DOCTOR OF PHILOSOPHY

Assessing the psychosocial impact of monoclonal gammopathy of undetermined significance (MGUS)

Murphy, Blain

Award date:
2020

Awarding institution:
Queen's University Belfast

Assessing the psychosocial impact of monoclonal gammopathy of undetermined significance (MGUS).

Presented to:

The School of Medicine, Dentistry and Biomedical Sciences,

Queen's University Belfast

for the degree of

DOCTOR OF PHILOSOPHY

by

Blain Murphy

BSc (Hons) Psychology

MSc Applied Psychology (Mental Health and Psychological Therapies)

October 2019

Volume 1/2: Thesis

Table of Contents

Table of Figures

Table of Tables

Acknowledgements

I would like to thank my supervisors, Dr. Lesley Anderson, Dr. Olinda Santin and Professor Michael Donnelly for guiding my research and providing the opportunities and encouragement to develop my research interests. I would also like to thank Dr. Charlene McShane, without whom that path would have been a lot bumpier and more difficult. She is a star.

To all the staff in the Centre for Public Health in QUB, who were always willing to give a helping hand or direction. In particular, Dr. Charlene Treanor, Dr. Michael O'Rourke and the Cancer Epidemiology and Health Services research group for their support. I would also like to thank those who helped getting the projects off the ground; Nurses Jackie Quinn and Louise Gribben, Prof. Brian Johnson, Prof. Liam Murray, Dr. Michael McMullan and all the patients and charities that helped promote the research.

To those who have helped me in travelling and disseminating my research over my PhD; specifically, the Centre of Excellence NI, the Helen Ramsey-Turtle committee, QUB School of Medicine, Dentistry and Biomedical Sciences, PsyPAG, the Haematology Association Ireland and the Department of Education and Learning for helping provide these opportunities to travel.

To my PhD cohort in CPH (Niamh, Shannon, Andrea, Hannah, Caroline, Kishan and Emma). Their support (and cake) are key!

Finally, to my family and Aisling. Thank you for all the support through my extended education!

Abbreviations

Abbreviation	Category	Full name
CLL	Cancer	Chronic Lymphocytic Leukaemia
MM	Cancer	Multiple Myeloma
WM	Cancer	Waldenström's Macroglobulinemia
HAI	Conference	Haematology Association of Ireland
WONCA	Conference	World Organization of National Colleges, Academies and Academic Associations of General Practitioners/Family Physicians
HCP	Health Service	Health Care Professional
GERD	Medical Condition	Gastroesophageal reflux disease
HPV	Medical Condition	Human Papilloma Virus
BO/BE	Premalignancy	Barrett's Oesophagus
CIN	Premalignancy	Cervical intra-epithelial neoplasia
DCIS	Premalignancy	Ductal Carcinoma in Situ
IgM	Premalignancy	Immunoglobulin M Protein
LCIS	Premalignancy	Lobular Carcinoma in Situ
MBL	Premalignancy	Monoclonal B Cell Lymphocytosis
MGUS	Premalignancy	Monoclonal Gammopathy of Undetermined/uncertain significance
OLP	Premalignancy	Oral lichen planus
PIN	Premalignancy	Prostate intra-epithelial neoplasia
SMM	Premalignancy	Smouldering Multiple Myeloma
VAIN	Premalignancy	Vaginal intra-epithelial neoplasia
VIN	Premalignancy	Vulval intra-epithelial neoplasia
BIS	Questionnaire	Body Image Scale

BDI	Questionnaire	Beck Depression Inventory
CCI	Questionnaire	Charlestown co-morbidity Index
CES-D	Questionnaire	Center for Epidemiological Studies Depression
EORTC QLQ	Questionnaire	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
EQ-5D	Questionnaire	EuroQol five-dimension scale
EPQ	Questionnaire	Eysenck personality questionnaire
FACT	Questionnaire	Functional Assessment of Chronic Illness Therapy
GASP	Questionnaire	Guilt and Shame Proneness Scale
GERQ	Questionnaire	Gastroesophageal reflux questionnaire
GERD-HRQOL	Questionnaire	Gastroesophageal reflux disease Health related QoL
GHQ-	Questionnaire	Goldberg's General Health Questionnaire
GIQLI	Questionnaire	Gastrointestinal Quality of Life index
IES (RIES)	Questionnaire	Impact of Events scale (Revised)
MHLCS	Questionnaire	Multi-Dimensional Health Locus of Control Scale
MOS-SS	Questionnaire	Medical Outcomes Study social support
PEAPS	Questionnaire	Psychosocial Effects of Abnormal Pap Smears
POSM	Questionnaire	process outcome specific measure,
PSI	Questionnaire	Psychiatric Symptom Index
QOLRAD	Questionnaire	Quality of Life in Reflux and Dyspepsia
RDQ	Questionnaire	Reflux Disease Questionnaire
SCL-90R,	Questionnaire	Revised Hopkins Symptom Checklist:
SF-(8,12,20,36)	Questionnaire	The Short Form Health Survey
STAI	Questionnaire	The State-Trait Anxiety Inventory
TIPS	Questionnaire	Trust in Physicians Scale
WHOQOL-BREF	Questionnaire	World Health Organization Quality of Life Instruments- Brief

AiMs	Study Name	Assessing the impact of MGUS
PIP	Study Name	Psychosocial impact of a Premalignant condition
BM	Study Team	Blain Murphy
CMcS	Study Team	Charlene McShane
CT	Study Team	Charlene Treanor
LAA	Study Team	Lesley A Anderson
MD	Study Team	Michael Donnelly
OS	Study Team	Olinda Santin
PPI	Research Term	Patient Public Involvement
ASCT	Research Term	Autologous Stem Cell Transplantation
IMWG	Research Organisation	International Myeloma Working Group
SERP	Diagnostic test	Serum Protein Electrophoresis
HMRN	Research Organisation	Haematological Malignancy Research Network

Abstract

Monoclonal gammopathy of undetermined significance (MGUS) is a premalignant plasma cell disorder which precedes multiple myeloma (MM), an incurable blood cancer. To date, limited research has focused on the psychosocial impact of receiving a MGUS diagnosis. This dissertation reports the findings from an exploratory-sequential mixed methods programme of work conducted to explore the lived experiences of MGUS patients with comparison to other premalignant conditions.

To enable comparison with other premalignant conditions, a mixed methods systematic review investigating the psychosocial impact of being diagnosed with a premalignant condition was conducted. A total of 75 studies (21 qualitative, 53 quantitative questionnaire based and one mixed methods studies) were included with quantitative data pooled using random-effects meta-analysis and qualitative data using meta-synthesis techniques. From the meta-synthesis, several themes were evident such as poor information provision, heightened anxiety post-diagnosis and unmet support needs. In contrast, no significant differences in quality of life measures were observed among patients with premalignant conditions compared to controls in pooled analysis of generic QoL or psychosocial wellbeing instruments.

Three separate studies focusing on MGUS were undertaken to investigate the viewpoints of MGUS patients and healthcare professionals (HCPs). The first study described is a qualitative study involving focus groups and individual telephone interviews with 14 MGUS patients undertaken in Northern Ireland to investigate the impact of receiving a MGUS diagnosis from a patient perspective. Transcripts were analysed using inductive thematic analysis. From this study three main themes were identified: (1) Experiences of MGUS health services, (2) The psychosocial impact of an MGUS diagnosis and (3) Knowledge of MGUS. These findings indicated unmet needs for MGUS patients; which left patients isolated and confused post-diagnosis.

The second study reports on findings from a paper-based cross-sectional survey carried out among haematology HCPs (such as haematologists and specialist nurses) attending an all-Ireland haematology conference to explore the words and language used to describe MGUS to patients at their diagnosis. They used terms such as a "*blood condition*" or compared it to "*like a mole we need to watch*". A total of 54 HCPs including 13 from Northern Ireland and 41 from Republic of Ireland responded to the survey. This study found that haematology staff attempted to use lay language to explain the diagnosis to patients and informed the majority of patients about their risk of progression to cancer. Less than half give out an information booklet to all patients and all believed that MGUS patients should be followed up; with the majority wanting haematology to provide care rather than primary care.

A separate online survey of GP/ GP trainees was undertaken to investigate GP/GP trainee knowledge of MGUS. The survey was promoted online using social media and the WONCA Europe Conference. A total of 58 GPs and GP Trainees from 25 countries responded. Overall, low levels of MGUS knowledge were observed for both GPs and GP trainees and the majority (88%) stated that they would not be confident in speaking with newly diagnosed MGUS patients. The increased risk of haematological malignancies was identified by 62.1% of GPs/GP trainees with MM, lymphoma and myelodysplastic syndromes the most commonly reported cancers associated with MGUS. The need for MGUS focused information and education resources for GPs was also highlighted.

Data from the previous studies was triangulated to develop an online mixed methods instrument to assess QoL and psychosocial wellbeing of premalignant patients; including MGUS (n=171) and smouldering multiple myeloma (SMM) (another premalignant plasma cell disorder) (n=60) patients. The survey was promoted using social media and online patient support groups and included validated instruments such as EQ-5D, SF-12, EQ-5D and HADS. The main findings identified a significant decrease in QoL and

psychosocial wellbeing (including increased levels of clinically relevant anxiety and depression) for MGUS patients compared to population norms and SMM patients. Qualitative analysis also indicated that MGUS and SMM patients lived with the fear of a future progression to cancer and a lack of both informational and psychosocial support from both their peers and their healthcare professionals. However, MGUS patients reported more detrimental effects of their diagnosis due to the higher levels of uncertainty and reported more concerns about their surveillance.

In summary, the studies included within this dissertation suggest that for some patients MGUS can have a significant psychosocial impact. This dissertation recommends the development of informational resources for clinicians and patients to help inform about MGUS, and better availability of peer and health service support for MGUS patients.

1 Chapter 1: Introductory chapter.

"(MGUS) is not something you hear (people) talking about, anybody talking about"

(Telephone interview 102, AiMs Study)

Monoclonal gammopathy of undetermined significance (MGUS) is a premalignant precursor of multiple myeloma (MM), a haematological malignancy with poor 5-year survival rates (1,2). MGUS is an asymptomatic condition, usually found upon routine screening or during investigations for other conditions (3).

1.1 Thesis Rationale

This research describes an investigation of the psychosocial and quality of life (QoL) factors associated with receiving and living with an MGUS diagnosis. The main objective of the research was to determine the psychosocial and QoL impact of an MGUS diagnosis. This was investigated through an exploratory sequential mixed methods design (4,5). This model was chosen due to a gap in the knowledge/literature on the psychosocial impact of MGUS on patients. The exploratory sequential design is useful as it initially collects and analyses qualitative data, whose themes drive the development of quantitative research to further explore the research problem and provide a more generalisable perspective in the final report (5,6); as shown in Figure 1-1.

This introductory chapter (i) sets out the research questions and aims that are addressed by the PhD study, (ii) provides a background to MGUS and associated conditions and (iii) considers and discusses the definitions and measurement of QoL and psychosocial wellbeing, respectively, that are used in the PhD study.

The first research activity that was undertaken as part of the PhD programme was a systematic review of studies that investigated the QoL/wellbeing of all

premalignant conditions (Chapter 2). The results of this review informed the design of a qualitative study of patients' views and experiences (Chapter 3). The recognition that other perspectives would improve the structure of the discussion of the psychosocial impact on patients led to the conduct of two surveys, one on haematology professionals and one on general practitioners (GPs) and trainees (Chapter 4). The final study was a survey of premalignant patients (Chapter 5). Collectively, the data generated informed a discussion of the psychosocial impact of MGUS in Chapter 6.

An exploratory sequential design was deemed to be the most appropriate design (compared to convergent, parallel and explanatory sequential designs) to investigate the psychosocial impact of MGUS. This paradigm was chosen as the exploratory component (qualitative study) allowed the research to identify the main issues for MGUS patients. This was important as there was a lack of prior knowledge/surrounding literature available in this area. Similarly, using a quantitative measure to identify if these issues were more generalisable to other premalignant conditions and to MGUS patients outside of Northern Ireland would provide greater insight and context/clarification. The final design utilised was similar to multi-phase design (4,5) as the quantitative surveys incorporated mixed methods and smaller qualitative components than initially envisioned.

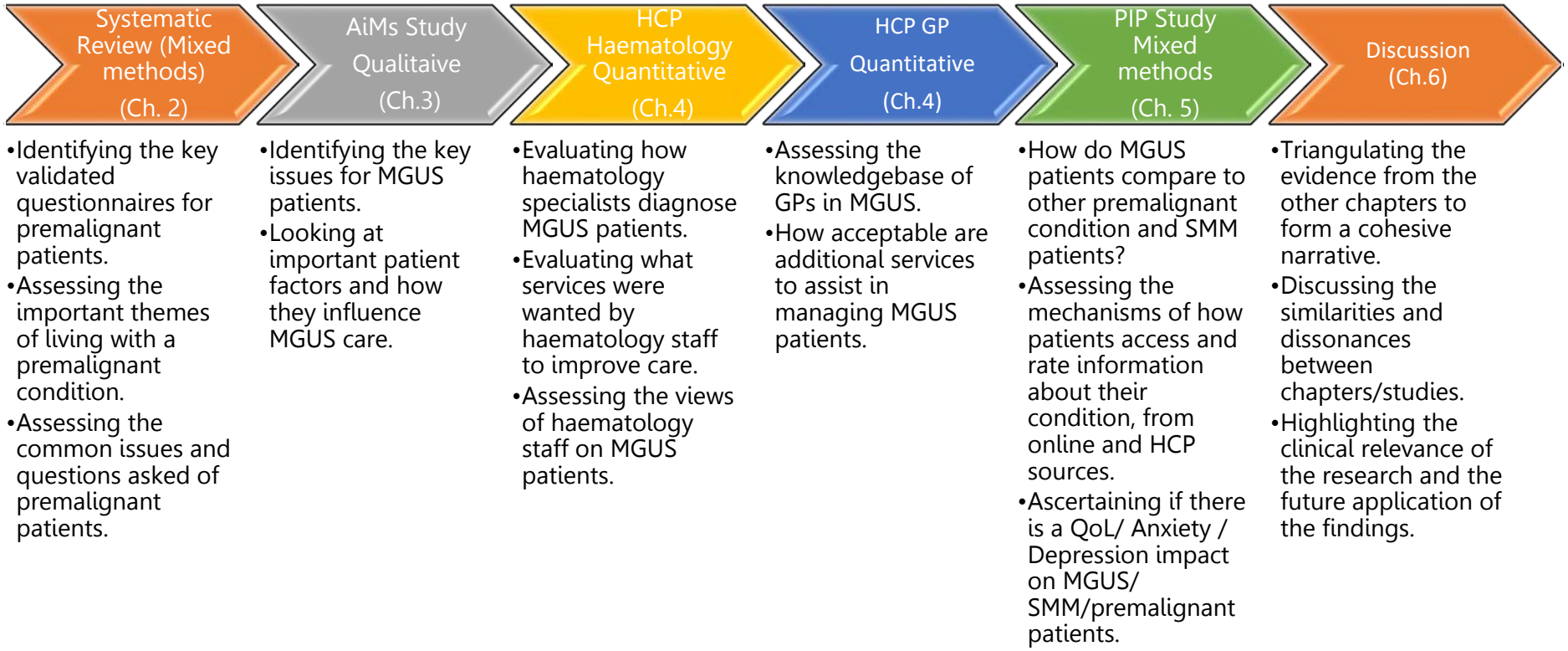


Figure 1-1 Exploratory Sequential design of the dissertation.

MGUS: Monoclonal gammopathy of undetermined significance; AiMs: Assessing the impact of MGUS; HCP: Healthcare professionals; GP: General practitioner; QoL: Quality of Life; PIP: Psychosocial impact of a Premalignant condition study; SMM: Smouldering Multiple Myeloma

1.2 Research Questions

This dissertation addressed the following research questions:

1. What is the perceived impact by patients of receiving a diagnosis of MGUS:
    a. on an individual's QoL and psychosocial wellbeing?
    b. compared to other pre-malignant conditions?
2. What are the health and social care needs of patients with MGUS?
3. How do key healthcare professionals interact with, and care (physical and psychosocial) for MGUS patients?
4. What is the formal or informal pathway that MGUS patients 'travel' to receive a diagnosis, treatment and care?

1.3 Thesis outline

1.3.1 Chapter 1: Introductory chapter

This chapter aimed to provide an overview of the dissertation and describe MGUS and related plasma cell disorders; including clinical relevance and known epidemiological evidence. The chapter also defined QoL and psychosocial well-being and the instruments used to measure these concepts.

1.3.2 Chapter 2: A Mixed Methodological systematic review of the psychosocial and QoL effects of a premalignant condition.

This chapter aimed to explore the experiences of patients with a premalignant diagnosis through a mixed methods systematic review, using meta-analysis and thematic synthesis, to inform the research on MGUS in the remainder of the dissertation.

1.3.3 Chapter 3: Assessing the impact of MGUS (AiMs study). A patient's perspective.

This chapter described and discussed an in-depth qualitative investigation which aimed to investigate the impact of MGUS on patients in Northern Ireland. Combining focus groups and individual telephone interviews; this chapter provided novel MGUS-specific data to inform on the issues and challenges (if any) encountered by MGUS patients to inform the subsequent studies.

1.3.4 Chapter 4: MGUS as viewed by healthcare professionals (HCPs) in Haematology and General Practice.

This chapter described and discussed two surveys conducted with HCPs involved in MGUS care. The first survey at a national haematology conference assessed how haematology professionals (haematology doctors, nurses and allied health professionals) diagnosed and communicated the diagnosis with MGUS patients. The second survey assessed the knowledge and experience of GPs and GP trainees with MGUS in an international online survey. This chapter provides a primary healthcare perspective on MGUS care informing the healthcare pathway of patients and the clinical relevance of the dissertation findings for clinical recommendations.

1.3.5 Chapter 5: The impact of an MGUS/SMM (smouldering multiple myeloma) diagnosis. Results from the Psychosocial impact of a Premalignant condition study (PIP).

This chapter described and discussed an online mixed methods survey on premalignant conditions which combined validated QoL/wellbeing instruments with a researcher-created questionnaire; based upon the previous research. The results primarily focused on MGUS and SMM (an asymptomatic plasma cell disorder similar to MGUS (7) but with a higher progression risk to MM than MGUS) patients, with comparison to other premalignant patients and population norms. This survey examines relevant questions gleaned from the previous research and was the first large-scale QoL/wellbeing survey on MGUS or SMM.

1.3.6 Chapter 6: Discussion Chapter.

Chapter 6 brought the findings together and discussed these in relation to MGUS and the surrounding literature on other premalignant conditions identified in the review and cancers. The findings indicated that the experience of MGUS patients is similar to that of other premalignant conditions but some issues affected MGUS patients more than other conditions. These are explored in the chapter under four topics; 'The psychosocial impact of an MGUS diagnosis', 'Becoming informed on MGUS', 'MGUS supports and health services' and finally comparing MGUS to its progressions (SMM and MM). The chapter concludes by highlighting the strengths and weaknesses of the dissertation, outlining the clinical recommendations from the findings and highlights the future direction the research can take to answer further questions.

As the research was conducted as part of a team, Figure 1-2 highlights the input of each member of the team in developing each study.

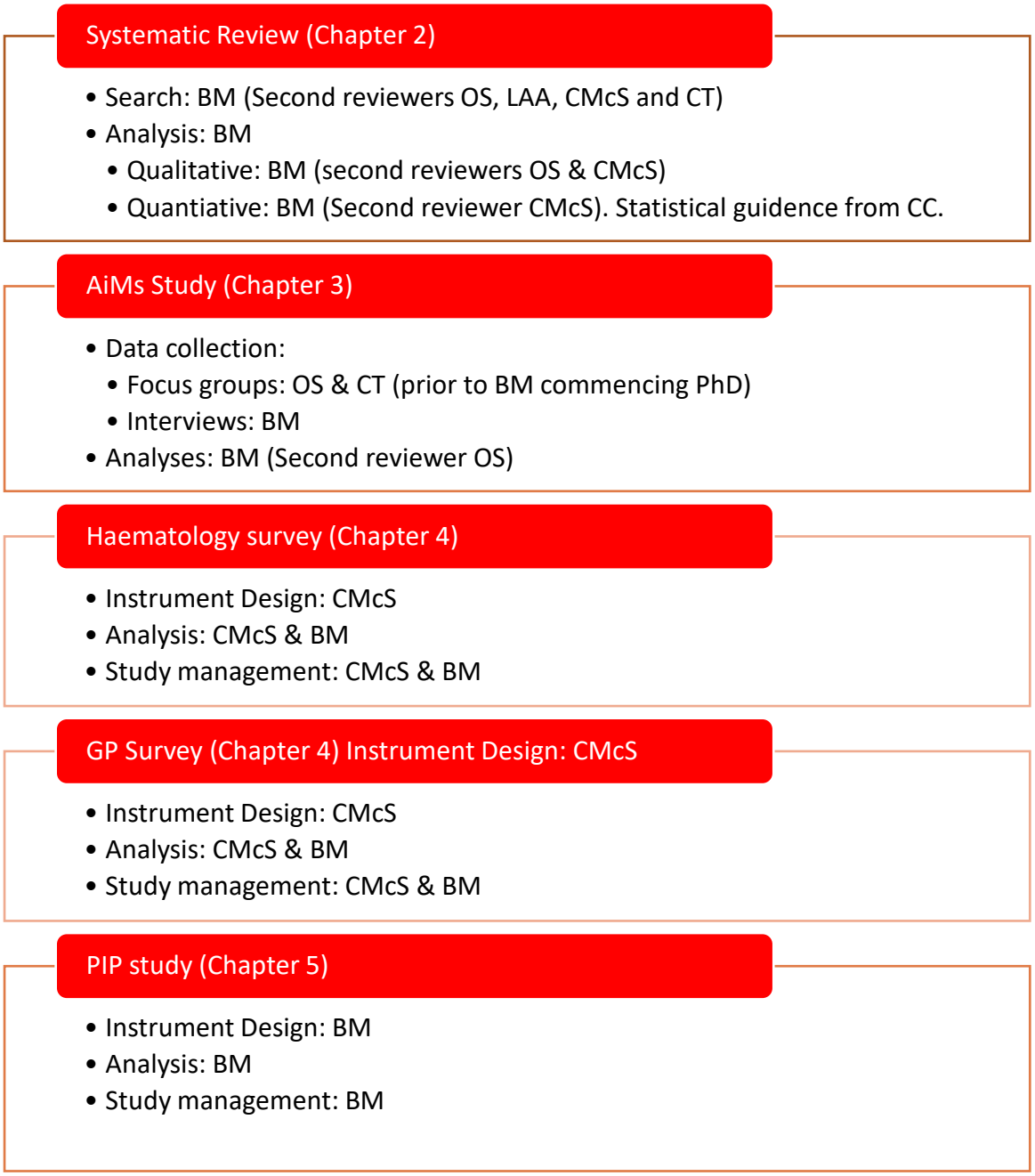


Figure 1-2 Visual representation of division of work in the dissertation [i].

[i] BM: Blain Murphy (Author), OS: Dr. Olinda Santin (Supervisor), LAA: Dr. Lesley A. Anderson (Supervisor), CMcS: Dr. Charlene McShane (Post-doctoral researcher), CT: Dr. Charlene Treanor (Post-doctoral researcher) & CC: Dr. Chris Cardwell (Statistician).

1.4 Introduction

This chapter focuses on two areas; the current knowledge of MGUS and related conditions and how QOL/ well-being is measured and defined throughout the dissertation, Figure 1-3.

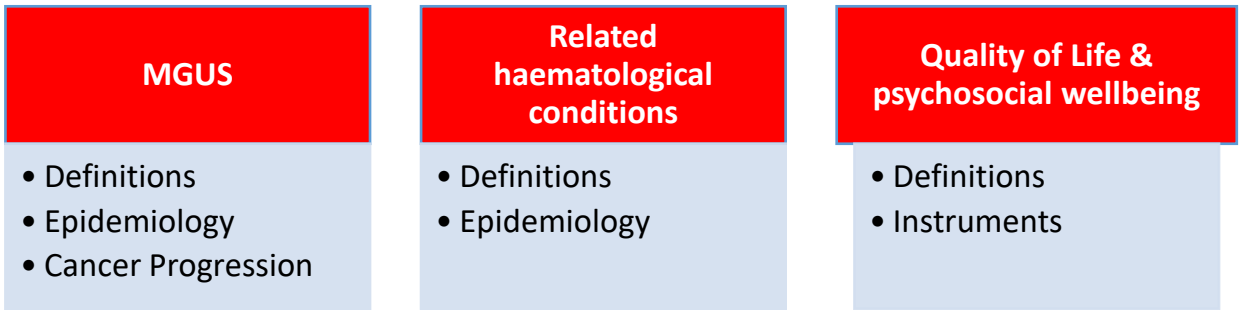


Figure 1-3 Chapter 1 overview of central themes.

1.5 Definitions and diagnostic criteria of MGUS and related disorders

1.5.1 Plasma Cell disorders

Plasma cells develop from B lymphocytes, a type of white blood cell, and are part of the bodies defence mechanism against disease. Plasma cells produce immunoglobulins, also known as antibodies. When plasma cells multiply uncontrollably, they release excessive amounts of a single antibody, a monoclonal antibody, leading to plasma cell disorders/dyscrasia which are an "inclusive designation for the monoclonal or unbalanced proliferation of immunoglobulin-secreting cells" (8). One of the plasma cell disorders that can be diagnosed as a result is MGUS. Other plasma cell disorders[i] include SMM, MM, Waldenström's macroglobulinemia (WM) and Systematic immunoglobulin light chain (AL) amyloidosis. These conditions are discussed separately below.

1.6 Monoclonal gammopathy of undetermined significance (MGUS)

1.6.1 What is MGUS?

MGUS was coined by Robert Kyle and colleagues in the Mayo Clinic (Minnesota, USA) in 1972 to describe the proliferation of a monoclonal gammopathy related to progression to MM (9). This created a new class of non-malignant monoclonal gammopathy-based upon the level of M protein in the plasma cells and an absence of end-stage organ damage- whose progression was linked to MM and other haematological malignancies (9).

---

[i] Monoclonal gammopathy of undetermined significance (MGUS): Page: 25

Smouldering multiple myeloma (SMM): Page 39

Multiple myeloma (MM): Page 40

Waldenström's macroglobulinemia (WM): Page 41

Systematic immunoglobulin light chain (AL) amyloidosis: Page 42

1.6.2 Clinical guidelines on MGUS; clinical criteria, testing/diagnosis and monitoring procedures

MGUS is an asymptomatic condition, usually found upon routine screening or during investigations for other conditions (3). MGUS is diagnosed using the serum protein electrophoresis (SERP) test after "clinical suspicion of an M-protein related disorder or when the results of other tests raise the possibility of the presence of an M-protein" (10,11). Abnormal SERP results which indicate MGUS are (12):

- raised erythrocyte sedimentation rate (ESR) or plasma viscosity.
- unexplained anaemia, hypercalcaemia or renal failure.
- raised total protein/globulin or immunoglobulins, particularly if one or more immunoglobulin classes (IgG, IgA, IgM) are reduced.
- reduction of one or more immunoglobulin class (IgG, IgA and IgM) levels.

Following initial SERP testing, further testing (complete blood count, serum calcium, creatinine, free light chain count (FLC), immunofixation, and 24-hour urine protein electrophoresis) is performed to determine MGUS type (IgM, non-IgM or light chain MGUS, Table 1-1) (13). These subtypes have different clinical features, progression rates and are related to progression to different haematological malignancies, Table 1-1.

The International Myeloma Working Group (IMWG) defines the parameters of MGUS as having a serum M protein <30g/l, <10% clonal plasma cells (PCs) in the bone marrow and, most importantly, the absence of end-organ damage that can be attributed to the PC proliferative disorder or other B-cell proliferative disorders (10,11) (Table 1-1). End-organ damage is assessed using the CRAB criteria (hypercalcemia, renal insufficiency, anaemia, bone lesions), when referring to a clonal plasma cell proliferative disorder (10,11). The absence of end-stage organ damage (CRAB criteria) indicates MGUS or the higher risk precursor (smouldering multiple myeloma/SMM) rather than the malignant stage MM.

MGUS patients are stratified as low or high risk by the Mayo clinic risk stratification model (14); based on <1.5 gm/dL, IgG type, normal FLC ratio or IgM <1.5gmdL or

light chain MGUS with FLC <8. The majority of MGUS patients are placed on active surveillance (AS) protocols. Some patients are deemed unfit for surveillance due to competing life-reducing comorbidities. Higher risk patients can have skeletal imaging (either conventional radiographic survey or low-dose whole body CT) and bone density central dual-energy x-ray absorptiometry conducted based on clinician experience and judgement; as these procedures are invasive and costly for asymptomatic patients (13). Current guidelines do not support routine screening for MGUS, as there are no curative or preventative treatments for progression to malignancy (12,15,16).

The current International Classification of Diseases (ICD)-10 (code D47.2) classifies MGUS as a "neoplasm of uncertain or unknown behaviour" (17). There are currently no UK National Institute for Health and Care Excellence (NICE) guidelines for MGUS, with the only guidance based within their guidelines for MM (18).

Table 1-1 International Myeloma Working Group criteria and classification of MGUS: adapted from International Myeloma Working Group criteria 2014 (9)

Name	**Features**	**Proliferative disorders progression**	**Malignancies** (14)
IgM monoclonal gammopathy of undetermined significance	• Serum IgM monoclonal protein <30 g/L. • Bone marrow lymphoplasmacytic infiltration <10%. • No evidence of anaemia, constitutional symptoms, hyper-viscosity, lymphadenopathy, hepatosplenomegaly, or other end-organ damage that can be attributed to an underlying lymphoproliferative disorder.	1.5% (19)	IgM myeloma, Waldenström's macroglobulinemia, Immunoglobulin-related amyloidosis (19)
Non-IgM monoclonal gammopathy of undetermined significance	• Serum monoclonal protein (non-IgM type) <30 g/L. • Clonal bone marrow plasma cells <10%. • Absence of end-organ damage (CRAB criteria) or amyloidosis that can be attributed to the plasma cell proliferative disorder.	1% (19)	Multiple myeloma, Solitary plasmacytoma, Immunoglobulin-related amyloidosis (20)

Name	• **Features**	**Proliferative disorders progression**	**Malignancies** (14)
Light-Chain monoclonal gammopathy of undetermined significance	• Abnormal FLC ratio (<0·26 or >1·65). • Increased level of the appropriate involved light chain (increased κ FLC in patients with ratio >1·65 and increased λ FLC in patients with ratio <0·26). • No immunoglobulin heavy chain expression on immunofixation • Absence of end-organ damage (CRAB criteria) or amyloidosis that can be attributed to the plasma cell proliferative disorder. • Clonal bone marrow plasma cells <10%. • Urinary monoclonal protein <500 mg/24hr.	0.3% (21)	Light Chain Myeloma, Immunoglobulin-light-chain amyloidosis (21)

1.6.2.1 Surveillance and monitoring procedures

MGUS patients undergo active surveillance; which is consistent lifelong/long-term follow-up (10,22). MGUS surveillance consists of a; "complete blood count, SPEP, FLC, calcium, and creatinine testing to determine clinical stability and detect rapidly evolving lymphoplasmacytic malignancies (LPMs)" at regular intervals (13). The International Myeloma Working Group risk stratification model is the current gold standard for monitoring practices; stating all MGUS patients should be monitored every 6 months for the first two years (10). After two years, high risk patients should be monitored annually and low risk patients every 2/3 years or if any symptoms emerge (10). The British Society for Haematology recommends surveillance every 6/12 months for all MGUS patients indefinitely (22).

Surveillance frequency is important as progression rates do not alter with time and surveillance incurs significant costs (23,24). MGUS has a continued progression rate (approximately 1% per annum) more than 20 years post-diagnosis (16). However, optimal monitoring (seen at least every 36 months, 69% of patients) leads to more diagnoses of SMM and earlier diagnoses of MM (25).

Previous research promotes the individualisation of MGUS monitoring, taking into consideration risk factors associated with progression (age, race and occupational factors) to determine optimal surveillance frequency and method (26,27). This may help reduce the monetary and staff burden on the health services and the potential emotional cost of monitoring for patients at low risk of progression (27). Discontinuing surveillance for those with low life expectancy (<5 years due to advanced age and/or significant co-morbidities) can reduce monetary, staff and potential patient emotional burden, as these populations are likely to die of competing causes (16,27). Evidence suggests surveillance should be consistent irrespective of type as despite lower progression rates (0.3% per annum), light chain MGUS patients have a high risk of developing renal disease (21,26).

The terms of watchful waiting and active surveillance are used interchangeably in literature published about prostate cancer surveillance (28,29). These terms have similar meanings but often used in different contexts. It is important to clarify there use within the dissertation as the terms can have different connotations to readers.

Watchful waiting is considered in the literature as more closely related to palliative care approach (28–30); while active surveillance is more associated with the practice of closer monitoring of predefined thresholds for potential early treatment with signs of progression (30,31). To maintain consistency within the dissertation, active surveillance is the terminology used; as MGUS is asymptomatic and a non-palliative/fatal condition, which is monitored through the use of predefined thresholds.

Outreach surveillance services, such as telephone clinics for low risk cases, can reduce waiting times and patient and staff costs, and have high patient satisfaction (26,32). The procedure consists of phlebotomy conducted at GP clinics and samples sent to a central lab for testing. Haematology nurses telephone patients with results and assess patients about their general health (32).

1.6.3 Epidemiology of MGUS

This section reports on the incidence, prevalence and survival statistics related to MGUS to describe the nature and size of the problem. The final section outlines the rate of progression to MM from MGUS.

1.6.3.1 Incidence

MGUS is an asymptomatic condition usually diagnosed incidentally or during investigation for another condition; therefore, the true incidence, i.e. the number of new cases in a specified timeframe, is difficult to ascertain with many individuals unaware that they have MGUS, remaining undiagnosed. Evidence regarding incidence rates is limited to three studies internationally, which were conducted in USA, Iceland and the Netherlands (33–35).

The Olmsted county study (USA), a cohort study in a single county, reported an incidence rate of 65 and 122 per 100,000-person years (PY) follow-up for females and males aged 50 years old and older respectively. Incidence increased with age, with those over 70 years having an incidence rate of 188 and 278 per 100,000 PY for

females and males respectively (35,36)[i]. An Icelandic registry study reported an age standardised incidence rate of 8.5 and 10.6 per 100,000 PY for females and males respectively (33). A Dutch registry study reported an incidence rate of 31 per 100,000 PY for females and males combined (34). Neither the Icelandic or Dutch studies reported an age-standardised incidence[ii]. Therefore, it can be difficult to compare these studies with studies which report age-standardised incidence, such as the Olmsted county study respectively (35,36); which indicates the incidence in more relevant age categories (over 50 years old). Individuals are estimated to have MGUS for an average of 15 years (mean 10-19 years) preceding diagnosis (35,36); due to the lack of population-wide SERP screening conducted.

Published data on MGUS incidence underestimates the true incidence in the population (35) in the absence of a comprehensive screening trial. Therefore, there may be large numbers of individuals living with MGUS who are unaware and undiagnosed. A large scale study, iStopMM (37), is currently being conducted in Iceland by Prof. Sigurdur Kristinsson, consisting of 140,000 Icelanders over the age of 40 years. There are currently no substantial findings released on this study.

1.6.3.2 Prevalence

MGUS prevalence, i.e. the number of people living with a condition within a specified timeframe, has been documented in various populations (9,36,38–43). Kyle's seminal 1972 paper reported a prevalence of 1.52% in over 50-year-olds in Thief River Falls, Minnesota (USA) (44) . The landmark prevalence paper in Olmsted County, Minnesota reported a prevalence of 3.2% (over 50 years old) in the first population-based study of MGUS (36). This increase may be due to the technological advances in blood screening (SERP (2006) compared to cellulose acetate (1972) and a more robust sampling strategy, with a high participation rate (80.1%). The study performed

[i] As will be described in Section 1.6.4.2 (page 36), males are more likely to have an MGUS diagnosis (10,11,36,69,70). However, there is currently no evidence as to the reason for this difference.

[ii] As will be described in Section 1.6.4.1 (page 36), as MGUS risk increase greatly after the age of 50 years (33–35,621), age standardization is important in relation to incidence rates.

further analysis on non-residents prior to 1972 (moved into Olmsted county post 1972), which had a similar demographic and prevalence rate (prevalence 3.7%) (36).

A systematic review on MGUS prevalence reported a large variation; ranging from 0.05% to 6.1% (45). Studies had a range of designs; including population-based (36,38) and hospital-based cross-sectional designs (46,47). A subset of recent articles (since 1990) reported prevalence rates of approximately 3% (range 2.1% to 6.1%) (36,38,46–48). The highest prevalence rates used the most sensitive measures, (agarose gel electrophoresis), to detect MGUS and focused on the over 50 year old age group (36,38,45,47,48). Lower prevalence studies included younger age groups (43,49,50), and/or used less sensitive testing agents (Cellulose acetate) (49,50).

Asian populations have reported lower prevalence of MGUS; indicating a lower susceptibility to MGUS (39–41). A Thailand-based study (40) using high-resolution gel electrophoresis reported a prevalence of 2.3% from 3,260 people over 50 years of age. However, this cohort had a lower median age than the USA study (USA (65.9 years) (36):Thailand (57.0 years) (40)). The Thai study also only included visitors to community health centres on one day; which was not a representative sample. A Hong Kong based study (41) reported a prevalence of 0.8%; but had a small sample size (n=1000) and limited age range (50-65 years old; median 57 years).

UK MGUS prevalence is limited; however, the Haematology Malignancy Research Network (HMRN) reported 3,601 per 100,000 patients (3.6%) diagnosed with MGUS in 2011 (51). An MGUS registry is currently under construction to assess prevalence and advise future policy and service provision in Northern Ireland. Overall, more sensitive testing and population ageing is increasing the reported prevalence of MGUS.

1.6.3.3 Progression rate of MGUS to MM

MGUS patients have a 1% risk of progression to MM each year, consistent over at least 20 years (16). Progression rates are variable dependent on MGUS type (IgM, Non-IgM or Light chain MGUS), Table 1-1. Why some patients progress, and others have ‘long lasting’ MGUS is not fully understood in the literature. Progression

involves serial changes in the levels of monoclonal immunoglobulin and the serum free light chains (FLC) (52). An increasing abnormal serum FLC increases the risk of progression (26). Other studies have reported that those with higher levels of bone marrow cells (6-9% compared to 0-5%), increased bone marrow angiogenesis and circulating peripheral blood plasma cells have an increased risk of progression (53–55). The risk stratification model for MGUS is described in Table 1-2. One theory is that MGUS is a very slowly growing myeloma, which changes to a faster growth rate given an internal or external yet unknown stimulus leading to the development of MM (56).

Table 1-2 Risk stratification Model adapted for stratifying MGUS risk. (57)

Risk level	Relative risk (%)	Absolute risk (%) of progression at 20 years	Absolute risk (%) of progression at 20 years accounting for death as a competing risk
Low risk Serum m-protein <15 g/dl, IgM subtype, normal FLC ratio (0.26-1.65)	1	5	2
Low-intermediate (any 1 factor abnormal)	5.4	21	10
High-intermediate (any 2 factors abnormal)	10.1	37	18
High-risk (all 3 factors abnormal)	20.8	58	27
Low risk Serum m-protein <15 g/dl, IgM subtype, normal FLC ratio (0.26-1.65)	1	5	2

1.6.3.4 Survival

MGUS patients have poorer overall survival (measured through relative survival ratios) than the general population (1-year survival: 0.98, 5 years: 0.93, 10 years: 0.82, 15 years: 0.70) (58). That study identified no difference in mortality rate between different MGUS subtypes or M-protein concentration levels. This survival difference is likely affected by other factors as many patients were incidentally detected as a result of investigation for other co-morbidities (59–61). A Dutch registry study reported a survival rate of 4.6 years less than population norms for MGUS patients with similar gender and age distribution (60). They also found a higher serum albumin level (over 40g/l) had a median survival time of 8.5 years compared to a low rate (under 30g/l) which had a median survival rate of 1.9 years (60).

A prior diagnosis of MGUS before the development of MM was associated with increased survival times after MM diagnosis (32 months vs 25 months, respectively; 2.7% had a prior MGUS diagnosis) (61). The reasons were unclear but may be due to earlier diagnosis and lead time bias (MM was detected at an earlier stage in MGUS patients but had no effect on mortality rate). A Surveillance Epidemiology and End Results (SEER)-Medicare/ linked study reported similar findings (23 vs 18 months survival, respectively; 6% had a prior MGUS diagnosis) (62).

1.6.4 Aetiology of MGUS

Several risk factors have been suggested to increase the risk of developing MGUS. Many of these aetiological factors have been found and supported by large scale cohort studies (20,63,64) and systematic reviews (45,65,66).

1.6.4.1 Age

Older age is associated a higher risk of MGUS (11,12,19,34,36,45,56,66). The prevalence of MGUS increases with age; with a rate of 1.7% in those aged 50 to 59 years, which rises to over 5% in those older than 70 years (67). There is no accepted rationale to explain the increased prevalence of MGUS in relation to age, due to no accepted "cause" of MGUS (68).

1.6.4.2 Sex

Males are more likely to have an MGUS diagnosis than females (10,11,36,69,70); with MGUS 1.3 to 1.8 times more likely in males (45). The Haematological Malignancy Research Network indicated that prevalence was higher in males than females in the UK (71). While males are more likely to have an MGUS diagnosis, there is currently no evidence as to the reason for this difference.

1.6.4.3 Race/ethnicity

MGUS is more prevalent in those of African descent with a prevalence of 5.9% and 9.4% (compared to 3.2% in white populations (36,45)) reported in studies conducted in the USA and Ghana respectively (38,48). US African-American veterans had a 3-fold increased prevalence than Caucasian veterans; but both races had similar progression rates (17% vs 15% of MGUS cases) over 10 years of surveillance (43). It has been suggested that the higher risk levels for black individuals may be due to

racial predisposition rather than dietary or environmental factors, however, research is limited (38,43).

Asian populations have a lower prevalence of MGUS than Caucasian and Black populations (39–41); approximately a 50% low rate than Caucasians in the USA (36). Mexicans also have lower prevalence rates (0.7%) (72). For Persian descent, an Iranian hospital-based population reported a prevalence rate of 3.98% (42). Their sample were patients in their district who had been referred to a local pathobiology lab. This may have artificially increased prevalence as blood samples are more likely to have come from patients which a suspected health problem and the break-down of why patients were referred was not provided (42). Comparisons across races/ethnicities have been limited by the lack of large co-ordinated screening programmes conducted.

1.6.4.4 Lifestyle Factors

Alcohol (73), obesity (121) and tobacco (74) use have been associated with an increased risk of MGUS in observational studies. The increased risk of MGUS from alcohol consumption was linked to heavy alcohol users having more contact with health services and increased blood testing; which led to an incidental MGUS diagnosis (73). Obesity is linked to higher progression rates to malignancy (75). This also may be linked to higher co-morbidities and health service utilisation (76). Heavy tobacco usage is a risk factor for haematological malignancies (77), including MGUS (74). Smokers have generally higher co-morbidities (78).

1.6.4.5 Occupational factors

Farmers, industrial workers and groups working with toxins have an increased risk of MGUS (45). Specifically, exposure to; fertiliser, pesticides, asbestos, radiation, aromatic hydrocarbons and paint related products increase the risk of MGUS significantly (45,79,80). Individuals over 70 years old involved in Operation Ranch Hand -which involved herbicide spray missions utilising Agent Orange in the

Vietnam war- were 2.4 times more likely to be diagnosed with MGUS (prevalence 7.1% compared to 3.1% in controls) (45,64).

Previous studies found a significantly higher prevalence of MGUS in those who had received a higher dose of radiation (39,77,80). However, a study on atomic bomb survivors in Japan (39) reported a lower prevalence rate (2.1%) than Mexican, Caucasian and Black populations (36,38,72). The Japanese study is considered an accurate cohort study as the cohort from Hiroshima and Nagasaki were measured through health screening annually since the 1980s for a multitude of cancers including MM (39). This may be confounded by the lower rate of MGUS in Asian populations previously described (39–41)

1.6.4.6 Genetic/Familial

Some small studies have suggested genetic links as a risk factor. Italian (81) and Icelandic (82) studies have indicated links but have been undermined by small samples sizes focusing on individual families and not adjusting for confounding risk factors (81). A review has indicated that the research into both the biological mechanisms and genetic markers lacks the confirmatory evidence and randomised controlled trials are needed to validate the genetic basis of MGUS (83). More research is needed to indicate a genetic influence.

1.6.4.7 Comorbid conditions

MGUS is more common in patients with autoimmune conditions, infections and neuropathies (62,65). Having any autoimmune condition was associated with a 42% increased risk of MGUS (65); with pernicious anaemia patients having a 67% increased risk. Bacterial and viral infections have been associated with an increased risk of MGUS (84,85). Interactions of the peripheral nerves and the monoclonal proteins are suggested rationale for the increased prevalence (69,86–88). This may be related to increased healthcare utilisation of these patients; however, a gap remains in the literature.

1.6.4.8 Associated conditions in MGUS patients

MGUS patients have a higher risk of other health conditions compared to the general population; such as heart problems (ischemic heart disease and congestive heart failure), liver issues, liver failure, cirrhosis, and renal disease (failure and glomerular) (58,69); likely due to an incidental diagnosis of MGUS. Irrespective of progression to malignancy, MGUS patients are more likely to develop bone disorders, such as fractures and osteoporosis (69).

1.6.5 Other haematological conditions related to MGUS

This section provides a short synopsis of the other haematological conditions which MGUS can progress to; SMM, MM, WM and AL amyloidosis. There is also a small section on another haematological premalignant condition: monoclonal B-cell lymphocytosis (MBL). Each section refers to the historical background, treatment options and epidemiology of the conditions

1.6.5.1 Smouldering multiple myeloma (SMM)

SMM is an asymptomatic plasma cell disorder similar to MGUS (7) but with a higher progression risk to MM than MGUS (89). Robert Kyle coined the term "smouldering multiple myeloma" to describe patients with abnormally high M-protein levels and percentage of plasma cells (above MGUS criteria) but lacking symptoms or CRAB criteria (monoclonal proliferation of plasma cells in the bone marrow, the presence of monoclonal (M) protein in the serum and/or urine, and disease-related end organ damage) (65).

A SMM diagnosis requires "the presence of a monoclonal protein level of >30g/l or more or a proportion of clonal plasma cells in the bone marrow of 10% or more but the absence of end-organ damage" due to a clonal plasma cell proliferative disorder (10). SMM patients undergo active surveillance, similar to MGUS patients, but with more frequent review (for intermediate and high risk patients) (90).

The incidence and prevalence of SMM is not well defined, but is estimated to be 8-20% of MM patients (90,91); with an estimated age-standardised incidence of 0.44 per 100,000 persons (90,92). SMM patients have a higher progression rate to MM than MGUS patients (10% per year for the first 10 years progression in SMM compared to 1% per annum in MGUS patients) (27).

There are two subtypes of SMM; evolving and non-evolving (93,94). Evolving SMM has a shorter progression time than non-evolving SMM (1.3 vs 3.9 years, respectively) due to increased M protein size (56,94); non-evolving SMM's M protein is more stable. The 2- and 5-year progression rates between evolving and non-evolving were 66% and 88% vs 12% and 58% respectively (93,94).

1.6.5.2 Multiple Myeloma (MM)

MM is a "cytogenetically heterogeneous clonal plasma cell proliferative disorder" (19,95), characterised by the production of monoclonal immunoglobulin by the malignant cells; with high levels of relapse (1,2). MM is diagnosed by "clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extra medullary plasmacytoma", evidence of end organ damage (CRAB criteria) or "uninvolved serum free light chain ratio≥100" (19) (Table 1-3).

MM patients often present late to healthcare services with non-specific symptomology, such as anaemia, fatigue and bone pain (due to intramedullary bone lesions) (96–98). Mean delay from initial healthcare visit to diagnosis is 99 days but this can range from 0 to 365 days (98).

Treatment is based upon risk-stratification at diagnosis; dependent on age, performance status, renal function and disease stage (95). The most prevalent methodology for staging is the Durie-Salmon staging (99) and the international staging system (100). These have been criticised for their complexity and subjectivity and lack of focus to disease burden and non-specificity for MM (95) respectively.

Autologous stem-cell transplantation (ASCT) and non-melphalan induction therapy is considered the optimal treatment for all patients (95). However, ASCT combined with high dose chemotherapy is the contemporary treatment for MM patients under

65 years (101). ASCT is usually conducted after induction (early) or after first relapse (delayed). Previous studies have shown no differences in survival between early or delayed ACST (95,102–104). The recommended pharmaceutical-based treatment is the combination of an alkylating agent and a proteasome inhibitor, such as bortezomib and carfilzomib (105). Combined with dexamethasone or prednisone (corticosteroids), it remains the stable combination for drug use for those not eligible for bone marrow transplant (95,106). Maintenance therapy involves bortezomib initially and ASCT can be utilised as a salvage therapy if sufficient stem cells were harvested previously. Survival rates have been improving consistently as pharmaceutical and ASCT use has increased (97).

MM has an age-adjusted incidence of 6 per 100,000 in the USA and Europe, is more common in males and the median age of diagnosis is 69 years (107). The HMRN estimates 4,470 MM diagnoses in the UK annually (108). Incidence has been rising in the UK since the early 1990s (109). There was an annual average increase of MM cases in NI (men 2.1%: women 0.6%) (110); which is expected to continue (110). Within Northern Ireland, there are approximately 158 cases annually (110). Diagnosis under 50 years old is rare, with only 5 cases of MM before 50 years in NI between 2013-2017 and none under 40 years (111); similar to UK values from the HMRN (22). Cancer Research UK (CRUK) estimates 17,600 individuals were living with MM in the UK (112). MM has an average survival rate (for older patients) 5.2 years (113) and a five year survival rate of 47.4% in NI (111); while 33% of patients survive MM for 10+ years (112).

1.6.5.3 Waldenström's macroglobulinemia (WM)

WM is an "indolent but incurable B-cell non-Hodgkin lymphoma characterized by the presence of a lymphoplasmacytic infiltrate in the bone marrow and immunoglobulin M monoclonal gammopathy" (114,115). WM is characterised by; "the presence of any size serum IgM MGUS, bone marrow infiltration with small lymphocytes demonstrating plasmacytoid/plasma cell differentiation, intertrabecular pattern of bone marrow infiltration and certain immunophenotypes)" (116), (Table 1-3). Adverse prognostic factors are; advanced age (over 65 years old), haemoglobin level less than

9 g/dL, weight loss, and cryoglobulinemia (67,117). IgM MGUS has a 1-1.5% annual progression risk to WM (118). Treatment is similar to MM, involving ASCT and rituximab alone or rituximab with alkylators (119).

WM has an age-adjusted incidence rate of 0.57 [0.92 (male) and 0.30 (female)] per 100,000 PY. An incidence level of 0.55 per 100,000 PY was reported in the UK (120). Five year survival rate for those under 70 years was 70% and over 70 years was 50% (120).

1.6.5.4 Systematic immunoglobulin light chain (AL) amyloidosis

Systematic AL amyloidosis is a type of amyloidosis involving aberrant de novo synthesis and abnormal proteolytic processing of light chains (67); caused by "a usually modest monoclonal B-cell-derived population synthesizing amyloidogenic immunoglobulin light chains" (121). It is diagnosed with a positive amyloid staining on a tissue biopsy and evidenced to be from immunoglobulin light chains (67). It is diagnosed by a positive amyloid staining on a tissue biopsy and evidenced to be from immunoglobulin light chains (67). Systematic AL amyloidosis can be suspected from nephrotic syndrome, axonal neuropathy or restrictive cardiomyopathy presenting as clinical symptoms (67).

The prognosis of systematic AL amyloidosis is dependent on the organ effected, with cardiac amyloidosis having the worst prognosis (122). The recommended treatment is ASCT, which has a median survival of 42 months compared to non-transplantation which has median survival of 18 months (67,122). Pharmaceutical treatment is similar to MM (67).

Incidence is estimated at between 0.3 and 0.5 per 100,000 population and is the cause of 1 per 1,500 deaths in the UK (123). The age-adjusted incidence in the US is between 0.51 and 1.28 per 100,000 (Kyle 1992). Prevalence has been calculated as 0.8 per 100,000, which translates to 1051 patients in the UK living with systematic AL amyloidosis (123,124). Those with an MGUS diagnosis are more than 8 times more likely than the USA SEER population (risk ratio (RR) 8.4, 95% confidence (CI) 4-16 to

be diagnosed with AL amyloidosis (10,68,125). However, this is still a smaller risk than MM (RR 25 95% CI (20-32) or WM (RR 46, 95% CI 19-95) patients (10).

1.6.5.5 Monoclonal B-cell lymphocytosis (MBL)

MBL is a premalignant blood precursor to chronic lymphocytic leukaemia (CLL) (126). It is considered the "cellular counterpart" to MGUS in CLL (127). MBL patients are diagnosed with having lower B-Cell counts and B-Cells in peripheral blood but have no evidence of lymphoma, infection, or autoimmune conditions, Table 1-3 (126). High count/risk MBL patients undergo active surveillance in haematology (128), whilst no specific follow-up is recommended for low count/risk patients, due to no increased progression risk for these patients. However, an annual complete blood count was recommended for low count patients in primary care by Mayo clinic guidelines (128).

MBL prevalence is estimated between 6.7% (129) and 12% (130) of those over 40 years. The progression rate for high count/risk patients is 1-2% (128,131) but there is no significant difference in survival compared to population norms (131). Risk factors for MBL are previous MBL/CLL family history (132), advancing age (129,133) and certain infection (hepatitis C & pneumonia (134). Vaccination against influenza and pneumonia are protective factors (135).

Table 1-3 Diagnostic criteria and progression information for other relevant haematological conditions.

Name	• **Diagnostic criteria** (19,126,136)	Annual progression rates to malignancy	Primary progression events
Smouldering multiple myeloma (SMM) (19)	• Serum monoclonal protein (IgG or IgA) ≥30 g/L or urinary monoclonal protein ≥500 mg per 24 h and/or clonal bone marrow plasma cells 10–60%. • Absence of myeloma defining events or amyloidosis.	10% (89)	Multiple Myeloma (89)
Multiple myeloma (MM) (19)	• Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma. • Evidence of end-stage organ damage (CRAB criteria). • Any one or more of the following biomarkers of malignancy: ➢ Clonal bone marrow plasma cell percentage ≥60%. ➢ Involved: uninvolved serum free light chain ratio§ ≥100. ➢ >1 focal lesions on MRI studies.	N/A	N/A

Name	• **Diagnostic criteria** (19,126,136)	Annual progression rates to malignancy	Primary progression events
Waldenström's macroglobulinemia (WM)(136)	• Bone marrow infiltration by small lymphocytes showing plasmacytoid/ • plasma-cell differentiation. • Intertrabecular pattern of bone marrow infiltration[i] • Surface IgM+, CD5±, CD10-, CD19+, CD20+, CD22+, CD23_, CD25+, CD27+, FMC7+, CD103-, CD138 immunophenotype	N/A	N/A

[i] Supportive of but not necessary for the diagnosis of WM.

Name	• **Diagnostic criteria** (19,126,136)	Annual progression rates to malignancy	Primary progression events
Systematic immunoglobulin light chain (AL) amyloidosis (19)	• Presence of an amyloid-related systemic syndrome (e.g., renal, liver, heart, gastrointestinal tract, or peripheral nerve involvement). • Positive amyloid staining by Congo red in any tissue (e.g., fat aspirate, bone marrow, or organ biopsy). • Evidence that amyloid is light-chain-related established by direct examination of the amyloid using mass spectrometry-based proteomic analysis, or immunoelectron microscopy, • Evidence of a monoclonal plasma cell proliferative disorder (serum or urine monoclonal protein, abnormal free light-chain ratio, or clonal plasma cells in the bone marrow)	N/A	Some patients might develop multiple myeloma (19)

Name	• **Diagnostic criteria** (19,126,136)	Annual progression rates to malignancy	Primary progression events
Monoclonal B-cell lymphocytosis (126)	• Documentation of a clonal B-cell population in peripheral blood (light-chain restriction [abnormal k/l ratio or low sIg in >25% B cells] or heavy-chain monoclonal IGHV rearrangement). • B-cell count <5 x 10^9/L. • Presence of CLL phenotype (CD5, CD19, CD23 positive; CD20 and sIg dim [reduced]). • No evidence of lymphoma, infection, or autoimmune conditions.	1-2% per annum (128,131)	Chronic lymphocytic leukaemia (CLL) (126)

1.6.6 Background of Psychosocial wellbeing

The minimal evidence available suggests that there is some psychosocial impact on patient wellbeing as a result of an MGUS diagnosis. Go and Rajkumar have previously highlighted the potential harms of an MGUS diagnosis and the need for further investigations on the potential harms of an MGUS diagnosis; due to the lack of academic debate or concern from doctors (13). Other research has indicated that MGUS patients may experience similar levels of psychosocial distress and poorer Quality of Life (QoL) compared to patients with haematological malignancies (137–139)

Recent work in the USA found MGUS patients reported lower QoL scores and felt less in control of their progression risk than SMM patients (140). This study was limited in size, including only 17 MGUS and 29 SMM patients in the preliminary analysis and a full text report of this study is not yet available (conference abstract only). However, the study provided insight as it utilised the validated QLQ-C30 cancer QoL instrument and the MY20 myeloma-specific module (141) and measured cancer worry in MGUS patients; a new development in the field of premalignant research.

Research in Monoclonal B-cell lymphocytosis (MBL), "*the cellular counterpart of MGUS*" has highlighted how disclosing an ambiguous and uncertain haematological diagnosis was an ethical concern for clinicians (127). The main issues highlighted were that informing a patient of the diagnosis may cause *"possible psychological and social harm and may not even truly be 'information' when the significance of the findings is unknown"* (127); which parallels MGUS in some ways. Informing patients is an important consideration in MGUS and is discussed in Chapter 6: Discussion.

1.7 Quality of Life and Wellbeing

This section describes how Quality of Life (QoL) and psychosocial wellbeing are used in the dissertation. Further description of the main QoL/psychosocial wellbeing instruments used in the systematic review and the research studies is located within the systematic review chapter (page 61). A list and location of where each validated questionnaires utilised throughout the dissertation is located within that section.

1.7.1 Defining quality of Life and uses

Quality of life (QoL) is a complex topic, whose conceptualisation and operationalisation is consistently disputed. The World Health Organisation QOL Group (WHOQOL-G) defined QOL as *"individuals' perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, values and concerns"* (142). QoL is a subjective perception shaped by individuals' preferences, objective, culture and life experiences influenced by individuals emotions, reactions and physical health status (143). Within oncological research, four domains have been identified to compartmentalise QoL and wellbeing (Physical, Psychological, Social and Spiritual wellbeing) (144).

QoL measurement is common within healthcare; to measure the effectiveness of a treatment (139,145,146) or intervention (147,148), allocate healthcare resources (149) and to create measurements to value individuals lives and wellbeing with scores such as the use of quality adjusted life years (QALYs) (150–152). However, QoL instruments ability to measure patient-centred QoL for all patients is controversial. This has been linked to a lack of consensus of what QoL is (153,154), what each instrument measures (and relevancy to quality of life) (154) and how each component is weighted, especially in instruments which provide global/component scores in large studies (154).

I believe the difficulties of comparing defining and contrasting QoL are best encapsulated by this quote from Storrs McCall in 1980.

"Not only do we not know what quality of life is, we don't even know what category of thing it is. Is quality of life a state of mind or a state of society? Does its definition vary from individual to individual, from culture to culture, from geographical area to geographical area, or is it the same for all people everywhere? Is quality of life measurable, and if so why do there continue to be profound differences of opinion over which social indicators are relevant to its determination?" (155).

Levine's conceptualisation defined QoL as "the complete social and psychological well-being: the individual's performance of social roles, mental acuity, emotional state, sense of well-being and relationships with others" (156); which provides a comprehensive conceptualisation of QoL. To maintain uniformity in the definition of QoL within the dissertation, Levine's conceptualisation has been chosen as the most consistent to my beliefs and perspective of QoL.

1.7.2 Psychosocial wellbeing

Similar to QoL, psychosocial wellbeing is a complex topic with various conceptual and organisational constituents within the literature (157). Wellbeing is broadly defined as 'the quality and state of a person's life' (158). Health science research views wellbeing an ascendant public health concept, with focuses on both individuals lifestyle and their wider contextual determinants (159); which is inconsistently defined and subjectively understood in public health (160). From a policy level, psychosocial wellbeing is determinable by economic standards and living conditions (160,161).

The European Social Survey (ESS) Well-being Module conceptualises the area by integrating the traditional models of wellbeing of psychosocial distress and mental health with more policy-driven aspects of the "economic, social and environmental influences on well-being" (162). While the definitions of psychosocial wellbeing are conceptually complex and wide-ranging, this dissertation uses the term psychosocial wellbeing in relation to participant's general psychosocial health and ill-health; focusing on anxiety, depression, fear, worry and social influences. This holistic view of psychosocial health proposes the inter- and intra-personal experiences of

individuals' as key determinants of the psychosocial impact of a medical condition (157).

A descriptive list of the QoL and psychosocial well-being instruments used in the dissertation is located within Chapter 2: Systematic review, Page 61.

1.8 Chapter Conclusion

MGUS is an asymptomatic blood condition which occurs in 3.2% of the over 50-year-old population but is frequently undiagnosed for long periods. MGUS patients have a high risk of developing MM or other haematological malignancies. There has been minimal research on the QoL and psychosocial wellbeing impact on MGUS patients; which this dissertation aims to provide. To inform the research, a systematic review on the QoL and psychosocial wellbeing impact of premalignant conditions was conducted and described in in Chapter 2.

Chapter 2: A Mixed Methodological systematic review of the psychosocial and QoL effects of a premalignant condition.

2.1 Introduction

This chapter presents the results of a novel systematic review of studies to compare and contrast the psychosocial impact of a range of premalignant conditions. The results were used subsequently to facilitate the study design and content of the studies in the dissertation (Chapters 3, 4 and 5). For example, the MGUS patient studies were designed in ways that avoided the limitations and barriers that identified in the review. Furthermore, the review was conducted with a view to improving understanding about the comparability (or otherwise) of psychosocial impacts across a range of premalignant conditions; thereby illuminating the problems and issues that may be relevant to MGUS patients.

Premalignant conditions are diagnosable conditions which significantly increase the risk of developing a related cancer (163). Premalignancies are defined as *"being associated with an increased risk of cancer, the cancer develops from cells within the precancer, the precancer is different from the normal tissue, the precancer is different to the cancer insofar it has some but not all of the molecular and phenotypical properties of the cancer and the precancer can be diagnosed"* (163).

Physiologically, premalignant conditions can present differently; varying from an asymptomatic condition diagnosed from abnormal blood results (MGUS (164)) to conditions with life-affecting symptoms (acid reflux) with invasive surveillance (endoscopy) (Barrett's oesophagus (165)). Post diagnosis, some conditions have immediate treatment (surgical excision in high-grade cervical intraepithelial neoplasia (CIN)) or patients undergo long-term surveillance (Barrett's oesophagus (166)).

Premalignant conditions have major epidemiological differences; with prevalence rates ranging from rare conditions like giant cell tumour (0.016 per 100,000 people) (167) to more common conditions such as colorectal polyps which affect approximately 30% of males aged over 50 years old (168), Table 2-1. The annual risk of progression to cancer also varies between conditions with Barrett's oesophagus and oral lichen planus having progression rates of 0.5% (169) and 0.65% (170),

respectively, while smouldering multiple myeloma (SMM) is associated with a 10% annual progression rate (89).

New technology and enhanced screening practices have led to a rise in the incidence of some premalignant conditions, such as ductal carcinoma in situ (DCIS) (171) and CIN (172). A short synopsis of each premalignancy including; name, site, diagnostic criteria, epidemiological information (incidence/prevalence and progression rate) and related cancer(s) is located in Table 2-1. A pictorial representation of the progression of some of the premalignancies is shown in Figure 2-1.

Table 2-1 Premalignant condition information

Premalignant Condition	Site of the Premalignancy	Definition	Future Cancer and associated Progression rate	Prevalence rate PR[i]	Treatment/Care
Actinic keratosis	Skin	Rough lesions on the skin, commonly appearing as a red scaling papule or plaque on an area of skin commonly exposed to sunlight (173)	Squamous cell carcinoma	46% (Australia, Adults aged 30-69) 11-25% (Northern Hemisphere, adults) (174)	Destruction of lesions (such as cryotherapy, laser treatment and dermabrasion) or topical treatment (Imiquimod, 5-Fluorouracil and Diclofenac sodium) (175)
Barrett's oesophagus	Oesophagus	A condition in which the cells lining the lower part of the oesophagus have changed or been replaced with abnormal cells that could lead to cancer of the oesophagus. (176)	Oesophageal Cancer	1.3-1.9% (177–180) (China, Italy, Sweden)	Predominantly regular (3-5 years) endoscopic screens. Oesophagostomy can be conducted in some cases. (181)

[i] For some conditions (DCIS, Giant bone cell tumour), Prevalence rates were not available. Incidence rates are reported in their place.

Premalignant Condition	Site of the Premalignancy	Definition	Future Cancer and associated Progression rate	Prevalence rate PR[i]	Treatment/Care
CIN (Cervical intraepithelial neoplasia) (Also known as CIS or Cervical dysplasia, as referenced in the 2000 guidelines (182)	Cervix	"Abnormal cells are found on the surface of the cervix. CIN is usually caused by certain types of human papillomavirus (HPV) and is found when a cervical biopsy is done. CIN is not cancer but may become cancer and spread to nearby normal tissue. It is graded on a scale of 1 to 3, based on how abnormal the cells look under a microscope and how much of the cervical tissue is affected." (176)	Cervical Cancer	1.11% of US women (183)	CIN 1 is observed for 18 months. If progression to CIN2/3, large loop excision of the transformation zone (LLETZ) is performed. (184).

Premalignant Condition	Site of the Premalignancy	Definition	Future Cancer and associated Progression rate	Prevalence rate PR[i]	Treatment/Care
Colorectal polyps	Colon	"Abnormal cells are found in the mucosa (innermost layer) of the colon and/or rectal wall. These abnormal cells may become cancer." (176)	Colon Cancer	Age 55-59 Males 6.2% Female 3.4% Age >80 Males 9.5% Female 7.3% (185)	Endoscopic follow-up and resection of the polyps (186)
DCIS (Ductal carcinoma in-situ)	Breast	"A non-invasive condition in which abnormal cells are found in the lining of a breast duct. The abnormal cells have not spread outside the duct to other tissues in the breast. In some cases, DCIS may become invasive cancer and spread to other tissues." (176)	Breast Cancer	32.5 per 100,000 (USA) (187) (Incidence)	Complete surgical excision, breast conserving surgery and mastectomy with or without postoperative radiotherapy. (188)

Premalignant Condition	Site of the Premalignancy	Definition	Future Cancer and associated Progression rate	Prevalence rate PR[i]	Treatment/Care
Giant cell tumour	Bone	Characterized by a proliferation of mononuclear stromal cells and the presence of many multi-nucleated giant cells with homogenous distribution." (189)	Bone Cancer	.016 per 100,000 (167) (Incidence)	Intralesional curettage followed by bone grafting and/or bone cement packing (190)
MGUS (Monoclonal gammopathy of undetermined significance)	Plasma Cells/Blood	An asymptomatic plasma cell disorder that affects the plasma cells (36)	Haematological cancers, usually Multiple Myeloma	3.2% in those aged >50 years (36)	Active surveillance (13)
OLP (Oral lichen planus)	Oral	White striations, white papules, white plaques, erythema, erosions, or blisters (191)	Oral Cancer	1-2% of the population (192)	Systemic and topical steroid therapy using corticosteroids under active surveillance (191).
SMM (Smouldering multiple myeloma)	Plasma Cells/Blood	An asymptomatic plasma cell disorder that affects the plasma cells (36)	Haematological cancers, usually Multiple Myeloma	0.9 per 100,000 (193) (USA) (Incidence) 0.4 per 100,000 (92) (Sweden) (Incidence)	Active Surveillance (90)

Premalignant Condition	Site of the Premalignancy	Definition	Future Cancer and associated Progression rate	Prevalence rate PR[i]	Treatment/Care
VAIN (Vaginal intraepithelial neoplasia)	Vagina	Abnormal cells are found in tissue lining the vagina (birth canal). These abnormal cells may become cancer and spread into the vaginal wall. (176)	Vaginal Cancer	0.23 Per 100,000 (194) (Incidence)	Excision of the premalignancy or chemical treatment (Intravaginal 5-fluorouracil cream) (195)
VIN (Vulvar intraepithelial neoplasia)	Vulva	"Abnormal cells are found on the surface of the vulvar skin." (176)	Vulvar Cancer	2.86 per 100,000 (196) (Incidence)	Local superficial excision of high grade lesions (197)

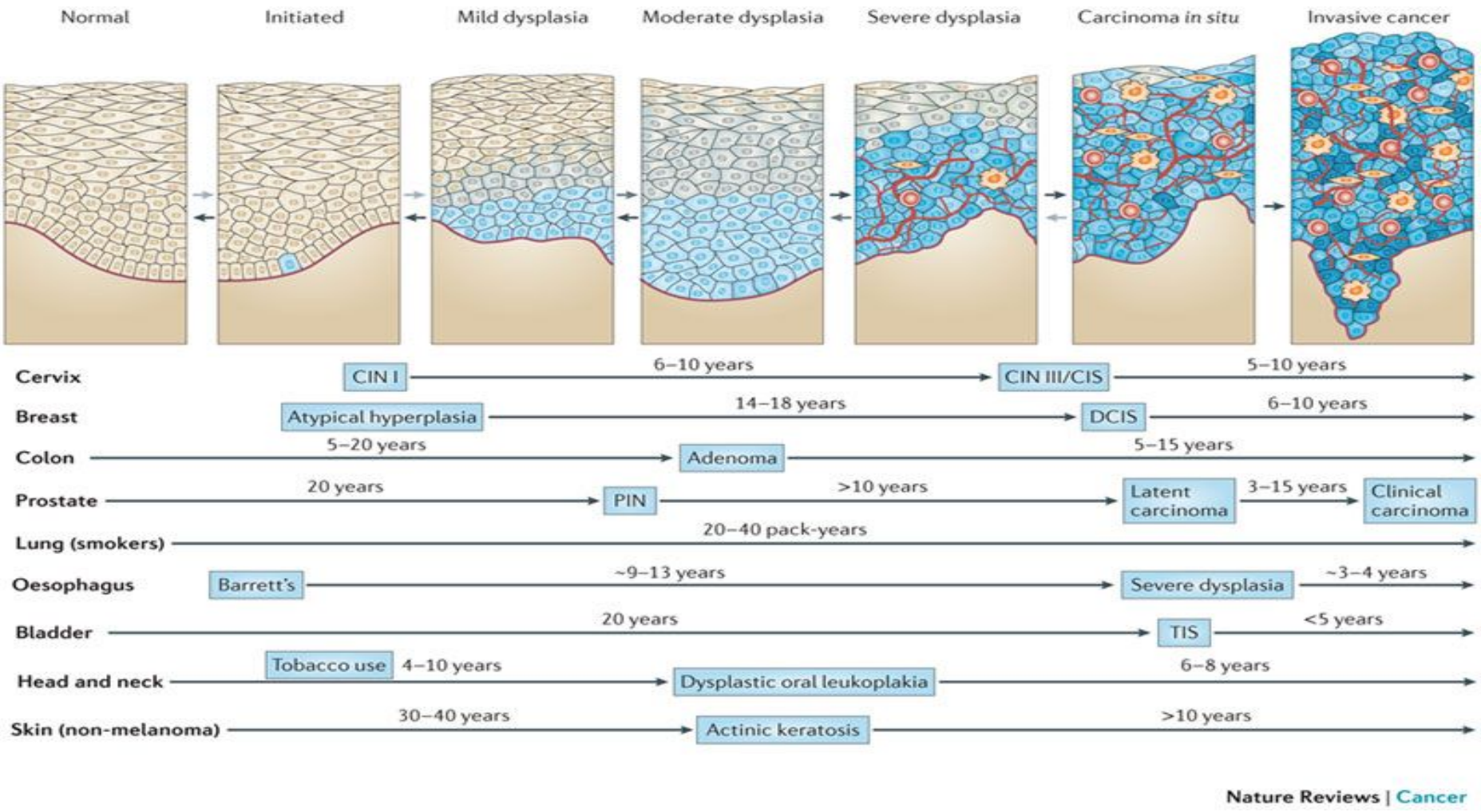


Figure 2-1 Progression of Premalignant conditions to cancers. Reproduced with permission (198)

(Copyrighted)

2.1.1 Previous Systematic reviews

Systematic reviews on psychosocial well-being and QoL of premalignant conditions have been conducted for Barrett's oesophagus (199), CIN (200) and oral premalignant conditions (201). These reviews highlighted the major areas of patient concern as; the need for information and help to address anxiety. The reviews shared the conclusion that many of the included studies were of poor quality; particularly the use of inappropriate comparison groups; such as no healthy control groups. This limited the confidence of their conclusions.

Crockett *et al* reviewed 25 Barrett's oesophagus studies identified in 3 databases (PubMed, CINAHL and PsychInfo) (199). Reviewed using a narrative summary, Barrett's oesophagus patients; had reduced QoL compared to population norms, viewed endoscopic surveillance as "burdensome", sought information -especially cancer risk-related- and often overestimated their risk of progression to oesophageal cancer, especially immediately post-diagnosis (199). Crockett *et al* postulated that progression from Barrett's oesophagus to dysplasia, a more advanced disease state, would lead to a further decline in QoL (199). The study highlighted difficulties and a lack of evidence on assessing cancer risk comprehension among patients with Barrett's oesophagus (199).

Fredericksen *et al* reviewed 17 CIN studies identified in PubMed only (200). Reviewed using a narrative summary, CIN patients; viewed their CIN diagnosis similarly to cervical cancer patients or those given an abnormal smear diagnosis at screening with patients experiencing short-term anxiety (declining post diagnosis) but reported no additional psychosocial impact of CIN treatment (cold-knife conisation (202). The reviewers postulated the uncertainty of the diagnosis and potential progression triggered short-term screening-induced anxiety (200). The review was limited by the included studies being difficult to interpret; due to a range of methodologies and different questionnaires utilised. It was also limited to one database; which may lead to indexing bias (203).

Tadakamalda *et al* reviewed 14 oral premalignant condition studies identified in 3 databases (PubMed, Medline and CINAHL) (201). Using a narrative review, oral premalignant patients (predominantly oral lichen planus patients (n=16/17 articles))

had no significant QoL detriment compared to healthy patients. The review highlighted significant issues in reporting quality [most studies were of weak (n=13/17) or moderate (n=4/17) quality), a lack of appropriate control groups (only one study compared to healthy controls), low generalisability as data was collected in specialist oral medicine centres and inadequate validity in the QoL instruments used (201).

2.1.2 QoL and psychometric Instruments/Questionnaires

Measuring QoL and/or the psychosocial wellbeing of an individual is complex, due to the difficulties in capturing all the important features and clinically relevant findings for each individual in a scale (204) and whether these scales are appropriately patient-centred (154). In this dissertation, a choice was made to use validated instruments to increase confidence in its findings; as validated instruments reduce bias' and provide better evidenced data (205,206). Five instruments were used throughout the dissertation. Each is described below and their scoring system explained.

2.1.2.1 Short Form Health Survey Questionnaires

The Short Form Health Survey (MOS SF) was developed for the Medical Outcomes Study (MOS), a multi-year study of patients with chronic conditions (207). There are several versions of the MOS SF questionnaires, with 8-,12-, 12v2, 20- and 36-item variants. Previous reviews on the validity and consistency indicated that combining the different versions of the SF questionnaires (SF-36, SF-20, SF-12, SF-8) is appropriate across studies and languages (208).

The instrument splits into 8 sub-scales (vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning and mental health). These scores combine to form two component scores (Physical and Mental component scores) to measure physical and mental health. Each sub-scale and component scale is scored 0 (very poor QoL) to

100 (perfect QoL). The MOS SF instruments are considered excellent measures for chronic health conditions (209–213).

2.1.2.2 EuroQol-5 dimension (EQ-5D)

The EQ-5D is a quality of life measure used in health research and to create quality adjusted life years (QALYs) for economic analysis (214,215). The EQ-5D consists of 2 parts; the EQ-5D descriptive system (part 1), and EQ visual analogue scale (EQ-VAS) (part 2). The descriptive system assesses health-related quality of life across five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). The EQ-VAS is a vertical scale ranging from "worst imaginable health state" [0] to "best imaginable health state" [100], which provides a quantitative measurement of health outcome (214,215). The EQ-5D questionnaire has previously been validated for use within adult populations throughout the world, including the UK and is considered simple and time efficient to complete (214,215).

2.1.2.3 Hospital Anxiety and Depression Scale (HADS)

The HADS consists of 14 questions which assess respondents anxiety and depression levels (216). The HADS is one of the most widely used anxiety and depression measures in both clinical and academic studies. A systematic review by Bjelland *et al.* found the HADS had high reliability and internal consistency (217). It has high levels of accuracy in assessing symptom severity in both clinical and general populations (218). Heightened scores (>7) are indicative of clinical levels of anxiety (216).

2.1.2.4 Center for Epidemiologic Studies Depression Scale (CES-D)

The CES-D scale is a short self-report scale designed to measure "depressed affect, positive affect, somatic problems and retarded activity, and interpersonal relationship problems, with an emphasis on depressed affect" (219); recalled over the previous week" (220). There are various versions, with the 20- and 10-item versions being the most common (219). Each question is scored 0 (rarely/none of the time) to

3 (most/all days). The score range (on the 20-item version) is 0-60, with a higher score more indicative of depression. Depending on the cut-off, clinical depression is indicated by a score over 16 (221) or 22 (222).

2.1.2.5 The State-Trait Anxiety Inventory (STAI)

The STAI is a 40-item scale used to measure state and trait anxiety (221). State anxiety evaluates current anxiety "right now", based upon subjective questions about feelings of "apprehension, tension, nervousness, worry, and activation/arousal of the autonomic nervous system" (223). Trait anxiety evaluates the more stable components of anxiety, such as "general states of calmness, confidence, and security" (223). Scores range from 20-80, with higher scores positively associated with higher levels of anxiety (221). Internal consistency is high (0.86 - 0.95) (221,223).

Table 2-2 Validated questionnaires used in the dissertation

Questionnaire	Usage
EuroQol-5 dimension (EQ-5D) (214)	Chapter 2: Systematic Review Chapter 5: PIP study
Short Form Health Survey Questionnaires (224)	Chapter 2: Systematic Review Chapter 5: PIP study
Hospital Anxiety and Depression Scale (HADS) (216)	Chapter 2: Systematic Review Chapter 5: PIP study
Center for Epidemiologic Studies Depression Scale (CES-D)(220)	Chapter 2: Systematic Review
The State-Trait Anxiety Inventory (STAI) (221)	Chapter 2: Systematic Review

2.1.2.6 Conducting a mixed method review

The mixed-methods systematic review that is presented here reflects the mixed methods approach used in the empirical studies of the dissertation. The approach integrates, for example, quantitative results about benefit and harm with qualitative research understanding about people's experiences (225). Previous reviews did not include the results of qualitative studies regarding the impact of premalignant conditions (199–201). Therefore, potentially, this novel mixed methods review provides a more comprehensive and integrated assessment of the results from existing studies about the psychosocial impact of having a premalignant condition.

The rationale for conducting the review was to highlight the potential areas which may concern MGUS patients. As the psychosocial impact of MGUS is a novel topic, it was anticipated that premalignant patients as a collective would experience similar psychosocial concerns. The review informed the development of the mixed methods survey of premalignant patients (Chapter 5). The survey focused on multiple premalignancies to provide a wide evidence base to compare and contrast the included premalignant conditions.

Mixed methods reviews *"broaden the conceptualisation of evidence, [are] more methodologically inclusive and produce syntheses of evidence that will be accessible to and usable by a wider range of consumers"* (226). Mixed methods reviews either integrate the quantitative and qualitative data together to create a framework (227) or analyse the data separately and discuss the results as a collective narrative (228). This review used the collective narrative approach as the qualitative data provided the context for evaluation of the quantitative results. As such, this review incorporates a meta-synthesis of qualitative research as well as a meta-analysis of studies using validated questionnaires to evaluate the impact of being diagnosed with a premalignant condition. The data from the dissertation is integrated within the main discussion chapter (Chapter 6); with the review providing the evidence base from which to evaluate the findings in relation to MGUS.

Qualitative meta-synthesis is a commonly used term which describes combining the experiences of individuals over multiple studies to develop a more in-depth understanding than is feasible within a single study. Multiple meta-synthesis

techniques are available; with the choice dependent on the author's epistemological position and the rationale for the review.

For example, authors whom intend to inform best practice or "lines of action" for patients use a meta-aggregate approach (229); while developing the theoretical background of a phenomenon is most appropriate for a meta-ethnographic approach (230). The main rationale and results of the various meta-synthesis approaches are highlighted in Table 2-2.

In line with the aims of the review, which were to evaluate the psychosocial impact of a premalignant condition, it was not appropriate to constantly compare the findings to generate abstract theory (grounded theory (231). Similarly, the aim was not to generate best practice guideline, as would be the purpose of conducting a meta-aggregation (229).

Thematic synthesis is a widely used technique which can provide broader answers than other techniques and traditional reviews, to "formalise the identification and development of themes" (232). Thematic synthesis has previously been used in reviews in breast (233), prostate (234) and multiple myeloma (235) cancers. Thematic synthesis develops both broad overview themes and more specific subthemes; which are used within the discussion chapter to compare premalignant conditions in general to MGUS. This method involves summarisation of each study, which allow the reader to judge the transferability and relationship to their own areas of interest (232). This summarisation improves methodological rigour and reflexive awareness for both reader and author and encourages a higher level of abstraction by providing the details and showcasing the spectrum of responses within the studies (230,232). These summaries are in Appendix 5.

As outlined previously (Previous Systematic reviews, page 60), previous systematic reviews did not perform a meta-analysis due to poor reporting quality (201), use of different methodologies and questionnaires (200) and high heterogeneity (199). To overcome these issues, this review used validated instrument which were used in multiple studies (minimum of three studies) to perform the meta-analysis and evaluate the impact of a premalignant condition across the different dimensions of

QoL and psychosocial wellbeing. This is a common practice in other conditions where multiple validated questionnaires are available (205,206).

2.1.2.7 Aims

The aim of the systematic review was to evaluate the psychosocial impact, in terms of QoL[i] , and psychosocial wellbeing[ii], on people living with a premalignant condition. This relates to the research questions[iii]; specifically, Q1 (What is the perceived impact of receiving a diagnosis of MGUS/premalignant condition) and Q2 (What are the health and social care needs of patients with MGUS).

[i] Defined in Chapter 1, Defining quality of Life and uses, page 49

[ii] Defined in Chapter 1, Psychosocial wellbeing, Page 50

[iii] Research questions outlined, Page 20.

Table 2-3 A short overview of the various meta-synthesis approaches for healthcare related systemic reviews.

Approach	Rationale	Result of synthesis
Meta-aggregation (229)	To aggregate the findings of included studies	To create guidelines and best practice and policy decisions
Meta-Ethnography (230)	To create a new theoretical understanding of a phenomenon	To transfer ideas and concepts across studies, while retaining their meaning.
Thematic Synthesis (232)	To bring together the findings of original research	A summary of the findings, under themes.
Content analysis (236)	To quantify and count the occurrence of themes	To collate the occurrences of themes within the literature. This can be deductive or inductive.
Grounded theory (231)	To generate theoretical models of an experience	An interpretive method that generates theoretical interpretations from the literature utilising constant comparative methods

2.2 Methods

This methods section has four main components.

- Search strategy.
- Study criteria and quality assessment procedures.
- Plan of quantitative meta-analysis.
- Plan of qualitative thematic meta-synthesis.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was followed in the reporting of this review (237), supplementary material (Appendix 3).

2.2.1 Systematic Review search strategy and information sources

Five online databases (PubMed (OvidSP), Medline (OvidSP), EMBASE (OvidSP), PsychInfo (OvidSP), Web of Science) were searched from inception to January 2020. A combination of keywords and controlled vocabulary/subject headings for premalignant conditions (such as "Precancer", Premalignant", "Ductal carcinoma in-situ" and "DCIS") and psychosocial wellbeing/QoL (such as "Quality of life", "QoL", "Depression" and "Psychology") were used (Appendix 8). Premalignant terms were identified through the NCI Cancer dictionary (176), premalignant consensus articles (163,238,239) and advice from premalignant researchers. An unpublished protocol for the study was followed in the review and has been included within Appendix 8.

The search was restricted to human studies with no language restrictions imposed. Search results were transferred into RefWorks and duplicate records removed (exact matches were removed automatically with probable matches reviewed individually).

Titles and abstracts were reviewed by the primary reviewer (BM) and secondary reviewers (CMcS, CT & OS) against the eligibility criteria, Table 2-3. Reference lists of articles included in the systematic review were also searched. Discrepancies were resolved by an independent reviewer (LAA).

2.2.2 Eligibility Criteria

The study eligibility criteria are separated into 4 sections based on the PICOS criteria (227).

Using the PICOS criteria:

- **Participants:** Patients with a confirmed premalignant diagnosis.
- **Interventions**: Not relevant
- **Comparisons:** Premalignant patients are compared to population norms or a control group without a cancer diagnosis or severe co-morbidities (quantitative studies only).
- **Outcomes:** QoL, Psychosocial wellbeing scores from validated instruments.
- **Study design:** Any quantitative, qualitative or mixed methods design.

2.2.3 Study selection

Several decisions were made to increase the validity and rigour of the findings. Patients without a confirmed diagnosis or those who had "abnormal test results" only were excluded as these patients would not be on a care pathway at that point and were still under investigation. This distinction is most common within the CIN literature and these groups (CIN and abnormal smear test results) are separated in the literature (240,241). Studies based on genetic heritability-based premalignancies (such as familial adenomatous polyposis) were excluded, as their experience of care would not be similar to other premalignant conditions which were not hereditary (242,243). Genetic heritability-based conditions are more likely to be detected through predictive genetic testing, had mixed/unclear effects on QoL/wellbeing and have a different care pathway than most premalignant conditions (243,244). All criteria are depicted in Table 2-3.

Table 2-4 Eligibility criteria for inclusion/exclusion

	Inclusion Criteria	Exclusion Criteria
Population of premalignant conditions within the papers.	• Patients aged 18 years or older. • Patients had received a confirmed (to patient and healthcare professional (HCP) premalignant condition diagnosis	• Studies where patients did not have a confirmed diagnosis. • Patients with severe comorbidities (such as HIV or late stage dementia). • Patients aged under 18 years. • Data from HCPs or carers only. • Studies of premalignant conditions which were: 1. High risk associated with genetic predisposition (such as familial adenomatous polyps) 2. Abnormal test results but diagnosis was not confirmed as premalignant (e.g. abnormal pap smear).
Outcome measures	Quantitative • Validated instrument that measured a psychosocial concept such as depression, anxiety, QoL, trauma. Qualitative • Studies which qualitative methodology (e.g. thematic analysis, grounded theory).	Quantitative • Studies which did not use validated questionnaire or had created their own, non-validated instruments. • Validated measures utilised in <3 studies. • Instruments which only measured sexual function or pleasure as this was not comparable across premalignant types.
Study design and publication type.	• Original research studies which used a quantitative, qualitative or mixed methods design.	• Previous reviews were excluded; however, the reference lists were checked. • Drug trials, case studies, abstracts only and non-human articles were excluded. • Studies in non-peer reviewed journals.

2.2.4 Data collection process/ Risk of bias assessment

Data was extracted into tabular format using a predesigned proforma by the principal reviewer (BM). Information extracted included: author, year, premalignant condition, study design, times since diagnosis, control group, study location, instruments used and sample size[i].

Risk of bias assessment was conducted using the Mixed Methods Appraisal Tool (MMAT) (2018 version) (245) to inform about the reliability of the studies, Figure 2-2. The MMAT was chosen due to its ability to reliably assess methodological quality across diverse study designs, including qualitative, quantitative, and mixed methods studies. The 2018 version of the MMAT was used due to: it's improved logic chart of selecting study category (randomised control trial, observational study or non-randomised trial) and excluded the use of a summative numerical score (246), as proposed in the literature (247,248). The exclusion of summative scores has been viewed as obsolete due to the high subjectivity, little/no effect on improving the utility of meta-analysis and potential introduction of bias (248–250).

[i] Specific information is located in Quantitative meta-analysis and forest-plots Page 73 and Qualitative meta-synthesis Page 76.

Part I: Mixed Methods Appraisal Tool (MMAT), version 2018

Category of study designs	Methodological quality criteria	Responses			
		Yes	No	Can't tell	Comments
Screening questions (for all types)	S1. Are there clear research questions?				
	S2. Do the collected data allow to address the research questions?				
	Further appraisal may not be feasible or appropriate when the answer is 'No' or 'Can't tell' to one or both screening questions.				
1. Qualitative	1.1. Is the qualitative approach appropriate to answer the research question?				
	1.2. Are the qualitative data collection methods adequate to address the research question?				
	1.3. Are the findings adequately derived from the data?				
	1.4. Is the interpretation of results sufficiently substantiated by data?				
	1.5. Is there coherence between qualitative data sources, collection, analysis and interpretation?				
2. Quantitative randomized controlled trials	2.1. Is randomization appropriately performed?				
	2.2. Are the groups comparable at baseline?				
	2.3. Are there complete outcome data?				
	2.4. Are outcome assessors blinded to the intervention provided?				
	2.5 Did the participants adhere to the assigned intervention?				
3. Quantitative non-randomized	3.1. Are the participants representative of the target population?				
	3.2. Are measurements appropriate regarding both the outcome and exposure/intervention?				
	3.3. Are there complete outcome data?				
	3.4. Are the confounders accounted for in the design and analysis?				
	3.5. During the study period, is the intervention/exposure administered as intended?				
4. Quantitative descriptive	4.1. Is the sampling strategy relevant to address the research question?				
	4.2. Is the sample representative of the target population?				
	4.3. Are the measurements appropriate?				
	4.4. Is the risk of nonresponse bias low?				
	4.5. Is the statistical analysis appropriate to answer the research question?				
5. Mixed methods	5.1. Is there an adequate rationale for using a mixed methods design to address the research question?				
	5.2. Are the different components of the study effectively integrated to answer the research question?				
	5.3. Are the results adequately brought together into overall interpretations?				
	5.4. Are divergences and inconsistencies between quantitative and qualitative results adequately addressed?				
	5.5. Do the different components of the study adhere to the quality criteria of each tradition of the methods involved?				

Figure 2-2 Mixed Methods Appraisal Tool (MMAT), v.2018

2.2.5 Synthesis of results: Quantitative meta-analysis and forest-plots

Studies presenting quantitative research findings were extracted into tabular format using a predesigned proforma by the principal reviewer (BM). Information extracted included; author, year, premalignant condition, study design, time of data collection, control group, study location, instruments used[i], sample size and quality assessment. Instrument scores were extracted in separate proforma designed for each specific instrument. This included scale and subscale score, standard deviation and number of participants for all instruments; for premalignant and control groups. The study characteristics table for quantitative studies is located in Appendix 4.

Data analytics was performed using StatsDirect v3.1.17 (251). After inserting the extracted data, the following sequence was run on all the extracted questionnaire data.

- Analysis
    - Meta-analysis
        - Effect size
            - Weighted effect (d) from mean, n and S.D.

Statistical heterogeneity was assessed using Cochran's Q-test. The I-Squared statistic (I^2) was utilised to calculate the variation of effect measure across the articles, due to the heterogeneity. Within the I^2 categorisation, low, moderate and high heterogeneity were considered at 25%, 50% and 75% respectively (252).

Substantive heterogeneity was expected to be high; due to varied instruments, study administration and respondent characteristics. Analysis by validated instrument was used to reduce this substantive heterogeneity (253); as validated instruments provide a better-quality and reproducible assessment. Unvalidated instruments are often poorly conceptualised or evaluated, difficult to compare across studies and can

---

- [i] Each of the questionnaires utilised within the meta-analysis is described in Chapter 2: (page 61).

introduce bias, such as measurement bias (254,255), while validated questionnaires provide better evidenced data (205,206). As many validated questionnaires are generic, it allows comparison to validated populations and norms across conditions (256); which is important in comparing across premalignant conditions. The most common validated instruments were used in the premalignant study (Chapter 5).

A random-effects model (DerSimonian-Laird (257) was deemed most appropriate as; heterogeneity was high, the populations varied in age and by premalignant condition and sample sizes varied (258).

Meta-analyses were conducted for all validated instruments which: were included in 3 or more published studies and reported a mean, standard deviation (or confidence intervals) and sample size for both the premalignant condition group and a control group[i]. For instruments which were not included in 3 or more published studies, a narrative review was conducted (on page 9999).

The meta-analysis was based on a weighted mean difference between premalignant patient and control groups/population norms; this summary measure is common in questionnaire-based systematic reviews (259,260) and is the most appropriate method when measuring on the same scale as a continuous outcome (261,262). Other approaches (such as standardised effect size) were not required due to the use of per instrument analysis (261,262).

2.2.5.1 Considerations and rationale for meta-analysis procedures

For studies with multiple time-points, the first time-point with confirmed diagnosis was used. For example, in Juraskova *et al,* (263), the 6-month score (rather than the baseline) was reported; as CIN diagnosis was not confirmed at baseline.

Some studies contained multiple groups with subtypes of the same premalignancy. As the review focused on the differences between premalignancies, these groups (of

[i]The control group had to contain a "healthy" group (no premalignant or malignant condition) or provided population-based norms.

subtypes) were combined into one score by weighting their means according to the number of patients in each group (264); based upon advice from statisticians[i].

$$\sum_{i=1}^{3} (wgt_i)^2 \operatorname{Var}(\bar{x}_i)$$

Where the weight is:

$$\frac{Number\ of\ observations\ in\ a\ group}{Total\ observations\ in\ all\ groups.}$$

Figure 2-3 Equation of Calculating weighted mean.

Within the forest plots, studies were weighted by sample size[ii]. Study identities were arranged by alphabetical order of; the premalignant condition, year and author name. This was performed to guide the reader on the differences between conditions. The vertical line within the forest plot is a population mean or weighted control mean. The mean score for control groups was computed in StatsDirect (251) by calculating the weighted mean average from the control groups. The source of the vertical line is highlighted in in Table 2-4 & Table 2-6 for each instrument. Studies which did not report a standard deviation, but provided a mean, were plotted on the forest plots to provide a visual representation.

Both component and subscale scores are provided; due to the differing physiological impacts in premalignant conditions. Some conditions reported similar component/global scores to other conditions but vastly differing subscale scores. For example, Barrett's oesophagus patients would likely have more physical function detriment than CIN patients - due to the average age of participants, surveillance procedures and treatment provided- which were apparent in subscale scores rather than component scores.

[i] To calculate the variance of this weighted mean, a standard formula for a sum of [weighted] random variables, assuming the two means were statistically independent, was adapted from Mood, Graybill and Boes 1974, page 179) (264).

[ii] For studies that did not include standard deviations, they were given a standard deviation of 0 for the purpose of visualisation on the forest plot. These studies were not included within the meta-analysis.

SF subscale analysis has been conducted in systematic reviews on the Health-related QoL (HRQoL) impact after burn injuries (53), herbal medicine in hypertension (54) and exercise interventions (55). A review in rheumatoid arthritis (56) used meta-analysis on SF instrument subscale and component scores to compare different roles of each (subscale) dimension on patient's QoL.

2.2.6 Synthesis of results: Qualitative meta-synthesis

Studies presenting qualitative research findings were extracted into tabular format using a predesigned proforma by the principal reviewer (BM). Information extracted included; study authors, publication year, summary of themes, premalignancy type, sample size and demographics (Example: mean age, sex of respondents); were extracted into tabular format using a predesigned proforma by the principal reviewer (BM) (Appendix 5).

All "results" or "findings" sections of the papers were initially coded on paper and then imported into NVIVO (265). This involved independent coding of each line to translate concepts between studies (232). These codes were developed into coherent themes within each article and checked against the study themes to increase rigour (232), Figure 2-12. A second level of coding constructed "descriptive themes" across the studies (232). Using these descriptive themes, researchers can "go beyond" to generate more analytical and abstract themes. These major themes brought together a mix of the descriptive themes to describe and explain the descriptive themes. The major themes also identified the barriers and implications of a premalignant condition which could be used in clinical practice and policy and intervention development (232).

All coding (descriptive and analytical) was independently audited by an experienced qualitative systematic review specialist, with strong inter-rater reliability assessed using triangulation between researchers through discussing and negotiating agreements/disagreements on the coding (266,267). Within each descriptive theme, the framework (containing the descriptive and analytical themes) is visually presented via coding trees.

2.3 Results

In total, 20,091 articles were identified across five databases. Following the exclusion of duplicates, 14,953 were reviewed in duplicate with 75 studies meeting the inclusion criteria [quantitative (n=53), qualitative (n=21) and mixed methods (n=1)], PRISMA diagram, Figure 2-4.

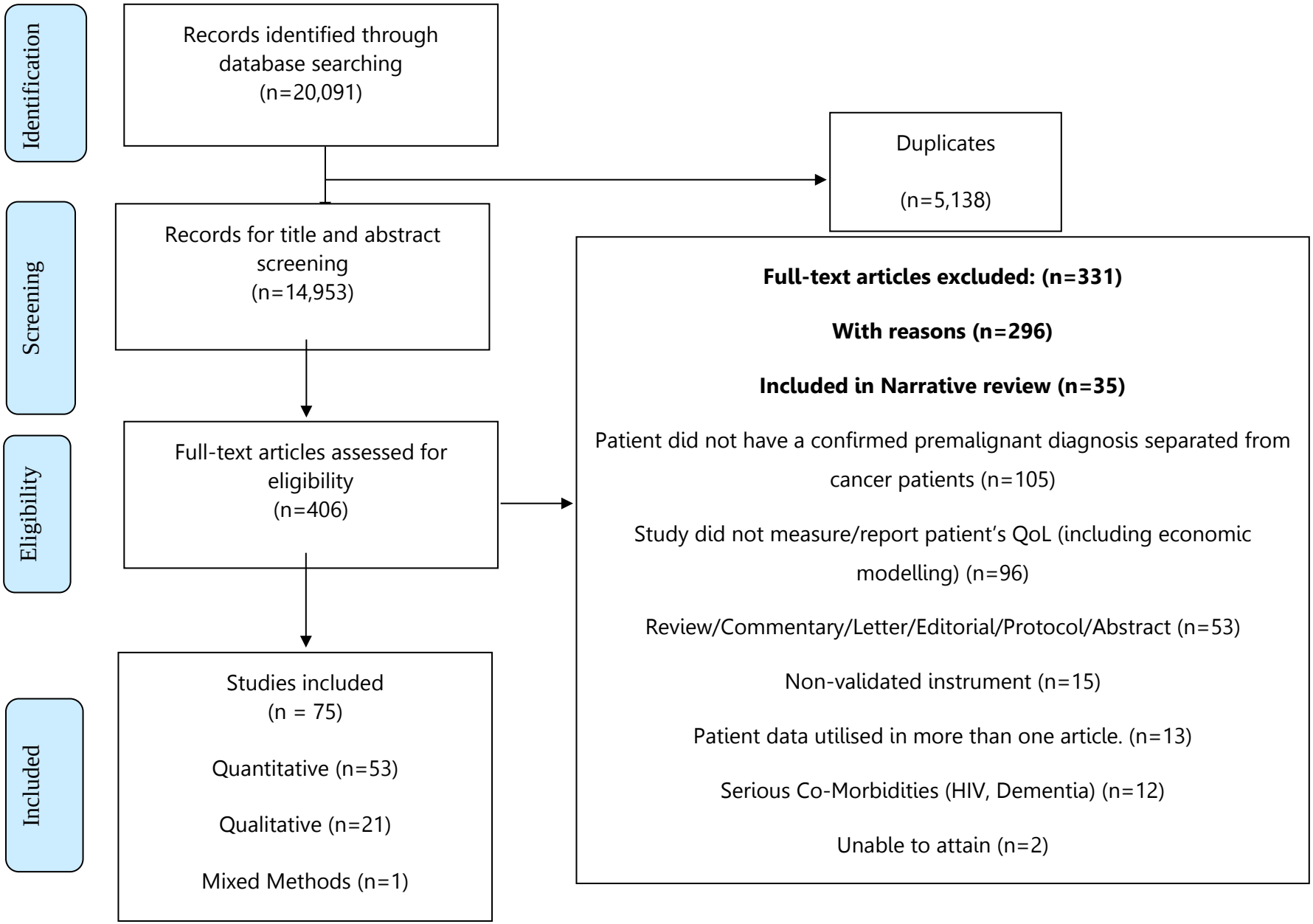


Figure 2-4 PRISMA Flowchart Systematic Review

2.3.1 Quantitative results

Summary of Quantitative Study characteristics

In total, 53 quantitative and 1 mixed methods studies containing 13,675 patients with 11 morphologically different premalignancies were reviewed. The premalignant conditions identified included ductal carcinoma in-situ (DCIS) (n=18), cervical intra-epithelial neoplasia (CIN)/cervical dysplasia (n=17), Barrett's oesophagus (n=13), actinic keratosis (n=7), colorectal polyps (n=5), oral premalignancies (n=5), vulval intra-epithelial neoplasia (VIN) (n=4), MGUS/SMM (n=2) and giant bone tumour (n=1).

Studies were conducted in numerous locations, the most common locations being the UK (n=17), USA (n=16) and Australia (n=6). Publication dates of the studies ranged from 1999-2019.

Study populations ranged from clinical case studies with 20 participants (268) to large case-control studies with 1604 participants (269). In total, 24 studies were limited to one sex (23 Female: 1 Male) with the remaining studies including both sexes (n=29). The mean age was approximately 54 years old although not all studies reported age; CIN patients were younger (mean age 21 years) (270) and actinic keratosis patients older (mean age 79.9 years) than average (271).

Five validated instruments were utilised >3 times. These were the Short Form Health Surveys (SF Questionnaires) (n=26), the Hospital Anxiety and Depression Score (HADS) (n=10), the State-Trait Anxiety Inventory (STAI) (n=7), EuroQol five-dimension scale (EQ-5D) (n=5) and Center for Epidemiological Studies Depression (CES-D) (n=4)[i]. Study designs included cross-sectional surveys (n=37), cohort (n=12) and case-control (n=8) studies.

[i] Further details of each instrument are in Chapter 2: QoL and psychometric Instruments/Questionnaires (page 61).

2.3.1.1 Short Form Health Surveys (SF instruments)

The SF instruments were the most commonly used instruments (n=26), Table 2-4. Collectively, 4,857 patients filled out an SF instrument across its different versions (SF-36, SF-20, SF-12, SF-8). Previous reviews on the validity and consistency indicated that combining the different versions of the SF questionnaires (SF-36, SF-20, SF-12, SF-8) is appropriate across studies and languages (208). Multiple articles reported only subscales or component scores with five articles (272–276) reporting both subscales and component scores, Table 2-4.

There were no statistically significant differences between premalignant patients and controls within the subscales or component scores, Table 2-5. However, the radar plot (Figure 2-5) highlighted differences between premalignant conditions, with Barrett's oesophagus patients reporting the lowest QoL scores. This was supported within the forest plots (Appendix 7), with a trend of Barrett's oesophagus (277–279) and giant cell tumour (280) patients reporting lower scores than control groups in all forest plots. The other conditions clustered around the control group mean in each forest plot (except those with colorectal polyps (272), who reported lower general health scores).

The physical component score forest plot highlighted differing physical effects between premalignancies with Barrett's oesophagus patients reporting higher physical component score detriment, while CIN patients reported an improved physical component score compared to the control mean Figure 2-6. There were no significant outliers in the mental component score forest plot,.

The CIN cohort from Xie *et al*, (281) reported mixed results, with scores being above or below the mean on various subscales (5/8 subscales higher, 3/8 lower than the mean). This study had a low-quality rating in the quality assessment (Appendix 4) and was excluded from the component score meta-analysis and forest plots due to statistical errors in the calculations. The study had calculated the physical and mental component scores using "PCS = (PF + RP + BP + GH)/4; MCS = (VT + SF + RE + MH)/4" rather than using the correct formula, which takes a weighted measure of all subscales (224,282).

There was high heterogeneity in the subscale and component score analysis. The Cochran's *Q* for each subscale was significant ($p<0.001$); and the I^2 statistic was >95% for all analyses (Table 2-4). A score of over 75% is considered high heterogeneity using the I^2 statistic (252). This high heterogeneity indicates caution should be used when assessing these results. Further discussion of the influence of heterogeneity is presented within the strengths and limitations section (page 137).

Table 2-5 SF Questionnaire study details

	SF Subscales	Physical Component Score (PCS)	Mental Component Score (MCS)
Studies which utilised SF Questionnaire and was included in forest plots	n=19 (210,211,279,280,283–289,213,272–278)	n=17 (28,240,269,272–276,290–299)	n=18 (240,269,293–300,272–276,290–292)
Overall population	n=2422	n=2764	n=3599
Studies excluded from meta-analysis and rationale	Insufficient detail on control groups (n=11) (210,213,289,274–276,278,279,283,284,288)	Insufficient detail on control groups (n=7) (275,292–296,298)	Insufficient detail on control groups (n=9) (272,275,292–296,298,300)
	Control group was cancer only (n=2) (280,285)	Control group was cancer only (n=1) (297)	Control group was cancer only (n=1) (297)
		Incorrect component scores calculation[i] (n=1) (281)	Incorrect component scores calculation [1] (n=1) (281)
Control group mean (forest plot vertical line)	See per Forest plot (Appendix 7) Weighted control group mean	Mean=46.07 Weighted control group mean	Mean= 48.79 Weighted control group mean

Table 2-6 SF instrument meta-analysis results

Questionnaire	Average Score (Range)	Pooled effect size (95% CI) ^	I^2 & Cochran's Q	Publication bias	Meta-analysis studies Participants (n=)
Role Limitation Physical (RLP)	52.7 (22.38 - 83.38)	3.519 (-1.77 to 5.27)	96.7% (p<.001*)	Begg-Mazumdar p=0.817 Egger p=0.550.	Articles (n=5) DCIS (n=3) (211,273,286) Barrett's oesophagus (n=1) (277) Colorectal polyps (n=1) (272) Participants (n=949)
Role Limitation Emotion (RLE)	78.99 (58.34 - 91.81)	-3.384 (-13.97 to 7.20)	96.7% (p<.001*)	Begg-Mazumdar p=0.817 Egger p=0.557	
Physical Function (PF)	73.75 (40.00 - 84.61)	-8.605 (-18.07 to 0.86)	97.5% (p<.001*)	Begg-Mazumdar p=0.233 Egger p=0.161	
Social Function (SF)	81.14 (62.50 - 88.91)	-5.391 (-13.38 to 2.60)	96.6% (p<.001*)	Begg-Mazumdar p=0.233 Egger p=0.476	
Mental Health (MH)	76.34 (68.00 - 80.27)	-0.99 (-6.42 to 4.44)	95.6% (p<.001*)	Begg-Mazumdar p=0.817 Egger p=0.890	
Bodily Pain (BP)	71.83 (43.75 - 90.21)	-5.03 (-20.70 to 10.65)	97.7% (p<.001*)	Begg-Mazumdar p=0.233 Egger p=0.479	
General Health (GH)	61.67 (37.50 - 77.50)	-5.72 (-13.94 to 2.49)	96.9% (p<.001*)	Begg-Mazumdar p=0.483 Egger p=0.568	
Vitality	57.81 (38.75 - 70.54)	-6.40 (-14.67 to 1.86)	97.2% (p<.001*)	Begg-Mazumdar p=0.817 Egger p=0.966	

Questionnaire	Average Score (Range)	Pooled effect size (95% CI) ^	I^2 & Cochran's Q	Publication bias	Meta-analysis studies Participants (n=)
Physical component score (PCS)	45.58 (41.80 – 53.00)	-0.79 (-2.78 to 1.20)	93.5% (p<.001*)	Begg-Mazumdar p=0.905 Egger p=0.932	Articles (n=8) DCIS (n=2) (212,269,297) Barrett's oesophagus (n=3) (290,291,299) Cervical Dysplasia (n=1) (274) CIN (n=1) (240) Colorectal polyps (n=1) (272) Participants (n=1968)
Mental Component score (MCS)	48.77 (44.32 – 53.00)	0.17 (-1.54 to 1.87)	87.1% (p<.001*)	Begg-Mazumdar p=0.562 Egger p=0.623	Articles (n=7) Barrett's oesophagus (n=3) (290,291,299) DCIS (n=2) (212,269) Cervical Dysplasia (n=1) (274) CIN (n=1) (240) Participants (n= 1807)

* p<0.05, ** p<0.001, ^ Compared to control groups.

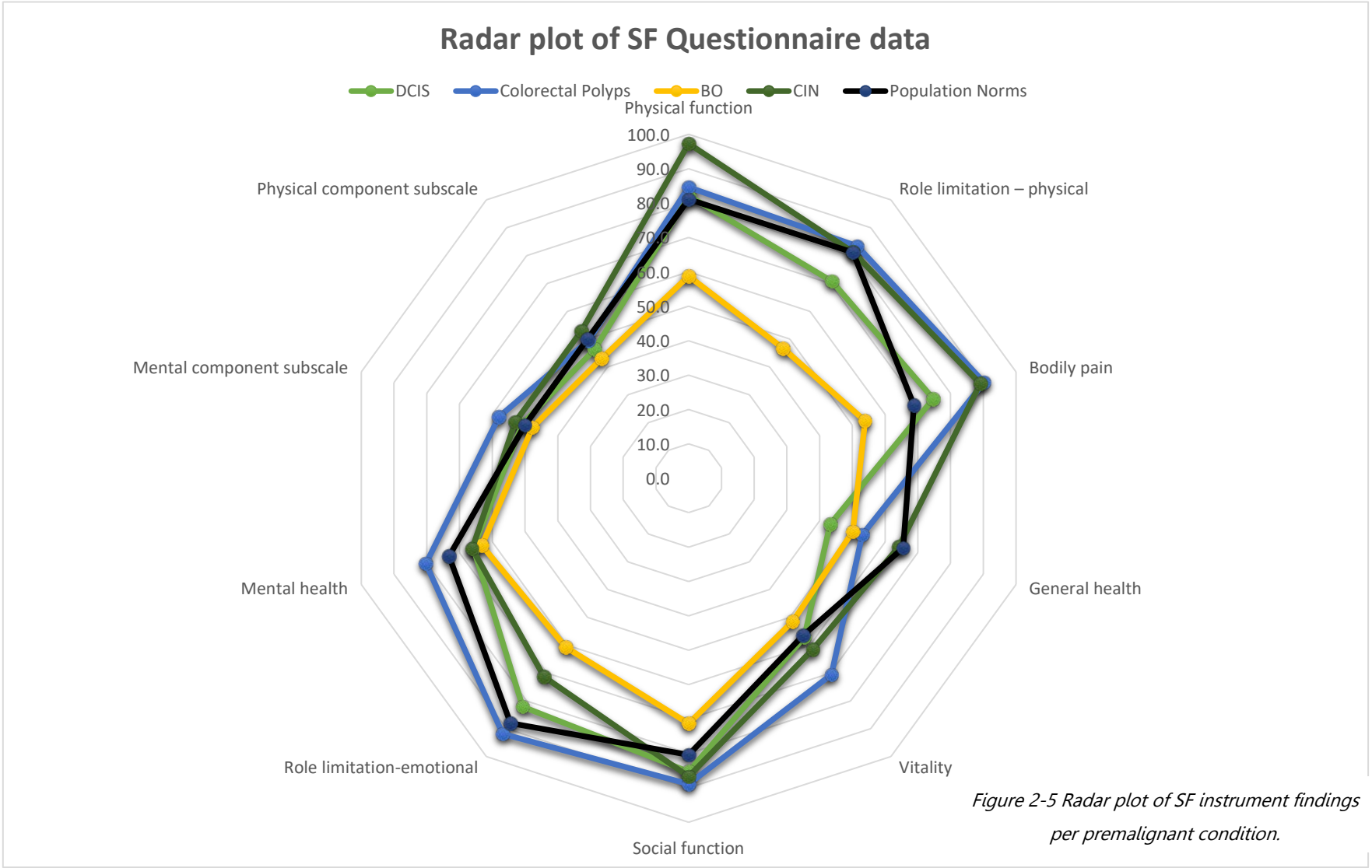


Figure 2-5 Radar plot of SF instrument findings per premalignant condition.

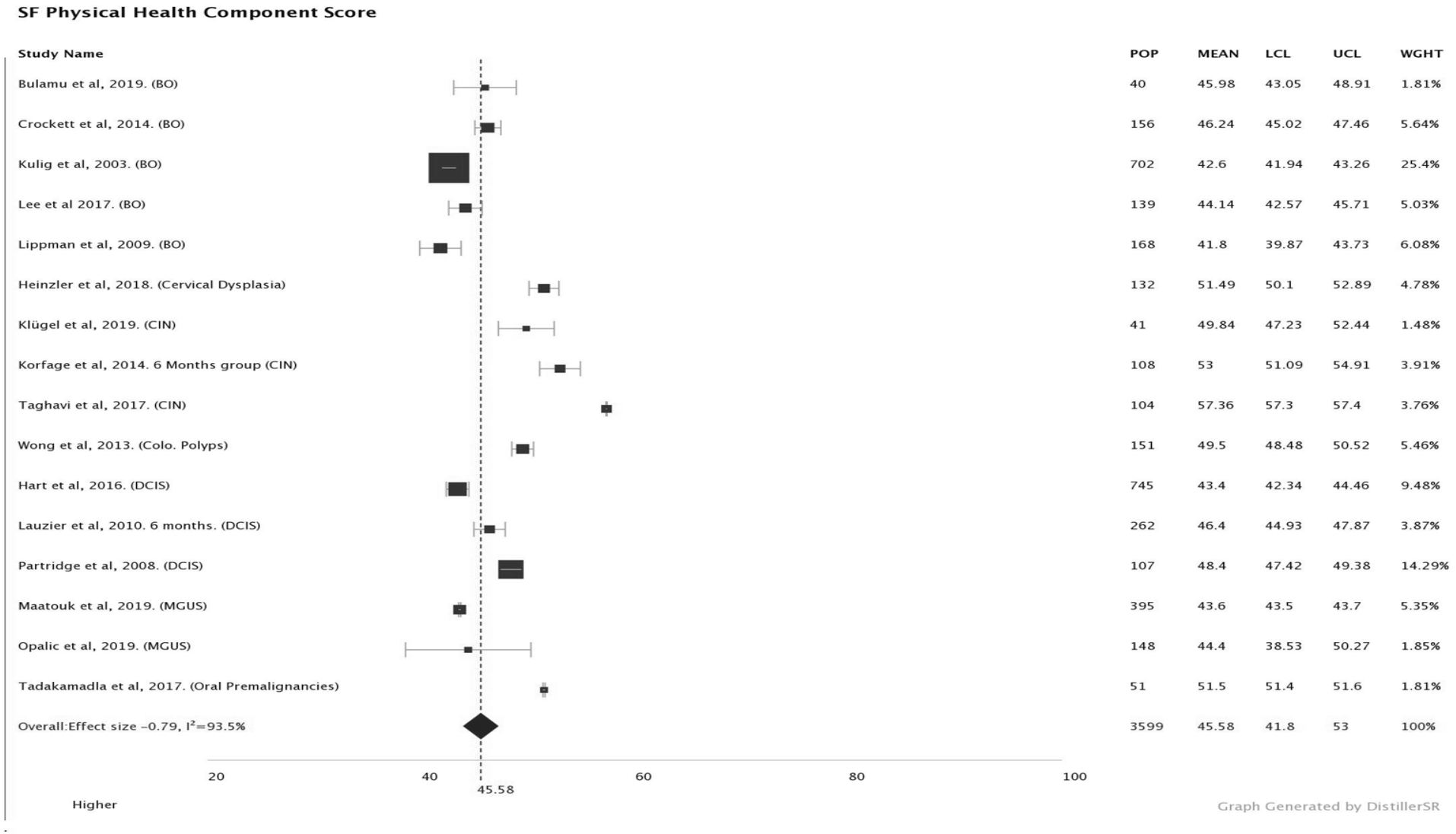


Figure 2-6 Physical component scores (PCS) Forest plot

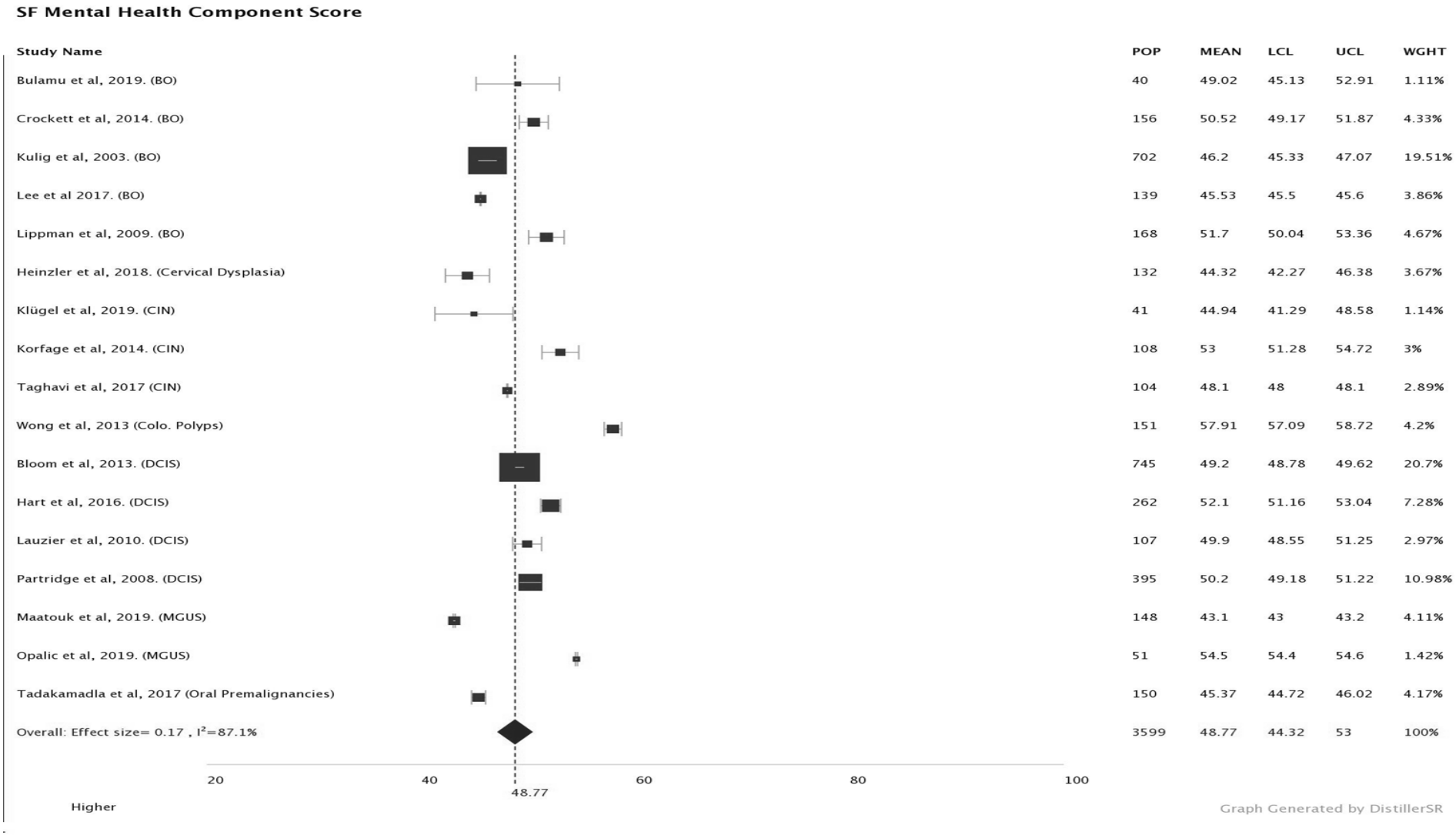


Figure 2-7 Mental component scores (MCS) Forest plot

2.3.1.2 Hospital Anxiety and Depression Scale (HADS)

The HADS[i] is a 14 item scale used to assess levels of anxiety and depression in individuals, Table 2-6 & Table 2-7. Heightened scores (>7) are indicative of clinical levels of anxiety. The meta-analysis found a statistically significant decrease in HADS score in premalignant patients compared to the general (non-clinical) population, Table 2-7. However, this significant finding must be interpreted with caution; due to the high heterogeneity ($p<0.001$; I^2 =94.5%) and clinical scoring system used in the scale.

Three outliers were identified in the forest plot (Figure 2-8). The VIN study by Shylasree et al, (301) and CIN study by Klugel et al, (296) reported heighted anxiety, which was linked to the younger age (compared to other premalignant conditions) and sexual unhappiness/inactivity as a result of the condition. From the quality assessment, both studies included no non-responder related data and were medium quality studies. The colorectal polyps study by Thiis-Evensen et al, (302) had lower anxiety than norms, but this study only included those who attended screening; which was a limitation of the study.

The average score (4.92) was below population norms (6.14) and also below the clinical score associated with anxiety (<7) (218). When interpreting the clinical scoring system used in the scale, scoring 4.92 (meta-analysis) or 6.14 (population norm) (218) equates to the same conclusion, the patient does not have a clinically significant level of anxiety. With the heterogeneity (from the I^2 statistic) considered, there is likely no clinically relevant differences between premalignant patients and the population on HADS score, Table 2-7.

More details are explained in Chapter 2: (page 61).

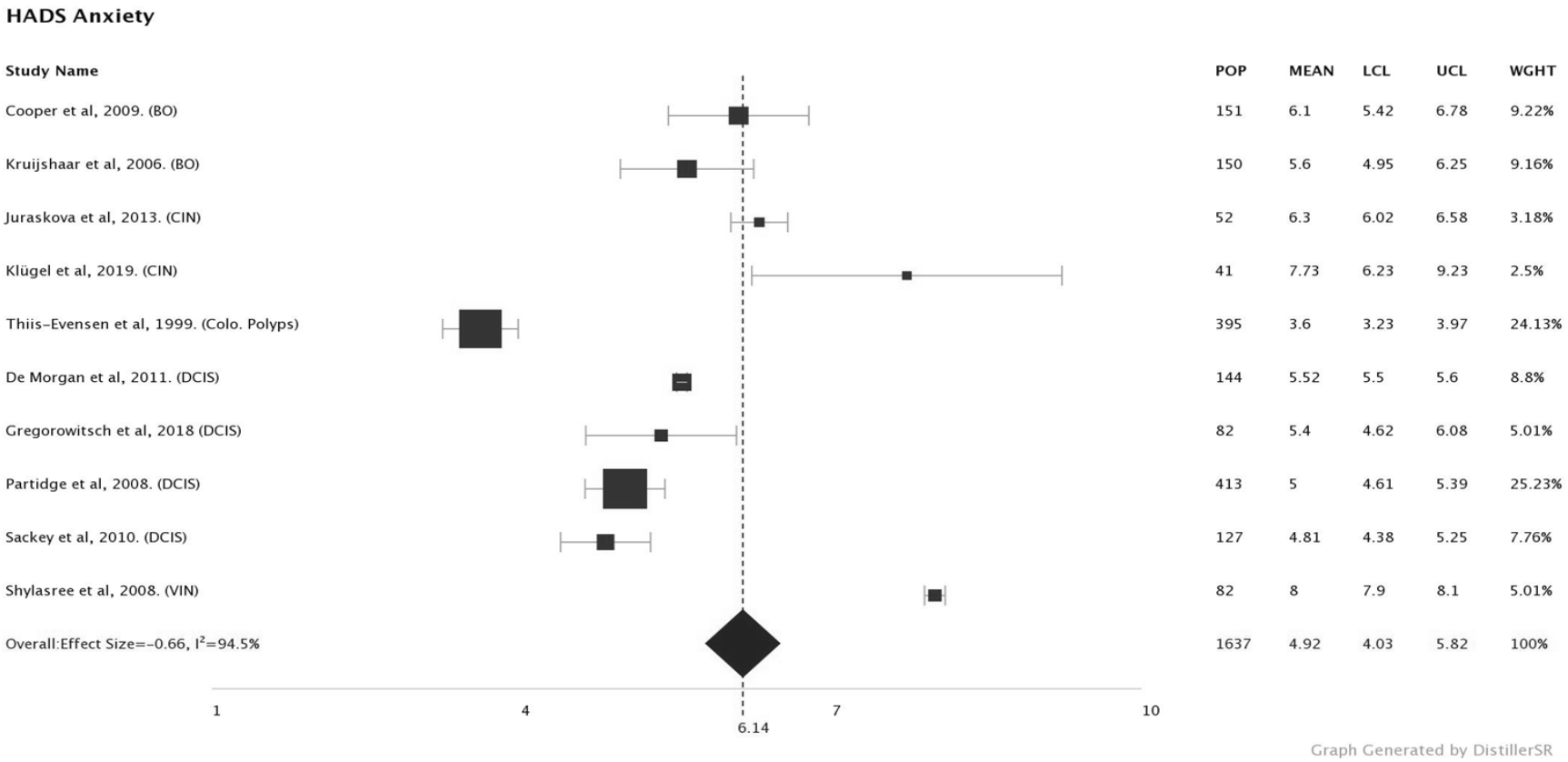


Figure 2-8 HADS Anxiety Forest Plot

2.3.1.3 Center for Epidemiologic Studies Depression Scale (CES-D)

The CES-D[i] is a 20 item scale used to self-report depression (220). Heightened scores (>16) are indicative of clinical levels of depression, Table 2-6 & Table 2-7. The meta-analysis found no significant difference in depression scores between premalignant patients collectively compared to population norms (10.24) (303), Table 2-7.

From the Forest plot (Figure 2-9) it was clear from the large confidence intervals that there was a wide variation both between studies and within studies. This led to high heterogeneity ($p<0.001$; $I^2=82.6\%$). The low number of studies (4 studies) implies that further rigorous investigation is required but depression was unlikely to be clinically relevant to most premalignant patients, Table 2-7.

[i] More details are explained in Chapter 2: (page 61).

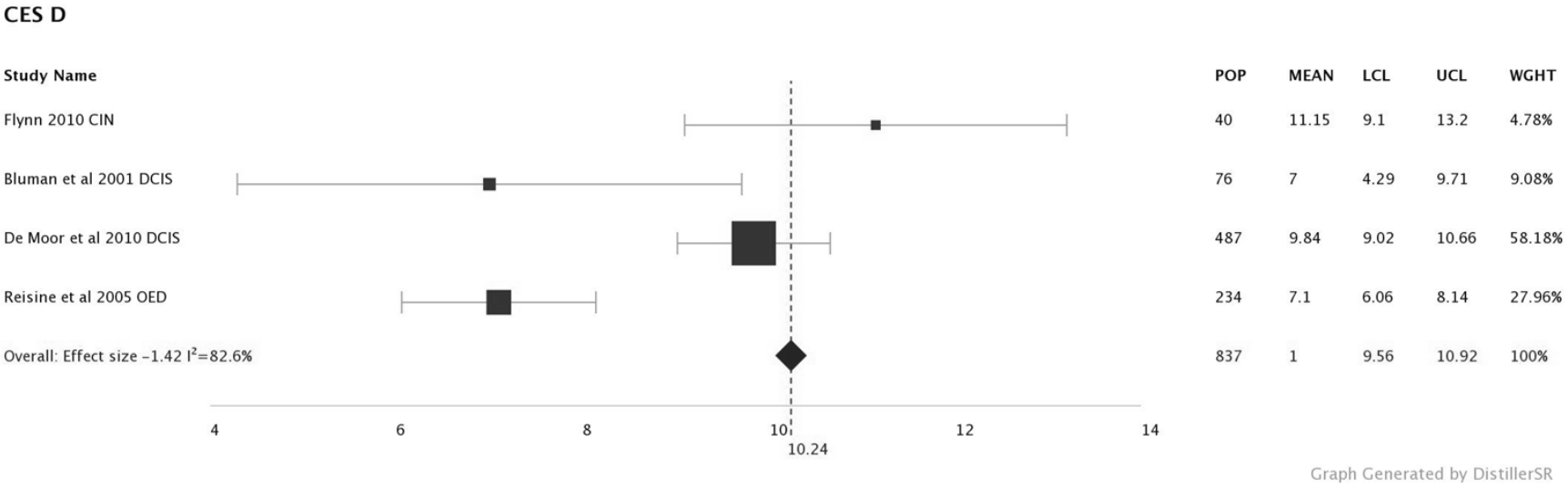


Figure 2-9 CES-D Forest Plot

2.3.1.4 EuroQol 5D (EQ-5D)

The EQ-5D[i] is a measure of quality of life commonly used in health research to create QALYs for economic analysis (214), Table 2-6 and Table 2-7. Scores range from -0.594 (worst health) to 1.0 (perfect health). The meta-analysis found no significant difference in QoL in premalignant patients compared to controls. As with the other questionnaires, there was a high level of high heterogeneity ($p<0.001$; $I^2=72.5\%$), However, these results indicate that it is unlikely to be a clinically relevant QoL effect for most premalignant patients, Table 2-7.

From the Forest plot (Figure 2-10), there was a clustering around the mean score (0.866), with the exception of in the VIN study (304), which reported a lower average QoL. The authors reported that the VIN 2/3 patients had more issues in all dimensions of the EQ-5D compared to population norms, especially in anxiety/depression. The authors attributed this to a higher clinical significance (to other conditions included, such as genital warts) and a significant effect on sexual functioning (304).

[i] More details are explained in More details are explained in Chapter 2: (page 61).

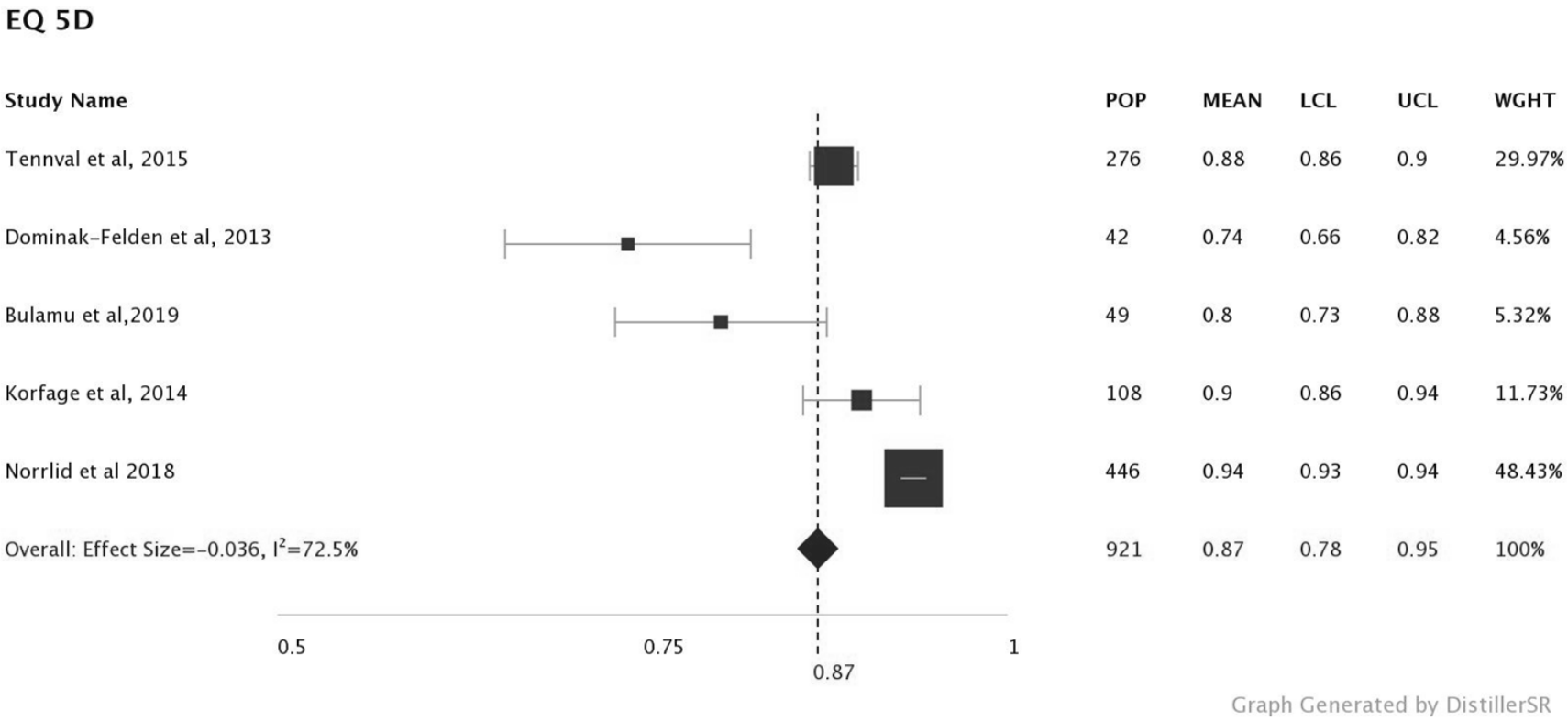


Figure 2-10 EQ-5D Forest Plot

2.3.1.5 The State-Trait Anxiety Inventory (STAI)

The STAI[i] is a 40-item scale that measures trait and state anxiety. Scores range from 20-80, with higher scores positively associated with higher levels of anxiety (221), Table 2-6 and Table 2-7. The meta-analysis found no significant difference in state anxiety between premalignant patients and controls.

There was no significant effect of heterogeneity using Cochran's Q (p=0.095) and medium heterogeneity using the I^2 statistic (I^2=57.5). The colorectal polyps study (305) had a strong weighting, potentially skewing the analysis. Further analysis using a standardised weighting structure provided similar findings. With the medium heterogeneity (from the I^2 statistic) considered, there is likely no clinically relevant differences between the premalignant patients and controls.

From the forest plot (Figure 2-11), there was a wide range in scores, even between studies investigating the same premalignant condition (example CIN), which highlights heightened heterogeneity in the analysis.

[i] More details are explained in Chapter 2: (page 61).

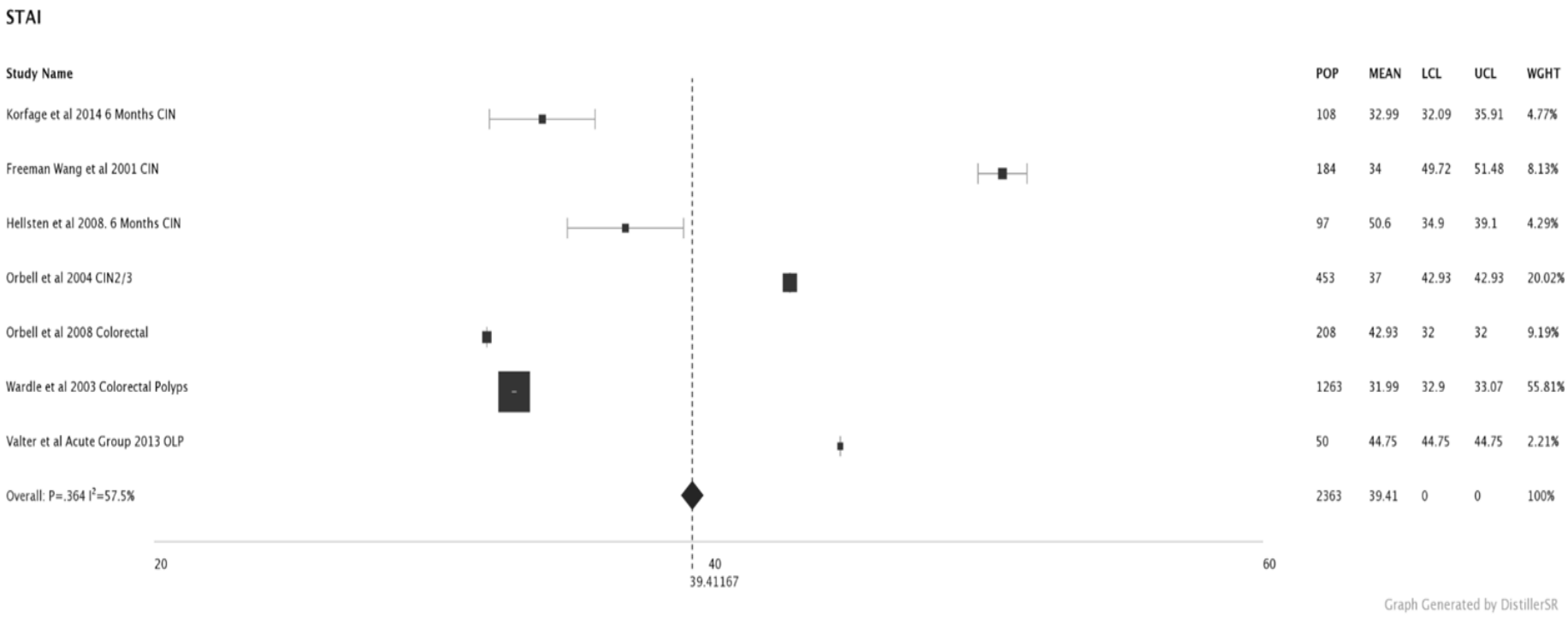


Figure 2-11 STAI Forest Plot

Table 2-7 Study details for the HADS, CES-D, EQ-5D and STAI instruments

SCALE SCORE	HADS	CES-D	EQ-5D	STAI
Studies which utilised scale and included in forest plots	n=10	n=4	n=5[i]	n=7
Overall population	n=1637	n=837	n=475	n=2363
Studies excluded from meta-analysis and rationale	No standard deviation reported (or calculable) (n=2) (301,306)	No excluded studies	No standard deviation reported (or calculable) (n=1) (307) No control group (n=1) (308,309)	No control group (n=1) (308) No standard deviation reported (or calculable) (n=3) (241,310,311)
Control group- forest plot vertical line	Score=6.14 Population norm (218)	Score=10.24 Population norm (303)	Score=0.869 Control Group mean.	Score=39.41 Control Group mean.

[i] One paper (307) on AK was not included as no scores were reported for the EQ-5D (Diagram only).

Table 2-8 HADS, CES-D, EQ-5D and STAI instrument meta-analysis results

Questionnaire	Average Score (Range)	Pooled effect size (95% CI)	I^2 & Cochran's Q	Publication bias	Studies included in the meta-analysis Participants (n=)
HADS	4.923 (3.60 – 7.73)	- 0.66 (-1.45 to 0.12) p= 0.101	94.5% p<.001*	Begg-Mazumdar p=0.109 Egger p=0.003*	Articles (n=8) DCIS (n=3) (273,286,312) Barrett's oesophagus (n=2) (284,313) CIN (n=2) (263,299) Colorectal polyps (n=1) (302) Participants (n=1411)
CES D	8.77 (7.00 - 11.15)	-1.42 (-3.36 to 0.51) p= 0.150	82.6% p<.001*	Begg-Mazumdar p=0.750 Egger p=0.894	Articles (n=4) DCIS (n=2) (314,315) CIN (n=1) (270) Oral Epithelial Dysplasia (n=1) (316) Participants (n=837)

Questionnaire	Average Score (Range)	Pooled effect size (95% CI)	I^2 & Cochran's Q	Publication bias	Studies included in the meta-analysis Participants (n=)
EQ-5D	0.866 (0.779 - 0.951)	-0.036 (-0.100 to 0.003) p= 0.259	72.5% p=0.012*	Begg-Mazumdar p=0.333 Egger p=0.636	Articles (n=4) Actinic keratosis (n=1) (317) Barrett's Oesophagus (n=1) (291) CIN (n=1) (240) VIN (n=1) (304) Participants (n=475)
STAI	39.20 (32.99 - 50.60)	-0.55 (-1.74 to 0.64) p= 0.364	57.% p=0.095	Too few studies were included in the analysis to perform Begg-Mazumdar or Egger tests	Articles (n=3) CIN (n=2) (240,318) Colorectal polyps (n=1) (305) Participants (n=1544)

2.3.2 Brief narrative review of studies not included in the meta-analyses.

In total, 35 studies fulfilled the inclusion/exclusion criteria of the systematic review (Table 2-3) but did not have a sufficient number of studies (>3) using the same validated instrument to be included in a meta-analysis. To ensure that the review provides a systematic and complete picture, these studies were included in a narrative review. The narrative review identifies each study, highlights the validated instrument utilised and reports the study conclusions. Conditions with multiple studies were summarised. All other study details can be found in Appendix 6.

2.3.2.1 Actinic Keratosis

Alarcon *et al,* 2017 (319) utilised the Actinic Keratosis Quality of Life (AKQoL) and Dermatology Life Quality Index (DLQI) in 74 patients with actinic keratosis. This was part of a cultural adaptation of the AKQoL into Spanish. The findings indicated that there may be lower scores (less HRQoL impairment) in Spanish patients compared to Danish patients in similar studies by the group. However, comparison was not a main aim of the article.

Diepgen *et al, 2019* (320) utilised the Skindex-16 in 826 patients with actinic keratosis. This was a randomised trial to assess the use of ingenol mebutate as a topical therapy for AK. The findings indicated ingenol mebutate improved skin-related QoL, was well tolerated by patients and significantly reduced clinically visible AK lesions.

Gholam *et al*, 2013 (321): This study utilised the Dermatology Life Quality Index (DLQI) in 22 actinic keratosis patients with no control/comparator group. The study compared actinic keratosis patient's QoL from screening to 4 weeks post treatment using photodynamic therapy. They concluded that

photodynamic therapy had a temporary detrimental effect on patient's QoL due to side effects of the treatment.

Ianhez *et al,* 2019 (322) utilised the Dermatology Life Quality Index (DLQI) in 61 patients with actinic keratosis. This was a randomised trial to assess the use of isotretinoin and tretinoin over 6 months. Both treatments improved QoL but there were no QoL-related differences between the treatments.

Jubert-Esteve *et al,* 2015 (323): This study utilised the Skindex-29 and Treatment Satisfaction Questionnaire for Medication (TSQM 1.4) in 19 actinic keratosis patients. This study piloted the use of an ingenol mebutate treatment over three weeks. Actinic keratosis patients reported improved scores relating to symptom severity, emotional response and overall Skindex-29/QoL score post-treatment. Actinic keratosis patients also rated ingenol mebutate treatments superior (effectiveness and global satisfaction) than previous treatments on the TSQM 1.4.

Longo *et al,* 2018 (324) utilised the Actinic Keratosis Quality of Life (AKQoL) in 1159 patients with actinic keratosis. The findings indicated that patients with higher levels of concern were more likely to show more impaired QoL, female sex and previous treatment for AK were linked to higher QoL impact from AK.

Meier *et al,* 2018 (325) utilised the Actinic Keratosis Quality of Life (AKQoL) and Dermatology Life Quality Index (DLQI) in 113 patients with actinic keratosis. This was part of a cultural adaptation of the AKQoL for the German-language region of Switzerland. The findings indicated their scores were similar to other studies; indicating a "rather light impairment in quality of life".

Neri *et al,* 2019 (326) utilised the Actinic Keratosis Quality of Life (AKQoL), Treatment Satisfaction Questionnaire on Medications version 2 (TSQM–V2) and Dermatology Life Quality Index (DLQI) in 1136 patients with actinic keratosis. All patients had a prescription of ingenol mebutate (IMB) (n=961)

or either diclofenac 3% in hyaluronic acid (DHA) or imiquimod 5% (IMQ) (n=175). The findings indicated their treatment satisfaction increased with follow-up, DLQI scores improved (improved QoL) from baseline to the second follow-up visit (approximately 30 days under treatment).

Pflugfelder *et al,* 2012 (327): This study utilised the Dermatology Life Quality Index (DLQI) in 418 actinic keratosis patients. This study included two patient groups using 3% diclofenac in 2.5% hyaluronic acid gel for 3 and 6 months. The QoL of 48% of patients using the gel improved; irrespective of time-period used (3- or 6-month).

Sanclemente *et al,* 2017 (328) utilised the Skindex-29 in 41 patients with actinic keratosis. This was a large-scale study on multiple skin-related diseases. The findings indicated AK patients appeared to report higher Skindex-29 global scores than the average skin conditions but no formal statistical tests were conducted for the AK patients.

The studies reported that treatment for actinic keratosis had mixed effects. Photodynamic therapy caused some temporary QoL detriment (321) while gel treatments improved QoL (320,322,323,326,327).

2.3.2.2 Barrett's Oesophagus

Baldaque-Silva *et al,* 2017 (329) utilised the gastroesophageal reflux disease health related quality of life questionnaire (GERD/HRLQ) in 54 patients with Barrett's oesophagus. These were separated into two groups; with (n=30) and without (n=24) anti-reflux surgery (fundoplication > 5 years prior to inclusion). The findings indicated that normalisation of acid reflux was associated with a significant reduction in GERD/HRQL symptoms compared to baseline values.

Drahoňovský *et al,* 2008 (324): This study utilised the Gastrointestinal Quality of Life Index (GIQLI) in 47 patients with Barrett's oesophagus. The findings indicated that successful surgery (laparoscopic anti-reflux surgery) returned

patients with Barrett's oesophagus's QoL to the population norm however no control/comparison group was included in the study.

Fisher *et al,* 2002 (325): This study utilised the Quality of Life in Reflux and Dyspepsia (QOLRD) in 15 patients with Barrett's oesophagus. The study found patients with Barrett's oesophagus reported improved QoL compared to previous published endoscopic patients, but provided no comparison to healthy controls. Using a separate utility measure rating potential surveillance outcome (for Barrett's oesophagus), the researchers suggested that patients with Barrett's oesophagus had concerns about surveillance not related to reflux symptoms. The article is unclear of these concerns but focused on the *"value of diagnosing cancer at an early stage balanced against patient preferences for the risks of surveillance or surgical intervention"* (325).

Han *et al,* 2019 (332) utilised Patient-Reported Outcomes Measurement Information System (PROMIS) Global 10 survey v1.0 and the Gastroesophageal Reflux Disease Questionnaire (GerdQ) in 144 patients with Barrett's oesophagus referred for endoscopic eradication therapy. The findings indicated that 53.9% had poor QoL and the degree of dysplasia was independently associated with poor QOL.

Markus *et al,* 2001 (326): This study utilised the gastrointestinal Quality of Life Index (GIQLI) in 14 patients with Barrett's oesophagus. The study compared patients with Barrett's oesophagus to those with gastro-oesophageal reflux disease (GERD). The study found no QoL differences between the groups. The treatment (laparoscopic Nissen fundoplication) improved QoL scores for both groups.

Miller *et al,* 2010 (327): This study utilised the linear analogy self-assessment (LASA) to measure QoL in 489 patients with Barrett's oesophagus comparing QoL scores to oesophageal cancer patients. patients with Barrett's

oesophagus reported better QoL compared to patients with oesophageal cancer.

Peerally *et al,* 2019 (335) utilised the EQ-5D and QLQ-C30 in 76 patients with Barrett's oesophagus undergoing radiofrequency ablation (RFA) or argon plasma coagulation (APC). This was a randomised pilot study. QoL scores were indicated on a graph, which was not suitable for accurately deciphering scores. The findings indicated both treatments had similar QoL effects on patients and minimal changes were evident after treatment.

Patients with Barrett's oesophagus who had successful surgery had improved QoL scores and could return to population normative scores (330) and reduce symptom severity (329). Patients with Barrett's oesophagus reported better QoL scores than patients with oesophageal cancer (327) and no different compared to other published endoscopic patients (325) and patients with GERD (326).

2.3.2.3 Cervical Dysplasia

Kesic *et al,* 2018 (336) utilised the FACIT-CD (Functional Assessment of Chronic Illness Therapy - Cervical Dysplasia), Beck's Anxiety Inventory (BAI), Beck Depression Inventory and Short Form-36v2 questionnaire (SF-36v2) in 160 cervical dysplasia patients. This was part of a cross-cultural adaptation and validation of the FACIT-CD in Serbia. Only scores from the FACIT-CD were presented. The findings indicated that the mean FACIT-CD were high; signifying a good HRQoL.

2.3.2.4 Cervical intraepithelial neoplasia (CIN)

Rueckert,*et al,* 2018 (337) utilised the Impact of Event Scale-Revised (IES-R) in 96 CIN and High grade squamous intraepithelial lesion (HSIL) patients. These were split into pregnant (n=52) and non-pregnant CIN (n=44) patients.

The findings indicated pregnant patients coped better with their CIN diagnosis than non-pregnant CIN patients.

Sparić,*et al,* 2019 (338) utilised Beck's anxiety (BAI) and depression (BDI) inventory Beck's Anxiety Inventory (BAI) and Beck Depression Inventory (BDI) in 146 CIN patients. The findings indicated approximately one-third of women over two years post-treatment have relatively greater anxiety and depression than norms and are concerned about the possibility of disease progression.

Taneepanichskul *et al,* 2011 (328): This study utilised the Functional Assessment of Cancer Therapy-General (FACT-G) questionnaire in 25 CIN 2/3 patients. The study compared CIN patients to cervical cancer patients, with no QoL difference observed between CIN 2/3 and cervical cancer patients. The authors suggested higher risk of emotional difficulties for younger patients and those with higher education.

Wang *et al,* 2011 (329): This study utilised the HPV impact profile (HIP) in 478 CIN patients. The study compared the QoL of CIN patients to normal HPV/pap tests respondents. CIN patients reported lower QoL than normal controls, especially in "sexual impact, self-image and control/life impact".

The two studies reported some QoL impact of CIN patients, with similar QoL impact as cervical cancer (328) and lower QoL compared to controls (329). Pregnancy (337) can also be a protective factor against anxiety.

2.3.2.5 Colorectal polyps

Nolthenius *et al,* 2016 (330): This study utilised the Impact of Events Scale (IES) in 65 colorectal polyps patients. The study compared IES scores pre- and post-surveillance (CT colonoscopy). The study found no clinically relevant change in IES score post-CT colonoscopy.

2.3.2.6 Ductal Carcinoma in Situ (DCIS)

Hamer *et al,* 2017 (342) utilised the Functional Assessment of Cancer Therapy for Breast Cancer (FACT-B) in 141 DCIS patients. The findings indicated DCIS patients had a better quality of life than breast cancer patients at any stage (early, locally advanced or metastatic).

Mercieca-Bebbe*et al,* 2017 (343) utilised the Health Literacy Questionnaire (HLQ) in 38 DCIS patients. The findings indicated fatigue-related symptoms (82%) and ''fear of progression'' (50%) were the most frequently experienced issues and health literacy was high across all nine HLQ scales.

Mertz *et al,* 2017 (344) utilised the Hospital Anxiety and Depression Scale (HADS) in 473 DCIS patients. The findings indicated that 20% of DCIS patients reported clinically relevant anxiety, while 6% reported clinically relevant depression.

The studies indicate that DCIS patients report a better quality of life than breast cancer patients but there is heighted anxiety and fears amongst this population.

2.3.2.7 Gastric cardia precursor

Wen *et al* 2015 (331): This study utilised the European Organisation for Research and Treatment of Cancer (EORTC) QoL questionnaire (QLQ)-C30 and -OES18 in 59 gastric cardia precursor lesions patients (including dysplasia). The study compared precursor lesions patients to early stage and advanced cancer patients over 12 months. Patients with gastric precursor lesions reported similar QoL to early stage and advanced cancer patients prior to treatment; various treatments including endoscopic mucosal resection (EMR) for precursor and early-stage patients, and surgery and combination therapies (advanced cancer only) for cancer patients. Patients with precursor lesions reported improved QoL compared to early and

advanced cancer patients' post-treatment and had similar scores to baseline 12 months' post-treatment.

2.3.2.8 Oral Premalignancies

Adamo *et al,* 2013 (332):This study utilised the Pittsburgh sleep quality index, the Epworth sleepiness scale and the Hamilton rating scale for depression and anxiety in 50 oral lichen planus (OLP) patients. OLP patients reported more sleep problems, lower sleep quality, more depressed mood and higher anxiety than healthy age- and sex-matched controls.

Karbach *et al,* 2014 (333): This study utilised the Oral Health Impact Profile (German) (OHIP 14) in 73 oral lichen planus (OLP) and 44 oral leukoplakia (OL) patients. The study compared the HRQoL of OLP and OL patients with oral squamous cell carcinoma patients. Culminative OHIP-14 scores did not differ between the groups but OLP patients reported higher "physical pain" and lower "social disability" than oral squamous cell carcinoma patients. Further analysis highlighted that symptomatic OLP (compared to asymptomatic) caused greater HRQoL impact.

Kono *et al,* 2016 (334): This study utilised the Voice Handicap Index and Voice-Related Quality of Life Measure in 25 laryngeal leukoplakia patients. The study compared patients under observation only with those receiving treatment with laser cordectomy. Patients who underwent additional surgery reported diminished vocal quality compared to patients in the observation arm and healthy control group and diminished voice-related QoL compared to the observation arm and healthy control group.

Rana *et al,* 2014 (335): This study utilised the Oral Health Impact Profile (German) (OHIP 14) and University of Washington Quality of Life Questionnaire (UW-QOL v4) (336) in 106 oral leukoplakia, erythroplakia, oral lichen planus (OLP) patients. The study compared these oral premalignancies

to oral cancer and reoccurrence patients. Oral premalignant patients reported superior QoL to cancer and reoccurrence patients in both the OHIP and the UW-QOL v4 measures.

Rzepakowska *et al,* 2018 (351) utilised the Voice Handicap Index (VHI), and the World Health Organization Quality of Life Scale- Brief Version (WHOQoL-BREF) in 34 oral premalignancy patients. The findings indicated microdirect Laryngoscopy surgery had no significant QoL-related improvement for premalignant (Vocal fold leukoplakia and Chronic laryngitis) patients compared to benign or malignant patients.

Rzepakowska *et al,* 2019 (352) utilised the Voice Handicap Index (VHI), Voice-Related Quality of Life questionnaire; and World Health Organization Quality of Life Scale- Brief Version (WHOQoL-BREF) in 19 oral premalignancy patients. The findings indicated microdirect laryngoscopy surgery had no significant QoL-related improvement for premalignant glottis lesion (leukoplakia, chronic laryngitis with hypertrophic changes of the mucosa, and erythroplakia) patients.

The studies reported that oral premalignancy patients; reported more sleep and sleep quality issues and greater anxiety and depression (332) than healthy controls and reported higher physical pain and lower social disability (333) but higher QoL (335) than oral cancer patients and diminished vocal quality (337). Microdirect laryngoscopy surgery has no significant QoL-related improvement for oral premalignancy patients (351,352).

2.3.2.9 Prostatic intraepithelial neoplasia (PIN)

Alberts *et al,* 2006 (338): This study utilised the UNI-SCALE, the Profile of Mood States (POMS) and the Health Status Questionnaire (HSQ) version of the SF-36 in 60 prostatic intraepithelial neoplasia (PIN) patients. The HSQ is different and not comparable to the SF-36 (339). Patients were split into two

groups; one using an experimental treatment (flutamide; which selectively inhibits androgen receptors (340)) and placebo controls. The findings indicated no QoL effect of flutamide, however no healthy or cancer controls were reported to provide context for the results.

2.3.2.10 Vulvar intraepithelial neoplasia (VIN)

McFadden *et al* 2009 (341): This study utilised the Dermatology Life Quality Index (DLQI) and the Family Relationships Index (FRI) in 8 VIN patients. The study compared QoL in VIN patients to non-clinical samples (population norms); VIN patients had lower QoL (DLQI). No conclusion was made by the authors on the Family Relationships Index due to "inconsistent and incomplete results" and no suitable non-clinical sample. This study also included the HADS questionnaire and found a clinically significant anxiety score compared to non-clinical population (17% compared to 12.6%). This was not included in the HADS meta-analysis as only the percentage of cases and not the score was presented.

2.3.2.11 Narrative review summary

Overall, the narrative review contained mixed findings under QoL, psychosocial wellbeing and treatment effects. By comparing premalignant patients with cancer patients, some studies reported premalignant patients having higher/improved QoL than cancer patients (334,349), while other studies reporting similar/no difference to cancer patients (339,345,347). Two QoL studies in Barrett's oesophagus reported no differences to GERD patients (333) and better than previous endoscopic patients (331).

Under the wider scope of psychosocial wellbeing, CIN patients had lower QoL than normal controls on the impact of HIP (329) and colonoscopy for colorectal polyps patients had no clinically relevant change in IES score.

Treatment had positive effects in multiple studies (320–323,327,330,345), (320–323,327) predominantly in actinic keratosis and no effect in one prostatic intraepithelial neoplasia (PIN) study (338). Treatment for laryngeal leukoplakia led to diminished vocal quality and QoL on patients (334).

Both the narrative review and meta-analysis reported similar findings; that there were minimal differences between premalignant and population scores. However, the narrative review included comparisons to cancer patients (which were not included in the meta-analysis), which indicted that premalignant conditions can have a similar effect to cancer for some conditions. This difference in findings is discussed within the discussion part of this chapter.

2.3.3 Qualitative findings

Twenty-one[i] qualitative articles covering 11 premalignant conditions (DCIS (342–347), CIN/cervical dysplasia (348–355), VIN (301,356), actinic keratosis (357), Barrett's oesophagus (358), colorectal polyps (359) and oral lichen planus (OLP) (360,361)) were included in the thematic synthesis. These studies varied by study location; UK (n=7), Denmark (n=3), Australia (n=2), USA (n=2), Sweden (n=2), Spain (n=2) and single studies from India, Ireland and Mexico. Publication years of studies ranged from 1999-2019.

In total[ii], 679 participants were included, ranging from n=6 (356) to n=231 (342) participants, with a median size of n=22. Sixteen studies included females only, one of men only and the remaining four were mixed sex. The mean age for all included studies was approximately 54 (not all studies reported mean age); ranging from younger individuals with CIN (mean age 31.75) (349) to older individuals with actinic keratosis (mean age 68) (357). Data analysis was conducted using thematic analysis (n=11/21), content analysis (n=3/21) or other[iii] (n=7/21). The study characteristics table (including quality assessment) is in appendix 5.

---

[i] Two studies (Freijomil-Vázquez et al., 2019a, 2019b) shared the same sample for their analysis. For clarity, they will be described as separate articles except when stated (such as participant numbers). The studies had different viewpoints and focused on different experiences for the participant, and are therefore included separately.

[ii] As described previously, Freijomil-Vázquez et al., 2019a, 2019b results are different.

[iii] The other 7 studies were; grounded theory (348), naive reading, structured analysis & critical interpretation (349), discursive theoretical analysis (350), interpretive analysis (360) or were unclear (301,351,352). Two unclear studies were considered content analysis (301,351) and one was a mix of content and thematic analysis (352).

Four descriptive themes were identified in the thematic meta-synthesis; Understanding and acquiring information, Patient's reaction to diagnosis, Health service interaction and Support for patients.

Three figures are presented to orientate the reader on the themes. A coding tree (Figure 2-12) presents the subthemes per premalignant condition and article. A thematic matrix (Table 2-9) presents the themes and sub-themes by occurrence per condition. Finally, a coding framework is presented for each major theme, Figure 2-14, Figure 2-15 and Figure 2-17.

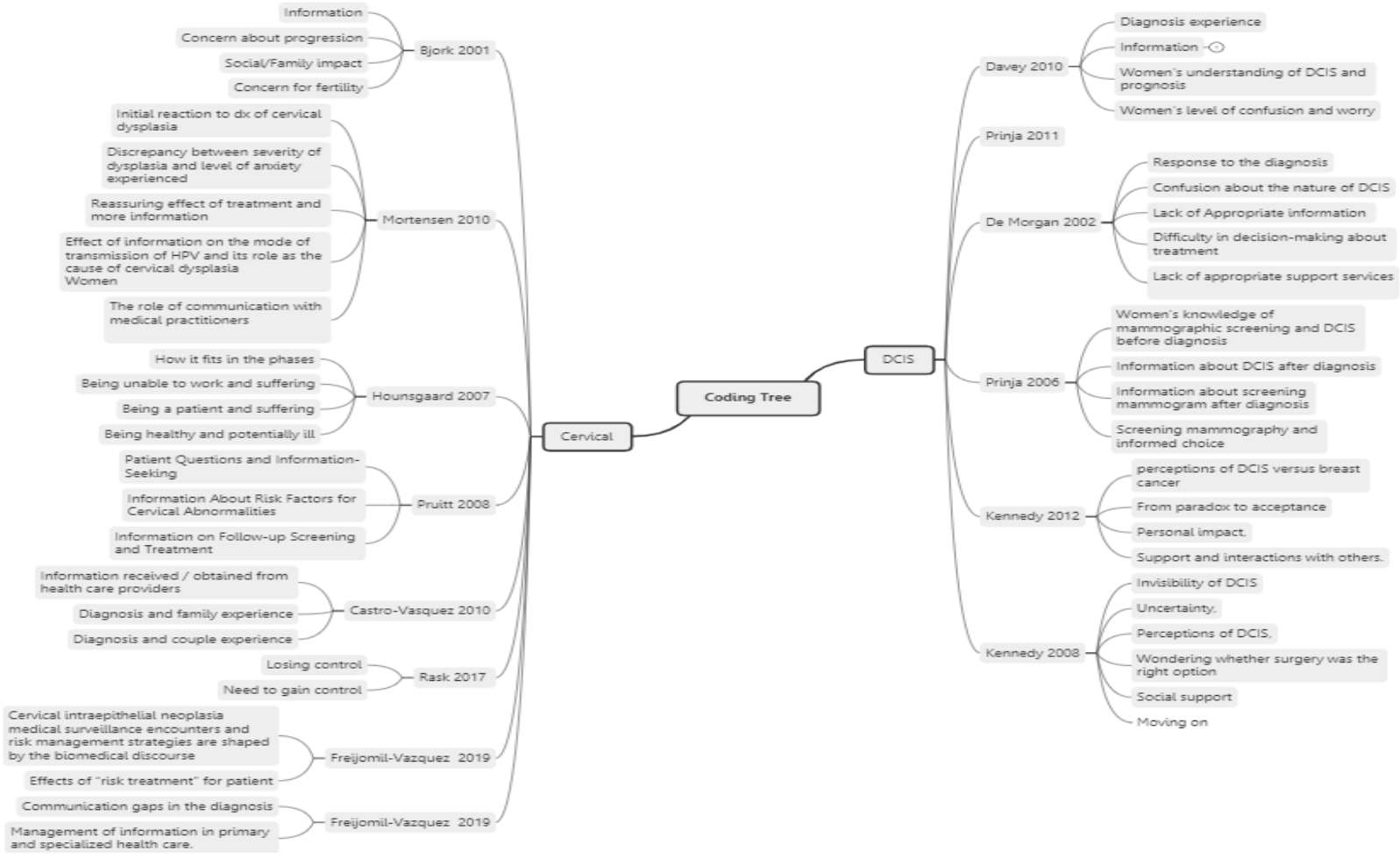


Figure 2-12 Qualitative Coding Tree (A) [i]

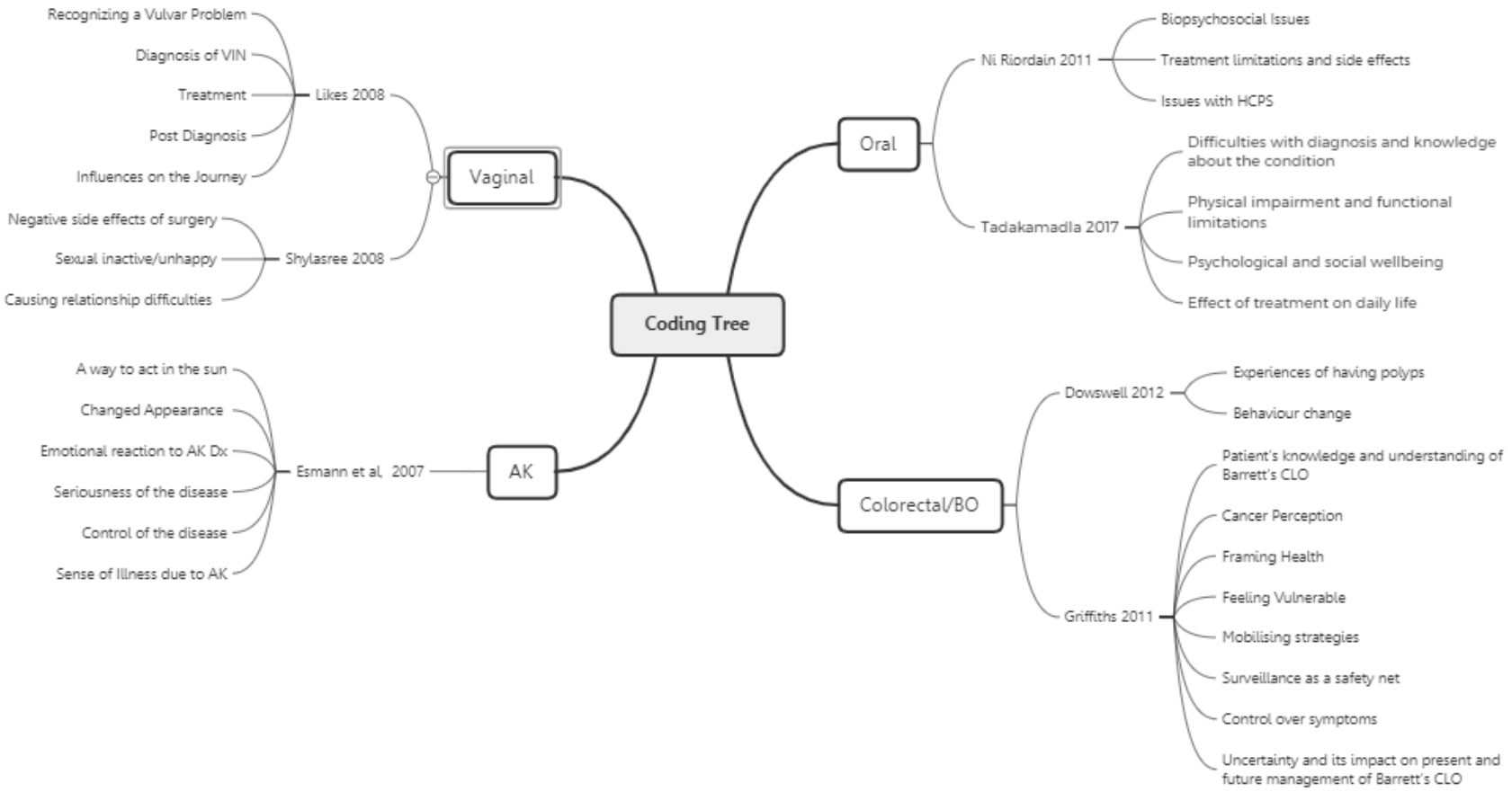


Figure 2-13 Qualitative Coding Tree (B)

Table 2-9 Matrix of Qualitative Themes and Sub-themes

Theme[i]	DCIS (n=6)	CIN (n=8)	VIN (n=2)	AK (n=1)	BO (n=1)	Colorectal Polyps (n=1)	OLP (n=2)
Understanding and acquiring information	Present	Present	Present	Absent	Present	Present	Present
Clarity of Diagnosis	Present	Present	Absent	Absent	Present	Absent	Present
Spectrum of Information	Present	Present	Present	Absent	Present	Present	Present
Using the internet for health needs/Information	Present	Present	Present	Absent	Absent	Absent	Absent
Patients' understanding of condition/ Confusion & Uncertainty	Present	Present	Present	Absent	Present	Present	Present

[i] DCIS: ductal carcinoma in situ, CIN: cervical intra-epithelial neoplasia, VIN: vulval intra-epithelial neoplasia, AK: actinic keratosis, BO: Barrett's oesophagus & OLP: Oral lichen planus

Patient's reaction to Diagnosis	Present	Present	Present	Present	Present	Present	Present
Shock	Present	Present	Present	Absent	Absent	Absent	Absent
Anxiety	Present	Present	Present	Present	Present	Present	Present
Behavioral Change	Present	Present	Absent	Present	Present	Present	Present
Guilt	Present	Present	Absent	Absent	Absent	Present	Absent
The Premalignant condition as a beneficial/negligible impact	Present	Present	Absent	Absent	Present	Present	Present
Medical service interaction	Present	Present	Present	Present	Present	Present	Present
Surgery/ Treatment	Present	Present	Present	Absent	Absent	Absent	Present
Surveillance/ Continued follow-up	Absent	Present	Absent	Absent	Present	Absent	Present
Support for Patients	Present	Present	Present	Present	Present	Present	Present
Social Support	Present	Present	Present	Present	Absent	Absent	Present
HCP Support	Present	Present	Present	Absent	Present	Present	Absent

The thematic overlap highlights the similarities between conditions, Table 2-9. The main divergences were a lack of information sought by actinic keratosis patients discussed in the literature (which may be linked to only one article being included), different emotional reactions between the conditions and different utilisation of health services. These differences and the similarities are elaborated upon within the relevant major themes and sub-themes below.

2.3.3.1 Understanding and acquiring information

Understanding and acquiring information was identified as a major theme in 19/21 studies (342,343,356,358–361,344–351) across the premalignant conditions investigated (except actinic keratosis),Figure 2-14. Four subthemes were developed; Clarity of diagnosis, Spectrum of information, Using the internet for health needs/ information and Understanding of their condition/ Uncertainty & Confusion, Figure 2-14.

This theme highlighted the importance of appropriate, comprehensive and clear information being available for patients at diagnosis (written) and post-diagnosis (online format). Similarly, many studies highlighted a need for greater HCP awareness of their use of medical terminology that may be difficult for patients to understand and appreciation of their role as providers of information. Better information provision may lead to less uncertainty and anxiety for patients.

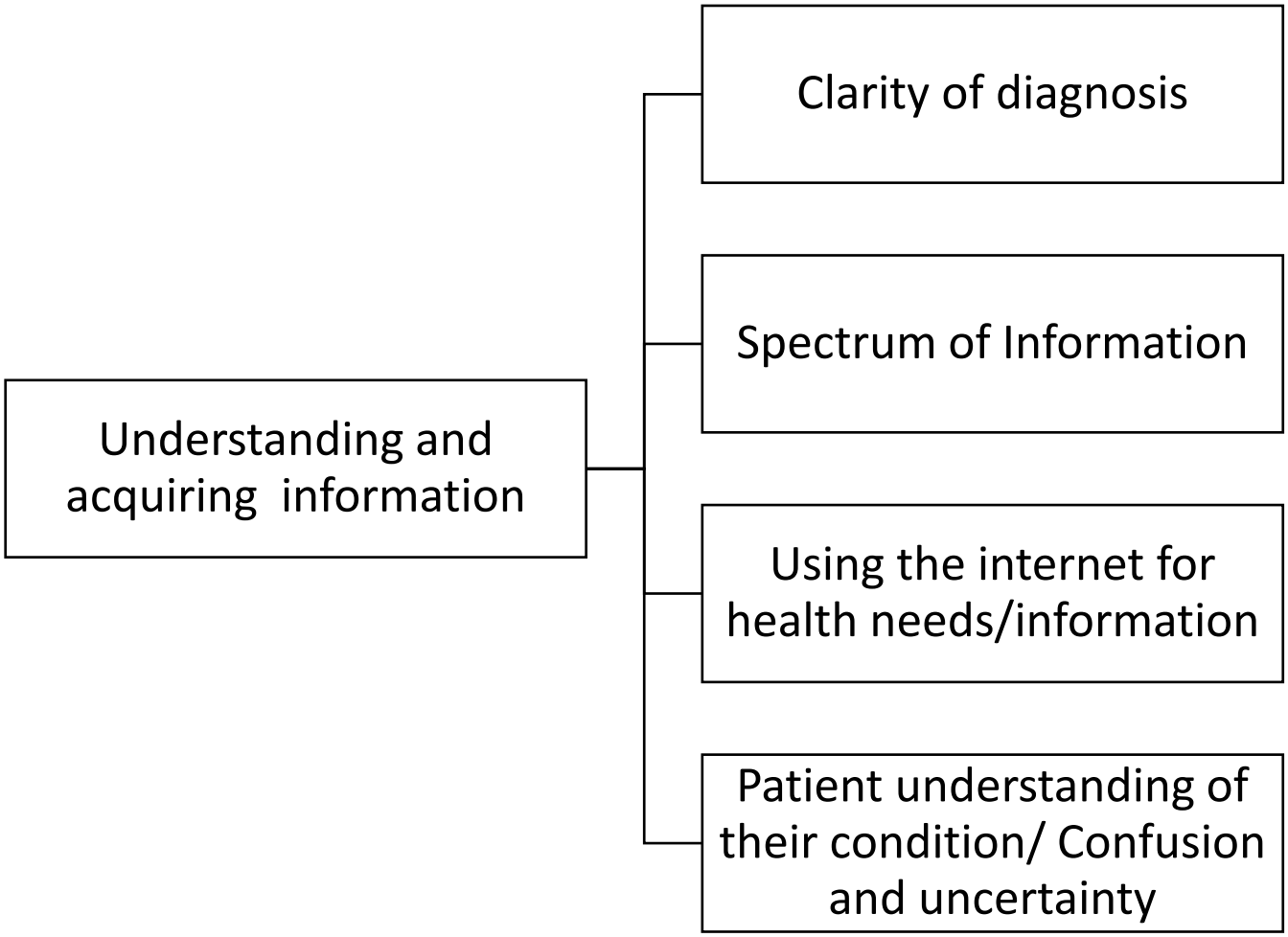


Figure 2-14 Coding Framework Understanding and acquiring information

2.3.3.1.1 Clarity of Diagnosis

Patients reported difficulties being informed of their diagnosis in 11/21 studies (342–344,348,350,353–355,358,360). This subtheme focused on two components, what patients were told they had and the communication style used by their HCP.

Patients reported difficulties interpreting and comprehending medical terminology at diagnosis in 5/21 studies (342–344,355,358). HCPs used 11 different terms during consultations to describe DCIS in two studies; "ductal carcinoma in situ, DCIS, MCIS (mammary carcinoma in situ) and carcinoma" (343), and the terms "breast cancer", "early cancer", "in situ", "pre-malignant", "ductal carcinoma in situ", "DCIS", "abnormal cells", "non-invasive" and "pre-cancer(ous)" (344). Patients were confused by the range of terminology comparing it to being "blinded by science" due to the use of "medical jargon" (358). While the use of multiple terms for their condition was most prominent for DCIS patients, difficult to understand terminology was relevant across the premalignant conditions (342–344,348,350,358,360).

Patients perceived HCPs as being ambiguous and vague explaining their condition in four studies (343,348,350,360). This was linked by patients to a hierarchal/paternalistic perception of doctors and seen as a barrier to further clarification by not wanting to irritate the doctor to repeat the details of the diagnosis or ask questions (348,358). Patients who did not fully grasp the premalignancy concept and required further information to fully comprehend their condition were more likely to want further clarification from their HCPs (343).

2.3.3.1.2 Spectrum of Information

The range of information sought by patients was discussed in 11/21 articles (342,344,360,346,349–351,353,356,358,359). Patients reported differing levels of written information provision at diagnosis; ranging from high levels of receiving an initial booklet/written information (82% (342)), to other patients reporting not receiving written information at diagnosis (356,358,359). For some patients, the

scarcity of information provided at diagnosis created confusion and increased anxiety levels (343,344,348). Patients wanted information on the: causes of their condition (352) and potential future impact and treatments available (both the premalignant condition and potential cancer) (343,344,348,353).

2.3.3.1.3 Using the internet for health needs/information

The internet for health needs/information resource for patients was discussed in 10/21 studies (342–346,348,352,353,355,356). Internet use was most common in DCIS and CIN patients, whose populations were younger (342,344,345,353,355). Many patients reported seeking information online to formulate informed questions about their condition and seek clarifications from HCPs (358). One recommendation to improve patient health literacy was guidance from their HCP to evidence-based websites (344).

Patients found it difficult to find and understand these websites without assistance; as the information was often complicated and not written in a patient friendly way. While patients reported improved knowledge about their condition as a result of their online information-seeking, the internet was perceived as potentially anxiety-inducing for some patients (348,353,355,356). Accessing online information and online forums led to encountering more extreme outcomes and progressions/treatments; which increased distress and concerns for patients (348,353,356).

2.3.3.1.4 Patient understanding of their condition/ Confusion and Uncertainty

Patients' understanding of their condition, and associated confusion and uncertainty was discussed in 14/21 studies (342,343,355,357–359,344–346,348,350,351,353,354). The findings were similar across conditions.

Understanding their future prognosis was difficult for many patients (343,353–355). Some patients were unsure of the cause of their condition, believing it to be due to genetic (359) or lifestyle (353,357) factors. Patient confusion about their diagnosis was on a spectrum; which varied from minimal/some confusion reported (342,343,345,346,350,354,355,358) to individuals under a number of misconceptions about their condition (such as believing they had cancer) (348,353).

Uncertainty about whether patients had a cancer diagnosis or not (even after receiving premalignant condition information) was presented in 8/21 studies (343,344,346,348,351,353–355). This was especially prominent for DCIS patients who frequently conducted further research for further information and were confused by the inconsistency of the literature (342,346). DCIS is considered in the literature as a non-invasive cancer, which can progress. It is referred to as premalignant in some literature (362) and a non-invasive cancer in other literature (363), which led to confusion.

Conflicting and contradictory information from various HCPs involved in their healthcare or the internet also confused some patients (344,360). Surveillance appointment intervals were highlighted as confusing, with little justification provided to patients as to the reasoning behind the intervals between appointments or the rationale for an interval change (350).

2.3.3.2 Patient's reaction to diagnosis

Patient's reaction to diagnosis was identified as a major theme in 19/21 studies (343,344,355–361,345–347,349,350,352–354) and present in all premalignant conditions (Table 2-9 & Figure 2-15 Coding Framework Patient's reaction to Diagnosis

). Five subthemes themes were developed which described; The initial shock of diagnosis, Anxiety about the risk of progression and surveillance, Behavioural

changes made by patients, Patient's guilt post-diagnosis and Premalignancy having a beneficial/negligible effect on patients.

Overall, there was a spectrum of reactions from patients to their diagnosis. For many patients, there was shock at diagnosis, related to the (often) asymptomatic presentation of the conditions. Anxiety was heavily related to the potential of cancer and the uncertainty of the future. Guilt about how patient's lifestyle choices was associated with their diagnosis and the unexpected impact (or benefits) of a premalignant condition were highlighted. This shows that patients have varying reactions to their diagnosis and care should be taken in providing individualised psychosocial care.

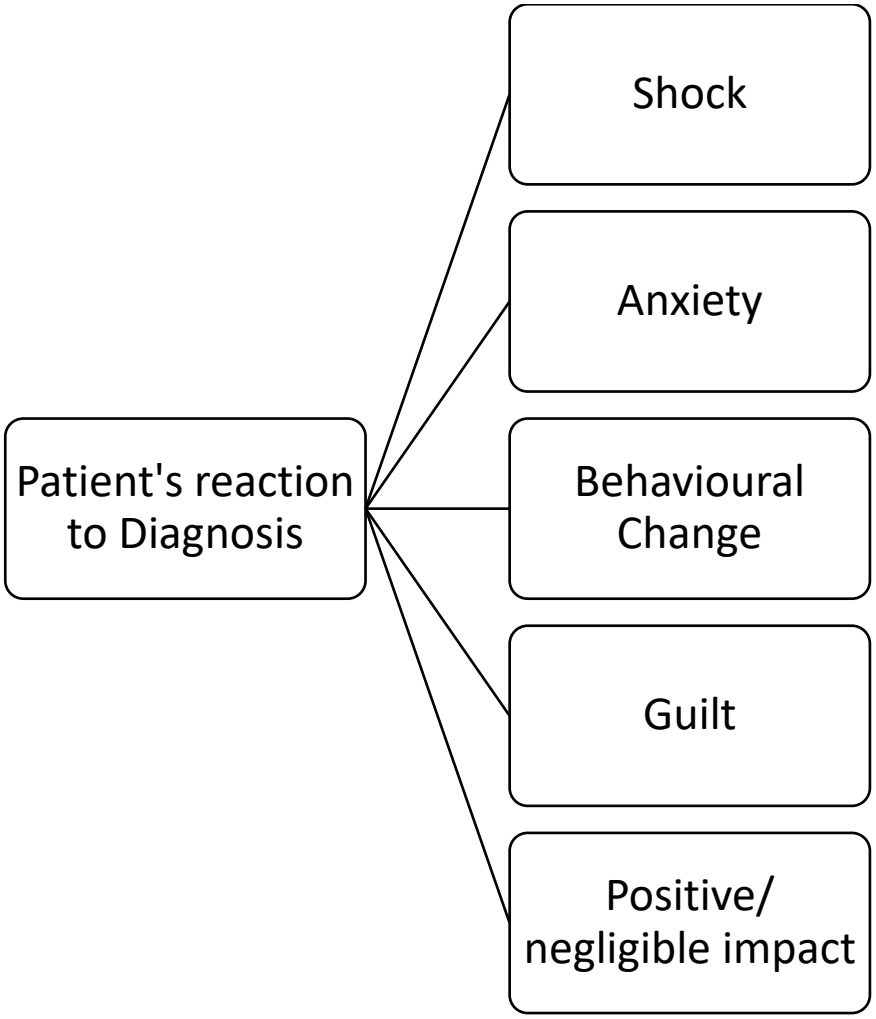


Figure 2-15 Coding Framework Patient's reaction to Diagnosis

2.3.3.2.1 Shock

Shock was the first reaction post-diagnosis for most patients (343,344,347,350,353–356). Shock was linked to the (usually) asymptomatic presentation and being diagnosed through screening or a routine medical visit (344,353–356). Many patients had no warning or signs that they had a potentially fatal undiagnosed condition. Shock was most common in conditions with surgical implications and physical changes (CIN, DCIS, VAIN & VIN); such as a mastectomy or repeat vulvar biopsies (344,356). This shock was intensified by the short interval provided to make treatment decisions (344,347).

2.3.3.2.2 Anxiety

Post-diagnosis, many patients expressed anxiety about: the risk of progression to cancer, recurrent-follow-up and the fear of reoccurrence of the premalignancy (post-surgery in DCIS and CIN patients) (344,345,358,360,361,349,350,352–357); nearly universal across conditions (with the exception of colorectal polyps' (359)).

Many patients were profoundly anxious and fearful about progression to cancer (345,350,353–355,357,358,360). Anxiety related to the lack of preventative steps available to avert progression caused intrusive thoughts for some patients (345). This lack of opportunity for prevention was perceived as cancer being manifest destiny/unavoidable, akin to a *"sword hanging above your head"* (344). This perspective was especially prominent in patients who reported a family history of cancer (358); and was associated with increased anxiety. Two articles reported young women worried about their unborn children (if pregnant or wanting to) as additional worries (352–355).

Fear of premalignancy reoccurrence was reported in three studies of surgically treatable conditions (344,345,356) related to potential repeat surgeries of the vulvar/cervix to remove the tissue (VIN/CIN) (344,356) or the premalignancy arising in the other breast conditions (DCIS) (345). This anxiety was stated but little detail

was provided on the impact this had on patients; highlighting a need for further research in this area.

Anxiety connected to post-diagnosis surveillance was common (350,356,357,360). Surveillance had a mixed response from patients who felt safer with being watched but anxious about waiting for the future and potentially dealing with an adverse outcome (350,356,360)[i].

The anxiety of diagnosis was a primer for some patients to have existential thoughts, thoughts about death and making sure that their affairs were in order, if they progressed to malignancy (349,350,352,353,358). This highlighted the impact that a diagnosis can have on patients and was linked to behavioural changes for many patients (349,350,352–355,358).

2.3.3.2.3 Behavioural change.

Diagnosis was a catalyst for behavioural change in 8 studies (344,353,354,357–361); with the unpredictable potential and the symptom burden provided as rationale for patient's behavioural changes (360). Patients with Barrett's oesophagus, oral lichen planus, CIN and colorectal polyps (353,358–361) reported changes to their diet to: reduce symptom burden (e.g. avoiding spicy foods, alcohol and coffee) (358,361), manage unexpected flare-ups (357,360,361) and potentially improve their future prognosis by eating more fibre, fruit and vegetables and a healthier diet (353,359).

Some patients saw their condition as an opportunity to improve positive behaviours and lifestyle changes by improving their physical activity levels (359). These changes

[i] This is discussed from a health service interaction perspective on page 130.

were mediated by other life changes/changes in circumstances, such as retiring and increased free time as a result.[i]

2.3.3.2.4 Guilt

Some patients experienced guilt (344,345,350,357,364); with two sub-components. One component related to potentially preventable premalignancies (actinic keratosis and CIN), as patients believed the diagnosis was attributable to their lifestyle choices and decisions (353,357). These patients felt responsible/guilty for causing their conditions.

In the second component, some patients felt guilty as they perceived themselves as over-reacting to their diagnosis or received HCP support that they didn't feel entitled to. This was prominent when patient's compared themselves to cancer patients (344,345,350). When patients received support for their condition, such as a dedicated nurse, they sometimes felt guilty or like a *"fraud"* (344,345) for using the available resources as they felt should have been reserved for *"real"* cancer patients.

2.3.3.2.5 The Premalignant condition as a beneficial/negligible occurrence

A more positive reaction to a premalignant condition diagnosis was reported in 7 studies (345–347,350,357–359); highlighting the relief of receiving a premalignant condition diagnosis or/and viewing the diagnosis as an inconsequential medical event which had relatively minimal psychosocial impact on their lives (345–347,350,357–359). Some patients were relived it wasn't cancer (345,347,350,359), viewing themselves as *"lucky"* that it was only a premalignant condition; especially after prolonged investigations (344). Some patients found treatment a positive outcome which eradicated symptoms, primarily for CIN and VIN patients (301,350).

---

[i] Behavioural changes related to altered perception on life and existential thinking are highlighted within the anxiety section above.

For others, their diagnosis had limited impact (357,358); with some deciding their condition would not define them as a person and would not let it take over their life (357,358). This was despite some patients having visible effects of their premalignant condition (actinic keratosis) (357) or other deleterious health effects (reflux in Barrett's oesophagus) (358).

2.3.3.3 Medical services Interaction

The theme of Medical service interaction focused on the medical decisions and interactions with health services after diagnosis in 14/21 studies (343,344,360,361,345–347,350,351,353,356,358). The two sub-themes explored included Surgery/treatment and Surveillance/continued follow-up. The main findings highlighted the influence and impact of surgery/treatment, especially when it caused physical changes, and the lack of available support, both psychosocially and informatively. The findings also highlighted the role of surveillance and similarities across premalignant conditions for the positive (keeping the patient safe) and negative (anxiety around progression) impacts of surveillance.

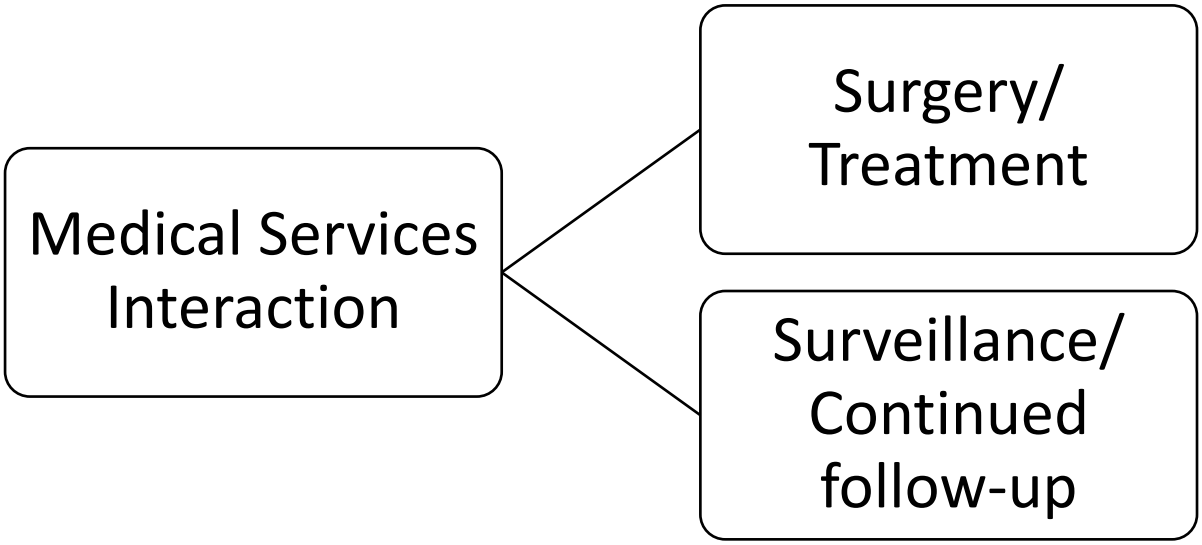


Figure 2-16 Coding Framework Medical Services interaction

2.3.3.3.1 Surgery/Treatment

Treatment/surgery was discussed in 10 studies (343–347,353–356,361), many of which focused on patients with DCIS (343–347) or VIN (356). Treatment/surgery decisions were commonly decided shortly after diagnosis. Many patients acknowledged surgery as necessary but many patients found it difficult to accept. However, not proceeding with the recommended treatment/surgery was rare within the studies reviewed. Many perceived the procedure as protecting themselves from potential progression to cancer but were disconcerted being diagnosed with a potentially fatal condition (in terms of progression) and receiving a surgical intervention, despite them having little/no symptoms and feeling fit and healthy (343,344,350). Some patients also felt that treatment/surgery was imposed on them without being convinced by the decision or fully informed about its impact (344,346,353,356); leading to some patients feeling "fast-tracked" and "railroaded" into treatment/surgery by clinicians (344–347).

Patients also framed their health by comparing their premalignant condition with their own co-morbidities (358). Patients with co-morbidities had poorer psychosocial wellbeing, and the premalignancy was perceived as a greater threat to mortality (358).

Some patients were clear they were not cancer patients but compared themselves to cancer patients, especially if similar treatment was conducted (343,344,356). Having treatment/surgery was perceived by patients as being indicative and similar to cancer. Patients perceived themselves as receiving the same treatment as cancer patients, such as mastectomies and lumpectomies; especially in DCIS (343,344,347). Surgical ramifications, such as losing part of/full breast, negatively affected patients wellbeing (343–345). This created an inconsistency in their minds by having similar treatment to cancer patients, but no access to similar support services (343).

2.3.3.3.2 Surveillance/Continued Follow-up

The impact of surveillance/continued follow-up on patients' lives was discussed in six studies (350,351,354,355,358,360) in Barrett's oesophagus, oral premalignancies, cervical dysplasia/CIN and colorectal polyps. Regular surveillance was positively viewed by many patients. Surveillance; allowed patients to question their HCP/healthcare team, improved perceptions of care and allowed the HCP/healthcare team to reinforce any pertinent messages about screening or health to patients (351).

However, extended intervals between surveillance appointments were viewed negatively, especially by patients with heightened fears of progression (350,355). Overall, surveillance was viewed as a burdensome and painful (358), but an essential safety net for patients; which would be missed if not available (358,360).

2.3.3.4 Support for patients

Support for patients was a major theme in 19/21 articles (342,343,352–360,344–351). The main findings highlighted the role of social support from patient's families, friends and peers in premalignant conditions and the role of HCP support post-diagnosis. Some patient groups (CIN and VIN) reported greater barriers accessing these supports due to the cause of their condition, especially if it was related to an STI. Overall, patients desired more support from their family and peers and the role of good HCP psychosocial support and guidance was emphasised (344,345,348,352–357,360).

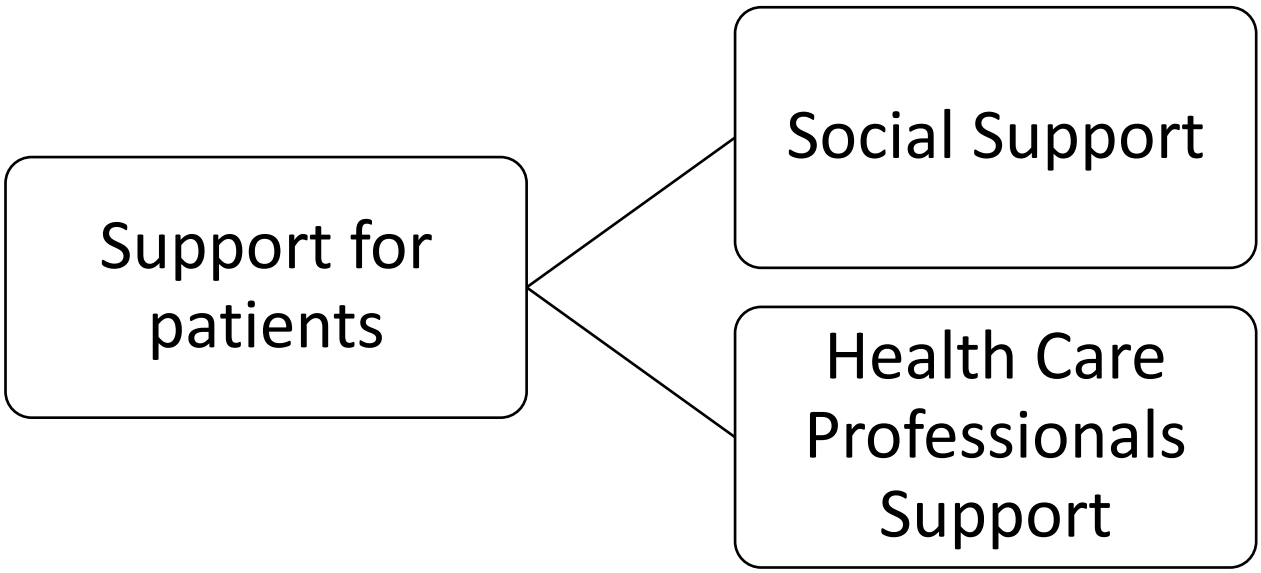


Figure 2-17 Coding Framework Psychosocial health factors

2.3.3.4.1 Social Support

Social support was a sub-theme in 9 studies (344,345,348,352–357,360); predominantly based on family and social network support (344,345,348,352–357,360). The family and social network support (such as friends and other patients) included informing family and friends and relying on them for support.

Family were perceived as a great comfort (344,345,353,356) and an "amazing support system" (356) for patients; but were also a source of stress that heightened anxiety levels (348,356,360). This was linked to families lacking knowledge about the premalignant condition or the future ramifications (344,360). To avoid this, patients sometimes avoided informing or disclosing information about their condition, to reduce or prevent anxiety (345). Some family members viewed patients as having cancer, which led to patients feeling overwhelmed with care (357).

CIN and VIN patients reported more complex support issues (348–351,354–356). These conditions are associated with the sexually transmitted infection human papillomavirus (HPV), which caused stigmatisation and patients feared being judged by their families and social networks (348,356). This also affected HCP relations, with one patient reporting that the doctor made her feel like *"some kind of degenerate"* post HPV/VIN diagnosis (356). Some patients endured relationship difficulties as treatment left some patients sexually unhappy due to their condition causing pain and fearful of passing on HPV to others (301,352,354,355).

Premalignant patients expressed a desire for peer-support networks (343–345,347,359). These networks were seen as; potentially providing positive examples of coping with a premalignant diagnosis (359), introducing a social aspect through meeting fellow patients (343,359) and providing opportunities to ask others about potential treatment decisions to feel better informed (344,347).

Many studies reported comparisons to cancer peer support networks, from which premalignant condition patients were excluded (343). Patients who believed they had cancer were more likely to seek out social support compared to other patients (343,344). However, some patients were concerned about meeting others with the same issue: who had undergone different treatments or had different

viewpoints/individualised experiences (356,359). This minority view was more common if patients used online support groups (348,356), which had increased anxiety[i]. More research is required to ascertain how premalignant conditions would benefit from social network supports and be provided (such as online, face-to-face or a combination).

2.3.3.4.2 HCP (Health care professional) Support

HCP support was discussed in 13/21 studies (342,343,356,358,359,344,345,348–350,353–355). There was a mix of responses from studies and patients on the quality of psychosocial support offered by HCPs. Many patients seen their HCPs as positive influences, a source of psychosocial support (342–344,348,349,353,355,356,359) and knowledgeable and trustworthy (344,348,353–356,359).

However, patients reported in six studies (344,345,349,350,353,355,356,360) poor communication and inadequate psychosocial support from their healthcare team. Some patients perceived their condition and treatment as trivialised by HCPs (344,353) and felt they were treated as less important than other patients (predominantly compared to cancer patients) (344). Some of this was related to poor patient understanding and a lack of confidence to ask the doctor for clarification (358). The articles did not make a link between this and how patients were diagnosed; which is explored within this dissertation in Chapter 3 (MGUS patient qualitative study) and Chapter 6 (discussion chapter).

[i] Discussed previously in 'Using the internet for health needs/information', page 120.

2.4 Discussion

2.4.1 Summary of evidence

This review aimed to evaluate the psychosocial impact, in terms of QoL, and psychosocial wellbeing, of living with a premalignant condition and identify similarities/ differences across conditions. While no detrimental QoL or psychosocial wellbeing (anxiety and depression) effects were reported using the quantitative instruments; the qualitative data highlighted multiple subclinical issues which had a psychosocial impact. These issues -information provision, social support and emotional issues- were similar across premalignant conditions. This novel systematic review integrates the results of studies investigating the psychosocial health and QoL across premalignant conditions as a collective concept. The findings of the review in relation to the background cancer literature and the main subject of the dissertation (MGUS) is discussed in Chapter 6: Discussion. This discussion outlines a short summary of the findings and outlines the strengths and potential improvements from the review.

2.4.2 Implications of the findings

The quantitative meta-analysis found no detrimental QoL or psychosocial wellbeing (anxiety and depression) effect of having a premalignant condition; in all components and scale scores in the SF questionnaire group (365), HADS (366), CES-D (220), EQ-5D (367) and STAI (221). This was similar to previous systematic reviews which focused on defined premalignant conditions (199–201). As explained within the introduction, the previous systematic reviews did not use meta-analytic procedures (Previous Systematic reviews, page 59) and the rationale of the approach of this review (validated questionnaire focused meta-analysis) was outlined in Conducting a mixed method review (page 64).

Forest plots comparing the conditions indicated that different premalignant conditions have different effects on QoL. There was a clear demarcation between Barrett's oesophagus and other premalignant conditions. The previous systematic review on Barrett's oesophagus (199) had indicated that Barrett's oesophagus

patients reported lower QoL than population norms, which was not found in this review. One reason for this discrepancy may be that the previous review was a narrative review which did not pool data for a meta-analysis. This review included a broader range of control groups/norms and a larger patient pool to increase power. The previous review also incorporated different instruments (10 instruments) (while this review conducted analysis per instrument), which would not have measured the same constructs/questions.

Variation in QoL measurements between premalignant conditions was expected; with similar reviews which compare patients with different types of cancer highlighting the varied impact on patients dependent on cancer site (368,369).

However, the psychosocial impact of premalignant conditions investigated in this review provides a more holistic perspective of premalignant conditions, which is important within the later chapters when comparing the results of the systematic review to the data collected from MGUS patients.

The qualitative findings highlighted patients using various approaches to describe their premalignant condition and how it impacted upon them. Several themes were identified; revolving around the areas of information, reaction to diagnosis, medical service interaction and social support. These themes describe a comprehensive account of the impact of diagnosis, highlighting potential subclinical issues that may not be picked up by the conventional QoL measuring instruments.

2.4.3 Integrating the quantitative and qualitative findings

Despite the common usage of mixed methods in health services research, the findings are often not integrated to explore their complementarity and independent findings through triangulation (370,371). In this review, the two main research paradigms, quantitative and qualitative investigation were triangulated to provide this integration. Overall, the qualitative and quantitative components in the review reported contrasting findings. Premalignant patients reported no detrimental effect from a quantitative perspective but the qualitative data indicated that many patients encountered barriers and difficulties post-diagnosis. The integration of the findings

will focus on three areas; validated instruments in premalignancies, the role of anxiety and issues not amenable to quantitative measurement.

There were major differences between the validated instruments and the qualitative findings. The meta-analysis and the narrative review consistently reported no/minimal effect on QoL or psychosocial wellbeing; whereas the qualitative findings consistently found that many patients were psychosocially impacted by their condition.

This contradiction of evidence can be interpreted in multiple ways. Integrating the findings, the low level of effects reported by the majority of patients would influence the overall mean but overshadow higher effects in certain individuals. The minority of patients who experienced greater QoL/psychosocial wellbeing impact would not be obvious from the pooled data. Another interpretation would be conventional generalised QoL/psychosocial wellbeing instruments (such as the EQ-5D and SF-36) are not suitable for the nuances of a premalignant condition. This is illustrated by the differences between the HADS instrument and the anxiety-related qualitative data.

The HADS was used in nine studies (meta-analysis n=6, excluded from meta-analysis but included in the forest plot n=2 & narrative review n=1) and reported no increased anxiety in premalignant patients. However, patients reported increased anxiety post-diagnosis in nine qualitative studies (344,345,349,350,352,356–358,360); across conditions[i]. One interpretation from triangulating and integrating the findings was that using a clinical measure (HADS (218) may not be appropriate for a condition which does not cause clinical levels of anxiety but does increase anxiety in patients. The review indicates the anxiety is linked to the uncertainty experienced by patients about their condition and future prognosis. A more appropriate scale and relevant anxiety and uncertainty scale may find different results in this population.

As the first review to utilise a mixed methods design to investigate the psychosocial impact of premalignant conditions, it was difficult to identify the triggers for anxiety for patients. The themes of information provision, patient understanding and

[i] With the exception of the single colorectal polyps study (359).

healthcare services interaction indicated these to be the main triggers of anxiety in patients. However, much of this anxiety was not captured by the generic validated questionnaires in the meta-analysis.

The narrative review indicated that more condition-specific instruments (such as the Dermatology Life Quality Index (DLQI) in actinic keratosis & Oral Health Impact Profile (OHIP 14) in oral premalignancies) may provide a more nuanced perspective of QoL/psychosocial wellbeing impact in premalignant patients.

Integrating the quantitative and qualitative review findings provided insight into the psychosocial impact of premalignant conditions. The systematic review findings provided the background of evidence from other premalignant conditions to compare with the MGUS-related findings in Chapter 6: Discussion. As many of the topics were similar across the conditions and the studies conducted, it was decided to focus the discussion in one chapter rather than in each individual chapter. Within Chapter 6, the four main topics discussed are; "The psychosocial impact of an MGUS diagnosis", "Becoming informed on MGUS", "MGUS supports and health services" and finally comparing MGUS to its progressions (SMM and MM).

Similarly, the other elements of future directions of the work and clinical guidance/recommendations are combined in Chapter 6. The future directions focuses on; more mixed methods studies in premalignant conditions (only one study included was mixed methods (301)), the development of better guidelines in premalignant conditions and providing improved materials to develop the care pathway for MGUS patients and their treating physicians. This review also informed the later studies conducted in the dissertation; the qualitative MGUS study, the healthcare professional studies and the online survey of premalignant conditions (Chapters 3-5).

2.4.4 Strengths and Limitations

Including all premalignant conditions as a collective concept can be viewed as both a strength and weakness of the review. Premalignant conditions vary in site, physical manifestations and symptoms/treatments; which means that patients encounter

different barriers and experiences. As highlighted, some premalignancies (such as Barrett's oesophagus) have issues specific for that premalignancy rather than the collective concept. For example, Barrett's oesophagus patients reported more physical effects which can influence their QoL/ psychosocial wellbeing differently; due to being unable to complete activities or have reduced physical function. Premalignant conditions have been classed as an appropriate taxonomy previously by Berman et al (163,238); who viewed the identification (and subsequent elimination) of premalignant conditions as a key goal in reducing cancers (372). To reduce the influence of the varied sites, physical manifestations and symptoms/treatments, premalignant conditions in the forest plots and the narrative review were grouped to highlight if an issue was more prominent in a certain premalignant condition.

The review was rigorously developed and reproducible, which gives confidence in its findings. Experts in; systematic review methods, premalignant conditions, psychosocial and QoL researchers, epidemiologists and patients were consulted to develop and adapt the search strategy over the 5 databases. Scoping exercises were used to refine the search strategy prior to the search.

With the scope of premalignant conditions, some conditions may not have been included in the search terms or captured as part of the search. However, a comprehensive scoping of premalignant classifications using the guidelines of defining premalignancies (163) and a comprehensive search strategy minimises this risk, Appendix 8. The search terms for QoL and psychosocial wellbeing were also comprehensive and identified a large number (17,506) of potentially relevant articles. The reference lists of all included articles and reviews were checked and experts within the area were contacted to further increase the rigour and reduce the chances of missed studies. Articles which did not use similar terms to "premalignant" or "precancer", were unlikely to have informed patients of their condition as a precursor and were likely to have been excluded on this basis. Therefore, we feel that this review was systematically conducted and includes all relevant patients.

The high heterogeneity of the studies included in the meta-analysis is a limitation which reduces the validity of the results. The sources of this heterogeneity are not

fully definable but are likely related to the; multiple premalignant conditions, varied methodologies used and poor reporting quality (as highlighted in previous reviews) (200,201).

The lack of design consistency and the use of various instruments (n=21) across studies complicated the meta-analysis. There were some issues with studies not adequately reporting the instrument scores (some studies did not report standard deviations, control group scores or results were only presented as a graph and not in a tabular form/within the results making data abstraction difficult). All efforts were made to ensure strong data quality during stringent data abstraction procedures and quality assessment using the MMAT tool Figure 2-2. The MMAT tool highlighted quality issues in several studies (Appendices 4, 5 & 6) may have biased the results and led to data from one article (Xie et al, 2013) (98) being excluded from part of the meta-analysis due to incorrect procedures calculating the component scores [i].

Meta-analyses are susceptible to certain bias. While the search strategy was robust, issues with premalignant patients being included as control groups or added into results (rather than the focus of a study) in other studies increase the risk of reporting bias. As there were minimal studies included in the meta-analyses (range 3-7 studies per instrument), the guidance was to not conduct funnel plot asymmetry tests in analyses that contain under 10 studies, especially if there is high heterogeneity present in the analyses. Similarly, the Egger test is not appropriate in analyses with fewer than 10 studies (373). However, these tests are provided in the results section to inform the reader of the issues with high heterogeneity.

Some studies utilised premalignant patients as controls in cancer patient studies, which meant that comparative meta-analysis was not appropriate as it lacked an adequate (disease-free/healthy) control group. Meta-analysis was only conducted using questionnaire data if the instrument scores fulfilled two criteria; clearly demarked premalignant patient scores (not mixed with cancer patients or control groups) and the studies provided a standard deviation or information to allow

[i] As described in Short Form Health Surveys (SF instruments) page 80.

calculation of this score (such as confidence intervals). Studies which did not fulfil these criteria were not included within the meta-analysis. However, studies which clearly demarked premalignant patient scores (not mixed with cancer patients or control groups) but did not provide confidence intervals or standard deviations were included within the forest plots to provide a visual representation of the data and reduce bias. Similarly, a narrative review was conducted on studies/questionnaires that did not meet the threshold (3+ studies) to reduce selection bias. These choices provided a wider perspective of the psychosocial impact of a premalignant diagnosis.

Most premalignant patients live with their condition for long periods between surveillance intervals and the impact on QoL and psychosocial burden may be heightened during hospital visits and during surveillance as suggested by the qualitative meta-synthesis. However, many of the included studies were clinic-based, with responses undertaken prior to surveillance or within the hospital setting. To reduce this potential confounder in this dissertation, the research was conducted at different intervals for patients away from clinical settings to provide a better insight into how these conditions impact patients outside of the hospital setting.

The appropriateness of meta-synthesis has been questioned by researchers who compared it to summing up poetry; you may have the idea that the poems are about loss but lose the uniqueness of each poem (374). As the qualitative research included in the review ranged across disciplines, qualitative experience of the researchers, methodology and premalignant conditions, care should be taken in evaluating the qualitative findings of this review. Similarly, when synthesising findings, the review was reliant on accurate reporting and analysis from the studies themselves. As shown by the quality assessment, some studies had missing data (such as missing response rates) in reporting (Appendices 4,5 &6). However, the loss of uniqueness of the studies by conducting a review needs to be balanced against the wider perspective of investigating how a premalignant condition psychosocially impacts a patient rather than the specific impact of each premalignancy. As shown in the studies, there was a spectrum of impacts both across and within conditions.

2.5 Chapter Conclusions

In conclusion, receiving a premalignant condition has a highly individualised and contextual impact on patients' lives. There were significant differences in the psychosocial impact of premalignancy reported between the quantitative and qualitative findings. The quantitative data indicated no significant effect on psychosocial wellbeing or QoL from the validated instruments. This is compared to the qualitative findings, which highlighted multiple impacts for premalignant patients, such as heightened uncertainty about their diagnosis and sub-clinical anxiety/worry about potential progression to cancer.

The evidence from the review indicates that many premalignant patients share a similar experience, especially in relation to poor information provision, an emotional reaction to the diagnosis and inadequacies interacting with the healthcare system. Other conditions can have more condition-specific issues, especially in regards to surgery and surveillance.

This review highlights that premalignant patients; desire user-friendly information that is communicated clearly by health professionals, have some level of anxiety about their condition at diagnosis and a minority of patients' experience anxiety which would benefit from psychosocial intervention. However, the mixed findings of the review and the high heterogeneity of the meta-analysis indicates that research in premalignant conditions in still in the embryonic phase and care should be taken in responding appropriately to individual patients with premalignant conditions. Further discussion of the clinical application of the research and research implications is located in Chapter 6.

3 Chapter 3: Assessing the Impact of MGUS (AiMs) study

3.1 Introduction

3.1.1 Rationale/Prelude

The systematic review highlighted the lack of quantitative or qualitative studies about the impact of MGUS on the QoL and well-being of patients and pointed to a gap in the literature regarding the need to investigate 'the lived experiences' of MGUS patients. This qualitative study aimed to address this knowledge gap by undertaking for the first time an exploration of living with MGUS from the patient perspective. Qualitative methods were used to develop an in-depth understanding of the issues faced by MGUS patients (375).

Within the study design framework provided in Chapter 1 (Figure 1-1, page 19), this exploratory component of the mixed methods design (4,5) identified the key issues in MGUS needed to develop the further research with healthcare professionals (HCPs) in Chapter 4 and the premalignant survey in Chapter 5.

3.1.2 Qualitative methodology

"Qualitative research is concerned with developing explanations of social phenomena. It aims to help us to understand the social world in which we live and why things are the way they are" (376).

Qualitative research incorporates a wide variety of techniques such as case studies, interviews, focus groups, observations and workshops to collect data in multiple forms such as text, audio and images for analysis. Similarly, there are multiple analysis techniques such as thematic, framework and content analyses (377–379). This range of approaches allows researchers to explore lay theories and participant's perceptions on any given topic in different ways. In this study, a multi-method approach to data collection was used in an attempt to overcome recruitment difficulties. Telephone interviews were used to supplement low FG participation. This strategy increased the number and range of study participants (380).

In this study, a multimethod approach to data collection was used; due to recruitment difficulties. Poor focus group recruitment led to incorporating telephone interviews to increase numbers, which provided a wider range of opinions and individuals than available with a focus group approach (380).

Focus groups are an *"informal discussion among selected individuals about specific topics"* (381); *"which allows a multiplicity of views and feelings to be expressed within a group environment and collection of a large amount of rich data in a shorter time"* (382). From the focus group, theories and hypotheses can be generated using the attitudes, feelings, beliefs and experiences expressed by participants towards the study topic (382). Patients are more likely to disclose more sensitive details in focus groups (383). Focus groups benefit from participants challenging each other, encouraging elaboration of each other's feelings and thought not found in other approaches (384).

An interview is "an interchange of views between two persons conversing about a theme of common interest" (385). In contrast to focus groups, individual interviews allows participants to articulate their views and feelings in a private setting and allows the interviewer to further explore emergent themes through prompting (385). The interview style selected -semi-structured- helps the researcher *"identify theories and hypotheses from the attitudes, feelings, beliefs and experiences expressed by the participant towards the study topic"* (385).

Telephone interviewing is a valid and productive tool in qualitative research, which reduces travel expenditure and allows greater flexibility for both the interviewer and interviewee than face to face interviews (386). Interview data can also be used to develop questions for questionnaires (386).

Using a multi-method monostrand design (combining focus groups and interviews) promoted a more complete method of dealing with the richness of the real world and was a pragmatic choice made due to the practical difficulties experienced in the study (387). A critical review endorsed this integration of the methods as it *"leads to an enhanced description of the phenomenon's structure and its essential characteristics"* (380). Theme development and effectiveness are similar between the methods (380,383); with other premalignant studies also combining focus groups

and interviews as a result of low recruitment (350). In the review (Chapter 2), interviews were used in eight studies; five studies used focus groups, one used a combination and three used open-text survey responses (Appendix 5).

3.1.3 Why is a Qualitative approach important in health research?

In a health setting, qualitative research is useful when the research question involves people's experiences and views on; *"exploration or identification of concepts or views, the real-life context and sensitive topics where flexibility is needed to avoid causing distress"* (376).

Quantitative approaches attempt to measure experience by quantifying how often or to what extent things occur; using large numbers of respondents to quickly and effectively answer questions, rather than seek more detailed and expensive interviewer dependent qualitative methods (388).

Both methodological approaches are important, and the researcher should be led by the best possible way to answer or discover the question rather than a favoured paradigm (388). However, qualitative approaches are particularly useful in areas with little previous exploration, such as MGUS.

Specific to MGUS, the study sought to understand the different barriers and facilitators in how patients understand MGUS, access services and live/are impacted by their condition. To identify the issues and what priority patients place on these issues, a qualitative investigation was the most appropriate paradigm to use. This study informed the other studies in the dissertation.

This use of studies informing each other as part of the exploratory sequential model is linked to the idea of developing "*quantitative data on qualitative judgement*" (389). This perspective outlines that when engaged in explorative research in which the questions are not known, qualitative research can provide the data to develop the questions for later investigation. A quantitative research design is often not the best tool to discover these questions (389). However, using qualitative methods also has drawbacks.

Qualitative methods can be burdensome; with recruitment, time commitments (from researchers and participants) and expense to complete, practical issues to overcome (377–379). Qualitative research has also been criticised about reliability, validity and credibility from a methodological perspective (390,391). Having a clearly defined question can reduce these issues; however, this is particularly difficult in novel research on a hitherto under-researched topic such as MGUS.

Using the Nowell et al (392) criteria in the methods section (page 152), we illustrate the steps taken through the use of method and researcher triangulation (validity) and developing saturation (reliability) to increase the rigour and credibility of the study (393–396). As part of this criteria, researchers are encouraged to take ownership of the choices and decision made through the use of personal pronouns, such as 'me' and 'we'.

Showing the decision trail of the process can help establish the trustworthiness/rigour in qualitative research. This trail enables the reader to follow the steps, while remaining mindful of the actions and influences on the researcher, to believe that the findings are reliable and valid (397). This trail is improved through presenting faithful descriptions of the participants experiences, with a clear derivation of how the themes were developed (397,398).

The terms "reliability" and validity" are contentious amongst qualitative researchers (399), but the concepts of ethically appropriate, relevant and rigorously described methodology are important cornerstones in qualitative research and developing rigour (400,401).

One important measure of rigour in qualitative studies is developing rigour; through reliability" and validity. Reliability is the transferability/applicability of the findings to contexts outside the study's setting (400). This is usually shown in qualitative research through saturation, where the data ceases to provide new questions/directions or is repetitive (375). Saturation is often related to sample size, but it is a difficult measure to pin down, as quality of data is a more important measure than sample size (402,403).

Studies are deemed credible if, with adequate context-building, the experience is recognisable for patients who have experienced the phenomenon (400,404). This is achieved through the development of validity in the research process and establishing credibility though practices such as triangulation, reflexivity and substantial description of the interpretation process (including congruent verbatim data/quotes) (400,404).

The COREQ (405) criteria was also used to guide the reporting of the study, Appendix 9.

This study explores the under-researched experiences of patients with MGUS (in Northern Ireland) in order to inform the development of MGUS-related HCP studies and a quantitative study of premalignant patients which focused on MGUS.

3.1.4 Aims

The main aims of this study were to:

- Conduct an exploratory qualitative study about the experiences of patients diagnosed with MGUS (in Northern Ireland).
- Explore patient's understanding about MGUS.
- Explore perceived life changes and impacts of receiving a MGUS diagnosis and living with MGUS.
- Explore current service provision and delivery for MGUS patients in relation to unmet need, especially with respect to the provision of active surveillance.

This relates to all of the research questions[i].

[i] Research questions outlined, Page 20.

3.2 Methods

3.2.1 Creation of the interview schedule

The results of a scoping review of research about premalignant conditions were used to develop a semi-structured interview schedule. The review identified the main issues in premalignant conditions which may be relevant for MGUS patients. This scoping work was further refined by the preliminary findings from the systematic review[i] and in-team discussion. The final version of the semi-structured schedule contained a fixed topic (about the impact of MGUS) and fixed questions but the schedule was used in a flexible and conversational style way that encouraged spontaneous responses from interviewees whilst being mindful of the need to gather reliable data (406). A structured interview would not have provided the flexibility that was required to explore a novel area such as MGUS care (406). As experienced interviewers who were not MGUS experts were used, an unstructured interview style may have missed patient experiences such as the topics that were highlighted in the reviewing activity regarding premalignant and haematological malignancy.

The study documentation (the invitation letter, information booklet, consent form, contact information sheet, demographic questionnaire and focus group interview schedule) was reviewed by a subset of (non-MGUS) patients involved in the Northern Ireland Clinical Trials Centre 'Personal and Public Involvement in Research' committee. This was to ensure the study documentation was understandable and appropriate to the target audience. This committee provided feedback (specifically about the wording of some questions), which were implemented; as deemed appropriate by the study team.

Prior to patient interviews, the interview schedule was pilot-tested among PhD students at QUB, to provide training and experience in facilitating focus groups/

---

[i] The systematic review (Chapter 2) identified 4 main themes in the qualitative synthesis (descriptive themes (1) that were incorporated into the schedule; Understanding and acquiring information, Patient's reaction to diagnosis, Health service interaction and Support for patients.

telephone interviews for BM. A copy of the interview schedule can be found in Appendix 11.

3.2.2 Inclusion/ Exclusion criteria

To be included in the study, patients had to have a confirmed MGUS diagnosis (to both the patient and healthcare team) and were deemed fit (mentally and physically) by their healthcare team (clinical nurse specialists and consultants).

Patients were excluded if their healthcare team (clinical nurse specialists and consultants) deemed the patient too physically frail to participate, had neurocognitive difficulties which affected consent or recall of information (such as dementia or learning difficulties) or had a severe mental health issue (such as clinical depression). Patients were also excluded if they were not informed that they had MGUS (due to other health issues) and their care was managed through a guardian/carer.

3.2.3 Sampling and recruitment procedure

Patients were recruited from a clinical nurse specialist-led (CNS) telephone clinic within two Health and Social Care Trusts within Northern Ireland (Belfast and Southern Health and Social Care Trusts).

Patients were informed about the study by the CNS during their routine telephone surveillance appointment. This was completed by the CNS as a requirement that was specified by the committee that granted ethical approval in order to protect a patient's details and anonymity. Patients were asked if they would like to take part in a study on their experiences of having MGUS and a pre-prepared statement giving a brief overview of the study was read to potential participants by the CNS.

If interested, patients were mailed a study information pack (containing a study information booklet, a consent sheet, a contact information sheet, a pen and a prepaid envelope to return the consent and contact information forms (Appendix 12). Patients who returned forms were contacted by the researchers to arrange

suitable times for the focus group/interview. Non-responders received a reminder telephone call by the nurse specialist after two weeks. If a patient expressed that they did not want to take part in the study or they did not respond to the reminder, no further contact was made.

3.2.4 Procedure for focus groups/ interviews

Each focus group (OS, CT) and telephone interview (BM) was facilitated by a research team member who had prior qualitative experience and no prior relationship to participants[i]. CMcS was present at the focus groups as an expert advisor and to make fieldnotes (the clinical nurse specialist was available outside the room but was not required). Focus groups (FG) were conducted within a neutral environment outside of the hospital (hotel conference rooms and university buildings) and lasted approximately one hour and 20 minutes. Telephone interviews were conducted at a time convenient for patients and lasted between 20 and 30 minutes. Participants were informed of the rationale of the study and the role of the facilitator in conducting the FG/interview.

At the beginning of each FG/interview, consent was checked with each participant and the distress protocol described (Appendix 12). Prior to recording commencing, participants were reminded that they were being audio-recorded and the interview would be transcribed verbatim.

During the FG/interview, the facilitators followed the schedule and encouraged patients to express their views on MGUS through appropriate probing and prompting behaviours (407). Field notes and descriptive memos were made to help the researchers interpret the information at analysis (408), assist reflection and inform and aid understanding (409).

---

[i] OS (Dr. Olinda Santin PhD) and CT (Dr. Charlene Treanor PhD) are experienced female qualitative researchers, who employed as a lecturer and postdoctoral fellow when conducting the focus groups. BM was a male PhD student, who had completed qualitative training prior to conducting the interviews. CMcS (Dr. Charlene McShane PhD) is an experienced female MGUS and cancer researcher.

The focus group was audio-recorded and transcribed verbatim using the 'Jefferson-lite' transcription method (410). This transcription included untimed pauses, speech repetitions and overlapping talk, but not all the finer-grained components of speech and interactional style. The fine level of detail of full Jeffersonian transcription (411), normally associated with conversation analysis (CA), was deemed unnecessary for this project.

After the FG/interview, draft transcripts were sent to patients (n=7) for member-checking/respondent validation (394). All participants were provided with an information pack containing an information leaflet and contact details for agencies (example: Myeloma UK), which they could use for additional information or support if interested, as per the distress protocol. This was handed to focus group participants and mailed to telephone participants. After the focus groups, the clinical nurse specialist was available for any questions. For the telephone interviews, patients were advised to contact their healthcare team if they had any further questions about MGUS.

3.2.5 Researcher reflexivity

I am a 27-year-old male completing a PhD in Public Health[i]. I have previously completed a bachelor's degree in psychology and a Master's degree in 'Applied psychology: Clinical specialism'. I come from a family of mental health professionals and worked in mental health services as an assistant psychologist prior to commencing my PhD. This has given me an interest in helping others and wanting to understand how people deal with an illness, especially from a mental perspective.

Conducting the qualitative research early in my PhD meant that I was only coming to grips with the MGUS and wider premalignant literature, meaning that I was inductively building my knowledge of the literature, combined with engrossing myself in patient experiences through the interviews. Learning through doing

[i] This section is referenced in other areas of the thesis, as an exploration of my reflexivity as a research and how this was developed.

enabled me to build up my skills and develop my own personal style, in both interviewing and analysis as the project continued. This experience has developed my empathy, resilience and given me an understanding of the mental processes of dealing with a medical condition.

Qualitative researcher's beliefs, perceptions and bias can affect the interpretation (412). Being objective in qualitative research can be difficult, therefore the researcher's ontological and epistemological stance are central and worthy of consideration (413).

Ontology refers to "assumptions about the nature of the world" (414) and concerns whether reality is an objective (realism) or subjective and socially constructed (constructivism). Epistemology refers to "assumptions about how the world can be investigated" (414).

The range of diverse attitudes and experiences and the different topics (such as information provision, contact with health services and life impact) more suitable from a pragmatic stand-point; as I have taken within this dissertation (415,416). A pragmatic stand-point is underpinned by the view that knowledge is based on experience and individuals' perceptions of the world are influenced by their experiences or experiences created from socially-shared experiences. This knowledge is constructed to help individuals to manage their existence, rather than consider the knowledge as reality itself (417).

The pragmatic viewpoint is also more relevant in the mixed methods paradigm used in the dissertation; which incorporates a range of stakeholders (patients and HCPs) through a variety of qualitative methods (interviews, focus groups and open-text responses (Chapters 4&5) (415,416).

3.2.6 Qualitative analysis methods

Inductive thematic analysis was chosen as it was the most appropriate methodology to explore the research aims of this chapter and the wider research questions. It is considered to be flexible yet structured in terms of accommodating theoretical perspectives, highlighting commonalities and differences in a data set and

generating insights (392,418). It was also the most commonly used qualitative approach in the studies in the systematic review (392). This has the additional benefit of being able to compare the themes developed from the MGUS sample to other premalignant conditions, which were analysed in a similar way (inductive thematic analysis). Inductive thematic analysis allows for data to be viewed from patient experience rather than theoretical assumptions. Within this study, thematic analysis allowed the research to develops themes in response to broad patterns; which can be further developed in later work. The lack of theory or previous research in MGUS meant an inductive methodology linked to the data was appropriate (393,418).

3.2.7 Outline of the qualitative methodology and data analysis

As proposed by Nowell et al (392), the analysis procedure used for the inductive thematic analysis is described in 6 phases, Figure 3-1. The pronouns ' I' and 'we' are used; I make choices in the research but the analysis was conducted within a team, which provided oversight and exposed different areas from different perspectives (419).

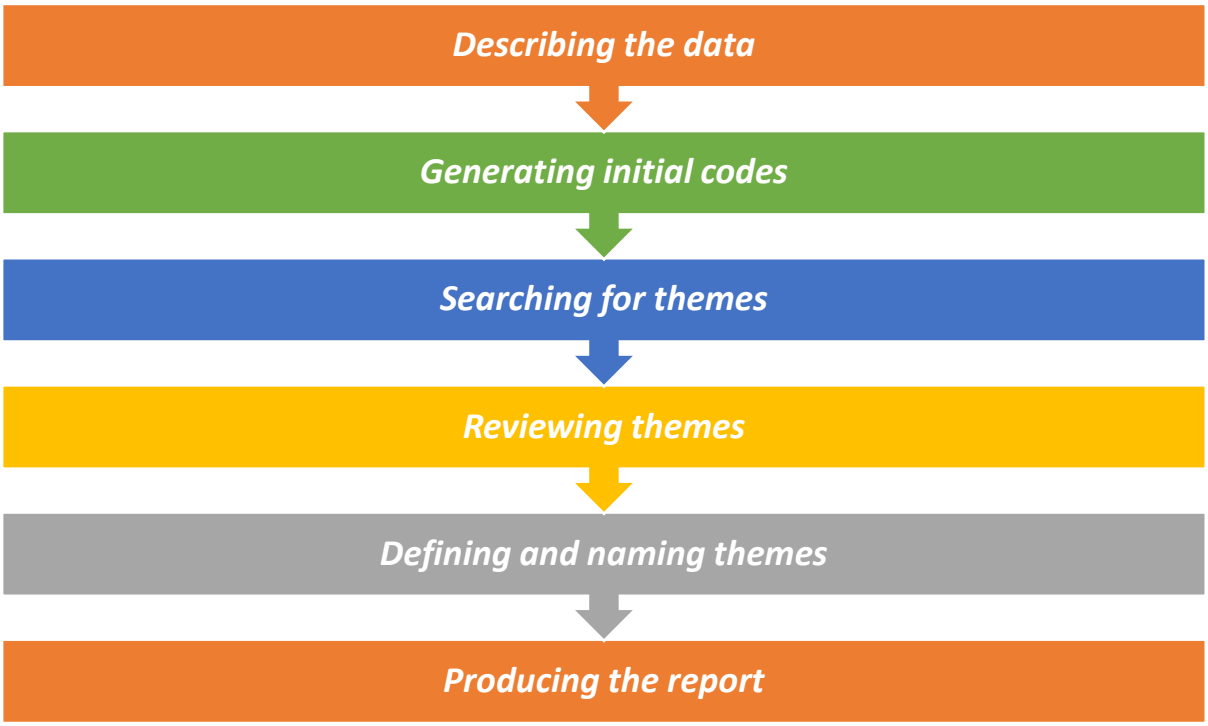


Figure 3-1 Nowell et al qualitative process

3.2.7.1 Describing the data

This phase describes the data and data storage. The data for the study was produced in two formats; audio recordings and verbatim transcripts. There was also fieldnote memos from the researchers who conducted the interviews/FGs. As I had conducted the interviews[i], I had some prior knowledge of the interviews and their content. However, I immersed myself in the content to familiarise myself with the content using repeated listening and reading of the material, as per the methodology (418). Post familiarisation, we began to identify codes for analysis.

All the data was logged onto NVivo (265) to organise and examine large data to facilitate insightful and sophisticated analysis (419). Programs like NVivo assist in the audit trail as they have a traceable process of analysis (397).

On data storage, audio recordings and full transcripts were stored in a safe confidential environment within the Centre for Public Health, Institute of Clinical Sciences B, Royal Victoria Hospital, QUB, and within encrypted computers and available for independent inspection. Participants were not identifiable from any data source including tapes, field notes and transcripts. Data was only shared with members of the study team who undertook appropriate ethics training and who held a good clinical practice (GCP) certificate.

3.2.7.2 Generating initial codes

This phase describes the initial production of codes and the processes in creating codes. Coding requires reflection on the data and deep thinking of the process of how to interact with the data (420). This reflection and *'deep thinking'* develops the unstructured data to a more meaningful development of ideas and codes. The codes (and themes) were derived post-hoc from the transcripts. I was also able to receive

[i] Focus groups had been conducted prior to the PhD commencing.

feedback on a thematic matrix system that assisted me in visualising the data and how pervasive a theme was between participants and between the two methods (FG and interviews); as a complementary analytic strategy (421), Figure 3-2. Within this project, we developed a hierarchical coding system (Figure 3-3) which focused on aspects relevant to the research. After developing the coding system on the hard copies of the transcripts, the codes were checked to ensure that codes had explicit boundaries. Codes with the same meaning but different names/terms were joined together to reduce excessive hierarchical layers. Collapsing codes into more meaningful and comprehensive themes is recommended as excessive hierarchical layers can be counterproductive (419).

As part of the criterion of rigor in qualitative research, we (BM and OS, the second reviewer) held collaborative meetings to discuss the data (and my interviewing technique) and the coding systems to explore how the analysis was proceeding as part of peer debriefing (392). This improved internal validity of the study through the creation of credibility (400,404). Our use of practices such as triangulation, reflexivity and substantial description of the interpretation process (including congruent verbatim data/quotes) supports high credibility/internal validity (400,404).

I used a reflection framework (the Gibb's reflective cycle (422) to evaluate my decisions and actions within interviews and analysis. These were part of my reflexive practice and to note how my ontological and epistemological beliefs influenced the research[i]. By using action plans and analysing my performances, I was able to develop my skills and improve as the interviews proceeded.

[i] Further explored in Researcher reflexivity, page 150.

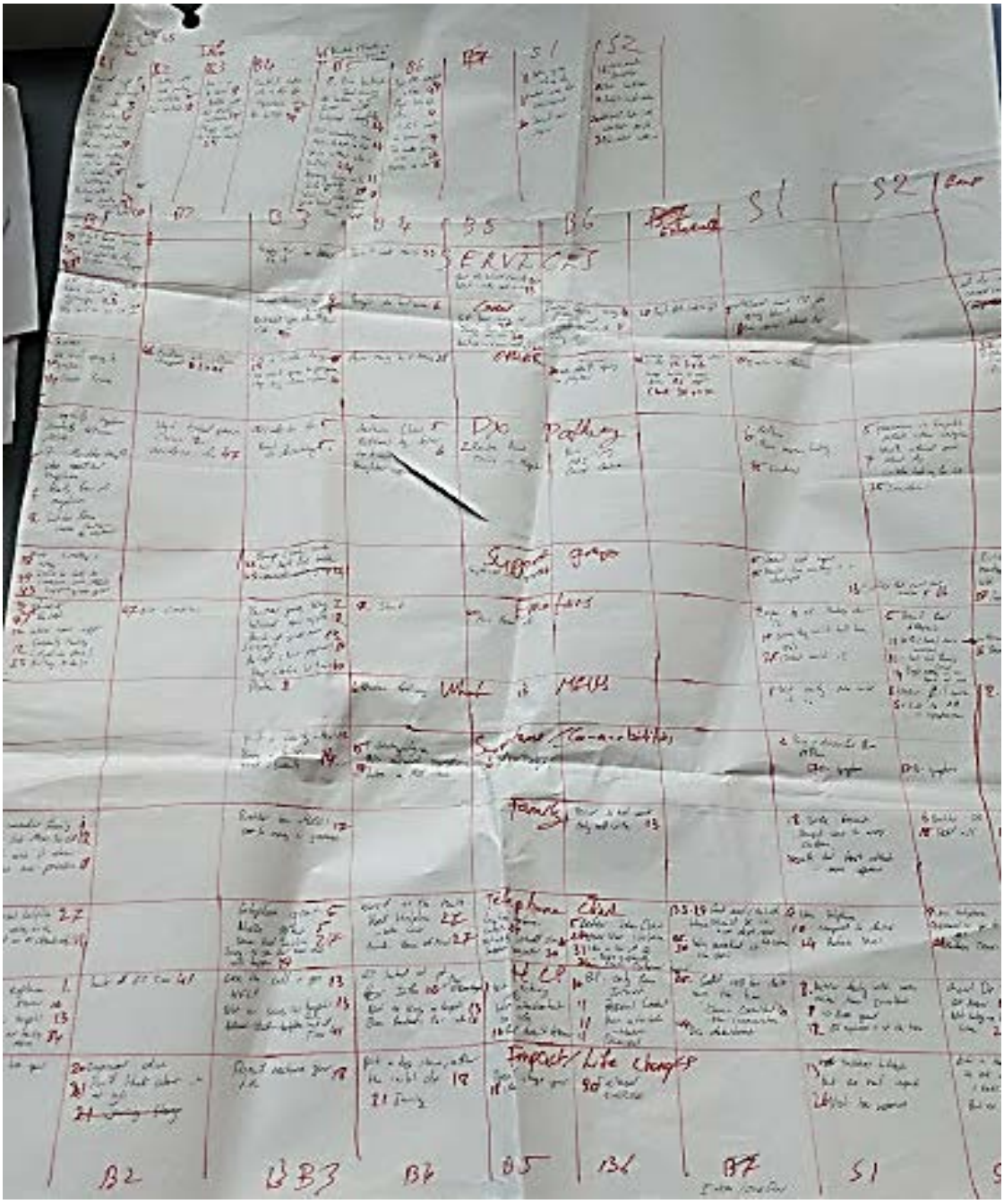


Figure 3-2 Thematic Matrix for Focus group: AiMs study

3.2.7.3 Searching for themes

After coding and collating the data in NVivo, we sorted the data extracts into sensitising/abstract (temporary and developing) concepts (418). These concepts were further developed into more concrete themes (418). *" A theme is an abstract entity that brings meaning and identity to a recurrent experience and its variant manifestations. As such, a theme captures and unifies the nature or basis of the experience into a meaningful whole"* (p. 362) (423).

These themes were inductively conceived from the data using mind-maps. A mind-map is provided for each theme in the results section. To do this, we used XMind v.8 (424) to visual the mind-maps. However, NVivo was used to organise the data fragments for each code to assist. These were organised using parent and child nodes within NVivo to maintain a clear audit trail.

3.2.7.4 Reviewing themes

After the themes were devised, it was important to refine these further; to increase their accuracy and specificity to the broader narrative, while remaining true to participant's voices and the voices of deviant cases. Some themes were removed, due to a lack of supportive data, while other themes were altered to create subthemes; to develop a more manageable and coherent piece (425).

3.2.7.5 Defining and naming themes

Naming and defining a theme that is both apparent to the reader and "punchy" (418), while remaining scientifically accurate and relevant to the wider narrative can be one of the most difficult decisions in the research (419). I enlisted help of more experienced qualitative researchers through peer debriefing to assist development and more clearly articulate the themes. We took care of the ordering of the themes to represent the issues in order of meaningfulness and relevance to clinical significance.

3.2.7.6 Producing the report

After fully establishing the themes, I wrote the chapter. After a number of revisions, the chapter reached a stage where the writing was concise, coherent, had minimal repetition and was displayed in a logical way (418). The Consolidated Criteria for Reporting Qualitative Studies (COREQ) (426) guided the reporting (Appendix 9).

We chose to embed patient quotes in the results; to aid the understanding of the reader and show the prevalence of the themes (419). We used a mix of short and long quotes (with a unique identifier), to highlight the richness of the data and to sensitise readers to the raw data. This provides depth to the analysis, rather than a purely descriptive account (419).

While some researchers advocate interweaving literature in the findings (427); we decided MGUS had insufficient literature to compare directly and that it would weaken Chapter 6: Discussion; as comparing the results when more significant data was available. This would be more coherent and reduce repetition.

3.2.8 Ethical approval

Ethical approval for this study was granted by the Office for Research Ethics Committees Northern Ireland (ORECNI); reference number 13/NI/0073. A copy of the approval letters can be found in Appendix 10. Governance approval was agreed with the relevant Health and Social Care Trusts within Northern Ireland through the Integrated Research Application System (IRAS).

3.2.9 Funding for the study

Funding was received in March 2012 from the Cancer Translational Research Group Small Grants Scheme to assist in setting up the study and providing the facilitates and stationary for the study.

3.3 Results/Findings

3.3.1 Demographic Information

In total, fourteen individuals participated in this study: eight focus group participants (an urban focus group (FG1, n=6) & a rural focus group (FG2, n=2)), and six participated in telephone interviews (TI 1-6). The participating patients were predominantly male (n=8/14), married (n=13/14) and educated to at least GCSE or O-level/high school standard (n=14) (Table 3-1). All patients received surveillance from their health care team in relation to their MGUS at 3-12 month intervals via the telephone clinic. Six patients reported co-morbid long-term conditions; however, the exact conditions were not recorded.

Non-response from those asked to participate in the study was not available; despite efforts made by the research team. Due to privacy concerns, all recruitment was conducted by the CNS'; whom were provided with log sheets to record the number of patients approached, declined or where accepted. However, over the long recruitment stage of the study, this was not consistently adhered to and therefore not reportable.

Table 3-1 AiMs: Demographic Information

Characteristics	**No. patients/ Mean (%/Range)**
Gender	
Male	8 (57.0)
Female	6 (43.0)
Age (Years)	
41-50	2 (14.3)
51-60	5 (35.7)
61-70	6 (42.8)
71-80	1 (7.2)
Marital Status	
Married	13 (92.8)
Divorced	1 (7.2)
Level of Education	
Finished Secondary School ('O' Levels)	3 (21.4)
Finished Secondary School ('A' Levels)	3 (21.4)
Further Education (attended a Technical College)	3 (21.4)
Undergraduate/ master's degree	5 (35.8)
Age at diagnosis	
Mean age in years	55.9 (45-74)
Telephone Review	
Follow-up time in months	5.6 (3-12)
Place of Residence	
Urban	9 (54.0)
Rural	5 (36.0)
Other long-term conditions	
Yes	6 (43.0)
No	8 (57.0)

3.3.2 Qualitative Findings

The thematic analysis identified 3 overarching themes and these themes were further categorised into 9 sub-themes. The overarching themes were; Experiences of MGUS health services, The psychosocial impact of an MGUS diagnosis and Knowledge of MGUS, Figure 3-3 AiMs Study Coding Tree.

The first major theme identified was 'Experiences of MGUS health services'. Commonly, participants discussed their interaction with the health service and health care staff from diagnosis to present. Participants' accounts identified various challenges and experiences, which differed extensively depending on where patients were on the patient pathway (pre-diagnosis, immediately post- diagnosis or a long-term MGUS patient). Some of these challenges were in relation to routine care and surveillance, communication and interactions with health care professionals and gaps or unmet needs in services.

The second major theme identified was 'The Psychosocial Impact of an MGUS diagnosis'. Participants identified particular psychosocial challenges that fluctuated across the MGUS pathway. In particular, patients discussed heightened emotions at diagnosis, including shock and fear. Psychosocial challenges were also discussed in relation to interaction with cancer services which evoked social comparisons with cancer patients and increased fears of progression. The majority of patients also discussed how their family and social network acted as a mediator to how they coped with the MGUS diagnosis, with many patients reporting that good social support reduced the overall disease impact. In addition, this theme discussed that the psychosocial impact of living with MGUS, can for many, reduce over time. Many patients do not worry about their MGUS daily but it remains dormant in their mind until a trigger, such as a surveillance appointment, occurs.

The final theme identified by participants was 'Knowledge of MGUS'. Patients experienced particular challenges due to the lack of information and confusing terminology provided by their HCP. When patients received information, it was often confusing and complex, which limited their ability to understand what MGUS was. Patients identified a number of information needs, which varied; with some patients requiring lots of information and others not wishing to receive any. Participants

discussed the lack of available written information and how information from health care professionals such as the GP can be limited due to their lack of experience with the condition.

In the paragraphs that follow a detailed account of each theme is presented.

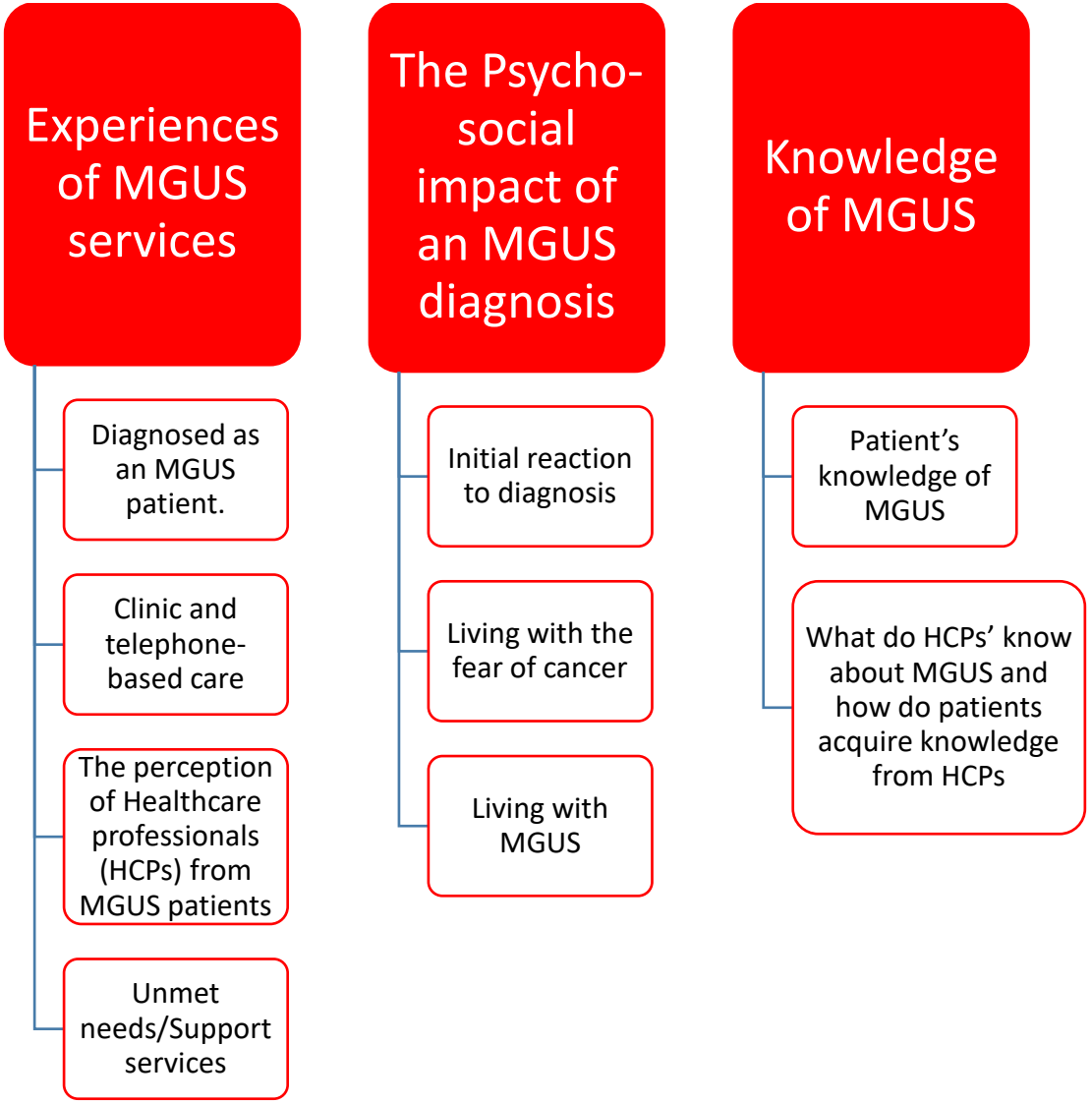


Figure 3-3 AiMs Study Coding Tree

3.3.2.1 Experiences of MGUS health services

A major theme identified was that patient's interaction with the health service was an important experience in the MGUS journey. This overarching theme describes how patients accessed MGUS health services from different pathways and the symptoms or illness that prompted a referral. Experiences of the health service were particularly discussed around the how and where patients were diagnosed. MGUS patients were typically informed by a haematologist in haematology clinic in the "cancer centre" of the hospital. Patients discussed how attending the "cancer centre" for diagnosis and their initial clinic appointment was anxiety inducing for them.

Experiences with health services were discussed in relation to their position on the MGUS care pathway. When patients were further on the MGUS care pathway (post-diagnosis), their appointments were co-ordinated by a clinical nurse specialist via a virtual telephone clinic. Patient's related positive experiences of the telephone clinic, which reduced the burden associated with attending clinics particularly in relation to travel/waiting time and personal time off work. Patients who experienced good psychosocial care and information support found MGUS easier to cope with and reported less negative reactions, such as heightened anxiety. On the other hand, poorer psychosocial care was linked by patients to greater anxiety. Through their experience of the health service, patients provided ideas on how to overcome some of the barriers and shortcomings in current MGUS health service provision. The theme and subthemes are depicted in Figure 3-4.

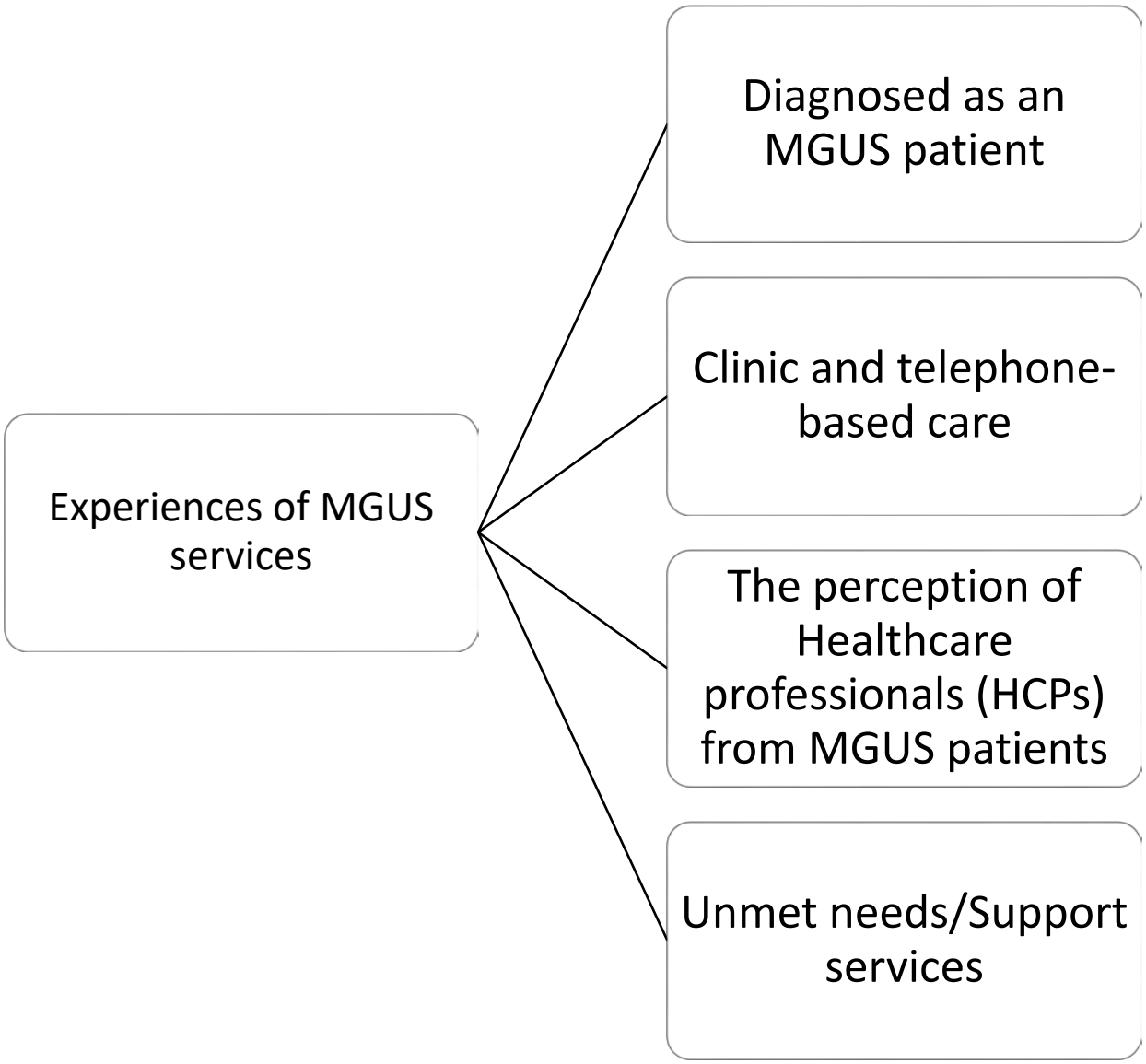


Figure 3-4 Coding Tree: Experiences of MGUS services

3.3.2.1.1 Diagnosed as an MGUS patient.

This subtheme discusses patient's narratives in relation to their interactions with the health services that led to their diagnosis or described their diagnostic experience. Most patients described being diagnosed incidentally when being investigated for non-related medical issues, therefore patients had varied pathways to diagnosis. Patients reported their being diagnosed with MGUS after; routine high blood pressure testing, co-morbidity appointments (asthma, COPD and acid reflux), hospitalisation for acute illness (pneumonia) and acute injuries (back and knee trauma). One patient was under investigation for MM for 9 months before being diagnosed as MGUS. These varied diagnosis pathways highlighted the inherent challenges in preparing MGUS patients for their diagnosis due to their varied interactions with various departments within the MGUS health services.

Different diagnostic pathways resulted in different experiences. For many patients, diagnosis occurred within the haematology clinic, this clinic was located within the cancer centre. The association with the "cancer centre" led patients to perceive that they had the potential to be diagnosed with a cancer, which generated anxiety. The physical association with cancer was associated with anxiety for many patients. Their experience of fear and anxiety of attending the "cancer centre" for an unknown reason/previously unheard-of condition was shared amongst a number of patients. However, this fear was intensified for one patient who was informed of the referral by post; which contained technical terminology ("Bence-Jones protein **(FG1.1)**". The patient was unable to make contact with haematology/health services and this led to confusion and anxiety. Whilst this was an isolated case, it highlights a short-coming in MGUS health services (and terminology use in correspondence), which can cause anxiety.

> *"I have to say this, because this really irked me, and I think it was because it was done over in (Local Hospital's Cancer Centre). That very place. God bless everyone".* ***FG1.3***

> *"Scary"* ***FG1.6***

"God bless everyone that has to go there. But I think that very place, when you have something like this, is the scariest thing in this world." ***FG1.6***

"Many, many, many people have MGUS but don't know they have it. Because we found out by accident." ***FG1.3***

"That's right, I found out by accident." ***FG1.6:***

I found out, because I took this rash --this thing on my arm, this itch, that just was relentless, absolutely relentless. And it was the um, the dermatology, who just done this --she done tests and she actually done for this specific one and it came back (as MGUS)." ***FG1.3***

In another case, a patient under investigation for MM was relieved to have MGUS; as they were not a "cancer patient" **(FG1.1)** who required treatment; unlike their previous status (as an MM patient)[i]. Therefore, their experience of entering the MGUS health services was vastly different and more positive than other patients.

3.3.2.1.2 Clinic and telephone-based care

This subtheme discusses patient's experiences of care after their diagnosis and their ongoing experience of initial surveillance for MGUS within the health service. All of the patients in the study were given ongoing surveillance by a clinical nurse specialist via a telephone clinic[ii]. Patients were informed on the telephone of the results of their surveillance-mandated blood tests by the nurses. This routine surveillance typically included a discussion of the blood result scores, if there had been any changes, inquiries about the patient's general health and an opportunity

[i] The emotional impact of being diagnosed is developed further within Psychosocial impact of an MGUS diagnosis page 186.

[ii] The telephone clinic is described in Chapter 1: Intro, page 30.

for the patient to ask any questions. Some patients kept track and detail the blood results at each appointment; to track any changes. Patients discussed an overwhelming sense of satisfaction with telephone surveillance, with no participants discussing negative experiences.

Patients valued the telephone clinic for several reasons; such as reduced travel time, greater convenience and the perception that they were reducing the burden on the health services. The telephone clinic offered an alternative to consultant-led appointments based in the hospital by offering collaborative management between the haematology department and their GP. Therefore, patients did not have to take time off or travel to the hospital for blood tests; but attended their local GP practice. This was beneficial for all patients, especially those who lived rurally as for many of the rural patients visiting the hospital in another town/city was seen as unnecessary.

"I think that -- that telephone follow up is --is a god send. Because going to that (Local Hospital's Cancer Centre), is the scariest thing. That people, because you do think worst, um, and why does it have to be done there. And I know you're going to say because that's where haematology is, but, no. There has to be something". **FG1.6**

In addition to the convenience of the telephone clinic, patients felt relieved that they were reducing the burden on haematology staff (especially doctors/consultants); as participants had the perception that HCP time was more appropriately spent treating cancer patients. Patients felt that doctors perceived them as of lesser importance[i]. Patients also described that not encountering cancer patients in the "cancer centre" reduced their anxiety; as seeing cancer patients acted as a trigger or fear of what their MGUS may progress to and they did not see what may be their future (if they progress to MM).

Patients found the nature of the telephone clinic offered a better environment/interaction in which to ask questions they had prepared. Participants

[i] The effects of this are discussed within the next sub-theme.

reported being more comfortable with the nurses because they were perceived as easier to talk to than the doctors. The nurses were seen providing excellent psychosocial care and information that provided reassurance and reduced anxiety. Patients also had access to a helpline; but only one patient had ever used it (due to other health concerns). The helpline was a 24-hour number; which haematology patients could call if they required assistance or were worried about a possible symptom.

"The telephone clinic I think it's a-... I think to me that's probably really all I need it would seem, it would seem to me you know an awful waste of time to come down and taking up the doctor's time perhaps in the-... in the hospital or anything I mean this is only a... quite a quick telephone conversation". **TI.4**

Despite an overall sense of satisfaction, the telephone clinic was still perceived as a necessary evil for patients, akin to visiting the dentist. Patients identified issues with the telephone clinic as a service. Patients seen surveillance as important for their health, but also something that they worried about. The waiting period, which may be some weeks, between testing and results was highlighted as particularly challenging. Patients reported feeling anxious about the wait and wondered whether this time, the nurse would tell them that the blood result scores had increased and they might have progressed/got worse. One patient routinely consulted their GP 3 days after testing (minimum period for testing) to reduce the anxiety of waiting. Patients who had attended physical clinics in the early part of their MGUS trajectory found the telephone component a significant upgrade and that that the telephone service had continually developed and improved since its inception

" *The dentist scenario, I hope it's another year or two till I see (the nurse). Because if see her someday, I'm probably getting slightly worse".* **FG2.1**

"When you see the phone, and the withheld number, and you know it's (Nurse Specialist) and you just think, [Made squeak Noise] Help! But it's not as scary as going to that hospital". **FG1.3**

3.3.2.1.3 The perception of Healthcare professionals (HCPs) from MGUS patients

A common theme discussed in relation to health service was patient's experiences of their interactions with health care professionals. Patients encountered a range of communication styles from HCPs when being diagnosed and when they sought information in relation to MGUS. The style of communication was said to mediate their experience of the health service and overall satisfaction. Some patients reported excellent psychosocial care, with clinicians (both specialists and GPs) taking time to explain the MGUS diagnosis and these patients experienced less diagnosis-related anxiety as a result of feeling sufficiently informed and cared for.

The haematology nursing staff were discussed as having a positive communication style. Patients felt the nursing staff provided individualised care and provided opportunities for them to ask questions. The nurses were praised for providing patients with "peace of mind" through their provision and explanation of information. This was appreciated by patients, who felt more at ease and less anxious about their diagnosis as a result of this individualised care and the impression of taking their time for caring for patients.

> *"(Nurse Specialist) always seems to ask me, round winter there, with me having asthma, I always get chest infections. I've had three antibiotics and three steroids, from January there. And she's always asking, you know, how many I've had, and all, how many you feel-- you know, how do I feel after it."* ***FG1.4***

Other patients reported their interactions with HCPs who had with poor communication skills, and this negative experience was linked to patients feeling isolated and uncertainty about their diagnosis, especially immediately post-diagnosis. Patient's reported doctors not taking the time to describe their condition and making the patient feel like they weren't important. Several patients described their doctor as detached and dismissive of MGUS patients. While patient's understood that other patients in haematology (such as cancer patients) would

require more care, they were disappointed at the lack of psychosocial care and empathy offered to them; with no signposting to other information or where they could talk to someone about their diagnosis. This resulted in patients having increased anxiety, feeling less informed and increased their worry about their diagnosis.

"Classic consultant. They go in and out of that every day, and they don't see it. They see people a lot worse that you. And there just delivering a line, to say, "Away you go". And the next patient in after you has got six months to live, or year. So they're focusing on him or her, rightly so. But just as a person, I think consultants are always criticized for treating you a bit more like a human being". **FG1.5**

"I'd say it's none of the -- the healthcare professionals, because they're dealing with serious cancers and things like that. So we're coming along and all we register as MGUS. They probably think, well you know, "Maybe you shouldn't even be here", you know".

[Background agreeance]

"Away you go, you're dismissed." But you're in (Local Hospital's Cancer Centre), and you're in the middle of it, and plus you're -- I had the scan done as well and you're in the cancer centre for that, so all your kind of mind is cancer this and cancer that". ***FG1.5***

3.3.2.1.4 Unmet needs/Support services

A common theme discussed in relation to MGUS patient's experiences of health services was the lack of psychosocial support services available and what supports were required to meet these needs. These unmet needs were mainly discussed in relation to social support.

Patients reported a sense of isolation/ uncertainty regarding their MGUS diagnosis, which many patients felt this could be alleviated by providing formal support structures for meeting and interacting with other MGUS patients. To alleviate this need, patients proposed developing two structures; in-person support groups

(similar to cancer support groups) and volunteer (local) MGUS patients' contactable post-diagnosis if a patient had questions or worries. This would reduce their isolation and uncertainty by being able to speak to their peers, whom had similar experiences in the MGUS health services.

> *"There's nothing (to help coping if individuals are struggling). you know, I just get through it, eventually. But it's not like I can lift the phone and ring (FG1.3). Lift the phone and ring (FG1.4), and say "How are you feeling today?" You know, "I'm feeling pretty shit". There's nothing out there, there's nobody out there. And that's because we're in limbo."* ***FG1.1***

Patient highlighted that this service would need to be co-ordinated by the health service; with the low numbers of MGUS patients (in NI) and some individuals not wanting to travel long distances identified as threats to the long-term stability of physical meet-ups. Those who attended a focus group (rather than the telephone interviews) were more positive about having meetings/support groups.

> *Yeah, but this is actually making me --has made me feel a lot better, than I have done."* ***FG1.3***

> *"You've started a support group."* ***FG1.5***

For other patients, there was an unmet need that did not require formal support through the health service in a support group, but a less invasive and lower cost intervention. Some patients valued the availability of a contactable MGUS patient who could speak to a newly diagnosed patient over *a "coffee or glass of wine"* FG**2.1** in the future. Developing this indirect type of support may be useful in the future for a charity or the health service to address this unmet need.

> *"So wouldn't it be nice to have a volunteer there, who's been through it. And who can talk to the person and say 'Look. Look at me. I'm fine.' You know, 'Really try not to focus everything on it.*

There is a positive outcome'. Because, I mean, if it's myeloma, the numbers are off the scale. So they have a far idea, very quickly, that you're going the MGUS trail instead. So it would be very nice if there was a volunteer". FG1.1

3.3.2.2 The psychosocial impact of an MGUS diagnosis

A major theme identified was that patients discussed how being diagnosed with MGUS affected their lives from a psychosocial perspective. This overarching theme describes the psychosocial impact of MGUS and how the impact of MGUS varied across the diagnosis/surveillance pathway. Patients felt isolated with their condition, especially if a family members had poor health (such as cancer). Patients felt unable to talk about their MGUS as it was perceived as less important by the patients themselves compared to their relative's illness. Patients also compared themselves to others with a serious illness and reported feeling a sense of guilt for using resources such as clinic hours; which made them feel less important and being less likely to discuss or seek support. The theme and subthemes are depicted in Figure 3-5.

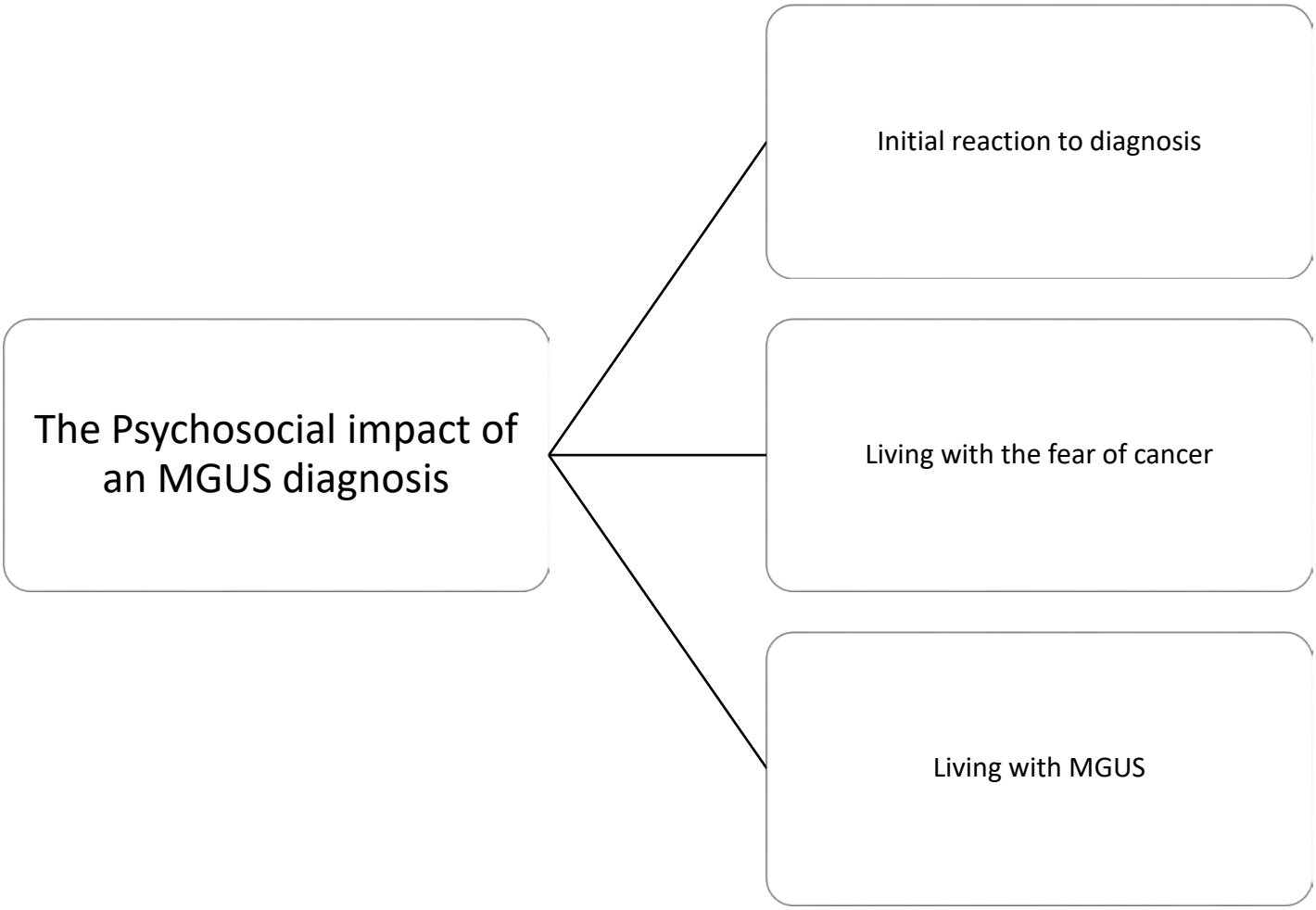


Figure 3-5 Coding tree: The Psychosocial impact of an MGUS diagnosis

3.3.2.2.1 Initial reaction to diagnosis

This subtheme discusses patient's narratives in relation to their initial diagnosis of MGUS. Patient's highlighted diagnosis as a particularly vulnerable psychosocial point in their pathway. Patients described their diagnosis as "the shock of my life" **(TI.2),** with some feeling their diagnosis was an existential threat to their mortality and future. Patients who had concerns regarding mortality reported making preparations for death with some completing wills and purchasing cemetery plots. These patients were more likely to want more information and reported being more anxious at diagnosis than other participants. However, all patients were aware of the potential life-shortening impact of MGUS and reported some initial anxiety about their diagnosis.

This concern regarding a fear of death was linked to the increased chance of having a fatal cancer in the future. This reaction was potentially heightened for patients as the diagnosis created a sense of shock that they were not prepared for; as they felt "fit and healthy" **(FG1.3).**

> "*To realise that this had the potential to be cancerous was also a shock and it certainly made me think about my mortality which I had-…obviously had thought about before but I thought about it even more and I did make a will and I did buy a grave (laughing). Basically I thought "Right I better start getting organised just in case this leads to something awfully terrible".* **TI.2**

For many patients, the shock developed into anxiety in the weeks' post-diagnosis; with patients describing consistent thoughts about their mortality in this time and calling this period as "horrific". Patients described the impact of the initial diagnosis of a cancer-related condition and the shock of hearing the term cancer leading to many of them missing some or all of the important MGUS information; including what MGUS was, their risk of progression to cancer and how they will be treated in the future (placed on active surveillance) at diagnosis. This shock and anxiety continued until the second appointment/first follow-up; usually 3 months' post-diagnosis; when patients could ask questions and process the information better.

Some patients reported that the diagnosis of MGUS came as a relief; providing a diagnosis after prolonged investigations, which was not cancer. Similarly, after overcoming the initial shock of diagnosis, patients were relieved that they don't have cancer.

"At the beginning, I mean we're all thinking, eh, cancer. I mean, really, MGUS comes down the line. And that's when the relief comes. But for those few months, that --before bloods and biopsies and all the rest of it. I mean, you really are going with, you know, Myeloma. You are not going with MGUS". ***FG1.1***

3.3.2.2.2 Living with the fear of cancer

A common theme discussed in relation to MGUS was living with the fear of cancer and their experiences of the "cancer world". For many patients, their initial diagnosis occurred within the cancer centre; with the waiting room often shared with patients undergoing cancer treatment. Many of these patients displayed signs of cancer, for example hair loss. This exposure to cancer patients lead to patients having increased anxiety about potentially receiving a cancer diagnosis and going through treatment in the future (and the associated physical changes).

This fear of cancer continues post-diagnosis, with the fear of progression to cancer being compared to "*Damocles sword*" **FG2.2**. MGUS patients had a consistent fear in the back of their mind at telephone surveillance, that this could be the appointment that they received bad news from the nurse and were progressing to cancer. This had a small but consistent psychosocial impact on patients.

"I think it's sort of a Damocles, hanging very high-- you know, it sort of-- not likely-- Sort of a high percentage chance of not developing anything". **FG2.2**

MGUS patients described living in "*kind of in a cancer world but not* "(**FG1.4)** post-diagnosis. Patients had consistent surveillance appointments, had regular blood tests and had the fear of cancer, but didn't experience cancer symptoms or the physical effects of treatment. This left some patients to feel like "*frauds*", whom were using

resources meant for cancer patients more deserving or in need of care than them. They were in need of care but seen other's needs as greater than theirs and felt guilty that they were using the resources of cancer patients but did not have cancer themselves.

"When that buzzer goes off (that it is cancer related), and it scares the crap out of you. **FG1.3**

3.3.2.2.3 Living with MGUS

A common theme amongst patients was how the psychosocial impact of MGUS reduced over time; as patients came to terms with their condition and other issues in their lives became more important. Most of the patients had lived with MGUS for a prolonged amount of time (multiple years) and reported their worries about MGUS or its consequences lessened over time. MGUS was predominantly an unseen condition, in the back of their mind during everyday life; that became important at surveillance appointments and while waiting on results. Due to the lack of symptoms, MGUS was compared to a mental health diagnosis; where patients were healthy on the outside but unwell inside but which had minimal consistent impact on their lives.

"Cause it's asymptomatic, so there are no symptoms associated with MGUS. It's seems to be that it's a hidden illness. So that may be one of the reasons why people don't really know much about it. You know, if-- like you said early, if you were to say to somebody they wouldn't understand what you were talking about, that kind of thing. How's that make you feel knowing that it not like eh, an illness that people can see". **FG2.2**

Overall, patients were positive on their low risk of progression to cancer; with the explanation of the low risk percentage (1%) helping patients to rationalise and understand their low risk of progression. One focus group participant was rebuked in the session for their pessimistic outlook on progression, with the majority believing they were not going to progress.

"*It's a strange thing to live with, because, we feel fit and healthy. But you're right, coming up to that, for me it's six months, that week or two weeks before hand, it's, you're not the same person".* **FG1.3**

"We're not going to progress. Would you stop being so doom and gloom?" **FG1.3**

For some patients, MGUS acted as a spur to improve their lives and make lifestyle changes, with patients reporting increased physical activity and improving diet for a result of their diagnosis and to lessen their risk of progression.

"I'm trying to do a bit of running. So it maybe gave me a little bit a kick in the backside to go out and do something, lose a bit weight. It's-- it was good that way. Was it because of that? Yeah, but that was only maybe more in the mind to, you know, I've got to do something to look after. I thought I was going to die from a heart rather than of MGUS". **FG2.2**

MGUS was overshadowed for some patients by medical issues in their family, especially if cancer-related. Patients felt that their MGUS diagnosis was less important than other family member's issues and tried to avoid causing worry and anxiety in their family by not talking about MGUS. As a result, some patients felt isolated with their diagnosis; having no-one to speak to about their worries or whom had similar experiences. Some male participants in particular were reluctant to speak about their MGUS as they had a poor understanding of what MGUS was and did not want to be perceived as sickly/in need of help by their family and friends.

*"It's like someone, god bless them, with mental health issue, because you can't see it, you -- you can't really be the same sympathetic". **FG1.3***

"Only other person in my life who knows is my wife. My kids don't know; I would spare them any worries of concerns. It would need to be something pretty serious, not just this for me to tell them" **FG2.1**

3.3.2.3 Knowledge of MGUS

A major theme identified was that patient's knowledge of MGUS was a vital component of the MGUS experience; with their seeking of knowledge and having more knowledge was linked to lessen psychosocial impact. Experiences were particularly discussed around acquiring knowledge from HCPs and the internet. This overarching theme describes what patients know about their condition and how they acquired this information. Patients discussed how good information helped them to lessen the impact of diagnosis; leading to patients being more confident about their diagnosis and taking an active role in their own care.

Patients described how information on MGUS was difficult to acquire; with many of their GPs lacking MGUS-specific knowledge; and the internet being difficult to find accurate and understandable information. Patients illustrated how they found negative and fear-inducing stories when searching online at diagnosis; as they lacked the understanding to differentiate MGUS information from MM information. The coding tree is provided in visual form, Figure 3-6.

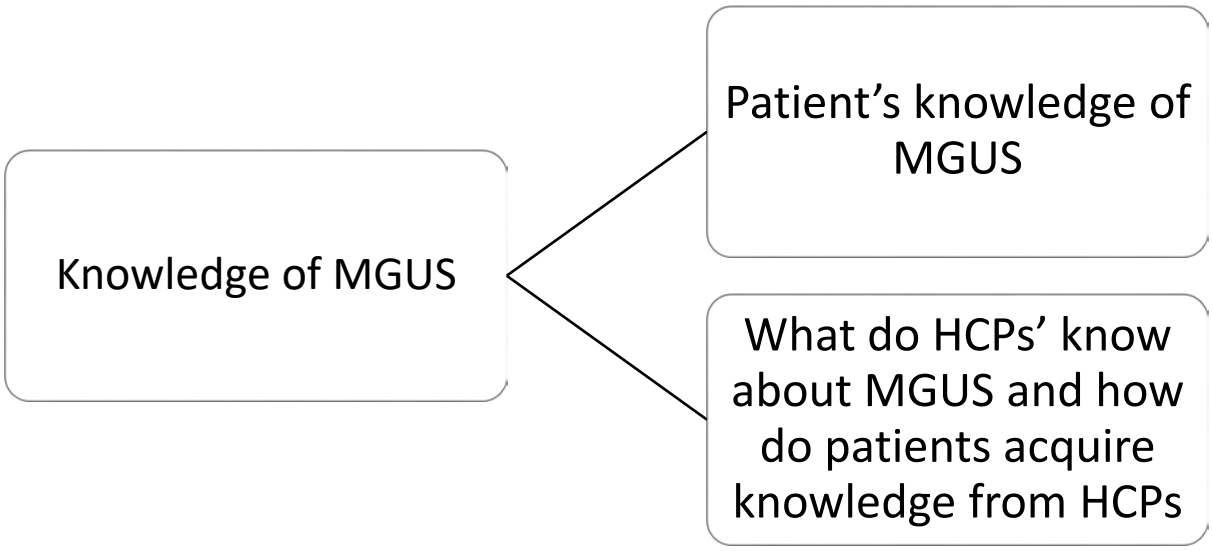


Figure 3-6 Coding Tree: Knowledge of MGUS

3.3.2.3.1 Patient's knowledge of MGUS

This subtheme discusses patient's knowledge of MGUS and how this affected the level of impact and confusion patients experienced. Patients found the full name (monoclonal gammopathy of undetermined significance) difficult to understand, remember and explain to others; such as family and friends. Confusion was heightened by the differing terminology used by HCPs when they were trying to explain the condition to patients. Patients reported that MGUS was described to them by HCPs as a; "*protein deficiency*" **(FG1.4)**, "*raised protein*" **(TI.4)**" "*benign blood abnormality*" **(TI.2)** and a *"rouge blood*" **(TI.3)**. The different terms were confusing for patients and many felt that this was a contributing factor to the confusion and anxiety they experienced at their diagnosis.

"What does the word (MGUS)-- what does the 4 letters mean?" **FG1.2**

"Monoclonal gammopathy of undermined significance." **Interviewer:**

"And that's why nobody can remember it." **FG1.2**

There were significant differences in the knowledge of patients and how much knowledge they wanted to have. Some patients reported wanting to "*live in a bubble*" **(FG1.3)** and did not want to know anything beyond the essential information; such as when their appointments were. On the other hand, other patients kept detailed records of their blood scores (light chain ratios and kappa lambda ratios). For these patients, feeling informed created a sense of empowerment for patients and they felt an active part of their care. These patients were able to describe the link between MGUS and MM and lymphoma and define the progression risk to MM (1% per annum **(TI.4**); which reduced their fears of progression. Other patients' knowledge ranged from low to medium levels and many desired to acquire more knowledge; highlighting the differing information needs and knowledge of MGUS patients.

"MGUS is a monoclonal gammopathy of undetermined significance" "It's sort of an indicative of being likely to develop some sort of cancer, most likely multiple myeloma or um, lymphoma, but, um, by no means guaranteed". **FG2.2**

"I like to see the results you know the blood results come through even though I don't understand them very much but I always have to go after them. I don't get that as a matter of course and I think that I should. It's just, I also I find that, that I there-... something my blood, results would show something to do with light chains, I've asked about that several times and I keep being told not to worry about it but I have a very abnormal ratio of light chains in my blood and I, I again, a little knowledge is a dangerous thing" **TI.2**

Patients described their experiences of using the internet to acquire information about MGUS. Patients found searching for MGUS information online to be challenging and websites being difficult to navigate; with most of the information connected to MM, used unfamiliar and difficult to understand language or referred to information in other countries (especially the USA). As a result, many patients were linked/directed to MM (not MGUS) information, which caused significant anxiety and worry. This was especially apparent if this information was being sought shortly after diagnosis when some patients believed they had cancer.

Over time, patients were less likely to search for MGUS-knowledge online; highlighting the difficulties and the "scary" stories as barriers and reasons to stop seeking information. Patients who received information leaflets at diagnosis reported less extensive online knowledge seeking than those who did not receive an information leaflet. To help future patients, an official MGUS website with understandable and clear information in lay language was proposed; to reduce the confusion and to help UK patients to interpret the often contradictory and unclear available currently.

"I sort of looked up what MGUS was I looked up online and I sort of had a fair idea what it was well sort of an idea what it was so I was probably a wee bit apprehensive

because I thought it's possible-…I could not have cancer but I could possibly be getting cancer so I did feel a bit (shocked) ". **TI.2**

"I know the internets a dodgy place to go to find anything medically, but, you can think that even at diagnosis, if there was an official, recommended and supervised support group for this, which might then set your mind at ease, then at the time you get the diagnosis, you can say well here's a link to a website, and official website and with some sort of support group. That people might post comments, and that's -- and if you could focus your attention rather than googling the word, and it takes you to all asundries." **FG1.5**

3.3.2.3.2 What do HCPs know about MGUS and how do patients acquire knowledge from HCPs on

This subtheme discusses how patients interacted with HCPs in order to gain information in relation to MGUS to educate and empower themselves. Patients sought information from three types of HCP; their haematology team (doctors and clinical nurse specialists), their GP and personal contacts within healthcare who were HCPs. Patients described how receiving good communication from their haematology team at diagnosis facilitated less anxiety and greater understanding. Good communication was described as the HCP taking the time to explain the condition and providing written materials at diagnosis.

Written information allowed patients to investigate the issue online or with contacts (if they wished) with some direction/knowledge; as patient's only retained part of what they had been told at diagnosis. One patient who received a leaflet from their haematology team after the first surveillance appointment (in clinic) was more confident after reading the leaflet and believed it would have been easier for them if that had been received and talked about at diagnosis.

"No information sheet, nothing. You were just kind of send away. And I actually had to try and remember what it was, because as everybody knows, when you're in with a

medical professional you probably retain about a quarter of what they said. So I came way, and the only thing I remembered was Mono. And I thought, "What was that? What was the rest of that?" And I was trying to remember, cause that was it." **FG1.5**

Patients described how their GPs were important providers of information, where they had their blood tests and general healthcare but generally reported poor MGUS-specific knowledge. Patients reported that they often felt they were more knowledgeable than their GP about their condition as a result of their research and that the more resources should be available for GPs to help patients understand MGUS and help patients cope with the impact of their condition. However, there was little indication of what resources that could involve.

When GPs were knowledgeable about MGUS, patients understood more about their diagnosis and felt reassured that they were receiving the best care possible. Patients with less knowledgeable GPs felt isolated and in need of further informational support; which was difficult to access due to the lack of awareness of MGUS amongst GPs. Patients were aware that GPs (and HCPs in general) had a lack of time available to inform themselves about all conditions, especially uncommon conditions like MGUS; but felt less anxious when their GP had knowledge.

" *So after the information, what I was told, it sinks in. and you do hear thing like "you should be ok" [Laugh] Um, but when it sinks in you first port of call, beyond the internet, is the GP. So I placed a call to the GP, and said to me "I don't know. I've never heard of this".* **FG1.5**

"It's a bad job when your GP doesn't know". **FG1.1**

"My doctor was on top of it the whole time like my doctor's been really good, and she has, she was she keeps me informed of everything that's happening and she explains everything she's my doctor. She's one of the only doctors that speaks my language if you know what I mean. I have all the confidence of the day in her cause she'll always go over the, the extra to help you." **TI.1**

Patients with family/friends who are qualified health care professionals (such as doctors, nurses and pharmacists) reported an improved knowledge and understanding of their condition post-diagnosis. Patients felt that by talking to their healthcare-knowledgeable family/friends they were able to understand more about MGUS, which lessened the psychosocial impact of living with MGUS. Some patients whose partners were healthcare staff described how they would prepare questions for haematology staff and keep records of surveillance results. Patients used a number of HCPs to acquire information to help cope with the psychosocial impact from MGUS.

"My wife had lists of questions, that she wanted me to ask. Now, and every time (Nurse Specialist) phones me now, I have those lists of questions now. **FG1.6**

"Y*ou have your list?"* **Interviewer**

"I have her (partner) sitting beside me and she makes sure I go through them. Because she checks everything and she's recorded everything herself, so that she sees everything progressing." **FG1.6**

3.4 Discussion

This novel study highlights that MGUS can have a negative psychosocial impact on patients which is most prominent at diagnosis and causes intermittent anxiety and worry around surveillance appointments. However, anxiety reduced over time for most patients and MGUS rarely had a life-changing impact on individual's lives long-term. However, it caused many patients to re-evaluate their lives and was a sobering event which caused patients' to question their mortality. Most patients had a poor level of understanding of MGUS. Patients highlighted some issues in current MGUS service provision, especially in relation to information provision, but were positive on the telephone clinic utilised for active surveillance. Information was a powerful tool for patients, with good information and explanation leading to improved understanding and lessened anxiety.

As per the other results chapters, this discussion outlines a short summary of the findings and outlines the strengths and limitations of the study before discussing the findings in relation to the background literature and the other dissertation studies in Chapter 6: Discussion.

3.4.1 Experiences of MGUS health services

The first theme of 'Experiences of MGUS health services' highlighted the different paths to diagnosis experienced by MGUS patients. This was the first exploration of the healthcare pathway of MGUS patients but similar work in myeloma has shown that haematological conditions often involve multiple investigations and testing before a diagnosis is provided (428).

Post-diagnosis, all patients underwent life-long surveillance via a telephone clinic; which was praised and credited with reducing their anxiety and improving patient's knowledge; similar to telephone clinics for other conditions (32). Patients were more at ease with talking with nurses about their condition; as many found their haematology doctors had poor communication skills and provided poor of psychosocial care and empathy to them as MGUS patients; compared to other conditions. This included doctors being dismissive and not providing clear

information to patients. This is in line with similar findings in the premalignant literature overall (Chapter 2: Systematic review).

Patients felt that the existing MGUS health services could be augmented to assist in their initial adjustment to their MGUS diagnosis through the implementation of formal support structures and peer groups for MGUS patients; overseen by the health service or a volunteer.

The disconnect between doctors and patients was one of the key messages from patients; and presents a barrier to improve services in the future (explored further in Chapter 6). The acceptability of these services to HCPs (Chapter 4: Haematology and GP studies) and patients (Chapter 5: premalignant patient survey) were important outcomes of this study, which are investigated further within the later chapters.

3.4.2 The psychosocial impact of an MGUS diagnosis

The emotional impact of MGUS was complex and nuanced to each individual. At the initial diagnosis, all patients experienced shock at being diagnosed with an asymptomatic condition linked to cancer. This shock was similar to population-level cancer screening positives (343,347), other premalignant conditions (301,344,349,429) and haematological malignancies (430). This shock developed into anxiety and fear for many patients; with the potential of developing cancer an active concern in the weeks and months following diagnosis. This is similar to the experiences of MM patients who reported similar experiences of having a sudden and shocking confrontation with their mortality, by a condition that they had never heard of (431). This anxiety often regressed when patients become accustomed to their diagnosis and the uncertainty was reduced (432); as expressed by the MGUS patients in this study. MGUS patients outlined this time period (shortly after diagnosis) as having the highest psychosocial impact on their lives and an area where intervention could be implemented in the future. As most of the patients were several years' post-diagnosis, further research on newly diagnosed patients would provide greater insight into that group.

3.4.2.1 Knowledge of MGUS

Knowledge of MGUS was one of the strongest messages from the collective voice of the participants. Overall, patients had poor knowledge of MGUS at diagnosis which only developed after the initial shock of diagnosis reduced. There was a clear distinction between the patients with MGUS knowledge and those with less knowledge. Those with knowledge experienced less anxiety and reported improved coping. In the wider literature, MM patients reported the initial gathering of information and developing knowledge as important to acquaint themselves with their condition and reduce their distress (431).

Patients are often unable to absorb verbal information at the time of diagnosis for medical conditions (433). Anxiety and isolation can result if the information from HCPs is considered to be lacking, confusing, or inadequately explained (347). Many MGUS patients reported not receiving an information leaflet, one of the most frequent sources of healthcare information for patients (434,435), at their diagnosis. However, those who received the information leaflet reported a more positive experience of their post-diagnosis experience. Within Chapter 4, the frequency of written information provision by haematology professionals was investigated, as a response to the low provision reported by MGUS patients in this chapter.

Online activity was described by many patients as potentially problematic if one was not medically literate; with patients reporting contradictory and confusing information about MGUS. Haematological conditions are generally amongst the least well understood malignancy by patients (436).

One of the issues raised was the legitimacy and the trustworthiness of the online material. This has previously been indicated as a major weakness in online content, as there is little stringent regulation, as would be the case in other avenues of information (437). One of the main aims of Chapter 5 was to assess what information MGUS (and other premalignant) patients wanted online.

3.4.3 Strengths and Limitations

As described in the introduction, MGUS is typically diagnosed for older adults over 70-years-old (67). The average age of our sample (55.9 years old) was considerably younger than the average age for MGUS patients (74 years old) (438). Therefore, some issues raised by this study may not be appropriate to all age groups with MGUS.

Due to the small numbers and that most patients were of a similar age (approximately 55 years old), we were unable to compare patients by age or discern patterns to their responses. However, in the later studies, different age ranges of MGUS patients are compared. However, as patients diagnosed with MGUS at a younger age live longer with the knowledge of their condition and have an increased lifetime risk of developing MM; this younger group may receive a greater benefit from future interventions.

The initial plan for the study included conducting focus groups and interviews with patients across Northern Ireland; which included patients who attended a clinic and on telephone-clinic care. However, this was not realised due to issues with recruitment and governance approvals.

All the participants were on the telephone-clinic at data collection; however, some patients had been attended clinics prior. We feel that collecting data on patients who physically attended the clinic would have added further insight into certain themes; especially the impact of waiting alongside cancer patients; which was mentioned as distressing for some patients.

During the study, several delays were experienced, with governance approval extending the study by several years. This was due to issues with slow progress through initially the lead trust's (Belfast) governance system, which was furthermore increased by slow progress through the second trust's (Southern) governance system, which has to conduct a separate review of the project (not connected to the lead trust's review). The study timetable was further extended due to recruitment difficulties for MGUS patients, as shown by the low numbers of participants (14) recruited . These recruitment difficulties shaped the thinking for the other

components of the studies and dissertation, as it moved towards incorporating haematology healthcare professional and GP views (Chapter 4) and online questionnaire methodology (Chapter 5) to overcome small numbers and governance issues in Northern Ireland.

The small number of participants limits the confidence we can place of the findings and the representativeness of the study. Additional participants would have provided a more representative sampling of attitudes of the impact of MGUS; However, this is a common issue comparable to other premalignant studies; six articles included within the review had 6-16 participants (344,346,349–351,356). However, despite this, we feel as a research team that this was an accurate representation of the views of NI MGUS patients but that there were further insights that could found with more participants in some sub-themes; which may have not reached data saturation.

Differences in telephone versus face to face interviews have been shown to have no significant effect on the results/ patient responses (439,440). Telephone interviews benefit from reduced social desirability effects; especially as cancer-related conditions can be a sensitive topic for patients (441). Telephone interviews also reduces travel expenditure and allowing greater flexibility for both the interviewer and interviewee than face to face interviews (32). However, telephone interviews reduce both time and monitory costs on both participants and researchers; which is important in studies with low funding such as this (442). It was important to outline the reasoning and pitfalls of utilising telephone contact as this is often not reflected upon in academic work (442).

The researchers used a variety of techniques, such as method triangulation and member-checking (credibility) (443), multiple interviewers/analysis (inter-observer reliability) (408) and strong replicability (with clear steps and protocols provided) (408) to develop the study's rigor and methodological robustness. Reporting was guided by the COREQ (405,426) criteria to focus the writing (Appendix 9). However, rigor could have been improved with a better audit trail/logbook and external validity through generalisability using a larger sample. This was a learning experience for me as a researcher, and improving my audit trail and rigour was a valuable lesson from conducting the study.

Inductive thematic analysis has several potential pitfalls for researchers (444). We were able to mitigate these effects through providing a personal statement prior to analysis (Researcher reflexivity, page 150) which discloses the potential bias of the author (BM) which could affect the data analysis. We (BM and OS) maintained a close relationship to the data and immersed ourselves in the data collection through multiple re-readings and interpretations of the data. We also used a third reviewer to examine the codes and interpretations (CMcS), to verify the validity and reliability of the findings.

3.4.4 Chapter Conclusion

The data indicates that MGUS patients can feel isolated and confused from their diagnosis, in part due to poor information provision and poor communication and psychosocial care from doctors. Patients experience recurrent anxiety around their surveillance; which revolves around the potential progression to cancer. The issues raised by patients on the knowledgebase of their GPs and the care offered by haematology staff were central concepts that led to the development of studies involving HCPs, which is detailed in the next chapter.

4 Chapter 4 Healthcare Professional's (HCP) views on MGUS care.

4.1 Introduction

In the previous chapters, both MGUS (Chapter 3: AiMs study) and other premalignant patients (Chapter 2: Systematic review) highlighted issues regarding HCP knowledge about their condition and how they communicated information. No previous research has focused on the MGUS care pathway or HCPs communication with MGUS patients. Two medical specialities, haematology and general practice, were identified by patients as most important in MGUS care, in terms of providing information, support and conducting surveillance. In response, two surveys were constructed; with closed and free-text response options. The first study on haematology staff aimed to identify the terminology used in relaying the MGUS diagnosis to patients and to evaluate the perspective of the staff. The second survey (GP survey), which was informed from the findings of first survey (haematology survey), using the sequential design; sought clarification on issues raised by patients and haematology staff, such as GP knowledge of MGUS through knowledge-based questions. The combination of the findings of the two studies allows comparisons to patient perspectives and experiences outlined throughout the dissertation. The surveys also provide an outline of the care pathway for MGUS patients.

In the context of the dissertation, this chapter provides the HCP perspective of MGUS care; informing how HCPs communicate and care for MGUS patients. This chapter focuses on two of the main dissertation research questions: "How do healthcare professionals interact and care for MGUS patients?" and "What is the healthcare pathway that MGUS patients navigate during their care?". This HCP perspective on MGUS care; informs the clinical recommendations of the dissertation and identifies future directions for MGUS health service research.

Compared to other health conditions, the care pathway for haematological patients can be; harder to understand (445) and more difficult for GPs to suspect (due to non-specific or lack of symptoms) (446). Haematological conditions are associated with more primary care visits before referral to specialist services such as haematology (428,446).

Furthermore, haematological malignancies with lower visible symptom burden than other malignancies (such as some myeloproliferative neoplasms) have been associated with HCP communication difficulties and poor patient understanding of their condition; irrespective of age, gender or educational level (447).

As MGUS is asymptomatic and diagnosis is predominantly incidental following routine blood work or diagnostic workup (13,90), the main aim of this research was to assess how HCPs view and communicate about MGUS. Premalignancy patients (systematic review and AiMs study) had outlined poor HCP communication about their diagnosis, particularly the use of complicated terminology, as adversely affecting their distress/anxiety levels (342–344,358).

4.1.1 Why was Content analysis appropriate?

Qualitative methodology is a useful method to deepen the understanding of individual's experiences and beliefs[i]. When planning the data collection, content analysis was chosen as the appropriate technique to gain an understanding of the terminology and communication style of respondents. Content analysis is a "research technique for making replicable and valid inferences from texts (or other meaningful matter) to the contexts of their use" (448). The technique involves analytical constructs/rules of inference to move from text to answer the research question (449). These analytical constructs can be derived from a combination of; existing theory, experience, expert knowledge or the literature (448). Content analysis can be subjected to independent tests and techniques for reliability and validity, comparable to quantitative research (449).

Conventional content analysis (450) was the most appropriate approach to describe a phenomenon (the treatment of MGUS) in an area with minimal existing theory or research literature (450). Conventional content analysis benefits from analysing participants' information without imposing preconceived ideas or a theoretical

[i] A description of the benefits and issues, and the reliability and validity of qualitative research is located in Chapter 3: Page 144.

perspective. The knowledge generated maximises the diversity of responses and is grounded in the data (450).

Content analysis has been criticised as lacking the sampling and analysis procedures to infer theoretical concepts from findings; however due to the lack of research in MGUS, it is important to be able to develop the novel concepts and models at this stage (451). Content analysis can fail to identify key categories and provide an inaccurate representation of the data if the context of the data is not understood (450). This can be mitigated through developing rigour through building credibility; using triangulation and negative/deviant case analysis (399).

Using social media as a dissemination tool has been used in patient (452,453) and HCP populations (454–456) to increase visibility and reach in difficult to research areas (457). The GP survey was conducted online using SurveyMonkey to collect responses and social media to disseminate the survey. Online surveys have anonymity, are easy to access and can be completed at any time; which is especially beneficial in HCP research (457–459).

4.1.2 Aims

These two studies aimed to identify how HCPs communicate a diagnosis of MGUS to their patients, what terminology is used to describe MGUS and its risk of progression and to compare the knowledge-base of GPs and GP trainees. Some open-text responses were provided by HCPs to guide the interpretation and offer some insight into the rationale behind their answer choices.

This relates to the research questions[i]; specifically Q3 (How do key healthcare professionals interact with, and care for, MGUS patients) and Q4 (What is the formal or informal pathway that MGUS patients 'travel' to receive a diagnosis, treatment and care).

[i] Research questions outlined, Page 20.

4.2 Methods

Two surveys were conducted on haematology healthcare professionals and general practice doctors and present separately below (unless stated).

4.2.1 Haematology survey

This work has been published in European Journal of Haematology (McShane, Charlene M., Murphy, Blain, Lim, Kah Heng, & Anderson, Lesley A.) (460).

4.2.1.1 Collaborators

CMcS (Post-doctoral fellow) overseen the running of the survey and liaised with HAI organiser (Sinead Cassidy) and other relevant members of HAI to ensure that the survey ran in accordance with the ethics protocol. CMcS and BM were involved in promoting and managing the survey at the conference. CMcS and BM were involved in data management, analysis and interpretation.

4.2.1.2 Sampling

Haematology professionals (haematologists, junior doctors and nurses) were surveyed at the Haematology Association of Ireland (HAI) conference in Athlone, Republic of Ireland (ROI), on the 14th and 15th of October 2016. This conference was chosen it is the largest gathering of haematology-related practice and research in Ireland, with approximately 280 ROI and Northern Ireland (NI) HCPs attending. Further details on the conference can be found at http://www.haematologyireland.ie/archive/.

Inclusion criteria

- Conference attendees who were health professionals working with haematology patients in Northern Ireland/ROI. These included doctors, nurses and allied HCPs.

Exclusion criteria

- Conference attendees who were not HCPs. This includes scientists, undergraduate students, conference sponsors and members of the admin/support team.

As all conference delegates did not meet the inclusion criteria (i.e. not a haematology professional), 250 were estimated to be eligible. Survey response rates were estimated to be between 20-35% for non-personalised responses (461,462); with this in mind, 50-88 responses were expected.

4.2.1.3 Instrument description

The haematology survey consisted of 9 questions which focused on; how HCPs diagnosed MGUS patients, provided information and their perspective on current MGUS surveillance practices. Questions also focused on the terminology used at diagnosis.. Questions were developed from issues raised in Chapter 2: Systematic review and Chapter 3: AiMs. All the questions were designed and pilot-tested within the study team for face validity and functionality. The survey was paper-based, anonymous and took approximately 5 minutes to complete. The survey is provided in Appendix 14.

4.2.1.4 Procedure and data collection

Surveys were disseminated in three ways; within each conference booklet (as a loose sheet), available at the conference administration desk and on seats within each session. Attendees were informed of the study several times during the sessions on slides presented by the research team and conference organisers.

Respondents completed the survey, which contained multiple choice questions' with skip logic to reduce time burden. Respondents returned completed surveys to boxes located at strategic locations in the venue. All attendees should have been aware of

the survey and offered the opportunity to complete. The protocol is located in Appendix 13.

To encourage participation, respondents were entered into a raffle for an 'iPad mini' tablet. A detachable slip of paper detailing the participant's personal details was provided with a separate box available for entry into the draw. The draw was conducted on the day of the conference and the winner was announced at the closing ceremony.

4.2.1.5 Analysis

Quantitative survey responses were transferred to Microsoft Excel before being coded and analysed using STATA v.14 (463). Statistical significance tests, Fisher's exact test (under 5 observations per group) and Chi-squared (5+ observations per group), were used for all variables (such as number of patients in their clinic).

Qualitative data was organised using NVivo (265). Content analysis[i] was conducted on the open-text responses; which focused on HCP views on diagnosing and using active surveillance with MGUS patients. Missing data was excluded from the analyses and missing responses are detailed within the results tables.

4.2.2 GP Survey

This work has been published in BMC Family Practice (McShane, Charlene M., Murphy, Blain, Santin, Olinda, & Anderson, Lesley A.) (464).

4.2.2.1 Collaborators

CMcS oversaw the running of the survey and liaised with Prof. Seifert and other relevant members of the WONCA Europe Organising Committee to ensure that the

[i] Content analysis is described on page 192.

survey ran in accordance with the ethics protocol. CMcS and BM were involved in promoting and managing the survey. CMcS and BM were involved in data management, analysis and interpretation of the findings.

4.2.2.2 Sampling

GPs and GP trainees were surveyed using SurveyMonkey (465); which was launched at the World Organization of National Colleges, Academies and Academic Associations of General Practitioners/Family Physicians (WONCA) Europe Conference (Prague: 28/06 to 01/07/2017) and promoted online through social media (Twitter). The WONCA conference was chosen as the launch event as it was the largest GP conference worldwide, with approximately 3,000 GP/family doctors from approximately 62 countries attending and a strong social media presence.

Inclusion Criteria

- GPs/GP trainees who completed the survey online
- GPs/GP trainees attended the WONCA Europe conference

Exclusion Criteria

- Anyone not a GP or GP trainee. This included doctors from other specialities and scientists, undergraduate students and the general public/patients.

4.2.2.3 Instrument description

The GP survey was designed to assess MGUS awareness and knowledge of GPs/Trainees. The survey consisted of 31 questions, which focused on; respondent demographics, MGUS diagnosis, surveillance, knowledge and potential support needs. The questions were developed from issues raised in Chapters 2 (Systematic review,) Chapter 3 (AiMs) and in response to the findings of the haematology survey;

which had highlighted primary care integration as important in MGUS surveillance. All the questions were designed and pilot-tested within the study team for face validity and functionality. The survey took approximately 10 minutes to complete, was based online (SurveyMonkey) and responses were anonymous.

4.2.2.4 Procedure and data collection

The survey commenced with a study information and consent form. Respondents then completed the survey, which contained multiple choice questions with skip logic to reduce time burden. A copy of the survey is located in Appendix 16 and a copy of the protocol in Appendix 15.

The GP survey was launched at the WONCA Europe conference through social media and visual presentations and posters at the conference. A study specific twitter account (@QUB_GPSurvey) was used tweet to relevant bodies/organisations and prominent social media influencers. The survey was also highlighted on the WONCA conference website. This combination of dissemination aimed to reduce undercoverage as participants could be conference attendees who seen the posters or those following the conference online though social media or the website.

Tweet examples:

- "ARE YOU A GP/GP IN TRAINING? We want to hear your views on a blood disorder. You could win an Android tablet! **[Survey link]**"
- "ARE YOU A GP/GP IN TRAINING? Do you have 10 mins to answer a survey on a blood disorder? You could win an Android tablet! **[Survey link]**"

Within SurveyMonkey, IP (Internet Protocol address) tracking was switched off in the collector settings as requested by ethics (i.e. the study team would not receive the IP addresses) to safeguard anonymity.

To encourage participation, respondents were entered into a raffle for an 'Android tablet'. Participants who wished to be included in the prize draw completed a

separate survey (not linked to the GP survey) which collected their name, location and email address and was not matched to the GP survey itself; to ensure anonymity. The draw was conducted using an online random number generator tool (e.g. www.randomresult.com) and the winner contacted through the email provided to confirm postal address. Upon confirmation of postal delivery, information relating to respondent names and addresses was deleted from SurveyMonkey, study team computers and e-mail accounts.

4.2.2.5 Analysis

Survey responses were transferred to Microsoft Excel. The quantitative data was coded and analysed using STATA v.14 (463). Statistical significance tests Fisher's exact (under 5 observations per group) and Chi-squared (5+ observations per group) tests were used for categorical variables (such as which type of MGUS surveillance procedure was preferred) and the students t-test for comparing scaled, normally distributed, data (such as familiarity with MGUS). Content analysis[i] was conducted on the open-text responses in Excel; which focused on GP/Trainee views on diagnosing and using surveillance with MGUS patients and challenges in supporting MGUS patients in primary care. Missing responses are detailed within the results tables and excluded from the analysis.

4.2.3 Ethical approvals for healthcare professional studies

Participation was voluntary, participants did not have to complete the survey and were not identifiable from the completed surveys. Hard copies were stored in a locked filing cabinet and soft copies stored on a Queens University Belfast password protected encrypted laptop within a secure alarmed building (Centre for Public Health, Queens University Belfast) and are available for independent inspection.

[i] Content analysis was described on page 192.

Ethical approval was granted from the School of Medicine, Dentistry and Biomedical Sciences Research Ethics Committee, Queen's University Belfast, Appendices 13 &15.

4.3 Results

This results section reports on two surveys; Irish haematology professionals (the Haematology survey) and the international survey of GPs and GP trainees (the GP survey) reporting on their experiences of MGUS and MGUS care. Table 4-1 highlights the study information and the main topics discussed in each.

Table 4-1 Healthcare professional study information and main topics.

	Haematology survey	**GP survey**
Conference/Survey	Haematology Association Ireland (HAI)	World Organization of National Colleges, Academies and Academic Associations of General Practitioners/Family Physicians (WONCA)
Survey Size	54	58
Survey modality	Paper-based	Online
Occupations of respondents	Consultant haematologists Junior doctors (haematology) Nurses Specialist nurses Allied Health professionals	GP GP Trainee
	Topics	
Diagnosis of MGUS	✓	✓
Describing MGUS	✓	✓
Risk (to malignancy)	✓	✓
Information Leaflets	✓	✓
Knowledge of MGUS	✗	✓
Signs and Symptoms	✗	✓
Supports for MGUS	✗	✓

4.3.1 Haematology Survey

4.3.1.1 Demographics

In total, 55 surveys were collected at the conference. One respondent was removed from the analysis; as they were not a healthcare professional as per the inclusion/exclusion criteria, Table 4-2. Respondents were primarily based in the Republic of Ireland (ROI) (n=41/54; 75.9%), with the remainder based in Northern Ireland (NI) (n=13/54; 24.1%). The majority of respondents were doctors (n=32/55; 58.1%); with consultant haematologists comprising half of this population (n=16/32). 57% of nursing attendees (n=21/54; 38.9%) were clinical nurse specialists (n=12/21). There was one allied health professional.

The higher proportion of ROI participants was likely due to the all-Ireland conference being held in ROI, between 3-5 hours travel for the majority of NI HCPs, Table 4-2. Most respondents encountered MGUS patients a daily/weekly basis (63.0%, n=34/54) and had small numbers of MGUS patients with their clinic (<50 patients) (n=23/47; 48.9%), Table 4-2.

4.3.1.2 MGUS diagnosis

Most HCPs informed "all patients" they had MGUS using the terms "MGUS" or "monoclonal gammopathy of undetermined/uncertain significance" (n=38/48; 79.2%)[i]. Informing the patient of their diagnosis is common medical practice and expected in most conditions.

"I believe most patients want to know and take some ownership. Also, it allows patients to educate themselves." ***(Consultant 7, ROI)***

For HCPs who reported not informing "all patients", patients who were not informed were elderly with co-morbid dementia or lacked significant cognitive capacity (n=6/9; 67.7%). HCPs explained their rationale of not informing patients as MGUS

[i] 6 respondents were excluded as they stated informing patients of their diagnosis was not applicable to their job role (nurse/allied healthcare professional).

being a lesser concern to these patients (due to other co-morbidities) and lessened understanding/capacity (in patients) meant this information was deemed as unnecessary by the HCP.

*"Not all patients have cognitive ability to retain complex info. Some families will request limited information. Other impending clinical concerns may preclude disclosure. "***(Junior Doctor 4, ROI)**

"Usually tell younger, interested or inquisitive patients in detail. Older patients with poor understanding-, do not give in depth detail." ***(Junior Doctor 10, NI)***

The terms "premalignant" or "precancer" were used by a minority of HCPs (9%, n=5/54), of which none were consultant grade haematologists. Clinicians used lay language to inform patients of their daignosis, with two-thirds using terms "abnormal protein" or "increased/high protein" to describe MGUS. HCPs also used analogies such as; "*like a mole we need to watch*" or "*finding a paraprotein is a bit like finding a lump"* to describe MGUS. These analogies were used as metaphors or compared to similar aliments by some HCPS to help explain what MGUS was to patents; as shown below.

"MGUS is a premalignant condition, which is your body is making defective proteins against some unknown enemy" **(Junior Doctor 13, ROI)**

*"I sometimes explain to patients that finding a paraprotein is a bit like finding a 'lump' and needing to investigate further whether benign or malignant - generally patients find this concept easier to understand. "(***Consultant 4, ROI)**

4.3.1.3 Informing patients on the risk of progression to a haematological malignancy.

Most respondents (38/54; 68.5%) reported telling 'all patients' about the associated risk of progressing to a haematological malignancy, while 13.0% (n=7/54) did not

inform patients[i], Table 4-2. Those informing patients stressed the low risk of progression and explained the reasoning for continued follow-up to patients. Some respondents (n=9/54; 16.4%) used numerical values to express the risk of progression; predominantly 1% per year reported by the Mayo clinic (118). HCPs explained the benefits and risks of providing risk information to patients and their use of clinical judgement/experience.

"You have some cells in your blood which are making a little too much protein. This will probably not cause you any harm, but you need to be followed up long-term". ***(Consultant 6, NI)***

[To patients] "All patients should be aware of the possibility of progression that would mean beginning of treatment and not just wait and watch." ***(Consultant 10, ROI)***

"Explain small risk of progression to a malignant disease multiple myeloma. They will look up on internet and find out or better to tell and in most cases, say risk is low." ***(Consultant 6, NI)***

"Some elderly patients- who may become very anxious and find this risk (of progressing to cancer) quite distressing ". ***(Specialist Nurse 11, ROI)***

One respondent stated that they avoid using the terms progression to "cancer" or "malignancy" and instead describe progression to a "*blood condition*" unless the patient enquires further; when progression to *"a type of blood cancer"* is discussed.

"Don't tend to say cancer or malignancy, [I] tend to say, "Blood Condition" or if they push it I might say "a type of blood cancer." ***(Consultant 15, ROI)***

[i] All respondents were non-physicians (n=4 nurses, n=2 specialist nurses and n=1 allied healthcare professional).

4.3.1.4 HCP views on MGUS surveillance.

All HCPs[i] recommended surveillance for MGUS patients with a split on surveillance frequency (3-4 months, 6 months or annually). Some suggested risk of progression should influence surveillance intervals.

HCPs differed on whether to review all patients frequently (n=27/51; 52.9%), only intermediate/high risk patients (n=11/51; 21.6%) or by primary care (n=7/51; 13.0%). In total, six respondents favoured a combined approach involving a mix of primary care (low risk) and haematology care (intermediate/high risk Table 4-2. Others proposed telephone-based nurse-led follow-up (10%, n=5) to reduce the stress for *"well patients*" of attending clinic appointments. Watch and wait/active surveillance was highlighted as a potential source of psychosocial difficulty for patients, with MGUS patients representing *"a hugely neglected cohort of patients from a nursing input"* **(Specialist Nurse 12, ROI)**.

"Frequency of attending hospital should be determined by stratified risk - high risk --> hospital; telephone clinic/community - intermediate/low." ***(Specialist Nurse 12, ROI)***

*"Depending on co-morbidities, haematology follow-up may not be needed - but annual full blood count and MGUS assessment is reasonable - sometimes in primary care. "****(Consultant 7, ROI)***

"Clinic appointments create unnecessary stress to well patients." ***(Nurse 7, NI)***

4.3.1.5 Working with Primary Care/GPs.

Respondents highlighted a lack of MGUS awareness outside of haematology; especially in primary care. HCPs believed GPs required additional support to avoid over-diagnosing and over-referring patients to haematology with abnormal serum protein electrophoresis results. HCPs recommended easy to understand guidelines

[i] 3 respondents (nurses) were excluded as they stated this was not part of their role.

for detecting and acting on paraprotein detection and education on signs and symptoms (of progression) as steps to improve primary care integration. This could reduce *"unnecessary anxiety*" in referrals and reduce the burden on haematology services.

"The overall awareness among GPs and other health care professionals on MGUS is generally poor". ***(Consultant 14, ROI)***

GPs don't understand this [MGUS] and need support to avoid over diagnosing myeloma [and MGUS]" ***(Consultant 5, ROI)***

"With the ageing population nationally, assessment for MGUS happens more frequently and integration with haematology to develop guidelines on when to test (for paraproteins) because often knowledge of paraprotein can cause unnecessary anxiety". ***(Consultant 7, ROI)***

4.3.1.6 Usage of informational materials by clinicians.

Less than half (42.6%, n=23/54) of respondents provided all MGUS patients with an information leaflet at diagnosis; with many only providing leaflets if requested (n=15/54 27.8%) or not at all (n=13/54; 24.1%), Table 4-2. Nurses (specialists and general) were significantly more likely to give an information leaflet to all patients than doctors (p=0.03). Respondents raised concerns about the lack of appropriate information leaflets (n=2) and difficulties accessing these resources (n=2).

"We have no access to info leaflets". ***(Nurse 9, ROI)***

[On whether to give an information leaflet at diagnosis] "If [an information sheet] is in the clinic". ***(Junior Doctor 9, ROI)***

Respondents highlighted the difficulties in explaining MGUS to patients, who have difficulties in understanding their condition. A patient-friendly information leaflet was proposed to help patients.

"Many patients find it difficult to understand what MGUS actually means; they have not been well-informed. Patient-friendly information leaflet would be useful".

(Consultant 14, ROI)

Table 4-2 Summary of survey responses. Haematology survey

	ROI n=41 (75.9%)	NI n=13 (24.1%)	p-value*
Position			0.015*
Consultant	13 (31.7)	3 (23.1)	
Junior Doctor	15 (36.6)	1 (7.7)	
Specialist Nurse	9 (22)	3 (23.1)	
Nurse	3 (7.3)	6 (46.2)	
Allied Healthcare professional	1 (2.4)	0	
Frequency of encountering MGUS patients			0.664
Daily	6 (14.6)	1 (7.7)	
Weekly	22 (53.7)	5 (38.5)	
Monthly	7 (21.8)	4 (30.8)	
Never	4 (10.9)	2 (15.4)	
Prefer not to say	2 (5.5)	1 (7.7)	
Number of patients in their clinic			0.255
0-50	16 (40.0)	7 (53.9)	
51-100	13 (32.5)	1 (7.7)	
101-200	7 (17.5)	2 (15.4)	
Prefer not to say	4 (10)	3 (23.1)	
Do you tell patients they have MGUS?			0.196
Yes, all patients	31 (77.5)	7 (58.3)	
Yes, some patients	6 (15.0)	2 (16.7)	
No	3 (7.5)	3 (25.0)	
Missing	1	1	
Do you tell MGUS patients about risk of progression?			0.149
Yes, all patients	29 (70.7)	8 (66.7)	
Yes, some patients	8 (19.5)	1 (8.3)	
No	4 (9.8)	3 (25.0)	
Missing/other	0	1	

	ROI n=41 (75.9%)	NI n=13 (24.1%)	p-value*
Do you give MGUS patients an information leaflet?			0.247
Yes, all the time	16 (41.0)	7 (58.3)	
Only if the patient asks	14 (35.9)	1 (8.3)	
Never	9 (23.1)	4 (33.3)	
Missing/Other	2	1	
Do you recommend that MGUS patients are followed-up?			0.008*
Yes, all MGUS patients should be followed up frequently	22 (53.7)	5 (38.5)	
Yes, intermediate/high risk MGUS patients	9 (22.0)	2 (15.4)	
Yes, but followed-up in primary care	7 (18.2)	0 (0)	
Combination	3 (7.3) [i]	3 (23.1)[ii]	

[i] Two clinicians recommended "Yes, intermediate/high risk MGUS patients" and "Yes, but followed-up in primary care". One clinician recommended "Yes, all MGUS patients should be followed up frequently" and "Yes, intermediate/high risk MGUS patients"

[ii] Three clinicians recommended "Yes, intermediate/high risk MGUS patients" and "Yes, but followed-up in primary care".

4.3.2 GP Survey

In total, 58 respondents participated in the GP survey, Table 4-3. All respondents were registered GP/Family physicians (n=35) or trainee GP/Family physicians (n=23). Respondents practiced medicine in 25 different countries worldwide[i]. GPs were majority urban-based, male, had over 10 years' experience (post-graduation) and involved in large practices (over 1000 patients) including 1-10 MGUS patients, Table 4-3. GP trainees were majority female, urban-based, had under 5 years' experience, and involved in large practices (over 1000 patients) including 1-10 MGUS patients, Table 4-3. The only significant difference between GPs and Trainees was experience post-graduation; which was expected, Table 4-3.

[i] Respondents were based in Portugal (n=8), UK (n=6), Spain (n=6), Ireland (n=4), Greece (n=3), Croatia (n=3), Serbia (n=2), Lithuania (n=2), Luxembourg (n=2). Single respondents practiced in Brazil, Finland, Hong Kong, Indonesia, Israel, Lebanon, Mexico, Romania, Saudi Arabia. Sweden, Switzerland, Tunisia, Turkey and the United States.

Table 4-3 Demographic Information GP survey

Question	GP Trainee n=23 (100%)	GP n=35 (100%)	p-value*
Current Job			n/a
Registered GP/Family Physician	0 (0)	35 (100)	
Registered GP/Family Physician trainee	23 (100)	0 (0)	
Sex			0.147
Male	10 (43.5)	13 (37.1)	
Female	13 (56.5)	22 (62.9)	
Years working as a GP/Family Physician (or trainee) since completing medical degree?			0.001**
0-5 years	20 (87.0)	5 (14.3)	
6-10 years	2 (8.7)	11 (31.4)	
11-20 years	0	13 (37.1)	
More than 20 years	1 (4.3)	6 (17.1)	
Location of Practice			0.410
Rural	5 (21.7)	10 (28.6)	
Metropolitan/urban	17 (73.9)	25 (71.4)	
Prefer not to say/Not applicable	1 (4.3)	0 (0)	
N of patients within the GP practice			0.825
0-500 patients	2 (8.7)	1 (2.9)	
501-1000 patients	1 (4.3)	2 (5.7)	
1001-2000 patients	9 (39.1)	16 (45.7)	
2001+ patients	11 (47.8)	16 (45.7)	
N of MGUS patients within the GP practice			0.191
0 (none)	3 (13.0)	5 (14.3)	
1-10 patients	6 (26.1)	18 (51.4)	
11-50 patients	3 (13.0)	2 (5.7)	
51+ patients	0	1 (2.9)	
Don't know/Prefer not to say/Not applicable	11 (47.8)	9 (25.7)	

4.3.2.1 MGUS diagnosis and surveillance

Most GPs/Trainees believed that patients should be referred to haematology if a M-protein was detected, Table 4-4. GPs/Trainees felt they had limited expertise/experience with MGUS and wanted haematology assistance to confirm diagnosis. After referral to haematology and patients were attending the GP clinic, GPs/Trainees did not feel confident discussing MGUS with newly diagnosed patients. In particular, no trainee reported being confident in discussing MGUS with a newly diagnosed patient, Table 4-4.

"In my case I refer that patients to haematology to decide what to do. I don't have knowledge enough to manage these patients" ***(GP Trainee 7, Portugal)***

"Probably an initial check to the Haematologists should be done for each and every patient." ***(GP Trainee 1, Romania)***

On surveillance, GPs and Trainees favoured frequent surveillance (annually/biennially for life), Table 4-4. GPs/Trainees believed that haematologists were the most effective for MGUS surveillance but supported primary care surveillance for at least some patients; either themselves within a practice (74.5%) or through a nurse-led telephone clinic (74.5%), Table 4-4.

"I have to know well something for me to feeling comfortable. And that's why I would send to specialist. But I would prefer having a consultant by phone or mail." ***(GP 29, Portugal)***

"I think (a nurse-led clinic) may be a fastest way and enough for some patients" ***(GP 16, Croatia)***

However, there were some concerns about introducing a telephone clinic to patients, as this may be interpreted as not providing adequate (physical and psychosocial) care for patients.

"[Regarding a nurse-led clinic] "A phone communication at least in the beginning is not a good choice as the patient would interpret it like "no one wants to receive me and explain what is happening". After the situation is being controlled maybe a phone communication would be an option." ***(GP 7, Spain)***

Most GPs/Trainees (60%) were unfamiliar with MGUS in general and lacked awareness of the signs/symptoms of progression to malignancy, Table 4-4 and Figure 4-1. However, they also felt that they were not able to care for every condition that arises in primary care and this should be considered in future service provision.

*"I have limited knowledge and would not be able to advise on exact monitoring and long term consequences (of MGUS)" (***GP 24, UK)**

"GPs cannot be expected to look after every rare condition and interpret subtleties in results" ***(GP Trainee 18, Ireland)***

Over 85% of GPs and Trainees were unaware of MGUS patient information leaflets, despite generally providing patients with these leaflets for other conditions, Table 4-4.

"Unfortunately there are no available information leaflets on disease/diagnosis [of MGUS]." ***(GP trainee 1, Romania)***

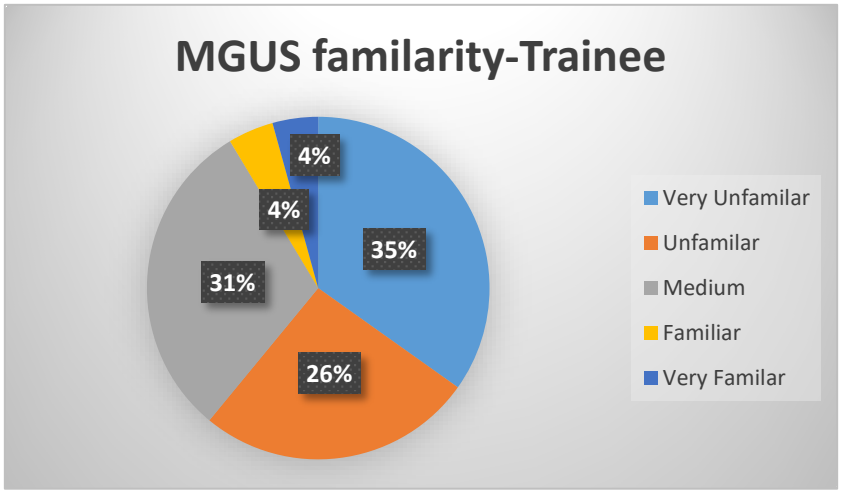
"Not on MGUS but patients with some of the most common conditions like hypertension or diabetes when they are diagnosed or have some questions. Also to children with acute conditions like gastroenteritis." ***(GP Trainee 22, Portugal)***

Table 4-4 MGUS diagnosis and surveillance

Question	Trainee Number (%)	GP Number (%)	p-value*
Do you think patients with a monoclonal (M) protein irrespective of the isotype/size, should be referred to haematology for further investigations?			0.344
Yes, all patients	16 (69.6)	19 (54.3)	
Yes, some patients	2 (8.7)	9 (25.7)	
No	0	1 (2.9)	
Don't know	5 (21.7)	6 (17.1)	
Would you feel confident discussing MGUS with a newly diagnosed patient?			0.072
Yes	0	6 (18.8)	
No	19 (100.0)	26 (81.3)	
Missing	4	3	
Which healthcare providers would be most effective at following-up MGUS patients?			0.714
General Practitioners	3 (13.0)	5 (14.3)	
Haematologists	10 (43.5)	11 (31.4)	
Haematology Nurses	0	2 (5.7)	
Community nurses	0	0	
All of the above	3 (13.0)	8 (22.9)	
Don't know	2 (8.7)	4 (11.4)	

Question	Trainee Number (%)	GP Number (%)	p-value*
Would you be willing to follow-up low/low-intermediate* risk MGUS patients solely within your GP/Family practice?			0.868
Yes, all patients	5 (27.8)	8 (26.7)	
Yes, some patients	9 (50.0)	17 (56.7)	
No	4 (22.2)	5 (16.7)	
Missing	5	5	
Would you support a nurse led MGUS telephone clinics within your practice?			0.681
Yes, for all patients	7 (38.9)	16 (51.6)	
Yes, for some patients	7 (38.9)	10 (32.3)	
No	4 (22.2)	5 (16.1)	
Missing	5	4	
What treatment/surveillance should be used for MGUS patients?			0.994
Reviewed frequently (annually/biennially for life)	10 (43.5)	17 (48.6)	
Reviewed for the first 2 years and if no changes, no further follow-up is required	2 (8.7)	3 (8.6)	
Placed on "watch and wait" (i.e. active surveillance with no treatment prescribed)	9 (39.1)	10 (28.6)	
Prescribed treatment to reduce symptoms and to reduce risk of progression	0 (0)	3 (8.6)	
Don't know	5 (21.7)	9 (25.7)	

Question	Trainee Number (%)	GP Number (%)	p-value*
How familiar with the term "MGUS"?			0.854
1 (not very familiar/never heard of it)	8 (34.8)	11 (31.4)	
2	6 (26.1)	10 (28.6)	
3	7 (30.4)	10 (28.6)	
4	1 (4.3)	3 (8.6)	
5 (Very familiar)	1 (4.3)	1 (2.9)	
Are you aware of any signs/symptoms that may be indicate progression in MGUS patients?			0.218
Yes	6 (26.1)	17 (48.6)	
No	9 (39.1)	8 (22.9)	
Don't know	7 (30.4)	10 (28.6)	
Are you aware of the existence of MGUS patient information leaflets?			0.392
Yes	1 (5.3)	5 (15.6)	
No	18 (94.7)	27 (84.4)	
Missing	4	3	
Do you provide information leaflets to all patients who ask for information on their diagnosis?			0.930
Yes, all patients	4 (20.0)	7 (21.9)	
Yes, some patients	11 (55.0)	15 (46.9)	
No	5 (25.0)	10 (31.3)	
Missing	3	3	



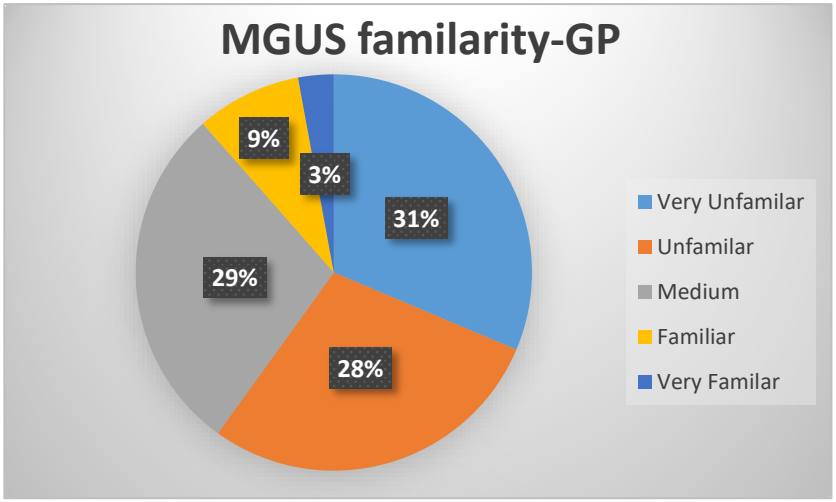


Figure 4-1 GP/Trainee familiarity with MGUS

4.3.2.2 Knowledge of MGUS

GPs/Trainees' MGUS knowledge was poor, with many not aware of what MGUS was or the increased risk of cancer; especially for lymphoplasmacytic lymphoma/ Waldenström's macroglobulinemia (15.5%), Table 4-5.

To assess knowledge, 3 questions were asked regarding what MGUS is, the average age of diagnosis and the biological/diagnostic profile; with only 19% of GPs/Trainees correctly answering all three questions, Figure 4-2. GPs were more likely than trainees to answer all three correctly (p=0.036), Table 4-5.

"I don't think I know enough about the disease and its treatment/surveillance to enlighten patients." **(GP 17, Portugal)**

Table 4-5 GP/Trainee knowledge on progression to cancer in MGUS.

Question[i]	**Trainee Number (%)**	**GP Number (%)**	**p-value***
MGUS patients have an increased risk of developing cancer.			0.774
True^^	15 (65.2)	21 (60.0)	
False	1 (4.3)	4 (11.4)	
Don't know	7 (30.4)	10 (28.6)	
Which cancers do you think MGUS patients have an increased risk of progressing to?			
Multiple myeloma^^	13 (56.5)	16 (45.7)	0.430
Polycythaemia Vera (myeloproliferative disorder)	4 (17.4)	3 (8.6)	0.418
Kaposi sarcoma (multi-centric vascular tumour)	0	0	
Lymphoma	5 (21.7)	7 (20.0)	0.873
Lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia^^	4 (17.4)	5 (14.3)	0.749
Pseudomyxoma peritonei (very rare digestive cancer)	0	0	
Leukaemia	1 (4.3)	5 (14.3)	0.386
Myelodysplastic syndromes	8 (34.8)	6 (17.1)	0.125
Don't know	1 (4.3)	3 (8.6)	

[i] ^^ denotes a correct answer.

Question	Trainee Number (%)	GP Number (%)	p-value*
What is MGUS?[i]			0.501
A malignant plasma cell disorder characterised by the presence of monoclonal (M) protein in the serum/urine.	4 (17.4)	5 (14.3)	
A very rare blood disorder caused by multiple protein abnormalities which may be genetic in nature.	3 (13.0)	8 (22.9)	
A pre-malignant plasma cell disorder characterised by the production of monoclonal (M) protein.	13 (56.5)	18 (51.4)	
A condition characterised by cytopenia and which arises from poorly developed or dysfunctional blood cells.	1 (4.4)	2 (5.7)	
Don't know	6 (26.1)	8 (22.9)	
Individuals in which age group are most likely to be diagnosed with MGUS?			0.693
Individuals aged <30 years old	1 (4.4)	1 (2.9)	
Individuals aged 30-50 years old	2 (8.7)	6 (17.1)	
Individuals aged ≥50 years old^^	11 (47.8)	18 (51.4)	
All of the above	1 (4.4)	0	
Don't know	8 (34.8)	10 (28.6)	

[i] Some respondents had more than one answer.

Question	Trainee Number (%)	GP Number (%)	p-value*
Which one of the following profiles is most consistent with a diagnosis of MGUS?			0.030*
Serum monoclonal protein **<30g/l,** clonal bone marrow plasma cells <10%, and **no evidence of end-organ damage^^**	3 (13.0)	12 (34.3)	
Serum monoclonal protein **≥30g/l,** clonal bone marrow plasma cells <10%, and **no evidence of end-organ damage**	8 (34.8)	2 (5.7)	
Serum monoclonal protein **≥30g/l,** clonal bone marrow plasma cells <10%, and **evidence of end-organ damage**	3 (13.0)	7 (20.0)	
Serum monoclonal protein **<30g/l,** clonal bone marrow plasma cells <10%, and **evidence of end-organ damage**	0	1 (2.9)	
Don't know	9 (39.1)	13 (37.1)	
Do you think MGUS is a common blood condition within the general population?			0.336
No, very rare	1 (4.4)	6 (17.1)	
No, rare ^^	16 (69.6)	17 (48.6)	
Yes, common	3 (13.0)	4 (11.4)	
Yes, very common	0	0	
Don't know	3 (13.0)	8 (22.9)	

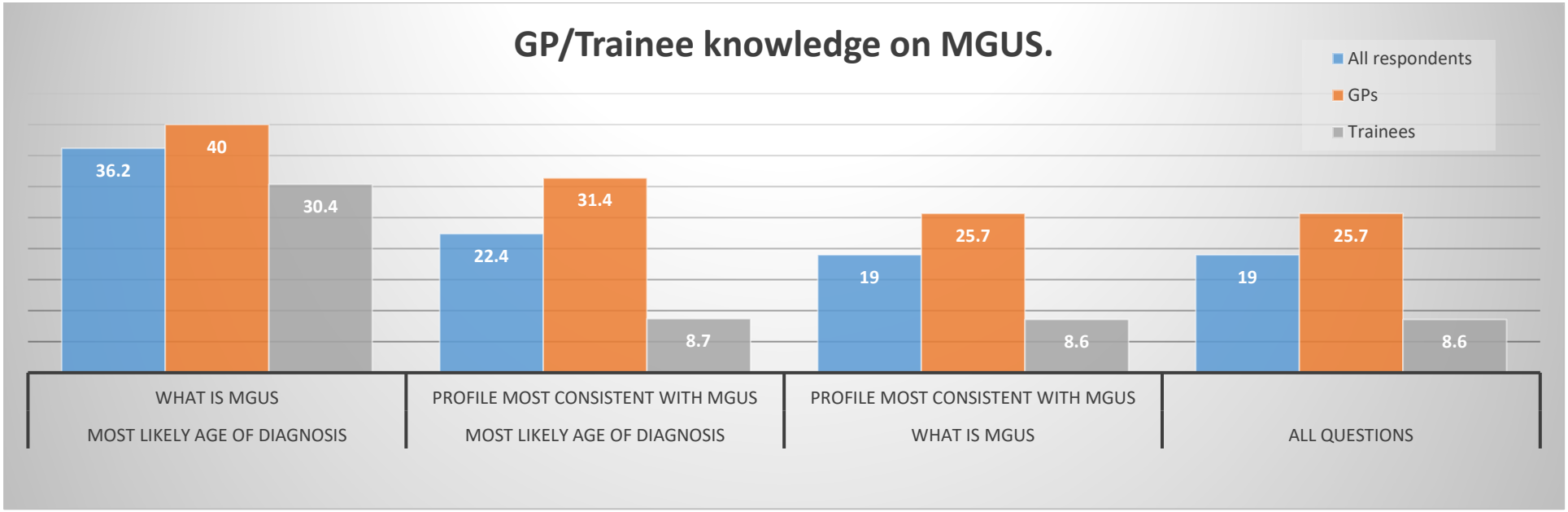


Figure 4-2 GP/Trainee knowledge on MGUS.

4.3.2.3 Supports for Primary Care

To assist in the development of services for GPs, we asked what clinical supports would be most useful for assisting surveillance. Haematology providing information leaflets to patients at diagnosis to advice patients and GPs was supported, Table 4-4. Most GPs/Trainees were unaware that MGUS patient information leaflets are available (88.2%).

Other useful clinical supports were alerts by the clinical software system or the blood profile laboratory report that there were indications of possible MGUS and direct telephone contact from haematology, Table 4-4. GPs/Trainees were also able to provide some open-text responses of what clinical supports they found useful.

"Detailed information on the diagnostic criteria, follow-up parameters and detailed information for patients (diagnostic, risks etc.)" ***(GP Trainee 1, Romania)***

"Funding. E.g. A locally enhanced service or commissioned federation service." ***(GP 2, UK)***

Table 4-6 Clinical Supports for HCPs

Which of the following options could usefully assist you in following-up MGUS patients in your practice?[i]	**Trainee Number (%)**	**GP Number (%)**	**P value**
Alert by the clinical software system used within your practice	9 (39.1)	17 (44.8)	0.479
Laboratory report on a blood profile alerting to possible MGUS/blood malignancy	12 (52.2)	25 (71.4)	0.136
Direct telephone call from the laboratory/haematology team	11 (47.8)	17 (48.6)	0.956
Information leaflet from haematology team at time of patient diagnosis	10 (43.5)	20 (57.1)	0.308
Access to a website or app	6 (26.1)	16 (45.7)	0.132
All of the above	3 (13.0)	10 (28.6)	0.165
Don't know	3 (13.0)	3 (8.6)	0.673

[i] Respondents who replied "all of the above" were included in each option to show their support for specific options.

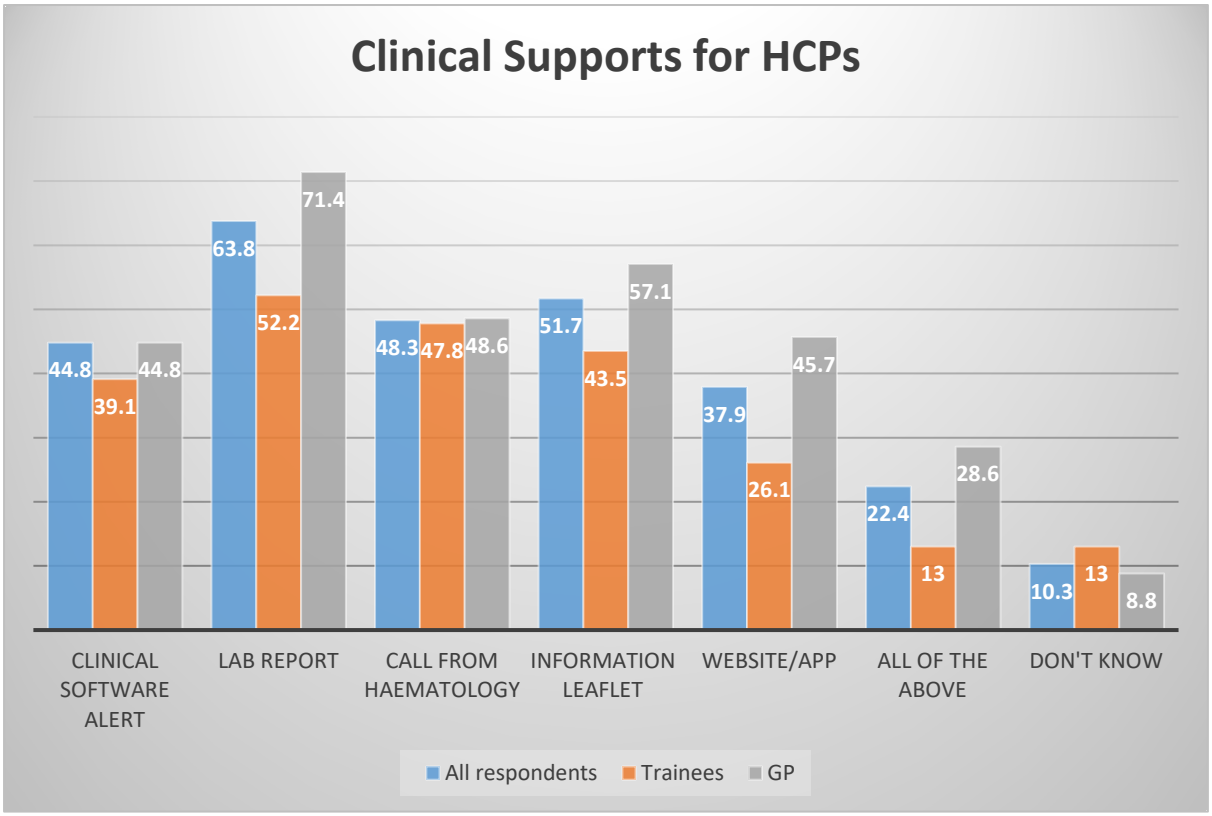


Figure 4-3 Clinical supports for HCPs.

4.4 Discussion

4.4.1 Overview

These surveys provided a unique insight into the challenges and experiences of HCPs in MGUS care; previously unexplored in the published literature. Haematology professionals reported communicating the MGUS diagnosis to most patients (some were not informed due to cognitive difficulties) and reported using metaphors/simplifications when appropriate to help explain the condition. HCPs reported using varied terminology to describe MGUS. Most haematology professionals informed patients about the progression risk to cancer. In general, GPs/Trainees had a poor comprehension of this risk for patients.

The results demonstrate that GPs and trainees have a low level of knowledge and awareness of MGUS. This was found in relation to the signs/symptoms of progression (to cancer) and average age of diagnosis. Furthermore, the findings indicated low utilisation of resources such as patient information booklets across both specialities (haematology and primary care).

This discussion focuses on a short discussion of the 3 main themes; MGUS knowledge, informing patients, and active surveillance; with the findings integrated in Chapter 6.

4.4.2 MGUS knowledge (GP survey only)

Only 11.5% of GPs and 8.6% of GP trainees were quite or very familiar with the term MGUS. This was supported by less than 20% of GP respondents answering the knowledge-based questions correctly (Table 4-5 and Figure 4-2). This was lower for GP Trainees, which indicates that experienced GPs are more likely to know about MGUS. Poor HCP knowledge contributes to diagnosis delays for haematological conditions (466). As MM is consistently preceded by MGUS (164), diagnostic delays can reduce the possibility of early action to delay MM stage progression. While there has only been preliminary studies on early treatment in MM, the results are promising for SMM patients (467), any delay in diagnosing MGUS may contribute to poorer long-term survival. However, as MGUS (and SMM) are commonly

observed/under active surveillance rather than treated, treatment may not necessarily be given sooner to these patients (467).

Improving educational resources and improved supports for GPs/Trainees is a key clinical application of this research. Due to the infrequent presentation of MGUS, any supports need to be easy to access and incorporated into routine clinical practice. Respondents were clear that most patients with an M-protein should be referred as they felt too inexperienced to diagnose patients. Knowing the correct procedures and ordering the appropriate immunoglobulin test was a challenge for GPs (468). One suggestion was clinical software to identify when a referral (to haematology) was required. This would be on either the GP clinical management system used or highlighted on laboratory reports. This type of clinical software is partly utilised within Northern Ireland through the electronic care record (ECR), which holds all healthcare data on one system; which is strongly supported by NI clinicians (469). It is evident from the results that incorporating this in future clinical practice could assist in providing MGUS surveillance through primary care.

4.4.3 Informing patients

Three areas were highlighted by haematology professionals and GPs as important when informing patients of their diagnosis; the terminology used, communicating risk and providing information resources. These were similarly highlighted in the previous studies (Chapters 2&3) as important parts of the care experience which affected patients' wellbeing.

The results indicated that predominantly haematology consultants and junior doctors informed patients of their diagnosis. Clinicians used the term "monoclonal gammopathy of undetermined significance" for most patients. Patients who were not informed were generally determined as cognitively unable to process the diagnosis; due to comorbid dementia or low educational attainment. Haematology professionals reported using simplified language and analogies such as "abnormal or raised protein" to describe MGUS. However, using different terminology can confuse

patients and cause misunderstanding, as shown in the systematic review in DCIS (342–344,358) and the AiMs study (Chapter 3).

The systematic review (Chapter 2) identified similar issues in other premalignancy conditions on HCP communication about (350); specifically explaining the condition to patients and not having access to information leaflets/materials at diagnosis (356,358,359).

The term precancer has been highlighted previously as potentially "creating a new disease from risk factor" (470). Only 5 haematology HCPs (9%) used the term premalignant or precancer when describing MGUS to patients (4 junior doctors and one nurse). The systematic review (342–344,358) and precancer consensus statements (163) highlighted that premalignant conditions terminology is variable and can cause confusion for patients. However, when doing research in the area, it is difficult to use other terms. When classifying the premalignant conditions into taxonomies, Berman and Henson (163,238), the term precancer was used as it could be applied to multiple disciplines and be widely understood. When naming the survey of all premalignant conditions (the psychosocial impact of premalignant conditions; PIP survey) described in Chapter 5, we were aware of the potential issues in using the terminology but decided that it was the most appropriate for disseminating the survey. However, care was used to promote the survey per condition (such as MGUS, SMM or Barrett's oesophagus) in light of this issue.

Information leaflets are one of the most frequent sources of healthcare information for patients (434,435) and are important supports to encourage shared decision making (471). This is especially relevant for MGUS patients as there are can be long intervals (6 months-2 years) between appointments and is considered a difficult condition for patients to understand, by patients (Chapter 3) and haematology professionals (haematology survey) (471). Some haematology respondents reported discussing sections of the leaflets with patients, which may provide a better diagnostic experience for future patients (471).

MGUS patient information leaflets are available from organisations such as Bloodwise and Myeloma UK. The National Cancer Patient Experience Survey 2016 (NCPES) (445) reported 92% of haematological malignancy patients received

information leaflets; compared to 70.4% (haematology) and 71.1% (GP) of HCPs in MGUS. GPs linked this to low awareness of the availability of these supports.

4.4.4 Risk of progression

Risk of progression was a prominent fear for MGUS patients (Chapter 3: AiMs study), with a progression rate of approximately 1% per annum for the remainder of patient's lives (43). The content of the message and the source of risk information are important influences can have a large influence on individual's reactions (472). Informing patients of their risk of cancer requires strong communication skills and confidence from the HCP to avoid negative experiences; such as fear and unnecessarily increased uncertainty and anxiety (473,474). Risk information can be distressing but is viewed as important for some premalignancy patients (343,344,347,350,356) but low importance to others (357–359).

Haematology HCPs reported being clear with patients of the low risk of progression and that MGUS was unlikely to develop into a malignancy. For some respondents (primarily nurses), the discussion of risk of progression to cancer was less common, with many indicating that it was the role of the doctor.

It is important for GPs to have a working knowledge of what MGUS is and risk of progression to cancer when treating MGUS patients; particularly the signs and symptoms that patients should be aware of which can indicate progression. Communication with patients and ensuring that progression is detected early through their healthcare team (including GPs) are the key messages that patients outlined with the AiMs study (Chapter 3). That many GPs and trainees were unaware of the increased risk of cancer (Table 4-5); especially multiple myeloma indicates that further work is needed to upskill GPs.

4.4.5 Active surveillance in MGUS

MGUS guidelines advocate patients undergo active surveillance approximately twice per annum for the rest of patient's life post diagnosis (12). Both surveys supported

continued surveillance but differed on how to provide surveillance. Haematology professionals were divided evenly between; haematology departments conducting all surveillance; and a division of intermediate/high risk patients being seen in haematology with lower risk patients being followed up in primary care; as supported by Mayo clinic guidelines (25). Both haematology and GP/trainees highlighted the importance of identifying high and low risk MGUS patients and ensuring that only suitable (low-risk) patients were transferred to primary care surveillance.

GPs and trainees supported nurse-led telephone clinics (32) and following low/low-intermediate risk patients in primary care, with abnormal blood findings in lower risk patients referred to haematology. Most GPs/trainees felt that they could provide MGUS surveillance, with appropriate technological and specialist (haematology) support. The AiMs (Chapter 3) and Rawstron *et al* (32) studies showed patients supported nurse-led telephone clinics. As the majority of GPs also supported this service (for at least some patients), this could be explored as a new surveillance strategy in the UK and further afield.

While the AiMs study highlighted the acceptability of the telephone clinic in a UK (state-sponsored) healthcare system, it may be less acceptable at pay at point of access (i.e. private insurance in the USA) systems. Reduced hospital admissions and specialist care can lead to decreased hospital funding and insurance rebates (475–477). Therefore, it is important to consider the cultural context when interpreting the results and the role that free healthcare can play on this. The survey responses indicate that many HCPs would find it acceptable within their clinics; but only one respondent was based in the USA.

4.4.6 Strengths and Limitations

No previous research has been published on HCP awareness of MGUS or their preferences for surveillance. These surveys included a variety of specialities, job roles and international diversity to accurately assess MGUS care from different HCP perspectives. By utilising two different cohorts of HCPs (haematology-based and

general practice physicians), the surveys were able to focus on the aspects most relevant to each specialty (diagnosing and informing patients for haematology professionals: knowledge and future directions/supports for general practice). This multi-lens perspective can be used depicted the care pathway of MGUS and outlined gaps in MGUS car; such as poor information provision and a need for increased haematology and primary care integration/co-operation. Research across healthcare specialities is rare, and these combined findings are a vital component in discovering more of how the condition is treated and a viable future direction for service provision and research (457).

Conducting two separate studies had positive and negative aspects. Employing the sequential design was useful in developing the previously under-researched topic of MGUS care. By assessing the haematology perspective initially, issues were identified which may have affected both the primary care survey and potential integration of surveillance between the specialties in the future. Haematology staff identified issues in the knowledge of GPs and trainees and this led to including questions within the GP survey on recognising the signs and symptoms of progression (to cancer) in MGUS patients and what cancers is MGUS related to a heightened risk.

Self-report was used for haematology respondents to describe how they inform patients of an MGUS diagnosis; rather than a more controlled procedure measure such as an observation study. The use of self-report lay language was therefore envisioned to give respondents an avenue to expand on how they inform patients about MGUS. In self-report instruments, clinicians may be more likely to describe how they inform patients as per clinical guidelines (478,479); rather than what is actually communicated to patients. Response bias in self-report data is a common phenomenon in healthcare research, including social desirability bias (480). To reduce this bias, respondents completed the survey themselves (rather than with an interviewer) and were informed the survey was anonymous (480).

Using online survey companies such as SurveyMonkey (465) increases the diversity and reach of respondents, are more economically viable for under-researched and low funded topics and easy to disperse through social media, especially through

organisations such as WONCA and influential social media personalities (481)[i]. As MGUS is a relatively niche condition, with low symptom burden, it is not a pressing concern for many haematology or general practice staff. Despite the recruitment efforts of the study team, it was a difficult topic to disseminate and generate buy-in and low numbers were recruited for both surveys.

When conducting research in previously unresearched areas, it is more financially and time efficient to address the hypothesis using a small and convenient sample (482). However, the low number of respondents means that the results must be interpreted with caution and any conclusions are limited by the small sample and lack of representativeness. This can provide quick results but imprecise estimates (482).

The initial plan for the research was to conduct focus groups to explore how clinicians communicated with MGUS patients, including terminology use. This has been completed in other hard-to-research areas (483). However, this was attempted by the research group and closed due to a lack of interest from the HCPs. Future research should include qualitative interviews with HCPs in MGUS care (including haematology nurses, haematologists and GPs).

Replicating and extending this study in other domains and contexts is necessary to test the applicability of the findings. However, the findings provide an insight into the perspectives of GPs and trainees and the methodology used provided valuable lessons in social media dissemination; which were implemented in Chapter 5: The Psychosocial impact of a Premalignant condition (PIP) study.

[i] The role of social media dispersal is commented upon more within the online patient study (Chapter 5).

4.5 Chapter Conclusion

In conclusion, the role of healthcare professionals in MGUS care is vital but there are barriers that may reduce the efficacy of patient care; specifically, in GP/trainee knowledge and how surveillance is conducted. The differences between haematology staff and GPs show that improved communication between the specialities is required but the implementation of support aids can lead to a better patient experience. Further discussion about how these findings can improve the knowledge of the role of healthcare professionals in MGUS care and how this relates to the patient studies is located in Chapter 6: Discussion.

5 Chapter 5: The impact of an MGUS/SMM diagnosis. Results from the Psychosocial impact of a Premalignant condition study (PIP)

5.1 Introduction

No large-scale psychosocial wellbeing or QoL-related study has been conducted on MGUS. The limited available evidence suggests that living with MGUS may impact on wellbeing, but only one unpublished study utilised validated instruments (SF-12) (484); thus demonstrating a need for robust data collection in this area. This chapter presents the findings of a survey which aimed to measure and explore the psychosocial well-being and QoL of patients living with MGUS. In response to the lack of psychometrically validated measures available in premalignant conditions (as discussed in Chapter 2) to measure needs in this population; a survey was constructed to measure the nature and prevalence of needs identified and described in Chapters 2 and 3, Figure 5-1.

The survey was disseminated using online methods in order to ensure widespread dispersal, lower costs, real-time tracking and anonymity of respondents (457). Online surveys are increasingly utilised to access hard to reach and difficult to recruit populations (452,453,485,486); as MGUS had proved to be in Chapter 3: AiMs study.

In order to draw accurate conclusions regarding the psychosocial well-being of patients, it was important to compare and contrast findings with the 'normal'[i] population and/or other patient comparator groups. SMM was chosen as the main comparator to MGUS in this study due to the similar biological make-up, asymptomatic presentation and care pathway. SMM patients have a higher risk of progression to cancer, with 10% of SMM patients progressing per annum (27) versus 1% of MGUS patients per annum (19). In order to assess the psychosocial impact of MGUS, we also compared MGUS to other premalignant conditions. These conditions, such as Barrett's oesophagus, monoclonal B cell lymphocytosis and cervical intra-epithelial neoplasia (a full list of eligible conditions is located in Table 2-1 page 54) were selected as comparators. The systematic review highlighted that premalignant

[i] 'Normal' is defined as population norms from the literature. The population norms used are described per questionnaire within the methods section, page 242.

condition patients shared similar issues in adjusting to and living with their condition. The evidence suggests that the uncertainty and complex reactions of a possible cancer progression would be psychosocial similar across premalignant conditions; similar to cancer worry from different cancer screening programs (487). However, it was important that the varying physical and symptom differences between premalignant conditions were taken into account when making comparisons between asymptomatic MGUS patients and other premalignant conditions (such as Barrett's oesophagus) which have symptoms.

This study aimed to measure the psychosocial impact of MGUS (and other premalignant conditions including SMM) using a series of validated instruments and additional questionnaire items developed from the previous dissertation chapters.

5.1.1 Research Aims

- What is the psychosocial wellbeing (anxiety and depression) and QoL impact of being diagnosed with MGUS?
- To compare the psychosocial health and wellbeing and QoL of premalignant patients using validated instruments to population norms.
- To compare the psychosocial health and wellbeing and QoL of MGUS patients to patients diagnosed with SMM and other premalignant conditions, using a series of validated questionnaires and a researcher-developed survey.
- To compare premalignant patient (MGUS, SMM and other premalignant condition) scores from validated QoL and psychosocial wellbeing measures to population norms.
- To identify unmet needs, if any, among patients diagnosed with MGUS or SMM using open ended questions.

This relates to all of the research questions[i].

[i] Research questions outlined, Page 20.

5.2 Methods

5.2.1 Development of the Questionnaire

The survey was developed from identifying the main challenges and issues from the previous research studies in the dissertation and combining this with the most common validated questionnaires utilised in the premalignant literature. A total of 78 questions were included; in four distinct sections identified as core to understanding the impact of MGUS/SMM. The creation matrix of the questionnaire is located at Figure 5-1 and a copy of the survey in Appendix 19.

Section 1 included items to measure the demographic and characteristics of the sample. There were 22 questions in this section, which included; participants age, gender, country of healthcare, previous cancer history (personal and blood relatives) and educational attainment.

Section 2 included items to measure the role of healthcare interaction. There were 16 questions in this section, which included; participant's age at diagnosis, prior illness, surveillance (frequency, rating and where their surveillance was conducted), provision of written information, understanding of their condition and how they utilised the internet for accessing information.

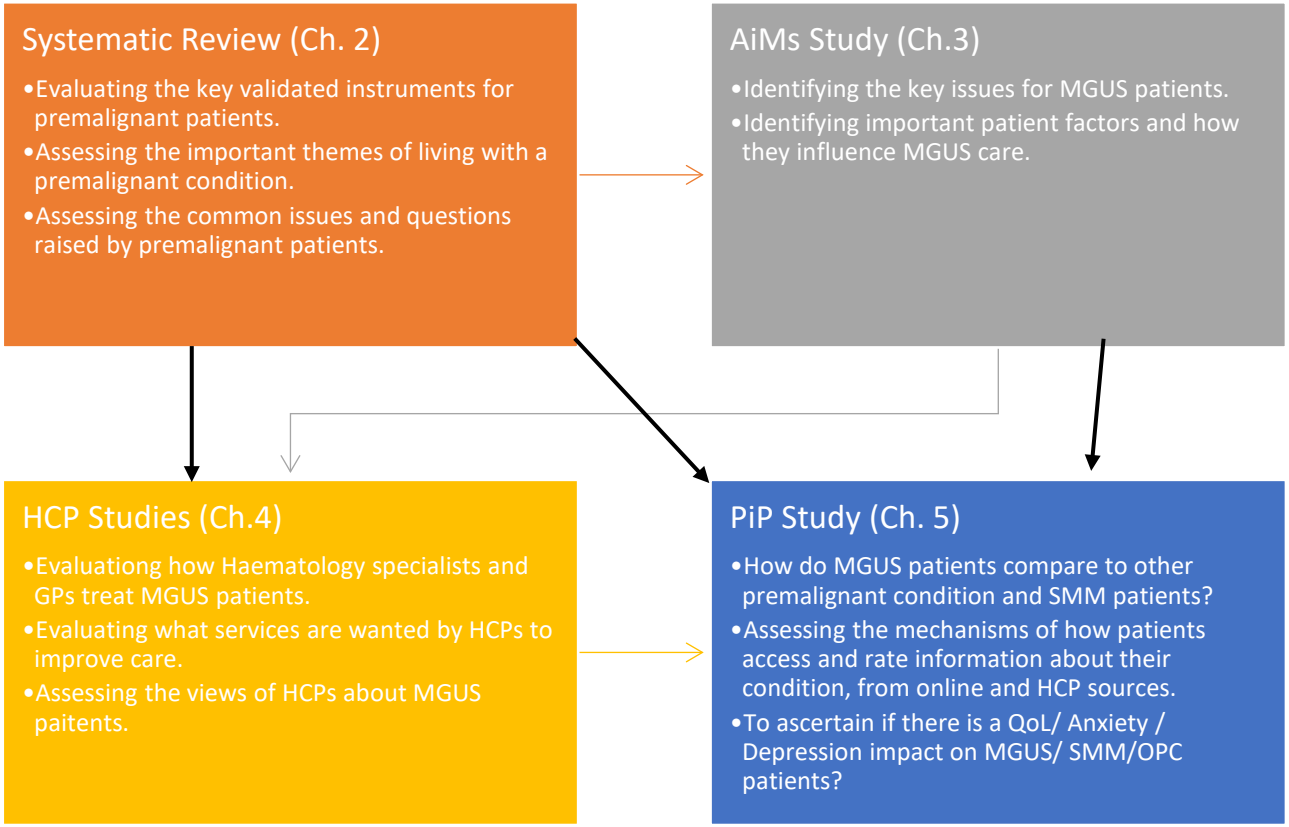
Section 3 included items to measure the psychosocial impact of their premalignant condition. There were 8 questions in this section, which included; their lifestyle changes (as a result of their condition), if they sought a second opinion, how often they thought about their condition, had they informed their family/friends and their communication with HCPs.

Section 4 included the validated questionnaires utilised. These were the SF12v2 (488) (12 questions), EQ-5D (214) (6 questions) and HADS (218) (14 questions); which were discussed in Chapter 2 (page 61).

Patients and clinicians were involved in designing the study and finalising the questionnaire by providing feedback and guidance on the important issues and relevant information required. The questionnaire was circulated to the members of the PPI advisory panel and their advice was also sought on how to disseminate the study and developing connections with charity partners (such as the Barrett's

Wessex, a prominent UK regional patient support & education charity and Bloodwise, a UK-based blood cancer charity).

The questionnaire was piloted amongst a researcher-chosen cohort of healthy individuals with a range of age and educational attainment levels before being launched online. The pilot group assessed if closed questions had sufficient response categories available, whether the language had appropriate readability and that any open question was understandable; as per best practice guidelines (489). The pilot group also assessed any technical issues when piloting the questionnaire in SurveyMonkey (490).



[i] MGUS: Monoclonal gammopathy of undetermined significance. SMM: Smouldering Multiple Myeloma. QOL: Quality of Life. OPC: Other Premalignant condition

Figure 5-1 Creation of the PIP Study[i]

5.2.2 Inclusion/Exclusion

- Individuals completed a screening question to assess their eligibility to take part in the study. Patients who did not have a premalignant condition were screened out using SurveyMonkey exclusion methods; if they answered they did not have a premalignant condition. If patients who completed the survey were later deemed ineligible (as per inclusion/exclusion criteria), their data was removed from the analysis. This is detailed within the results (124 participants were excluded).

Inclusion

- Have a diagnosis of MGUS, SMM or other premalignant condition.
- Patients were eligible to participate at any point of the post-diagnosis pathway (newly diagnosed to long term follow-up).
- Over the age of 18 years.

Exclusion

- Patient did not report a premalignant condition.
- Patient reported a previous cancer directly related to their premalignant condition (example: reporting an MGUS/SMM diagnosis and later stating they had multiple myeloma, the malignant form)
- Patients with severe psychosocial or medical co-morbidities, e.g. Psychosis, Alzheimer's disease or Multiple Sclerosis.
- Patient under the age of 18 years.
- Patient who did not complete at least one validated questionnaire.
- Patients who did not provide consent (on online questionnaire).

5.2.3 Sampling

The survey launched on 5th February 2018 and the data was collected in January 2019. The survey was disseminated exclusively online through social media and charity organisations internationally using Twitter/Tweeting influential individuals/organisations, contacting relevant Facebook groups and working with

charities to promote the study. While the study includes many premalignant conditions, such as Barrett's oesophagus, cervical intraepithelial neoplasia (CIN) and ductal carcinoma in situ (DCIS), the primary focus of the research was on MGUS and SMM patients and promotion of the study focused on these patient groups.

The aim was to recruit >75 patients per condition to ensure that moderate differences between conditions could be detected (491): 64 patients per group would have 80% power to detect a statistically significant (at the two-sided 5% level) difference in the mean of the validated QOL measure with 0.5 standard deviations between conditions. This was completed using G-Power calculations (491) under the advice of a senior statistician (Dr. Chris Cardwell).

Prominent researchers, known as "influencers", were contacted with links to the survey asking for retweets and sharing on Twitter. Influencers are identified as key individuals/accounts on social media, who had multiple (>100) followers involved in premalignant or cancer research were targeted. Similar methods for Twitter recruitment have been used previously in cancer studies (452,453). Some examples of the influencers contacted were Dr. Ola Landgren (@DrOlaLandgren), Dr. Robert Z. Orlowski (@myeloma_doc), the Mayo clinic (@mayomyeloma) and @MGUS_Info (a patient account with many followers). Examples of the tweets are as follows:

- We want to hear the experiences of #MGUS #SMM patients. (LINK) Please RT.
- Please RT Want to support our work into #Precancer? Help us understand your views (weblink)
- We are doing a survey into quality of life in #MGUS patients (LINK)

Further examples of tweets are in Appendix 18 (PIP protocol).

Facebook

- Facebook patient support/information groups were identified through Google, Facebook and Twitter searching, expert advice from the PPI group and snowballing from participant's responses (an option was available for patients to indicate where they found the survey link). These 'groups' were

contacted using an approved scripted message to the administrator of the group or an email (if possible).

- This message outlined a description of the survey, a request to join the group and sought permission to post a link (maximum of twice as a requirement of ethics) to the survey within the 'group'. If the administrator did not feel it appropriate for the researcher to join the 'group' (to protect privacy), administrators were asked to post the message in the 'group' on behalf of the research team. Similar methods have been used in cancer research (485,486). A Facebook profile and page were created to publicise the survey. In total, the study was a "member" of 8 MGUS/SMM/MM related groups despite '33 groups' being contacted about the study.

Charities and blogs

Several charities and blogs posted information about the study:

- Bloodwise, a UK Blood cancer charity, @Bloodwise_res also posted about the study on their social media.
- Margaret's Blog (https://margaret.healthblogs.org/2018/02/16/your-help-is-needed-for-the-first-large-scale-survey-on-mgus-and-smm-patients-experiences-and-quality-of-life/), popular patient blog.
- Watch and Wait Blood cancers (https://www.watchandwaitbloodcancers.com/), a research information site headed by Dr. Terry Golombick (prominent blood cancer researcher).

These platforms/blogs posted about the survey, using the template (Appendix 18). Previous research for clinical trials (492) and cancer research (485,486,493) have used Facebook and blogs to disperse their research and recruit participants.

5.2.4 Data analysis

5.2.4.1 Quantitative analysis

Analyses were undertaken as per instrument published methodologies (SF12v2, EQ-5D, HADS) (207,221,494) using STATA v.14 (463), as described on page 61.

Group scores were compared with published population norms (UK and USA norms), comparing MGUS patients with SMM and OPC (other premalignant condition) by total and dimension scores in the validated instruments (EQ-5D and HADS) using t-tests, ANOVAs and logistic and linear regressions adjusting for potential confounders[i] (gender, educational attainment, race, time since diagnosis, age, healthcare location and if they had a significant comorbidity) where appropriate.

The EQ-5D was stratified into two groups, chosen by dichotomisation of the participants' mean age and the population norm groups in the literature (495). Both the UK and US crosswalk values were included (495) to show the variability of the measures. The UK value is considered the worldwide standard as it is the oldest and most commonly utilised tariff (496).

The SF12v2 was analysed using software developed by QualityMetric Incorporated (488). This software provided accurate scaling and comparison to 2009 USA norms. These norms have not been published separately. The output from this software was imported to STATA for further analysis, in line with the other questionnaires.

Subscale and component scores in the EQ-5D and SF12v2 were analysed using linear regression, while all other regressions were logistical regressions after passing the assumptions needed for regression (normal distribution, linear relationship between independent and dependant variables, reliable measurement and homoscedasticity) (497). Missing data was excluded from any percentages presented, marked clearly with each table and participants with missing data were excluded from regression

[i] Confounders included within the models were age (continuous variable), sex (male; female), educational attainment (non-university; university), race (white; other), time since diagnosis (<1 year; 1-2 years; 3-5 years; 5+ years), comorbidity (heart attack, heart disease, diabetes, stroke, lung disease, autoimmune condition, liver disease, previous cancer) (yes, no)

analysis. The STROBE guidelines were used to guide the quantitative elements of the chapter (498) (Appendix 20).

5.2.4.2 Qualitative analysis

Researchers aimed to present insightful and transparent themes from the open-ended questions, which were relevant to clinical practice:

- Do you have any concerns about your diagnosis?
- Are there any additional services or supports you would like to put in place for people with your condition?
- Have you made any lifestyle changes since your diagnosis?
- Can you tell us more about why you sought a second opinion on your diagnosis? (Example: Who did you receive the second opinion from, why did you seek a second opinion, etc.).

Inductive thematic analysis was the qualitative paradigm chosen for analysis (418). Thematic analysis was chosen as content analysis was deemed inadequate to infer the theoretical relationships between concepts that were highlighted in the previous work (Chapter 3) (450). Summative content analysis was inappropriate as the purpose of the questions were to infer meaning rather than identifying or quantifying word use (499) and as the sample was anonymous and online, it was impossible to check the meanings of alternative words and intended meaning through patient validation (399,450).

The spectrum of experiences reported in premalignant conditions in the systematic review and Chapter 3 indicated a more comprehensive method of analysis (such as thematic analysis) to provide the context for differences between MGUS and SMM was required.

The previous lack of theory or previous research in MGUS meant that using an inductive methodology was appropriate and was linked to the data (393,418). The

methodology of analysis -using the Nowell et al (392) framework for describing the qualitative process- and researcher reflexivity was described in Chapter 3, page 152. The Consolidated Criteria for Reporting Qualitative Studies (COREQ) (426) was used to guide the reporting of the qualitative elements of the study (Appendix 17).

5.2.5 Governance

Participation was voluntary and participants had the right to withdraw from the study at any stage prior to commencing the online survey. However, once a response was submitted to the online survey, it was not possible for the participants to remove their data from the dataset; due to the anonymous format of the survey. The IP address capturing feature in SurveyMonkey was disabled to anonymise the participant's location.

Data was held in SurveyMonkey cloud data servers, which may be located outside the European Union however for "compliance with European personal data export requirements SurveyMonkey have been certified under the EU-US Privacy Shield Program." https://help.surveymonkey.com/articles/en_US/kb/SurveyMonkey-Data-Transfers-and-EU-Laws.

All completed surveys were stored on a Queens University Belfast password protected encrypted laptop within a secure alarmed building (Centre for Public Health, Queens University Belfast) and are available for independent inspection. Survey responses are retained for at least 5 years, in line with university policy, post data analysis. Patients were advised to contact their healthcare team if they had any issues as a result of participating in the study.

5.2.6 Collaborators

This study was conducted collaboratively as part of an interdisciplinary research team with guidance from supervisors Anderson, Santin and Donnelly and inputs from Dr. McShane; who is leading a programme of research on MGUS and SMM, Dr McMullan, a patient representative and Prof. Brian Johnston, a clinician specialising in gastroenterology.

5.2.7 Ethics

Ethical approval was granted from the UK Office for Research Ethics Committee (Reference: 17/EM/0390) through proportionate review.

5.3 Quantitative Results

The results are split into 4 sections; focusing on the aims of the study with MGUS patients compared to SMM and OPC patients:

- Demographics (Table 5-1)
- Healthcare Interaction (Table 5-3)
- Impact of diagnosis (Table 5-5)
- Validated questionnaires; HADS, EQ-5D & SF12v2 (Table 5-6, Table 5-7, Table 5-8 & Table 5-9).

5.3.1 Demographics

In total, 478 individuals completed the survey (Figure 5-3) with 354 patients included in the analysis; 171 MGUS (48.3%), 60 SMM (n=16.9%) and 123 OPC[i] patients (34.8%).

Overall, 124 patients were excluded due to; not having a premalignant condition (n=50), not completing at least 1 validated questionnaire (n=39), not providing consent (n=14), having a previous related cancer (n=17) or having a severe co-morbidity (such as dementia, HIV or MS) (n=4) , Figure 5-3. Excluded individuals were similar to included individuals on all confounders.

The overall included sample was predominantly female and white; with a mix of educational attainment and country of healthcare provision, Table 5-1. One third had a major comorbidity[ii] and patients were on average 54 years old. Most patients lived in the US (41.8%) or UK (37.5%), however many countries were represented including; Australia (n=17), Canada (n=15) and Italy (n=11) across all continents, Figure 5-2.

---

[i] The other premalignant conditions (OPC) group was comprised of a mix of premalignant conditions (n=123); Barrett's oesophagus (BO) (n=81), monoclonal B cell lymphocytosis (n=15), cervical intra-epithelial neoplasia (CIN) (n=9), ductal carcinoma in situ (DCIS) (n=5), vulvar intra-epithelial neoplasia (VIN) (n=3), gastric premalignancies (n=4), colorectal polyps (n=3), actinic keratosis (AK) (n=2) and lobular carcinoma in situ (LCIS) (n=1).

[ii] Comorbidities were classified having or have had a; heart attack, heart disease, diabetes, stroke, lung disease, any autoimmune condition, liver disease or previous cancer.

Figure 5-2 Map of included patients. Included countries in red.

There were a number of differences between MGUS patients and the comparator (SMM and OPC) patients. MGUS patients were more likely than OPC patients to; live in the UK (rather than the US), have a co-morbidity, been diagnosed in a GP surgery (compared to a hospital/specialist) and reviewed in a "cancer centre". MGUS patients were less likely to have been ill prior to diagnosis and have multiple hospital appointments, Table 5-1. MGUS and SMM patients differed on age; with MGUS patients younger on average.

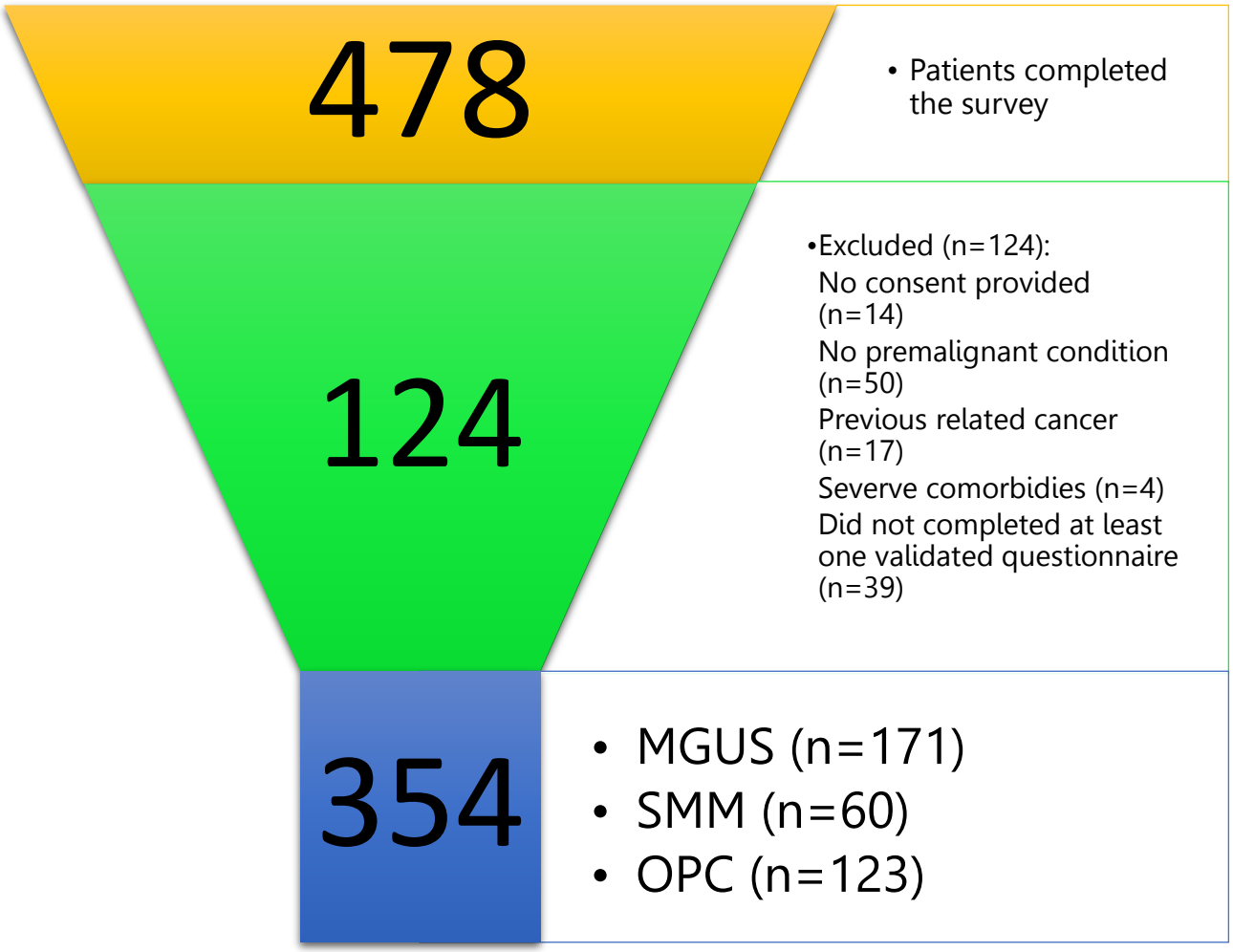


Figure 5-3 Flowchart of participants and reasons for exclusion

Table 5-1 Demographics tables of included MGUS, SMM and Other Premalignant condition (OPC) patients.

Premalignant condition	**MGUS**[i] **n= 171**	**SMM n=60**	**OPC**[ii] **n=123**
Sex			
Male	24 (14.0)	15 (25.0)	31 (25.2)
Female	147 (86.0)	45 (75.0)	92 (74.8)*
Missing	0	0	0
Age (years)			
Mean (SD)	54.3 (11.1)	57.5 (10.2)*	52.8 (12.8)
Min-Max	19-87	38-79	23-77
Missing	5	0	2
Age at diagnosis (years)			
Mean (S.D.)	50.3 (10.8)	53.7 (10.3)*	48.7 (13.1)
Range	17-75	34-75	22-76
Missing	1	1	0
Race			
White	166 (97.1)	54 (90.0)*	119 (96.7)
Other	5 (2.9)	6 (10.0)	4 (3.3)

[i] * p<0.05 ** p<0.001 compared to MGUS

[ii] OPC- Other Premalignant Condition

Premalignant condition	MGUS[i] n= 171	SMM n=60	OPC[ii] n=123
Time since diagnosis			
<1 Year	36 (21.1)	13 (21.7)	30 (24.4)
1-2 Years	30 (17.5)	10 (16.7)	19 (15.4)
3-5 Years	54 (31.6)	18 (30.0)	41 (33.3)
5+ Years	46 (26.9)	17 (28.3)	30 (24.4)
Missing	5 (2.9)	2 (3.3)	3 (2.4)
Educational attainment			
Non-University	83 (48.5)	21 (35.0)	60 (48.8)
University	79 (46.2)	35 (58.3)	55 (44.7)
Missing	9 (5.3)	4 (6.7)	8 (6.5)
Country of Healthcare			
UK	55 (32.2)	11 (18.3)	72 (58.5) **
US	78 (45.6)	29 (48.3)	43 (35.0)*
Other	37 (21.6)	18 (30.0)	17 (13.8)
Missing	1 (0.6)	2 (3.3)	2 (1.6)

Premalignant condition	MGUS[i] n= 171	SMM n=60	OPC[ii] n=123
Does the patient have any other major comorbidities?[i]			
No	49 (28.7)	23 (38.3)	51 (41.5)
Yes	113 (66.1)	33 (55.0)	64 (52.0)*
Missing	9 (5.3)	4 (6.7)	8 (6.5)
Was a second opinion sought?			
No	113 (66.1)	32 (53.3)	91 (74.0)
Yes	56 (32.8)	28 (46.7)	32 (26.0)
Can't remember/Prefer not to say	2 (1.2)	0	0
Was the patient ill prior to diagnosis?			
No			
Yes	60 (36.1)	29 (49.2)	59 (49.2)*
Don't Know	96 (57.8)	28 (47.5)	55 (45.8)
	10 (6.0)	2 (3.4)	6 (5.0)

[i] Comorbidities were classified having or have had a: Heart attack, Heart disease, Diabetes, Stroke, Lung disease, Any autoimmune condition, Liver disease or previous cancer (non-related cancer).

Premalignant condition	MGUS[i] n= 171	SMM n=60	OPC[ii] n=123
Location of Active Surveillance[i]			
Cancer Centre	58 (38.9)	24 (40.0)	8 (6.9)**
Consultant-led hospital appointment	67 (45.0)	31 (51.7)	86 (74.1)**
GP-led appointment	30 (20.1)	9 (15.0)	22 (18.9)
Not Reviewed	6 (4.0)	0 (0.0)	13 (11.2)*
Missing	22 (12.9)	0	7 (5.7)

[i] Some patients had more than one type of appointment.

Some patients had a previous (non-related) cancer[i] (14.4%) and the majority had a blood relative with a cancer (60.4%), Table 5-2. A higher than expected percentage of patients reported either having another premalignant themselves[ii] (17.2%) or having a blood relative[iii] (7.6%) with a premalignant condition.

[i] In total, 46 patients reported their cancer as; Skin (melanoma, basal & squamous) (n=21), breast (n=7), thyroid (n=6), uterine (n=3) prostate (n=1) and single cases of; cervical, endometrial, intestinal, lung, multiple myeloma (OPC patient), oral and testicular.

[ii] In total, 61 patients reported their other premalignant condition as; colorectal polyps (n=19), actinic keratosis (n=11), cervical dysplasia/CIN (n=11), Barrett's oesophagus (n=9), gastric premalignancies (n=7), DCIS (n=2) and single cases of MGUS and LCIS.

[iii] In total, 16 patients reported their blood relatives' premalignant condition; colorectal polyps (n=7), actinic keratosis (n=2), Barrett's oesophagus (n=2), CIN (n=2), MGUS (n=2) and one case of monoclonal B-cell lymphocytosis.

Table 5-2 Cancer history of participants and blood relatives.

Question	MGUS[i] n=171 (%)	SMM n=60 (%)	OPC n=123 (%)
Respondent previously diagnosed with a cancer[ii].			
Yes	28 (16.4)	6 (10.0)	17 (13.8)
No	130 (76.0)	49 (81.7)	98 (79.7)
Missing	13 (7.6)	5 (8.3)	8 (6.5)
Respondent having another premalignant condition			
Yes	26 (15.2)	7 (11.7)	28 (22.8)
No	90 (52.6)	40 (66.7)	69 (56.1)
Missing	55 (32.2)	13 (21.7)	26 (21.1)
Blood relative diagnosed with a cancer			
Yes	106 (62.0)	31 (51.7)	77 (62.6)
No	48 (22.0)	22 (36.7)	35 (28.5)
Don't Know	4 (2.2)	1 (1.7)	3 (2.4)
Missing	13 (7.6)	6 (10.0)	8 (6.5)

[i] * $p<0.05$ ** $p<0.001$ compared to MGUS

Question	MGUS[i] n=171 (%)	SMM n=60 (%)	OPC n=123 (%)
Blood relative diagnosed with a premalignant condition			
Yes	12 (7.0)	1 (1.7)	14 (11.4)
No	121 (70.8)	46 (76.7)	79 (64.2)
Missing	38 (22.2)	12 (20.0)	30 (24.4)

[i] * p<0.05 ** p<0.001 compared to MGUS

5.3.2 Healthcare Interaction

MGUS patients had longer intervals between surveillance appointments and rated their surveillance lower than SMM patients (Figure 5-4A): but had shorter intervals between surveillance appointments than OPC patients. Patients spoke to similar HCPs[i] about their condition. However, MGUS patients rated condition specific knowledge of HCPs outside their direct healthcare team lower than OPC patients, Table 5-3. Overall, many patients rated HCP knowledge as poor or fair (45.2%).

MGUS patients were less likely to receive an information leaflet about their condition at diagnosis compared to SMM patients, however overall only a small proportion of patients with a premalignant condition received an information leaflet (35.6%). MGUS patients were more likely to seek information online (and ranked the information available lower) than SMM patients (Figure 5-4B).

In general, patient understanding of their condition improved post-diagnosis; the percentage of individuals rating their understanding as poor/fair at diagnosis decreased from 46% (n=165) to 18.6% (n=66) currently. Similarly, 52.5% of patients rated their understanding currently as very good/ excellent, increasing from 24.3% after diagnosis. The majority of patients (81%) rated their current understanding at least "good" (Figure 5-4C).

[i] Specific specialities (such as haematologists in MGUS) were classified as "Consultant/Specialist".

Table 5-3 Patient's surveillance, contact with HCPs, information access and understanding of their condition.

Question	MGUS n=171	SMM n=60	OPC n=123	Adjusted OR[i] (MGUS vs SMM)	Adjusted OR (MGUS vs OPC)
How often between patient's surveillance appointments?					
1/3 Months	34 (19.9)	31 (51.7)	7 (5.7)	1.0	1.0
4/6 Months	67 (39.2)	22 (6.7)	12 (9.8)	4.44* (1.06 - 18.56)	1.19 (0.22 - 6.37)
7/12 Months	45 (26.3)	3 (5.0)	27 (22.0)	41.26** (5.04 - 338.02)	0.38 (0.07 - 2.22)
Multi-year follow-up	3 (1.8)	0 (0.0)	42 (34.1)		
New diagnosis	8 (4.7)	3 (5.0)	12 (9.8)		0.64 (0.08 - 5.50)
Missing/ *Trend*	13 (8.2)	1 (1.7)	23 (18.7)	<0.001**	<0.001**
Patient rating of surveillance					
Poor/Fair[ii]	69 (40.4)	10 (16.7)	44 (35.8)	1.0	1.0
Good	39 (22.8)	12 (20.0)	28 (22.8)	0.68 (0.16 - 2.87)	1.09 (0.38 - 3.17)
VG/Excellent	52 (30.4)	38 (68.3)	33 (26.8)	0.31 (0.09 - 1.07)	0.84 (0.30 - 2.32)
Missing/ *Trend*	11 (6.4)	0 (0.0)	18 (14.6)	0.048*	0.741

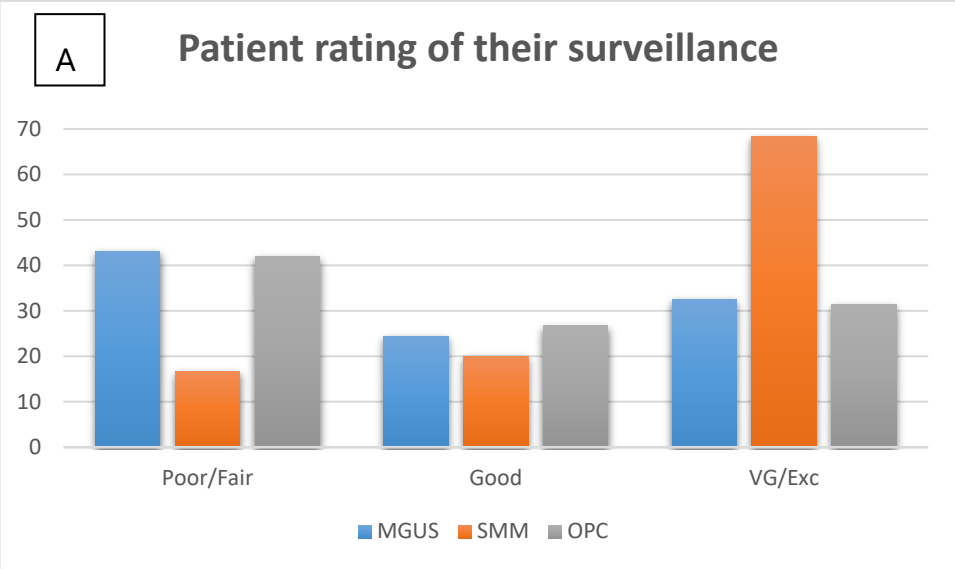
[i] *Adjusted for: Age, Gender (male; female), educational attainment (Non-college-college) and race (White; other), Time since Diagnosis (<1 Year; 1-2 Years; 3-5 Years; 5+ Years), Have a significant Comorbidity (No: Yes), Healthcare country (UK, USA, Other)

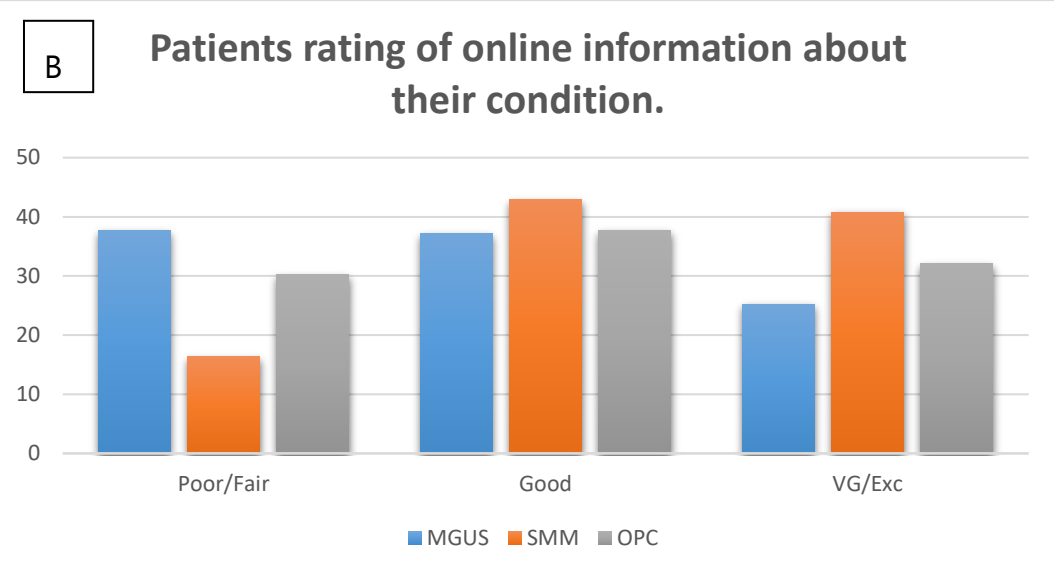
[ii] Combined due to small numbers

Question	MGUS n=171	SMM n=60	OPC n=123	Adjusted OR[i] (MGUS vs SMM)	Adjusted OR (MGUS vs OPC)
Which healthcare professional does the patients talk to the most about their diagnosis?					
GP	50 (29.2)	12 (20.0)	41 (33.3)	1.0	1.0
Consultant/Specialist	56 (32.7)	27 (45.0)	33 (26.8)	0.48 (0.20 - 1.14)	1.19 (0.62 - 2.30)
Other Healthcare	37 (21.6)	12 (20.0)	17 (13.8)	1.95 (0.34 – 2.69)	1.39 (0.63 – 3.04)
Not Spoken to a HCP	17 (9.9)	4 (6.7)	20 (16.3)	1.09 (0.29 – 4.12)	0.61 (0.27 - 1.41)
Missing	11 (6.4)	5 (8.3)	12 (9.8)		
How did patients rate healthcare professional's (outside of their healthcare team) knowledge of their condition?					
Poor	64 (37.4)	13 (21.7)	17 (13.8)	1.0	1.0
Fair	34 (19.9)	13 (21.7)	19 (15.4)	0.68 (0.27 - 1.73)	0.43 (0.19 - 1.01)
Good	10 (5.8)	8 (13.3)	14 (11.4)	0.40 (0.12 - 1.35)	0.14 (0.05 - 0.42)**
Very Good/Excellent	12 (7.0)	9 (15.0)	10 (8.1)	0.35 (0.11 - 1.10)	0.29 (0.10 – 0.87)**
N/A	41 (24.0)	16 (26.7)	48 (39.0)		
Missing/ *Trend*	10 (5.8)	1 (1.7)	13 (12.2)	p=0.307	P=0.055
Was there an information leaflet provided?					
Yes	53 (31.0)	26 (43.3)	47 (38.2)	1.0	1.0
No	113 (66.1)	30 (50.0)	73 (59.4)	2.46 (1.19 - 5.12)*	1.09 (0.63 – 1.91)
Can't remember	5 (2.9)	4 (6.7)	3 (2.4)		

Question	MGUS n=171	SMM n=60	OPC n=123	Adjusted OR[i] (MGUS vs SMM)	Adjusted OR (MGUS vs OPC)
Has the patient searched for information online of their condition?					
No	8 (4.7)	9 (15.0)	11 (8.9)	1.0	1.0
Yes	162 (91.7)	50 (83.3)	109 (88.6)	5.10 (1.59 – 16.30)*	2.58 (0.89 – 7.51)
Missing	1 (0.6)	1 (1.7)	3 (2.4)		
How do patient's rate the information available online on their condition?					
Poor/Fair	60 (35.1)	8 (13.3)	32 (26.0)	1.0	1.0
Good	59 (34.5)	21 (35.0)	40 (32.5)	0.31* (0.11 - 0.85)	0.71 (0.37 - 1.38)
Very Good/Excellent	40 (23.4)	20 (33.3)	34 (27.6)	0.30* (0.10 - 0.89)	0.58 (0.28 - 1.21)
N/A	9 (5.3)	10 (16.7)	14 (11.4)		
Missing/ *Trend*	3 (1.8)	1 (1.7)	3 (2.4)	P=0.849	P=0.959
How did patients rate their understanding of their condition prior to diagnosis?					
Poor	141 (82.5)	38 (63.3)	89 (72.4)	1.0	1.0
Fair	21 (12.)	13 (21.7)	16 (13.0)	0.57 (0.24 - 1.37)	0.47 (0.35 - 1.58)
Good/Very Good/Excellent	7 (4.1)	8 (13.3)	15 (12.2)	0.20* (0.06 - 0.69)	0.30* (0.11 - 0.83)
Missing/ *Trend*	2 (1.2)	1 (1.7)	3 (2.4)	P=0.438	P=0.081

Question	MGUS n=171	SMM n=60	OPC n=123	Adjusted OR[i] (MGUS vs SMM)	Adjusted OR (MGUS vs OPC)
How did patients rate their understanding of their condition after diagnosis?					
Poor	29 (17.0)	5 (8.3)	17 (13.8)	1.0	1.0
Fair	63 (36.8)	17 (28.3)	34 (27.6)	0.56 (0.17 - 1.84)	1.14 (0.51 - 2.52)
Good	42 (24.6)	18 (30.0)	36 (29.3)	0.50 (0.15 - 1.62)	0.55 (0.24 - 1.26)
Very Good/Excellent	34 (19.9)	19 (31.7)	33 (26.8)	0.53 (0.16 - 1.74)	0.61 (0.26- 1.42)
Missing/ *Trend*	3 (1.8)	1 (1.7)	3 (2.4)	P=0.618	p=0.279
How did patients rate their understanding of their condition currently?	43 (25.1)	6 (10.0)	17 (13.8)	1.0	1.0
Poor/Fair	55 (32.2)	15 (25.0)	26 (21.1)	0.70 (0.23 - 2.14)	0.66 (0.29 – 1.50)
Good	71 (44.5)	38 (63.3)	77 (62.6)	0.42 (0.14 - 1.22)	0.24** (0.11 - 0.53)
Very Good/Excellent	2 (1.2)	1 (1.7)	3 (2.4)	P=0.440	P=0.163
Missing/ *Trend*					


A
Patient rating of their surveillance
70
60
50
40
30
20
10
0
Poor/Fair
Good
VG/Exc
MGUS
SMM
OPC


B
Patients rating of online information about their condition.
50
40
30
20
10
0
Poor/Fair
Good
VG/Exc
MGUS
SMM
OPC

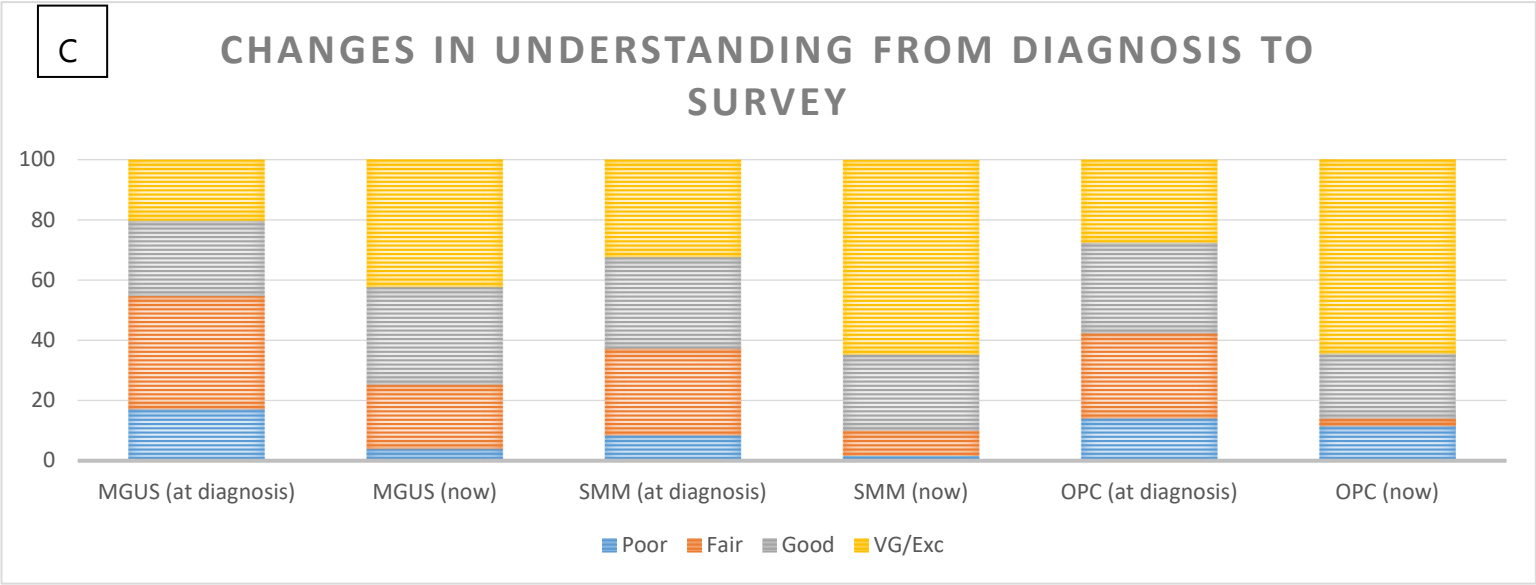


Figure 5-4: Differences by premalignant condition on; (A) patient rating of their surveillance, (B) Patient's rating of information, (C) Changes in understanding for patients over time.

The analysis showed that MGUS patients were most likely to want more information, although nearly all (99.4%) premalignant patients sought knowledge about their condition; predominantly their risk of progress to cancer, new scientific research and what do their test results mean (Table 5-3).

Compared to SMM patients, MGUS patients wanted more online information about; potential signs/symptoms, what investigations they should be getting and frequency of surveillance. Compared to OPC patients, MGUS patients wanted more information about; which tests they should get and their meaning, new research and the potential signs/symptoms (Table 5-4).

Table 5-4 What information do patients want about their condition?

Question	MGUS[i] n=171 (%)	SMM n=60 (%)	OPC n=123 (%)
What are my risks of progression for?	148 (90.8)	49 (87.5)	107 (92.2)
What do my test results mean?	143 (87.7)	46 (82.1)	79 (68.1)**
New scientific/medical research	137 (84.1)	48 (85.7)	84 (72.4)*
What symptoms/signs should I look out for?	133 (81.6)	36 (64.3)*	78 (67.2)*
What tests/investigations should I be getting?	126 (77.3)	36 (64.3)*	73 (62.9)*
How often should I be followed-up?	111 (68.1)	27 (48.2)*	83 (71.6)
Who gets (premalignant condition)?	88 (54.0)	29 (46.4)	53 (55.2)
Is (premalignant condition) common/rare?	77 (47.2)	24 (42.9)	62 (53.5)
None of above	1 (0.7)	1 (1.8)	0 (0)
Missing	7 (4.1)	3 (5.0)	7 (5.7)

[i] * $p<0.05$ ** $p<0.001$ compared to MGUS

5.3.3 Impact of Diagnosis

Three quarters of patients thought about their condition at least daily in the first year. SMM patients were more likely to think about their diagnosis than MGUS patients (p=0.42). Most patients changed their lifestyle because of their diagnosis (84.3%). This was contextualised in the qualitative evidence with patients describing increasing physical activity, improving their diet and making healthier lifestyles choices. MGUS patients were less likely to inform others about their condition and more likely to only inform their close-knit social groups than SMM or OPC patients (Table 5-5).

Table 5-5 Making life and cognitive changes because of their diagnosis.

Question [i]	MGUS	SMM	OFC	Adjusted OR[ii] (MGUS vs SMM)	Adjusted OR (MGUS vs OPC)
How often did patients think about their diagnosis in year one?					
Less than Daily	43 (25.1)	7 (11.7)	34 (27.6)	1.0	1.0
Daily	122 (71.3)	50 (83.3)	81 (65.9)	0.38* (0.15 – 0.97)	1.20 (0.66 – 2.18)
Missing	6 (3.5)	3 (5.0)	8 (6.5)		
How often did patients think about their diagnosis currently?					
Less than Daily	101 (59.1)	25 (41.7)	68 (55.3)	1.0	1.0
Daily	68 (39.8)	34 (56.7)	52 (42.3)	0.40* (0.19 - 1.84)	0.90 (0.51 – 1.57)
Missing	2 (1.2)	1 (1.7)	3 (2.4)		
Has the patient changed their lifestyle as a result of their diagnosis?					
No	29 (17.0)	5 (8.3)	12 (9.8)	1.0	1.0
Yes	103 (60.2)	47 (78.3)	97 (78.9)	0.47 (0.16 - 1.38)	0.56 (0.25 - 1.24)
Missing	39 (22.8)	8 (13.4)	14 (11.4)		

[i] * $p<0.05$ ** $p<0.001$ compared to population norms

[ii] Adjusted for: Age, Gender (male; female), educational attainment (Non-college-college) and race (White; other), Time since Diagnosis (<1 Year; 1-2 Years; 3-5 Years; 5+ Years), Have a significant Comorbidity (Yes; No), Healthcare country (USA, UK, Other).

Question	MGUS	SMM	OFC	Adjusted OR[i] (MGUS vs SMM)	Adjusted OR (MGUS vs OPC)
Has the patient informed anyone of their diagnosis?					
Anyone	22 (12.9)	19 (31.7)	38 (30.9)	1.0	1.0
Family only	32 (18.7)	9 (15.0)	15 (12.2)	3.00* (1.08 – 8.32)	3.54** (1.457 - 7.99)
Family and Friends	83 (48.5)	24 (40.0)	42 (34.1)	3.49** (1.54 – 7.91)	4.11** (2.09 - 8.09)
Partner or friends only	8 (4.7)	2 (3.3)	3 (2.4)	10.71* (1.51-75.97)	14.75** (2.73 – 79.65)
Other	21 (12.3)	4 (6.7)	16 (13.0)		
Missing/ Trend	5 (2.9)	2 (3.3)	9 (7.3)	P= 0.971	P=0.079

[i] Adjusted for: Age, Gender (male; female), educational attainment (Non-college-college) and race (White; other), Time since Diagnosis (<1 Year; 1-2 Years; 3-5 Years; 5+ Years), Have a significant Comorbidity (Yes; No), Healthcare country (USA, UK, Other).

5.3.4 Validated Instruments

5.3.4.1 Anxiety and Depression (HADS)

The HADS questionnaire measures anxiety and depression, with higher scores more indicative of clinical anxiety and depression (Table 5-6). MGUS and OPC patients reported high levels of clinically relevant anxiety and depression. SMM patients reported similar levels to population norms. MGUS patients had the highest levels of both clinical anxiety and depression. MGUS patients were nearly three times as likely to have moderate (or severe) anxiety and over 5 times more likely to have moderate (or severe) depression compared to the general population, Table 5-6.

Table 5-6 Clinically relevant anxiety and depression identified using the HADS questionnaire.

Question	Population norms[i]	MGUS	SMM	OPC	Adjusted OR[ii] (MGUS vs SMM)	Adjusted OR (OPC vs MGUS)
Clinical anxiety>8 (HADS)						
Not anxious	67%	57 (39.3)	29 (56.9)	53 (47.3)	1.0	1.0
Anxious	33%	88 (60.7) **	22 (43.1)	59 (52.7) **	2.19* (1.05 – 4.59)	1.36 (0.78 - 2.36)
Clinical anxiety>11 (HADS)						1.0
Not anxious	87.4%	94 (64.8)	44 (86.3)	77 (68.8)	1.0	1.24 (0.69 – 2.22)
Anxious	12.6%	51 (35.2)**	7 (13.7)	35 (31.2)**	3.13* (1.24 – 7.93)	
Mean score (SD)	6.14 (3.76)	8.7 (4.6) **	6.7 (4.0)	8.5 (4.7) **	1.12* (1.02 - 1.22)	1.02 (0.96 – 1.08)
Missing		25 (14.6%)	9 (15%)	11 (8.9%)		

[i] * $p<0.05$ ** $p<0.001$ compared to population norms

[ii] Adjusted for: Age, Gender (male; female), educational attainment (Non-college-college) and race (White; other), Time since Diagnosis (<1 Year; 1-2 Years; 3-5 Years; 5+ Years), Have a significant Comorbidity (Yes; No), Healthcare country (USA, UK, Other).

Question	Population norms[i]	MGUS	SMM	OPC	Adjusted OR[ii] (MGUS vs SMM)	Adjusted OR (OPC vs MGUS)
Clinical depression>8 (HADS)						
Not Depressed	88.6%	80 (54.4)	44 (84.6)	81 (74.3)	1.0	1.0
Depressed	11.4%	67 (45.6) **	8 (15.4)	28 (25.7) **	4.46** (1.75 –11.35)	2.34** (1.29 - 4.26)
Clinical depression>11 (HADS)						
Not Depressed	96.4%	1122 (76.2)	51 (98.1)	93 (85.3)	1.0	1.0
Depressed	3.6%	35 (23.8)**	1 (1.9)	16 (14.7) **	10.97* (1.40 –86.11)	1.64 (0.80 - 3.36)
Mean score (SD)	3.68 (3.07)	7.3 (4.2)**	3.8 (3.4)	4.9 (4.2)*	1.30** (1.16 - 1.47)	1.14** (1.06 - 1.22)
Missing		24 (14.0%)	8 (13.3%)	14 (8.9%)		

[i] * p<0.05 ** p<0.001 compared to population norms

[ii] Adjusted for: Age, Gender (male; female), educational attainment (Non-college-college) and race (White; other), Time since Diagnosis (<1 Year; 1-2 Years; 3-5 Years; 5+ Years), Have a significant Comorbidity (Yes; No), Healthcare country (USA, UK, Other).

5.3.4.2 QoL Measures- EQ-5D

The EQ-5D is a commonly used QoL instrument. Table 5-7 compares MGUS patients to SMM and OPC patients on the 5 dimensions. Table 5-8 compares MGUS patients to SMM and OPC patients and the three groups to population norms using the index (QoL) score.

MGUS patients were more likely to have 'slight' problems conducting their usual activities, Table 5-7. MGUS patients were more likely to have pain/discomfort compared to SMM patients (p=0.003) and more mobility issues compared to OPC patients (p=0.015).

Compared to population norms in both the UK and USA[i], MGUS and OPC patients had reduced QoL (except OPC patients >55 years compared to US norms) in both index and VAS scores. This difference was not present for SMM patients, Table 5-8.

[i] As per methods, the use of both crosswalk values when scoring the EQ 5D is best practice (495).

Table 5-7 Differences in EQ-5D dimensions by premalignant group.

Question	MGUS	SMM	OPC	Adjusted OR[i] (MGUS vs SMM)	Adjusted OR (MGUS vs OPC)
Mobility					
No problem	84 (49.1)	41 (68.3)	96 (78.0)	1.0	1.0
Slight problem	38 (22.5)	5 (8.3)	11 (8.9)	2.13 (0.60 - 7.53)	3.27* (1.11 - 9.68)
Moderate problem	30 (17.5)	6 (10.0)	3 (2.4)	2.97 (0.65 - 13.52)	13.10* (1.28 - 133.79)
Severe problem	8 (4.7)	4 (6.7)	5 (4.1)	1.13 (0.13 - 9.71)	2.39 (0.25 - 23.08)
Unable to move	2 (1.2)	0 (0)	1 (0.8)		
Missing	9 (5.3)	4 (6.7)	7 (5.7)		
Self-care					
No problem	132 (77.2)	50 (83.3)	106 (86.2)	1.0	1.0
Slight problem	21 (12.3)	5 (8.3)	7 (5.7)	1.71 (0.33 - 8.87)	1.51 (0.39 - 5.76)
Moderate problem	5 (2.9)	1 (1.7)	2 (1.6)		
Severe problem	1 (0.6)	0 (0.0)	1 (0.8)		
Unable to wash/dress	3 (1.8)	0 (0.0)	0 (0.0)		
Missing	9 (5.3)	4 (6.7)	7 (5.7)		

[i] Adjusted for: Age, Gender (male; female), educational attainment (Non-college-college) and race (White; other), Time since Diagnosis (<1 Year; 1-2 Years; 3-5 Years; 5+ Years), Have a significant Comorbidity (Yes; No), Healthcare country (USA, UK, Other).

Question	MGUS	SMM	OPC	Adjusted OR[i] (MGUS vs SMM)	Adjusted OR (MGUS vs OPC)
Usual activities					
No problem	60 (35.1)	39 (65.0)	89 (72.4)	1.0	1.0
Slight problem	53 (31.0)	7 (11.7)	13 (10.6)	3.57**(1.02 -12.45)	3.92* (1.31 - 11.72)
Moderate problem	30 (17.5)	8 (13.3)	6 (4.9)	1.97 (0.49 - 7.96)	4.74 (0.96 - 23.41)
Severe problem	13 (7.6)	1 (1.7)	8 (6.5)		3.09 (0.56 - 16.89)
Unable to perform	6 (3.5)	1 (1.7)	0 (0.0)		
Missing	9 (5.3)	4 (6.7)	7 (5.7)		
Pain/Discomfort					
No pain/discomfort	29 (17.0)	27 (45.0)	33 (26.8)	1.0	1.0
Slight pain/discomfort	56 (32.7)	16 (26.7)	51 (41.5)	3.06 (0.97 - 9.68)	2.06 (0.68 - 6.27)
Moderate pain/discomfort	48 (28.1)	9 (15.0)	24 (19.5)	8.86*(1.78 - 44.13)	2.43 (0.69 - 8.59)
Severe pain/discomfort	23 (13.5)	4 (6.7)	7 (5.7)	11.62*(1.06-127.02)	3.75 (0.64 - 21.95)
Extreme pain/discomfort	6 (3.5)	0 (0.0)	1 (0.8)		
Missing	9 (5.3)	4 (6.7)	7 (5.7)		

Table 5-8 QoL compared to population norms and comparison of MGUS (to SMM & OPC) using the EQ-5D.

Question	MGUS	SMM	OPC	Adjusted OR[i] (MGUS vs SMM)	Adjusted OR (MGUS vs OPC)
Anxiety/Depression					
Not Anxious/depressed	31 (18.1)	20 (33.3)	38 (30.9)	1.0	1.0
Slightly Anxious/depressed	67 (39.2)	23 (38.3)	42 (34.1)	2.87 (0.90 - 9.11)	1.80 (0.62 - 5.22)
Moderately Anxious/depressed	49 (26.9)	12 (20.0)	28 (22.8)	3.29 (0.86 - 12.58)	1.43 (0.44 - 4.70)
Severely Anxious/depressed	12 (7.0)	0 (0.0)	5 (4.1)		2.29 (0.25 - 20.49)
Extremely Anxious/depressed	3 (1.8)	1 (1.7)	3 (2.4)		
Missing	9 (5.3)	4 (6.7)	7 (5.7)		

EQ-5D	Population Norms[i]	MGUS	SMM	OPC	Adjusted coefficients[ii] (MGUS vs SMM)	Adjusted coefficients (MGUS vs OPC)
EQ-5D [iii]						
n	N/A	162	56	116		
UK Index Scores Mean (SD)		0.624 (0.264)	0.773 (0.207)	0.740 (0.200)	-0.106 (-0.181 - -0.031)*	-0.088 (-0.146 - -0.031)*
US Index Scores Mean (SD)		0.719 (0.179)	0.820 (0.143)	0.801 (0.140)	-0.073 (-0.124 - -0.022)*	-0.064 (-0.104 - -0.025)*
VAS Mean (SD)		63.2 (20.3)	75.3 (18.1)	69.2 (19.4)	-10.1 (-16.3 - -3.9)*	-4.9 (-10.0 – 0.1)
Missing		9	4	7		

[i] Population norms (495) were taken from the TTO values for the 45-54 and 55-64 age groups for the <55 and >55 groups respectively.

[ii] **Adjusted for: Age, Gender (male; female), educational attainment (Non-college-college) and race (White; other), Time since Diagnosis (<1 Year; 1-2 Years; 3-5 Years; 5+ Years), Have a significant Comorbidity (Yes; No), Healthcare country (USA, UK, Other).

[iii] *$p<0.05$ **$p<0.001$ compared to MGUS

EQ-5D	Population Norms	MGUS	SMM	OPC	**Adjusted coefficients** (MGUS vs SMM)	**Adjusted coefficients** (MGUS vs OPC)
EQ-5D Index Scores [i]						
<55 years						
n		79	23	60		
Compared to UK norms	UK 0.847	0.615 (0.278)**	0.769 (0.232)	0.733 (0.225)**	-0.087 (-0.217 - 0.042)	-0.109 (-0.196 - -0.022)*
Compared to US norms	USA 0.855	0.710 (0.192)**	0.818 (0.162)	0.796 (0.157)*	-0.062 (-0.151 - 0.028)	-0.079 (-0.140 - -0.019)*
>55 years						
n		83	34	56		
Compared to UK norms	UK 0.799	0.634 (0.250)**	0.776 (0.192)	0.747 (0.173)*	-0.123 (-0.214 - -0.033)*	-0.074 (-0.150 - 0.002)
Compared to US norms	USA 0.830	0.728 (0.165)**	0.821 (0.131)	0.806 (0.119)	-0.082 (-0.143 - -0.021)*	-0.052 (-0.104 - -0.001)*

[i] * p<0.05 ** p<0.001 from UK mean ^p<0.05 ^^ p<0.001 from USA mean

EQ-5D	Population Norms	MGUS	SMM	OPC	Adjusted coefficients (MGUS vs SMM)	Adjusted coefficients (MGUS vs OPC)
EQ-5D VAS Scores [i]						
<55 years						
n		79	22	60		
Compared to UK norms	UK 82.0	P<0.001**	P=0.028*	P<0.001**		
Compared to US norms	USA 79.2	P<0.001**	P=0.125	P=0.016*		
Mean score (SD)		61.4 (22.2)	73.4 (17.1)	72.1 (17.9)	-10.0 (-20.5 – 0.5)	-10.4 (-17.4 - -3.3)*
>55 years						
n		83	34	56		
Compared to UK norms	UK 81.7	P<0.001**	P=0.117	P<0.001**		
Compared to US norms	USA 76.9	P<0.001**	P=0.902	P<0.001**		
Mean Score (SD)		65.0 (18.3)	76.5 (18.8)	66.0 (20.5)	-11.1 (-18.5 - -3.7)*	2.3 (-5.2 – 9.9)

[i] * p<0.05 ** p<0.001 from UK mean ^p<0.05 ^^ p<0.001 from USA mean

5.3.4.3 QoL Measures- SF 12v2

The SF12v2 is a commonly used QoL instrument, with subscales (which range from 0 (worst health)-100 (perfect health) and component scales (which amalgamate scores) and are norm-based around 50 (range 0-100) respectively.

There were minimal differences within the subscale scores between conditions although MGUS patients had statistically significant impaired physical function compared to SMM ($p<.05$). However, MGUS patients had lower scores than SMM patients across all domains (except general health). Within the component scores, approximately 60% of patient's mental component scores were under population norms, Table 5-9.

The scoring software developed by QualityMetric (488) highlighted a higher proportion of premalignant patients were at risk of depression (20% norm: <51% all premalignant). This was not broken down by the scoring software by condition.

Table 5-9 Regression Analysis of SF12v2 between conditions (MGUS vs SMM & MGUS vs OPC)

Questionnaire[i]	MGUS Mean (SD)	SMM Mean (SD)	OPC	Adjusted coefficients [ii] (MGUS vs SMM)	Adjusted coefficients (MGUS vs OPC)
N	163	57	81		
Physical Function	64.1 (38.6)	69.3 (37.5)	68.8 (34.4)	-10.1 (-16.3 - -3.9)*	-4.9 (-10.0 – 0.1)
Role Limitation Physical	60.4 (35.3)	64.0 (34.2)	60.6 (31.9)	-2.1 (-13.7 – 9.5)	2.6 (-7.4 – 12.5)
Bodily Pain	65.0 (33.3)	70.6 (31.0)	65.4 (31.8)	-2.7 (-13.4 – 8.0)	1.7 (-7.7 – 11.2)
General Health	57.2 (30.5)	56.2 (29.0)	57.7 (28.8)	0.8 (-9.2 – 10.8)	-1.9 (-10.6 – 6.7)
Vitality	37.0 (28.8)	43.4 (30.4)	37.3 (26.6)	-5.6 (-15.0 – 3.9)	-0.7 (-8.7 – 7.3)
Social Function	58.6 (29.4)	67.1 (29.9)	56.8 (31.6)	-8.4 (-18.1 – 1.3)	5.4 (-3.3 – 14.1)
Role Limitation Emotional	66.4 (30.6)	72.4 (29.2)	67.4 (30.1)	-6.2 (-16.2 – 3.8)	1.2 (-7.7 – 10.0)
Mental Health	54.4 (22.5)	57.0 (19.9)	52.2 (22.0)	-4.1 (-11.2 – 3.0)	3.2 (-3.1 – 9.4)

[i] $^{*}p<0.05$ $^{**}p<0.001$ compared to MGUS

[ii] Adjusted for: Age, Gender (male; female), educational attainment (Non-college-college) and race (White; other), Time since Diagnosis (<1 Year; 1-2 Years; 3-5 Years; 5+ Years), Have a significant Comorbidity (Yes; No), Healthcare country (USA, UK, Other).

Questionnaire[i]	MGUS Mean (SD)	SMM Mean (SD)	OPC	Adjusted coefficients [ii] (MGUS vs SMM)	Adjusted coefficients (MGUS vs OPC)
Physical Component Score[iii]	46.6 (8.6)	47.6 (8.6)	47.6 (8.3)	0.2 (-2.7 – 3.0)	-0.2 (-2.7 – 2.2)
At or Above Population Norm (%)	112 (69.6%)	42 (75.0%)	57 (70.4%)	1.0	1.0
Below Population Norms (%)	49 (30.4%)	14 (25.0%)	24 (29.6%)	2.6 (0.6 - 10.2)	0.9 (0.5 - 1.7)
Mental Component Score[iv]	41.2 (10.5)	43.5 (10.0)	40.4 (11.7)	-3.0 (-6.4 – 0.4)	1.3 (-1.9 – 4.4)
At or Above Population Norm (%)	63 (39.1%)	25 (44.6%)	32 (39.5%)	1.0	1.0
Below Population Norms (%)	98 (60.9%)	31 (55.4%)	49 (60.5%)	2.7 (0.8 - 8.7)	0.98 (0.53 - 1.8)
Missing	9	4	42		

[i] *p<0.05 ** p<0.001 compared to MGUS

[ii] Adjusted for: Age, Gender (male; female), educational attainment (Non-college-college) and race (White; other), Time since Diagnosis (<1 Year; 1-2 Years; 3-5 Years; 5+ Years), Have a significant Comorbidity (Yes; No), Healthcare country (USA, UK, Other).

[iii] Compared to USA 2009 population norms as per patient age and gender

[iv] Compared to USA 2009 population norms as per patient age and gender

5.4 Qualitative Findings

In total, 197 (142/171 MGUS and 55/60 SMM) respondents provided at least one qualitative response in the survey. Their responses ranged significantly; from short answers (such as "no" (MGUS patient 2) to detailed accounts describing patient's fears, lifestyle changes and journeys through the health system.

The thematic analysis identified 2 overarching themes from the data, categorised into 8 sub-themes. The overarching themes were 'Living with the fear of progression from MGUS/SMM to cancer" and 'Issues with support for MGUS/SMM patients', Figure 5-5.

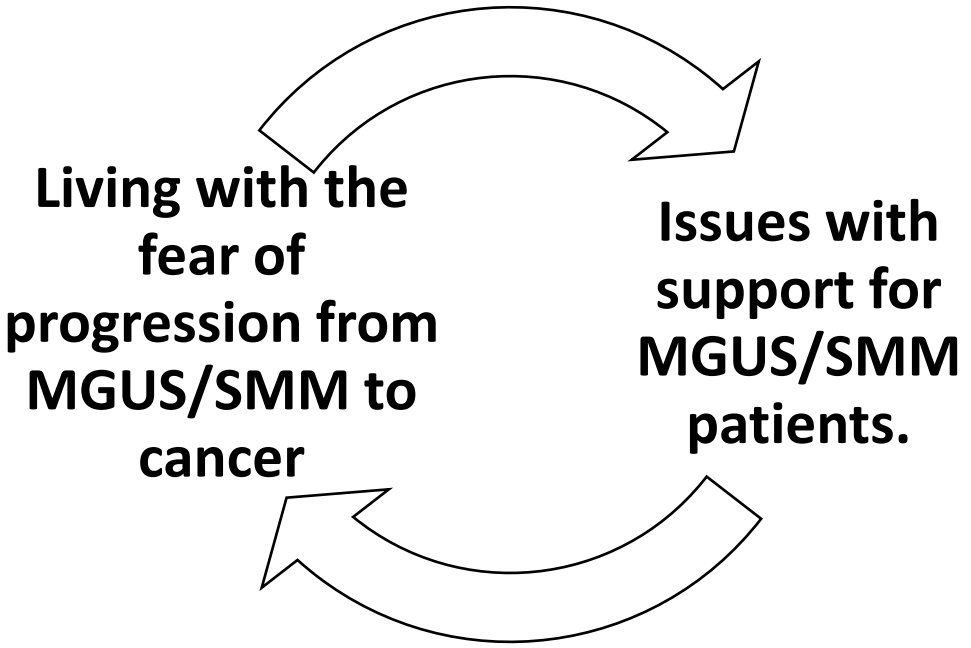


Figure 5-5 MGUS/SMM Qualitative themes

The first major theme identified was 'Living with the fear of progression from MGUS/SMM to cancer'. Both MGUS and SMM patients identified several

psychosocial challenges they faced living with their condition. The fear of progressing to cancer in the future was identified by patients as the main challenge of living with an MGUS/SMM diagnosis; especially if other family members had/have had a blood cancer. This fear was a common thread through the responses, with patients describing the methods of how they coped with this fear, such as changing their diet to reduce their risk of progression. Patients described watchful waiting/active surveillance as risking their future health, believing that waiting on starting treatment when a cancer progression occurs was too late. Patients also highlighted that waiting on the results of the surveillance caused increased anxiety; as this may be the time they progressed to cancer.

Overall, an MGUS/SMM diagnosis had varying impacts on patients', dependent on the patient's life circumstances; such as age and co-morbidities. Some patients viewed MGUS as inconsequential and not having an impact on their lives. On the other hand, some patients reported extreme reactions with one patient attempting suicide as a result of their diagnosis and others reporting severe distress. As a result of their diagnosis, both MGUS and SMM patients attempted to reduce their risk of progression by; increasing physical activity, improving diet and taking nutritional supplements. The thematic tree for the theme is presented in Figure 5-6.

The second major theme identified by patients was 'Issues with support for MGUS/SMM patients''. Patients viewed support for their condition as two constructs; informational support and psychosocial support. This theme describes the barriers experienced by patients to access information and psychosocial support.

Both MGUS and SMM patients wanted more information about their condition from HCPs and online resources, such as their risk of progression and updates about the latest MGUS and SMM research. Patients described how their doctors were often poor communicators; specifically, failing to answer their questions and lacking a detailed knowledge of MGUS/SMM. In particular, GPs were described as lacking knowledge and providing

inadequate patient care as a result. Patients illustrated why they sought second opinions on their care and why several changed their doctor after poor doctor communication and knowledge. Patients also described how they sought to improve their knowledge through the use of online groups and websites. However, many patients lacked the understanding to access evidence-based research and to interpret results/ findings.

The second component of support identified by both MGUS and SMM patients was a lack of psychosocial support from the health services/HCPs, specifically doctors, and their peers (fellow MGUS/SMM patients). Patients described barriers in accessing the psychosocial supports in the health service; specifically, accessing mental health professionals. Specialist doctors (haematologists) were perceived as poor psychosocial support post-diagnosis to patients.

The other component of lacking support identified by patients was peer support. Patients desired peer-support which involved meeting other patients but reported a lack of opportunities to meet other patients face-to-face. In response, many used online groups and forums to access information about the current research and read other patient's experiences of MGUS/SMM. The thematic tree for the theme is presented in Figure 5-7.

5.4.1 Living with the fear of progression from MGUS/SMM to cancer

A major theme identified was that both MGUS and SMM patients viewed their diagnosis in the context of the future rather than the present. This was exemplified by the consistent fear of progressing to cancer in the future reported by many patients. Patients described how living with this uncertainty was difficult for them. This was illustrated by how patients viewed their surveillance; a safety net designed to protect them but also a recurrent trigger which heightened anxiety. Patients feared that their next surveillance results would indicate progression and they would become a cancer patient.

Patients reported different reactions to living with MGUS/SMM long-term; with patients varying from extreme psychosocial reactions such as clinical anxiety, to others who considered their condition as inconsequential. When patients discussed their future, they highlighted steps they took to lower their risk of progression, such as improved diet and increased physical activity; despite the minimal evidence behind these steps. The thematic tree for the theme is presented in Figure 5-6.

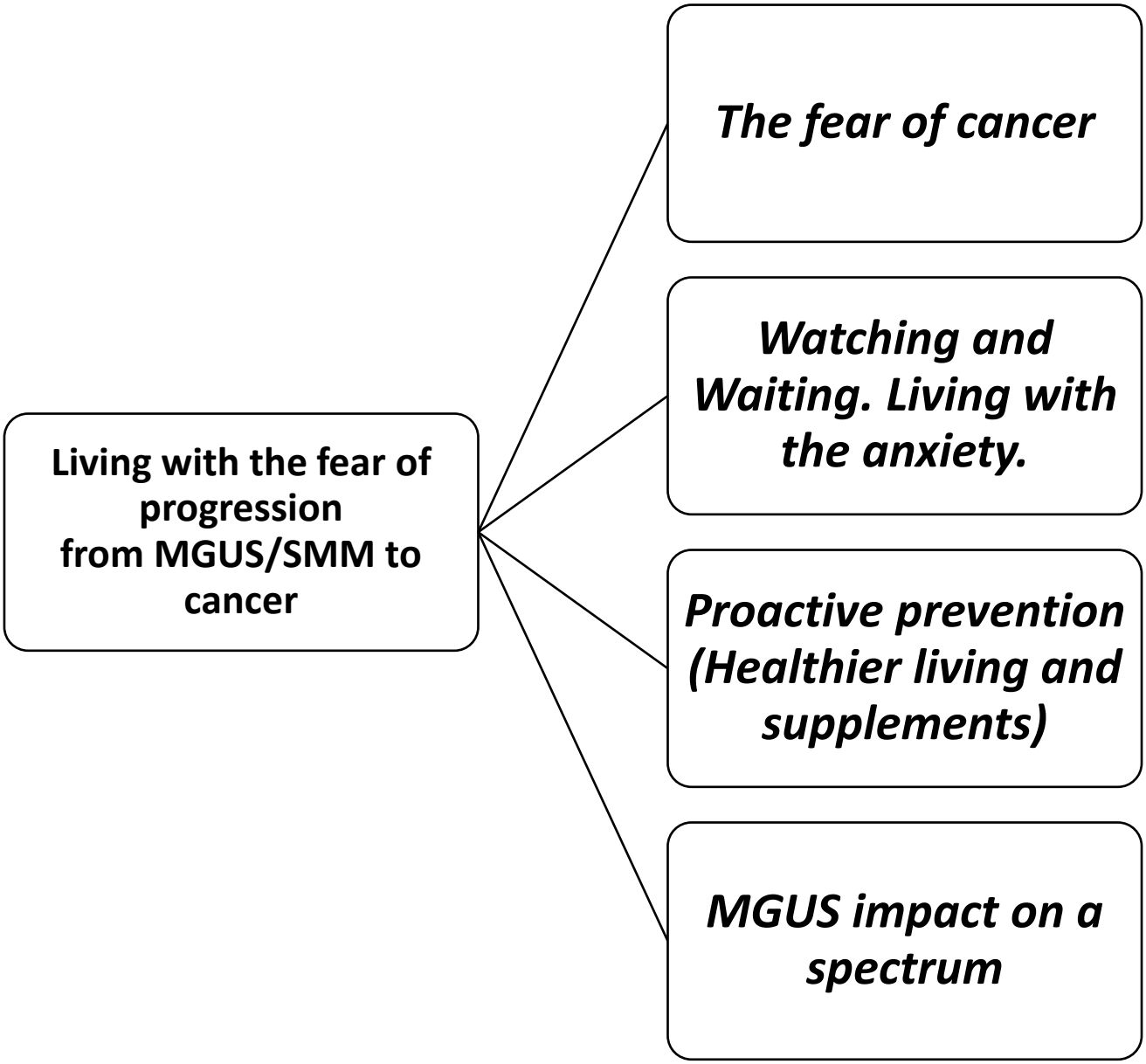


Figure 5-6 Living with the fear of progression from MGUS/SMM to cancer: Thematic Tree

5.4.1.1 The fear of cancer

Both MGUS and SMM patients discussed their uncertainty and fear of the future potential cancer they could be diagnosed with. Patients described how the uncertainty of the potential progression was one of the most difficult parts of processing and living with their diagnosis. Many MGUS and SMM patients described how they lived in continuous fear of a potential cancer diagnosis and viewed their surveillance appointments as triggers of increased anxiety. They feared the blood results of the next appointment would indicate that progression had occurred and they transitioned to being a cancer patient. This uncertainty was consistent for patients both newly diagnosed and those living with MGUS and SMM for a prolonged period. Living with the uncertainty was compared by one patient 32 years post MGUS diagnosis to *"living under the Sword of Damocles*" **(MGUS patient 37).**

"Psychologically, I have been trying to wrap my head around all this while trying not to worry about it too much. Sometimes I'm "okay" with it. Other times I worry about every little ache and the potential for progression. It has been disconcerting to be given this diagnosis and then told not to worry about it, but to just "wait and see." **(MGUS patient 49)**

"I am not afraid to die but I have young grandchildren and I worry about the impact on them when I die. On the other hand, we must all die of something so now I know it will almost certainly be MM that does me in." ***(SMM patient 29)***

SMM patients reported less uncertainty about their future; describing their future more negatively and predestined than MGUS patients. SMM was compared to waiting on "a time bomb that (they) don't really have any control over**" (SMM patient 44).** SMM patients were more accepting of their future than MGUS patients and took steps to make the most of their time prior to progression; such as having a positive attitude to life, spending time with family and enjoying every day.

Fear of a future cancer was especially concerning for the younger patients with both MGUS and SMM; who feared the impact on their children and health due to living with their condition longer than the average patient.

*"How do you live a normal life now? Where is the support for young people with MGUS?" (**MGUS patient 108, aged 33 years**)*

5.4.1.2 Watching and Waiting. Living with the anxiety.

Many patients discussed how active surveillance/watchful waiting appointments caused anxiety; as patients feared that their next appointment could be the appointment that they would be informed of progression to cancer. Some SMM patients perceived active surveillance as "risky" and frustrating when they were "*not receiving treatment*" (**SMM patient 17**). Both MGUS and SMM patients wanted to take proactive steps to reduce their risk or to start treatment for their condition, as they had read about in clinical trials rather than wait until they had a cancer before starting treatment.

*"Whether watch & wait is risky and should there be some sort of treatment to stop possible progression. Doctors and healthcare professionals (apart from oncology & haematologist) have very little or no knowledge of MGUS and testing." **(MGUS patient 26)***

Several MGUS and SMM patients highlighted the period between the surveillance appointments and receiving results, usually a number of weeks, as the most anxiety-inducing period post diagnosis. Patients who identified a lack of confidence in their healthcare team on MGUS/SMM (poor communication and knowledge) were more likely to have higher anxiety during this period; especially if their HCP was a GP rather than a specialist/haematologist.

*"Not unduly concerned and really don't give it much thought, except when bloods are due to be checked." **(MGUS patient 126)***

*"I'm concerned that my new GP doesn't understand MGUS enough. I'm concerned that my new haematologist isn't making an appointment soon enough" **(MGUS patient 18)***

The responses of MGUS patients focused heavily on the intervals (usually 3 to 6 months) between surveillance appointments/tests. They described moving from a three-monthly to a six-monthly interval between appointments as scary. Patients believed that any progression to cancer was more likely to be missed by their healthcare team during a six-monthly interval compared to a three-month interval. Similarly, individuals who felt their HCP was not adhering to clinical guidelines (for interval between appointments and clinical investigations) reported heightened anxiety.

5.4.1.3 MGUS impact on a spectrum

There was a varied reaction from both MGUS and SMM patients on the impact of their condition; with some patients from both conditions reporting a high negative impact and other patients reporting little to no impact as a result of their diagnosis.

On one end of the spectrum, some patients reported limited concerns for their future and minimal impact on their lives; perceiving it as inconsequential. Patients highlighted advanced age, the lack of treatment available, other co-morbidities or prolonged surveillance as reasons that MGUS/SMM was not that important to them.

"There isn't anything I can do about MGUS) so there is no point in worrying about it. At 71 and alone, I have already made up my mind that I will not pursue therapy should I develop multiple myeloma or lymphoma". ***(MGUS patient 57)***

"I'm not convinced that (MGUS) is a condition. The NHS is very overstretched, and I do not want to burden it further by being a member of the worried well" ***(MGUS patient 9)***

On the other end of the spectrum, some diagnoses of MGUS and SMM created an overwhelming sense of despair for patients; with severely detrimental effects on their psychosocial wellbeing. The MGUS/SMM diagnosis was described as a "death sentence" (MGUS patient 63), with one patient reporting a suicide attempt as a result

of their MGUS diagnosis. Patients diagnosed at younger ages were at higher risk at heightened anxiety; due to their extended time living with the condition.

"It feels like a death sentence may have been passed. I never had a health problem/issue. Prior to this. I hadn't visited a G.P in over twenty years and when I finally did I got this MGUS diagnosis - without any really proper explanation." ***(MGUS patient 63)***

"Prior to seeing consultant, I was so low because of what my GP said and a nursing girlfriend I attempted to take my own life." ***(MGUS patient 87)***

"Concerned over whether I will progress despite being told that I have a low risk of progression. Concerned when I am effectively being followed up and receiving the proper testing. Concerned that, because I was diagnosed at a fairly young age, that I will eventually progress." ***(MGUS patient 16)***

5.4.1.4 Proactive prevention (Healthier living and supplements)

A common theme discussed in relation to their future was how both MGUS and SMM patients made lifestyle changes to prevent their progression risk, such as altered physical activity and improved diet. At least some lifestyle change was made by the majority of patients. Some examples of this increased physical activity were patients starting yoga and increasing their step counts. Other patients lowered their physical activity levels as a result of their diagnosis; citing symptom burden from MGUS and other co-morbidities. These symptoms were often described as fatigue and pain. One third of patients reported making positive dietary changes; such as decreasing alcohol and red meat consumption, decreasing sugar intake and increasing fruit and vegetables and/or going vegan/vegetarian/pescatarian. Patients seen these changes as taking an active role in slowing their progression.

"Concerned with progression to Active Myeloma but also if it would be beneficial to start treatment now, before the Myeloma becomes active. I believe this is in a trial at the moment and if the trial concludes that it is beneficial then it would mean an opportunity to manage my Myeloma has been missed. I accept that it is impossible

for my team to know this, and that it is highly likely that the trial will conclude that it "depends on the patient" as Myeloma is different for everyone." ***(SMM patient 36)***

Both MGUS and SMM patients reported taking supplements to reduce their risk of progressing in the future. However, SMM patients were more likely to report taking supplements. The most common supplement taken by patients was curcumin/turmeric. Patients described it as a *"golden paste"* (**SMM patient 9)** and ingested between 2-10 grams per day. Patients seen taking curcumin as reducing their risk, and several MGUS and SMM patients adhered to research and clinical trial protocols for curcumin they researched/found online. Other supplements taken by patients included iron pills, CBD oil and vitamin D. Some patients reported barriers from HCPs when seeking alternative medicine; especially regarding nutriments and supplements. These patients sought alternative sources and HCPs for help with this.

"Taking curcuforte (4g curcumin), removed refined sugar from diet, no white carbs, reduced red meat, increased fish intake, increased vegetable intake, increased water intake, taken a lower stress job and increased exercise" ***(MGUS patient 51)***

"My concerns have to do with the fact that in the US, nutritional benefits of living with SMM are not recognized and therefore cannot be even talked about with my specialist. Therefore, I've had to go contact doctors in other parts of the world to find out something to do other than "watch and wait!" ***(SMM patient 22)***

5.4.2 Issues with support for MGUS/SMM patients.

A major theme identified that both MGUS and SMM patients discussed was the poor support they received for their condition. This poor support was described as detrimental to their general wellbeing. Patients identified barriers to acquiring knowledge and understanding about their condition, particularly from HCPs and the internet. Patients also described barriers when they sought psychosocial support from their healthcare teams and peers.

The first part of this overarching theme describes how HCPs were important information supports for both MGUS and SMM patients. HCPS can empower and disempower patients by their communication style and knowledge of health conditions. Patients discussed how a lack of knowledge and poor communication from HCPs weakened their trust in their HCPs and led to patients becoming less confident of their care. Some patients sought second opinions and more specialised care as a result of this. GPs were highlighted as having poor MGUS-specific knowledge and do not provide adequate care; however, GPs were less involved in SMM care in general.

This lack of confidence led to both sets of patients seeking further information from other sources; such as research articles and online sources. Many patients sought specific knowledge to assist in monitoring their test results and clinical investigations; however, their lack of understanding led to difficulties in interpreting this information. Patients used online forums such as Facebook groups to help understand this information with their fellow patients.

The second component of support identified by patients was psychosocial support from the health services/HCPs and their peers (fellow MGUS/SMM patients). Psychosocial support from their healthcare team was described as important mechanisms to increase patient's coping skills. This was perceived as inadequate by their specialists (haematology) and GPs; due to a lack of knowledge and training in mental health. Patients also desired more contact with their peers; highlighting a lack of opportunities to meet other patients to share their experiences. As a result, may patients recounted their experience of using online groups and forums to access peer support. The thematic tree for the theme is presented in Figure 5-7.

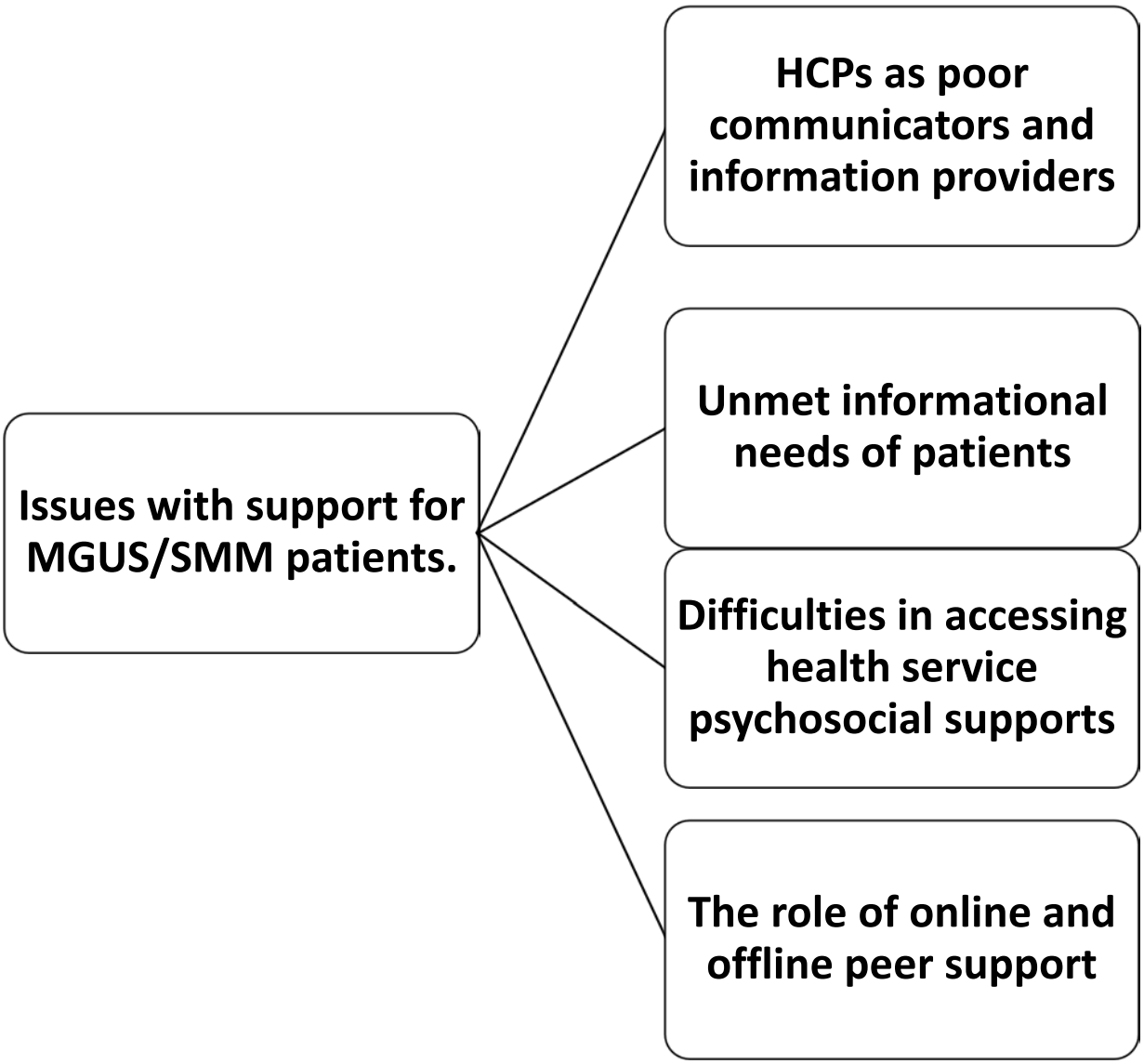


Figure 5-7 Issues with support for MGUS/SMM patients: Thematic Tree

5.4.2.1 HCPs as poor communicators and information providers.

This subtheme discusses how patients experienced interacting with HCPs about their condition. Both MGUS and SMM patients felt that their HCPs did not provide the knowledge and understanding many patients sought and MGUS patients specifically felt their HCPs trivialised their concerns about their condition when they tried to develop their understanding. Patients felt they did not receive the informational support desired, even if they prepared questions for their HCP. Patients found this increased their anxiety about their condition.

"Oncologist got mad that I had questions and printed all my records and said, here your go stick this in your Dr. Durie book." ***(MGUS patient 154)***

"I think (their doctor) is very diminishing, making me feel like I don't have anything going on and I shouldn't be even think about it and if I have some questions she puts me down and thinks I am stupid." ***(MGUS patient 103)***

"My first oncology doctor was very rude and did not want to answer my questions". ***(MGUS patient 99)***

Patients identified their GP as their primary points of contact for care and knowledge but believed GPs did not have the knowledge or the skillset to provide care for their MGUS/SMM. This was defined by patients as GPs not being aware of the correct protocols for their care and that specialists (haematologists) provided more appropriate care; such as the correct intervals between surveillance appointments. This was more prominent for UK/European patients (who are commonly monitored in primary care) than US patients (who predominantly seen specialists' post-diagnosis). In general, these issues with GPs were more prominent for MGUS patients than SMM patients as SMM patients were generally under the care of specialists than GPs; due to the higher progression risk.

"I have a concern that my GP doesn't really know much about MGUS and really thinks it is insignificant." ***(MGUS patient 138)***

*"Primary care doesn't have a clue about MGUS and trivialises concerns" (**MGUS patient 84)***

*"I would prefer to be seen and tested by haematologist rather than my GP who had never heard of MGUS and only takes blood tests, no 24-hour urine for analysis that was done in Spain by haematologist. Basically, I don't feel secure in the GP's hands." **(MGUS patient 26)***

5.4.2.2 Unmet informational needs of patients

This subtheme discusses the information that MGUS and SMM patients wanted about their condition and how they understood this information. Patients described how information on their condition was difficult to acquire; especially for interpretation of their blood test results.

Many patients sought their test results; with several patients from both conditions including their clinical investigation results (e.g. SERP and M-Spike levels) in their response. Many patients recounted difficulties in accessing these results initially; specifically, their HCPs being reluctant to provide the raw scores of these blood tests. This was related to most patients lacking the medical knowledge and understanding to interpret the findings correctly. Even patients who reported "*some medical knowledge*" (**MGUS patient 84)** found it difficult to interpret due to the lack of clear information on how to interpret the results. Not understanding and being unable to interpret the results led to increased anxiety for some patients.

*"I still don't understand my diagnosis completely. My biopsy, I don't understand the results". **(SMM patient 40)***

*"I monitor my analyses and when they are not good" (Kappa Lampata score), I think of death… and I become anxious" **(SMM patient 18).***

Many MGUS and SMM patients sought information online; especially though forums and Facebook groups. These groups contained information about ongoing clinical trials, guides to interpret test results and answers for patient's commonly asked

questions (and the ability to ask other questions). However, these groups were usually patient-led groups with minimal HCP or scientific input; meaning the information may not correct or evidenced. Patients reported using online sources, such as Myeloma UK and Luekiemia.org, to inform themselves. However, these resources were considered hard to find amidst complicated terminology and MM-dominant research rather than MGUS/SMM research.

"More education on 'WHAT IS GOING ON' "when you make a new chromosome"? How to read the charts I see on FB groups. I'm not dumb, but for sure (I am) not schooled in this." ***(MGUS patient 43)***

"I am unsure whether to question a follow up on my free light chain ratios. It seems from what I have recently researched that this ratio can be a big indicator for progression." ***(MGUS patient 55)***

"Access to the most recent research that relates directly to MGUS - one portal with only MGUS research." ***(MGUS patient 171)***

5.4.2.3 Difficulties in accessing health service psychosocial supports

This subtheme discusses how patients wanted greater access to psychosocial supports to assist in coping with their diagnosis. Both MGUS/SMM patients highlighted barriers in accessing care and a lack of trained psychosocial support personnel to provide them with the skills to increase their resilience and improve their coping strategies.

MGUS and SMM patients wanted greater access to *"mental health professionals who deal with these types of diagnoses"* **(SMM patient 41)** for this to occur. Patients felt this access was often not available or difficult to access after diagnosis. As stated, many patients felt that doctors were poor suppliers of psychosocial care; the doctors being perceived as dismissive, "blasé" and difficult to access by MGUS and SMM patients.

"I wish it were easier to access those services and supports that are supposedly available. It all took so long and so much work when my disease worked so quickly, and I struggled incredibly while applying for help." ***(MGUS Patient 121)***

MGUS patients highlighted the positive role of haematology specialist nurses in providing psychosocial care. This was clarified by patients as nurses being more accessible and more open to questions than doctors. Specialised nursing support was an unmet need to patients; which would increase the support available for patients. Multiple patients from both MGUS and SMM desired a specialist haematologist nurse whom they could contact to discuss their condition. Patients who received dedicated psychosocial care reported this support reduced their distress and improved their understanding.

"Counselling if needed and recognition support from a nurse." ***(SMM patient 1)***

"I would love to be able to talk to a specialist nurse when I have concerns." ***(MGUS patient 55)***

"I am glad that my doctor offered a social worker on staff to help me- they are giving me six sessions (included in my care fee) which I felt was really awesome. I am also starting to see a spiritual counsellor. I just got diagnosed this month (it's only been about 3 weeks) so I am not sure what else I need other than a cure!" ***(MGUS Patient 89)***

5.4.2.4 The role of online and offline peer support

This subtheme discusses how patients felt the lack of peer support- both in-person and online- affected their psychosocial wellbeing. Patients described how they accessed social support from their peers and the unmet needs.

Both MGUS and SMM patients were disappointed that to have minimal contact with their peers. Patients felt that meeting other patients could help increase their awareness of their condition, provide insight on what the future could hold for them and provide opportunities to speak with someone who they felt understand them. 'Newly diagnosed' patients (under 2 years' post-diagnosis) were highlighted as a

group that would benefit the most from this contact; providing advice and sharing their experiences of care. Patients proposed setting up community groups that MGUS/SMM patients could attend to share their stories, concerns and experiences; similar to cancer support groups.

"There should be some community support groups set up for this condition where people who have it can meet other likewise people." ***(MGUS patient 149)***

"I would like to see more support groups organized in order to help with the anxiety. I do not want to make a big deal out of MGUS, however it does feel as if you are waiting for the other shoe to fall off. Not meaning to sound dramatic, however there is no support network whereby you meet others that have the same concerns." ***(MGUS patient 42)***

Both MGUS and SMM patients reported that using online forums (such as Facebook, message boards & blogs) to communicate with other patients and access support. This support involved sharing current research, providing emotional support and educating each other on how to read medical results. Patients found these forums as safe spaces to explore their condition and ask questions. However, not all patients viewed online support as appropriate or desirable; preferring face-to-face contact.

"There are several Facebook groups which provide great information and support. It would be awesome if info on these were provided to the newly diagnosed. Printed material should also be provided at that time" ***(MGUS patient 96)***

5.5 Discussion

MGUS patients experienced increased anxiety, depression and diminished QoL from their diagnosis compared to the general population and SMM patients; due to heightened uncertainty and fear of progression to cancer. Patients reported the negative psychosocial impact of surveillance; such as heightened anxiety, a lack of available psychosocial support, a continuing fear of progression to cancer. Patients also reported taking proactive measures to help prevent progression/cancer. This

study provides a unique insight into the challenges and experiences of MGUS and SMM patients; previously unexplored in the published literature.

There has been limited research investigating the psychosocial impact of an MGUS or SMM diagnosis on patients. This study specifically is amongst one of the first and largest to investigate the impact and to compare the MGUS and SMM. A study by Maatouk *et al,* found that 148 MGUS and SMM patients had similar HRQoL and anxiety to levels to MM patients but have not published any comparisons between MGUS and SMM patients (293).

On the psychosocial impact, MGUS patients were more likely to think about their diagnosis daily, had higher rates of clinically relevant anxiety and depression and had decreased QoL compared to patients with SMM. Both patient groups reported about symptoms that they attributed to their MGUS/SMM diagnosis. However, MGUS patients emphasised their symptoms more than SMM patients; despite both conditions being considered asymptomatic (500). MGUS patients predominantly reported pain, recurrent infection and peripheral neuropathy; of which the latter two are linked to MM (501) and MGUS respectively (15). However, these claims have not been substantiated. The fact that many MGUS patients experience symptoms that they attribute to MGUS but HCPs maintain MGUS is asymptomatic may contribute to why MGUS patients feel they have poor HCP care; as highlighted in the qualitative analysis within this Chapter and the AiMs chapter.

A premalignant condition causing a demonstrative and significant impact on QoL using validated questionnaires is a novel finding in the area; as highlighted in the systematic review; where no such effect was found. This was also validated across two QoL measures (SF12v2 & EQ-5D), which increases the reliability and validity of the finding. In a deeper analysis in the subscales of the measures, heightened pain, a reduction in normal activities, increased anxiety/depression (EQ-5D) and diminished physical function (SF12v2) were highlighted as important factors in the diminished QoL for MGUS patients. From integrating the qualitative findings, anxiety was also found to be a major potential factor in the diminished QoL of MGUS patients.

Many MGUS patients reported clinical levels of anxiety (according to the HADS questionnaire) at both the lower and higher clinical thresholds (218); highlighting

that an MGUS diagnosis had a substantial effect on patient's anxiety. From the qualitative analysis, this anxiety was linked to the heightened uncertainty about their risk of progression to MM. This was complex, with SMM patients (who have a higher progression risk) seemingly more "at peace" with their diagnosis. In an abstract from MD Anderson in Texas, MGUS patients felt less in control of their progression risk compared to SMM patient (140). In a study of MM patients (502), who had similar characteristics, their percentage of clinically relevant anxiety and depression was lower than the MGUS population in this study. The current low level of research on MGUS (and SMM) highlights the need for increased research and greater integration/collaboration on research studies that incorporate MGUS, SMM and MM patients within one study.

Overall, patients (84.3%) described how they had implemented some type of behavioural/lifestyle change as a result of their diagnosis. The most common step taken was the use of supplements as part of an anti-cancer regime to prevent/reduce their chance of progression to cancer. The most common supplement was curcumin/turmeric. Recent research has indicated that these supplements help in prevention of myeloma and general anti-cancer properties (503); however, results are mixed so far (504). Much of the early research in curcumin/turmeric as an "anti-cancer" agent was conducted by Dr. Bharat Aggarwal (505–507); which has been since redacted due to poor data quality and concerns about the interpretation of the results. Patients also reported improving their diet (healthier eating), increasing their physical activity levels and using other health supplements (such as iron pills) to reduce their risk of progression.

Another observation was that MGUS patients wanted clear and comprehensive information available at diagnosis and online. MGUS patients were less likely to receive information leaflets at diagnosis, were more likely to seek information online and rate this poorer than SMM patients. Two thirds of MGUS patients didn't receive any information at diagnosis and desired information on their risk of progression, testing/surveillance and current research; similar to the systematic review findings for patients with other haematological conditions (508). Being able to understand available information was also important (509,510) and patients in this study

reported using Facebook groups/blogs to help understand and share information. It is important in future research to determine whether less information provision is correlated with the lower QoL and higher anxiety/depression experienced by MGUS patients.

In relation to MGUS support and health services, MGUS patients rated their surveillance worse and had longer intervals between appointments than SMM patients. They were also less open about their condition and less willing to speak about their condition to others.

In comparison to MGUS patients, SMM patients appear to receive better information at diagnosis, have better communication with HCPs and are able to speak about their condition easier. This along with better outcomes on QoL measures suggests that simple interventions may help to improve how MGUS patients cope with their diagnosis. Having their condition explained at diagnosis and receiving time and written information to process it in their own time is an important recommendation of the research presented within this dissertation that could reduce the overall psychosocial impact experienced by some MGUS patients.

5.5.1 Strengths and Limitations

This was a novel study targeting an under-researched group (MGUS and SMM) using an online recruitment strategy to provide a large international sample. Clinical and PPI involvement provided insight and understanding of MGUS care (511).

Previous systematic reviews, including Chapter 2, have highlighted the proliferation of non-validated instruments measuring QoL/Wellbeing in premalignant conditions. Validated instruments (EQ-5D, SF 12v2 and HADS) increase the confidence of the findings and enable comparison to norms, published research and other premalignant conditions. However, utilising the Cancer Worry Scale (140,512) could have added evidence to the qualitative findings of cancer worry and informed future research. This scale was not utilised as it was uncommon in the premalignant literature.

Utilising online surveying and recruitment leads to faster, more cost-efficient research with less risk of social desirability bias of health risk behaviours (513–516). Online surveys have similar responses to paper-based surveys (517,518), allow wider dispersal of participants and reduce the risk of human error in data imputation (514). Response rates can be difficult to assess as social media recruitment does not provide metrics of how many eligible participants seen the survey but didn't complete it. Instead in this study, the researchers focused on contacting as many groups as possible to have the most representative and largest sample possible. Charities disseminated the study to encourage individuals without social media accounts to participate.

A study on MGUS from MD Anderson used the QLQ-C30 cancer QOL instrument, MY20 myeloma-specific module and measured cancer worry (140). When developing the PIP study, the study team felt that using a cancer QoL instrument was not the best option for the study. There were three main reasons for this decision. The first reason was the lack of cancer worry instruments used by premalignant studies in the systematic review. Within the review, generic QoL instruments (such as the SF-12 and EQ-5D) were the most common instruments used [i]. Using the same instruments as the other premalignant studies enabled comparisons to be made between MGUS, SMM and other premalignancies. Thirdly, generic instruments provide population norms to enable comparisons between the general population and MGUS/SMM patients. We felt comparing the impact to the general population was more appropriate and impactful in the future. The aim of the research was to investigate the impact on MGUS patients rather than comparing to cancer patients; as would be more relevant when using QLQ-C30 cancer QOL instrument.

Some demographics limit the representativeness and generalisability of the findings. The sample was; majority white females (MGUS has a higher prevalence in those of African descent (38,48) and males (51)), aged approximately 54 years-old (average age of diagnosis is 70 years-old (58)) and had other co-morbidities (69.7%). This may

[i] As described in QoL and psychometric Instruments/Questionnaires, page 61.

have confounded the analysis (although the analysis was adjusted for age, sex and race). Younger MGUS and SMM patients live longer with the knowledge of their condition (58) and have an increased lifetime risk of developing MM over their lifetime; they are also more suitable for future intervention studies.

5.6 Chapter Conclusion

In conclusion, MGUS patients have increased anxiety and face uncertainty on their future due to their heightened risk of cancer. Patients felt unsupported by staff, unable to access supports and lacked understanding about their condition immediately post-diagnosis. There were clear differences between MGUS and SMM patients, which indicate psychosocial differences in experiences and show that these conditions should be separated in studies rather than combined as a premalignant group. There was a clear need from patients for improved services with regards information provision, psychosocial support and HCP education about their condition. Further discussion about how these findings can be utilised to improve the experiences or MGUS patients and how this relates to the healthcare professional studies is located in Chapter 6: Discussion.

6 Chapter 6: Discussion

This chapter provides an overview of the dissertation and a critical reflection across all studies presented in this dissertation. Three main topics were identified: 'The psychosocial impact of an MGUS diagnosis', 'Becoming informed about MGUS' and 'MGUS supports and health services'. Each topic provides an overview of the findings and the context from the literature of how this affects patients living with cancers and premalignant conditions; especially haematological malignancies where available. To re-orientate the reader of the methods and function of each chapter, a short overview is provided below along with a visual guide that describes the research undertaken, Figure 6-1. The research questions[i] from the introductory chapter are also provided.

1. What is the perceived impact by patients of receiving a diagnosis of MGUS:
    a. on an individual's QoL and psychosocial wellbeing?
    b. compared to other pre-malignant conditions?
2. What are the health and social care needs of patients with MGUS?
3. How do key healthcare professionals interact with, and care (physical and psychosocial) for MGUS patients?
4. What is the formal or informal pathway that MGUS patients 'travel' to receive a diagnosis, treatment and care?

6.1 Chapter overview

Chapter 1, the introductory chapter provided an overview and description of the main topic of the dissertation (MGUS) and related plasma cell disorders. This chapter also outlined how QoL and psychosocial well-being are defined in the dissertation and describes the quantitative instruments used throughout the dissertation.

Chapter 2 described a mixed methods systematic review that assessed the impact of premalignant conditions on patients. A meta-analysis and meta-synthesis of the

[i] Research questions outlined, Page 20.

quantitative and qualitative data were undertaken, respectively. The findings indicated that having a premalignant condition did not have a detrimental effect on QoL or psychosocial well-being as assessed using validated questionnaires. However, the qualitative synthesis highlighted that patients appeared to experience multiple detrimental psychosocial impacts such as increased anxiety and uncertainty, fear of progression to cancer, and inadequate information provision, particularly at diagnosis. This provided evidence that generic quantitative QoL instruments were unable to capture the impact of having a premalignant condition which was discernible from qualitative methods.

Chapter 3 described a qualitative study- Assessing the Impact of MGUS **(AiMs)-** which explored the lived experiences of MGUS patients in Northern Ireland. A thematic analysis identified three main themes which revolved around MGUS patients' 'experiences of health services', 'the psychosocial impact of receiving an MGUS diagnosis' and 'knowledge about MGUS' in relation to key 'stakeholders' in MGUS care. The findings indicated that MGUS patients experienced anxiety about the potential for MGUS to progress to cancer. Patients reported feeling isolated and confused about their diagnosis due to a lack of information and poor communication and psychosocial care from healthcare professionals. Most MGUS patients adjusted well to their diagnosis over time. However, they encountered difficulties as users of MGUS services and anxiety levels were heightened at initial diagnosis and subsequent surveillance appointments. Finally, patients reported that they needed more, clearer information about their condition.

Chapter 4 presented the results of two surveys that investigated the experiences and views of (i) haematology healthcare professionals on the island of Ireland and (ii) GPs and GP trainees across the globe. The survey instruments asked HCPs about their general awareness of MGUS, how they diagnosed MGUS and how they communicated the diagnosis of MGUS to patients. Primary care professionals (unlike haematology HCPs) appeared to lack awareness and understanding about MGUS. Haematologists reported used terminology and analogies to describe MGUS that they believed patients found easy to understand. Both haematology staff and GPs supported the direct management and surveillance of MGUS patients in primary care

but wanted more collaboration with the specialism of haematology, whose assistance and support was required in order to provide these services.

Chapter 5 described an online mixed methods survey - The psychosocial impact of a premalignant condition (**PIP**) - that evaluated the QoL and wellbeing of patients with a premalignant condition. The survey compared the experiences of MGUS patients and patients with SMM, a more advanced precursor to MM, and other premalignant conditions. MGUS patients reported lower QoL, higher anxiety and higher depression scores than SMM patients, patients with other premalignant conditions and population norms. In addition, MGUS patients reported problems accessing relevant information and they encountered issues (beyond the issues experienced by SMM patients) regarding the active surveillance of their condition.

Chapter 6. This chapter integrates the findings from the above noted studies and discusses them in the context of relevant literature regarding MGUS, premalignant conditions and cancer. Overall, the research indicated that while the experience of MGUS patients is similar to patients with other premalignant conditions MGUS patients experience poorer QoL, more anxiety and depression. This chapter presents and discusses these issues including 'The psychosocial impact of an MGUS diagnosis', 'Becoming informed about MGUS' and 'MGUS supports and health services'. The chapter concludes with the strengths and weaknesses of the PhD research and presents research-informed recommendations that could improve the psychosocial wellbeing of MGUS patients.

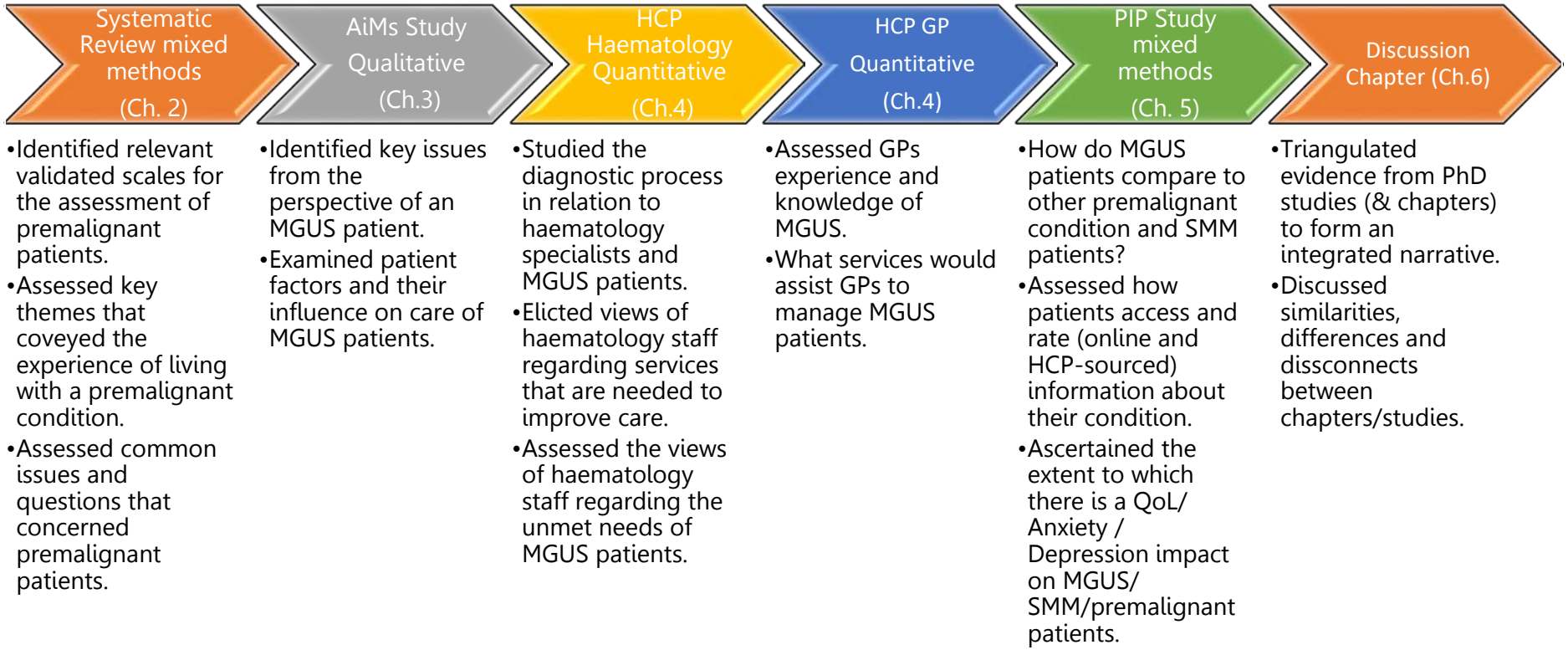


Figure 6-1 Exploratory Sequential design of the dissertation.

6.2 Psychosocial impact of an MGUS diagnosis

The psychosocial impact that was experienced by MGUS patients varied across the care pathway[i]. One of the main research questions[ii] in the dissertation was to identify what is the impact of a diagnosis of MGUS on; on an individual's QoL and psychosocial wellbeing and compared to other pre-malignant conditions. While developing the research, three distinct phases that patients experienced were apparent; the diagnosis phase, shortly after diagnosis and a longer-term phase beyond the initial year after diagnosis. This topic describes the psychosocial impact expressed by MGUS patients and other premalignant conditions identified in the systematic review as comparators at each phase of the care pathway.

6.2.1 The Diagnosis phase

Patients in the systematic review, AiMs and PiP studies described their shock of being diagnosed with a potentially cancerous condition. This diagnosis phase was a vulnerable time for patients. Patients in the AiMs study described how waiting outside the haematology clinic, surrounded by patients with the visible signs of cancer treatment (such as lost hair and general ill health), was particularly anxiety inducing and how the fear of becoming one of these patients was shocking for them. In this state of heightened agitation, the term 'cancer' and how MGUS, a 'precancerous' condition, can lead to a future cancer diagnosis, was described as shocking by patients[iii]. This shock led to some patients not comprehending the remainder of the consultation and missing important information. Patients

[i] A care pathway which describes the diagnostic pathway for MGUS patients is described in Pathway of MGUS care page 333.

[ii] Research questions outlined, Page 20.

[iii] The psychosocial impact of an MGUS diagnosis is described on page 172 and page 265.

reported that the shock persisted throughout the diagnosis phase and developed into anxiety about the potential for progression to cancer [i].

The shock of an unexpected cancer-related diagnosis was also reported in the systematic review for patients with multiple premalignant conditions and has also been reported in a review of screen-detected cancers, such as breast, cervical and colorectal cancers (519). A meta-aggregation of MM patients (431) highlighted that MM patients also experienced shock (from the qualitative data) at the time of diagnosis as similar to MGUS patients they were not expecting this diagnosis. In the wider literature, abnormal and indicative (of cancer) results in screening have been linked to adverse psychosocial effects including shock and anxiety (346,350); especially in asymptomatic patients and in individuals with non-specific symptoms. Therefore, as patients did not have any warning signs (or symptoms) that could have prepared them psychosocially; MGUS patients may be at a higher risk of experiencing shock at the time of diagnosis.

In the haematology survey, haematology professionals reported breaking the diagnosis down into simpler language and analogies to help the patient understand their diagnosis. However, in the PIP survey patients reported confusion about the range of terminology used to describe MGUS. GPs also reported not being confident or experienced in speaking to newly diagnosed MGUS patients about their diagnosis. Many GPs were unaware of the increased risk of developing cancer, or the specific types of cancer (MM or WM) commonly associated with MGUS. This mismatch appears to point to a need to give concentrated attention to the ways in which doctors communicate with MGUS patients. Research and reports from patients and clinicians about doctor-patient communication in relation to imparting a

[i] The psychosocial impact of an MGUS diagnosis is described on page 172 and page 265.

diagnosis suggest this is a vital period for HCPs to inform patients[i] and can have beneficial effects (520).

Within the diagnosis phase, a subgroup of patients was identified who were relived rather than shocked by their MGUS diagnosis. This subgroup had often experienced prolonged medical investigation prior to receiving their MGUS diagnosis and in some cases, had believed they had MM. The relief was associated with transitioning from believing they were a cancer patient to becoming a non-cancer patient. This expression of relief was supported by patients with other premalignant conditions in the systematic review, such as DCIS and breast cancer (345,347,350,359)[ii].

6.2.2 Shortly after diagnosis phase

Many patients reported anxiety [iii], depression and uncertainty about their potential to progress to cancer following a diagnosis of MGUS.

Within the systematic review, all qualitative studies of premalignant conditions (except colorectal polyps) reported anxiety about progression to cancer (344,345,349,350,352,356–358,360). This was supported by similar experiences described by MGUS patients in the AiMs and PIP studies. Patients described their waiting on progression to cancer as *"Damocles' sword"* **(AiMs)** and a *"time bomb"* waiting to explode **(PIP).** This anxiety manifested in more serious issues for a small minority of patients; with one patient attempting suicide **(PIP)** and others questioning their mortality **(AiMS).**

---

[i] This was highlighted in MGUS diagnosis page 202 by haematology staff and in initial reaction to diagnosis page 174 and in Living with the fear of progression from MGUS/SMM to cancer page 283 by patients.

[ii] As described in 'the Premalignant condition as a beneficial/negligible occurrence' page 126.

[iii] The psychosocial impact of an MGUS diagnosis is described on page 172 and page 265.

A review article by a selection of cancer patients (various sites) highlighted the initial period post diagnosis as a *"roller coaster of emotions and feelings including anxiety, fear, hope, helplessness, courage, despair, strength and depression"* (521); which was a similar experience to that reported by many MGUS patients in the dissertation.

A number of MGUS patients with clinically relevant anxiety and depression were identified in the PIP survey using reliable, validated assessment tools. This is in contrast to what was found for patients with other premalignant conditions in the systematic review; where the caseness of clinically relevant anxiety and depression were not above population norms. The term clinically relevant anxiety and depression is used as clinical anxiety and depression cannot be measured using only the HADS questionnaire (522) and requires further investigation to assess using DSM-IV criteria (523). Clinically relevant anxiety and depression was more common in MGUS patients in the PIP study than in the general population (218), other premalignant conditions **(PIP and Systematic review)** and SMM patients. These heightened anxiety and depression levels in MGUS patients were apparent at both mild and moderate thresholds (218).

These findings were a surprise as the systematic review and the AiMs study had indicated that anxiety and depression were unlikely to be relevant for most premalignant patients, including those with MGUS. It highlights that a subgroup of MGUS patients would benefit from a formal mental health service intervention and that MGUS patients may require more psychosocial care than patients with other premalignant conditions. No type of psychosocial intervention has been trialed in patients with other premalignant conditions, as the research to date had not supported a significant psychosocial effect of diagnosis.

MGUS patients in both the AiMs and PIP studies experienced high levels of uncertainty after their diagnosis; and identified uncertainty as a greater problem for them than SMM patients. A systematic review of Barrett's oesophagus postulated that the uncertainty of diagnosis and potential

progression to oesophageal cancer triggered anxiety (200), while other premalignant condition studies highlighted uncertainty as part of the difficulty patients had in understanding and living with their diagnosis (343,344,346,348,351). Similar issues of living with uncertainty, attending follow-up and fearing relapse were also common themes in a systematic meta-aggregation review of MM patients experiences (431).

One explanation for the lessened uncertainty from the qualitative responses was that SMM patients appeared more at peace with their future than MGUS patients. Being *"at peace"* with their prognosis has also been associated with lower psychological distress in cancer patients (524). A study found that strong relationships with their HCP, the provision of clear and honest information and HCPs recognising their fears are key components which helped cancer patients 'achieve peace' with their diagnosis (520). The findings of this dissertation **(Systematic review, AiMs and PiP)** have consistently highlighted that positive HCP care can mitigate and reduce a proportion of the uncertainty and negative psychosocial effects of a diagnosis, through informing patients and providing psychosocial care[i].

Overall, there was a consistent message from MGUS patients throughout the dissertation; that MGUS had psychosocial effects particularly in the period shortly after diagnosis which, for the majority of patients, abated over time However, a minority of patients, who experienced clinically relevant anxiety and depression, may benefit from a structured clincal psychological intervention. HCPs involved in the MGUS care pathway should be made aware of the potential impact that an MGUS diagnosis can have on patients.

[i] This was highlighted in MGUS diagnosis page 202 by haematology staff and in initial reaction to diagnosis page 174 and in Living with the fear of progression from MGUS/SMM to cancer page 283 by patients.

6.2.3 Living with MGUS long-term

In this sub-theme, the long-term effects of MGUS are discussed. This section describes how patients viewed the impact of their diagnosis in different ways, from attempted suicide **(PIP)** to making positive lifestyle changes **(PIP and AiMs) to** reduce their risk of progression to cancer and how patients described living under active surveillance for a premalignant condition.

6.2.3.1 MGUS impact on a spectrum

Throughout the dissertation, including the systematic review, AiMs and PIP studies, the impact of diagnosis varied between MGUS patients including both negative to positive impacts as well as those who viewed their condition as inconsequential.

Some studies in the systematic review reported that patients experienced considerable emotional turmoil (343,344,347,350,356). This was supported by the PIP study findings, which included one participant who attempted suicide as a result of their MGUS diagnosis. Attempted suicide as a result of cancer diagnosis has not been extensively reported but has previously been linked to increased stress and anxiety related to a cancer diagnosis (525–527). Haematological malignancies have also been linked to higher rates of suicidal intent compared to a matched (age and sex) cancer-free control in Sweden (528). There were no other reports of attempted suicide in the premalignant literature included in the systematic review; however, this may be an isolated case. As previously discussed in the shortly after diagnosis period, cancer patients encountered considerable psychosocial distress (521). Multiple systematic reviews (369,529–532), including one of MM patients (431), have outlined the emotional turmoil of a cancer diagnosis. The findings throughout the dissertation suggest that turmoil was also experienced by a subset of MGUS patients.

For other patients, a premalignant condition had a minimal impact on their lives; it was something that only came into their thoughts around the time of

surveillance. Within the systematic review of pre-malignant conditions, some studies reported on patients who did not want their condition to define them as a person or take over their life and subsequently described a limited impact on their lives (357,358). Within both the AiMs and PIP studies, the majority of patients reported that their MGUS diagnosis had minimal impact on their lives. Some patients reported that they were not sure if they should even be treated for it and they felt that they were potentially wasting valuable clinical time.

A review on how patients interpret the term 'cancer survivor' found that a small group of cancer patients perceived themselves as 'non-salient' (they did not find their lives after cancer any different from their lives before the cancer diagnosis) (533). These patients found the label 'cancer survivor' as making them feel they were dwelling on the condition and not moving on with their lives. Similarly, other life events were more important (533); similar to those patients who described their MGUS as having a minimal effect on their lives.

On the other end of the spectrum, some patients described how their MGUS diagnosis had a beneficial impact on their everyday lives and long-term health. This included increased physical activity and introducing a healthier diet. Many patients described that these changes were to reduce their risk of developing cancer in the future.

Within the PIP study, many patients increased their levels of physical activity to reduce the risk of progression to cancer; such as taking up yoga or going on more walks. Similarly, in the AiMs study, the patient's MGUS diagnosis was one of the drivers that encouraged them to be healthier. Increased physical activity levels are commonly reported in studies of individuals at higher risk of cancer (534), and in those with a premalignant (344,357–360) or a review of cancer patients (535).

The other component of positive life changes reported by 60% of MGUS patients in the PIP study was adoption of a healthier diet. Many MGUS and SMM patients reported taking supplements to reduce their risk of cancer in

particular curcumin/turmeric. Previous *in-vitro* research on curcumin has suggested that it can inhibit the growth of a variety of cell lines that can have a measurable biological effect in cancer patients, including those with MM (536). Research on MGUS patients has shown positive risk reduction of MM, but the studies have been limited by small sample sizes (10 and 36 participants in the 2 published studies) (537,538). In a recently published article from Iceland, increased fruit intake (at least three times a week) was associated with a reduced risk of progression to MM (hazard ratio 0.34) in 575 patients with MGUS using a retrospectives food frequency questionnaire (539). Within the systematic review (Chapter 2), only one study reported premalignant (colorectal polyps) patients eating more fibre, fruit and vegetables to potentially improve their future prognosis (359).

A cancer-related diagnosis has been shown to be an incentive for improved health and having a positive effect on patient's lives (533). Patients who embrace their condition are more likely to report better psychological well-being than those who perceive themselves as 'victims' (533). In one study of prostate cancer patients, for example, patients who perceived their cancer as a 'good cancer' (i.e. not life-threatening and curable) were more likely to report a positive impact on their health than those who perceived it as a 'bad cancer' (540); similar to MGUS patients viewed their premalignant (rather than malignant) status as a positive.

Overall, the positive aspects of an MGUS diagnosis were related to providing motivation to patients to change their lives for the better. This could help reduce the negative aspects of the condition improving patient's general health and fitness; which may help if progression occurs and MM treatment is initiated (541). Cases studies have shown exercise having positive effects for SMM patients (542,543) but the research has not commenced at trial/RCT level.

6.2.3.2 Surveillance

Active surveillance is a common clinical management strategy for patients with premalignant conditions, such as Barrett's Oesophagus (544–546), oral lichen planus (547) and actinic keratosis (548). These studies described surveillance as the most difficult period for patients; with uncertainty and anxiety[i] more prominent than at any other time post initial diagnosis (350,351,358,360). MGUS patients in the AiMs and PIP studies identified similar issues with uncertainty and anxiety about surveillance.

Active surveillance for MGUS patients was supported by both the haematology professionals and GPs in the survey responses presented in Chapter 4. The consensus was that MGUS patients with a lower risk of progression to cancer should be followed up in primary care with intermediate/high risk patients monitored in secondary care by haematology professionals. This was due to the need to monitor high risk patients more closely by clinicians who are experienced and knowledgeable about clinical signs of progression to MM and other haematological neoplasms. However, most GPs in Chapter 4 felt confident in their ability to conduct MGUS surveillance (through a nurse-led telephone clinic system (32)), with appropriate assistance from haematology healthcare professionals. This is potentially problematic though as most GPs are not knowledgeable and confident enough to discuss MGUS adequately with patients.

Active surveillance, with no treatment, is also a management pathway for prostate cancer but can have issues with long-term adherence (549). A pilot study in prostate cancer active surveillance has recently started which will utilise an electronic registry to track men for their testing to improve adherence to guidelines (550); which may benefit GPs in managing MGUS patient surveillance It has been reported that surveillance can have adverse

[i] This was highlighted in HCP views on MGUS surveillance page 205 by haematology staff and Living with the fear of cancer, page 175) and Healthcare Interaction, page 256 by patients.

psychological effects on prostate cancer patients; including heightened anxiety from the uncertainty about their future (29). Cancer and premalignant patients who are 'under surveillance' reported wanting more information about surveillance procedures and desired more shared decision-making in their care (551). Moving towards alternative surveillance procedures; such as the telephone clinics[i] may reduce the anxiety for some MGUS patients; however less patient contact may reduce the chances of detecting maladaptation to their MGUS diagnosis, such as anxiety or depression. Further training/provision of specialist haematology nurses would also be required to staff such services.

Overall, the findings of this dissertation supports the use of surveillance for MGUS patients but highlights issues from both patient and practitioner perspectives. For patients, further work is required to adequately inform patients about the role of surveillance and to reduce the distress experienced by patients under surveillance. For practitioners, despite GPs confidence in their ability to facilitate surveillance in low risk MGUS patients, further education and oversight from haematology professionals would be required.

6.2.3.3 QOL

There was conflicting evidence identified throughout the dissertation about the effect that MGUS and other premalignant conditions can have on QoL. Within the systematic review, there was no quantitative evidence that supported a link between having a premalignant condition and an adverse effect on a patient's general QoL. Other published systematic reviews of Barrett's oesophagus, CIN and oral premalignancies also found no detrimental effect of having a premalignant condition, in relation to QoL

[i] This was highlighted in Clinic and telephone-based care page 166 by patients.

measures or psychosocial wellbeing (anxiety and depression) measured using validated questionnaires (199–201).

From the evidence obtained from the PIP survey, MGUS patients differed from patients with other premalignant conditions based on validated QoL measures (EQ-5D, SF 12v2 and HADS), with MGUS patients more likely to have clinically relevant depression (HADS) and reduced QoL (EQ-5D). Compared to population norms, MGUS patients were also significantly more likely to have reduced QoL (EQ-5D and SF 12v2) and more likely to have clinically relevant depression (HADS). Through the AiMs study and open questions on the PIP survey, it was evident that MGUS patients experienced increased anxiety and diminished QoL as a result of their diagnosis. As the PIP study is one of the largest to include MGUS and SMM patients to date; it is clear that future research should differentiate these two premalignancies as the QoL impact appears to differ.

Previous research has shown that patients with non-malignant and malignant haematological conditions report similar QoL scores (138). This study focused on a patient sample of a community-based oncology group practice in Germany. Their results highlighted that psychosocial wellbeing and distress were not dependent on whether the condition was malignant or non-malignant but that patients who had a strong trusting relationship with their doctor reported a lower level of distress. In a recent research study comparing MGUS (and SMM) patients to MM patients, there were no significant differences in HRQoL or anxiety levels between the conditions (293). Being newly diagnosed with MM was associated with a negative psychosocial impact (484); similar to the negative psychosocial impact reported by MGUS patients at diagnosis in the AiMs and PIP studies. However, MM patients encounter additional challenges to MGUS patients, such as treatment effects and body changes (431).

While these findings highlight that some MGUS patients may have significant psychosocial impact as a result of their diagnosis, the representativeness of the online modality of the survey means this may not be true for all MGUS

patients. A clinical prospective longitudinal study would help to identify the needs of MGUS patients over time and how to identify those at most need. MGUS patients may require extra support not needed by patients with other premalignant conditions. However, given the variation in the findings from the quantitative and qualitative studies identified in the systematic review a new validated questionnaire to evaluate the impact of diagnosis should be considered for premalignant conditions. This would aid healthcare professionals identifying those with most need.

6.3 Becoming informed about MGUS

A common topic derived from the dissertation findings highlighted that MGUS patients became informed about MGUS from two key sources; HCPs and the internet. One of the main research questions[i] in the dissertation was to identify how healthcare professionals (such as haematology staff and GPs) interacted with MGUS patients?

6.3.1 Information from HCPs

In the AiMs and PIP studies, HCPs were identified as one of the main providers of information about MGUS at diagnosis and during follow-up.

6.3.1.1 At diagnosis

Within the systematic review (Chapter 2), poor information provision was consistently highlighted as an issue with many studies reporting that premalignant patients did not receive information leaflets from their HCP at diagnosis (342,344,346,349–351,356,358–360). This issue was also identified

[i] Research questions outlined, Page 20.

as an issue for MGUS patients, supported by the findings of both the AiMs and PIP (31%, Table 5-3) studies. These emphasised a lack of constructive information from HCPs about their condition and that the verbal information received was difficult to absorb at the time of diagnosis. As a result, many patients did not fully understand what MGUS was after diagnosis.

The initial consultation and the communication of risk of progression to cancer was highlighted as a particular challenge for patients with a premalignant condition in the systematic review. HCPs, especially doctors, often overestimate the amount of information that patients understand from consultations; with patients reportedly understanding approximately 58% of presented information (552). This is lower if upsetting information is presented early in the consultation, such as receiving a potential cancer diagnosis (553).

In terms of the information provided to patients at the time of MGUS diagnosis, haematology professionals participating in the survey at the HAI conference reported modifying the level and content of information provided dependent on patients' life circumstances (such as age and cognitive ability) (460). These factors are considered vital in risk communication (473,474). Informing patients of their risk of cancer requires strong communication skills and confidence from the HCP to avoid negative experiences such as fear and unnecessary uncertainty and anxiety (473,474). Some haematology survey respondents highlighted that informing patients of the low risk of progression was an important part of their role in MGUS and only 68.5% reported telling 'all patients' about the associated risk of progressing to a haematological malignancy.

Risk is a difficult concept for the general public to understand; with many lacking sufficient health numeracy [i] especially in relation to probabilities

[i] Definition: "the degree to which individuals have the capacity to access, process, interpret, communicate, and act on numerical, quantitative, graphical, biostatistical, probabilistic health information needed to make effective health decisions" (622) [page 375].

(554) and overestimating 'rare risk' (555). For MGUS, the low annual risk of progression to cancer (approximately 1%) should reassure patients but the lack of understanding of risk (health numeracy), and the difficulties that patients have in understanding MGUS in general[i], highlights the need for strong risk communication skills by haematologists and other HCPs.

In summary, haematologists have been identified as the most appropriate HCP to inform patients about their diagnosis; due to their experience and knowledge of MGUS. However, greater awareness amongst haematologists of the potentially upsetting nature of an MGUS diagnosis (which patient responses indicated that many haematologists did not seem aware of) and more appreciation of the low health literacy and numeracy skills of their patients could help physicians to improve communication strategies and reduce the psychosocial impact of the diagnosis.

6.3.1.2 Leaflet provision

Articles identified in the systematic review (356,358,359) and patients in the AiMs and PIP studies identified that low levels of leaflet/ written material provision was an issue at and after diagnosis. In the PIP study, 68% of MGUS patients reported not having received an information booklet at diagnosis. Conversely, in the National Cancer Patient Experience Survey (NCPES) 2016; 92% of haematological malignancy patients received information leaflets at diagnosis (445). In the HCP studies only 41.8% of haematology professionals reported providing written information to patients at diagnosis and only 11.7% of GPs were aware of the availability of MGUS information leaflets. The lower provision of information leaflets for MGUS patients is a key take-away message from this dissertation.

[i] As discussed on in Patient understanding of their condition/ Confusion and Uncertainty page 120 and Healthcare Interaction page 256.

Information leaflets are an important source of healthcare information for patients (434,435) and are commonly used to encourage shared decision making between patients and doctors (556,557). Patients who receive information leaflets at diagnosis are less likely to have incorrect beliefs about their condition (471,558–560); for example believing they had a cancer when they have a premalignant condition as reported by some studies in the systematic review (343,344,346,348,351). However, reviews on interventions found little supportive evidence for simple literature provision (either in booklets or via online platforms) being beneficial for prostate cancer patients for example; with benefits only being transient (532,561). However, within the PIP study, one of the main differences identified between SMM and MGUS patients was that SMM patients were more likely to receive information leaflets at diagnosis than MGUS patients[i] and reported better knowledge of their condition post-diagnosis than MGUS patients; which was likely linked.

In the literature, patients with cancers (approximately 90% in one review article) reported high levels of understanding about their diagnosis (562). In comparison, 61.7% of SMM and 54.5% patients reported at least good understanding of their condition after diagnosis, which is considerably lower. Cancer patients who reported less satisfaction with the information provision reported more anxiety, depression and lower quality of life (369,562,563). Corresponding, patients who reported the highest negative psychosocial impact were those with unmet informational needs (369,562,563).

This dissertation highlights the importance of provision of patient-friendly information in both verbal and written formats at the point of diagnosis for MGUS patients. Multiple MGUS related patient information leaflets are

[i] Leaflet provision is discussed in detail in the discussion page 320.

available from organisations such as Bloodwise[i] and Myeloma UK[ii] within the UK and other organisations such as the International Myeloma Foundation.[iii]. From the body of evidence collated, the current situation of low leaflet provision is likely a contributing factor to the heightened anxiety and negative psychosocial impact experienced by some MGUS patients[iv].

6.3.1.3 GPs as information providers

In the AiMs study patients reported visiting their GP to obtain additional information about their diagnosis. This was corroborated in the PIP study with 31.3% of patients reporting that they spoke to their GPs the most about their diagnosis compared to other HCPs. However, the knowledge levels of GPs were raised as a concern by patients in both the AiMs and PIP studies and by haematology staff in the HCP survey. Haematologists were specifically concerned about GP knowledge of the signs and symptoms of progression from MGUS to MM as the patients' primary healthcare provider. This concern appears appropriate as GPs scored poorly on MGUS-related knowledge on the GP survey; especially regarding symptoms of progression (464).

GPs are vital in providing knowledge to empower, inform and advocate for patients; which can reduce negative experiences with healthcare (564). This is especially true for patients with haematological conditions as evidenced by a qualitative study of patients with haematological malignancies who viewed the time they spent with their GP as vital in providing understanding about hospital treatments and terminology used during specialist appointments

---

[i] https://bloodwise.org.uk/sites/default/files/documents/Monoclonal%20gammopathy%20of%20undetermined%20significance%20MGUS%20fact%20sheet%20August%202017.pdf

[ii] https://www.myeloma.org.uk/wp-content/uploads/2018/03/Myeloma-UK-MGUS-Infosheet.pdf

[iii] https://www.myeloma.org/sites/default/files/resource/u-mgus_smm.pdf

[iv] How this can be realised as a clinical outcome is discussed on page 341.

(565). Due to the lack of MGUS-specific knowledge that GPs had, this type of support was not available to most MGUS patients. In a qualitative systematic review of rare disease, multiple studies highlighted unwillingness of doctors to educate themselves about, or become involved in care of, rare conditions (566). Studies had also emphasised the reluctance of some HCPs to accept the information offered by patients (566); which was highlighted by patients in the PiP study[i]

Overall, the provision of tools, such as information factsheets for both patients[ii] and GPs[iii], may help to reduce the psychosocial impact of being diagnosed with MGUS diagnosis and help GPs effectively manage MGUS patients. The current guidelines for MGUS diagnosis are provided by the UK Myeloma Forum (UKMF) and the Nordic Myeloma Study Group (NMSG) which provide an excellent overview of clinical care recommendations for MGUS patients (12); the information is extensively detailed however, making it an unlikely source of information for busy GPs[iv].

6.3.1.4 MGUS terminology

In the systematic review, 7 studies reported that medical terminology used by HCPs when communicating about their premalignant condition left patients confused about their diagnosis (342–344,348,350,358,360). This was exemplified by two studies in which patients reported 11 different terms for DCIS utilised (343,345). Similarly, in the AiMs study, 9 different terms were reportedly used to describe MGUS[v]. The PIP study did not explore this area specifically, but the terminology used by HCPs to describe MGUS was

---

[i] As described in HCPs as poor communicators and information providers page 293.

[ii] As described in Leaflet provision page 320.

[iii] How this can be realised as a clinical outcome is discussed on page 341.

[iv] How this can be realised as a clinical outcome is discussed on page 341.

[v] These have been described in Patient's knowledge of MGUS page 180.

highlighted in the qualitative responses. From the haematology survey, staff reported using the terms "MGUS" or "monoclonal gammopathy of undetermined/uncertain significance" to describe MGUS for most (68.5%) patients; but also used "lay language" and analogies to improve patient's understanding.

A systematic review focusing on the information needs of haematological malignancy patients found that patients placed a high priority on understandable information provision, especially medical information (508). Over-medicalisation of terminology, contributing to a lack of patient understanding, is a regular occurrence for patients with uncommon medical conditions (566).

The point where a healthy individual becomes a patient was highlighted by MGUS patients as shocking and a time where patients are vulnerable to the terminology their HCP uses. Terminology which can generate fear and/or anxiety in patients can increase the difficulty of making informed care choices and reduce the capability of patients to be active participants in their care (567–569).

As MGUS patients have several HCPs involved in their care (commonly GPs, haematologists and specialist nurses), it is important that HCPs are considerate in their terminology used so as not to further confuse patients. A systematic review found when more medicalised terminology was used; patients exhibited a greater preference for more invasive management and surgery (570). While MGUS care does not have an invasive or surgical option, more medicalised condition labels can have greater emotional, physiological and psychosocial consequences, such as higher blood pressure (571) and lower self-esteem (569).

In addition to provision of information leaflets utilisation of a glossary of terms specific to MGUS should be explored. This has been shown to be effective in other chronic conditions (572,573). These studies found that their condition-specific glossary was useful for educating patients, especially those who struggled with the currently available materials, and defining terms

which were often used by HCPs but not defined for the patient (572,573). Avoiding unclear terminology (306,358) and assessing patients understanding of the condition before the end of the consultation (351,574) have been shown to improve patient understanding. In conclusion, the findings of the dissertation show that language and terminology use in describing MGUS and other premalignancies are important considerations which have the potential to influence patients' beliefs about their conditions.

6.3.2 Online information

The systematic review concluded that the internet was a common way for patients to inform themselves about their condition (342–346,348,352,356). Similarly, in both the AiMs and PIP studies, MGUS (and SMM) patients reported the internet as an information source. Within the PIP study, 95.3% of MGUS participants utilised online information; with many patients using Facebook groups to obtain information, in the absence of understandable and easy to find information about MGUS online. However, this may not be true for all MGUS patients as the use of online recruitment methods are likely to have led to a biased sample of patients. However, eight studies in the systematic review also highlighted that many patients obtained information online (342–346,348,352,356).

Both of the patient studies **(AiMs and PIP)** highlighted online information as difficult to understand and contradictory. Currently available online information on MGUS was rated as poor or fair by most patients in the PIP study with available information focusing on MM rather than MGUS.

In the UK, a survey suggested that 63% of individuals use the internet to obtain information on how to manage health conditions (575). However, research has shown that many patients are unsure of which sources of information to trust (576) and there is little regulation of online information (437). A study of German cancer patients found that patients want a trustable source, information from experts and "actual information" about their

condition; however, they raised similar issues in the level of trust they could place on the quality of information (577). Obtaining incorrect information from online sources can lead to distrust in HCPs (577).

MGUS patients in both the AiMs and PIP studies supported the promotion/creation of online healthcare resources focused on MGUS to provide patient-friendly evidence-based information (578,579). In studies which developed such resources, care was taken to; use a language level below grade 6 (USA, approximately aged 12/13 years-old) and to reduce information overload (580). The development of resources that can be accessed by different 'personas' of information seekers was highlighted; with 'fuzzy' search functions (example: a search box on a website) suitable for more experienced information seekers, while filters may be more beneficial to newer and inexperienced information seekers to narrow down their results (580). Utilisation of these 'virtual information consult' resources can help patients to find the answers to their questions and 'orientate' newer patients to their new condition (580).

Overall, most patients identified that the current online information was of mixed quality and confusing. A clear need was identified for online resources with evidence based information for MGUS patients that could be accessed after diagnosis. Suitable information sources should be explained to patients at diagnosis and a link provided in written materials or in the MGUS-specific information leaflets available.

6.4 MGUS supports and health services

6.4.1 Overview

Overall, the dissertation highlighted that some MGUS patients required additional support following their diagnosis of MGUS. One of the main

research questions[i] in the dissertation was to identify what were the health and social care needs of patients with MGUS. Patients reported seeking support from their healthcare providers, their peers and their family.

6.4.2 Psychosocial support from HCPs

One of the main research questions[ii] in the dissertation was to identify how healthcare professionals (such as haematology staff and GPs) provided psychosocial care for MGUS patients.

Across the systematic review, AiMs and PIP studies patients with premalignant conditions reported varied experiences of HCP support. HCPs were either perceived as positive influences and a source of psychosocial support for patients (342–344,348,349,356,359) or dismissive and "blasé" **(PIP)** to patients (344,345,349,350,356,360). This variation was supported by the AiMs and PIP studies with examples of excellent support and patients feeling trivialised on account of their MGUS[iii]. Within the AiMs and PIP studies, GPs were perceived as having the best interests of the patient; but many lacked the knowledge to provide adequate support for patients [iv].

The AiMs study respondents reported excellent support from their specialist nurses; who were able to provide information and psychosocial support. The PIP survey also highlighted nurses as more accessible than doctors; but many patients desired greater access to specialist nurses in the qualitative responses. Interactions with nursing staff however were not mentioned in the articles reporting on other premalignant conditions in the systematic review;

---

[i] Research questions outlined, Page 20.

[ii] Research questions outlined, Page 20.

[iii] As described in The perception of Healthcare professionals (HCPs) from MGUS patients page 169 and HCPs as poor communicators and information providers. page 293) by patients.

[iv] As described in What do HCPs know about MGUS page 182 by patients, in Working with Primary Care/GPs, page 205 by haematology staff and in Knowledge of MGUS page 218 by GPs.

indicating that specialist nurses may be more available for MGUS patients than patients with other premalignant conditions. It may also be that specialist nurse input is specific to NI MGUs clinics and further research is required outside of Northern Ireland of its potentially beneficial effects.

Asymptomatic life-long conditions which have a 'silent development'/ progression phase creates an alternative framework for management compared to acute conditions; which are more relatable to patients due to prior personal or familial experiences (581). This presents a challenge to both MGUS patients and their HCPs as they often don't have frames of reference for their situation. In this dissertation, a model of the 'MGUS experience' was developed to help guide clinicians in managing MGUS care[i].

One of the biggest issues presented by MGUS patients was a lack of support regarding symptoms that they attributed to MGUS. Patients felt that as MGUS is described in the literature as asymptomatic (500), HCPs disregarded their symptoms saying that they were not connected to MGUS. Effective doctor-patient communication can positively influence patient satisfaction and potentially health outcomes through acting as a source of motivation, reassurance and support (574); while poor HCP communication effects patients negatively (582,583).

6.4.3 Telephone Clinics

The AiMs and haematology professional studies advocated increased usage of telephone/nurse-led clinics[ii] (32). There was no such system for follow up of patients with other premalignant conditions identified in the systematic review and telephone clinics were not common practice for most patients in the PIP study; who were geographically dispersed. In the AiMs study, patients

[i] A care pathway which describes the diagnostic pathway for MGUS patients is described in Pathway of MGUS care page 333.

[ii] As described in the introduction page 30.

found the telephone clinic used in the Belfast Health and Social Care Trust decreased the burden of travelling to the hospital, encouraged them to prepare questions from the safety of their own surroundings and reduced contact with cancer patients in the hospital, which was reportedly distressing. However, the high wait time between phlebotomy and the nurse calling with their results extended their anxiety over a longer period than patients felt was necessary. Mechanisms to reduce the length of this waiting period should be considered.

Both Haematology HCPs and GPs supported nurse-led telephone clinics for low/low-intermediate risk patients; with blood testing done in primary care with a qualified nurse contacting patients with results by telephone. Telephone clinics are an area of potential growth to reduce surveillance burden for many patients; especially outside the UK with a number of telephone clinics for MGUS patients already established in the UK (32) and Northern Ireland (personal communication).

As a main point of contact for patients and through facilitating the telephone clinic, nurses provided opportunities for patients to seek information and improve their MGUS health literacy. Similar to our findings, cancer patients highlighted telephone clinics as more accessible and convenient to patients and allowed more personalised care post treatment (colorectal (584,585) and breast (586) cancers). UK patients and GPs with indolent B-cell and plasma cell disorders in the Rawstron et al study supported the wider implementation of a telephone clinic review model (32); due to its greater flexibility and releasing more appointment slots for other patients respectively.

6.4.4 Peer Support

6.4.4.1 Offline

Peer support was identified as important for premalignant patients in many studies identified in the systematic review (343–345,347,359) and in MGUS

patients in the AiMs and PIP studies. Overall, there was a lack of in-person support groups for patients with premalignant conditions, with many patients reporting their desire for a peer support network (343–345,347,359). DCIS patients in the systematic review were often treated surgically, undergoing more extensive surgical procedures than some cancer patients (587), but did not have the same support systems to assist them in adjusting to their new reality/dealing with the ramifications of their condition (post breast conserving surgery/ mastectomy) (347).

MGUS patients rarely encountered other patients for peer support. In the AiMs study, the focus group was the first time many were able to see and talk to other patients with MGUS. These patients agreed that there was benefit in meeting other patients to discuss their shared experience; leading to calls for organised peer support.

As shown by the recruitment difficulties experienced throughout the dissertation, a mix of face-to-face and telecommunication could be used. This has previously been found effective in "hardly reached" (588) populations (individual, demographic, and cultural–environmental factors such as transients, from disadvantaged backgrounds and rural areas), who are difficult to access (588).

Peer support is common for cancer patients, with large numbers of charities and group sessions available (589,590) which have been shown to be effective in improving patient's psychosocial wellbeing (591,592). However, reviews have highlighted that the current literature on cancer support groups can lack theoretical frameworks, adequate program descriptions and a lack of validated instruments for measuring effects; which can make it difficult to evaluate the effects (589). These peer supports should be available to MGUS patients and based on evidence-based theoretical frameworks and measured using validated instruments.

6.4.4.2 Online

Online forums, blogs and online groups were used by patients to access social support in the systematic review (348,356), AiMs and PIP studies. Patients in the PIP study used these groups to access information and as safe spaces to explore their condition and ask questions. Patients in the AiMs study highlighted the presence of "scary" stories as barriers to seeking support online. However, these forums were opportunities for patients to read about the experiences of other MGUS (and SMM) patients **(PIP)** and patients with other premalignant conditions (348,356).

The internet is now a large component of the everyday life of most individuals and as discussed previously, many patients use it for information and resources for health conditions (575,593). Social media platforms, such as online forums, YouTube and Facebook groups are often utilised by patients with cancer (594,595), diabetes (596) and chronic diseases (597) for support. The use of online support groups have previously been associated with empowering patients, through providing emotional and informational support in cancer (598–600) and chronic conditions, such as fibromyalgia (601). Patients that used these groups felt better informed, more accepting of their condition and had better self-esteem and wellbeing (601,602). These forums and groups were avenues of; both indirect (597) and peer (603) social support; which provided patients with information on their condition, how to manage it and an important avenue for speaking about their physical, mental and emotional wellbeing (603). A systematic review proposed higher utilisation of online support groups as they were beneficial in providing cancer patients with "encouragement, empowerment, information and a sense of cohesion'' (590).

An official, recommended, website featuring patient life stories and blogs but supplemented by scientific facts, with experiential information was advocated by MGUS patients **(AiMs and PIP)**. One example is Cancer, Caring, Coping set-up for carers of cancer patients, which provides information and video clips with advice for carers, that had strong stakeholder buy-in (604). A

similar system for MGUS patients could provide a safe place to find information and contact other MGUS patients.

6.4.5 Family support

Premalignant patients the findings of the systematic review (344,345,356), AiMs and PIP studies highlighted that the support of their family was important in coping with the psychosocial impact of their condition.

In the systematic review, studies reported that premalignant patients felt they did not receive as much support from their family as other patients, especially those with cancer, due to a lack of knowledge about premalignant conditions (344,360). Many MGUS patients in the AiMs and PIP studies felt isolated as they often did not inform family and friends about their condition. In one study looking at men with urologic problems, patients who received greater perceived family support reported fewer adjustment problems and lower psychological distress (605). This was also reported by MGUS patients in the AiMs and PIP studies. Within the AiMs study, some MGUS patients stated that they did not inform others about their condition so as not to burden them especially their children.

In the cancer research field, family and friends have been identified as providing an important support system for patients (430,606,607). This support reportedly reduces the negative psychosocial effects of the condition (430,606,607). However, in some conditions, such as prostate cancer, disclosure of their diagnosis is low, to maintain a 'normal' life, in both social circles and the workplace (608,609). Similar findings were observed in the AiMs study, as some patients reported not informing their friends to maintain a 'normal' life. This was to avoid others potentially treating them differently as a result of their MGUS diagnosis, similar to what has been reported by patients with other premalignant conditions (357). As MGUS is asymptomatic and patients have no physical symptoms that would attract attention; it is easy for patients to hide their diagnosis from others.

6.4.6 Location of diagnosis

A specific unmet need identified for MGUS patients in the AiMs study was where their clinical appointment for diagnosis and surveillance was based. As discussed previously (Chapter 3), a number of patients were diagnosed within the local "cancer centre", which invoked fear and anxiety. Seeing cancer patients in waiting rooms was difficult for MGUS patients; who seen this as what may happen them in the future. These MGUS patients desired to have their surveillance provided away from the "cancer centre". While this seems to be specific for MGUS patients in Northern Ireland and was not highlighted in the PiP study, many MGUS patients are diagnosed and followed up in haematology clinics where cancer patients are also treated. Alternative surveillance strategies, such as telephone review clinics, appear to be helpful in this regard; with strong support for this from patients in the AiMs study and from HCPs in the HCP studies (Chapter 4). From searching the literature, this seems to be unique issue for NI patients; however, it may be more relevant for patients with other non-cancerous conditions.

6.5 Pathway of MGUS care

One of the main research questions[i] in the dissertation was to identify what is the formal or informal pathway that MGUS patients 'travel' to receive a diagnosis, treatment and care. This led to the development of a pathway model of the 'MGUS experience' by identifying where on the diagnostic pathway interventions could be most effective. This has previously been documented for MM patients from the Haematological Malignancy Research Network (HMRN) (428). There were multiple similarities of the pathways for both MGUS in this dissertation and MM patients in the study (428); and the

[i] Research questions outlined, Page 20.

comparisons are depicted throughout this section. A visual presentation of the MGUS care pathway is depicted below (Figure 6.2).

Patient care pathways are defined as "tools that assist in providing general guidelines for dealing with individuals and groups of patients suffering for a wide variety of diseases" (610). There is currently no consensus in the literature for documenting patient pathways to care; with many of the current "pathways" available via the NHS being flow diagrams for clinical decision making rather than patient friendly guides (611).

Pathways for care are rarely prescriptive; with multiple investigations and testing occurring prior to diagnosis. However, the pathway typically evolves from symptoms and primary care, to being diagnosed and the outcome of living with the condition (and surveillance in MGUS).

In the early stages (before being informed of the diagnosis), both MM and MGUS patient groups reported low awareness of their condition and having multiple investigations before being confirmed as a MGUS or MM patient. However, many of the MM patients reported health issues prior to diagnosis, (such as bone pain and fatigue), which were not reported for most MGUS patients. Some patients in the AiMs study did report fatigue and pain, but MGUS is considered as an asymptomatic condition in the literature (3) and subsequently by HCPs. At this stage, clinicians should explain key parts of the diagnostic pathway, including what tests are required/have been conducted and why, and patients should have the time and opportunity to ask questions. This can be via the doctor or another informed HCP; such as a haematology nurse specialist. Similar issues were raised by MGUS patients on the role of primary care; with both groups indicating that awareness of their condition amongst GPs was low. This was especially related to knowledge of the signs of progression in MGUS.

Specifically in MGUS, there was a clear unmet need presented in the studies (from patients, haematology HCPs and GPs) on the important role of written information/leaflets (Leaflet provision, page 320). This was not reported in

the MM patient pathway study; indicating patients may have felt sufficiently informed (428).

The pathway model (Figure 6.2) highlights several recommendations informed by the dissertation studies to improve care for MGUS patients; such as clearly informing patients of the diagnosis and associated risk of progression to cancer, giving patients time to reflect on their diagnosis and ask question and wide implementation of telephone clinics (32). While the pathway requires further refinement, it can provide an insight into the care pathway for MGUS patients; a previously unavailable resource in the literature.

Figure 6.2 MGUS experience care pathway model

6.6 Strengths and Limitations

While conducting the research contained within this dissertation and evaluating it after completion, clear strengths of the research were identified along with potential strategies that would have improved the rigour and credibility of the research. Each chapter contains a strengths and potential improvements section relevant to its methodological approach. This section describes the larger impact of how the methodology and research design influenced the research and its findings.

The novel nature of investigating the psychosocial impact of MGUS led to multiple challenges. Previous research was limited to some comments by clinicians and researchers that there may be potential harms from being diagnosed with MGUS (13). As there was no surrounding literature in the area a wide spectrum of viewpoints (patients and HCPs) and mixed methods designs were used to identify how the condition impacted patients.

Herein, the value of developing a mixed methods project to show the psychosocial impact of MGUS from a multi-lens perspective can be shown. This started with a mixed methods systematic review and pilot qualitative study to establish a research base, determine potential areas of investigation and develop an informed program of research.

The mixed methods systematic review was a large undertaking involving all known premalignant conditions. This was done as the research team leads, experienced in this field, were unaware of published literature investigating the psychosocial impact of MGUS. This was confirmed within the findings of the systematic review. By identifying potentially relevant issues for patients with premalignant conditions as a whole and assessing comparability between patients with different premalignant conditions key areas of investigation were identified. The pilot qualitative study (AiMs study) similarly set the scene for the PIP survey by determining if the issues experienced by patients with other premalignant conditions identified in the systematic review were similar for MGUS patients. In short, the factors affecting MGUS

patients in the AiMs and PIP studies mirrored many of those identified for patients with other premalignancies identified through the systematic review. Using a mixed methods approach is a pragmatic method of generating research questions using the strengths of qualitative research and naturalistic enquiry, while attempting to answer these questions using empirically-based and precise quantitative data to assess the generalisability of the qualitative findings (612).

Patients and clinicians were involved in the development of the PIP survey. PPI involvement provides a greater understanding and insight into the research area (613,614) and allows the community to have greater input into research (511). In hindsight, greater PPI involvement for the healthcare professional surveys would have benefited the research; but time constraints meant that this was not viable at the time.

Despite the strength and novelty of the research question several limitations need to be taken into consideration. Two of the studies (PIP and GP survey) used online methods to recruit participants. Previous research has highlighted the potential pitfalls of online data collection, especially in relation to potential selection bias (481). This responder bias, with respondents being more likely to be highly motivated and/or engaged in the topic compared to the rest of the target population (481); may have influenced the results, with actual MGUS-specific knowledge lower within the global GP population. This is especially true of doctors, as the targeted population (GPs) tend to only interact with research studies salient to them (457,615) and relevant to their interests as physicians (616). Doctors who attend conferences and seek out (and participate in) studies of this nature are more likely to be knowledgeable about the topic area than non-participants (617,618). Unfortunately, this level of bias was not able to be detected.

Accurate (reliable and valid) instruments for patient-reported data is vital for benchmarking between conditions (and patients) and to provide an objective measure of patient outcomes (255); such as an MGUS diagnosis. The use of

validated questionnaires in the PIP survey increased confidence in the findings and enabled comparison with the findings of the systematic review.

Overall, the average age of MGUS patients who participated in the research studies included in this dissertation (AiMs: approx. 57 years-old, PIP: 54.3 years-old) was considerably younger than the average age of diagnosis for MGUS patients (74 years old) (438). However, it is important to determine the impact of MGUS on younger individuals as these patients will live longer with the knowledge of their condition and have an increased lifetime risk of developing MM (125). Focusing interventions on this younger cohort may have optimal benefit.

6.7 Future Directions

The findings of this dissertation support the need for further research on MGUS patients; specifically building a longitudinal study to assess the impact of MGUS over time, developing a questionnaire to enable clinical care teams to identify patients requiring additional support, creating strategies to improve psychosocial care of MGUS patients and further HCP involvement and training.

The findings support a larger longitudinal study, where MGUS patients are followed from diagnosis with psychosocial evaluation/testing at multiple time points; such as at diagnosis, after the initial surveillance appointment and 2 and 5 years' post-diagnosis. This would provide time for patients to live with their condition and experience long-term follow-up. This would improve the evidence base on the psychosocial impact of MGUS giving an indication of where support is most needed. A large scale population trial is currently underway in Iceland (iStopMM) to screen the population for MGUS (37). This provides an opportunity to fully evaluate the impact of diagnosis. Furthermore, Future research should include patients across all three disease stages (MGUS, SMM and MM) to create a more complete picture of the

effects of diagnosis on QoL, health service utilisation and the psychosocial impact and wellbeing of these haematological conditions.

Incorporating more comprehensive qualitative interviews/focus groups with the healthcare staff involved in MGUS care, such as the GPs and haematologists and nursing staff would provide further information of the care pathway for MGUS patients. While the GP study was able to get a worldwide viewpoint as to how MGUS patients are treated in-depth interviews in a local context would provide more detailed information on how to improve the wellbeing of MGUS patients. This was considered as a potential component of this dissertation, but was not pursued due to difficulties recruiting these individuals.

At the time of submission, there are no MGUS specific NICE guidelines, which focus only on MM but these propose recommendations regarding communication and support, which would also be relevant to MGUS patients (18). The importance of providing information to the patient and family members/carers about MGUS and its prognosis and how to access peer and patient support groups would be particularly helpful.

This research further strengthens the call for improved educational resources on MGUS for GPs, which highlights the key clinical indicators and possible signs and symptoms of progression to MM. In practical terms, having these educational materials as easy to access and understandable is an important consideration in upskilling GPs on MGUS care. This is especially important as GPs are likely to be more involved in MGUS care in the near future in Northern Ireland conducting surveillance for low and low-intermediate risk MGUS patients. From the knowledge gained from the AiMs study, the GP as an information provider was key to the patient experience. A feasibility study of how to integrate MGUS care into GP practice would be the next step in determining the viability of this; building on the foundations this project has established.

6.8 Clinical Applications

Patient friendly information and support is necessary at the point of diagnosis and thereafter for all MGUS patients. This is in line with the UK/Nordic guidelines [i] (12). This information should be offered to patients in a variety of formats (verbal, paper and online) as patient needs differ and should contain information on future follow-up procedures, disease progression and signs/symptoms to be aware of. Inclusion of 'life stories' of other MGUS patients in information leaflets was also suggested by patients who want to 'see' what other MGUS patients look like. Currently, a number of free patient friendly information booklets are available online (e.g. Myeloma UK, Macmillan or the International Myeloma Foundation) but not all patients are aware of these resources as they are not routinely provided at diagnosis.

HCPs supported improved services to assist MGUS management; especially implementation/expansion of telephone review clinics. The use of telephone clinics was positively endorsed by MGUS patients. Telephone clinics conducted by specialist nurse practitioners reduce patient burden by reducing hospital visits, which can incur both financial and psychosocial costs (32,619).

Utilisation of a single healthcare database may also assist clinical care teams in their management of patients in primary care. This type of clinical software is partly utilised within Northern Ireland already, the electronic care record (ECR), which holds the majority of healthcare data on one system. This is considered by doctors to be an excellent resource to improve patient care by providing one, easy-to-access location for medical notes (469). Previous research in personalised computer-based information for cancer patients has shown that information on patients specific clinical investigation scores can be easily and inexpensively provided, with appropriate reference material

[i] As described in Clinical guidelines on MGUS; clinical criteria, testing/diagnosis and monitoring procedures page 26.

(620). This type of technology may be the next step in improving MGUS care and expertise in GPs. Other supported options were computer-based clinical alert system with a laboratory report alerting to possible MGUS/blood malignancy, better contact with haematology (GPs) and access to a website/app/leaflet for patients with MGUS. Northern Ireland is currently introducing a digital integrated care record (Encompass[i]) that can improve health outcomes and provide a greater overview for haematology staff and GPs to co-ordinate care and allow patients to access their test results if desired (as highlighted by some patients in the AiMs study[ii]).

6.9 Dissertation Conclusion

In conclusion, being diagnosed with MGUS has a variety of effects on patients. Patient's journeys and transition through their condition are individual to each patient but share commonalities which enables this research to suggest mechanisms to improve the "MGUS experience". The anxiety and uncertainty experienced by the MGUS patients who took part in this research, and the research captured in the systematic review of patients with other pre-malignant conditions, could be improved with service improvements that increase the knowledge and health literacy at/post-diagnosis for patients and HCPs. Establishing mechanisms to detect patients experiencing difficulties with their diagnosis and creating pathways to help patients cope with their diagnosis are crucial. The majority of patients are most impacted near diagnosis, and this is where intervention strategies to better the lives of patients with M

GUS and reduce the costs (both psychosocially for the patients and financially for the health service) could be implemented.

---

[i] http://www.hscboard.hscni.net/encompass/

[ii] As described in Patient's knowledge of MGUS page 180.

7 References

1. Dimopoulos MA, Terpos E, Niesvizky R, Palumbo A. Clinical characteristics of patients with relapsed multiple myeloma. Cancer Treat Rev. 2015 Dec;41(10):827–35.

2. Palumbo A, Anderson K. Multiple Myeloma. N Engl J Med. 2011 Mar 17;364(11):1046–60.

3. Madan S, Greipp PR. The incidental monoclonal protein: Current approach to management of monoclonal gammopathy of undetermined significance (MGUS). Blood Rev. 2009 Nov;23(6):257–65.

4. Ozawa S, Pongpirul K. 10 Best Resources on … Mixed Methods Research in Health Systems. Health Policy Plan. 2014;29(3):323–7.

5. Creswell JW, Clark VLP. Designing and Conducting Mixed Methods research. Sage, editor. Thousand Oaks, CA: Sage Publications, Inc.; 2011.

6. Berman E. An Exploratory Sequential Mixed Methods Approach to Understanding Researchers' Data Management Practices at UVM: Integrated Findings to Develop Research Data Services. J eScience Librariansh. 2017;6(1):e1104.

7. Kyle RA, Greipp PR. Smoldering Multiple Myeloma — NEJM [Internet]. Vol. 302, The New England Journal of Medicine. 1980. p. 1347–9. Available from: http://www.nejm.org/doi/full/10.1056/NEJM198006123022405

8. Takatsuki K, Sanada I. Plasma cell dyscrasia with polyneuropathy and endocrine disorder: clinical and laboratory features of 109 reported cases. Jpn J Clin Oncol. 1983;13(3):543–56.

9. Kyle RA. Monoclonal gammopathy of undetermined significance: natural history in 241 cases. J Am Med. 1978;64(5):814–25.

10. Kyle RA, Durie BGM, Rajkumar S V, Landgren O, Blade J, Merlini G, et al. Monoclonal gammopathy of undetermined significance (MGUS) and smoldering (asymptomatic) multiple myeloma: IMWG consensus perspectives risk factors for. Leukemia. 2010 Jun;24(6):1121–7.

11. International Myeloma Working Group. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders. Br J Haematol. 2003 Jun;121(5):749–57.

12. Bird J, Behrens J, Westin J, Turesson I, Drayson M, Beetham R, et al. UK Myeloma Forum (UKMF) and Nordic Myeloma Study Group (NMSG): guidelines for the investigation of newly detected M-proteins and the management of monoclonal gammopathy of undetermined significance (MGUS). Br J Haematol. 2009;147(1):22–42.

13. Go RS, Rajkumar SV. How I manage monoclonal gammopathy of undetermined significance. Blood. 2018 Jan 11;131(2):163–73.

14. Rajkumar SV, Kyle RA, Buadi FK. Advances in the diagnosis, classification, risk stratification, and management of monoclonal gammopathy of undetermined significance: Implications for recategorizing disease entities in the presence of evolving scientific evidence. Mayo Clin Proc. 2010;85(10):945–8.

15. Berenson JR, Anderson KC, Audell R a, Boccia R V, Coleman M, Dimopoulos M a, et al. Monoclonal gammopathy of undetermined significance: a consensus statement. Br J Haematol. 2010 Jul;150(1):28–38.

16. van de Donk NWCJ, Palumbo A, Johnsen HE, Engelhardt M, Gay F, Gregersen H, et al. The clinical relevance and management of monoclonal gammopathy of

undetermined significance and related disorders: recommendations from the European Myeloma Network. Haematologica. 2014;99(6):984–96.

17. World Health Organization (WHO). International Statistical Classification of Diseases and Related Health Problems 10th Revision. 10th ed. Vol. Volume 2 I. Geneva: WHO; 2010.

18. National Institute for Health and Care Excellence. Myeloma: diagnosis and management. 2016.

19. Rajkumar SV, Dimopoulos MM a, Palumbo A, Blade J, Merlini G, Mateos M-V, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol. 2014 Nov;15(12):e538-548.

20. Landgren O, Kyle R a., Rajkumar SV. From myeloma precursor disease to multiple myeloma: New diagnostic concepts and opportunities for early intervention. Clin Cancer Res. 2011 Mar 15;17(6):1243–52.

21. Dispenzieri A, Katzmann JA, Kyle RA, Dirk R, Iii LJM, Colby CL, et al. Prevalence and Risk of Progression of Light-Chain Monoclonal Gammopathy of Undetermined Significance (LC-MGUS): A newly defined entity. Lancet. 2010;375(9727):1721–8.

22. Smith A, Wisloff F, Samson D. Guidelines on the diagnosis and management of multiple myeloma 2005. Br J Haematol. 2006;132(4):410–51.

23. Kyle RA, Therneau TM, Rajkumar SV, Remstein ED, Offord JR, Larson DR, et al. Long-term follow-up of IgM monoclonal gammopathy of undetermined significance. Blood. 2003;102(10):3759–64.

24. Doyle LM, Go RS. A monoclonal gammopathy in search of clinical significance: 57 years later. Blood. 2009;114(11):2355–7.

25. Bianchi G, Kyle RA, Colby CL, Larson DR, Kumar S, Katzmann JA, et al. Impact of optimal follow-up of monoclonal gammopathy of undetermined significance on early diagnosis and prevention of myeloma-related complications. Blood. 2010;116(12):2019–25.

26. Rajkumar SV, Kyle R a, Therneau TM, Melton LJ, Bradwell AR, Clark RJ, et al. Serum free light chain ratio is an independent risk factor for progression in monoclonal gammopathy of undetermined significance. Blood. 2005 Aug;106(3):812–7.

27. Pérez-Persona E, Mateo G, García-Sanz R, Mateos MV, De Las Heras N, De Coca AG, et al. Risk of progression in smouldering myeloma and monoclonal gammopathies of unknown significance: Comparative analysis of the evolution of monoclonal component and multiparameter flow cytometry of bone marrow plasma cells. Br J Haematol. 2010;148(1):110–4.

28. Bellardita L, Valdagni R, Van Den Bergh R, Randsdorp H, Repetto C, Venderbos LDF, et al. How does active surveillance for prostate cancer affect quality of life? A systematic review. Eur Urol. 2015;67(4):637–45.

29. Ruane-McAteer E, Porter S, O'Sullivan JM, Santin O, Prue G. Active surveillance for favorable-risk prostate cancer: Is there a greater psychological impact than previously thought? A systematic, mixed studies literature review. Psychooncology. 2017;26(10):1411–21.

30. Parker C. Active surveillance: towards a new paradigm in the management of early prostate cancer. Lancet Oncol. 2004 Feb;5(2):101–6.

31. Adolfsson J. Watchful waiting and active surveillance: the current position. BJU Int. 2008;102(1):10–4.

32. Rawstron AC, Jones RA, Ferguson C, Hughes G, Selby P, Reid C, et al. Outreach

monitoring service for patients with indolent B-cell and plasma cell disorders: a UK experience. Br J Haematol. 2007;139(5):845–8.

33. Ögmundsdóttir HM, Haraldsdóttir V, Jóhannesson GM, Ólafsdóttir G, Bjarnadóttir K, Sigvaldason H, et al. Monoclonal gammopathy in Iceland: A population-based registry and follow-up. Br J Haematol. 2002;118(1):166–73.

34. Ong F, Hermans J, Noordijk EM, Wijermans PW, Seelen PJ, de Kieviet W, et al. A population-based registry on paraproteinaemia in The Netherlands. Comprehensive Cancer Centre West, Leiden, The Netherlands. Br J Haematol. 1997;99(4):914–20.

35. Therneau TM, Kyle RA, Melton LJ, Larson DR, Benson JT, Colby CL, et al. Incidence of monoclonal gammopathy of undetermined significance and estimation of duration before first clinical recognition. Mayo Clin Proc. 2012;87(11):1071–9.

36. Kyle RA, Therneau TTM, Rajkumar SV, Larson DR, Plevak MF, Offord JR, et al. Prevalence of monoclonal gammopathy of undetermined significance. N Engl J Med. 2006;354(13):1362–9.

37. International Myeloma Foundation. iStopMM [Internet]. 2018. Available from: https://www.myeloma.org/istopmm

38. Landgren O, Katzmann J, Hsing A. Prevalence of monoclonal gammopathy of undetermined significance among men in Ghana. Mayo Clin Proc. 2007;82(12):1468–73.

39. Iwanaga M, Tomonaga M. Prevalence of monoclonal gammopathy of undetermined significance in Asia: a viewpoint from nagasaki atomic bomb survivors. Clin Lymphoma Myeloma Leuk. 2014;14(1):18–20.

40. Watanaboonyongcharoen P, Na Nakorn T, Rojnuckarin P, Lawasut P, Intragumtornchai T. Prevalence of monoclonal gammopathy of undetermined significance in Thailand. Int J Hematol. 2012;95(2):176–81.

41. Wu SP, Minter A, Costello R, Zingone A, Lee CK, Au WY LO. MGUS prevalence in an ethnically Chinese population in Hong Kong Recent. Blood. 2015;121(12):2364–7.

42. Mohammadnia-Afrouzi1 M, Aghili B, Gholamrezaei M, iAdel Ghavami M, Matin Z, Samira B, et al. Monoclonal Gammopathy in Iran : Prevalence and Isotype Distribution. MOJ Immuniology. 2014;1(5):2–4.

43. Landgren O, Gridley G, Turesson I, Caporaso NE, Goldin LR, Baris D, et al. Risk of monoclonal gammopathy of undetermined significance (MGUS) and subsequent multiple myeloma among African American and white veterans in the United States. Blood. 2006;107(3):904–6.

44. Kyle RA. Incidence of monoclonal proteins in a Minnesota community with a cluster of multiple myeloma. Blood. 1972;40(5):719–24.

45. Wadhera RK, Rajkumar SV. Prevalence of monoclonal gammopathy of undetermined significance: a systematic review. Mayo Clin Proc. 2010 Oct;85(10):933–42.

46. Aguzzi F, Bergami M. Occurrence of monoclonal components in general practice: clinical implications. Eur J Haematol. 1992;48(4):192–5.

47. Anagnostopoulos A, Evangelopoulou A. Incidence and evolution of monoclonal gammopathy of undetermined significance (MGUS) in Greece. Ann Haematol. 2002;81(7):357–61.

48. Cohen HJ, Crawford J, Rao MK, Pieper CF, Currie MS. Racial differences in the prevalence of monoclonal gammopathy in a community-based sample of the elderly. Am J Med. 1998;104(5):439–44.

49. Carrell R, Colls B, Murray J. The Significance of Monoclonal Gammopathy in a Normal Population*. Aust N Z J Med. 1971;1(4):398–401.

50. Malacrida V, De Francesco D. Laboratory investigation of monoclonal gammopathy during 10 years of screening in a general hospital. J Clin Pathol. 1987;40(7):793–7.

51. Smith A, Howell D, Patmore R, Jack A, Roman E. Incidence of haematological malignancy by sub-type: a report from the Haematological Malignancy Research Network. Br J Cancer. 2011;105(11):1684–92.

52. Weiss BM, Abadie J, Verma P, Howard RS, Kuehl WM. A monoclonal gammopathy precedes multiple myeloma in most patients. Blood. 2009 May;113(22):5418–22.

53. Cesana C, Klersy C, Barbarano L, Nosari AM, Crugnola M, Pungolino E, et al. Prognostic factors for malignant transformation in monoclonal gammopathy of undetermined significance and smoldering multiple myeloma. J Clin Oncol. 2002;20(6):1625–34.

54. Kumar S, Rajkumar SV, Kyle R a., Lacy MQ, Dispenzieri A, Fonseca R, et al. Prognostic value of circulating plasma cells in monoclonal gammopathy of undetermined significance. J Clin Oncol. 2005;23(24):5668–74.

55. Rajkumar SV, Mesa RA, Fonseca R, Schroeder G, Plevak MF, Dispenzieri A, et al. Bone marrow angiogenesis in 400 patients with monoclonal gammopathy of undetermined significance, multiple myeloma, and primary amyloidosis. Clin Cancer Res. 2002;8(7):2210–6.

56. Bladé J, Rosiñol L, Cibeira MT, de Larrea CF. Pathogenesis and progression of monoclonal gammopathy of undetermined significance. Leukemia. 2008;22(9):1651–7.

57. Korde N, Kristinsson SY, Landgren O. Monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM): Novel biological insights and development of early treatment strategies. Blood. 2011 May 26;117(21):5573–81.

58. Kristinsson SY, Björkholm M, Andersson TM-L, Eloranta S, Dickman PW, Goldin LR, et al. Patterns of survival and causes of death following a diagnosis of monoclonal gammopathy of undetermined significance: a population-based study. Haematologica. 2009;94(12):1714–20.

59. Kristinsson SY. Population-Based Studies on Familiality and Prognosis in Patients With Monoclonal gammopathies. Karolinska University Hospital Solna and Karolinska Institutet, Stockholm, Sweden; 2009.

60. Schaar CG, Le Cessie S, Snijder S, Franck PFH, Wijermans PW, Ong C, et al. Long-term follow-up of a population based cohort with monoclonal proteinaemia. Br J Haematol. 2009;144(2):176–84.

61. Sigurdardottir EE, Turesson I, Lund SH, Lindqvist EK, Mailankody S, Korde N, et al. The Role of Diagnosis and Clinical Follow-up of Monoclonal Gammopathy of Undetermined Significance on Survival in Multiple Myeloma. JAMA Oncol. 2015;1(2):1–7.

62. Go RS, Gundrum JD, Neuner JM. Determining the Clinical Significance of Monoclonal Gammopathy of Undetermined Significance: A SEER–Medicare Population Analysis. Clin Lymphoma Myeloma Leuk. 2015;15(3):177-186.e4.

63. Melton LJ, Rajkumar SV, Khosla S, Achenbach SJ, Oberg AL, Kyle R a. Fracture risk in monoclonal gammopathy of undetermined significance. J bone Miner Res. 2004 Jan;19(1):25–30.

64. Landgren O, Shim YK, Michalek J, Costello R, Burton D, Ketchum N, et al. Agent Orange Exposure and Monoclonal Gammopathy of Undetermined Significance. JAMA Oncol. 2015 Sep 3;1(8):1061.

65. McShane CM, Murray LJ, Landgren O, O'Rorke M a, Korde N, Kunzmann AT, et al. Prior autoimmune disease and risk of monoclonal gammopathy of undetermined significance and multiple myeloma: a systematic review. Cancer Epidemiol biomarkers Prev. 2014 Feb 1;23(2):332–42.

66. Alexander DD, Mink PJ, Adami H-O, Cole P, Mandel JS, Oken MM, et al. Multiple myeloma: a review of the epidemiologic literature. Int J Cancer. 2007 Jan;120 Suppl:40–61.

67. Rajkumar SV, Dispenzieri A, Kyle RA. Monoclonal Gammopathy of Undetermined Significance, Waldenström Macroglobulinemia, AL Amyloidosis, and Related Plasma Cell Disorders: Diagnosis and Treatment. Mayo Clin Proc. 2006 May;81(5):693–703.

68. Kyle RA, Buadi F, Vincent Rajkumar S. Management of monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM). Oncology. 2011;25(7):578–86.

69. Bida JP, Kyle RA, Therneau TM, Melton LJ, Plevak MF, Larson DR, et al. Disease associations with monoclonal gammopathy of undetermined significance: a population-based study of 17,398 patients. Mayo Clin Proc. 2009;84(8):685–93.

70. Cabrera Q, Macro M, Hebert B, Cornet E, Collignon A, Troussard X. Epidemiology of Monoclonal Gammopathy of Undetermined Significance (MGUS): The experience from the specialized registry of hematologic malignancies of Basse-Normandie (France). Cancer Epidemiol. 2014;38(4):354–6.

71. Smith A, Roman E, Howell D, Jones R, Patmore R, Jack A. The Haematological Malignancy Research Network (HMRN): a new information strategy for population based epidemiology and health service research. Br J Haematol. 2010;148(5):739–53.

72. Ruiz-Delgado G, Gómez R. Monoclonal gammopathy of undetermined significance (MGUS) in Mexican mestizos: one institution's experience. Gac Med Mex. 2004;140(4):375–9.

73. Gregersen H, Jensen P, Gislum M, Jørgensen B, Sørensen HT, Nørgaard M. Fracture risk in patients with monoclonal gammopathy of undetermined significance. Br J Haematol. 2006 Oct;135(1):62–7.

74. Landgren O, Kyle RA, Hoppin JA, Beane Freeman LE, Cerhan JR, Katzmann JA, et al. Pesticide exposure and risk of monoclonal gammopathy of undetermined significance in the Agricultural Health Study. Blood. 2009 Apr 22;113(25):6386–91.

75. Chang S-H, Luo S, Thomas TS, O'Brian KK, Colditz GA, Carlsson NP, et al. Obesity and the Transformation of Monoclonal Gammopathy of Undetermined Significance to Multiple Myeloma: A Population-Based Cohort Study. J Natl Cancer Inst. 2017;109(5):djw264.

76. Reidpath DD, Crawford D, Tilgner L, Gibbons C. Relationship between body mass index and the use of healthcare services in Australia. Obes Res. 2002;10(6):526–31.

77. Pasqualetti P, Festuccia V, Acitelli P, Collacciani A, Giusti A, Casale R. Tobacco smoking and risk of haematological malignancies in adults: a case-control study. Br J Haematol. 1997;97(3):659–62.

78. Jiménez-Ruiz CA, Andreas S, Lewis KE, Tonnesen P, van Schayck CP, Hajek P, et al. Statement on smoking cessation in COPD and other pulmonary diseases and in smokers with comorbidities who find it difficult to quit. Eur Respir J. 2015;46(1):61–79.

79. Pasqualetti P, Collacciani A, Casale R. Risk of monoclonal gammopathy of undetermined significance: a case-referent study. Am J Hematol. 1996;52(3):217–20.

80. Pasqualetti P, Casale R. Occupational risk for hematological malignancies. Am J Hematol. 1991;38(2):147–9.

81. Bizzaro N, Pasini P. Familial occurrence of multiple myeloma and monoclonal gammopathy of undetermined significance in 5 siblings. Haematologica. 1989;75(1):58–63.

82. Steingrímsdóttir H, Einarsdóttir HK, Haraldsdóttir V, Ogmundsdóttir HM. Familial monoclonal gammopathy: hyper-responsive B cells in unaffected family members. Eur J Haematol. 2011;86(5):396–404.

83. Greenberg AJ, Rajkumar SV, Vachon CM. Familial monoclonal gammopathy of undetermined significance and multiple myeloma : epidemiology , risk factors , and biological characteristics. Blood. 2013;119(23):5359–66.

84. Brown LM, Gridley G, Check D, Landgren O. Risk of multiple myeloma and monoclonal gammopathy of undetermined significance among white and black male United States veterans with prior autoimmune, infectious, inflammatory, and allergic disorders. Blood. 2008 Apr 1;111(7):3388–94.

85. Lindqvist EK, Goldin LR, Landgren O, Blimark C, Mellqvist U-H, Turesson I, et al. Personal and family history of immune-related conditions increase the risk of plasma cell disorders: a population-based study. Blood. 2011;118(24):6284–91.

86. Kelly J, Adelman L. Polyneuropathies associated with IgM monoclonal gammopathies. Arch Neurol. 1988;45(12):1355–9.

87. Chassande B. Peripheral neuropathy associated with IgM monoclonal gammopathy: correlations between M-protein antibody activity and clinical/electrophysiological features in 40. Muscle Nerve. 1998;21(1):55–62.

88. Bollensen E, Steck A, Schachner M. Reactivity with the peripheral myelin glycoprotein Po in serum from patients with monoclonal IgM gammopathy and polyneuropathy. Neurology. 1988;38(8):1266–1266.

89. Kyle RA, Remstein ED, Therneau TM, Dispenzieri A, Kurtin PJ, Hodnefield JM, et al. Clinical course and prognosis of smoldering (asymptomatic) multiple myeloma. N Engl J Med. 2007;356(25):2582–90.

90. Ghobrial IM, Landgren O. How I treat smoldering multiple myeloma. Blood. 2014 Nov 27;124(23):3380–8.

91. Dispenzieri A, Stewart AK, Chanan-Khan A, Rajkumar SV, Kyle RA, Fonseca R, et al. Smoldering multiple myeloma requiring treatment: Time for a new definition? Blood. 2013;122(26):4172–81.

92. Kristinsson SY, Holmberg E BC. Treatment for High-Risk Smoldering Myeloma. N Engl J Med. 2013 Oct 31;369(18):1762–3.

93. Rosinol L, Carrio A, Blade J, Queralt R, Aymerich M, Cibeira M, et al. Comparative genomic hybridisation identifies two variants of smoldering multiple myeloma. Br J Haematol. 2005;130(5):729–32.

94. Rosiñol L, Bladé J, Esteve J, Aymerich M, Rozman M, Montoto S, et al. Smoldering multiple myeloma: Natural history and recognition of an evolving type. Br J Haematol. 2003;123(4):631–6.

95. Rajkumar SV. Treatment of multiple myeloma. Nat Rev Clin Oncol. 2011;8(8):479–91.

96. George ED, Sadovsky R. Multiple myeloma: recognition and management. Am Fam

Physician. 1999 Apr 1;59(7):1885–94.

97. Renshaw C, Ketley N, Møller H, Davies EA. Trends in the incidence and survival of multiple myeloma in South East England 1985-2004. BMC Cancer. 2010 Dec 1;10(1):74.

98. Friese CR, Abel GA, Magazu LS, Neville BA, Richardson LC, Earle CC. Diagnostic delay and complications for older adults with multiple myeloma. Leuk Lymphoma. 2009;50(3):392–400.

99. Durie BGM, Salmon SE. A clinical staging system for multiple myeloma correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival. Cancer. 1975 Sep;36(3):842–54.

100. Greipp PR, Miguel JS, Dune BGM, Crowley JJ, Barlogie B, Bladé J, et al. International staging system for multiple myeloma. J Clin Oncol. 2005;23(15):3412–20.

101. Attal M, Lauwers-Cances V. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. N Engl J Med. 2012;366(19):1782–91.

102. Fermand P.; Chevret, S.; Divine, M.; Leblond, V.; Belanger, C.; Macro, M.; Pertuiset, E.; Dreyfus, F.; Mariette, X.; Boccacio, C.; Brouet, J. C. JP. R. High-dose therapy and autologous peripheral blood stem cell transplantation in multiple myeloma: up-front or rescue treatment? Results of a multicenter sequential randomized clinical trial. Blood. 1998;92(9):3131–6.

103. Facon, T., Mary, J.Y., Harousseau, J.A.E., Attal, M., Bosly, A., Michaux, J.L., Maloisel, F., Sadoun, A., Muron, T., Anglaret, B. and Rossi JF. Bone marrow transplantation (ABMT) following a first course of high dose melphalan (HDM) in multiple myeloma (MM). Preliminary results of a prospective .... Blood. 1996;88(10):2729.

104. Barlogie B, Kyle RA, Anderson KC, Greipp PR, Lazarus HM, Hurd DD, et al. Standard chemotherapy compared with high-dose chemoradiotherapy for multiple myeloma: Final results of phase III US intergroup trial S9321. J Clin Oncol. 2006;24(6):929–36.

105. Lonial S, Durie B, Palumbo A, San-Miguel J. Monoclonal antibodies in the treatment of multiple myeloma: Current status and future perspectives. Leukemia. 2016;30(3):526–35.

106. Raab MS, Podar K, Breitkreutz I, Richardson PG, Anderson KC. Multiple myeloma. Vol. 374, The Lancet. 2009. p. 324–39.

107. Röllig C, Knop S, Bornhäuser M. Multiple myeloma. Lancet. 2015 May;385(9983):2197–208.

108. The Haematological Malignancy Research Network (HMRN). Myeloma Statistics [Internet]. 2018 [cited 2018 Sep 28]. Available from: https://www.hmrn.org/statistics/disorders/24

109. Cancer Research UK. Myeloma incidence statistics [Internet]. 2018 [cited 2019 Apr 9]. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma/incidence#ref-

110. DR D.W. Donnelly (Queen's University Belfast) DAG (Queen's UB. Cancer Incidence Trends 1993-2013 with Projectections to 2035. 2014;89–96.

111. Northern Ireland Cancer Registy. Multiple Myeloma Official statistics [Internet]. 2018 [cited 2019 Apr 9]. Available from: https://www.qub.ac.uk/research-centres/nicr/CancerInformation/official-statistics/BySite/Blood/#d.en.620923

112. Cancer Research UK. Myeloma statistics [Internet]. [cited 2018 Jun 18]. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma

113. Buadi FK, Pandey S, Kapoor P, Kumar SK, Dispenzieri A, Lacy MQ, et al. Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. Leukemia. 2014;28(5):1122–8.

114. Norris FRCPA D. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues (4th Edition) - Lymphoma Classification in the Third Millennium. QML Pathol Newsl. 2012;(4):1–12.

115. D'Sa S. Lymphoplasmacytic Lymphoma / Waldenström's Macroglobulinaemia. London Cancer LPL/WM Guidelines 2015-16 v1.0. 2015.

116. Fonseca R, Hayman S. Waldenström macroglobulinaemia. Br J Haematol. 2007;138(6):700–20.

117. Gobbi PG, Bettini R, Montecucco C, Cavanna L, Morandi S, Pieresca C, et al. Study of prognosis in Waldenström's macroglobulinemia: a proposal for a simple binary classification with clinical and investigational utility. Blood. 1994;83(10):2939–45.

118. Kyle RARA, Therneau TM, Rajkumar SV, Offord JR, Larson DR, Plevak MF, et al. A long-term study of prognosis in monoclonal gammopathy of undetermined significance. N Engl J Med. 2002 Feb 21;346(8):564–9.

119. Treon SP. How i treat Waldenström macroglobulinemia. Blood. 2015;126(6):721–32.

120. Phekoo KJ, Jack RH, Davies E, Møller H, Schey SA. The incidence and survival of Waldenström's Macroglobulinaemia in South East England. Leuk Res. 2008;32(1):55–9.

121. Bellotti V, Mangione P, Merlini G. Review: immunoglobulin light chain amyloidosis--the archetype of structural and pathogenic variability. J Struct Biol. 2000;130(2–3):280–9.

122. Dispenzieri A, Lacy MQ, Kyle RA, Therneau TM, Larson DR, Rajkumar SV, et al. Eligibility for Hematopoietic Stem-Cell Transplantation for Primary Systemic Amyloidosis Is a Favorable Prognostic Factor for Survival. J Clin Oncol. 2001 Jul 15;19(14):3350–6.

123. Pinney JH, Smith CJ, Taube JB, Lachmann HJ, Venner CP, Gibbs SDJ, et al. Systemic Amyloidosis in England: An epidemiological study. Br J Haematol. 2013;161(4):525–32.

124. Gillmore JD, Wechalekar A, Bird J, Cavenagh J, Hawkins S, Kazmi M, et al. Guidelines on the diagnosis and investigation of AL amyloidosis. Br J Haematol. 2015;168(2):207–18.

125. Kyle RA, Therneau TM, Rajkumar SV, Larson DR, Plevak MF, Melton LJ. Long-term follow-up of 241 patients with monoclonal gammopathy of undetermined significance: the original Mayo Clinic series 25 years later. Mayo Clin Proc. 2004 Jul;79(7):859–66.

126. Strati P, Shanafelt TD. Monoclonal B-cell lymphocytosis and early-stage chronic lymphocytic leukemia: diagnosis, natural history, and risk stratification. Blood. 2015;126(4):454–62.

127. Hardy NM, Grady C, Pentz R, Stetler-Stevenson M, Raffeld M, Fontaine LS, et al. Bioethical considerations of monoclonal B-cell lymphocytosis: Donor transfer after haematopoietic stem cell transplantation. Br J Haematol. 2007;139(5):824–31.

128. Shanafelt TD, Ghia P, Lanasa MC, Landgren O, Rawstron AC. Monoclonal B-cell lymphocytosis (MBL): Biology, natural history and clinical management. Leukemia. 2010;24(3):512–20.

129. Dagklis A, Fazi C, Sala C, Cantarelli V, Scielzo C, Massacane R, et al. The immunoglobulin gene repertoire of low-count chronic lymphocytic leukemia (CLL)-

like monoclonal B lymphocytosis is different from CLL: diagnostic implications for clinical monitoring. Blood. 2009 Jul 2;114(1):26–32.

130. Nieto WG, Almeida J, Romero A, Teodosio C, López A, Henriques AF, et al. Increased frequency (12%) of circulating chronic lymphocytic leukemia-like B-cell clones in healthy subjects using a highly sensitive multicolor flow cytometry approach. Blood. 2009;114(1):33–7.

131. Molica S, Mauro FR, Giannarelli D, Lauria F, Cortelezzi A, Brugiatelli M, et al. Differentiating chronic lymphocytic leukemia from monoclonal B-lymphocytosis according to clinical outcome on behalf of the GIMEMA chronic lymphoproliferative diseases working group. Haematologica. 2011;96(2):277–83.

132. Rawstron AC, Yuille MR, Fuller J, Cullen M, Kennedy B, Richards SJ, et al. Inherited predisposition to CLL is detectable as subclinical monoclonal B-lymphocyte expansion. Blood. 2002;100(7):2289–91.

133. Hillmen P, Morgan GJ, Kennedy B, Green MJ, Richards SJ, O'Connor SJ, et al. Monoclonal B lymphocytes with the characteristics of "indolent" chronic lymphocytic leukemia are present in 3.5% of adults with normal blood counts. Blood. 2002;100(2):635–9.

134. Anderson LA, Landgren O, Engels EA. Common community acquired infections and subsequent risk of chronic lymphocytic leukaemia. Br J Haematol. 2009 Nov;147(4):444–9.

135. Casabonne D, Almeida J, Nieto WG, Romero A, Fernández-Navarro P, Rodriguez-Caballero A, et al. Common Infectious Agents and Monoclonal B-Cell Lymphocytosis: A Cross-Sectional Epidemiological Study among Healthy Adults. PLoS One. 2012;7(12).

136. Dimopoulos MA, Kyle RA, Anagnostopoulos A, Treon SP. Diagnosis and management of Waldenstrom's macroglobulinemia. J Clin Oncol. 2005;23(7):1564–77.

137. Cole CE, McHugh VL, Mathiason MA, Schroeder JE, Bottner WA, Farnen J. et al. Comparative Assessment of Significant Psychological Distress In Patients with Malignant and Non-Malignant Hematologic Disorders. Blood. 2010;116(21):1538.

138. Mergenthaler U, Heymanns J, Kippler H, Thomalla J, van Roye C, Schenk J, et al. Evaluation of psychosocial distress in patients treated in a community-based oncology group practice in Germany. Ann Oncol. 2011;22(4):931–8.

139. Allart-Vorelli P, Porro B, Baguet F, Michel A, Cousson-Gélie F. Haematological cancer and quality of life: a systematic literature review. Blood Cancer J. 2015;5(February):e305.

140. Hildebrandt MAT, Callender RA, Belachew AA, Classen C, Lee HC, Patel KK, et al. Quality of life and cancer worry in a follow-up cohort of patients with asymptomatic monoclonal gammopathies. J Clin Oncol. 2018 May 20;36(15_suppl):8049–8049.

141. Proskorovsky I, Lewis P, Williams CD, Jordan K, Kyriakou C, Ishak J, et al. Mapping EORTC QLQ-C30 and QLQ-MY20 to EQ-5D in patients with multiple myeloma. Health Qual Life Outcomes. 2014;12(1):1–9.

142. WHOQoL group. Development of the World Health Organization WHOQOL-BREF Quality of Life Assessment. Psychol Med. 1998;28(3):551–8.

143. Youssef NFA. Health-related quality of life, symptoms experience and perceived social support among patients with liver cirrhosis: a cross-sectional study in Egypt. University of Stirling; 2013.

144. Curbow B. Quality of life among long-term cancer survivors. Oncology-Huntington.

1997;11(4):572–5.

145. Augustin M, Tu JH, Knudsen KM, Erntoft S, Larsson T, Hanke CW. Ingenol mebutate gel for actinic keratosis: The link between quality of life, treatment satisfaction, and clinical outcomes. J Am Acad Dermatol. 2015;72(5):816–21.

146. Bloom JR, Stewart SL, Chang S, Banks PJ. Then and now: Quality of life of young breast cancer survivors. Psychooncology. 2004;13(3):147–60.

147. Galway, K., Black, A., Cantwell, M., Cardwell, C. R., Mills, M., & Donnelly M, Galway K, Black A, Cantwell M, Cr C, Mills M, et al. Psychosocial interventions to improve quality of life and emotional wellbeing for recently diagnosed cancer patients. Cochrane Database Syst Rev. 2012;2012(11).

148. Chambers SK, Pinnock C, Lepore SJ, Hughes S, O'Connell DL. A systematic review of psychosocial interventions for men with prostate cancer and their partners. Patient Educ Couns. 2011;85(2):e75–88.

149. Makai P, Brouwer WBF, Koopmanschap MA, Stolk EA, Nieboer AP. Quality of life instruments for economic evaluations in health and social care for older people: A systematic review. Soc Sci Med. 2014;102:83–93.

150. Phillips C. What is a QALY ? London Hayward Med Commun. 2009;(April):6.

151. Whitehead SJ, Ali S. Health outcomes in economic evaluation: The QALY and utilities. Br Med Bull. 2010;96(1):5–21.

152. Jansen F, Zwieten V Van, Coupé VMH, Leemans CR. A Review on Cost-Effectiveness and Cost-Utility of Psychosocial Care in Cancer Patients. Asia Pac J Oncol Nurs. 2016;3:125–36.

153. Fayers PM, Machin D. Quality of life : the assessment, analysis, and interpretation of patient-reported outcomes. John Wiley & Sons; 2007. p.

154. Carr AJ, Higginson IJ. Are quality of life measures patient centred? BMJ Br Med J. 2001;322:1357–60.

155. McCall S. What is quality of life? Philosophica. 1980;25(1):5–14.

156. Levine S. The changing terrains in medical sociology: emergent concern with quality of life. J Health Soc Behav. 1987;28(1):1–6.

157. Dean G, Orford A, Staines R, McGee A, Smith KJ. Psychosocial well-being and healthrelated quality of life in a UK population with Usher syndrome. BMJ Open. 2017;7(1):1–9.

158. Maggino F. Assessing the Subjective Wellbeing of Nations. In: Global Handbook of Quality of Life. Dordrecht: Springer Netherlands; 2015. p. 803–22.

159. Dooris M, Farrier A, Froggett L. Wellbeing: the challenge of 'operationalising' an holistic concept within a reductionist public health programme. Perspect Public Health. 2018;138(2):93–9.

160. La Placa V, Knight A. Well-being: Its influence and local impact on public health. Public Health. 2014;128(1):38–42.

161. Singh-Manoux A, Macleod J, Davey Smith G. Psychosocial factors and public health. J Epidemiol Community Health. 2003;57(8):553–6.

162. Huppert FA, Marks N, Clark A, Siegrist J, Stutzer A, Vittersø J, et al. Measuring Well-being across Europe: Description of the ESS Well-being Module and preliminary findings. Soc Indic Res. 2009;91(3):301–15.

163. Berman JJ, Albores-Saavedra J, Bostwick D, DeLellis R, Eble J, Hamilton SR, et al.

Precancer: A conceptual working definition. Results of a Consensus Conference. Cancer Detect Prev. 2006;30(5):387–94.

164. Landgren O, Kyle R a., Pfeiffer RM, Katzmann J a., Caporaso NE, Hayes RB, et al. Monoclonal gammopathy of undetermined significance (MGUS) consistently precedes multiple myeloma: A prospective study. Blood. 2009 May 28;113(22):5412–7.

165. Li N, Pasricha S, Bulsiewicz WJ, Pruitt RE, Komanduri S, Wolfsen HC, et al. Effects of preceding endoscopic mucosal resection on the efficacy and safety of radiofrequency ablation for treatment of Barrett's esophagus: results from the United States Radiofrequency Ablation Registry. Dis Esophagus. 2015;

166. Shaheen NJ, Falk GW, Iyer PG, Gerson LB. ACG Clinical Guideline: Diagnosis and Management of Barrett's Esophagus. Am J Gastroenterol. 2016;111(1):30–50.

167. Beebe-Dimmer JL, Cetin K, Fryzek JP, Schuetze SM, Schwartz K. The epidemiology of malignant giant cell tumors of bone: an analysis of data from the Surveillance, Epidemiology and End Results Program (1975-2004). Rare Tumors. 2009;1(2):e52.

168. Heitman SJ, Ronksley PE, Hilsden RJ, Manns BJ, Rostom A, Hemmelgarn BR. Prevalence of Adenomas and Colorectal Cancer in Average Risk Individuals: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol. 2009;7(12):1272–8.

169. Murray L. Risk of adenocarcinoma in Barrett's oesophagus: population based study. Bmj. 2003;327(7414):534–5.

170. van der Meij EH, Mast H, van der Waal I. The possible premalignant character of oral lichen planus and oral lichenoid lesions: A prospective five-year follow-up study of 192 patients. Oral Oncol. 2007;43(8):742–8.

171. CRUK. DCIS statistics [Internet]. [cited 2019 Jan 5]. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/incidence-in-situ#ref-

172. CRUK. CIN Statistics [Internet]. [cited 2019 Jan 5]. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/cervical-cancer/incidence-in-situ

173. Alam M. Actinic keratoses: Prevalence, pathogenesis, presentation, and prevention. Johns Hopkins Adv Stud Med. 2006;785–90.

174. Siegel JA, Korgavkar K, Weinstock MA. Current perspective on actinic keratosis: a review. Br J Dermatol. 2017;177(2):350–8.

175. Englert C, Hughes B. A review of actinic keratosis for the nurse practitioner: Diagnosis, treatment, and clinical pearls. J Am Acad Nurse Pract. 2012;24(5):290–6.

176. NCI. NCI Dictionary of Cancer Terms [Internet]. 2017 [cited 2017 Mar 21]. Available from: NCI Dictionary of Cancer

177. Ronkainen J, Aro P, Storskrubb T, Johansson SE, Lind T, Bolling-Sternevald E, et al. Prevalence of Barrett's esophagus in the general population: An endoscopic study. Gastroenterology. 2005;129(6):1825–31.

178. Zou D, He J, Ma X, Chen J, Gong Y, Man X, et al. Epidemiology of symptom-defined gastroesophageal reflux disease and reflux esophagitis: The systematic investigation of gastrointestinal diseases in China (SILC). Scand J Gastroenterol. 2011;46(2):133–41.

179. Zagari RM, Fuccio L, Wallander MA, Johansson S, Fiocca R, Casanova S, et al. Gastro-oesophageal reflux symptoms, oesophagitis and barrett's oesophagus in the general population: The Loiano-Monghidoro study. Gut. 2008;57(10):1354–9.

180. Schoofs N, Bisschops R, Prenen H. Progression of Barrett's esophagus toward

esophageal adenocarcinoma: an overview. Ann Gastroenterol. 2016;30(1):1–6.

181. de Jonge PJF, van Blankenstein M, Grady WM, Kuipers EJ. Barrett's oesophagus: epidemiology, cancer risk and implications for management. Gut. 2014;63(1):191–202.

182. Benedet JL, Bender H, Jones III H, Ngan HYS, Pecorelli S. Staging classifications and clinical practice guidelines of gynaecologic cancers. Int J Gynecol Obstet. 2000;70:207–312.

183. Sanad AS, Kamel HH, Hasan MM. Prevalence of cervical intraepithelial neoplasia (CIN) in patients attending Minia Maternity University Hospital. Arch Gynecol Obstet. 2014;289(6):1211–7.

184. Petry KU, Gynaecology O. Best Practice & Research Clinical Obstetrics and Gynaecology Management options for cervical intraepithelial neoplasia. Best Pract Res Clin Obstet Gynaecol. 2011;25(5):641–51.

185. Brenner H, Hoffmeister M, Stegmaier C, Brenner G, Altenhofen L, Haug U. Risk of progression of advanced adenomas to colorectal cancer by age and sex: Estimates based on 840 149 screening colonoscopies. Gut. 2007;56(11):1585–9.

186. Veitch AM, Barbour JA, Loughrey MB, Rutter MD, Pullan R, Saunders BP, et al. British Society of Gastroenterology/Association of Coloproctologists of Great Britain and Ireland guidelines for the management of large non-pedunculated colorectal polyps. Gut. 2015;64(12):1847–73.

187. Virnig BA, Tuttle TM, Shamliyan T, Kane RL. Ductal carcinoma in Situ of the breast: A systematic review of incidence, treatment, and outcomes. J Natl Cancer Inst. 2010;102(3):170–8.

188. Toss M, Miligy I, Thompson AM, Khout H, Green AR, Ellis IO, et al. Current trials to reduce surgical intervention in ductal carcinoma in situ of the breast : Critical review. The Breast. 2017;35:151–6.

189. Sobti A, Agrawal P, Agarwala S, Agarwal M. Current Concepts Review: Giant Cell Tumor of Bone -An Overview. Arch Bone Jt Surg. 2016;2(41):2–9.

190. Balke M, Schremper L, Gebert C, Ahrens H, Streitbuerger A, Koehler G, et al. Giant cell tumor of bone: Treatment and outcome of 214 cases. J Cancer Res Clin Oncol. 2008;134(9):969–78.

191. Sugerman PB, Savage NW. Oral lichen planus: causes, diagnosis and management. Aust Dent J. 2002;47(4):290–7.

192. Scully C, Beyli M, Ferreiro MC, Ficarra G, Gill Y, Griffiths M, et al. Update On Oral Lichen Planus: Etiopathogenesis and Management. Crit Rev Oral Biol Med. 1998 Jan;9(1):86–122.

193. Ravindran A, Bartley AC, Holton SJ, Gonsalves WI, Kapoor P, Siddiqui MA, et al. Prevalence, incidence and survival of smoldering multiple myeloma in the United States. Blood Cancer J. 2016;6(10):e486.

194. Watson M, Saraiya M, Wu X. Update of HPV-Associated Female Genital Cancers in the United States, 1999–2004. J Women's Heal. 2009;18(11):1731–8.

195. Rome RM, England PG. Management of vaginal intraepithelial neoplasia: A series of 132 cases with long-term follow-up. Int J Gynecol Cancer,. 2000;10(5):382–90.

196. Judson PL, Habermann EB, Baxter NN. Situ Vulvar Carcinoma. Obstet Gynecol. 2006;107(5):1018–22.

197. Joura EA. Epidemiology, diagnosis and treatment of vulvar intraepithelial neoplasia. Curr Opin Obstet Gynecol. 2002;14(1):39–43.

198. Umar A, Dunn BK, Greenwald P. Future directions in cancer prevention. Nat Rev Cancer. 2012;12(12):835–48.

199. Crockett SD, Lippmann QK, Dellon ES, Shaheen NJ. Health-related quality of life in patients with Barrett's esophagus: a systematic review. Clin Gastroenterol Hepatol. 2009;7(6):613–23.

200. Frederiksen ME, Njor S, Lynge E, Rebolj M. Psychological effects of diagnosis and treatment of cervical intraepithelial neoplasia: a systematic review. Sex Transm Infect. 2015;91(4):248–56.

201. Tadakamadla J, Kumar S, Johnson NW. Quality of life in patients with oral potentially malignant disorders: a systematic review. Oral Surg Oral Med Oral Pathol Oral Radiol. 2015;119(6):644–55.

202. Santesso N, Mustafa RA, Wiercioch W, Kehar R, Gandhi S, Chen Y, et al. Systematic reviews and meta-analyses of benefits and harms of cryotherapy, LEEP, and cold knife conization to treat cervical intraepithelial neoplasia. Int J Gynecol Obstet. 2016;132(3):266–71.

203. Felson DT. Bias in meta-analytic research. J Clin Epidemiol. 1992 Aug;45(8):885–92.

204. Higginson IJ, Carr AJ. Measuring quality of life: Using quality of life measures in the clinical setting. BMJ. 2001;322(7297):1297–300.

205. Cerruto MA, D'Elia C, Siracusano S, Porcaro AB, Cacciamani G, De Marchi D, et al. Is Health-Related Quality of Life after Radical Cystectomy Using Validated Questionnaires Really Better in Patients with Ileal Orthotopic Neobladder Compared to Ileal Conduit: A Meta-Analysis of Retrospective Comparative Studies. Curr Urol. 2017;10(2):57–68.

206. Adam S, Feller A, Rohrmann S, Arndt V. Health-related quality of life among long-term (≥5years) prostate cancer survivors by primary intervention: A systematic review. Health Qual Life Outcomes. 2018;16(1):1–14.

207. RAND. 12-Item Short Form Survey (SF-12) [Internet]. [cited 2016 Sep 1]. Available from: http://www.rand.org/health/surveys_tools/mos/12-item-short-form.html

208. Treanor C, Donnelly M. A methodological review of the Short Form Health Survey 36 (SF-36) and its derivatives among breast cancer survivors. Qual Life Res. 2014;36:339–62.

209. Claus EB, Petruzella S, Carter D, Kasl S. Quality of life for women diagnosed with breast carcinoma in situ. J Clin Oncol. 2006;24(30):4875–81.

210. Nekhlyudov L, Kroenke CH, Jung I, Holmes MD, Colditz GA. Prospective changes in quality of life after ductal carcinoma-in-situ: Results from the Nurses' Health Study. J Clin Oncol. 2006;24(18):2822–7.

211. Jeffe DB, Perez M, Liu Y, Collins KK, Aft RL SM. Quality of life over time in women diagnosed with ductal carcinoma in situ, early-stage invasive breast cancer, and age-matched controls. Breast Cancer Res Treat. 2012;134(1):379–91.

212. Partridge A, Winer JP, Golshan M, Bellon JR, Blood E, Dees EC, et al. Perceptions and management approaches of physicians who care for women with ductal carcinoma in situ. Clin Breast Cancer. 2008;8(3):275–80.

213. Rosmolen WD, Nieuwkerk PT, Pouw RE, Henegouwen MI va. B, Bergman JJGHMGHM, Sprangers MAGG, et al. Quality of life and fear of cancer recurrence after endoscopic treatment for early Barrett's neoplasia: A prospective study. Dis Esophagus. 2016;30(3):1–9.

214. EuroGroup. EuroGroup. EQ-5D-3L.

215. Rabin R, Charro F. EQ-SD: a measure of health status from the EuroQol Group. Ann Med. 2001;337–43.

216. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand. 1983 Jun;67(6):361–70.

217. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. J Psychosom Res. 2002;52(2):69–77.

218. Crawford JR, Henry JD, Crombie C, Taylor EP. Normative data for the HADS from a large non-clinical sample. Br J Clin Psychol. 2001;40(Pt 4):429–34.

219. Smarr KL, Keefer AL. Measures of depression and depressive symptoms: Beck Depression Inventory-II (BDI-II), Center for Epidemiologic Studies Depression Scale (CES-D), Geriatric Depression Scale (GDS), Hospital Anxiety and Depression Scale (HADS), and Patient Health Questionna. Arthritis Care Res (Hoboken). 2011 Nov;63(S11):S454–66.

220. Ces-d T. Source: Radloff, L.S. (1977). The CES-D scale: A self-report depression scale for research in the general population. Jisp. 2006;(1977):1–2.

221. Spielberger CD, Gorsuch R.L., Luschene R. VPR, G.A. J. Manual for the State-Trait Anxiety Inventory STAI (form Y)(" self-evaluation questionnaire"). 1983.

222. Haringsma R, Engels GI, Beekman ATF, Spinhoven P. The criterion validity of the Center for Epidemiological Studies Depression Scale (CES-D) in a sample of self-referred elders with depressive symptomatology. Int J Geriatr Psychiatry. 2004;19(6):558–63.

223. Julian LJ. Measures of anxiety: State-Trait Anxiety Inventory (STAI), Beck Anxiety Inventory (BAI), and Hospital Anxiety and Depression Scale-Anxiety (HADS-A). Arthritis Care Res. 2011;63(SUPPL. 11):467–72.

224. Ware JE. SF-36 Health Survey Manual & Interpretation Guide. Boston, Massachusetts: The Health Institute, New England Medical Center; 1993.

225. Harden A. FOCUS Mixed-Methods Systematic Reviews: Integrating Quantitative and Qualitative Findings Key Features of a Systematic Review. Natl Cent Dissem Disabil Res. 2010;(25):8.

226. Sandelowski M, Leeman J, Knafl K, Crandell JL. Text-in-context: A method for extracting findings in mixed-methods mixed research synthesis studies. J Adv Nurs. 2013;69(6):1428–37.

227. Alderfer MA, Long KA, Lown EA, Marsland AL, Ostrowski NL, Hock JM, et al. Psychosocial adjustment of siblings of children with cancer: a systematic review. Psychooncology. 2009 Oct 27;19(8):789–805.

228. Pearson A, White H, Bath-Hextall F, Salmond S, Apostolo J, Kirkpatrick P. A mixed-methods approach to systematic reviews. Int J Evid Based Healthc. 2015;13(3):121–31.

229. Hannes K, Lockwood C. Pragmatism as the philosophical foundation for the Joanna Briggs meta-aggregative approach to qualitative evidence synthesis. J Adv Nurs. 2011;67(7):1632–42.

230. Britten N, Campbell R, Pope C, Donovan J, Morgan M, Pill R. Using meta ethnography to synthesize qualitative research: A worked example. J Heal Serv Res. 2002;7(4):209–15.

231. Dixon-Woods M, Agarwhal S, Jones D, Young B, Sutton a. Synthesising qualitative and quantitative evidence: a review of possible methods. J Heal Serv Res Pol. 2005;10(1):45-53b.

232. Thomas J, Harden A. Methods for the thematic synthesis of qualitative research in systematic reviews. BMC Med Res Methodol. 2008;8:19.

233. Jones CEL, Maben J, Jack RH, Davies EA, Forbes LJL, Lucas G, et al. A systematic review of barriers to early presentation and diagnosis with breast cancer among black women. BMJ Open. 2014;4(2).

234. King AJLJL, Evans M, Moore THMHM, Paterson C, Sharp D, Persad R, et al. Prostate cancer and supportive care: a systematic review and qualitative synthesis of men's experiences and unmet needs. Eur J Cancer Care (Engl). 2015;24(5):618–34.

235. Walpole G, Clark H, Dowling M. Myeloma patients' experiences of haematopoietic stem cell transplant: A qualitative thematic synthesis. European Journal of Oncology Nursing. 2018.

236. Finfgeld-Connett D. Use of content analysis to conduct knowledge-building and theory-generating qualitative systematic reviews. Qual Res. 2014;14(3):341–52.

237. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015;349(3):g7647.

238. Berman JJ, Henson DE. Classifying the precancers: a metadata approach. BMC Med Inform Decis Mak. 2003;3:8.

239. O'Shaughnessy JA, Kelloff GJ, Gordon GB, Dannenberg AJ, Hong WK, Fabian CJ, et al. Treatment and prevention of intraepithelial neoplasia: an important target for accelerated new agent development. Clin Cancer Res. 2002;8(2):314–46.

240. Korfage IJ, Essink-Bot M-LL, Westenberg SM, Helmerhorst T, Habbema JDF, Van Ballegooijen M. How distressing is referral to colposcopy in cervical cancer screening?: A prospective quality of life study. Gynecol Oncol. 2014;132(1):142–8.

241. Orbell S, Hagger M, Brown V, Tidy J. Appraisal theory and emotional sequelae of first visit to colposcopy following an abnormal cervical screening result. Br J Health Psychol. 2004;9:533–55.

242. Half E, Bercovich D, Rozen P. Familial adenomatous polyposis. Orphanet J Rare Dis. 2009 Dec 12;4(1):22.

243. Douma KFL, Aaronson NK, Vasen HFA, Gerritsma MA, Gundy CM, Janssen EPA, et al. Psychological distress and use of psychosocial support in familial adenomatous polyposis. Psychooncology. 2010;19(3):289–98.

244. Broadstock M, Michie S, Marteau T. Psychological consequences of predictive genetic testing: a systematic review. EJHG Eur J Hum Genet. 2000 Oct 3;8(10):731–8.

245. Hong QN, Pluye P, Sergi F, Bartlett G, Boardman F, Cargo M, et al. Mixed Methods Appraisal Tool (MMAT), version 2018. McGill Dep Fam Med. 2018;1–11.

246. Hong QN, FÀBregues S, Bartlett G, Boardman F, Cargo M, Dagenais P, et al. The Mixed Methods Appraisal Tool (MMAT) version 2018 for information professionals and researchers. Educ Inf. 2018;1–7.

247. Chandler J, Higgins J, Deeks J, Davenport C, Clarke M. Cochrane Handbook for Systematic Reviews of Interventions Handbook for Systematic Reviews of Interventions Chapter 1 : Introduction. 2017;1–12.

248. Herbison P, Hay-Smith J, Gillespie WJ. Adjustment of meta-analyses on the basis of quality scores should be abandoned. J Clin Epidemiol. 2006;59(12).

249. Greenland S. On the bias produced by quality scores in meta-analysis, and a hierarchical view of proposed solutions. Biostatistics. 2001 Dec 1;2(4):463–71.

250. Greenland S. Invited commentary: A critical look at some popular meta-analytic methods. Am J Epidemiol. 1994;140(3):290–6.

251. StatsDirect Ltd. StatsDirect statistical software. England; 2013.

252. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ Br Med J. 2003;327(7414):557–60.

253. Rao SR, Graubard BI, Schmid CH, Morton SC, Louis TA, Zaslavsky AM, et al. Meta-analysis of survey data: Application to health services research. Heal Serv Outcomes Res Methodol. 2008;8(2):98–114.

254. Linton MJ, Dieppe P, Medina-Lara A. Review of 99 self-report measures for assessing well-being in adults: Exploring dimensions of well-being and developments over time. BMJ Open. 2016;6(7).

255. Dowrick AS, Wootten AC, Murphy DG, Costello AJ. We used a validated questionnaire: What does this mean and is it an accurate statement in urologic research? Urology. 2015;85(6):1304–11.

256. Patrick DL, Deyo RA. Generic and disease-specific measures in assessing health status and quality of life. Med Care. 1989 Mar;27(3 Suppl):S217-32.

257. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986 Sep;7(3):177–88.

258. Borenstein M, Hedges L V., Higgins JPT, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. Res Synth Methods. 2010;1(2):97–111.

259. Shan L, Shan J, Saxena A, Robinson D. Quality of life and functional status after carotid revascularisation: A systematic review and meta-analysis. Eur J Vasc Endovasc Surg. 2015;49(6):634–45.

260. Maragkos GA, Geropoulos G, Kechagias K, Ziogas IA, Mylonas KS. Quality of Life After Epilepsy Surgery in Children: A Systematic Review and Meta-Analysis. Neurosurgery. 2018;0(0):1–9.

261. Zlowodzki M, Poolman RW, Kerkhoffs GM, Tornetta P, Bhandari M. How to interpret a meta-analysis and judge its value as a guide for clinical practice. Acta Orthop. 2007;78(5):598–609.

262. Higgins JP, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. 2011.

263. Juraskova I, Butow P, Bonner C, Robertson R, Sharpe L. Sexual adjustment following early stage cervical and endometrial cancer: Prospective controlled multi-centre study. Psychooncology. 2013;22(1):153–9.

264. Mood AMFAG, Boes DC. Introduction to the Theory of Statistics. 3rd ed. McGraw-Hill Kogakusha; 1974. 179 p.

265. QSR International Pty Ltd. NVivo qualitative data analysis Software. 2015.

266. Armstrong D, Gosling A, Weinman J. The Place of Inter-Rater Reliability in Qualitative Research: Sociology. 1997;31(3):597–606.

267. Waitzkin H. The politics of medical encounters: How patients and doctors deal with social problems. Yale University Press; 1991.

268. Le T, Hopkins L, Menard C, Hicks-Boucher W, Lefebvre J, Fung Kee Fung M. Psychologic morbidities prior to loop electrosurgical excision procedure in the treatment of cervical intraepithelial neoplasia. Int J Gynecol Cancer. 2006

May;16(3):1089–93.

269. Hart V, Sprague BL, Lakoski SG, Hampton JM, Newcomb PA, Gangnon RE, et al. Trends in health-related quality of life after a diagnosis of ductal carcinoma in situ. J Clin Oncol. 2016;34(12):1323–9.

270. Flynn SE. Shame , Guilt , and Knowledge of Hpv in Women Recently Diagnosed With Hpv-Related Cervical Intraepithelial Neoplasia (Cin). 2010.

271. Imedio IL, Serra-guillén C. Adaptation and Validation of the Spanish Version of the Actinic Keratosis Quality of Life Questionnaire &. Actas Dermo-Sifiliográficas (English Ed. 2016;107(6):474–81.

272. Wong CKH, Lam CLK, Poon JTC, Kwong DLW. Clinical Correlates of Health Preference and Generic Health-Related Quality of Life in Patients with Colorectal Neoplasms. PLoS One. 2013;8(3):e58341.

273. Partridge A, Adloff K, Blood E, Dees EC, Kaelin C, Golshan M, et al. Risk perceptions and psychosocial outcomes of women with ductal carcinoma in situ: longitudinal results from a cohort study. J Natl Cancer Inst. 2008;100(4):243–51.

274. Heinzler J, Brucker J, Bruckner T, Dinkic C, Hoffmann J, Dornhöfer N, et al. Impact of a cervical dysplasia and its treatment on quality of life and sexual function. Arch Gynecol Obstet. 2018;298(4):737–45.

275. Opalic M, Peric S, Palibrk A, Bozovic I, Bjelica B, Stevic Z, et al. Quality of life in patients with polyneuropathy associated with different types of monoclonal gammopathy of undetermined significance. Acta Neurol Belg. 2019;(0123456789).

276. Min Ang X, Chi Khang Au P, Kwok K, Yeon Park K, Kujan O, Frydrych AM, et al. Quality of life in patients with oral leukoplakia. J Oral Pathol Med. 2019;48(7):574–80.

277. Eloubeidi M a, Provenzale D. Health-related quality of life and severity of symptoms in patients with Barrett's esophagus and gastroesophageal reflux disease patients without Barrett's esophagus. Am J Gastroenterol. 2000;95(8):1881–7.

278. Gerson LB, Ullah N, Hastie T, Goldstein MK. Does cancer risk affect health-related quality of life in patients with Barrett's esophagus? Gastrointest Endosc. 2007;65(1):16–25.

279. Marano S, Mattacchione S, Luongo B, Mingarelli V, Campagna G, Vietri F, et al. Laparoscopic Nissen-Rossetti fundoplication for gastroesophageal reflux disease patients after 2-year follow-up. J Laparoendosc Adv Surg Tech A. 2012;22(4):336–42.

280. Shchelkova OY, Usmanova EB. Quality of life and relation to disease in patients with bone sarcoma. Psychol Russ State Art. 2015;8(1):22–31.

281. Pan XF, Xie Y, Zhang SK, Lv SH, Zhao FH, Qiao YL YC. Quality of life in women with cervical precursor lesions and cancer: a hospital-based study. Value Heal. 2013;16:A146.

282. Ware J E J, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). Med Care. 1992;30(6):473–83.

283. Chang LC, Oelschlager BK, Quiroga E, Parra JD, Mulligan M, Wood DE, et al. Long-term Outcome of Esophagectomy for High-Grade Dysplasia or Cancer Found During Surveillance for Barrett ' s Esophagus. J Gastrointest Surg. 2006;10(3):341–6.

284. Cooper SC, El-agib A, Dar S, Mohammed I, Nightingale P, Murray IA, et al. Endoscopic surveillance for Barrett's oesophagus: the patients' perspective. Eur J Gastroenterol Hepatol. 2009;21(8):850–4.

285. Xie Y, Zhao F-H, Lu S-H, Huang H, Pan X-F, Yang C-X, et al. Assessment of quality of

life for the patients with cervical cancer at different clinical stages. Chin J Cancer. 2013;32(5):275–82.

286. Sackey H, Sandelin K, Frisell J, Wickman M, Brandberg Y. Ductal carcinoma in situ of the breast. Long-term follow-up of health-related quality of life, emotional reactions and body image. Eur J Surg Oncol. 2010;36(8):756–62.

287. van Duijnhoven FJB, Jenab M, Hveem K, Siersema PD, Fedirko V, Duell EJ, et al. Circulating concentrations of vitamin D in relation to pancreatic cancer risk in European populations. Int J Cancer. 2018;142(6):1189–201.

288. Rosmolen WD, Phoa NKYN, Nieuwkerk PT, Pouw RE, Weusten BLAM, Bisschops R, et al. Impact of ablation of Barrett's esophagus with low-grade dysplasia on patients' illness perception and quality of life: a multicenter randomized trial. Gastrointest Endosc. 2019;90(2):215–21.

289. van der Ende-van Loon MCM, Rosmolen WD, Houterman S, Schoon EJ, Curvers WL. Cancer risk perception in relation to associated symptoms in Barrett's patients: A cross sectional study on quality of life. United Eur Gastroenterol J. 2018;6(9):1316–22.

290. Lippmann QK, Crockett SD, Dellon ES, Shaheen NJ. Quality of life in GERD and Barrett's esophagus is related to gender and manifestation of disease. Am J Gastroenterol. 2009;104(11):2695–703.

291. Bulamu NB, Chen G, Ratcliffe J, Schloite A, Bright T, Watson DI. Health-Related Quality of Life Associated with Barrett's Esophagus and Cancer. World J Surg. 2019;43(6):1554–62.

292. Lee SW, Lien HC, Chang C Sen, Ko CW, Tung CF, Yeh HZ. Health-related quality of life of subjects with Barrett's esophagus in a Chinese population. PLoS One. 2017;12(12):8–15.

293. Maatouk I, He S, Hummel M, Hemmer S, Hillengass M, Goldschmidt H, et al. Patients with precursor disease exhibit similar psychological distress and mental HRQOL as patients with active myeloma. Blood Cancer J. 2019;9(2):1–4.

294. Tadakamadla J, Kumar S, Lalloo R, Babu G, Johnson NW, Gandhi Babu DB, et al. Impact of oral potentially malignant disorders on quality of life. J Oral Pathol Med. 2017;47(1):60–5.

295. Taghavi K, Morell S, Lamb J, MacNab H, Innes C, Coffey K, et al. Initial observation of CIN2 does not appear to reduce quality of life in women under 25 years of age. Aust New Zeal J Obstet Gynaecol. 2017;57(4):473–8.

296. Klügel S, Lücke C, Mehren A, Malik E, Philipsen A, Schild-Suhren M, et al. Patients with cervical intraepithelial neoplasms show different states of health-related quality of life and different coping styles depending on the choice of therapy: Findings from the CIN study. Int J Womens Health. 2019;11:511–7.

297. Lauzier S, Maunsell E, Levesque P, Mondor M, Robert J, Robidoux A, et al. Psychological distress and physical health in the year after diagnosis of DCIS or invasive breast cancer. Breast Cancer Res Treat. 2010;120(3):685–91.

298. Crockett SD, Lipkus IM, Bright SD, Richard E, Wang KK, Boolchand V, et al. Overutilization of endoscopic surveillance in non-dysplastic Barrett's Esophagus: A multi-center study. Gastrointest Endosc. 2014;75(1):23–31.

299. Kulig M, Leodolter A, Vieth M, Schulte E, Jaspersen D, Labenz J, et al. Quality of life in relation to symptoms in patients with gastro-oesophageal reflux disease - an analysis based on the ProGERD initiative. Aliment Pharmacol Ther. 2003;18(8):767–76.

300. Bloom JR, Stewart SL, Napoles AM, Hwang ES, Livaudais JC, Karliner L, et al. Quality of

life of Latina and Euro-American women with ductal carcinoma in situ. Psychooncology. 2013;22(5):1008–16.

301. Shylasree TS, Karanjgaokar V, Tristram A, Wilkes AR, MacLean AB, Fiander AN. Contribution of demographic, psychological and disease-related factors to quality of life in women with high-grade vulval intraepithelial neoplasia. Gynecol Oncol. 2008;110(2):185–9.

302. Thiis-Evensen E, Wilhelmsen I, Hoff GS, Blomhoff S, Sauar J. The psychologic effect of attending a screening program for colorectal polyps. Scand J Gastroenterol. 1999;34(1):103–9.

303. Crawford J, Cayley C, Lovibond PF, Wilson PH, Hartley C. Percentile Norms and Accompanying Interval Estimates from an Australian General Adult Population Sample for Self-Report Mood Scales (BAI, BDI, CRSD, CES-D, DASS, DASS-21, STAI-X, STAI-Y, SRDS, and SRAS). Aust Psychol. 2011;46(1):3–14.

304. Dominiak-Felden G, Cohet C, Atrux-Tallau S, Gilet H, Tristram A, Fiander A. Impact of human papillomavirus-related genital diseases on quality of life and psychosocial wellbeing: results of an observational, health-related quality of life study in the UK. BMC Public Health. 2013 Dec 12;13(1):1065–76.

305. Wardle J, Williamson S, Sutton S, Biran A, McCaffery K, Cuzick J, et al. Psychological impact of colorectal cancer screening. Heal Psychol. 2003;22(1):54–9.

306. De Morgan S, Redman S, D'Este C, Rogers K. Knowledge, satisfaction with information, decisional conflict and psychological morbidity amongst women diagnosed with ductal carcinoma in situ (DCIS). Patient Educ Couns. 2011;84(1):62–8.

307. Hanke WC, Norlin JM, Mark Knudsen K, Larsson T, Stone S. Quality of life in treatment of AK: Treatment burden of ingenol mebutate gel is small and short lasting. J Dermatolog Treat. 2016;27(5):450–5.

308. Hellsten C, Lindqvist PG, Sjostrom, K. A longitudinal study of sexual functioning in women referred for colposcopy: A 2-year follow up. BJOG An Int J Obstet Gynaecol. 2008;115(2):205–11.

309. Norrlid H, Norlin JM, Holmstrup H, Malmberg I, Sartorius K, Thormann H, et al. Patient-reported outcomes in topical field treatment of actinic keratosis in Swedish and Danish patients. J Dermatolog Treat. 2018;29(1):68–73.

310. Valter K, Boras VV, Buljan D, Juras DV, Susić M, Pandurić DG, et al. The influence of psychological state on oral lichen planus. Acta Clin Croat. 2013;52(2):145–9.

311. Orbell S, O'Sullivan I, Parker R, Steele B, Campbell C, Weller D. Illness representations and coping following an abnormal colorectal cancer screening result. Soc Sci Med. 2008;67(9):1465–74.

312. Gregorowitsch ML, van den Bongard HJGD, Young-Afat DA, Pignol JP, van Gils CH, May AM, et al. Severe depression more common in patients with ductal carcinoma in situ than early-stage invasive breast cancer patients. Breast Cancer Res Treat. 2018;167(1):205–13.

313. Kruijshaar ME, Kerkhof M, Siersema PD, Steyerberg EW, Homs MY V., Essink-Bot, M. L. &, et al. The burden of upper gastrointestinal endoscopy in patients with Barrett's esophagus. Endoscopy. 2006;38(9):873–8.

314. Bluman LG, Borstelmann NA. Knowledge, Satisfaction, and Perceived Cancer Risk among Women Diagnosed with Ductal Carcinoma In Situ. J Womens Health Gend Based Med. 2001;10(6):589–98.

315. De Moor JS, Partridge AH, Winer EP, Ligibel J, Emmons KM. The role of

socioeconomic status in adjustment after ductal carcinoma in situ. Cancer. 2010;116(5):1218–25.

316. Reisine S, Morse DE, Psoter WJ, Eisenberg E, Cohen D, Cleveland D, et al. Sociodemographic risk indicators for depressive symptoms among persons with oral cancer or oral epithelial dysplasia. J Oral Maxillofac Surg. 2005;63(4):513–20.

317. Tennvall GR, Norlin JM, Malmberg I, Erlendsson AM, Hædersdal M. Health related quality of life in patients with actinic keratosis – an observational study of patients treated in dermatology specialist care in Denmark. Health Qual Life Outcomes. 2015;13(1):111.

318. Freeman-Wang T, Walker P, Linehan J, Coffey C, Glasser B, Sherr L. Anxiety levels in women attending colposcopy clinics for treatment for cervical intraepithelial neoplasia: a randomised trial of written and video information. BJOG. 2001;108(5):482–4.

319. Alarcon I, Vinding GR, Christensen KB, Esmann S, Malvehy J, Puig S, et al. Spanish version of the Actinic Keratosis Quality of Life questionnaire. J Eur Acad Dermatology Venereol. 2017;31(6):986–91.

320. Diepgen TL, Eicke C, Bastian M. Ingenol mebutate as topical treatment for actinic keratosis based on a prospective, non-interventional, multicentre study of real-life clinical practice in Germany: efficacy and quality of life. Eur J Dermatology. 2019;29(4):401–8.

321. Gholam P, Kroehl V, Enk AH. Dermatology life quality index and side effects after topical photodynamic therapy of actinic keratosis. Dermatology. 2013;226(3):253–9.

322. Jubert-Esteve E, Del Pozo-Hernando LJ, Izquierdo-Herce N, Bauza-Alonso A, Martin-Santiago A, Jones-Caballero M. Quality of Life and Side Effects in Patients with Actinic Keratosis Treated With Ingenol Mebutate: A Pilot Study. Actas Dermosifiliogr. 2015;106(8):644–50.

323. Pflugfelder A, Welter AK, Leiter U, Weide B, Held L, Eigentler TK, et al. Open label randomized study comparing 3 months vs. 6 months treatment of actinic keratoses with 3% diclofenac in 2.5% hyaluronic acid gel: A trial of the German Dermatologic Cooperative Oncology Group. J Eur Acad Dermatology Venereol. 2012;26(1):48–53.

324. Drahoňovský, V., Vrbenský, L., Hnuta, J., & Pecák P. The positive effect of laparoscopic antireflux surgery on the development of mucosal changes in Barrett's esophagus for five years or more after the operation. Čes Slov Gastroenterol Hepatol. 2008;62(4):190–202.

325. Fisher D, Jeffreys A, Bosworth H, Wang J, Lipscomb J, Provenzale D. Quality of life in patients with Barrett's esophagus undergoing surveillance. Am J Gastroenterol. 2002;97(9):2193–200.

326. Markus PM, Horstmann O, Kley C, Neufang T, Becker H. Laparoscopic fundoplication: Is there a correlation between pH studies and the patient's quality of life? Surg Endosc Other Interv Tech. 2002;16(1):48–53.

327. Miller RC, Atherton PJ, Kabat BF, Fredericksen MB, Geno DM, Deschamps C, et al. Marital status and quality of life in patients with esophageal cancer or Barrett's esophagus: the mayo clinic esophageal adenocarcinoma and Barrett's esophagus registry study. Dig Dis Sci. 2010;55(10):2860–8.

328. Taneepanichskul S, Lertmaharit S, Pongpanich S, Termrungruanglert W, Havanond P, Khemapech N, et al. Quality of life among Thai women diagnosed with cervical cancer and cervical intraepithelial neoplasia at King Chulalongkorn Memorial Hospital. J Med Assoc Thai. 2011 Aug;94(8):902–7.

329. Wang S-M, Shi J-F, Kang D-J, Song P, Qiao Y-L. Impact of Human Papillomavirus-Related Lesions on Quality of Life. Int J Gynecol Cancer. 2011;21(1):182–8.

330. Tutein Nolthenius CJ, Boellaard TN, de Haan MC, Nio CY, Thomeer MGJ, Bipat S, et al. Burden of waiting for surveillance CT colonography in patients with screen-detected 6–9Â mm polyps. Eur Radiol. 2016;26(11):4000–10.

331. Wen Y, Pan XF, Huang WZ, Zhao ZM, Wei WQ, Chen F, et al. Quality of life for patients with esophageal/gastric cardia precursor lesions or cancer: A one-year prospective study. Asian Pacific J Cancer Prev. 2015;16(1):45–51.

332. Adamo D, Leuci S, Ruoppo E, Martina S, Mignogna M. The prevalence and associations of sleep disturbances, anxiety, and depression in patients with premalignant chronic inflammatory diseases: A case-control study. Oral Oncol. 2013;49:S99.

333. Karbach J, Al-Nawas B, Moergel M, Daubländer M. Oral health-related quality of life of patients with oral lichen planus, oral leukoplakia, or oral squamous cell carcinoma. J Oral Maxillofac Surg. 2014;72:1517–22.

334. Kono T, Saito K, Yabe H, Ogawa K. Phonosurgical resection using submucosal infusion technique for precancerous laryngeal leukoplakia. Laryngoscope. 2016;127(1):1–6.

335. Rana M, Gellrich N-C, Rana M. Comparison of health-related quality of life of patients with different precancer and oral cancer stages. Clin Oral Investig. 2015;19(2):481–8.

336. Weymuller EA, Alsarraf R, Yueh B, Deleyiannis FWB, Coltrera MD. Analysis of the performance characteristics of the University of Washington Quality of Life instrument and its modification (UW-QOL-R). Arch Otolaryngol Head Neck Surg. 2001;127(5):489–93.

337. Kono T, Saito K, Yabe H, Uno K, Kaoru Ogawa KO, Takeyuki Kono, MD (presenter); Koichiro Saito, MD, PhD; Haruna Yabe, MD; Kosuke Uno, MD; Kaoru Ogawa, MD P, et al. Postoperative Glottal Function and Voice-Related QOL after Type1 and Type2 Cordectomy against Laryngeal Leukoplakia. Otolaryngol Head Neck Surg. 2014;151:52.

338. Alberts S, Novotny P, Sloan J, Danella J, Bostwick D, Sebo T, et al. Flutamide in men with prostatic intraepithelial neoplasia: a randomized, placebo-controlled chemoprevention trial. Am J Ther. 2006;13(4):291–7.

339. Claiborne N, Krause TM, Heilman AE, Leung P. Measuring Quality of Life in Back Patients. Soc Work Health Care. 1999 Jun 15;28(3):77–94.

340. Neri R. Pharmacology and pharmacokinetics of flutamide. Urology. 1989 Oct;34(4):19–21.

341. McFadden KM, Sharp L, Cruickshank ME. The prospective management of women with newly diagnosed vulval intraepithelial neoplasia: Clinical outcome and quality of life. J Obstet {&} Gynaecol. 2009;29(8):749–53.

342. Davey C, White V, Warne C, Kitchen P, Villanueva E, Erbas B. Understanding a ductal carcinoma in situ diagnosis: Patient views and surgeon descriptions. Eur J Cancer Care (Engl). 2011;20(6):776–84.

343. De Morgan S, Redman S, White KJ, Cakir B, Boyages J. "Well, have I got cancer or haven't I?" The psycho-social issues for women diagnosed with ductal carcinoma in situ. Heal Expect. 2002;5:310–8.

344. Kennedy F, Harcourt D, Rumsey N. The challenge of being diagnosed and treated for ductal carcinoma in situ (DCIS). Eur J Oncol Nurs. 2008;12(2):103–11.

345. Kennedy F, Harcourt D, Rumsey N. The shifting nature of women's experiences and perceptions of ductal carcinoma in situ. J Adv Nurs. 2012;68(4):856–67.

346. Prinjha S, Evans J, McPherson A. Women's information needs about ductal carcinoma in situ before mammographic screening and after diagnosis: a qualitative study. J Med Screen 2006. 2006;13(3):110–4.

347. Prinjha S, Evans J, Ziebland S, McPherson a. "A mastectomy for something that wasn't even truly invasive cancer". Women's understandings of having a mastectomy for screen-detected DCIS: a qualitative study. J Med Screen. 2011;18(1):34–40.

348. del Carmen Castro-Vásquez M, del Carmen Arellano-Gálvez M. Acceso a la información de mujeres con VPH, displasia y cáncer cervical in situ. Salud Publica Mex. 2010;52(3):207–12.

349. Hounsgaard L, Petersen LK, Pedersen BD. Facing possible illness detected through screening-Experiences of healthy women with pathological cervical smears. Eur J Oncol Nurs. 2007;11(5):417–23.

350. Lee Mortensen G, Adeler AL. Qualitative study of women's anxiety and information needs after a diagnosis of cervical dysplasia. J Public Health (Bangkok). 2010 Oct 31;18(5):473–82.

351. Pruitt SL, Parker PA, Follen M, Basen-Engquist K. Communicating colposcopy results: what do patients and providers discuss? J Low Genit Tract Dis. 2008;12(2):95–102.

352. Björk S, Hagstrom H, Bjork. Of what significance is abnormal results of smear test? Anxiety Because of insufficient information in connection with abnormal results of cervical smear test. Lakartidningen. 2001;98(23):2796–800.

353. Rask M, Swahnberg K, Lindell G, Oscarsson M. Women's experiences of abnormal Pap smear results – A qualitative study. Sex Reprod Healthc. 2017;12:3–8.

354. Freijomil-Vázquez C, Gastaldo D, Coronado C, Movilla-Fernández MJ. When risk becomes illness: The personal and social consequences of cervical intraepithelial neoplasia medical surveillance. PLoS One. 2019;14(12):1–19.

355. Freijomil-Vázquez C, Gastaldo D, Coronado C, Movilla-Fernández MJ. Health care informational challenges for women diagnosed with cervical intraepithelial neoplasia: A qualitative study. BMC Womens Health. 2019;19(1):1–10.

356. Likes WM, Russell C, Tillmanns T. Women's Experiences With Vulvar Intraepithelial Neoplasia. J Obstet Gynecol Neonatal Nurs. 2008;37(6):640–6.

357. Esmann S, Jemec GBE. Management of actinic keratosis patients: a qualitative study. J Dermatolog Treat. 2007;18(1):53–8.

358. Griffiths H, Davies R. Understanding Barrett's columnar lined oesophagus from the patients' perspective: qualitative analysis of semistructured interviews with patients. Frontline Gastroenterol. 2011;2(3):168–75.

359. Dowswell G, Ryan A, Taylor A, Daley A, Freemantle N, Brookes M, et al. Designing an intervention to help people with colorectal adenomas reduce their intake of red and processed meat and increase their levels of physical activity: a qualitative study. BMC Cancer. 2012;12(1):255.

360. Ni Riordain R, Meaney S, Mccreary C, Ní Riordain R, Meaney S, Mccreary C. Impact of chronic oral mucosal disease on daily life: preliminary observations from a qualitative study. Oral Dis. 2011;17(3):265–9.

361. Tadakamadla J, Kumar S, Lalloo R, Johnson NW. Qualitative analysis of the impact of Oral Potentially Malignant Disorders on daily life activities. PLoS One. 2017;12(4):1–14.

362. Costa A, Zanini V. Precancerous lesions of the breast. Nat Clin Pract Oncol. 2008;5(12):700–4.

363. The Consensus Conference Committee. Consensus Conference on Consensus Conference on the Classification of Ductal Carcinoma In Situ. Cancer. 1997;80:1798–802.

364. Rask M, Oscarsson M, Ludwig N, Swahnberg K. The Swedish translation and cross-cultural adaptation of the Functional Assessment of Chronic Illness Therapy - Cervical Dysplasia (FACIT-CD): Linguistic validity and reliability of the Swedish version. BMC Womens Health. 2017;17(1):1–10.

365. Cheak-Zamora NC, KW W, TD. M. Reliability and Validity of the SF-12v2 in the Medical Expenditure Panel Survey. Qual Life Res. 2009;18(6):727–35.

366. Zigmond, AS; Snaith R. HADS scale - depression. Acta Psychiatr Scand. 1983;67(D):21.

367. Association TEG. EQ 5D 5L [Internet]. 2016 [cited 2016 Jun 22]. Available from: http://www.euroqol.org/about-eq-5d/eq-5d-nomenclature.html

368. Lintz K, Moynihan C, Steginga S, Norman A, Eeles R, Huddart R, et al. Prostate cancer patients' support and psychological care needs: Survey from a non-surgical oncology clinic. Psychooncology. 2003 Dec;12(8):769–83.

369. Harrison JD Young JM PMABPNSMJ, Harrison JD, Young JM, Price MA, Butow PN, Solomon MJ. What are the unmet supportive care needs of people with cancer? A systematic review. Support Care Cancer. 2009 Aug 25;17(8):1117–28.

370. Tonkin-Crine S, Anthierens S, Hood K, Yardley L, Cals JWL, Francis NA, et al. Discrepancies between qualitative and quantitative evaluation of randomised controlled trial results: Achieving clarity through mixed methods triangulation. Implement Sci. 2016;11(1).

371. Wagner KD, Davidson PJ, Pollini RA, Strathdee SA, Washburn R, Palinkas LA. Reconciling incongruous qualitative and quantitative findings in mixed methods research: Exemplars from research with drug using populations. Int J Drug Policy. 2012;

372. Seidman JD, Berman JJ. Premalignant nonepithelial lesions: a biological classification. Mod Pathol. 1993 Sep;6(5):544–54.

373. Sterne JAC, Sutton AJ, Ioannidis JPA, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ. 2011;343(7818):1–8.

374. Sandelowski M, Docherty S, Emden C. Qualitative metasynthesis: Issues and techniques. Res Nurs Health. 1997 Aug;20(4):365–71.

375. Denzin N, Lincoln Y. The Sage handbook of qualitative research. Thousand Oaks, California 91320: Sage Publications, Inc.; 2005.

376. Hancock, BevHancock B (2006). An Introduction to Qualitative Research Au t hors. Qual Res. 2006;4th:504.

377. Dean M, Raats MM, Lähteenmäki L, Food-related MI. Methods Investigating Food-Related Behaviour. In: Nutrition Research Methodologies. Chichester, UK: John Wiley & Sons, Ltd; 2015. p. 151–68.

378. Silverman D. Doing Qualitative Research: A Practical Handbook. 3rd edn. 3rd ed. London: SAGE Publications Ltd.; 2010.

379. Silverman D. Interpreting Qualitative Qata: Methods for Analyzing Talk, Text and Interaction. 3rd ed. London: SAGE Publications Ltd.; 2006.

380. Stokes D, Bergin R. Methodology or "methodolatry"? An evalution of focus and depth interviews. Qual Mark Res An Int J Artic. 2006;9(2):26–37.

381. Beck LC, Trombetta WL, Share S. Using focus group sessions before decisions are made. N C Med J. 1986 Feb;47(2):73–4.

382. Powell RA, Single HM. Focus Groups. Int J Qual Heal Care. 1996;8(5):499–504.

383. Guest G, Namey E, Taylor J, Eley N, McKenna K. Comparing focus groups and individual interviews: findings from a randomized study. Int J Soc Res Methodol. 2017;20(6):693–708.

384. Wilkinson S. Focus Groups. Psychol Women Q. 1999 Jun 24;23(2):221–44.

385. Kvale S. Doing Interviews. Vol. 2, Sage, London. London: Sage Publications, Inc.; 2008. 160 p.

386. Stephens N. Collecting data from elites and ultra elites: telephone and face-to-face interviews with macroeconomists. Qual Res. 2007;7(2):203–16.

387. Barbour CR. Doing Focus Groups. London: Sage Publications, Inc.; 2014. 160–172 p.

388. Hubberman A., Miles MB. Qualitative data analysis: An expanded sourcebook. Thousand Oaks, California 91320: SAGE Publications Ltd.; 1994.

389. Atieno OP. An analysis of the strengths and limitations of qualitative and quantitative research paradigms. Probl Educ 21st century. 2009;13(1):13–8.

390. Pope C, Mays N. Qualitative Research: Reaching the parts other methods cannot reach: an introduction to qualitative methods in health and health services research. BMJ. 1995 Jul 1;311(6996):42–5.

391. Pope C, Mays N. Critical reflections on the rise of qualtitative research in health services research. Bmj. 2009;339:1–6.

392. Nowell LS, Norris JM, White DE, Moules NJ. Thematic Analysis : Striving to Meet the Trustworthiness Criteria. 2017;16:1–13.

393. Fereday J, Muir-Cochrane E. Demonstrating Rigor Using Thematic Analysis: A Hybrid Approach of Inductive and Deductive Coding and Theme Development. Int J Qual Methods. 2017;5(1):80–92.

394. Birt L, Scott S, Cavers D, Campbell C, Walter F. Member Checking : A Tool to Enhance Trustworthiness or Merely a Nod to Validation ? 2016;

395. Barbour RS. Checklists for improving rigour in qualitative research: a case of the tail wagging the dog? BMJ. 2001;322(7294):1115–7.

396. Hussein A. The use of Triangulation in Social Sciences Research: Can qualitative and quantitative methods be combined? J Comp Soc Work. 2009;1:1–12.

397. Koch T. Establishing rigour in qualitative research: the decision trail. J Adv Nurs. 1994 May;19(5):976–86.

398. Guba E, Lincoln Y. Fourth generation evaluation. Thousand Oaks, California 91320: SAGE Publications Ltd.; 1989.

399. Lincoln YS, Guba E. Naturalistic Inquiry. The Blackwell Encyclopedia of Sociology. Newbury Park, CA: Sage Publications; 1985.

400. Hammarberg K, Kirkman M, de Lacey S. Qualitative research methods: when to use them and how to judge them. Hum Reprod. 2016;31(3):498–501.

401. Cohen DJ, Crabtree BF. Evaluative criteria for qualitative research in health care:

Controversies and recommendations. Ann Fam Med. 2008;6(4):331–9.

402. Guest G, Bunce A, Johnson L. How Many Interviews Are Enough?: An Experiment with Data Saturation and Variability. Field methods. 2006;18(1):59–82.

403. Barker S, Edwards R. How many qualitative interviews is enough? National Centre for Research Methods; 2007.

404. Sandelowski M. The problem of rigor in qualitative research. ANS Adv Nurs Sci. 1986;8(3):27–37.

405. Booth A, Hannes K, Harden A, Noyes J, Harris J, Tong A. COREQ (Consolidated Criteria for Reporting Qualitative Studies). Guidel Report Heal Res A User's Man. 2014;214–26.

406. Lowe A. The real life guide to accounting research — A behind-the-scenes view of using qualitative research methods. Vol. 40, The International Journal of Accounting. 2005. 294–298 p.

407. Tourangeau R, Rips LJ, Rasinski K. The Psychology of Survey Response. Cambridge: Cambridge University Press; 2000.

408. Schensul JJ, LeCompte MD. Ethnographer's toolkit. Walnut Creek, CA: AltaMira Press.; 1999.

409. Phillippi J, Lauderdale J. A Guide to Field Notes for Qualitative Research: Context and Conversation. Qual Health Res. 2018;28(3):381–8.

410. Holstein J, Gubrium J. Inside interviewing: New lenses, new concerns. Thousand Oaks, California 91320: sage; 2003.

411. Jefferson G. Glossary of transcript symbols with an introduction. In 2004. p. 13–31.

412. Shaw R. Embedding reflexivity within experiential qualitative psychology. Qual Res Psychol. 2010;7(3):233–43.

413. Lyons E, Coyle A, Coyle A. Introduction to Qualitative Psychological Research. In: Analysing Qualitative Data in Psychology. 2012. p. 9–30.

414. Rohleder P, Lyons AC. Qualitative Research in Clinical and Health Psychology. London: Macmillan International Higher Education; 2015.

415. Attia M, Edge J. Be(com)ing a reflexive researcher: a developmental approach to research methodology. Open Rev Educ Res. 2017;4(1):33–45.

416. Morgan DL. Paradigms Lost and Pragmatism Regained: Methodological Implications of Combining Qualitative and Quantitative Methods. J Mix Methods Res. 2007;1(1):48–76.

417. Kaushik V, Walsh CA. Pragmatism as a research paradigm and its implications for Social Work research. Soc Sci. 2019;8(9).

418. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol. 2006;3(2):77–101.

419. King N, Cassell C, Symon. G. Using templates in the thematic analysis of text. Essent Guid to Qual methods Organ Res 2. 2004;256–70.

420. Savage J. One voice , different tunes : issues raised by dual analysis of a segment of qualitative data. 2000;31(6):1493–500.

421. Averill JB. Matrix Analysis as a Complementary Analytic Strategy in Qualitative Inquiry. Qual Health Res. 2002;12(6):855–66.

422. Gibbs G. Learning by Doing: A Guide to Teaching and Learning Methods. Gibbs G,

editor. Oxford: Further Education Unit at Oxford Polytechnic, UK; 1988.

423. Desantis L, Ugarriza DN. The Concept of Theme as Used in Qualitative Nursing Research. 2000;22(3):351–72.

424. XMind Ltd. XMind.

425. Attridge-Stirling J, Attride-Stirling J. Thematic networks: an analytic tool for qualitative research. Qual Res. 2001 Dec 7;1(3):385–405.

426. Tong A, Sainsbury P, Craig J. Consolidated criterio for reporting qualitative research (COREQ): a 32- item checklist for interviews and focus group. Int J Qual Heal Care. 2007;19(6):349–57.

427. Aronson J. A pragmatic view of thematic analysis. Qual Rep. 1994;2(1):3.

428. Howell DA, Hart RI, Smith AG, Macleod U, Patmore R, Cook G, et al. Myeloma: Patient accounts of their pathways to diagnosis. PLoS One. 2018;13(4):e0194788.

429. Gough MD, Gilliam AD, Stoddard CJ, Ackroyd R. Barrett's esophagus : patient information and the Internet. The patient's perspective. Dis Esophagus. 2003;57–9.

430. Swash B, Hulbert-Williams N, Bramwell R. 'Haematological cancers, they're a funny bunch: A qualitative study of non-Hodgkins lymphoma patient experiences of unmet supportive care needs. J Health Psychol. 2016;July:1–12.

431. Hauksdóttir B, Klinke ME, Gunnarsdóttir S, Björnsdóttir K. Patients' Experiences With Multiple Myeloma: A Meta-Aggregation of Qualitative Studies. Oncol Nurs Forum. 2017;44(2):E64–81.

432. Mishel M. Uncertainty in chronic illness. Annu Rev Nurs Res. 1999;17(November):269–94.

433. Kessels RPC. Patients' memory for medical information. J R Soc Med. 2003;96(5):219–22.

434. Kenny T, Wilson RG, Purves IN, Clark J, Newton LD, Newton DP, et al. A PIL for every ill? Patient information leaflets (PILs): a review of past, present and future use. Vol. 15, Family practice. 1998. p. 471–9.

435. Meredith P, Emberton M, Wood C. New directions in information for patients. BMJ. 1995 Jul 1;311(6996):4–5.

436. Department of Health. Cancer patient experience survey 2011/12. National report. London; 2012.

437. Rider T, Malik M, Chevassut T. Haematology patients and the internet - The use of on-line health information and the impact on the patient-doctor relationship. Patient Educ Couns. 2014;97(2):223–38.

438. Li J, Smith A, Crouch S, Oliver S, Roman E. Estimating the prevalence of hematological malignancies and precursor conditions using data from Haematological Malignancy Research Network (HMRN). Cancer Causes Control. 2016;27(8):1019–26.

439. Holt A. Using the telephone for narrative interviewing: a research note. Qual Res. 2010 Feb 15;10(1):113–21.

440. Susan Vogl. Telephone versus face to face interviews: Mode on Semi-structured interviews with children. Sociol Methodol. 2016;43(August 2013):133–77.

441. Malta S. Qualitative Interviewing of Older Adults: Offline versus Online Methods. In: Proceedings 8th National Conference of Emerging Researchers in Ageing A New Era for Ageing Research: What's in Your Toolkit? 2009. p. 133–7.

442. Oltmann SM. Qualitative interviews: A methodological discussion of the interviewer and respondent contexts. Forum Qual Sozialforsch. 2016;17(2):1–11.

443. Guba E, Lincoln Y. Effective evaluation. San Francisco: Jossey-Bass Publishers; 1981. 423 p.

444. Boyatzis R. Transforming qualitative information: Thematic analysis and code development. Thousand Oaks, CA, US: Sage; 1998.

445. Quality Health. National Cancer Patient Experience Survey 2016. Chesterfield; 2016.

446. Shephard EA, Neal RD, Rose P, Walter FM, Litt EJ, Hamilton WT. Quantifying the risk of multiple myeloma from symptoms reported in primary care patients: A large case-control study using electronic records. Br J Gen Pract. 2015;65(631):e106–13.

447. McMullin MF, James G, Duncombe AS, de Vocht F, Fritschi L, Clarke M, et al. Patient perspectives of a diagnosis of myeloproliferative neoplasm in a case control study. Exp Hematol Oncol. 2016;5(1):1–5.

448. Krippendorff K. Content Analysis: An Introduction to Its Methodology Ch2 and 4. Content Analysis: An Introduction to Its Methodology. 2003. 440 p.

449. White MD, Marsh EE. Content Analysis: A Flexible Methodology. Libr Trends. 2006;55(1):22–45.

450. Hsieh HF, Shannon SE. Three approaches to qualitative content analysis. Qual Health Res. 2005;15(9):1277–88.

451. Lindkvist K. Approaches to textual analysis. In: Advances in content analysis. 1981. p. 23–42.

452. Rabin C, Horowitz S, Marcus B. Recruiting Young Adult Cancer Survivors for Behavioral Research. J Clin Psychol Med Settings. 2013 Mar 19;20(1):33–6.

453. Sugawara Y, Narimatsu H, Hozawa A, Shao L, Otani K, Fukao A. Cancer patients on Twitter: a novel patient community on social media. BMC Res Notes. 2012;5(1):699.

454. Thoma B, Paddock M, Purdy E, Sherbino J, Milne WK, Siemens M, et al. Leveraging a Virtual Community of Practice to Participate in a Survey-based Study: A Description of the METRIQ Study Methodology. AEM Educ Train. 2016;1(2):110–3.

455. Choo EK, Ranney ML, Chan TM, Trueger NS, Walsh AE, Tegtmeyer K, et al. Twitter as a tool for communication and knowledge exchange in academic medicine: A guide for skeptics and novices. Med Teach. 2015;37(5):411–6.

456. Chan TM, Jo D, Shih AW, Bhagirath VC, Castellucci LA, Yeh C, et al. The Massive Online Needs Assessment (MONA) to inform the development of an emergency haematology educational blog series. Perspect Med Educ. 2018;

457. Cunningham CT, Quan H, Hemmelgarn B, Noseworthy T, Beck CA, Dixon E, et al. Exploring physician specialist response rates to web-based surveys. BMC Med Res Methodol. 2015 Dec 9;15(1):32.

458. Pit SW, Vo T, Pyakurel S. The effectiveness of recruitment strategies on general practitioner's survey response rates - a systematic review. BMC Med Res Methodol. 2014;14(1):1–14.

459. Pushparajah DS, Manning E, Michels E, Arnaudeau-Bégard C. Value of Developing Plain Language Summaries of Scientific and Clinical Articles: A Survey of Patients and Physicians. Ther Innov Regul Sci. 2018;52(4):474–81.

460. McShane CM, Murphy B, Lim KH, Anderson LA. Monoclonal gammopathy of undetermined significance (MGUS) as viewed by haematology healthcare

professionals. Eur J Haematol. 2017;(August):1–7.

461. Cook C, Heath F, Thompson RL. a Meta-Analysis of Response Rates in Web-or Internet-Based Surveys. Educ Psychol Meas. 2000;60(6):821–36.

462. Levine R, Kaplowitz MD, Hadlock TD. A Comparison of Web and Mail Survey Response Rates. Public Opin Q. 2004;68(1):94.

463. StataCorp. Stata Statistical Software. College Station, TX: StataCorp; 2015.

464. McShane CM, Murphy B, Santin O, Anderson LA. Low knowledge and awareness of monoclonal gammopathy of undetermined significance (MGUS) among general practitioners. BMC Fam Pract. 2019 Dec 14;20(1):61.

465. SurveyMonkey Inc. SurveyMonkey Inc. San Mateo, California, USA;

466. Pierucci P, Lenato GM, Suppressa P, Lastella P, Triggiani V, Valerio R, et al. A long diagnostic delay in patients with Hereditary Haemorrhagic Telangiectasia: A questionnaire-based retrospective study. Orphanet J Rare Dis. 2012;7(1):1–13.

467. Jagannath S, Laubach J, Wong E, Stockerl-Goldstein K, Rosenbaum C, Dhodapkar M, et al. Elotuzumab monotherapy in patients with smouldering multiple myeloma: a phase 2 study. Br J Haematol. 2018;182(4):495–503.

468. Cadogan SL, McHugh SM, Bradley CP, Browne JP, Cahill MR. General practitioner views on the determinants of test ordering: A theory-based qualitative approach to the development of an intervention to improve immunoglobulin requests in primary care. Implement Sci. 2016;11(1):1–12.

469. Purvis J. NIECR--a quiet revolution. Ulster Med J. 2015;84(1):1–2.

470. Jewell MD. Using the term pre-cancer creates a new disease out of a risk factor. BMJ. 2014;349(December):g7226.

471. Young A, Tordoff J, Leitch S, Smith A. Doctors and pharmacists provision and opinions of medicines information leaflets in New Zealand. Int J Clin Pharm. 2018;1–10.

472. Frewer LJ, Miles S. Temporal stability of the psychological determinants of trust: Implications for communication about food risks. Heal Risk Soc. 2003;5(3):259–71.

473. Thornton H, Edwards A, Elwyn G. Evolving the multiple roles of "patients" in health-care research: Reflections after involvement in a trial of shared decision-making. Heal Expect. 2003;6(3):189–97.

474. Thornton H. Patients' understanding of risk. BMJ. 2003;327(7417):693–4.

475. Fineberg H V. A Successful and Sustainable Health System — How to Get There from Here. N Engl J Med. 2012 Mar 15;366(11):1020–7.

476. Kaplan RS, Porter ME. Interaction - How to solve the cost crisis in health care. Vol. 89, Harvard business review. 2011. p. 2011–3.

477. Porter ME, Teisberg EO. How Physicians Can Change the Future of Health Care. JAMA. 2007 Mar 14;297(10):1103.

478. Baile WF. SPIKES--A Six-Step Protocol for Delivering Bad News: Application to the Patient with Cancer. Oncologist. 2000;5(4):302–11.

479. Keefe-Cooperman K, Savitsky D, Koshel W, Bhat V, Cooperman J. The PEWTER Study: Breaking Bad News Communication Skills Training for Counseling Programs. Int J Adv Couns. 2018;40(1):72–87.

480. Rosenman R, Tennekoon V, Hill LG. Measuring bias in self-reported data. Int J Behav

Healthc Res. 2011;2(4):320.

481. Teixeira E, Borlido-Santos J, Brissot P, Butzeck B, Courtois F, Evans RW, et al. The importance of the general practitioner as an information source for patients with hereditary haemochromatosis. Patient Educ Couns. 2014;96(1):86–92.

482. Hackshaw A. Small studies: strengths and limitations. Eur Respir J. 2008;32(5):1141–3.

483. Wenrich MD, Curtis J, Shannon SE, Carline JD, Ambrozy DM, Ramsey PG. COmmunicating with dying patients within the spectrum of medical care from terminal diagnosis to death. Arch Intern Med. 2001;161(6):868–74.

484. Maatouk I, He S, Becker N, Hummel M, Hemmer S, Hillengass M, et al. Association of resilience with health-related quality of life and depression in multiple myeloma and its precursors: results of a German cross-sectional study. BMJ Open. 2018;8(7):e021376.

485. Gunasekaran B, Jayasinghe Y, Fenner Y, Moore EE, Wark JD, Fletcher A, et al. Knowledge of human papillomavirus and cervical cancer among young women recruited using a social networking site. Sex Transm Infect. 2013;89(4):327–9.

486. Hawkins DM, Eide MJ, Lim HW. Perception of xeroderma pigmentosum support group members of xeroderma pigmentosum lifestyle impact. Photodermatol Photoimmunol Photomed. 2012;28(6):338–9.

487. Hay JL, Buckley TR, Ostroff JS. The role of cancer worry in cancer screening: A theoretical and empirical review of the literature. Psychooncology. 2005;14(7):517–34.

488. Maruish ME (Ed.). User's manual for the SF-12v2 Health Survey (3rd ed.). 3rd ed. Lincoln, RI: QualityMetric Incorporated; 2012.

489. Kelley K, Clark B, Brown V, Sitzia J. Good practice in the conduct and reporting of survey research. Int J Qual Heal Care. 2003;15(3):261–6.

490. van Teijlingen E, Hundley V. The importance of pilot studies. Nurs Stand. 2002 Jun 19;16(40):33–6.

491. Faul F, Erdfelder E, Lang A-G, Buchner A. G*Power: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods. 2007;39(2):175–91.

492. Hookway N. "Entering the blogosphere": Some strategies for using blogs in social research. Qual Res. 2008;8(1):91–113.

493. Kapp JM, Peters C, Oliver DP. Research recruitment using facebook advertising: Big potential, big challenges. J Cancer Educ. 2013;28(1):134–7.

494. Euroqol Group. EuroQol Group EQ-5D™ Health Questionnaire. Http://WwwEuroqolOrg/Eq-5D-Products/How-To-Obtain-Eq-5DHtml. 2009;3.

495. Szende A, Janssen MB, Cabasés JM, Ramos Goñi JM. Self-Reported Population Health: An International Perspective based on EQ-5D. Vol. 16, Value in Health. 2014. A464 p.

496. Stavem K, Augestad LA, Kristiansen IS, Rand K. General population norms for the EQ-5D-3 L in Norway: Comparison of postal and web surveys. Health Qual Life Outcomes. 2018;16(1):1–10.

497. Osborne JW, Waters E. Four assumptions of multiple regression that researchers should always test. Pract Assessment, Res Eval. 2001;8(2):1–5.

498. Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): Explanation and elaboration. Int J Surg. 2014 Dec;12(12):1500–24.

499. Potter WJ, Levine-Donnerstein D. Rethinking validity and reliability in content analysis. J Appl Commun Res. 1999;27(3):258–84.

500. Sirohi B, Powles R. Epidemiology and outcomes research for MGUS, myeloma and amyloidosis. Eur J Cancer. 2006;42(11):1671–83.

501. Anderson LA, Atman AA, McShane CM, Titmarsh GJ, Engels EA, Koshiol J. Common infection-related conditions and risk of lymphoid malignancies in older individuals. Br J Cancer. 2014;110(11):2796–803.

502. Molassiotis A, Wilson B, Blair S, Howe T. Unmet supportive care needs, psychological well-being and quality of life in patients living with multiple myeloma and their partners. Psycho-. 2011;

503. Nida Fathima D. Curcumin -Role in cancer. J Pharm Sci Res. 2014;6(11):351–5.

504. Bar-Sela G, Epelbaum R, Schaffer M. Curcumin as an Anti-Cancer Agent: Review of the Gap Between Basic and Clinical Applications. Curr Med Chem. 2009;17(3):190–7.

505. Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB. Bioavailability of Curcumin: Problems and Promises. Mol Pharm. 2007 Dec;4(6):807–18.

506. Aggarwal BB, Sundaram C, Malani N, Ichikawa H. Curcumin: The Indian solid gold. Vol. 595, Advances in Experimental Medicine and Biology. Boston, MA: Springer US; 2007. p. 1–75.

507. Goel A, Kunnumakkara AB, Aggarwal BB. Curcumin as " Curecumin": From kitchen to clinic. Biochem Pharmacol. 2008;75(4):787–809.

508. Rood JAJ, Eeltink CM, van Zuuren FJ, Verdonck-de Leeuw IM, Huijgens PC. Perceived need for information of patients with haematological malignancies: A literature review. J Clin Nurs. 2015;24(3–4):353–69.

509. Hallowell N, Mackay J, Richards M, Gore M, Jacobs I. High-Risk Premenopausal Women's Experiences of Undergoing Prophylactic Oophorectomy: A Descriptive Study. Genet Test. 2004 Jun;8(2):148–56.

510. Glassey R, Ives A, Saunders C, Musiello T. Decision making, psychological wellbeing and psychosocial outcomes for high risk women who choose to undergo bilateral prophylactic mastectomy - A review of the literature. Breast. 2016;28:130–5.

511. Department of Health. Equity and excellence: Liberating the NHS (White Paper). The Stationery Office. 2010. 61 p.

512. Custers JAE, Van Den Berg SW, Van Laarhoven HWM, Bleiker EMA, Gielissen MFM, Prins JB. The cancer worry scale: Detecting fear of recurrence in breast cancer survivors. Cancer Nurs. 2014;37(1).

513. Crutzen R, Göritz AS. Social desirability and self-reported health risk behaviors in web-based research: Three longitudinal studies. BMC Public Health. 2010;10(1):720.

514. McPeake J, Bateson M, O'Neill A. Electronic surveys: How to maximize success. Nurse Res. 2014;21(3):24–6.

515. Kreuter F, Presser S, Tourangeau R. Social desirability bias in CATI, IVR, and web surveys: The effects of mode and question sensitivity. Public Opin Q. 2008;72(5):847–65.

516. Hunter RF, Gough A, O'Kane N, McKeown G, Fitzpatrick A, Walker T, et al. Ethical Issues in Social Media Research for Public Health. Am J Public Health. 2018;e1–6.

517. Miller ET, Neal DJ, Roberts LJ, Baer JS, Cressler SO, Metrik J, et al. Test-retest reliability of alcohol measures: Is there a difference between internet-based assessment and

traditional methods? Psychol Addict Behav. 2002;16(1):56–63.

518. Riva G, Teruzzi T, Anolli L. The Use of the Internet in Psychological Research: Comparison of Online and Offline Questionnaires. CyberPsychology Behav. 2003;6(1):73–80.

519. Walter LC, Covinsky KE. Cancer screening in elderly patients: A framework for individualized decision making. Jama. 2001;285(21):2750–6.

520. Best M, Butow P, Olver I. The doctor's role in helping dying patients with cancer achieve peace: A qualitative study. Palliat Med. 2014;28(9):1139–45.

521. McCaughan E, McKenna H. Never-ending making sense: Towards a substantive theory of the information-seeking behaviour of newly diagnosed cancer patients. J Clin Nurs. 2007;16(11):2096–104.

522. Cuijpers P, Smit F. Subklinische depressie: Een klinisch relevante conditie? Tijdschr Psychiatr. 2008;50(8):519–28.

523. Lux V, Kendler KS. Deconstructing major depression: A validation study of the DSM-IV symptomatic criteria. Psychol Med. 2010;40(10):1679–90.

524. Ray A, Block SD, Friedlander RJ, Zhang B, Maciejewski PK, Prigerson HG. Peaceful Awareness in Patients with Advanced Cancer. J Palliat Med. 2006 Dec;9(6):1359–68.

525. Crocetti E, Arniani S, Acciai S, Barchielli A, Buiatti E. High suicide mortality soon after diagnosis among cancer patients in central Italy. Br J Cancer. 1998;77(7):1194–6.

526. Fang F, Keating NL, Mucci LA, Adami H-O, Stampfer MJ, Valdimarsdóttir U, et al. Immediate Risk of Suicide and Cardiovascular Death After a Prostate Cancer Diagnosis: Cohort Study in the United States. JNCI J Natl Cancer Inst. 2010;102(5):307–14.

527. Henson KE, Brock R, Charnock J, Wickramasinghe B, Will O, Pitman A. Risk of Suicide after Cancer Diagnosis in England. JAMA Psychiatry. 2019;76(1):51–60.

528. Mohammadi M, Moradi T, Bottai M, Reutfors J, Cao Y, Smedby KE. Risk and predictors of attempted and completed suicide in patients with hematological malignancies. Psychooncology. 2014;23(11):1276–82.

529. Schubart JR, Stuckey HL, Ganeshamoorthy A, Sciamanna CN. Chronic health conditions and internet behavioral interventions: A review of factors to enhance user engagement. CIN - Comput Informatics Nurs. 2011;29(2):81–92.

530. Lang H, France E, Williams B, Humphris G, Wells M. The psychological experience of living with head and neck cancer: A systematic review and meta-synthesis. Psychooncology. 2013;22(12):2648–63.

531. Piet J, Würtzen H, Zachariae R. The effect of mindfulness-based therapy on symptoms of anxiety and depression in adult cancer patients and survivors: A systematic review and meta-analysis. J Consult Clin Psychol. 2012;80(6):1007–20.

532. Faller H, Schuler M, Richard M, Heckl U, Weis J, Kuffner R. Effects of psycho-oncologic interventions on emotional distress and quality of life in adult patients with cancer: Systematic review and meta-analysis. J Clin Oncol. 2013;31(6):782–93.

533. Cheung SY, Delfabbro P. Are you a cancer survivor? A review on cancer identity. J Cancer Surviv. 2016;10(4):759–71.

534. Caswell S, Anderson AS, Steele RJC. Short Communication Bowel health to better health : a minimal contact lifestyle intervention for people at increased risk of colorectal cancer British Journal of Nutrition. Br J Nutr. 2009;102(11):1541–6.

535. Demark-Wahnefried W, Aziz NM, Rowland JH, Pinto BM. Riding the crest of the teachable moment: Promoting long-term health after the diagnosis of cancer. J Clin Oncol. 2005;23(24):5814–30.

536. Kotecha R, Takami A, Espinoza JL. Dietary phytochemicals and cancer chemoprevention: A review of the clinical evidence. Oncotarget. 2016;7(32):52517–29.

537. Golombick T, Diamond TH, Manoharan A, Ramakrishna R. Addition of Rice Bran Arabinoxylan to Curcumin Therapy May Be of Benefit to Patients with Early-Stage B-Cell Lymphoid Malignancies (Monoclonal Gammopathy of Undetermined Significance, Smoldering Multiple Myeloma, or Stage 0/1 Chronic Lymphocytic Leukemia). Integr Cancer Ther. 2016;15(2):183–9.

538. Golombick T, Diamond TH, Manoharan A, Ramakrishna R. Monoclonal gammopathy of undetermined significance, smoldering multiple myeloma, and curcumin: A randomized, double-blind placebo-controlled cross-over 4g study and an open-label 8g extension study. Am J Hematol. 2012;87(5):455–60.

539. Thordardottir M, Lindqvist EK, Lund SH, Costello R, Burton D, Steingrimsdottir L, et al. Dietary intake is associated with risk of multiple myeloma and its precursor disease. PLoS One. 2018;13(11):1–15.

540. Maliski SL, Mccorkle R. Couples ' Transformation of a Prostate Cancer Diagnosis. Nurs Res. 1994;391–7.

541. van Haren IEPM, Staal JB, Potting CM, Atsma F, Hoogeboom TJ, Blijlevens NMA, et al. Physical exercise prior to hematopoietic stem cell transplantation: A feasibility study. Physiother Theory Pract. 2018;34(10):747–56.

542. Kaynak E. Original articles. J Int Consum Mark. 1993;5(2):1–4.

543. Boullosa DA, Abreu L, Tonello L, Hofmann P, Leicht AS. Exercise is medicine: Case report of a woman with smoldering multiple myeloma. Med Sci Sports Exerc. 2013;45(7):1223–8.

544. Maes S, Sharma P, Bisschops R. Review: Surveillance of patients with Barrett oesophagus. Best Pract Res Clin Gastroenterol. 2016;30(6):901–12.

545. Tan WK, di Pietro M, Fitzgerald RC. Past, present and future of Barrett's oesophagus. Eur J Surg Oncol. 2017;43(7):1148–60.

546. Lindblad M, Bright T, Schloithe A, Mayne GC, Chen G, Bull J, et al. Toward More Efficient Surveillance of Barrett's Esophagus: Identification and Exclusion of Patients at Low Risk of Cancer. World J Surg. 2017;41(4):1023–34.

547. Al-Hashimi I, Schifter M, Lockhart PB, Wray D, Brennan M, Migliorati CA, et al. Oral lichen planus and oral lichenoid lesions: diagnostic and therapeutic considerations. Oral Surgery, Oral Med Oral Pathol Oral Radiol Endodontology. 2007;103(SUPPL.).

548. Kirby JS, Gregory T, Liu G, Leslie DL, Miller JJ. Variation in the cost of managing actinic keratosis. JAMA Dermatology. 2017;153(4):265–9.

549. Hefermehl LJ, Disteldorf D, Lehmann K. Acknowledging unreported problems with active surveillance for prostate cancer: A prospective single-centre observational study. BMJ Open. 2016;6(2).

550. Cedars B, Lisker S, Borno HT, Kamal P, Breyer B, Sarkar U. An electronic registry to improve adherence to active surveillance monitoring among men with prostate cancer at a safety-net hospital: protocol for a pilot study. Pilot Feasibility Stud. 2019;5(1):1–7.

551. Kim C, Wright FC, Look Hong NJ, Groot G, Helyer L, Meiers P, et al. Patient and provider experiences with active surveillance: A scoping review. PLoS One.

2018;13(2):1–17.

552. Bryne TJ, Edeani D. Knowledge of Medical Terminology among Hospital Patients. Nurs Res. 1984 May;33(3):178–81.

553. Fallowfield LJ, Baum M. Psychological Welfare of Patients with Breast Cancer. J R Soc Med. 1989 Jan 29;82(1):4–5.

554. Reyna VF, Brainerd CJ. Numeracy, ratio bias, and denominator neglect in judgments of risk and probability. Learn Individ Differ. 2008;

555. Lea DH, Kaphingst KA, Bowen D, Lipkus I, Hadley DW. Communicating genetic and genomic information: Health literacy and numeracy considerations. Public Health Genomics. 2011;14(4–5):279–89.

556. Griffin J, McKenna K, Tooth L. Written health education materials: Making them more effective. Aust Occup Ther J. 2003;50(3):170–7.

557. Kinnersley P, Edwards A, Hood K, Ryan R, Prout H, Cadbury N, et al. Interventions before consultations to help patients address their information needs by encouraging question asking: Systematic review. Bmj. 2008;337(7665):335–9.

558. Friedman DB, Hoffman-Goetz L. A Systematic Review of Readability and Comprehension Instruments Used for Print and Web-Based Cancer Information. Heal Educ Behav. 2006 Jun 30;33(3):352–73.

559. SEMPLE CJ, McGOWAN B. Need for appropriate written information for patients, with particular reference to head and neck cancer. J Clin Nurs. 2002 Sep;11(5):585–93.

560. Mills ME, Sullivan K. The importance of information giving for patients newly diagnosed with cancer: a review of the literature. J Clin Nurs. 1999 Nov;8(6):631–42.

561. Bourke L, Boorjian SA, Briganti A, Klotz L, Mucci L, Resnick MJ, et al. Survivorship and Improving Quality of Life in Men with Prostate Cancer. European Urology. 2015.

562. Faller H, Koch U, Brähler E, Härter M, Keller M, Schulz H, et al. Satisfaction with information and unmet information needs in men and women with cancer. J Cancer Surviv. 2016;10(1):62–70.

563. Fiszer C, Dolbeault S, Sultan S, Brédart A. Prevalence, intensity, and predictors of the supportive care needs of women diagnosed with breast cancer: A systematic review. Psychooncology. 2014 Apr;23(4):361–74.

564. Knight A, Senior T. The common problem of rare disease in general practice. Med J Aust. 2006;185(2):2–3.

565. Bulsara C, Ward A, Joske D. Haematological cancer patients: Achieving a sense of empowerment by use of strategies to control illness. J Clin Nurs. 2004;13(2):251–8.

566. von der Lippe C, Diesen PS, Feragen KB. Living with a rare disorder: a systematic review of the qualitative literature. Mol Genet Genomic Med. 2017 Nov;5(6):758–73.

567. Cassell EJ, Leon AC, Kaufman SG. Preliminary evidence of impaired thinking in sick patients. Ann Intern Med. 2001;134(12).

568. Spurio MG razi. Words that heal. Psychiatr Danub. 2015;27:S21–7.

569. Copp T, Mccaffery K, Azizi L, Doust J, Mol BWJ, Jansen J. Influence of the disease label polycystic ovary syndrome' on intention to have an ultrasound and psychosocial outcomes: A randomised online study in young women. Hum Reprod. 2017;32(4):876–84.

570. Nickel B, Barratt A, Copp T, Moynihan R, McCaffery K. Words do matter: A systematic review on how different terminology for the same condition influences management

preferences. BMJ Open. 2017;7(7).

571. Pickering TG. Now we are sick: labeling and hypertension. J Clin Hypertens (Greenwich). 2006;8(1):57–60.

572. Koch-Weser S, Dejong W, Rudd RE. Medical word use in clinical encounters. Heal Expect. 2009;12(4):371–82.

573. Rudd RE, Zobel EK, Fanta CH, Surkan P, Rodriguez-Louis J, Valderrama Y, et al. Asthma: In Plain Language. Health Promot Pract. 2004 Jul 23;5(3):334–40.

574. Ha JF, Longnecker N. Doctor-patient communication: a review. Ochsner J. 2010;10(1):38–43.

575. Statista Research Department. Share of individuals who have used the internet to search for health care information in the United Kingdom (UK) in 2015 [Internet]. 2015 [cited 2019 Sep 26]. Available from: https://www.statista.com/statistics/505053/individual-use-internet-for-health-information-search-united-kingdom-uk/

576. Meyer SB, Coveney J, Ward PR. A qualitative study of CVD management and dietary changes: problems of "too much" and "contradictory" information. BMC Fam Pract. 2014;15(1):25.

577. Ebel MD, Stellamanns J, Keinki C, Rudolph I, Huebner J. Cancer Patients and the Internet: a Survey Among German Cancer Patients. J Cancer Educ. 2017;32(3):503–8.

578. Lee SP, Sung I-K, Kim JH, Lee S-Y, Park HS, Shim CS. The effect of emotional stress and depression on the prevalence of digestive diseases. J Neurogastroenterol Motil. 2015;21(2):273–82.

579. Caiata-Zufferey M, Abraham A, Sommerhalder K, Schulz PJ. Online health information seeking in the context of the medical consultation in switzerland. Qual Health Res. 2010;20(8):1050–61.

580. Papadakos J, Trang A, Cyr AB, Abdelmutti N, Giuliani ME, Snow M, et al. Deconstructing Cancer Patient Information Seeking in a Consumer Health Library Toward Developing a Virtual Information Consult for Cancer Patients and Their Caregivers: A Qualitative, Instrumental Case Study. JMIR Cancer. 2017;3(1):e6.

581. Leventhal H, Alison Phillips L, Burns E. Modelling management of chronic illness in everyday life: A common-sense approach. Psihol Teme. 2016;25(1):1–18.

582. Stewart M, Brown JB, Boon H, Galajda J, Meredith L, Sangster M. Evidence on patient-doctor communication. Cancer Prev Control. 1999 Feb;3(1):25–30.

583. Stewart MA. Effective physician-patient communication and health outcomes: a review. CMAJ. 1995;152(9):1423–33.

584. Beaver K, Campbell M, Williamson S, Procter D, Sheridan J, Heath J, et al. An exploratory randomized controlled trial comparing telephone and hospital follow-up after treatment for colorectal cancer. Color Dis. 2012 Oct;14(10):1201–9.

585. Williamson S, Chalmers K, Beaver K. Patient experiences of nurse-led telephone follow-up following treatment for colorectal cancer. Eur J Oncol Nurs. 2015;19(3):237–43.

586. Kimman ML, Dirksen CD, Voogd AC, Falger P, Gijsen BCM, Thuring M, et al. Nurse-led telephone follow-up and an educational group programme after breast cancer treatment: Results of a 2×2 randomised controlled trial. Eur J Cancer. 2011 May;47(7):1027–36.

587. Agarwal S, Pappas L, Neumayer L, Kokeny K, Agarwal J. Effect of breast conservation

therapy vs mastectomy on disease-specific survival for early-stage breast cancer. JAMA Surg. 2014;149(3):267–74.

588. Sokol R, Fisher E. Peer Support for the Hardly Reached: A Systematic Review. Am J Public Health. 2016;106(7):1308.

589. Campbell HS, Phaneuf MR, Deane K. Cancer peer support programs - Do they work? Patient Educ Couns. 2004;55(1):3–15.

590. Hoey LM, Ieropoli SC, White VM, Jefford M. Systematic review of peer-support programs for people with cancer. Patient Educ Couns. 2008 Mar;70(3):315–37.

591. Kingod N, Cleal B, Wahlberg A, Husted GR. Online Peer-to-Peer Communities in the Daily Lives of People with Chronic Illness: A Qualitative Systematic Review. Qual Health Res. 2017;27(1):89–99.

592. Allen C, Vassilev I, Kennedy A, Rogers A. Long-term condition self-management support in online communities: A meta-synthesis of qualitative papers. J Med Internet Res. 2016;18(3):1–21.

593. Fox S, Duggan M. Health online 2013. Health (Irvine Calif). 2013;1–55.

594. Chou WYS, Hunt Y, Folkers A, Augustson E. Cancer survivorship in the age of YouTube and social media: a narrative analysis. J Med Internet Res. 2011;13(1).

595. Bender JL, Jimenez-Marroquin MC, Jadad AR. Seeking support on facebook: A content analysis of breast cancer groups. J Med Internet Res. 2011;13(1).

596. Greene JA, Choudhry NK, Kilabuk E, Shrank WH. Online social networking by patients with diabetes: A qualitative evaluation of communication with Facebook. J Gen Intern Med. 2011;26(3):287–92.

597. Partridge SR, Gallagher P, Freeman B, Gallagher R. Facebook Groups for the Management of Chronic Diseases. J Med Internet Res. 2018;20(1):e21.

598. Klemm P, Bunnell D, Cullen M, Soneji R, Gibbons P, Holecek A. Online cancer support groups: a review of the research literature. Comput Inform Nurs. 2003;21(3):136–42.

599. Groen WG, Kuijpers W, Oldenburg HSA, Wouters MWJM, Aaronson NK, Van Harten WH. Empowerment of cancer survivors through information technology: An integrative review. J Med Internet Res. 2015;17(11):1–17.

600. Hong Y, Peña-Purcell NC, Ory MG. Outcomes of online support and resources for cancer survivors: A systematic literature review. Patient Educ Couns. 2012;86(3):288–96.

601. van Uden-Kraan CF, Drossaert CH, Taal E, Shaw BR, Seydel ER, van de Laar M a. Empowering processes and outcomes of participation in online support groups for patients with breast cancer, arthritis, or fibromyalgia. Qual Health Res. 2008;18(3):405–17.

602. Klemm P, Bunnell D, Cullen M, Soneji R, Gibbons P, Holecek A. Online cancer support groups: a review of the research literature . ClN Comput Informatics, Nurs. 2003;21(3):136–42.

603. Laukka E, Rantakokko P, Suhonen M. Consumer-led health-related online sources and their impact on consumers: An integrative review of the literature. Health Informatics J. 2017;146045821770425.

604. Santin O, McShane T, Fowler C, McCarry S, McManus M, Mills M, et al. Cancer, Caring, Coping. Cancer Caring Coping: The co-design development and evaluation of an online resource to support cancer caregivers. A report for HSC R&D Office. 2018.

605. Baider L, Ever-Hadani P, Goldzweig G, Wygoda MR, Peretz T. Is perceived family support a relevant variable in psychological distress? A sample of prostate and breast cancer couples. J Psychosom Res. 2003;55(5):453–60.

606. Swash B, Hulbert-Williams N, Bramwell R. Unmet psychosocial needs in haematological cancer: A systematic review. Support Care Cancer. 2014;22(4):1131–41.

607. Ashing-Giwa KT, Kagawa-Singer M, Padilla G V, Tejero JS, Hsiao E, Chhabra R, et al. The impact of cervical cancer and dysplasia: a qualitative, multiethnic study. Psychooncology. 2004;13(10):709–28.

608. Gray RE, Fitch M, Phillips C, Labrecque M, Fergus K. To tell or not to tell: Patterns of disclosure among men with prostate cancer. Psychooncology. 2000;9(4):273–82.

609. Brown D, Oetzel J. Men's use of networks to manage communication tensions related to a potential diagnosis of prostate cancer. Eur J Oncol Nurs. 2016 Feb;20:106–12.

610. Coughlan J, Eatock J, Eldabi T. Evaluating telemedicine: A focus on patient pathways. Int J Technol Assess Health Care. 2006;22(1):136–42.

611. Jones K. The Remodelling of Patient Care Pathway for e health. Computing. 2009;(September).

612. Johnson RBB, Onwuegbuzie AJJAJ. Mixed Methods Research: A Research Paradigm Whose Time Has Come. Educ Res. 2004;33(7):14–26.

613. Brett J, Staniszewska S, Mockford C, Herron-Marx S, Hughes J, Tysall C, et al. A Systematic Review of the Impact of Patient and Public Involvement on Service Users, Researchers and Communities. Patient. 2014;7(4):387–95.

614. Mockford C, Staniszewska S, Griffiths F, Herron-Marx S. The impact of patient and public involvement on UK NHS health care: a systematic review. Int J Qual Heal Care. 2012;24(1):28–38.

615. C Thorpe, B Ryan, SL McLean, A Burt, M Stewart, JB Brown GR and SH. How to obtain excellent response rates whensurveying physicians. Fam Pract. 2016;26:65–8.

616. Hummers-Pradier E, Scheidt-Nave C, Martin H, Heinemann S, Kochen MM, Himmel W. Simply no time? Barriers to GPs' participation in primary health care research. Fam Pract. 2008;25(2):105–12.

617. Rehan H, Sah R, Chopra D. Comparison of knowledge, attitude and practices of resident doctors and nurses on adverse drug reaction monitoring and reporting in a tertiary care hospital. Indian J Pharmacol. 2012;44(6):699.

618. McDonald FS, Zeger SL, Kolars JC. Associations of Conference Attendance With Internal Medicine In-Training Examination Scores. Mayo Clin Proc. 2008 Apr;83(4):449–53.

619. Overend A, Khoo K, Delorme M, Krause V, Avanessian A, Saltman D. Evaluation of a nurse-led telephone follow-up clinic for patients with indolent and chronic hematological malignancies: A pilot study. Can Oncol Nurs J. 2008;18(2):64–8.

620. Jones R, Pearson J, Mcgregor S, Cawsey AJ, Barrett A, Craig N, et al. Information in practice Randomised trial of personalised computer based information for cancer patients. Br Med J. 1999;319:1241–7.

621. Neriishi K, Nakashima E, Suzuki G. Monoclonal gammopathy of undetermined significance in atomic bomb survivors: incidence and transformation to multiple myeloma. Br J Haematol. 2003;121(3):405–10.

622. Golbeck AL, Ahlers-Schmidt CR, Paschal AM, Dismuke SE. A definition and

operational framework for health numeracy. Vol. 29, American Journal of Preventive Medicine. 2005. p. 375–6.