STAKEHOLDERS' PERSPECTIVES ON PREVENTIVE APPROACHES TO RHEUMATOID ARTHRITIS

BY

IMOGEN WELLS

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Institute of Inflammation and Ageing

College of Medical and Dental Sciences

University of Birmingham

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ABSTRACT

Background

There is a strong research focus on the identification of individuals at risk of RA, to facilitate preventive interventions. To inform the development of effective predictive and preventive approaches for RA, it is important to gain a thorough understanding of the views of those who may affected by these approaches. Therefore, this thesis aimed to explore stakeholder's perspectives towards predictive and preventive approaches for RA, including RA patients, their first degree relatives (FDRs) and healthcare professionals (HCPs).

Method

Due to the limited existing literature within the field of RA, a mixed-methods systematic literature review was conducted to examine the acceptability of predictive testing for ischemic heart disease (IHD) in those with a family history, to gain insights that may be relevant in the context of RA. Two cross-sectional surveys were conducted to assess the views of patients with RA and their FDRs regarding predictive testing. FDRs' surveys assessed their interest in predictive testing, and potential predictors of interest. Patients' surveys assessed their likelihood of communicating RA risk information to their FDRs, and potential predictors of this likelihood. Finally, one-to-one qualitative interviews were conducted on rheumatologists, rheumatology nurse specialists and GPs to assess their views on predictive and preventive approaches.

Results

The systematic review examined five quantitative and two qualitative studies. Surveys were completed by 396 FDRs and 482 patients, and interviews were conducted with 16 HCPs. Those with a family history of RA (and IHD) were interested in taking a

predictive test for the disease. Patients were willing to communicate information about RA risk to their FDRs, and HCPs were willing to provide predictive and preventive approaches to those at-risk. Several factors influencing stakeholders' perceptions towards these approaches, including the introduction of these approaches, were identified. These included demographic characteristics, perceived risk of developing RA, understanding of prediction and prevention, the need for patient autonomy, and the potential for tests to cause psychological harm.

Conclusion

Stakeholders were generally interested in predictive and preventive approaches for RA, and reported various factors influencing their perceptions that could be used to inform the development of effective strategies to support the implementation of such approaches into clinical practice.

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Publications and presentations

Abstracts:

- **Wells I,** Simons G, Wöhlke S, Schicktanz S, Hansson M, Raza K, et al. QUALITATIVE STUDY OF PUBLIC PERCEPTIONS OF PREDICTIVE GENETIC TESTING FOR RHEUMATOID ARTHRITIS. Rheumatology. 2019;58(3): kez110.066.
    - Poster presentation.

- **Wells I,** Simons G, Stack R, Mallen C, Nightingale P, Raza K, et al. OP0264-HPR PERSPECTIVES ON APPROACHES TO PREDICT THE DEVELOPMENT OF RHEUMATOID ARTHRITIS: A QUANTITATIVE ASSESSMENT OF PATIENTS AND THEIR FIRST DEGREE RELATIVES. Annals of the Rheumatic Diseases. 2020;79:165-166.
    - Oral presentation.

- **Wells I,** Nightingale P, Simons G, Mallen C, Raza K, Falahee M. POS1483-HPR A QUANTITATIVE ASSESSMENT OF THE LIKELIHOOD THAT PATIENTS WITH RHEUMATOID ARTHRITIS WILL COMMUNICATE INFORMATION ABOUT RHEUMATOID ARTHRITIS RISK TO RELATIVES. Annals of the Rheumatic Diseases. 2021;80:1026-1027.
    - Poster presentation.

Submitted publications

- **Wells I,** Davenport C, Mallen C, Raza K, Falahee M. Acceptability of predictive testing for ischemic heart disease in those with a family history and the impact of results on behavioural intention and behaviour change: a systematic review. 2021.
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- **Wells I,** Zemedikun DT, Simons G, Stack RJ, Mallen CD, Raza K, Falahee M. Predictors of interest in predictive testing for rheumatoid arthritis among first degree relatives of rheumatoid arthritis patients. Rheumatology, 2021; keab890

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- **Wells I,** Simons G, Stack R, Mallen C, Raza K, Falahee M. Predictors of the likelihood that patients with rheumatoid arthritis will communicate information about rheumatoid arthritis risk to relatives: a quantitative assessment. 2021.

    - To be submitted to Arthritis Care & Research.

I have included parts of chapters 2, 3 and 4 in the manuscripts detailed above, which were unpublished at the time of thesis submission. The relevant text was written by me, with revisions suggested by my PhD supervisors.

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List of abbreviations

RA	Rheumatoid arthritis
ACR-EULAR	American College of Rheumatology-European League against Rheumatism
PIP	Proximal Interphalangeal
MCP	Metacarpophalangeal
CRP	C-Reactive Protein
ESR	Erythrocyte Sedimentation Rate
UK	United Kingdom
MTP	Metatarsophalangeal
BD	Boutonniere Deformity
SND	Swan Neck Deformity
DMARD	Disease-Modifying Antirheumatic Drug
CVD	Cardiovascular Disease
cs	Conventional synthetic
b	Biologic
ts	Targeted synthetic
NSAID	Non-Steroidal Anti-Inflammatory Drug
MTX	Methotrexate
TB	Tuberculosis
Anti-CCPs	Anti-Cyclic Citrullinated Protein/Peptide Antibodies
RF	Rheumatoid Factor
FDR	First Degree Relative
HLA	Human Leukocyte Antigen
BMI	Body mass index
OC	Oral contraceptive
ACPA	Anti-Citrullinated Protein/Peptide Antibodies
MRI	Magnetic Resonance Imaging

CSA	Clinically Suspect Arthralgia
UA	Unclassified Arthritis
NAO	National Audit Office
DCE	Discrete Choice Experiment
PREFER	Patient Preferences in Benefit-Risk Assessments during the Drug Life Cycle
PTT	Probabilistic Threshold Technique
HCP	Healthcare professional
GP	General practitioner
IHD	Ischemic Heart Disease
DM	Diabetes Mellitus
IBD	Inflammatory Bowel Disease
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
CRD	Centre for Reviews and Dissemination
PROSPERO	International Prospective Register of Systematic Reviews
ECG	Electrocardiograms
SES	Socioeconomic Status
RCT	Randomised Controlled Trial
SDR	Second Degree Relative
T2D	Type 2 diabetes
Brief IPQ	Brief Illness Perceptions Questionnaire
IPQ-R	Revised Version of the Illness Perception Questionnaire
LOT-R	Life Orientation Test-Revised
SHAI	Short Health Anxiety Inventory
RAID	Rheumatoid Arthritis Impact of Disease
GVIF	Generalised Variance Inflation Factors
GEE	Generalised Estimating Equations
PRP	Patient Research Partners

HCM	Hypertrophic Cardiomyopathy
PCP	Primary Care Practitioner
GC	Genetic Counsellor
COREQ	Consolidated Criteria for Reporting Qualitative Research
TDF	Theoretical Domains Framework

Chapter 1 General Introduction

1.1 Overview

Rheumatoid arthritis (RA) is a common chronic autoimmune condition for which early treatment is important. If treatment is delayed, irreversible joint destruction and disability are more likely to occur. Research efforts have been increasingly directed towards early RA, and more recently towards those at risk of RA, to facilitate early treatment and preventive interventions. The clinical translation of this research will mean that at-risk groups will be offered risk assessment. Therefore, it is important to understand the views of this group, as well as others who might be affected by predictive and preventive approaches, to ensure these approaches are sensitive to the needs and concerns of each group. In this thesis, I explore perceptions of predictive and preventive approaches to RA amongst patients with RA, their first degree relatives and healthcare professionals from primary and secondary healthcare services.

1.2 Rheumatoid arthritis

RA is a chronic autoimmune disease causing inflammation, painful swelling and tenderness of the joints.(1) Persistent inflammation and swelling can result in erosion of the articular cartilage and bone, which can cause deformity and loss of function.(2) RA can also affect extra-articular sites, including the lungs, blood vessels and eyes. Furthermore, fatigue and depression are common symptoms of RA.(3) Fatigue resulting from RA is often described by patients as overwhelming, and uncontrollable.(4)

1.2.1 Classification of RA

Patients are classified as having RA according the American College of Rheumatology-European League against Rheumatism 2010 (ACR-EULAR 2010) classification criteria.(5) Before the development of these criteria, patients were classified based on the 1987 criteria. These criteria were well accepted and widely used to define the development of RA for many years.(6) They were demonstrated to have 91-94% sensitivity and 89% specificity for RA compared with non-RA rheumatic disease controls.(7) Using these criteria, a diagnosis of RA was made based on the presence of four or more of the following categories: [1] morning stiffness in and around the joints before maximal improvement; [2] soft tissue swelling of 3 or more joint areas observed by a physician; [3] swelling of the proximal interphalangeal (PIP), metacarpophalangeal (MCP), or wrist joints; [4] symmetric swelling; [5] rheumatoid nodules; [6] the presence of rheumatoid factor, and; [7] radiographic erosions and/or periarticular osteopenia in hand and/or wrist joints. Categories 1-4 must have been present for at least six weeks. A limitation of these 1987 criteria, however, is that they were generated to distinguish between those who had established RA from those with other forms of rheumatic diagnoses.(6) As such, they were not optimal for classifying patients with early disease who would benefit most from early intervention.(5) The 1987 criteria were also developed before the importance of ACPAs in the development of RA was recognised.(5) Therefore, the ACR and EULAR developed a new criteria (ACR-EULAR 2010 criteria) to overcome these issues, allowing the identification of patients early in their disease course.

Table 1: Categories within the ACR-EULAR 2010 criteria for RA and points provided for each category.

Category	Points
Joint involvement	
1 large joint	0
2-10 large joints	1
1-3 small joints (large joints not counted)	2
4-10 small joints (large joints not counted)	3
>10 joints including at least one small joint	5
Serology	
Negative RA and negative ACPA	0
Low positive RF and low positive ACPA	2
High positive RF or high positive ACPA	3
Acute-phase reactants	
Normal CRP[a] and ESR[b]	0
Abnormal CRP or ESR	1
Duration of symptoms	
<6 weeks	0
≥6 weeks	1

[a]C-reactive protein,[b] Erythrocyte sedimentation rate

1.2.2 Epidemiology of RA

RA is the second most common form of arthritis in the United Kingdom (UK), affecting approximately 1% of the UK adult population,(8) and 0.24% of the population worldwide.(9,10) The prevalence rate of RA globally has increased by 7.4% from 1990 to 2017, reaching higher than expected levels during the recent years in which this was explored. (9) The highest prevalence of RA is found in older age groups, peaking at 70-79 years and, as with various other chronic autoimmune diseases, the majority of patients with RA are women. (9) However, RA can affect individuals of all ages and genders, and with the rapid decline in mortality, the number of people living with RA is expected to continue increasing substantially over the coming decades.(10)

1.3 Articular features

RA manifests primarily in the synovial joints, most commonly in the small joints of the hands and feet, including the MCP, PIP and metatarsophalangeal (MTP) joints.(11,12) Larger joints (ankles, wrists, knees, and elbows) can also be affected.(12) The synovial lining of these joints becomes inflamed, causing pain and tenderness of the joints.(12) Prolonged inflammation of the synovial lining in those with RA is associated with hyperplasia, cartilage destruction and bone erosions.(13) Bone erosions can occur in the early stages of RA, as approximately 13% of patients with RA were found to develop bone erosions within eight weeks of the onset of RA, and around 60% developed bone erosions after one year of their diagnosis.(13,14)

Persistent inflammation of the joints can also cause permanent deformities,(15) including ulnar deviation of the MCP joints, boutonniere deformity (BD) and swan neck

deformity (SND). These deformities can have a substantial effects on functional capacity in relation to hand function and in performing daily activities, as well as causing permanent disability.(15) It was found that 44%, 24% and 23.5% of RA patients had ulnar deviation, BD and SND, respectively, after 10 years of their diagnosis, with almost half of these patients having multiple deformities. The majority of these deformities occurred within the first two years of their diagnosis.(15) However, with modern management including treat to target approaches and the use of biological and targeted synthetic disease-modifying antirheumatic drugs (DMARDs), these deformities are becomes less frequent.

1.4 Extra-articular features

The chronic inflammation caused by RA can also result in a number of potential extra-articular complications. For example, RA-related osteoporosis is known to significantly increase the rate of hip and spine fractures.(16,17) These fractures occurred significantly earlier for patients with RA compared to the control group (71 years and 76 years, respectively),(16) and women with RA were at an increased risk of these fractures at an even younger age (below 50 years).(16)

In addition to skeletal complications, RA is associated with a twofold increased risk of cardiovascular disease (CVD).(18) The risk is increased because RA can cause inflammation of the blood vessels (vasculitis) and generalised endothelial dysfunction leading to the development of atheroma and plaque rupture.(19) RA is also associated with an increased risk of pulmonary complications, due to inflammation or fibrosis of the lungs, airways and pleura.(20-22)

RA is also associated with reduced life expectancy. All-cause death rates were found to be higher in patients with RA compared to the general population.(23) Another study found that, in a 15-year time-span, RA patients lost about one life-year compared to the general population.(24) Complications associated with RA, such as CVD and pulmonary diseases, also contributed to a significant increase in morbidity and mortality.(20-22) As RA and the complications associated with this disease can have a serious impact on patients' health, treating RA is paramount to preventing these problems from occurring.

1.5 Current treatment

To date, it is not possible for RA to be cured, and long-term treatment is often required. There are a number of pharmacological interventions available to manage pain, and suppress synovial inflammation and disease progression in RA. These include conventional synthetic (cs), biologic (b), and targeted synthetic (ts) disease modifying anti-rheumatic drugs (DMARDs), non-steroidal anti-inflammatory drugs (NSAIDs), and glucocorticoids.

The csDMARD methotrexate (MTX), a csDMARD, is the mainstay of RA treatment, recommended by the 2019 EULAR guidelines as the first-line treatment for RA,(25) and is also cited for use in treatment guidelines internationally.(26) It is fairly inexpensive (certainly when compared with bDMARDs and tsDMARDs), and around a third of patients respond well to this drug, with the drug reducing disease activity, damage and mortality in RA patients.(27-29) MTX and other csDMARDs are generally slow-acting, often taking around four to six weeks to take effect. The precise mechanism responsible for the efficacy of MTX is not fully known, but some suggest

that MTX acts as an inhibitor of the JAK/STAT pathway.(30) This pathway is central to both immune and inflammatory systems, and is now the target of tsDMARDs.(30) Small doses of MTX are taken once weekly, administered orally or via a subcutaneous injection.(30) Oral administration is recommended in the first instance,(31) with injections typically used when the oral preparation causes nausea.(31,32) Other types of csDMARDs include Leflunomide, Sulfasalazine, and Hydroxychloroquine, which are also recommended as a potential first-line treatment for RA.(31) If remission or low disease activity has not been achieved with one of these csDMARDs, a combination is recommended as the next course of action.(31) Leflunomide, Sulfasalazine and Hydroxychloroquine were found to be effective at improving clinical outcomes of RA when used either as a monotherapy, or in combination with MTX.(33,34)

bDMARDs and tsDMARDs, such as anti-TNF-alpha monoclonal antibodies and JAK inhibitors, have been developed over recent years to target individual cytokines, cells and signalling pathways directly implicated in the inflammatory process. These drugs can work more quickly than csDMARDs and are effective in many patients who fail to respond to csDMARDs. Due to the cost of bDMARDs and tsDMARDs, in the UK they are only prescribed to patients who have failed to respond to at least two csDMARDs and have moderate (as of 2021) or high ongoing disease activity.(25) These b/ts DMARDs are usually prescribed in addition to csDMARDs.(25) Treatment of RA using DMARDs is particularly effective within the first three months after symptoms first appear as there is a higher chance of achieving DMARD-free remission.(35) These first three months are commonly known as the “window of opportunity” for DMARD initiation.(35)

NSAIDs, such as ibuprofen and naproxen are often used to manage pain and reduce inflammation associated with RA.(36) Clinical trials have found that NSAIDs reduce symptoms such as pain and stiffness in patients with RA within one to two weeks.(37,38) In a recent systematic review, those taking NSAIDs reported improved physical function, and a reduction in pain and the number of painful joints compared to a placebo.(39) NSAIDs reduce pain and inflammation by inhibiting cyclooxygenase enzymes 1 and 2, and restraining the formation of prostaglandins.(36,40,41) However, they do not slow down the progression of disease or prevent additional joint damage.(36) DMARD therapy is thus critical and NSAIDs should only ever supplement these.

Glucocorticoids are potent anti-inflammatory drugs that act to rapidly control synovial inflammation and have been reported to delay radiographic progression through, amongst other mechanisms of action, suppression of expression of proinflammatory gene expression.(36,42,43) Glucocorticoids are commonly used in the treatment of RA; around 50% of RA patients reported using this treatment.(44) Numerous studies have shown glucocorticoids to be effective at reducing symptoms of RA when taken alongside csDMARDs. A higher number of patients taking glucocorticoids alongside csDMARDs achieved remission at 16 weeks compared with those taking csDMARDs alone.(44,45) In another study, greater improvement in disease activity at 12 weeks was found for those taking glucocorticoids alongside csDMARDs, compared to those taking csDMARDs alone.(44,46) Glucocorticoids are fast-acting, and are recommended for short-term use as part of the initial treatment strategy alongside csDMARDs as well as to manage flares.(31,44)

The use of these pharmacological treatments, however, are associated with potentially severe side effects. For example, significantly higher incidences of renal and hepatic dysfunction were found in those taking csDMARDs.(47) csDMARDS were also found to be associated with an increased risk of neutropenia, lymphopenia and pulmonary complications including interstitial pneumonitis and pulmonary fibrosis.(48) Furthermore, many DMARDs are highly teratogenic.(49) bDMARDs have been linked to an increased risk of congestive heart failure and non-melanoma skin cancers.(50,51) These drugs also significantly increase the risk of serious infections including tuberculosis (TB), and may lead to the induction or reactivation of autoimmune conditions such as multiple sclerosis and psoriasis.(36)

NSAID-related complications include peptic ulceration and an increased risk of CVD, due to the inhibition of cyclooxygenase enzymes and reduction of prostaglandin production in the gastrointestinal mucosa.(37,52,53)

Glucocorticoids can cause a number of potentially severe side effects, especially when higher doses are provided for longer periods of time.(44) However, lower doses can also cause side effects.(44) A EULAR taskforce highlighting recommendations for the management of glucocorticoids in the treatment of rheumatism found this treatment to be associated with a number of major adverse events, including: [1] CVD; [2] gastrointestinal diseases, including peptic ulcer disease and pancreatitis; [3] psychological disorders, such as mood disorders and steroid psychosis; and [4] musculoskeletal disorders, including osteoporosis and myopathy.(44,54)

Due to the risk of potentially serious side effects from prolonged RA treatment, there is an increasing drive to focus on the earliest stages of RA, before symptom onset, to

develop short term interventions to prevent the development of RA and thus avoid the need to take potentially harmful medication in the long-term.

1.6 Risk factors for RA

1.6.1 Genetic risk factors

To generate effective preventive interventions for RA, it is important that risk factors associated with RA are identified. By identifying these risk factors, we can define a subsection of the population that may benefit from preventive treatment. Additionally, preventive interventions can be developed that are aimed at managing or modifying specific risk factors, thereby reducing an individual's likelihood of developing RA. The exact cause of RA is unknown, and indeed there may be different causes between various individuals. For example those with seropositive RA (the presence of anti-cyclic citrullinated protein/peptide antibodies (anti-CCPs) and / or rheumatoid factor (RF)), and seronegative RA (the absence of anti-CCPs and RFs). Genetic factors contribute significantly towards the risk of developing RA. Population-based epidemiological studies have found that a family history of RA can increase the risk of the disease by approximately 3-5 fold, with the risk being higher for first degree relatives (FDRs) compared to second or third degree relatives, and for seropositive RA compared to seronegative RA. (55-57) One study identified a heritability estimate of ~50% for seropositive RA, and ~20% for seronegative RA.(55)

Numerous genetic variants are associated with the development of RA. HLA-DRB1, part of the human leukocyte antigen (HLA) complex, is one of the strongest genetic risk factors for RA, particularly for seropositive RA.(58,59) This gene has been found

to increase RA susceptibility and radiographic damage.(60,61) Specific alleles of this gene that predispose an individual to RA include the HLA-DRB*01, *04 and *10 alleles.(58) These alleles share a specific amino acid sequence, termed the “shared epitope”.(57,58) This “shared epitope” has been identified by many studies as having a strong association with seropositive RA.(57,58,62) In contrast, HLA-DRB3 has been identified as a possible risk factor for seronegative RA, as well as a milder prognosis.(62) Genome-wide association studies have identified over 100 RA susceptibility loci, including the PTPN22 gene and the PAD14 locus, which are associated with an increased risk of seropositive RA,(36,57,62) and the STAT4 gene, which has been found to increase the risk of both seropositive and seronegative RA.(62)

1.6.2 Environmental risk factors

A range of modifiable environmental factors have also been found to contribute towards the risk of RA, including cigarette smoking, dietary factors, body mass index (BMI), periodontitis, the gut microbiome, sex hormones, and breast feeding, with distinct factors being more associated with either seropositive or seronegative RA.

Cigarette smoking is the strongest and most consistently identified environmental risk factor for RA. The risk of developing RA was almost twice as high for smokers compared to non-smokers, with the risk being significantly greater for those with seropositive RA compared to seronegative RA.(63,64) An estimated 25% of all RA, and 35% of seropositive RA, can be attributed to smoking.(58) A dose-response relationship was identified between smoking and the risk of seropositive RA, as this risk significantly increased the more cigarettes participants smoked per day, and the

longer they had been smoking for.(65,66) Studies found mixed results for a dose-response relationship between smoking and the risk of seronegative RA.(65,66)

In terms of diet, studies have found that high levels of red meat consumption were associated with an increased risk of developing RA.(67,68) Furthermore, higher red meat consumption was associated with early onset of RA; those who had a high intake of red meat developed RA six years earlier, on average, than those who had a low intake of red meat.(68) In a study examining dietary intake and the risk of developing seropositive and seronegative RA, those eating an unhealthy diet, including excess consumption of red meats and sugar sweetened drinks, had an increased risk of developing both seropositive and seronegative RA, but the risk was stronger for those with seropositive RA.(69) In terms of BMI, the risk of developing RA increased by 13% for every 5kg/m increase in BMI. (70) Additionally, the risk of developing RA in those who were obese was higher for seronegative RA compared to seropositive RA (47% vs 8%, respectively).(70)

The pathogenesis of periodontitis, a bacterial-induced, chronic inflammatory disease of the gums,(71) is suggested to be similar to RA, as both involve chronic inflammation and bone erosion. Risk factors between these two diseases are also found to be similar.(71,72) Due to their strong clinical associations, researchers have examined the association between periodontitis and RA risk, and identified a significant association between the two.(71,73) In pre-symptomatic individuals, severe periodontitis was found to be associated with an increased risk of RA, particularly seropositive RA.(71,74)

The oral and gut microbiome have also been associated with the risk of RA. Alterations in the both oral and gut microbiome were found in a study comparing RA patients with healthy controls.(58,75) More specifically, the presence of Haemophilus spp. were reduced in those with RA. Conversely, the presence of Lactobacillus salivarius was higher in those with RA, and was associated with more active RA.(75)

The prevalence of RA is higher in females than males, suggesting that hormonal factors, such as oestrogen and prolactin, are likely to play a role in the development of disease.(71) Oral contraceptives (OCs), which can increase oestrogen levels, were found to influence the risk of RA. One study found that the use of these contraceptives increased the risk of seropositive RA compared to seronegative RA.(76,77). However, other studies have found that prolonged use of OCs was associated with a reduced risk of RA.(78) These contradictory findings may be due to the fact that oestrogen can have both pro and anti-inflammatory effects.(71) Women who were post-partum, or who have had more than one pregnancy were found to be at an increased risk of developing seronegative RA.(79) Increased levels of prolactin have been cited as a potential cause, but studies examining this association provided inconsistent results.(76) In one study, breastfeeding for a longer duration of time was also found to be associated with a greater risk of RA, especially seropositive RA.(78) However, this was not found in other studies,(80) and therefore may not be a strong risk factor.

Identifying the various environmental factors involved in the development of RA is important as it can help to establish potential lifestyle modifications that at-risk populations could incorporate to decrease their risk of RA. However, the majority of the research examining environmental risk factors has focused on the relationship between smoking and RA, with the epidemiology of other environmental factors being

much less developed. Therefore, at this stage it is difficult to draw conclusions regarding the contribution of other factors to the development of RA.

1.6.3 Markers of autoimmunity

Markers of autoimmunity present in seropositive RA, such as anti-citrullinated protein/peptide antibodies (ACPAs e.g. anti-CCPs), and RFs can be detected early in the course of the disease, and even prior to the development of arthritis, and thus can be used to identify those at risk. ACPAs are an important clinical biomarker associated with RA as they provide a high positive predictive value for the disease.(81) ACPAs are found to be present in approximately 50% of patients with early RA (82) and, in some cases can be detectable years before disease onset, up to 10 years before onset in some cases.(58,83). Although ACPAs provide the strongest predictive value for the development RA, the presence of other autoantibodies in combination with ACPA further increase the risk of RA. For example, it has been found that the presence of RF alongside ACPA is associated with a higher risk of developing RA compared to the presence of ACPA alone.(83) The combination of ACPA, RF and anti-carbamylated protein (anti-CarP) antibodies also significantly increase the risk of developing RA.(84)

1.6.4 Interaction between risk factors

Researchers have begun to explore the interaction between genetic factors, environmental factors and markers of autoimmunity to further inform the development of RA, and identify those at risk. The main focus of these studies has been on the interaction between smoking and the HLA-DRB1 shared epitope, which was found to increase the risk of RA.(85,86) A dose-response relationship was also found for the interaction between smoking and the HLA-DRB1 shared epitope, as an increased

number of HLA-DRB1 alleles present, and pack-years of smoking further increased the likelihood of developing seropositive RA.(85,87) The interaction between these two factors is likely mediated by markers of autoimmunity, as smoking is found to be important in the development of ACPA,(88) and the shared epitope has been identified as important in the transition from having ACPA antibodies to a diagnosis of RA (89-91). The interaction between smoking, ACPAs and the HLA-DRB1 shared epitope in the development of RA has likely been the focus of research to date as these risk factors show the strongest association with RA. However, it is likely that RA is caused by multiple interactions,(87) highlighting the complexity of this disease.

Current prospective observational studies are underway to further determine the optimal use of autoantibody and other blood / biological material (e.g. stool) based biomarkers, in combination with genetic factors to predict the development of RA, particularly for FDRs. These include the PREVeNT study,(92) currently recruiting in the UK, the Arthritis Check-up study taking place in Switzerland (93) and the SERA study in the USA.(94) The studies are also collecting environmental exposures and other data; for example questionnaires are being used to collect information on family history, lifestyle, environment and wellbeing. More recently, the Arthritis Check-up study has extended their project to examine genetic markers and immune responses in FDRs who have tested positive for COVID-19, to examine whether COVID-19 infection is capable of triggering an autoimmune response, potentially leading to the development of RA.

Advanced imaging such as magnetic resonance imaging (MRI) and ultrasound scans are also being used to predict the onset of RA. MRI scans are sensitive at detecting inflammatory changes in the bone marrow, synovium and tendon sheaths.(95)

Inflammation assessed via MRI was found to be associated with the progression of RA in individuals at risk including those with clinically suspect arthralgia.(96) Ultrasound-defined synovial thickening, power Doppler signal, tenosynovitis, and bone erosion at peripheral joints were also found to provide predictive value for the development of RA in those at risk.(97,98)

A recent EULAR task force have created guidelines for the conduct of observational studies and clinical trials in those at-risk of RA, to optimise the data produced from future studies.(99) Two key elements of these guidelines were: to inform individuals about their risk of RA using a tailored approach, and to support at-risk individuals to understand their risk, to help inform their decision to participate in future studies.(99)

1.7 Opportunities for preventive intervention for RA

Knowledge of the genetic, environmental and inflammatory risk factors of RA has aided in identifying distinct stages of RA development. These phases represent windows in which treatment could be initiated to reduce the risk of RA developing. Figure 1 summarises the various stages which individuals may progress through before developing RA. The earliest stages depict those who are at risk but who have not yet developed any symptoms whilst the latter stages represent phases in which individuals have joint symptoms /arthritis but have not yet developed full blown RA.

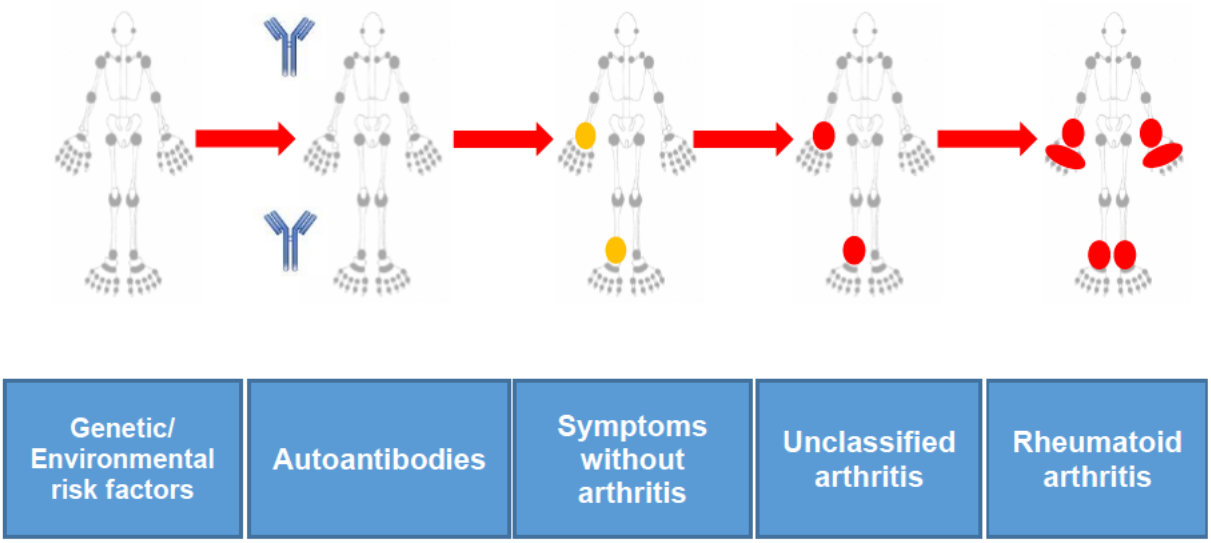


Figure 1. Flow diagram illustrating the stages of RA development from genetic and environmental risk factors to a diagnosis of RA, developed by EULAR.

1.7.1 Stage 1: Genetic/ environmental factors

The earliest stage focuses on individuals who may have genetic or environmental risk factors for RA, such as those discussed above. At this stage, individuals may not have any inflammatory markers associated with the disease, or exhibit any symptoms, but by identifying those with genetic risk factors, and obtaining information about their lifestyle, we can determine who would be at higher risk of developing RA, and potentially initiate treatment long before any irreversible damage may occur.

1.7.2 Stage 2: Autoantibodies

The second stage of development focuses on those who have progressed to develop systemic autoimmunity. At this stage, individuals may have developed specific autoantibodies such as ACPAs or RFs, but do not yet exhibit any symptoms or signs of arthritis such as joint pain or swelling. The presence of these autoantibodies identifies a period in which treatment could be provided prior to symptom onset, and before any potentially irreversible damage occurs. Additionally, identifying specific patterns of biomarkers may help to identify precise immunologic pathways that can be targeted for prevention that relate to an individual's 'personal' stage of RA development.(84) For example, if an individual has a combination of ACPAs and RFs, this may identify a specific target for prevention.

1.7.3 Stage 3: Symptoms without arthritis

The third stage of RA development relates to individuals who are further along the journey towards the development of RA. This stage is characterised by the presence of symptoms without clinical arthritis, also known as clinically suspect arthralgia (CSA).(99) A EULAR task force has identified a set of clinical characteristics that are present in individuals with CSA, including: joint symptoms which have developed within the last year; symptoms of MCP joints; morning stiffness lasting ≥ 60 minutes; most severe symptoms present early in the morning; the presence of a first degree relative with RA; and, on examination, difficulty making a fist, and a positive squeeze test of MCP joints.(100) The predictive utility of autoantibodies (such as ACPAs) and of MRI-detected subclinical inflammation in CSA individuals has been assessed. It was found

that the risk of developing arthritis within one year was 31% in CSA patients who had a positive MRI, and 71% in patients who were ACPA-positive and had a positive MRI.(101) The association between genetic factors and CSA in RA development has also been explored. It was found that specific polymorphisms in IL-7R and IGF-1 genes were independently associated with the development of RA in those with CSA.(102) The presence of genetic and inflammatory biomarkers in those with CSA can thus be helpful in predicting which individuals with CSA may go on to develop RA in the future.

1.7.4 Stage 4: Unclassified arthritis

The fourth and final stage leading up to the development of RA focuses on individuals with unclassified arthritis (UA). UA is defined as a clinically apparent inflammatory arthritis without a specific diagnosis (i.e. criteria for RA are not fulfilled, nor for other defined arthritides).(5,103) Individuals at this stage are usually considered to be most proximate to the development RA, as up to 32% progress to develop this disease within one year, and up to 40% within three years.(104,105) Treatment for those with UA may delay or stop disease progression, minimising joint damage.(106) Therefore, studies are attempting to identify UA patients who have a high probability of developing RA to determine who may benefit most from early treatment. Criteria have been developed for identifying these patients, which include: increased age; female gender; family history of RA; early morning stiffness; elevated CRP and swollen joint count; positive RF or ACPA autoantibodies; joint involvement pattern; and duration of symptoms for 8 weeks or longer.(107,108) These criteria have been validated as useful in identifying those with UA who are at the highest risk for developing RA.(108,109)

It is important to remember, however, that not all those who proceed through these stages will go on to develop RA. In addition, some people will go on to develop RA without having been through any of the previous stages. Therefore, whilst these stages are important in helping to identify opportunities for preventive intervention, it should be noted that progression from one stage to another is seen in only a proportion of individuals.

It is also important to recognise the physical and psychological burden present in individuals at certain stages of development, including those with who are anti-CCP positive, and those with CSA. For example, studies examining anti-CCP positive individuals found that they were more likely to be taking an antidepressant than those with arthritis.(110) Other anti-CCP positive individuals reported the presence of a number of psychological symptoms such as fear, uncertainty, shame and frustration surrounding the chance of developing RA.(111) Other studies found that the physical and psychological burden associated with CSA was similar to that of RA patients.(112-115) Common symptoms present in both RA patients and those with CSA included joint pain, stiffness, fatigue, sleep difficulties, lower quality of life and psychological distress, which impacted on their daily functioning.(112-115) This further indicates the need for effective predictive and preventive approaches, to effectively identify those at risk and provide them with the appropriate treatment to improve both the physical and psychological burden associated with their risk.

1.8 Studies of preventive interventions for RA

1.8.1 Preventive pharmaceutical interventions for RA

An increasing focus on the identification of those at risk of developing RA highlights the opportunity for research addressing potential interventions to prevent or delay the development of this disease. Clinical trials of treatments in the early stages of RA development have been conducted, and found that methotrexate, rituximab and abatacept delayed the progression of RA in those at risk.(106,116,117) Further trials are currently ongoing to determine the effectiveness of established RA treatments and novel therapies at preventing or delaying RA development. These studies include those at various stages of RA development, including FDRs, ACPA-positive individuals, individuals with CSA and those with undifferentiated arthritis. Both the completed and ongoing trials are summarised in Table 2. The findings from these trials could generate a paradigm shift from treatment of RA to prevention.

Table 2: Studies examining the efficacy of established RA treatment in the pre-RA stages.

Study	Patients	Completion Status	Intervention	Control	Primary Outcome/Findings
StopRA (118)	ACPA FDRs Subjects at health fairs	Ongoing	Hydroxychloroquine (HCQ) 200-400mg daily for 1 year.	Placebo	**Outcome:** Diagnosis of clinical synovitis or RA.
PRAIRI (116)	Autoantibody -positive arthralgia, and either an inflammatory response as measured by CRP or subclinical synovitis on imaging	Completed	Rituximab 1000mg, single infusion.	Placebo	**Findings:** Single infusion of rituximab significantly delayed the onset of RA by approximately 12 months.
Bos et al (119)	ACPA or RF inflammatory arthralgia	Completed	Dexamethasone 100mg at baseline and 6 weeks	Placebo	**Findings:** Dexamethasone decreased autoantibody levels (ACPA and IgM-

					RF), but did not prevent the development of arthritis.
ARIAA (120)	ACPA Arthralgia Synovitis on MRI scan	Completed	Abatacept 125mg weekly for 6 months	Placebo	**Outcome:** Improvement of synovitis on MRI scan. Currently no findings published.
STAPRA (121)	ACPA> 3xULN or ACPA plus RF inflammatory arthralgia	Completed	Atorvastatin 40mg daily for 3 years	Placebo	**Findings:** Atrovastatin was not found to have a protective effect on the development of arthritis on the small sample size included.
APPIPRA (122)	ACPA>3xULN or ACPA plus RF and inflammatory arthralgia	Recruitment completed	Abatacept 125mg weekly for 1 year.	Placebo	**Outcome:** Diagnosis of clinical synovitis or RA

TREAT EARLIER (123)	CSA and recent onset arthralgia (<1 year), synovitis on MRI	Ongoing	Methotraxate up to 25mg weekly for 1 year.	Placebo	**Outcome:** Diagnosis of clinical synovitis.
PROMPT (106)	UA	Completed	Methotrexate 15mg weekly for 1 year. Dosage increased every 3 months if DAS score was >2.4.	Placebo	**Findings:** Methotrexate postponed progression of RA in UA patients with a high risk of RA.
ADJUST (117)	Anti-CCP2 positive patients with UA and clinical synovitis of two or more joints	Completed	Abatacept ~10 mg/kg for 6 months, administered on days 1, 15, 29, 57, 85, 113, 141, and 169.	Placebo	**Findings:** Abatacept delayed the progression to RA in some UA patients.
STIVEA (124)	Early inflammatory polyarthritis	Completed	Intramuscular glucocorticoid injection	Placebo	**Findings:** Intramuscular methylprednisolone

			(methylprednisolone acetate) 80mg. Three injections provided, each one week apart.		acetate postponed the prescription of DMARDs, and prevented 1 in 10 patients with early inflammatory polyarthritis from progressing to RA within the next 12 months.
SAVE (125)	UA ACPA or RF	Completed	Methylpredisolone 120mg single dose, intramuscularly	Placebo	**Findings:** Methlypredisolone did not delay the development of RA. The need to start DMARDs was also not influenced by Methlypredisolone.
Saleem et al (126)	UA ACPA or RF	Completed	Infliximab 3mg/kg at weeks 0,2,4,6,14.	Placebo	**Findings:** Infliximab provided moderate, short term relief but did not prevent RA development.

Durez et al, (127)	UA ACPA	Completed	Infliximab 3mg/kg at weeks 2,6,14,22.	Placebo	**Findings:** Infliximab improved ACR20/50/70 responses, but did not prevent the development of RA.
EMPIRE (128)	UA ACPA or RF	Completed	Etanercept 50mg/kg alongside methotrexate up to 20 mg/kg weekly for one year.	Placebo	**Findings:** Clinical responses, including DAS28-CRP<2.6, were achieved earlier than the placebo.

Whilst the studies highlighted above indicate the potential for preventive treatment for RA in at-risk individuals, studies examining the perspectives of those who both declined and participated in some of these prevention trials (121,129,130) highlighted challenges of recruitment and retention. These included unwillingness to use study medication, adverse events experienced from the medications, and their perceptions regarding the benefits and risks of these therapies. Such challenges indicate the importance of understanding at-risk individual's perceptions regarding preventive treatment, and show that the perceptions of this group should be taken into account when designing preventive interventions.(130)

1.8.2 Preventive lifestyle interventions for RA

Several studies have examined the association between lifestyle modification, such as smoking cessation, diet and physical activity, and the risk of developing RA. Prospective cohort studies have found that, after 10-20 years of smoking cessation the risk of RA was reduced by approximately 30%, with the relative risk of RA becoming similar to that of non-smokers.(64,131,132)

High adherence to a Mediterranean diet reduced the risk of developing RA by 21%. (133) In addition, those who were under 55 years of age and had a healthy overall dietary pattern reduced their risk of developing RA by 33% compared to those with an unhealthy dietary pattern.(69) Omega 3 fatty acids were found to have a beneficial effect on individuals with a shared epitope who were at risk of developing RA. Higher levels of these essential fatty acids were associated with a lower prevalence of RF and anti-CCP antibodies in this population group,(134) thereby lowering the risk of developing RA.

Those who engaged in over one hour per week of exercise, and over 20 minutes per day of leisure activity had a 35% decreased risk of developing RA compared to those who spent less time engaging in such activities.(135) Lifestyle interventions are generally low-risk, and so can be effectively utilised in the earliest stages of RA development to reduce the risk of RA.

1.9 Potential benefit of preventive interventions for RA

RA costs the NHS almost £700 million a year in healthcare expenses. (136) In addition, a report from the National Audit Office (NAO) found that around 30% of patients with RA stop work within two years of their diagnosis, and 50% within 10 years due to the

impact of their disease.(137) This costs the UK economy almost £8 billion per annum in productivity losses.(136) As such, the development of short-term interventions to prevent RA may benefit not only those who may be at risk of developing RA but also the NHS and the wider economy, by contributing to a reduction in the number of individuals requiring long-term, costly treatment for RA.

1.10 Perceptions of predictive and preventive approaches

The clinical translation of research to predict and prevent RA will mean that at-risk groups will be offered risk assessment and thus be faced with a complex decision about whether to accept an assessment of their risk status. Provision of information about disease risk is associated with several ethical and social challenges. For example, risk information may cause psychological harm, stigmatisation and discrimination, as well as affect individual's life, family and financial planning.(138) In addition, receiving information about disease risk status can lead to a perceived responsibility for individuals to inform their relatives about their risk, which may conflict with their own or their relatives' wishes about communicating this information.(138-140) It is therefore important to understand the views of those at risk and other stakeholders to ensure that risk information is communicated in an ethical way that is sensitive to recipients' needs and concerns.(141)

1.11 Perceptions of predictive and preventive approaches among at-risk groups

Perspectives on predictive testing among those at risk have been explored across several diseases, including breast cancer,(142) CVD,(143) and Alzheimer's disease

(AD).(144,145) These studies found that most participants were interested in taking a predictive test for a specific disease. The reasons at-risk individuals were interested to take a predictive test were: to increase feelings of control over their risk;(142) to allow them to plan for the future;(143-145); and to promote engagement in risk-reducing behaviour.(143)

Perceptions of preventive approaches have also been examined across several diseases for which such approaches are available or are becoming available, such as breast cancer and CVD. For breast cancer, most participants who were at risk of this disease would consider chemoprevention, with 17 of the 27 participants being likely to take this treatment within the next five years. Participants felt that this treatment would help them to feel proactive and in control of their health, but stated that they would need evidence of its efficacy in reducing breast cancer risk.(146) This group also highlighted concerns regarding potential side effects.(146) In another study examining perceptions of chemoprevention among those at risk of breast cancer, interest in taking this treatment was low, despite its potential efficacy.(147) For CVD, most at-risk participants were interested in the idea of a combination of statins and hypertensives to reduce risk, but only if those taking the treatment were at high risk of developing the disease.(148) These participants also highlighted concerns regarding the potential side effects of this treatment.(148)

Few studies to date have explored perceptions towards predictive testing for RA in those at risk. One qualitative study, conducted on 34 at-risk individuals who had previously taken a predictive biomarker test for RA, (10 asymptomatic participants, and 24 with arthralgia (149)) examined their reasons for taking a predictive test, and found important differences between those with and without symptoms. For example, those

with arthralgia wanted to receive confirmation about the causes of their symptoms, and that something was wrong. Conversely, asymptomatic individuals were motivated to take a predictive test for research purposes only. Arthralgia patients were also more likely to agree to further predictive tests and investigations involving tissue sampling compared to those who were asymptomatic.(149)

Another qualitative study examined perceptions towards predictive testing amongst 34 FDRs, and found that the majority of these participants had favourable perceptions towards predictive tests for RA.(150) They felt that predictive tests could inform early intervention, increase awareness of early symptoms of RA, and allow them to 'mentally prepare' for the future. However, negative views were also highlighted relating to concerns about the accuracy of predictive tests and the type of information these tests could provide. Some relatives wanted a test that would provide certainty about whether or not they would develop RA, but felt that it was unlikely that a predictive test for RA would provide such a conclusive result. Relatives also highlighted concerns regarding the potential for these test results to cause anxiety for their family members, as well as stress or feelings of guilt for their relatives with RA.

Quantitative studies have explored the effect of the provision of web-based personalised risk information, including genetic and autoantibody results to FDRs on their motivation to adopt risk-reducing behaviours.(151,152) A significant increase in willingness to alter risk-related behaviours was found in the intervention arm that was not found in a control group receiving standard education about RA.(152) This effect was carried over up to 12 months after the intervention. A higher number of participants in the intervention arm were also found to adopt risk-reducing behaviours.(152)

Participants in the intervention arm were less concerned about their risk of developing RA compared to those receiving standard information.(153)

Four further qualitative studies have explored perceptions towards preventive treatments among those at risk of RA.(149,154-156) Novotny and colleagues (154) examined the perspectives of 20 FDRs, and found that they were interested in taking preventive treatment if their baseline risk of developing RA was high. If a predictive test were to indicate less than 30% risk within the next five years, FDRs were unlikely to consider a preventive treatment. FDRs also reported concerns about adverse effects, particularly in relation to suppression of the immune system. Factors that would motivate FDRs to accept preventive treatment included a feeling of involvement (as a result of having an affected relative) and hope for personal benefit. Finally, whilst FDRs expected a therapeutic intervention to prevent the development of RA, treatment that delayed development was also considered to be useful.

Munro and colleagues (155) studied perceptions of preventive treatment among five FDRs, 13 patients with RA and seven rheumatologists. The perspectives of RA patients and rheumatologists will be explored later on in this chapter. In terms of FDRs, this group were found to prefer more natural, “herbal” treatments in comparison to medications, and wanted more information on the reasons for needing preventive treatment. This included information about the extent to which RA is hereditary, and differences between RA and other types of arthritis such as osteoarthritis.(155) FDRs also sought more information about preventive treatments, including the side effects of the treatment, method of administration, how it has been tested, the dosing schedule, and evidence regarding the effectiveness of the treatment in preventing RA.(155)

Simons and colleagues (156) explored the perspectives of preventive treatments among 24 FDRs. This study found that most participants had positive views towards lifestyle-related interventions, such as smoking cessation, diet and exercise, to reduce the risk of RA or delay the development of RA, but felt that they would need information about how lifestyle interventions may impact on their risk before deciding whether or not to engage in this intervention.(156) Participants generally had more negative views regarding preventive medication, highlighting concerns regarding possible side effects (this was a particularly prominent concern from those who had seen the side effects of medications, such as DMARDs, on their family members with RA), the effect of this medication on existing medical conditions, and its potential impact on family planning.(156)

Mosor and colleagues (149) examined perspectives towards preventive treatment among those with arthralgia and those who were asymptomatic. They found that nine of the 24 arthralgia patients would take preventive medication compared to none of the asymptomatic participants.(149) Conversely, 20 of the 24 arthralgia patients would consider lifestyle changes to reduce RA risk compared to two out of 10 of the asymptomatic individuals. This indicates the potential impact that risk and type of treatment may have on perceptions towards preventive treatments for RA.

A small number of quantitative studies have also examined preferences for preventive treatments among those at risk. One survey study examining the perspectives of 133 individuals with arthralgia and positive ACPA/RF, found that 53% of these participants would take medication that was 100% effective and had no side effects, if they had a 30% risk of developing RA. On the other hand, 69% would take the same medication if they had a 70% risk of developing RA. In regard to lifestyle interventions, participants

reported being willing to change lifestyle-related behaviours such as smoking cessation, diet and exercise.(157)

A pilot choice-based treatment preference study with 32 FDRs of RA patients found that treatments to reduce risk of RA would need to show substantial efficacy before their use was considered, and would need to have a low probability of causing serious adverse events (≤10%).(158) Two discrete choice experiments (DCEs) also examined FDRs' preferences for preventive treatments.(159,160) One of these studies examined the preferences of 30 FDRs, 78 patients with RA and 39 rheumatologists,(160) but FDRs' preferences will be the focus of this section. FDRs reported a strong preference for preventive treatments that were administered orally, and would provide the greatest risk reduction for the development of RA (from 60% to 24%). FDRs were least likely to choose a treatment that had irreversible side effects, or which offered the smallest risk reduction for the development of RA (from 60% to 44%). The type of treatment also influenced FDRs' preferences, as this group were most likely to choose methotrexate, hydroxychloroquine or steroids compared with abatacept, rituximab or statins.

The 'Patient Preferences in Benefit-Risk Assessments during the Drug Life Cycle' (PREFER) project is currently underway to develop evidence-based recommendations regarding how and when to include patient preferences in the drug life cycle.(161) One PREFER case study addresses the preferences of up to 500 FDRs regarding preventive pharmacological treatments for RA, using DCEs and probabilistic threshold technique (PTT).

To date, no quantitative study has assessed perceptions of FDRs relating to their risk of developing RA in the future and their interest in predictive testing. This thesis will

address this gap. The information obtained can be used alongside that from the PREFER project to develop effective prediction and prevention strategies and information to support shared decision-making regarding the use of these strategies.

1.12 Perceptions of predictive and preventive approaches among patients with RA

Whilst the studies described above are useful to help understand perceptions of those at-risk towards predictive and preventive approaches, it is also important to examine the perspectives of other groups that may be affected by these approaches, including patients with RA. This population group are integral to the success of predictive and preventive strategies, as access to FDRs is usually obtained via patients with RA. If patients are unwilling or unable to pass on information to their FDRs about their risk of developing RA or about opportunities for predictive testing and preventive strategies, then access to this group may be restricted. Therefore, it is important to explore patients' perceptions in this context to understand the process and determinants of family communication about RA risk. An understanding of this process will enable the development of effective communication strategies to support family communication and access to FDRs.

Family communication of risk information has been studied within other disease contexts such as cancer (breast and ovarian), and CVD.(162-165) These studies have found that risk communication is influenced by the perceived desirability of risk information,(162,163) the closeness of their family relationships,(162,163), patterns within the family i.e. who is best placed to share the information and receptivity of those receiving the information,(162) as well as the perceived responsibility of patients to inform their relatives of their risk.(164)

One qualitative study to date has examined perceptions of predictive testing and preventive intervention for RA, and of communicating RA risk information among 21 patients with RA.(166) Most patients held positive views towards tests to predict the risk of RA in their FDRs. Patients felt that information about RA risk would enable individuals to prepare for their future, and cope better if they developed RA symptoms. Some patients also highlighted that predictive testing for their relatives could bring them peace of mind. However, these positive viewpoints were associated with the misperception that test results would provide a high degree of certainty, and be able to rule in or out future RA development. Negative viewpoints were associated with an understanding of the inherent uncertainty of risk information.

In terms of RA risk communication, patients expressed a general willingness to communicate with their FDRs about their risk of RA.(166) However, despite this willingness, patients described a process of selecting which relatives to communicate with. This process was based on the perceived receptivity of their FDRs, FDRs' likelihood to act on this information, and patients' feelings of guilt and responsibility for passing on a hereditary predisposition to their FDRs. The reasons patients provided for not wanting to communicate risk information included a lack of closeness with their FDRs, and wanting to prevent their FDRs from unnecessary anxiety.

One qualitative and one quantitative study have examined patients' perceptions towards preventive treatment for RA.(155,160) The qualitative study found that patients were worried about the potential for serious side effects from preventive treatment, and felt that FDRs should only take medication if their risk for RA was high.(155) Patients were particularly hesitant about preventive treatments as they

believed there to be significant gaps in the current knowledge and understanding of the causes of RA.

In a DCE examining patients' perceptions towards preventive treatment for RA,(160) it was found that patients were less likely to choose a treatment which offered only a small (27%) reduction in the risk of developing RA, or had irreversible side effects. Patients were more likely to prefer treatments which offered a greater reduction in the risk of developing RA (30-40%). Of the treatments being studied for prevention of RA (methotrexate, hydroxychloroquine, abatacept, rituximab, statins, and steroids), methotrexate, hydroxychloroquine and steroids were preferred by this group.

No quantitative studies to date have examined determinants of family communication about RA risk, which are needed to provide a comprehensive understanding of this area. This understanding could be used to inform risk information resources that address patients' needs and concerns, and support family communication about RA risk.

1.13 Perceptions of predictive and preventive approaches among healthcare professionals

The implementation of predictive and preventive strategies for RA would generate considerable changes to the organization of healthcare services, which are currently focused on the treatment of established disease. These changes may have a significant impact on the work of healthcare professionals (HCPs), and how they interact with patients in both primary and secondary care settings. It is also likely that HCPs have an influential impact on individual's perceptions towards predictive and preventive approaches, given their professional role. A study examining FDRs' preferences for preventive treatment found that FDRs reported stronger preferences

for a specific type of treatment if that treatment was also preferred by a HCP.(159) Given the potential influence of predictive and preventive strategies on healthcare services, and the impact of HCPs on the perceptions of other stakeholders, it is imperative that an understanding of HCPs' views regarding the value, efficacy and integration of predictive testing and preventive treatment for RA is sought. An understanding of these views will help in identifying any potential barriers and training needs.

HCPs' perspectives towards predictive and preventive approaches have been explored within other disease areas, including CVD. HCPs believed that it was their duty to prescribe preventive CVD medications, with lifestyle changes being a secondary focus.(167) Some HCPs advised patients to take preventive medication irrespective of their risk status, and believed that it was more important than lifestyle recommendations. However, some concerns were expressed regarding the potential for medications to encourage patients' continuation of unhealthy behaviours.(167)

One qualitative study has assessed HCPs' perceptions towards predictive and preventive approaches to RA.(155) This study found that rheumatologists were concerned about the impact of tests that predict the development of RA in individuals at high risk of the disease. They highlighted concerns regarding the cost of these tests, insurance implications, and the potential for test results to cause anxiety for those who are at risk, especially in the case of a false positive test result.

In terms of preventive treatment for RA, rheumatologists highlighted concerns about the appropriateness of pharmaceutical treatment, due to the potential side effects and absence of high quality evidence regarding its effectiveness.(155) In the absence of

this evidence, rheumatologists suggested lifestyle-mediated interventions, such as smoking cessation, as suitable treatments to recommend currently. In terms of implementation, rheumatologists highlighted concerns about the ability of predictive tests to identify those at high risk, their capacity to see more patients, and their suitability for providing preventive interventions. Nevertheless, rheumatologists would consider providing preventive treatments to certain high-risk populations including FDRs.(157)

Two quantitative studies assessed HCPs' perceptions towards preventive treatment for RA.(157,160) A DCE study found that HCPs had similar treatment preferences to FDRs and RA patients, with a stronger preference for treatments that would offer the greatest risk reduction for RA (60% to 24%), and least likely to choose a treatment that had irreversible side effects.(160) The views of FDRs and RA patients were also found to be an important factor in HCPs' views towards preventive treatment, as they reported preferring a treatment that FDRs and RA patients preferred. This may indicate the importance HCPs place on shared decision-making. HCPs were more likely to choose a preventive treatment for at-risk individuals (88%) over no treatment for now, compared to patients and FDRs (62%). They were also more likely to choose hydroxychloroquine, methotrexate or steroids to treat at-risk individuals compared to biologic treatments.

A second survey study found that, from the 49 rheumatologists examined, 35% of them reported providing lifestyle advice to ≥50% of those at-risk of RA.(157) In addition, 74% of these rheumatologists stated that they would prescribe medication that was 100% effective and had no potential side effects to patients who had a 30% risk of developing RA, and 92% would prescribe this medication to patients at 70% risk. This willingness

to prescribe preventive medication was substantially higher than at-risk individual's willingness to take the same medication (53% for 30% risk, and 69% for 70% risk).(157)

Understanding the perceptions of rheumatologists is important in supporting efficient integration of predictive testing and preventive treatment into clinical practice. However, to further understand the perceptions of HCPs, it is important that all professionals who may be involved in the management of RA are studied, including nurse specialists and primary care HCPs such as general practitioners (GPs). There are no studies to date that examine the perspectives of both primary and secondary HCPs regarding predictive and preventive approaches for RA. This thesis will therefore address that gap.

1.14 Overview and aims

As there is a growing trend towards prediction and prevention in healthcare generally, there is a need to gain a thorough understanding of the perspectives of all relevant stakeholders. This will help to inform the development of efficient predictive and preventive strategies that are acceptable to patients and those at risk, as well as the development of informational resources that are sensitive to the needs and concerns of all stakeholders. These resources can be used to support shared decision-making, as well as family communication surrounding RA risk. Therefore, the overarching aim of this thesis was to explore stakeholder's perspectives towards predictive and preventive approaches for RA. This includes the views of RA patients, their FDRs and HCPs. Specific aims (highlighted below) are addressed in relation to this overarching aim in subsequent chapters.

1.14.1 Relatives of patients with RA

It is important to understand the acceptability of predictive strategies for RA. However, relevant literature in the context of RA is limited. Therefore, an examination of the existing evidence in another chronic disease where predictive testing is already part of routine clinical practice, such as ischemic heart disease (IHD), is needed to inform RA-related research. As a result, **the aims of chapter 2 were to examine [1] the willingness of those with a family history of IHD to accept a test to predict their risk of developing IHD, and [2] the effect of such testing on intentions to change risk-related behaviours or actual behaviour change for this group**. To address these aims, a mixed-methods systematic review was conducted and a narrative synthesis was used to synthesise findings and identify patterns within the literature in relation to the study aims.

Whilst a small number of qualitative studies provide some insight into FDRs' perspectives of predictive testing for RA, further quantitative studies are needed to provide a more robust understanding, including the impact of FDR's demographic and psychosocial characteristics on willingness to accept predictive testing. Studies in other disease areas have found that patients' characteristics, such as their experience of their disease, affected their FDRs' perceptions towards taking a predictive test, though this has yet to be explored in the context of RA.(168,169) **Therefore, the aims of chapter 3 were to identify: [1] cognitive, affective and demographic predictors of FDRs' interest in predictive testing, [2] RA patients' disease and demographic characteristics that predicted their FDRs' interest in predictive testing, and [3]**

FDRs' beliefs about the causes of RA. These aims were addressed using cross-sectional surveys, provided to patients and their FDRs. FDRs' surveys assessed their interest in predictive testing, and potential demographic and psychosocial predictors of interest, and patients' surveys assessed their disease status and potential demographic predictors of their FDRs' interest. Binary logistic regression examined the association between FDRs' characteristics and their interest in predictive testing. Generalised estimating equations assessed associations between patient characteristics and FDRs' interest in predictive testing.

1.14.2 Patients with RA

In order to access FDRs, it is often necessary to do so via patients with RA. To do this, patients need to feel able to introduce the topic of RA prediction to their FDRs, and inform them of their potential elevated risk. As such, it is important to gain understanding of the potential determinants of family communication about RA risk. **Therefore, the aims of chapter 4 are to identify [1] cognitive, affective and demographic predictors of the likelihood that people with existing RA will communicate with their FDRs about their risk of developing RA, [2] barriers to family communication about risk of RA, as perceived by people with existing RA, and [3] beliefs about the causes of RA among people with existing RA**. These aims were addressed using a cross-sectional survey for patients with RA, which assessed their reported likelihood of communicating RA risk information to each of their FDRs, and demographic and psychosocial predictors of their likelihood to

communicate risk. A binary regression was used to examine the association between patient characteristics and their likelihood of communicating RA risk.

1.14.3 Healthcare professionals

As the introduction of predictive and preventive approaches for RA would generate a shift in healthcare services from treatment to prevention, it is important that these services are developed in a way that addresses not only the needs of those who may be provided with these approaches, but also those who will deliver such approaches. **Therefore, the aims of chapter 5 were to explore [1] the perceptions of rheumatologists, specialist nurses and GPs regarding the utility of predictive and preventive approaches for RA within healthcare services, and factors that may affect their utility, and [2] information and support needs of rheumatologists, specialist nurses and GPs for the introduction of predictive and preventive approaches into clinical practice.** No existing studies have examined the views of all HCPs involved in the management of RA, including specialist nurses and primary care professionals. Therefore, an exploratory approach was needed to provide insight into the views of these stakeholders. Therefore one-to-one qualitative interviews were conducted, and data were analysed using an inductive thematic approach.

Chapter 2: Acceptability of predictive testing for ischemic heart disease in those with a family history: a systematic review.

2.1 Introduction

Healthcare services are moving away from a 'one-size-fits-all' approach to an era of personalised medicine, with a focus on early intervention and disease prevention.(170) As discussed earlier in the thesis, there is growing interest in preventive pharmacological interventions for RA; indeed RA treatments such as methotrexate and rituximab, currently used for patients with established RA, have been found to delay RA progression in at-risk groups.(106,116,117) Lifestyle interventions, such as smoking cessation, improved diet and physical activity may also reduce the risk of developing RA in those at risk.(65,69,134,135) An increasing focus on preventive approaches for this disease increases the need for effective identification of those at risk.(171,172) This is particularly important for those with a positive family history of RA, as the presence of a family history can be used to identify individuals at increased risk of that disease. Specific tests can then be applied to these individuals, to help to identify subgroups with particularly high risk, who may benefit most from preventive interventions. To ensure that these approaches are effective and suitable for this group, it is imperative that the viewpoints of those with a positive family history are explored. It is also important to determine whether the provision of risk information from these predictive approaches would motivate behavioural intentions or behaviour change to reduce an individual's risk of RA, as predictive tests may be a useful tool for motivating engagement in preventive interventions.

There are currently only two studies that have examined the views of those with a positive family history of RA about predictive testing for this disease and the effect of risk information on health-related behaviours, discussed in detail within the introduction of this thesis.(150,152) In brief, the first study found that individuals with a positive

family history of RA generally had positive views towards predictive testing for this disease, highlighting that it promoted early awareness of RA symptoms. However, concerns were mentioned regarding the accuracy of the tests.(150) The second study found that the provision of web-based personalised risk information increased motivation to engage in risk-reducing behaviours, as well as the reported adoption of behaviours such as smoking cessation, increased omega-3 fatty acid intake, and dental hygiene practices.(152)

Given the lack of relevant literature in the context of RA, it is informative to review studies that explore perceptions of predictive testing for other chronic diseases of multifactorial aetiology where predictive testing is currently part of routine clinical practice, such as IHD, a heart condition caused by narrowed coronary arteries that supply blood to the heart (173). IHD is the most common type of heart disease, with approximately 300,000 people with the disease in the UK.(174) This condition also has connections with RA, as RA increases the risk of developing IHD.(18) Risk factors for IHD, such as smoking, BMI and blood pressure, are routinely assessed in clinical care, and are incorporated into risk calculators to predict the likelihood of developing future disease.(175-179) Risk assessments such as genetic testing and imaging are currently being explored within this disease context, and will likely be incorporated into existing IHD prediction algorithms.(180-182) Interventions to reduce the risk of IHD are also incorporated into routine clinical care.(183-185)

A comprehensive review of existing literature on the views of those at increased risk of IHD as a result of a positive family history, will usefully inform the development of future research regarding perceptions of predictive testing for RA and the likely impact of predictive testing. A comprehensive review of IHD literature can also help to identify

potential barriers and facilitators to the acceptability of risk prediction, and inform the development of information and resources to support decision making for those considering predictive tests, preventive treatment or participation in prevention research for IHD and other chronic multifactorial diseases such as RA.

Three systematic reviews of studies on interest in predictive testing for IHD and other chronic diseases were identified as part of a scoping search for this review. A review of 11 qualitative studies assessing diabetes mellitus (DM), IHD and inflammatory bowel disease (IBD), published between 1989 and 2015, found that study participants believed predictive testing to be effective at quantifying risk, and a reliable way to ease concerns about risk status, but some highlighted concerns relating to confidentiality of risk information.(186) That review did not search for potentially relevant studies from the grey literature. A systematic review of eight observational and experimental studies focusing on DM, IHD and obesity between 1806 and 2012 found a high level of public interest in predictive testing for these diseases.(187) The included studies for that review only addressed hypothetical predictive tests. A systematic review of 13 randomised controlled trials (RCTs) (2003-2015) that assessed DM, IHD and obesity found no consistent effect of predictive testing on intention to engage in risk-reduction behaviours (diet and physical activity) or actual behaviour change.(188)

No systematic reviews that focussed exclusively on perceptions of predictive testing for IHD were identified. In addition, no review identified in this context focussed specifically on the perceptions of predictive testing held by individuals who are at risk due to having a family history, or the impact of the test on risk-reducing behaviour for this at-risk group. The current systematic review will therefore examine [1] the willingness of those with a family history of IHD to accept a test to predict their risk of

developing IHD, and [2] the effect of such testing on intentions to change risk-related behaviours or actual behaviour change for this group.

2.2 Method

This review was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations.(189) The protocol for this review was registered with the University of York, Centre for Reviews and Dissemination (CRD) International Prospective Register of Systematic Reviews (PROSPERO) database: CRD42019124524.

2.2.1 Search strategy

The search strategy for this review was generated with support from a systematic review expert, and informed by search strategies used in previous related reviews.(187,188) The search was limited to publications involving adult participants aged 18 and over, and to those written in the English language, as limited resources were available to support the translation of non-English language studies. The search strategy specified no start date, and the end date was 8th March 2019. The electronic databases searched were: OVID MEDLINE, psycINFO and EMBASE. Terms relating to or describing the population, disease and intervention were investigated. Both keywords and medical subject headings were included and adapted for use in each of the bibliographic databases searched. Grey literature was also searched using Google, EThOS and ProQuest. References from review papers identified in scoping searches and those from studies included in the present review were also checked for relevance to the current objectives.(187,188) The search terms used for each source are provided in Appendix 1.

2.2.2 Eligibility Criteria

In order to be eligible for review, studies identified by the search strategy above had to meet each of the following criteria:

Type of study: Any primary research was eligible for review. This included both quantitative and qualitative studies. Systematic reviews were excluded but their included studies were eligible for inclusion.

Type of participants: Eligible participants were adults (aged 18 or over) with a family history of IHD. Studies including both participants with and without a family history of IHD were eligible for inclusion, provided that results were presented separately.

Type of intervention: Eligible studies assessed a predictive test for IHD, defined as a test that can provide information about the likelihood that a person will develop IHD in the future. The information provided by such a test should be additional to that provided by standard physical examination (defined as examination of IHD risk using blood pressure, weight and BMI). The test should involve further investigation, including, but not restricted to: blood tests (to assess genetic variants or cholesterol levels), saliva tests, electrocardiograms (ECGs) and imaging as appropriate. Tests could be actual or hypothetical.

Outcome measures: Both quantitative and qualitative outcomes were included. Outcomes of interest were willingness to take a predictive test and the effect of predictive test results on health behaviour, behavioural intentions or clinical outcomes.

Willingness to take a predictive test could be measured by self-reported interest, test uptake or attitudes (positive or negative) towards predictive testing.

A range of health behaviours, behavioural intentions and associated clinical outcomes could be measured to examine the effect of predictive test results. These include, but

are not limited to: smoking cessation, dietary modification, physical activity modification, treatment/ medication adherence (for example the use of statins), weight loss and changes in serum lipid profile.

2.2.3 Study selection

Titles and abstracts of studies identified by the search strategy were screened by IW using Endnote X8. If studies were deemed potentially eligible at this stage, they were subject to a full-text review. All full texts were reviewed independently by both IW and MF (IW's secondary supervisor, a health psychologist). Disagreement occurred over the eligibility of two of the 24 full texts reviewed. These discrepancies were discussed and resolved with a third reviewer (KR-IW's primary supervisor, an academic rheumatologist).

2.2.4 Patient research partner input

The review objectives and search strategy were informed by discussion with patient research partners involved in a previous study.(186) A group of three patient research partners also contributed to the analysis and interpretation of findings for this review. As a result of their input, additional demographic data (age, gender, education levels, socioeconomic status (SES) and ethnicity) were extracted from each study, if reported. The impact of these demographic variables on willingness to take a predictive test for IHD and the effect of such testing on health behaviours was assessed.

2.2.5 Data collection and items

Data for all included papers were assessed and extracted in duplicate between IW and two other reviewers (GM and NW, summer interns) in accordance with the items outlined in table 3. Discrepancies were discussed with two other authors (MF and KR).

Table 3: Data items that were extracted across included studies.

Items of study	Data items extracted
Background	Aim, source of funding and ethical approval.
Method	Study design and setting, sample size, participant characteristics (including demographic data), defined family history, patient and public involvement, intervention(s) and predictive test(s) used.
Results	Any quantitative or qualitative outcome measuring willingness to take a predictive test and the effect of test results on risk reducing behaviours and subsequent outcomes, including but not restricted to: smoking cessation, dietary modification, physical activity modification, treatment/medication adherence, weight loss and serum lipid profile.

2.2.6 Risk of bias assessment

The quality of each study was assessed in duplicate between three reviewers (IW, GM and AB, a research nurse) using the Standard Quality Assessment Criteria for Evaluating Research Papers from a Variety of Fields.(190) This validated tool uses a 14-item checklist to evaluate the quality of quantitative studies relating to the reporting of study methods (description of objectives, recruitment, allocation, outcome measures, sampling size and strategy) and results (description of analytic methods, potential confounders and detail of results). A separate, 10- item checklist was used to evaluate qualitative studies relating to the reporting of study methods (description of objectives, study context, sampling strategy and data collection methods) and results (description of analysis, verification procedures, conclusions and reflexivity). Each study was scored based on the degree to which specific criteria were met (Yes= 2, Partial= 1, No=0). Items that were not applicable to a particular study design in the quantitative checklist were marked N/A, and were excluded when calculating the total score. Assigning N/A was not permitted for any of the items in the qualitative checklist. Any study that had a total score ≥75% of the maximum possible score was judged as having good quality, scores between 55%-75% indicated moderate quality and scores below 55% indicated poor quality.(190,191) Due to heterogeneity in study designs, the quality indicators for each study type are not directly comparable. However, an overall assessment score can be used as a guide for interpreting the relative and overall quality of evidence from individual studies. Inter-rater agreement was high between researchers (97% agreement for quantitative studies; 92% agreement for qualitative studies). Disagreement between assessors was resolved through discussion amongst the research team. Quality scores were summarised across studies.

2.2.7 Data synthesis

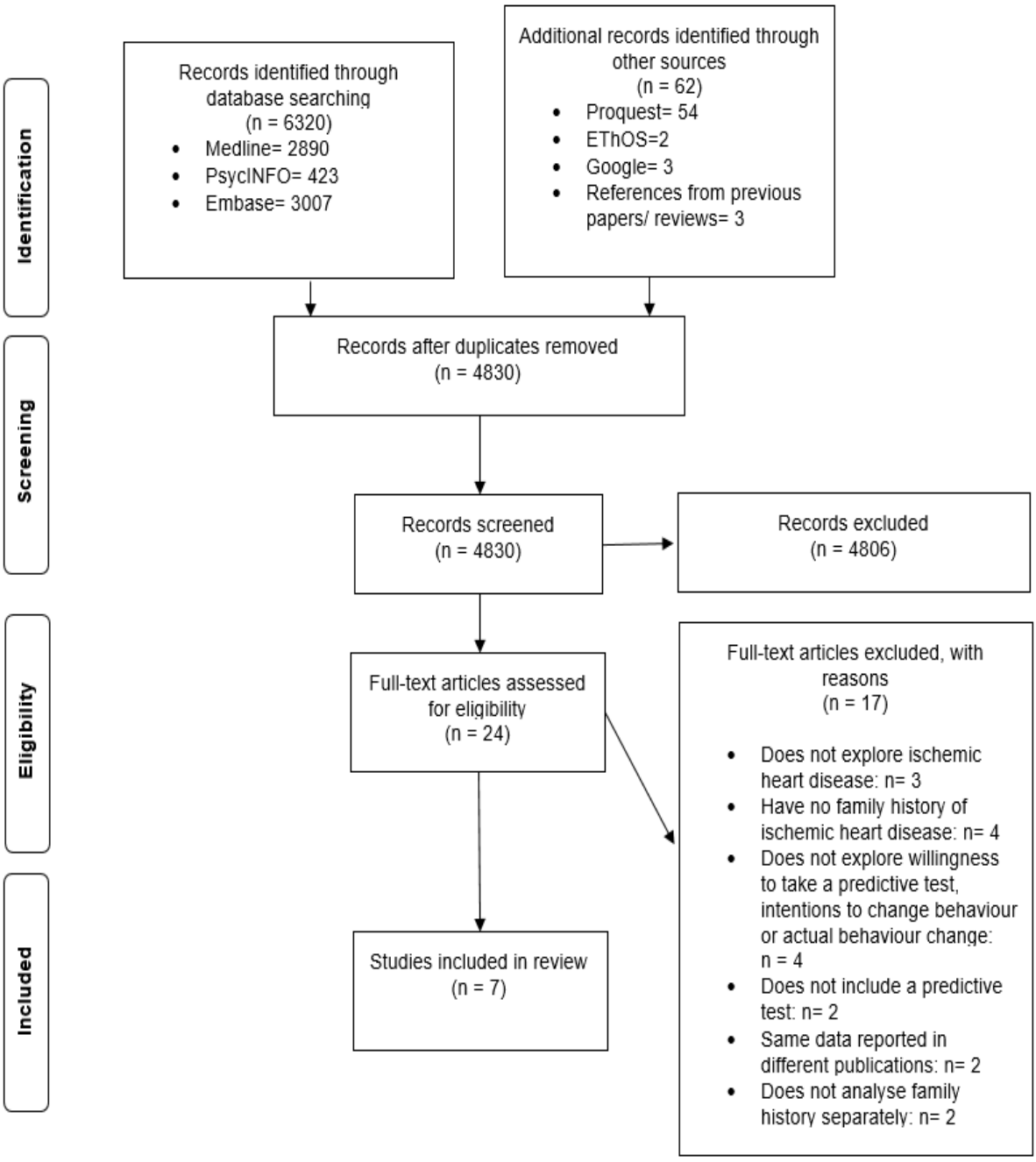
A narrative synthesis was used to synthesise the findings across all studies included within this review.(192) This approach has been widely used in mixed-method systematic reviews,(193,194) and is particularly useful when synthesising findings in which the review objectives dictate the inclusion of a wide variety of research designs.(195) Quantitative and qualitative data were integrated based on guidance by Popay and colleagues.(192,196) A framework analysis was conducted, where outcomes from quantitative studies that were relevant to the objectives of this systematic review were used to develop a framework. Concepts from qualitative studies were then synthesised using this framework, and any additional concepts were added as necessary. Similarities and differences between and within each study contributing to a specific theme were then assessed and discussed.

2.3 Results

2.3.1 Study selection

Of the 6382 papers identified across all databases, 24 full-text papers were considered, of which seven were included in the review. One of these seven studies identified from the database search was also identified in the reference list of a previous review used to inform the search strategy, and two of the seven included studies were also identified from an included study.(187,197) Reasons for exclusion of 17 studies are provided in figure 2.

Figure 2: PRISMA flow diagram of the selection process of included studies



2.3.2 Characteristics of studies

Of the seven studies identified, five employed a quantitative design (two observational, one experimental pre-post-test, and two randomised controlled trials (RCTs)), and the remaining two employed a qualitative design (one employed individual interviews and the other utilised individual and couple interviews). Studies were published between 2004 and 2016, and were conducted in the Netherlands (*n*=1), Australia (*n*=1), USA (*n*=1) and the UK (*n*=4). Study settings included primary care practices (*n*=2), tertiary care cardiovascular wards (n=1), university campuses (*n*=2), and participants' homes (*n*=2). The proportion of participants at risk due to a family history of IHD ranged from 22%-100% across studies, with the average being 65%. From the data reported in these studies, most study participants were between 40-65 years of age, 28%-87% were female, 21%-47% had low levels of education, 24%-52% had intermediate levels of education, 20%-47% had high levels of education, and 67%-97% were of a white ethnicity. Two studies included participants as young as 16 years of age.(198,199) Whilst this challenges the exclusion criteria, the mean age for participants in each of these studies was 47 [*SD*=18.2] years (198) and 30-34 [*SD*=10-12] years, across all experimental groups.(199) As a limited number of studies were identified as eligible for inclusion in this review, these studies were included. Two studies examined predictive genetic tests, three examined predictive cholesterol tests and two examined both. Willingness to take a predictive test was assessed by three studies. Four studies explored the effect of predictive test results on health behaviours (two investigated behavioural intentions, and two explored self-reported adoption of health behaviours). No studies examined actual health behaviours. The preventive behaviours examined in these studies were physical activity, dietary intake, medication adherence and

smoking cessation. All four studies included an intervention informing participants of preventive treatment options alongside risk results.

Table 4 describes the aims, participants, design and setting, type of predictive test, intervention, and findings of each of the included studies. Additional study characteristics are provided in Appendix 2.

Table 4: Characteristics of included studies

Reference	Aims	Population	Demographic characteristics	Study design and setting	Intervention and Predictive test	Findings
Claassen et al (200) 2012	To examine differences in self-reported perceived risk, causal attributions of IHD[a], perceived efficacy of preventive behaviour and adoption of preventive behaviour between people with and without a known genetic predisposition of IHD. **Hypotheses:** Those with a known genetic predisposition to IHD compared to those without will: -Have higher perceptions of IHD risk. -Attribute IHD more strongly to genetics and less to an unhealthy lifestyle.	100 participants: *n*= 51 individuals with a GP[b] to IHD, who had a recent diagnosis of familial hypercholesterolemia through DNA testing in a national family cascade screening program in the Netherlands. 15 had one FDR[d], and 28 had two or more FDRs. *n*=49 individuals with NGP[c] but still at risk for IHD. These participants were from a larger intervention study. 16 had one FDR and 12 had two or more FDRs.	**Age (mean (SD))-** GP- *n*=54 (13) NGP- *n*=55(8) **Gender-** GP- Female- *n*=27 Male- *n*=24 NGP- Female- *n*= 23 Male- *n*=26 **Education-** GP- Low- *n*=19 Medium- *n*=15 High- *n*=16 NGP- Low- *n*=23 Medium- *n*=14 High- *n*=10	**Design-** Cross-sectional postal survey that measured self-reported cholesterol levels, blood pressure, number of FDRs with IHD, perceived risk (susceptibility and comparative risk within the next 10 years), causal attributions of IHD (genetic e.g. hereditary/ predisposition and lifestyle e.g. unhealthy diet/lack of exercise/smoking), perceived efficacy of preventive behaviours (medication use for those who were prescribed medication, dietary behaviour, exercise and smoking cessation) and reported preventive behaviour (medication adherence, diet, exercise and smoking).	**Intervention-** The study directly compared two different populations who experienced different types of risk assessments (genetic and cholesterol). **Predictive test(s)-** DNA test (for those in the GP condition) and blood test to measure cholesterol levels.	Perceived comparative risk, genetic attributions to developing IHD and perceived efficacy of taking medication was significantly higher in those who had a genetic compared to a cholesterol test (28% higher for perceived comparative risk (p=0.003), 11% higher for genetic attributions (p=0.02) and 16% higher for perceived efficacy of taking medication (p=0.001)).No significant differences between groups in terms of perceived susceptibility of IHD, lifestyle attributions for developing IHD, perceived efficacy of a healthy lifestyle or preventive behaviour.

Reference	Aims	Population	Demographic characteristics	Study design and setting	Intervention and Predictive test	Findings
Claassen et al (200) 2012 (cont.)	**Hypotheses (cont.):** -Have more confidence in the efficacy of medication, and less confidence in efficacy of a healthy lifestyle to reduce IHD risk. -No hypotheses for the adoption of preventive behaviour.			**Setting-** Netherlands.		Those with a higher number of FDRs with IHD reported higher perceived susceptibility to IHD (p=0.04), stronger genetic attributions (p=0.03), increased perceived efficacy of medication (p=0.04) and reported engaging in physical activity and a healthy diet more often than those with a lower number of FDRs (p=0.005). Medication adherence was high for those who took a genetic or cholesterol test (96% and 97%, respectively), and did not differ based on family history. The number of participants who reported not smoking was high for those who took a genetic or cholesterol test (88% and 82%, respectively), and did not differ based on family history.

Reference	Aims	Population	Demographic characteristics	Study design and setting	Intervention and Predictive test	Findings
Imes et al (201) 2016	To examine the effect of a pilot intervention for young adults with a family history of IHD on IHD knowledge, perceived IHD risk, and intention to engage in IHD risk-reducing behaviours. **Hypothesis:** Perceived IHD risk, IHD knowledge and IHD risk-reducing behaviours will increase from baseline to post-intervention.	*n*=15 undergraduate and postgraduate students. One participant had an FDR with IHD, and 12 had at least one SDR[e] with IHD. The remaining two were unspecified.	**Age (mean(SD))** 20.8 (2.2) **Gender-** Female- *n*=13 Male- *n*=2 **Ethnicity-** Caucasian- *n*=10. Asian- *n*=2. Asian and Native Hawaiian- *n*=1 Hispanic or latino- *n*=2. Black- *n*=0	**Design-** Experimental pre-post test pilot study. A self-report questionnaire measured IHD knowledge, perceived IHD risk and intention to engage in IHD risk-reducing behaviours (diet and physical activity) at baseline and two weeks post-intervention. **Setting-** Pacific Northwest University, Washington, USA	**Intervention-** IHD risk assessment incorporating information on family history (three-generation pedigree), a blood test to assess lipid levels, and a brief educational counselling intervention on increasing physical activity and dietary behaviours. **Predictive test-** Blood test to assess lipid levels associated with elevated IHD risk (LDL-C, HDL-C and triglyceride levels).	Participants' IHD knowledge significantly increased post-intervention compared to baseline (p=0.02). Participants' perceived risk of IHD was significantly higher post-intervention compared to baseline (p=0.048). However, when adjusting for multiple comparisons (perceived lifetime risk, perceived susceptibility, and perceived lifetime risk after receiving family history information only) this effect was no longer significant.

Reference	Aims	Population	Demographic characteristics	Study design and setting	Intervention and Predictive test	Findings
Imes et al (201) 2016 (cont.)						Participants expressed a higher intention to engage in exercise after receiving the intervention (p=0.036), with a medium effect size (d=0.58). However, after adjustment for multiple comparisons (engagement in exercise, diet, health-promoting lifestyles (total score for exercise and diet), and likelihood to engage in a health-promoting lifestyle after receiving family history information only) this effect was no longer statistically significant. Participants' intention to adopt a healthy diet did not differ from baseline to post-intervention (p=0.064). Those with a higher number of first and second degree relatives with IHD had significantly higher risk perceptions of IHD (p=0.014), and a significantly higher intention to exercise after receiving the intervention than those with a lower number of first and second degree relatives (p=0.035). This result was not found for diet.

Reference	Aims	Population	Demographic characteristics	Study design and setting	Intervention and Predictive test	Findings
Middlemass et al[1] (197) 2014	To explore how patients who had a recent IHD assessment perceive additional information from genetic testing for IHD, and perceptions of whether this additional genetic information influenced their behaviour.	n= 29 individuals from primary care practices who were part of a larger ongoing study and who had received a conventional IHD risk assessment within 18 months prior to this study and had agreed to have a genetic test. 17 had either an FDR or SDR with IHD.	**Age (median (IQR))-** 59 (53.5-62) **Gender-** Female- *n*=8 Male- *n*=21 **Ethnicity-** Caucasian- *n*=28 Asian- *n*=0 Mediterranean- *n*=1 Black- *n*=0 **Education-** No formal qualifications- *n*= 6 GCSE- *n*=2 Vocational qualification- *n*=3 A-level- *n*=2 First degree- *n*= 10 Other- *n*=5 Missing- *n*=1	**Design-** Qualitative interview study. Interviews were conducted four months after receiving risk results (conventional, genetic, and overall risk, communicated by letter). Participants were asked about their conventional risk assessment, experience of the genetic test, their interpretations of the genetic and conventional risk results, and whether the results had influenced any change in their behaviours. **Setting-** 12 primary care practices from both urban and rural settings in Nottinghamshire, UK.	**Intervention-** There was no intervention for this study, as all participants had a genetic (and conventional) test. **Predictive test-** Saliva sample which involved an IHD panel of nine risk alleles to produce a combined risk profile score. For the conventional IHD risk assessment conducted previously, a blood sample was taken to measure cholesterol levels.	Family history was cited as the primary motivation for having a genetic test, so they can clarify their family history further and are able to discuss their results with their children. Testing was seen as beneficial as it could motivate behaviour change, particularly in those with high genetic and conventional risk results. However, for some individuals identified as at high risk from a conventional IHD risk assessment, an average genetic risk score provided false reassurance that they did not have to modify their lifestyle to reduce their risk. Genetic testing was cited as being more appropriate for a younger age group as prevention is more likely to lead to health benefits.

Reference	Aims	Population	Demographic characteristics	Study design and setting	Intervention and Predictive test	Findings
Stocks et al (202) 2015	**Primary aim:** To determine whether the provision of advice promoting IHD risk assessment to FDRs of patients with premature IHD (PIHD) would increase the proportion of relatives who undertake IHD risk assessment. **Secondary aim:** To ascertain absolute IHD risk of relatives in the intervention group.	*n*= 97 FDRs (siblings and children) of patients hospitalised with PIHD in tertiary care cardiovascular wards in South Australia. *n*=55 were in the intervention group for this study. *n*=42 were in the control group.	**Age-** 18 and over. **Gender-** Female- *n*=59 Male- *n*=38	**Design-** Prospective randomised-controlled trial. Patients were randomly allocated to provide an information pack (either intervention or control) to their FDRs either in the hospital or via post. Evidence that relatives in the intervention group had an IHD risk assessment was provided by GPs through a postcard returned to the University, detailing relatives' risk results and self-reported attendance.	**Intervention-** Written advice/ recommendation to attend their GP for a risk assessment. **Predictive test-** Blood test to measure total cholesterol: HDL ratio.	52% of all FDRs attended their GP for an IHD risk assessment within six months of the trial, 75% from the intervention group and 21% from the control group. More FDRs from the control group compared to the intervention group did not see their GP at all during the 6 month follow-up (41% vs 15%, respectively). A small portion of FDRs from the control and intervention groups attended the GP for a risk assessment after six months (17% and 2%, respectively). The majority of FDRs from the intervention group who attended their GP had low IHD risk (66%). All FDRs who had moderate to very high IHD risk (34%) were siblings.

Reference	Aims	Population	Demographic characteristics	Study design and setting	Intervention and Predictive test	Findings
Stocks et al (202) 2015 (cont.)				Evidence that the control group had risk assessment was through self-reported attendance alone. All FDRs were also phoned six months after providing consent to ascertain whether they had attended their GP for a IHD risk assessment within those six months, whether any IHD risk factors were identified and whether any lifestyle changes had been made. **Setting-** Tertiary care cardiovascular wards at Royal Adelaide Hospital, Flinders Medical Centre and Flinders Private Hospital, Australia.		

Reference	Aims	Population	Demographic characteristics	Study design and setting	Intervention and Predictive test	Findings
Saukko et al[1] (203) 2012	To explore how individuals who are at high risk of heart disease configure risk information provided by an IHD risk assessment, and how their understanding of their risk may shape their preventive behaviours.	*n*= 30 participants who were taking part in a trial assessing the utility of family history in an IHD risk assessment. 20 participants from the current study were in the intervention group in the trial, and 10 were in the control group. Maximum variation sampling was conducted in the current study based on gender, socioeconomic status and family history. 11 participants in the intervention group had a family history of IHD. The degree of family history was not disclosed. Family history was not assessed in the control group.	**Age (range)-** 30-49- *n*=2 50-59- *n*=11 60-65- *n*=17 **Gender-** Female- *n*=10. Male- *n*=20. **Employment-** Managerial and professional- *n*=10 Intermediate- *n*=5 Manual and unemployed- *n*=15	**Design-** Qualitative interview study, nested within a larger trial. Participants took part in interviews at two weeks and six months after receiving risk results. These interviews asked participants what they thought about being classed as at high risk of IHD, their thoughts about the risk assessment, what interaction they'd had with their clinicians about their risk, and what they'd done with the information.	**Intervention-**The current study was not an interventional study, but for the nested trial participants were invited to discuss their risk, lifestyle and medications with their clinicians. The intervention arm of the trial had their family history of IHD formally assessed (using a self-report questionnaire). **Predictive test-** Blood test to measure cholesterol (conducted as part of the trial).	Initially, most participants were shocked to be identified at high risk of IHD, and planned some preventive actions to reduce their risk. At the six month follow up, 23 participants reported engaging in health behaviours; 13 reported taking statins only, five reported taking part in lifestyle behaviours (diet and physical activity) and five reported taking statins and engaging in lifestyle behaviours. Seven reported not engaging in any health behaviours, which was often due to overwhelming personal and social circumstances. Participants in this group often had a lower socioeconomic status than those who engaged in risk-reducing behaviours, and had poor communication with their clinicians.

Reference	Aims	Population	Demographic characteristics	Study design and setting	Intervention and Predictive test	Findings
Saukko et al[1] (203) 2012 (cont.)				**Setting-** 24 general practices in diverse socioeconomic areas in the East Midlands and South West of the UK.		No substantial difference was found in these results between those in the intervention and control groups of the nested trial, or those with and without a family history.
Sanderson and Michie (199) 2007	To investigate the impact of IHD risk test type (genetic high risk, genetic low risk and oxidative high risk) on intention to quit smoking. To examine whether the impact of test type is the same for individuals with a family history compared to without.	*n*=261 smokers overall: *n*=75 were undergraduate students from a UK university. *n*=161 were undergraduate students' family/friends or staff from a UK university. *n*=25 were recruited through Quitline- a telephone quit-smoking service. All participants smoked seven or more cigarettes per week.	**Age (mean (SD))-** Genetic high risk- 34(12) Genetic low risk- 30(12) Oxidative high risk- 30(10) **Gender-** Female- *n*=116 Male- *n*=145 **Ethnicity-** Caucasian- *n*= 217 Non-Caucasian- *n*=44 **Education-** GCSE- *n*= 49 A-level- *n*=88 Bachelor's degree- *n*=89 Higher degree- *n*=34	**Design-** Randomised controlled trial. Self-reported family history was measured at baseline, intention to quit smoking was measured at baseline and post- intervention.	**Intervention-** Hypothetical predictive test result from one of three types of predictive test: high genetic risk vs low genetic risk vs high oxidative stress risk. **Predictive test-** Hypothetical genetic or oxidative stress test, described as a blood test that tests for different genes (genetic risk) or enzymes and antioxidants (oxidative stress) associated with IHD risk.	Those who received a high genetic risk result had significantly higher outcome expectations (p<0.001), more positive attitudes towards quitting smoking (p=0.039) and had a higher intention to quit smoking than those who received a high oxidative risk result (p=0.009). No significant difference was found for perceived control or social pressure. The genetic high risk group also had significantly higher outcome expectations (p=0.003), greater perceived control over quitting smoking (p=0.012) and a stronger intention to quit (p<0.001) than those who received a genetic low risk result.

Reference	Aims	Population	Demographic characteristics	Study design and setting	Intervention and Predictive test	Findings
Sanderson and Michie (199) 2007 (cont.)	**Hypotheses:** -Smokers in the genetic high risk group would have lower outcome expectations about quitting smoking, and lower perceived control over quitting than the oxidative high risk group. -Outcome expectations and perceived control would partly mediate the effect of test type on intention to quit smoking.	58 had a family history of IHD. The degree of history was not disclosed.		Self-reported attitudes towards quitting smoking, outcome expectations, perceived control over quitting, and perceived social pressure were measured post-intervention using a questionnaire. **Setting-** UK.		No significant difference was found for perceived attitudes towards quitting or perceived social pressure. 30.3% of the effect of risk results on intention to quit smoking was mediated by stronger beliefs that quitting smoking would reduce risk of IHD (outcome expectations) (p=0.011). When examining the interaction between family history and risk results, the effect of a high genetic risk result on outcome expectations was greatest amongst smokers with no family history of heart disease. (p=0.04). The interaction between family history and risk results was not significant for attitudes towards quitting (p=0.61), perceived control over quitting (p=0.27), perceived social pressure (p=0.58) or intention to quit (p=0.34).

Reference	Aims	Population	Demographic characteristics	Study design and setting	Intervention and Predictive test	Findings
Sanderson et al (198) 2004	To examine interest in genetic testing for IHD and cancer, and the influence of factors such as family history, age, gender, education and ethnicity on interest. **Hypotheses:** -The same factors that predict interest in genetic testing for cancer (previously, younger adults, women and those with a higher level of education) will predict interest in genetic testing for IHD.	*n*=1960 respondents from a stratified random probability sample as part of the Office for National Statistics Omnibus survey. 830 respondents had at least one FDR or SDR with IHD.	**Age (mean(SD))-** 47(18.2) **Gender-** Female- *n*=999 Male- *n*=961 **Education-** No formal qualifications- *n*= 629 GCSEs- *n*=524 A-levels- *n*=559 Degree- *n*=247 **Ethnicity-** Caucasian- *n*= 1843. Non-Caucasian- *n*=112.	**Design-** Cross-sectional survey study. The survey questions were delivered by researchers through telephone calls to participants. Participants were asked if they would take a genetic test for IHD (and cancer) in the next six months. They were also asked about their age, gender, ethnicity, education, and family history. **Setting-** UK.	**Predictive test-** Hypothetical genetic test.	Respondents were significantly more likely to be interested in taking a predictive test for IHD than for cancer (69% and 64%, respectively, $p<0.001$). 42% of participants would definitely take a predictive test for IHD and 28% would probably take a test. Men were significantly more likely to say they would take a predictive test for IHD than women (72% vs 68%, respectively, $p=0.03$). Middle-aged respondents (46-60 years) had the highest interest in testing for IHD (78%), and older respondents had the lowest interest (49%, $p<0.001$). Those with school-based qualifications had the highest interest in testing (75%) compared with those who had no formal qualifications (64%). Those with the highest level of education had the lowest interest (62%, $p<0.001$).

Reference	Aims	Population	Demographic characteristics	Study design and setting	Intervention and Predictive test	Findings
Sanderson et al (198) 2004 (cont.)	**Hypotheses (cont.):** -People will be more interested in genetic testing for IHD than for cancer.					No significant difference in interest in testing for IHD was found for ethnicity (p=0.16). Participants who had at least one FDR or SDR with IHD had a significantly higher interest in predictive testing compared to those who did not know their family history and those who did not have a family history (74%, 70% and 67%, respectively, p=0.005).

[a]IHD= ischemic heart disease, [b]GP= genetic predisposition, [c]NGP= no genetic predisposition, [d]FDR= first degree relative, [e]SDR= second degree relative. [1] = Qualitative studies.

2.3.3 Risk of bias

Individual and total quality scores for each of the included studies are presented in Tables 5 and 6. Total quality across all studies was moderate to good, with scores ranged from 60%-100%; 79-100% across quantitative studies and 60-85% across qualitative studies.

Table 5: Quality appraisal checklist and total quality score for included quantitative studies

Criteria[a]	Claassen et al (200)	Imes et al (201)	Stocks et al (202)	Sanderson and Michie (199)	Sanderson et al (198)
Question / objective sufficiently described?	2	2	2	2	2
Study design evident and appropriate?	2	2	1	2	2
Method of subject/comparison group selection or input variables described and appropriate?	2	2	2	2	2
Subject characteristics sufficiently described?	2	2	2	2	2
If interventional and random allocation was possible, was it described?	N/A	N/A	2	2	N/A
If interventional and blinding of investigators was possible, was it reported?	N/A	N/A	0	0	N/A
If interventional and blinding of subjects was possible, was it reported?	N/A	N/A	1	0	N/A
Outcome and (if applicable) exposure measure(s) well defined and robust to measurement / misclassification bias?	2	2	2	2	2
Sample size appropriate?	0	0	1	2	2
Analytic methods described/justified and appropriate?	2	2	2	2	2

Some estimate of variance is reported for the main results?	1	2	2	1	2
Controlled for confounding?	1	0	1	2	N/A
Results reported in sufficient detail?	2	2	2	2	2
Conclusions supported by the results?	2	2	2	2	2
Total score (%)	82%	82%	79%	82%	100%

[a]Yes= 2, Partial = 1, No = 0, or not applicable (N/A). Summary score calculated as: (number of yes x 2) + (number of partials x1)) / (28-(number of N/A x 2).

Table 6: Quality appraisal checklist and total quality score for included qualitative studies.

Criteria[a]	Middlemass et al (197)	Saukko et al (203)
Question / objective sufficiently described?	2	1
Study design evident and appropriate?	1	2
Context for the study clear?	1	2
Connection to a theoretical framework / wider body of knowledge?	0	2
Sampling strategy described, relevant and justified, and includes full range of relevant cases?	1	2
Data collection methods clearly described and systematic?	1	2
Data analysis clearly described and systematic?	2	2
Use of verification procedure(s) to establish credibility?	2	2
Conclusions supported by the results?	2	2
Reflexivity of the account?	0	0
Total score (%)	60%	85%

[a]Yes= 2, Partial = 1, No= 0. Summary score calculated as: (number of yes x 2) + (number of partial x1) / 20.

2.3.4 Summary of quality across studies

A range of sampling strategies were used to recruit participants across the five quantitative studies, including stratified random probability sampling (*n*=1), convenience sampling (*n*=1) and purposive sampling (*n*=3, with one of these studies being selected those from larger, ongoing studies). The majority of studies measured outcomes using self-report data (*n*=4). In one study, participants' general practitioners (GPs) reported their outcome (uptake of a predictive test) in addition to participants' self-report.(202) Three studies were judged to have issues relating to small sample sizes and/or limited generalisability.(200-202) Two studies reported methodological issues. These issues included the employment of a single group design,(201) no manipulation checks to determine participants' understanding of the information provided,(199) and the use of a 2x1 instead of a 2x2 ANCOVA design.(199) The use of a 2x2 ANCOVA design would have generated a more rigorous examination of interaction effects.

One of the two qualitative studies used maximum variation sampling to identify participants from an ongoing trial,(203) and the other used a self-selected sample from a larger ongoing study.(197) Both studies were rated zero for reflexivity.

2.3.5 Themes

The themes identified for each outcome are as follows. For willingness to take a predictive test, themes included attitudes towards predictive tests and uptake of predictive tests. For the effect of predictive testing on behaviour change, themes were based on the type of behaviour examined, for example: physical activity, diet,

medication adherence and smoking cessation. This synthesis was conducted across both quantitative and qualitative research.

2.3.6 Willingness to take a predictive test

2.3.6.1 Attitudes towards predictive tests

Participants' attitudes towards taking a predictive test were examined in one quantitative (198) and one qualitative study.(197) In the qualitative study, where all participants accepted genetic testing in addition to having a standard risk assessment previously, those with a family history of IHD (FDR or second degree relative (SDR)) reported that genetic information could increase their awareness of their risk, enable them to inform their children of their risk, and was more likely to motivate preventive behaviour change. However, receiving an average genetic risk result provided false reassurance (reassurance that they did not need to take action to reduce their risk) to some individuals who had previously been identified as at high risk from a conventional IHD risk assessment, which included a cholesterol test.(197) Relatives communicated a desire to clarify their risk from their family history further, convey their risk results to their children and protect their children from developing the disease: "*So all I am interested in, in reality, is protecting my kids and myself. And I think through this genetic thing we should be able to do it hopefully"* [197(p.e284)]. However, some were sceptical of the value of informing their children, suggesting that they were too young to be concerned about IHD, despite the majority of their children being adults. Another participant stated that predictive testing would be most appropriate for a younger age-group, where preventive measures would be more likely to lead to health benefits: *"I think 25 ... At least it would point to them and, er, give them plenty of time to adjust to*

the lifestyle" [197(p.e286)]. Family history was seen as an important motivator for predictive testing (both hypothetical and genuine) across both studies. In the quantitative study (which assessed interest in a hypothetical genetic test using a survey), those with at least one FDR or SDR with IHD expressed greater interest in taking a genetic test than those who did not know if they had a family history and those without a family history (74% vs 70% vs 67%, respectively, $p<0.05$,(198)). This quantitative study measured the impact of age on interest across a wider range of age groups and found that middle-aged participants (defined as those aged 46-60 years) were more interested in predictive testing (78%) than younger (67%) and older participants (49%; $p<0.001$, (198)). In addition, the study also found that gender and education levels influenced interest in predictive testing for IHD. Males were more interested in predictive testing than females (72% vs 68%, respectively; $p<0.05$), and interest in testing was higher for those whose highest level of education was school-based qualifications (75%) than those with higher qualifications including university degrees (62%), and those with no qualifications (64%; $p<0.001$).(198) It should be noted that analysis of the effect of demographic variables on interest in predictive testing in the quantitative study was not conducted separately for those with a family history compared to those without a family history.

2.3.6.2 Uptake of predictive tests

One prospective RCT investigated FDR's uptake of a blood test to measure cholesterol levels to assess risk of IHD.(202) That study explored whether an intervention involving a recommendation to attend a GP for a risk assessment for IHD would increase the number of relatives who would take this risk assessment within six months. Seventy five percent of those who received the intervention attended their GP for a risk

assessment within six months of the trial, compared to 21% in the control group. The majority of participants in the intervention and control group were siblings (84% and 55%, respectively).

2.3.7 Effect of predictive testing on behaviour change

2.3.7.1 Physical Activity

The effect of predictive cholesterol test results on intention to engage in physical activity were examined using a pre-post-test experimental design.(201) After being informed of their cholesterol test results alongside information about the degree of their family history and an educational counselling intervention, relatives reported a significantly greater intention to engage in physical activity than at baseline (p<0.05). However, this was no longer statistically significant after applying a Bonferroni adjustment for multiple comparisons across intentions to adopt different health behaviours. The degree of family history significantly influenced intention to engage in physical activity. Those who had a higher number of FDRs or SDRs with IHD reported a higher intention to engage in physical activity after receiving their predictive test results, degree of family history and counselling intervention than those with a lower number of relatives with IHD (r=.55, p<0.05).(201)

Two further studies, one quantitative and one qualitative, explored the influence of predictive test results on self-reported physical activity.(200,203) The former investigated self-reported physical activity in those who had a predictive genetic test or conventional IHD risk assessment (which included a cholesterol test) and had received an intervention informing them of risk-reducing behaviours. That study found no difference in self-reported physical activity between those who had a genetic test

and those who had a cholesterol test. Family history was more predictive of physical activity than the type of predictive test in that study, as those who had a higher number of FDRs reported engaging in daily physical activity after receiving their test results more often than those with a lower number of FDRs.(200) In a qualitative study of participants identified from a cholesterol test as being at high risk of developing IHD (who were interviewed either alone or with their partner), ten out of 30 reported engaging in increased physical activity.(203) The accounts of those with a family history in that study were not substantially different to those without a family history. Participants in that study were invited to discuss their lifestyle and medications with their clinicians prior to interview. Participants stated that, over the six month period being investigated, they increased their activity levels as they had negative attitudes towards preventive pharmacological interventions, and felt that physical activity was more 'natural'. When a doctor suggested to a participant that he take medication to reduce his cholesterol, he said he was "*not one to pop pills*"[203(p.569)] and would rather do it "*naturally*" [203(p.569)].

2.3.7.2 Diet

A pre-post-test experimental design was used to examine the effect of predictive test results on intentions to adopt a healthy diet.(201) No evidence of an increased intention to adopt a healthy diet after receiving cholesterol test results, alongside information about the degree of family history and an educational counselling intervention, was found (p=0.06). This was not influenced by the number of FDRs or SDRs with IHD.(201)

One cross-sectional survey and one qualitative interview study examined the influence of predictive test results on reported dietary behaviour. The cross-sectional survey study (200) found no difference in self-reported dietary behaviour between those who had a genetic test and those who had a cholesterol test. Participants' degree of family history was more predictive of dietary behaviour than the type of predictive test in that study, as more individuals who had a higher number of FDRs reported eating healthily every day after receiving their test results compared to those with a lower number of FDRs.(200) The qualitative interview study found that 10 out of 30 participants reported adopting a healthy diet after receiving cholesterol test results identifying them as at high risk for developing IHD. The accounts of participants in this study did not substantially differ between those who had a family history and those who did not.(203) Those who reported adopting a healthy diet after receiving their test results did so because they felt it was more 'natural' than preventive medication. Those who reported not adopting a healthy diet after finding out their risk attributed this to their confusion regarding the effectiveness of dietary change for reduction of IHD risk. Participants felt that inconsistent information had been presented to them by various sources, including HCPs: '"*We've got one book that says you can eat eggs and another book that says you can't eat eggs*" [203(p.566)]. One participant added that in the list healthcare professionals gave him about foods to eat "*there was nothing there that you can grasp hold of*" [203(p.566)].

2.3.7.3 Medication adherence

One cross-sectional survey study and one qualitative interview study explored the influence of the results of predictive testing on reported medication adherence. The cross-sectional study found no difference in reported medication adherence (to statins

or anti-hypertensives) between those who had a genetic test compared with those who had a cholesterol test. Reported medication adherence was exceptionally high in both groups (96% and 97%, respectively).(200) This was not influenced by the number of FDRs with IHD. In the qualitative interview study, the majority of participants (18 out of 30) also reported adhering to prescribed statins after receiving cholesterol test results. This medication was prescribed once they received their risk results. Participants' accounts did not substantially differ in those with or without a family history.(203) Factors motivating adherence were varied, with some reporting that they had tried engaging in lifestyle-related behaviours, such as diet and physical activity, but were informed by a HCP that this alone did not lower their risk of IHD. Instead, HCPs cited that statins were a more effective way of lowering risk. For example, a participant reported that a nurse had mentioned *"you can eat the best diet and [be] best weight and God knows what, but you won't bring your cholesterol down. You've got to have tablets"*[203(p.566)]. This meant that some participants felt they had no behavioural control over their risk of IHD, and so drug treatment was felt to be necessary. Participants who did not report adhering to taking medication in this study, or any other risk-reducing behaviours generally had lower SES.(203) Those with lower SES reported having poor communication with their clinicians, which often left them confused about preventive treatment. One such participant mentioned that she was dissatisfied with doctors, who kept *"pooh poohing"* [203(p.571)] her and made her feel like she was *"a bit of a waste of space"* [203(p.571)] when she asked them to take her blood pressure.

2.3.6.4 Smoking cessation

One RCT investigated the effect of the type of predictive test result on intention to stop smoking. Only 22% of participants in this study had a family history of IHD. Participants

were provided with hypothetical test results and information about how smoking cessation can reduce IHD risk.(199) Participants were randomly assigned to a genetic test scenario, where they received either a high or low risk result, or an oxidative stress test scenario, where they received a high risk result. Those who received a genetic risk result indicating that their risk of developing IHD was high had a greater intention to stop smoking than groups presented with a low genetic risk result (3.71 vs 2.98, $p<0.001$) or high oxidative risk result (3.71 vs 3.29, $p<0.05$). This effect did not differ between participants with FDRs or SDRs with IHD and those without ($p=0.34$). However, thirty percent of the effect of test type (genetic or oxidative stress) on intention was mediated by stronger beliefs that stopping smoking would reduce their chance of developing IHD (outcome expectations) and this effect was greatest among those with no first or second degree relatives with of IHD, compared to those with first or second degree relatives ($p<0.05$).(199) Therefore, while a genetic high risk result significantly increased intention to stop smoking in those with a family history, this effect was not as strongly influenced by outcome expectations as those without a family history.

One cross-sectional survey study explored the effect of predictive test results on reported smoking behaviour.(200) That study found no difference in smoking cessation between those who had a genetic test compared with those who had a cholesterol test, or between those who had more or fewer FDRs with IHD. A relatively high number of participants reported not smoking across both groups (88% of those who had a genetic test and 82% of those who had a cholesterol test).

2.4 Discussion

This review has summarised the literature on willingness to take a predictive test in those with a family history of IHD and the effect of results of such tests on approaches to risk-reducing interventions. These results increase understanding of perspectives towards predictive tests for IHD and their impact among those with a positive family history, which can inform future research on predictive approaches for other chronic diseases such as RA, as well as inform the development of these strategies for RA.

Only three studies explored attitudes towards predictive testing or uptake of predictive testing, highlighting the limited evidence available in this area. The evidence available suggests that participants' degree of family history may be an important determinant of willingness to take a predictive test but further good quality research in this area is needed across those who are at risk due to their family history to provide a comprehensive account.

The relationship between willingness to take a predictive test and family history aligns with literature for other chronic diseases such as RA, breast and ovarian cancer, where the opportunity to inform children, increase awareness of the disease, and the potential for early treatment intervention are key motivators for acceptance of predictive testing.(150,204) The influence of family history has been identified across both quantitative and qualitative studies and across various diseases,(197,198,204) suggesting that risk status due to family history is likely to be important to support decision-making around taking a predictive test for both IHD and other multifactorial diseases, including RA.

Evidence from one included study suggested that interventions recommending predictive testing promoted uptake.(202) However, further research is needed on the effectiveness of interventions to promote testing, to inform shared decision making. This finding identifies a potential area that could be explored within other disease contexts, such as RA.

In the current review, age was observed to influence willingness to take a predictive test.(198) This aligns with previous literature in other disease areas, including DM and dementia.(205) However, the conclusions that can be drawn from this finding, specifically for individuals with a family history of IHD, are limited as no included study examined the effects of individuals' age on their willingness to take a test separately for those with and those without a family history. This highlights the need for further research exploring the influence of demographic variables on willingness to take a predictive test for those at risk of the condition, as well as those at risk of other multifactorial conditions for which there is limited literature within this area, such as RA.

The limited evidence examining the effect of predictive tests on risk-reducing behaviours reported a positive impact of predictive testing on behavioural intentions or self-reported behaviour change. However, no studies assessed the impact of predictive testing on independently observed behavioural change.

After receiving genetic or cholesterol test results and information about preventive behaviours, higher perceived risk (through family history or personal genetic risk, identified by a positive test result) increased physical activity and smoking cessation intentions.(199,201) Additionally, the majority of participants reported engaging in at least one preventive behaviour, particularly medication adherence.(200,203) This may

be because medication adherence requires less effort compared to lifestyle change, and was promoted by HCPs. Additionally, contradictory messages about diet were provided by HCPs.(203) This indicates the importance of HCPs' views in supporting decision-making for those at risk from a positive family history of IHD. As such, it is integral that HCPs' views are examined in more detail across other diseases, including RA. Other factors appeared to influence participants' reported physical activity and dietary behaviours, which varied across study designs. This includes the degree of family history in the quantitative study,(200) and participants' preferences for certain behaviours in the qualitative study.(203) This indicates the importance of examining different types of health behaviours within IHD and other chronic diseases. The type of predictive test (a genetic or cholesterol test) did not appear to influence reported behaviour change.

Studies exploring other chronic diseases such as RA and DM have found mixed results for the effect of the provision of information about personal risk status on behavioural intentions, as higher personal risk increased intentions to engage in dietary change, physical activity and smoking cessation for some yet had no effect on intention for others.(152,206,207) Further research in this area could usefully shed light on the variation of behavioural intentions from increased personal risk across chronic diseases. Studies exploring reported behaviour change across multiple chronic conditions including DM and obesity in healthy participants or those at risk due to clinical characteristics such as raised BMI, found mixed results for the effect of predictive genetic test results on reported lifestyle behaviours.(208-211) The effect of predictive test results on reported behaviour change may differ across chronic diseases, which may be attributable to the perceived severity of a disease.(212,213)

For example, RA is perceived as less severe than other diseases such as cancer and heart disease.(213) Therefore, the influence of predictive test results on reported behaviour change should be explored in further detail within RA.

2.4.1 Strengths and limitations

This review has several methodological strengths, including a comprehensive search strategy, multidisciplinary contributors, patient partner involvement, and independent assessment for the inclusion of studies, data extraction and quality assessment.

The evidence available for inclusion in this review was limited in its extent - only a small number of studies focused on those with a family history.

Some of these only included a small proportion of participants with a family history, and for one study the total number of those with a family history could not be established.(203) Furthermore, the degree of family history was not fully defined within some studies, for example a distinction between first and second degree relatives was not always made.

2.4.2 Implications

The current review highlights opportunities for further research both for IHD and for other chronic diseases where predictive testing for those at risk due to a family history may be useful, such as RA. As only a few studies have explored perceptions of predictive testing for RA and its impact in those at risk,(150,152) understanding of predictors of interest in predictive testing for this disease is limited.

The findings of this review are informative for the development of interventions to support decision making around taking a predictive test for IHD and other chronic diseases where prevention is possible, including RA.

2.4.3 Conclusions

Evidence found in this review suggests that first and second degree relatives were willing to take a predictive test and reported willingness to adopt preventive behaviours, which was primarily motivated by increased perceived risk of IHD (through family history or personal risk from a positive test result), promotion from HCPs, or a preference for engaging in a certain type of behaviour. However, few studies were identified, highlighting a need for further research to provide more robust evidence to inform strategies to support decision-making in individuals considering a predictive test or preventive intervention for IHD, as well as other chronic diseases where prevention is possible, including RA.

Chapter 3: Predictors of interest in predictive testing for rheumatoid arthritis (RA) amongst first degree relatives of RA patients.

3.1 Introduction

FDRs of patients with RA have an increased risk of developing RA and are being increasingly recruited to studies developing predictive algorithms for this disease.(92-94) It is important to understand their beliefs about the causes of RA, their views on whether or not they would be interested in taking a predictive test, and predictors of their interest. Such an understanding would enable the development of informational resources and support for this group to support their decisions surrounding predictive testing and management of their risk status.

As discussed earlier on in the thesis, previous qualitative studies have examined FDRs' views towards predictive approaches for RA.(150) These studies identified perceived advantages and disadvantages of tests to predict the development of RA. Perceived advantages include the potential for tests to allow FDRs to prepare for the future and initiate early intervention, and perceived disadvantages include the potential for the test to cause anxiety for themselves and their relatives. Positive viewpoints about predictive testing for RA were associated with an expectation that such tests would be able to rule in, or rule out RA. However, large-scale quantitative investigations examining interest in predictive testing are lacking.

Findings from studies examining predictive testing for other diseases have highlighted several variables that are predictive of interest in predictive testing. These include demographic variables such as age, gender, education, and smoking status. Older individuals were more likely to be interested in taking a predictive test for CVD and type 2 diabetes (T2D). In contrast, those who were younger tended to have an optimistic bias towards their disease susceptibility.(198,205,214-216) Mixed results

were found for gender, as males were found to be more interested in predictive testing in some studies, whereas females were found to be more interested in others.(198,217) Previous studies examining interest in predictive testing for lung cancer among smokers found that they were generally interested in taking a predictive test for this disease.(218) Positive attitudes towards predictive testing were highlighted, including the potential for the test to motivate them to quit smoking.(218) Those with lower education levels were found to be more interested in taking a predictive test for CVD, cancer and T2D than those with higher education levels.(198,214,205) This may be due to misperceptions that test results would provide a high degree of certainty.(150,166) In contrast, those who are more highly educated may have a more realistic understanding of risk information.(214) Identifying the influence of demographic variables on interest in predictive testing can help to identify subsections of the population where information and support resources may be most suitable.

Individuals' understanding of health information, such as their health literacy and numeracy, has been identified as influential in decision-making regarding healthcare utilisation and disease prevention.(219, 220) Higher levels of health literacy have been shown to be associated with an increase in physical activity and the adoption of a healthier diet, as well as an increase in self-reported health status. (221) Interventions to increase health literacy have also been found to improve behavioural outcomes.(219) As interest in predictive testing is likely to be associated with the uptake of a predictive test, a type of preventive health behaviour,(222) an individual's health literacy and numeracy may be predictive of interest in predictive testing for RA, but this has yet to be explored.

The rise in patient autonomy within healthcare services (223) identifies another potential influence (i.e. autonomy preferences) on interest in predictive testing for RA. Previous research has found that individuals' preferences regarding their autonomy in seeking information about their health, and making decisions about their health have been identified as predictors of interest in predictive testing for diseases such as Alzheimer's disease,(145,224,225) though not for hereditary breast and ovarian cancer.(226) With contradictory findings identified across different disease contexts, it is important to determine whether these factors influence interest in predictive testing for RA.

An individual's coping style may influence their interest in taking a test to predict disease risk, as some individuals have been found to minimise their perceived susceptibility when faced with potentially distressing information regarding their disease risk.(198,227) Therefore, those with an avoidant coping style may have different views towards finding out their risk of a disease, compared to those who take a more active approach, which may influence their likelihood of finding out their risk. Previous research has found that an active, problem-focused coping response was associated with more health-related behaviours.(228) However, understanding of the influence of coping strategies on individual's interest in predictive testing is limited, and has not yet been explored within the context of RA.

Individuals' attitudes towards predictive tests (positive or negative) are thought to be critical in shaping their decisions surrounding the uptake of predictive testing.(229) Positive attitudes towards predictive testing, such as the perceived benefits of taking a test, were found to influence interest in taking a predictive test for DM, CVD and breast cancer. Negative attitudes including concerns regarding potential distress and

discrimination decreased interest.(229,230) These studies provide an understanding of the influence of individuals' attitudes towards predictive testing on their interest in testing across several chronic diseases, which may indicate the potential influence of individuals' attitudes towards predictive testing for RA. However, no quantitative studies have examined this within RA.

The effect of individuals' perceived benefits of predictive testing on their interest in testing may be influenced by dispositional optimism. Optimists have been found to be more receptive of potentially threatening information, and more responsive towards the use of health information in relation to disease management and prevention.(231) Therefore, optimists may be more likely to seek out risk information to inform their health-related decisions. It has been found that individuals with a high level of optimism reported greater interest in taking a predictive test for a genetic condition, and greater intentions to use this information to change health behaviours.(231) However, the influence of optimism on interest in taking a predictive test for a specific chronic disease, including RA, remains unknown.

Individuals with high levels of health anxiety tend to seek out health-related information and reassurance, especially from healthcare professionals.(232) and may therefore have higher levels of interest in predictive testing. Surprisingly however, there is limited literature on the influence of health anxiety on interest in taking a predictive test, and no studies examining this factor within the context of RA. As such, further information regarding the influence of this factor is needed.

The influence of an individual's perceptions towards an illness, that is, their beliefs and expectations regarding an illness (233) are particularly important to explore. This is

because they have been identified by both theory and empirical evidence as an important factor influencing health behaviours. The self-regulation model of health and illness (233) identifies illness perceptions as a key motivator in individuals' decisions to engage in health behaviours in response to a health threat. Additionally, a review of previous literature identified illness perceptions as an important determinant of numerous health behaviours and health outcomes across a number of studies.(234) Therefore, illness perceptions may also influence interest in predictive testing. There is limited literature examining this, but there is some evidence that individuals who perceived a disease such as lung or colon cancer to be more threatening reported a higher interest in taking a predictive test.(229) The influence of this factor on interest in predictive testing for RA remains to be explored.

Perceptions of the risk of developing a disease is also particularly important to explore in regards to interest in predictive testing for RA, as this factor has been identified by numerous studies as a key motivator in the use of predictive testing and other protective behaviours across diseases.(229,235,236). Additionally, risk perceptions are often targeted in health behaviour change interventions.(236) Previous studies examining the influence of different measures of perceived risk (worry about risk, absolute risk, experiential risk and comparative risk) in a number of disease areas, including cancers (colon, breast and lung), heart disease and DM found that those who were more worried about their risk of developing a disease were more interested in taking a predictive test for that disease.(229,230,237) However, findings relating to the influence of measures of perceived absolute risk, experiential risk, and comparative risk on interest in taking a predictive test and health behaviours, were mixed.(230,231,237,238) For example, these risk perception measures were not

significantly associated with interest in predictive testing or engagement in preventive health behaviours for breast cancer,(230,238) but were for colon cancer.(237) In the context of RA, individuals who received personalised risk information reported an increased likelihood of engaging in preventive health behaviours.(152) Therefore, perceived risk may be an important motivator for interest in predictive testing. Further investigation is needed to clarify the specific influence of perceived risk on interest in predictive testing for RA.

The relationship individuals have with their family members, including their closeness and the frequency of contact they have with these members may also be important in predicting their interest in taking a predictive test. Previous studies examining acceptance of predictive testing for breast cancer found that participants were more willing to take a predictive test if their relative was interested in them taking a test,(239) and that less contact with family members was associated with a lower uptake of predictive genetic testing.(240) However, there are limited data addressing the role of relational factors on interest in predictive testing. In addition, healthcare services do not often consider the impact relational factors may have on an individual's health-related decision-making.(239) Therefore, the impact of an individual's relationships with their family members should be examined further to inform both research and clinical practice.

As the influence of family relationships on FDRs' interest in testing may be important, the potential influence of patients' characteristics on their FDRs' interest in predictive testing are also important to explore. A small number of studies have examined the influence of patients' characteristics on their relatives' interest in taking a predictive test in other disease areas, including cancers, CVD and diabetes. These studies have

found that witnessing a family member being affected by that disease increased relatives' beliefs about their susceptibility to and the perceived threat of that disease, which influenced individuals' motivation to engage in predictive approaches.(168,169) Whilst these studies indicate the potential influence of patients' disease status on their relatives' interest in predictive testing, this has seldom been explored. In addition, the influence of patients' demographic factors, which may be indicative of patients' disease severity (e.g. from their age/smoking status), are yet to be explored. No studies to date have examined the influence of RA patients' disease status, or their demographic characteristics on their FDRs' perceptions towards predictive testing for RA. Quantitative examination of the influence of RA patients' characteristics on their FDRs' interest in predictive testing will address this gap.

Alongside interest in predictive testing, it would be informative to examine FDRs' beliefs about the causes of RA. Previous qualitative studies have examined perceived causes of RA among FDRs,(150) and members of the public.(241) Members of the public cited older age, diet, and 'wear and tear' of the joints as possible causes for RA.(241) FDRs cited hereditary factors, environmental factors, and biological factors such as gender, as possible causes for RA.(150) However, information regarding FDRs' beliefs about the causes of RA have not yet been quantified. This information could help identify specific educational needs that may be required for FDRs.

The aims of this study were therefore to identify [1] cognitive, affective and demographic predictors of FDRs' interest in predictive testing, [2] RA patients' disease and demographic characteristics that predict their FDRs' interest in predictive testing, and [3] FDRs' beliefs about the causes of RA.

In relation to these aims, health behaviour theories and previous literature in the field, it was hypothesised that:

1. FDRs would be interested in taking a predictive test for RA, and that a higher perceived risk of developing RA and more threatening perception of RA would be associated with an increased interest in taking a predictive test for the disease.

   Other factors identified in previous literature on other chronic diseases, including demographic factors, health literacy and health numeracy, preferences for autonomy in seeking information and making decisions about health, coping strategies, optimism, health anxiety, and attitudes towards predictive testing, were also hypothesised to predict FDRs' interest in predictive testing for RA.

2. FDRs' interest in predictive testing would be associated with their family members' RA disease status and duration.

3.2 Method

3.2.1 Design

Two cross-sectional surveys, one for patients with RA and another for their FDRs, (see Appendix 3 and 4) assessed interest in predictive testing and potential demographic and psychosocial predictors of such interest. These predictors include: health literacy, health numeracy, autonomy preferences, coping styles, optimism, health anxiety, perceived risk of developing RA, and attitudes towards predictive testing. The primary outcome for this study is FDRs' interest in predictive testing.

3.2.2 Procedure

Patients with a confirmed diagnosis of RA were identified via rheumatology outpatient clinics in the West Midlands, England. Participants were recruited between March 2017 and January 2020. FDRs were eligible if they a) were biological children and/ or full siblings of a patient with a confirmed diagnosis of RA; b) were aged 18 years or over; c) did not have a diagnosis of RA; and d) were able to complete the printed survey in English and indicate consent.

Patients were provided with a survey pack containing a survey for them and two surveys for FDRs, along with a freepost envelope to return the completed anonymous survey to the research team at the University of Birmingham. Patients were invited to pass the FDR surveys onto their FDRs and were able to request additional surveys if they wished to invite more than two FDRs to participate. Patients were advised that their FDRs were able to take part in the survey even if they themselves did not wish to take part. All surveys within each pack were labelled with a unique code, allowing the

research team to link returned FDR and patient surveys. All surveys were completed anonymously.

3.2.3 Measures

Interest in predictive testing was assessed using two items; “if, in the next 6 months your doctor offered you a test that predicted your risk of developing rheumatoid arthritis, would you take the test?” and “if, in the future your doctor offered you a test that predicted your risk of developing rheumatoid arthritis, would you take the test?”. Responses were measured on a 4-point Likert scale ranging from 0 (“no definitely not”) to 3 (“yes definitely”). A higher score indicates higher interest in taking a predictive test for RA.

FDRs’ reported gender, age, ethnicity (following the format recommended by the Office for National Statistics (242)), postcode (used to calculate deprivation using the multiple deprivation index,(243) scored between 1-10 with 1 indicating the most deprived areas and 10 indicating the least deprived areas) employment status, highest level of education, smoking status, relationship to the index patient (child or sibling), whether they live with the patient who provided them the survey and how often they talk to this patient (measured using a 4 point Likert scale ranging from “never” to “every day”).

Data were also collected from FDRs using the following questionnaires:

[1] The Brief Illness Perceptions Questionnaire (Brief IPQ), which measured FDRs’ illness perceptions of RA using eight items: consequences (potential consequences of the illness), timeline (how long the illness will last), personal control (individual’s control over the illness), treatment control (perceived effectiveness of treatment), identity (experience of symptoms), concern (concern about illness), understanding (degree of

understanding of the illness) and emotion (how much the illness would affect an individual emotionally) (244) The wording of these items was rephrased to make it appropriate for at-risk individuals, rather than patients.(244) Items were scored on an 11-point scale, with a higher score indicating a more threatening view of RA. The revised version of the illness perception questionnaire (IPQ-R) was used to assess perceived causes of an illness (in this case RA). As with the brief IPQ, the wording of items was rephrased to make it appropriate for at-risk individuals. Additional items were also included, based on perceived causes identified in earlier qualitative investigations.(150,166) The IPQ-R identified possible causes for RA, and assessed the extent to which participants agreed that those specific factors cause RA, using a 5-point Likert scale ranging from 0 (“strongly disagree”) to 4 (“strongly agree”). This questionnaire also included free text responses for participants to identify, in rank order, the three most important factors they believe cause RA.

[2] The single item literacy screener, which assessed FDRs’ health literacy asks “how often do you need to have someone help you when you read instructions, pamphlets, or other written material from your doctor or pharmacy?”. Responses were measured on a 5-point Likert scale ranging from 0 (“never”) to 4 (“always”). This scale demonstrates good sensitivity (54%) and specificity (83%). Scores above 2 indicate some difficulty reading printed health-related material.(245)

[3] The three-item subjective numeracy scale, which measured FDRs’ self-reported ability to understand and use numerical information, using three items which assessed participants’ perceived ability to work with fractions, work with percentages and how often they find numerical to be useful.(246) Each item was scored on a 6-point scale with overall summary scores ranging from 3-18. A higher overall score indicates

stronger perceived mathematical ability. This scale has fair internal consistency (α=.78).(246)

[4] The autonomy preference index, which includes two sub-scales measuring health-related decision-making (six items) and information seeking preferences (eight items). Both domains were measured using a 5-point Likert scale ranging from 0 (“strongly disagree”) to 4 (“strongly agree”). Scores were converted into a scale from 0-100, with higher scores indicating greater autonomy preferences. This index has been found to have good internal consistency (α=.82).(247)

[5] The Brief Approach/Avoidance Coping Questionnaire, which measures approach/avoidant coping style in stressful situations in three domains: cognitive, socioemotional and action-related.(248) This measure is comprised of 12 items, each measured using a 5-point Likert scale ranging from 0 (“strongly disagree”) to 4 (“strongly agree”). Items 1-6 represent approach coping and items 7-12 represent avoidance coping. Total scores range from 0 (low approach/ high avoidance) to 48 (high approach/ low avoidance).

[6] Dispositional optimism, which was assessed using the three items from the Life Orientation Test-Revised (LOT-R). Each was assessed using a Likert scale ranging from 0 (“strongly disagree”) to 4 (“strongly agree”) and demonstrates strong internal consistency (α=.85).(249) Total scores for this measure range from 0-12, with a higher score indicating increased optimism.(249)

[7] The Short Health Anxiety Inventory (SHAI), which assessed worry about health, awareness of bodily sensations and feared consequences of illness using 18 items.(250) For each item, participants were asked to select one of four statements

that best reflect their feelings over the past 6 months. Total scores range from 0-54, with a score above 27 indicating health anxiety.(251) This scale has been found to demonstrate high test-retest reliability (r=0.87) and internal consistency (α =.95).(250)

Four items assessed FDRs' perceived lifetime risk of RA; absolute risk, comparative risk, experiential risk and concern about risk. These items were adapted from previous studies examining the association between perceived risk and interest in predictive testing or engagement in health behaviours.(229-231,237,252) These items were measured using a 5-point response scale. Higher scores indicate higher perceived risk.

Twenty three attitudinal statements measuring perceived advantages (12 items) and disadvantages (11 items) of "finding out how likely it is that you will develop rheumatoid arthritis in the future" were adapted from Cameron and colleague's (229) study of the impact of genetic risk information on interest in genetic testing and attitudes towards such testing, with additional items based on themes identified in previous qualitative investigations of perceptions about predictive testing for RA.(150,166,186,253) Participants were asked to indicate the extent to which they agreed with each statement using a 5-point Likert-type scale ranging from "Strongly disagree" to "Strongly agree".

For those FDRs for whom linked survey data were available from their index patient, measures of patients' demographic and clinical characteristics were assessed, including patients' reported gender, age, ethnicity, postcode, employment status, highest level of education, smoking status, years with RA, current treatment for RA, and RA status, measured using the Rheumatoid Arthritis Impact of Disease (RAID) scale.(254) This scale used seven items to assess the extent to which patients' RA

affected the following domains in the previous week: pain, ability, fatigue, sleep, physical wellbeing, emotional wellbeing and coping. Each domain was measured on an 11-point scale from 0 to 10, where 0 indicates no impact, and 10 indicates extreme impact of RA. A total score was calculated based on the sum of scores, taking into account the weight of each domain. The weights of each domain were as follows: pain 0.21, ability 0.16, fatigue 0.15, sleep 0.12, emotional wellbeing 0.12, physical wellbeing 0.12 and coping 0.12. Total score range between 0-10, where a higher score indicates worse reported disease status.(255)

3.2.5 Analysis

Statistical analyses were performed using IBM SPSS Statistics version 27.0 and R version 4.0.3.

3.2.5.1 Association between FDR characteristics and their interest in predictive testing

Descriptive statistics were used to summarise demographic and psychosocial characteristics, and FDRs' perceived causes of RA (free text responses from this measure were categorised thematically, and the number of times each theme occurred was noted). Principal components analysis with direct oblimin rotation was conducted to reduce the 23 attitudinal items into a smaller number of underlying factors. Factor loadings for each item were multiplied by the original item score to obtain a weighted score. From this, a mean score was calculated.

Kruskal-Wallis H and Mann-Whitney U tests were performed to assess the effects of categorical variables on FDRs' interest in predictive testing. Spearman's rank correlations were used to investigate associations between ordinal variables and

interest in predictive testing. Predictor variables with a significance level <0.05 were used to inform a binary logistic multivariate model, with interest in predictive testing recoded as a binary variable (definitely interested versus all other responses).

A backward stepwise logistic regression was conducted, using the default cut-off p-value of 0.1.(256) To determine which variables to include in this regression, multi-collinearity amongst categorical and continuous predictor variables was assessed using generalised variance inflation factors (GVIFs) with a cut-off value of 1.414.(257)

Ordinal variables included in the model were assessed for linearity by plotting logs of the odds ratio and corresponding confidence limits for each variable category.

3.2.5.2 Association between patients' characteristics and FDRs' interest in predictive testing

To examine the association between RA patients' characteristics and their FDRs' interest in predictive testing, measures of patients' demographic and clinical characteristics were paired with FDRs' interest in testing (recoded as a binary variable as above).

Descriptive statistics were used to describe patients' demographic and clinical characteristics.

Generalised estimating equations (GEEs) were conducted, using an exchangeable working correlation matrix, to assess the ability of patient characteristics to predict their FDRs' interest in predictive testing, thereby allowing for possible non-independence of FDRs paired with the same patient. An additional variable indicating whether the FDR

was the first, second, third or fourth linked to the index patient accounted for cases where two or more FDRs were paired with the same index patient.

3.2.6 Sample size calculation

A sample size of 288 FDRs would provide 95% confidence that an estimate of the proportion of positive and negative responses for the primary outcome variable was within 0.06 of the true value, allowing for the inclusion of up to five explanatory variables in a multivariate logistic regression, provided that neither outcome occurs in less than 20% of cases.

3.2.7 Patient and public involvement

Three patient research partners (PRPs) contributed to the design and development of surveys. They highlighted that issues raised in the survey might cause anxiety for some patients and FDRs, who may not have considered that they or their relatives might have an elevated risk status. As a result, potential patient participants were approached during scheduled clinic appointments by a member of the healthcare team rather than by mail, so they had the opportunity to ask questions and raise any concerns. Potential participants were further provided an information resource about RA risk for family members of RA patients, which was developed as part of the 'EuroTEAM' project.(258) Patients diagnosed with RA within the previous six months were not approached to take part in the survey, as suggested by PRPs. This suggestion was made as these patients may already be experiencing anxiety associated with the diagnosis and adjustment to their treatment, and thus it was not

felt to be appropriate to invite these patients to a study that may raise additional concern. As a result of further PRP input, a subjective rather than an objective measure of numeracy was used, the patients' survey was divided into two parts to allow for a break if necessary, tables of contents were included so participants were aware of the nature of survey questions before deciding to respond, additional space was included between each item, and opportunities for open ended responses were included.

PRPs also advised on the wording and content of all study documents, and on the analysis and interpretation of data, including re-coding interest in predictive testing as definitely interested versus all other responses, and revising the classification of free text responses into thematic groups.

3.3 Results

Survey packs were provided to 1720 patients. 396 eligible FDRs returned a survey; for 292 of these FDRs, paired data from 214 patients were available. In some cases FDRs who returned a survey did not have a linked patient return a survey. In other cases, multiple FDRs were associated with one patient survey. 148 patients had one FDR complete the survey, 56 had two FDRs, eight had three FDRs and two had four FDRs. Analyses are presented separately for predictor variables relating to FDRs and to index patients.

The median age of the FDR sample was 42 years, 65% of participants were female, 76% were employed, and 83% were white British.

3.3.1 FDRs' interest in predictive testing

Interest in taking a predictive test within six months and in the future were highly inter-correlated (r=0.92, p<0.001). As it has been suggested previously that 6 months is as far in the future as most people plan a specific behaviour change,(259) interest in predictive testing within six months was chosen for subsequent analyses.

The distribution of scores for FDRs' interest in taking a predictive test within the following six months is described in Table 7. The majority (91.3%) of FDRs reported that they were definitely or probably interested in taking a predictive test.

Table 7: Distribution of scores for FDRs' interest in taking a predictive test.

Interest in taking a predictive test	Number of relatives (N=393)[a]	Percentage (%)
Yes definitely	218	55.5
Yes probably	141	35.9
No probably not	29	7.4
No definitely not	5	1.3

[a]N=3 (0.8%) missing responses from relatives.

Principal components analysis of the 23 items describing advantages and disadvantages of predictive testing was conducted. Factor loadings with an absolute value less than 0.3 were disregarded.(260) The KMO measure of sampling adequacy was 0.84. Bartlett's test of sphericity was significant (p<0.001). A six-factor solution (Table 8) explained 64.44% of the variance. Interpretation of the factor loadings labelled the factors as: 1) Desire for risk knowledge; 2) Psychological harm to self as a result of knowing risk; 3) Increased empowerment over health; 4) Family (di)stress associated with experience of getting a test; 5) Accuracy of predictive testing and 6) Social consequences as a result of testing.

Table 8: Factor labels and factor loadings from a PCA of items measuring attitudes towards predictive testing.

Factors	Items	Factor loadings
1.Desire for risk knowledge	"I prefer not to think about things that might never happen"	-0.73
	"I should find out my risk of developing rheumatoid arthritis to determine whether my children might be at risk"	0.70
	"I should find out my risk of developing rheumatoid arthritis for the sake of my family"	0.66
	"Not knowing my risk of developing rheumatoid arthritis could make me anxious"	0.63
	"I should find out my risk of developing rheumatoid arthritis at an early age"	0.54
2. Psychological harm to self as a result of knowing risk	"If I was found to be at high risk of developing rheumatoid arthritis I would be likely to worry unnecessarily about my health"	0.86
	"If I was found to be at high risk of developing rheumatoid arthritis I may become anxious as a result"	0.85
	"If I was found to be at high risk of developing rheumatoid arthritis I may become depressed as a result"	0.73
	"Knowing that I was at high risk of developing rheumatoid arthritis would harm my self-image"	0.46
	"If I was found to be at high risk of developing rheumatoid arthritis I would be likely to feel guilty about the possibility of passing the risk on to my children"	0.43
3. Increased empowerment over health	"If I was found to be at high risk of developing rheumatoid arthritis, I would be able to lower my risk by making changes to my lifestyle"	0.82
	"Finding out my risk of developing rheumatoid arthritis would help me feel prepared if I developed symptoms of rheumatoid arthritis"	0.79

	“Finding out my risk of developing rheumatoid arthritis would help me to get treated quickly if I developed symptoms of rheumatoid arthritis”	0.71
	“If I was found to be at high risk of developing rheumatoid arthritis, I would be able to take medicines to lower my risk”	0.65
	“Finding out my risk of developing rheumatoid arthritis would give me control over my health”	0.64
	“Finding out my risk of developing rheumatoid arthritis would help me to make important decisions about how to live my life”	0.64
	“Knowing that my risk of developing rheumatoid arthritis was low would give me peace of mind”	0.37
4. Family (di)stress associated with experience of getting a test	“Getting a test to predict my risk of developing rheumatoid arthritis would be a stressful experience for my relatives”	0.93
	“My relatives would be upset if I was found to be at high risk of developing rheumatoid arthritis”	0.75
	“Getting a test to predict my risk of developing rheumatoid arthritis would be a stressful experience for me”	0.70
5. Accuracy of predictive testing	“Getting a test to predict my risk of developing rheumatoid arthritis would tell me that I definitely would, or definitely wouldn’t develop rheumatoid arthritis”	0.86
6. Social consequences as a result of testing	“If I was found to be at high risk of developing rheumatoid arthritis I may not be able to get insurance”	0.84
	“If I was found to be at high risk of developing rheumatoid arthritis I may be discriminated against”	0.80

FDRs' demographic and psychosocial characteristics, and univariate analyses of their relationships with interest in predictive testing, are summarised in Table 9; 20 predictor variables were significantly associated with interest in predictive testing.

Table 9: Descriptive statistics and univariate analyses for FDRs' characteristics and associations with interest in testing (N=396).

FDRs' characteristics	**Descriptive statistics**	**Association with interest in predictive testing**	
		Statistics	**P**
Age (years) (*N*=16 missing); median (IQR)	42 (30-53)	-0.07 [rs]	0.16
Deprivation index (*N*=82 missing); median (IQR)	4 (2-7)	-0.05 [rs]	0.41
Gender (*N*=6 missing); frequency (%)			0.15
Male	137 (35.1)	3(2-3) [U]	
Female	253 (64.9)	3(2-3) [U]	
Employment (*N*=6 missing); frequency (%)			0.08
Employed	297 (76.2)	3(2-3) [H]	
Unemployed	62 (15.9)	3(2-3) [H]	
Other	31 (7.9)	3(2-3) [H]	
Ethnic Group (*N*=2 missing); frequency (%)			0.76
White	328 (83.2)	3(2-3) [H]	
Mixed	15 (3.8)	3(2-3) [H]	
Asian	36 (9.1)	3(2-3) [H]	
Black	14 (3.6)	3 (2-3) [H]	
Other	1 (0.3)	3 (3-3) [H]	
Smoking (*N*=8 missing); frequency (%)			0.62
Current	40 (10.3)	3(2-3) [H]	
Ever	111 (28.6)	3(2-3) [H]	
Never	237 (61.1)	3(2-3) [H]	
Education (*N*=17 missing); frequency (%)			0.65
A level or lower	187 (49.3)	3(2-3) [U]	
Higher than A level	192 (50.7)	3(2-3) [U]	
Type of Relative (*N*=4 missing); frequency (%)			<0.001

Child	295 (75.3)	3(2-3) [U]	
Sibling	97 (24.7)	2(2-3) [U]	
Living with index patient (*N*=2 missing); frequency (%)			0.45
Yes	77 (19.5)	2(2-3) [U]	
No	317 (80.5)	3(2-3) [U]	
Frequency of talking to index patient (*N*=4 missing); frequency (%)		0.12 [rs]	0.02
Never	0		
Rarely	4 (1)		
Sometimes	20 (5.1)		
Often	154 (39.3)		
Daily	214 (54.6)		
Perceived absolute risk (*N*=2 missing); median (IQR)	3 (2-3)	0.33 [rs]	<0.001
Perceived relative risk (*N*=2 missing); median (IQR)	3 (2-3)	0.34 [rs]	<0.001
Perceived experiential risk (*N*=1 missing); median (IQR)	3 (2-3)	0.32 [rs]	<0.001
Worry about risk (*N*=1 missing); median (IQR)	3 (2-3)	0.29 [rs]	<0.001
Health literacy (*N*=4 missing); median (IQR)	0 (0-0)	0.004 [rs]	0.95
Subjective numeracy (*N*=4 missing); median (IQR)	15.00 (11.25-17.75)	-0.05 [rs]	0.33
Brief illness perception questionnaire; median (IQR)			
Consequences (*N*=5 missing)	8 (7-9)	0.14 [rs]	0.006
Timeline (*N*=5 missing)	10 (9-10)	0.14 [rs]	0.007
Personal control (*N*=5 missing)	5 (3-7)	-0.03 [rs]	0.52
Treatment control (*N*=5 missing)	7 (5-8)	-0.02 [rs]	0.71
Identity (*N*=4 missing)	8 (7-8)	0.11 [rs]	0.03
Concern (*N*=2 missing)	8 (7-10)	0.21 [rs]	<0.001
Understanding (*N*=2 missing)	7 (6-9)	0.10 [rs]	0.04
Emotional (*N*=2 missing)	7 (6-9)	0.11 [rs]	0.03

Information Seeking (*N*=4 missing); median (IQR)	84.38 (75.00-93.75)	0.34 [rs]	<0.001
Decision making (*N*=1 missing); median (IQR)	58.33 (45.83-70.83)	-0.02 [rs]	0.73
Brief Avoidance Coping Questionnaire (*N*=9 missing); median (IQR)	30 (26-34)	0.12 [rs]	0.02
Optimism (*N*=5 missing); median (IQR)	7 (6-9)	0.06 [rs]	0.25
Health anxiety overall (*N*=17 missing); median (IQR)	12 (8-18)	0.14 [rs]	0.006
Attitudes towards testing– median (IQR)			
Desire for risk knowledge (*N*=62 missing)	1.08 (0.72-1.37)	0.47 [rs]	<0.001
Psychological harm to self as a result of knowing risk (*N*=49 missing)	1.00 (0.66-1.41)	-0.18 [rs]	0.001
Increased empowerment over health (*N*=7 missing)	1.98 (1.79-2.35)	0.42 [rs]	<0.001
Family (di)stress associated with experience of getting a test (*N*=2 missing)	1.29 (0.79-1.84)	-0.15 [rs]	0.003
Accuracy of predictive testing (*N*=6 missing)	1.72 (0.86-2.58)	0.17 [rs]	0.001
Social consequences as a result of testing (*N*=4 missing)	1.24 (0.82-1.64)	-0.06 [rs]	0.27

[rs]= Spearman's rank correlation, [H]= Kruskal-Wallis H test, [U]= Mann-Whitney U test. Correlation coefficients are reported for Spearman's rank correlations, medians and IQRs are reported for Kruskal-Wallis H and Mann-Whitney U tests.

Measures of FDRs' perceived risk of developing RA were inter-correlated (r=0.62, p<0.001(absolute risk and comparative risk); r=0.80, p<0.001(absolute risk and experiential risk); and r=0.64, p<0.001(comparative risk and experiential risk)). Risk framed as absolute rather than comparative is less likely to affect health behaviour.(261) Therefore, as these results are informative for the development of information to support shared decision-making, rather than intended to influence it, absolute risk was the measure of risk perception included in the multivariate analysis presented here.

The factors 'desire for risk knowledge' and 'family (di)stress associated with experience of getting a test' had a GVIF score above 1.414 and thus were excluded from the first backward stepwise logistic regression. The backward stepwise logistic regression performed on the remaining 16 significant variables identified a new model with seven variables.

Upon re-calculating the GVIF scores, when 'desire for risk knowledge' and 'family (di)stress associated with experience of getting a test' were added to the model to determine whether their multicollinearity extended to the new model of variables, all scores were below 1.414. Therefore, a final backward stepwise logistic regression was conducted on the seven variables identified by the previous regression, 'desire for risk knowledge' and 'family (di)stress associated with experience of getting a test'. The effect of the ordinal variable 'perceived absolute risk' appeared to follow a linear pattern and so was treated as linear for this analysis. A final model was identified which included seven variables, outlined in table 10.

Table 10: Final binary logistic regression model to predict FDRs' interest in predictive testing.

FDRs' predictors	Odds ratios (95% CI)	P Value
Desire for RA risk knowledge	5.81 (2.61 to 12.97)	<0.001
Increased empowerment over health	2.28 (0.95 to 5.49)	0.066
Information seeking preferences	1.04 (1.01 to 1.07)	0.007
Perceived absolute risk	1.68 (1.15 to 2.44)	0.007
Concern about RA risk (reference category-extremely concerned (9))		0.056
1 (not at all concerned)	1.14 (0.15 to 8.59)	0.897
2	2.45 (0.16 to 37.56)	0.521
3	0.22 (0.02 to 2.18)	0.197
4	0.63 (0.16 to 2.58)	0.523
5	0.49 (0.13 to 1.95)	0.313
6	0.23 (0.10 to 0.56)	0.001
7	0.34 (0.15 to 0.76)	0.008
8	0.55 (0.22 to 1.37)	0.199
Psychological harm to self as a result of knowing risk	0.39 (0.22 to 0.69)	0.001
Frequency of talking to index patient (reference category-everyday)		0.018
Rarely	0.33 (0.02 to 5.66)	0.446
Sometimes	0.22 (0.05 to 1.06)	0.058
Often	1.85 (1.02 to 3.34)	0.043

FDRs' desire to obtain risk knowledge, perceived absolute risk of RA, regular versus daily contact with the index patient, and information seeking preferences predicted increased interest in predictive testing. FDRs' belief that predictive testing would result in psychological harm predicted decreased interest in testing.

Preliminary analyses found a significant difference between children's and siblings' interest in predictive testing. As children constitute the majority of the FDR sample (75.3%), factor analysis and univariate analyses were undertaken for children only as a sensitivity analysis (Appendix 5).

For the factor analyses conducted, no differences in the arrangement of factor items was found between the whole FDR sample and the children only sample. Univariate analyses showed that most of the significant associations between predictor variables and FDRs' interest in testing in the main analysis were also identified as significant for the children's sample. Illness perceptions including consequences, identity, understanding and emotion, health anxiety, beliefs that tests would cause family distress and talk frequency were significantly associated with interest for FDRs overall but not for children.

3.3.2 The association between patients' characteristics and FDRs' interest in predictive testing

Descriptive statistics summarising the demographic and clinical characteristics of index patients, and test statistics with corresponding p-values for the relationship between patients' characteristics and FDRs' interest in predictive testing for RA are presented in Table 11.

Table 11: Descriptive statistics and generalised estimating equations examining impact of patient characteristics on FDRs' interest in testing (N=214).

Patients' characteristics	**Descriptive statistics for patients**	**Descriptive statistics for patients whose relatives were definitely interested in taking a test (N=150)**	**Descriptive statistics for patients whose relatives were not definitely interested in taking a test (N=140)**	**Wald Chi-square**	**P value**
Age (years) (*N*=7 missing); median (IQR)	64 (55-73)	64 (55-73)	64 (54-71)	0.85	0.36
Deprivation index (*N*=32 missing); median (IQR)	4 (2-6)	4 (2-6)	4 (2-6)	8.15	0.52
Gender (*N*=6 missing); frequency (%)				2.54	0.11
Male	50 (24)	39 (26.7)	25 (18.2)		
Female	158 (76)	107 (73.3)	112 (81.8)		
Employment (*N*=1 missing); frequency (%)				1.28	0.26
Employed	63 (29.6)	37 (24.8)	43 (30.7)		
Unemployed	148 (69.5)	109 (73.2)	97 (69.3)		
Other	2 (0.9)	3 (2.0)	0		
Ethnic Group (*N*=2 missing); frequency (%)				4.34	0.23
White	180 (84.9)	124 (83.8)	119 (85.0)		
Mixed	4 (1.9)	2 (1.4)	5 (3.6)		
Asian	18 (8.5)	17 (11.5)	9 (6.4)		
Black	10 (4.7)	5 (3.4)	7 (5.0)		
Other	0	0	0		

Smoking (*N*=3 missing); frequency (%)				1.03	0.60
Current	17 (8.1)	12 (8.1)	9 (6.5)		
Ever	70 (33.2)	58 (39.2)	49 (35.3)		
Never	124 (58.8)	78 (52.7)	81 (58.3)		
Education (*N*=13 missing); frequency (%)				2.84	0.09
A level or lower	135 (67.2)	103 (73)	86 (64.2)		
Higher than A level	66 (32.8)	38 (27)	48 (35.8)		
RA duration (years) (*N*=43 missing); median (IQR)	10 (4-20)	10 (4-16)	10 (4-20)	0.24	0.63
RAID score (*N*=8 missing); median (IQR)	5.00 (3.00-7.00)	5.23 (2.95-7.00)	5.30 (2.22-6.99)	0.62	0.43
Pain	5 (3-7)	5 (3-7)	5 (3-7)	18.41	0.04
Ability	5 (2-7)	6 (2-8)	5 (2-8)	12.33	0.26
Fatigue	6 (3-8)	6 (4-8)	6 (3-8)	9.57	0.48
Sleep	5 (2-8)	6 (3-8)	5 (2-8)	6.73	0.75
Physical wellbeing	5 (3-7)	5 (3-8)	5 (3-7)	9.24	0.42
Emotional wellbeing	4 (2-7)	5 (3-7)	4 (1-7)	17.17	0.07
Coping	4 (2-6)	4 (2-6)	4 (1-6)	17.70	0.06
Current treatment; frequency (%)					
No treatment	4 (1.9)	3 (2.0)	3 (2.1)	0.04	0.85
Conventional synthetic DMARDs and glucocorticoids	189 (88.3)	135 (90)	118 (84.3)	1.56	0.21

Biologic DMARDs	67 (31.3)	47 (31.3)	47 (33.6)	0.18	0.67

Patients' reported pain due to their RA weakly predicted their FDRs' interest in predictive testing (p=0.04). However, this would not remain statistically significant if correction for multiple comparisons was applied. No other patient variables predicted FDRs' interest in testing.

FDRs' beliefs about the causes of RA are summarised in tables 12 and 13. From the list of perceived causes provided, the three most cited causes for RA were hereditary factors (82.8%), wear and tear (75.4%), and ageing (74.2%). From the free text responses, hereditary factors were ranked as the most important cause for RA, followed by age, and then wear and tear of the joints.

Table 12: Response frequencies for FDRs' perceived causes of RA.

Perceived causes	Response frequency (%)					
	Strongly agree (%)	Agree (%)	Neither agree nor disagree (%)	Disagree (%)	Strongly disagree (%)	% Agree /strongly agree
Stress or worry	25 (6.4)	103 (26.2)	86 (21.9)	118 (30.0)	61 (15.5)	32.6
Hereditary	166 (41.9)	162 (40.9)	48 (12.1)	14 (3.5)	6 (1.5)	82.8
Germ or virus	24 (6.1)	50 (12.8)	95 (24.2)	120 (30.6)	103 (26.3)	18.9
Diet	25 (6.3)	118 (29.9)	108 (27.3)	98 (24.8)	46 (11.6)	36.2
Chance/ bad luck	35 (8.9)	105 (26.7)	92 (23.4)	65 (16.5)	96 (24.4)	35.6
Poor medical care	10 (2.5)	45 (11.4)	110 (27.9)	138 (35.0)	91 (23.1)	13.9
Pollution	3 (0.8)	41 (10.5)	144 (36.7)	119 (30.4)	85 (21.7)	11.3
Own behaviour	14 (3.6)	97 (24.7)	115 (29.3)	98 (24.9)	69 (17.6)	28.3
Mental attitude (e.g. thinking about life negatively)	3 (0.8)	50 (12.7)	88 (22.4)	132 (33.6)	120 (30.5)	13.5
Family problems	14 (3.5)	54 (13.7)	96 (24.3)	127 (32.2)	104 (26.3)	17.2
Overwork	38 (9.6)	113 (28.6)	101 (25.6)	92 (23.3)	51 (12.9)	38.2
Emotional state	12 (3.1)	69 (17.9)	1-5 (27.2)	126 (32.6)	74 (19.2)	21.0
Ageing	91 (23.0)	199 (51.2)	42 (10.8)	37 (9.5)	20 (5.1)	74.2

Alcohol	9 (2.3)	59 (15.2)	148 (38.0)	114 (29.3)	59 (15.2)	17.5
Smoking	23 (5.9)	76 (19.4)	136 (34.7)	103 (26.3)	54 (13.8)	25.3
Accident or injury	44 (11.3)	161 (41.3)	86 (22.1)	59 (15.1)	40 (10.3)	52.6
Personality	3 (0.8)	8 (2.0)	86 (22.0)	139 (35.5)	155 (39.6)	2.8
Altered immunity	63 (16.2)	147 (37.8)	108 (27.8)	46 (11.8)	25 (6.4)	54
Overweight	30 (7.7)	168 (42.9)	88 (22.4)	72 (18.4)	34 (8.7)	50.6
Hormonal changes	19 (4.8)	139 (35.5)	143 (36.5)	62 (15.8)	29 (7.4)	40.3
Wear and tear	110 (28.2)	184 (47.2)	43 (11.0)	39 (10.0)	14 (3.6)	75.4
Gum disease	6 (1.5)	19 (4.9)	157 (40.3)	119 (30.5)	89 (22.8)	6.4

Items shaded in grey indicate the five items where participants responded with ‘applies’ and ‘definitely applies’ most frequently.

Table 13: Ranked responses for FDRs' perceived causes of RA

Causal factor 1[a]	Frequency (%)	Causal factor 2[b]	Frequency (%)	Causal factor 3[c]	Frequency (%)
Hereditary	41	Age	21	Wear and tear	20
Immunity	18	Wear and tear	20	Lifestyle	19
Wear and tear	13	Lifestyle	15	Age	17
Age	10	Hereditary	13	Hereditary	11
Lifestyle	4	Immunity	12	Immunity	8
Mental health[d]	4	Accident/injury	8	Accident/injury	6
Accident/injury	2	Mental health	4	Mental health	5
Chance	2	Hormonal	4	Chance	5
Physical health conditions[e]	1	Chance	2	Hormones	4
Outside environment	1	Issues with medical care	1	Physical health conditions	3
Hormones	1	Physical health conditions	1	Issues with medical care	1
No opinion	1			Outside environment	1
Issues with medical care[f]	1				

[a]N=377. [b]N=364. [c]N=359. [d] Includes any condition affecting mental health, such as stress, anxiety, or trauma. [e] Includes any physical comorbidities, previous physical health problems and operations. [f] Includes any problems in relation to patients' medical care, for example, misdiagnosis, delay in diagnosis, or medications prescribed.

3.4 Discussion

This chapter provides the first quantitative assessment of the causal beliefs for RA held by FDRs of RA patients, interest in predictive testing for RA amongst FDRs of RA patients, and the impact of RA patients' characteristics on FDRs' interest in predictive testing.

FDRs expressed a high level of interest in predictive testing for RA. This is consistent with results from previous qualitative work.(149,150) This study also confirms qualitative findings (150,166) that interest in predictive testing for RA was associated with the belief that such tests would be extremely accurate, and able to rule in/ out future RA development. Such beliefs may help individuals to deal with complex probabilistic risk information.(166,262) However, these mechanisms may impede understanding of risk information provided by healthcare professionals. Therefore, effective communication of the probabilistic nature of risk information for diseases such as RA presents a challenge for approaches to support shared decision-making in this context.

Several predictors were associated with FDRs' interest in predictive testing, including greater preferences for seeking information about their health, higher perceived absolute risk of RA, regular contact with the index patient, and attitudinal items reflecting a desire to obtain risk knowledge about RA. The influence of FDRs' desire to obtain risk knowledge of RA on interest in testing is consistent with findings from studies assessing interest in predictive testing in other diseases including heart disease, diabetes and cancer.(229,230) Increased health information seeking preferences aligned with previous research examining this factor in other diseases

such as heart disease, DM (225) and Alzheimer's disease (AD),(145), but was not evident in a cross-sectional study of interest in predictive genetic testing for hereditary breast or ovarian cancer.(226) The relationship between information seeking preferences and interest in predictive testing may be influenced by the type of disease being tested for, or by a number of other factors, such as the characteristics of the test (for example, the type of test offered).

The influence of perceived risk on interest in predictive testing in this study aligns with findings in other disease areas. (231,237,238,263) As perceived risk is found to be associated with interest in predictive testing and health behaviours across diseases, it may be an important factor in individual's decisions around predictive and preventive approaches for chronic diseases, including RA. As such, it is imperative that risk information is communicated in a way that will support FDRs' decision-making.

The influence of FDRs' frequency of talking to the index patient on interest in testing contradicts findings in other disease areas, which found a dose effect between contact and interest.(239,240) As such, this result may need to be interpreted with caution. Further studies are needed to confirm this finding within the context of RA, to assess whether regular contact with the proband predicts higher interest in testing for RA compared to daily contact.

FDRs were less interested in taking a predictive test if they agreed that risk information could cause psychological harm. This aligns with previous qualitative research highlighting concerns about the potential for anxiety about risk status.(150,166) Predictive approaches therefore should incorporate appropriate information and support.

FDRs' demographic variables, such as their age, gender, and education were not associated with their interest in predictive testing for RA. This contradicts previous studies examining other disease areas.(198,205,214-216) It may be that these factors are not influential within the context of RA. Alternatively, as most FDRs who took part in this study were interested in taking a predictive test, these factors may be more associated with a lack of interest in predictive testing for RA, rather than an increased interest.

The present study found no evidence to suggest that patient characteristics were associated with their FDRs' interest in predictive testing. It is possible that the cumulative impact of the patient's RA over the course of their illness, rather than over the previous week as captured by the RAID questionnaire, may have been predictive here.

Whilst the majority of FDRs in the current study were aware that there is a hereditary component to RA, aligning with the findings from a previous qualitative study,(150) many also reported common misperceptions associated with RA – particularly, that RA is caused by 'wear and tear' on the joints. There is no data to suggest that overuse is a risk factor for RA. This misperception was also identified by members of the public.(241) This highlights the need for easily accessible informational resources that clarify common misperceptions such as 'wear and tear' of the joints, so that FDRs can gain a thorough understanding of the development of RA.

3.4.1 Implications

The findings from this study increase understanding of perceptual variation amongst those at risk of developing RA and identify a range of factors that should be addressed

via informational resources for those considering predictive testing to support shared decision-making. Further research is needed to explore interest in different types of predictive tests for RA (for example genetic tests, multi-omics technologies and imaging techniques) and tests with different performance characteristics (tests with a high positive predictive value versus high negative predictive value).

3.4.2 Strengths and limitations

This chapter has several methodological strengths, including a large sample size, paired data linking FDRs with index patients, multidisciplinary contributors, and extensive patient partner involvement. A further strength is the recruitment of FDRs via participants with a confirmed diagnosis of RA, rather than individuals self-reporting a family history of RA. This is important as members of the general public often confuse RA with other conditions, such as osteoarthritis.(241)

However, as FDR recruitment relied on RA patients passing the survey to their FDRs, the study may be subject to selection bias. Recruitment of FDRs is challenging (264) and further research is needed to compare alternative strategies and investigate predictors of the likelihood that patients will pass on RA risk information to their relatives. Female participants of white British ethnicity are over-represented in the present sample.

Additionally, the surveys provided to FDRs contained numerous questionnaires, which likely took a significant amount of time to complete. Some of the questionnaires included have been found to be fairly complex, including for example the Brief IPQ.(265) Because of this, bias might have occurred as participant performance may

have declined due to increased fatigue and loss of motivation.(266) This may be reflected by the low return rate identified in this study. Of course, indirect recruitment of FDRs may also account for the low return rate for this study. The survey was pre-tested by patient partners and an FDR, who did not think it was overly burdensome and felt that all the of the measures included were relevant. However, their views may not be representative of those who were approached for the study. As the current study aimed to explore potential predictors of FDRs' interest in predictive testing for RA, many potential predictors were assessed. As a result, key predictors have now been identified which can be the focus of future research, thereby reducing the length of future surveys. However, if a survey of this length was to be provided again, the use of alternative formats, such as an online survey rather than a postal survey that needed to be returned by mail, or approaching FDRs directly, may increase the return rate of this at-risk group. It would also be important to review the experience with the present survey with a new PRP panel to identify approaches to boost completion rates. For example, enhanced explanation about the scientific and clinical value of the study via the Participant Information Sheet, and/ or financial incentives may improve completion rates. However, an independent ethics committee would clearly need to make a final judgement on any approaches proposed and ultimately it is important that any incentive does not interfere with the voluntariness of participants' consent by acting as an inducement.

3.4.3 Conclusions

Interest in predictive testing for RA was high amongst FDRs. Several predictors of interest were identified, including information seeking preferences, desire for RA risk knowledge, regular contact with the index patient, and perceived absolute risk of RA.

Beliefs that testing could lead to psychological harm predicted lower levels of interest. These findings will inform the development of effective predictive strategies and information to support decision-making in individuals considering predictive tests for RA, or taking part in prospective and preventive research.

Chapter 4: Predictors of rheumatoid arthritis (RA) patients' likelihood of communicating RA risk information to relatives.

4.1 Introduction

FDRs have been identified as an important target population for the development of predictive and preventive approaches for RA. Therefore, an understanding of their perspectives towards these approaches is integral to the development of effective strategies. However, access to this group may be limited, as FDRs may not be aware of their risk of developing RA, or of any potential predictive or preventive approaches that could reduce their risk. One important way in which FDRs could be informed of their risk and the potential for RA prediction and prevention is through patients with RA, who have access to this at-risk group.

Communication of this information, however, depends on whether or not the patient is willing to pass on this information to their FDRs. Therefore, it is important to examine patients' perceptions towards family communication regarding RA risk, to understand the process and potential determinants of risk communication among families. This will inform the development of resources to support family communication and facilitate access to FDRs. One qualitative study, discussed within the introduction of this thesis, explored family risk communication among patients with RA.(166) That study found that patients were generally willing to communicate risk information to their relatives. However, their willingness to communicate involved a complex decision-making process about who would be receptive to this risk information. This decision was based on whether or not they had close contact with their relative, whether their relative was too busy, or whether their relative would feel anxious about their risk.(166) This decision was also influenced by patients' perceived responsibility to promote awareness of RA to their relatives. These findings provide important insight into patients' decision-making processes regarding RA risk communication, including

potential barriers and facilitators towards risk communication. However, large-scale quantitative investigations examining potential determinants of RA risk communication, as well as potential barriers such as relatives being too busy or not having a close relationship with their relatives, are currently lacking.

Studies examining family communication about the risk of other diseases have identified several variables that are predictive of patients' likelihood of communicating disease risk information to their relatives. These include demographic factors such as age and gender. Previous research within the field of breast cancer found that younger adults were more likely to inform their relatives about their risk compared to older adults.(267) Females were found to be more likely to communicate information about the risk of breast and ovarian cancer to their relatives compared to males.(163,268,269) Identifying the influence of patients' demographic factors on their likelihood of communicating risk information to their relatives can help to identify subsections of the population where the provision of information and support resources might be most relevant.

Patients' understanding of genetic risk information has been found to significantly influence their likelihood of communicating this information. Those with a higher comprehension of autosomal dominant inheritance in regards to hypertrophic cardiomyopathy (HCM) were more likely to communicate risk information to their children and siblings compared with those who had a lower comprehension.(270) Another study found that around 71% of patients with a genetic heart condition felt that a strong understanding of genetic test results made it easier to communicate risk information to their relatives.(271) A higher understanding of risk information may increase individuals' confidence in communicating this information to their relatives

effectively, influencing their likelihood of communicating about risk.(272,273) Individual's health literacy and numeracy have a significant influence on their knowledge of genetic risk information.(274,275) Lower levels of health literacy and numeracy have been shown to be associated with less knowledge about genetic risk.(274,275) An individual's health literacy and numeracy also impacts on their ability to discuss risk with healthcare providers, further impairing their understanding of risk information and confidence in communicating this information with their family.(274,275) As such, patients' health literacy and numeracy may predict their likelihood to communicate about RA risk information. However, this has yet to be explored. Identifying the influence of health literacy and numeracy can determine whether specific educational strategies focused on increasing understanding of genetic risk information are needed for patients with RA.

Patients' knowledge concerning other aspects of RA development is also important to explore, as previous qualitative research has identified several misperceptions from patients regarding the causes of RA.(166) For example, some did not believe that RA was a heritable disease, or that smoking could be a risk factor, but did believe that 'wear and tear' was a risk factor for the development of RA.(166) However, information regarding patients' beliefs about the causes of RA are yet to be quantified. Identification of patients' perceived causes of RA across a larger subsection of the population could indicate whether further education surrounding the development of RA is also needed for this group.

Patients' attitudes towards risk knowledge (positive or negative) may influence their likelihood of communicating about RA risk. These attitudes have been found to influence risk communication in other disease contexts. Studies examining patients

with breast, ovarian or bowel cancer found that those who were apprehensive about communicating risk information to family members believed that this information may generate unnecessary worry, anxiety and upset for their relatives.(162,163) Patients were more likely to inform their relatives of their risk if they believed that knowing about risk would help their relatives prevent the development of the disease through risk-reduction strategies.(163) These studies provide an understanding of the influence of patients' attitudes towards risk knowledge on communication about disease risk, which may indicate the potential influence of these attitudes on RA risk communication. Patients' attitudes towards RA risk knowledge have been identified in a previous qualitative study,(166) highlighting that risk information would help their relatives prepare for the future, and bring them peace of mind.(166) However, the influence of these attitudes on RA patients' likelihood of communicating about risk remains to be explored.

The severity of patients' disease may also influence their likelihood of communicating disease risk information. Previous research has found mixed results regarding the influence of this factor, as one study examining heart disease found that those whose disease was less severe were less concerned about their disease and thus found it easier to communicate risk.(276) In contrast, another study examining Huntington's disease found that the onset of symptoms (and thus an increase in disease impact) was a driving force in their decision to communicate about risk with their relatives.(273) This contrast in findings may be due to the prognosis of these specific diseases. Therefore, it would be informative to examine the influence of disease severity in relation to communication about the risk of RA.

Patients' coping style may influence their likelihood of communicating RA risk information with their relatives. Studies examining other chronic diseases found that some individuals highlighted avoiding communication about risk to protect their family members from potentially anxiety-provoking information.(163,277-279) Conversely, others wanted to protect their family by providing information that can initiate decision-making regarding risk reduction and prevention of a disease.(162,279) In particular, some saw communication of risk information as a way to encourage their relatives to take a predictive test for the disease.(270,271,280) Therefore, those with avoidant coping strategies (i.e. those who want to avoid generating anxiety for their relatives) may be less likely to communicate risk information compared to those with more active coping strategies, where communicating risk is seen as a way to enact risk-reduction behaviours in their relatives. Those with avoidant coping strategies may also include individuals who want to avoid uncomfortable feelings (such as guilt) around having passed on risk to their family members, or avoid feelings of responsibility surrounding the management of their relatives' risk.(160) The influence of coping styles on risk communication among patients with RA has yet to be explored. Therefore, to increase understanding of the potential impact of these coping styles, research examining this area is needed. This research also identifies the potential influence of patients' interest in their relatives taking a predictive test on their likelihood to communicate disease risk information,(270,271,280) which has also yet to be explored within the context of RA.

Studies have also found that individuals who were more optimistic were more likely to communicate about cancer compared to those who were less optimistic.(281) This may be because those who are more optimistic might perceive the emotional demands of communicating this information as more manageable, or are more likely to believe

that relatives will receive this information more positively and act on the information than those who are less optimistic.(281) However, there is limited literature examining the influence of optimism on disease risk communication, and the influence of optimism on RA risk communication is currently unknown. Therefore, patients' levels of optimism may be important to explore as a potential predictor of their likelihood of communicating RA risk information.

Patients' preferences for autonomy in decision-making and information seeking about health may also influence their likelihood of communicating RA risk information. Studies have found that patients communicating risk to their relatives for other diseases such as breast and ovarian cancer felt that their relatives had a right to information which could facilitate their decision-making around health behaviours.(282) Another study also found that patients were motivated to communicate risk information to their relatives to empower them to discuss any concerns about risk, obtain more information about their health, and make important life decisions.(283) The finding that patients are motivated to provide autonomy for their relatives may reflect their own preferences regarding autonomy in decision-making and information seeking about health. However, the influence of patients' preferences for autonomy and their likelihood of communicating risk information has seldom been explored, and there is currently no research that has examined its influence in the context of RA. Therefore, patients' preferences for autonomy in relation to decision-making and seeking information about health are important to explore regarding RA risk communication.

Several studies assessing patients with heart disease or with cancer found that dispositional openness predicted increased likelihood of communicating risk

information to relatives.(165,276,284). As dispositional openness has been found to increase risk communication across various chronic diseases, it may be an important factor influencing family risk communication for RA, and thus would be important to explore within this context. Currently, there are no studies that have examined the influence of dispositional openness on RA risk communication. Examining this could help to identify subsections of the population where further support is needed.

Patients' perceptions of their illness are particularly important to explore within the context of family disease risk communication, due to it being identified by both theory and empirical evidence as an important determinant of numerous health behaviours across various chronic diseases.(233,234,285) The influence of illness perceptions on health behaviours may indicate the potential for these perceptions to predict family risk communication in patients, to enable their relatives to engage in health behaviours. However, there is limited literature examining the influence of patients' illness perceptions on their likelihood to communicate disease risk. Certain aspects relating to patients' perceptions of their illness, such as their perceived control over the illness, and their beliefs that treatment could help with their illness (233) have been found to influence patients' likelihood of communicating disease risk information. Patients were more likely to communicate risk information about a disease if treatment or prevention were available for that disease.(286) For diseases where no such interventions are available and people are likely to interpret the disease as out of their control (e.g. Huntington's disease), a larger number of patients reported being less likely to communicate risk information to their relatives.(279,286) As patients' illness perceptions, specifically their perceived control over an illness, have been found to influence their likelihood to communicate risk in other chronic diseases, it is important

that this is explored within the context of RA. Identifying inaccurate beliefs regarding RA and how they may influence communication could provide opportunities to modify these beliefs, which could influence patients' likelihood of communicating disease risk as well as the accuracy of the information patients can provide.

The influence of patients' family dynamics is also particularly important to explore within the context of RA risk communication, as it has been identified as an integral factor influencing family risk communication across numerous studies and disease contexts. (286-289) Open communication within families has been identified as one of the most reliable ways to predict whether an individual will communicate about the genetic risk of a disease with their relatives.(286,288) Previous research on a number of disease areas have found that families who emphasised open communication were more likely to communicate risk, whereas those who highlighted complex relationships within the family, family conflict and trauma were less likely to communicate about disease risk with their relatives.(271,290,291) Specific relationships within the family have also been found to influence risk communication, as patients were more likely to communicate information about the risk of breast and ovarian cancer, or Huntington's disease, to their children compared to their siblings.(273,279) An understanding of the type of family environment that is less likely to result in open communication about disease risk is important to identify ways to generate effective resources to support communication in families at risk. As such, it is integral that this is explored within the context of RA. The influence of specific family relationships, such as whether a patients' relative is a child or sibling, is also important to explore within RA as it could indicate whether a certain type of relative may be less likely to receive risk information, identifying a specific group that might need additional information or support.

The aims of this study were to identify [1] cognitive, affective and demographic predictors of the likelihood that people with existing RA will communicate with their FDRs about their risk of developing RA, [2] barriers to family communication about risk of RA, as perceived by people with existing RA, and [3] beliefs about the causes of RA among people with existing RA.

In relation to these aims, health behaviour theories and previous literature within the field, it was hypothesised that:

1. Patients with RA would be willing to communicate RA risk information to their FDRs, and that higher family functioning and more perceived control over their RA would be associated with an increased likelihood to communicate RA risk information to their relatives.

   Other factors identified in previous literature examining other chronic diseases, including demographic factors, health literacy and health numeracy, preferences for autonomy in seeking information and making decisions about health, the severity of their disease, coping strategies, optimism, interest in their FDRs taking a predictive test and attitudes towards risk knowledge, were also hypothesised to predict patients' likelihood of communicating RA risk information to their FDRs.

2. Patients would be more likely to communicate about RA risk information with their children, or with female relatives compared to siblings or male relatives.

4.2 Method

4.2.1 Design

A cross-sectional survey was provided to patients with RA, which assessed their reported likelihood of communicating RA risk information to each of their FDRs, and potential demographic and psychosocial predictors of their likelihood to communicate risk. These predictors include: disease impact, illness perceptions, autonomy preferences, health literacy, health numeracy, coping styles, optimism, dispositional openness, interest in their relatives taking a predictive test for RA, and attitudes towards finding out about RA risk.

4.2.2 Procedure

Information about the study procedure is described in the previous chapter. Any information pertaining to patients that was not mentioned in the previous chapter is covered in the current chapter. Patients were eligible if they a) had received a diagnosis of RA (satisfying the 2010 ACR-EULAR classification criteria (6)) at least six months before they were approached to take part in the study; b) were aged 18 or over; c) had one or more FDRs (biological offspring or full siblings); and d) were able to complete the printed survey in English. All patients provided written informed consent.

Patients were introduced to the study by a member of their healthcare team during a scheduled visit to the rheumatology outpatient clinic and were provided with the survey pack discussed in the previous chapter. Patients were advised that they could take the survey pack home and decide whether or not to participate in their own time.

4.2.3 Measures

Patients' likelihood of communicating RA risk to FDRs was assessed by asking the patient to identify their relationship to each FDR (daughter, son, sister or brother), and their likelihood of communicating RA risk information to each of those FDRs ("How likely would you be to pass on information to this relative about their risk of developing rheumatoid arthritis?", assessed on a Likert scale ranging from extremely unlikely (0) to extremely likely (4), with higher scores indicating increased likelihood).

Data were also collected about the patients' gender, age, ethnicity, (following the format recommended by the Office of National Statistics,(242)) postcode,(used to calculate deprivation using the multiple deprivation index,(243) scored between 1-10, with higher scores indicating less deprivation) employment status, highest level of education, smoking status, years with RA and their current treatment for RA (measured as "no treatment", "steroids", "DMARDs" and "biological treatments"). The following measures were also completed (those used in the previous chapter will be described briefly here; those that are specific to the current chapter will be described in detail):

(1) The RAID scale, which measured patients' RA status on an 11 point scale from 0 (no impact) to 10 (extreme impact). Higher scores indicate worse disease status.(254)

(2) The Brief IPQ, which measured patients' illness perceptions of their RA on an 11-point scale, with higher scores indicating a more threatening view of RA.(292) The IPQ-R was used to assess patients' perceived causes of their RA,(244) with additional items based on perceived causes identified in earlier qualitative investigations.(150,166) The extent to which participants agreed that a specific factor

caused their RA was assessed using a 5-point Likert scale ranging from 0 (“strongly disagree”) to 4 (“strongly agree”). Free text responses options were also included for participants to identify the three most important factors they believed caused their illness.

(3) The single item literacy screener, which assessed patients’ health literacy. Responses were scored on a 5-point Likert scale from 0 (“never”) to 4 (“always”), with scores above 2 indicating some difficulty reading health-related material.(245)

(4) The three-item subjective numeracy scale, which measured patients’ self-reported ability to understand numerical information. Each item was scored on a 6-point Likert scale, with higher scores indicating stronger perceived mathematical ability.(246)

(5) The autonomy preference index, which measured health-related decision-making and information seeking preferences. Each item was measured on a 5-point Likert scale from 0 (“strongly disagree”) to 4 (“strongly agree”). Higher scores indicate greater autonomy preferences.(247)

(6) The Brief Approach/Avoidance Coping Questionnaire, which measured approach/avoidant coping style in stressful situations. Items were measured using a 5-point Likert scale from 0 (“strongly disagree”) to 4 (“strongly agree”). Higher scores indicate higher approach/ lower avoidance coping styles.(248)

(7) Dispositional optimism (assessed using the three items from the LOT-R). These items were measured using a 5-point Likert scale from 0 (“strongly disagree”) to 4 (“strongly agree”). Higher scores indicate increased optimism.(249)

(1) Dispositional openness, which measured patients’ general disclosure of information using one item; “I am a person who usually talks to other people about my problems,

concerns, and daily life events". This item was assessed using a 5-point Likert scale ranging from 0 ("strongly disagree") to 4 ("strongly agree"). Higher scores indicate increased openness to communicate.(293)

(8) Twenty three attitudinal statements measured perceived advantages and disadvantages of someone finding out how likely they are to develop rheumatoid arthritis in the future.(150,166,186,229,253) Items were scored on a 5-point Likert scale ranging from 0 ("strongly disagree") to 4 ("strongly agree"). Higher scores indicated increased agreement with an attitudinal statement.

(9) The General Functioning Subscale of the McMaster Family Assessment Device, which measured family functioning across six domains: general problem solving, communication, roles, affective responses, affective involvement and behavioural control. These items were measured on a 4-point Likert scale ranging from 0 ("strongly disagree") to 3 ("strongly agree"). Scores above 2 indicate good family functioning. This subscale has been found to have good internal consistency (α=.70).(294)

(10) Patients' interest in their children and/or siblings taking a predictive test within 6 months and in the future were assessed using four items, one assessing each timeframe and each FDR subgroup (children or sibling); "if, in the next six months, your doctor offered your children/sibling a test that predicted their risk of developing RA, would you like them to take the test?" and "if, sometime in the future, your doctor offered your children/sibling a test that predicted their risk of developing RA, would you like them to take the test?". Responses were measured on a 4-point Likert scale ranging from 0 ("no definitely not") to 3 ("yes definitely"). A higher score indicates higher interest in their FDR(s) taking a predictive test for RA.

4.2.4 Analysis

Statistical analyses were performed using IBM SPSS Statistics version 27.0 and R version 4.0.3.

Descriptive statistics were used to summarise demographic and psychosocial characteristics, reasons patients were likely/ unlikely to communicate RA risk information to their relatives, and patients' perceived causes of RA (free text responses from this measure were categorised thematically, and the number of times each theme occurred was noted). Principal components analysis with direct oblimin rotation was conducted to reduce the 23 attitudinal items into a smaller number of underlying factors. Factor loadings for each item were multiplied by the original item score to obtain a weighted score. From this, a mean score was calculated.

For patients' reported likelihood of communicating RA risk to their FDRs, the median score across all FDRs was calculated for each patient. These scores were then used as the primary outcome in subsequent analyses.

Kruskal-Wallis H and Mann-Whitney U tests were performed to assess the effects of categorical variables on patients' reported likelihood of communicating RA risk to their FDRs. Spearman's rank correlations were used to investigate associations between ordinal predictor variables and likelihood of communicating RA risk. Wilcoxon signed-rank tests were conducted on patients who reported having both children and siblings, as well as patients who reported having both male and female relatives, to examine differences in patients' likelihood of communicating RA risk information to their children compared to their siblings, and to male relatives compared to female relatives. All

predictor variables with a significance level <0.05 were used to inform a binary logistic multivariate model, with likelihood of communicating RA risk recoded as a binary variable (extremely likely to communicate RA risk information vs not extremely likely).

A backward stepwise logistic regression was conducted, using the default cut-off value of 0.1.(256) To determine which variables to include in this regression, multi-collinearity amongst categorical and continuous predictor variables was assessed using GVIFs with a cut-off value of 1.414.(257)

4.2.5 Sample size calculation

A sample size of 480 patients would provide 95% confidence that an estimate of the proportion of responses for the primary outcome variable was within 0.046 of the true value, and would allow the inclusion of up to 9 explanatory variables in a multivariate logistic regression provided that neither outcome occurs in less than 20% of the cases.

4.2.6 Patient and public involvement

Three PRPs contributed to the design and development of surveys. The involvement of these PRPs is described in detail in the previous chapter. In brief, changes that were made as a result of PRP input to reduce anxiety were: approaching potential patient participants during scheduled clinic appointments rather than by mail; and not approaching patients diagnosed with RA within the previous six months to take part in the survey study. General changes that were made to the survey as a result of PRP input were: providing a subjective rather than objective measure of numeracy; dividing the survey into two parts; adding a table of contents; providing additional space between each item; and the opportunity for open ended responses. PRPs also advised

on the wording and content of all study documents, and on the analysis and interpretation of data, including validation of the thematic categorisation of free text responses.

4.3 Results

Surveys were provided to 1720 patients. 482 of these patients returned a survey. The median age for this sample was 65 years, 72% of participants were female and 50% were retired. Patients reported having had a diagnosis of RA for a median of 10 years, and most reported taking conventional synthetic DMARDs and glucocorticoids to manage their condition (89%).

4.3.1 Patients' likelihood of communicating RA risk information to their FDRs

Most patients reported being "likely" or "extremely likely" to communicate RA risk information to their FDRs (38.2% and 36.9%, respectively) (Table 14). 81.2% of patients reported being "likely" or "extremely likely" to communicate RA risk information to their children, 69.3% to their siblings, 75.8% to male relatives, and 77.2% to female relatives.

Table 14: Response frequencies for patients' likelihood of communicating RA risk information to their relatives.

	Response frequencies (%) for patients' likelihood of communicating RA risk				
	Extremely unlikely	**Unlikely**	**Neither likely nor unlikely**	**Likely**	**Extremely likely**
All relatives (n=1684)	**124 (7.4)**	**158 (9.4)**	**137 (8.1)**	**644 (38.2)**	**621 (36.9)**
Relationship of relative to the patient*					
Children (n=792)	34 (4.3)	63 (8)	52 (6.5)	327 (41.3)	316 (39.9)
Siblings (n=511)	63 (12.3)	56 (11)	38 (7.4)	167 (32.7)	187 (36.6)
Gender of relative*					
Male (n=623)	44 (7)	64 (10.3)	43 (6.9)	231 (37.1)	241 (38.7)
Female (n=680)	53 (7.8)	55 (8.1)	47 (6.9)	263 (38.7)	262 (38.5)

*Response frequencies for specific relatives (children vs siblings; male vs female) includes only those cases where patients indicated the characteristics of the relative (child, sibling, male, female) in relation to whom they were reporting their likelihood of communicating RA.

The 190 patients who reported their likelihood of communicating RA risk to both children and siblings were more likely to communicate about risk to their children rather than their siblings ($p<0.001$) (Table 15). Of the 221 patients who reported their likelihood of communicating RA risk information to both male and female relatives, their likelihood of communicating risk information was not significantly influenced by their FDRs' gender ($p=0.32$) (Table 15).

Table 15: Wilcoxon signed-rank tests for reported relatives' characteristics and their association with patients' median likelihood of communicating RA risk to relatives.

Reported relatives' characteristics	Medians (IQRs)	P Value
Relationship to the patient		<0.001
Children	3.00 (3.00-4.00)	
Siblings	3.00 (1.38-4.00)	
Gender		
Male	3.00 (2.00-4.00)	0.32
Female	3.00 (2.75-4.00)	

Principle components analysis of the 23 items describing advantages and disadvantages of predictive testing was conducted. Factor loadings with an absolute value of less than 0.3 were disregarded.(260) The KMO measure of sampling adequacy was 0.87. Bartlett's test of sphericity was significant (p<0.001). A five-factor solution (Table 16) explained 63.16% of the variance. After interpretation of the factor loadings, the factors were labelled as: 1) Increased empowerment over a person's health; 2) Psychological harm as a result of knowing risk; 3) Responsibility to obtain risk information; 4) Social consequences as a result of predictive testing and 5) Stress and avoidance around taking a predictive test.

Table 16: Factor labels and factor loadings from a factor analysis measuring patients' attitudes towards taking a predictive test.

Factors	Items	Factor loadings
1. Increased empowerment over person's health	"Finding out they were at high risk of developing RA would help a person feel prepared if they developed symptoms of RA"	0.848
	"Finding out their risk of developing RA would help a person to make important decisions about how to live their lives"	0.835
	"Finding out they were at high risk of developing RA would help a person get treated quickly if they developed symptoms of RA"	0.782
	"A person found to be at high risk of developing RA would be able to lower their risk by making changes to their lifestyle"	0.778
	"Finding out their risk of developing RA would give a person control over their health"	0.745
	"A person found to be at high risk of developing RA would be able to lower their risk by taking medications"	0.620
	"Knowing that their risk of developing RA was low would bring a person peace of mind"	0.550
2.Psychological harm as a result of knowing risk	"People found to be at high risk of developing RA may become anxious as a result"	0.918
	"People found to be at high risk of developing RA may become depressed as a result"	0.842
	"People found to be at high risk of developing RA are likely to worry unnecessarily about their health"	0.745
	"The relatives of someone found to be at high risk of developing RA would be upset"	0.651
	"Parents found to be at high risk of developing RA are likely to feel guilty about the about the possibility of passing the risk on to their children"	0.605

	"Knowing that they were at high risk of developing RA would harm a person's self-image"	0.449
3. Responsibility to obtain risk information	"People should find out their risk of developing RA to determine whether their children might be at risk"	-0.836
	"People should find out their risk of developing RA for the sake of their family"	-0.828
	"People should find out their risk of developing RA at an early age"	-0.765
	"Getting a test to predict their risk of developing RA would tell a person that they definitely would, or wouldn't develop RA"	-0.674
	"Not knowing their risk of developing RA could make a person anxious"	-0.623
4. Social consequences as a result of testing	"People found to be at high risk of developing RA may not be able to get insurance"	0.902
	"People found to be at high risk of developing RA may be discriminated against"	0.844
5. Stress and avoidance around taking a predictive test	"Getting a test to predict their risk of developing RA would be a stressful experience for a person"	0.639
	"I prefer not to think about things that might never happen"	0.623
	"Getting a test to predict the risk of a person developing RA would be a stressful experience for their relatives"	0.614

Patients' demographic and psychosocial characteristics, and univariate analyses of their relationship with their likelihood of communicating RA risk, are summarised in Table 17; 13 predictor variables were significantly associated with patients' likelihood of communicating RA risk information.

Patients' interest in their children/ siblings taking a predictive test for RA in six months and in the future were highly inter-correlated (r=0.92, p<0.001 for children, and r=0.94, p<0.001 for siblings). Therefore, as it has been suggested previously that six months is as far into the future as most people plan a specific behaviour change,(259) interest in predictive testing within six months was chosen for subsequent analyses.

Table 17: Descriptive statistics and univariate analyses for patients' characteristics and their associations with patients' median likelihood of communicating RA risk information to their relatives (N=482).

Patient characteristics	**Descriptive statistics**				
	Frequency for patients' characteristics	**Medians (IQRs) for patients' characteristics**	**Medians (IQRs) for patients' likelihood of communicating risk**	**Test statistics**	**P value**
Age (N= 17 missing);median (IQR)		65 (55-72)		-0.19	<0.001 [rs]
Deprivation index (N= 85 missing);median (IQR)		4(2-7)		-0.08	0.10 [rs]
Gender (N= 11 missing); frequency (%)					0.87 [U]
Male	131 (27.8)		3 (3-4)		
Female	340 (72.2)		3 (3-4)		
Employment (N= 6 missing); frequency (%)					0.001 [H]
Employed	146 (30.7)		3 (3-4)		
Unemployed	86 (18.1)		3 (3-4)		
Retired	240 (50.4)		3 (2-4)		
Other	4 (0.8)		4 (4-4)		
Ethnic group (N= 3 missing); frequency (%)					0.26 [H]
White	406 (84.8)		3 (3-4)		
Mixed	9 (1.9)		3 (3-4)		
Asian	37 (7.7)		3 (3-4)		
Black	26 (5.4)		3 (3-4)		
Other	1 (0.2)		4 (4-4)		
Smoking (N= 9 missing); frequency (%)					0.20 [H]
Current	53 (11.2)		3 (3-4)		
Ever	158 (33.4)		3 (3-4)		
Never	262 (55.4)		3 (2-4)		
Education (N= 35 missing); frequency (%)					0.36 [U]
A level or lower	300 (67.1)		3 (3-4)		

Higher than A level	147 (32.9)		3 (3-4)		
Current treatment; frequency (%)					
No treatment	11 (2.3)		3 (3-3)		0.51 [U]
Conventional synthetic DMARDs and glucocorticoids	428 (89.4)		3 (3-4)		0.69 [U]
Biologic DMARDs	156 (32.6)		3 (3-4)		0.67 [U]
RA duration (N= 97 missing);median (IQR)		10 (4-20)		-0.18	0.001 [rs]
RAID score (N= 15 missing); median (IQR)					
Pain (*N*=2 missing)		5(3-7)		0.03	0.52 [rs]
Ability (*N*=4 missing)		5 (2-7)		-0.01	0.77 [rs]
Fatigue (*N*=7 missing)		6 (3-8)		0.05	0.28 [rs]
Sleep (*N*=3 missing)		5 (2-7)		0.03	0.58 [rs]
Physical wellbeing (*N*=4 missing)		5 (3-7)		-0.002	0.97 [rs]
Emotional wellbeing (*N*=4 missing)		4 (2-7)		-0.001	0.98 [rs]
Coping (*N*=4 missing)		4 (2-6)		-0.02	0.68 [rs]
Brief illness perception questionnaire; median (IQR)					
Consequences (*N*=5 missing)		6 (4-8)		0.02	0.72 [rs]
Timeline (*N*=15 missing)		10 (9-10)		-0.02	0.73 [rs]
Personal control (*N*=7 missing)		5 (4-7)		-0.04	0.34 [rs]
Treatment control (*N*=4 missing)		8 (6-9)		-0.01	0.79 [rs]
Identity (*N*=3 missing)		6 (5-8)		0.03	0.51 [rs]
Concern (*N*=7 missing)		7 (5-9)		0.07	0.13 [rs]
Understanding (*N*=3 missing)		8 (6-9)		0.04	0.34 [rs]
Emotional (*N*=7 missing)		6 (3-8)		0.04	0.35 [rs]
Health literacy (*N*=7 missing); median (IQR)		0 (0-1)		-0.05	0.33 [rs]

Health numeracy (*N*=8 missing); median (IQR)	14 (11-17)	0.003	0.95 [rs]
Information Seeking (*N*=8 missing); median (IQR)	84 (75-97)	0.26	<0.001 [rs]
Decision making (*N*=7 missing); median (IQR)	54 (42-67)	0.09	0.048 [rs]
Brief Avoidance Coping Questionnaire (*N*=17 missing); median (IQR)	28 (25-31)	0.09	0.07 [rs]
Optimism (*N*=5 missing); median (IQR)	8 (6-9)	0.03	0.51 [rs]
Openness (*N*=1 missing); median (IQR)	2 (1-3)	0.13	0.004 [rs]
Interest in predictive testing			
Children (*N*=65 missing); median (IQR)	3 (2-3)	0.44	<0.001 [rs]
Siblings (*N*=87 missing); median (IQR)	2 (2-3)	0.44	<0.001 [rs]
Family functioning (*N*=40 missing); median (IQR)	2 (2-3)	0.23	<0.001 [rs]
Attitudes towards testing – median (IQR)			
Increased empowerment over person's health (*N*= 9 missing);	2.21 (1.98-2.45)	0.36	<0.001 [rs]
Psychological harm as a result of knowing risk (*N*=8 missing)	1.62 (1.37-1.99)	-0.16	0.001 [rs]
Responsibility to obtain risk information (*N*=5 missing)	-1.96 (-2.24-1.55)	-0.30	<0.001 [rs]
Social consequences as a result of predictive testing (*N*=4 missing)	1.72 (0.87-2.17)	-0.03	0.48 [rs]
Stress and avoidance around taking a predictive test (*N*=7 missing)	1.25 (1.04-1.67)	-0.33	<0.001 [rs]

[rs]= Spearman's rank correlations, [H]= Kruskal-Wallis H test, [U]= Mann-Whitney U test. Correlation coefficients are reported for Spearman's rank correlations, medians and IQRs are reported for Kruskal-Wallis H and Mann-Whitney U tests.

The factors ‘age’ and ‘interest in children taking a predictive test’ both had a GVIF score above 1.414 and thus were excluded from the first backward stepwise logistic regression. The backward stepwise logistic regression performed on the remaining 11 significant variables identified a new model with four variables.

Upon re-calculating the GVIF scores, when ‘age’ and ‘interest in children taking a predictive test’ were added to the new model, all scores were below 1.414. Therefore, a final backward stepwise logistic regression was conducted on the four variables identified by the previous regression, ‘age’ and ‘interest in children taking a predictive test’. A final model was identified which included four variables, outlined in Table 18.

Table 18: Final binary logistic regression model to predict patients’ reported likelihood of communicating RA risk information to their relatives.

Patients’ predictors	**Odds ratios (95% CI)**	**P Value**
Family functioning	2.02 (1.14-3.58)	0.017
Increased empowerment over health	3.92 (2.00- 7.86)	<0.001
Stress and avoidance around taking a predictive test	0.35 (0.19-0.62)	<0.001
Interest in siblings taking a predictive test (reference category- yes definitely (3))		<0.001
No	0.25 (0.10-0.64)	0.003
Yes probably	0.31 (0.17-0.58)	<0.001

Patients who had a higher interest in their siblings taking a predictive test for RA, had higher family functioning, and believed that risk knowledge would increase a person's empowerment over their health were more likely to communicate about RA risk. Patients' beliefs that tests to predict the risk of RA would cause stress to a person and their relatives decreased their likelihood of wanting to communicate RA risk.

Reasons patients were likely / unlikely to communicate RA risk information to their relatives are summarised in Table 19. The three most cited reasons that patients were unlikely to communicate RA risk information to their relatives include the fact that their relatives feel healthy at the present time (45%), that they do not want to worry their relatives (36%) and that their relatives have other problems to deal with (34%).

Table 19: Response frequencies for reasons patients were unlikely to communicate RA risk information to their relatives.

Items	Response frequency (%)					
	Definitely does not apply	**Does not apply**	**Neutral**	**Applies**	**Definitely applies**	**% Applies /definitely applies**
Not concerned about RA risk						
"They feel healthy at the present time"	55 (16.8)	49 (15)	76 (23.2)	121 (37)	26 (8)	45
"I'm not worried about the possibility that they might develop RA"	62 (18.9)	56 (17.1)	138 (42.1)	52 (15.9)	20 (6.1)	22
"I think that their risk of developing RA is low"	49 (14.6)	57 (17)	161 (48.1)	50 (14.9)	18 (5.4)	20.3
Nothing will be done to lower risk						
"They would be unlikely to do anything about their risk of developing RA"	33 (10.1)	57 (17.4)	131 (40.1)	92 (28.1)	14 (4.3)	32.4
"There is nothing that can be done to lower their risk of developing RA"	52 (15.7)	52 (15.7)	138 (41.6)	67 (20.2)	23 (6.9)	27.1
Avoidance of risk knowledge						
"They would rather not think about the possibility that they might develop RA"	35 (10.7)	57 (17.4)	124 (37.9)	85 (26)	26 (8)	34

"I would rather not think about the possibility that they might develop RA"	57 (17.2)	60 (18.1)	118 (35.5)	69 (20.8)	28 (8.4)	29.2
"I don't like talking about my RA with them"	95 (29.3)	81 (25)	81 (25)	57 (17.6)	10 (3.1)	20.7
"It is not my responsibility"	86 (26.6)	79 (24.5)	116 (35.9)	37 (11.5)	5 (1.5)	13
"They don't like it when I talk about my RA"	109 (32.8)	105 (31.6)	89 (26.8)	23 (6.9)	6 (1.8)	8.7
"I don't want them to know that I've got RA"	165 (49.8)	108 (32.6)	47 (14.2)	9 (2.7)	2 (0.6)	3.3
Age						
"They are too old"	109 (34.2)	88 (27.6)	80 (25.1)	34 (10.7)	8 (2.5)	13.2
"They are too young"	115 (36.4)	86 (27.2)	75 (23.7)	29 (9.2)	11 (3.5)	12.7
Privacy issues						
"I would feel that I was invading their privacy"	98 (30.3)	99 (30.7)	82 (25.4)	39 (12.1)	5 (1.5)	13.6
"They would feel that I was invading their privacy"	100 (31.1)	100 (31.1)	87 (27)	31 (9.6)	4 (1.2)	10.8
Anxiety/guilt surrounding RA						
"I don't want to worry them"	53 (16.3)	54 (16.6)	101 (31)	96 (29.4)	22 (6.7)	36.1
"The conversation would make me feel anxious"	74 (23.2)	83 (26)	98 (30.7)	50 (15.7)	14 (4.4)	20.1
"I would feel guilty"	99 (30.7)	111 (34.4)	76 (23.5)	31 (9.6)	6 (1.9)	11.5

"They might feel embarrassed"	91 (28.3)	83 (25.9)	113 (35.2)	26 (8.1)	8 (2.5)	10.6
"They might blame me"	103 (32)	112 (34.8)	74 (23)	28 (8.7)	5 (1.6)	10.3
"I might feel embarrassed"	121 (37.2)	124 (38.2)	62 (19.1)	16 (4.9)	2 (0.6)	5.5
Other life issues						
"They have other problems to deal with"	63 (19.5)	50 (15.5)	99 (30.7)	87 (26.9)	24 (7.4)	34.3
"They are busy"	68 (21.2)	68 (21.2)	113 (35.2)	60 (18.7)	12 (3.7)	22.4
"I have other problems to deal with"	79 (24.9)	76 (24)	95 (30)	55 (17.4)	12 (3.8)	21.2
"I am busy"	89 (27.8)	97 (30.3)	110 (34.4)	18 (5.6)	6 (1.9)	7.5
Lack of knowledge surrounding RA						
"Doctors cannot tell them for certain that they will, or won't develop RA"	56 (16.7)	46 (13.7)	121 (36)	81 (24.1)	32 (9.5)	33.6
"They do not understand the impact that RA has on my life"	74 (22.8)	80 (24.6)	65 (20)	81 (24.9)	25 (7.7)	32.6
"I don't have enough information about their risk of developing RA"	67 (20.1)	58 (17.4)	104 (31.2)	77 (23.1)	27 (8.1)	31.2
"They think RA is something that affects older people"	90 (27.6)	83 (25.5)	86 (26.4)	55 (16.9)	12 (3.7)	20.6
Closeness with relatives						

“They live far away from me”	114 (35.5)	83 (25.9)	59 (18.4)	40 (12.5)	25 (7.8)	20.3
“I am not currently in contact with them”	141 (43.9)	83 (25.9)	46 (14.3)	29 (9)	22 (6.9)	15.9
“I do not have a close relationship with them”	132 (41)	91 (28.3)	56 (17.4)	22 (6.8)	21 (6.5)	13.3

Items shaded in grey indicate the ten items where participants responded with ‘applies’ and ‘definitely applies’ most frequently.

Patients’ perceived causes of RA are summarised in tables 20 and 21. From the list of perceived causes provided, the three most cited causes for RA were wear and tear (66.4%), altered immunity (61.1%), and hereditary factors (56.3%) (Table 20). Of the ranked, free text responses, hereditary factors were ranked as the most important causal factor for RA, followed by mental health (which includes trauma, stress and anxiety), and finally wear and tear (Table 21).

Table 20: Response frequencies for patients' perceived causes of RA.

Perceived causes	Response frequency (%)					
	Strongly agree (%)	Agree (%)	Neither agree nor disagree (%)	Disagree (%)	Strongly disagree (%)	% Agree/ strongly agree
Stress or worry	80 (17)	148 (31.5)	126 (26.8)	69 (14.7)	47 (10)	48.5
Hereditary	137 (29.1)	128 (27.2)	110 (23.4)	46 (9.8)	50 (10.6)	56.3
Germ or virus	51 (10.6)	90 (19.3)	149 (31.9)	97 (20.8)	80 (17.1)	29.9
Diet	21 (4.5)	112 (23.8)	162 (34.4)	111 (23.6)	65 (13.8)	28.3
Chance/ bad luck	56 (11.9)	121 (25.7)	116 (24.6)	72 (15.3)	106 (22.5)	37.6
Poor medical care	12 (2.6)	38 (8.1)	115 (24.6)	150 (32.1)	153 (32.7)	10.7
Pollution	14 (3.0)	57 (12.2)	184 (39.4)	129 (27.6)	83 (17.8)	15.2
Own behaviour	9 (1.9)	72 (15.4)	135 (28.8)	123 (26.3)	129 (27.6)	17.3
Mental attitude (e.g. thinking about life negatively)	16 (3.4)	54 (11.5)	106 (22.6)	137 (29.2)	156 (33.3)	14.9
Family problems	35 (7.4)	96 (20.4)	117 (24.8)	115 (24.4)	108 (22.9)	27.8
Overwork	58 (12.3)	124 (26.3)	113 (23.9)	97 (20.6)	80 (16.9)	38.6
Emotional state	38 (8.3)	108 (23.6)	130 (28.4)	114 (24.9)	67 (14.7)	31.9
Ageing	35 (7.6)	210 (45.4)	86 (18.6)	77 (16.6)	55 (11.4)	53

Alcohol	3 (0.7)	49 (10.7)	168 (36.5)	136 (29.6)	104 (22.6)	11.4
Smoking	27 (5.8)	56 (12.1)	163 (35.3)	108 (23.4)	108 (23.4)	17.9
Accident or injury	24 (5.1)	163 (34.8)	120 (25.6)	88 (18.8)	73 (15.6)	39.9
Personality	4 (0.9)	32 (6.9)	128 (27.6)	149 (32.1)	151 (32.5)	7.8
Altered immunity	100 (21.5)	184 (39.6)	121 (26.0)	32 (6.9)	28 (6)	61.1
Overweight	24 (5.2)	141 (30.3)	135 (29.0)	99 (21.2)	67 (14.4)	35.5
Hormonal changes	32 (6.9)	129 (27.7)	178 (38.3)	78 (16.8)	48 (10.3)	34.6
Wear and tear	108 (22.9)	205 (43.5)	66 (14.0)	50 (10.6)	42 (8.9)	66.4
Gum disease	14 (3.0)	41 (8.8)	202 (43.5)	116 (25.0)	91 (19.6)	11.8

Items shaded in grey indicate the five items where participants responded with ‘agree’ and ‘strongly agree’ most frequently.

Table 21: Ranked responses for patients' perceived causes of their RA.

Causal factor 1[a]	**Frequency (%)**	**Causal factor 2[b]**	**Frequency (%)**	**Causal factor 3[c]**	**Frequency (%)**
Hereditary	25	Mental health	18	Wear and tear	17
Mental health[d]	14	Wear and tear	15	Lifestyle	14
Wear and tear	13	Lifestyle	13	Immunity	13
Don't know	12	Immunity	12	Mental health	13
Immunity	10	Hereditary	11	Don't know	9
Accident/ injury	5	Age	6	Hereditary	8
Outside environment	4	Outside environment	6	Issues with medical care	6
Lifestyle	3	Physical health conditions	5	Outside environment	5
Physical health conditions[e]	3	Issues with medical care	4	Physical health conditions	4
Age	3	Don't know	3	Chance	3
Issues with medical care[f]	2	Hormones	3	Hormones	3
Chance	2	Chance	2	Accident/ injury	3
Hormones	2	No cause	1	Age	2
No cause	1	Accident/ injury	1		

[a]N=442. [b]N=337. [c]N=268. [d] Includes any condition affecting mental health, such as stress, anxiety, or trauma. [e] Includes any physical comorbidities, previous physical health problems and operations. [f] Includes any problems in relation to patients' medical care, for example, misdiagnosis, delay in diagnosis, or medications prescribed.

4.4 Discussion

This chapter provides the first quantitative assessment of the causal beliefs for RA held by patients with RA, and the likelihood that patients with RA would communicate RA risk information to their FDRs.

Patients were generally willing to communicate RA risk information to their FDRs. This is consistent with results from previous qualitative work in RA.(166) This study's findings also align with those of previous studies, with patients being more likely to communicate risk information to their children compared with their siblings.(273,279) Patients in those previous studies felt a greater responsibility to inform their children about their risk.(273,279) This may be because they feel responsible for passing on a hereditary predisposition.(166)

The finding that patients' likelihood of communicating RA risk was not significantly influenced by their FDRs' gender contradicts previous research examining risk communication for other chronic diseases.(162,268,269) The majority of the previous studies, however, assessed family communication about risk for breast and ovarian cancer, which may explain why a gender difference was found in those studies.

Several patient characteristics were associated with patients' likelihood of communicating RA risk information to their FDRs. These included younger age, shorter RA duration, increased dispositional openness, higher family functioning, stronger beliefs that risk knowledge would increase a person's empowerment over their health, and higher interest in their FDRs taking a predictive test.

Patients' age appeared to be an important determinant of their likelihood to communicate RA risk information. This is consistent with previous research findings

from studies assessing risk communication in breast and ovarian cancer.(267,268) Younger adults were more likely to communicate risk information to their FDRs compared to older adults as they felt that it was better for their FDRs to find out their risk earlier.(268) Younger patients may be more likely to have been treated earlier, or be more aware of the importance of early intervention as healthcare services move towards an era of personalised medicine, with a focus on early intervention.(170) For these reasons, younger patients may be more likely to communicate risk information to their FDRs compared to older patients.

The finding that dispositional openness and family functioning increased patients' likelihood of communicating risk information was also found in studies assessing CVD and cancer.(165,276,283,284) Open communication (originating from either an intrinsic characteristic of an individual or as part of a family dynamic) may thus be an important factor in whether patients are likely to communicate RA risk information to their FDRs. With this knowledge, resources can be developed to support individuals with low openness to make it easier for them to communicate more openly with their relatives regarding RA risk.

The influence of patients' beliefs that risk knowledge would increase a person's empowerment over their health on their likelihood of communicating RA risk is consistent with findings from studies in other disease areas.(271,283) These previous studies also align with the current study's findings regarding the influence of a preference for autonomy in information seeking and decision-making on their likelihood of communicating RA risk.(283) This indicates the importance of promoting autonomy when developing informational and support services for family communication of RA risk.

Previous studies exploring CVD and Huntington's disease (270,271,280) also support the current study's finding that patients who had a higher interest in their FDRs taking a predictive test were more likely to communicate RA risk information. This is likely to be because, by communicating risk information, patients can encourage their FDRs to take a predictive test to establish their risk.(270,271,280) This reasoning may be associated with patients' beliefs that such tests would provide a high degree of certainty, and be able to rule in/ out future RA development.(150,166)

Patients were less likely to communicate RA risk information to their FDRs if they believed that tests to predict the risk of RA would cause stress to a person and their FDRs. This is consistent with previous qualitative studies highlighting concerns about stress and anxiety for relatives regarding their risk status (166) and underlines the importance of incorporating appropriate information and support services to predictive and preventive strategies.

Many patients in the current study reported a common misperception regarding the cause of RA, that is, RA is caused by 'wear and tear' of the joints. This finding suggests that patients may be confusing RA with other musculoskeletal conditions associated with overuse. Such misperceptions about RA are consistent with previous research on both patients with RA, and the general public.(166,241) RA patients are usually provided with information resources about RA. Therefore, the fact that misperceptions still appear indicates that patients may not understand the information provided from these resources, or that patients may not read the resources provided. As such, information resources that are more accessible to patients are needed, to ensure that they obtain a good understanding of their condition.

4.4.1 Implications

The findings from this study increase understanding of the process and determinants of communication about RA risk in families, and should inform the development of risk information resources that are sensitive to patients' needs and concerns. Such resources should be used to support family communication and allow patients and their FDRs to have a supported and informed discussion. Further research is needed to explore patients' likelihood of communicating RA risk information to their FDRs through different channels (for example preferences for face-to-face, online or written communication).

4.4.2 Strengths and limitations

The research presented in this chapter has several methodological strengths, including a large sample size, the use of previously validated questionnaires, multidisciplinary contributors, and extensive patient partner involvement.

However, retired patients of white British origin were over-represented in the present sample and their views may not fully represent those of other groups. This study was also limited to those within the West Midlands of the UK, and questionnaires were provided in English only. Further work is needed to capture the perspectives of diverse communities regarding communication about RA risk in families. The sample for this study were also self-selected and therefore may be open to selection bias.

Finally, the surveys provided to patients contained a large number of questionnaires (more than the surveys provided to relatives), which likely took considerable time to

complete. Some of the questionnaires, such as the Brief IPQ and RAID, have also been identified as fairly complex to complete, with some items reported as being difficult to understand. (265, 295) The cognitive burden that may be generated by long and complex questionnaires can lead to response error or incompletion of survey measures.(296) This may be reflected by the low return rate identified in this study. This survey was pre-tested by patient partners and an FDR who felt that, similarly to the survey for FDRs, all items included within the patients' survey were relevant. Of course, these views may not be representative of the population. Due to the length of this survey however, PRPs suggested dividing it into two parts to allow for a break, if necessary.

As this study was the first to explore potential predictors of patients' likelihood of communicating RA risk information to their FDRs, many potential predictors were assessed. As a result, key predictors have been identified which can be utilised in subsequent studies. However, if a survey of this length were to be provided again, alongside the information suggested in the previous chapter for FDRs' surveys it is suggested that follow-up surveys/ reminders from clinical staff could be provided, as this has been found to increase response rates in a previous study.(297) Whilst providing follow-up surveys may increase the cost of the study, it has been identified that due to higher response rates the approach may more cost-effective in obtaining an equivalent number of responses compared to only providing one copy of the survey to participants.(297)

4.4.3 Conclusions

Patients were willing to communicate RA risk to their FDRs, and were more likely to communicate about risk to their children than their siblings. Factors including information seeking and decision-making preferences, dispositional openness, interest in FDRs taking a predictive test, family functioning and beliefs that risk knowledge would increase a person's empowerment over their health were associated with increased likelihood of communicating RA risk information to FDRs. Increased age and RA duration, beliefs that risk information would cause psychological harm or stress to a person and their relatives, and less strongly held beliefs that people are responsible for obtaining risk information were associated with decreased likelihood. These findings are informative for the development of risk information resources to support family communication about RA and RA risk, and facilitate access to FDRs to participate in risk reduction approaches or prediction/prevention studies.

Chapter 5: Healthcare professionals' perspectives on predictive and preventive strategies for RA

5.1 Introduction

As genomic medicine becomes more advanced, and predictive and preventive measures for RA are introduced into the healthcare system, it is likely that the operation of healthcare services will change significantly. Both specialist and non-specialist HCPs may be required to deliver predictive and preventive services to a group of patients who are at risk of RA, but who have not yet developed the disease. The needs of this new group of patients will likely differ from the patients with existing RA that they currently manage.

At present, HCPs' responsibilities focus primarily around the diagnosis and management of RA, including identification of signs and symptoms of RA, communication of treatment options and provision of pharmacological and lifestyle treatments for those with RA, and monitoring requirements for pharmacological treatments.(31) With the introduction of predictive and preventive services for RA, recommendations for HCPs may shift towards identifying those at risk and reducing this risk. As the introduction of these approaches would likely affect HCPs' roles within the healthcare service, it is important that their views around predictive and preventive approaches for RA are explored to identify any potential barriers towards integration, or support needs that need to be addressed prior to integration.

A review examining other chronic diseases such as familial hypercholesterolemia, kidney disease, diabetes, and neurogenerative disorders found that HCPs had concerns related to predictive testing. For example, they were cautious of the potential psychosocial consequences for those at risk and their families and the wider community. (253) They also felt under pressure to respond to an increased demand

for predictive services, but were conscious of the limited resources available to support this. However, they highlighted the utility of the tests that encourage positive lifestyle modification in patients. Another review examined HCPs' views towards preventive treatment for CVD, and found that they expressed a preference for lifestyle intervention over medication, rejecting the idea of medicalising healthy patients.(298) HCPs also noted that their decision around whether or not to provide preventive medication for CVD was dependent on organisational constraints, such as commissioning arrangements, guidelines, national health policies and costs of pharmaceutical treatments.

Research examining other diseases has also highlighted important differences between the perspectives of HCPs and patients. For example, a cross-sectional study found that significantly more patients compared with HCPs felt that predictive genetic testing for cancer (lung, breast and ovarian) should be included in the national screening programme (67.7% and 30.1%, respectively).(299) Patients also tended to overestimate the potential benefit of predictive testing compared to HCPs, who more often expressed concerns. A review identified differences in patients' reasons for taking a preventive treatment for CVD compared to HCPs' reasons for prescribing them.(300) For patients, their willingness to take preventive treatment was influenced by their experience of their family and friends with CVD, and beliefs regarding the risks and benefits of the treatment. HCPs' willingness to prescribe these treatments was dependent on their responsibility to address CVD risk in patients, and follow clinical guidelines.(300) The experiences of patients and HCPs in regards to prediction and prevention are varied, likely to be reflected in the context of RA, which further illustrates the importance of examining the perspectives of HCPs as an independent group.

The introduction of predictive and preventive approaches for RA would affect both primary and secondary care services, and thus it is important that HCPs from both services gain a thorough understanding of these approaches, and feel equipped to provide them to those at risk. However, the needs of those from each service may differ, depending on their roles and experience. For example, the role of GPs in the context of RA currently involves performing initial diagnostic tests and referring to secondary care for more detailed assessment.(31) HCPs in secondary care are also more involved in the initial prescribing of pharmacological therapies such as DMARDs, whereas GPs are typically more involved in ongoing monitoring and the management of co-morbidities.(31) The responsibilities specific to each role may influence HCPs' perceptions towards prediction and prevention. Therefore, it is important to explore the perceptions of those from both primary and secondary care services, to determine whether specific information and support needs should be addressed when developing and implementing these approaches.

Studies examining other chronic diseases such as breast and ovarian cancer have identified important differences in the views of different HCPs. One study highlighted that primary care practitioners (PCPs) felt they may not have enough time to discuss and provide predictive genetic tests, as there are often time restrictions associated with primary care.(301) They also felt that more evidence regarding the benefit of these tests is needed, to justify and encourage the use of these tests. Genetic counsellors (GCs) felt that predictive tests need to be more clearly defined, as they felt that other HCPs and patients may confuse prediction with diagnosis. GCs also felt that predictive tests would allow other HCPs to understand where to refer the patient to provide the most suitable care. In terms of communicating risk results, PCPs again highlighted

concerns regarding time constraints, which may prevent them from having a comprehensive conversation with patients about their risk. GCs felt that, without someone to appropriately address patients' questions about their risk, patients would experience considerable stress.

Another study found differences in the knowledge of predictive genetic testing for ovarian cancer between different HCPs.(302) GPs were found to know significantly less about predictive genetic testing compared to clinical geneticists, oncologists and gynaecologists. This study also found that, compared with oncologists and GPs, significantly fewer clinical geneticists were willing to offer genetic testing to all their adult female patients (68.9%, 50% and 18.2%, respectively). Whilst these studies provide valuable insight of the views towards prediction and prevention of other diseases from HCPs with various roles, it is important to explore these perspectives in the context of RA.

Currently, a small number of studies have been conducted exploring rheumatologists' views towards predictive and preventive approaches for RA, which have been discussed in detail in the introduction of this thesis. These studies highlighted rheumatologists' concerns regarding the cost of predictive tests, and a lack of evidence concerning the efficacy and safety of pharmacological treatments to reduce risk. Rheumatologists expressed a preference for lifestyle interventions until there is sufficient evidence of the benefit of pharmacological treatment.(155,160) Whilst these studies provide some understanding of HCPs views towards predictive and preventive approaches to RA, no study to date has examined the perspectives of other relevant HCPs, including those from primary care services. This is needed to help determine whether there are any needs that must be met when developing these approaches, so

that they can be effectively utilised by all professionals who may be involved in the management of RA.

Therefore, the aims of the present study were to explore:

(1) The perceptions of rheumatologists, specialist nurses and GPs regarding the utility of predictive and preventive approaches for RA within healthcare services, and factors that may affect their utility.

(2) Information and support needs of rheumatologists, specialist nurses and GPs for the introduction of predictive and preventive approaches into clinical practice.

5.2 Method

5.2.1 Design

This study was a qualitative interview study, with an inductive approach, using a semi-structured interview schedule. Semi-structured interviews (interviews which are guided by a schedule but allow for flexibility in the questions asked (303)) were used to ensure that key areas were covered to meet the study aims, and also to take opportunities to seek clarity or development of participant responses, which can help to provide novel insights.(303) This method of interview is also known to generate rich and detailed qualitative data.(303)

The initial draft of the interview schedule used within this study was developed by IW, a PhD student with a background in health psychology, with input from MF and KR, a psychologist and rheumatologist, respectively. MF and KR's research interests involve the examination of patient preferences towards the development of predictive and preventive strategies for RA, to inform engagement in these strategies. Several open-ended questions were developed at this stage to address the study aims, with the first half of the schedule focused on predictive testing for RA, and the second half addressing preventive treatment. The questions generated were informed by previous related studies.(150,166,253) Open-ended questions (questions that allow the participant to provide a free-form answer) were used for this study as they allow the interviewee to describe their views towards a topic in further detail than closed-ended questions, which can generate more holistic and comprehensive information surrounding the topic explored.(304-306) Due to the exploratory nature of this study, it is important that a comprehensive insight into the views of HCPs are obtained. It was

decided at this stage that a small number of vignettes (hypothetical scenarios) relating to the potential provision of predictive testing would be provided. Vignettes can be used to obtain key information on how an individual would respond to a situation, prompting the individual to reflect on the situation and their potential action, including the consequences of this action.(307) As such, seeing how HCPs respond to individuals at different stages of RA risk, and whether or not they would provide them with a predictive test, could provide insight into their views towards the utility of these tests.

Once the initial draft of the interview schedule was developed, it was sent to five research partners, who provided their input on the schedule. These research partners included an FDR of a patient with RA, a GP, a rheumatology nurse specialist and a rheumatologist. As a result of their input, the interview schedule was modified to clarify the type of preventive interventions the research team wished to discuss, including pharmaceutical treatments, lifestyle interventions, or both, and include prompts relating to the type of predictive test that HCPs may consider (for example inflammatory markers or imaging). This was felt to increase the clarity of the interview questions and promote meaningful discussions that would help meet the aims of the study.

A pilot interview was also conducted to determine the effectiveness of the interview schedule at addressing the aims of the study. This was done by carrying out a face-to-face interview with a rheumatology nurse specialist. Following feedback from this interview, the schedule was revised further. For example, interview prompts were generated to further clarify questions relating to perceived challenges and benefits associated with preventive interventions.

One-to-one interviews were conducted by IW, a female PhD student with a background in health psychology and previous experience of conducting one-to-one interviews with patients with a chronic condition. These interviews were conducted with GPs, rheumatologists and rheumatology nurse specialists within the Midlands, UK, between November 2019 and July 2021. These were done either face-to-face in a private room at the participant's workplace, or by telephone. One-to-one interviews were chosen over focus groups for pragmatic reasons, to facilitate efficient scheduling of interviews at a time that was convenient for busy healthcare professionals. IW made field notes after each interview, which included observations of salient points made by HCPs, questions where HCPs asked for further clarity or appeared confused, HCPs' confidence in answering the questions provided and their assumptions of the interviewer, if provided (for example, one HCP asked if IW was in the medical field). These notes were reviewed by IW with a reflexive approach to recognise and manage the potential for the researchers to influence the study conduct, as well as modify the interview schedule to further clarify specific questions.

Ethical approval was granted by the University of Birmingham Science, Technology, Engineering and Mathematics Ethical Review Committee (ERN_18-1781). This chapter was reported following the Consolidated Criteria for Reporting Qualitative Research (COREQ) guidelines.(308)

5.2.2 Recruitment

Eligible participants were [1] HCPs who managed patients with RA within primary or secondary care settings, and [2] proficient in English. HCPs were excluded if they [1] did not manage patients with RA within primary or secondary care settings, [2] worked predominantly with patients under 18 years of age and [3] were not proficient in English.

HCPs from various professional backgrounds were recruited to provide a comprehensive understanding of their information and support needs surrounding predictive and preventive strategies for RA, which could inform the successful implementation of these strategies at different stages of the patient journey. Those involved in providing primary care (GPs) and secondary care (rheumatologists and rheumatology nurse specialists) to RA patients were recruited as both levels of care serve distinct and important roles in the management of RA, and thus are likely to be affected by a shift towards provision of predictive and preventive strategies for this disease. In addition, once predictive and preventive strategies for RA are introduced, primary HCPs may be more likely to see asymptomatic individuals e.g. asymptomatic FDRs, compared to secondary HCPs whose roles would likely only involve the management of symptomatic individuals. Therefore, examining both groups will provide key information on the perspectives of those who will be involved in the provision of predictive and preventive strategies across various at-risk groups.

A sample size of around 10-20 interviews has been suggested as sufficient to achieve data saturation for this type of study.(309-311) Therefore, at study initiation 20 HCPs (10 GPs and 10 secondary care professionals), was deemed likely to be sufficient for the current study, though we anticipated that we could cease recruitment once saturation had been reached. For this study, information redundancy and thematic

saturation were assessed alongside recruitment. Information redundancy occurs when no new information is discovered in interviews.(312-313) Thematic saturation occurs when no new codes or themes emerge in the data.(312) These two types of saturation were assessed in this study as information redundancy can provide a good indication that enough participants have been recruited at interview stage, and thematic saturation can reinforce this at the analysis stage.(312) Assessing these types of saturation can increase the consistency and credibility of the research,(312,314,315) as well as provide confidence that further data collection would generate similar results, and confirm emerging themes.(316) In this study, information redundancy was found when IW heard the same points repeated in interviews, with no new information provided.(312) Thematic saturation was achieved when IW did not identify any new codes or themes when comparing data both within and between HCP groups (primary care and secondary care). Due to the COVID-19 pandemic response, 16 HCPs were recruited. While this did not meet the initially anticipated sample size, information redundancy and thematic saturation were reached prior to the final three interviews, with these final interviews confirming that saturation was achieved.

A convenience sample of GPs, rheumatologists and rheumatology nurse specialists was recruited to ensure efficient recruitment of these groups.(317) GPs were identified either through the NIHR CRN (West Midlands), or with support from CM (an NIHR professor of general practice) at the Midlands Partnership NHS Foundation Trust (MPFT), who identified individuals who met the inclusion criteria for the study, and contacted them via email on behalf of the research team. GPs who expressed an interest in participating were asked to respond directly to IW, who arranged interviews with them at a convenient time and place. Any GP who expressed an interest in taking

part in this study and who met the inclusion criteria was recruited.(317) Rheumatologists and rheumatology nurse specialists were identified by KR (a senior consultant in rheumatology) at Sandwell and West Birmingham (SWB) NHS Trust, and by research staff at MPFT, who contacted potential participants either face-to-face or via email. Those who were interested in taking part were asked to email IW, who arranged interviews. As with GPs, any secondary care professional who expressed an interest in taking part and who met the inclusion criteria was recruited. (317) Potential participants were provided with a participant information sheet when invited to take part, which informed them that the purpose of the study was to understand their thoughts regarding strategies to predict the development of RA and treatments to reduce the risk of developing RA. All participants were aware that the interviewer was a PhD student supervised by KR (a senior rheumatology consultant) and MF (a psychologist).

Recruitment for this study was put on hold in March 2020 and recommenced in July 2021. The decision to put this study on hold was made as it did not seem appropriate to ask HCPs to take part in this qualitative research study during the COVID-19 pandemic response.

5.2.3 Data collection

Potential participants were provided with a background questionnaire and consent form to complete prior to their interview (Appendix 6 and 7) The background questionnaire contained questions regarding participants' gender, role and length of time in practice. For face-to-face interviews, background questionnaires and consent

forms were provided in person to complete prior to interview. For telephone interviews, these questionnaires and forms were posted to the participant's place of work along with free post envelopes to be completed and returned to the research team prior to their scheduled interview. Each participant was assigned a unique identification number, which was used to identify their background questionnaires.

Interviews were guided by a semi-structured interview schedule shown in Appendix 8 Participants were first provided with some brief background information relating to current research developing predictive strategies for RA. Pre-prepared text covering this topic was included in the interview schedule. Participants were then asked general open-ended questions about their views regarding the utility of predictive testing for RA, referred to as 'any test that can provide information about whether a person is likely to develop a specific condition in the future' and the use of this approach in clinical practice. Specific questions were also asked relating to two short vignettes that were presented, which described individuals sharing some concerns about their health. The first described a patient presenting with joint pain and stiffness, but no swelling, and the second focused on a patient with a family history of RA. Following this, participants were provided with some brief background information about the type of treatments that may be used to prevent the onset of RA, described as 'any form of intervention that can lower the likelihood of developing a specific disease', and asked questions about their views regarding the utility of these treatments, and the potential introduction of these measures into clinical practice. Participants were told that all questions addressing preventive treatments related to both lifestyle and pharmaceutical treatments, and if their opinion differs for each type of intervention, to mention this and state why.

5.2.5 Analysis

The interviews were audio-recorded and transcribed verbatim using an independent transcription company (The Transcription Company). Data were analysed thematically (through identification of patterns of meaning across a dataset (318)) using the approach developed by Braun and Clarke,(318) with codes and themes identified using an inductive approach, based on the data obtained rather than any preconceived notion.(318,319) Thematic analysis is a widely-used analytic approach within health research which provides a more flexible approach to analysis than other analyses such as grounded theory or interpretive phenomenological analysis, and can be applied across a range of epistemological approaches.(318) It can also provide a rich and detailed account of the data.(318) An inductive approach is commonly used when there is limited information surrounding a topic, as it allows for findings to emerge directly from the data, without restraints imposed by structured methodologies or preconceptions.(319) Such an approach fits well with the exploratory nature of this study.

A critical realist framework was utilised to make sense of HCPs' perspectives. Sitting between both realist and constructionist schools of thought, this framework posits that an objective reality exists, but that it exists independently from human perception, and it is only these perceptions and experiences of what is observable that can be examined.(318,320,321) This framework also proposes that individual's perceptions and experiences can be influenced by their social context or structures.(318,320,321)

Using this framework to inform analysis, IW identified HCPs' perceptions towards predictive and preventive approaches for RA, including their potential utility and impact, and also examined how social structures, for example their professional role and the current operation of healthcare services, may have impacted on their perceptions towards RA prediction and prevention.(318,320,321)This analysis was facilitated by the NVivo software (version 12.0), which enabled IW to record codes identified from the raw data, and arrange them into overarching themes. NVivo is commonly used to aid in the analysis of qualitative studies, and is highly compatible with numerous qualitative study designs and data analysis methods, including thematic analysis.(322) IW read each transcript in full to familiarise herself with the data, and then coded the data line by line. Three of the transcripts were also independently coded by GS (a health psychologist). In relation to the HCP perspective, agreement occurred between the two researchers. IW used these codes and the notes she made after each interview to develop initial themes and subthemes, which were refined and developed through regular discussions with KR and MF. This was facilitated by a document collating coded data extracts from all interviews organised into overarching categories. Data analysis was conducted in parallel with data collection, to facilitate assessment of the semi-structured interview schedule and revision of the prompts used if necessary. Information redundancy and thematic saturation were assessed during data collection and analysis. Both types of saturation were reached prior to the final three interviews. The final interviews further confirmed that saturation was achieved, as no new information was found in these interviews (information redundancy) and no new codes or themes were identified during analysis (thematic saturation).(312,313)

5.3 Results

5.3.1 Participant characteristics

Sixteen interviews were conducted, including ten GPs, three rheumatologists and three rheumatology nurse specialists. Ten of the 16 participants were female, (62.5%) and had been qualified for between 10 months and 29 years, with an average of 13 years. Out of the 10 GPs interviewed, four had a specialist interest in rheumatology (40%), and an additional two had some research or clinical experience in rheumatology (20%). The characteristics of HCPs are summarised in Table 22. The durations of these interviews were between 30 and 80 minutes. One participant took part in a face-to-face interview, and 15 took part in a telephone interview.

Table 22: Participant characteristics.

Participant ID number	Gender	Role	Years since qualification	Specialist interest in rheumatology
1	Male	Rheumatologist	8	N/A
2	Female	Rheumatology clinical nurse specialist	16	N/A
3	Female	Rheumatology clinical nurse specialist	23	N/A
4	Male	Rheumatologist		N/A
5	Female	Rheumatology clinical nurse specialist	12	N/A
6	Female	GP	9	No
7	Female	Rheumatologist	20	N/A
8	Male	GP	10	Interest in MSK in general practice
9	Female	GP	9	Yes, but no formal qualifications
10	Female	GP	10	No, but has been involved in research

				into the epidemiology/ management of rheumatological conditions in primary care
11	Male	GP	7	No
12	Male	GP	29	Yes
13	Female	GP	2.8	No, but has previously been an FY2 in rheumatology.
14	Female	GP	6	No
15	Male	GP	20	Yes
16	Female	GP	14	No

5.3.2 Codes and themes

Four key themes were identified: professional roles, impact of prediction and prevention on healthcare systems, integration of prediction and prevention within healthcare systems, and comparison with other chronic diseases. The key themes and subthemes are described below using supporting quotations, which are presented in the text followed by key characteristics of the participant who provided the quote, or referred to in the text using ‘Q’ followed by the code number. The supporting quotations referred to as ‘Q’ are summarised in Tables 23-26.

5.3.3 Professional Roles

HCPs described their perceived current role within the assessment and treatment of RA, as well as the role of other HCPs. These discussions highlight where their experience and knowledge base lies in relation to this disease, and where they may need further training or education. This theme describes the following areas: knowledge of predictive and preventive approaches, responsibilities, referral, influence of guidelines, and expectations. Supporting quotations are shown in Table 23.

Table 23: Quotations Relating to Professional Roles

Code	Quotations	HCP role	Predictive testing or preventive treatment
Knowledge of predictive and preventive approaches			
Q1	I don't know what you can do in terms of preventing RA but as far as I know there's not much you can do.	GP	Preventive treatment
Q2	I know we are looking into it and blood tests can predict which type of RA you've got which driver you have you know.	Rheumatology nurse specialist	Predictive testing
Q3	You can do a combination of tests and anti-CCP antibodies obviously increases your risk of developing RA in the future and there are a variety of different HLA proteins but again, these aren't widely used in clinical practice for the prediction of RA	Rheumatologist	Predictive testing
Q4	I know there have been studies done looking at giving intramuscular steroids for patients with symptoms and I mean positive serology but not actual joint inflammation. I know there is the APPIPRA study but I don't think the results are there yet	Rheumatologist	Preventive treatment
Q5	The evidence base isn't strong. I think there is some evidence that it [methotrexate] delays the to time to onset but not that is changes the eventual outcome	Rheumatologist	Preventive treatment
Responsibilities			
Q6	The only thing I would say in primary care that I would be willing to offer is like a lifestyle intervention, you know, going through risks and being able to say that you know, stop smoking, lose weight, they should be general lifestyle changes anyway that we recommend to everyone	GP	Preventive treatment

Q7	This [lifestyle intervention] is something we do all the time, every day and would do it sort of routinely with patients so smoking cessation is something that, yeah, it's bread and butter general practice	GP	Preventive treatment
Q8	Proper counselling is often better done by specialist nurses really than doctors. Doctors can be a bit blunt about these things sometimes	GP	Predictive testing
Q9	I think nurse appointments.. I don't know for sure, but I believe are a bit longer and I hope that… they certainly seem to do in this trust and some others, they actually talk about those things [lifestyle interventions] and they talk about the importance of activity and things	Rheumatologist	Preventive treatment
Q10	With exercise, like I say, the physios should have an input. I think when we're looking at that, perhaps more patients should have a chance to see a physio and get advice from that point of view and perhaps see the occupational therapist at the same time.	Rheumatologist	Preventive treatment
Q11	It would be physios and OTs who are very good at doing the lifestyle interventions, keeping patients moving, keeping them active	Rheumatology nurse specialist	Preventive treatment
Referral			
Q12	I would just ask them to see their GPs to help with, to get the new approach to anti-CCP popular then for treatment refer them to a Rheumatologist	Rheumatology nurse specialist	Predictive testing
Q13	I would advise them [patient] that the GP would be the first point of call for assessment and they will give you tests and if any of that was positive then the GP would refer them on	Rheumatology nurse specialist	Predictive testing
Influence of guidelines			
Q14	When I worked in rheumatology as an FY2, it was a few years ago and at that point, as	GP	Predictive testing

	a GP, you weren't able to request anti-CCP antibodies in the community		
Q15	I think that's probably the only thing I can request [genetic test] other than sending somebody to rheumatology	GP	Predictive testing
Unrealistic expectations			
Q16	I have sympathy for GPs because we're expected to know everything and highly criticised when we miss stuff and we don't do stuff	GP	Predictive testing
Q17	People expect doctors to have a response to everything and you kind of develop a… maybe you are the first line of defence, but having the humility to, you know, appreciate that you don't know everything and maybe someone else is better placed	Rheumatologist	Preventive treatment
Q18	We're expected to know so much about so much and you can't know everything	GP	Preventive treatment

5.3.3.1 Knowledge of predictive and preventive approaches

HCPs displayed varying levels of knowledge regarding predictive and preventive approaches to RA, depending on their role within the healthcare service. GPs appeared to have less knowledge of these approaches compared with secondary care professionals (Q1-3).

"I'm not particularly aware of any risk prediction tools for patients who are still asymptomatic" (GP, predictive testing)

Some rheumatologists were also aware of the research being conducted in relation to prediction and prevention for RA, which was not mentioned by GPs.(Q4-5)

5.3.3.2 Responsibilities

HCPs described the nature of their role within the healthcare service, and their specific responsibilities regarding the assessment and treatment of RA, as well as the responsibilities of other HCPs. They identified potential responsibilities they could take on in the prediction and prevention of RA, as well as those for other HCPs. GPs were described to be more commonly involved in prescribing lifestyle interventions.(Q6-7) Conversely, HCPs in secondary care would be more involved in prescribing pharmacological treatments.

"If it's drugs, then I would say that currently, unless the methotrexate and rituximab come with very, very, very specific instructions, then I'd still suspect that that would need to be done in secondary care, or certainly initiated in secondary care" (GP, preventive treatment)

Rheumatology nurse specialists were described as being more suited to having discussions with patients around risk information and preventive treatment for RA, as they generally spend more time with patients than other HCPs, and have the relevant skills to discuss this information in a sensitive manner (Q8-9).

Participants also identified the use of other HCPs such as occupational therapists and physiotherapists in the facilitating preventive interventions for RA, specifically lifestyle interventions (Q10-11).

5.3.3.3 Referral

HCPs described the importance of a multidisciplinary team in the assessment and treatment of RA, as well as the prediction and prevention of RA. They recognised the limits of their knowledge and skills, and described when they should refer a patient to

a HCP who is better suited to dealing with a specific issue. A rheumatology nurse specialist stated that, in a hypothetical scenario where they saw a patient with a family history of RA, they would refer a patient to a GP to provide a predictive test for RA, and then onto a rheumatologist for treatment (Q12-13). A GP stated that that they would refer a patient on to a rheumatologist to provide a more detailed physical examination.

"I wouldn't examine their hands and feet, I'd leave that to the rheumatologist." (GP, predictive testing)

5.3.3.4 Influence of guidelines

Some HCPs highlighted that their use of specific tests and treatments for RA are influenced by the guidelines specific to their role, which dictate the type of tests and treatments they are able to prescribe. GPs stated that they were able to request genetic tests but not tests for anti-CCPs,(Q14-15) and were not able to prescribe treatments such as methotrexate or rituximab.

"Generally, as far as I'm aware, they're [methotrexate and rituximab] on the amber list, which is they need to be started in secondary care and then they can be transferred over to primary care" (GP, preventive treatment)

These tests and treatments are currently being studied in the context of RA prediction and prevention,(92,93,106,116) and thus these guidelines may influence HCPs' use of predictive and preventive measures of RA.

5.3.3.5 Unrealistic expectations

A small number of the GPs and rheumatologists in this study discussed the unrealistic expectations placed on them by patients regarding their knowledge of health conditions, and the diagnosis and treatment options for these conditions, including RA. These expectations impact on the pressure they feel at work, and their health-related decisions, such as when to refer. They stressed the importance of remembering the limits to their knowledge and ability to provide appropriate care (Q16-18).

5.3.4 Impact of predictive and preventive approaches on healthcare systems

This theme describes HCPs' perceptions regarding the potential impact of predictive tests and preventive treatments for RA on healthcare resources and clinical care. HCPs described the short and long-term impacts of the prediction and prevention for RA, including: cost, resources vs demand, monitoring and access to services. Supporting quotations are shown in Table 24.

Table 24: Quotations relating to impact of prediction and prevention on healthcare systems

Code	Quotations	HCP role	Predictive testing or preventive treatment
Cost			
Q19	Clearly we'd be using very high cost drugs, thinking about rituximab, for a much bigger proportion of the population	GP	Preventive treatment
Q20	Reduce the healthcare costs associated with treatment and reduce things like joint surgery and so on. So the cost savings could be very big.	GP	Preventive treatment
Q21	If we could predict, you could get people on treatment a little bit sooner […] which would obviously improve people's ability to carry on working, reduce sick days	Rheumatology nurse specialist	Predictive testing/preventive treatment
Q22	Obviously, by carrying on working, they're [patients] contributing to the economy and obviously paying for the NHS	Rheumatology nurse specialist	Predictive testing/preventive treatment
Resources and demand			
Q23	There's a risk that we could become overwhelmed by people worrying about rheumatic disease, there's people that are not clear about the difference between osteoarthritis and rheumatoid disease	GP	Predictive testing
Q24	If we tested everybody just because they've got a family member, you would be inundated with referrals and it wouldn't be feasible	Rheumatology nurse specialist	Predictive testing
Q25	If there was a prediction there that said if your mum had RA, you need to be tested to see if there's a chance you've got it, more than half the population that haven't got RA would be wanting that test. Could the service cope with that demand?	Rheumatology nurse specialist	Predictive testing
Q26	Actually, just keeping up-to-date with it, as a rheumatologist, it's obviously day to day but, as GPs, we can't do that. We	GP	Preventive treatment

	can't keep up-to-date with all the latest immunotherapies		
Q27	I guess a demand for surveillance in that kind of later period you've predicted and currently services aren't really set up or commissioned or have capacity to do that	GP	Predictive testing
Q28	I guess the longer-term impact would be that if RA was being prevented then the burden on the healthcare services in the longer-term would be reduced	GP	Preventive treatment
Q29	People won't get referred for the more advanced treatments as quickly and eventually, that would slow down as well	Rheumatology nurse specialist	Preventive treatment
Monitoring			
Q30	I'm slightly more reticent about the use of drugs as a preventive strategy given that they have a monitoring requirement associated with them based on the fact that they carry innate risks of their own	GP	Preventive treatment
Q31	There are costs to patients in terms of monitoring requirements and costs to the health service in terms of monitoring requirements, like chest x-rays or that sort of thing	Rheumatologist	Preventive treatment
Increased access to services			
Q32	You might have rapid access [to healthcare services] for people who are at high risk or that sort of thing. You might be able to stratify how you saw patients in the rheumatology services	Rheumatologist	Predictive testing
Q33	It might be that you prioritise people differently or offer people different services according to risk	Rheumatologist	Predictive testing
Q34	Even if it [a predictive test] was a negative rheumatoid negative CCP but was a positive CRP, that would guide me to do more urgent referral or speak to the on-call Rheumatologist	GP	Predictive testing

5.3.4.1 Cost

HCPs believed that the introduction of predictive tests and preventive treatments would generate additional costs to healthcare services in the first instance as these tests and treatments can be very expensive, and they would need to be made available to a larger proportion of the population compared to their current use (Q19).

"I think I recognise that some of the tests are very expensive and if you just did them on every person that came in with joint pain, you'd bankrupt your local CCG" (GP, predictive testing)

However, it was felt that in the long term these measures would lead to a reduction in healthcare costs, as earlier detection and treatment would lead to delayed progression, less serious prognosis or even complete prevention, which would increase the number of patients who are still able to work, and reduce costs associated with long-term treatment for RA (Q20-22).

"In healthcare benefits longer term they would be treated earlier its much less of a burden for NHS money and not relying so much on medications like biologic drugs" (Rheumatology nurse specialist, preventive treatment)

5.3.4.2 Resources and demand

HCPs stated that the introduction of predictive and preventive approaches would initially increase the demand on services, as they would need to provide care for those who are at risk of RA, as well as provide their current care for those who have a diagnosis of RA. With the current resources available, HCPs felt that they would be unable to cope with this increase in demand (Q23-25). An increase in demand of those who were asymptomatic (e.g. were at risk on the basis of a family history of RA) was felt more by HCPs than those who presented with RA-related symptoms (e.g. joint pain

and early morning stiffness) as currently, asymptomatic patients seldom access healthcare services in the context of musculoskeletal disease (Q24-25), whilst individuals commonly present to healthcare services when they develop symptoms or signs.(90)

While most HCPs felt there were a lack of resources available to deal with the increase in demand, this was highlighted as a key concern for GPs due to them having to care for patients with a variety of conditions.(Q26-27)

"At the moment we are really struggling with just the basic cardiovascular disease, diabetes, you know, taking a lot of manpower as well as, having the resources available so practice nurses, people to take bloods and follow up" (GP, preventive treatment)

However, by seeing more patients initially, HCPs felt that this would decrease the demand on services in the long term as more people would be provided with early treatment, and so would not reach a more advanced stage of RA where they may require long-term treatment (Q28-29). Approaches to preventing RA, in particular lifestyle interventions (e.g. smoking cessation), may also have other health benefits and as a result reduce demand on healthcare services, particularly primary care services.

"It would probably have a knock-on effect easing problems with diabetes, obesity and other conditions, if we solved the prevention in one area" (Rheumatology nurse specialist, preventive treatment)

"I think if you can suggest to patients that smoking cessation, improving their lifestyle, so their sort of exercise and diet, is going to reduce their risk of these chronic conditions, which, you know, probably overlaps with lots of chronic conditions, then that'd be very very helpful" (GP, preventive treatment)

5.3.4.3 Monitoring

HCPs emphasised that the introduction of preventive pharmacological interventions would lead to an increased monitoring requirement for patients, which may increase HCPs' workloads and costs to healthcare services (Q30-31), as well as presenting an additional burden for those at risk.

"But equally then they would have the additional treatment burden associated with it. Whether that be taking injections or blood tests for monitoring" (GP, preventive treatment)

5.3.4.4 Increased access to services

Some HCPs stated that predictive tests for RA could lead to more urgent and targeted referral for those at risk, and increase their access to specific healthcare services that would be the most beneficial at reducing risk (Q32-34). This can include the initiation of treatment to reduce their risk.

"If the bloods are positive, then you could actually initiate treatment from that" (Rheumatology nurse specialist)

"If the rheumatoid factor was high and you think that they're more rheumatoid factor positive, then initiate the first line DMARDs to try and get control" (Rheumatology nurse specialist)

HCPs who felt that predictive tests would lead to more referrals to secondary care (including urgent referrals) generally discussed this in relation to those who would present with RA-related symptoms. When discussing a scenario describing a person who came to them with joint pain and early morning stiffness, HCPs mentioned that they would likely still refer the person as their symptoms were indicative of potential

RA development, but that the tests would increase their urgency at which they would refer.

"I think it [a predictive test] would determine how quickly I would refer them. So obviously if they were positive and indicative of rheumatoid arthritis I'd be more likely to refer them urgently. But it sounds like they need a rheumatology referral anyway" (GP, predictive testing).

"*I would probably still refer [the symptomatic patient] onto rheumatology, just for an opinion, obviously if I get back a positive rheumatoid factor, I probably will refer more urgently then*" (GP, predictive testing).

5.3.5 Integration of prediction and prevention within healthcare systems

This theme describes HCPs' views on how prediction and prevention for RA can be integrated into healthcare systems most effectively. HCPs identified various information and support needs, and how these needs could be addressed to ensure successful implementation of predictive and preventive services. These included: funding, resource allocation, expansion of guidelines, a standardised pathway, training, performance characteristics of tests and cost-effectiveness of treatment. Supporting quotations are shown in Table 25.

Table 25: Quotations Relating to Integration of Prediction and Prevention within healthcare systems

Code	Quotations	HCP role	Predictive testing or preventive treatment
Funding			
Q35	You need to think of a setup that's going to be sustainable and that's going to be able to be funded and supported	GP	Predictive testing/preventive treatment
Q36	All for it if we have good, effective predictive things, then implement them with the proper funding	GP	Predictive testing
Resource allocation			
Q37	If you wanted to talk generally just about lifestyle interventions at length obviously you know you would probably need extra clinic space	Rheumatology nurse specialist	Preventive treatment
Q38	It [preventive interventions] would need to be integrated properly into the system, you need to pay the professionals to do it and you need to give them time to do it, you can't just add it on to everything else	GP	Preventive treatment
Expansion of guidelines			
Q39	I think predictive testing does have an important role but I think it needs to be taken up and integrated into our national guidelines like NICE etc.	GP	Predictive testing
Q40	Like I say all this stuff needs to go into teaching programmes and national guidelines and things	GP	Predictive testing/preventive treatment
Standardised pathway			

Q41	Accessibility to tests as well varies region to region, so I've come from the West Midlands, where you have access to anti-CCP but that's not always available in each region so I think in the East Midlands you get rheumatoid factor rather than CCP	GP	Predictive testing
Q42	The tools that we've got are probably adequate but I think it goes beyond that in that we probably don't have a clear pathway that is widely understood to be best practice that everybody adheres to	GP	Predictive testing
Q43	You'd have to develop very clearly a sort of pathway for bringing these patients in and explaining to them what you were doing and why you were doing it and getting their consent and doing whatever your test would be for that risk prediction	GP	Predictive testing/preventive treatment
Q44	I'd clearly want to ask about some of the other concerns and other symptoms that could go along with inflammatory arthritis.	GP	Predictive testing
Q45	I would be likely to request bloods on this [symptomatic] patient, including inflammatory markers and CCP, rheumatoid factor. I'd probably request some X-rays of their hands and refer them.	GP	Predictive testing
Q46	I'd probably proceed to do an ultrasound scan of their [symptomatic patients'] hands looking for joint inflammation. I'd like to do some blood tests to particularly check their rheumatoid factor and anti-CCP.	Rheumatologist	Predictive testing
Q47	I would talk them [the asymptomatic patient] through the symptoms they need to look out for. I'd probably try and do some education with them in terms of when you should be worried and how you can get help.	GP	Predictive testing
Q48	I would not refer. I would explain obviously I would acknowledge that	GP	Predictive testing

	the [asymptomatic] patient has a slightly higher chance of developing it [RA].		
Q49	We don't have a test at the moment, as far as I'm aware, to tell us what the likelihood is of you [the asymptomatic patient] developing any symptoms.	GP	Predictive testing
Q50	It would have to be done at a national level that you've got a standardised clinical risk tool that you could use and implement in the computer system so you need to identify the patients early	GP	Predictive testing
Q51	Something pops up and says 'ask them these questions'. You might not remember as a GP, to say, 'have you had knee pain? Have you had a dry mouth? Are you tired all the time? I don't know. You tick the boxes and then it gives you a risk score. It has to be driven by technology I think	GP	Predictive testing
Training			
Q52	I think there are some training needs there but also GPs are going to just say 'is this going to be part of our role or do we just transfer to specialty?' I think that would have to be worked out. There has to be a pathway.	GP	Predictive testing/preventive treatment
Performance characteristics of the test			
Q53	If we had a test that was able to do it [predict RA development] with sufficient accuracy, that would be useful	Rheumatologist	Predictive testing
Q54	I think the predictive tests, to be useful and beneficial, have to be	Rheumatologist	Predictive testing

	sufficiently strong in their conclusions		
Q55	I think any tool would need to be very sensitive and very specific	GP	Predictive testing
Q56	If you were going to give somebody a biologic, you'd want your test to be 80% plus accurate at predicting rheumatoid arthritis	Rheumatologist	Predictive testing
Q57	In terms of giving immunosuppressive treatments, like a biologic, I think you want something that's 100% accurate	Rheumatologist	Predictive testing
Q58	If you could reassure somebody with a good level of accuracy that they weren't going to develop RA, that would be useful at a rheumatology service level	Rheumatologist	Predictive testing
Q59	I think an ultrasound scan would be useful in that scenario [patient presenting with joint pain but no swelling] for helping you to find things that might predict the development or to reassure yourself that no the patient doesn't need treatment at that point	Rheumatologist	Predictive testing

Cost-effectiveness

Q60	Well again that [prescribing preventive interventions] would depend partly on economic costs if you're thinking about the NICE threshold for economic effectiveness	GP	Preventive treatment
Q61	I guess this is one of those things where you'd want to see an economic analysis. Does starting preventive treatment actually save money in the long run?	GP	Preventive treatment
Q62	I'd be very careful in making any kind of risk benefit assessment and then GP economic assessment	GP	Preventive treatment

	before you decided to prescribe treatments to patients who don't have RA but might develop RA		
Q63	If it's [pharmacological treatment] going to reduce the risk by 40% to 50% and not going to cause too many problems, then I would say even if they only had a 20% risk or a 10% risk, then it's still worthwhile going on it	GP	Preventive treatment

5.3.5.1 Funding

HCPs emphasised that there is currently not enough funding provided to healthcare services for predictive and preventive approaches to be effectively integrated. To ensure successful integration, additional funding would need to be provided to these services, (Q35-36) or the funding would need to be relocated from other areas within the healthcare service, such as treatment for established RA.

"I mean if you can repurpose some of the funding that's currently spent on treatment of rheumatoid and have people to support ongoing change in people of high risk, then that's absolutely fine" (GP, preventive treatment)

However, one HCP mentioned that obtaining this funding may be challenging, as commissioners may be less likely to provide funding for services aimed at people who have not yet developed the disease, and potentially may not end up developing the disease.

"The funding aspect, so getting CCG to pay for drugs for the practice on diseases that they've not yet got might be a challenge" (Rheumatology nurse specialist, preventive treatment)

5.3.5.2 Resource allocation

The limited number and availability of resources across healthcare services was thought to affect the quality of care HCPs could provide to those at risk. To overcome this, HCPs recommended allocating additional resources towards healthcare services such as extra clinic space, an increased number of staff and additional time to effectively discuss and review the impact of these approaches (Q37-38).

"I'm not sure that it would be appropriate for healthcare services to keep on reviewing them [patients] and reminding them and talking through behaviour change programmes. At least not without dedicated additional resources for that" (GP, preventive treatment)

5.3.5.3 Expansion of guidelines

HCPs described working according to the current healthcare guidelines, which primarily focus on assessing and treating patients with RA. They suggest that, to effectively integrate predictive and preventive approaches into the healthcare system, national guidelines would need to be extended to include these approaches (Q39-40). By doing this, it is more likely that HCPs will provide these services.

"They then need to be integrated into recognised guidelines if you want them to be taken up by practitioners I think" (GP, predictive testing)

5.3.5.4 Standardised pathway

One HCP, who had worked in practices in both the West and East Midlands, discussed the differences in accessibility to certain tests across each region, and how this limited what they could prescribe (Q41). Because of this, they suggested that predictive tools should be standardised nationally so that all HCPs have access to, and therefore can provide, the same tests.

"The variability in what you have access to varies and I think that is something that would need to be addressed as a national issue, if you're going to put something in place, prediction, you have to be able to offer the tools to General Practitioners for that" (GP, predictive testing)

Other HCPs suggested that there needs to be a standardised pathway for how predictive tests and preventive treatments are provided, which includes a set of criteria regarding the requesting of predictive tests and the initiation of preventive treatments for RA that is widely understood by HCPs (Q42-43).

This pathway should provide guidance on the requesting of predictive tests and preventive treatments for those who are both symptomatic and asymptomatic, as HCPs described providing different types of care for these groups (from the scenarios provided to them), based on their current experience. For those who were symptomatic (e.g. who presented with joint pain and early morning stiffness), HCPs stated that they would provide further examination and tests (Q44-46), reflecting the care pathway currently in place for the diagnosis of RA.(31) For those who were asymptomatic (e.g. had a family history only) HCPs described providing information only, and were unsure of what else they could provide to them at that stage (Q47-49). The type of care HCPs described providing to those who were either symptomatic or asymptomatic in the

scenarios provided was similar across both primary and secondary care HCPs. Therefore, a pathway that provides information on the use of prediction and prevention strategies in those who are both asymptomatic and symptomatic is needed.

To aid in developing a standardised pathway, HCPs felt that this pathway would need significant technological underpinning. This would enable HCPs to ask the appropriate questions, perform suitable tests, and enter the information into an online system that would generate a risk score to communicate with patients (Q50-51).

5.3.5.5 Training

Some HCPs identified training needs to be met in order for them to deliver predictive and preventive approaches for RA most effectively. One such need, identified by a rheumatology nurse specialist, was the communication of RA risk information. For example, training in counselling to help patients deal with potentially distressing information.

"I think general nurses might need a little bit more input you know, with those communication skills, the ability to handle this kind of information [risk information]" (Rheumatology nurse specialist, predictive testing)

"I think it's just down to having those skills to manage that situation, knowing it might upset the patient and the patient being in denial […] so maybe a bit more training how to do that" (Rheumatology nurse specialist, predictive testing)

One GP stated that any training that would be provided to GPs should be clarified within a care pathway as being part of their role, as this may affect whether or not GPs would take part in this training (Q52).

5.3.5.6 Performance characteristics of the test

HCPs stated that, in order for predictive tests to be effectively integrated into healthcare services, and for preventive pharmacological treatments to be provided, they need to have a good positive predictive value (Q53-57). Some have suggested that tests would need to have a very high positive predictive value to be used (Q56-57). While false positive results are seen as a potential issue for the prescription of pharmaceutical treatments, HCPs describe them as being less of an issue for lifestyle interventions.

"If it's lifestyle intervention or stopping smoking, I couldn't give you an accuracy cut off level but you want something that is pretty accurate" (Rheumatologist, predictive testing)

"In terms of lifestyle modifications […] I think you'd accept a much lower level because they're generally good things to do anyway" (Rheumatologist, predictive testing)

HCPs also described wanting tests that would have a good negative predictive value. This would allow patients who take a predictive test and get a 'negative' result to feel reassured that they will not go on to develop RA in the future, and will inform HCPs that no further action needs to be taken at that time (Q58-59).

5.3.5.7 Cost-effectiveness

For preventive pharmaceutical treatments to be successfully integrated into healthcare services, HCPs felt that there needed to be sufficient evidence showcasing the benefit of these treatments, and that the benefit outweighs any potential risks. Risks include side effects from the treatment, or the cost of providing such treatments. Benefits include the reduction of risk, or long-term savings for healthcare services (Q60-63).

"You need to know quite a lot of detail about what the test is going to be able to do and how beneficial their treatment was in terms of cost benefit in reducing the need for services" (GP, preventive treatment)

Lifestyle interventions were described as having much less risk compared to pharmaceutical treatments, and so would not need the same kind of evidence showcasing its cost-effectiveness.

"Smoking cessation, lifestyle stuff, I don't think it matters but I think, you know, if you're going to be exposing patients to methotrexate they've got to have, you know, a high impact on the prevention of rheumatoid arthritis" (GP, preventive intervention)

I have no issue with preventive interventions in terms of lifestyle interventions, like smoking cessation, because I think it's easy to implement and it has a low risk of causing harm" (Rheumatologist, preventive intervention)

5.3.6 Comparison with other chronic diseases

This theme describes how HCPs compared their experience and knowledge of other diseases where methods of prediction and prevention are more established (such as DM, CVD and cancer) with predictive and preventive approaches for RA to inform their responses about how these approaches could be successfully implemented. Areas of comparison included: guidelines, knowledge of the disease, risk communication, and preventive treatment. Supporting quotations are shown in Table 26.

Table 26: Quotations Relating to Comparison with Other Chronic Diseases

Code	Quotations	HCP role	Predictive testing or preventive treatment
Guidelines			
Q64	How are they [healthcare professionals] going to identify it [RA risk] so is it a clinical scoring tool, in cardiovascular, you use QRISK, is there a clinical scoring risk tool for that	GP	Predictive testing
Q65	Like for example the QRISK, I'm sure you know what that is, that is in all our guidelines and it's very well integrated and we get paid for it with QOF essentially	GP	Predictive testing
Knowledge of the disease			
Q66	I think, generally speaking, patients know about the risk of developing diabetes, heart disease, and things like that and can buy into preventive actions for that. I think RA is poorly understood at a population level and so I think patients would struggle to appreciate where RA fits in	Rheumatologist	Predictive testing
Q67	In that illness [biliary cirrhosis], they [HCPs] can almost predict the day you'll need a liver transplant. That's helpful in that you can arrange donors and things like that in order to make sure that when you need it, it's there for you. I don't think RA is necessarily the same	GP	Predictive testing
Q68	The problem with rheumatoid arthritis is it's just very rare. That's why it's easier	GP	Predictive testing

	to do it [provide predictive services] in things like cardiac disease because there is so much of it. You can look at those patterns and you can do that statistical analysis. That's the challenge with rheumatoid arthritis		

Risk communication

Q69	So take a population of people similar to the person in front of me and estimate it over a period of time, cardiovascular disease for example ten years and show how many of that group would then turn out to have the condition and then if there was an intervention how many of those people would be helped. So cardiovascular disease, 10% risk over ten years you'd have 100 people, 10 would look glum at the end of a 10 year period	GP	Predictive testing
Q70	When we're talking about the risk of stroke with the NOACs and stuff like that, we're talking about a 4% or 5% risk. When you see the smiley faces and the sad faces, you might be getting four sad faces of getting a stroke. You're given the medication and now two people are having the stroke. On 100 faces, it doesn't look like an awful lot but you could say, 'This is a 50% reduction of your risk,' or something like that	GP	Predictive testing

Treatment

Q71	With something like a cardiac event, if you've got a 10% cardiac risk, over a ten year period this is, then we should be giving people statins which they have to take on a daily basis but actually, most people don't even notice it. Actually, the biggest faff about it is taking it on a daily basis and remembering because there are no consequences to that. It's that kind of	GP	Preventive treatment

	balance and it really depends on the toxicity of the treatment to prevent RA		
Q72	Hopefully it [lifestyle interventions for RA] would be something like pre-diabetes where you've identified that risk, you go on a diabetes prevention course and that's enough for the patients to change their behaviour so that they don't become diabetic, that's what I'd say from a prevention course	GP	Preventive treatment
Q73	If I'm comparing it with diabetes, it's until their risk reduces	GP	Preventive treatment

5.3.6.1 Guidelines

HCPs discussed the current guidelines in place for the prediction and prevention of diseases such as CVD and DM, and their experience of working according to these guidelines. This experience is used as an example to make suggestions about how guidelines for the prediction and prevention of RA should be developed. One HCP believed that the guidelines for the prediction of RA development should not follow the same approach as the guidelines for CVD, as these guidelines 'pathologise' the natural ageing process.

"My feeling is it's like statins; the requirement of the guidance was about the risk of a heart attack being cut from 20% to 10% over ten years and it effectively meant that, you know, every single male over 60, regardless of how healthy they were, should be on a statin. At which point, I don't think it's individualised or personalised medicine, I think it's just pathologising old age" (GP, preventive treatment)

Other HCPs identified the widespread use of the QRISK score for classifying those at risk of developing CVD as an example of how healthcare guidelines could be developed for the prediction of RA (Q64-65).

5.3.6.2 Knowledge of the disease

Participants believed that both patients and HCPs were less knowledgeable of RA compared with other diseases such as DM and CVD, and highlighted the impact that this lack of knowledge may have on clinical care and uptake of preventive treatments (Q66-67).

One HCP mentioned that the reason for the lack of knowledge about RA compared to other chronic diseases such as CVD and DM is that RA is much less common, and thus has not been researched as extensively (Q68).

"We've been able to research that [CVD] quite robustly with the tools we've got because it's such a common disease. Whereas, with rheumatoid arthritis, it's quite rare actually, isn't it?" (GP, predictive testing)

Another HCP used their knowledge of the current research surrounding predictive approaches for DM to make suggestions about how RA could be predicted.

"I guess if you compare it to the diabetes literature where you identify people before they've got diabetes and they've determined pre-diabetes and we're starting to treat people now with pre-diabetes. So I guess if the science is similar, maybe you get to a stage where you have pre-RA" (GP, predictive testing)

5.3.6.3 Risk communication

When discussing communication of risk information and opportunities for risk reduction strategies for RA, HCPs highlighted their experiences of communicating risk for other

chronic diseases like CVD, and used these experiences as a guide for how risk information and risk reduction strategies could be communicated with those at risk of RA most effectively. From this, HCPs generally suggested using pictographs to indicate patients' risk and risk reduction when using a preventive strategy (Q69-70)

Using their experience in CVD prevention, one HCP suggested communicating RA risk to patients when trying to motivate them to engage in lifestyle interventions such as exercise and smoking cessation.

"We do this in vascular disease prevention all the time [use CVD risk as a motivator for behaviour change] and its variably effective, and often people need to start doing something or they need a jolt or something like that, something to go wrong for them to get warning shots, that they're actually going to change" (GP, preventive treatment)

5.3.6.4 Treatment

HCPs described their experiences of prescribing preventive interventions for other chronic diseases such as CVD and DM, and used these to make suggestions about the sort of interventions that would be most effective for those at risk of developing RA (Q71-72). One HCP suggested providing a prevention course for those at risk, similar to one provided in those with pre-DM, to motivate patients to change their behaviour (Q72).

Another HCP, who discussed the length of time a treatment should be recommended for, suggested following the current guidelines for preventive treatments in pre-DM (Q73).

"So with pre-diabetes it would be their HBA1C, so one of their diabetes markers reducing back down to normal. So I guess if there was a cut-off for the blood test results, whenever that goes back to the normal range" (GP, preventive treatment)

Finally, one HCP used their knowledge of studies currently being conducted within DM to suggest monitoring patients identified as being at risk by using regular blood tests, in order to manage their risk rather than expose them to treatment.

"I'm aware of a study being done in type 1 diabetes where they look for a genetic marker and if that genetic marker is present then they do a blood test every year to see if antibodies start to be developed. So they're doing sort of blood testing as opposed to exposing patients to treatment so I see that as being perhaps a better and less burdensome way of managing potential risk" (GP, preventive treatment)

5.4 Discussion

5.4.1 Summary of findings

This qualitative study explored HCPs' perceptions towards predictive and preventive approaches to RA, identifying four key themes: professional roles, impact of prediction and prevention on the healthcare system, integration of prediction and prevention within the healthcare system, and comparison with other chronic diseases. HCPs identified important needs that should be addressed to enable successful implementation of predictive and preventive approaches. These include the need to establish the cost-effectiveness of predictive and preventive approaches, appropriate resource allocation, and the development of easy-to-use clinical prediction tools and associated guidelines. This is the first study to examine the perspectives of prediction and prevention of RA from HCPs working in both primary and secondary care services.

HCPs' understanding of their responsibilities regarding the diagnosis and management of RA, for both themselves and other HCPs, closely reflect their knowledge and use of what is stated in the current NICE guidelines,(31) particularly in regards to HCPs in secondary care, where pharmaceutical therapies for RA are usually initiated. HCPs in this study also mentioned the influence these guidelines have on healthcare decisions, which align with previous findings examining CVD.(300) This highlights the importance of developing appropriate guidelines to accompany implementation of preventive strategies within the healthcare system.

The finding that GPs' knowledge regarding the prediction and prevention of RA was lower than secondary care professionals' knowledge was consistent with previous research.(301) Because of this, the previous study suggested that a clear definition of

predictive testing is needed for GPs.(301) This highlights the need for GPs to receive appropriate training regarding predictive and preventive approaches for RA, before they are introduced into the healthcare system.

The potential impact of prediction and prevention for RA on the demand for services, and the lack of current resources highlighted by GPs was also found in previous studies examining other disease areas, where GPs felt unable to provide sufficient care, due to demand 'outstripping supply'.(253,301,323) As this issue extends across GPs in multiple studies, it illustrates the importance of allocating appropriate resources to this group to support them in providing care for those at risk of RA. The current finding that the increase in demand is more likely to be associated with an increase in asymptomatic individuals compared to symptomatic patients further indicates the need for additional resources for GPs, as asymptomatic patients are more likely to present to this group.

The potential for predictive and preventive approaches for RA to increase healthcare costs aligns with previous research within both CVD and RA.(298,155) However, participants in this study also mentioned the potential savings that predictive and preventive services could provide through reduced long-term treatment of established disease that may balance out any short-term increase in cost, and the need to establish the cost-efficiency of preventive approaches.

The need to establish the cost-effectiveness of predictive and preventive approaches for RA found in the current study was consistent with previous research.(155,160) Therefore, further research in this area is needed to enable HCPs to assess the

benefits of these approaches alongside potential risks, including side effects, costs or psychosocial impacts.

HCPs in the current study also identified the need for standardised, technology-based, easy-to-use prediction tools that can be applied to those who present both with and without symptoms. The use of such a tool has been identified by these HCPs to be utilised effectively for other chronic diseases such as CVD. For example the QRISK calculator has been found to identify approximately 2.8 million people at high risk of CVD in England, facilitating preventive intervention and a reduction in CVD-related deaths and events by approximately 9000 per annum.(324) Therefore, development of prediction tools for RA that can be easily implemented into clinical practice to support identification of at-risk individuals will be an important element of preventive strategies. Prospective observational studies are underway to predict the development of RA in those at various stages of RA development, including those who have RA-related symptoms and those with a family history.(92-94,101) Due to the current research efforts across those who are symptomatic and asymptomatic, it is important that when these easy-to-use prediction tools are developed for use within healthcare services, they can be provided to both groups. This will also be important as, in the context of musculoskeletal disease HCPs generally see those who have developed symptoms and thus are more knowledgeable about what could be provided to this specific group compared to those who are asymptomatic, as evidenced by HCPs in this study. Therefore, tools that can be applied to those who are asymptomatic and symptomatic will ensure that appropriate measures are in place for those at various at-risk stages.

The need for these tools to have a strong predictive value was also stressed by HCPs in the current study, as well as by rheumatologists in a previous study.(155) Due to the

potential risks associated with predictive test results, such as the inappropriate prescription of potentially harmful treatment, insurance and anxiety-related issues,(155) or even delayed treatment for those who were told they would not develop RA, HCPs want to be confident that the results they provide are accurate. Therefore, it is important to ensure that these strategies are as accurate as possible before introducing them into clinical practice.

The themes and subthemes identified within the current study map onto the domains within the Theoretical Domains Framework (TDF).(325) This framework identifies 12 domains describing factors that may influence behaviour change relevant to the successful implementation of a healthcare intervention.(325,326) The TDF domains, which the themes and subthemes of the current study map onto, are: [1] knowledge; [2] skills; [3] professional role and identity; [4] beliefs about capabilities; [5] beliefs about consequences; [6] motivations and goals; [7] memory, attention and decision processes; [8] environmental context and resources; [9] social influences [10] emotion; [11] behavioural regulation; and [12] nature of behaviours.(21) The findings of the current study may therefore be informative for the design of future implementation studies of predictive and preventive initiatives for RA.

5.4.2 Strengths and limitations

To my knowledge, this is the first qualitative study to explore perceptions of predictive and preventive approaches for RA from HCPs working in both primary and secondary care settings. As such, this study provides novel insights into the information and support needs of all those who are likely to be involved in the provision of predictive and preventive approaches for RA, further informing the development and successful

implementation of these approaches across services. The use of interviews within this study, as well as an inductive thematic analytical approach provided the opportunity for new concepts to be explored in depth, generating rich and informative data.(318,319) This study also includes extensive research partner involvement and a pilot interview in the design of the interview schedule, which allowed for the generation of more relevant questions, leading to more relevant data that can be applied more readily to practice.(327) The findings of this study also reflect a wide range of professional experience, as those interviewed ranged from being in the first year of the role, to being in their position for almost 30 years. In addition, the fact that data saturation (assessed using two different types of saturation: information redundancy and thematic saturation) was achieved illustrates the consistency and credibility of the data.(312,314,315)

However, aside from one HCP, interviews were conducted on HCPs working in the West Midlands, UK. This may not be representative of HCPs working in other regions. Additionally, whilst the use of a convenience sample is often an efficient approach, it could have led to potential bias in the types of participants recruited,(328) as the majority of GPs recruited in this study had a specialist interest in rheumatology. Those who did not have a specialist interest in rheumatology may have different information and support needs. Additionally, the recruitment of some GPs via a senior colleague (CM) may also cause potential bias within this sample, as they may have felt more obliged to take part to please this colleague. As such, their views and motivations may not reflect all HCPs likely to be involved in the prediction and prevention of RA.

The predominant use of telephone interviews within this study may have impacted on the data received, as non-verbal cues cannot be detected through this method. In

addition, a stronger rapport between the interviewer and participant is generally provided through face-to-face contact, which may influence the data that participants are willing to provide.(329) However, telephone interviews have been judged to provide rich, detailed and high quality data, and some participants have been reported to feel more relaxed and less judged than when they were interviewed face-to-face.(329,330)

5.4.3 Recommendations for future research

To provide insight into the information and support needs of GPs without a specialist interest in rheumatology, future studies should examine the perceptions of this group. As this group may be less likely to engage in research with a musculoskeletal focus compared to those who do have a specialist interest, a potential financial incentive may need to be provided.

Future qualitative studies may also benefit from the use of an online communication platform to perform interviews, such as Zoom or Microsoft Teams. This provides the option for participants to communicate either face-to-face or via audio only. Interviews conducted on these platforms have been cited as useful in forming rapport, and have been described as convenient, non-intrusive and comfortable for the interviewee.(331,332) The use of online communication platforms also removes the physical security arrangements surrounding the use of Dictaphones.

The information and support needs identified by HCPs in this study could be used to inform the development of services so that HCPs are prepared to provide predictive and preventive approaches, as well as the development of these approaches so that they are appropriate for use within healthcare services. However, an implementation

study is needed to examine the feasibility of introducing predictive and preventive strategies that are developed to address the needs identified in this study. In line with the current findings, the intervention should provide further education for GPs surrounding predictive and preventive approaches for RA, training in counselling skills for rheumatology nurse specialists, a standardised prediction tool (similar to the QRISK tool for CVD), and the development of appropriate guidelines that include recommendations on the provision of predictive and preventive approaches for RA. This intervention can then be piloted within current healthcare services, and feasibility indicators can be assessed. These include (1) economic evaluations such as the cost of implementing the intervention within the current healthcare service and potential cost savings associated with such an approach, (2) resources needed to effectively implement the intervention, (3) acceptability of implementing predictive approaches, and (4) potential barriers to the intervention. Outcomes of the intervention can also be assessed, including satisfaction with the service, knowledge of prediction/prevention for GPs, confidence in discussing RA risk with patients for rheumatology nurse specialists and risk assessment for patients to determine whether this service helped in reducing their risk of RA.

5.4.4 Conclusion

For successful implementation of predictive and preventive approaches for RA, HCPs identified specific information and support needs, including evidence of cost-efficiency, appropriate resource allocation, official guidelines, and the development of easily implemented clinical prediction tools. Some of the needs identified by HCPs, including

the need to provide further education to GPs, counselling training for rheumatology nurse specialists and a standardised prediction tool could be used to inform the development of a predictive and preventive intervention for RA to be used within healthcare services. The feasibility of this intervention could then be assessed, where the feasibility indicators used are informed by this study's findings. For example, examination of the cost effectiveness of providing the intervention, and the resources needed to implement the intervention. This could inform the implementation of predictive and preventive approaches for RA across healthcare services nationally. Additional qualitative research is also required to further inform implementation studies. This research should examine GPs who do not have a specialist interest in rheumatology, to identify any additional insights that could further inform implementation. This could be done using an online communication platform.

Chapter 6: General Discussion

6.1 Overview

This thesis increases understanding about the views of stakeholders who are likely to be affected by the introduction of predictive and preventive approaches for RA, including patients with RA, their FDRs and HCPs. It includes the first quantitative assessments of interest in predictive testing among FDRs of RA patients, as well as the likelihood that patients with RA would communicate RA risk information to their relatives. This thesis also provides the first detailed exploration of the views of HCPs from both primary and secondary care services towards predictive and preventive approaches for RA. As a result of the research undertaken for this thesis, several novel findings have been identified that are informative for the development of predictive and preventive approaches for RA.

This thesis identified that FDRs expressed a high level of interest in predictive testing for RA, with several factors, including perceived risk of developing RA, predicting increased interest. This is consistent with findings from studies examining the influence of perceived risk in other disease areas, including several types of cancers.(229,237,238)

This thesis also found that patients with RA reported willingness to communicate RA risk information to their relatives. Higher family functioning was identified as an important factor influencing risk communication among this group, which aligns with previous studies examining CVD and Huntington's disease.(271,286,288)

The idea that risk knowledge could cause psychological harm for FDRs and other family members negatively impacted FDRs' interest in taking a predictive test, and RA patients' likelihood of communicating risk information to their relatives. This supports

previous qualitative findings examining these groups.(150,166) FDRs and RA patients also agreed with the common misperception that RA is caused by wear and tear of the joints. This is consistent with previous qualitative research on patients with RA and members of the public, (166,241) and highlights key opportunities for educational interventions.

HCPs within this thesis identified important needs to be addressed to ensure successful integration of predictive and preventive approaches for RA into clinical practice, which have not been identified in other studies within this context.(155,157,160) Primarily, the need to develop a standardised, easy-to-use prediction tool, as well as the need to allocate appropriate resources, particularly for those working in primary care, were identified. A standardised prediction tool has been identified as successful in CVD.(324)

This final chapter will discuss how well the overarching aim of the thesis, as well as the aims identified for specific chapters, were addressed. The salient findings identified across chapters will be discussed in the context of the strengths and limitations of this thesis, and recommendations for future research and practice will be developed.

6.2 Aims of the thesis

The overarching aim of this thesis was to explore stakeholders' perspectives towards predictive and preventive approaches for RA. To achieve this aim, a mixed methods approach was used to examine the perspectives of those likely to be directly affected by predictive and preventive strategies for RA, including patients with RA, their FDRs,

and HCPs. While there is some debate around the definition of mixed and multi methods research, multi methods research generally refers to the collection of data through multiple research methods (including the use of two or more exclusively qualitative approaches, or two or more exclusively quantitative approaches in a single programme of enquiry).(333) Mixed methods research is a specific form of multi methods research that refers specifically to the combination of quantitative and qualitative research methods within a research project.(333,334) The different methods involved in mixed methods research may address specific, distinct research questions but contribute to the same overarching research goal, as is the case with the current thesis.(334) Therefore, the use of a mixed methods approach was appropriate to address the overall aims of this thesis. The use of a mixed methods approach within research is rapidly expanding, and is both well accepted and commonly used in health sciences.(334,335) This approach combines the strengths of each methodology, including the rich insight provided by qualitative research, alongside the more generalisable data generated through quantitative research, which usually captures data from a larger number of participants.(334,335) As a result, studies using this approach can lead to a more comprehensive understanding of the research topic and yield more complete evidence surrounding the topic.(333-335) The use of a mixed methods approach within this thesis has generated a thorough understanding of the perceptions of those likely to be affected by the introduction and provision of predictive and preventive approaches for RA. Several needs and concerns across the various stakeholders examined within this thesis have been identified (discussed in further detail later on in this chapter), which can be used to develop effective prediction and prevention strategies that are sensitive to these concerns. Therefore, the overarching

aim of this thesis has been successfully addressed. The findings from this thesis can also be used to inform the development of information resources to support decision-making regarding both the use and provision of these strategies.

To help address the overarching aim of this thesis, specific aims were generated for each chapter, which are discussed below.

Chapter two aimed to examine [1] the willingness of those with a family history of IHD to accept a predictive test for this disease, and [2] the effect of these tests on intentions to change risk-related behaviours, or actual behaviour change, to inform further RA-related research. To achieve these aims, a mixed methods systematic review of the literature was conducted, identifying seven studies (five quantitative and two qualitative) which examined these aims. From these studies, several factors were identified that influenced an individual's willingness to take a predictive test, with the most important being family history. In addition, higher perceived risk (through family history or personal genetic risk from a positive predictive test result) and a preference for engaging in a certain type of behaviour were found to influence an individual's motivation to engage in preventive behaviours or actual behaviour change. The information obtained from this review shed light on individuals' willingness to take a predictive test, and the effect of these tests on intentions to engage in health behaviours and actual behaviour change, thereby successfully addressing the aims of the chapter. In addition, the factors identified within the current review highlight opportunities for further research within RA. Providing a mixed methods review of the literature allowed for the identification of a wider range of studies and generated a deeper understanding regarding willingness to take a predictive test and its effect on preventive behaviours. Additionally, examining a disease with multifactorial aetiology,

where predictive and preventive approaches are part of routine clinical care was advantageous in informing RA-related research, where prediction and prevention for those at risk due to a family history may be useful. However, further insight into these aims could have been obtained if more studies were available examining the perspectives of those with a family history. Nevertheless, this review indicates the importance of examining the perspectives of those with a family history regarding prediction and prevention for chronic diseases, including RA.

The aims for the third chapter were to identify [1] predictors of FDRs' interest in predictive testing, [2] RA patients' disease and demographic characteristics that predicted their FDRs' interest in testing and [3] FDRs' beliefs about the causes of RA. To achieve these aims, cross-sectional surveys were provided to FDRs and their patient probands, assessing several potential predictors (based on the factors identified as predictive of interest in other disease contexts) and FDRs' interest in predictive testing. Cross-sectional surveys are useful at examining the attitudes of a chosen population towards a specific topic area and are commonly used to examine associations between specific factors and the outcome of interest (in this case, predictive testing for RA).(336) Therefore, the use of cross-sectional surveys were appropriate to address the aims of chapter 3. The surveys used enabled the collection of data for a large number of potential predictors, as well as data on beliefs around the causes of RA from a large sample of FDRs. The surveys also incorporated a robust method to link FDR and patient responses (using a unique survey code), to identify whether patient characteristics influence FDRs' interest in testing. However, the use of surveys can result in low response rates.(336) Nevertheless, the target sample size was achieved. This chapter identified several predictors of FDRs' interest in predictive

testing, as well as a number of perceived causes for RA (discussed in further detail later on in this chapter). Whilst chapter 3 examined patients' demographic and disease characteristics on FDRs' interest in predictive testing, no evidence was found suggesting that these characteristics were associated with their FDRs' interest in predictive testing. Nevertheless, this chapter successfully assessed potential predictors of FDRs' interest in predictive testing, as well as their beliefs about the causes of RA and thus successfully addressed the aims of the chapter. This chapter also identified a range of factors to be addressed through informational resources for those considering predictive testing to support shared decision making. However, relying on RA patients to recruit FDRs to this study may have led to selection bias, as patients might have selected those who they felt would be most interested in RA prediction. Therefore, the views obtained may not reflect those who are not as interested in taking a predictive test. Nevertheless, FDRs are a hard to recruit group (264) and this method of data collection ensured that those recruited were FDRs of patients with a confirmed diagnosis of RA.

The fourth chapter aimed to identify [1] predictors of the likelihood that RA patients would communicate with their FDRs about their risk of developing RA, [2] perceived barriers towards family communication about RA risk, and [3] patients' beliefs about the causes of RA. Cross-sectional surveys provided to patients with RA were used to address these aims, assessing several potential predictors (identified as factors influencing risk communication within other disease contexts) and their likelihood of communicating RA risk information to their FDRs. As this study aimed to examine the association between potential predictors and patients' likelihood of communicating RA risk information, a cross-sectional survey was identified as a suitable methodological

approach that could provide this information and extend existing qualitative investigations.(166,336) As well as obtaining data on the potential predictors and beliefs about the causes of RA, these surveys also provided the opportunity to collect data on the reasons patients may be unlikely to communicate RA risk information to their FDRs across a large sample. This chapter identified several demographic and psychosocial factors that influence patients' likelihood of communicating RA risk information to their FDRs, as well as their perceived causes of RA (discussed in further detail later in the chapter). Reasons that RA patients were unlikely to communicate RA risk information to their relatives were also identified, including the fact that their relatives feel healthy at present, and that they wanted to protect their relatives from anxiety-provoking information. Therefore, these findings successfully addressed the aims of the chapter and can be used to inform the development of risk information resources that are sensitive to patients' concerns, which can support family risk communication. However, due to the self-selected sample obtained for this study these findings may be more applicable to RA patients who are more interested in communicating RA risk information to their family. Therefore, the views of those who are less interested in family communication of RA risk may be under-represented in this thesis.

The fifth chapter aimed to explore [1] the perceptions of rheumatologists, specialist nurses and GPs regarding the utility of predictive and preventive approaches for RA within healthcare services and factors that may affect their utility, as well as [2] the perceived information and support needs of these HCPs to support the introduction of predictive and preventive approaches into clinical practice. Due to the exploratory nature of these aims and the absence of existing evidence, one-to-one interviews were

conducted with these HCPs. One-to-one interviews can provide more in-depth information around the topic being explored compared to other qualitative methods such as focus groups.(337,338) As such, a deeper understanding of HCPs' needs and concerns can be gained from this approach, which can then be used to inform further research in this area. From the interviews conducted, HCPs identified several potential benefits towards the introduction of predictive and preventive approaches for RA, including increased access to healthcare services for those at-risk, as well as a long-term reduction in healthcare costs. Increased access to healthcare services was seen to be more of a benefit for those who were symptomatic compared to those who were asymptomatic. Several information and support needs were also identified, such as the need for additional funding and training, including education surrounding predictive and preventive approaches for GPs, and counselling training for rheumatology nurse specialists. These findings successfully addressed the aims of chapter 5 by providing insight into HCPs' views on the utility of RA prediction and prevention and factors that may affect their utility, as well as their information and support needs regarding implementation. However, the use of a convenience sample within this study may have led to the predominant recruitment of GPs with a specialist interest in rheumatology. As such, the views of GPs identified in this thesis are more representative of those who have a specialist interest in rheumatology.

6.3 Summary of findings

As discussed, this thesis has successfully addressed the specific aims for each chapter, as well as the overarching aim of exploring stakeholder's perspectives

towards predictive and preventive approaches for RA. To provide a broader understanding of these perspectives, the following section will discuss the overall findings of the thesis across the studies.

Within this thesis, it was found that those with a family history of RA (and IHD) were willing to take a predictive test for the disease, patients were willing to communicate information about RA risk to their relatives, and HCPs were willing to provide predictive and preventive approaches for those at risk. Several factors influencing stakeholders' perceptions towards predictive and preventive approaches, and the introduction of these approaches into clinical practice, were identified across these studies. The main factors identified across studies are summarised below.

6.3.1 Demographic variables

The influence of demographic variables, such as age, gender and education levels, on willingness to take a predictive test were identified in the systematic review.(198) Lower SES was found to influence risk-reducing behaviour in this review, after receiving predictive test results.(203) The influence of these demographic variables on interest have also been found in previous research exploring other chronic diseases, including cancer and DM.(205,215,217) However, no association between demographic variables and interest in predictive testing for RA was found among FDRs in this thesis. There are several potential reasons for this contrast in findings. First, the association between demographic variables and interest in testing may be disease-specific. There is often a lack of awareness surrounding RA, and this disease is perceived to be less severe than other diseases such as heart disease.(213) These perceptions may affect whether or not demographic variables impact interest in predictive testing for RA.

Second, assessment of the influence of demographic variables on willingness to take a test in the systematic review was not separated for those with and without a family history.(198) Therefore, the influence of these variables in the systematic review may be more indicative of public interest in testing, rather than interest from those with a family history. Demographic variables may still be important in the prediction and prevention of RA, however, as younger age was found to be associated with increased patient likelihood of communicating RA risk information to relatives within this thesis. They may also be associated with the engagement of risk-reduction behaviours in FDRs who have received predictive test results, which should be explored in future studies.

Both patients with RA and those with a family history of IHD were interested in communicating disease risk information to their children. RA patients highlighted wanting to communicate RA risk information to their children over their siblings, and those with a family history of IHD identified the opportunity to communicate disease risk to their children as a key motivator for accepting a predictive test. The fact that the majority of FDRs who returned their surveys for this thesis were children (75.3%) suggests that RA patients were more likely to communicate RA risk information to their children. As there is likely to be increased access to this at-risk group compared to other FDRs such as siblings, specific interventions are required to promote communication of RA risk to siblings as well as children.

6.3.2 Perceived risk

Perceived risk of developing RA was identified as an important motivator towards FDRs' interest in taking a predictive test. Perceived risk of developing IHD was also

found to be an important motivator towards interest, as well as intentions to engage in risk-reducing behaviour. The findings from this thesis align with previous findings from other chronic diseases,(231,238,263) This demonstrates that risk perceptions are an important factor in decision-making regarding predictive testing across various diseases. The influence of an individual's perceived risk of RA should be considered when developing predictive tests, and when discussing risk information obtained from these tests. This will ensure that risk is communicated in a way that supports decision-making around engagement in predictive and preventive approaches.(261)

6.3.4 Understanding of prediction and prevention

Misperceptions regarding predictive testing, for example beliefs that tests could determine for certain whether or not someone would develop RA, influenced FDRs' interest in taking a predictive test for RA in this thesis. The systematic review also found that engagement in health behaviours was, in part, associated with an individual's understanding of the efficacy of preventive behaviours (i.e. whether they believed the behaviour would reduce or prevent their risk of developing IHD). This understanding was influenced by information that was provided by HCPs regarding the efficacy of these behaviours in reducing IHD risk (i.e. contradictory information provided about the efficacy of dietary change influenced individual's likelihood to change their diet).(203) This indicates the importance of developing effective communication strategies between HCPs and patients, to enhance understanding for those at-risk. GPs in this thesis identified a need for further education regarding predictive and preventive approaches for RA, and both primary and secondary care HCPs identified the need to develop a standardised pathway for the requesting of predictive tests and initiation of preventive treatments. As such, further education may

need to be provided to HCPs, as well as easily implemented, standardised care pathways, to increase HCPs' understanding of these approaches, and to enhance communication with those at-risk to increase their comprehension of predictive and preventive approaches and further support shared decision-making around these approaches.

Further education regarding the development of RA is also needed for FDRs and RA patients, as both groups identified common misperceptions such as 'wear and tear' of the joints (a factor commonly associated with other musculoskeletal conditions) as a potential cause of RA. The information provided to these groups will need to be easily accessible, and address common misperceptions, to enhance their understanding of RA and thus their understanding of potential risk factors for this disease.

6.3.5 Patient preferences for autonomy

Preferences for autonomy, in terms of obtaining information about health, and having control over health, were highlighted as important factors in FDRs' interest in predictive testing, and RA patients' likelihood of communicating RA risk to relatives. The importance of patients' preference for autonomy for the prediction and prevention of RA aligns with the focus of current healthcare services, which value patients' choices when making healthcare decisions, compared to a more paternalistic approach used in the past.(339,340) As patient autonomy, and preferences for autonomy, appear to be highly valued across at-risk, patient and healthcare groups, it is integral that predictive strategies are developed in a way that emphasises autonomy for those at-risk. This will support shared decision-making for those considering predictive tests, as well as those considering communicating information about RA risk to their relatives.

6.3.6 Potential for harm

The perceived potential for predictive tests to cause psychological harm, such as stress and anxiety, was found to lower FDRs' interest in taking a predictive test for RA and patients' likelihood of communicating RA risk information in this thesis. These findings align with previous qualitative literature examining perspectives of predictive testing for RA and communication about RA risk,(150,166) as well as research examining other chronic diseases, such as breast and ovarian cancer.(163,277) This highlights the importance of this issue in regards to the prediction of RA and other chronic diseases, and indicates the need for support services for individuals considering taking a test that could provide potentially distressing information about their risk of a disease. Rheumatology nurse specialists recruited for the qualitative study described in this thesis also identified that risk information has the potential to upset those at risk, and highlighted the need for such specialists to receive training in how to manage that situation.

HCPs also highlighted the importance of the negative predictive value of a test, which could provide reassurance to patients that they would likely not develop RA in the future. As such, ensuring that predictive tests can state with accuracy that a person will not go on to develop the disease is important when generating these strategies. The possibility of obtaining a negative result should also be emphasised to FDRs who are anxious about predictive test results, as well as patients with RA who may want to protect their relatives from anxiety-provoking information.

6.4 Strengths and limitations

This thesis has made a substantial contribution to the field of RA prediction and prevention by providing extensive insight into the perceptions of those who will be directly affected by the provision and uptake of these approaches. The use of a mixed methods approach has led to both a deeper and wider understanding of the perspectives of stakeholders that will usefully inform future research and practice surrounding the development and implementation of predictive and preventive approaches for RA.

The extensive input of PRPs in the development, design and analysis of studies involved within this thesis has further increased the value of this research. The input provided by those who hold a lived-experience perspective has likely increased the quality, coherence and relevance of this research.(341)

The large sample of patients with RA and their FDRs was another significant strength of this thesis. A large sample size increases the statistical power and precision of data analysis, as well as the generalisability and reliability of results.(342,343) Therefore, the findings obtained from FDRs and RA patients in this thesis likely provide a valid and reliable representation of the views of these groups. The insights obtained from stakeholders through the approaches utilised within this thesis can be used to inform information and support services for RA patients and their families. Such services can support family communication of disease risk, increase access to FDRs (a hard to recruit subsection of the population (264)) and ensure that predictive and preventive approaches are introduced in a way that can improve instead of burden the current healthcare system.

While this thesis makes a significant contribution to the field, it is not without limitations. The exclusion of non-English studies within the systematic review and, for the cross-sectional survey studies, the exclusion of those who are unable to complete the survey in English, may impact on the generalisability of the findings obtained within this thesis. Non-English speakers often experience issues related to their healthcare as a result of language and cultural barriers.(344,345) These barriers have been found to prevent them from accessing healthcare services, and can lead to lower quality care for those who do access the service.(344,345). Therefore, it is likely that non-English speakers have specific needs that have not been captured in this thesis, due to its focus on English speakers.

The potential for sampling bias in the cross-sectional survey studies and the qualitative interview study may have also impacted the findings of this thesis. The self-selected (and patient selected) sample that comprised these studies likely means that those who were more interested in the topic of RA prediction and prevention (or those perceived by their proband to be more interested) volunteered to take part. As such, the findings from this thesis may reflect the perceptions of these specific groups only, and the needs of those who are not as interested in this area may not have been captured.

Finally, FDRs within this thesis were only linked with one family member with RA. While this was useful in determining whether this patient proband influenced their interest in taking a predictive test for RA, they may have had experience of other relatives (including those from previous generations) who may be affected by RA differently (either more or less severely). As such, these relatives may have also impacted on their interest. In addition, the severity of patients' RA was assessed using the RAID

scale, which only assesses the impact of the patients' disease over the previous week. As such, this measure may not capture the cumulative impact of the patients' RA over the entire course of their illness, and the potential influence of this on FDRs' interest in predictive testing.

6.5 Future work

The findings generated from this thesis provide valuable insights into the perspectives of those likely to be affected by predictive and preventive approaches for RA, which can inform future research and clinical practice. Further details on how these findings could inform research and practice are detailed below.

6.5.1 Research

The findings produced from this thesis can be used to inform future research regarding the perspectives of those likely to be affected by the prediction and prevention of RA, as well as inform further studies developing predictive and preventive approaches for RA. Recommendations based on the findings of the current thesis are provided.

This thesis identified key predictors influencing interest in predictive testing among FDRs of patients with RA that can be used in future research examining this group or other at-risk individuals. The experiences and perceptions of RA prediction and prevention among individuals at different at-risk stages may vary. For example, individuals generally present to HCPs as a result of clinical symptoms or signs, with those who do not have any symptoms rarely accessing healthcare services in the context of musculoskeletal disease.(99) Therefore, it is important that the perceptions of those at various at-risk stages are examined. Surveys assessing the key predictors

identified within the current thesis, and the measure of interest used within this thesis could be provided to individuals at varying stages of risk for RA. Predictors of interest within each group could then be assessed and compared to other at-risk groups to determine whether differences exist. This could inform information and support strategies specific to the needs of each at-risk group, to support decision-making around the uptake of predictive tests and promote optimal engagement in prediction and prevention studies, identified as important by the EULAR task force.(99)

This thesis found no evidence to suggest that RA patients' characteristics were associated with their FDRs' interest in predictive testing. This may be because FDRs were only linked with one family member with RA, or that the cumulative impact of their family member's RA over the course of the disease was not assessed within this thesis (discussed in the limitations section of this chapter). As such, further investigation is needed to comprehensively assess relationships between at-risk individuals' interest in predictive testing and their experience of the impact of RA across all relatives with RA. To do this, the disease and demographic characteristics of several family members with RA should be assessed, and their impact on at-risk individuals' interest in predictive testing examined. The items assessing RA patients' characteristics within the current thesis could be used to assess other family members with RA, with the inclusion of an additional measure examining the impact of RA, including for example a modification of the RAID which asks about the impact of their RA overall rather than in the previous week. This could provide key information on whether an at-risk individuals' experience of RA from different family members with the disease impacts on their interest in taking a predictive test. Patients' likelihood of communicating RA risk information to relatives could also be assessed across other family members with

RA. This could provide important information on the influence of different family relationships (for example RA patients who are grandparents of at-risk individuals) on patients' likelihood of communicating RA risk information.

The findings of this thesis illustrate the importance of examining perceptions of predictive strategies for RA among those at risk in informing and promoting engagement in prediction research. To further inform prevention research, large-scale quantitative research examining the perceptions of preventive treatment among FDRs is needed. As discussed in the introduction of this thesis, a project examining FDRs' preferences towards pharmaceutical preventive treatments is currently underway.(161) One case study from that research project assesses FDRs' preferences using DCE and PTT methods, to assess the relative importance of treatment attributes, as well as potential factors that may influence treatment preferences. The information obtained from that study will help to promote engagement in research into preventive approaches for RA from this hard to recruit group, and inform the development of preventive strategies that are suitable to FDRs' needs and concerns. As suggested for future research regarding predictive strategies, this study could also be expanded in the future to include those within other at-risk stages, to compare responses across those who may have different perceptions and experiences regarding prevention.

Promoting participation and engagement of those who are at the early stages of RA risk in RA prevention trials is important, as there is currently limited evidence on the efficacy of preventive approaches for RA in these groups. Additionally, a recent RA prevention trial was stopped prematurely due to the difficulty in identifying individuals who were willing to take part.(121) A recent EULAR taskforce highlight the importance

of developing effective risk information for those at-risk who are considering taking part in prevention trials, which could promote engagement.(99) The findings from this thesis highlight important factors that could be used to inform the information provided to these at-risk groups. For example, information about an individual's risk through their family history as well as their personal risk (identified as important in influencing intentions to engage in health behaviours in the systematic review of this thesis) could be provided, and this information could be presented to them in the form of pictographs, which could increase at-risk individual's understanding of their risk (suggested by HCPs in this thesis). Additionally, information about the potential efficacy of these preventive trials in reducing RA risk or delaying progression to RA should be provided to those considering taking part in a trial. This would help inform an individual's decision and may help to reduce their anxiety or stress surrounding a preventive treatment, which has been found to decrease FDRs' interest in taking a predictive test in this thesis. Information about the efficacy of a preventive behaviour was also found in the systematic review of this thesis to influence decision-making around engaging in that behaviour. Research examining the impact of communicating risk information in this format on at-risk individuals' willingness to take part in a preventive trial (pharmaceutical or lifestyle-modification), compared to providing no risk information, could be conducted to determine its efficacy. Further suggestions on how RA risk could be best communicated to at-risk individuals could also be assessed in those who are at-risk.

The findings from this thesis, in particular the information and support needs identified by HCPs, can inform the successful integration of predictive and preventive approaches for RA into healthcare services. To further ensure successful integration,

an implementation study is needed to determine the feasibility of implementing such approaches, and their effect on HCPs' resources and at-risk individuals' risk status. An intervention providing predictive and preventive strategies for RA, which incorporates information and support needs identified by HCPs in this thesis could be examined within healthcare services. Based on the needs identified by HCPs, this intervention could include [1] further education for GPs regarding predictive and preventive approaches for RA, [2] training in counselling skills for rheumatology nurse specialists, [3] a standardised prediction tool and [4] guidelines that include recommendations for providing predictive and preventive approaches for RA. The feasibility of this approach could then be assessed, using feasibility indicators that address several factors identified by HCPs as potentially being impacted by the introduction of predictive and preventive approaches. This includes the cost of implementing the intervention and potential cost savings associated with this approach, along with the resources needed to implement this intervention. A risk assessment could also be provided to at-risk individuals to determine the efficacy of this intervention at reducing their risk.

6.5.2 Clinical Practice

The findings from this thesis could benefit all stakeholders who are likely to be involved in the uptake and provision of predictive and preventive approaches for RA. They could inform the development and implementation of effective predictive and preventive strategies that address the needs and concerns of FDRs, patients with RA and HCPs. Recommendations are made regarding the development of these approaches for use in clinical practice, based on the findings of this thesis. These recommendations will

help to ensure that predictive and preventive approaches will be of benefit to all stakeholders.

Due to the influence of perceived risk on views towards RA prediction and prevention found within this thesis, it is important that individuals are informed of their risk of RA, and that this is done in an effective way that individuals can understand. Doing so will help to inform individuals' decisions around taking a predictive test or preventive treatment for RA. As discussed earlier, the EULAR task force also recommended informing individuals about their risk of RA, and to use a tailored approach to provide this information.(99) As part of this tailored approach, it is recommended that individuals' absolute risk of developing RA is provided to them, as this was found to predict interest in predictive testing in the current thesis. Absolute risk is also less likely to influence health behaviours compared to other forms of risk assessment such as relative risk,(261) making it the most appropriate form of risk communication to support shared decision-making around taking a predictive test or preventive treatment. As discussed in the previous section, pictographs could be used to present this risk information to individuals to increase understanding of their risk. RA patients should also be informed that their FDR is at an increased risk of developing RA due to their family history using the recommendations above. This will facilitate patients' understanding of RA risk, and support family risk communication.

As this thesis found that both FDRs and RA patients believed in common misperceptions regarding the causes of RA, it is recommended that education strategies focused on the potential causes for RA are developed. Informing these groups about the causes of RA can increase awareness of risk factors involved in the development of RA, which could influence healthcare utilisation and behaviour

modification in those at risk. To increase access to this information, public awareness raising initiatives addressing common misperceptions of RA should be provided in an easily comprehensible manner. Previous research demonstrates the influence of public awareness raising initiatives on increasing symptom recognition and appropriate help-seeking behaviours in other chronic diseases including cancers.(213) Therefore, these initiatives may help to increase awareness around the causes of RA. Such initiatives could be informed by those addressing other chronic diseases, such as breast cancer, that have proven to be effective.(346)

The findings from this thesis, along with the recommendations of the EULAR task force,(99) highlight the need for additional support for at-risk individuals, as well as for patients with RA who may have to communicate information about risk. Support services centred around reducing anxiety in those at risk and supporting family communication should be provided alongside predictive and preventive approaches for RA. It may be useful to provide at-risk individuals and probands with RA the opportunity to visit a genetic counsellor, who can provide support surrounding psychological issues such as anxiety, refer individuals to in-depth counselling and provide information about community resources and support groups.(347) Rheumatology nurses could also be trained to offer support and counselling to at-risk individuals and patients, as suggested by HCPs in this thesis. Given their expertise in the area, this training could be provided, or informed, by genetic counsellors.

To successfully implement predictive and preventive approaches into clinical practice, current healthcare services may need to be modified to account for the increase in demand and required resources, as identified within this thesis. As such, it is recommended that the appropriate allocation of resources is considered prior to

implementation, particularly within primary care services. For example, a care service focused on RA prediction and prevention for those at risk could be implemented into secondary healthcare services, while current primary care services operate as normal, referring those identified as at risk to these secondary care services. By doing this, no additional strain would be put onto primary care services. The resource requirement of providing this care service would need to be carefully assessed and the adequacy of this resource monitored and adjusted, if necessary.

6.6 Conclusions

Considerable interest within the medical research community in the development of predictive and preventive strategies for RA has led to an important need to understand the perspectives of those who may be directly affected by these approaches. This includes FDRs, who are likely candidates for predictive and preventive approaches, patients with RA who provide access to this at-risk group, and HCPs, who will likely prescribe these approaches. This thesis provides valuable insight into the perspectives of these stakeholders, increasing understanding of their needs and concerns around RA prediction and prevention. To obtain this insight, this thesis employed the first quantitative assessments of FDRs' views towards predictive testing and RA patients' likelihood of communicating RA risk information to their relatives. It also provided the first detailed examination of views towards RA prediction and prevention from HCPs in both primary and secondary healthcare services. Several key findings were identified from these approaches that can inform the development of effective predictive and preventive strategies for RA. FDRs were found to be interested in taking a predictive

test for RA, patients were willing to communicate RA risk information to their relatives and HCPs were willing to provide predictive and preventive approaches for RA to those at risk. Several factors influencing these perspectives were also identified, including perceived risk, understanding of RA prediction and prevention, and the potential for these approaches to cause psychological harm. Such findings can inform the development of information resources to support family communication of RA risk, and decision-making surrounding the uptake of predictive and preventive approaches. They can also inform strategies to promote engagement in prediction and prevention research. To further inform the development of information resources and effective predictive and preventive strategies, further research should examine the perspectives of various at-risk groups. To increase understanding of the risk factors for RA, and support decision-making regarding predictive and preventive approaches, it is important that public awareness raising initiatives surrounding the causes of RA are provided, as well as additional support services for at-risk individuals and patients who may have to communicate about RA risk. To ensure successful implementation of these approaches, a care service focused on RA prediction and prevention should be implemented into secondary care services, so that no additional strain is put onto primary care services.

Appendix 1
Search strategies from each database used in the systematic review

Medline

1	(family adj2 histor*).ti,ab. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
2	"first degree relative".ti,ab.
3	"relative".ti,ab.
4	or/1-3
5	"CVD".ti,ab.
6	exp Heart Diseases/
7	exp Myocardial Ischemia/
8	"ischemic heart disease".ti,ab.
9	ischaemic heart disease.ti,ab.
10	exp Cardiovascular Diseases/
11	Cardiovascular Diseases/px [Psychology]
12	Cardiovascular Diseases/pc [Prevention & Control]
13	exp Coronary Artery Disease/
14	exp Coronary Disease/
15	"coronary heart disease".ti,ab.
16	or/5-15
17	"DNA based test".ti,ab.
18	"gene* screen*".ti,ab.
19	"predict* test".ti,ab.
20	exp Genetic Testing/
21	"genetic risk".ti,ab.
22	Genetic Carrier Screening/
23	(risk adj2 assessment).ti,ab. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary

	concept word, rare disease supplementary concept word, unique identifier, synonyms]
24	(risk adj2 test).ti,ab. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
25	(gene* adj2 test*).ti,ab.
26	(predict* adj2 test*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
27	exp Genetic Predisposition to Disease/
28	*Genetic Testing/
29	*Risk Factors/
30	*CHOLESTEROL, LDL/
31	*CHOLESTEROL, HDL/
32	*TRIGLYCERIDES/
33	*Lipoproteins/
34	"lipoprotein (a)".ti,ab.
35	"LP (a)".ti,ab.
36	"CRP".ti,ab.
37	or/17-36
38	4 and 16 and 37
39	limit 38 to (English language and humans and “all adult (19 plus years)”)

Embase

1	(family adj2 histor*).ti,ab. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
2	"first degree relative".ti,ab.
3	"relative".ti,ab.
4	or/1-3

5	"CVD".ti,ab.
6	exp Heart Diseases/
7	exp Myocardial Ischemia/
8	"ischemic heart disease".ti,ab.
9	ischaemic heart disease.ti,ab.
10	exp Cardiovascular Diseases/
11	Cardiovascular Diseases/pc [Prevention & Control]
12	exp Coronary Artery Disease/
13	exp Coronary Disease/
14	"coronary heart disease".ti,ab.
15	or/5-14
16	"DNA based test".ti,ab.
17	"gene* screen*".ti,ab.
18	"predict* test".ti,ab.
19	exp Genetic Testing/
20	"genetic risk".ti,ab.
21	Genetic Carrier Screening/
22	(risk adj2 assessment).ti,ab. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
23	(risk adj2 test).ti,ab. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
24	(gene* adj2 test*).ti,ab.
25	(predict* adj2 test*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
26	exp Genetic Predisposition to Disease/
27	*Genetic Testing/
28	*Risk Factors/
29	*CHOLESTEROL, LDL/
30	*CHOLESTEROL, HDL/
31	*TRIGLYCERIDES/

32	*Lipoproteins/
33	"lipoprotein (a)".ti,ab.
34	"LP (a)".ti,ab.
35	"CRP".ti,ab.
36	or/16-35
37	4 and 15 and 36
38	limit 37 to (human and english language and embase and (adult <18 to 64 years> or aged <65+ years>))

Psycinfo

1	(family adj2 histor*).ti,ab. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
2	"first degree relative".ti,ab.
3	"relative".ti,ab.
4	or/1-3
5	"CVD".ti,ab.
6	"ischemic heart disease".ti,ab.
7	ischaemic heart disease.ti,ab.
8	"coronary heart disease".ti,ab.
9	or/5-8
10	"DNA based test".ti,ab.
11	"gene* screen*".ti,ab.
12	"predict* test".ti,ab.
13	exp Genetic Testing/
14	"genetic risk".ti,ab.
15	(risk adj2 assessment).ti,ab. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
16	(risk adj2 test).ti,ab. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
17	(gene* adj2 test*).ti,ab.

18	(predict* adj2 test*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
19	*Genetic Testing/
20	*Risk Factors/
21	*Lipoproteins/
22	"lipoprotein (a)".ti,ab.
23	"LP (a)".ti,ab.
24	"CRP".ti,ab.
25	or/10-24
26	exp Heart Disorders/
27	exp ISCHEMIA/
28	exp Cardiovascular Disorders/
29	coronary artery disease.mp.
30	coronary disease.mp.
31	or/26-30
32	genetic carrier screening.mp.
33	genetic predisposition to disease.mp.
34	*CHOLESTEROL/
35	CHOLESTEROL, LDL.mp.
36	CHOLESTEROL, HDL.mp.
37	triglycerides.mp.
38	or/32-37
39	9 or 31
40	25 or 38
41	4 and 39 and 40
42	limit 41 to (human and english language and adulthood <18+ years>)

ProQuest

(AB, TI("family histor*")) OR (AB, TI("first degree relative")) AND (AB, TI("cardiovascular disease*")) OR (AB, TI("ischaemic heart disease")) OR (AB, TI("ischemic heart disease")) AND (AB, TI("gene* test*")) OR (AB, TI("lipoproteins")) OR (AB, TI("triglycerides")).

EThOS

Genetic test AND heart disease AND family history.

Google

(genetic screening) AND (ischemic heart disease) AND (family history).

Appendix 2
Table of additional information extracted from studies included in the systematic review

References	Ethical Approval	Funding Sources	PPI Involvement
Claassen et al (200)	Does not state.	Societal Component of Genomics Research of the Netherlands Organization for Scientific Research (NWO).	No
Imes et al (201)	Approved by the University of Washington's institutional review board.	National Institute of Nursing Research of the National Institutes of Health.	No
Middlemass et al (197)	Approved by Derby Research Ethics Committee (reference number: 08/H0401/).	National Health Service Task-linked Research and Development funding for 'Clinical Genetics in Primary care' programme.	No
Stocks et al (202)	Approved by the Royal Adelaide Hospital Research Ethics committee and Flinders research ethics committee, and approved for conduct at Flinders Private Hospital.	National Health and Medical Research Council (NHMRC) Project.	No
Saukko et al (203)	Approval obtained by the Mutlicentre Research Ethics Committee for	UK Department of Health's Genetics Based Health Services Programme.	No

	Scotland (06/MRE10/9).		
Sanderson and Michie (199)	Approved by the Psychology Ethics Board of University College London	MRC-ESRC Postdoctoral Research Fellowship.	No
Sanderson et al (198)	Does not state.	Department of Health and Department of Technology, Industry to the London IDEAS Genetics Knowledge Park, Cancer Research UK and the British Heart Foundation.	No

Appendix 3
Survey for FDRs of patients with RA

UNIVERSITY OF BIRMINGHAM

Survey for relatives of people with rheumatoid arthritis

Participant Number:

Thank you for taking the time to complete this survey. Your answers are very important to us, and will help us to improve support and care for people affected by rheumatoid arthritis and for their relatives. You will **not** have to take part in further research or follow up activities as a result of completing this survey, unless you would like to.

There are no right or wrong answers to the questions in this survey - we just want to know your own opinion. All of your answers will be **anonymous**, so please answer honestly. Please complete all sections of the survey.

Before you complete this survey, please make sure that you have read the enclosed Participant Information Sheet dated 08/03/2016 (version 1). Please contact the researchers if you have any questions about the information sheet or the survey.

Please note that by completing the consent form on the following page and returning the completed survey you agree to take part in this study, and give permission for the research team to use the information you have provided.

It is up to you whether you want to take part in this survey. If you change your mind you can contact us to withdraw your answers within 2 weeks. You do not need to give a reason, and your medical care or your legal rights would not be affected. As the survey is anonymous, you need to keep a record of your participant number (above) to be able to withdraw

Participant consent form

Study Title: Rheumatoid Arthritis Risk Survey

Lead Researchers: Professor Karim Raza, Dr Marie Falahee, Dr Gwenda Simons, Dr Rebecca Stack

Please put a cross or tick in the boxes to show:

1. I confirm that I have read and understand the Participant Information Sheet dated 08/03/16 (version 1) for the above study and have been offered the opportunity to ask questions about the study. Any questions I have asked have been answered to my satisfaction.	☐
2. I agree to take part in the study.	☐
3. I understand that the survey data collected during the study may be looked at by individuals from the University of Birmingham, or from my NHS Trust. I give permission for these individuals to have access to this information.	☐
4. I understand that taking part in this study is voluntary.	☐
5. I understand that even if I complete the survey and return it to the researchers, I am free to contact the research team to withdraw my survey data, without giving a reason, and without my medical care or legal rights being affected.	☐

Survey for relatives of people with rheumatoid arthritis

CONTENTS

Section 1: This section asks about your background

Please tick the answer that best describes you, or write in the correct answer.

What is your gender? ☐ Male ☐ Female

What is your age (in years)?

What is your postcode?

What is your current employment status? (Tick all that apply)

Employed: ☐ Full time ☐ Part time
Self-employed: ☐ Full time ☐ Part time
Student: ☐ Full time ☐ Part time
☐ Homemaker
☐ Carer
☐ Retired
☐ Not working due to illness / disability
☐ Other (please describe):

What is your highest level of education?

☐ No qualification
☐ CSE or equivalent
☐ GCSE / O level or equivalent
☐ A level or equivalent
☐ Vocational qualification
☐ Degree level or equivalent
☐ Postgraduate qualification
☐ Other (please describe):

Do you smoke now?

☐ Yes ☐ No, never ☐ No, but I have smoked in the past

What is your ethnic group? Choose one option that best describes your ethnic group or background:

White:	☐ English/Welsh/Scottish/Northern Irish/British ☐ Irish ☐ Gypsy or Irish Traveller ☐ Any other White background
Mixed/Multiple ethnic groups:	☐ White and Black Caribbean ☐ White and Black African ☐ White and Asian ☐ Any other Mixed/Multiple ethnic background
Asian/Asian British:	☐ Indian ☐ Pakistani ☐ Bangladeshi ☐ Chinese ☐ Any other Asian background
Black/African/ Carribean/Black British	☐ African ☐ Caribbean ☐ Any other Black/African/Caribbean background

☐ Any other ethnic group, please describe:

☐ I do not wish to disclose this information

Is there a history of rheumatoid arthritis in your family?

☐	☐	☐	☐	☐
Definitely not	Probably not	Don't know	Probably	Definitely

Which relative gave you this survey?

☐ Mother ☐ Father ☐ Sister ☐ Brother

Are you currently living in the same home as this relative?

☐ Yes ☐ No

How often do you talk to this relative?

☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Every day

How many children do you have (not including step-children)?

Number of daughters:

Number of sons:

☐ I don't have any children

How many siblings do you have (not including step-siblings or half-siblings)?

Number of sisters:

Number of brothers:

☐ I don't have any siblings

Section 2: This section asks how you think you would feel if you were to develop rheumatoid arthritis.

Obviously you cannot know for sure what it would be like - please give your best guess of what you think might happen, basing your guess on what you know about yourself and about rheumatoid arthritis.

For each of the following questions, please TICK the number that best corresponds to your views:

If you were to develop rheumatoid arthritis, how much do you think it would affect your life?

0	1	2	3	4	5	6	7	8	9	10

Not affect me at all — Severely affect my life

If you were to develop rheumatoid arthritis, how long do you think it would continue?

0	1	2	3	4	5	6	7	8	9	10

A very short time — Forever

If you were to develop rheumatoid arthritis, how much control do you think you would you have over it?

0	1	2	3	4	5	6	7	8	9	10

Absolutely no control — Extreme amount of control

If you were to develop rheumatoid arthritis, how much do you think your treatment would help it?

0	1	2	3	4	5	6	7	8	9	10

Not at all helpful — Extremely helpful

If you were to develop rheumatoid arthritis, how much do you think you would experience symptoms from it?

0	1	2	3	4	5	6	7	8	9	10

No symptoms at all Many severe symptoms

If you were to develop rheumatoid arthritis, how concerned do you think you would you be about it?

0	1	2	3	4	5	6	7	8	9	10

Not at all concerned Extremely concerned

If you were to develop rheumatoid arthritis, how well do you think you would understand it?

0	1	2	3	4	5	6	7	8	9	10

Not understand at all Understand very clearly

If you were to develop rheumatoid arthritis, how much do you think it would affect you emotionally? (e.g. would it make you angry, scared, upset, or depressed)

0	1	2	3	4	5	6	7	8	9	10

Not at all affected emotionally Extremely affected emotionally

Section 3. This section asks what you think the causes of rheumatoid arthritis are.

For each of the following possible causes, please tick one box to show how much you agree or disagree that it is a cause of rheumatoid arthritis:

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
Stress or worry	☐	☐	☐	☐	☐
Hereditary - it runs in the family	☐	☐	☐	☐	☐
A germ or virus	☐	☐	☐	☐	☐
Diet or eating habits	☐	☐	☐	☐	☐
Chance or bad luck	☐	☐	☐	☐	☐
Poor medical care	☐	☐	☐	☐	☐
Pollution in the environment	☐	☐	☐	☐	☐
Own behaviour	☐	☐	☐	☐	☐
Mental attitude (e.g. thinking about life negatively)	☐	☐	☐	☐	☐
Family problems or worries	☐	☐	☐	☐	☐
Overwork	☐	☐	☐	☐	☐

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
Emotional state (e.g. feeling down, lonely, anxious, empty)	☐	☐	☐	☐	☐
Ageing	☐	☐	☐	☐	☐
Alcohol	☐	☐	☐	☐	☐
Smoking	☐	☐	☐	☐	☐
Accident or injury	☐	☐	☐	☐	☐
Personality	☐	☐	☐	☐	☐
Altered Immunity	☐	☐	☐	☐	☐
Overweight	☐	☐	☐	☐	☐
Hormonal changes	☐	☐	☐	☐	☐
Wear and tear on the joints	☐	☐	☐	☐	☐
Having gum disease	☐	☐	☐	☐	☐

Please list in rank-order the three most important factors that you think cause rheumatoid arthritis. *The most important causes are:*

1. _____

2. _____

3. _____

Section 4: This section asks how likely you think it is that you will develop rheumatoid arthritis in the future.

For each of the following, please tick the box that best describes you:

How likely do you think it is that you will develop rheumatoid arthritis in your lifetime?

☐	☐	☐	☐	☐
Very unlikely	Unlikely	Neither unlikely nor likely	Likely	Very likely

Compared with other people your age, gender and race, how likely do you think it is that you will develop rheumatoid arthritis in your lifetime?

☐	☐	☐	☐	☐
Much less unlikely	Less likely	About the same	More likely	Much more likely

I feel that I am at risk of getting rheumatoid arthritis in my lifetime.

☐	☐	☐	☐	☐
Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree

I am worried about getting rheumatoid arthritis in my lifetime.

☐	☐	☐	☐	☐
Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree

How likely are you to talk to a healthcare professional (e.g. doctor, nurse, counsellor) about your risk of developing rheumatoid arthritis?

☐	☐	☐	☐	☐
Very unlikely	Unlikely	Neither unlikely nor likely	Likely	Very likely

If, in the next 6 months, your doctor offered you a test that predicted your risk of developing rheumatoid arthritis, would you take the test?

☐	☐	☐	☐
No definitely not	No probably not	Yes probably	Yes definitely

If, sometime in the future, your doctor offered you a test that predicted your risk of developing rheumatoid arthritis, would you take the test?

☐	☐	☐	☐
No definitely not	No probably not	Yes probably	Yes definitely

Section 5. This section asks for your views on the advantages and disadvantages of finding out how likely it is that you will develop rheumatoid arthritis in the future.

For each of the following statements, please tick one box to show how much you agree or disagree:

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly Agree
Finding out my risk of developing rheumatoid arthritis would help me to get treated quickly if I developed symptoms of rheumatoid arthritis	☐	☐	☐	☐	☐
If I was found to be at high risk of developing rheumatoid arthritis, I would be able to take medicines to lower my risk	☐	☐	☐	☐	☐
If I was found to be at high risk of developing rheumatoid arthritis, I would be able to lower my risk by making changes to my lifestyle	☐	☐	☐	☐	☐
Finding out my risk of developing rheumatoid arthritis would help me feel prepared if I developed symptoms of rheumatoid arthritis	☐	☐	☐	☐	☐

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly Agree	Does not apply
Finding out my risk of developing rheumatoid arthritis would give me control over my health	☐	☐	☐	☐	☐	
Finding out my risk of developing rheumatoid arthritis would help me to make important decisions about how to live my life	☐	☐	☐	☐	☐	
Knowing that my risk of developing rheumatoid arthritis was low would give me peace of mind	☐	☐	☐	☐	☐	
Not knowing my risk of developing rheumatoid arthritis could make me anxious	☐	☐	☐	☐	☐	
I should find out my risk of developing rheumatoid arthritis for the sake of my family	☐	☐	☐	☐	☐	
I should find out my risk of developing rheumatoid arthritis to determine whether my children might be at risk	☐	☐	☐	☐	☐	☐
I should find out my risk of developing rheumatoid arthritis at an early age	☐	☐	☐	☐	☐	

			Neither agree			

	Strongly disagree	Disagree	nor disagree	Agree	Strongly Agree
I prefer not to think about things that might never happen	☐	☐	☐	☐	☐
Getting a test to predict my risk of developing rheumatoid arthritis would tell me that I definitely would, or definitely wouldn't develop rheumatoid arthritis	☐	☐	☐	☐	☐
Getting a test to predict my risk of developing rheumatoid arthritis would be a stressful experience for me	☐	☐	☐	☐	☐
Getting a test to predict my risk of developing rheumatoid arthritis would be a stressful experience for my relatives	☐	☐	☐	☐	☐
My relatives would be upset if I was found to be at high risk of developing rheumatoid arthritis	☐	☐	☐	☐	☐
Knowing that I was at high risk of developing rheumatoid arthritis would harm my self-image	☐	☐	☐	☐	☐
If I was found to be at high risk of developing rheumatoid arthritis I may become depressed as a result	☐	☐	☐	☐	☐
			Neither agree		Does not apply

	Strongly disagree	Disagree	nor disagree	Agree	Strongly Agree	
If I was found to be at high risk of developing rheumatoid arthritis I may become anxious as a result	☐	☐	☐	☐	☐	
If I was found to be at high risk of developing rheumatoid arthritis I would be likely to worry unnecessarily about my health	☐	☐	☐	☐	☐	
If I was found to be at high risk of developing rheumatoid arthritis I would be likely to feel guilty about the possibility of passing the risk on to my children	☐	☐	☐	☐	☐	☐
If I was found to be at high risk of developing rheumatoid arthritis I may not be able to get Insurance	☐	☐	☐	☐	☐	
If I was found to be at high risk of developing rheumatoid arthritis I may be discriminated against	☐	☐	☐	☐	☐	

Section 6. This section asks how easy you find it to understand written and numerical information.

These questions help us to ensure that health information is delivered in a way that is easy to understand.

Please tick the answer that best describes you:

How often do you need to have someone help you when you read instructions, pamphlets, or other written material from your doctor or pharmacy?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Always

How good are you at working with fractions?

1	2	3	4	5	6
Not good at all					Extremely good

How good are you at figuring out how much a shirt will cost if it is 25% off?

1	2	3	4	5	6
Not good at all					Extremely good

How often do you find numerical information to be useful?

1	2	3	4	5	6
Never					Very often

Section 7. This section asks about your views on how much information you need about your health, and how involved you think you should be in decisions about your health.

For each of the following statements, please tick one box to show how much you agree or disagree:

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
As you become sicker you should be told more and more about your illness	☐	☐	☐	☐	☐
You should understand completely what is happening inside your body as a result of your illness	☐	☐	☐	☐	☐
Even if the news is bad you should be well informed	☐	☐	☐	☐	☐
Your doctor should explain the purpose of your laboratory tests	☐	☐	☐	☐	☐
You should be given information only when you ask for it	☐	☐	☐	☐	☐
It is important for you to know all the side effects of your medications	☐	☐	☐	☐	☐
	Strongly disagree	Disagree	Neither agree	Agree	Strongly agree

			nor disagree		
When there is more than one way to treat a problem, you should be told about each	☐	☐	☐	☐	☐
Information about your illness is as important to you as treatment	☐	☐	☐	☐	☐
The important medical decisions should be made by the doctor, not by you	☐	☐	☐	☐	☐
You should go along with your doctor's advice even if you disagree with it	☐	☐	☐	☐	☐
When hospitalized, you should not be making decisions about your own care	☐	☐	☐	☐	☐
You should feel free to make decisions about everyday medical problems	☐	☐	☐	☐	☐
If you were sick, as your illness became worse you would want the doctor to take greater control	☐	☐	☐	☐	☐
You should decide how frequently you need a check-up	☐	☐	☐	☐	☐

Section 8: This section asks about how you usually cope with problems and illness

For each of the following statements, please tick one box to show how much you agree or disagree:

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
I say so if I am angry or sad	☐	☐	☐	☐	☐
I like to talk with a few chosen people when things get too much for me	☐	☐	☐	☐	☐
I make an active effort to find a solution to my problems	☐	☐	☐	☐	☐
Physical exercise is important to me	☐	☐	☐	☐	☐
I think something positive could come out of my complaints/problems	☐	☐	☐	☐	☐
I firmly believe that my problems will decrease (and my situation improve)	☐	☐	☐	☐	☐
I try to forget my problems	☐	☐	☐	☐	☐
I put my problems behind me by concentrating on something else	☐	☐	☐	☐	☐

			Neither agree		

	Strongly disagree	Disagree	nor disagree	Agree	Strongly agree
I bury myself in work to keep my problems at a distance	☐	☐	☐	☐	☐
I often find it difficult to do something new	☐	☐	☐	☐	☐
I am well on the way towards feeling I have given up	☐	☐	☐	☐	☐
I withdraw from other people when things get difficult	☐	☐	☐	☐	☐
In uncertain times I usually expect the best	☐	☐	☐	☐	☐
I'm always optimistic about my future	☐	☐	☐	☐	☐
Overall, I expect more good things to happen to me than bad	☐	☐	☐	☐	☐

Section 9. The section asks how much you worry about your health

For each of the following, please tick ONE box that best describes your feelings OVER THE PAST SIX MONTHS:

1. ☐ I do not worry about my health.
   ☐ I occasionally worry about my health.
   ☐ I spend much of my time worrying about my health.
   ☐ I spend most of my time worrying about my health.

2. ☐ I notice aches/pains less than most other people (of my age).
   ☐ I notice aches/pains as much as most other people (of my age).
   ☐ I notice aches/pains more than most other people (of my age).

- ☐ I am aware of aches/pains in my body all the time.

3.
- ☐ As a rule I am not aware of bodily sensations or changes.
- ☐ Sometimes I am aware of bodily sensations or changes.
- ☐ I am often aware of bodily sensations or changes.
- ☐ I am constantly aware of bodily sensations or changes.

4.
- ☐ Resisting thoughts of illness is never a problem.
- ☐ Most of the time I can resist thoughts of illness.
- ☐ I try to resist thoughts of illness but am often unable to do so.
- ☐ Thoughts of illness are so strong that I no longer even try to resist them.

5.
- ☐ As a rule I am not afraid that I have a serious illness.
- ☐ I am sometimes afraid that I have a serious illness.
- ☐ I am often afraid that I have a serious illness.
- ☐ I am always afraid that I have a serious illness.

6.
- ☐ I do not have images (mental pictures) of myself being ill.
- ☐ I occasionally have images of myself being ill.
- ☐ I frequently have images of myself being ill.
- ☐ I constantly have images of myself being ill.

7.
- ☐ I do not have any difficulty taking my mind off thoughts about my health.
- ☐ I sometimes have difficulty taking my mind off thoughts about my health.
- ☐ I often have difficulty in taking my mind off thoughts about my health.
- ☐ Nothing can take my mind off thoughts about my health.

8.
- ☐ I am lastingly relieved if my doctor tells me there is nothing wrong.
- ☐ I am initially relieved but the worries sometimes return later.
- ☐ I am initially relieved but the worries always return later.

☐ I am not relieved if my doctor tells me there is nothing wrong.

9.
☐ If I hear about an illness I never think I have it myself.
☐ If I hear about an illness I sometimes think I have it myself.
☐ If I hear about an illness I often think I have it myself.
☐ If I hear about an illness I always think I have it myself.

10.
☐ If I have a bodily sensation or change I rarely wonder what it means.
☐ If I have a bodily sensation or change I often wonder what it means.
☐ If I have a bodily sensation or change I always wonder what it means.
☐ If I have a bodily sensation or change I must know what it means.

11.
☐ I usually feel at very low risk for developing a serious illness.
☐ I usually feel at fairly low risk for developing a serious illness.
☐ I usually feel at moderate risk for developing a serious illness.
☐ I usually feel at high risk for developing a serious illness.

12.
☐ I never think I have a serious illness.
☐ I sometimes think I have a serious illness.
☐ I often think I have a serious illness.
☐ I usually think that I am seriously ill.

13.
☐ If I notice an unexplained bodily sensation I don't find it difficult to think about other things.
☐ If I notice an unexplained bodily sensation I sometimes find it difficult to think about other things.
☐ If I notice an unexplained bodily sensation I often find it difficult to think about other things.
☐ If I notice an unexplained bodily sensation I always find it difficult to think about other things.

14. ☐ My family/friends would say I do not worry enough about my health.
☐ My family/friends would say I have a normal attitude to my health.
☐ My family/friends would say I worry too much about my health.
☐ My family/friends would say I am a hypochondriac.

Section 10. This section asks what you think it might be like if you had a serious illness of a type which particularly concerns you (e.g. heart disease, cancer, multiple sclerosis and so on).

Obviously you cannot know for definite what it would be like; please give your best estimate of what you think might happen, basing your estimate on what you know about yourself and serious illness in general.

For each of the following, please tick ONE box that best describes you:

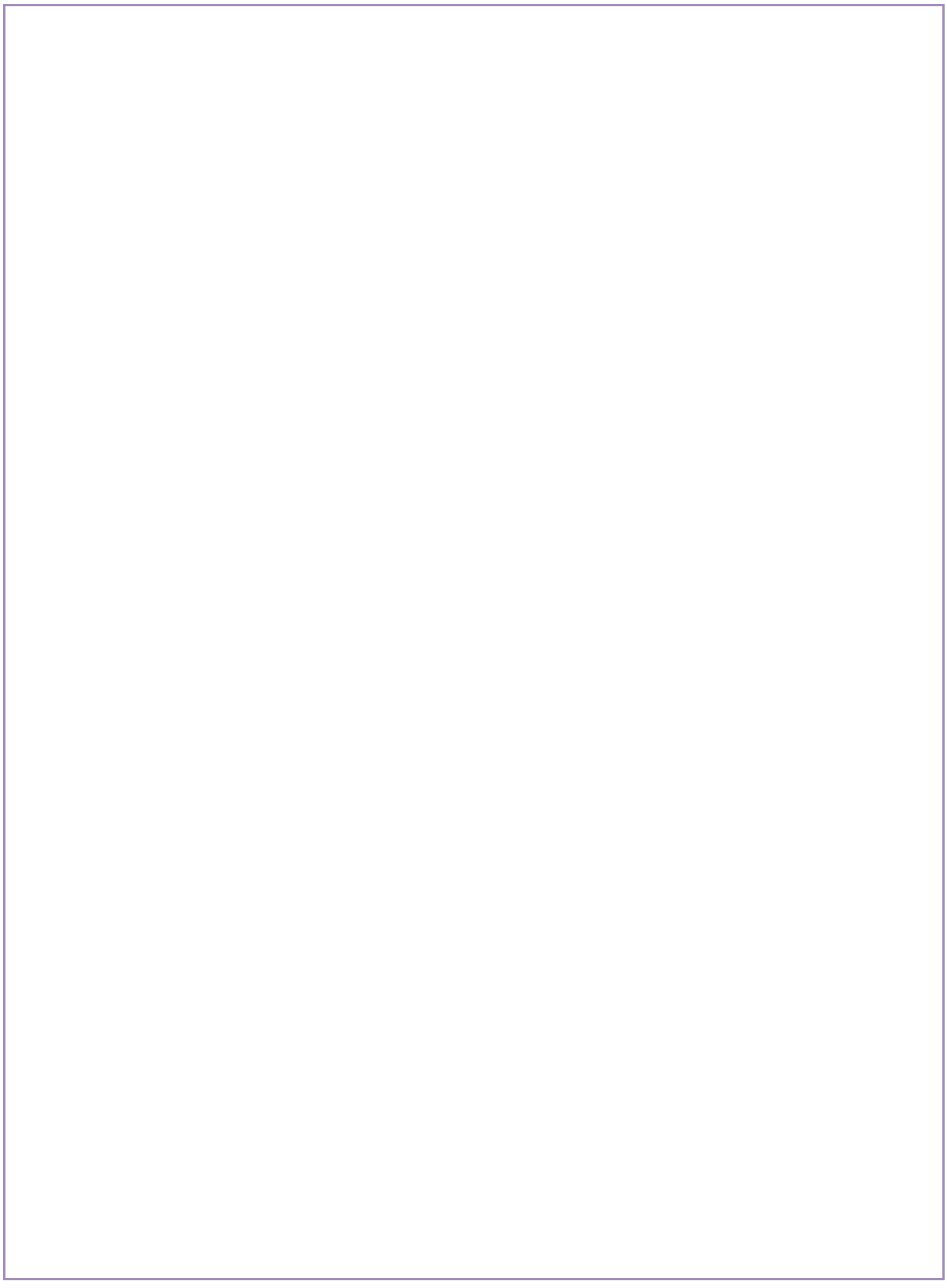
1 ☐ If I had a serious illness I would still be able to enjoy things in my life quite a lot.
☐ If I had a serious illness I would still be able to enjoy things in my life a little.
☐ If I had a serious illness I would be almost completely unable to enjoy things in my life.
☐ If I had a serious illness I would be completely unable to enjoy life at all.

2 ☐ If I developed a serious illness there is a good chance that modern medicine would be able to cure me.
☐ If I developed a serious illness there is a moderate chance that modern medicine would be able to cure me.
☐ If I developed a serious illness there is a very small chance that modern medicine would be able to cure me.
☐ If I developed a serious illness there is no chance that modern medicine would be able to cure me.

3 ☐ A serious illness would ruin some aspects of my life.
☐ A serious illness would ruin many aspects of my life.
☐ A serious illness would ruin almost every aspect of my life.
☐ A serious illness would ruin every aspect of my life.

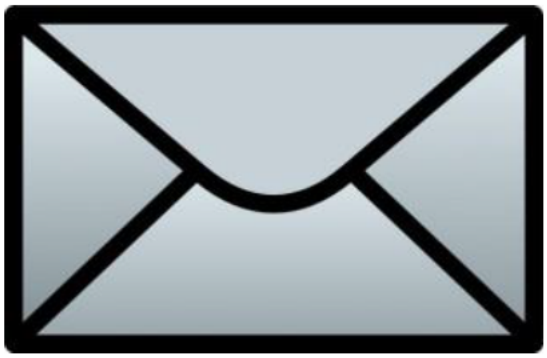
4 ☐ If I had a serious illness I would not feel that I had lost my dignity.
☐ If I had a serious illness I would feel that I had lost a little of my dignity.
☐ If I had a serious illness I would feel that I had lost quite a lot of my dignity.
☐ If I had a serious illness I would feel that I had totally lost my dignity.

If you would like to tell us about any feelings you have about the issues raised in this survey, please use the space below.



END OF SURVEY

You have reached the end of this survey. Thank you very much for taking the time to complete it. Your views are very important to us and will help us to ensure that we are meeting the needs of patients and their relatives in the future.



Please check that you have completed all sections of the survey, and return it to us in the reply paid envelope provided.

A leaflet containing information for relatives of people with rheumatoid arthritis about the risk of developing rheumatoid arthritis in the future can be found www.birmingham.ac.uk/Arthritis-Booklet-Relatives. If you would like us to send you a printed copy of this leaflet, please send your name and address to [redacted], or telephone [redacted] or write to:

Dr Marie Falahee, Rheumatology Research Group, Institute of Inflammation and Ageing, University of Birmingham, Queen Elizabeth Hospital, Birmingham B15 2WB.

If you would be interested in taking part in other research projects like this one, or have any questions about this survey, please get in touch with us using the contact details above.

If you are concerned about any issues related to your health, or issues that you came across while completing this questionnaire, please contact your GP in the first instance. If you would like more information about rheumatoid arthritis you can contact Arthritis Research UK (www.arthritisresearchuk.org; telephone 01246 558033), or the National Rheumatoid Arthritis Society (www.nras.org.uk; Freephone helpline 0800 2987650)

There are also Patient Advice and Liaison Services at City Hospital. You can contact PALS services over the phone (0121 507 5836), via email (swb-tr.pals@nhs.net), or by visiting the hospital and asking to be directed towards the PALS office.

Appendix 4
Survey for patients with RA

UNIVERSITY OF BIRMINGHAM

Survey for people with rheumatoid arthritis

Participant Number:

Thank you for taking the time to complete this survey. Your answers are very important to us, and will help us to improve support and care for people affected by rheumatoid arthritis and for their relatives. You will **not** have to take part in further research or follow up activities as a result of completing this survey, unless you would like to.

There are no right or wrong answers to the questions in this survey - we just want to know your own opinion. All of your answers will be **anonymous**, so please answer honestly.

We have divided the survey into two parts. You may want to take a break when completing the survey but please try to complete all sections of the survey.

Before you complete this survey, please make sure that you have read the enclosed Participant Information Sheet dated 08/03/2016 (version 1). Please contact the researchers if you have any questions about the information sheet or the survey.

Please note that by completing the consent form on the following page, and returning the completed survey you agree to take part in this study, and give permission for the research team to use the information you have provided.

It is up to you whether you want to take part in this survey. If you change your mind you can contact us to withdraw your answers within 2 weeks. You do not need to give a reason, and your medical care or your legal rights will not be affected. As the

survey is anonymous, you need to keep a record of your participant number (above) to be able to withdraw.

Participant consent form

Study Title: Rheumatoid Arthritis Risk Survey

Lead Researchers: Professor Karim Raza, Dr Marie Falahee, Dr Gwenda Simons, Dr Rebecca Stack

Please put a cross or tick in the boxes to show:

6. I confirm that I have read and understand the Participant Information Sheet dated 08/03/16 (version 1) for the above study and have been offered the opportunity to ask questions about the study. Any questions I have asked have been answered to my satisfaction.	☐
7. I agree to take part in the study.	☐
8. I understand that the survey data collected during the study may be looked at by individuals from the University of Birmingham, or from my NHS Trust. I give permission for these individuals to have access to this information.	☐
9. I understand that taking part in this study is voluntary.	☐
10. I understand that even if I complete the survey and return it to the researchers, I am free to contact the research team to withdraw my survey data, without giving a reason, and without my medical care or legal rights being affected.	☐

Survey for people with rheumatoid arthritis

PART 1

Part 1 of the survey asks questions about you, your rheumatoid arthritis and how you cope with problems or illness. It contains the following sections:

Section 1.1. This section asks about your background.

Please tick the answer that best describes you, or write in the correct answer.

What is your gender? ☐ Male ☐ Female

What is your age (in years)?

What is your postcode?

What is your current employment status? (Tick all that apply)

Employed:	☐ Full time	☐ Part time
Self-employed:	☐ Full time	☐ Part time
Student:	☐ Full time	☐ Part time

☐ Homemaker
☐ Carer
☐ Retired
☐ Unemployed
☐ Not working due to rheumatoid arthritis
☐ Not working due to other illness / disability
☐ Other (please describe):

What is your highest level of education?

☐ No qualification
☐ CSE or equivalent
☐ GCSE / O level or equivalent
☐ A level or equivalent
☐ Vocational qualification
☐ Degree level or equivalent
☐ Postgraduate qualification
☐ Other (please describe):

Do you smoke now?

☐ Yes ☐ No ☐ No, but I have smoked in the past

What is your ethnic group? Choose one option that best describes your ethnic group or background:

White:	☐ English/Welsh/Scottish/Northern Irish/British ☐ Irish ☐ Gypsy or Irish Traveller ☐ Any other White background
Mixed/Multiple ethnic groups:	☐ White and Black Caribbean ☐ White and Black African ☐ White and Asian ☐ Any other Mixed/Multiple ethnic background
Asian/Asian British:	☐ Indian ☐ Pakistani ☐ Bangladeshi ☐ Chinese ☐ Any other Asian background
Black/African/ Carribean/Black British	☐ African ☐ Caribbean ☐ Any other Black/African/Caribbean background

☐ Any other ethnic group, please describe:

☐ I do not wish to disclose this information

Is there a history of rheumatoid arthritis in your family?

☐	☐	☐	☐	☐
Definitely not	Probably not	Don't know	Probably	Definitely

How many children do you have (not including step-children)?

☐ I don't have any children

Number of daughters: _____ Number of sons: _____

If you have children, have any of your children been diagnosed with rheumatoid arthritis (RA)?

☐ Yes ☐ No

If yes, how many of your children have rheumatoid arthritis?

Number of daughters with RA: _____ Number of sons with RA: _____

How many siblings do you have (not including step-siblings or half-siblings)?

☐ I don't have any siblings

Number of sisters: _____ Number of brothers: _____

If you have siblings, have any of your siblings been diagnosed with rheumatoid arthritis (RA)?

☐ Yes ☐ No

If yes, how many of your siblings have rheumatoid arthritis?

Number of sisters with RA: _____ Number of brothers with RA:_____

Section 1.2. This section asks about your rheumatoid arthritis (RA), and the impact that it has on your life.

Please tick the answer that best describes you, or write in the correct answer.

How long ago were you diagnosed with RA (in years)?

What treatments / medication are you currently taking for your RA?
Please tick all that apply.

- ☐ None
- ☐ Steroids (e.g. prednisolone)
- ☐ Disease modifying anti-rheumatic drugs (DMARDs; e.g. methotrexate, leflunomide, hydroxychloroquine, sulfasalazine)
- ☐ Biological treatments (e.g. anti-TNF drugs (etanercept, infliximab, adalimumab, certolizumab, golimumab), rituximab, abatacept, tocilizumab)

Pain

Please tick the number that best describes the pain you felt due to your RA **during the last week:**

0	1	2	3	4	5	6	7	8	9	10
None										Extreme

Ability

Please tick the number that best describes the difficulty you had in doing daily physical activities (e.g. walking, washing etc.) due to your RA **during the last week:**

0	1	2	3	4	5	6	7	8	9	10
No difficulty										Extreme difficulty

Fatigue

Please tick the number that best describes how much fatigue you felt due to your RA **during the last week:**

0	1	2	3	4	5	6	7	8	9	10

No fatigue — Totally exhausted

Sleep

Please tick the number that best describes the sleep difficulties (resting at night) you felt due to your RA **during the last week:**

0	1	2	3	4	5	6	7	8	9	10

No difficulty — Extreme difficulty

Physical well-being

Considering your RA overall, how would you rate your level of physical well-being **during the past week**?

Please tick the number that best describes your level of physical well-being:

0	1	2	3	4	5	6	7	8	9	10

Very good — Very bad

Emotional well-being

Considering your RA overall, how would you rate your level of emotional well-being **during the past week**?

Please tick the number that best describes your level of emotional well-being:

0	1	2	3	4	5	6	7	8	9	10

Very good — Very bad

Coping

Considering your RA overall, how well did you cope with your condition **during the past week**?

Please tick the number that best describes how well you coped:

0	1	2	3	4	5	6	7	8	9	10
Very well										Very poorly

The previous questions asked about how your RA has affected you in the last week. The following questions ask how you feel <u>in general</u> about your RA and the way if affects your life.

Please tick the number that best describes your feelings:

How much does RA affect your life?

0	1	2	3	4	5	6	7	8	9	10
No affect at all										Severely affects my life

How long do you think your RA will continue?

0	1	2	3	4	5	6	7	8	9	10
A very short time										Forever

How much control do you have over your RA?

0	1	2	3	4	5	6	7	8	9	10
Absolutely no control										Extreme amount of control

How much do you think your treatment can help your RA?

0	1	2	3	4	5	6	7	8	9	10
Not at all										Extremely helpful

How much do you think you experience symptoms from your RA?

0	1	2	3	4	5	6	7	8	9	10
No symptoms at all										Many severe symptoms

How concerned are you about your RA?

0	1	2	3	4	5	6	7	8	9	10
Not at all concerned										Extremely concerned

How well do you feel you understand your RA?

0	1	2	3	4	5	6	7	8	9	10
Don't understand at all										Understand very clearly

How much does your RA affect you emotionally? (e.g. does it make you angry, scared, upset, or depressed)

0	1	2	3	4	5	6	7	8	9	10
Not at all affected emotionally										Extremely affected emotionally

Please list in rank-order the three most important factors that you believe caused <u>your</u> RA. *The most important causes for me are:*

1. _____

2. _____

3. _____

Section 1.3. The previous section asked about the possible causes of your rheumatoid arthritis. This section asks what you think the possible causes of rheumatoid arthritis in general are.

For each of the following possible causes, please tick one box to show how much you agree or disagree that it is a cause of rheumatoid arthritis:

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
Stress or worry	☐	☐	☐	☐	☐
Hereditary - it runs in the family	☐	☐	☐	☐	☐
A germ or virus	☐	☐	☐	☐	☐
Diet or eating habits	☐	☐	☐	☐	☐
Chance or bad luck	☐	☐	☐	☐	☐
Poor medical care	☐	☐	☐	☐	☐
Pollution in the environment	☐	☐	☐	☐	☐
Own behaviour	☐	☐	☐	☐	☐
Mental attitude (e.g. thinking about life negatively)	☐	☐	☐	☐	☐
Family problems or worries	☐	☐	☐	☐	☐

Overwork	☐	☐	☐	☐	☐

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
Emotional state (e.g. feeling down, lonely, anxious, empty)	☐	☐	☐	☐	☐
Ageing	☐	☐	☐	☐	☐
Alcohol	☐	☐	☐	☐	☐
Smoking	☐	☐	☐	☐	☐
Accident or injury	☐	☐	☐	☐	☐
Personality	☐	☐	☐	☐	☐
Altered Immunity	☐	☐	☐	☐	☐
Overweight	☐	☐	☐	☐	☐
Hormonal changes	☐	☐	☐	☐	☐
Wear and tear on the joints	☐	☐	☐	☐	☐
Having gum disease	☐	☐	☐	☐	☐

Section 1.4. This section asks how easily you understand written and numerical information.

These questions help us to ensure that health information is delivered in a way that is easy to understand.

Please tick the answer that best describes you:

How often do you need to have someone help you when you read instructions, pamphlets, or other written material from your doctor or pharmacy?

☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

How good are you at working with fractions?

1	2	3	4	5	6
Not good at all					Extremely good

How good are you at figuring out how much a shirt will cost if it is 25% off?

1	2	3	4	5	6
Not good at all					Extremely good

How often do you find numerical information to be useful?

1	2	3	4	5	6
Never					Very often

Section 1.5. This section asks for your views about how much information you need about your health, and how involved you think you should be in decisions about your health.

For each of the following statements, please tick one box to show how much you agree or disagree:

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
As you become sicker you should be told more and more about your illness	☐	☐	☐	☐	☐
You should understand completely what is happening inside your body as a result of your illness	☐	☐	☐	☐	☐
Even if the news is bad you should be well informed	☐	☐	☐	☐	☐
Your doctor should explain the purpose of your laboratory tests	☐	☐	☐	☐	☐
You should be given information only when you ask for it	☐	☐	☐	☐	☐
It is important for you to know all the side effects of your medications	☐	☐	☐	☐	☐

When there is more than one way to treat a problem, you should be told about each	☐	☐	☐	☐	☐

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
Information about your illness is as important to you as treatment	☐	☐	☐	☐	☐
The important medical decisions should be made by the doctor, not by you	☐	☐	☐	☐	☐
You should go along with your doctor's advice even if you disagree with it	☐	☐	☐	☐	☐
When hospitalized, you should not be making decisions about your own care	☐	☐	☐	☐	☐
You should feel free to make decisions about everyday medical problems	☐	☐	☐	☐	☐
If you were sick, as your illness became worse you would want the doctor to take greater control	☐	☐	☐	☐	☐
You should decide how frequently you need a check-up	☐	☐	☐	☐	☐

Section 1.6: This section asks how you usually cope with problems and illness.

For each of the following statements, please tick one box to show how much you agree or disagree:

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
I say so if I am angry or sad	☐	☐	☐	☐	☐
I like to talk with a few chosen people when things get too much for me	☐	☐	☐	☐	☐
I make an active effort to find a solution to my problems	☐	☐	☐	☐	☐
Physical exercise is important to me	☐	☐	☐	☐	☐
I think something positive could come out of my complaints/problems	☐	☐	☐	☐	☐
I firmly believe that my problems will decrease (and my situation improve)	☐	☐	☐	☐	☐
I try to forget my problems	☐	☐	☐	☐	☐
I put my problems behind me by concentrating on something else	☐	☐	☐	☐	☐
I bury myself in work to keep my problems at a distance	☐	☐	☐	☐	☐

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
I often find it difficult to do something new	☐	☐	☐	☐	☐
I am well on the way towards feeling I have given up	☐	☐	☐	☐	☐
I withdraw from other people when things get difficult	☐	☐	☐	☐	☐
In uncertain times I usually expect the best	☐	☐	☐	☐	☐
I'm always optimistic about my future	☐	☐	☐	☐	☐
Overall, I expect more good things to happen to me that bad	☐	☐	☐	☐	☐
I am a person who usually talks to other people about my problems, concerns and daily life event	☐	☐	☐	☐	☐

END OF PART 1

If you would like to, you could take a break before completing Part 2.

Survey for people with rheumatoid arthritis

PART 2

Part 2 of this survey asks how you would feel about tests that predicted someone's risk of developing rheumatoid arthritis, and how you would feel about giving information to family members about their chances of developing rheumatoid arthritis in the future. It contains the following sections:

Section 2.1. This section asks if you would like your relatives to take a test that predicted how likely they are to develop rheumatoid arthritis (RA).

Please note that throughout this survey, the word 'relative' refers to close, biological (blood) relatives. This includes sons and daughters (but not step-children) and sisters and brothers (but not half-siblings).

Please complete this section if you have biological children or full siblings who do not have rheumatoid arthritis. Otherwise, please continue to the next section (Section 2.2, page 21).

For each of the following statements, please tick one box that best describes your views:

If, in the next 6 months, your doctor offered your children a test that predicted their risk of developing RA, would you like them to take the test?

☐	☐	☐	☐	☐
No definitely not	No probably not	Yes probably	Yes definitely	Does not apply to me

If, sometime in the future, your doctor offered your children a test that predicted their risk of developing RA, would you like them to take the test?

☐	☐	☐	☐	☐
No definitely not	No probably not	Yes probably	Yes definitely	Does not apply to me

If, in the next 6 months, your doctor offered your siblings a test that predicted their risk of developing RA, would you like them to take the test?

☐ No definitely not	☐ No probably not	☐ Yes probably	☐ Yes definitely	☐ Does not apply to me

If, <u>sometime in the future</u>, your doctor offered your <u>siblings</u> a test that predicted their risk of developing RA, would you like them to take the test?

☐ No definitely not	☐ No probably not	☐ Yes probably	☐ Yes definitely	☐ Does not apply to me

Section 2.2. This section asks about for your views on the advantages and disadvantages of someone finding out how likely they are to develop rheumatoid arthritis (RA) in the future.

For each of the following statements, please tick one box to show how much you agree or disagree:

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly Agree
Finding out they were at high risk of developing RA would help a person get treated quickly if they developed symptoms of RA	☐	☐	☐	☐	☐
A person found to be at high risk of developing RA would be able to lower their risk by taking medicines	☐	☐	☐	☐	☐
A person found to be at high risk of developing RA could lower their risk by making changes to their lifestyle	☐	☐	☐	☐	☐
Finding out they were at high risk of developing RA would help a person feel prepared if they developed symptoms of RA	☐	☐	☐	☐	☐
Finding out their risk of developing RA would give a person control over their health	☐	☐	☐	☐	☐
Finding out their risk of developing RA would help a person to make important decisions about how to live their lives	☐	☐	☐	☐	☐

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly Agree
Knowing that their risk of developing RA was low would bring a person peace of mind	☐	☐	☐	☐	☐
Not knowing their risk of developing RA could make a person anxious	☐	☐	☐	☐	☐
People should find out their risk of developing RA for the sake of their family	☐	☐	☐	☐	☐
People should find out their risk of developing RA to determine whether their children might be at risk	☐	☐	☐	☐	☐
People should find out their risk of developing RA at an early age	☐	☐	☐	☐	☐
I prefer not to think about things that might never happen	☐	☐	☐	☐	☐
Getting a test to predict their risk of developing RA would tell a person that they definitely would, or wouldn't develop RA	☐	☐	☐	☐	☐
Getting a test to predict their risk of developing RA would be a stressful experience for a person	☐	☐	☐	☐	☐
Getting a test to predict the risk of a person developing RA	☐	☐	☐	☐	☐

would be a stressful experience for their relatives					
	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly Agree
The relatives of someone found to be at high risk of developing RA would be upset	☐	☐	☐	☐	☐
Knowing that they were at high risk of developing RA would harm a person's self-image	☐	☐	☐	☐	☐
People found to be at high risk of developing RA may become depressed as a result	☐	☐	☐	☐	☐
People found to be at high risk of developing RA may become anxious as a result	☐	☐	☐	☐	☐
People found to be at high risk of developing RA are likely to worry unnecessarily about their health	☐	☐	☐	☐	☐
Parents found to be at high risk of developing RA are likely to feel guilty about the possibility of passing the risk on to their children	☐	☐	☐	☐	☐
People found to be at high risk of developing RA may not be able to get insurance	☐	☐	☐	☐	☐

People found to be at high risk of developing RA may be discriminated against	☐	☐	☐	☐	☐

Section 2.3. This section asks about how likely you would be to pass on information from a healthcare professional to your relatives about their risk of developing rheumatoid arthritis.

Please note that throughout this survey, the word 'relative' refers to close biological (blood) relatives. This includes sons and daughters (but not step-children) and sisters and brothers (but not half-siblings).

Please complete this section if you have biological children or full siblings who do not have rheumatoid arthritis. Otherwise, please skip both this section and the next and continue to section 2.5 on page 32

For each of your children and siblings who do not have rheumatoid arthritis, please tick the appropriate boxes to show:

1. how they are related to you
2. how likely you would be to pass on information from a healthcare professional to them about their risk of developing rheumatoid arthritis
3. whether or not you will invite them to take part in the survey for relatives

Relative 1: **How likely would you be to pass on information to this relative about their risk of developing rheumatoid arthritis?**

This is my...
☐ Daughter
☐ Son
☐ Sister
☐ Brother

☐	☐	☐	☐	☐
Extremely unlikely	Unlikely	Neither likely nor unlikely	Likely	Extremely likely

I will invite Relative 1 to take part in the survey for relatives: ☐ Yes ☐ No

Relative 2: **How likely would you be to pass on information to this relative about their risk of developing rheumatoid arthritis?**

This is my…	☐ Extremely unlikely	☐ Unlikely	☐ Neither likely nor unlikely	☐ Likely	☐ Extremely likely
☐ Daughter ☐ Son ☐ Sister ☐ Brother					

I will invite Relative 2 to take part in the survey for relatives: ☐ Yes ☐ No

Relative 3: How likely would you be to pass on information to this relative about their risk of developing rheumatoid arthritis?

This is my…	☐ Extremely unlikely	☐ Unlikely	☐ Neither likely nor unlikely	☐ Likely	☐ Extremely likely
☐ Daughter ☐ Son ☐ Sister ☐ Brother					

I will invite Relative 3 to take part in the survey for relatives: ☐ Yes ☐ No

Relative 4: How likely would you be to pass on information to this relative about their risk of developing rheumatoid arthritis?

This is my…	☐ Extremely unlikely	☐ Unlikely	☐ Neither likely nor unlikely	☐ Likely	☐ Extremely likely
☐ Daughter ☐ Son ☐ Sister ☐ Brother					

I will invite Relative 4 to take part in the survey for relatives: ☐ Yes ☐ No

Relative 5: How likely would you be to pass on information to this relative about their risk of developing rheumatoid arthritis?

This is my…	☐ Extremely unlikely	☐ Unlikely	☐ Neither likely nor unlikely	☐ Likely	☐ Extremely likely
☐ Daughter ☐ Son ☐ Sister ☐ Brother					

I will invite Relative 5 to take part in the survey for relatives: ☐ Yes ☐ No

Relative 6: **How likely would you be to pass on information to this relative about their risk of developing rheumatoid arthritis?**

This is my...
☐ Daughter
☐ Son
☐ Sister
☐ Brother

☐ Extremely unlikely	☐ Unlikely	☐ Neither likely nor unlikely	☐ Likely	☐ Extremely likely

I will invite Relative 6 to take part in the survey for relatives: ☐ Yes ☐ No

Relative 7: **How likely would you be to pass on information to this relative about their risk of developing rheumatoid arthritis?**

This is my...
☐ Daughter
☐ Son
☐ Sister
☐ Brother

☐ Extremely unlikely	☐ Unlikely	☐ Neither likely nor unlikely	☐ Likely	☐ Extremely likely

I will invite Relative 7 to take part in the survey for relatives: ☐ Yes ☐ No

Relative 8: **How likely would you be to pass on information to this relative about their risk of developing rheumatoid arthritis?**

This is my...
☐ Daughter
☐ Son
☐ Sister
☐ Brother

☐ Extremely unlikely	☐ Unlikely	☐ Neither likely nor unlikely	☐ Likely	☐ Extremely likely

I will invite Relative 8 to take part in the survey for relatives: ☐ Yes ☐ No

Do you have more than 8 biological children or full siblings?

☐ Yes ☐ No

If yes, please tell us how many more:

I have ..... more children and/or I have ..... more siblings

If yes, please tell us how many of these additional children/siblings you would be likely to pass on information to about their risk of developing rheumatoid arthritis:

I would be likely to pass on information to ..... of these additional

children and/or ..... of these additional siblings

For those relatives listed above who will NOT be invited to take part in the survey for relatives, please tell us why.

Please tick the box, or boxes below that best describe the reason(s) why (please tick all the boxes that apply):

☐ I do not have enough copies of the survey

☐ They are under 18

☐ They are too elderly

☐ They do not speak / understand English

☐ They cannot read / write

☐ They might not have time to complete the survey

☐ I don't have time to pass the survey on to them

☐ They might not be interested in completing the survey

☐ They might be upset if I ask them to complete the survey

☐ They might worry about some of the issues raised by the survey

☐ They are dealing with illnesses other than rheumatoid arthritis

☐ I don’t see them very often

☐ I am not in touch with them

☐ I don’t have a close relationship with them

☐ They live far away

☐ I don’t like talking to them about my rheumatoid arthritis

☐ Other (please write in):

Section 2.4. This section asks about possible reasons why you might be unlikely to pass on information to your relative(s) about their risk of developing rheumatoid arthritis (RA).

Please complete this section if you have biological children or full siblings who do not have rheumatoid arthritis. Otherwise, please skip this section and continue to section 2.5 on page 32

If you answered "extremely likely" for every relative listed in the previous section (section 2.3), please skip this section and continue to section 2.5 on page 31.

The following statements are possible reasons why you might prefer NOT to pass on information to a relative about their risk of developing RA. For each of the possible reasons, please tick one box to show whether it applies to ANY of the relatives that you listed in the previous section:

I am unlikely to pass on information to one or more of my relatives because…	Definitely does not apply	Does not apply	Neutral	Applies	Definitely applies
I think that their risk of developing RA is low	☐	☐	☐	☐	☐
I'm not worried about the possibility that they might develop RA	☐	☐	☐	☐	☐
There is nothing that can be done to lower their risk of developing RA	☐	☐	☐	☐	☐

I would rather not think about the possibility that they might develop RA	☐	☐	☐	☐	☐
I am unlikely to pass on information to <u>one or more</u> of my relatives because…	Definitely does not apply	Does not apply	Neutral	Applies	Definitely applies
They would rather not think about the possibility that they might develop RA	☐	☐	☐	☐	☐
They would be unlikely to do anything about their risk of developing RA	☐	☐	☐	☐	☐
It is not my responsibility	☐	☐	☐	☐	☐
They are too young	☐	☐	☐	☐	☐
They are too old	☐	☐	☐	☐	☐
I don't want to worry them	☐	☐	☐	☐	☐
The conversation would make me feel anxious	☐	☐	☐	☐	☐
They have other problems to deal with	☐	☐	☐	☐	☐
I have other problems to deal with	☐	☐	☐	☐	☐
They are busy	☐	☐	☐	☐	☐
I am busy	☐	☐	☐	☐	☐

They might feel embarrassed	☐	☐	☐	☐	☐
I am unlikely to pass on information to <u>one or more</u> of my relatives because…	Definitely does not apply	Does not apply	Neutral	Applies	Definitely applies
I would feel embarrassed	☐	☐	☐	☐	☐
I would feel guilty	☐	☐	☐	☐	☐
They might blame me	☐	☐	☐	☐	☐
I would feel that I was invading their privacy	☐	☐	☐	☐	☐
They would feel that I was invading their privacy	☐	☐	☐	☐	☐
They think RA is something that affects older people	☐	☐	☐	☐	☐
They do not understand the impact that RA has on my life	☐	☐	☐	☐	☐
They feel healthy at the present time	☐	☐	☐	☐	☐
I do not have a close relationship with them	☐	☐	☐	☐	☐
I am not currently in contact with them	☐	☐	☐	☐	☐
They live far away from me	☐	☐	☐	☐	☐

I don't like talking about my RA with them	☐	☐	☐	☐	☐
I am unlikely to pass on information to <u>one or more</u> of my relatives because…	Definitely does not apply	Does not apply	Neutral	Applies	Definitely applies
They don't like it when I talk about my RA	☐	☐	☐	☐	☐
I don't want them to know that I've got RA	☐	☐	☐	☐	☐
I don't have enough information about their risk of developing RA	☐	☐	☐	☐	☐
Doctors cannot tell them for certain that they will, or won't develop RA	☐	☐	☐	☐	☐

Section 2.5. This section asks about how your family members support each other in general.

Please tick one box to show how much you agree or disagree with each statement:

	Strongly disagree	Disagree	Agree	Strongly Agree
Planning family activities is difficult because we misunderstand each other	☐	☐	☐	☐
In time of crisis we can turn to each other for support	☐	☐	☐	☐
We cannot talk to each other about sadness we feel	☐	☐	☐	☐
Individuals are accepted for what they are	☐	☐	☐	☐
We avoid discussing our fears and concerns	☐	☐	☐	☐
We can express feelings to each other	☐	☐	☐	☐
There are lots of bad feelings in the family	☐	☐	☐	☐
We feel accepted for what we are	☐	☐	☐	☐
Making decisions is a problem for our family	☐	☐	☐	☐

We are able to make decisions about how to solve problems	☐	☐	☐	☐

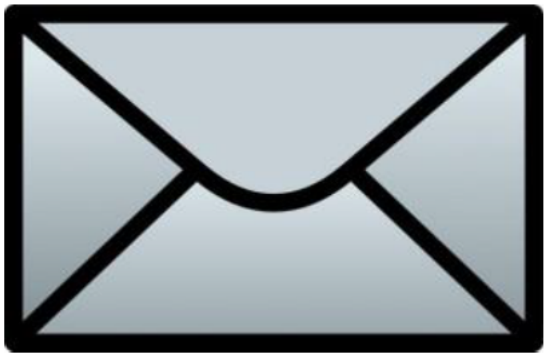
	Strongly disagree	Disagree	Agree	Strongly Agree
We don't get along well together	☐	☐	☐	☐
We confide in each other	☐	☐	☐	☐

END OF PART 2

If you would like to tell us about any feelings you have about the issues raised in this survey, please use the space below.

END OF SURVEY

You have reached the end of this survey. Thank you very much for taking the time to complete it. Your views are very important to us and will help us to ensure that we are meeting the needs of patients and their relatives in the future.



Please check that you have completed all sections of the survey, and return it to us in the reply paid envelope provided.

A leaflet containing information for relatives of people with rheumatoid arthritis about the risk of developing rheumatoid arthritis in the future can be found at www.birmingham.ac.uk/Arthritis-Booklet-Relatives. If you would like us to send you a printed copy of this leaflet, please send your name and address to , or telephone or write to:

Dr Marie Falahee, Rheumatology Research Group, Institute of Inflammation and Ageing, University of Birmingham, Queen Elizabeth Hospital, Birmingham B15 2WB.

If you would be interested in taking part in other research projects like this one, or have any questions about this survey, please get in touch with us using the contact details above.

If you are concerned about any issues related to your health, or issues that you came across while completing this questionnaire, please contact your GP in the first instance. If you would like more information about rheumatoid arthritis you can contact Arthritis Research UK (www.arthritisresearchuk.org; telephone 01246 558033), or the National Rheumatoid Arthritis Society (www.nras.org.uk; Freephone helpline 0800 2987650)

There are also Patient Advice and Liaison Services at City Hospital. You can contact PALS services over the phone (0121 507 5836), via

email (swb-tr.pals@nhs.net), or by visiting the hospital and asking to be directed towards the PALS office.

Appendix 5

Sensitivity analysis for children, including a factor analysis and univariate analyses

Factor labels and factor loadings from a principal components analysis of items measuring perceived advantages and disadvantages of learning about RA risk status.

Factors	Items	Factor Loadings
1. Psychological harm to self as a result of knowing risk	"If I was found to be at high risk of developing rheumatoid arthritis I would be likely to worry unnecessarily about my health"	0.79
	"If I was found to be at high risk of developing rheumatoid arthritis I may become anxious as a result"	0.79
	"If I was found to be at high risk of developing rheumatoid arthritis I may become depressed as a result"	0.68
	"Knowing that I was at high risk of developing rheumatoid arthritis would harm my self-image"	0.49
	"If I was found to be at high risk of developing rheumatoid arthritis I would be likely to feel guilty about the possibility of passing the risk on to my children"	0.41
2. Increased empowerment over health	"If I was found to be at high risk of developing rheumatoid arthritis, I would be able to lower my risk by making changes to my lifestyle"	0.81
	"Finding out my risk of developing rheumatoid arthritis would help me feel prepared if I developed symptoms of rheumatoid arthritis"	0.75
	"Finding out my risk of developing rheumatoid arthritis would give me control over my health"	0.70
	"Finding out my risk of developing rheumatoid arthritis would help me to make important decisions about how to live my life"	0.65
	"If I was found to be at high risk of developing rheumatoid arthritis, I would be able to take medicines to lower my risk"	0.64
	"Finding out my risk of developing rheumatoid arthritis would help me to get treated quickly if I developed symptoms of rheumatoid arthritis"	0.48
	"Knowing that my risk of developing rheumatoid arthritis was low would give me peace of mind"	0.39
3.Desire for risk knowledge	"I should find out my risk of developing rheumatoid arthritis to determine whether my children might be at risk"	-0.79
	"I should find out my risk of developing rheumatoid arthritis for the sake of my family"	-0.74
	"I should find out my risk of developing rheumatoid arthritis at an early age"	-0.70

	“Not knowing my risk of developing rheumatoid arthritis could make me anxious”	-0.65
	“I prefer not to think about things that might never happen”	0.63
4. Family (di)stress associated with experience of getting a test	“Getting a test to predict my risk of developing rheumatoid arthritis would be a stressful experience for my relatives”	0.91
	“My relatives would be upset if I was found to be at high risk of developing rheumatoid arthritis”	0.69
	“Getting a test to predict my risk of developing rheumatoid arthritis would be a stressful experience for me”	0.67
5. Social consequences as a result of predictive testing	“If I was found to be at high risk of developing rheumatoid arthritis I may not be able to get insurance”	0.86
	“If I was found to be at high risk of developing rheumatoid arthritis I may be discriminated against”	0.78
6. Accuracy of predictive testing	“Getting a test to predict my risk of developing rheumatoid arthritis would tell me that I definitely would, or definitely wouldn’t develop rheumatoid arthritis”	-0.78

Univariate analyses for children's characteristics and their associations with interest in predictive testing for RA (N=295)

Children's characteristics	Association with interest in predictive testing	
	Statistics	**P**
Age (years)	0.05 [rs]	0.36
Deprivation index	-0.12 [rs]	0.06
Gender		0.04
Male	3 (2-3) [U]	
Female	3 (2-3) [U]	
Employment		0.77
Employed	3 (2-3) [H]	
Unemployed	3 (2-3) [H]	
Other	3 (3-3) [H]	
Ethnic Group		0.95
White	3 (2-3) [H]	
Mixed	3 (2-3) [H]	
Asian	3 (2-3) [H]	
Black	3 (2-3) [H]	
Other	3 (3-3) [H]	
Smoking		0.73
Current	3 (2-3) [H]	
Ever	3 (2-3) [H]	
Never	3 (2-3) [H]	
Education		
A level or lower	3 (2-3) [U]	0.15
Higher than A level	3 (2-3) [U]	
Living with index patient		0.11
Yes	3 (2-3) [U]	
No	3 (2-3) [U]	
Frequency of talking to index patient	0.02 [rs]	0.79
Perceived absolute risk	0.34 [rs]	<0.001
Perceived relative risk	0.37 [rs]	<0.001
Perceived experiential risk	0.32 [rs]	<0.001
Worry about risk	0.24 [rs]	<0.001
Health literacy	0.02 [rs]	0.73
Subjective numeracy	-0.05 [rs]	0.42
Brief illness perception questionnaire		
Consequences	0.07 [rs]	0.22
Timeline	0.16 [rs]	0.005
Personal control	0.01 [rs]	0.92
Treatment control	-0.04 [rs]	0.53
Identity	0.11 [rs]	0.05
Concern	0.21 [rs]	<0.001
Understanding	0.06 [rs]	0.34
Emotional	0.11 [rs]	0.06
Information Seeking	0.28 [rs]	<0.001

Decision making	-0.09 [rs]	0.12
Brief Avoidance Coping Questionnaire	0.12 [rs]	0.04
Optimism	0.08 [rs]	0.20
Health anxiety overall	0.09 [rs]	0.12
Attitudes towards testing		
Desire for risk knowledge	-0.45 [rs]	<0.001
Psychological harm to self as a result of knowing risk	-0.14 [rs]	0.02
Increased empowerment over health	0.34 [rs]	<0.001
Family (di)stress associated with experience of getting a test	-0.10 [rs]	0.11
Accuracy of predictive testing	-0.18 [rs]	0.002
Social consequences as a result of testing	-0.06 [rs]	0.34

[rs]= Spearman's rank correlation, [H]= Kruskal-Wallis H test, [U]= Mann-Whitney U test. Correlation coefficients are reported for Spearman's rank correlations, medians and IQRs are reported for Kruskal-Wallis H and Mann-Whitney U tests.

Appendix 6
Background questionnaire for the qualitative interview study

Background Questionnaire

Study ID:

Date:

What is your gender?

☐ Male ☐ Female ☐ Prefer not to disclose

What is your role in practice?

How many years since qualification?

Are you a rheumatologist/rheumatology nurse specialist?

☐ Yes ☐ No

If you answered no, do you have a specialist interest in rheumatology?

Appendix 7
Consent form for the qualitative interview study

Participant Consent Form

Stakeholder perceptions of preventive approaches to rheumatoid arthritis: Qualitative study of healthcare professionals' perspectives on predictive and preventive strategies

Chief Investigator: Marie Falahee, Rheumatology Research Group, Institute of Inflammation and Ageing (IIA), University of Birmingham; Queen Elizabeth Hospital, Birmingham, B15 2WB
Direct Line: + E mail:

This form should be produced in conjunction with the participant information sheet. Please read the statements below. If you agree to the statements, please initial each box and sign the consent form to confirm that you agree to take part in this study.

	Please initial each box
I have read the information sheet dated xx version XX regarding this study and I have had an opportunity to ask questions or discuss any concerns about it. Any questions have been answered to my satisfaction	
I was given sufficient time to decide whether I am willing to participate in this study	
I understand that my participation is voluntary and that I am free to withdraw my participation prior to and during the interview, without my legal rights being affected. I understand that I still have the right to withdraw from this study for up to 1 week after the interview by contacting the research team	
I am aware that all my responses to the background questionnaire and my contributions to the interview will be identified by a participant number, not my name	
I agree that the researchers will collect information about me as described in the information sheet dated xx version XX: including information on gender and occupation, and for them to enter this information into a secure electronic database	
I understand that content from the interview will be looked at by researchers from the University of Birmingham and I agree for these individuals to have access to this information	
I agree that direct quotations can be taken from my interview and published anonymously	
I agree that my interview will be audio recorded, and that this recording will be identified by a participant number, not my name. The recording will be kept on	

secure servers using password protected and networked devices. The recording will be deleted after the interview has been transcribed.	
I understand that the researchers make use of an external company to transcribe the interview. The transcription company will receive the recording of the interview identified only by a unique number. The transcription company is bound to a strict confidentiality agreement	
I agree that my anonymised data can be shared among the research team.	
I agree that my coded data may be used to address research questions in future studies complying to national and international data protection regulations.	
I agree to my data collected during the study being looked at by individuals from the research team, representatives of the sponsor, from regulatory authorities or from the NHS Trust, where this is relevant to my taking part in this research. I agree for these individuals to have direct access to my records.	
I agree that the study results can later be used for publications as well as educational purposes	
I hereby confirm my voluntary participation in this project	

Please indicate your response to the statement below:

I would like to receive a summary of the study findings, and agree that the researchers hold my contact details for this purpose. I am aware that once I have been given a summary of the findings, my contact details will be deleted.

☐ **Yes** ☐ **No**

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Name of Researcher	Date	Signature

Appendix 8
Interview schedule for the qualitative interview study

Interview Schedule

Predictive testing

General introduction:

This study will explore your perceptions towards predictive and preventive interventions for rheumatoid arthritis (RA). There are currently a number of studies working on creating predictive strategies to identify those who are at risk of developing RA in the future. There is also a strong research focus on identifying effective treatments for the early stages of RA, including even before the onset of symptoms in those "at risk" of RA.

In light of these current developments, we would like to gain an understanding of your thoughts about the use of these approaches and their potential impact within clinical practice. This information is important as it can help to inform the design of future predictive and preventive strategies.

The initial questions will relate to your perceptions regarding predictive testing for RA for anyone who might be at risk of RA but hasn't yet developed it. In this context, predictive testing will include any test that can provide information about whether a person is likely to develop a specific condition in the future.

- **Do you think it's important to be able to predict RA development in those at risk?**
    - Why/why not?

- **Do you think the tools we have at the moment are adequate**?
    - Why/why not?
    - E.g. bloods for inflammatory markers, ACPA, RF, ultrasound/ MRI scans.

- **What do you currently know about measures that could increase the ability to predict the likelihood of developing Rheumatoid Arthritis?**

You will now be provided with some short scenarios describing individuals who come to you sharing some concerns about their health. Once you have been presented with a scenario, you will be asked a series of questions related to that scenario.

Vignette 1:

A patient has mentioned that they find it difficult to get out of bed in the morning because their joints are very stiff. They state that their finger and wrist joints hurt in particular and hurt most when they wake in the morning, but can last all day. The patient has not reported any swelling of the joints and there was none to find on examination.

Vignette 2:

A patient comes to you mentioning that they are concerned about developing RA because their mother has been living with RA for a number of years.

Questions to be asked after the presentation of each vignette:

1. **What would you do?**
   - Prompt: Are there any (other) tests that might be useful in this situation e.g. blood tests (RF, ACPA, inflammatory markers (e.g. CRP/ESR?) or imaging (e.g. ultrasound /MRI)
   - Why / why not?

2. **How useful would you find the results of these tests? How would these results impact on your decision making (what you would do next)?**
   - Prompt: how useful would a test be which indicates a high likelihood/ low likelihood/ intermediate likelihood that an individual will develop RA?
   - What would count as a high/low/intermediate likelihood?

You will now be asked some more general questions about predictive testing:

3. **How likely to develop RA in the future would someone need to be in order for medical action (preventive intervention) to be needed. What action (if any) would be appropriate?**
   - For example, would a person need to be 20%, 50%, or 70% likely to develop RA for a preventive intervention to be needed, in your opinion?
   - There are no right or wrong answers.
4. **How would you explain the results of predictive tests to patients?**
   - Risk score, graphical, other?

5. **How may measures that increase the current ability to predict that someone will develop RA in the future affect healthcare services if at all?**
   - How might they impact on your role within the healthcare service?
   - What impact might predictive tests have on current healthcare resources?

6. **How do you think healthcare services could be set up to provide predictive approaches for RA most effectively?**
   - What resources might be most beneficial to allocate to existing healthcare services to facilitate integration of predictive approaches?

7. **In what situations would an increased ability to predict RA be most useful?**
   - Why?

8. **What is most important to predict: Development of RA? Time to onset of RA? Severity of RA? Other outcomes?**

9. **What issues or concerns would you have about doing tests to predict future development of RA in people who don't currently have RA?**
   - What issues are there with integrating it into clinical practice?

10. **What benefit might there be in predicting future development of RA in people who don't currently have RA?**
    - What benefits might there be to integrating this into clinical practice?

11. **What type of healthcare professional do you think would provide predictive tests?**
    - What are your reasons for thinking this?

Preventive Treatment

General introduction:

- What do you currently know about interventions to prevent the development of RA?

Preventive interventions refer to any form of intervention that can lower the likelihood of developing a specific disease. These interventions can take the form of lifestyle interventions to decrease disease risk through, for example, changing nutrition and physical activity, or smoking cessation. Alternatively, drug treatments can be provided to lower RA risk. There are currently trials exploring the preventive efficacy of treatments such as hydroxychloroquine, methotrexate, rituximab and abatacept for those who are at different stages of risk for developing RA.

The following questions will relate to both lifestyle-interventions and pharmacological treatments, unless specifically stated otherwise. If your opinion differs for each type of intervention, feel free to mention this and explain why.

Questions:

1. **What are your views regarding the potential for preventive interventions for RA? Do you think RA can be prevented in people at risk?**

2. **What type of healthcare professional do you think would provide preventive interventions?**
    - What are your reasons for thinking this?
    - Prompt – is there a difference in your answer between drug treatments and another type of intervention?
3. **In what situation would you be most likely to suggest a lifestyle mediated preventive intervention such smoking cessation?**
    - Why?

4. **In what situation would you be most likely to suggest a preventive treatment in the form of a pharmacological agent such as methotrexate?**
    - Why?

5. **How do you think the introduction of preventive interventions would affect healthcare services if at all?**
    - How might they impact on your role within the healthcare service?
    - What impact might preventive treatment have on current healthcare resources?

6. **How do you think healthcare services could be set up to provide preventive approaches for RA most effectively?**

- What resources might be most beneficial to allocate to existing healthcare services to facilitate integration of preventive approaches?

7. **What issues might there be surrounding the introduction of these interventions into clinical practice?**
    - Prompt: concerns about risks of interventions especially re: drug treatments. What's the acceptable risk of the treatment or of the development of RA for it to be used?
    - Issues surrounding introduction for those at risk of developing RA?

8. **What benefits might there be surrounding the introduction of these interventions to clinical practice?**
    - Benefits surrounding introduction for those at risk of developing RA?

9. **What level of risk for developing RA should a patient have for a preventive intervention to be considered?**
    - E.g. high/ low/intermediate risk?
    - What are your reasons for thinking this?

10. **How would a patient's risk status affect the type of preventive intervention you would prescribe?**
    - E.g. would lower risk make you more likely to prescribe lifestyle, or drugs?
    - 20%, 50%, 70% risk?

11. **What level of benefit should a preventive intervention offer to be considered?**
    - E.g. complete prevention, delayed onset?

12. **How long should preventive interventions be recommended for?**
    - What are your reasons for thinking this?
    - Prompt: Is there a difference in your answer between drug treatments and another type of intervention?

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