Abstract (296 words):

Effective treatments for rheumatoid arthritis (RA) are available and can lead to remission for some patients but most patients remain on potentially toxic and expensive medications in the long term. Interest is increasingly turning to the disease phases preceding the development of RA that represent opportunities for preventive interventions. ‘At risk’ target populations include individuals with genetic and environmental risk factors, those who have developed systemic autoimmunity, and those who have developed clinically suspect symptoms (e.g. arthralgias without synovitis, or an early arthritis).

Ongoing prospective studies will inform the development of increasingly accurate predictive tools to identify individuals at risk of developing RA. Furthermore a range of preventive approaches have been suggested, including lifestyle modification (e.g. smoking cessation) and pharmacological interventions (e.g. hydroxychloroquine, methotrexate, abatacept, rituximab) that are currently the subject of randomised controlled trials.

As prediction and prevention of RA evolve, it is increasingly likely that those at risk (including asymptomatic individuals) may be faced with complex decisions about whether to accept assessment of their risk status or to take a preventive intervention associated with risk of serious adverse events and uncertain benefit. Acceptance of preventive medication in other contexts can be low. For example, less than 25% of women at high risk for breast cancer are willing to take preventive hormonal treatments. Actual uptake is lower still.

Patients’ beliefs and preferences predict treatment uptake and adherence. Before the dream of preventing RA can become reality, healthcare providers need to understand the perspectives of individuals in the target population, to identify barriers and facilitators for this approach. This commentary will review what is currently known about the perspectives of patients and individuals at risk about predictive and preventive approaches for RA and identify gaps to be addressed to inform the development of efficient preventive strategies.
Rheumatoid arthritis (RA) is a common chronic inflammatory disease affecting approximately 1% of the population. Painful swelling of the joints is typically accompanied by fatigue and depression, and without effective treatment RA can lead to joint destruction and deformity. A number of treatments are now available for patients with RA that can, in some cases, lead to disease remission, but most patients have to remain on potentially toxic and often expensive medications in the long term. Furthermore, many patients have persistent synovial inflammation despite current therapeutic approaches and some experience significant extra-articular complications of their RA, including cardiovascular disease and osteoporotic fractures. RA presents a significant burden not only to the individual and their families, but also to society through increased healthcare utilisation, disability and reduced ability to work. Given this, interest is increasingly turning to the phases of disease leading up to the development of RA during which interventions may be put in place to reduce the risk of RA development. Accurate identification of individuals at risk of developing RA and effective prevention would likely provide a highly cost-effective strategy for the management of this condition.

European League Against Rheumatism (EULAR) recommendations for prospective studies identify distinct ‘at risk’ groups, each of which represents a potential opportunity for preventive intervention. Individuals without RA who are key target groups for preventive approaches may have one or more of the following: [1] genetic risk factors for RA; [2] environmental risk factors for RA; [3] systemic autoimmunity associated with RA (typically associated with the development of rheumatoid factor and/or anti-citrullinated protein/peptide antibodies in the blood); [4] musculoskeletal symptoms suggestive of underlying inflammation but without clinically apparent synovial swelling (also known as clinically suspect arthralgias); [5] an early arthritis that does not yet fulfil classification criteria for RA.

Predictive tools are currently available that can estimate the risk of RA development for patients in different at risk phases. For example, tools have been developed to predict RA development in patients with arthralgias and systemic autoimmunity and undifferentiated arthritis. These rules include a range of clinical and laboratory variables including inflammatory markers and the levels of a range of RA related autoantibodies. Additional predictive variables have also been explored. In
patients with arthralgias these include the interferon signature and B cell signatures and ultrasound findings in the joints. In patients with unclassified arthritis the presence of ultrasound defined subclinical synovitis and tenosynovitis have also been investigated. Furthermore, tools are being developed to predict RA in individuals in earlier ‘at risk’ stages, for example in individuals with a family history of RA. Having identified individuals as being at risk of RA, a range of potential approaches may be available to reduce RA risk. These include lifestyle modification and pharmacological interventions. Of lifestyle modifications, smoking cessation is likely to be most beneficial but other environmental risk factors have been defined for RA including silica dust and air pollution which may also be amenable to environmental modification. Amongst pharmacological interventions, the first to be assessed in the context of a clinical trial was intramuscular glucocorticoid, which did not delay arthritis development in patients with autoantibody positive arthralgias, but prevented 1 in 10 patients with very early inflammatory polyarthritis from progressing to RA and delayed prescription of disease modifying antirheumatic drugs (DMARDs). A trial of rituximab in patients with autoantibody positive arthralgias and either imaging synovitis or evidence of an acute phase response on blood tests showed that a single infusion of the B cell depleting agent significant delayed the onset of arthritis – but did not reduce the number of patients who eventually developed arthritis. However, the preventive effect of a number of additional drugs (e.g. hydroxychloroquine, atorvastatin, methotrexate, abatacept) is currently being assessed in randomised controlled trials. Further work is needed to define which lifestyle / pharmacological intervention is most effective in which at risk stage – with different stages likely to be amenable to different preventive approaches.

Importance of understanding ‘patient’ preferences for preventive approaches

Any preventive treatment will carry risks of adverse events without certainty of preventing the development of RA. Individuals at risk will need to understand their own risk of developing RA and be able to balance it against the risk of drug-related adverse events and the potential benefits of a preventive treatment. Communication of probabilities of risks and benefits is a complex task. Physicians can find it difficult to interpret and communicate risk effectively and patients struggle to accurately estimate and understand their own risks. The manner in which benefits and risks of treatment are presented to patients further influences health decisions. The most effective way of
conveying risk information may differ according to the individuals’ characteristics, such as personality, education, literacy and numeracy.\textsuperscript{26}

Risk aversion to adverse events has been consistently found to influence the uptake of preventive medication,\textsuperscript{27-29} which can be amplified by a general distrust in medication.\textsuperscript{30} Effectiveness of treatment seems to have a more variable impact on decision making and depends on the specific context. Participants’ willingness to take treatment for cardiovascular prevention changed little with variations in treatment effectiveness.\textsuperscript{31} In order to take preventive therapy patients may actually require a higher benefit than the medication can achieve.\textsuperscript{32} Other attributes of preventive treatments, such as the method of administration may have an important impact on treatment acceptance. Patients evaluating preventive medication for osteoporosis deemed the route of administration to be as important as the likelihood of adverse events.\textsuperscript{33}

Acceptance of and adherence to preventive interventions for RA will be dependent not just on the treatment risks and benefits but also on patients’ beliefs and preferences. In the context of other diseases, acceptance of preventive medication is low. Fewer than 25% of women at high risk for breast cancer are willing to take preventive hormonal treatment. Effective uptake of medication is even lower\textsuperscript{28}, and predicted by patients’ beliefs about medicine\textsuperscript{34}. Acceptance of treatment for osteoporosis is somewhat higher, but still only about half of post-menopausal women would accept preventive medication at the recommended fracture risk threshold.\textsuperscript{35}

There is therefore an increasing need for formative research to be conducted in the potential target populations for preventive intervention, to identify the most important considerations in decision making about treatments, the weight given to various treatment characteristics and how these vary according to the clinical setting. The remainder of this commentary will review what is currently known about the perspectives of patients and individuals at risk about predictive and preventive approaches for RA, and identify knowledge gaps that could usefully be addressed to inform the development of ethical and efficient preventive strategies.

Preferences for assessment of the risk of developing RA

Effective risk stratification is an essential precursor to preventive approaches and an important consideration for proof-of-concept trials as preventive efficacy may be difficult to demonstrate in
heterogeneous populations. Existing models to predict the development of RA in different ‘at risk’ groups have discriminative ability though further evidence from prospective studies is needed to validate and improve risk prediction in pre-clinical disease stages.

As prediction and prevention of RA evolve, individuals are increasingly likely to be provided with disease risk estimates, whether by healthcare professionals or via commercial providers (e.g. direct-to-consumer genetic testing). Early evidence suggests that a web-based tool providing personalized RA risk education for first degree relatives of RA patients increases participants’ knowledge of RA risk factors, intentions to change risk related behaviours, and results in risk-reducing lifestyle changes. However evidence of the impact of biomarker-based risk information on health behaviour change across disease areas is limited. Further research is needed to understand the extent to which inconsistent findings can be explained by heterogeneity in individuals’ responses to risk information.

It is important that risk information is communicated in a tailored way that is sensitive to the needs and concerns of those affected. Reviews of qualitative studies of stakeholder perceptions of predictive testing in other chronic diseases have highlighted challenging social and ethical issues associated with the provision of risk information, including concerns relating to information security and the potential for risk information to have a negative impact. Qualitative studies of the symptoms experienced by patients with a diagnosis of clinically suspect arthralgia demonstrate that being ‘at risk’ of disease progression can have a considerable negative psychological impact. On the other hand, a recent randomized controlled trial showed that personalized risk communication provided reassurance to first degree relatives of RA patients. It is therefore essential to understand the perspectives of all those likely to be affected by predictive testing for RA, to identify support needs and address preferences for the communication of risk information.

The first study to report on the perspectives of individuals at risk on predictive approaches for RA used qualitative interviews to explore the views of first-degree relatives of existing RA patients in three European countries. Participants described a lack of awareness about RA and risk factors for RA. Though participants appreciated the value of predictive approaches to facilitate early treatment and preventive intervention, concerns were raised about the accuracy of risk information and the potential for it to have a negative impact on future decision-making and the wellbeing of participants themselves and of other family members.

Reliable access to first degree relatives is usually indirect and via existing patients with a diagnosis of RA. This in turn depends on patients’ willingness to pass on information to their relatives about RA risk. It is therefore important to understand patients’ perspectives in this context to identify barriers
and facilitators to approaches targeting first-degree relatives. This was the focus of a UK based qualitative study \(^52\) which described selective and restricted family communication about RA and further emphasised a demand for informational resources about RA and risk factors for RA to support predictive approaches and communication amongst family members. Positive attitudes towards risk assessment for their relatives were associated with an expectation that the results would be able to rule in, or rule out RA. Negative viewpoints were associated with an appreciation of the probabilistic nature of risk information.

A qualitative interview study of the perspectives of both asymptomatic and symptomatic (clinically suspect arthralgias without inflammatory arthritis) individuals who had received a positive test result for anti-citrullinated protein antibodies (ACPA), that was conducted across three European countries \(^53\), found that symptomatic individuals were more likely to describe feelings of anxiety in response to learning about their risk status, and were more receptive to further predictive tests, including tissue sampling. All participants described the need for tailored, accessible informational resources to support predictive and preventive strategies for RA.

Taken together these qualitative studies highlight educational and psychological support needs for the provision of information about future development of RA. Positive viewpoints were associated with high perceived predictive accuracy and availability of highly effective preventive strategies. This aligns with findings from other chronic diseases. \(^54, 55\) Communication of the imprecision of probabilistic estimates has been shown to affect decision making about RA treatments \(^56\) and effective communication of the accuracy of prognostic models is an important challenge for predictive approaches \(^57\).

Preferences for interventions to reduce risk of developing RA

Several European qualitative studies have explored preferences relating to preventive interventions for RA of first-degree relatives \(^58-60\), RA patients \(^52, 59\), and ACPA positive individuals without arthritis \(^53\). Lifestyle change was preferred over pharmacological interventions to reduce RA risk \(^52, 53, 58-60\), however positive viewpoints were associated with the perspective that any intervention would need to substantially reduce or completely remove their risk of RA. Symptomatic individuals were more likely than asymptomatic individuals to consider preventive medications, subject to their efficacy and side-effect profile \(^53\).
Some North American indigenous populations have a prevalence of RA estimated to be 5-7% higher than in the general population, and in some populations approximately 50% of patients have relatives with the disease. A qualitative study of 14 family members of RA patients in two First Nations (Cree and Oji-Cree Nations) in Manitoba suggested that a preventive approach with oral drug intervention with low toxicity, communicated appropriately, within the context of a research study led by a known and trusted researcher might be acceptable. However, discussions in that study suggested that lifestyle change, for example smoking cessation, was of limited interest. Fear of drug side effects was highlighted as a central theme, which has also been identified in qualitative studies in Europe.

Further research has involved linked qualitative and quantitative studies to assess the preferences of at-risk populations for preventive treatments for RA. These approaches use qualitative studies to identify key aspects of decision-making, which are subsequently used to develop choice-based surveys to quantify preferences.

The first study of this kind was based in Switzerland and included interviews with 20 first-degree relatives of RA patients. The findings showed that in addition to treatment effectiveness, treatment safety (few adverse effects preferred) and mode of administration (oral tablet taken infrequently at home preferred) are likely to be the key features of a preventive treatment. The choice-based (best-worst scaling) study derived from this qualitative work confirmed that preventive treatment would have to be targeted to those at high risk of developing RA and offer a high reduction in the risk of developing RA with a low-risk of serious side effects for prevention to be acceptable. Overall, predicted uptake of preventive intervention was low, and results suggested the avoidance of risks of side effects was key to prevention; some individuals would accept a 10% risk of serious side effects for a highly effective treatment, but most would prefer a moderately effective treatment with a very low risk of serious side effects.

A similar North American study sought perspectives from patients with RA, first-degree relatives of patients, and rheumatologists to understand what might influence preferences for preventive treatment strategies to inform the development of a choice-experiment. The key features identified related to the testing (who recommends the test, accuracy of predictive testing, an individual’s risk of developing RA) and the type of preventive treatment used (how a treatment is given, reduction in the risk of developing RA, risks and seriousness of side effects, strength of supporting evidence of risks and benefits, and other people’s opinions of the treatment). Patients and first-degree relatives described wanting to hear the evidence about preventive treatments from multiple trusted sources, including people with the disease and health care professionals. Preferences elicited from
subsequent discrete choice experiments suggested that the decision to take preventive medication will depend primarily on factors other than the reduction in risk of RA.\textsuperscript{65, 66} For first-degree relatives of patients this is more likely to be how treatment is taken, the opinion of the health care professionals, and the potential risk and reversibility of side effects.\textsuperscript{65} Results from studies of patients and rheumatologists also emphasized the primary importance of the shared decision-making process, with results indicating the opinion of the rheumatologist (for patients) and patient (for rheumatologists) as having the strongest influence on preferences.\textsuperscript{66} The results from these studies indicated that of the preventive pharmaceutical treatments currently being evaluated in randomized controlled trials, non-biologic DMARDs such as hydroxychloroquine and potentially methotrexate are much more likely to be acceptable preventive options than biologic DMARDs.\textsuperscript{65, 66}

Discussion and Conclusions

This commentary has highlighted the importance of understanding the beliefs and preferences of the target population about predictive and preventive approaches to the management of RA and provided a narrative review of existing studies in this context. A range of qualitative studies have explored the perceptions of at risk groups on the quantification of an individual’s risk of developing RA and have highlighted important informational and support needs that should accompany risk assessment and the challenges of communicating risk effectively and ethically. Quantitative studies are now needed to assess and predict preference heterogeneity in relation to predictive testing and inform the development of tailored strategies. Studies of the perspectives of other stakeholders are also needed to provide a comprehensive understanding and assessment of feasibility and cost effectiveness. For example, it is important to address the perceptions of healthcare professionals in both primary and secondary care in this context, to understand the feasibility of implementing potentially complex prediction algorithms in routine clinical care. For the development and assessment of publically funded interventions it can also be argued that the preferences of members of the general public (tax-payers) should also be taken into account.\textsuperscript{67} Furthermore, genetic risk information relating to common multifactorial conditions is increasingly available to consumers outside of traditional healthcare settings.

Both qualitative and quantitative studies have addressed the preferences of first-degree relatives in relation to preventive treatments for RA, and have shown that a range of treatment attributes impact on decision making, in addition to treatment effectiveness and risks. Further work is needed to identify effective predictors of preference heterogeneity. No quantitative studies have addressed
the preferences of seropositive or symptomatic at risk individuals, despite the fact that these groups are perhaps the most likely candidates for most of the immunomodulatory agents that are currently being evaluated for prevention of RA.

It is important to note that concerns about barriers to access to preventive services were not salient themes in the studies reviewed here. These studies were conducted in Canada and in European countries where there is universal healthcare, and the findings are unlikely to be representative of populations in, for example, insurance-based healthcare systems such as the United States of America where financial barriers to preventive interventions may be a key concern. Further work is needed to explore the impact of political and sociocultural context on perceptions of risk and preventive intervention.

Decisions to take predictive tests or preventive treatments for RA are highly complex. For predictive testing to be worthwhile and RA prevention a reality, preventive interventions will need to offer a favourable benefit-harm trade-off whilst satisfying the preferences and needs of at risk individuals. Patients’ beliefs are strong predictors of adherence to treatments of RA, and there is growing evidence that choice-based preference studies predict actual health behaviours. Understanding the preferences of individuals at risk of RA and other stakeholders for prevention of RA is crucial to facilitate cost-effective clinical translation of investment in prevention research, and efficient and ethical recruitment of participants to preventive trials. The studies reviewed here are an important step towards achievement of these objectives.
References


**Conflict of Interest statement**

MF, AF and MH have no conflicts of interest. KR has received honoraria / speaker fees from Abbvie, BMS, Janssen, Lilly, Pfizer, Roche, Sanofi and UCB and grants from Abbvie and Pfizer.

**Acknowledgements**

This work was partially supported by the Swedish Foundation for Humanities and Social Sciences (Riksbankens Jubileumsfond) [grant number M13-0260:1].

KR is supported by the NIHR Birmingham Biomedical Research Centre.

MH is supported by a Young Investigator Salary Award 2016 from The Arthritis Society (YIS-16-104) and a Michael Smith Foundation for Health Research Scholar Award 2017 (#16813).