Polygenic risk scores and rheumatic diseases

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The two major goals of common disease genetics research have been dissection of the aetiopathogenesis of common diseases, and the development of genetic predictors or diagnostic tools of disease. The former goal has clearly been successfully achieved, with successes in genomics driven repositioning of therapeutic agents (e.g. of interleukin [IL]-17/23 inhibition into psoriasis and ankylosing spondylitis based on genome-wide association study [GWAS] findings, particularly of association of IL-23 receptor variants with those diseases [1,2]), and in ongoing drug development programs informed by GWAS associations.[3] Early hopes that GWAS-associations would prove useful as diagnostic tests were not realised, because GWAS demonstrated that common disease heritability is truly polygenic, with very large numbers (likely thousands to tens of thousands) of genetic variants involved, each contributing a small fraction of the total genetic effect on the disease.[4] The recent development of approaches that combine findings across the genome has revolutionised this field though,[5] and will in turn have major effects on the practice of medicine. In this paper we review what polygenic risk scores (PRS) are, how they are developed, and their potential applications in rheumatology.

PRS are quantitative scores that measure an individual genetic risk for the condition or trait involved. Early PRS used only variants that had been definitively associated with the condition, typically defined by achieving 'genome-wide significance' for association usually considered to be $P < 5\times10^{-8}$. As for nearly all diseases only a minority of the total heritable component of diseases has yet been defined at this level of significance, these scores have limited informativity, although they perform better than scores of individual single-nucleotide polymorphisms (SNPs). Including SNPs that show less definitive evidence of association captures a higher proportion of the total heritability of the disease, but also increases the number of variants included that are false positive findings that add statistical noise to the score and reduce its performance. True PRS have been optimised such that the number of SNPs involved maximises the performance of the score, and typically include hundreds to thousands of SNPs. For example, a PRS in ankylosing spondylitis shows that using only 103 non-major histocompatibility complex (MHC) SNPs that have been shown to achieve definitive genome-wide significant associations with the disease, the score could discriminate cases from healthy subjects with an area under the curve (AUC) of 0.66, which is moderately informative (0.5 = no capacity to discriminate, 1.0 = perfect ability to discriminate).[6] However, a PRS involving 1750 non-MHC SNPs selected effectively for their strength of association with the disease had AUC = 0.78, a marked increase in performance, even though many of the 1750 SNPs involved may ultimately turn out not to be associated with the disease.

Different methods of selecting SNPs for PRS have been developed, and further improvements are likely with for example machine learning approaches. Whilst they have typically been developed using data from SNP microarrays, they can also use inputs data from whole genome sequencing as well. Development of the PRS though normally requires very large sample sizes, typically >5000 cases and controls. The greater the sample size, generally the better the performance of the PRS, because the ability to discriminate between true positive and false positive associated SNPs increases.[7]

The performance of the PRS is influenced by several other factors in addition to the discovery dataset size.[7] The more comprehensive the performance of the genetic characterisation, the better will be the performance of the PRS. Therefore, whole genome sequence data will perform better than SNP microarrays, which do not reliably detect copy number variants or rare variants, and only capture a moderate proportion of the total number of

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SNPs. Approaches that incorporate epigenetic profiles may also improve the performance of SNP based scores. Epigenetic characterisation is much more complicated and is affected by non-heritable variables including gender, age, smoking status, diet and medications, as well as the cellular composition of the source DNA, which are very hard to control for. It is therefore not clear at this point whether inclusion of epigenetic data will increase the performance of PRS.

The discovery dataset needs not only to be large, but also preferably to be diagnostically homogenous, as clinical heterogeneity will increase heterogeneity of the genetic factors involved in the cases studied. Thus, for most diseases, large well characterised GWAS datasets are the optimal datasets for PRS development, rather than biobank style datasets, where there is less diagnostic certainty about many diseases or traits.

This issue also applies to validation sets. It is clearly essential to validate any PRS, to ensure it is generalisable when used in datasets or individuals other than those in the discovery cohorts. Validation can be either internal, involving the same cohorts used to develop the PRS, or completely external. Cross-validation is one strategy for internal validation, in which the discovery cohort is divided in two with one part used to develop the PRS, and the other to test that PRS. This process is repeated multiple times and the results of the tested sets are used to define the PRS and to validate the score. This approach has the advantage that the validation uses cohorts which reflects the disease characteristics of the discovery cohorts, but the disadvantage that it is not truly independent. Also the discovery cohorts never use the whole dataset, and are therefore not optimally powered. External validation involving a completely separate dataset is truly independent. However, often external validation cohorts are not as clinically homogenous as the discovery set, and may have subtle ethnic differences, leading to apparent loss of performance of the PRS. Failure to validate in external datasets may therefore simply reflect clinical differences between the datasets rather than true failure of the PRS.

Ethnicity also has effects on the performance of PRS, although for most common diseases these effects are likely to be modest, because the common variants that drive susceptibility to those diseases arose long ago in human ancestry, before most human ethnic divergence occurred. As most PRS have been developed from GWAS datasets, these typically have studied people of western European descent. Similarly, most validation studies have involved large scale publicly available biobank datasets, such as UK Biobank and FinnGen, and therefore the performance of these PRS in other ethnic groups has yet to be determined. This may be because either no GWAS data is available such as understudied populations of African or south Asian ancestry, or due to the GWAS data is not publicly available such as in Chinese or other east Asian ancestries. There is clearly a great need to increase the diversity of datasets available for discovery and validation of PRS.

There are now PRS available for a large number of traits and diseases. The PGS Catalogue is a public repository of such scores [https://www.pgscatalog.org/].[8] The catalogue currently (6/8/2021) includes scores for over 800 diseases, involving African ($n = 149$), south Asian ($n = 79$), east Asian ($n = 132$), Hispanic/Latin American ($n = 80$) and European ($n = 811$) ancestries. Clearly there is a great need to extend PRS research and development into non-European ancestries.

Clinical use of PRS: Whilst PRS have typically been developed to be used in diagnosis, they have multiple other potential clinical and research uses. These include improving disease classification, predicting likelihood of future development of disease, stratifying people according to need and optimal frequency of screening tests, prediction of natural history of disease, pharmacogenomics and more. As PRS are typically developed in carefully assessed, clinically homogenous GWAS datasets, they can be used in disease classification, as people with clinical similar conditions with low PRS have a different though potentially overlapping aetiopathogenesis for their disease. This suggests they either have a different disease, or a disease subset.

PRS are stable from the point of conception, and therefore have predictive ability for disease, and do not depend on development of the disease to have utility. This means they can be applied to determine the optimal frequency of screening tests for the disease, and there are currently studies underway for example to stratify people for breast or prostate cancer screening frequency according to their PRS. There are many potential usages of PRS in rheumatology in this regard, such as stratifying people at risk of systemic lupus erythematosus or rheumatoid arthritis, to reduce inappropriate autoantibody testing in those at low risk of disease. Additionally they can be used to predict the likelihood of future development of disease, or facilitate early disease diagnosis, enabling preventative therapy where such exists, or early interventional therapies for those with disease. Given the strong evidence that early intervention leads to better outcomes for many rheumatic diseases such as rheumatoid arthritis and ankylosing spondylitis, the potential utility of PRS in rheumatology is obviously high.

As most diseases individually affect a minority of the population, and most PRS have at most moderate discriminatory capacity, PRS on their own are not particularly useful for predictive screening in the general population. Rather, they are of utility in combination with other tests, or in groups at high risk of the disease concerned. For example, the ankylosing spondylitis PRS mentioned above has a maximum positive predictive value (likelihood of disease given a positive test) of 15% when used in the general population, which is not high enough to justify widespread usage. However, if used in a setting such as patients <45 years of age with >3 months of chronic back pain, where the prior probability of ankylosing spondylitis is high (30%), then the maximum positive predictive value of the PRS is 93%, which is high enough to be nearly diagnostic on its own. In clinical practice we typically use tests in combination with each other tests and imaging, and with our clinical assessment of the patient. Very few PRS to date have been assessed for their utility in

clinical settings and performance in relation to or in combination with other currently available tests. There are large scale programs underway internationally to do this, such as the 'Our Future Health' program in the United Kingdom, which will study PRS performance and acceptability in five million Britons over the next 5 years [https://ourfuturehealth.org.uk/].

As disease severity and complications for many diseases have genetic underpinnings, PRS are therefore also of use in predicting disease complications and natural history. An emerging field of research is the use of PRS to predict response to or toxicity of pharmacologic treatments. Current pharmacogenomics focus on individual SNP, or in some cases copy number variants, and their association with drug efficacy and toxicity, but it is likely that these characteristics are also polygenic in nature.

PRS in Rheumatology: As most rheumatological diseases have low prevalence and moderate to high heritability, PRS for many rheumatological diseases have demonstrated high discriminatory capacity [Table 1].[9-16] Very few though have been developed or validated for other than European ethnicities, and there are still many major rheumatic diseases for which no PRS has been published to date.

Whilst several of these AUC may seem moderate, with few exceptions ranging between 0.65 and 0.80, it should be borne in mind that many of our diagnostic tests actually have lower AUC and yet are considered valuable and are widely used in clinical practice. For example, CRP has an AUC of 0.7 when used in the diagnosis of ankylosing spondylitis[17] and 0.61 for rheumatoid arthritis.[18] MRI when used to screen chronic back pain for patients with ankylosing spondylitis has an AUC of 0.62 to 0.885.[19,20] Therefore PRS already perform similarly to widely used tests in rheumatological clinical practice, and are only likely to improve in performance in future.

These scores are already potentially of clinical utility. The current ankylosing spondylitis PRS is more informative than human leukocyte antigen (HLA)-B27 testing alone, which has AUC of 0.869 to 0.901 in Europeans and East Asians respectively.[6] As the PRS is easily calculated from anyone who has had a SNP microarray performed, its cost to these people is far lower than that of HLA-B27 genotyping. Even in those who have not had SNP microarray genotyping performed, its cost is already lower than current HLA-B27 testing costs within the National Health Service in the United Kingdom, as so clearly should replace it.

Table 1: Exemplar PRS for common rheumatic diseases.

Disease	Ethnicity	AUC
Ankylosing spondylitis	European	0.924[6]
Ankylosing spondylitis	East Asian	0.948[6]
Acute anterior uveitis	European	0.96[9]
Systemic sclerosis	European	0.673[10]
Systemic lupus erythematosus	European	0.67–0.72[11]
Systemic lupus erythematosus	East Asian	0.76[12]
Rheumatoid arthritis	European	0.78[13]
Gout	European	0.664[14]
Osteoporotic hip fracture	European	0.798[15]
Psoriatic arthritis	European	0.91–0.92[16]

In each case the AUC is reported for use of the PRS to discriminate cases from healthy subjects. AUC: Area under the curve; PRS: Polygenic risk scores.

A potential rheumatological application of PRS is to assist in diagnosis either prior to or in combination with other tests performed as part of standard diagnostic workup. A recent paper reported the development of a suite of PRS ('G-PROB') for this application, which provides a probability of a patient with inflammatory arthritis having either gout, psoriatic arthritis, rheumatoid arthritis, spondyloarthropathy, or systemic lupus erythematosus.[21] In patients presenting with undiagnosed inflammatory arthritis, the PRS suite was able to deprioritise one disease in 100% of patients, two or more diseases in 84% of patients, three or more diseases in 40% of patients, and four diseases in 11% of patients, with a negative predictive value 0.98. Whilst clinicians did a little better, the disease with the highest G-PROB matched the final diagnosis in roughly half of patients (53%). Combining the PRS with clinical information is likely to improve the performance of this score, but the study shows that this is close to being usable as a triage tool in clinical practice.

Whilst PRS are available across multiple diseases, there remain many diseases including major rheumatic diseases where no score has yet been reported. Further, for many rheumatological diseases the sample size used for discovery sets has been modest, and larger sample sizes will lead to better performance. New statistical approaches may also lead to modest gains in PRS performance, but the key areas where much further work is required are multiomic scores combining PRS with other biomarkers and clinical factors, and extension of PRS research further into non-European ancestries. Health economic assessment of the impact of PRS is underway but given the low cost of SNP microarray genotyping, likely to be <£20 per patient shortly. The widespread availability of SNP microarray data from direct-to-consumer testing companies such as 23andMe and MyHeritage, means that it is near certain that PRS will be widely introduced into clinical practice in the near future. We then need to work out best how to use them as diagnostic and predictive tools, and integrate the tests into our clinical pathways. There will clearly need to be educational programs about how to interpret these tests, but in reality this is quite easy, once it is realised that they are interpreted in the same way as any other numeric biomarker test we use every day in clinical practice, the only difference being that they don't change during life. This will significantly benefit prediction, diagnosis and treatment of disease, and potentially enable accurately targeted preventative or early intervention approaches to disease management. Wouldn't that be a great outcome!

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