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EDITORIAL

Finding the Right Fit for Genes in Rheumatology Clinical Care

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April 2023 marked 20 years since the completion of the Human Genome Project, a groundbreaking international collaboration generating the first comprehensive sequence of the human genome.[1] Today, advancements in genetics, analytic methods, and computing platforms have made it possible to distill vast amounts of genetic data for use in an expanding array of clinical settings, including oncology, cardiovascular disease, and endocrinology. How best to do this in rheumatology remains an open question.

Hum et al take an initial step in addressing this unmet need.[2] In their study, the authors externally validate a tool designed to aid in the diagnosis of early inflammatory arthritis. The method, a genetic probability tool (G-PROB), uses an individual's genomic data to calculate the probability that they have one of five different inflammatory arthritides: rheumatoid arthritis, systemic lupus erythematosus, spondyloarthropathy, psoriatic arthritis, and gout.[3] Because inflammatory arthritis in the very early stages is often undifferentiated, G-PROB was designed to assist clinicians in making an accurate diagnosis in this time window by providing a focused summary of their genomic data relevant to this group of conditions.

The original G-PROB study started with a simulation study, followed by two rounds of cross-sectional validation combining data from multiple biobanks. Lastly, G-PROB was tested with data from a small cohort (n = 243 participants) from one of the biobanks, assessing the probability of each of the five types of inflammatory arthritis at the first visit with the final diagnosis based on review of the electronic health record (EHR) data. In the present study, Hum et al applied G-PROB to the Norfolk Arthritis Register, a primary care–based cohort of patients prospectively followed after a new diagnosis of early inflammatory arthritis. A total of 1,047 patients were examined from this study, based on available data on genotype and clinician diagnosis. This study provided an independent external validation of the original G-PROB method, finding a similarly strong correlation between the probability generated by G-PROB and the final diagnosis across the five types of inflammatory arthritis. The authors observed that G-PROB could discriminate among conditions with a pooled area under the curve of 0.85 (95% confidence interval 0.84–0.86). Probabilities provided by G-PROB for one of the five inflammatory arthritides of <5% corresponded to a negative predictive value (NPV) of 96.0%, and when it was possible to suggest >2 unlikely diseases, the NPV was 94%. Probabilities estimated by G-PROB at >50% for a specific type of inflammatory arthritis had a positive predictive value of 70.4%. In 55.7% of patients, the disease with the highest probability from G-PROB corresponded to the final diagnosis. Based on these data, the strength of G-PROB was in its ability to exclude diagnoses.

In general, many research findings cannot be validated in independent studies.[4,5] Referred to as the "replication crisis,"[6] the study presented by Hum et al beats the current validation odds.[2] One might argue that the results were anticipated because the G-PROB risk scores consisted of the main risk alleles associated with each condition and would be expected to correlate closely with the final diagnosis. However, this study represents a necessary first step in evaluating the G-PROB tool for clinical care.

Several important key steps remain for the meaningful translation of G-PROB into the clinic. Future studies will need to examine whether the method is helpful in making an accurate diagnosis of patients earlier, the intended use for G-PROB. In other words, among patients without a clear diagnosis in the first few months of presentation or in whom the diagnosis changed during follow-up, would the use of G-PROB help the clinician come to the final diagnosis earlier?

Importantly, data are needed regarding how to incorporate the probabilities generated from G-PROB into our own clinical decision-making process when formulating a diagnosis. Given the substantial nongenetic determinants of inflammatory arthritis,

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future studies are needed to address whether genomic data improve upon current diagnostic practice for inflammatory arthritis, which includes the history, physical, laboratory measurements, and imaging. It is in this context that we need to assess the utility of the genomic information rather than in isolation. For example, in cardiovascular disease, the clinical utility of polygenic risk scores has been defined by their ability to improve risk stratification beyond what is already achieved with more common risk factors and measures such as cholesterol levels, smoking status, and coronary calcium scores.[7,8] Similarly, a polygenic risk score for breast cancer would not be clinically implemented alone for risk prediction, but rather as one risk factor among others, such as hormonal and reproductive factors and prior mammographic data.[9] Beyond such comparative analyses, prospective trials would offer additional rigor to the question of whether genomic data improve rheumatologic diagnosis and management; such trials are currently underway in breast cancer, cardiovascular disease, and many others.[10–12] The time might be right for a similar trial in inflammatory arthritis.

It is worth noting that this type of question would have been difficult to consider even a decade ago. The exponential growth of population genomic data, acquired through biobanks, other research studies, or commercial platforms, has enabled unprecedented discovery and the development of models such as G-PROB. The Human Genome Project's tantalizing promise is the application of these discoveries to clinical care, but developing a valid and effective genomic test for rheumatology practice will require additional effort. Using a research model to develop a clinical grade laboratory assay suitable for use in patient care is not trivial and must consider the inclusion of diverse patient populations, model calibration, and selection of an appropriate reference population for the clinical population in question.[13] Even then, myriad implementation questions remain, including how to educate providers about a new technology and how to represent probabilistic data in the EHR.

For inflammatory arthritides, earlier diagnosis and treatment lead to better outcomes.[14,15] The barrier for obtaining genetic data has decreased significantly over the past decade with improved high-throughput technologies reducing cost and advancements in the analytic methods as well as the computing platforms; one can imagine a scenario in which genomic data can become a standard part of clinical care in rheumatology in the next decade. Similar to when we first meet a patient presenting with bilateral wrist synovitis and a positive antibody to cyclic citrullinated peptide (anti-CCP), the genetic data may one day be provided in a way that is easily interpretable at that first or second visit like the anti-CCP, allowing us to initiate the optimal therapy based on an individual patient's characteristics.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published.

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