Using the Genomics England data set to propose updated global guidelines to improve rare disease diagnosis

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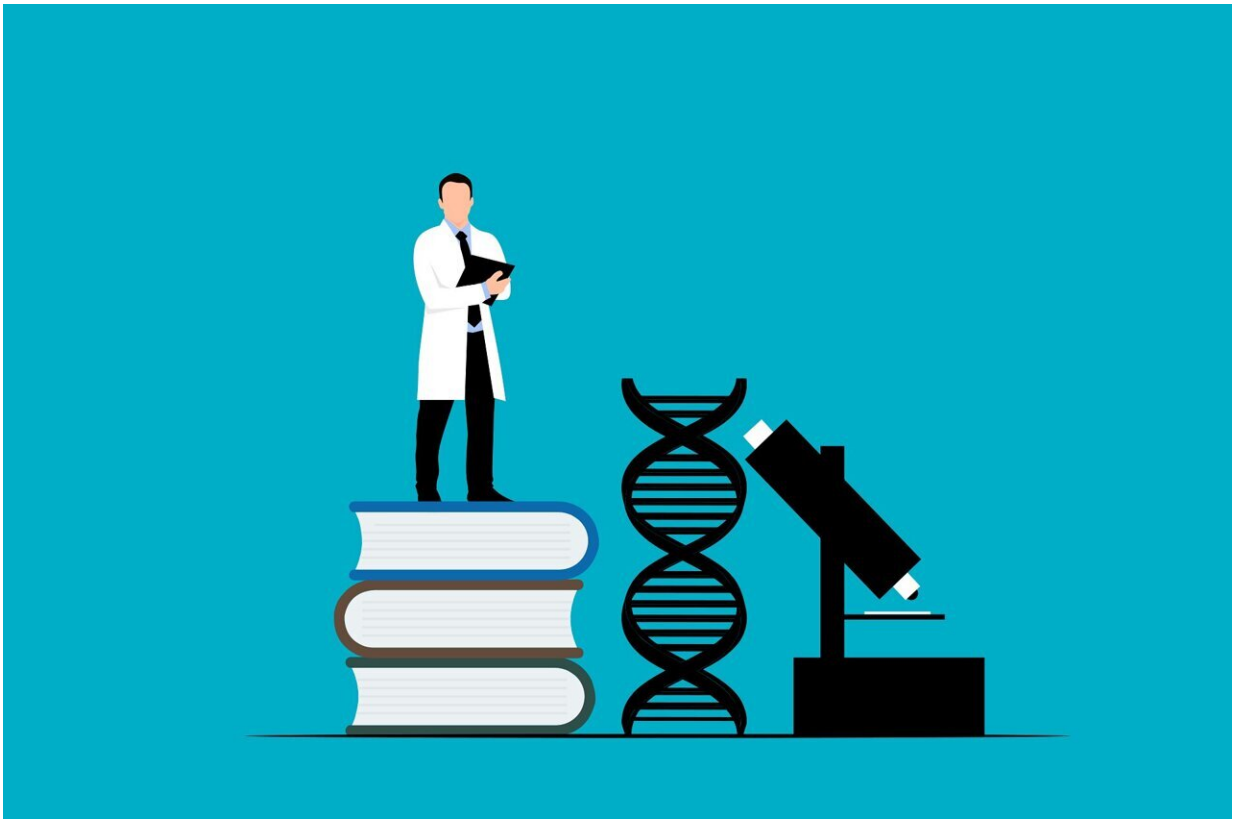

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Today, an international group of leading scientists publish recommendations for updating existing standards for determining the

disease-causing potential of genomic variants, harnessing insights from Genomics England rare disease participants. The work was led by scientists at Genomics England, The University of Manchester and The University of Oxford, coordinating an expert team of scientists and clinicians from academic and healthcare institutions across the UK, US and Australia.

The proposed expanded guidelines will enable clinicians and researchers to take better advantage of the full range of variation in whole-genome sequence (WGS) data. They are presented in a paper appearing today in the online edition of the open-access journal *Genome Medicine*.

The recommendations address a major challenge in the diagnosis and understanding of rare disease: to date, most genetic testing has been focused on coding sequence variants—that is, those variants that disrupt regions of genes that directly encode proteins. The standards and guidelines developed over the past decade for interpreting the results of these tests—including single-gene assays and gene panels, as well as whole-exome sequencing, which encompasses all of the coding regions of the genome—have similarly focused on these types of variants.

Yet while these standards have provided a solid, evidence-driven framework for delivering consistent and reliable diagnoses using such tests, coding regions account for at most 2% of the genome. With the advent of affordable WGS and its growing use in clinical practice, ever larger numbers of potentially disease-causing variants of many different types are being detected, but without similarly systematic criteria for the community to assess their impact on disease. The result has been the proliferation of "variants of uncertain significance" (VUS), some of which have the same downstream clinical impact as pathogenic coding variants but work through different mechanisms and so are more difficult to assess.

In proposing updates to these guidelines for the WGS era, the authors focus explicitly on recommending adaptations and expansions that sit alongside the existing guidance, and using the same strategy of consultation and consensus-building that was used to create them. Taking advantage of Genomics England's leading expertise in clinical WGS, and data from the 100,000 Genomes Project participants, the recommendations were drafted by a panel of nine clinical and research scientists from major genomics laboratories in the UK.

These include four of the NHS Genomic Laboratory Hubs serving the Genomic Medicine Service (GMS) and the Wellcome Centre for Human Genetics at the University of Oxford. The draft recommendations were tested by an additional group of clinical scientists using 30 test variants; refined by a group of variant interpretation experts from the UK, the Broad Institute in Cambridge, Massachusetts, and the Garvan Institute and Murdoch Children's Research Institute in Australia, among others.

The recommendations were subsequently presented in late 2021 at the Association for Clinical Genomic Science (ACGS) meeting for further feedback, and will also be presented for discussion in a workshop at the upcoming American Society of Human Genetics (ASHG) annual meeting to be held in Los Angeles in October.

"We are very pleased to be able to present these recommendations to the global clinical and scientific community," said Dr. Jamie Ellingford, lead genomic data scientist for rare disease at Genomics England, Research Fellow at The University of Manchester, and co-lead of the study. "We hope that their adoption will serve as a useful starting point for standardizing and refining the characterization of ever more VUS. In doing so we believe that we will be able to target a subset of VUS, and provide guidelines for how to create appropriate functional evidence to interrogate pathogenicity for these variants and deliver more diagnoses for patients in the UK and around the world."

"Our aim is to catalyze getting more valuable genetic diagnoses to patients", said Dr. Nicky Whiffin, group leader and Sir Henry Dale fellow at the University of Oxford, and co-lead of the study. "As we have access to more and more whole genome sequencing data it is becoming increasingly clear that variants in regions of the genome that do not directly encode protein play an important role in rare disease. These recommendations enable us to fully interpret these variants and harness them in the clinic, improving diagnosis and personalized treatment."

"This is an important and timely response to a pressing need in the rare disease community, and one that we are proud that Genomics England research participants data has contributed to. Even with the great improvements brought with new sequencing technologies and the interpretation of DNA variation, many families remain without a diagnosis, often for years. Work like this is vital to changing that, allowing identification of causes of disease that have been hard to identify, hiding between the genes ", said Dr. Rich Scott, Chief Medical Officer at Genomics England.

"Working with the NHS we are proud of the impact whole genome sequencing has already had in the UK, through the 100,000 Genomes Project and now in the NHS Genomic Medicine Service. This paper illustrates both the increasing power of the technology. It also emphasizes the importance—with participants consent—of linking clinical care to research at national scale"

"The NHS made a huge contribution to the 100,000 Genomes Project, and the use of this extra information in our genomes demonstrates the value of research insights in genomics and how whole genome sequencing has the potential to transform diagnoses for patients living with a rare disease," said Professor Dame Sue Hill, Chief Scientific Officer for England and Senior Responsible Officer for Genomics in the

NHS. "It is an important step in unraveling the mystery of the non-coding regions in our genomes and the role they could play in contributing to the development of rare diseases."

"I am very excited for the release of these new evidence standards for non-coding variation as it provides a path to understand the pathogenicity of more variants", said Dr. Heidi Rehm, Professor of Pathology at the Massachusetts General Hospital and Broad Institute of MIT and Harvard. "We plan to use the framework as a starting point for providing more explicit guidance for evaluating non-coding variation in the next version of the ACMG/AMP standards, actively under development."

More information: Jamie M. Ellingford et al, Recommendations for clinical interpretation of variants found in non-coding regions of the genome, *Genome Medicine* (2022). DOI: 10.1186/s13073-022-01073-3

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