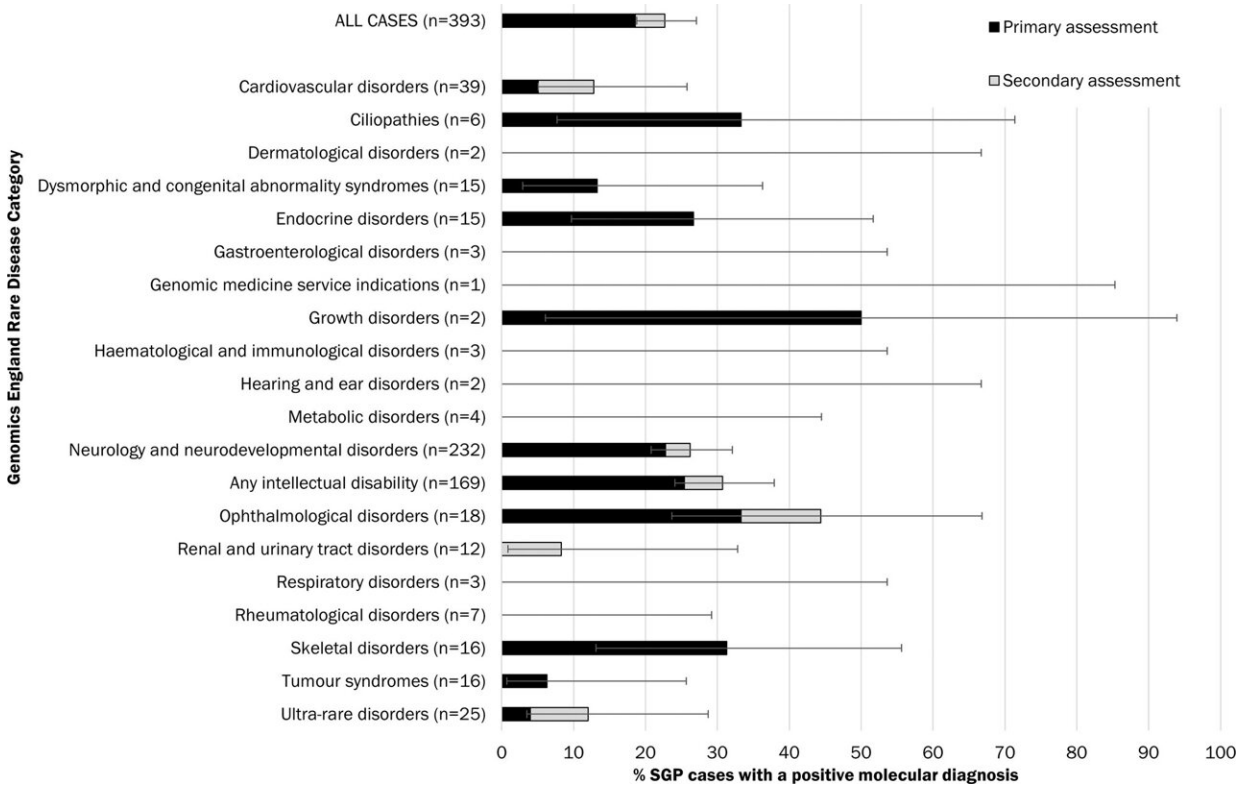
Genome technologies bring long-awaited answers to families in Scotland

December 19 2022



Diagnostic yield following primary (black) and secondary (gray) assessment, for all cases and by Genomics England rare disease category. Diagnostic yield is also included for probands with any ID (a subset of the Neurology and Neurodevelopmental Disorders category). The number of probands in each category is shown in brackets. Some probands are in more than one category and are included for both categories where the variant fully explained their phenotype. Bars indicate 95% confidence intervals for the overall diagnostic yield after primary and secondary assessment. Credit: *European Journal of Human Genetics* (2022). DOI: 10.1038/s41431-022-01226-3

The detection and management of inherited rare and serious conditions in routine care can be improved by genome sequencing, a new study involving the University of Aberdeen has found.

Until recently standard genetic testing focused on small numbers of genes but as thousands of genes are implicated in disease a new approach is being developed.

Genome sequencing reads out the sequence of all a person's genes and identifies variants that differ from the normal pattern. Specialists compare these digitally against lists of genes known to cause disease and then examine this short list of variants to identify which one might be the key to the person's condition.

Rare conditions affect an estimated 8% of the population of Scotland and around 80% of these conditions have a genetic cause. There are more than 150,000 gene abnormalities known to cause developmental and learning difficulties and a host of conditions that impact long term health. But many patients are undiagnosed which has a huge impact on their life and their families.

Published in the *European Journal of Human Genetics* the findings of the project, known as the Scottish Genomes Partnership, will be used to inform health care policy and funding decisions.

The partnership between Scottish universities, NHS genetics labs and clinics and Genomics England, offered whole genome sequencing to families with rare, inherited conditions where previous genetic testing had not identified a genetic cause.

The major research program sequenced 1,000 genomes from Scottish

residents with rare conditions and their family members and sent the data for processing and storage into the 100,000 Genomes Project—a flagship project set up in England to advance clinical care through genome research. NHS Scotland genetic scientists and doctors then interpreted the analyzed data and passed useful results to participants. A genetic diagnosis has been found in 23% so far and more answers are coming from research on the data being carried out in Genomics England's protected online research environment and from an SGP extension project, funded to look for more complex genome rearrangements.

The project chief investigator, Professor Zosia Miedzybrodzka of the University of Aberdeen, said, "We have set up a system for Scottish patients to have genomes sequenced as part of their care. But we have also found that a more targeted genome wide approach—the exome—recently funded by the Scottish Government as part of routine care—can give us similar numbers of diagnoses at less cost.

"The Scottish Government is using the study results to inform policy on what will be available in NHS Scotland in coming years. If analysis of genome sequence improves as expected, and the costs fall, Scotland will be well placed to implement the technology.

"Having an undiagnosed genetic condition brings a huge amount of worry for those affected but it is our hope that diagnosis through genome sequencing can bring answers and improve the lives of patients and their families."

Professor Tim Aitman, University of Edinburgh, said, "The publication of the SGP results represents a landmark for application of genome technology to the healthcare of Scottish patients with rare genetic disorders.

"With over 1,000 high quality genome sequences now generated at the Edinburgh Genomics facility; new diagnoses have been found for dozens of patients who previously remained undiagnosed after standard genetic testing.

"The SGP focus on genome technology and genome informatics has increased the available expertise in these areas and the insights gained from the SGP are now being fed into Scottish healthcare policy, giving a long-term legacy of the SGP rare diseases project for Scottish patients.

"Continuously reducing costs of genome sequencing stand to increase future availability of genome-based testing for patients with rare diseases in Scotland."

Natalie Frankish, policy and engagement manager for Scotland, Genetic Alliance U.K., said, "Many people with rare conditions face significant challenges in getting a diagnosis, with more than a third of people with a rare condition having to wait more than five years. This diagnostic odyssey can have a significant impact on the quality of life and well-being for a person with a rare condition and their family.

"A diagnosis can lead to improved medical management and can open doors to accessing care, treatment and support services. It is encouraging to see that recent investment in genome-based testing through the Scottish Genomes Partnership has given 88 patients new diagnoses, we hope that this news will help these families access the care and support that they need.

"Ensuring a fast and accurate diagnosis is important for people with rare conditions. We hope that the findings published by the Scottish Genomes Partnership in this paper will help make the case for further investment in genomic, diagnostic and screening services within NHS Scotland, but we must recognize that speed of diagnosis is only part of

the picture.

"How a person is supported on their journey to diagnosis is equally important and we must see investment in clinical services to ensure people with rare conditions and their families receive the support that they need throughout their diagnosis journey."

More information: Lynne J. Hocking et al, Genome sequencing with gene panel-based analysis for rare inherited conditions in a publicly funded healthcare system: implications for future testing, *European Journal of Human Genetics* (2022). DOI: 10.1038/s41431-022-01226-3

Provided by University of Aberdeen