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Genomic Results Return Study Underscores Clinical Value, Takeaways for Expanded Implementation

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NEW YORK – A new study by investigators at Brigham and Women's Hospital (BWH), Massachusetts General Hospital, and Harvard Medical School highlights the potential value of returning actionable genomic findings to research participants, as well as the benefit of comprehensive genomic testing in individuals with known familial or other risk factors.

Published in the *American Journal of Human Genetics* on Monday, the study describes takeaways from an effort by BWH's Genomes2People (G2P) program to disclose actionable genetic results to research participants who volunteered to contribute to the Mass General Brigham Biobank.

The study's authors wrote that as genomic biobank cohorts proliferate, the question of why and how to return medically actionable information to participants has become more pressing. However, relatively few of these programs have implemented or experimented with return of results policies.

Considering that research participants are expected to increasingly demand access to this type of information, the BWH team hoped to provide details and insights that might help other research programs who are cautious or confused about the costs and logistics of developing their own protocols.

"These data will help other groups planning for the return of genomic results in research, and remind us that across the entire health care landscape, we are missing an opportunity to help patients avoid cancer and heart disease by not applying published recommendations for genomic testing," said co-senior author, Harvard Medical School physician and G2P director Robert Green, in a statement.

The investigators described their findings from an analysis of approximately 36,000 biobank samples, focusing on 59 genes for conditions designated by the American College of Medical Genetics and Genomics as medically actionable. They offered to clinically confirm and return results to any subjects with variants detected that met the criteria for being deemed pathogenic or likely pathogenic.

Biobank volunteers were largely genotyped using array-based methods, targeting specific, pre-determined sites. But a subset of the cohort also underwent next-generation sequencing.

The team initially identified 425 individuals with potentially returnable findings. Of these, 293 were deemed eligible, and 256 were successfully contacted regarding a preliminary variant finding. Of these, 65 actively declined to receive confirmatory testing and results, and another 31 passively declined.

In a subset who were surveyed about their reasons for declining follow-up, the most common responses were that the results weren't relevant, as the subject was already aware of their elevated risk, or that they had more pressing health concerns.

According to the authors, 76 percent of the individuals who received confirmation and risk results met clinical criteria for genetic testing but had never been offered it and were otherwise unaware that they carried a variant that put them at increased risk.

"Many people have a personal or family health history already documented in their medical record indicating they should have been offered genetic testing but never had it, and there are others who had no family history or symptoms to clinically tip doctors off but still carry a dangerous genetic risk variant," co-lead author Carrie Blout Zawatsky, a senior genetic counselor for the G2P research program, said in a statement. "Our findings demonstrate the lifesaving benefit that genomic screening will bring to patients by identifying individuals who do not know that they are at risk," she added.

As part of the process of confirming results for those who consented to follow-up and return, the team found that 45 percent of initially detected variants were incorrect when clinical sequencing was performed on new samples.

Additionally, genotyping failed to identify 72 percent of the dangerous variants that were detected by comprehensive sequencing in the subset of individuals whose samples had been tested by both methodologies.

The authors wrote that this could be variable depending on the type of genotyping array used in biobanks or other studies, but they cited other recent analyses where even the most comprehensive global research arrays have shown similar results.

"Many biobanks rely on genotyping technology instead of genomic sequencing. Our study shows that genotyping, while a useful tool in research, may miss important results that more comprehensive sequencing detects," co-senior author Matthew Lebo, chief laboratory director at the Mass General Brigham Laboratory for Molecular Medicine, said. "In this study, confirmation of the genotype findings through sequencing was critically important as it allowed us to filter out false positives."

The researchers also calculated the costs of returning genomic results to biobank volunteers under their model (above and beyond the initial costs of the initial biobank analyses) concluding that the program had an overall cost of $14 per participant across the entire Biobank population, or about $3,000 for each person who had results successfully confirmed and returned to them.

Although planning for return of genomic results in a research context can be complex, the authors wrote that they hope their findings offer helpful takeaways for groups seeking to find a balance between

"conducting scientific research, preserving participant autonomy and privacy, and offering information that could reduce morbidity and mortality among those that have generously contributed their DNA for the benefit of science."

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