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Genetic tests unexpectedly find genes linked to heart disease—now what?

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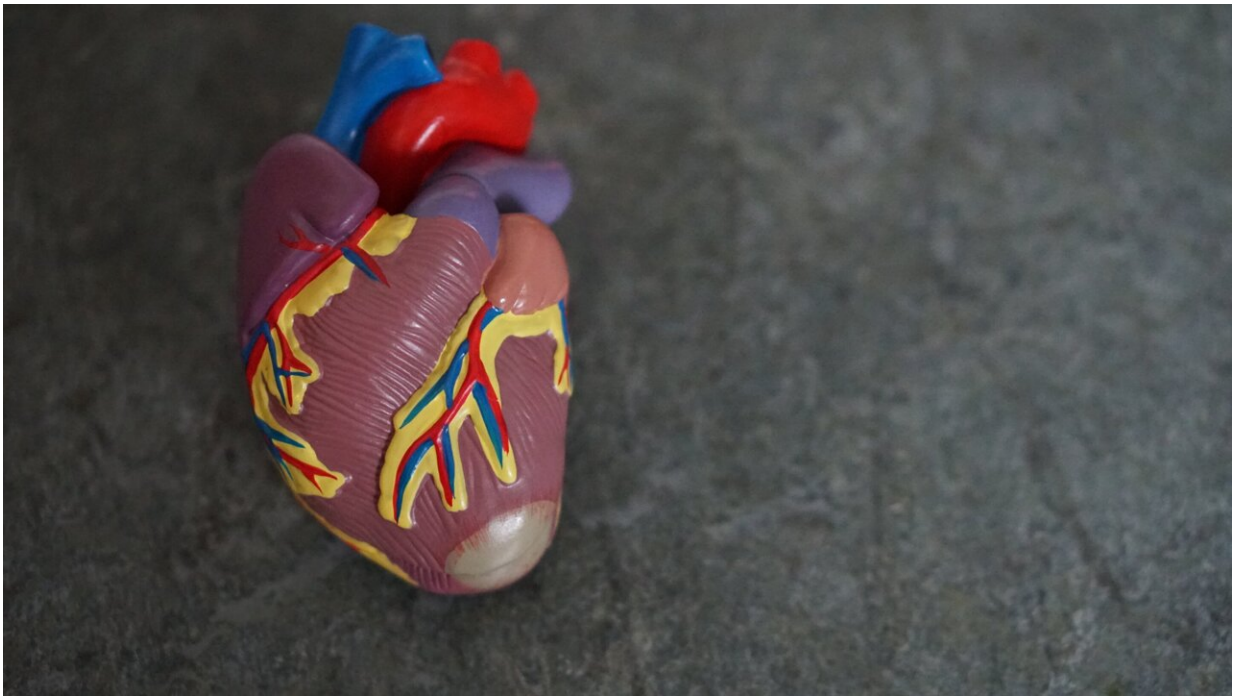

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Increasing use of genetic testing means people may discover they have a gene variant associated with some types of cardiovascular disease (CVD). A new scientific statement, published today in the American Heart Association journal *Circulation: Genomic and Precision Medicine*, aims to help individuals and health care professionals understand what to do when a variant is discovered.

An American Heart Association scientific statement is an expert analysis of current research and may inform future guidelines. The new statement, "Interpreting Incidentally Identified Variants in Genes Associated with Heritable Cardiovascular Disease," suggests next steps to determine whether a variant truly carries a health risk, provides support to health care professionals on how to communicate with people and their families, and suggests appropriate follow-up actions to care for people with variants deemed higher risk for CVD.

Variants associated with cardiovascular disease risk are often found "incidentally" when people undergo genetic testing for non-cardiac reasons, including screening or diagnosis of other diseases. These unexpected genetic variants may also be discovered with genetic testing through direct-to-consumer DNA testing kits.

Pretest genetic counseling is strongly encouraged to prepare patients for the possibility of incidental findings, how and whether findings will be communicated, and potential implications for themselves and family members.

"The scope and use of genetic testing have expanded greatly in the past decade with the increasing ease and reduced cost of DNA sequencing," said Andrew P. Landstrom, M.D., Ph.D., FAHA, chair of the scientific statement writing committee and associate professor of pediatrics and cell biology at Duke University School of Medicine in Durham, North Carolina. "Where we would once look for genetic changes in a handful of genes, we can now sequence every gene and, potentially, the whole genome, allowing us to make genetic diagnoses that would have been impossible in the past. However, with increased genetic testing comes more surprises, including finding unexpected variants in genes that might be associated with cardiovascular disease.

"If we interpret these incidental variants incorrectly, it may lead to

inappropriate care, either by suggesting patients have a risk of cardiac disease when they do not, or by not providing care to those with increased risk for a serious condition."

This statement is the first to focus on inherited monogenic, or single-gene, diseases for CVD which can be passed on within families, such as hypertrophic cardiomyopathy or long QT syndrome. There are currently 42 clinically treatable, secondary variant genes that increase the risk of sickness or death from sudden cardiac death, heart failure and other types of cardiovascular disease, according to the American College of Medical Genetics and Genomics. Genetic variants that cause long QT syndrome cause the heart to electrically reset slower than normal after each contraction, which may cause electrical instability of the heart and may lead to fainting, arrhythmias or even sudden death.

Once an incidental genetic variant for CVD is found, the statement authors suggest a framework for interpreting the variant and determining whether it is classified as benign, uncertain or pathogenic (disease-causing):

- Health care professionals should only relay information to patients about incidentally identified variants if they are among the cardiovascular disease genes already known to be associated with CVD and if patients agreed during pretest genetic counseling to be informed about incidental findings.
- Incidentally identified variants in genes with an uncertain association with CVD should not be reported.
- If the discovered variant may increase the risk of CVD, a family history and medical evaluation by an expert health care professional are suggested, preferably a specialist working with or within a multidisciplinary team to address in the disease in question. The goal of this evaluation is to determine whether the individual has evidence of the disease, such as symptoms or

relevant test results, or if there are any warning signs in the family history.
- The genetic variant itself should be re-evaluated periodically by an expert or expert team to ensure whether the CVD link remains accurate. As knowledge about a variant evolves over time, its link to disease may be reclassified.
- Finally, the medical evaluation and genetic re-evaluation should guide next steps, which may vary from dismissing the incidental variant as not likely to cause CVD to starting medical interventions. This may also involve periodic re-evaluation with appropriate tests (echocardiogram, blood tests, etc.) and possibly screening other family members for the variant.

"The list of incidental variants related to cardiovascular disease continues to evolve. This statement provides a foundation of care that may help people with a CVD-related genetic variant and their health care professionals take the next step in determining the individual and familial risk that a variant may or may not carry," Landstrom said. "It's also important to consult with genetics specialists to custom-tailor an evaluation and treatment plan to both the individual and the genetic variant in order to ensure the highest level of care possible."

This scientific statement was prepared by the volunteer writing group on behalf of the American Heart Association's Data Science and Precision Medicine Committee of the Council on Genomic and Precision Medicine and the Council on Clinical Cardiology; the Council on Cardiovascular and Stroke Nursing; the Council on Hypertension; the Council on Lifelong Congenital Heart Disease and Heart Health in the Young: Council on Peripheral Vascular Disease; and the Stroke Council. American Heart Association scientific statements promote greater awareness about cardiovascular diseases and stroke issues and help facilitate informed health care decisions. Scientific statements outline what is currently known about a topic and what areas need additional

research. While scientific statements inform the development of guidelines, they do not make treatment recommendations. American Heart Association guidelines provide the Association's official clinical practice recommendations.

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More information: Interpreting Incidentally Identified Variants in Genes Associated With Heritable Cardiovascular Disease: A Scientific Statement From the American Heart Association, *Circulation Genomic and Precision Medicine* (2023). DOI: 10.1161/HCG.0000000000000092

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