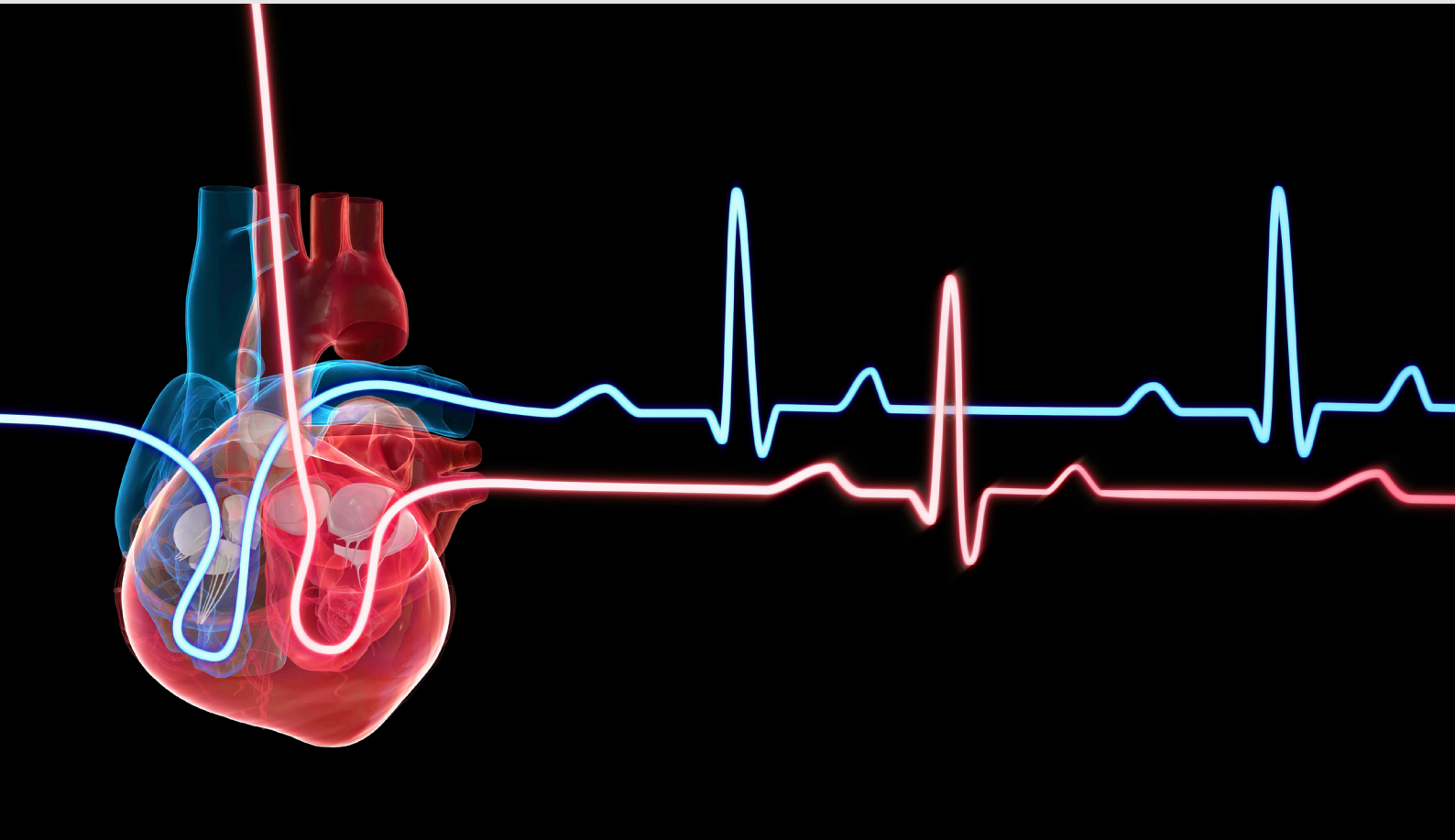


GENOMIC DISCOVERIES AT THE HEART OF CARDIOVASCULAR DISEASE

Testing for genetic variants is gaining momentum in cardiovascular disease, and it is helping improve diagnosis and precision treatment. What are the latest advancements in cardiogenomics, and what are the barriers to broad scale adoption?



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GENOMIC DISCOVERIES AT THE HEART OF CARDIOVASCULAR DISEASE

For 20 years, scientists have gathered data on genetic polymorphisms. Testing for genetic variants is gaining momentum in cardiovascular disease, and it is helping improve diagnosis and precision treatment. What are the **LATEST ADVANCEMENTS IN CARDIOGENOMICS**, and what are the barriers to broad scale adoption?

“Many cardiovascular diseases caused by single gene variants are underdiagnosed because clinical sequencing is underused,” says Dan Rader, a physician-scientist heading the Division of Translational Medicine and Human Genetics at Penn Medicine. His team is sequencing large heterogeneous populations to understand how rare genetic variants contribute to cardiovascular disease. They are finding that treatable causes are being missed because doctors are not looking at patients’ genes.

Since the 1990s, genetic testing in cardiology practice has been recommended for patients who present with symptoms of an inherited cardiovascular disease or are at high risk because there is a known pathogenic variant in their family (see ‘Cardiogenomics enables better patient outcomes’). The decision to undergo genetic

testing is shared between the patient and the healthcare provider after consideration of potential benefits, risks, and limitations of the test.

In 2020, the American Heart Association (AHA) issued a statement recommending genetic testing for patients diagnosed with all forms of cardiomyopathy, arrhythmic disorders, vascular disorders and lipid disorders such as familial hypercholesterolemia. The AHA also highlighted 30 medically actionable genes related to cardiovascular diseases, from a list by the American College of Medical Genetics and Genomics.¹ “Even in patients who have a clinical diagnosis of an inherited cardiovascular disease, genetic testing could identify the responsible mutation and help tailor their care,” says Kiran Musunuru, lead author of the statement, and cardiologist and geneticist at Penn Cardiovascular Institute.

“MANY CARDIOVASCULAR DISEASES CAUSED BY SINGLE GENE VARIANTS ARE UNDERDIAGNOSED BECAUSE CLINICAL SEQUENCING IS UNDERUSED.”

because it serves to further knowledge of gene-disease relationships. Such studies are revealing that there are often multiple small-effect common gene variants (single nucleotide polymorphisms) that cumulatively increase the risk of cardiovascular

Physicians can order genetic tests that range from sequencing a single gene or a panel of genes that have been associated with the disease, to unbiased whole-exome or whole-genome sequencing that queries all genes. At present, whole-genome sequencing is more common in research settings than in the clinic

disease. Researchers can use this information to generate polygenic risk scores that reflect a person’s susceptibility to disease before they even present any symptoms.

The opportunity to adopt preventive measures is likely to accelerate the use of high-coverage genetic sequencing in a clinical setting. “Although physicians still prioritise clinical screening, genotyping is an inevitable trend because, ultimately, cardiovascular disease has a lot of clinical solutions,” says Wilson Tang, a heart failure and transplant cardiologist at Cleveland Clinic’s Heart, Vascular and Thoracic Institute. “If cardiovascular disease is identified early, there are medicines and procedures to ameliorate the risk and improve patient outcomes.”

Cardiogenomics can save lives

As researchers learn more about the mechanisms by which genetic variation contributes

to disease, they can start to examine the effects of known drugs on selected groups of patients or use this knowledge to develop new ones.

For example, mutations in genes encoding ion channel subunits are responsible for 75% of cases of long QT syndrome (LQTS), an inherited heart rhythm problem that may be responsible for around 3,000 unexpected deaths in children and young adults in the United States each year. Testing for these genes (*KCNQ1*, *KCNH2*, *SCN5A*) not only confirms diagnosis, but can also guide treatment decisions since only patients with certain mutations will benefit from beta-blockers.² Thus genetic testing not only brings clinical benefit but is also cost effective.

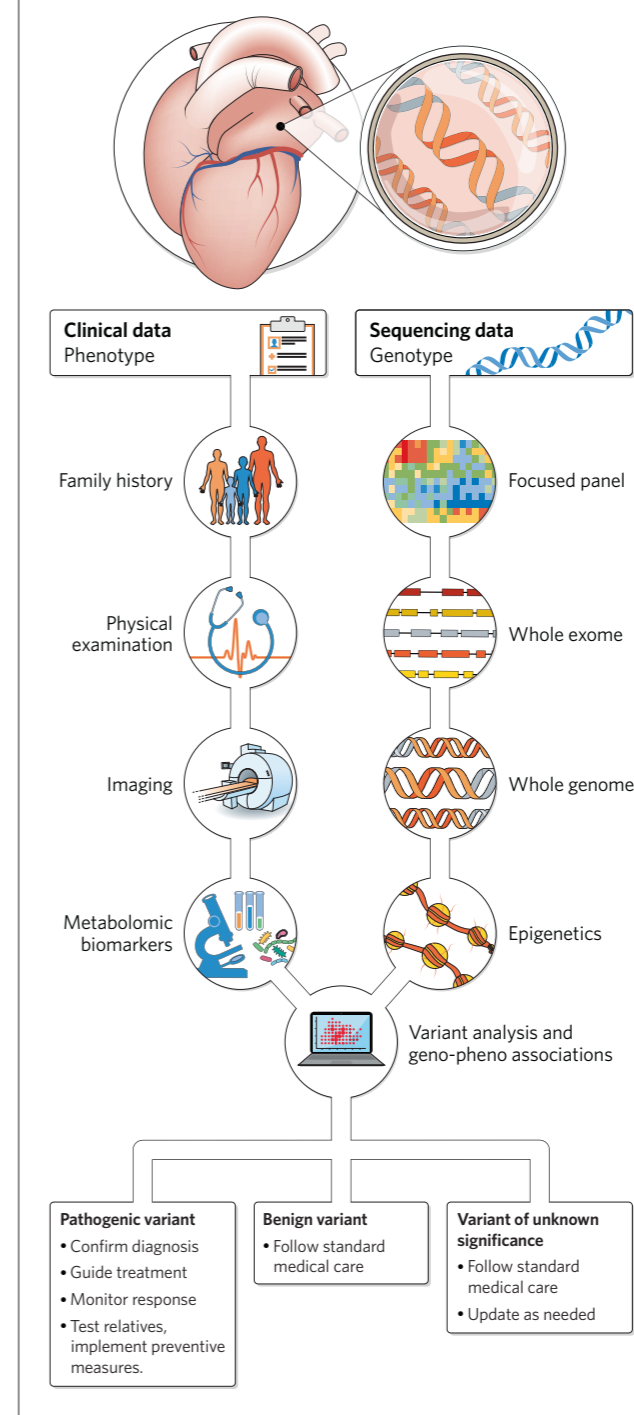
It takes time for newly discovered mutations associated with heart disease to become part of the clinical testing regimen. Many gene variants with proven influence on the course or treatment of cardiovascular disease are not yet tested for.

One of the best examples involves mutations in the *TTR* gene, which are linked to hereditary cardiac amyloidosis, where deposition of amyloid in cardiac muscles hampers the heart’s ability to pump blood. “There is an effective treatment on the market for hereditary cardiac amyloidosis. But because it is underdiagnosed, and *TTR* testing is not routinely carried out, these patients are not eligible for the drug,” Rader explains.

Similarly, patients are not being sequenced for mutations in the *LMNA* gene, which is associated with dilated cardiomyopathy.³ “Mining data from the Penn Medicine

CARDIOGENOMICS ENABLES BETTER PATIENT OUTCOMES

The cardiology community is increasingly aware of the benefits of combining genetic testing and phenotypic data to improve disease management and identify at-risk relatives.



Biobank we find quite a few people who have deleterious mutations in *LMNA* and heart failure, but where a genetic diagnosis had not been considered,” says Rader. Testing for *LMNA* could speed up diagnosis, identify at-risk family members, and encourage routine surveillance with cardiovascular screening tests.

And then there are mutations in three genes associated with familial hypercholesterolemia, which encode the low-density lipoprotein receptor (LDLR), apolipoprotein B (APOB), and proprotein convertase subtilisin/kexin 9 (PCSK9). Genetic testing for mutant versions of these genes is rarely done, even though they elevate the risk of this increasingly common and potentially fatal, but treatable, condition.⁴

Barriers to implementation

As the genetic underpinnings of many cardiovascular diseases are revealed, why are genetic tests not more widely used? “The biggest obstacle is a lack of knowledge about genetic testing on the part of cardiologists and healthcare providers in general,” says Musunuru. “If it’s not on their radar, they won’t order the tests.”

In addition, practitioners may fail to suspect an inherited condition given the emphasis on family history (or lack thereof) in clinical diagnosis. “Family history has its limitations in terms of deciding whether a condition is inherited,” says Rader. “If a patient presents with idiopathic dilated cardiomyopathy, and no one else in their family has the condition, the cardiologist may have no reason to suspect that it has a genetic cause.”

Engaging cardiologists with the emerging data is crucial. “When we have presented *TTR* data to cardiologists, they have recognized that they probably aren’t thinking of, or looking for, cardiac amyloidosis as aggressively as they should be,” says Rader.

Although the use of genetic testing in cardiology is not as common as in cancer, Tang notes that cardiologists are becoming more confident and comfortable using it. “As in other disciplines, it is recognized that some variants are much more malignant than others,” he explains. “Identifying them allows us to be better prepared for progression in terms of both the phenotypic manifestation and therapeutic response.”

But counselling is not always easy to put in place. Patients should be aware of the implications of genetic testing, with sessions before and after the results are known. “This should be done by genetic counsellors, who are in relatively short supply,” says Musunuru.

Finally, there are also concerns about the cost and reimbursement for the tests. Although most insurance policies acknowledge the benefit of genetic testing for cardiovascular disease, particularly to identify asymptomatic at-risk relatives, coverage varies. “The uncertainty of whether testing will be reimbursed can put cardiologists off ordering it,” says Rader. Many professionals are calling for more consistent payer policies.

Addressing the gaps

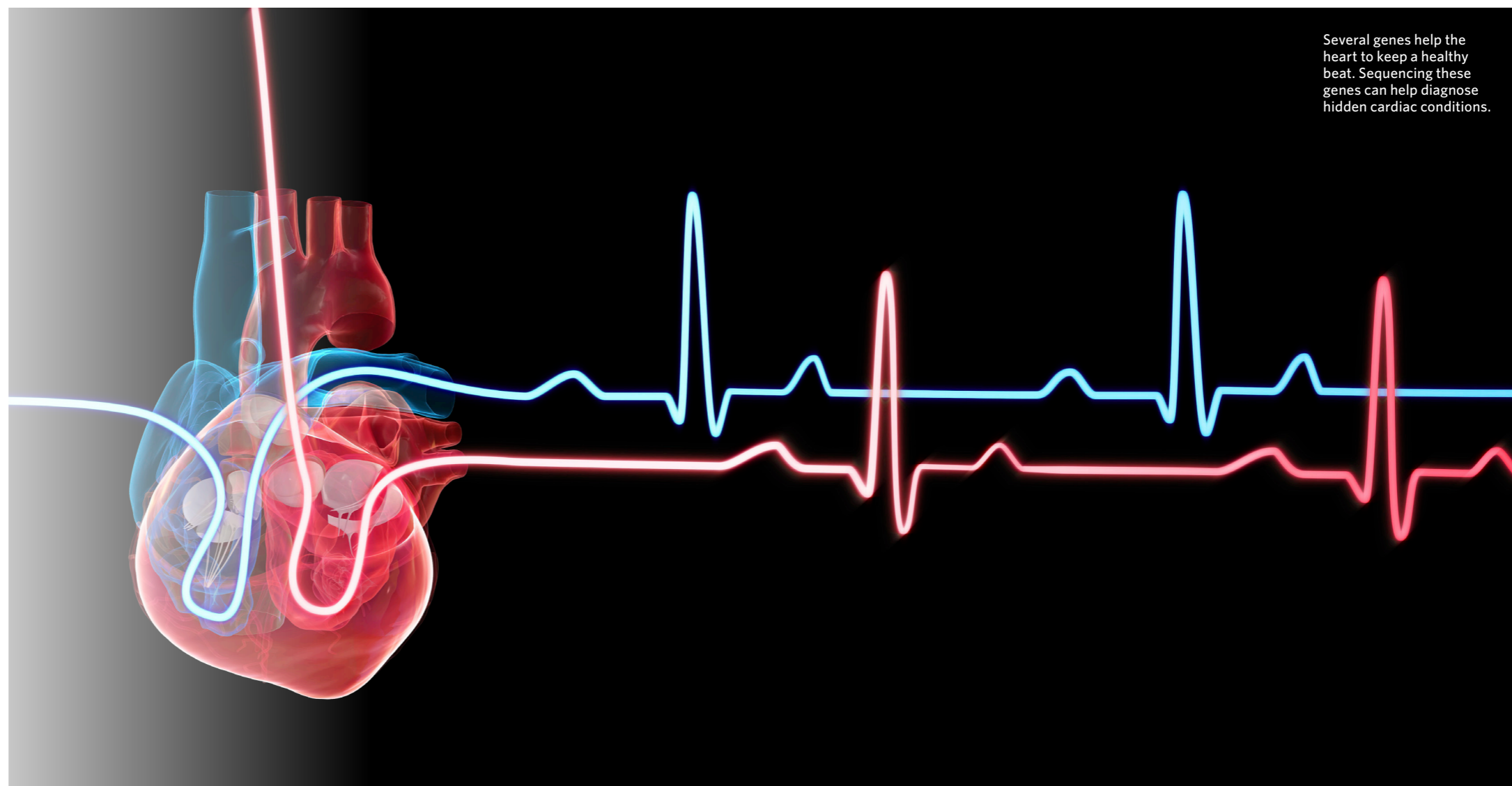
Cardiogenomics is still a young field. Many gene variants associated with

cardiovascular disease are of unknown significance and thus of limited clinical utility. Further understanding of how these variants interact with other genes and environmental factors will help determine their pathogenicity.

There is still a lot to learn about disease-causing ancestral gene variants. Most genetic data come from people with European ancestry, who have different genetic vulnerabilities to disease than people from other ethnicities. Initiatives to sequence African populations are starting to address this issue. For example, a specific *TTR* variant associated with cardiac amyloidosis is found at higher frequency in people of African ancestry than in those of European ancestry, highlighting the usefulness of *TTR* testing in specific ethnic groups.⁵

Another important consideration is that some cardiovascular diseases disproportionately affect women, yet treatment guidelines are largely based on clinical trials in men. As more women participate in research studies and more sex-specific analyses are published, there is a growing number of gender-specific interventions for the treatment and management of cardiovascular disease.⁶

Several initiatives are aiming to help shed light on potential genetic mechanisms underlying the observed sex differences. The Women’s Genome Health Study (WGHS) has been examining the genomes of more than 25,000 initially healthy US women to identify potential gene variants associated with major health incidents, including myocardial infarction and stroke.⁷ But it’s a complicated relationship. “There are many gene-



Several genes help the heart to keep a healthy beat. Sequencing these genes can help diagnose hidden cardiac conditions.

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environment interactions at play,” says Tang, “some related to co-expressed or modifier genes and others likely due to dietary, lifestyle or sex-specific (hormonal) effects.”

Integrating other ‘omic’ data will also help clarify the picture of cardiovascular disease. “The development of methods to assess epigenetic marks in heart tissue, to look at large-scale proteomics in blood, and for metabolomics, is going to take us to another level of understanding,” says Rader.

“THE BIGGEST OBSTACLE IS A LACK OF KNOWLEDGE ABOUT GENETIC TESTING ON THE PART OF CARDIOLOGISTS AND HEALTHCARE PROVIDERS IN GENERAL.”

Cardiogenomics and disease prevention

Deciphering how the genetic code is transcribed and expressed is key for personalized care. “Single-cell sequencing and spatial transcriptomics have revolutionized our ability to subclassify diseases according to their underlying mechanisms at the molecular level,” says Tang. He is particularly interested in metabolomics and understanding how environmental factors, such as diet, affect gene expression. “This dynamic interaction is very

important at the clinical level as it can inform interventions that ameliorate risk,” he explains.

Identifying potentially pathogenic mutations that have actionable effects will have a substantive impact on the practice of cardiology. “We are continuously learning about the genetic basis of, not just classic inherited cardiovascular conditions, but also common diseases such as heart attack and atrial fibrillation,” says Musunuru.

This knowledge is helping disease prevention through

early intervention. “In the coming years, it should be possible to use whole-genome sequencing very early in life to better forecast a person’s future health and encourage choices to reduce the lifetime risk of disease,” Musunuru adds, “which should hopefully lead to longer and healthier lives.” ■

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