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Cardiology Embraces Whole-Genome Sequencing:

CardioSeq Trial Demonstrates Pragmatic Path to Routine Clinical Genomics

A Precision Medicine Online / Illumina Webinar Report

David E. Lanfear, MD, MS, FAHA, FACC, FHFSA

Chief Scientific Officer, Vice President of Research

Henry Ford Health

Denise L. Perry, MS, CGC

Senior Director, Medical Genomics Lab Services

Illumina

In a Precision Medicine Online webinar titled "Are We Ready for Routine Clinical Genomics in Cardiovascular Disease:

Implementation of a Pragmatic Approach and Initial Results from the CardioSeq Clinical Trial," two leaders in cardiovascular genomics made a compelling case that the integration of genetic testing into cardiology practice is now a reality, and its clinical implementation is more achievable than many clinicians realize.

David Lanfear, Chief Scientific Officer and Vice President of Research at Henry Ford Health (HFH), teamed up with Denise Perry, senior director of medical genomics lab services at Illumina Laboratory Services, to share findings from the prospective CardioSeq clinical trial, designed to evaluate the diagnostic yield and impact of comprehensive genomic sequencing in 1,000 patients from the cardiology clinic at HFH. This groundbreaking collaboration between their institutions involves a pragmatic genetic testing approach using the TruGenome Cardiovascular Disease Test, a single comprehensive clinical genetic test for cardiovascular diseases.

The webinar, sponsored by Illumina, showed how comprehensive genomic sequencing can be integrated into cardiology practice.

The Testing Gap in Cardiology

Lanfear began by pointing out a significant gap in cardiovascular genetics. Although many professional guidelines now recommend genetic testing for conditions like cardiomyopathies, arrhythmias, and familial hypercholesterolemia, these recommendations are still not widely implemented in clinical practice.

"Despite the fact that we have all this potential clinical impact of genetic testing, genetic testing remains very poorly utilized," Lanfear explained, citing recent data showing that "about 1 percent of patients that have a recommended indication for testing actually get that test."

The barriers are multifaceted: limited availability of genetic counselors, physicians' lack of confidence in interpreting results, concerns about insurance coverage, and lingering perceptions that genetic information won't meaningfully impact patient care.

Yet the clinical landscape is shifting quickly. Lanfear highlighted emerging precision therapies for genetically defined cardiomyopathies, noting that "as the years go on, we're getting more and more trials, and more Phase III trials now in terms of specific therapies for genetically inherited cardiovascular disease."

Lanfear gave several examples of situations in which genetic testing can directly impact clinical management, including cardiomyopathy-associated mutations treatable with enzyme replacement therapy and aortopathy-related mutations that indicate a need for earlier aortic repair. "Marfan's is a perfect example where if you know the genetic diagnoses and you can get in front of it, you actually can almost normalize outcomes," he said.

A Whole-Genome Approach

Genomic tests for cardiovascular disease have traditionally tested for pathogenic variants in single genes or a targeted panel of relevant genes. However, cardiovascular presentations often overlap, so narrowly focused testing can lead to false negatives, and it can miss pathogenic variants under investigation in clinical trials, those with emerging evidence, and those in regions that are challenging to sequence.

Whole-genome sequencing (WGS) covers the breadth of actionable variants, it can provide additional pharmacogenomic and risk information, and it can replace a complex assortment of single-marker tests or small panels with as a "one-stop shop." While its adoption has previously been hindered by sequencing costs and demanding analysis, WGS is more accessible than ever, Lanfear said, thanks to the falling cost of sequencing and more advanced informatics tools and electronic health records.

"With this in mind," he said, "We sought to create an intervention that would be optimally practical for use in the cardiology clinic, capturing common uses of genetic testing as well as the monogenic findings that we are mostly going to run into."

HFH partnered with Illumina for the CardioSeq trial, implementing the TruGenome Cardiovascular Disease Test, a clinically validated LDT developed by Illumina Laboratory Services, which consists of a WGS backbone followed by a virtual panel analysis. The study investigated the diagnostic yield and clinical utility of the test as well as the patient and physician experience.

The TruGenome Cardiovascular Disease Test: Rigorous Development

Perry detailed the meticulous process of developing the Cardiovascular Disease Test. The team conducted a comprehensive literature review, examining gene-disease validity curations from ClinGen, the Gene Curation Coalition, and Illumina's internal database, while assessing the content of commercially available cardiovascular genetic testing panels.

Critically, the team applied the ClinGen gene-disease validity framework and made a consequential decision:

"We decided to only include genes that met the highest confidence association with cardiovascular disease on our panel, so a definitive or strong association with disease," Perry explained.

This rigorous approach resulted in 215 high-confidence gene-disease pairs across six disease categories: cardiomyopathy, arrhythmia, aortopathy, dyslipidemia, coronary artery disease, and thrombophilia. The test also incorporated carefully selected risk alleles and offered optional reporting of non-cardiovascular genes from the ACMG secondary findings list — primarily hereditary cancer predisposition genes.

A pharmacogenomics component rounded out the offering, with clinical interpretation for 10 well-characterized pharmacogenes. Three of these — affecting warfarin, clopidogrel, and simvastatin metabolism — are particularly relevant for cardiovascular patients.

Illumina Lab Services' Streamlined Workflow

Perry described the laboratory workflow behind this clinical WGS test, highlighting both its technological sophistication and practical efficiency. The end-to-end workflow results in a 15 to 30-day turnaround time from sample receipt to clinical reporting — a timeline that makes routine clinical use practical.

Illumina high-throughput sequencing instruments were used for sequencing, laying the groundwork for comprehensive genomic analysis. After sequencing, the data moves through a carefully orchestrated pipeline designed to transform raw genomic information into actionable insights.

For secondary analysis — the computationally intensive process of transforming raw sequencing data into identified genetic variants — Illumina uses DRAGEN (Dynamic Read Analysis for GENomics). This platform manages the essential task of aligning sequencing reads to the reference genome and calling variants with high accuracy and speed.

The tertiary analysis and reporting stage uses Emedgene, Illumina's variant interpretation platform for genetic disease research, hosted in the AWS cloud. Here, variant calls are converted into streamlined reports through advanced variant filtering, prioritization, and annotation algorithms.

Perry highlighted the strategic methods the Illumina laboratory team used to improve interpretation efficiency. "As you sequence and test more patients, and you're curating and classifying variants and adding them to your variant knowledge base, then the next time you encounter that variant, that work is already done," she explained.

When asked about the interpretation burden per case, Perry explained: "When we look across the cardiovascular disease panel, which is the bulk of genes, the secondary findings, and risk alleles, we're seeing about anywhere between zero and 10 variants per person to review and curate and classify."

The result is a scalable workflow that balances thoroughness with efficiency —forming a strong analysis workflow capable of managing large volumes while upholding accuracy.

Striking Results in an Unselected Population

The CardioSeq trial enrolled a highly diverse population. The final cohort of 1,000 patients was evenly split between men and women, with 40 percent identifying as Black or African American and nearly 60 percent as white-non Hispanic. The genetic findings even surprised the investigators. The study found 88 pathogenic or likely pathogenic mutations in cardiovascular genes, affecting 7.4 percent of participants (See Figure 1). An additional 1.4 percent had ACMG secondary findings, bringing the overall monogenic finding rate to 8.8 percent.

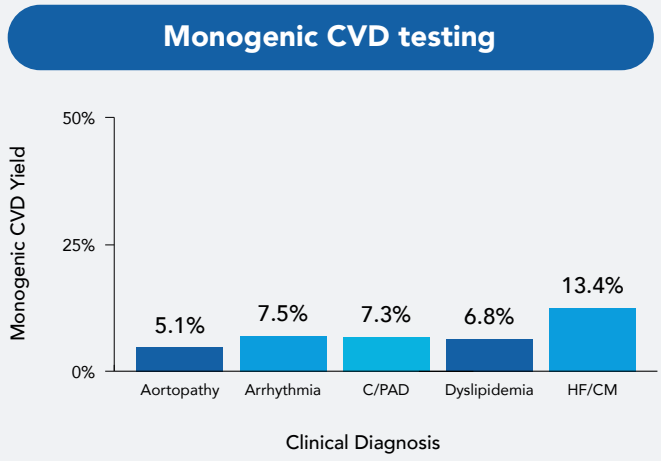

Figure 1. The rate of CV monogenic findings in the cohort was 7.4 percent, but it varies across disease presentation. The rate roughly doubles in patients with heart failure/cardiomyopathy.

The most frequently identified genes with variants were TTR (transthyretin, linked to cardiac amyloidosis), TTN (associated with dilated cardiomyopathy), and LDLR (responsible for familial hypercholesterolemia). An additional 10 percent of patients had clinically significant risk allele findings (see Figure 2).

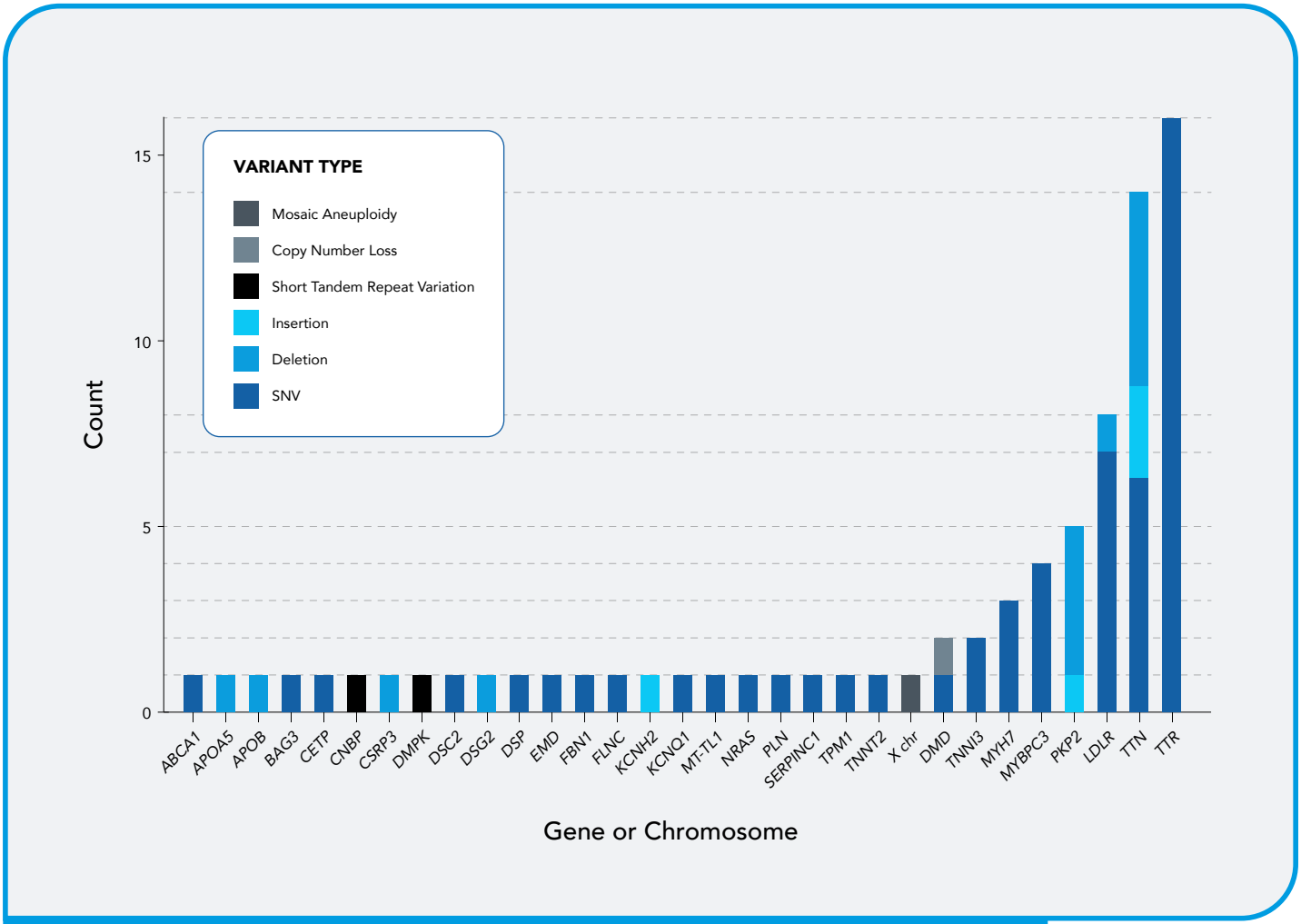

Figure 2. Diagnostic Findings included a range of variant types across CVD conditions.

Pharmacogenetic findings were nearly universal — "almost everyone has an important variant in one of those pharmacogenetic genes that we tested," Lanfear reported.

"When I saw the top line results, I was a little surprised at how common we had monogenic findings," Lanfear admitted. However, he pointed out external validation was obtained through comparison with the HeartCare study at Baylor.

Notably, 97 percent of patients opted in to receive non-cardiovascular ACMG secondary findings. "I think this is one of those areas where I wanted to leave it open. I wasn't sure everyone would embrace it, but the vast, vast majority did," Lanfear said.

Patient Enthusiasm Versus Physician Readiness

Perhaps the most striking contrast was between patient and physician reactions. Patients embraced participation enthusiastically, even those receiving concerning diagnoses. "There weren't any patients that were unhappy with their participation or, even when they got bad news, were angry or regretful," Lanfear said. "They literally were all quite happy or felt fortunate to have the information and then be able to do something with it."

Physicians faced a steeper learning curve. "I think it was a little harder on the physician side, actually. I don't think are well prepared to deal with this information," Lanfear acknowledged. The path forward requires "a lot better education about how to practically handle genetic testing, as well as help from our friends like genetic counselors."

Implications and Next Steps

The CardioSeq findings have important implications. Since nearly 10 percent of unselected cardiology patients hold actionable monogenic results, routine genetic testing provides real benefits for patients and their families.

Lanfear emphasized key takeaways: "There really is widespread utility to whole-genome-based routine genetic testing." Additionally, "pharmacogenes, as previously known, are nearly universally present. It's only a matter of time until someone gets a medication that will be differentially metabolized compared to others."

Perry added: "It really takes a village — patient advocacy groups, professional societies, genetic counselors, cardiologists, industries, and pharma companies — coming together to really move the needle for patients."

The CardioSeq clinical trial shows that technical and logistical barriers to routine cardiovascular genomics can be overcome. With streamlined whole-genome sequencing workflows, comprehensive genetic testing can be implemented widely in everyday cardiology practice.

Interested in exploring comprehensive cardiovascular disease genetic testing at your Institution? Illumina Laboratory Services is an accredited clinical laboratory with the aim of supporting Illumina customers on accelerating their goals through clinical test send out services and peer-to-peer engagement.

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