MAYO CLINIC

Precision Cardiovascular Medicine: State of Genetic Testing

John R. Giudicessi, MD, PhD; Iftikhar J. Kullo, MD; and Michael J. Ackerman, MD, PhD

From the Department of Internal Medicine, Internal Medicine Residency Program, Clinician-Investigator Training Program (J.R.G.), Department of Cardiovascular Diseases (I.J.K., M.J.A.), Gonda Vascular Center (I.J.K.), Division of Heart Rhythm Services (M.J.A.), Department of Pediatric and Adolescent Medicine, Division of Pediatric Cardiology (M.J.A.), and Department of Molecular Pharmacology and Experimental Therapeutics, Windland Smith Rice Sudden Death Genomics Laboratory (M.J.A.), Mayo Clinic, Rochester, MN

CME Activity

Target Audience: The target audience for *Mayo Clinic Proceedings* is primarily internal medicine physicians and other clinicians who wish to advance their current knowledge of clinical medicine and who wish to stay abreast of advances in medical research.

Statement of Need: General internists and primary care physicians must maintain an extensive knowledge base on a wide variety of topics covering all body systems as well as common and uncommon disorders. *Mayo Clinic Proceedings* aims to leverage the expertise of its authors to help physicians understand best practices in diagnosis and management of conditions encountered in the clinical setting.

Accreditation: Mayo Clinic College of Medicine and Science is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Credit Statement: Mayo Clinic College of Medicine and Science designates this journal-based CME activity for a maximum of 1.0 *AMA PRA Category 1 Credit(s).*™ Physicians should claim only the credit commensurate with the extent of their participation in the activity.

MOC Credit Statement: Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 1 MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

Learning Objectives: On completion of this article, you should be able to (1) summarize clinical indications for cardiovascular disease genetic testing, (2) recognize common pitfalls and current limitations of genomic-aided approaches, and (3) appraise the current clinical utility of genetic testing to individualize the diagnosis, risk stratification, and management of patients with an array of cardiovascular diseases.

Disclosures: As a provider accredited by ACCME, Mayo Clinic College of Medicine and Science (Mayo School of Continuous Professional Development) must ensure balance, independence, objectivity, and scientific rigor in its educational activities. Course Director(s), Planning Committee members, Faculty, and all others who are in a position to control the content of this educational activity are required to disclose all relevant financial relationships with any commercial interest related to the subject matter of the educational activity. Safeguards against commercial bias have been put in place. Faculty also will disclose any off-label and/or investigational use of pharmaceuticals or instruments discussed in their presentation. Disclosure of this information will be published in course materials so that those participants in the activity may formulate their own judgments regarding the presentation.

In their editorial and administrative roles, William L. Lanier, Jr, MD, Terry L. Jopke, Kimberly D. Sankey, and Nicki M. Smith, MPA, have control of the content of this program but have no relevant financial relationship(s) with industry.

Dr Kullo has received honoraria from Amgen Inc. Dr Ackerman is a consultant for Boston Scientific Corporation, Gilead Sciences, Inc, Invitae, Medtronic, MyoKardia, Inc, and St. Jude Medical, LLC, and has licensing agreements with AliveCor. From 2004 through 2016, Dr Ackerman and Mayo Clinic received sales-based royalties from Transgenomic, Inc, for their FAMILION-LQTS and FAMILION-CPVT genetic tests. However, none of these entities participated in this study.

Method of Participation: In order to claim credit, participants must complete the following:

1. Read the activity.
2. Complete the online CME Test and Evaluation. Participants must achieve a score of 80% on the CME Test. One retake is allowed.

Visit www.mayoclinicproceedings.org, select CME, and then select CME articles to locate this article online to access the online process. On successful completion of the online test and evaluation, you can instantly download and print your certificate of credit.

Estimated Time: The estimated time to complete each article is approximately 1 hour.

Hardware/Software: PC or MAC with Internet access.

Date of Release: 4/1/2017

Expiration Date: 3/31/2019 (Credit can no longer be offered after it has passed the expiration date.)

Privacy Policy: http://www.mayoclinic.org/global/privacy.html

Questions? Contact dletcsupport@mayo.edu.

Abstract

In the 15 years following the release of the first complete human genome sequences, our understanding of rare and common genetic variation as determinants of cardiovascular disease susceptibility, prognosis, and therapeutic response has grown exponentially. As such, the use of genomics to enhance the care of patients with cardiovascular diseases has garnered increased attention from clinicians, researchers, and regulatory agencies eager to realize the promise of precision genomic medicine. However, owing to a large burden of "complex" common diseases, emphasis on evidence-based practice, and a degree of unfamiliarity/discomfort with the language of genomic medicine, the development and implementation of genomics-guided approaches designed to further individualize the clinical management of a variety of cardiovascular disorders remains a challenge. In this review, we detail a practical approach to genetic testing initiation and interpretation as well as review the current state of cardiovascular genetic and pharmacogenomic testing in the context of relevant society and regulatory agency recommendations/guidelines.

Since the sentinel discovery of the first heritable monogenic cardiovascular disease (CVD) genes in the early to mid 1990s, genetic testing for familial aortopathies,[1,2] cardiomyopathies,[3,4] cardiac channelopathies,[5,6] and hypercholesterolemia[7,8] has transitioned rapidly from early research-based endeavors to a full complement of reimbursable commercially available genetic tests. Furthermore, following the release of the first complete human genome sequences in 2001,[9,10] ensuing genome-wide association studies (GWASs) have identified a plethora of common genetic variants that underlie risk for development of common CVDs such as coronary heart disease (CHD)[11] and atrial fibrillation (AF)[12] as well as interindividual variability in cardiovascular drug response. Collectively, genetic testing for rare monogenic CVDs, ongoing development of genetic risk scores (GRSs) for common polygenic CVDs, and the implementation of pharmacogenomic testing to predict response to cardiovascular drugs represent the spectrum of genetic tests that currently impact the diagnosis, risk stratification, and clinical management of patients with rare and common CVDs.

With the announcement of the Precision Medicine Initiative in early 2015, interest in precision genomic medicine has intensified, and the stage has been set for an unprecedented proliferation of genetics- and genomics-guided approaches. Although cardiovascular health care professionals stand to benefit from these advances, the rapid pace of genomic discoveries, gaps in genomics education/literacy, and the paucity of data from randomized controlled trials (RCTs) designed to determine the clinical utility of genomics-aided approaches have left many overwhelmed and thereby ill-prepared to deliver high-quality, genomics/genetics—guided care. As such, this review aims to summarize the current clinical utility, commonly encountered pitfalls, and areas of emerging interest pertaining to the use of genetic and pharmacogenomic testing to individualize the clinical management of an array of CVDs.

BASIC PRINCIPLES GOVERNING THE INITIATION AND INTERPRETATION OF CARDIOVASCULAR GENETIC TESTS

With each passing year, cost-lowering technological advances, improved payer reimbursement, and legislation aimed at eliminating genetic discrimination make genetic testing increasingly accessible and appealing. However, as the pendulum has swung from inaccessible to more readily available, the increased, and at times inappropriate, utilization of genetic testing has brought a new set of obstacles.[13] As such, the ensuing paragraphs aim to help physicians avoid common pitfalls associated with the inappropriate use of genetic testing, namely, poor phenotyping, inappropriate genetic test selection, and misinterpretation of results, by outlining common indications, expected results, and basic interpretive strategies when considering CVD genetic testing.

At present, CVD genetic testing is reserved typically for 1 of 3 clinical indications: (1) comprehensive genetic testing to aid or confirm the diagnosis of a heritable CVD for which there is a strong index of clinical suspicion (class I recommendation for many, but not all, monogenic CVDs),[6] (2) mutation-specific cascade screening of appropriate relatives (class I recommendation for all monogenic CVDs),[6] and (3) the selected use of pharmacogenomic testing to aid in the selection and/or dosing of certain cardiovascular medications (variable society and regulatory agency recommendations). It is important to note that due to variable expressivity and incomplete penetrance of monogenic CVDs coupled with substantial background genetic variation in many monogenic CVD-causative genes, diagnostic genetic testing should be viewed as probabilistic rather than binary/deterministic.[5,14,15]

As such, the clinical utility of a given genetic test is highly dependent on the pretest probability of disease (ie, strength of clinical phenotype/diagnosis) and disease-specific genetic test performance metrics (eg, diagnostic yield, signal to noise ratio). In other words, in patients with weak/nonequivocal clinical phenotypes, the diagnostic yield of genetic testing declines, the signal to noise ratio rises, and the risk of encountering false-positive results increases exponentially. Therefore, a "one size fits all" mentality to genetic testing is ill-advised, and genetic testing should be undertaken only if considerable suspicion for an underlying genetic CVD remains after a thorough clinical evaluation, including, but not limited to, a detailed family history,