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FELLOWS-IN-TRAINING & EARLY CAREER PAGE

Training in Cardiovascular Genetics

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The last 2 decades have borne witness to a rapid and vigorous expansion of our understanding of the genetic basis underlying many cardiovascular diseases. As fellows-in-training, this marks an exciting time with a rapid tempo of discovery that keeps us in constant motion, which challenges us to keep up with current developments to provide optimal cardiovascular care to our patients. Since the discovery in 1990 that a mutation in the β cardiac myosin heavy chain, a component of the sarcomere, caused familial hypertrophic cardiomyopathy (1,2), investigators in the field of cardiovascular genetics have developed an increasingly complex understanding of the pathophysiologic basis of inherited cardiac diseases (3). Genetic testing for these heritable diseases has rapidly advanced from basic scientific discovery to clinical application, and commercially targeted gene testing and comprehensive disease panels have entered mainstream cardiology practice in the past several years (4). Clinical screening tools for whole-exome or -genome sequencing are becoming exponentially more affordable and accessible and are now entering the clinical world. However, technical advances in deoxyribonucleic acid sequencing methodology have outpaced our ability to confidently understand the clinical significance of these findings. Increasingly, both adult and pediatric cardiologists are being called upon to serve as interpreters of the genetic language relevant to cardiovascular disease. This will necessitate focused training pathways for fellows to acquire the fluency to understand the rapidly expanding landscape of cardiovascular genetics and the requisite expertise to accurately recognize the cardiac and extracardiac phenotypes of inherited cardiovascular disorders.

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We will briefly consider 5 likely referrals to a cardiovascular medicine specialist. First, an 18-year-old competitive swimmer presents for evaluation of exertional syncope in the context of a family history of sudden cardiac death. He is found to have a borderline QT interval, with a QTc of 480 ms on the electrocardiogram. How can genetic testing help with the care of this patient? Second, a 34-year-old woman with pre-hypertension is found to have moderate concentric left ventricular hypertrophy on a screening echocardiogram performed for evaluation of a murmur. Should this patient have genetic testing for hypertrophic cardiomyopathy–associated mutations, including β-myosin heavy chain gene (*MYH7*) and myosin binding protein C (*MYBPC3*)? Third, a 55-year-old man with normal low-density lipoprotein cholesterol and Framingham risk score is referred for recommendations regarding primary prevention of atherosclerotic cardiovascular disease. His family history is notable because his father had a myocardial infarction at 50 years of age. The patient has read about testing for genetic variants at the 9p21 locus and asks if he "should get this test?" Fourth, as part of an unrelated research study, a 45-year-old woman undergoes whole-exome sequencing that reveals a variant in the titin (*TTN*) gene, which has been associated with nonischemic dilated cardiomyopathy. She has no clinical phenotype and is not aware of family members with cardiac disease. How should she be counseled regarding this finding? Finally, a 46-year-old patient is referred for implantable cardioverter-defibrillator (ICD) extraction after device infection. Her ICD was placed for primary prevention in the setting of a syncopal episode and commercial genetic testing, revealing a variant in *SCN5A* (1 of the genes involved in Brugada syndrome and long QT syndrome), which at the time, was thought to be likely pathogenic, but has since been downgraded to a variant of unknown significance. Was initial ICD implantation appropriate, and should it be replaced?

Many cardiovascular trainees might feel underprepared to care for these patients. Indeed, despite

the rapid expansion in cardiovascular genetics, trainees generally have limited exposure to cardiovascular genetics during their fellowships. Although such patients are increasingly, and appropriately, referred to specialized clinics, a fundamental understanding of the management of such patients is incumbent on all cardiologists. Determining the optimal elements of training during general adult or pediatric cardiology fellowship as well as defining the structure and role of novel advanced training pathways are both key to filling this gap.

As illustrated, the field of cardiovascular genetics encompasses a wide variety of inherited cardiac conditions from monogenic diseases, such as channelopathies (long QT syndrome, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia), cardiomyopathies (dilated, hypertrophic, and arrhythmogenic), connective tissue diseases (Marfan syndrome and Loeys-Dietz syndrome), and familial dyslipidemias, to those with a more complex inheritance pattern, such as certain forms of congenital heart disease and perhaps even coronary artery disease. Additionally, the pleiotropy of many genes and increasingly recognized overlap syndromes add to the clinical complexity. With genetic testing for these conditions and others becoming more available, and even publicly accessible in some cases (5), cardiologists will be increasingly looked upon to help navigate these tests, ideally including pre-test counseling to ensure that expectations regarding the benefits and limitations of testing are appropriate. Cardiologists with knowledge of genotype and phenotype are also needed to accurately interpret the results of genetic testing in the context of the patient and family under their care. As genetic testing advances and next-generation sequencing become more accessible, policy makers may seek out cardiologists to help chart a course for responsible use of these technologies (6).

Current cardiovascular genetics specialists have evolved from various backgrounds, including electrophysiology, heart failure, advanced imaging, and preventive cardiology. In the absence of precedent or standardization, such specialists have generally defined their own learning pathways, curricula, and clinical exposures. Clearly, there is an evolving need to train specialists in cardiovascular genetics, and such programs are needed and sought after by fellows-in-training. To facilitate this training, 2 alternate, but not exclusive, pathways could be chosen: 1) continue with the current approach of adding supplemental cardiovascular genetics training to 1 of the traditional cardiovascular subspecialties; or 2) define this as a brand-new training opportunity.

The core elements of either trajectory would include: 1) development of expertise in thorough clinical phenotyping of probands and family members, using the family as the unit of care; 2) development of an approach to the (often gray) indications for genetic testing, including selection of appropriate tests (targeted sequencing, disease-panels, whole genome sequencing, and so on) and optimal testing strategy (selection of the family proband, directing cascade screening); 3) proficiency in interpreting genetic testing results, including the technical aspects of variant classification, and integrating results in the context of a patient's and family's phenotype; 4) proficiency in genetic counseling; 5) knowledge of appropriate management of various common cardiovascular disorders with a genetic basis; and 6) research training, including the ethical, social, and legal implications of genetic investigation, genetic testing, and familial disease.

Examples of important experiences for the trainee, which could accomplish these learning objectives, include participation in an outpatient family clinic focused on inherited cardiovascular disorders and associated molecular genetics. Working with genetic counselors to facilitate family interactions would also be a critical foundational exposure. Finally, there should be formal training to develop an informed and critical approach to interpreting genetic testing results, including exposure to key gene variant analytic platforms and training on the use of publicly available databases of human genomic variation. Associated imaging for diagnosis and risk stratification of genetic conditions for key diseases also would be an important cornerstone.

In conclusion, cardiovascular genetics is rapidly emerging as a new paradigm for diagnosing and managing cardiovascular diseases. Its relevance to the practice of clinical medicine has transcended the laboratory, and clinicians now require expertise in this field to make appropriate, informed patient care decisions. Training fellows in cardiovascular genetics will be critical to ensure that the cardiovascular community is able to provide efficient, high-quality, personalized care for the next generation of patients.

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RESPONSE: Cardiovascular Genetics Training

Robustness and Certification

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Dr. Beauséjour Ladouceur is to be thanked for bringing the issues about fellowship training in cardiovascular genetics (CVG) to the forefront. As she correctly points out, CVG has moved well beyond the research laboratory over the past 25 years and has become an increasingly important part of our diagnostic armamentarium. Increasingly, guidelines for care are including genetic testing and phenotype surveillance for patients and family members for certain cardiovascular disorders (1,2). CVG programs have arisen at increasing numbers of academic institutions, overseen by physicians with varying expertise and experience but who are, inevitably, self-appointed, as there is no formal process for certifying CVG practitioners.

Because Dr. Beauséjour Ladouceur has discussed the critical issues about CVG training, I will only attempt to amplify or expand a bit on a few of those points. First and foremost, all cardiology trainees—adult and pediatric alike—need exposure to CVG (albeit, not the exact same information). Genetic testing is here to stay. It will continue to evolve as technologies advance and the underlying genetic data about populations and diseases expand. Eventually, it is likely that the genome sequences of all patients will be available as part of the electronic medical record from early in life. Moreover, the utility of genetic information will continue to move beyond mere testing for diagnosis and prognosis to the realm of determining therapies. Best clinical practices for the disciplines within cardiovascular medicine will increasingly demand that cardiologists be aware of the implications of the underlying genetics for their patients, as is already the case for certain diagnoses such as long QT syndrome (1). Although we are developing advanced training pathways in CVG, it will still be incumbent on all practitioners to know enough about the genetics relevant to their scope of practice.

A second issue concerns the formalities for an area of cardiovascular medicine to rise to the level of being certifiable. Here, we must note a difference between adult and pediatric cardiology. At the current time, the American Board of Internal Medicine sponsors certification in several advanced practices beyond cardiology per se (adult congenital heart disease, advanced heart failure and transplant cardiology, clinical cardiac electrophysiology, and interventional cardiology). In contrast, the American Board of Pediatrics only cosponsors certification in adult congenital heart disease, administered through the American Board of Internal Medicine. Both boards have criteria for establishing new certificate-granting subspecialties, but doing so is laborious and time consuming. There are also substantial attendant costs, both for programs to support trainees in these advanced practice tracks and for the boards to sustain the infrastructure needed for certification and maintenance of certification. Practically, the latter issue necessitates that enough cardiologists pursue certification for it to even be economically feasible.

In the meantime, it would be worthwhile for program directors, both of general cardiology training programs as well as CVG programs, to develop guidelines for training in both contexts.

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