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A Model for the Integration of Genome Sequencing Into a Pediatric Cardiology Clinic

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Genetic testing in cardiology improves the management of patients and families. Genome sequencing (GS) is a comprehensive, nontargeted approach to genetic testing and an established pillar of precision medicine used to increase genetic discoveries, diagnoses, and provide individualized care. Challenges with integrating GS into cardiology include a lack of genomic literacy, recurrent data interpretation, and returning results to patients. The Cardiac Genome Clinic proposes a multidisciplinary model to support the integration of GS into pediatric cardiology. Preliminary data show that use of this model supported new diagnoses, identification of medically actionable secondary findings, and improved medication management.

Genetic Testing in Cardiology

Making a genetic diagnosis can guide cardiologists' approach to management of disease, inform proactive screening regimens for at-risk relatives, empower families by identifying the cause of patients' conditions, and enable appropriate counselling for family planning and risk of recurrence.[1] In current practice, targeted genetic testing is initiated in patients with heart disease in specific clinical circumstances such as the presence of multiple congenital anomalies, a high suspicion of a genetic syndrome, a positive family history, or in specific subtypes of cardiac disease (eg, cardiomyopathy, arrhythmia, and aortopathy).[1] This approach relies on the clinician's ability to recognize these criteria and leaves a large group of patients without genetic testing options. Despite affecting many patients followed in pediatric cardiology, genetic testing in congenital heart disease remains underdeveloped.

GS assesses many types of genetic variation across the genome in 1 comprehensive test and can be appropriately ordered without a specific differential diagnosis. In addition, GS data can be continually reinterpreted in the context of new information about a patient or a disease. When compared with traditional testing (eg, microarray and targeted gene panels), GS improves the diagnostic yield and reduces the number of tests ordered.[2] Finally, GS provides the opportunity for novel gene discovery, which contributes to our understanding of disease mechanisms and provides the opportunity for the development of new treatments.[1]

The era of precision medicine necessitates the use of GS as a tool to increase genomic diagnoses and enable targeted

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prevention and treatment of disease. The advantages of GS are recognized in other specialties, such as oncology, neurology, and neonatology, in which it is being used as a first-tier diagnostic test, prognostic tool, and precursor to therapeutic management.[3] In cardiology, the transition to genomics remains unrealized. Although GS is not currently publicly funded, it is anticipated to become more widely available, and workflows to support its implementation into cardiology will be essential.

Challenges of Implementing GS in Cardiology

Despite evidence that GS contributes to an increase in genetic diagnoses in heart disease, challenges to the effective integration of GS into clinical cardiology remain. First, there is a lack of understanding of the cost—benefit ratio for GS. Economic models and clinical utility studies are required to fill this knowledge gap. Second, clinicians without formal training in genetics cannot always discern the optimal use and potential limitations of GS. The complexity and rapid evolution of genomic technology demands that ordering clinicians have a thorough understanding of its application and implications for their patients, including the possibility of uncovering secondary results.[4] A thoughtful informed-consent discussion with patients highlighting the risks and benefits of GS is necessary, as most families lack sufficient genomic literacy to make informed decisions independently.[4] This highlights the need for educational support for both patients and cardiologists. Finally, the amount of time and expertise needed for the ongoing and evolving interpretation of GS data is a challenge for most clinicians.[4] It is important that these challenges be considered when developing models of care to facilitate the use of genomic technologies in the clinic. Such models must enable increased access to GS; facilitate ongoing provider and patient education; and have frameworks to guide data analysis, reanalysis, and the return of relevant results to patients.

The GS Multidisciplinary Team

Recent literature highlights the value of using a multidisciplinary approach to incorporate GS into clinical care. Here, we propose a model for integrating GS into pediatric cardiology. This multidisciplinary workflow was developed for use in the Ted Rogers Centre for Heart Research, Cardiac Genome Clinic (CGC) research study to investigate the underlying genetic etiology for patients with—or at risk of—heart failure using GS.[5] Figure 1 highlights the varied expertise of the CGC, composed of professionals from several specialties and programs across The Hospital for Sick Children's Hospital and Research Institute, including Cardiology, Genetic Counselling, Clinical and Metabolic Genetics, Pharmacology and Toxicology, Genome Diagnostics (the clinical laboratory) and The Center for Applied Genomics (the research laboratory). Our integrative approach was critical for addressing the complexities and challenges associated with adopting GS in cardiology.

Genetic counsellors play an integral role in the translation of new genomic technology into clinical care.[4] They facilitate engagement with—and education for—patients, families, and health care providers and support the informed consent process. Genetic counsellors also offer valuable insight into the prioritization of genes for analysis and their relevance to patient phenotypes as well as counsel patients on complex results and associated risk. It is increasingly common for genetic counsellors to be integrated into multidisciplinary clinical settings, such as cardiology clinics, and the success of our model hinges on their involvement throughout the GS process.

Given the complexity of genomic analysis, interpretation is most successful when detailed phenotypic information is collected and incorporated. Geneticists, genetic counsellors, and cardiologists collaborate to provide deep phenotyping of patients via a detailed physical examination, family history, and imaging. Bioinformaticians are critical data analysts who can manage big data and develop filtering pipelines, together with the genetic counsellors and geneticists, to ensure the appropriate data are prioritized for analysis. Genome analysts leverage the filtered genomic and phenotypic data in the context of each family to make meaningful and relevant interpretations. Finally, the pharmacogenetics (PGx) pharmacist analyzes GS data for variants with Food and Drug Administration (FDA)-recognized guidelines that support modification in prescribing of medication.

The CGC multidisciplinary case review brings together the team's expertise to review the interpreted data collectively and determine the clinical relevance of results related to a genetic diagnosis (primary) or other medically actionable genetic findings (secondary/PGx). Further examples of multidisciplinary models of care are needed to understand how to best incorporate GS in other diverse clinical settings.

Our Experience and Outcomes With Using a Multidisciplinary Model

Our experience using the proposed CGC workflow was successful in engaging with—and facilitating educational opportunities for—clinical staff, facilitating informed consent for GS (including primary and secondary findings), analyzing genomic data, and returning clinically relevant results[5] (Fig. 2). There were 409 families of pediatric patients with heart disease enrolled in the study over a 5-year period; the majority had congenital heart disease and were recruited during their routine cardiology follow-up at a tertiary care centre. The CGC initiated a new-patient or updated clinical genetics assessment for the majority (71%) of participants. Integrating multidisciplinary care for these patients through the CGC enabled access to genetic services that might not otherwise have been initiated. The remaining participants did not require an updated genetics assessment before their enrollment.

Fifty-seven percent of the 409 participants have received results from GS to date, the remainder of which were pending sequencing and analysis at the time of manuscript preparation, owing to rolling enrollment. The diagnostic yield of GS was 15%. Specific primary findings identified are reported in a previous CGC publication;[5] this is not an accurate reflection of the expected yield in this population, as patients with previously known genetic etiologies for their heart disease were excluded from participating in the study.

For CGC participants, the potential benefits of GS extended beyond primary diagnosis. First, 3% of participants received medically actionable secondary findings based on

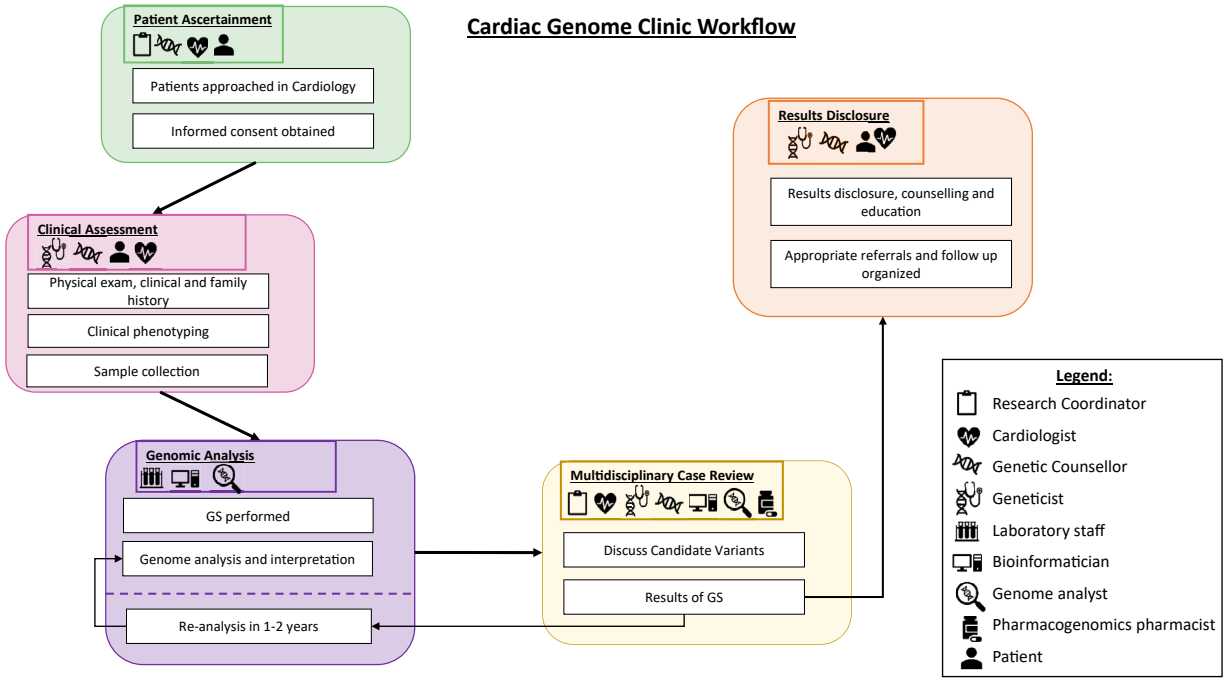
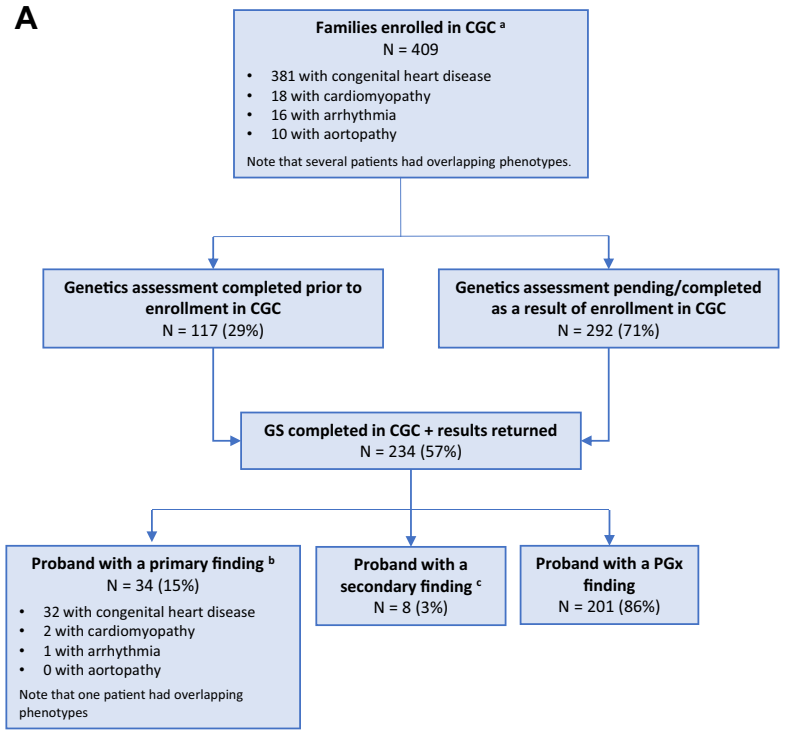


Figure 1. Proposed components of a cardiology-focused, multidisciplinary, genome sequencing (GS) workflow. Model developed and used by the Ted Rogers Centre for Heart Research Cardiac Genome Clinic study.



B

Genes with Secondary Findings:
PTEN
KCNH2
DSC2
PTEN
DSG2
PKD2
MSH6
COL3A1

a) Enrollment Criteria: Patients with heart disease of unknown etiology (i.e., no known genetic, metabolic, or environmental cause). Heart disease includes congenital heart disease, cardiomyopathy, arrhythmia, aortopathy and others at risk for heart failure.
b) Primary findings were previously reported.[5]
c) Specific secondary findings identified are outlined in Figure 2B.

Figure 2. Outcomes of research whole genome sequencing through the Ted Rogers Centre for Heart Research Cardiac Genome Clinic (CGC) study.

recommendations from The American College of Medical Genetics and Genomics. Specific secondary findings identified are presented in Figure 2B. These findings allowed for proactive surveillance or intervention for the patients and presymptomatic genetic testing for their at-risk relatives. Notably, one-third of these secondary findings affected the patient's cardiac care, including risk genes for additional cardiac complications that were previously unknown (eg, hereditary arrhythmias and cardiomyopathies). Second, 86% of participants had at least 1 medically actionable PGx variant. PGx results provide proactive guidance through predicting the absence of therapeutic benefit or presence of adverse drug reactions of certain medications for individual patients. In many cases, these results affected the patients' current medication therapy. Finally, the ability to reinterpret GS data over time provides opportunity for future diagnoses for patients and their posterity.

Conclusions

GS is on the horizon and will necessitate multidisciplinary care to overcome the challenges to its clinical integration. The CGC successfully integrated GS into the care of pediatric cardiology patients in the clinical research setting. It identified genetic diagnoses for patients who otherwise may not have received a clinical genetics assessment or testing. Furthermore, secondary and PGx findings provided patients with information enabling proactive and preventative surveillance, screening, or drug-dose modifications. As more precision medicine strategies such as GS are translated into clinical practice, it is critical that clinicians are supported and equipped to deliver individualized care to their patients. The CGC multidisciplinary model provides an approach to address the challenges presented by GS and support its integration into pediatric cardiology.

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Disclosures

The authors have no conflicts of interest to disclose.

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