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*Original Article*

# High burden of genetic conditions diagnosed in a cardiac neurodevelopmental clinic

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**Abstract** *Background:* There is a known high prevalence of genetic and clinical syndrome diagnoses in the paediatric cardiac population. These disorders often have multisystem effects, which may have an important impact on neurodevelopmental outcomes. Taken together, these facts suggest that patients and families may benefit from consultation by genetic specialists in a cardiac neurodevelopmental clinic. *Objective:* This study assessed the burden of genetic disorders and utility of genetics evaluation in a cardiac neurodevelopmental clinic. *Methods:* A retrospective chart review was conducted of patients evaluated in a cardiac neurodevelopmental clinic from 6 December, 2011 to 16 April, 2013. All patients were seen by a cardiovascular geneticist with genetic counselling support. *Results:* A total of 214 patients were included in this study; 64 of these patients had a pre-existing genetic or syndromic diagnosis. Following genetics evaluation, an additional 19 were given a new clinical or laboratory-confirmed genetic diagnosis including environmental such as teratogenic exposures, malformation associations, chromosomal disorders, and single-gene disorders. Genetic testing was recommended for 112 patients; radiological imaging to screen for congenital anomalies for 17 patients; subspecialist medical referrals for 73 patients; and non-genetic clinical laboratory testing for 14 patients. Syndrome-specific guidelines were available and followed for 25 patients with known diagnosis. American Academy of Pediatrics Red Book asplenia guideline recommendations were given for five heterotaxy patients, and family-based cardiac screening was recommended for 23 families affected by left ventricular outflow tract obstruction. *Conclusion:* Genetics involvement in a cardiac neurodevelopmental clinic is helpful in identifying new unifying diagnoses and providing syndrome-specific care, which may impact the patient's overall health status and neurodevelopmental outcome.

Keywords: Genetic evaluation; medical; heart defects; development

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CHD ARE COMMON IN THE GENERAL POPULATION, and are present in an estimated 50 per 1000 live births.[1] The long-term care needs of this population are becoming increasingly important as an estimated 85% of children with CHD survive into adulthood.[2] It has become apparent that survivors of CHD, with brain immaturity at times of corrective or palliative operative interventions with altered cerebral blood flow and requisite intensive care support, have neurocognitive effects including developmental disabilities.[3,4]

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It is also understood that there is a high burden of genetic diagnosis in individuals with CHD with over 750 associated syndromes described.[3] Genetic syndromes can potentially cause more severe developmental delay than would be expected by surgical intervention alone; 8–13% of patients with CHD have abnormal chromosome analysis.[5] An additional 20% or more patients with CHD may be identified as having a confirmed genetic syndrome with re-examination by a geneticist at 1 year of age,[5,6] lending support for genetic follow-up and serial examinations. The presence of a genetic syndrome is highly associated with more severe neurodevelopmental delay in children with widely varying congenital heart anomalies.[6–8]

A cardiovascular genetics approach with a personalised genetic differential based on CHD findings may lead to a higher diagnostic rate – for example, 80% of individuals with certain characteristic heart lesions have 22q11.2 deletion syndrome confirmed by genetic testing.[9] In addition, clinically available genetic testing has increased dramatically, including chromosome microarray, gene panels utilising NextGen sequencing, and whole exome or genome analysis. Beyond genetic testing, a trained geneticist can request additional specialist referrals for phenotyping that may lead to refining the differential, as well as imaging that may detect other congenital or skeletal findings characteristic of a suspected syndrome.

Owing to the presumed likelihood of undiagnosed genetic causes of CHD in the Cincinnati Children's Hospital Medical Center (CCHMC) Heart Institute Neurodevelopmental and Educational Clinic (NDEC), and with the premise that knowledge of a unifying diagnosis would affect health as well as developmental and educational recommendations, a cardiovascular geneticist was recruited to see patients as part of the multidisciplinary team evaluation. The purpose of this study was to describe the prevalence of new genetic syndromic diagnosis and medical management needs in a selected population seen in a cardiac neurodevelopmental follow-up clinic.

## Materials and methods

### *Study design*

This study was a retrospective case series approved by the CCHMC Institutional Review Board (2013–2632).

### *Patient population*

In the course of the Heart Institute NDEC evaluation at CCHMC, 214 consecutive patients were evaluated from 6 December, 2011 to 16 April, 2013. All patients were referred by physicians who cared for them within the Heart Institute. Eligible patients for this clinic were assessed to be at high-risk of developmental delay by previously described American Heart Association guidelines:[4] open heart surgery, cyanotic heart lesion, prematurity and/or developmental delay recognised in infancy, genetic abnormality or syndrome associated with developmental delay, mechanical support or heart transplantation, cardiopulmonary resuscitation, prolonged hospitalisation (>2 weeks), perioperative seizures related to heart repair, and significant abnormalities on neuroimaging or microcephaly. No referred patients were excluded. All patients were evaluated by a multidisciplinary neurodevelopmental team including a paediatric cardiologist, developmental-behavioural paediatrician, cardiovascular geneticist, neurologist, psychologist, educational specialists, social worker, nutritionist, child life specialist, and occupational/physical therapists. After a half-day evaluation, the team created an integrated global impression and plan with specific recommendations, which was shared with the parent/guardian, primary cardiologist, and primary care provider. Follow-up assessments by other ancillary medical providers and scheduling for specific neuropsychological testing were coordinated by the clinic's advanced practice nurse who functioned as the programme manager. Educational specialists coordinated implementation of NDEC team recommendations in each patient's school. Follow-up evaluations were recommended based on the specific needs of the child, team consensus, and the 2012 American Heart Association/American Academy of Pediatrics neurodevelopmental follow-up guidelines for children and adolescents with CHD.[3]

### *Data collection*

This study was approved by the CCHMC Institutional Review Board. Demographic, clinical, and genetic data were obtained via chart review, electronic and/or paper chart. Demographic data included date of birth, date of visit, gender, and race. Clinical data included cardiac and pre- and post-visit genetic diagnosis, which were classified as "isolated heart defect", heart defect without other known congenital anomalies or dysmorphic features, "multiple congenital anomalies", that is, >1 congenital anomaly, inclusive of dysmorphic features, with unknown unifying diagnosis, "clinical syndrome", clinical features of a recognisable genetic syndrome or prenatal exposure without laboratory confirmation, or "laboratory-confirmed syndrome", clinical laboratory results consistent with diagnosis of syndrome. Clinical diagnosis was established using peer-reviewed

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published guidelines for clinical diagnosis when available.[10–12] Genetic data included clinical genetic testing results, family history, and pedigree.

### *Statistical analysis*

Summary statistics were performed to tabulate categorical variables. The cohort was divided into the four discrete diagnosis categories as noted above. Pearson's $\chi^2$ analysis was used to compare the distribution of diagnostic categories before and after visit. Stata 11 software[13] was used for analysis (StataCorp, College Station, Texas, United States of America).

## Results

### *Patient population*

We report 214 consecutive NDEC patients who were seen by a medical geneticist with genetic counselling support during the course of the Heart Institute NDEC multidisciplinary evaluation at CCHMC. Demographic data are summarised in Table 1; 56% of the patients were male, and the primary race/ethnicity group was Caucasian (Non-Hispanic). The median age was 5.1 years (2 months–18 years 9 months). The majority of patients were older than 1 year of age (88%), with 44% aged 1–5 years. Of the 214 patients, 144 (67%) had biventricular CHD with (27) or without (117) aortic arch obstruction and 70 (33%) had single ventricular CHD with (34) or without (36) aortic arch obstruction.

### *Clinical and genetic findings*

In all, 64 patients (30%) had a previously identified clinical (26) or laboratory-confirmed syndrome (38) (Table 2). In the 176 patients without a laboratory diagnosis (82%), the following normal testing had been performed previously: chromosome microarray (48), chromosome analysis (32), fluorescent *in situ* hybridization (FISH) probe for 22q11 deletion syndrome (33) or Williams Syndrome (1), single-gene sequencing (*ZIC3, DNAI2, MYH7, C0L3A1*), seven NextGen panels (heterotaxy or Noonan Syndrome), three metabolic screens, and one chromosome breakage study for Fanconi anaemia.

After examination by a dysmorphologist specialising in cardiovascular genetics, the following recommendations were made: 112 patients (52%) were recommended to have additional genetic testing; 73 patients (34%) were referred to additional medical specialists; 17 patients (8%) were recommended to have radiological imaging recommended by the geneticist, for example, bone age and MRI of the brain; and 14 patients (6%) were recommended to have clinical laboratory studies, for example, thyroid stimulating harmone. The referred services included, in order of frequency, the following: ophthalmology, endocrinology, urology, craniofacial team, gastroenterology, psychiatry, dentistry, and nutrition.

Healthcare management based on diagnosis was provided for 32 patients (15%) who received syndrome-specific published guideline healthcare management recommendations. Healthcare management was performed for 26 patients with the following diagnoses: 22q11.2 deletion, Noonan syndrome, and Williams syndrome;[14–16] six additional patients with heterotaxy syndromes and asplenia or polysplenia received recommendations according to the American Academy of Pediatrics Red Book Guideline for asplenia,[17] including additional immunisations, and discontinuation and/or initiation of antibiotic prophylaxis may have been recommended. Cardiac imaging was recommended for first-degree relatives in 23 families (11%) because of diagnoses of left ventricular outflow tract obstruction defects such as bicuspid aortic valve or hypoplastic left heart syndrome or cardiomyopathy in the proband.

Following these cardiovascular genetic evaluations, 19 patients (13%) received a new clinical or laboratory-confirmed diagnosis (Table 3). Recommended studies that led to diagnosis and initial management are

Table 1. Study population demographics (n = 214).

| | |
|---|---|
| Gender | 119 Male (55.6%) |
| Age at visit | Median 5.1 years (2 months–18 years 9 months) |
| <1 year | 25 (12%) |
| 1–5 years | 95 (44%) |
| 6–11 years | 61 (28%) |
| 12 years or more | 33 (15%) |
| Race/ethnicity | |
| Caucasian, non-Hispanic | 183 (86%) |
| Caucasian, Hispanic | 5 (2%) |
| African-American, non-Hispanic | 24 (11%) |
| Pacific Islander, non-Hispanic | 1 (0.5%) |
| Other, non-Hispanic | 1 (0.5%) |

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Table 2. Diagnoses before Neurodevelopmental and Educational Clinic visit (n = 64)* and primary heart lesion.

22q11.2 Deletion syndrome (21)
- Tetralogy of Fallot (8)
- Tetralogy of Fallot with pulmonary atresia (1)
- Interrupted aortic arch type B (3)
- Truncus arteriosus (2)
- Septal defects (ASD and/or VSD) (5)
- Double-outlet right ventricle (1)
- Aberrant left subclavian artery (1)

VATER/VACTERL association (10)
- Tricuspid atresia (4)
- Left pulmonary artery sling (2)
- VSD (2)
- Truncus arteriosus (1)
- Tetralogy of Fallot with pulmonary atresia (1)

Noonan syndrome (3)
- Pulmonary stenosis with (1)/without ASD (1)
- ASD alone (1)

Marfan syndrome (2)
- Aortic root dilation (1)
- Cardiomyopathy (1)

Cri du Chat syndrome (1)
- Deletion 5p15.33p15.31; dup 8p23.3p21.2
- Double outlet right ventricle

Jacobsen syndrome (1)
- Mosaic deletion 11q24.2q25
- Shone's Complex

Primary ciliary dyskinaesia (1)
- AV canal

7q11.23 duplication (1)
- Aortic root dilation

Dent's disease (1)
- Total anomalous venous connection

Heterotaxy syndrome (13)
- Double-outlet right ventricle (5)
- AV canal (3); one also with D-TGA
- Tricuspid atresia (2)
- Total anomalous pulmonary venous return (1)
- Hypoplastic left heart syndrome (1)
- Tetralogy of Fallot with pulmonary atresia (1)

Familial cardiomyopathy (3)
- *MYH7* mutation (2)
- *LDB3* mutation (1)
- Dilated cardiomyopathy (2)
- Restrictive cardiomyopathy (1)

Williams syndrome (2)
- Supravalvular aortic stenosis (1)
- VSD (1)

Mosaic trisomy 8 (1)
- VSD

Unbalanced translocation (1)
- *GATA4* deletion (8p23.3p23.1); dup 5p15.33p15.2
- AV canal with pulmonary atresia

Kleefstra syndrome (1)
- 9q34.3 deletion
- Atrial and VSDs

1q43q44 deletion (1)
- VSD

16p11.2 deletion (1)
- Double-outlet right ventricle

Axenfeld–Rieger syndrome (1)
- Total anomalous pulmonary venous return

ASD = atrial septal defect; AV = atrioventricular; D-TGA = D-transposition of the great arteries; VATER/VACTERL = vertebral anomalies, anal atresia, cardiac defects, TE fistula, esophageal atresia, renal dysplasia, limb defects; VSD = ventricular septal defect
*One patient had both cardiomyopathy and Marfan syndrome

Table 3. New diagnoses following Neurodevelopmental and Educational Clinic genetics evaluation (n = 19) and primary heart lesion.

Heterotaxy syndrome (2)
- Double-inlet left ventricle (1)
- Hypoplastic left heart syndrome(1)

CHARGE syndrome (2)
- Double-outlet right ventricle (1)
- VSD (1)

22q11.2 deletion syndrome (1)
- VSD

Noonan syndrome (1)
- Double-inlet left ventricle

Rubinstein–Taybi syndrome (1)
- Hypoplastic left heart syndrome

MURCS association (1)
- Atrial and VSDs

2q13 deletion (1)
- AV canal with pulmonary valve atresia

*MYH7* related Ebstein's anomaly (1)
- Ebstein's anomaly

Prenatal depakote exposure (2)
- Tetralogy of Fallot with pulmonary atresia (1)
- Shone's Complex (1)

Kabuki syndrome (2)
- Total anomalous venous connection (1)
- Hypoplastic left heart syndrome (1)

Williams syndrome (1)
- Pulmonary valve stenosis

VACTERL (1)
- Double-outlet right ventricle with pulmonary atresia

Ohdo syndrome (1)
- VSD with coarctation of the aorta

16p13.11 duplication (1)
- AV canal with coarctation

Unbalanced translocation (1)
- del 10q26.2q26.3; dup 11q24.2q25
- AV canal

AV = atrioventricular; CHARGE syndrome = coloboma, heart defects, atresia choanae, retardation of growth or development, GU anomalies and hypogonadism, ear anomalies and deafness; Müllerian = duct, renal, and cervical vertebral defects; VSD = ventricular septal defect

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Table 4. Genetic evaluation leading to diagnosis.

| | |
|---|---|
| Heterotaxy syndrome | Prenatal depakote exposure |
| Abdominal ultrasound | Prenatal history |
| Microarray | Microarray |
| Liver scan (nuclear medicine) | Ophthalmology |
| Heterotaxy panel | |
| CHARGE syndrome | Kabuki syndrome |
| Ophthalmology evaluation | *KMT2D, KMD6A* analysis |
| Audiology | Immunoglobulins |
| CT scan of temporal bone | Temporal bone CT |
| Microarray | Microarray |
| Endocrine consult (growth) | |
| *CHD7* sequencing | |
| 22q11.2 Deletion Syndrome | Williams syndrome |
| Microarray or 22q11 FISH | Williams FISH |
| Calcium, parathyroid | Calcium, urine Ca/Cre |
| Thyroid panel | Thyroid panel |
| CBC with differential | Renal ultrasound |
| Ophthalmology | |
| Velopharyngeal insufficiency clinic | |
| Renal ultrasound | |
| Noonan syndrome | VACTERL |
| Noonan RASopathy panel | Spine films |
| CBC with differential | Renal ultrasound |
| PT, PTT | Microarray |
| Thyroid panel | Chromosome breakage studies |
| Rubinstein–Taybi syndrome | Ohdo syndrome |
| Microarray | Ophthalmology evaluation |
| *CREBBP* and *EP300* analysis | Dental evaluation |
| Hand, foot, chest, spine, pelvis films | *KAT6B* and *MED12* analysis |
| Ophthalmology | |
| MURCS association | 16p13.11 duplication |
| Pelvic ultrasound | Microarray |
| Microarray | Parental studies |
| X-ray elbow to hand | |
| Thyroid panel | |
| Renal ultrasound | |
| Spine films | |
| 2q13 deletion | Unbalanced translocation |
| Microarray | (del 10q26.2q26.3; dup 11q24.2q25) |
| Parental studies | Microarray |
| | Renal ultrasound |
| | Foot imaging |
| | Parental studies |
| *MYH7* related Ebstein's anomaly | |
| *MYH7* sequencing | |
| Microarray | |
| Parental studies | |

CBC = complete blood count; PT = prothrombin time; PTT = partial thromboplastin time

Table 5. Comparison of pre-visit and post-visit diagnostic classification (n = 214).

| Diagnostic categories | Pre-visit (n (%)) | Post-visit (n (%)) |
|---|---|---|
| Isolated heart | 114 (53) | 90 (42) |
| Multiple congenital anomalies | 36 (17) | 41 (19) |
| Clinical syndrome | 26 (12) | 36 (17) |
| Laboratory diagnosis of syndrome | 38 (18) | 47 (22) |

outlined in Table 4. Overall, in the NDEC cohort, the clinical and laboratory-confirmed diagnosis rate increased from 30% (64/214) to 39% (83/214).

Pre- and post-visit patient classifications were compared (Table 5). Before evaluation, more than half of the patients were considered to have isolated

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cardiac defects without multiple congenital anomalies; however, after genetic evaluation, there was a significant decrease in the number of patients considered to have CHD as an isolated finding and an increase in the post-visit number of patients with clinical and laboratory-confirmed genetic diagnoses in the between-group analysis ($p < 0.0001$).

## Discussion

In this study, consecutive patients were screened by a cardiovascular geneticist in a cardiac neurodevelopmental follow-up clinic. Before NDEC evaluation, the population was well characterised from a genetics standpoint with 30% having a known clinical or laboratory-confirmed genetic diagnosis. As this was a cardiac at-risk population referred for multidisciplinary developmental evaluation, not all genetic diagnoses were necessarily associated with neurodevelopmental delay, such as VATER/VACTERL, Marfan, and heterotaxy syndromes, as well as cardiomyopathy.

The important finding was that an additional 13% of the aggregate undiagnosed patients were given a new genetic diagnosis following initial brief evaluation by a geneticist in the context of the multidisciplinary evaluation. Most of these patients had not seen a geneticist previously. With these diagnoses, 39% of the patients in the cardiac neurodevelopment clinic had an identifiable environmental or genetic cause of their heart disease.

In addition to identifying new unifying diagnoses, this study shows the value of consultation with a genetics subspecialist for ongoing evaluation and management in patients with identified clinical or laboratory-confirmed syndromes. Of those patients with pre-existing genetic diagnoses, there were additional interventions recommended by the geneticist, including additional genetic testing, for example, chromosome microarray or chromosome breakage studies in patients with VACTERL to assess for Fanconi anaemia, additional imaging studies to screen for associated anomalies, for example, renal ultrasound and scoliosis series, additional consultations, for example, ophthalmology, and laboratory testing. Patients with identified syndromes with health supervision recommendations were given medical management for these conditions. Many of these patients were not followed-up by a geneticist on a regular basis, and these evaluations would not have occurred otherwise.

The findings of new genetic diagnoses in this study are similar to previous studies at The Children's Hospital of Philadelphia, where a geneticist evaluated 359 patients with CHD at 1 year of age and an additional 8% were diagnosed with a new syndrome, as well as an additional 15% were suspected of having a syndrome;[6] two other cardiac defect-specific papers from this group described newly confirmed or suspected diagnoses in 35% of patients with ventricular septal defect[8] and in 18% of patients with tetralogy of Fallot.[8] These studies found that confirmed or suspected genetic syndrome was the most important predictor of neurodevelopmental outcomes in patients with CHD at 1 year of age.[6–8] It can be difficult to discern dysmorphic features in newborns who are critically ill with CHD, and all congenital anomalies as well as developmental concerns may not yet be apparent, underscoring the importance of genetic re-evaluation over time.

The burden of genetic disease in individuals with CHD is becoming more apparent with revolutionary improvements in genetic testing. Previously, a unifying diagnosis was determined by genetics screening or consultation, possibly with studies of metabolic aetiologies, and chromosome analysis. Many school-aged and adolescent patients in NDEC were assessed as newborns with these technologies, with no further genetics follow-up. With more sophisticated clinical testing available, older patients should have the benefit of re-evaluation by a medical geneticist to determine whether additional testing would be beneficial.

Genetic diagnosis has multiple benefits, including providing a unifying context for multiple co-morbidities, and potentially uncovering genetic disorders that may affect a patient's developmental performance;[6–8] for example, a suspicion of CHARGE syndrome in a toddler patient in NDEC led to evaluations that discovered retinal colobomas and abnormal semicircular canals, clarifying difficulties with vision, imbalance, and gross motor delay. With genetic evaluation, there may be an end of a diagnostic odyssey and costly diagnostic evaluations and a shift in focus of care to healthcare management and developmental/educational support. Finally, having a genetic or syndromic diagnosis offers families the opportunity to connect with other families via social media, non-profit support groups, and syndrome-specific conferences.

Evaluation by a cardiovascular geneticist identified a number of families who may be at risk for cardiac anomalies or cardiomyopathy. Bicuspid aortic valve is a common CHD present in 0.5–1.4% of the general population.[18] This common heart defect is highly heritable and may be present in parents or siblings of an affected patient.[19,20] There is an increased risk of bicuspid aortic valve in other family members of individuals with hypoplastic left heart syndrome.[21] Echocardiograms are recommended for first-degree

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family members of individuals with a bicuspid aortic valve or hypoplastic left heart syndrome.[22] Any affected individuals in the family should have cardiology care and follow-up.

Cardiomyopathy is a common and progressive condition. Cardiomyopathy can be familial, most commonly with autosomal dominant inheritance due to sarcomeric mutations, but in paediatric populations there can also be underlying metabolic or syndromic aetiologies that may elevate the risk for neurodevelopmental delay.[23] Thus, echocardiograms of first-degree relatives of affected individuals are recommended, and cascade genetic screening should be performed if a disease-causing mutation is identified in the proband.[24] In total, four families of patients with cardiomyopathy – restrictive, dilated, and left ventricular non-compaction – were seen in NDEC, and following unremarkable genetics examination surveillance echocardiograms, genetic testing for cardiomyopathy of the proband, or known familial mutation testing were recommended as appropriate.

As a member of the multidisciplinary team, cardiovascular geneticists have a responsibility for educating team members regarding a patient's unifying diagnosis and potential developmental, educational, neurological, and nutrition implications – for example, in NDEC, the geneticist may inform the developmental paediatricians regarding syndrome-specific developmental and neurocognitive profiles, education strategies, co-morbidities, and growth charts. The multidisciplinary setting facilitates immediate communication between the geneticist and other subspecialists, resulting in a more personalised and informed evaluation.

Our study does have some limitations. This study may have a possible ascertainment bias in that patients referred to NDEC may have had suspected genetic disorders or more severe developmental concerns prompting the referral to NDEC. Arguing against bias is the fact that the cardiovascular geneticist had an independent genetics clinic and was available for referrals from specialists both within and outside CCHMC, the geneticist was embedded in the Heart Centre on a full-time basis, and our findings were similar to the study by Fuller et al, which found new genetic diagnoses in 8% of patients. A second limitation of this retrospective case series may be that the data are historic and may be incomplete – for example, not all medical data were available for patients who were initially seen at other institutions or where records were lost. Some families did not follow-up with the recommended genetic testing, and the ascertainment of genetic diagnosis is likely underestimated. No patients were studied with whole-exome or whole-genome sequencing, which may have increased the yield of genetic evaluation. Finally, this case series reflects evaluations by a single medical geneticist, and additional geneticist input might have increased the diagnostic yield.

## Conclusion

Participation by a medical geneticist in the Heart Institute cardiac Neurodevelopmental and Educational Clinic was associated with significantly increased clinical and laboratory-confirmed diagnoses in patients. The healthcare management of patients and families with a variety of diagnoses was specifically addressed using the most current guidelines. Identifying an underlying genetic aetiology for CHD can improve the care team's ability to provide the best-informed developmental guidance, ensure that patients receive the most appropriate medical surveillance and treatment, and provide important information and psychosocial support to patients with CHD and their families.

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## Conflicts of Interest

None.

## Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation (Cincinnati Children's Hospital Medical Center Institutional Review Board) and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the institutional committee of Cincinnati Children's Hospital Medical Center.

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