



# Genetic counseling for congenital heart disease – Practice resource of the national society of genetic counselors

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## Abstract

Congenital heart disease (CHD) is an indication which spans multiple specialties across various genetic counseling practices. This practice resource aims to provide guidance on key considerations when approaching counseling for this particular indication while recognizing the rapidly changing landscape of knowledge within this domain. This resource was developed with consensus from a diverse group of certified genetic counselors utilizing literature relevant for CHD genetic counseling practice and is aimed at supporting genetic counselors who encounter this indication in their practice both pre- and postnatally.

## KEYWORDS

complex disease, congenital heart disease, genetic counseling, genetic testing, practice resource

## 1 | INTRODUCTION

Congenital heart disease/defects (CHD/CHDs) constitute a heterogeneous group of cardiovascular malformations and represent the most common birth defects in humans. These malformations have a

birth incidence of 0.8%–1%, with an estimated global prevalence of approximately 1%–2% due to improved diagnosis, surgical interventions, and survival in the last three decades (Pierpont et al., 2018). The prevalence of adults with CHDs is now greater than that of children, with approximately 90% of individuals surviving into adulthood

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(Mazor Dray & Marelli, 2015). Given this, we anticipate a greater need for genetic counselors, across several specialties, to be familiar with CHDs, as they may encounter this indication more frequently in both their patient population and/or while obtaining a family history.

The American Heart Association (AHA) and European Society of Cardiology (ESC) have recently highlighted the current understanding of the genetic underpinnings of CHDs and the utility of genetic counseling and genetic testing for the pediatric and adult CHD populations (Baumgartner et al., 2020; De Backer et al., 2019; Pierpont et al., 2018). Given the clinical and etiologic heterogeneity of CHDs, as well as the rapidly changing nature of diagnostic genetic testing options available, genetic counseling for this indication can be complex. Because of this recognized need, we aimed to create a resource that provides CHD-specific counseling strategies and approaches for genetic counselors of any experience level or specialty that is supported by narrative literature review. A group of genetic counselors representing multiple specialties with significant professional experience counseling in the setting of CHDs convened in 2019 and developed this resource over the course of approximately 15 months (2019–2020).

In this practice resource, we review topics that can assist with guiding CHD counseling strategies including cardiac development, genetic testing approaches, and strategies for recurrence risk counseling and family risk assessment in syndromic and apparently isolated CHDs. A broad overview of these strategies can be found in

Table 1. We also review the benefits of caring for patients with CHD using a multidisciplinary team approach involving genetic counselors, medical geneticists, and cardiologists. Last, we briefly review resources for the unique setting of prenatal genetic counseling for CHDs. This resource assumes readers have some basic prior knowledge of contemporary practice and genetic technologies (e.g., chromosome microarray, next-generation sequencing, and noninvasive cell-free fetal DNA screening). This practice resource was developed to serve as a solid foundation for genetic counseling approaches to CHDs in an area that has been changing rapidly in the last decade, with advances in genetic and genomic testing technologies increasing the understanding of the genetic basis of CHDs. As a brief note, the terms ‘congenital heart defect(s)’ and ‘congenital heart disease’ can be interchangeably used, and both are acceptable disease descriptions with the same acronym (CHD).

## 2 | CARDIAC DEVELOPMENT

A basic understanding of cardiac embryogenesis can provide insight into the genetic etiology of CHDs. By common convention, the classification of CHDs is often centered on the physiological effects or outcomes such as cyanotic (lesions which decrease the amount of blood flow to the body, e.g., tetralogy of Fallot) and acyanotic CHDs. This classification scheme guides the surgical and medical

**TABLE 1** Genetic counseling considerations for CHDs in different scenarios: CHDs with syndromic features vs. isolated CHDs (sporadic and familial)

Genetic counseling considerations for congenital heart disease			
	Multiple Congenital Anomalies	Apparently Isolated	
		Familial	Sporadic
Differential	<ul style="list-style-type: none"> <li>• Suspected underlying genetic syndrome (single gene or chromosomal)</li> </ul>	<ul style="list-style-type: none"> <li>• Single gene or chromosomal cause associated with isolated CHD</li> <li>• Single gene or chromosomal cause associated with syndromic CHD and more mild presentation</li> </ul>	<ul style="list-style-type: none"> <li>• Multifactorial</li> <li>• Single-gene cause associated with isolated CHD</li> </ul>
Genetic testing	<ul style="list-style-type: none"> <li>• Guided by etiology of suspected syndrome</li> <li>• Consideration of CMA as first-line test ± additional molecular genetic testing</li> </ul>	<ul style="list-style-type: none"> <li>• CMA</li> <li>• Consider CHD Panel if CMA negative</li> <li>• Consider ES/GS if CHD Panel negative and family is interested (with affected family members as part of a family analysis)</li> </ul>	<ul style="list-style-type: none"> <li>• CMA</li> <li>• Consider CHD gene sequencing or panel based on lesion (e.g., <i>ELN</i> for <i>SVAS</i>)</li> </ul>
Recurrence risk	<ul style="list-style-type: none"> <li>• Based on inheritance of particular syndrome identified and if inherited from a parent</li> <li>• If no diagnosis is made, counseling on recurrence risk is less specific</li> </ul>	<ul style="list-style-type: none"> <li>• Positive Testing: Based on inheritance pattern, reduced penetrance, and variable expressivity</li> <li>• Negative Testing: Unable to provide exact recurrence risk but could be as high as 50%</li> </ul>	<ul style="list-style-type: none"> <li>• Positive Testing: Based on inheritance pattern, reduced penetrance, and variable expressivity</li> <li>• Negative Testing: Refer to empiric data based on lesion type</li> </ul>
Family screening	<ul style="list-style-type: none"> <li>• Fetal echocardiography in future pregnancies is reasonable if pregnancy considered at-risk for syndrome</li> <li>• Cardiac screening may be appropriate based for at-risk family members</li> </ul>	<ul style="list-style-type: none"> <li>• Fetal echocardiography in future at-risk pregnancies</li> <li>• If LVOTO, cardiac screening for first-degree relatives</li> </ul>	<ul style="list-style-type: none"> <li>• Fetal echocardiography in future at-risk pregnancies</li> <li>• If LVOTO, cardiac screening for first-degree relatives</li> </ul>

management decisions for patients with CHDs. While this classification scheme is useful to cardiologists, surgeons, and other physicians, a different classification system that centers on the underlying developmental processes is often more useful from the perspective of clinical genetics and genetic counseling.

The dynamic process of cardiac development requires numerous sequential and time-sensitive steps within the first few weeks of embryogenesis. These steps are orchestrated by a complex genetic network of transcription factors, cell signalers, histone/chromatin modifiers (e.g., *NKX2.5*, *JAG1*, *NOTCH1*, *GATA4*, and *CHD7*), and, in some instances, sarcomeric and other structural-encoding proteins. Disruption of these genes can lead to different 'categories' of CHDs. For instance, *NOTCH1* is more strongly associated with left ventricular outflow tract defects (LVOTO), such as bicuspid aortic valve and coarctation of the aorta (Preuss et al., 2016).

In order to meet the challenge of categorizing cardiovascular malformations, the 'Botto' classification scheme categorizes CHDs reflective of development (for instance, whether a lesion is due to an aberration in conotruncal development vs. septal development) (Botto et al., 2007). The Botto criteria consider several higher-level categories for which varieties of simple and complex CHDs can be grouped (see Table 2). The advantage of this classification scheme is that knowledge of the cardiac malformation embryological stage is reflective of, to a degree, the underlying genetics of heart development. Having a basic understanding of this process can assist with informing the selection of differential diagnoses for syndromic presentations and relevant genes to prioritize for analysis. See Table 3 for a list of genes and genetic syndromes associated with the various Botto classes and Appendix S1 for examples of how to utilize the Botto classification scheme.

**TABLE 2** Embryological classification of CHDs using the Botto criteria

Level 3 class	Detailed cardiac phenotypes (Level 1) comprising the class
Anomalous pulmonary venous return (APVR)	TAPVR, PAPVR
Atrioventricular Septal Defect (AVSD)	Primum ASD, inlet VSD, complete AVSD/complete AV canal defect, AVSD +outflow tract obstruction
Complex	Multiple complex heart anomalies, complex single ventricle defects, L-TGA ( $\pm$ LVOTO)
Conotruncal	DORV, DORV-TOF type, DORV-TGA type, TA, IAA, IAA-B, D-TGA, D-TGA $\pm$ VSD or outflow tract obstruction, TOF
Heterotaxy	Heterotaxy <sup>a</sup> , situs inversus totalis/ambiguus $\pm$ CHD, dextrocardia, mesocardia, persistent L-SVC (i.e., bilateral SVC), interrupted IVC, asplenia/polysplenia +CHD, midline or left-sided liver +CHD, other gastrointestinal situs anomalies +CHD
Left Ventricular Outflow Tract Obstruction (LVOTO)	BAV, HLHS, AS ( $\pm$ CoA), CoA ( $\pm$ VSD), MA, Shone's complex
Right Ventricular Outflow Tract Obstruction (RVOTO)	PA ( $\pm$ VSD), PVS ( $\pm$ ASD or any noninlet VSD), Ebstein anomaly, tricuspid atresia
Septal	VSD (nonspecific), VSD (perimembranous, muscular, or noninlet), secundum ASD, multiple co-occurring ASD or VSD

Note: Abbreviations: APVR, anomalous pulmonary venous return; AS, aortic stenosis; ASD, atrial septal defect; AVSD, atrioventricular septal defects (i.e., atrioventricular canal defects/AV canal defects); BAV, bicuspid aortic valve; CHD, congenital heart defect (not specified); CoA, coarctation of the aorta; DORV, double-outlet right ventricle; D-TGA, dextro-transposition of the great arteries; HLHS, hypoplastic left heart syndrome; IAA, interrupted aortic arch; IAA-B, interrupted aortic arch type B; IVC, inferior vena cava; L-SVC, left superior vena cava; LVOTO, left ventricular outflow tract obstruction; MA, mitral valve atresia; PA, pulmonary atresia; PA-IVS, pulmonary atresia with intact ventricular septum; PAPVR, partial anomalous pulmonary venous return; PVS, pulmonary valve stenosis; SVC, superior vena cava; TA, truncus arteriosus; TAPVR, total anomalous pulmonary venous return; TGA, transposition of the great arteries (not specified); TOF, tetralogy of Fallot; VSD, ventricular septal defect (not specified).

Examples provided are not fully inclusive, and genetic counselors should collaborate with cardiologists familiar with these criteria for accurate CHD phenotype classification, or to resolve classification uncertainty (Sources: Botto et al., 2007).

<sup>a</sup>This category may also include laterality-spectrum disorder malformations, and examples that are more inclusive of these malformations are provided here compared to what was originally reported by Botto et al. (2007).

### 3 | CONGENITAL HEART DEFECT ETIOLOGIES

#### 3.1 | Genetic contribution to CHD

When thinking about the possible genetic etiologies of CHDs, it can be helpful to focus the approach on two categories: monogenic/chromosomal vs. polygenic/multifactorial. Combining genetic testing techniques, a monogenic or cytogenetic etiology can be determined in around 20%–30% of cases, meaning that the underlying cause of the majority of individuals with CHDs (~60%–70%) currently remains unclear (Blue et al., 2017; Cowan & Ware, 2015). In instances of isolated/sporadic CHD, Mendelian causes with a single locus and large effect is a less common cause and is suspected to be more likely due to a complex aggregate of polygenic/oligogenic loci with additive effects (Blue et al., 2017; Marian et al., 2011). However, polygenic models for CHD etiology are still being explored. Even in instances of apparently autosomal dominant inheritance of CHDs within a family, identifying a monogenic cause has proven to be challenging, indicating there may be a stronger oligogenic component to isolated CHD (both sporadic and familial) (Reuter et al., 2020). In contrast, individuals with extracardiac anomalies and/or dysmorphic features are more likely to have a diagnostic finding with genetic testing, especially chromosomal abnormalities or single-gene Mendelian syndromes (Cowan & Ware, 2015; Jin et al., 2017). Because of this, patients should be assessed by a medical geneticist or experienced dysmorphologist, when possible, for subtle noncardiac malformations, dysmorphisms, and developmental differences that may represent a mild presentation of a genetic syndrome. This may ultimately alter genetic testing strategies, anticipated yields of genetic testing, and recurrence/familial risk counseling. When an underlying genetic cause is identified, it is currently most commonly due to chromosomal copy-number variants, followed by aneuploidy, and finally, single-gene variants (Figure 1).

Studies have shown that de novo genetic variants in developmental genes critical for heart development may be more enriched in individuals with CHDs compared with unaffected controls (Pasipoularides, 2018; Zaidi et al., 2013). Additionally, studies have shown that de novo variants are more likely to be associated with syndromic CHD, while inherited protein-truncating variants may be more common for nonsyndromic CHDs (Jin et al., 2017; Paige et al., 2018; Sifrim et al., 2016). Understanding the underlying genetic etiology of CHDs is complex, and there is still much to be learned. With the increased implementation of exome and genome sequencing into clinical care, it is likely that our understanding of this topic will evolve over the years, shifting the counseling and testing strategy.

#### 3.2 | Environmental causes

In addition to genetic causes, previous epidemiologic studies suggest environmental causes could explain approximately 2% of

CHDs, highlighting roles for environmental teratogenic risk factors in a subset of cases (Jenkins et al., 2007; Kučienė & Dulskienė, 2008). These environmental exposures (i.e., any nongenetic risk factor affecting the fetal–placental–maternal environment) have been limited to those occurring in the periconceptional period. This period has been defined as three months prior to conception extending through the first trimester of pregnancy, with special attention to the first 2–6 weeks of gestation during critical cardiac developmental stages (Patel & Burns, 2013). However, quantifying risk estimates for cardiac teratogens has been difficult owing to challenges in teratology study design, recall bias by study participants, limited animal model studies, and the possibilities of confounding variables in many studies (Mahler & Butcher, 2011). Given the incomplete understanding of cardiac teratogens and difficulty in providing definitive causal evidence supporting a single environmental risk factor's role in CHD occurrence, genetic counselors should exercise caution in excluding a genetic etiology, even when a teratogenic cause is plausible.

Obtaining information on the prenatal history and the possible presence of external risk factors can be valuable for the genetic counselor risk assessment and should be considered. Patel and Burns (2013) reviewed previous case–control studies assessing numerous CHD-related teratogens with reported odds ratios. Across all CHDs, one of the strongest environmental risk factors was pregestational diabetes mellitus. Due to the dose-dependent relationship between hemoglobin A1c and risk for fetal malformations, a high A1c level early in pregnancy would increase the concern for maternal diabetes as a contributor to the development of fetal CHDs (Helle & Priest, 2020; Nielsen et al., 2006; Wender-Ozegowska et al., 2005). Additional environmental risk factors for CHD include, but are not limited to, first-trimester maternal rubella infection, maternal phenylketonuria (hyperphenylalaninemia), exposure to particular classes of medications, and advanced maternal age given its association with aneuploidy. Jenkins et al. (2007) also provide a comprehensive review of environmental and maternal health risk factors for fetal CHDs. See Figure 2 for additional environmental risk factors. Given this, we recommend assessing for the following prenatal history: dosage and timing of any maternal medication exposure, maternal A1c levels (both pre-pregnancy and during pregnancy), level of gestational or pre-gestational diabetes control in mothers with diabetes, and the timing and diagnosis (if known) of any maternal illness. See the recurrence risk section for additional details on how one might counsel in the presence of a possible environmental risk factor.

An in-depth review of various cardiac teratogens and their quantified risks is beyond the scope of this work, and there are helpful peer-reviewed published resources for genetic counselors to consider when further investigation of prenatal exposures is needed (Jenkins et al., 2007; Patel & Burns, 2013). Teratogen information databases such as *Reprotox* (<https://www.reprotox.org/>), *Teris* (<https://deohs.washington.edu/teris/>), and *MotherToBaby* (<https://mothertobaby.org/>) are helpful resources to use when determining the risks associated with a particular exposure.

**TABLE 3** Lesion types based on the Botto classification system and reported associated genetic causes of such lesions broken down by CNVs, single genes, and chromosomal aberrations

Botto classification	Lesion	CNVs and CNV syndromes	Monogenic Syndromes	Genes also associated with apparently isolated CHDs	Chromosomal
APVR	TAPVR, PAVPR	<ul style="list-style-type: none"> <li>16p12.1 microdeletion (APVR)</li> <li>17p11.2 deletion/Smith–Magenis syndrome (APVR)</li> </ul>	<ul style="list-style-type: none"> <li>Smith–Lemli–Opitz (TAPVR)</li> </ul>	<ul style="list-style-type: none"> <li>BMPR2 (pulmonary HTN +PAPVR)</li> </ul>	<ul style="list-style-type: none"> <li>Trisomy 8 mosaicism (TAPVR)</li> <li>Chromosome 22 partial tetrasomy – Cat Eye Syndrome (APVR)</li> </ul>
AVSD	AVSD, AVSD+outflow tract obstruction	<ul style="list-style-type: none"> <li>3p25 deletion syndrome (AVSD)</li> <li>8p23.1 deletion syndrome (AVSD)</li> </ul>	<ul style="list-style-type: none"> <li>CHARGE (AVSD)</li> <li>Coffin–Siris (AVSD)</li> <li>Ellis–Van Creveld (AVSD)</li> <li>Holt–Oram (AVSD)</li> <li>McKusick–Kaufman (AVSD)</li> <li>Noonan (AVSD)</li> <li>Smith–Lemli–Opitz (AVSD)</li> </ul>	<ul style="list-style-type: none"> <li>BMPR2 (pulmonary HTN +AVSD)</li> <li>CRELD1 (AVSD)</li> <li>GATA4 (AVSD)</li> <li>NR2F2 (AVSD)</li> <li>TBX5 (AVSD)</li> </ul>	<ul style="list-style-type: none"> <li>T13 (AVSD)</li> <li>T21 (AVSD)</li> </ul>
Conotruncal	TOF, IAA, TGA, DORV, TA	<ul style="list-style-type: none"> <li>1q21.2 deletion syndrome (TA, TOF, IAA, TGA)</li> <li>1q21.1 duplication syndrome (TOF, TGA)</li> <li>1q21.1 deletion syndrome (TA, TGA)</li> <li>4p14.3 deletion/Wolf–Hirschhorn syndrome (TOF)</li> <li>4q deletion syndrome (TOF)</li> <li>5p15.2 deletion syndrome/Cri-du-chat syndrome (TOF)</li> <li>8p23.1 deletion syndrome(TOF)</li> <li>9q34.3 deletion/Kleefstra syndrome (TOF)</li> <li>11q terminal deletion syndrome/Jacobsen syndrome (TGA, DORV, TA, IAA type B)</li> <li>16p11.2p12.2 microdeletion/16p11.2 deletion syndrome (TOF)</li> <li>17p11.2 deletion/Smith–Magenis syndrome (TOF)</li> <li>22q11.2 deletion syndrome/DiGeorge syndrome (IAA type B, TOF, DORV, TA)</li> <li>22q11.2 duplication syndrome (TGA, TOF)</li> </ul>	<ul style="list-style-type: none"> <li>Adams–Oliver (TOF, DORV)</li> <li>Alagille (TOF)</li> <li>Baller–Gerold (TOF)</li> <li>Carpenter (TOF, TGA)</li> <li>CHARGE (TOF, DORV, IAA)</li> <li>Ellis–Van Creveld (TGA)</li> <li>Holt–Oram (TOF, DORV)</li> <li>Kabuki (TOF, TGA)</li> <li>RA Sopathies (TOF)</li> <li>Simpson–Golabi–Behmel (TGA)</li> <li>Timothy (TOF)</li> <li>Townes–Brocks (TOF)</li> </ul>	<ul style="list-style-type: none"> <li>FLT4 (TOF)</li> <li>GATA4 (TOF)</li> <li>GATA5 (TOF, DORV)</li> <li>GATA6 (TOF, TA)</li> <li>GDF1 (TOF)</li> <li>HAND2 (TOF)</li> <li>JAG1 (TOF)</li> <li>MED13L (TGA)</li> <li>NKX2.5 (TOF)</li> <li>NKX2.6 (TA)</li> <li>NODAL (D-TGA, DORV, TOF)</li> <li>NOTCH1 (DORV)</li> <li>NRF2 (TOF, DORV)</li> <li>SMAD2 (DORV)</li> <li>TAB2 (TOF)</li> <li>TBX1 (TOF, IAA)</li> <li>TBX5 (TOF)</li> <li>TBX20 (TOF, TA, DORV)</li> <li>ZFPM2 (TOF, DORV)</li> </ul>	<ul style="list-style-type: none"> <li>Trisomy 8 mosaicism (TA)</li> <li>T13 (DORV, TGA)</li> <li>T18 (TOF, TGA, DORV)</li> <li>T21 (TOF)</li> </ul>

(Continues)

TABLE 3 (Continued)

Botto classification	Lesion	CNVs and CNV syndromes	Monogenic Syndromes	Genes also associated with apparently isolated CHDs	Chromosomal
Heterotaxy	Heterotaxy +CHD	<ul style="list-style-type: none"> <li>• 2p25.1 duplication syndrome</li> <li>• 3p24.1 deletion syndrome</li> <li>• 22q11.2 deletion syndrome</li> <li>• Xq26.2 deletion syndrome</li> </ul>	<ul style="list-style-type: none"> <li>• Carpenter</li> <li>• Meckel-Gruber</li> <li>• Primary Ciliary Dyskinesia (12% of heterotaxy patients)</li> </ul>	<ul style="list-style-type: none"> <li>• ANKS3</li> <li>• ACVR2B</li> <li>• CCDC11</li> <li>• CFC1</li> <li>• CRELD1</li> <li>• DNAH11</li> <li>• FOXH1</li> <li>• GDF1</li> <li>• GRK5</li> <li>• LEFTY2</li> <li>• NKX2.5</li> <li>• NODAL</li> <li>• SHROOM3</li> <li>• SMAD2</li> <li>• ZIC3</li> </ul>	
LVOTO	HLHS, CoA, AS, BAV	<ul style="list-style-type: none"> <li>• 1q43q44 microdeletion (CoA, HLHS)</li> <li>• 1q21.1 deletion syndrome (BAV, CoA)</li> <li>• 4q deletion (AS, CoA)</li> <li>• 9p23.1 deletion (CoA)</li> <li>• 9q34.3 deletion/Kleefstra syndrome (BAV, CoA)</li> <li>• 10p deletion (BAV, CoA)</li> <li>• 11q terminal deletion syndrome/Jacobsen syndrome (HLHS, BAV, AS, CoA, Shone's Complex)</li> <li>• 16p11.2 deletion syndrome (BAV, AS)</li> <li>• 16p12.1 microdeletion (BAV, HLHS)</li> <li>• 17q21 microdeletion (BAV)</li> <li>• 22q11.2 duplication (HLHS)</li> </ul>	<ul style="list-style-type: none"> <li>• Adams-Oliver (BAV, CoA, HLHS)</li> <li>• Andersen-Tawil (BAV, CoA)</li> <li>• Beckwith-Wiedemann (HLHS)</li> <li>• Cantu (BAV, CoA, AS)</li> <li>• Ellis-Van Creveld (CoA, HLHS)</li> <li>• Kabuki (CoA, BAV, HLHS)</li> <li>• Loey-Dietz (BAV)</li> <li>• Marfan (BAV)</li> <li>• Meckel-Gruber (CoA)</li> <li>• Mowat-Wilson (CoA)</li> <li>• Noonan (CoA, AS)</li> <li>• Rubenstein-Taybi (HLHS, BAV, CoA)</li> <li>• Simpson-Golabi-Behmel (BAV, CoA, AS)</li> <li>• Smith-Lemli-Opitz (HLHS, CoA)</li> </ul>	<ul style="list-style-type: none"> <li>• GJA1 (HLHS)</li> <li>• GATA5 (BAV)</li> <li>• MEIS2 (CoA)</li> <li>• MYH6 (HLHS)</li> <li>• NKX2.5 (HLHS)</li> <li>• NOTCH1 (CoA, HLHS)</li> <li>• NFATC1 (BAV, CoA)</li> <li>• NR2F2 (AS, CoA, HLHS)</li> <li>• SMAD6 (HLHS, AS, CoA, BAV)</li> <li>• TAB2 (BAV, AS)</li> <li>• TBX5 (CoA, BAV)</li> </ul>	<ul style="list-style-type: none"> <li>• T13 (HLHS, AS)</li> <li>• T18 (CoA, HLHS, AS)</li> <li>• Turner (CoA, AS, HLHS, BAV)</li> </ul>

(Continues)

**TABLE 3** (Continued)

Botto classification	Lesion	CNVs and CNV syndromes	Monogenic Syndromes	Genes also associated with apparently isolated CHDs	Chromosomal
RVOTO	PVS, PA, PS, TrA, Ebstein	<ul style="list-style-type: none"> <li>1q21.2 deletion syndrome (PVS)</li> <li>1q21.1 duplication syndrome (PVS)</li> <li>3p25 deletion syndrome (TrA)</li> <li>4p14.3 deletion/Wolf-Hirschhorn syndrome (TrA)</li> <li>7q11.23 deletion/Williams syndrome (pulmonary artery branch stenosis)</li> <li>8p23.1 deletion syndrome (PVS)</li> <li>16p11.2p12.2 microdeletion/16p11.2 deletion syndrome (PA)</li> <li>17p11.2 deletion/Smith-Magenis syndrome (PS, PA)</li> <li>17q21 microdeletion (PVS)</li> <li>20p12 microdeletion/Alagille syndrome (peripheral or branch PS)</li> <li>22q11.2 duplication (PVS)</li> <li>Deletion 9p (PVS)</li> <li>Deletion 10p (PVS)</li> </ul>	<ul style="list-style-type: none"> <li>Alagille (peripheral or branch PS, PA)</li> <li>Beckwith-Wiedemann (PS)</li> <li>Carpenter (PS)</li> <li>Coffin-Siris (PS)</li> <li>Cornelia de Lange (PVS)</li> <li>Cranioectodermal dysplasia (PS)</li> <li>Peters Plus (PS)</li> <li>RA Sopathies (PVS)</li> <li>Simpson-Golabi-Behmel (PVS)</li> <li>Smith-Lemli-Opitz (PS)</li> </ul>	<ul style="list-style-type: none"> <li>ELN (SVAS)</li> <li>GATA4 (PS, PVS)</li> <li>GATA6 (TrA)</li> <li>GJA1 (PA)</li> <li>HAND2 (PS)</li> <li>JAG1 (PVS, PA)</li> <li>NKX2.6 (TrA)</li> </ul>	<ul style="list-style-type: none"> <li>Chromosome 22 partial tetrasomy – Cat eye Syndrome (TrA)</li> </ul>
Septal	ASD, VSD, ASD+VSD, ASD+CoA, ASD+VSD+CoA/AS, PDA	<ul style="list-style-type: none"> <li>1p36 deletion syndrome (VSD, ASD)</li> <li>1q21.1 deletion syndrome (VSD, ASD)</li> <li>3p25 deletion syndrome (VSD)</li> <li>4p14.3 deletion/Wolf-Hirschhorn syndrome (ASD, VSD, PDA)</li> <li>4q deletion (VSD, PDA, ASD)</li> <li>5p15.2 deletion/Cri-du-chat syndrome (VSD, ASD, PDA)</li> <li>7q11.23 deletion/Williams syndrome (ASD, VSD)</li> <li>8p23.1 deletion syndrome (ASD, AVSD)</li> <li>9p23.1 deletion (VSD, PDA)</li> <li>10p deletion (ASD, VSD, PDA)</li> <li>11q terminal deletion syndrome/Jacobsen syndrome (VSD)</li> <li>17q21 microdeletion (ASD, VSD)</li> <li>17p11.2 deletion/Smith-Magenis syndrome (ASD, VSD)</li> <li>22q13 deletion (VSD, ASD)</li> <li>22q11.2 deletion syndrome (ASD, VSD)</li> </ul>	<ul style="list-style-type: none"> <li>Adams-Oliver (ASD, VSD)</li> <li>Bardet-Biedel (VSD)</li> <li>Carpenter (ASD, VSD)</li> <li>CHARGE (ASD, VSD)</li> <li>Costello (ASD, VSD)</li> <li>Coffin-Siris (ASD, VSD, PDA)</li> <li>Cornelia De Lange (VSD, ASD, PDA)</li> <li>Cranioectodermal Dysplasia (ASD, VSD, PDA)</li> <li>Char (PDA, VSD)</li> <li>Ellis-Van Creveld (ASD, VSD)</li> <li>Holt-Oram (VSD, ASD)</li> <li>Joubert (ASD, VSD)</li> <li>Kabuki (ASD, VSD)</li> <li>Noonan (ASD, VSD, PDA)</li> <li>McKusick-Kaufman ASD, VSD, PDA)</li> <li>Mowat-Wilson (ASD, VSD, PDA)</li> <li>Rubenstein-Taybi (VSD, ASD, PDA)</li> <li>Peters Plus (ASD, VSD)</li> <li>Saethre-Chotzen (VSD)</li> <li>Smith-Lemli-Opitz (ASD, VSD, PDA)</li> <li>Sotos (ASD, VSD, PDA)</li> <li>Townes-Brocks (ASD, VSD, PDA)</li> </ul>	<ul style="list-style-type: none"> <li>ACTC1 (ASD)</li> <li>CITED2 (ASD, VSD)</li> <li>CRELD1 (ASD)</li> <li>GATA4 (ASD, VSD)</li> <li>GATA5 (ASD, VSD)</li> <li>GATA6 (VSD)</li> <li>HAND1/2 (VSD)</li> <li>HEY2 (VSD)</li> <li>MEIS2 (ASD, VSD)</li> <li>MYH6 (ASD)</li> <li>MYBPC3 (ASD, VSD, PDA)</li> <li>MYH6 (ASD)</li> <li>NOTCH1 (ASD, VSD)</li> <li>NODAL (VSD)</li> <li>NKX2.5 (ASD)</li> <li>NR2F2 (VSD)</li> <li>SMAD2 (ASD, VSD, PDA)</li> <li>TBX1 (VSD, ASD)</li> <li>TBX5 (ASD, VSD)</li> <li>TBX20 (ASD, VSD)</li> </ul>	<ul style="list-style-type: none"> <li>T13 (ASD, VSD)</li> <li>T18 (ASD, VSD, PDA)</li> <li>T21 (ASD, VSD)</li> <li>Klinefelter (PDA, ASD)</li> <li>Turner (ASD, VSD)</li> </ul>

(Continues)

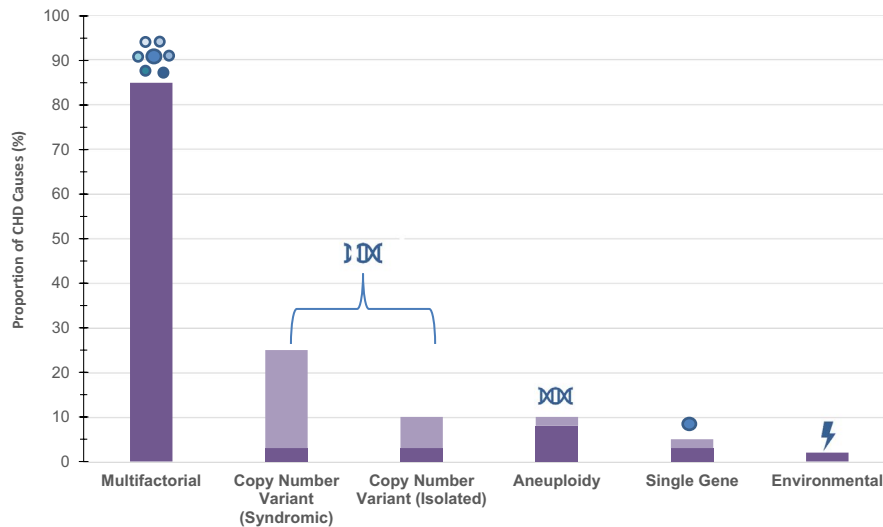
TABLE 3 (Continued)

Botto classification	Lesion	CNVs and CNV syndromes	Monogenic Syndromes	Genes also associated with apparently isolated CHDs	Chromosomal
NA	Other valvular defects	<ul style="list-style-type: none"> <li>1p36 deletion syndrome (Ebstein anomaly)</li> <li>7q11.23 deletion/Williams Syndrome (SVAS)</li> <li>11q terminal deletion syndrome/Jacobsen syndrome (mitral stenosis)</li> </ul>	<ul style="list-style-type: none"> <li>Coffin-Lowry (MVP)</li> <li>Fragile X (MVP)</li> <li>Marfan (MVP)</li> </ul>	<ul style="list-style-type: none"> <li>DCHS1 (MVP)</li> <li>MYBPC3 (mitral valve regurgitation)</li> <li>MYH7 (Ebstein anomaly)</li> </ul>	
NA	Overlap with Cardiomyopathy/Conduction Disease	<ul style="list-style-type: none"> <li>1p36 deletion syndrome (LVNC)</li> </ul>	<ul style="list-style-type: none"> <li>Cantu (HCM)</li> <li>CFC (HCM)</li> <li>Coffin-Lowry (LVNC)</li> <li>Costello (HCM)</li> <li>Holt-Oram (conduction defects)</li> <li>Noonan (HCM)</li> <li>Timothy (LQTS)</li> </ul>	<ul style="list-style-type: none"> <li>ACTC1 (HCM, DCM, LVNC)</li> <li>HAND2 (LVNC)</li> <li>MYH6 (HCM, DCM)</li> <li>MYH7 (LVNC, HCM, DCM)</li> <li>MYBPC3 (HCM)</li> <li>NFATC1 (LVNC)</li> <li>NKX2-5 (LVNC, conduction disease)</li> <li>TBX5 (conduction disease)</li> <li>TBX20 (LVNC, DCM)</li> </ul>	

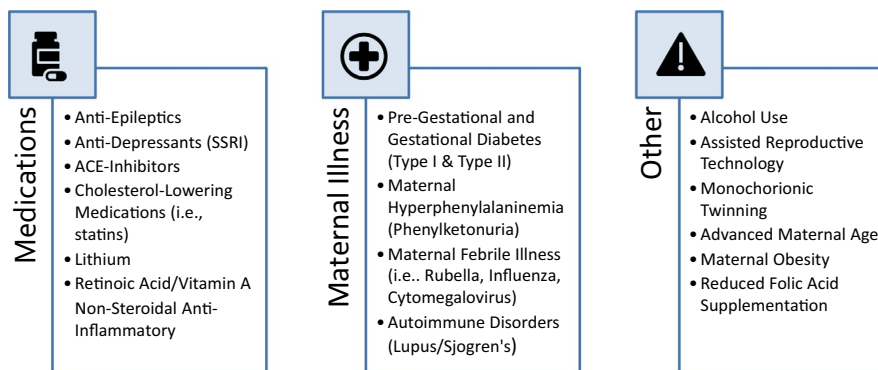
Note: It is important to note that this table does not necessarily represent a comprehensive list. It is likely that knowledge regarding these association will evolve as more is learned. The 'complex' Botto classification is not represented in this table, as this is defined as the presence of multiple cardiac anomalies spanning several Botto categories (Sources: Botto et al., 2007; De Backer et al., 2019; Jerves et al., 2020; Nees & Chung, 2020; Pierpont et al., 2018; Williams et al., 2019).

Abbreviations: APVR, anomalous pulmonary venous return; AS, aortic stenosis; ASD, atrial septal defect; AVSD, atrioventricular septal defect (AKA atrioventricular canal defect); BAV, bicuspid aortic valve; CoA, coarctation of the aorta; DCM, dilated cardiomyopathy; DORV, double-outlet right ventricle; HCM, hypertrophic cardiomyopathy; HLHS, hypoplastic left heart syndrome; IAA, interrupted aortic arch type B; LQTS, long QT syndrome; LVNC, left ventricular noncompaction cardiomyopathy; MVP, mitral valve prolapse; PA, pulmonary atresia; PAPVR, partial anomalous pulmonary venous return; PDA, patent ductus arteriosus; PS, pulmonic stenosis; PVS, pulmonary valve stenosis; SVAS, supraaortic stenosis; T13, trisomy 13, T18, trisomy 18, T21, trisomy 21, TA, truncus arteriosus; TAVPR, total anomalous pulmonary venous return; TrA, tricuspid atresia; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; VSD, ventricular septal defect.





**FIGURE 1** Estimated prevalence of monogenic, cytogenetic, and complex/multifactorial CHD etiologies. The prevalence of chromosome copy-number variants is specified for both syndromic and apparently isolated CHDs. A range is provided for many of these etiologies with the darker shade indicating the lower end of the range and the lighter shade indicating the greater end of the range. *Note:* these categories collectively may not sum to 100% due to incomplete knowledge of multifactorial etiologies and because some CHD cases can have >1 contributing genetic/chromosomal or environmental risk factors (Sources: Cowan & Ware, 2015)



**FIGURE 2** Overview of common CHD teratogens and other environmental risk factors (Sources: Donofrio et al., 2014; Kalisch-Smith et al., 2020; Lynch & Abel, 2015).

#### 4 | TARGETED FAMILY HISTORY ASSESSMENT FOR CONGENITAL HEART DISEASE

When assessing a family history of CHDs, genetic counselors should be prepared to obtain additional details on this history with the understanding that CHDs are clinically and etiologically heterogeneous. If possible, it is recommended that a four-generation pedigree is obtained to try to capture a broad overview. Relevant information to assess includes a) who else in the family has CHD(s) and how closely they are related to the proband (i.e., does this appear to be isolated or familial?), b) whether the affected individual has an underlying syndromic diagnosis or a presumed isolated defect, or whether other relatives have potentially syndromic features, and c) the findings of any previously performed genetic evaluation and genetic testing results (positive or negative). The purpose of obtaining this information is to assist with gaining clearer insight into the

possible etiology of CHD(s) in the proband and/or the family. To do this, it can be helpful to ask about when and how the individual was diagnosed, and whether the affected individual(s) had other congenital anomalies, and/or intellectual disability. Genetic counselors should keep in mind that due to variable expressivity and reduced penetrance, it may not always be clear if a CHD is truly isolated and/or sporadic.

#### 5 | GENETIC TESTING FOR CONGENITAL HEART DEFECTS

Given the variable genetic etiologies of CHDs (chromosome copy-number variation, aneuploidy, single-gene syndromes, single-gene nonsyndromic, etc.), there are a variety of genetic tests to consider in the genetic evaluation of CHD patients. This section aims to explore the utility of well-known testing modalities for individuals

with CHDs as well as key considerations when determining testing strategies.

## 5.1 | Cytogenetic testing strategies

Chromosomal microarray analysis (CMA) is widely used as the initial genetic test for individuals with CHDs and is recommended as the first-tier test for individuals with congenital anomalies (Manning & Hudgins, 2010; Miller et al., 2010). With few exceptions (e.g., conotruncal anomalies and supravalvular aortic stenosis), many guidelines do not directly address recommendations for use of CMA for individuals with apparently isolated CHD. However, institutions may perform, or at least offer, a CMA to all individuals with complex/critical CHD regardless of the presence or absence of recognized syndromic features. Though an individual may appear to have isolated CHD, genetic testing, particularly in the neonatal setting when additional extracardiac features may be mild and harder to identify, provides the opportunity to identify a genetic aberration which may have otherwise been missed and could impact clinical care and risk counseling. Overall, CMA has been found to currently have the greatest diagnostic yield across all testing modalities, identifying a diagnosis in 9%–25% of individuals with CHDs (Ahrens-Nicklas et al., 2016; Buckley et al., 2015; Geddes et al., 2019; Geng et al., 2014; Wang et al., 2018). The diagnostic yield of CMA is highest in those who have CHDs with extracardiac anomalies and/or neurodevelopmental disorders when compared to apparently isolated CHDs (15%–25% and 4%–17%, respectively) (Breckpot et al., 2010; Buckley et al., 2015; Geng et al., 2014; Turan et al., 2018; Wang et al., 2018). The yield and clinical utility of CMA for an older individual with CHD *without* extracardiac anomalies or developmental concerns remain to be explored (Ito et al., 2020). The European Society of Cardiology recently published recommendations for how best to navigate testing for this population of patients stating that there is currently no strong indication for CMA in the context of *adult* individuals with mild to moderately complex isolated CHD (De Backer et al., 2019). We encourage readers to review this resource when involved in the care of an adult individual with apparently isolated CHD (De Backer et al., 2019).

Researchers have examined whether the diagnostic yield of CMA differs based on the particular class of CHD. Some patterns have emerged (e.g., higher yields for conotruncal defects), leading the American Heart Association (AHA) to support CMA for any individual with specific conotruncal anomalies including, but not limited to, interruption of the aortic arch type B, truncus arteriosus, and tetralogy of Fallot (Pierpont et al., 2018). More robust, lesion-specific data remain limited due to relatively small cohorts available (Buckley et al., 2015; Wang et al., 2018). Therefore, teams may consider a broader approach for using CMA in the assessment of CHD patients regardless of the underlying CHD class.

Historically, fluorescence in situ hybridization (FISH) was the standard test methodology for diagnosing recurrent microdeletions

syndromes. While there are several proposed testing algorithms in the literature that include consideration of FISH with high suspicion for a specific CNV such as 22q11.2 deletion syndrome or Williams syndrome, multiple studies have demonstrated that starting with CMA is often more cost-effective and timely than performing FISH and/or karyotype then reflexing to CMA (Connor et al., 2014; Geddes et al., 2017). Karyotype and/or FISH are recommended with high suspicion for common aneuploidies like trisomy 13/18/21 and Turner syndrome and especially when there is a need to assess for chromosomal rearrangements that will guide recurrence risk counseling (e.g., chromosomal translocations). The recent AHA Scientific Statement also suggests that it is reasonable to consider offering FISH to all individuals with supravalvular aortic stenosis (SVAS) given a strong association with William's syndrome (Pierpont et al., 2018).

## 5.2 | Single-Gene, Next-Generation Sequencing (NGS) panels, and exome/genome sequencing

As opposed to structural variants, single-gene variants currently account for a less significant proportion of CHDs with genetic testing ranging from single-gene analysis to large multi-gene panels and exome/genome sequencing. Single-gene testing can be considered in specific cases based on cardiac lesion, presence or absence of extracardiac features, and family history of CHDs. For example, *ELN* single-gene analysis should be considered in an individual with isolated SVAS with or without a family history of SVAS. In a study by Blue et al., (2014), the yield of *ELN* sequencing in individuals with SVAS was estimated at ~3.4%. Single-gene analysis could also be considered for patients with suspected syndromic CHDs at the discretion of a medical geneticist and/or based on dysmorphology evaluation by an experienced clinician. Examples of this may include *CHD7* analysis for CHARGE syndrome, *JAG1* testing for Alagille syndrome, and *TBX5* analysis for Holt–Oram syndrome. However, these syndromes are individually rare, so the yield of single-gene testing approaches for CHDs will have decreased utility without a priori suspicion of a specific single-gene syndrome.

Targeted multi-gene panels commonly used for CHDs include RASopathy gene panels and heterotaxy gene panels. RASopathy gene panels should be considered in patients with features of Noonan-spectrum disorders, valvar pulmonic stenosis with another cardiovascular malformation, or valvar pulmonic stenosis with specific extracardiac features (Anderson et al., 2019). Heterotaxy panels with the inclusion of primary ciliary dyskinesia genes should be considered in patients with complex cardiac defects such as unbalanced atrioventricular canal defects or malposed great vessels with or without additional left-right patterning abnormalities (Geddes et al., 2020; Pierpont et al., 2018).

Large multi-gene CHD panels including both syndromic and isolated CHD genes can be considered in cases with a broad differential diagnosis or in cases of familial CHD. Some studies have reported a 31%–46% yield of molecular diagnosis using a 57-gene CHD panel in cases of familial CHD (Blue et al., 2014; Jia et al., 2015). However,

this is likely a higher yield than expected due to the strong familial pattern in these study cohorts and due to less stringent variant interpretation practices (Richards et al., 2015). Next-generation sequencing panels, which can vary greatly between laboratories, are not typically the clinical standard of care for isolated (nonfamilial) CHD, as the yield is low. Panel testing may have advantages in that there is assessment of a pre-specified group of both syndromic and nonsyndromic CHD genes and is arguably more cost-effective than single-gene approaches. However, studies in patient cohorts with more narrowly defined case definitions (e.g., isolated vs. syndromic, adult vs. pediatric, and/or familial vs. sporadic) would be needed to investigate the utility and diagnostic yield of CHD gene panels, especially for apparently isolated CHDs.

While exome and genome sequencing (ES and GS, respectively) is available clinically, at this time most centers do not routinely use exome or genome analysis for identification of underlying genetic etiology of isolated CHDs. However, it is suspected that over time these methodologies will be incorporated more regularly into clinical practice, especially in the presence of a strong family history of CHD. ES and GS are more frequently utilized in research studies in search of novel genes, novel structural variants, and additional variant types which are unable to be detected by standard sequencing (such as deep intronic/splice-site variants). An example of such discoveries using ES was recently published in a study by Jin et al., (2017). Findings included discovery of a recessive Ashkenazi Jewish founder variant in *GDF1*, possible association between *FTL4* loss-of-function variants with tetralogy of Fallot, and 12 additional novel genes with possible associations with CHDs. To date, the reported yield of ES and GS for CHDs has ranged widely in the literature due to variability in study design, case classifications, sample sizes, and variant interpretation stringency. Based on current literature, the diagnostic yield has been reported to range from 5 to 35+%, with generally higher yields for those with apparently syndromic CHDs (presence of extracardiac anomalies) (Blue et al., 2015; Homsy et al., 2015; Liu et al., 2020; Reuter et al., 2020; Sun et al., 2019; Szot et al., 2018; Zaidi et al., 2013). As with any use of ES, teams should be aware of the limitations of ES-based approaches, especially with variable/reduced exon coverage for certain genes and decreased ability for identifying types of genomic variants like copy-number variants, genes in highly repetitive genomic regions, or genes with multi-nucleotide repeats. These limitations may be largely addressed by oncoming adoption of GS-based testing approaches within the next few years.

Last, some institutions may utilize exome-based gene panel analysis strategies that involve analysis of the exome but only provide interpretation of variants in genes associated with CHDs. This testing approach can be beneficial for a more comprehensive analysis while minimizing the reporting of secondary findings or variants of unclear significance (VUS) in noncardiac genes. The ability to interpret variants found in genes with possible but low evidence supporting disease association complicates the use of broader genetic testing technologies. Some groups have also been able to identify chromosome copy-number variants from ES and GS data, and with

improved bioinformatics approaches for these genomic variants, ES and GS may supplant CMA for copy-number variant identification in the future (e.g., Shi et al., 2018).

### 5.3 | Genetic testing and counseling considerations

Identifying a genetic etiology of a patient's CHD may offer benefits to the patient and family. Genetic testing may diagnose a disorder with established medical management guidelines or may influence pre-surgical laboratory evaluations (e.g., 22q11.2 deletion syndrome and immune system studies, Noonan syndrome and need for coagulopathy workup) and medical care through the surgical process (e.g., William's syndrome and the increased risk of anesthesia complications) (Latham et al., 2016; Nugent et al., 2018). Even if a genetic diagnosis has no associated guidelines, medical management may be impacted. Multiple retrospective studies of patients undergoing CMA for any indication, including CHDs, have found that positive test results often warranted a referral to a subspecialist for surveillance and/or intervention for a previously unrecognized disease (Ellison et al., 2012; Hayeems et al., 2015; Henderson et al., 2014). Data also show that individuals, including those with CHDs, found to carry a copy-number variant were more likely to have increased health challenges such as decreased transplant-free survival and poor growth (Carey et al., 2013; Kim et al., 2016). Additionally, some disorders may have long-term implications beyond CHDs, including increased risk for arrhythmias. This is the case for *TBX5*, which has been associated with both Holt-Oram syndrome (CHDs and limb digit anomalies) and apparently isolated CHDs. In both cases, there is an increased risk to develop arrhythmias requiring long-term heart rhythm surveillance and risk counseling. A similar risk of arrhythmias is seen in people with pathogenic *NKX2-5* variants.

During pretest counseling, the genetic counselor should discuss the possible results of genetic testing including pathogenic copy number variants and/or VUSs. This also includes those that have variable or uncertain phenotypes and the potential difficulty in predicting outcomes. This may be particularly relevant as CMA testing becomes more routinely used for individuals with isolated CHD without established syndrome-specific guidelines. An example of this can be seen with deletions of the 1q21.1 region that are known to have wide clinical variability and may demonstrate incomplete penetrance (Brunetti-Pierri et al., 2008). If a CHD panel is offered to an individual with isolated CHD, even in cases in which there is a strong family history, careful counseling is recommended to set expectations around a likely lower diagnostic yield and a greater VUS rate.

In summary, several variables must be considered when choosing an appropriate genetic testing strategy. Multiple algorithms have been published providing suggested approaches to genetic testing for congenital heart disease (De Backer et al., 2019; Jerves et al., 2020; Zaidi & Brueckner, 2017). These algorithms provide similar guidance on the approach to testing in the instance of high suspicion for aneuploidy or 22q11.2 deletion syndrome, with use of karyotype or

FISH/CMA, respectively. For patients with syndromic presentations, the algorithms similarly suggest starting with either targeted testing when a specific disorder is highly suspected, or CMA with a broader differential (or after an uninformative targeted test result) and consideration of ES if initial testing is uninformative. For apparently non-syndromic presentations, the proposed genetic testing strategies account for family history, CHD class, and reproductive age/decision making, with some variation among the algorithms. Two algorithms also note consideration of use of GS for research purposes when an alternative cause has not been identified (De Backer et al., 2019; Jerves et al., 2020). While these algorithms can help in the development of testing protocols, institution-specific policies, procedures, and urgency of a clinical situation can affect genetic testing decisions.

## 6 | COUNSELING FOR CHD RECURRENCE RISK

Perhaps one of the most pertinent aspects of genetic counseling involves the discussion of recurrence risk. This risk is dependent on many factors, including the presence or absence of an identifiable genetic etiology, known environmental or teratogenic exposures, family history, and CHD class (see discussion above regarding the Botto classification scheme).

### 6.1 | In the presence of a genetic etiology

Individuals with CHDs co-occurring with other congenital anomalies, dysmorphic features, and/or developmental delays should be recommended for a formal genetics evaluation prior to estimating recurrence risk. If the CHD is explained by the identification of a Mendelian genetic syndrome, genetic counseling should proceed according to the inheritance of that particular syndrome and whether the variant was inherited or *de novo*.

If a monogenic cause of *isolated* CHD is identified and there is substantial evidence supporting the pathogenicity of the causative variant, reduced penetrance and variable expressivity should be emphasized to patients/families when appropriate, and when discussing the risk to family members. An example of this concept is highlighted in a recent study of familial CHD caused by *NOTCH1* variants, which demonstrated that penetrance was up to 75% for pathogenic variant carriers (Kerstjens-Frederikse et al., 2016). Similarly, incomplete penetrance was demonstrated in families with tetralogy of Fallot associated with *FLT4* gene variants (Reuter et al., 2019). However, most gene variants associated with nonsyndromic, isolated CHD do not have published penetrance information; therefore, it is reasonable to discuss the risk of an individual inheriting the variant (i.e., 50% risk to future children), but that the risk of CHD occurrence, as well as type/severity of CHD, may be less clear. As genotype-phenotype correlations improve, variant-specific risks will hopefully become available, allowing the risk assessment to be more tailored. However, the research

required to demonstrate gene- and variant-specific estimates of penetrance and fuller ranges of expressivity will be substantial.

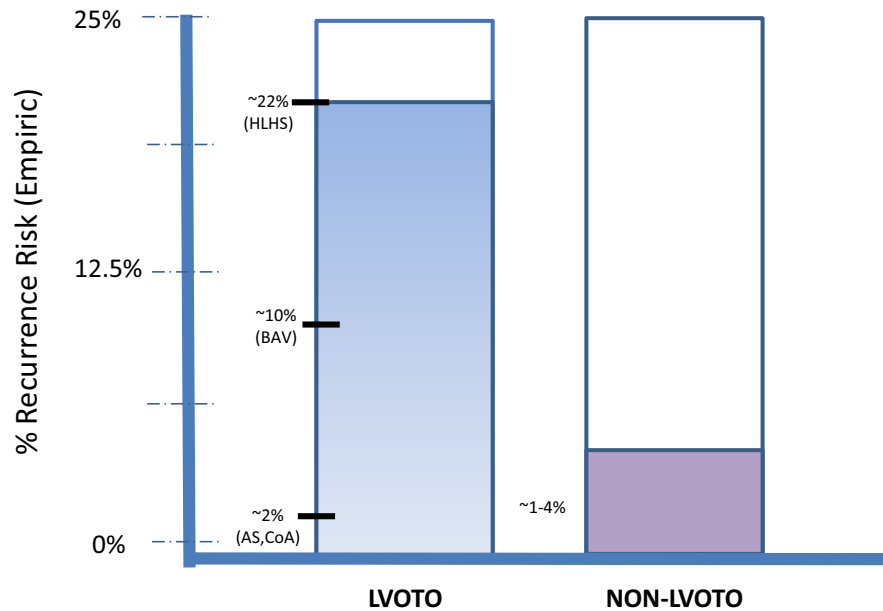
Some monogenic causes of CHD can be associated with an increased risk of developing other cardiac phenotypes such as arrhythmias and cardiomyopathies. These include, but are not limited to, *MYH7*, which can be associated with cardiomyopathy (Postma et al., 2011; Van der Linde et al., 2017), and *GATA4*, which has been associated with atrial fibrillation (Posch et al., 2010; Yang et al., 2011). In these cases, it is important to offer predictive testing to at-risk individuals, emphasize the risk to other family members, and highlight the variable features that may present in the family. It is also appropriate to counsel families that the risk of CHDs to individuals *without* the familial pathogenic variant is likely reduced to baseline risk.

Of note, in some cases, genes previously associated with genetic syndromes can cause apparently isolated CHD, further expanding our understanding of variable expressivity. For example, *TBX5* has been associated with nonsyndromic CHDs, Holt-Oram syndrome, and dilated cardiomyopathy, demonstrating the spectrum of phenotypes associated with this gene (Zhou et al., 2015). In other instances, identifying a variant in one of these genes may actually uncover an undiagnosed syndrome in the family that has thus far affected individuals relatively mildly (Blue et al., 2014).

Regardless of whether a pathogenic monogenic cause has been identified, the lines between Mendelian and complex multifactorial causes of CHDs are becoming increasingly blurred. This is especially salient when considering the complex interactions between cardiac developmental genes and their dependent activities in developmental gene networks (Waldron et al., 2016). It is likely that the underlying genetic complexities of CHDs drive the clinical and familial manifestations of incomplete penetrance and variable expressivity. In a study by Blue et al., (2017), individuals with CHDs, both in familial and in isolated cases, had a higher burden of variants in cardiac developmental genes than those without CHDs. Even in seemingly monogenic cases, there is likely an element of complex genetic or multifactorial contribution to the development of heart disease and related manifestations (e.g., cardiomyopathy and arrhythmias).

### 6.2 | In the absence of a known genetic etiology

In the absence of an identifiable genetic etiology or an uncertain genetic finding, the recurrence risk for isolated (apparently nonsyndromic) congenital heart disease has been estimated from several large population studies. A summary of recurrence risk by CHD class has been reported by Cowan and Ware (2015) and can be used as a 'baseline' risk. This risk can be modified (i.e., increased or lowered) by clinical observations such as a family history of CHDs and confirmed teratogenic exposures during pregnancy (e.g., limited control of maternal diabetes). When counseling a family concerned about recurrence, it is important to highlight the limitations of empiric risk calculations as they are based on population averages without knowledge of the actual underlying etiology.



**FIGURE 3** Schematic representing baseline recurrence risk for future children (based on empiric data), for apparently isolated CHD. Of note it is important to consider that this risk can be further modified by taking into consideration other risk factors such as the presence of maternal illness (ex. uncontrolled diabetes), teratogen exposure, and family history of CHD (especially if a parent or siblings is also affected by CHD – risk could be up to 50%) (Sources: Cowan & Ware, 2015; Freeze et al., 2016; Hales & Mahle, 2014). Abbreviations: AS, Aortic stenosis; BAV, Bicuspid aortic valve; CoA, Coarctation of the aorta; HLHS, Hypoplastic left heart; LVOTO, Left ventricular outflow tract obstruction; Non-LVOTO, None Left ventricular outflow tract obstruction defects (all other categories of congenital heart disease)

### 6.3 | Familial recurrences

The presence of more than one CHD within a family can increase risk of recurrence. As noted by population data, recurrence risk for any CHD is considered 2%–3% for a family with one affected child and may increase to up to 50% with more than two affected first-degree relatives (Harper, 2010). However, even in a family history that appears to follow a Mendelian pattern of inheritance, reduced penetrance, often speculated to be associated with an oligogenic or multifactorial etiology, complicates estimation of the recurrence risk. Thus, when there is a strong family history of isolated CHD(s) that appears to follow an autosomal dominant inheritance pattern, and no genetic cause has been identified, one could consider counseling that the risk to future offspring could potentially be up to 50%, but that it is also possible that this risk could be lower.

### 6.4 | CHD class

In the case of CHDs that are *not* suspected by the clinical team to be syndromic, lesion type can significantly affect the likelihood of recurrence (Figure 3). While there are studies suggesting increased risk of recurrence for almost any lesion type, left ventricular outflow tract lesions (LVOTO) have the highest recurrence risk of CHD classes. Common LVOTO lesions include hypoplastic left heart syndrome, aortic stenosis, coarctation of the aorta, or bicuspid aortic valve. It is important to note that an incidence of recurrence may not be of

the same lesion and may be of varying severity such that occurrence of aortic stenosis, coarctation, and bicuspid aortic valve can all be noted within one family. Many publications have cited this in the case of HLHS where recurrence in siblings was lower for HLHS (0%–8%) but higher for other defects (13%–31%) (Cowan & Ware, 2015; Kelle et al., 2015; Loffredo et al., 2004). Despite higher heritability of LVOTO CHDs, this does not necessarily mean that there will be a higher diagnostic yield of genetic testing or that other CHD classes do not have genetic contributions to their causes. It is still important to remember that all classes of CHDs likely have genetic causes, even if the LVOTO class is considered to have the highest heritability. This was explored by Øyen et al. (2009), reporting on the *relative risk* for all types of CHDs in individuals that had a first-degree relative with a CHD. Relative risks were substantial, ranging from ~3.0 to 79.0, and the overall relative risk for first-degree relatives to have the same or similar CHDs was ~8.0 to 12.0. Results from that study are difficult to use for genetic counseling practice because the relative risks in Øyen et al. (2009) do not translate easily to absolute recurrence risks (%).

### 6.5 | Environmental exposures

Finally, estimation of recurrence risk is not complete without a detailed review of environmental exposures during pregnancy (as noted in the genetic etiology section above). Well-known exposures such as maternal diseases or teratogen exposures that reoccur during a subsequent pregnancy can significantly increase one's risk for recurrence.

For instance, if a mother was known to have limited diabetes control during the pregnancy, this may decrease the concern for an underlying genetic etiology and may indicate a lower recurrence risk, unless the mother were to similarly have limited control during a subsequent pregnancy. This same approach can be applied to other types of environmental or maternal health teratogenic risk factors.

## 7 | CHD FAMILY SCREENING RECOMMENDATIONS

In the absence of an identified genetic risk factor, cardiac screening recommendations for family members of an affected individual varies based on CHD class (e.g., LVOTO vs. non-LVOTO), family history, and practices of the specific center (Figure 4).

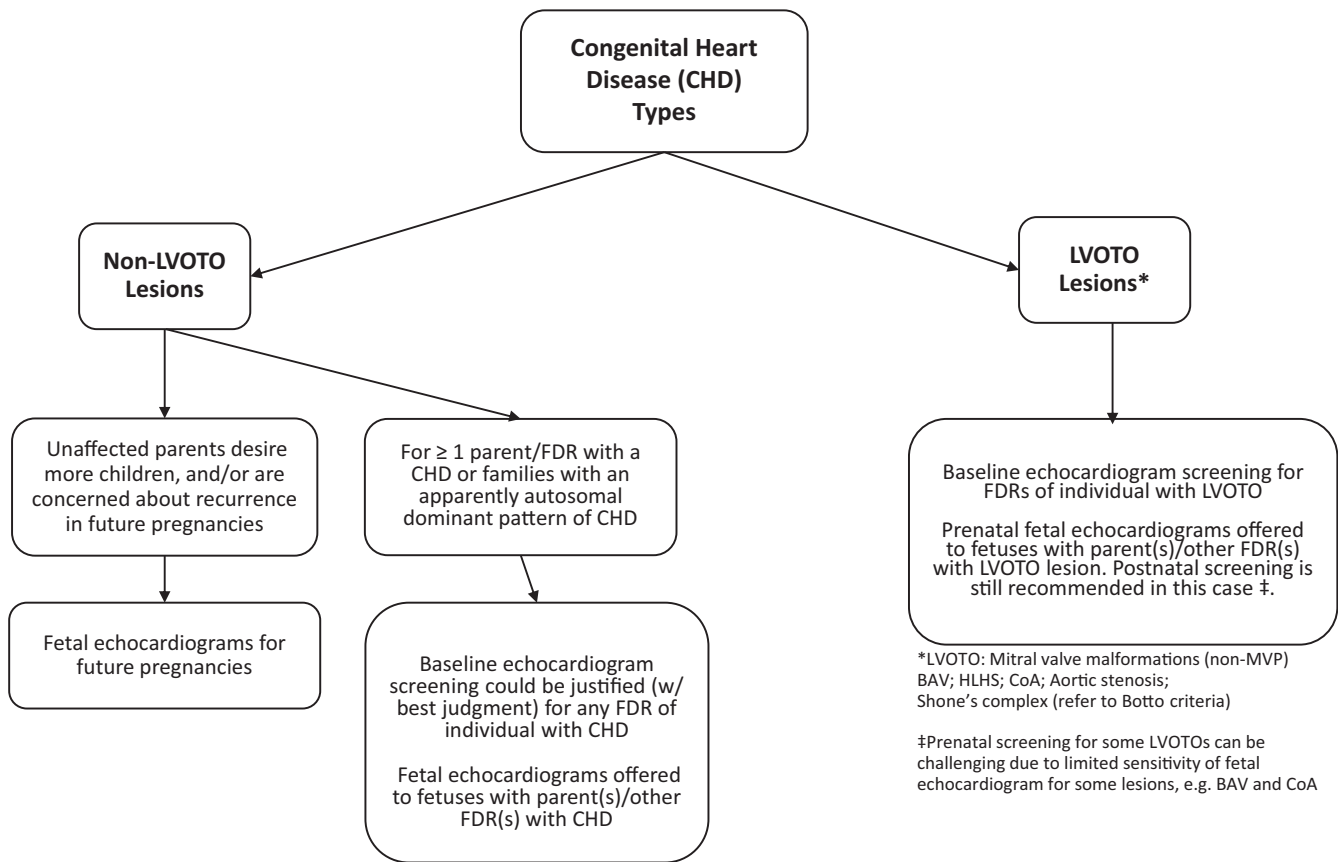
### 7.1 | LVOTO

As stated previously, left ventricular outflow tract obstruction (LVOTO) malformations are known to demonstrate one of the

greatest heritability risks compared with other cardiac malformations. Currently, few professional organizations have published screening recommendations for first-degree family members of individuals with CHDs, with the exception of Hiratzka et al. (2010). These guidelines recommend that all first-degree relatives of an individual with a bicuspid aortic valve undergo a screening echocardiogram; it does not address cardiac screening for relatives of individuals with other LVOTO malformations. However, due to the body of literature documenting the increased incidence of CHDs in relatives with various LVOTOs, many centers recommend a baseline screening echocardiogram for any first-degree relatives of an individual with any LVOTO (Demir et al., 2013; Hinton et al., 2007; Kelle et al., 2015; Kerstjens-Frederikse et al., 2011; McBride et al., 2005).

### 7.2 | Non-LVOTO screening considerations

For all other isolated cardiac lesions, there is a lack of formal guidance for clinical screening of seemingly unaffected family members. This is true for scenarios where there is a clear familial inheritance



**FIGURE 4** Family screening recommendations for individuals with isolated CHD for which the underlying genetic cause is unknown categorized by LVOTO and Non-LVOTO lesions. When screening for CHDs, generally it is recommended to have a single echocardiogram to confirm or exclude CHD. Generally, ongoing cardiac surveillance is not recommended if a previous echocardiogram was normal, unless there is indication to screen for other cardiac disease (i.e., cardiomyopathy). Abbreviations: BAV, Bicuspid aortic valve; CoA, Coarctation of the aorta; FDR, first-degree relative; HLHS, Hypoplastic left heart; LVOTO, Left ventricular outflow tract obstruction; Non-LVOTO, None Left ventricular outflow tract obstruction defects

due to a high incidence of CHDs within a family. Whether or not a seemingly unaffected family member should undergo echocardiography in these circumstances is primarily up to clinical judgment and/or familial concern or interest.

As discussed previously, some monogenic causes of CHDs can be associated with an increased risk of developing other cardiac phenotypes such as arrhythmias and cardiomyopathies. It is important to keep in mind that variants associated with both CHD and cardiomyopathy/arrhythmia can present with variable expression. For example, due to variable expressivity, individuals with pathogenic variants in *ACTC1* can present with ASDs as well as HCM, DCM, or LVNC. Therefore, it is possible for one individual in the family to be born with a CHD, and another to only present with cardiomyopathy and/or arrhythmia. If a family has a pathogenic variant in a gene that can cause additional cardiac phenotypes, predictive testing is recommended for all first-degree family members, and cardiac screening (e.g., echocardiogram and ECG) would be indicated for relatives who are found to carry the variant, even if they are seemingly unaffected, given that cardiomyopathy and arrhythmia can develop over time. It is also important that families understand that in these cases, a singular instance of cardiac screening may not be sufficient to rule out disease, and ongoing cardiac screening may be necessary to monitor for the development of cardiomyopathy and arrhythmia over time.

## 8 | CHD MULTIDISCIPLINARY TEAM APPROACHES

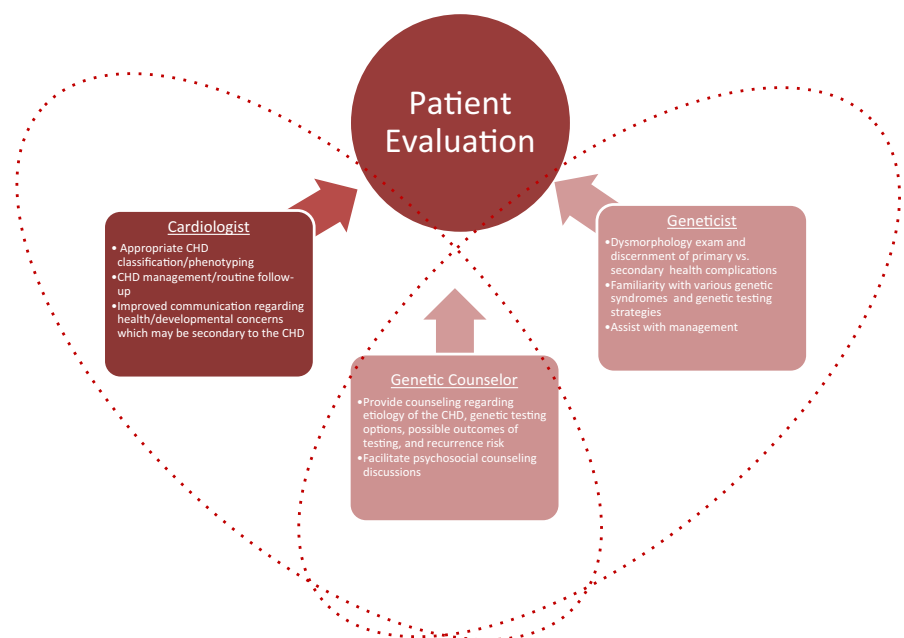
Multiple professional organizations including the AHA and ESC stress the importance of a multidisciplinary approach to delivery of care for individuals with CHDs, inclusive of a genetic counselor and/or clinical geneticist (De Backer et al., 2019; Stout et al., 2019).

However, there are limited data on the efficacy of different cardiogenetics clinic models. Individuals and families with CHDs have identified genetic counselors and cardiologists as primary sources for genetic information (Van Engelen et al., 2011; Kasparian et al., 2014, 2018; Shikany et al., 2019). In one study, 93% of parents of children with CHDs reported being most likely to attend a cardiogenetics clinical visit if there would be access to a geneticist and genetic counselor and in a timely manner (Kasparian et al., 2014).

Many individuals with CHDs are referred directly to a genetics clinic with a geneticist and genetic counselor, particularly in the presence of extracardiac anomalies. Studies have demonstrated improvement in diagnostic rate, appropriate management, and utilization of genetic testing when a geneticist is involved in care of individuals with CHDs in various clinical settings (Van Engelen et al., 2013; Goldenberg et al., 2017). Given that neonates may present with mild dysmorphic features that could go unnoticed and the inability to assess for developmental delays/learning disabilities at this stage in life, the geneticist can play a vital role in identification of subtle findings that may alter the differential and/or testing strategy.

Genetic counselors can add value to patient care by providing psychosocial support to families and education on the genetics of CHD, discussing cardiac screening recommendations for at-risk family members, providing information regarding recurrence risk estimates, interpreting genetic testing results, and performing predictive testing in the family when appropriate (Van Engelen et al., 2013). Dependent on institutional referral practices, a possible weakness of a cardiologist/genetic counselor-only model includes the exclusion of a dysmorphology evaluation. This can be especially important when genetic testing in an apparently nonsyndromic CHD case yields a variant in a gene that can have syndromic (i.e., extracardiac) features.

As genetic risk assessment in CHDs is often lesion-specific, close collaboration between experienced cardiology clinicians



**FIGURE 5** The multidisciplinary approach to CHD care and roles of the various specialists who may be involved in CHD practice models

can improve CHD classification and downstream risk assessment. For instance, close collaboration with a cardiologist may improve the separation of health outcomes that may be secondary to a patient's cardiac history (e.g., developmental delay due to the cardiac surgical intervention) as opposed to an independent primary diagnosis. Some multidisciplinary clinics may allow for both a geneticist and genetic counselor to work directly with cardiologists, while in other instances a genetic counselor may see patients with a cardiologist independent of a geneticist. With this approach, cardiologists and genetic counselors are encouraged to develop standard approaches for genetic testing and referring patients to a geneticist for syndromic evaluation, if indicated. In summary, cardiogenetics services can be diverse, consist of many models, and may employ a combination of genetic counselors, geneticists, and cardiologists dependent on institutional resources and preferences (Figure 5). It is important to consider the advantages and disadvantages of each model given referral patterns and provider utilization that often will differ between institutions, and to determine whether there are ways to supplement for resources that may not be available at one's institution. Last, a largely unexplored area includes multidisciplinary practice models targeted to adult CHD populations.

## 9 | CONSIDERATIONS FOR PRENATAL GENETIC COUNSELING

### 9.1 | Counseling on a Family History of CHD(s)

In the prenatal genetic counseling setting, it is common to identify a history of CHDs in a parent of the fetus, prior child, or other family member(s). The goal of the genetic counselor in these cases is to obtain as much detail as possible about the reported family history (e.g., relationship of affected relatives, type of CHD, and etiology if

**TABLE 4** Indications for fetal echocardiogram that may be pertinent for the prenatal genetic counseling setting

1st or 2nd degree relative of the fetus with CHD
1st or 2nd degree relative of fetus with Mendelian disorder that has CHD association
Fetal chromosome abnormality by diagnostic testing or cell-free DNA screening
Fetal cardiac abnormality suspected on ultrasound
Major fetal extracardiac abnormality suspected on ultrasound
Hydrops fetalis
Fetal increased NT >95% ( $\geq 3$ mm)
Abnormal fetal heart rate or rhythm suspected on ultrasound
Pregnancy achieved via IVF
Monochorionic twins
High-risk maternal medical conditions, medication exposures, or infections

Note: (Sources: Donofrio et al., 2014; Lee et al., 2020).

known) to inform risk assessment and offer testing options for the current pregnancy. See 'the Targeted Family History' section above for additional details on assessing for a family history of CHD.

Recurrence risk counseling is complicated by the fact that many prenatal patients do not know the underlying diagnosis in their affected relative. The same recurrence risk principles reviewed above apply in the prenatal setting. A referral for genetic evaluation and testing may be reasonable for the affected individual to help clarify specific risks. However, further evaluation and testing of relatives may not be a viable option within the time-sensitive window to facilitate prenatal testing or accurate recurrence risk provision for the current pregnancy.

In the case where a pregnant mother has a personal history of apparently nonsyndromic CHD, she should be referred to adult congenital cardiology and high-risk obstetrics specialists with expertise in caring for such high-risk pregnancies with appropriate maternal surveillance. CHD class-specific recurrence risk counseling, as outlined previously, is important. If a genetic syndrome is suspected in the mother, evaluation by a medical geneticist may be helpful.

Fetal echocardiogram should be considered in pregnancies where the fetus has a close relative with CHD or a Mendelian disorder associated with CHD. A suspected structural, chromosomal, or heart rate/rhythm abnormality in the fetus would also warrant fetal echocardiogram, among other indications (Donofrio et al., 2014; Lee et al., 2020). Table 4 lists common indications for which fetal echocardiogram is appropriate. Patients should be informed that certain types of CHDs may not be reliably detected even with fetal echocardiography and that postnatal echocardiography may be important.

Upon identifying a family history of a CHD, prenatal genetic counselors also have a unique opportunity to discuss the potential benefits of echocardiography screening for their pregnant patients and partners who may benefit from imaging themselves if their family history meets the recommendations outlined above.

### 9.2 | Counseling on a fetus with a CHD identified prenatally

When a CHD is present in a fetus, prenatal identification can allow for the most appropriate management, for example, planning for delivery at a tertiary care facility with specialized neonatal and surgical care which can maximize outcomes for the fetus and the family.

One of the main challenges when counseling about a fetus with a CHD is that some lesions may be difficult to diagnose or specifically characterize with a fetal echocardiogram or limitations of prenatal ultrasound. When a CHD is detected, a careful search for other malformations is important. Prenatal genetic counselors rely on the expertise of perinatology and pediatric cardiology specialists to determine the likely diagnosis, understanding that postnatal evaluation may provide additional information regarding the nature of the specific cardiac lesion or, more rarely, be normal. The family should be counseled that a diagnosis may change after delivery, additional findings may be identified, and a referral to a geneticist may be a necessary part of postnatal care. As discussed previously (see



Etiology/Genetic Testing sections above), the genetic etiologies of CHDs are heterogeneous. Petracchi et al., (2019) provide a comprehensive overview of the most common genetic causes of fetal CHD tailored for prenatal providers.

Chromosome abnormalities are a major cause of fetal CHDs, even more prevalent than in newborns due to spontaneous loss of pregnancies with chromosomal abnormalities. Published literature can be utilized to provide data on the chance of a chromosome abnormality based on the specific cardiac lesion and presence of other anomalies. For example, a 2018 prospective cohort study of 602 prenatal cases of fetal heart defects identified a pathogenic chromosomal abnormality in 20.8% of cases, with 52% of them being due to aneuploidy and the remainder being copy-number variants (Wang et al., 2018). The detection rate of a pathogenic chromosomal abnormality was lower in cases of an isolated congenital heart defect (14.3%) and increased in the presence of additional structural anomalies (48.9%) or intrauterine growth restriction (50.0%).

Studies of ES in the prenatal setting are emerging (Lord et al., 2019; Petrovski et al., 2019; Westphal et al., 2019). In a recent study published in 2020, CMA and ES were performed sequentially in 360 fetuses with CHDs. A genetic diagnosis was encountered in 84 cases (23.3%), with chromosomal abnormalities in 60 (16.7%) and sequence variants in 24 (6.7%). Of the 300 fetuses with normal CMA, 24 (8%) had a pathogenic/likely pathogenic variant identified through ES. Although aneuploidies were more frequent in fetuses with nonisolated CHDs, the frequency of copy number variants and sequence variants was not significantly different among fetuses with isolated vs. nonisolated CHDs. The authors of this study conclude that ES should be offered prenatally in all cases of CHDs with normal CMA results (Qiao et al., 2020).

### 9.3 | Prenatal genetic testing and additional considerations

In the setting of a fetus with CHD, patients should be offered both diagnostic testing and screening options. The American College of Obstetricians and Gynecologists (ACOG) issued a statement in December 2016 recommending CMA for patients with a fetus with one or more major structural abnormalities identified on ultrasound who are undergoing invasive prenatal diagnosis (Committee on Genetics & the Society for Maternal-Fetal Medicine, 2016). There have been numerous studies that demonstrate the utility of CMA as a first-tier test for a fetus with a CHD (Jansen et al., 2015; Turan et al., 2018; Wang et al., 2018).

Additional testing may be considered if CMA is normal such as a multi-gene panel or ES—especially if there are additional ultrasound findings suggestive of a genetic syndrome (e.g., extracardiac anomalies, growth restriction). See Appendix S2 for details on supporting guidelines for gene panels and ES.

Currently, ES in the prenatal setting is limited by turnaround time, cost, and insurance coverage. Additionally, interpretation of

secondary findings or VUS can be particularly challenging in the prenatal setting where clinical information is limited and the implications for pregnancy management, including termination of pregnancy, are significant.

Last, with ongoing developments in cell-free fetal DNA (cfDNA) screening, there may be options for screening fetuses with CHDs for common aneuploidies via this modality (Gregg et al., 2016; Committee opinion no. 640, 2015). However, it is important to discuss the limitations of cfDNA analysis, emphasizing it is not a replacement for diagnostic testing. Cell-free DNA screening for select microdeletion syndromes (e.g., 22q11.2 deletion syndrome), certain single-gene disorders and genome-wide copy-number variants are also now available through several laboratories. Preliminary studies have suggested increased rates of cfDNA-positive results in fetuses with ultrasound abnormalities using genome-wide cfDNA screening compared with standard cfDNA screening (Ehrich et al., 2017). While screening for microdeletion syndromes, single-gene disorders, and autosomal aneuploidies other than common aneuploidies is not currently recommended by ACOG/ACMG/SMFM due to lack of clinical validation studies, it could be considered in the setting of a fetus with a congenital anomaly when diagnostic testing is declined and with appropriate counseling on limitations.

Overall, amniocentesis with CMA should be offered to all families of a fetus with a CHD, regardless of screening results or presence/absence of additional sonographic findings. If amniocentesis is declined, postnatal CMA on cord blood should be considered. Genetic counselors should note whether the testing laboratory utilizes a different platform or different reporting criteria in prenatal vs. postnatal samples. From a cost-saving perspective, if available, reanalysis of the prenatal data may be preferred to repeat postnatal analysis.

The presence of additional family members with congenital anomalies or developmental delays or a family history of recurrent pregnancy loss, stillbirth/infant death or infertility may be suggestive of an underlying chromosome abnormality or genetic syndrome in the family, perhaps with recurrence in the fetus. In cases where the etiology remains elusive, affected relatives may consider a genetics evaluation. If counseling a couple with a history of recurrent miscarriage, parental chromosome analysis would be indicated and may help to uncover the cause of the CHD in the fetus.

In the setting of a perinatal loss, autopsy should be offered to evaluate for additional abnormalities, such as CHD, which may suggest an etiology. ACOG recommends a CMA be considered (Committee on Genetics and the Society for Maternal-Fetal Medicine). Additionally, in some instances, ES may want to be considered following an inconclusive CMA result.

Recurrence risk counseling for subsequent pregnancies following the prenatal diagnosis of a fetal CHD should be approached with caution unless a specific genetic diagnosis is made. Accurate risk assessment is challenging since the specific lesion can be difficult to characterize prenatally and it is not possible to be certain a CHD is truly isolated. See below for psychosocial considerations for prenatal genetic counseling.

## 10 | PSYCHOSOCIAL CONSIDERATIONS

Literature suggests that parents of a child with CHDs suffer from increased levels of hopelessness and distress, including anxiety and depression when compared with parents of healthy controls and importantly when compared to parents of children with other diseases (Blue et al., 2015; Grønning Dale et al., 2013; Lawoko & Soares, 2002, 2006). Additionally, families of children with more severe cardiac defects have shown more significant impact on social relationships, financial burden, personal strain, and challenges with siblings compared with families with milder CHDs (Almesned et al., 2013; Brosig et al., 2007; Connor et al., 2010).

Genetic counselors are uniquely posed to provide not only information to these patients and families, but psychosocial support as well. Studies have found that families who pursued genetic counseling reported increases in knowledge and decreases in depression, anxiety, and stress (Blue et al., 2015).

The questions of 'why' and 'how' a CHD occurs are at the forefront of the minds of parents of children with CHD. Receiving information related to the etiology of CHD through genetic counseling sessions results in increased personal control and decreased reports of guilt, depression, anxiety, and stress (Blue et al., 2015). Important considerations related to the timing, delivery, and type of information pertaining to genetic factors in CHDs have been studied. A significant number of parents (87%) report genetic factors as quite or extremely important; however, in the same study, only 36% recalled receiving such information (Kasparian et al., 2014). In another study related to genetic counseling services for parents of children with CHD, parents reported high satisfaction (96%) with genetic counseling services and would recommend genetic counseling sessions to other parents. Nearly all parents surveyed (98%) in one study reported information on recurrence risks of CHD is important, though only 7% recalled receiving this information from a healthcare provider (Blue et al., 2015). Evaluation of when and how families prefer to receive information related to the genetic factors of CHD shows a preference for a single appointment, with the presence of a clinical geneticist and genetic counselor, spoken and web-based information, and availability of the information within two weeks (Kasparian et al., 2018). Collectively, this work underscores the importance of including genetic counseling related to CHDs in the multidisciplinary care of these families. We encourage our community to continue to seek to understand, and publish findings related to, patient perception of CHD genetic counseling.

### 10.1 | Unique psychosocial considerations for prenatal genetic counseling

Genetic counseling in the setting of a fetal CHD is complex for the reasons outlined above. In addition, there are unique psychosocial issues. At the time of counseling, families are often struggling to come to terms with their unborn baby having significant medical needs and the genetic counselor may be the first person to discuss

the possibility the fetal CHD may not be 'isolated' even though it appears to be on prenatal ultrasound. Families are typically overwhelmed at the time of counseling, as the diagnosis may be recent, they may be learning about additional prenatal findings and they may need to deliver the baby far from home.

Discussion of the potential for an underlying genetic cause with associated developmental/medical concerns and/or a shortened lifespan can be especially difficult during pregnancy when they have yet to 'meet' their baby. The pervasive uncertainty surrounding the exact nature of the CHD, underlying diagnosis, and potential prognosis in the prenatal setting can be especially difficult for families to manage. In addition, some families may consider termination of pregnancy or compassionate postnatal care. Decisions regarding termination of pregnancy can be challenging since a CHD is typically not diagnosed until late in the second trimester and results from genetic testing may take several weeks.

During contracting, it is helpful to assess what the family understands about the fetal CHD and how they are coping with the diagnosis. It is also helpful to inquire about their support system and to provide contacts for local resources as appropriate (e.g., perinatal bereavement, palliative care, First Steps, and support groups).

Prenatal genetic counseling in the setting of a fetal CHD is complex, but essential. It prepares families for the possibility of additional noncardiac abnormalities. It also helps families understand the importance of genetic testing/evaluation to provide the best care for their baby and to provide accurate recurrence risk counseling for subsequent pregnancies.

## 11 | DISCUSSION & FUTURE PERSPECTIVES

The purpose of this practice resource is to serve as a foundation for genetic counselors approaching CHDs in their work, regardless of their underlying specialty. Despite being the most common birth defect in humans, genetic counseling approaches to CHDs can be complex because of the significant biological and genetic complexity, diversity of testing options, clinical indications, and varying practice models involving multidisciplinary teams of genetic counselors, medical geneticists, and cardiologists or other specialists. We encourage readers to refer to Table 5 for an outline of key considerations from each section of this manuscript.

We expect that the field will move more toward ES/GS as first-tier testing strategies for patients with CHDs, and this will lead to even greater need for genetic professionals well versed in the complexity of counseling in CHD settings and interpretation, management and counseling of CHD genetic testing results. Genomic-scale testing strategies have the capability to generate more information than can be meaningfully interpreted for clinical utility, and this will require multidisciplinary clinical teams that complement their respective domains of expertise. We encourage genetic counselors to contribute to research in this area, especially with the possible development of polygenic models of disease that incorporate diverse genomic variation across hundreds of genes involved in the

**TABLE 5** Summary of recommendations for CHD Counseling in practice**Targeted family history assessment for CHD**

- When possible, a four-generation pedigree should be obtained to provide a broad overview of the family history and assist with guiding the suspected etiology (environmental, monogenic, cytogenetic (microdeletion/duplication, aneuploidy, and/or structural rearrangements), or multifactorial/complex.
- It is recommended that the following information be obtained when assessing the family history:
  - Are there any other family members with congenital heart disease and/or congenital anomalies?
  - If yes, does the individual appear to have isolated or syndromic disease (dysmorphic features, intellectual disability, developmental delay, autism, etc.)? Have they undergone genetic testing? If so, is the family aware of the result and/or have the ability to obtain additional information on this history?
  - If there is a family history of CHD(s), do the CHDs appear to fall within the same Botto class (potentially indicating a similar underlying genetic etiology) or separate?
  - Is there a family history of recurrent miscarriages, infertility, stillbirths, or infantile death indicative of chromosomal structural rearrangements or severe syndromes?
  - Is there a family history of arrhythmias, pacemakers/implanted defibrillators, or sudden cardiac death? This question can assess for CHD genes which may present with arrhythmias/conduction disease (e.g., *NKX2.5*, *TBX5*, etc.).
- Given that CHDs can occur due to autosomal recessive inheritance, it is important to assess for consanguinity. Ancestry is less likely to assist with gene/disease differentials, but this may change as our understanding of the etiology of CHD(s) evolve. CHDs occur across all global geographic regions.
- It is important to keep in mind that due to reduced penetrance and variable expressivity, it is not always possible to determine if a CHD is truly isolated and/or sporadic in a proband and/or the family.

**Genetic testing for CHD**

- Based on current research, CMA has the highest diagnostic yield and has been shown to be cost-effective for both syndromic and nonsyndromic CHDs. Because of this, it should be considered a first-tier test to consider for those with CHDs.
- Those with syndromic presentations (e.g., extracardiac anomalies, developmental delay, etc.) should ideally be evaluated by a medical geneticist and other testing options may be prioritized (e.g., syndrome-specific genetic testing).
- At present, the diagnostic yield and clinical utility for CMA testing in adult CHD patients requires further exploration (especially for apparently isolated CHDs).
- Multigene panels for CHDs (both syndromic and non-syndromic) can be useful and likely cost-effective. However, studies are limited in demonstrating diagnostic yields for apparently isolated CHDs (familial and sporadic). Further research is required to determine diagnostic yield in different CHD cohorts: syndromic, apparently isolated, sporadic, and familial.

**Genetic counseling for CHD recurrence risk**

- If a pathogenic monogenic cause of isolated CHD is identified, a thorough assessment of the variant and data supporting its pathogenicity should be reviewed, and reduced penetrance and variable expressivity should be emphasized to patients/families when appropriate.
- If a *potential* monogenic cause of familial isolated CHD is identified (i.e., a variant of uncertain significance), and there is evidence suggesting its possible involvement in the familial cardiac disease, segregation testing can be considered for affected family members. Patients should receive careful counseling around the likelihood of the variant being reclassified based on this data, as well as the potential for the variant to remain a VUS despite segregation studies. Patients/families should be encouraged to check in with their team every few years to learn if there are updates to the classification of any uncertain variants detected.
- In the absence of a genetic etiology, empiric risks can be used as a baseline and modified based on other factors such as family history of CHDs or known teratogenic or environmental exposures (Figure 3). However, it should be made clear to families that this is only an estimate based on our current understanding of empiric risks and the patient's and family's histories. A family's true risk may be higher or lower than the estimate and based on population data and other risk factors present.

**CHD family screening recommendations**

- At this time, screening echocardiograms for first-degree relatives of an individual with an isolated LVOTO (like bicuspid aortic valve, aortic stenosis, coarctation of the aorta, mitral atresia, and hypoplastic left heart) has been specifically recommended in the literature.
- For non-LVOTO class of CHDs, family screening recommendations may depend on whether or not there is familial disease as well as parental concerns about recurrence risk in future pregnancies.
- When a causative genetic variant is identified, family screening can generally follow cascade genetic testing for individuals who inherited the variant. For some CHD genes that can present with risk of arrhythmia/cardiomyopathy, a single echocardiogram to exclude cardiac malformations may not suffice; long-term surveillance may still be recommended for these other cardiac manifestations.

**CHD and a multidisciplinary approach**

- It is recommended that genetic counselors interested in working with the CHD population assess their institutional dynamics and provider/specialist availability. Each institution will have unique contexts and different referral patterns requiring flexible approaches; close collaboration between genetics providers and the CHD care team is essential for both pediatric and adult CHD programs.

(Continues)

TABLE 5 (Continued)

**Considerations for prenatal genetic counseling**

- It is important to assess for the following prenatal history: dosage and timing of any maternal medication exposure, maternal A1c levels, level of gestational or pre-gestational diabetes control in mothers with diabetes, and the timing and diagnosis (if known) of any maternal illness and/or exposures to teratogens. This information should also be collected if seeing a patient postnatally in order to assess for potential secondary causes of the CHD.
- Fetal echo should be considered pursuant to Table 4.
- A woman with a personal history of CHD should be referred to both perinatology and cardiology specialists with expertise in caring for such high-risk pregnancies.
- If a CHD is diagnosed prenatally, the fetus should be carefully evaluated for the presence of additional extracardiac anomalies.
- Amniocentesis with chromosomal microarray analysis should be offered when a fetus is diagnosed with a CHD; if amniocentesis is declined, screening for chromosome abnormalities through cell free DNA testing should be offered.
- If amniocentesis is declined, CMA on cord blood should be considered.
- Newborns with prenatally diagnosed CHDs would benefit from evaluation by a medical geneticist familiar with cardiovascular conditions or cardiologist with expertise in genetics.
- Families should be counseled that a diagnosis may change after delivery and appropriate follow-up with a pediatric cardiologist is recommended for postnatal evaluation

complex interplay between cardiac developmental genes. As a formal Practice Resource, this will undergo periodic re-review according to the NSGC Practice Guidelines policy. Continuously improving genomic diagnostic testing and knowledge of the genetic architecture of CHDs will likely lead to changes in genetic counseling strategies for the CHD population in the future.

**AUTHOR CONTRIBUTIONS**

HEI and BMH lead the development and coordination of the manuscript as well as contributed substantially to the overall writing and editing of this document. AFS, KMS, and KLZ developed and wrote all prenatal content. The remainder of the manuscript was divided up among and written by all other authors (LM, ELG, AP, ARS, MJT, ES, EMD, KKF, SFB). All authors contributed significantly to the editing and iterating of the manuscript.

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**COMPLIANCE WITH ETHICAL STANDARDS****Conflict of interest**

The author group composition is in compliance with the National Society of Genetic Counselors Practice Guidelines Committee Conflict of Interest Policy. This policy requires all proposed authors to disclose conflict of interest prior to selection and imposes thresholds for conflict of interest with the potential for direct, personal financial benefit, or other real or perceived conflict of interest, through the development of the document. All authors declare that they have no conflict of interest pertaining to this work during the development of this practice resource.

**Human studies and informed consent**

No human studies were carried out by the authors for this article.

**Animal studies**

No animal studies were carried out by the authors for this article.

**Data sharing and data accessibility**

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

**DISCLOSURES**

This practice resource (PR) is provided by the National Society of Genetic Counselors (NSGC) solely to serve as a helpful practice management resource and tool for genetic counselors and other healthcare providers. NSGC's PRs are not based on a systematic evidence review; instead, they are based on the recommendations and experience of the authors.

Each NSGC PR focuses on a clinical or practice-based issue, includes points for the genetic counselor or other healthcare providers to consider, and is based on review and analysis of current professional literature that the authors believe to be reliable. As such, the information provided and ideas discussed in NSGC's PRs; (1) reflect only the current scientific and clinical knowledge at the time of publication; (2) are only current as of their publication date; and (3) are subject to change without notice as advances emerge.

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#### SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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