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The incremental yield of prenatal exome sequencing over chromosome microarray for congenital heart abnormalities: A systematic review and meta-analysis

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Abstract

Objectives: To determine the incremental yield of prenatal exome sequencing (PES) over standard testing in fetuses with an isolated congenital heart abnormality (CHA), CHA associated with extra-cardiac malformations (ECMs) and CHA dependent upon anatomical subclassification.

Methods: A systematic review of the literature was performed using MEDLINE, EMBASE, Web of Science and grey literature January 2010-February 2023. Studies

were selected if they included greater than 20 cases of prenatally diagnosed CHA when standard testing (QF-PCR/chromosome microarray/karyotype) was negative. Pooled incremental yield was determined. PROSPERO CRD 42022364747.

Results: Overall, 21 studies, incorporating 1957 cases were included. The incremental yield of PES (causative pathogenic and likely pathogenic variants) over standard testing was 17.4% (95% CI, 13.5%–21.6%), 9.3% (95% CI, 6.6%–12.3%) and 35.9% (95% CI, 21.0%–52.3%) for all CHAs, isolated CHAs and CHAs associated with ECMs. The subgroup with the greatest yield was complex lesions/heterotaxy; 35.2% (95% CI 9.7%–65.3%). The most common syndrome was Kabuki syndrome (31/256, 12.1%) and most pathogenic variants occurred de novo and in autosomal dominant (monoallelic) disease causing genes (114/224, 50.9%).

Conclusion: The likelihood of a monogenic aetiology in fetuses with multi-system CHAs is high. Clinicians must consider the clinical utility of offering PES in selected isolated cardiac lesions.

Key points

What is already known?

- Congenital heart abnormalities are the most commonly occurring congenital anomalies and can be associated with chromosomal or monogenic conditions.
- With the increasing use of fetal sequencing, there is a need to define the association between monogenic conditions and specific cardiac abnormalities, particularly when isolated to facilitate triaging for prenatal sequencing.

What does this study add?

- The incremental yield of prenatal exome sequencing over and above chromosome microarray for congenital heart abnormalities is 9.3% in isolated lesions and 35.2% in the presence of complex lesions/heterotaxy.
- Clinicians should consider the clinical utility of offering prenatal exome sequencing in selected isolated cardiac lesions dependent on resources available.

1 | INTRODUCTION

Congenital heart abnormalities (CHAs) are the most common congenital anomalies worldwide, occurring in 1% of live term births, with a high incidence of perinatal morbidity and mortality.[1-4] Prenatal identification can optimise outcome, facilitating early referral to tertiary units for investigation and management. Congenital heart abnormalities have a complex and heterogenous aetiology including environmental and genetic elements, although the pathophysiology is yet to be fully elucidated.[5] Timely detection is key to facilitate the identification of the cardiac phenotype, associated extra-cardiac malformations (ECM), and enable discovery of a possible underlying genetic diagnosis as this can have implications regarding pregnancy course, neonatal management and surgical planning.[6] It is estimated that over half of fetuses remain without a genetic diagnosis underlying their CHA phenotype following standard prenatal genetic testing with G-banding karyotype and/or chromosome microarray (CMA) with associated incremental diagnostic yields from either technology around 20% and 8%, respectively.[5,7] The recent introduction of prenatal exome sequencing (PES) has facilitated a significant shortening of the diagnostic odyssey for fetuses and ultimately children with congenital anomaly; however, it is a resource with limitations such as cost and interpretational burden with the potential for variants of uncertain significance (VUS).[8] Hence, case selection is important, as demonstrated by the high diagnostic yield generated when an evidence-based phenotypic inclusion criteria is utilised.[9]

A previous systematic review and meta-analysis assessed the incremental yield of PES for CHA and included 636 cases from January 2000 to October 2019, demonstrating an incremental yield in any prenatally detected CHA of 13%.[10] Since this time there has been an exponential rise in the literature published in this area, hence, there is a need for updated summation of evidence. The objectives of this systematic review and meta-analysis were to; (i) determine the incremental yield of PES over and above standard testing (G-banding karyotype and/or CMA) in fetuses with a CHA both isolated and in conjunction with other ECMs and; (ii) further elucidate the yield based on different CHA sub-classifications.

2 | METHODS

2.1 | Data sources

A systematic review was conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance.[11] A systematic electronic search of MEDLINE, EMBASE, Web of Science and the grey literature was conducted from January 2010 on February 2023 inclusive. Keywords including 'exome sequencing', 'prenatal' and 'anomaly' were used. Alternative terms for 'exome sequencing' included 'genome sequencing'. Alternative terms for 'prenatal' included 'fetal', 'fetus' or 'antenatal'. Alternative terms for 'anomaly' included 'abnormality' and 'defect'. Bibliographies of all relevant papers were searched to identify further potentially appropriate studies. Studies that were not in the English language or were not based on human studies were excluded. The full search strategy can be acquired from the corresponding author upon request. The systematic review was registered prospectively on 11th October 2022, PROSPERO No. CRD 42022364747.

2.2 | Eligibility criteria for study selection and data extraction

Once all searches were completed, the relevant abstracts were uploaded to Covidence®.[12] All study abstracts, and subsequently when required full texts, were screened by two reviewers (K.R. and S. S.). Where there was disagreement, this was decided by the senior author (F.M.). Studies that were selected for inclusion were those that had; (a) twenty or more cases of CHA, (b) testing initiated due to prenatal phenotyping only, and (c) a negative CMA and/or G-banding karyotype result. Where testing was carried out postnatally, the cases were included if the decision to test was based on the prenatal phenotype. The relevant data extracted included ultrasound phenotype, exome sequencing approach, genomic variants, source of fetal DNA, turnaround time for testing, gestational age and pregnancy outcome. The genomic variants considered diagnostic were those that were graded 'likely pathogenic' or 'pathogenic' and causative to the fetal phenotype in line with the American College of Medical Genetics and Genomic (ACMG) guidance and the Association for Clinical Genomic Science (ACGS) in line with authors' local reporting practice.[13,14] Where phenotypic information was incomplete, the corresponding authors were contacted for further information. All cases of CHA from the review were then categorized as being isolated, associated with ECMs (multisystem) and broken down in line with the anatomical sub-classification which was agreed upon by three paediatric cardiologists with expertise in prenatal CHA (N.M., F.C. and A.S.)

2.3 | Quality assessment and data synthesis

The incremental yield of PES in chromosomally normal fetuses was calculated for each study and reported as the proportion of pathogenic and likely pathogenic variants detected by ES in fetuses with non-diagnostic CMA and/or G-banding karyotype with 95% confidence intervals (CI), and as a pooled value for (a) all CHA; (b) isolated CHA; (c) CHA associated with ECM and; (d) CHA sub-classified using anatomical classification.[10] Studies that did not include full information on whether the CHA was isolated or not were not included in the subgroup analyses. Incremental yield estimates were pooled through a meta-analysis of proportions using the Freeman-Tukey double-arcsine transformation and inverse-variance weighting. Results for each of these analyses were displayed in forest plots with the associated 95% CI. Statistical heterogeneity was assessed using the Higgins I^2 statistic. The risk of publication bias was graphically assessed by inspecting the asymmetry of a funnel plot of standard errors against the double-arcsine transformed proportions only for the main analysis of all CHAs, and formally tested using the Peters' test for meta-analyses of proportions.[15] Analyses were conducted using the package meta in the statistical package R.[16,17] *p*-values below 0.05 were considered statistically significant. Quality assessment was evaluated using the modified Standards for Reporting of Diagnostic Accuracy criteria.[18] The quality criteria deemed most important to optimize accuracy were: (1) whether trio analysis was performed; (2) whether ACMG/ACGS criteria were used for variant interpretation; and (3) whether there was Sanger validation of variants. Owing to the limited number of studies available, beyond the predefined inclusion criteria, the quality of the studies could not be incorporated into the analysis.

3 | RESULTS

3.1 | Study selection and characteristics

In total, 73 studies were identified as suitable for inclusion; however, 52 of these were excluded for reasons including less than 20 cases, overlap with data reported in other papers, testing based on single gene sequencing and postnatal phenotype (Figure 1). Corresponding authors for 18 of the original 52 papers were emailed for further information where this was incomplete and four of these responded with complete data for inclusion, of which one was excluded as it had less than 20 cases.[19–22] This left 21 studies included in the final meta-analysis (incorporating 1957 cases).[19–21,23–40] Of the 21 studies in this paper, 8 were used in the previous analysis by Mone, et al.[10] Table S1 outlines the study characteristics. Supplementary Figure S1 demonstrates the quality assessment.

3.2 | Overall outcomes

Whether the fetus had an isolated CHA, or CHA associated with ECMs, was specified in 1793 cases (91.6%). Where recorded, the primary source of fetal DNA was amniocytes; 47.3% (864/1828), followed by fetal blood (cordocentesis); 40.8% (745/1828). Where reported (20.5%; 402), the median turnaround time for obtaining an

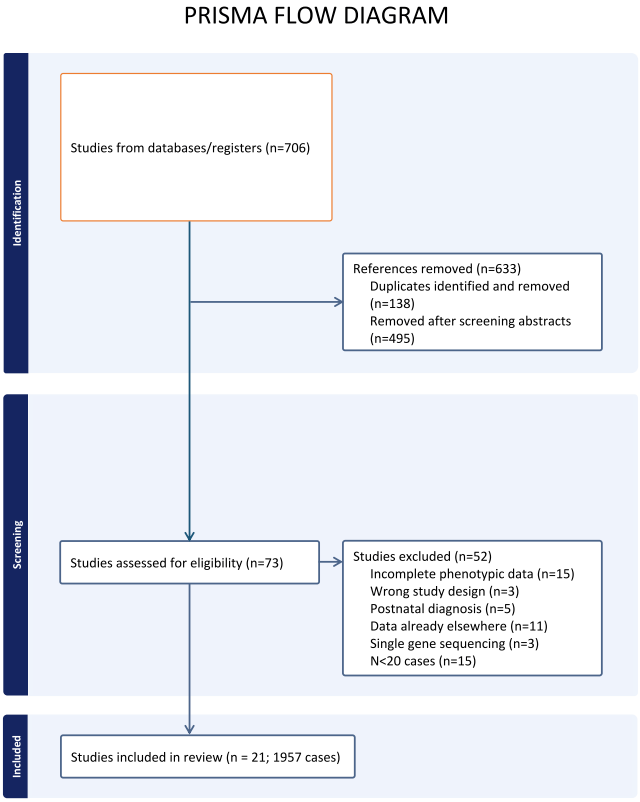

FIGURE 1 PRISMA flow diagram.

ES result was 42 days (range 14–271 days). The commonest pregnancy outcome for the entire cohort was termination of pregnancy; 52.8% (254/481).

3.3 | Incremental yield of pathogenic variants

The pooled incremental yields for all CHAs, isolated CHAs associated with ECMs were 17.4% (95% CI, 13.5%–21.6%), 9.3% (95% CI, 6.6%–12.3%) and 35.9% (95% CI, 21.0%–52.3%), respectively [Figure 2A–C], with significant asymmetry evident in the corresponding funnel plot (Peters' test p-value <0.001) [Figure S2].

In fetuses with non-isolated CHA associated with ECMs with a causative variant, the most common associated anomalies were gastrointestinal; 26.7% (35/131), central nervous system; 25.2% (33/131) and neck/skin anomalies (cystic hygroma and thickened nuchal); 22.1% (29/131).

Subgroup analyses of phenotypic categories of non-isolated cardiac lesions revealed the greatest yield in complex lesions/isomerism; 35.2% (95% CI, 9.7%–65.3%) and right-sided lesions; 23.2% (5.9%–45.9%) [Table 1 and Supplementary Figure S3–S9]. Further subgroup analysis of phenotypic categories in isolated cardiac lesions only [Table 2] overall demonstrated a lower yield for all categories other than conotruncal abnormalities and complex lesions/isomerism.

Where reported, causative pathogenic and likely pathogenic variants are demonstrated in Table S2. Where stated, the commonest genetic syndromes were Kabuki syndrome (31/256, 12.1%), Noonan syndrome (21/256, 8.2%), CHARGE (Coloboma, Heart defects, Atresia choanae, Retardation of growth, Genital abnormalities, ear abnormalities) syndrome (16/256, 6.3%), and Primary ciliary dyskinesia (14/256, 5.5%). Table 3 highlights the genes associated with these and the other most common syndromes alongside the presenting cardiac phenotype and the number of affected fetuses. The commonest nature of inheritance pattern was autosomal inheritance with de novo variants (114/224, 50.9%). In isolated cardiac lesions with a causative pathogenic variant, these syndromes were typically associated with multi-system anomalies in 32.8% (84/256).

Incidental findings and VUS were reported with incremental yields of 6.4% (95% CI, 3.1%–10.6%) and 15.5% (95% CI, 6.8%–26.5%) respectively [Tables S3 and S4].

4 | DISCUSSION

This meta-analysis has identified an apparent incremental yield for PES over standard prenatal genetic testing of 9.3%, with the highest yields identified in the presence of ECAs and in complex cardiac lesions/heterotaxy at 35.9% and 35.2%, respectively. The most common clinical syndromes identified, based on the variant genes detected, were Kabuki and Noonan syndrome. Over half of the causative pathogenic variants occurred de novo and in autosomal dominant (monoallelic) disease genes.

This is an extension to a previous meta-analysis conducted by Mone, et al., with over twice the number of cases included and considering a different anatomical classification, demonstrating a similar yield in isolated CHAs and a more significant yield for complex lesions/heterotaxy (35.2% vs. 23%).[10] The latter may be secondary to the greater number of cases included as well as potential selection bias for performing and reporting PES in such instances, where obtaining a genetic diagnosis may have a more significant clinical impact regarding management in pregnancy and postnatal surgical planning.[7] Analysis of the fetal heterotaxy cases in isolation and the complex cases in isolation, was not feasible due to too small numbers in each group. Rates of VUS were lower than previously reported, likely reflective of; (i) the fact that many more recent studies and clinical pathways do not routinely report prenatal VUS and; (ii) the predicted reduction of VUS reported with time as variant classification has become more refined and more population data and case reports have become available. This phenomenon is akin to what has occurred with microarray technology.[42]

Similar to our previous study, we echo the need for a robust prenatal CHA classification system which may or may not align with genetic diagnoses which will likely be based upon embryological origin. Where an isolated CHA and associated phenotype was described (n = 970) this did not fit into any of the four anatomical categories (i.e., septal, left-sided obstructive, right-sided conotruncal and complex) in 52 cases (5.4%) for example, cardiomyopathy and persistent left superior vena cava and in 70 cases (7.2%) fitted into more than one anatomical subcategory, highlighting the complexity and challenge with categorising cardiac lesions. Given a relatively

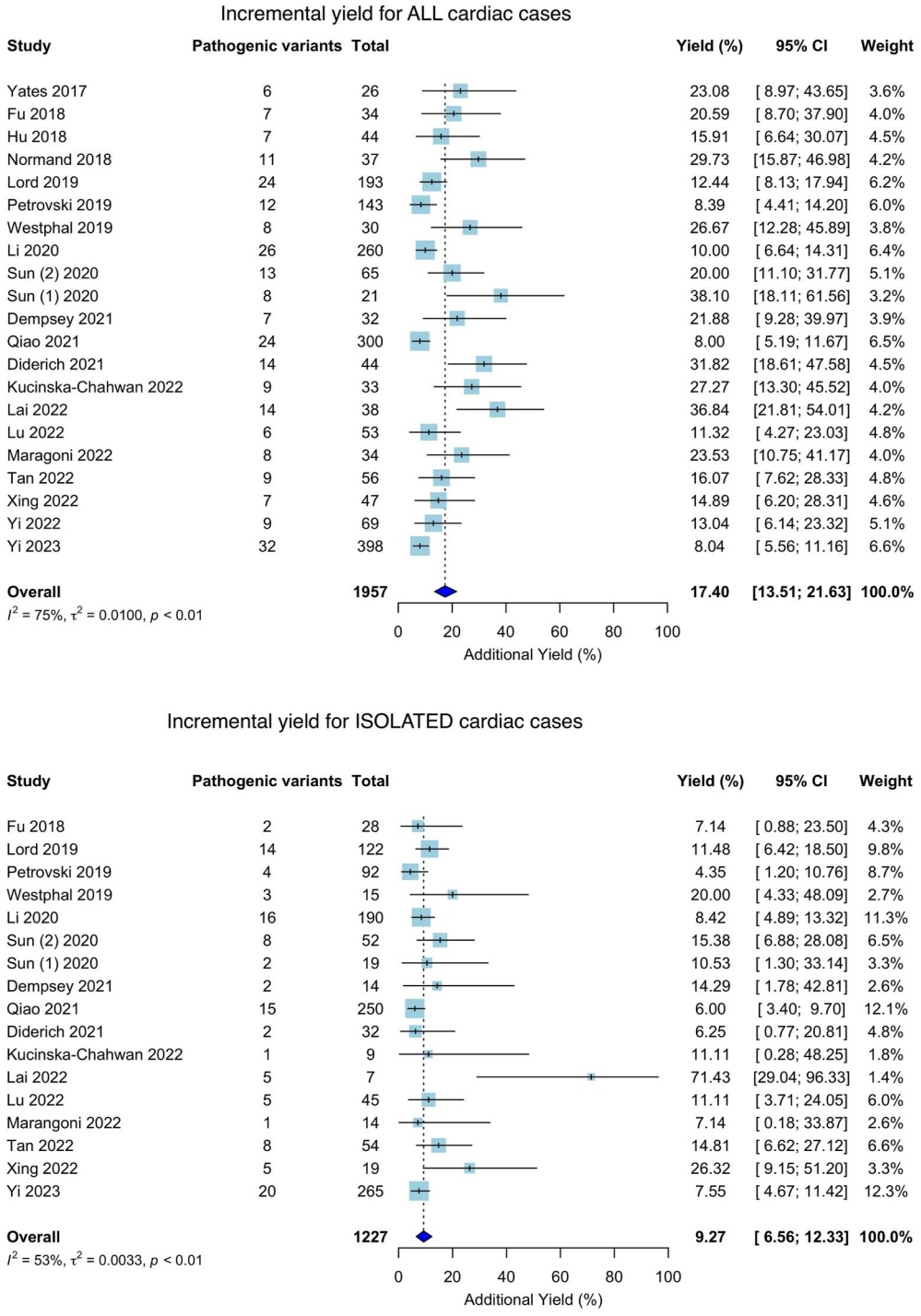

FIGURE 2 (A) Forest plot depicting the incremental yield of prenatal exome sequencing over standard testing in fetuses with prenatally detected congenital cardiac anomalies. Only the first author of each study is given. (B) Forest plot depicting the incremental yield of prenatal exome sequencing over standard testing in fetuses with prenatally detected isolated congenital cardiac anomalies. Only the first author of each study is given. (C) Forest plot depicting the incremental yield of prenatal exome sequencing over standard testing in fetuses with prenatally detected congenital cardiac anomalies associated with extra-cardiac anomalies. Only the first author of each study is given.

modest yield with PES compared to other structural anomalies for example, 68% in suspected skeletal dysplasia,[43] one could argue that isolated CHAs are not primarily due to single gene mutations, and propose that the association with post-translational modifications and epigenetic change needs to be elucidated further with a particular focus on transcriptomics. Embryological development of the

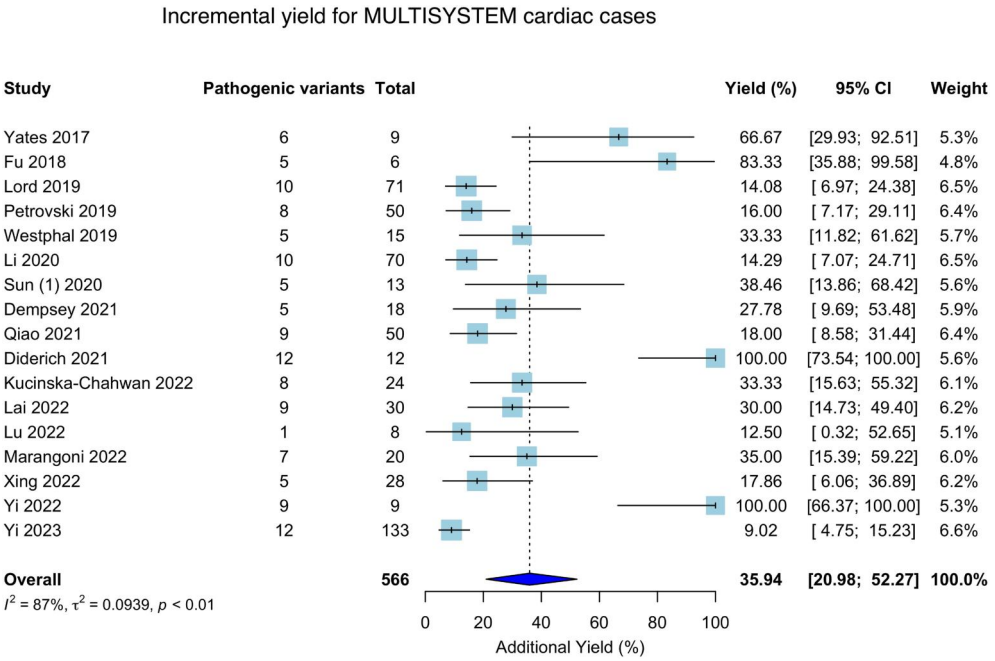

FIGURE 2 (Continued)

heart starts from the end of the second week of human development and involves an interplay of cell differentiation, migration, proliferation, folding, looping, compaction, and ultimate development of a four-chamber organ with outflow tracts and a conduction system. Regulation of development is highly complex, involving multiple genes controlling interacting molecular signalling pathways which can be influenced by a range of transcription factors (e.g., MESP1, GATA4/6, TBX5, SRF, ISL1) and micro-RNAs which can reappear at several steps in the embryological process. One example is that of the *NOTCH* signalling pathway which is important throughout embryological development and within which mutations may present with a range of cardiac phenotypes as evident through animal knock-out studies.[44,45] Further to this, the genes involved in embryological cardiac development do not fully explain the causative list of pathogenic variants from our study for example, the *KMT2D* gene where loss-of-function variants are associated with Kabuki syndrome, the commonest identified syndrome within our cohort. *KMT2D* encodes an enzyme called lysine-specific methyltransferase 2D which is a histone marker associated with DNA methylation and chromatin remodelling, core mechanisms in epigenetic modification,[46] supporting the theory that origins are beyond that of the genetic code.

From a clinical perspective, given the associated high mortality associated with complex CHA, obtaining a genetic diagnosis may be more important than in many other types of structural anomalies as it may influence surgical planning and prognostication.[47] This is especially true of those with complex CHA associated with ECAs as this may affect the suitability of patients for surgical procedures and the overall outcomes following intervention. To further the complexity, detection in the first instance and accurate prenatal classification of CHA remain limited internationally, although improved ultrasound technology has improved the ability to make more accurate diagnoses as early as the first trimester and specific fetal Human Phenotype Ontology terms are being developed.[48,49] A third of the syndromes identified in this study were typically those with a multi-system phenotype presenting as an isolated CHA in utero. While it is known that the postnatal examination of fetuses with a prenatally suspected 'isolated' CHA may reveal undiagnosed extra-cardiac anomalies in up to a quarter of cases prenatally, given that some of these may represent subtle dysmorphology or certain anomalies only evident at clinical or post-mortem examination, this highlights the need for deeper phenotyping and reconsideration of the description of syndromes prenatally and postnatally which has only come to light with the provision of next-generation sequencing.[50-52]

Postnatally CHAs have a low absolute sibling recurrence risk of around 2.5%, which is suggestive of the predominance of de novo variants (as seen in our own study), incomplete penetrance and somatic mosaicism.[53] This is important as given advances in the management of CHAs, many fetuses will survive into reproductive age where mitigation of recurrence in off-spring may be an option. Interestingly, abnormal dysmorphic facial features are almost always present neonatally where a single gene disorder is identified in a CHA, again highlighting the limitations of prenatal phenotyping.[54] Few post-natal studies have assessed the use of NGS in non-syndromic (i.e., apparently isolated) CHAs, although within a high-risk cohort with familial recurrence where a cardiac gene panel was applied, the yield ranged from 31% to 46% with variants in *NOTCH1* and *TBX5* most prevalent.[55]

The strength of this systematic review is that to our knowledge, it is the largest of its kind and the first to be classified by

TABLE 1 Incremental yield, heterogeneity (I^2) and commonest syndromes and genes for each subgroup for any congenital heart abnormality in both isolated and multisystem defects. NB: genotypes were not stated for all cases of causative class IV or V variants.[41]

Category	*N* (%) cases with causative class IV or V variants	Incremental yield (95% CI)	I^2 (%)	Most common genes *n*(%)	Corresponding syndromes
All cardiac (*n* = 1957)	261	17.4% (13.5%–21.6%)	75	*KMT2D* (*n* = 31, 12.1%)	Kabuki syndrome
Isolated (*n* = 1227)	113	9.3% (6.6%–12.3%)	53	*KMT2D* (*n* = 14, 12.4%)	Kabuki syndrome
Multisystem (*n* = 566)	126	35.9% (21.0%–52.3%)	87	*KMT2D* (*n* = 13, 10.3%)	Kabuki syndrome
Septal: *ASD, VSD, AVSD (n = 350)*	63	19.6% (10.9%–29.8%)	65	*PTPN11* (*n* = 5, 9.6%)	Noonan syndrome
Subgroup of septal: *VSD (n = 249)*	49	19.3% (11.1%–28.8%)	57	*PTPN11* (*n* = 3, 6.1%), *NIPBL* (*n* = 3, 6.1%), *CHD7* (*n* = 3, 6.1%)	Noonan syndrome Cornelia de Lange syndrome CHARGE syndrome
Subgroup of septal: *AVSD (n = 78)*	13	21.8% (5.8%–42.6%)	68	*ANKRD11* (*n* = 2, 18.2%), *DNAH11* (*n* = 2, 18.2%), *PTPN11* (*n* = 2, 18.2%)	KBG syndrome Primary Ciliary Dyskinesia Noonan syndrome
Left sided obstructive: *mitral stenosis/atresia, aortic stenosis/atresia, hypoplastic/borderline left ventricle, coarctation of aorta n = (263)*	35	11.6% (6.3%–17.9%)	46	*KMT2D* (*n* = 14, 40%),	Kabuki syndrome
Right sided: *Tricuspid stenosis/atresia, pulmonary stenosis/atresia, hypoplastic/borderline right ventricle (n = 172)*	27	23.2% (5.9%–45.9%)	84	*NONO* (*n* = 5, 18.5%),	Intellectual development disorder, X-linked syndromic 34
Conotruncal: *Tetralogy of Fallot, common arterial trunk, transposition of the great arteries, double outlet right ventricle, interrupted aortic arch (n = 427)*	39	8.0% (4.4%–12.4%)	12	*CHD7* (*n* = 4, 10.3%),	CHARGE syndrome
Complex/Isomerism: *Left/Right atrial isomerism, double inlet left ventricle, single ventricle/complex congenital heart disease (n = 131)*	28	35.2% (19.7%–65.3%)	85	*KMT2D* (*n* = 3, 10.7%)	Kabuki syndrome

Abbreviations: ASD, atrial septal defect; AVSD, atrioventricular septal defect; VSD, ventricular septal defect.

TABLE 2 Incremental yield, heterogeneity (I^2) and commonest syndromes and genes for isolated cardiac heart abnormalities only. NB: genotypes were not stated for all cases of causative class IV or V variants.[41]

Category (isolated cardiac subgroups)	*N* (%) cases with causative class IV or V variants	Incremental yield (95% CI)	I^2 (%)	Most common genes *n*(%)	Corresponding syndromes
Septal: (*n* = 180) *ASD, VSD, AVSD and combinations*	21	10.4% (3.9%–18.9%)	43	*PTPN11, SOS1* (*n* = 4; 19%)	Noonan syndrome
Subgroup of septal: *VSD (n = 92)*	10	8.4% (0.9%–20.1%)	0	*PTPN11, SOS1* (*n* = 3; 30%)	Noonan syndrome
Subgroup of septal: *AVSD (n = 71)*	6	7.3% (0.5%–18.6%)	44	No dominant gene	No dominant syndrome
Left sided obstructive: *mitral stenosis/atresia, aortic stenosis/atresia, hypoplastic/borderline left ventricle, coarctation of aorta (n = 215)*	25	9.2% (3.0%–17.3%)	56	*KMT2D* (*n* = 8; 32%) *NOTCH1* (*n* = 8; 32%)	Kabuki syndrome 1 Adams Oliver syndrome 5
Right sided: (*n* = 143) *Tricuspid stenosis/atresia, pulmonary stenosis/atresia, hypoplastic/borderline right ventricle*	15	12.0% (1.0%–29.1%)	77	*NONO* (*n* = 5, 33%)	Intellectual development disorder, X-linked syndromic 34
Conotruncal: *Tetralogy of Fallot, common arterial trunk, transposition of the great arteries, double outlet right ventricle, interrupted aortic arch (n = 243)*	25	8.2% (3.2%–14.7%)	47	*CCDC114, DNAH11, DHAH5* (*n* = 4, 16%)	Primary ciliary dyskinesia
Complex/Isomerism: *Left/Right atrial isomerism, double inlet left ventricle, single ventricle/complex congenital heart disease (n = 91)*	16	34.2% (2.3%–76.1%)	87	*CCDC114, CCDC103, CCDC40, DNAH11* (*n* = 6, 37.5%)	Primary ciliary dyskinesia

Abbreviations: ASD, atrial septal defect; AVSD, atrioventricular septal defect; VSD, ventricular septal defect.

TABLE 3 Most common syndromes, associated genes and the number of fetuses diagnosed.

Syndrome	Gene	Number diagnosed	Commonest cardiac phenotype
Kabuki	*KMT2D, KDM6A*	31	Single ventricle appearance/VSD/Complex
Noonan	*PTPN11, RIT1, LZTR1, SOS1, KRAS, RAF1*	21	VSD/valvular anomaly
CHARGE	*CHD7*	16	Complex/valvular anomaly
Primary ciliary dyskinesia	*CCDC103, DNAH5, CCDC114, DNAH11, ARMC4, CCDC40*	14	Conotruncal/heterotaxy/isomerism
Adams-Oliver	*NOTCH1*	10	Left ventricular outflow tract obstruction/aortic anomaly
Tuberous sclerosis	*TSC1, TSC2*	9	Rhabdomyoma
X-linked intellectual disability disorder	*NONO*	6	VSD/Ebstein's anomaly/abnormal aortic arch

Abbreviation: VSD, ventricular septal defect.

paediatric cardiologists. We had international collaboration from associated authors to ensure full data sets when possible. A robust methodology was applied and the quality of the included studies was also checked based upon the previously mentioned standards.[11] The main limitation is the high heterogeneity, which is evident and which we attempted to minimise by only including studies with case numbers greater than 20 and through subgroup analyses. Additionally, the cohort represents selection bias given the uptake of invasive testing in CHAs, particularly in isolated CHAs is low and that many affected fetuses will be terminated before genetic testing is performed.[7] Whilst we know that prenatal phenotyping is more limited than what can be done postnatally, a significant limitation of this meta-analysis is that we do not know when cases were scanned, the standard of scanning delivered, if CHAs were confirmed postnatally or if findings such as increased nuchal translucency were reported. These factors may inflate the rates of monogenic conditions in "isolated" lesions as we would not expect such high rates in postnatally ascertained cases.[56] A further limitation is that there were inadequate numbers in either complex or heterotaxy sub-groups to determine the incremental yield in isolation for either group.

5 | CONCLUSION

This meta-analysis has identified an apparent incremental yield for PES over standard prenatal genetic testing of 17.4% in cases of CHA, with highest yields identified in the presence of extra-cardiac anomalies and complex cardiac lesions/heterotaxy. While the overall yield in isolated lesions may be lower compared to other systems, it is still an important yield likely to contribute to clinical impact and clinicians must consider the clinical utility of offering prenatal exome sequencing in isolated cardiac lesions dependent on resources available and the potential outcomes.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The completed dataset is available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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