Cardiology in the Young

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The Kids Heart BioBank: supporting 20 years of patient care and research into CHD

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Review

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Abstract

Introduction: The cause of most CHD is unknown and considered complex, implicating genetic and environmental factors in disease causation. The Kids Heart BioBank was established in 2003 to accelerate genetic investigations into CHD. *Methods:* Recruitment includes patients undergoing interventions for CHD at The Children's Hospital at Westmead. Informed consent is obtained from parents/guardians, and blood is collected at the time of cardiac intervention from which DNA is extracted and stored. Associated detailed clinical information and a family history are stored in the purpose-designed database. *Results:* To date, the Kids Heart BioBank contains biospecimens and associated clinical information from over 4,900 patients with CHD and their families. Two-thirds (64.1%) of probands have been included in research studies with 28.9% of participants who underwent genomic sequencing receiving a molecular diagnosis with direct clinical utility. The value of this resource to patients and families is highlighted by the high consent rate (94.6%) and the low withdrawal of consent rate (0.4%). The Kids Heart BioBank has supported many large national and international collaborations and contributed significantly to CHD research. *Conclusions:* The Kids Heart BioBank is an invaluable resource and, together with other similar resources, the resulting research has paved the way for clinical genetic testing options for CHD patients, previously not possible. With research in the field moving away from diagnosing monogenic disease, the Kids Heart BioBank is ideally placed to support the next chapter of research efforts into complex disease mechanisms, requiring large patient cohorts with detailed phenotypic information.

Introduction

CHD encompasses structural defects of the heart and great vessels that are present at birth. CHD is the most prevalent birth defect globally[1] and is estimated to affect 6–8 per 1000 live births.[2] It is associated with significant mortality and morbidity, with up to a third of babies born requiring invasive treatment and lifelong care.[3] The cause of most CHD is unknown with most presenting cases considered multifactorial, implicating multiple (epi)genetic and environmental factors in disease causation.[4,5] Significant advances in genomics over the last decade have accelerated our understanding of genetic causes with over 140 genes associated with human CHD to date.[6,7] Indeed, the diagnostic rate for patients with familial forms of disease and those with extracardiac anomalies in addition to their heart defects is ~30%[5,8], which is in line with diagnostic yields for other rare monogenic diseases. Whereas non-syndromic monogenic forms of CHD displaying clear Mendelian inheritance do occur, they account for a small portion of presenting CHD cases (~2–5%).[8,9]

Biobanks are an integral part of medical research, with a primary purpose to facilitate research and improve our understanding of the genetic and molecular mechanisms underlying disease. A well-managed and maintained biobank is an invaluable resource, informing and enabling research discoveries through access to rich genotype–phenotype data via biospecimens and associated clinical information. Conversely, research also informs biobanking and demands continuous improvements in sample or data collection/access to maintain its usefulness and value. As such, there exists a reciprocal relationship between biobanking and research, one that is continuously evolving and adapting to the ever-changing landscape of advancing knowledge.

Several international biobanks incorporating biospecimens and clinical information from patients with CHD have been established. These include the Kids Heart BioBank in Australia, the Heart Centre Biobank in Canada, the Paediatric Cardiac Genomics Consortium in the

United States[10], and the CHD-Biobank in Germany[11]; individually, and in some cases, collectively, addressing important research questions in CHD. These biobanks have greatly contributed to understanding the causes of CHD and have revealed its genetic complexity.[12–17]

Genetic research in CHD is refocusing away from diagnosing seemingly monogenic forms of disease as these diagnostic processes and services are increasingly embedded within clinical workflows in line with current recommendations.[8] However, there is still a significant need for research to understand the complex origins and pathophysiological mechanisms underlying patients with isolated and sporadic CHD, especially as these patients represent most presenting cases. In this review, we describe the Kids Heart BioBank resource and highlight the important contributions biobanks have made, and continue to make, to the field and patient care.

Kids Heart BioBank

The Kids Heart BioBank was established in 2003 and operates within a high functioning cardiac service in a paediatric tertiary hospital to facilitate efficient participant recruitment, biospecimen collection, medical data collection, processing, and storage. It is fully certified by the New South Wales Heath Pathology Statewide Biobank Program and adheres to national biobanking standards.

The primary purpose of the Kids Heart BioBank is to understand the genetic and biological mechanisms underlying CHD to ultimately inform future clinical management and treatment in this patient group. Any patient with diagnosed CHD can participate. DNA is collected from all participants and stored with associated clinical data. To date, the Kids Heart BioBank has over 4,900 participants, mostly singleton probands; however, over 300 trios (affected child and both biological parents), ~200 additional family members (siblings, grandparents, etc), and over 400 healthy and/or study control subjects are included (Figure 1). The Kids Heart BioBank also houses several fibroblast and induced pluripotent stem cell lines and snap-frozen tissue samples.

An extensive range of CHD are represented in the Kids Heart BioBank with atrial and ventricular septal defects and tetralogy of Fallot, forming the majority. Other CHD types also highly represented in the Kids Heart BioBank are common AV canal, d-transposition of the great arteries, and coarctation of the aorta (Table 1). The Kids Heart BioBank can recontact participants to facilitate additional biospecimens and/or information collection, including surveys and updated clinical information. This is an important distinction between the Kids Heart BioBank and some other established biobanks in the field.

Kids Heart BioBank processes

Recruitment, biospecimen, and data collection

Routine recruitment includes patients undergoing interventions at The Children's Hospital at Westmead (Sydney, Australia); however, any patient with diagnosed CHD may be recruited. Neonates weighing less than 2 kgs and patients with a genetic syndrome known to be associated with CHD are excluded. Additionally, where probands have a family history of CHD or where they have a significant extracardiac abnormality, biological parents and additional family members may be recruited.

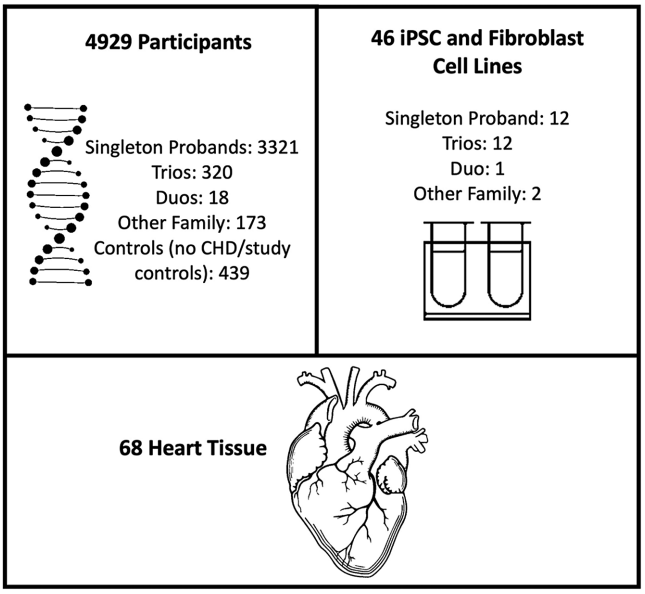

Figure 1. Overview of Kids Heart BioBank biospecimen types and numbers. Participants comprise probands, parents, other family members, and controls. Number of available trios and duos are indicated in the biospecimen types. Heart tissue samples comprise tissue routinely discarded during cardiac surgery, including resected right ventricle in patients with tetralogy of Fallot and resected infundibulum in patients with hypoplastic left heart syndrome. IPSC = induced pluripotent stem cell.

Approximately 70% of participant recruitment comes from outpatient appointments prior to cardiac surgery and ~ 30% of participants are recruited as inpatients from the neonatal/paediatric ICUs or the cardiac ward (Supplementary Figure S1). During the consenting process, all participants agree to genomic testing and indefinite storage of their re-identifiable biospecimen and data in heart-related research. Further, they can indicate their preferences regarding: (1) result dissemination, including incidental findings; (2) data sharing and storage, including data linkage; and (3) involvement in future ethically approved heart-related research.

During recruitment, a detailed family history is obtained, including self-reported medical/health history and ethnicity (Table 1). Each participant's CHD diagnosis is described using the European Paediatric Cardiac Code[18], and medical records are reviewed to obtain additional health/medical data. All associated demographic, clinical, and family data as well as data relating to sample collection, processing, storage, and usage is contained within a purpose-built database. The database is a control centre for organising the inventory and keeping track of clinical and research genetic testing for each participant.

Staffing

Staffing of the Kids Heart BioBank requires a full-time research assistant, with oversight from a clinical lead, to identify and recruit potential participants, provide informed consent, facilitate sample collection and processing, and record associated medical/health data. This role also includes involvement in specific research projects, laboratory activities, and regular database auditing and maintenance. Kids Heart BioBank staffing also includes a genetic counsellor who provides counselling support and facilitates appropriate referrals to clinical services as required. Importantly, and in-line with ethics approval, none of the

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Table 1. Kids Heart BioBank participant clinical and demographic data

Clinical and demographic data	Number of probands (%)
Family history of CHD – ≥1 affected first-degree relative	272 (7.4)
Ethnicity	
Aboriginal	32 (0.9)
Arabic	270 (7.4)
Asian	264 (7.2)
Caucasian	2339 (63.9)
India/Pakistan/Bangladesh/Sri Lanka	187 (5.1)
Melanesian	85 (2.3)
Polynesian	60 (1.7)
Other*	412 (11.3)
Not recorded or unknown by family	9 (0.2)
Genetic syndromes† (since 2006)	483 (13.2)
Genetic testing – clinical or research (since 2020)	742 (20.3)
ART/IVF pregnancy (since 2016)	104 (2.8)
Consanguinity (since 2006)	92 (2.5)
Medications in pregnancy (since 2006)	1197 (32.7)
Pregnancy complications & maternal disease (since 2006)	773 (21.1)
Extracardiac abnormality (since 2016)	867 (23.7)
Neurodevelopmental outcomes/assessments (since 2017)	138 (3.8)
CHD subtype††	
L-TGA	39 (1.1)
Complex functional single ventricle	159 (4.3)
DILV	11 (0.3)
DORV-transposition type	40 (1.1)
d-TGA	229 (6.2)
Heterotaxy	42 (1.1)
HLH	104 (2.8)
IAA	38 (1.0)
Pulmonary atresia – IVS	61 (1.7)
TAPVR	34 (0.9)
TA	58 (1.6)
Tricuspid atresia	40 (1.1)
TOF	404 (10.9)
ALCAPA	5 (0.1)
AP Window	9 (0.2)
CoA	230 (6.2)
Common AV canal	278 (7.5)
Cor triatriatum	1 (<0.1)
Coronary artery abnormality	4 (0.1)
DORV-Fallot type	36 (1.0)
Double chambered right ventricle	22 (0.6)
Ebstein anomaly	19 (0.5)
Hemitruncus	4 (0.1)
LVOTO (isolated)	164 (4.4)
Mitral valve abnormality	32 (0.9)
PAPVR	85 (2.3)
Pulmonary atresia + VSD	88 (2.4)
RVOTO (isolated)	101 (2.7)
Tricuspid valve abnormalities	3 (0.1)
ASD	399 (10.8)
ASD + minor abnormalities	100 (2.7)
BAV (isolated)	3 (0.1)
DORV	34 (0.9)
Other (e.g., isolated SVC abnormality)	2 (0.1)
PDA (isolated)	117 (3.2)
PFO (isolated)	5 (0.1)
Vascular ring	42 (1.1)
VSD	248 (6.7)
VSD + minor abnormalities	403 (10.9)

Note: Data are collected at the time of recruitment often in infancy/early childhood when certain medical/health issues may not have manifested/developed yet.
ALCAPA = anomalous left coronary artery from the pulmonary artery; AP Window = Aortopulmonary window; ART = assisted reprodcutive technology; ASD = atrial septal defect; AV = atrioventricular; BAV = bicuspid aortic valve; CoA = coarctation of the aorta; d-TGA = d-transposition of the great arteries; DILV = double-inlet left ventricle; DORV = double-outlet right ventricle; HLH = hypoplastic left heart; IAA = interrupted aortic arch; IVF = in vitro fertilisation; IVS = intact ventricular septum; KHB = Kids Heart BioBank; L-TGA = congenitally corrected transposition of the great arteries; LVOTO = left ventricular outflow tract obstruction; PAPVR = partial anomalous pulmonary venous return; PDA = patent ductus arteriosus; PFO = patent foramen ovale; RV = right ventricle; RVOTO = right ventricular outflow tract obstruction; SVC = superior vena cava; TA = truncus arteriosus; TAPVR = total anomalous pulmonary venous return; TOF = tetralogy of Fallot; VSD = ventricular septal defect.
*Other ancestry refers to participants who have parents with multi-ethnic backgrounds, or whose ethnicity doesn't fit into the pre-determined categories.
†Genetic syndromes diagnosed subsequent to participant recruitment.
††CHD subtype is classified according to the primary lesion. The Complex Functional Single Ventricle group includes participants with single-ventricle physiology and may include multiple CHD subtypes.

Kids Heart BioBank recruitment staff are involved in the clinical care of the patient.

Ethics and governance

All Kids Heart BioBank processes and activities are approved by the Sydney Children's Hospital Network, Human Research Ethics Committee, and Research Governance. Ethics renewal is required every 5 years.

The Kids Heart BioBank is administered by the Governance Committee which consists of the Head of the Biobank and committee members with expertise in cardiology, developmental biology, genetics/genomics, scientific methods, genetic counselling, and ethical conduct. The Governance Committee is responsible for the scientific and ethical decision-making of the Kids Heart BioBank with recourse to the Human Research Ethics Committee and Research Governance as required.

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Obtaining paediatric consent

The age at which a person becomes an adult in Australia is 18 years. In line with this, Kids Heart BioBank consent is sought from parents/guardians for most participants at our paediatric institute. However, from the age of 14 years, children/young adults may consent to their own participation with parental approval using age-appropriate participant information sheets and co-signing the consent form.

In line with biobanking regulations, the Kids Heart BioBank is required to seek approval for continued involvement in research when the participant reaches adulthood using an "opt out" approach.[19] To date, >1037 participants have been reconsented to the Kids Heart BioBank as adults. Notably, only 0.4% of reconsented participants have withdrawn their consent to date, highlighting the ongoing value of this resource to the adult CHD population.

Privacy and data security

Privacy is paramount, and Kids Heart BioBank protocol and processes have been established to minimise breaches in privacy, including the de-identification of biospecimens and all laboratory-based data. Further, database access by Kids Heart BioBank clinical and laboratory staff is separated, such that Kids Heart BioBank laboratory staff are unable to access any identifying information, including clinical and demographic data, and identify participants using their database generated code only. Kids Heart BioBank clinical staff can access all identifying data. All identifying data remain in the Kids Heart BioBank, and only de-identified biospecimens and/or clinical data are released to collaborators or external researchers. No biospecimens, clinical, or demographic data are released to third parties including the New South Wales or Australian Federal Police, except when enforced by court order.

Access to Kids Heart BioBank biospecimens

The Kids Heart BioBank considers applications for access to biospecimens and/or associated clinical data for both internal and external research studies and collaborations. Access is via the Kids Heart BioBank Access Policy, and all applications are considered by the Kids Heart BioBank Governance Committee. Access to Kids Heart BioBank biospecimens requires ethics approvals from the host institution where the research will be conducted. The application is reviewed by the Kids Heart BioBank Governance Committee where factors such as whether the proposed research aligns with the strategic and scientific aims of the Kids Heart BioBank and the impactful use of a limited resource are considered. Upon approval by the Kids Heart BioBank Governance Committee, the application is submitted to local ethics for final review and approval. Following local ethics approval, a material transfer agreement and other legal documents may be required and executed. For most access requests, the Head of the Kids Heart BioBank is considered a collaborator, in recognition of the foundational and ongoing work in maintaining the resource, oversight of the resource, and sample procurement.

Biobank funding and recruitment cost

The Kids Heart BioBank was established and initially supported through competitive grant funding from the National Heart Foundation of Australia. Ongoing biobanking costs, such as staffing and biospecimen management (including collection, processing, storage, and sample distribution), are supported by soft funding via donations, including from patients and their families. Biobanking processes that require funding are detailed in Supplementary Table S1. The total cost of recruiting, collecting, and storing a biospecimen is approximately AUD103 per participant (Supplementary Table S1), with the largest cost attributed to the salaried time taken to facilitate recruitment, participant data collation, and data entry. Additional costs include ongoing biospecimen storage, database maintenance, and data updates.

Kids Heart BioBank participation and consent rate

On average, the Kids Heart BioBank approaches ~75% of eligible research participants presenting to The Children's Hospital at Westmead for cardiac interventions as inpatient and outpatients. Reasons why eligible participants are not approached include (1) urgent/emergency surgery occurring outside of working hours (including on weekends) or with limited notification and no time to consent and (2) language or comprehension barriers. Eligible participants who are missed are often approached at subsequent cardiac procedures. Of those approached 94.1% of inpatients and 95.1% of outpatients consent to the Kids Heart BioBank. This consent rate is significantly higher than what is reported[20–22] and may be explained by the close alignment of biobanking processes with clinical care, including biospecimen collection at the time of intervention. It also likely reflects a strong desire and need by parents of children with CHD to understand the cause of their child's heart condition, which is well described.[5,23] Altruism is another factor, with many parents commenting that this research will hopefully benefit children with CHD in the future.[21]

Of the ~ 5% of eligible participants who do not consent to Kids Heart BioBank participation, reasons for non-consent include: (1) feeling overwhelmed; (2) needing more time to consider; (3) needing to consult with a partner not present during consent; and 4) concerns regarding blood collection at time of surgery (Supplementary Table S2) in line with previous reports.[22] The reasons for declining are similar between inpatients and outpatients (Supplementary Table S2); however, inpatients are more likely to decline due to "feeling overwhelmed" by the often-urgent cardiac care required. Interestingly, since 2022, there has been an increase in non-consent relating to concerns regarding blood loss during surgery; the reasons for this are not understood although under review.

Return of research results

There is little consensus as to what research results researchers are obliged to return to participants and best practice to facilitate this process.[24] In Australia, there is currently no legal requirement for researchers to inform research participants of clinically actionable results.[25] However, The National Statement on Ethical Conduct in Human Research[26] requires researchers to have an ethically defensible plan to manage the disclosure or non-disclosure of genetic research results, including what results are returned to participants. Additionally, researchers are obligated to inform research participants that research results must be clinically confirmed at a nationally accredited clinical testing laboratory, prior to clinical use.

Most Kids Heart BioBank participants (99.4%) indicate that they would like to be informed of research results, compared with 54–88% of biobank participants reported in the literature.[24] The strong preference in our cohort may be explained by access to genetic counselling and/or the genetics clinic, but it may also

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highlight parents' desires for access to genetic testing in the absence of clinically available options, until recently.

During the Kids Heart BioBank consenting process, participants can indicate their preferences relating to the return of research results for clinically actionable variants related to CHD and incidental findings. Most Kids Heart BioBank participants (98.4%) want to be informed of clinically actionable incidental findings, described as incidental findings associated with preventable or treatable health conditions. All clinically actionable variants are reviewed by the Kids Heart BioBank Governance Committee with respect to clinical utility and relayed to research participants in consultation with their treating clinician. Research findings that are uninformative, of unknown significance and/or non-actionable incidental findings (i.e., are not preventable or treatable) are not returned to research participants.

In line with significant advances in the field in recent years, a dedicated CHD Genetics Clinic has been established at The Children's Hospital at Westmead. The Kids Heart BioBank regularly refers patients with significant research findings to this service for clinical validation and subsequent clinical management (Supplementary Figure S1). Immediate and extended family members are also referred to this service where appropriate. Similarly, the CHD Genetics Clinic will refer patients with uninformative clinical genetic testing to the Kids Heart BioBank for inclusion in future research.

COVID-19 pandemic and impact on recruitment

During the COVID-19 pandemic of 2020–2022, biobanks worldwide were shut down or repurposed for COVID-19 research.[27] Similarly, the COVID-19 pandemic had a significant effect on Kids Heart BioBank recruitment and processes. The number of eligible research participants approached decreased from ~ 75 to 40% in 2020 following cessation of elective cardiac surgery. In 2021, the number of eligible participants approached decreased further to 25% due to a 107-day lockdown in New South Wales, Australia. Further, throughout this time, single parent attendance of children presenting to the hospital was enforced.

As of January 2022, the number of eligible Kids Heart BioBank participants approached has returned to pre-pandemic levels (~74%). Interestingly, non-consent has increased from 5–11/year prior to the pandemic to ~ 30/year in 2022, possibly reflecting continued societal stress post-pandemic and/or decreased interest in non-essential health activities.

Kids Heart BioBank contributions

CHD research

The Kids Heart BioBank has made significant and valuable contributions to the field of CHD genetics. Specific research outputs include over 30 publications that have resulted from in-house as well as large national and international collaborations (Figure 2, Supplementary Table S4). More recently established linkages to national and state-based administrative health, clinical, and registry databases provide important additional research opportunities. The significant impact likely relates to the focused nature of the Kids Heart BioBank, the co-location within the clinical programme and clinical workflows, the establishment of a multidisciplinary consortium including computer scientists and researchers, and its identifiable role in CHD research.

Since its establishment 20 years ago, the Kids Heart BioBank has contributed to many significant advances in the field of CHD genetics; from identifying new disease genes using single gene screening[28,29], identifying risk loci in the largest genome-wide association studies in CHD at the time[17,30,31], to the application of genomic technologies.[12–14,32,33] The Kids Heart BioBank has also contributed to important and timely psychosocial research related to advances in the field, including highlighting the value of genetic counselling provision for CHD patients and families.[23,34] Further, Kids Heart BioBank participant biospecimens have supported other functional genomics research, including studies to validate variant pathogenicity[35] and have indirectly facilitated the development of new protocols and methodologies that are used by researchers worldwide.[36–38] Research findings enabled by the Kids Heart BioBank, together with those of other researchers, as well as our experiences with patients and research participants have also been summarised in key reviews.[5,9]

Supporting patient care

The most common questions asked by patients with CHD and their families are "why did this happen?" and "what are the chances of it happening again?"[3,23] Finding an answer to these questions triggered the development of the Kids Heart BioBank and underpins its associated research. In Australia, until recently, genetic testing for patients and families affected by CHD was only available via research pathways. As such, for over a decade, the Kids Heart BioBank has provided an important avenue for access to genetic testing and counselling for patients and families who would otherwise not have had access to these services.

To date, over two-thirds (64.1%) of Kids Heart BioBank probands have participated in at least one research study. Of the Kids Heart BioBank participants who have undergone research genomic testing to identify the genetic cause of their CHD, 28.9% had a pathogenic or likely pathogenic variant identified according to American College of Medical Genetics and Genomics guidelines at the time[39] (Table 2, and Supplementary Table S3). Kids Heart BioBank participants with an affected first-degree relative (i.e., a family history of CHD) and participants with extracardiac anomalies had a higher chance of being identified as carrying a pathogenic or likely pathogenic variant (38.1% and 35.3%, respectively), compared with participants with sporadic CHD (13.5%).

These findings are largely in keeping with current literature on CHD diagnostic yields across the various CHD presentations which currently suggest an approximate diagnostic yield of 30–40% in patients with familial disease and those with extracardiac anomalies.[5,8] Some of the yields in the Kids Heart BioBank are inflated, which is likely reflective of selection bias associated with individual research projects.

Importantly, the findings and diagnoses made above occurred during a time when most patients with CHD and their families did not have access to genetic testing. The clinical utility and value of research to patients and their families cannot be underestimated with many participants using clinically validated research findings to provide reproductive options, including preimplantation genetic diagnosis. Further, research findings have had direct clinical utility for many patients and their families in terms of the ongoing management of their heart defects and the identification of heart defects in previously undiagnosed family members.

In addition to the direct benefits to patients of our research programme, the benefit to CHD patients has also been evidenced

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Table 2. Research genetic testing outcomes in Kids Heart BioBank probands. Genetic testing technologies utilised include a purpose-designed CHD gene panel, exome, and genome sequencing

Proband category (%)	P/LP variant results (%)*	Genes with P/LP variants	VUS/uninformative variants (%)*	Genes with VUS variants
Family history 63 (46.7)	**24 (38.1)** · Singleton 5 · Trio 19	*NOTCH1* (x4), chr 10del; *TFAP2β, SPTB, TBX5* (x2), *GATA4, DLL4, BCOR, CFC1, NODAL* (x2), *NF1, ACTC1, ELN, GATA6, TIE1, UPF2, FLT4, TEK, TLL1, USP34*	**39 (61.9)** · Singleton 11 · Trio 28	*CHD4, JAG1, CHD7, KMT2C (x2), NOTCH1* (x3), *GATA4, PRSS23, HMCN1, WDR1, JARID2, MYOCD, DCHS1, GDF1, TMEM2, SMAD5, PRMT5, NODAL, ZFPM2, BIN1, DNAH5, KDM5A*
Consanguinity 3 (2.2)	**2 (66.7)** · Singleton 1 · Trio 1	*HAAO, KIAA0586*	**1 (33.3)** · Singleton 0 · Trio 1	*GDF1*
Sporadic 52 (38.5)	**7 (13.5)** · Singleton 0 · Trio 7	22q11del, *JAG1, PBX1, KMT2C, INVS, NODAL, TEAD2, ZFP36L2*	**45 (86.5)** · Singleton 0 · Trio 45	*MYH6* (x2), *HNRNPK, SEMA3D, HAND1* promoter, *SMAD6, WDR90, ACVR1* intronic
ECA 17 (12.6)	**6 (35.3)** · Singleton 2 · Trio 4	*PTPN11* (x2), *SETD5, NFE2L2, CNOT1*	**11 (64.7)** · Singleton 1 · Trio 10	*PTPN23, KIF7, DCHS1, KMT2D*
Total 135 (100.0) · Total Singleton 20 (14.8) · Total Trio 115 (85.2)	**39 (28.9)** · Singleton 8 (40.0) · Trio 31 (27.0)		**96 (71.1)** · Singleton 12 (60.0) · Trio 84 (73.0)	

Note: Variant classifications reflect published literature and research reports at the time and have not been re-evaluated in accordance with updated American College of Medical Genetics and Genomics (ACMG) guidelines.
P = pathogenic; LP = likely pathogenic; VUS = variant of uncertain significance.
*Proportion of probands as a percentage of proband category.

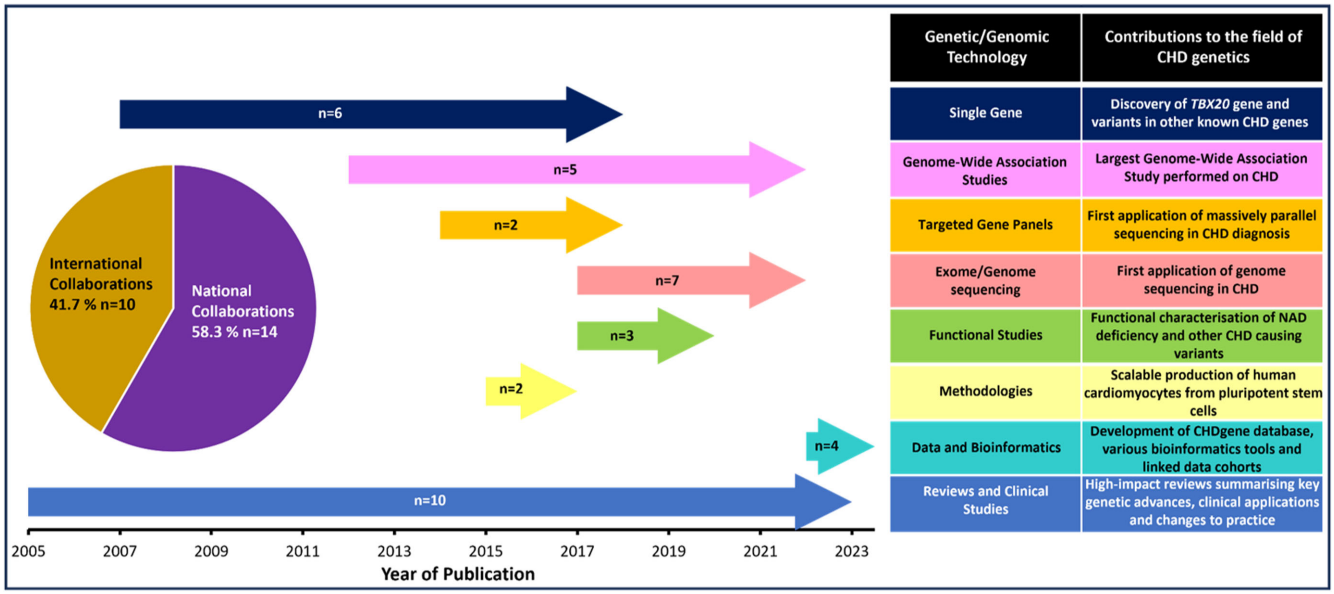

Figure 2. Contributions of the Kids Heart BioBank to CHD research over time. International/national collaborations and resulting peer-reviewed publications supported by Kids Heart BioBank participants and/or associated data are listed. *n* = number of collaborations/publications using Kids Heart BioBank participants and/or associated data.

more broadly. Novel technologies, including genomic technologies, were first adopted in a research capacity, with findings from our research and that of others leading to the development of clinical genetic testing pathways for this patient group. In Australia, government-funded clinical genetic testing options are now available for patients and families with familial forms of disease and in patients with extracardiac anomalies. For patients with sporadic and isolated disease, the Kids Heart BioBank continues to provide an avenue for research genetic testing, following limited clinical options. The Kids Heart BioBank regularly receives research referrals from Clinical Genetics services for sporadic CHD and for cases with uninformative clinical genetic testing. Similarly, the Kids Heart BioBank, which is intimately linked in with clinical processes, facilitates the appropriate referral of patients and families who are unaware of the clinical genetic testing options now available to them, further demonstrating the important reciprocal relationship between research and clinical care for this patient group.

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Conclusion and future directions

The Kids Heart BioBank has provided opportunities to investigate the complex mechanisms underpinning CHD development, thereby contributing towards our understanding of disease causation, especially in those with monogenic forms of disease to date. It has supported significant advances in the field of CHD genetics and improved patient care and management, including the establishment of a dedicated CHD genetics clinic.[12,13,23] For two decades, it has provided access to cutting-edge research technologies and genetic testing that was otherwise unavailable to patients with CHD and their families. Importantly, together with advances from others in the field, the resulting research has paved the way for clinical genetic testing options for CHD patients that were not possible a decade ago.

The value of this resource is demonstrated by the impact it has had on the field through in-house research as well as large national and international collaborations. Further, the value to patients and families is evidenced by the high consent rate (94.6%) and the low withdrawal of consent and reconsenting rate (0.4%). The high level of trust patient and families place in the Kids Heart BioBank is justified by ethically sound procedures and in the autonomy provided by the consenting process. Further, being embedded in the clinical workflow provides additional opportunities for interactions with participants and solidifies trust in the research process.

With genetic research in CHD moving away from diagnosing monogenic disease, biobanks, including the Kids Heart BioBank, are ideally positioned to support next research efforts to understand the complex multifactorial mechanisms underlying sporadic disease, which will require large patient numbers with detailed phenotypic data. Polygenic risk scores, epigenetic investigations, and data linkage approaches to investigate potential environmental factors affecting the fetal–placental–maternal environment are up and coming in the field and primarily rely on large numbers of patients with available biospecimens and associated clinical data.

With most CHD patients surviving to adulthood, there is also increasing research interest in improving immediate and long-term outcomes for patients in terms of their clinical management, prognosis, and associated comorbidities.[40,41] Combining biospecimen resources such as the Kids Heart BioBank with data linkage approaches to track patient outcomes provides the ideal tool and environment to begin addressing these important research questions. Artificial intelligence will likely play an important part in addressing these next research efforts.

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Competing interests. None.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the National Statement on Ethical Conduct in Human Research (2018) and with the Helsinki Declaration of 1975, as revised in 2008, and have been approved by the Sydney Children's Hospital Network, Human Research Ethics Committee and Research Governance.

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