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Novel initiatives of the National Institutes of Health to support congenital heart disease research

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Abstract

Purpose of review—In fiscally challenging times, scientists must seek creative strategies and leverage existing resources to advance research.

Recent findings—This review describes programmes supported by the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH) to promote research in paediatric cardiology and congenital heart disease (CHD).

Summary—An understanding of NHLBI-supported research programmes will help investigators identify opportunities to collaborate with existing systems and use scientific results from existing efforts to catalyse future research in CHD.

Keywords

congenital heart disease; paediatric cardiology; research

INTRODUCTION

Since surgical repair of congenital heart defects became a reality approximately 60 years ago, advances in diagnosis and management have been realized at an extraordinary pace. Such advances would not have been possible without the tireless efforts of scientists and clinicians, equipped with a passion for understanding the heterogeneous conditions that manifest as congenital heart disease (CHD) as well as with the creativity to test novel approaches to improve outcomes. Through this period of rapid knowledge acquisition, the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH) has been committed to supporting research in CHD and paediatric cardiology. This review describes the NIH structure and highlights specific NHLBI efforts to foster paediatric cardiology research. It also identifies challenges facing our field and suggests opportunities to facilitate moving the field forward in times of limited resources.

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Conflicts of interest

There are no conflicts of interest.

TEXT OF REVIEW

The NIH began in 1887 as a one-room workshop called the 'Hygienic Laboratory' within the Marine Hospital in Staten Island, New York. Its research initially focused on bacteriology, but soon expanded to vaccines. Despite the economic hardships of the Great Depression, the United States government acknowledged the importance of funding medical research, and thus granted the Hygienic Laboratory federal sponsorship in 1930, designating it the National Institute of Health. With the addition of institutes for research on heart disease, mental health and dental diseases in the 1940s, the name was updated to the National Institutes of Health [1]. Today, the NIH comprises 27 institutes and centres.

NHLBI is NIH's third largest institute. Its mission is to provide global leadership for research, training and education programmes to promote the prevention and treatment of heart, lung and blood diseases and enhance the health of all individuals so that they can live longer and more fulfilling lives.

Approximately 10% of the annual NHLBI budget funds research that is performed at NIH (intramural), whereas nearly 90% of the NHLBI budget supports extramural research performed at centres throughout the US and abroad. Most of the extramural research is investigator-initiated, that is, scientists request NHLBI funding to test a novel hypothesis. A smaller portion of NHLBI's extramural budget supports initiatives developed by the Institute.

National Heart, Lung, and Blood Institute programmes on congenital heart disease, past and present

NHLBI is committed to fostering paediatric cardiovascular research and applies several principles to build a foundation for evidence-based medicine: encourage innovation, be nimble and responsive to changing needs and opportunities, and build infrastructure to support science, leverage talent and avoid duplication of efforts. Investigator-initiated grants are NHLBI's fundamental source of innovation. They begin with a great idea from an inquisitive scientist, and over the years have resulted in a number of significant biomedical advances. NHLBI remains proactive and provides scientific leadership in specific areas through creative programmatic approaches and targeted releases of funding opportunity announcements. NHLBI has a particularly strong track record in developing programmes to encourage team science and provide economies of scale in scientific endeavours [2[■]]. Several of the NHLBI initiatives to support research in CHD are described here.

The Bench to Bassinet Program

In the mid-1980s, NHLBI released a series of requests for applications to promote interest in basic science research in cardiac development under the leadership of Constance Weinstein, an NHLBI programme official. This effort helped build a large, vibrant cardiac development research community, which served as the platform for the next stage of programmes. She then used the NHLBI Specialized Centers Program to bring the expanding cadre of basic biologists together with clinical researchers. Although it was still too early to apply the resulting basic knowledge directly to the clinic, these Centers provided a level of interaction

between the two groups of researchers necessary to direct their research efforts towards a common goal. However, there remained opportunities for more direct collaboration between basic scientists and clinical researchers.

To that end, the Bench to Bassinet (B2B) Program was launched by NHLBI in 2009 (www.BenchtoBassinet.org). This translational experiment brings together a basic science consortium, a genomics consortium and a clinical studies network as interacting components along the translation continuum [3] (Fig. 1).

The B2B basic science consortium, the Cardiovascular Development Consortium (CvDC), generates and disseminates comprehensive data about the molecular networks and pathways that regulate cardiovascular development using model organism systems. The Pediatric Cardiac Genomics Consortium (PCGC) identifies genetic causes of CHD and works to relate genetic variants to clinical outcomes [4[■]]. Since December 2010, the PCGC has enrolled over 5000 patients with CHD and many of their biological parents (trios) into a common protocol that collects phenotypic data and DNA samples for genomic analysis. Data from the PCGC will be made publicly available for additional analysis through the NIH Database for Genotypes and Phenotypes (dbGaP) and may be accessed by interested members of the scientific community. The Pediatric Heart Network (PHN), described below, completes the translational continuum by conducting clinical research on CHD and other cardiovascular disorders. Several consortium-wide cores, including a biorepository of genetic samples, model organism cores and data hubs, enable data sharing, collaboration and flexibility.

The Pediatric Heart Network

As early as 1997, the need for evidence-based approaches to paediatric cardiovascular problems was recognized at NHLBI. Yet, there were substantial barriers to conducting clinical trials in infants and children with heart disease, the most significant of which were the heterogeneity of conditions and the small number of individuals with a given condition that could be recruited at a single centre. Few centralized databases existed, standard of care varied significantly by centre, and multicentre studies were uncommon because of the absence of clinical research infrastructure. With input from paediatric cardiovascular researchers and under NHLBI leadership, the PHN came to fruition in 2001 [5] (www.PediatricHeartNetwork.com).

Currently, the PHN has nine main clinical sites, a data coordinating centre and many auxiliary sites (Fig. 2) [2[■]]. The use of auxiliary sites is an important strategy, which offers the PHN a unique opportunity to enhance recruitment and complete studies more quickly, to train more research teams, obtain data that have been standardized across a larger number of centres and supplement the PHN clinical and research expertise. The PHN considers new study proposals from investigators at the main clinical sites as well as from independent investigators who develop proposals in collaboration with PHN investigators.

To date, the PHN has conducted four clinical trials and five observational studies and published over 120 articles and abstracts. For example, the unprecedented Single Ventricle Reconstruction trial randomized 555 infants with single ventricle lesions to the right ventricle to pulmonary artery shunt (RVPAS) or the modified Blalock-Taussig shunt across

15 North American centres. At 12 months of age, there was a significant difference in transplant-free survival, the primary endpoint, favouring the RVPAS group, but analysis of longer term follow-up has shown an attenuation of this result [6]. This was the first large randomized surgical trial in CHD. It not only leveraged PHN infrastructure to garner statistical power by pooling eligible patients in a rare disease population, but it also dispelled a myth that paediatric cardiovascular surgeons would be unwilling to randomize their patients.

The Infant Single Ventricle Trial randomized 230 infants with single-ventricle physiology to enalapril or placebo and found no difference in somatic growth at 14 months, ventricular function or heart failure severity [7]. This trial illustrates that medications routinely used for adult heart failure may not be effective in paediatric heart failure. It also highlights the importance of conducting research in children rather than extrapolating from adult data and using hand-me-down therapies.

When NHLBI was approached in 2006 with compelling basic science evidence and pilot data in several children with Marfan syndrome that showed a dramatic arrest of aortic root growth with losartan, NHLBI leveraged the flexible PHN infrastructure to conduct a clinical trial comparing losartan with atenolol in individuals 6 months to 25 years old with Marfan syndrome. The trial was launched within 14 months, enrolled 608 patients and will complete follow-up in February 2014 [8]. This success could not have been realized without the unique partnerships between the PHN, the National Marfan Foundation, the Food and Drug Administration's (FDA) Office of Orphan Products Development, industry and the 14 participating auxiliary sites.

The PHN has trained more than 300 investigators, nurses and coordinators over the past 12 years through formal means (Career Day and Clinical Research Skills Development Cores [9]) and informal means (mentoring, participating in study committees and writing groups), thereby passing the passion along to the next generation. The PHN is unique in its commitment to nursing research by providing mechanisms for nurses to hone research and writing skills, as well as mentoring and funds to pursue research ideas.

The Children and Clinical Studies Campaign

During its early studies, the PHN identified an unmet need for information for parents considering participation in research and partnered with NHLBI, National Institute of Child Health and Human Development and others to create the Children and Clinical Studies campaign (www.nhlbi.nih.gov/childrenandclinicalstudies/index.php). This website invites children, families and healthcare providers to learn about paediatric clinical research through award-winning documentaries of parents, researchers and children sharing their experiences. This resource is used by research organizations, Institutional Review Boards and families around the world, is available in Spanish and addresses issues of concern to minority participants [10,11].

The Pumps for Kids, Infants and Neonates Program

Recognizing the paucity of available options for chronic circulatory support devices for children with CHD or heart failure, NHLBI launched the Pediatric Circulatory Support

Program in 2004 by funding the development of ventricular assist devices and advanced extracorporeal membrane oxygenators for infants and children. The second phase, the Pumps for Kids, Infants, and Neonates (PumpKIN) Program, was created in 2010 to support preclinical testing for the most promising of these devices, with the goal of gaining FDA approval to begin clinical trials [12]. This programme not only creates unique partnerships between scientists, engineers, industry and federal regulatory and research agencies, but it also encourages device development in areas of need that have been traditionally perceived by industry as having limited market potential.

Future challenges and opportunities

Although there have been significant improvements in outcomes among individuals with CHD over the last several decades, survival curves have plateaued, and this population remains at risk of significant morbidity and mortality [13]. Lowering mortality rates further will require novel approaches to tackling the inherent complexity of CHD. A fundamental step will be to develop a more comprehensive understanding of both cardiac development and the genetics underlying CHD [14[■],15[■]]. Moreover, the trend of diminishing biomedical research funding over the last decade, both by the federal government and by pharmaceutical and device companies, calls for restructuring of current business models and the development of strategic efforts to do more with less [16[■],17[■]].

Yet every challenge is accompanied by new opportunities. The community of scientists and providers invested in caring for individuals with CHD has a greater opportunity than ever before to leverage recent technological advances and collaborative initiatives to improve the tools we use to care for this population.

Traditional tools such as pulse oximetry, electrocardiography and echocardiography for the diagnosis and management of CHD are crude and operator dependent. Incorporation of newer technology, such as three-dimensional and functional imaging, may improve diagnosis, whereas three-dimensional printers, computational fluid dynamics, bioengineering and interventional MRI may complement surgical and interventional techniques.

Advances in the tools used to perform genomic analysis, such as massive parallel sequencing, will be critical not only in understanding the myriad causes of CHD but also in assessing the impact of genomics on outcomes and identifying potential therapeutic targets. The infrastructure for large-scale genomic analyses and the team science approach have been initiated by the PCGC, and further investigations will be facilitated by pooling data into large publicly available databases such as the NIH Database for Genotypes and Phenotypes (dbGaP). The use of standardized nomenclature, especially for cardiac anatomy, will be critical in facilitating these meta-analyses.

Bioinformatics will also play an important role in advancing CHD research. The PHN uses a bioinformatics grid to streamline data collection and analysis by allowing direct data transfer of echocardiograms and electrocardiograms from research sites to core laboratories. Bioinformatics tools will also facilitate the ability to pool existing data from electronic health records and registries.

In fiscally conservative times, it will be important to tap into the wealth of data that has already been collected in registries and databases rather than building systems from scratch. Global Unique Identifiers (GUID), as are used in the autism research community [18], are being piloted by the PCGC. The GUID is a unique code assigned to a patient on the basis of several inputs (name, date of birth, sex and city of birth). It will allow CHD researchers to link de-identified data among individuals who may already be enrolled in multiple existing registries and research studies. Although patients may move or transition to adult providers during their lifetime, and they may be enrolled in multiple databases and registries, the GUID will allow the research community to understand the full picture of a particular patient's experience by linking data from various fragmented registries and studies. Limited federal funding should encourage adoption of innovative collaborative models. For example, private companies, foundations, professional societies and universities could build resources and systems (registries, databases and biorepositories, and so on) and the NIH could fund research that leverages such resources.

Previous studies have documented significant practice variation among centres that care for individuals with CHD [19[■]]. Quality improvement initiatives may provide opportunities to decrease practice variation and improve outcomes in patients with CHD. Several successful models already exist. For example, the adult cardiovascular surgery field has demonstrated significant decreases in surgical mortality by comparing outcomes [20], and paediatric and neonatal ICUs have reduced catheter-based bloodstream infections and nosocomial infections using quality improvement techniques [21,22].

CONCLUSION

The future of research in paediatric cardiology will be propelled by innovative ideas from independent investigators and may be enhanced by leveraging existing infrastructure such as NHLBI's Bench to Bassinet Program, Pediatric Heart Network and PumpKIN programs. Tackling the complexity of CHD will require novel approaches that embrace new technology, genomics, bioinformatics, quality improvement initiatives, alternative funding strategies and team science.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 638).

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KEY POINTS

- NHLBI is committed to supporting research in CHD through investigator-initiated grants as well as large programmes such as Bench to Bassinet, the Pediatric Heart Network and PumpKIN.
- Although there have been significant improvements in outcomes among individuals with CHD over the last several decades, lowering mortality rates further will require novel approaches to tackling the inherent complexity of CHD.
- In addition to developing a more comprehensive understanding of both cardiac development and the genetics underlying CHD, further advances in CHD research will rely on embracing new technology, genomics, bioinformatics and quality improvement initiatives while leveraging existing resources.

FIGURE 1.

Organization of the Bench to Bassinet Program. This schematic illustrates the organizational structure of the Bench to Bassinet Program. This translational experiment brings together a basic science consortium, a genomics consortium and a clinical studies network as interacting components along the translation continuum. ACC, Administrative Coordinating Center; DCC, Data Coordinating Center; DSMB, Data Safety Monitoring Board; OSMB, Observational Study Monitoring Board; PRC, Protocol Review Committee.

FIGURE 2.

Pediatric Heart Network Participating Centers. This figure illustrates the geographic distribution of the Pediatric Heart Network centres, including nine main centres, a data coordinating centre, the funding agency (NHLBI) and many auxiliary sites. Reprinted with permission from [2¹].