Published in final edited form as:
Curr Opin Pediatr. 2009 October ; 21(5): 585–593. doi:10.1097/MOP.0b013e32832e48df.

Clinical Research Directions In Pediatric Cardiology

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Abstract

Purpose of review—Clinical research in pediatric cardiology is under-appreciated and under-funded, yet it has enormous implications for cardiovascular health and healthcare over the entire life-course. Renewed interest in federally funded clinical research makes it timely to propose a comprehensive research agenda that, with its associated rationale, will attract public funds for research into child cardiovascular health and disease.

Recent findings—We propose here a comprehensive pediatric cardiology research agenda consisting of 22 topics and associated research questions. We describe the following five topics in more detail: 1) the need for life-course studies of pediatric cardiac disease and epigenetic factors for later onset of cardiovascular effects; 2) the need to study cardiometabolic disease risk in children; 3) recent pediatric cardiology clinical trials and observational studies; 4) the need to explore the role of physical activity in preventing and treating pediatric cardiology patients; and 5) the need to develop and implement evidence-based interventions to manage pediatric cardiovascular problems.

Summary—If the field of pediatric cardiology can adopt a comprehensive research agenda that identifies the most-needed studies, then research could be better coordinated, long-term and collaborative studies would be more readily organized and funded, and the overall financial and scientific efficiency of research in pediatric cardiology would be improved. Targeted research efforts are more likely to realize potential breakthroughs in areas such as genetic and epigenetic screening, biomarkers, cardioprotective strategies, life-course studies, long-term monitoring technologies, environmental influences on disease, evidence-based practice guidelines, and more rapid and safer development of drugs.

Keywords

cardiology; epigenetics; clinical trials; late effects; pediatric; child

Introduction

Children comprise 26% of the US population but are the target of only 9% of research funds. Given this limited share of research funds, it is both desirable and necessary to establish research priorities. In fact, a clear research agenda can help guide not only pediatric cardiology research but public health policy as well; poor cardiac health at birth and during childhood has repercussions throughout life. For example, health status during the perinatal, postnatal, and childhood periods has a major impact on adult health status: poor cardiac health as a child equates to poor health as an adult.

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Disclosures: No conflicts of interest or sponsorships are noted.

Elsewhere, we have described a proposed pediatric cardiology research agenda [1-3•]. Here, we identify 22 topics and associated research questions that form a comprehensive research agenda (Table 1). We discuss five areas of pediatric cardiology research in detail, describing several advances illustrating the impact that such research can have on health throughout life. These five areas are: 1) life-course studies of cardiovascular disease, including the epigenetic fetal origins of disease as well as late effects and long-term cardiac consequences; 2) risk factors for pediatric cardiometabolic disease; 3) needed clinical trials and observational studies in pediatric cardiology; 4) the value of physical activity in treating cardiac disease in children; and 5) how to study pediatric cardiac problems and to implement evidence-based findings.

1. Life-course Studies of Pediatric Cardiovascular Disease

New information has recently been published on the late cardiovascular effects of anthracycline chemotherapy in long-term survivors of childhood cancer [4••,5••]. Anthracycline toxicity remains one of the best-studied environmental exposures during early childhood that is associated with pervasive, persistent, and, in many cases, progressive late cardiotoxicity. Despite improvements in dilated cardiomyopathy soon after anthracycline chemotherapy, especially in girls treated at younger ages and receiving higher doses of anthracycline, long-term follow-up of childhood cancer reveals a restrictive cardiomyopathy, the incidence of which increases with time. Cardiovascular-related morbidity and mortality rates are significantly increased in these patients at 20 and even 30 years after exposure. Radiation therapy is also associated with progressive late cardiovascular toxicity [6•].

These studies [4••,5••,6•] illustrate the need for life-course analyses of the relationships between early environmental exposures and late cardiovascular effects (Table 1, Topics 1 through 3, 5 through 10, and 12) in terms of the mechanisms and time course of injury, monitoring issues, screening techniques, epigenetic factors, environmental and genetic susceptibilities, biomarker development, individual and population disparities, and clinical trial designs.

The importance of long-term follow-up of the effects of medications and chronic illnesses for late cardiovascular health and diseases was recently illustrated in a study of HIV-infected children at high risk for cardiovascular diseases in which medications such as antiretroviral therapy and other disease factors markedly increased their risk of these diseases (Table 1, Topics 3, 5, 6, 9, and 11) [7••].

Other clinical situations have shown that otherwise healthy children may be put at risk by maternal exposures *in utero*. For example, children born to HIV-infected mothers have a persistent and progressive risk for cardiovascular disease, as well as mortality rates that appear to be related to maternal health and exposures, emphasizing the importance of fetal and developmental origins of subsequent disease [8•,9•,10•,11•]. Furthermore, maternal dietary intake may influence the child's subsequent cardiovascular health or risk. Second-trimester maternal calcium intake appears to affect systolic blood pressure during early childhood, for example [12•]. Thus, the fetal and developmental origins of adult cardiovascular disease and the importance of longer follow-up studies are parts of the proposed pediatric cardiology clinical research plan (Table 1, Topics 3 through 6,11,12).

Other topics in pediatric cardiology research are also of emerging interest. These topics include developing biomarkers and understanding the mechanisms of reversible and irreversible myocardial injury during early childhood that may be related to chronic adrenergic stimulation, as might occur in a child on inotropic therapy in a cardiac critical care unit (Table 1, Topics 1 through 3, 6, and 9) [13•]. Additionally, research into models of comprehensive long-term care of pediatric cardiology patients with chronic illnesses is now available (Table 1, Topics 3, 10, 11, 12, and 21) [14••]. Finally, studies comparing real-world clinical management of pediatric

cardiology patients with clinical practice guidelines indicate that new implementation strategies are needed because clinical practice in this field does not conform to known standards (Table 1, Topics 12, 14) [15••].

2. Risk Factors for Cardiometabolic Disease in Children

The importance of waist circumference and body mass index as predictors of the long-term risk of premature cardiovascular disease has also been recognized (Table 1, Topics 3 and 9 through 12 [16••]. More than 17% of children in the United States aged 2 to 19 years are obese, and another 34% are overweight and at risk for becoming obese [17••]. In the proposed research plan, childhood obesity and its complications are thus a top priority.

Recent studies have reported an association between childhood obesity and the development of a cluster of cardiometabolic disease risk factors characterized by variable combinations of insulin resistance, dyslipidemia, and hypertension, which some authors have termed “metabolic syndrome” [17,18••]. In turn, this clustering is associated with the onset of type 2 diabetes and long-term atherosclerotic cardiovascular complications in both childhood and adulthood [19,20].

Nearly one million adolescents aged 12 to 19 years in the US, or about 4% of the population in this age range, have signs and symptoms of metabolic syndrome [18••]. Among overweight adolescents, the prevalence is nearly 30%. Among 8- to 11-year-olds, national prevalence estimates of metabolic syndrome risk factors ranged from 2% to 9%, using two age-, sex-, and ethnicity-adjusted definitions [21••].

Identifying individual children and adolescents who either are at risk for or who have metabolic syndrome has remained more elusive and controversial. Much of the controversy surrounding metabolic syndrome in children is in its definition [18••,22]. Definitions of pathological processes are typically based on endpoints. The difficulty in defining these predictors of cardiovascular risk in childhood is that most children have not experienced the endpoint of interest (atherosclerotic cardiovascular disease). Thus, there is technically no single, established operational definition of metabolic syndrome in children [17••]. The challenge is to set an appropriate cut-point for each risk factor that takes into account age and sex, as well as continuous growth, the onset of puberty, and perhaps ethnic background and setting these cut-points should be a research priority as such. One approach has been to use age- and sex-adjusted percentiles as the cut-points for these risk factors, which raises the issues of which percentiles maximize both the sensitivity and specificity of the prediction and on what cohort these cut-points are determined: an historical cohort from before the current obesity epidemic, perhaps as far back as the first or second National Health and Nutrition Examination Surveys, or a more current cohort that may potentially be skewed toward higher risk.

The American Heart Association has stated that further research is necessary to define pediatric metabolic syndrome. Specific areas of inquiry include the need to: 1) assess large-scale observational and outcome studies to determine stability and predictive power of future chronic disease (e.g. diabetes and cardiovascular disease); 2) clarify the molecular basis of metabolic syndrome; 3) establish the importance of environmental exposures or toxins in the development of metabolic syndrome; 4) determine the appropriate use of medical management in treating insulin resistance, pre-hypertension, early vascular changes, elevated triglyceride levels, and low high density lipoprotein cholesterol levels; 5) identify the pathways linking insulin resistance and obesity with other metabolic syndrome components beginning early in life; 6) better understand leptin biology and the mechanisms of weight regulation; 7) assess any genetic predisposition and prenatal and neonatal factors that promote the development of insulin resistance and metabolic syndrome; and 8) determine whether the mechanisms and pathways of metabolic syndrome vary among racial or ethic groups [17••].

Only systematic, long-term follow-up of well characterized pediatric cohorts into adulthood will provide the information needed to define appropriate age-, sex-, and race or ethnicity-specific cardiovascular risks in childhood. Such studies should allow earlier and more aggressive lifestyle interventions as well as more appropriate pharmacologic treatment of these children.

3. Recent Clinical Trials and Observational Studies in Pediatric Cardiology

Results from the Pediatric Cardiomyopathy Registry (a study funded by the National Heart Lung and Blood Institute since 1995) indicate that children with Duchenne or Becker muscular dystrophy in addition to cardiomyopathy are at greater risk of premature mortality than are children with other causes of cardiomyopathy [23••]. As a result, regular cardiac evaluations can now be recommended for children with muscular dystrophy early in their presentation to optimize the application of potentially beneficial cardiac therapies.

In 2004, Lipshultz et al. reported the results of a randomized clinical trial in which dexrazoxane, a free radical scavenger, prevented or reduced the cardiac injury associated with doxorubicin treatment for childhood acute lymphoblastic leukemia [24]. Although a 2007 report suggested that dexrazoxane increased the incidence of secondary malignancies in children with Hodgkin's disease [25], a follow-up analysis of the 2004 study of high-risk children with acute lymphoblastic leukemia found that dexrazoxane was not associated with an increased risk of secondary malignant neoplasms [26••]. The authors of the 2004 study concluded that given the potential importance of dexrazoxane as a cardioprotectant, it should continue to be used and studied in doxorubicin-containing pediatric cancer treatment regimens.

Interest in the use of cardiac biomarkers to evaluate cardiac status in children is increasing (Table 1, Topic 9). Cardiac troponin T (cTnT) is a serum biomarker associated with myocardial injury from a variety of causes. In a study of 32 healthy newborns, cTnT levels were elevated in both cord (24 or 76%) and peripheral blood (30 or 94%) and were high enough to be associated with myocardial infarction in 2 (0.6%) of these infants [27••]. Other biomarkers associated with cardiac disease or dysfunction were also found in smaller proportions of this sample. The authors concluded that subclinical myocardial injury occurs in apparently healthy newborns, but whether this injury is pathologic or a response to the stress of the immediate perinatal period or to other prenatal factors remains to be determined.

Another biomarker used to assess cardiac status is N-terminal pro-hormone brain natriuretic peptide (NT-proBNP), which is secreted by myocytes in the cardiac ventricle. This biomarker is elevated in patients with both asymptomatic and symptomatic ventricular dysfunction, including congestive heart failure. Mangat et al. found that elevated and rising brain natriuretic peptide (BNP) levels, the active hormone, were associated with both abnormal echocardiographic measurements of left ventricular dysfunction as well as with clinical assessments of cardiac-related disability using either the New York Heart Association or the Ross (for non-ambulatory infants) classifications [28•]. In children with congestive heart failure, a serum BNP level greater than 290 pg/mL was associated with death, transplantation, or listing for transplantation [28•].

Maher et al. found that BNP was useful in identifying heart disease in children admitted to emergency departments. The mean BNP level was 3290 pg/mL in children with acute presentations of congenital or acquired heart disease and 17 pg/mL in children with respiratory or other infections [29••]. Another recent report found that neuroendocrine (NT-proBNP levels) and inflammatory activation (levels of C-reactive protein, tumor necrosis factor-alpha or soluble tumor necrosis factor receptor II) were associated with more severe symptoms and dilated cardiomyopathy in children with heart failure [30••].

4. The Role of Physical Activity in Preventing and Treating Cardiac Disease in Children

The benefits of a healthy life style in health and sickness are well documented [21••]. Substantial evidence currently indicates that among children with chronic disease that can lead to, or is a result of, cardiac dysfunction, structured exercise programs can improve some clinical endpoints and are safe in the right environment.

In light of the rapidly increasing rates of childhood obesity, interest is now even greater in ascertaining its cardiovascular effects in children with and without chronic illness (Table 1, Topic 11) [31••]. Children with chronic disease, especially those with cardiac dysfunction, are at risk for sedentary lifestyles and poor nutrition that can lead to overweight and exacerbate or promote cardiac dysfunction [32]. Massin et al. outlines the atherosclerotic cardiovascular risk of children with congenital heart disease [32]. Up to 25% of children with congenital or acquired heart disease are overweight [33]. Emerging evidence suggests that children with congenital heart disease, cardiomyopathy (congenital or acquired), cardiac transplantation, or metabolic cardiac risk (secondary to obesity) can benefit from increased physical activity and improved nutrition (Table 1, Topic 12) [34].

Children with congenital heart disease can show baseline de-conditioning, regardless of previous surgical repair. Children with hypoplastic left heart syndrome had a progressive age-related decline in exercise performance regardless of surgical strategy with children aged 13 to 17 years achieving only 60% of predicted maximum oxygen uptake [35••]. However, children with ventricular septal defects, repaired or not, had normal physical activity levels and fully participated in exercise [36•]. Other studies have shown that repair of the Fontan fenestration improves aerobic and exercise capacity [37], but some patients showed improvements only in ventilation [38]. Paridon et al. [39••] showed that although maximal aerobic capacity was reduced, higher oxygen saturation was associated with better exercise performance; boys and adolescents were particularly affected.

Similarly, it appears that children with congenital or acquired cardiomyopathy and those who have undergone cardiac transplantation benefit from a structured and supervised exercise rehabilitation program [34,40••]. Two children with idiopathic dilated cardiomyopathy completed a 3-month, hospital-based circuit-training program where their strength, body composition, quality of life and overall activity level improved over baseline [40••]. Another recent study showed that heart transplant recipients benefited from a home-based exercise rehabilitation program: endurance, peak oxygen consumption, and strength all improved [41]. Both studies showed the programs were safe and feasible in these populations. The potential for de-conditioning, along with increased metabolic risk and the likelihood that exercise programs can be beneficial, should also be considered in children with cardiac dysfunction as a result of cancer treatments [42], renal disease [43], and HIV infection [44], to name a few. Miller et al. outlines the response to a structured exercise program in children with HIV, a disease that presents metabolic and cardiomyopathic risk [44].

As discussed in other sections of this article, the prevalence of childhood obesity and its metabolic consequences are now out of control [45]. The risk of atherosclerotic disease in childhood is a real concern. Physical activity and nutrition are key components of any obesity intervention program, and recent studies have shown that those children with metabolic syndrome had a lower Healthy Eating Index and lower physical activity levels [45]. Metabolic syndrome, in turn, is associated with reduced cardiorespiratory fitness, low physical activity, and living in an urban environment [46]. A high-intensity, progressive, resistance training program improved central and whole body adiposity in overweight children, suggesting a conferred risk reduction for cardiometabolic sequelae [47••]. A Cochrane Review of 26 school-

based physical activity programs showed that these programs increased the duration of physical activity and maximum oxygen uptake and reduced television viewing and cholesterol levels [48•]. Participation in school sports programs substantially increased the number of endothelial progenitor cells, which in turn correlates with improved vascular function and that may protect against cardiovascular disease [49].

5. How to Study Pediatric Cardiac Problems and to Implement Evidence-based Findings

Several recent papers have described models for conducting and improving pediatric cardiac clinical research, such as establishing a clinical research division and conducting registry-based research, both of which have provided infrastructures that have lead to investigator successes [50••,51••]. Having a formal clinical research infrastructure improves both the planning and conducting of research by refining hypotheses; better controlling error, confounding, and bias; improving the accuracy of data collection and processing; and providing quality checks for analyzing and interpreting data.

The need for more and improved research is driven by the fact that prescribing medications to children in the absence of formal pediatric clinical trails can result in substantial risks to their health; an unfortunate but common occurrence in pediatric cardiology. Pediatric medications must be tested in an ethical and safe environment that is supported by scientific excellence (Table 1, Topics 3,12,15 through 17). In particular, we need to determine whether comparative trials, in which groups of patients are compared to determine the effectiveness of interventions, threaten the application of personalized medicine in pediatric cardiology, in which patient characteristics and individual genomic information are used to craft individual management strategies (Table 1, Topics 3 through 22) [52•,53•,54•]. The specialized statistical methods needed to analyze long-term follow-up studies with missing data illustrate the requirements for this kind of research [55•]. The components needed to develop a comprehensive research agenda, some research priorities, and some proposed directions in research for pediatric cardiology are detailed in Table 1.

Conclusions

We conclude the following:

- Clinical research in pediatric cardiology must accelerate rapidly in the near future if we are to reduce cardiovascular morbidity and mortality for the entire population.
- Epigenetic cardiovascular factors clearly affect development.
- We need a greater understanding of the timeframe over which cardiovascular risk remains modifiable.
- We need to identify validated biomarkers as surrogate endpoints for clinically important cardiovascular disease.
- Multi-disciplinary, multiple-site life-course study groups are essential for accurately determining the risk of exposures and to identify vulnerable sub-populations. Such study groups would also inform future clinical studies and trials.
- Local infrastructure [50••] and expertise in pediatric cardiology clinical research is highly variable and must be strengthened to increase the discovery of both incremental and break-through advances in care.

Acknowledgments

Supported by the NIH (HL072705, HL078522, HL053392, CA127642, CA068484, HD052104, AI50274, CA068484, HD052102, HL087708, HL079233, HL004537, HL087000, HL007188, HL094100, HL095127, HD80002), the

Children's Cardiomyopathy Foundation, the Women's Cancer Association, the Thrasher Foundation, and the STOP Children's Cancer Foundation.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

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

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Abbreviations

BNP	brain natriuretic peptide
cTnT	serum cardiac troponin T
DNA	deoxynucleic acid
HIV	human immunodeficiency virus
NT-proBNP	N terminal-prohormone brain natriuretic peptide

Table 1

Essential Topics and Research Questions of a Comprehensive Clinical Research Agenda in Pediatric Cardiology

1 The mechanisms of pediatric cardiovascular disease

- **A.** What is the best approach to understand the clinical presentation, diagnostic approaches, and evidence-based management and therapy of pediatric genetic and mitochondrial diseases?
- **B.** What is the importance of oxidative stress and the emerging use of antioxidants in pediatric cardiology?
- **C.** What developments are needed to refine anti-inflammatory and immunomodulatory therapies for immune-mediated cardiovascular diseases?

2 Enhanced physiologic and hemodynamic monitoring of pediatric cardiac status and outcomes, including the use of functional echocardiography.

3 Establishing birth cohorts to study the natural history of pediatric cardiac diseases and the effects of risk factors for cardiovascular disease over the life course. Such research may help determine the implications of chronic disease risk and protective strategies; the effects of maternal exposures on the health of children; and the public health implications of obesity and cardiovascular disease that begin early in life.

4 Fetal and developmental origins of adult cardiovascular health and disease

- **A.** What is the range of adult cardiovascular diseases that is impacted by developmental and fetal programming, and how does epigenetics affect developmental programming?
- **B.** What are the effects of intrauterine stress on post-natal health and on adult disease, including the effects of *in utero* epigenetic modifications on adult disease?
- **C.** What is the extent to which perinatal modification of DNA methylation and histones affect the subsequent phenotype?

5 Early childhood cardiovascular risks

- **A.** What are the associated maternal, infant, and environmental characteristics associated with increased cardiovascular risk?
- **B.** What prenatal and perinatal screening and assessment techniques might predict subsequent cardiovascular disease?

6 Environmental causes or exacerbations of cardiac health and disorders in children

- **A.** To what extent are early exposures to environmental chemicals linked to cardiac impairment in infants and children? Transplacental exposures can occur early during fetal development; postnatal exposures can occur through breast milk, other nutrition, or directly through the environment.
- **B.** To what extent are long-term changes in cardiac structure and function related to early exposures?
- **C.** What mechanistic causal pathways are potentially important; what new measures of sub-clinical phenotypes are important and what potential confounding effects may be posed by current therapies?
- **D.** How important are new measures of intermediate clinical phenotypes and what potential confounding effects may be posed by current therapies on cardiovascular disease or health?
- **E.** What methodological approaches are needed to understand and characterize children's responses and vulnerability to environmental exposures?
- **F.** What factors influence the relationship between environmental exposures and children's cardiovascular health?
- **G.** How can predisposing factors be characterized and evaluated?
- **H.** Which modifier genes are responsible for clinically adverse cardiovascular outcomes?
- **I.** What other factors influence the biological response to environmental agents, and what is the risk of adverse cardiovascular health outcomes in children? Approaches may include examining the role of the environment in children's health, including critical windows of vulnerability, early life exposures, various phenotypes, variability in biological response to several classes of environmental contaminants, the interplay between genetics and the environment, and the influence of complex mixtures and patterns on susceptibility of exposures and childhood outcomes.
- **J.** What factors influence environmental susceptibility and which are predictors of differential susceptibilities?

7 Promotion of the United States National Children's Study (an NIH life course study of 100,000 children)

- **A.** What epigenomic changes are related to environmental exposures in children?
- **B.** How do early life factors and exposures affect gene transcription?
- **C.** How do variants in the DNA sequence influence susceptibility to environmental stressors?
- **D.** How do epigenetic changes (those that result in stable changes in gene transcription with changes in DNA sequence) contribute to disease pathogenesis?

E. How do epigenomic responses to environmental exposures have long-lasting effects on intermediate biomarkers and disease occurrence?

8 Screening infants and children at risk for genetically-mediated cardiovascular disease

A. In the era of personalized and individualized medicine, what are the implications of testing for genetic diseases in pediatric cardiology? Issues include testing for genetic susceptibility, false positive screening results, whether screening should be voluntary or mandatory, and what should happen if parents opted out of screening.

B. What are the implications of genetic variations that are associated with increased susceptibility to common cardiovascular disorders with several causes?

C. What are the public policy, social, and ethical issues in screening for genetic cardiovascular disease and susceptibility that would occur if newborn, childhood and adolescent screening programs for cardiovascular disorders were implemented for newborns, children, and adolescents?

D. What are the clinical implications of advances in genome mapping and identifying variations associated with increased susceptibility to common cardiovascular disorders of multifactorial origins?

E. What is the value of screening for conditions with variable degrees of treatability or conditions for which no therapies currently exist, such as cardiomyopathy secondary to Duchenne Muscular dystrophy?

F. What is the role of bone marrow transplant in treating genetic diseases diagnosed at a pre-symptomatic stage?

9 Validated biomarkers for cardiovascular diseases

A. How can genomic and proteomic techniques be applied to discovering biomarkers?

B. How does transcriptional regulation of normal and abnormal cardiovascular development work and how do epigenetic mechanisms control transcriptional regulatory expression in cardiac development and disease?

10 Disparities in the quality and safety of pediatric health and cardiac care resulting in unequal treatment

A. How do the continuing racial, ethnic, and socioeconomic disparities of medically underserved populations affect pediatric cardiovascular health and diseases that linger or are exacerbated in adulthood, and what epidemiological, life-course, and policy research is needed to correct these disparities?

11 Morbidities and implications associated with childhood obesity

A. What are the predisposing factors and complications of morbidities in childhood obesity?

B. What is the pathogenesis of these morbidities?

12 Clinical trials and observational studies

A. What new and conventional therapies and devices need to be tested?

B. What new indications might be tested for existing therapies?

C. What complementary, alternative, and integrative therapies should be evaluated?

D. Which physical activity and fitness interventions should be evaluated?

13 Biologic-based therapies to reduce the incidence and severity of cardiovascular diseases

A. How can the most likely stem-cell-based therapeutic tools and reparative medicine be applied in the short-term?

B. How can patient-specific pluripotent stem cells improve transplantation therapies for genetic cardiovascular diseases in children?

C. Which genomic discoveries will most likely affect the delivery of pediatric cardiovascular medicine?

D. How can laboratory-based discoveries best inform the care of children with heart disease?

14 Streamline pediatric cardiology studies and trials to bring research findings to the bedside faster?

A. What are the most efficient and effective ways to implement evidence-based preventive and therapeutic strategies into clinical practice?

15 Ethical issues related to pediatric cardiovascular research, especially for under-served populations with chronic illnesses

16 Advocacy training to promote research and clinical education and care related to pediatric cardiology

17 Developing methods, expertise, and facilities to support clinical research

A. What support is needed to sustain the long-term success of pediatric cardiac specialist research networks and registries such as the NHLBI-funded Pediatric Cardiomyopathy Registry and Pediatric Heart Network?

B. Given that pediatric clinical cardiac diseases are relatively rare, relevant study outcomes are relatively infrequent and remote to disease onset; patient follow-up over long periods of time is difficult and expensive, and adequate sample sizes are impossible for individual institutions to obtain, what support is needed to sustain multi-institutional collaborative research in children's health care, given the different modes and missions of these research efforts?

C. What research and resources are needed to develop biological specimen repositories for pediatric cardiology research and what ethical issues do such repositories raise?

18 **Patient-based quality-of-care improvement research.**

A. Development of quality improvement translational efforts to close the gap between science and practice and to enhance evidence-based care to improve outcomes.

19 **Cardiovascular toxicities and late effects of pediatric medications, including the areas of toxicoproteomics for understanding individual susceptibilities and improved post-marketing surveillance to counter the current lack of reliable estimates of the prevalence of adverse drug events.**

20 **Pediatric cardiac medication safety**

A. What are the benefits and limitations of using medical informatics to augment good communication in assuring safety for children with cardiac disease?

B. How can communication theories be applied to improve team performance and patient safety?

C. What communication barriers affect quality of care and efforts to reduce medical errors?

21 **Chronic illness models for improving healthcare for medically complex, chronically ill children with cardiovascular abnormalities**

A. Given that children with special health care needs comprise more than 12% of all children but require more than half of pediatric healthcare dollars, how do we improve their access to preventive and early care?

B. What are the optimal management strategies and public policy options for these children?

C. Which models of care (e.g., medical home, dedicated inpatient services, and consult services) are best for these children?

D. What evaluation tools and research are needed to develop evidence-based practice guidelines for care that is specialized, complex, family-centered, and culturally competent in a subspecialty cardiac setting?

22 **Cost-effectiveness analyses of new technologies, to make the best use of limited resources in treating children with cardiac problems.**

A. Whether and how should cost-benefit and cost-effectiveness analyses help determine screening policies and practices.