National Heart,

Lung, and

Blood Institute

Report

of the

Task Force on

Research in

# Pediatric Cardiovascular Disease

The National Heart, Lung, and Blood Institute (NHLBI) provides leadership for a national program in diseases of the heart, blood vessels, lung, and blood; sleep disorders; and blood resources management. It plans, conducts, fosters, and supports an integrated and coordinated program of basic research, clinical investigations and trials, observational studies, and demonstration and education projects related to the causes, prevention, diagnosis, and treatment of heart, blood vessel, lung, and blood diseases, and sleep disorders. Research is conducted in the Institute's own laboratories and by other scientific institutions and individuals supported by research grants and contracts. The Institute also supports research training and career development for new and established researchers in basic and clinical research relating to these topics, and oversees management of the Women's Health Initiative.

U.S. DEPARTMENT OF
HEALTH AND
HUMAN SERVICES

For Administrative Use
May 2002

Public Health Service
National Institutes of Health

## Contents

## Executive Summary

Heart disease in infants, children, and adolescents is a large and under-appreciated public health problem. Diseases range from congenital structural defects present at birth to genetic abnormalities of the heart muscle and conduction system, acquired heart diseases, and adult diseases that begin in childhood. Because children have a long life ahead, the burden and cost of children's heart disease are substantial for families and society. More than 1 million adults are alive today who had a heart defect repaired during childhood.

In January 2001, the National Heart, Lung, and Blood Institute (NHLBI) convened the Task Force on Research in Pediatric Cardiovascular Disease to identify research priorities and scientific opportunities for addressing this significant public health problem. The Task Force recommends that the NHLBI support an aggressive research program in the basic, clinical, and population sciences to capitalize on recent advances in genetics, understanding of cardiovascular development, and clinical care.

This Task Force report encompasses three broad areas: basic research on cardiovascular development and the causes of cardiovascular disease, research to improve clinical outcomes, and population strategies to reduce cardiovascular disease in adults by altering risk factors during childhood. Implementation of the Task Force's recommendations could help to foster prevention of pediatric cardiovascular disease; improve outcomes for infants, children, and adolescents with heart disease; and promote cardiovascular health among adults.

The Task Force identifies eight research priorities over the next 5 years. These priorities reflect current scientific opportunities in the following areas:

- Fundamental studies of the formation of heart and blood vessels
- Development and use of new and improved technologies to image the heart
- Advanced repair of congenital heart defects in infants and children
- Refined surgical treatment of human fetuses with heart defects
- Exploration of stem cell biology for the repair of heart tissues
- Creation of improved biomaterials through tissue engineering
- Translational research to enhance clinical care
- Definition of the childhood antecedents and risk factors for atherosclerotic heart disease in adults.

The first opportunity, cardiovascular morphogenesis, or the formation of heart and blood vessels, deserves research emphasis, to define the mechanisms of normal and abnormal morphogenesis and the role of genetic and epigenetic (environmental) factors in the development of these tissues. Basic research on these processes will yield important information on the effects of genetic and environmental risk factors and the interactions between genes and the environment in the development of heart defects. Investigators will need resources to support comparisons of genetic factors in children who have congenital heart defects with experimental models. This research could yield options for preventing heart defects.

By using advanced technologies to image the heart, researchers also could greatly improve the clinical care of children with heart defects. The Task Force recommends support of targeted programs to develop and use new and improved technologies for creating two- and three-dimensional images and assessing heart function. To accomplish this work, pediatric heart centers and technology companies must establish partnerships to develop new equipment for assessing heart disease in infants and children, to define its appropriate applications, and to determine its cost effectiveness. Use of bioinformatics is particularly important for cardiologists and surgeons who need to have real-time images of the heart combined with sophisticated measures of vascular and muscle function.

Surgeons and cardiologists can enhance their repair of congenital heart defects in infants and children by using minimally invasive surgery guided by robotics, new types of therapy with catheters, and improved pre- and postsurgical support of heart and lung function. The Task Force recommends research to improve heart assist devices and technology for extracorporeal membrane oxygenation and to adapt this technology for use in infants and small children.

Surgical treatment of the human fetus is imminent. To take advantage of this opportunity to repair heart defects in utero, researchers need to develop new techniques and tools for imaging and surgically repairing the heart. Support of multicenter, collaborative studies of the natural history of heart defects in utero and the efficacy of interventions before birth would greatly help to facilitate this research.

Stem cell biology and tissue engineering also offer the potential to improve the outcomes of treatment for children with heart defects. Stem cells are a potential source of heart muscle cells and blood vessels which clinicians can use to rebuild or replace damaged heart tissue and thereby obviate the need for heart transplantation. In addition, researchers could program stem cells to produce artificial valves, blood vessels, and tissue for patches, thereby avoiding complications currently associated with the use of cardiac prosthetic materials.

Establishing a clinical trials network to implement multicenter, randomized studies for rapidly assessing new therapies will accelerate the translation of research advances into clinical care. Research on clinical outcomes also is critical to implementation and development of standards of care for pediatric cardiology. Because children potentially have a long life ahead, longitudinal studies and patient registries are important for, and integral to, defining the risk of specific heart defects, appropriate surgical management, and late postoperative complications. Clinicians need to develop surrogate markers to predict optimal outcomes and identify "best practices" for various diagnoses of heart disease and across heart research centers.

Atherosclerotic heart disease in adults begins early in life. The Task Force recommends studies that define the origins of atherosclerotic vascular disease during fetal life and childhood. Development of effective therapeutic and preventive regimens depends on research strategies to identify children at high risk for future cardiovascular disease.

In this report, the Task Force details specific recommendations for each priority area. In addition, the Task Force urges action to develop and nurture an adequate, well-trained work force in academic pediatric cardiology to conduct the research needed. The future of children's cardiovascular health depends on having an adequate work force of pediatric cardiologists, other pediatric specialists, and basic scientists to translate research findings and provide quality care. The Task Force notes concern that the number of physicians adequately prepared for these important roles is declining, at a time when the opportunity to achieve significant scientific advances is great. The Task Force urges the scientific community to devise ways to recruit and nurture the next generation of clinician scientists to conduct basic, clinical, and translational research in pediatric cardiovascular disease.

The issues and recommendations discussed by the Task Force are central to the long-term goals of understanding the causes of pediatric heart diseases, improving clinical care, and eventually preventing these diseases and their complications.

## Introduction

Heart disease in children involves abnormalities in heart structure and function. Children may be born with heart disease or may acquire it, for example, in association with other illnesses. Heart conditions in children include congenital cardiovascular malformations, cardiomyopathies, congestive heart failure, arrhythmias, coronary artery aneurysms, and myocardial infarction. The morbidity and mortality associated with these conditions are significant. The major goals of pediatric cardiologists and other pediatric cardiovascular researchers are to identify the cause(s) of these conditions, improve treatment of them, and ultimately prevent them.

In the United States, *congenital cardiovascular malformations* (CCVMs) are the most common birth defect, and birth defects are the leading cause of infant mortality. Congenital cardiovascular malformations arise in utero during development of the embryo. They affect 1 in every 100 U.S. infants born each year. Many of these infants need intervention, by catheter or surgically, during their first weeks of life, and they will need additional procedures as they grow. Most of the procedures are palliative rather than curative, and many of the children need to be closely followed medically to minimize complications. As many as one-third of children with CCVMs also have congenital or acquired conditions that affect their kidneys, brain, digestive system, lungs, bones, immune system, and other organs. These additional problems complicate their care further.

Some children have disorders specifically involving the myocardium, or heart muscle. These *cardiomyopathies* may be primary or secondary disorders of myocardial function. All of their causes are not known. For primary cardiomyopathies, researchers continue to identify an increasing number of specific gene defects. The various causes of secondary cardiomyopathies include toxic medications, chronic overload of left ventricular volume from chronic severe valvar regurgitation, and myocarditis, an inflammatory process primarily caused in children by infectious agents. Some children with cardiomyopathy are asymptomatic for years, whereas others may develop severe symptoms, including sudden death or life-threatening heart failure. Currently, heart transplantation is the only definitive therapy for children with cardiomyopathy who develop end-stage heart failure.

*Congestive heart failure* may arise in children who have congenital or acquired heart disease. Providing effective pharmacological therapy for these children is a special challenge. Researchers have established the safety and efficacy of only a few of the medications currently being used in children with heart disease and, instead, have extrapolated the use and dosages of most medications from studies in adults. Thus, children with heart disease may be receiving improper dosages of medications or medications that do not benefit them or are potentially dangerous. In addition, the developmental issues associated with long-term administration of drugs in children are not completely known.

*Arrhythmias*, or disorders of electrical conduction, also may be congenital or acquired. Disorders such as long QT syndrome may be caused by gene defects or may be associated with disease processes such as the cardiomyopathies. Other conduction disorders may be

associated with specific CCVMs or may be caused by various therapies, including surgery. The morbidity and mortality associated with all conduction disorders are substantial for pediatric patients who have cardiovascular disease. Achieving an increased understanding of the mechanisms of arrhythmia and developing effective and safe therapies are essential for improving care for the many children affected by these disorders. Similar to the treatments for heart failure in children, many therapies for arrhythmia have been extrapolated for pediatric use from physicians' experience with acquired heart disease in adults. However, the developmental issues associated with long-term consequences of arrhythmias and their treatment may differ dramatically between children and adults.

*Coronary artery aneurysms* are a specific complication of Kawasaki disease, which has replaced rheumatic fever as the most common cause of acquired heart disease among U.S. children. First identified in 1967, Kawasaki disease generally occurs in young children. Its incidence peaks among those ages 1-2 years, and 85 percent of the cases occur in children under age 5. The cause is not known. Administration of intravenous gamma globulin dramatically reduces the incidence of coronary artery aneurysms in this disease, but approximately 5 percent of the children will develop at least transient dilation of a coronary artery and 1 percent will develop giant aneurysms. Researchers have not defined the long-term outcomes for children with even apparently transient abnormalities of the coronary arteries, but children with large aneurysms are at risk for myocardial infarction.

Because of the remarkable innovations made in medical and surgical therapy, many pediatric patients with cardiovascular disease now survive into adulthood. Unfortunately, the incidence of residual disease is relatively high, and these children continue to be at increased risk for sudden death later in life. Currently, 1 million U.S. residents who are older than 21 years live with congenital heart disease. This population, which is expanding, needs specialized care that often is not available, and many clinical questions have yet to be resolved.

The link between childhood and heart disease in adults is strong for many additional Americans, for the atherosclerotic vascular disease process begins well before adulthood and perhaps even during fetal life. Atherosclerotic vascular disease is the leading cause of death among all adults in the United States. The extent of the early atherosclerotic process, for each adult, reflects the number and levels of risk factors present. Obesity, for example, is a major risk factor for both young and old. The severity and prevalence of obesity during childhood are increasing in U.S. society. Obesity during childhood predicts adult obesity, and obese children and adolescents have a larger number of other cardiovascular risk factors than those who are not obese. Development of effective strategies to reduce the burden of cardiovascular risk factors during childhood and adolescence is essential for improving the nation’s public health.

Because of the public health burden that cardiovascular diseases impose on children, the National Heart, Lung, and Blood Institute (NHLBI), in January 2001, convened a Task Force on Research in Pediatric Cardiovascular Disease. The NHLBI charged the Task Force to identify the most important research priorities and scientific opportunities over the next 5 years in basic science, clinical medicine, and epidemiology associated with pediatric

cardiovascular disease. To review the diverse topics within its charge, the Task Force formed three subcommittees: Basic Science, Clinical Science, and Population Science. Each subcommittee addressed the charge within its purview. The entire Task Force then met to review the work of the subcommittees and to decide on the most important recommendations that would form the research agenda.

The Task Force focused on the most promising research areas for making progress in the next 5 years to improve understanding, treatment, and prevention of pediatric cardiovascular disease. The members identified eight research priorities, as follows:

- Development of the normal and abnormal heart and vascular system
- Imaging
- Minimally invasive surgery and transcatheter therapy
- Intervention during fetal life
- Development of cardiovascular cell therapies
- Creation of materials for cardiovascular bioprostheses
- Translating research advances to clinical care
- Childhood antecedents of atherosclerotic vascular disease in adults.

In this report, the Task Force presents specific recommendations for each area and provides the background and rationale for each recommendation. The recommendations are not intended to be restrictive or to preclude creative work in other areas relevant to cardiovascular disease in children.

## Development of the Normal and Abnormal Heart and Vascular System

In this priority area for research on pediatric cardiovascular disease, the Task Force highlights scientific opportunities in four topics: development of the heart, development of the vascular system, laboratory cores for the study of animal models, and risk factors for CCVMs.

### Development of the Heart

*Recommendations*

- Encourage investigations of the specification of cardiomyocyte lineages and the molecular mechanisms underlying differentiation and proliferation of cardiomyocytes.
- Further characterize molecular and cellular mechanisms involved in cardiac morphogenesis, including the embryology of the conduction system.
- Increase understanding of the pathological processes underlying abnormal development of the heart.

Increased understanding of the processes that regulate normal and abnormal development of the cardiovascular system is essential for preventing and improving treatment of CCVMs. Research activity in this field has increased dramatically during the past decade. In studies of model

organisms, researchers have shown that development of the heart is an evolutionarily conserved program triggered by specific signaling molecules and mediated by tissue-specific transcription factors. This program controls the genesis of cardiomyocytes from mesodermal stem cells and the subsequent activation of genes responsible for cardiac contractility and morphogenesis. Understanding the mechanisms that underlie the specification and proliferation of myocytes (muscle cells) is important for understanding CCVMs and for possibly repairing heart tissues by genetically reprogramming nonheart cells for cardiogenesis.

After specification, heart muscle cells converge along the ventral midline of the embryo to form a beating linear heart tube composed of distinct myocardial and endocardial layers separated by an extracellular matrix. The endocardium differentiates into a unique subpopulation of endothelial cells when development begins. The interplay between the endocardium and myocardium during development is likely to be important for the ultimate form and function of the heart. Although these myocardial–endocardial interactions are potentially significant for the initial morphogenesis of heart tissue and for its subsequent remodeling, scientists have little understanding of the mechanisms that regulate this interchange.

The heart is formed through a precisely orchestrated series of molecular and morphogenetic events. Even subtle perturbations of them can result in CCVMs. For example, improper looping of the heart tube can cause a discordance of cardiac, pulmonary, and visceral location, which is known as heterotaxy syndrome. Also, abnormalities in the composition, production, or reabsorption of the extracellular matrix may underlie defects that involve incomplete septation of the atrioventricular valves. Furthermore, because neural crest cells contribute to formation of the aorta, ductus arteriosus, proximal subclavian artery, and carotid and pulmonary arteries, abnormal specification or migration of neural crest cells often results in complex defects of the outflow tract, such as tetralogy of Fallot or truncus arteriosus. And, a single abnormality, for example atresia of a valve, may lead to additional defects resulting from abnormal patterns of blood flow during development.

In studies of vertebrate and invertebrate animal models, researchers have identified genes that control development of the heart, which can now be investigated as possible culprits in the development of CCVMs in humans. Equally important is the mapping and identification of genes responsible for CCVMs in humans. That specific gene defects can lead to a variety of congenital heart defects, which appear during development, is increasingly clear. A single clinical entity, such as tetralogy of Fallot, can be associated with defects in several different genes (*NKX2.5*, *Jagged 1*, *del Chr. 22q11*) and with several clinical syndromes, such as DiGeorge syndrome or trisomy 21 syndrome.

Alternatively, defects in a single gene can cause multiple abnormalities. For example, mutations in the gene encoding the human NKX2.5 transcription factor result in tetralogy of Fallot, ventricular septal defects, atrial septal defects, tricuspid valve abnormalities, double-outlet right ventricle, and atrioventricular conduction delays. Because of the heterogeneity of CCVMs associated with single-gene defects, achieving a mechanistic understanding of gene function is a research challenge. Modifier genes, environmental factors, and genetic polymorphisms may all be important in determining the severity and type of CCVM.

To identify essential genes that act at critical steps in the development of the heart, researchers mostly use animal models of CCVMs created by causing homozygous mutations, which result in loss of function and, frequently, severely abnormal phenotypes that are lethal during early embryogenesis. In humans, however, malformations generally result from mutations in only one gene in a pair of genes and thus are not lethal during embryogenesis. Additional research is needed to translate findings from animal models to humans.

Examples of research in the above areas include, but are not limited to, the following:

- Studies to increase understanding of the role of the endocardium in development of the heart
- Study of the ontogeny of specialized conduction tissues, to help clarify the genesis of arrhythmias
- Construction of a repository of developmentally staged samples of cardiovascular genes and proteins from model organisms, to help characterize the expression of genes and proteins during development
- Correlation of particular amino acid substitutions with specific cardiac malformations, to gain insight into the structure–function relationships of encoded proteins in vivo
- Use of large-scale approaches to mutagenesis and gene modification in animal models, to discover additional genes responsible for CCVMs
- Development of new animal models that have mutations which are not lethal during embryogenesis and thus mimic the human condition more closely.

**Development of the Vascular System**

*Recommendation*

- Encourage investigations of angiogenesis and vasculogenesis, especially in relation to the development of the pulmonary vasculature and coronary arteries.

Many investigators have focused on factors that regulate the differentiation and organization of the myocardium during cardiac morphogenesis, but fewer investigators have explored the development of the associated systemic and pulmonary vasculature. At the earliest stages of differentiation, the endothelium of veins and arteries is molecularly distinct from the mesoderm which gives rise to most heart structures.

The pulmonary vasculature is unique because it develops by both angiogenesis (de novo differentiation of endothelial cells from the mesoderm) and vasculogenesis (remodeling of the primary vascular plexus and sprouting of new vessels from existing vessels). Development of the pulmonary vasculature is also inextricably linked to development of the heart. Recent investigations suggest that blood flow is a potent stimulus to vascular growth and remodeling. This finding is consistent with the observation that many patients with obstructed pulmonary

blood flow, such as in tetralogy of Fallot, also have abnormal pulmonary vasculature that persists even after surgeons repair the initial cardiac malformation.

The pulmonary circulation is a potentially accessible target for therapeutic intervention because it is one of the few vascular beds where the most expansive growth occurs during the perinatal and postnatal periods. However, before researchers can design rationally based therapies, they need to study further the mechanisms that regulate development and remodeling of the pulmonary vasculature. When mutated, many of the factors considered to be essential for development of the embryonic vasculature result in the demise of the embryo well before pulmonary development begins. For this research, investigators will need new models and approaches.

Coronary arteries, which are essential for later stages in the development of a fetus's heart, arise from tissue that subsequently forms the epicardial, or outer, layer of the heart. A cascade of cell–cell signaling and cell–fate specifications leads to the formation of blood vessels on the surface of the heart which eventually connect with their essential blood supply from the aorta. This process is still not completely understood. Isolated congenital abnormalities of the coronary arteries develop when the coronary arteries do not form proper connections with the aorta or form additional connections with other blood vessels or chambers of the heart. Also, many types of CCVMs are associated with abnormal positioning of the coronary arteries, which may affect clinical outcomes.

Examples of research in the above areas include, but are not limited to, the following:

- Characterization of the specification and proliferation of endothelial and vascular smooth muscle cells
- Investigation of the mechanisms that regulate development of the pulmonary vasculature in CCVMs
- Characterization of the development of the coronary vasculature.

**Laboratory Cores for Studying Animal Models**

*Recommendation*

- Develop core facilities for imaging and studying the physiology of the cardiovascular system in small animals, to serve as national resources for research on CCVMs.

Characterization of the physiological phenotype of diseases in animal models is essential for understanding completely the pathophysiology of these diseases and their relevance to human conditions. For research in mice and other small animals, investigators need sophisticated techniques and specialized equipment to characterize cardiac function, regulation of the circulation, and cardiovascular responses to pharmacological and physiological interventions. By having state-of-the-art core laboratories for studying animal physiology, investigators

could gain important information on the overall effect of specific genetic or other manipulations on cardiovascular performance.

To evaluate the efficacy of pharmacological and gene therapies in these animal models, researchers also need to be able to characterize the animals' functional physiological responses to specific interventions. Examples of the laboratory capabilities needed for these studies include isolated perfused heart preparations, open- and closed-chest instrumented animal models, advanced imaging modalities, electrophysiological analysis, and exercise/stress testing. Investigators could potentially modify some of these approaches for studies in other small animals, such as zebra fish.

By measuring cardiovascular performance in animal fetuses in utero, researchers may be able to derive new indices of fetal viability that would be applicable to assessments in human pregnancies. For example, many single-gene mutations affect different facets of cardiovascular development in mice. In the mouse model, investigators can precisely assess physiological developments under similar conditions because the mouse uterus contains multiple embryos, which may be wild type, heterozygous, or null mutant phenotypes. Multiple measurements can be made over time and the most informative indices determined, which could then be verified rapidly in humans. By developing strategies for analyzing cardiovascular performance in mice in utero, researchers will be able to enhance characterization of gene mutations and their effects and expedite translation of clinically relevant information.

Most of the imaging techniques currently used to diagnose cellular, molecular, and metabolic processes are limited. The new techniques of magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), magnetic resonance (MR) spectroscopy, positron emission tomography (PET), single-photon-emission computed tomography (SPECT), as well as other emerging imaging modalities, have the potential to define structural, physiological, and metabolic processes at molecular and cellular levels. Researchers, for example, can use specialized MRI scanners (7-9 Tesla) to study the morphology of the cardiovascular system and the expression of genes in mouse embryos. Having the ability to attain spatial resolution at the micron level and to image molecular and cellular processes with MRI-specific agents opens a new frontier in image-based cardiovascular research. (See also the section on "Imaging" later in this report.)

Because of the numerous experimental methods and sophisticated techniques needed to examine phenotypes fully, a multidisciplinary team approach is necessary for this research. Also, any plans to develop core physiology laboratory facilities must include sophisticated imaging facilities to correlate function and structure of the cardiovascular system. Support for a single comprehensive laboratory that serves as a national resource center could help to ensure uniform analyses and the use of appropriate experimental approaches for specific animal models and research questions. This component of an overall research program on the physiology of small animals could include studies of bioengineering and mathematical modeling.

## Risk Factors for CCVMs

*Recommendations*

- Evaluate the role of genetic and environmental risk factors and gene–environment interactions in the development of CCVMs.
- Establish a centralized core resource that includes a comprehensive DNA database, for analysis of CCVMs in humans and experimental models (mouse and zebra fish) using microarray technology.

Progress in preventing cardiovascular disease in adults, based on an understanding of risk factors identified in population-based studies, has been substantial. However, progress in preventing CCVMs has been limited because few population-based studies have addressed their risk factors.

Improved understanding of the causes and prevention of CCVMs depends on studies in large populations. Yet, these studies are complicated because CCVMs encompass different anatomical lesions and clinical manifestations and have various causes and because children with CCVMs are difficult to ascertain, diagnose, and classify within a population. Also, although researchers can identify and diagnose most children with serious heart defects in population-based studies, children with milder or asymptomatic heart defects tend to be missed. This incomplete ascertainment limits investigators' ability to evaluate the incidence of disease and to identify risk factors in a population. By addressing these challenges in the design and conduct of population-based studies, researchers can take a critical step toward advancing knowledge about the causes of CCVMs.

Having a complete understanding of the risk factors for CCVMs may lead to effective interventions to prevent them. Some disorders that affect a mother's metabolism, for example, diabetes mellitus, correlate with an increased risk of CCVM in the mother's offspring. Other factors, such as a mother's alcohol intake and nutrition and the use of certain medications, also are risk factors for CCVMs. Yet, despite this knowledge, scientists cannot explain the causes of CCVMs in most cases.

The opportunity to define the genetic causes of CCVMs has never been greater. With the completed sequencing of the human and mouse genomes and the development of DNA data sets that can be surveyed using microarray technology, scientists are likely to soon identify most, if not all, of the genes expressed during the development and maturation of the heart. Because the number of candidate genes is large, resources and strategies are needed to delineate which genes actually have a critical role in causing CCVMs. Already, researchers can characterize the full spectrum of allelic variants and exposures and estimate the allelic effects of genes, environmental factors, and gene–environment interactions in appropriately stratified population-based studies. They also can estimate some measures of risk (for example, the effect of genes or gene–environment interactions) in smaller studies without

using population-based sampling. Some study designs can yield a very useful initial screening of gene–environment interactions under certain circumstances.

One of the major limitations in linking the discovery of genes with clinically relevant analysis of them is access to genetic samples from patients with CCVMs and their families. Whereas "informative families" will continue to provide the critical substrate for analyzing the linkage between genes and disease, having access to large numbers of tissue samples from patients with clearly defined clinical defects is essential for thorough analysis of candidate genes and modifying factors. The complicating factors of partial penetrance (i.e., individuals who have the genotype for a disease but do not exhibit the disease phenotype), variable expressivity (i.e., individuals having identical genetic defects but varied phenotypes), and asymptomatic individuals (whose disease may be affected by important modifying factors) affect researchers' efforts to determine the role of specific genes in human CCVMs. Having a better understanding of the interplay between candidate genes and modifying factors (i.e., "genotype–phenotype" correlation) will improve therapeutic interventions and outcomes, and this information is essential for appropriate and effective genetic counseling.

To facilitate research on the causes of CCVMs, researchers must have a core resource and a comprehensive DNA database so that any investigator from any institution can conduct analyses to determine whether mutations in a gene are associated with specific forms of CCVMs. This resource also may foster development of advanced tools for gene discovery and creation of new and more rapid screens to identify agents that cause CCVMs.

Detailed genetic studies of experimental models of CCVMs, for example in mice and zebra fish, also are essential. These studies could include, for example, evaluation of the patterns of gene expression and the profiles of "downstream" genes in animals that have specific mutations of developmentally important genes. Most laboratories currently lack automated approaches to assess the altered expression of mutants in a small set of previously identified genes. Having a centralized core resource with microarray technology would be more efficient and cost effective and would enable investigators to identify a large number of genes with altered expression, as well as their multiple downstream targets.

With a centralized core resource and an associated database, researchers also will be able to conduct meta-analyses of microarray data sets derived from studies of individual mutants. For example, the mutation of a single transcription factor can alter patterns of expression for several hundred genes, whereas a mutation in a different transcription factor can effect a different set of altered patterns of expression. Researchers could analyze these differences using microarray technology. Investigators also could identify gene cohorts from experimentally manipulated embryos or the effects of alterations in a mother's diet or drug exposure. By conducting meta-analyses of microarray data from each single mutant, investigators could readily identify genes that are altered in two or more cohorts (from mutant or experimentally manipulated samples) and are thus likely to be central to cardiovascular development. Because microarray technology is currently in flux and standard approaches are lacking, adequate and informative meta-analyses of microarray data are virtually impossible unless the microarrays are performed on the same gene sets under standardized conditions.

With a centralized core resource, investigators could access the same genetic information and gene sets for further experimental analysis.

Examples of research in the above areas include, but are not limited to, the following:

- Studies to ascertain current trends over time in the incidence of CCVMs
- Evaluation of the role of metabolic and nutritional factors in causing CCVMs
- Collaboration with the National Birth Defect Prevention Study of the Centers for Disease Control and Prevention to foster further studies of the epidemiology of CCVMs
- Evaluation of the heterogeneity of CCVMs in relation to genetic and environmental risk factors
- Expansion of the DNA database to include samples suitable for nonparametric linkage approaches, such as the transmission disequilibrium test and the affected relative pair approach, to identify the genetic loci for susceptibility to CCVMs and modifying factors
- Facilitate connections between microarray analyses and human DNA databases so that researchers can consider human candidate genes for study when new gene cohorts are identified from microarray analyses of model systems (mice and zebra fish).

## Imaging

In this priority area for research on pediatric cardiovascular disease, the Task Force highlights four general scientific opportunities: development and modification of imaging technologies for patients with CCVMs, development of fetal diagnostic imaging technologies, use of imaging to guide transcatheter and minimally invasive surgery, and integration of multimodal imaging display and bioinformatics.

### Development and Modification of Imaging Technologies for Patients With CCVMs

*Recommendations*

- Assess the anatomy and function of the cardiovascular system in infants and children who have congenital and acquired heart diseases, using improved techniques such as MRI, MRA, MR spectroscopy, ultrafast and electron-beam computed tomography (CT), and real-time, three-dimensional and miniature echocardiography.
- Develop, validate, and integrate innovative imaging tools for noninvasive assessment of myocardial mechanics, flow dynamics, and metabolic and molecular processes in patients with congenital and acquired pediatric heart diseases.
- Stimulate development of new multidimensional imaging technologies.

- Design and implement prospective clinical studies to develop diagnostic algorithms with optimal cost effectiveness and risk-benefit profiles for specific clinical circumstances in pediatric cardiovascular medicine.

Being able to image the heart and blood vessels is essential for diagnosing and treating all forms of pediatric heart disease. From initial diagnoses of CCVMs before and after birth to therapeutic interventions in catheterization laboratories and operating rooms, clinicians rely on imaging tools for information to guide their prognoses and management of diseases. Diagnostic imaging of cardiovascular structures in a fetus, infant, or child is especially challenging compared with that in an adult because the cardiovascular structures are much smaller, the heart rates are faster, young patients are less able to remain still during procedures, the spectrum of congenital anomalies is much wider, and most disease processes are dynamic.

With the recent advances in noninvasive imaging techniques, such as MRI, CT, nuclear imaging, and PET, cardiologists and surgeons are able to acquire diagnostic information that cannot be obtained using traditional methods. In particular, the capabilities of MRI for diagnosing heart structures have increased dramatically during the past 5 years because of the remarkable progress made in computer technology, bioengineering, and software design.

Compared with other current imaging modalities, MRI has several advantages. It is noninvasive, uses harmless radio-frequency energy, provides three-dimensional images, and enables clinicians to receive information and manipulate signals obtained directly from tissue. This technology is ideally suited for defining the structure and function of the cardiovascular system. However, researchers in only a few heart centers for children are studying the use of MRI for pediatric patients, and they use equipment and diagnostic techniques for infants and children that are adapted from medical procedures for adults.

Because infants and children are not simply "small adults," researchers should concentrate on developing hardware and software for MRI designed specifically for fetuses, neonates, and children with congenital heart disease. Specific needs include (a) MRI hardware that accommodates patients ranging from premature infants weighing less than 1 kilogram to adults weighing more than 150 kilograms; (b) a new generation of cardiac-specific, multichannel, phased-array coils for a wide range of body sizes; and (c) new MRI sequences to improve spatial and temporal resolutions for the small, rapidly beating heart of a child.

Investigators also need to improve *echocardiography*, to move it from two-dimensional imaging to a high-resolution, real-time, three-dimensional imaging modality. Through research and development in engineering and computer sciences and extensive clinical testing, investigators could achieve the spatial and temporal resolutions needed for high-quality imaging of infants and children with heart disease. To expand use of echocardiography beyond tertiary care centers, researchers need to develop miniaturized cardiac ultrasound equipment. For example, hand-held echocardiographic equipment is likely to replace stethoscopes, and the use of this equipment will improve the sensitivity and diagnostic accuracy of assessments of the cardiovascular system in patients who reside in

geographic areas where access to tertiary health care is limited. Other technological advances in echocardiography also are likely to advance the field of pediatric cardiac imaging.

For the future, investigators need to develop other innovative, noninvasive diagnostic techniques specifically for fetuses, neonates, and children with congenital heart disease. In addition, they need to define the role of new imaging techniques, such as MRI, three-dimensional echocardiography, ultrafast and electron-beam CT, PET, SPECT, optical imaging and others, for research and clinical practice in pediatric cardiovascular disease. As manufacturers introduce expensive new imaging modalities for research and clinical use, researchers must determine their test characteristics (e.g., sensitivity, specificity, and predictive values) for fetuses, newborns, and children.

Examples of research in the above areas include, but are not limited to, the following:

- Development of innovative sequences and methods of analysis, including high-resolution, interactive, real-time MRI; on-line quantification of blood flow; automated myocardial strain analysis; and structure-specific tracking methods
- Provision of accurate quantitative data on specific domains, including global pump function, regional myocardial mechanics, perfusion, and cardiovascular metabolism
- Noninvasive quantification of blood flow pressure, energy, and shear stress
- Development of four-dimensional anatomical imaging (and three-dimensional spatial imaging over time)
- Determination of the safety, accuracy, and reproducibility of new imaging modalities in infants and children.

**Development of Fetal Diagnostic Imaging Technologies**

*Recommendations*

- Develop noninvasive tools and technologies to assess cardiovascular function in fetuses.
- Design a multicenter collaborative study of the natural history of prenatal congenital heart disease.
- Develop noninvasive imaging tools to guide cardiovascular therapy in fetuses.

The development of high-frequency ultrasound transducers and digital image processing has greatly improved diagnostic imaging of congenital heart disease in utero. Currently, clinicians can diagnose most structural congenital heart defects reliably after 16 weeks of pregnancy. However, although they can better visualize the fetal heart, their ability to assess the functioning of the cardiovascular system of fetuses is more primitive. To measure cardiovascular function, physicians are currently limited to estimating global ventricular function, determining variations in the velocity of blood flow using the Doppler technique, and assessing heart rate. Development and use of new noninvasive tools and techniques will help to improve assessments of cardiovascular function in the fetus.

Another research frontier is interventional therapy in utero. When developing transcatheter and surgical techniques specifically for the fetus, researchers must identify the patients who are most likely to benefit from these interventions. As a first step, they will need to delineate the natural history of congenital heart disease in utero.

Examples of research in these areas include, but are not limited to, the following:

- Development of methods to quantify accurately global ventricular function, myocardial mechanics, and the dynamics of blood flow in the fetus
- Definition of the natural history of congenital heart disease in utero, through a multicenter collaborative study.

**Use of Imaging to Guide Transcatheter and Minimally Invasive Surgery**

*Recommendation*

- Develop and integrate new tools, such as real-time MRI and three-dimensional echocardiography, for image guidance of transcatheter, minimally invasive, and robotic surgery for CCVMs.

As therapy for congenital heart disease advances, cardiologists and surgeons need accurate noninvasive imaging tools to guide their therapeutic interventions in children. Researchers could adapt real-time MRI, ultrafast CT, and ultrasound to guide minimally invasive and robotic surgery and transcatheter interventions. Physicians could then use these high-resolution, three-dimensional visualization systems to deliver drugs, genes, energy (e.g., radio-frequency, laser, electric, or focused ultrasound), instruments, and devices to targeted areas in the cardiovascular system. By using image guidance during cardiac therapy, physicians also will be able to evaluate, in real time, the effects of interventions, the prognoses, and the need for further treatment. New tools must be developed and tested.

Examples of research in this area include, but are not limited to, the following:

- Development of new MRI sequences for tracking catheters and instruments; high-performance gradient systems; and new hardware to optimize access to a patient during interventional procedures
- Development of a new generation of MRI-compatible instruments
- Integration of several imaging modalities (e.g., MRI, three-dimensional echocardiography, x-ray fluoroscopy) into one platform to achieve a more flexible and capable imaging system that can be used to guide various interventions and assess their effects
- Use of focused ultrasound energy to release bioactive substances, such as drugs or genes, in specific areas within the heart or to open up restrictive septa or valves.

### Integration of Multimodal Image Display and Bioinformatics

*Recommendations*

- Develop, validate, and implement new bioinformatics systems that combine input from multiple diagnostic and imaging modalities to derive anatomical and functional information.
- Design and implement studies to determine the optimal use of imaging technologies based on analyses of cost effectiveness and risk-benefit.

The use of bioinformatics in pediatric cardiology will improve the care of children with heart disease. From the exploration of new methods for bringing biomedical imaging data to the desktops of clinicians and researchers to the promotion of rational, science-based use of imaging technologies, research in bioinformatics can greatly enhance communication in clinical research and access to biomedical data. This sharing of information, in turn, will stimulate new opportunities for research collaboration and greater efficiency in clinical practice.

Because each of the current imaging modalities has different advantages and disadvantages and because these differences are likely to apply to new imaging modalities as well, the combining of the specific information obtained by various techniques into an integrated multimodal display will be advantageous. New technology that combines information into integrated displays may enable clinicians to directly correlate structural, functional, and molecular events in the cardiovascular system.

An example of research in this area is as follows:

- The combining of biochemical data obtained by MR spectroscopy or SPECT (which have poor spatial resolution) with high-resolution MRI, MRA, CT, or echocardiographic images to pinpoint metabolic processes within the myocardium or walls of blood vessels.

## Minimally Invasive Surgery and Transcatheter Therapy

*Recommendations*

- Use bioengineering and material science approaches to improve robotic technologies, endoscopic instruments, and minimally invasive and transcatheter techniques.
- Develop large-animal models to test various minimally invasive approaches to surgery for specific CCVMs.
- Develop left ventricular assist devices and extracorporeal membrane oxygenation systems that are appropriate for pediatric patients.

The improved outcomes for children with CCVMs over the past 30 years are largely due to advances in surgical technique and myocardial preservation. After the technique of cardiopulmonary bypass was established, the repair of congenital heart defects during childhood became common. The subsequent development of techniques for assuring successful surgery in infants, during the 1970s, enabled physicians to definitively repair CCVMs early in life. Today, even premature infants weighing as little as 3 pounds can successfully undergo open-heart surgery.

Minimally invasive surgery can improve the treatment of patients with CCVMs. It can speed recovery times, improve cosmetic results, and reduce wound complications. Furthermore, robotic technology has great potential for expanding the role of endoscopic surgery in procedures that are becoming increasingly complex. Robotic-assisted surgery enables physicians to manipulate and handle tissues more precisely than with conventional endoscopic instruments and is ideally suited for cardiovascular procedures in patients who have small chest cavities. Endoscopic repairs of CCVMs that surgeons currently correct using open-chest techniques may be possible in the future. The initial experience with video-assisted thoracoscopic approaches for patent ductus ligation and congenital subaortic resection is encouraging.

However, because of technical limitations, the development of less invasive surgical techniques for CCVMs has not been as rapid as for acquired heart disease in adults. One problem is that instruments are too large for infants and young children. Endoscopic instruments need to be miniaturized for use in small patients. In addition, researchers need to develop other equipment, such as suction devices, retractors, stabilizers, and catheters, for pediatric surgery involving endoscopic instruments. With miniaturization, robotic-assisted surgery will be applicable to ever-smaller patients, but further research is needed to improve the current robotic technology for surgery and to meet the rigorous demands of heart surgery in infants and young children. Because of the variety of lesions encountered in pediatric cardiovascular disease, researchers will first need to assess the feasibility of new procedures, which could be numerous, in large-animal models.

Patients with complex heart defects often need systemic support to recover from the stress of surgery and their compromised ventricular and pulmonary function. Investigators need to adapt and refine current techniques of left ventricular assist and extracorporeal membrane oxygenation for use in infants and small children.

Increasingly, research on transcatheter therapy is expanding the options for therapy and the alternatives to surgical intervention. Transcatheter therapy is likely to be an integral component of minimally invasive approaches. Rashkind developed transcatheter septostomy in the late 1960s, and physicians now routinely use catheters in children to dilate narrowed valves and blood vessels; close unwanted communications; repair septal defects (both simple and complex); create new communications; and open compressed, hypoplastic, and even discontinuous vascular structures with stents. Pediatric cardiologists recently developed catheter-based techniques to repair complicated defects in adults such as patent foramen ovale

(to prevent strokes), coronary arteriovenous fistulas, paravalvar leaks, and postinfarction septal ruptures.

In 2001, the Food and Drug Administration approved two transvascular catheter devices for closing atrial septal defects (holes between the two top chambers of the heart) and ventricular septal defects (holes between the two bottom, or pumping, chambers of the heart) within the heart. One of the most important new areas of biomechanical research is development of a practical, safe, successful, and long-lasting pulmonary valve that can be implanted during catheterization of the heart.

Examples of research in the above areas include, but are not limited to, the following:

- Application of robotic technologies in surgeries to create palliative shunts (e.g., the Blalock-Taussig shunt) or assist with percutaneous procedures and, in selected cases, cardiopulmonary bypass
- Development of new surgical techniques and instruments for treating CCVMs using minimally invasive approaches
- Adaptation of extracorporeal membrane oxygenation and left ventricular assist technology as adjuncts to care for infants and small children
- Development of tools for suturing heart tissues using transcatheter approaches
- Development of new materials that can be implanted safely in the circulation of growing children (e.g., tissue-engineered patch material and absorbable scaffolding for stents and umbrellas).

## Intervention During Fetal Life

*Recommendation*

- Refine techniques for interventions in the fetus, including improved technology for cardiopulmonary bypass and myocardial protection, reconstructive techniques, and transcatheter interventions.

Surgical and transcatheter interventions in the fetus to repair primary defects and to normalize blood flow patterns could improve function and minimize structural deformation. These benefits should improve the quality of life for individuals with congenital heart disease. Currently, a disproportionate share of the resources available for treating congenital heart disease is extended to patients with selected defects, such as hypoplastic left heart syndrome, because these conditions are complex and the options for treatment are only partially effective. Interventions during fetal life have special promise for these patients and could help to contain the costs of continued care. Furthermore, as researchers develop newer treatment modalities, such as gene therapy and genetic engineering, interventions during fetal life are likely to become possible for a wider range of cardiovascular defects.

Cardiac surgeons often use extracorporeal circulatory techniques to support heart surgery in fetuses. Because of the differences between fetuses and newborns, these techniques and most other surgical techniques need to be modified specifically for fetuses. Compared with newborns, fetuses are smaller in size and have less well developed cellular and subcellular systems in the myocardium, as well as immature and fragile tissues with less structural integrity. Sutures and staples are often ineffective in these conditions, and researchers will have to devise modified techniques to protect the fetus's heart muscle.

Clinicians have gradually introduced limited-access, endoscopic, and even robotic techniques into mainstream surgical practice, including open-heart surgery. The potential benefits of these techniques for interventions in fetuses are enormous. For example, to achieve direct access to a fetus's heart, a surgeon must cross the mother's abdominal and uterine walls and then the fetal chest wall. Techniques and methodologies that give surgeons an alternative to direct-access surgery could result in markedly reduced stress and trauma for both the mother and the fetus. Instruments that are appropriate in size and for the specific circumstance of fetal cardiovascular surgery, and associated methodologies, need to be developed.

Some congenital heart defects can be repaired by using transcatheter procedures postnatally. The recent report of a successful transabdominal, transuterine procedure to reverse the development of hypoplastic left heart syndrome in utero provides a powerful impetus to pursue catheter-based interventions in fetuses who have severe cardiovascular disease. The development of improved techniques, tools, and methodologies to position, immobilize, image, and catheterize the heart of human fetuses will almost certainly revolutionize the management of many infants with life-threatening CCVMs.

Examples of research in these areas include, but are not limited to, the following:

- Studies to optimize extracorporeal circulation and myocardial protection in the fetus
- Development of biological glue and laser tissue-welding techniques for reconstructing fragile fetal tissues
- Modification and development of surgical instruments specifically for use in fetuses
- Development of miniaturized and “semi-robotic” catheter tools specifically for interventions in fetuses
- Testing of newer imaging techniques, such as three-dimensional echocardiography and three-dimensional MRI, as necessary adjuncts to successful transcatheter procedures in fetuses.

## Development of Cardiovascular Cell Therapies

*Recommendation*

- Define the differentiation, proliferation, and interactions of stem cells during development as a basis for using them as potential sources of cardiomyocytes,

endothelial cells, and vascular smooth muscle cells for treating cardiovascular disease during childhood.

An improved understanding of stem cell biology is critical to the development of tissue-engineered implants (see the next priority) and clinically useful techniques for regeneration of damaged heart muscle. The lack of methods to deliver cells to affected tissues or organs hampers the development of cell therapies for diseases involving solid organs such as the heart. Scientists had long assumed that solid organs such as the heart do not have stem cells and that cells from them could not be reprogrammed to differentiate into other cell lines in adulthood. Recently, however, researchers have identified stem cells in solid organs such as the brain and skeletal muscle and have shown that adult stem cells can differentiate into other types of cells or tissues.

New data suggest that a subpopulation of adult myocytes, which may come from resident stem cells in the heart or from stem cells in the circulation that have migrated to the heart, is able to proliferate. By using human stem cells for therapy, physicians may some day be able to regenerate or repair heart muscle, conduction tissue, and blood vessels. A combination of gene therapy and stem cell therapy, such as genetically modifying stem cells with vectors that program the expression and secretion of therapeutic proteins, may eventually be possible. Moreover, patients who have inherited single-gene mutations such as the mutation at chromosome 1q32, which affects troponin T and causes cardiomyopathy, might benefit if myocyte stem cells that lack specific gene products could be reconstituted genetically with a normal copy of the defective gene.

Examples of research in this area include, but are not limited to, the following:

- Development of improved techniques for isolating and culturing human stem cells
- Studies to improve understanding of the mechanisms that regulate the survival and differentiation of stem cells in vitro and in vivo
- Development of methods to ensure proliferation of only desired cell types.

## Creation of Materials for Cardiovascular Bioprostheses

*Recommendation*

➢ Develop tissue-engineered structures for blood vessels, heart valve components, and materials for surgical repairs within the heart and for use in devices placed in the heart during surgery or cardiac catheterization.

The placement of artificial valves and conduits is an important facet of therapy for patients with CCVMs. However, artificial valves and conduits tend to deteriorate because of calcification and degradation of the extracellular matrix, and they do not grow with the patient. Pediatric patients who receive replacement heart valves or blood vessels have to undergo subsequent operations to replace these bioprostheses. Also, some patients must take

anticoagulant medication to avoid life-threatening thromboses associated with certain artificial valves. Physicians must manage this anticoagulant medication carefully, and patients are always at risk of serious bleeding. Development and use of improved substitutes for cardiovascular tissue will reduce the need for multiple surgeries for children with CCVMs. In addition, use of tissue-engineered structures may decrease the risks of thrombosis associated with prosthetic and bioprosthetic materials and, thereby, reduce the need to treat patients with anticoagulant medications.

Preliminary investigations involving tissue-engineering technologies are under way, to study the feasibility of developing substitutes for heart tissue that are durable, biocompatible, and able to grow with young patients. Approaches such as growing cells on biodegradable scaffolds configured to the shape of heart valves or conduit vessels may eventually provide superior substitutes for cardiovascular tissue.

Examples of research in this area include, but are not limited to, the following:

- Identification of polymers that function as workable scaffolds, but resorb after cellular and matrix remodeling has "bioengineered" a stable valve or vessel
- Investigation of the correct balance of endothelial cells, vascular smooth muscle cells, and fibroblasts needed to elaborate the appropriate extracellular matrix for bioprostheses
- Development of prosthetic, electrophysiologically active tissue implants to restore nodal function in patients with atrioventricular node block or sinus node dysfunction
- Testing of developed biomaterials in animal systems.

## Translating Research Advances to Clinical Care

In this priority area for research on pediatric cardiovascular disease, the Task Force highlights five general scientific opportunities: clinical trials, surrogate outcome measures, patient research registries, clinical effectiveness, and measuring general health status.

### Clinical Trials

*Recommendations*

- Support integrated networks and infrastructures for clinical trials.
- Conduct multicenter, randomized trials to test and assess new therapies for pediatric cardiovascular disease.

New strategies for treating heart disease in infants and children are likely to evolve in the near future from research on tissue engineering, stem cell replacement, pharmacogenomics and drug discovery, and possibly gene therapy. Collaborative multicenter trials will be needed to test their safety and efficacy and to seek their approval from regulatory agencies. Multicenter

trials are advantageous when (a) no single center has sufficient resources to answer a research question; (b) collaboration will speed the resolution of the research question; and (c) collaboration will resolve the question more authoritatively. Multicenter studies enable investigators to accrue the sample sizes needed in a reasonable amount of time and to generalize results because they involve a broader range of clinical settings than is possible with single centers. Even the largest clinical centers can individually enroll only small numbers of patients with rare CCVMs, and the findings are not as readily generalizable as in multicenter trials.

The barriers to conducting clinical trials of treatments for pediatric cardiovascular disease are substantial. First, this category of diseases comprises multiple rare and diverse disorders. Second, randomization of patients is difficult because regimens for treatment vary widely across clinical centers depending on the availability of appropriately trained individuals to perform treatments and the conviction of physicians about which treatments are effective. Third, analyzing the endpoints for pediatric heart patients is difficult because they are not likely to die, their symptoms are difficult to quantify, and they are "a moving target" as they grow and develop.

Fourth, the long-term effects of different therapies on variables that are unique to infants and children, such as their growth and development, may be expensive to measure, creating the need for investigators to define and validate surrogate outcomes. Finally, many pediatric cardiovascular centers have only recently begun to develop the infrastructure needed for clinical trials. This infrastructure largely did not exist before September 2001, when the NHLBI inaugurated the Pediatric Heart Network. Establishing this network is an important forward step for clinical research on pediatric cardiovascular disease. It establishes a collaborative clinical research structure and affords a suitable venue for training junior investigators in clinical research.

Examples of research in this area include, but are not limited to, prospective, randomized trials of the following:

- New biomechanical methods and drugs for better preservation of vital organs, including the brain and heart, during cardiopulmonary bypass and the early postoperative period
- New drugs for nonstructural pediatric cardiovascular diseases, such as myocarditis, Kawasaki disease, and heart failure
- Resynchronization therapy for dilated cardiomyopathy in infants and children.

**Surrogate Outcome Measures**

*Recommendation*

- Conduct short- and long-term studies to delineate validated and sensitive surrogate markers for clinical outcomes.

The proper conduct of prospective, randomized trials in children depends on delineation of appropriate outcome measures. Ideally, prospective studies should demonstrate whether a treatment or intervention results in better clinical outcomes, such as improved symptoms or survival. Because the outcome of greatest interest may take a long time to develop and be difficult to measure, investigators often use surrogate markers as outcome measures in prospective studies of children and adults. By relying on surrogate endpoints that predict clinical outcomes, clinicians often can bring the benefits of new treatments, at a relatively low cost, to patients years before information on long-term outcomes would be available. However, by relying on surrogates that do not fully predict the clinical benefit of a treatment, clinicians may adopt therapies that could be futile or even harmful in the long term. Still, because many pediatric cardiovascular diseases are rare, defining the benefit to survival may not be realistic, whereas using an intermediate endpoint (e.g., exercise tolerance, degree of cyanosis) as an outcome measure may be possible.

Examples of research in this area include, but are not limited to, the defining of valid surrogate outcome measures for development of the following:

- Arrhythmia or sudden death as a late consequence of CCVMs
- Complications in patients who have undergone a modified Fontan procedure, including those who are now adults
- Neurocognitive dysfunction in school-age children who undergo surgery for CCVMs using cardiopulmonary bypass.

**Patient Research Registries**

*Recommendation*

- Develop prospective, longitudinal databases and registries of patients with pediatric cardiovascular disease, including patients who are now adults.

Prospective, longitudinal registries of patients with pediatric cardiovascular disease contain valuable information about the epidemiology and outcomes of these diseases that investigators use to improve the clinical care of children. With the decline in deaths from surgery for CCVMs and the documentation of adverse, long-term cardiac and neurological sequelae in some survivors of CCVMs, investigators have shifted their research emphasis from ensuring survival to optimizing long-term outcomes.

For patients with pediatric cardiovascular disease, adverse long-term outcomes are a major issue. For example, repair of tetralogy of Fallot using a transannular patch causes long-term adverse effects on right ventricular function. Patients who undergo repair of coarctation of the aorta experience long-term alterations in vascular resistance. Patients with univentricular heart who undergo the Fontan procedure often have multiple serious, long-term sequelae such as arrhythmias and thromboses within the heart. Infants who undergo reparative heart surgery

frequently have later difficulties with cognitive and motor function and need significant remedial services when they enter school.

The next 5 to 10 years will be critical in the development of population-based clinical databases and registries of patients with pediatric cardiovascular disease. Some projects are already under way and could be expanded. Prospective studies and registries funded by the NHLBI include the Prospective Assessment After Pediatric Catheter Ablation (PAPCA) study and the Pediatric Cardiomyopathy Registry (PCMR). The databases and registries should include conditions and procedures, as well as important clinical risk factors and practice characteristics. An excellent model to follow is the New York State cardiovascular surgery database. Health care purchasers and provider groups could be invited to participate in research partnerships between public and private organizations to organize and support databases and registries.

Clinical centers that care for children with pediatric cardiovascular disease will need to have sophisticated infrastructures and sufficient financial resources to collect appropriate data, manage the data and assure quality control, and comply with regulatory requirements. Researchers will need centralized resources with improved data information systems, including population-based administrative databases, as well as consistently defined terminology within the field, tissue banks, and clinical research networks. Protecting the confidentiality of patients' records is an implicit challenge in striving for greater standardization and centralization of these databases.

Examples of research in this area include, but are not limited to, establishment of registries of patients who have the following conditions:

- High-risk arrhythmias and implanted cardioverter defibrillators
- Myocarditis
- Kawasaki disease with coronary artery disease
- Univentricular heart palliated with a modified Fontan procedure
- Transposition of the great arteries treated during infancy with Mustard or Senning atrial switch procedures.

## Clinical Effectiveness

*Recommendations*

- Develop and validate adjustment tools that are specific to procedures, conditions, and patients' risks, to facilitate clinical research on determinants of outcome across the many rare and diverse congenital heart lesions.
- Identify processes and structures of care that predict outcomes for children with heart disease.

Even when clinical research demonstrates that a particular treatment is clearly advantageous, instigating changes in medical practice is difficult because physicians often are unaware about best practices, healthcare systems may be inadequate, and outcomes depend on individuals' skills in performing procedures, such as during surgery. Methods to evaluate the effectiveness of clinical research have become increasingly powerful for determining how new knowledge improves the cardiovascular health of children and for identifying processes and structures of care that predict best outcomes. Partly because clinical research in pediatric cardiovascular disease typically involves small numbers of patients and different practices, published reports often provide incomplete, or even conflicting, guidance for pediatric cardiologists and surgeons. Researchers can apply methods such as decision analysis and meta-analysis to weigh and reconcile the results of clinical studies that yield different conclusions, in order to determine the best practices.

Because pediatric cardiovascular disease comprise rare and diverse conditions and are a leading cause of death in childhood, clinical researchers must use valid techniques, when assessing the efficacy of new treatments, to adjust for each patient's baseline risk for a poor outcome. To facilitate clinical research studies that examine the determinants of outcome across the many different congenital heart lesions, investigators will need to develop and validate adjustment tools that are specific to procedures, conditions, and patients' risks.

Clinical research on the effectiveness of treatments for pediatric cardiovascular disease is sparse. This research must be conducted using a multidisciplinary approach and with access to large data sets, systems and personnel for managing the data, and biostatisticians. Efforts to improve health services research in pediatric cardiology depend on the development of robust data and management information systems that can support the administration and use of massive databases. By ensuring high standards for data entry and including valuable clinical information in these databases, investigators could facilitate population-based research on linkages among variables across data systems. However, to enable investigators to access these databases and to record linkages without violating patients' privacy will be a challenge.

Examples of research in this area include, but are not limited to, the following:

- Elucidation of variables that underlie the relationship between institutions' volume of cases and patients' outcomes in pediatric heart surgery
- Identification of the effects of patients' characteristics and the processes and structures of care (e.g., race and ethnicity, insurance status, institutional characteristics) on morbidity and mortality
- Exploration of the effects of factors (e.g., an institution's volume of cases, patients' insurance status or race) on related outcomes, such as functional status, quality of life, and long-term cardiac and neurodevelopmental status.

### Measuring General Health Status

*Recommendation*

- Develop and validate instruments for assessing the functional status and quality of life of children with heart disease, to compare outcomes and practices across clinical centers and medical diagnoses.

Studies of clinical outcomes after heart surgery on infants document mortality and morbidity, but provide limited information on subsequent general health status or health-related quality of life. Many instruments are available to assess quality of life in adults who have undergone heart surgery, but researchers have only recently developed tools for use in pediatric patients. To compare the outcomes of interventions in children who have congenital heart disease, investigators need to develop and refine instruments for assessing the general health status or quality of life of these children. Tools could include documented reports of parents, parents' proxies, children, and teachers. Measures of functional status and quality of life that are validated in children with heart disease will be important when assessing the success of new therapies. Assessment of functional status and quality of life, in addition to the efficacy and cost of treatments, will enable researchers to better evaluate and compare interventions.

Examples of research in this area include, but are not limited to, the following:

- Validation of the current generic instruments for measuring general health status and quality of life, in children with heart disease
- Development of an assessment module for measuring general health status and quality of life specifically for pediatric cardiovascular disease
- Study of ways to track general health status over time in children with heart disease
- Exploration of the relationship between assessments by parents, or their proxies, and children.

## Childhood Antecedents of Atherosclerotic Vascular Disease in Adults

*Recommendations*

- Increase understanding of the origins of atherosclerotic vascular disease (ASVD) during fetal life and childhood.
- Develop strategies to identify children at high risk for ASVD and to develop effective therapeutic and preventive regimens.

Atherosclerotic vascular disease, particularly coronary artery disease (CAD), is the leading cause of death among adults in the United States. However, this disease process begins much earlier and perhaps even during fetal life. For example, low birthweight is associated with an increased frequency of subsequent hypertension, diabetes, and death from CAD. Autopsies of infants and young children show fatty streaks in their aortas, and specimens from adolescents

show intimal plaques as well. Risk factors such as high cholesterol, high blood pressure, and obesity during childhood and adolescence exacerbate the atherosclerotic process in children *and* predict increased cardiovascular risk in adulthood. Furthermore, children who have both increased levels of risk factors and first- and second-degree relatives with ASVD are at increased risk of morbidity and mortality from ASVD. Investigators can use noninvasive measures, such as thickness of the carotid artery wall and calcification of coronary arteries, to document manifestations of ASVD in children.

Scientists have determined that certain genotypes are related to adverse levels of blood lipids, blood pressure, and inflammatory processes associated with the atherosclerotic process in adults. These genotypes are present at birth and identifiable in children and adolescents who are at risk, later in life, for diseases resulting from atherosclerosis. Further studies are needed to determine whether genotyping at young ages augments information on known risk factors to help physicians identify young patients who could benefit from preventive measures for early atherosclerotic disease.

Three major, controllable risk factors for development of ASVD in children are obesity, high blood pressure, and increased levels of low-density lipoprotein (LDL) cholesterol. The severity and prevalence of obesity among U.S. children are increasing due to excessive intake of calories and insufficient exercise. Obesity in childhood predicts obesity in adulthood and is associated with the development of syndrome X, a metabolic syndrome characterized by hypertension, dyslipidemia, glucose intolerance, insulin resistance, and type II diabetes. Obesity is associated with a clustering of risk factors, and all of these complications confer an increased risk for ASVD. Yet, weight loss is difficult for both adults and children to achieve. Effective strategies for preventing obesity during childhood and adolescence must be developed and applied to promote healthy weight and to decrease the risk of ASVD among U.S. adults.

A child's blood pressure is determined partly by genetic factors, physical activity, diet, and body mass index. Because levels of blood pressure, grouped by percentiles, tend to track over time, increased blood pressure during childhood often correlates with hypertension in early adulthood. By increasing their physical activity and losing weight, adolescents with hypertension can lower their blood pressure.

Increased concentrations of LDL cholesterol are linked to development of atherosclerotic plaque at all ages and with increased rates of CAD. However, the age at which cholesterol concentrations should be a matter of concern and possibly treated is a current point of controversy. Logic suggests that modifying this risk factor early would increase the potential for reducing the severity of ASVD, but there is also concern about the consequences of long-term administration of lipid-lowering medications beginning in childhood. Therefore, further research is needed.

Control of weight, reduction of LDL cholesterol, treatment of hypertension, and cessation of smoking (another major risk factor) clearly decrease the probability that clinical manifestations of ASVD will arise in middle- and older-age adults. Even though researchers

now know that ASVD begins early in life, determining the best approach to control risk factors in children needs further study. Clinical trials of drugs to lower cholesterol and blood pressure in children and adolescents have demonstrated their short-term safety, efficacy, and acceptability, but their long-term consequences are not known. Researchers also have not adequately studied whether diets that reduce children's intake of total fats place them at risk for retarded growth, inadequate nutrition, or adverse psychosocial effects. The long-term effects of such interventions must be assessed carefully.

Because of the overwhelming problem of obesity in the United States, the Task Force endorses the pediatric component of a "top-tier" research priority recently recommended by the NHLBI Task Force on Research in Prevention of Cardiovascular Disease. This top-tier priority is to "support studies to facilitate reduction of the epidemic of obesity in American children and adults."

Examples of additional research in the above areas include, but are not limited to, the following:

- Investigations of the effects of socioeconomic status, gender, and ethnicity on childhood risk factors for ASVD
- Investigation of the effects of malnutrition during fetal development on physiology and metabolism
- Characterization of the relationship among specific genotypes, risk of ASVD, and response to therapy
- Examination of the mechanisms in childhood obesity that increase the risk for ASVD
- Development of effective strategies for reducing risk factors in families and through school- and community-based programs
- Evaluation of the efficacy and safety of therapies to reduce various risk factors, to include use of noninvasive measures to assess the burden of disease
- Development of effective strategies to integrate the results of clinical trials into community and clinical practice
- Determination of whether the genotyping of progeny of parents with early-onset atherosclerotic disease (fathers age 55 years or less and mothers age 65 years or less) improves identification of children and adolescents who are at high risk for early development of atherosclerosis.

## Work Force for Academic Pediatric Cardiology

*Recommendation*

- Continue to develop successive generations of scientists to study pediatric cardiovascular disease.

As science enters the postgenomic era, investigators from each clinical discipline must translate basic genetic information into clinical practice. This translational effort is much more complex than research to sequence the human genome, but it is likely to yield new strategies for treating and preventing birth defects and acquired diseases. The research work force to accomplish this task must be available, while clinicians continue to provide high-quality clinical care for a growing population of children who have congenital or acquired heart diseases. Without an adequate research work force, scientific advances will languish and implementation of new therapies will fail.

The research work force is aging, and the number of practitioners is probably inadequate to meet the need for evolving models of clinical care and for increased levels of service for a growing population of survivors of pediatric cardiovascular disease. In addition, the future availability of well-trained clinical researchers and practitioners is uncertain.

For example, the proportion of pediatric residents who choose advanced training has declined from 33 percent in 1986 to 21 percent in 2000, and pediatric cardiology is only the third most common choice for pediatric residents who do seek advanced training. Also, the number of current trainees preparing for a vigorous independent scientific career is not known. In addition, the ability of medical departments to sustain an expensive laboratory and clinical scientific effort in the foreseeable future is uncertain.

The revolution in health care funding has severely limited the finances needed for medical education and research. Many programs simply cannot afford to pay for faculty who pursue traditional academic paths. Even a fully funded research investigator needs to have an additional subsidy of 30-40 percent of total research costs, to support organizational expenditures for infrastructure. The recently initiated NIH Loan Repayment Program, which gives priority to pediatric researchers, is an important initiative for supporting new investigators. The Task Force applauds this initiative, but notes that additional efforts are needed to ensure that a well-trained cadre of researchers and practitioners will be available to sustain research on pediatric cardiovascular disease in the near future.

Examples of approaches to address the issues in this area include, but are not limited to, the following:

- Evaluation of strategies (e.g., the NIH Loan Repayment Program, the new NHLBI skills development provision for multicomponent clinically oriented research) to encourage and support clinicians interested in becoming independent investigators
- Optimization of strategies to develop centers for training scientists in developmental biology, genetics, population science, and information technology.

## Conclusion

We are entering an exciting era in medicine characterized by human genomics, cell engineering, and the promise of increasingly sophisticated technology. Predicting the future

is always hazardous. Contemplating opportunities, however, provides a framework for allocating resources and preparing the next generation of scientists and clinicians. The goal of the Task Force was to identify the high potential areas for basic science, clinical investigation, and population-based studies. The issues and recommendations discussed by the Task Force are central to understanding the causes of pediatric cardiovascular diseases, improving clinical care for them, and eventually preventing them and their complications. The utility of our efforts will only become apparent with time.

## Selected References

The following selected references are provided for individuals interested in research on pediatric cardiovascular disease. This list is not intended to be comprehensive or to convey important contributions from individual studies, but, rather, to reflect recent research in the field.


Anversa P, Nadal-Ginard B: Myocyte renewal and ventricular remodeling. *Nature* 2002; 415:240-3.

Care of the Adult With Congenital Heart Disease. Presented at the 32nd Bethesda Conference, Bethesda, Maryland, October 2-3, 2000. *J Am Coll Cardiol* 2001;37:1161-98.

Daniels SR: Cardiovascular disease risk factors and atherosclerosis in children and adolescents. *Curr Atheroscler Rep* 2001;3(6):479-85.

Deckelbaum RJ, Williams CL: Childhood obesity: The health issue. *Obes Res* 2001;Suppl 4:239S-43S.

Epstein JA: Developing models of DiGeorge syndrome. *Trends Genet* 2001;17(10):S13-17.

Franz WM, Muller OJ, Katus HA: Cardiomyopathies: From genetics to the prospect of treatment. *Lancet* 2001;358(9293):1627-37.

Gelb BD: Genetic basis of syndromes associated with congenital heart disease. *Curr Opin Cardiol* 2001 (May);16(3):188-94.

Godfrey KM, Barker DJ: Fetal programming and adult health. *Public Health Nutr* 2001;4(2B):611-24.

Goldmuntz E: The epidemiology and genetics of congenital heart disease. *Clin Perinatol* 2001 (March);28(1):1-10.

Hewitt M, for the Committee on Quality of Health Care in America and the National Cancer Policy Board: Interpreting the Volume–Outcome Relationship in the Context of Health Care Quality: Workshop Summary. Washington, DC: National Academy Press, 2000.

Hornberger LK, Barrea C: Diagnosis, natural history, and outcome of fetal heart disease. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu* 2001;4:229-43.

Jacobs S, Falk V: Pearls and pitfalls: Lessons learned in endoscopic robotic surgery - the da Vinci experience. *Heart Surg Forum* 2001;4(4):307-10.

Kaji EH, Leiden JM: Gene and stem cell therapies. *JAMA* 2001;285:545-50.

Lohr JL, Yost HJ: Vertebrate model systems in the study of early heart development: Xenopus and zebrafish. *Am J Med Genet* 2000;97(4):248-57.

Moorman AFM, de Jong F, Denyn MMFJ, Lamers WH: Development of the cardiac conduction system. *Circ Res* 1998;82:629-44.

Phoon CK: Circulatory physiology in the developing embryo. *Curr Opin Pediatr* 2001 (October);13(5):456-64.

Rosenquist TH, Finnell RH: Genes, folate and homocysteine in embryonic development. *Proc Nutr Soc* 2001 (February);60(1):53-61.

Saiki Y, Rebeyka IM: Fetal cardiac intervention and surgery. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu* 2001;4:256-70.

Small Clinical Trials: Issues and Challenges. Washington, DC: National Academy Press, 2001.

Smith BR: Magnetic resonance microscopy in cardiac development. *Microsc Res Tech* 2001 (February) 1;52(3):323-30.

Sodian R, Hoerstrup SP, Sperling JS, Daebritz SH, Martin DP, Schoen FJ, Vacanti JP, Mayer JE Jr.: Tissue engineering of heart valves: in vitro experiences. *Ann Thorac Surg* 2000;70:140-44.

Srivastava D: Genetic assembly of the heart: Implications for congenital heart disease. *Annu Rev Physiol* 2001;63:451-69.

Stainier DY: Zebrafish genetics and vertebrate heart formation. *Nat Rev Genet* 2001 (January);2(1):39-48.

Stock UA, Vacanti JP: Tissue engineering: Current state and prospects. *Annu Rev Med* 2001;52:443-51.

Stoddard JJ, Cull WL, Jewett EAB, Botherton SE, Mulvey HJ, Alden ER: Providing pediatric subspecialty care: A workforce analysis. *Pediatrics* 2000;106:1325-33.

Ten Eick AP, Reed MD: Clinical pharmacology research in the pediatric patient: The challenge continues. *Prog Pediatr Cardiol* 2000;12:29-35.

Towbin JA, Bowles NE: Arrhythmogenic inherited heart muscle diseases in children. *J Electrocardiol* 2001;34 Suppl:151-65.

Towbin JA, Bowles NE: The failing heart. *Nature* 2002;415:227-33.

Trivedi KR, Azakie A, Benson LN: Collaborative interventional and surgical strategies in the management of congenital heart lesions. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu* 2001;4:185-07.

Tunnessen WW, Gurerin RO, Stockman JA, Pediatric Workforce: Data from the American Board of Pediatrics. *Journal of Pediatrics* 2001;139(2):311-6.

Waitzman NJ, Scheffler RM, Romano PS: The Cost of Birth Defects: Estimates of the Value of Prevention. Lanham, MD: University Press of America, Inc., 1996.

Yelon D: Cardiac patterning and morphogenesis in zebrafish. *Dev Dyn* 2001;222(4):552-63.

## Task Force on Research in Pediatric Cardiovascular Disease

## Task Force Cochairs

Edward B. Clark, M.D.
*Wilma T. Gibson Presidential Professor and Chair*, Department of Pediatrics
University of Utah School of Medicine
*Medical Director*
Primary Children's Medical Center
Salt Lake City, Utah

Arthur Garson, Jr., M.D., M.P.H.
*Vice President*
Texas Children's Hospital
Houston, Texas

## Subgroup Chairs

### Basic Science

Arnold Strauss, M.D.
*James C. Overall Professor and Chair*
Department of Pediatrics
Vanderbilt University School of Medicine
Nashville, Tennessee

### Population Science

Ronald M. Lauer, M.D.
*Professor of Pediatrics and Epidemiology*
Department of Pediatrics
University of Iowa Hospitals and Clinics
Iowa City, Iowa

### Clinical Science

Jane W. Newburger, M.D., M.P.H.
*Professor of Pediatrics*
Harvard Medical School
*Associate Cardiologist-in-Chief*
Department of Cardiology
Children's Hospital
Boston, Massachusetts

## Basic Science

Arnold Strauss, M.D. (Chair)
*James C. Overall Professor and Chair*
Department of Pediatrics
Vanderbilt University School of Medicine
Nashville, Tennessee

Michael Artman, M.D.
*Professor of Pediatrics and Physiology*
Pediatric Cardiology
New York University School of Medicine
New York, New York

H. Scott Baldwin, M.D.
*Professor,* Pediatrics and Cell and Developmental Biology
*Vice-Chair in Pediatrics* for Laboratory Sciences
Vanderbilt University Medical Center
Nashville, Tennessee

Lynn Mahony, M.D.
*Professor of Pediatrics*
Department of Pediatrics
University of Texas Southwestern Medical Center
Dallas, Texas

Eric Olson, Ph.D.
*Professor and Chair*
Department of Molecular Biology
University of Texas Southwestern Medical Center
Dallas, Texas

H. Joseph Yost, Ph.D.
*Director, Center for Children*
Huntsman Cancer Institute
*Professor*
Department of Oncological Sciences
*Adjunct Professor*
Department of Pediatrics
University of Utah
Salt Lake City, Utah

## Clinical Science

Jane W. Newburger, M.D., M.P.H. (Chair)
*Professor of Pediatrics*
Harvard Medical School
*Associate Cardiologist-in-Chief*
Department of Cardiology
Children's Hospital
Boston, Massachusetts

Tal Geva, M.D.
*Director of Cardiac MRI and Senior Associate in Cardiology*
Department of Cardiology
Children's Hospital
*Associate Professor, Pediatrics*
Harvard Medical School
Boston, Massachusetts

Thomas Graham, M.D.
*Ann and Monroe Carell Jr. Family Professor of Pediatric Cardiology*
*Director,* Division of Pediatric Cardiology
Vanderbilt Medical Center
Nashville, Tennessee

Frank Hanley, M.D.
*Professor of Cardiothoracic Surgery*
*Director,* Children's Heart Center at
Lucile Packard Children's Hospital
Stanford, California

James Lock, M.D.
*Chairman and Cardiologist-in-Chief*
Department of Cardiology
Children's Hospital
Boston, Massachusetts

Robert E. Shaddy, M.D.
*Professor of Pediatrics*
Primary Children's Medical Center
University of Utah School of Medicine
Salt Lake City, Utah

Gary D. Webb, M.D.
Toronto General Hospital
Toronto, Ontario

## Population Science

Ronald M. Lauer, M.D. (Chair)
*Professor of Pediatrics and Epidemiology*
Department of Pediatrics
University of Iowa Hospitals and Clinics
Iowa City, Iowa

Terri H. Beaty, Ph.D.
*Professor*
Department of Epidemiology
The John Hopkins University School of
Hygiene and Public Health
Baltimore, Maryland

Adolfo Correa, M.D., Ph.D.
*Medical Epidemiologist*
Division of Birth Defects and Developmental
Disabilities
National Center on Birth Defects and
Developmental Disabilities
Centers for Disease Control and Prevention
Atlanta, Georgia

Curt D. Furberg, M.D., Ph.D.
*Professor of Public Health Science*s
Department of Public Health Science
Wake Forest University School of Medicine
Winston Salem, North Carolina

## Ex officio

Roberta G. Williams, M.D.
*Vice President of Pediatrics and*
*Academic Affairs*
Children's Hospital-Los Angeles
Los Angeles, California

**NHLBI Staff**

**Coordination:**

Carl A. Roth, Ph.D., LL.M.
*Associate Director for Scientific Program Operation*

Judy Corbett
*Program Analyst*
Office of Science and Technology

Nancy Eng
*Program Analyst*
Office of Science and Technology

**Resources:**

Gail D. Pearson, M.D., Sc.D.
*Leader, Heart Development, Function, and Failure Scientific Research Group*
Division of Heart and Vascular Diseases