Trends in Congenital Heart Disease
The Next Decade

John K. Triedman, MD; Jane W. Newburger, MD, MPH

Congenital heart disease (CHD) is the most common class of major congenital malformations. Although there is slight variation between many population-based studies, CHD occurs in ≈1% of live births, with similar prevalence throughout the world,1–3 and in 10% of aborted fetuses.4 It is also the leading cause of mortality from birth defects.5 Approximately one-quarter of the 40,000 children born with CHD annually in the United States require intervention in the first year of life. In the 60 years since the first successful repair of a congenital heart defect using cardiopulmonary bypass in 1953, the accurate diagnosis and effective treatment of even the most complex congenital heart lesions have become standard practice. Critical CHD is often lethal in the absence of treatment, and effective surgical, catheter, and medical therapies have dramatically extended life expectancy. With advances in the survival of patients with CHD, there have been major demographic shifts, so that adult patients with CHD now outnumber children even with complex CHD.6

The expected surgical outcomes for patients with simpler congenital cardiovascular lesions (eg, typical forms of septal defects) have continually improved7 and have long since reached a very high level of excellence. These procedures can now be reasonably viewed as a commodity, which is widely available in the developed world. In treatment of simpler lesions, research is increasingly focused on methods to increase the safety, efficiency, and value of therapeutic procedures, and to provide high-quality alternatives to children in nations with resource-constrained healthcare infrastructure and budgets, as well. On the other end of the spectrum of disease severity, outcomes continue to improve in patients with more complex lesions (Figure 1).8 Survival through childhood is now common even in the most complex and lethal malformations, such as hypoplastic left heart syndrome.9 However, as the dramatic early benefits of cardiac intervention and surgical repair in childhood have become routine, the sequelae of CHD and its treatments have increasingly emerged in adulthood10 (Figure 2).

Projecting the future evolution of pediatric cardiovascular medicine requires an appreciation of the historical trajectory of innovation and the current status quo. Innovative approaches to procedures, patient management, and clinical research have driven the field of pediatric cardiovascular medicine from its inception. Examples of life-saving technologies in CHD include advances in surgical technique, development of intensive care management and myocardial preservation techniques, and the introduction of interventional cardiology, high-resolution imaging, transplantation medicine and extracorporeal support, and interventional electrophysiology. Among the most notable are the introduction of techniques for stabilizing critically ill newborns (prostaglandin therapy, balloon septostomy) and neonatal reparative and palliative surgery for the most complex lesions, eg, primary repair of tetralogy of Fallot, the arterial switch procedure for d-transposition of the great arteries, and the Norwood procedure for hypoplastic left heart syndrome. Indeed, the maturation of the field of neonatal surgery is evidenced by a National Heart, Lung, and Blood Institute (NHLBI)–funded multicenter randomized clinical study comparing the outcomes of 2 types of palliative staged operations for children with hypoplastic left heart syndrome and other single right ventricle disorders.12–14

Patients with single ventricle are living longer with the evolutionary development of the Fontan procedure as a staged palliation.15

Management of CHD has been further refined by the design of catheter-delivered devices to close septal defects and replace insufficient valves. Cardiac MRI and other advanced imaging techniques have allowed unparalleled noninvasive quantification of anatomy and function, and the electrophysiological sequelae have been treated with catheter ablation and implantable cardioverter defibrillators and other cardiac rhythm management devices. Other devices originally designed for adults, such as ventricular assist devices, are being adapted to infants and children.16,17 The development of fetal echocardiography has provided a window into the evolution of CHD in utero, and fetal intervention, the possibility to potentially alter its course.18,19 The pharmacology of cardiovascular medications has been more rigorously studied in young children and in those with Fontan physiology, and clinical trials to obtain pediatric labeling have been promoted through the exclusivity extension provision under the Food and Drug Administration Modernization Act.20 Concurrent with these advances, we have seen the training and clinical maturation of a generation of physicians and allied healthcare practitioners, who have disseminated the knowledge and skills needed to treat pediatric and CHD globally.

This admittedly selective listing highlights the historical focus of the field on surgical and interventional management of children born with CHD. The research describing and
validating these extraordinary procedural and technical innovations has been described and communicated in reports and case series of children, often critically ill with their underlying heart disease. Recently, technical innovations in acute therapies have been complemented by increasing attention to the systematic study and improvement of clinical outcomes. This new focus exposes a fundamental challenge facing researchers in pediatric cardiovascular medicine: cardiovascular disease in children is anatomically diverse; it comprises many combinations and permutations of rare lesions. Even the highest-volume centers thus have small subpopulations of patients with specific heart lesions available for the study of therapies that have more incremental efficacy than the breakthrough interventions in the 1960s through the 1980s. In addition, given the continuous evolution of treatment strategies and the relatively long life expectancies of survivors of cardiac interventions, the long-term efficacy of different treatment strategies is difficult to compare over time. Moreover, treatment strategies are continuously evolving, and sequelae may take years or even decades to become manifest, hindering comparison of the efficacy of different approaches.
What Next?

Several emerging trends will change the landscape of pediatric cardiovascular medicine in the areas of basic and translational research, clinical practice, training, and organization of systems of care. Given the prevalence of anatomic congenital defects in the field, it seems very likely that in 10 years’ time, the foundation of practice will still be based on increasingly powerful imaging tools, surgical and catheter-based intervention, and physiological management of critically ill patients, especially those in the critical period of neonatal and infant life. Innovation will continue in many areas in the field, but increasing emphasis will be given to informing clinical practice as to the effective use of our expanding diagnostic and therapeutic armamentarium. The very strength of our present and growing abilities to diagnose and treat anatomic cardiovascular defects in a critical care setting highlights the need and the potential for development of new models of care. These models will be patient centered and increasingly personalized, and will take advantage of increasing opportunities for collaborative research performed across multiple centers. They will leverage recent advances in genetic medicine, regenerative biology and novel informatics, and bioengineering methods and technologies, and will provide a blueprint that will span the life cycle of the patient and family, integrating inpatient episodes of care with outpatient management and, in some cases, end-of-life care.

We will review the current state of the art in the many specialized components of diagnosis and care that currently impact cardiovascular disease in children and young adults. These include the genetics of cardiovascular disease, prenatal development, surgical and interventional management of patients with CHD, and the management of heart failure. We will discuss the transition of pediatric care into adult life, as these patients survive through their childhood with a novel set of cardiovascular problems rarely encountered before the era of effective cardiac intervention. We will then look forward to anticipating the trajectory of pediatric cardiovascular care over the next decade from the perspective of patient-centered care, recognizing both the scientific and societal changes that are currently affecting this broad area of practice. Pediatric noninvasive imaging and intervention will be detailed in greater depth in other articles in this series.

Genetics in CHD

Most congenital heart defects are believed to have a genetic basis, and an epidemiological study has shown that the overall relative risk of CHD among first-degree relatives ranges from 3 to 80 for concordant and $\approx 2$ for discordant defects.21,22 Certain genetic abnormalities occurring in a minority of patients, including chromosomal disorders, microdeletions, or mutations, have long been associated with CHD.23 Recently, analyses of exomic mutations, copy number variants, and candidate gene resequencing in CHD patients have identified de novo and deleterious variants in genes with critical functions in the regulation of developmental transcriptional networks.24 A wide range of mutations have been identified in CHD patients,25 affecting rare variants in molecules that modify chromatin, regulate proliferation/differentiation decisions, and broadly regulate transcription or more selectively activate cardiac gene transcription (Figure 3).26–28

Despite this progress, the genetic etiology of CHD is currently discernible in only 30% of cases, although damaging exomic mutations are more common among patients with neurodevelopmental disability and congenital anomalies.29 This fraction will continue to increase, as presently unidentified genetic causes of CHD are characterized. These will include variants in sequences that are poorly annotated (eg, synonymous variants that function as splice enhancers/
We can expect the future to bring the identification of new classes of CHD mutations and novel insights into the pathways that these mutations impact and a better understanding of genes that modify the responses to hemodynamic and environmental stress, as well. Because the number of causative variants is large and the frequency of causative variants for individual genes is low, sufficiently sizeable cohorts of probands and parents must be assembled across multiple centers, as is currently achieved in the NHLBI Pediatric Cardiac Genomics Consortium. Ongoing and future collaborations between pediatric cardiologists and surgeons, geneticists, developmental biologists, and bioinformaticians are expected to identify new classes of CHD mutations and provide novel insights into the pathways that these mutations impact, and to elucidate the relationship of particular genetic abnormalities with clinical outcomes, including postoperative course and neurodevelopment. In addition, increasing knowledge of developmental pathways will allow for the development of cellular models of CHD through production of induced pluripotent stem cells with mutations related to CHD and other cardiomyopathies and arrhythmias that are congenitally expressed. With precision medicine, these discoveries will advance opportunities to improve the health of CHD patients through earlier and more accurate diagnosis, prediction of response to therapies, and outcome prognostication.

Regenerative Medicine and 3-Dimensional Printing
Augmenting the historical importance of surgical procedure and catheter-based intervention in the field, the research domains of regenerative medicine and 3-dimensional printing are emerging into the translational stage of research and development. These technologies offer the promise of durable and patient-specific, bioengineered replacement parts, both singly and in combination. Direct stem cell therapies related to myocardial regeneration and growth in culture of usable tissue prostheses have to some degree been an unfulfilled promise to date, but the huge potential for major impact throughout medicine will hopefully lead to clinical applications targeting and perhaps originating within the field of pediatric cardiology. This potential impact in our field is large, given the anatomic diversity and current limitations on valve and conduit prostheses related to growth and durability, and further enhanced with the possibility of engineering and implanting functional tissue properties (eg, insertion of electrically competent conduction tissue). Further innovation in this area will include the development of more durable bioprosthetic valves. Three-dimensional printing techniques are already being used in demonstration for planning of complex surgical maneuvers in CHD (Figure 4), and the development of anatomically specific valve and vascular prostheses will also likely make use of this technology. Such innovation in this area will be further advanced and supported by exploration of the use of volume imaging technologies such as MRI for computational assessment of ventricular function, hemodynamics, and outcome risk and possibly even as a direct navigational tool for cardiac intervention. We also expect to see further development of novel robotic tools and augmented reality platforms for catheter-based and other less invasive cardiac interventions.

Neurodevelopment in CHD
As survival of patients with critical CHD continues to improve, long-term neurodevelopmental and cognitive disabilities have emerged as the most common comorbid outcome. In comparison with normative populations, survivors of infant heart surgery have more problems with reasoning, learning, executive function, inattention and impulsive behavior, language skills, and social skills. The past decade has heightened awareness of neurocognitive challenges in children with CHD, and American Heart Association recommendations now provide guidance to pediatric caregivers about the need for regular screening for those at high risk.
The earliest prospective trials focused on intraoperative bypass management strategies as a potential modifiable risk factor for adverse neurodevelopmental (ND) outcome. Subsequent data have shown the greater importance of sociodemographic patient and preoperative factors, and postoperative morbidity. However, these factors together explain only one-third of the variance in ND outcomes. The next decade will bring breakthroughs in understanding the sources for the remaining variance in neurocognitive outcomes. Using whole genome sequencing and other genetic technologies, we will better understand the role of genetic and epigenetic contributions to ND disabilities in CHD patients. In-exome sequencing of CHD parent-offspring trios gathered in the Pediatric Cardiac Genomics Consortium recently demonstrated an excess of protein-damaging de novo mutations; such mutations occurred most frequently in genes highly expressed in the developing heart and brain, and affected genes involved in morphogenesis, chromatin modification, and transcriptional regulation. These damaging mutations were present in 1 in 5 CHD patients who had ND disability or noncardiac anomalies, but only in 2% of those with CHD but without ND or noncardiac anomalies.

In addition, abnormalities of brain development and metabolism may relate to in utero disturbances, such as abnormalities in cerebral hemodynamics and substrate supply in fetal life, especially in fetuses with abnormalities of aortic outflow as in hypoplastic left heart syndrome and transposition of the great arteries, in which cerebral blood flow is more desaturated than normal. Therapies to improve fetal brain development such as maternal oxygen delivery may be tested and refined.

Many effects of ND comorbidities associated with CHD remain to be investigated. Neurocognitive function has not yet been well studied in the adult with CHD, and future research will delineate the relationship between deficits such as executive dysfunction and later employability, relationships, and quality of life. Advanced brain MRI techniques, such as brain surface topology, quantitative T1 and T2 mapping, and structural and functional connectivity, will better delineate the relationship between brain structure and function, and genetic underpinnings, as well, in the CHD population. Finally, although the high prevalence of ND disabilities has been described, novel interventions to help school performance, transition to adult care, and compliance with cardiological follow-up should be developed and tested in the future.

**Adults With CHD**

An important epidemiological consequence of the success of CHD management is that the population of adults with congenital heart disease (ACHD) has grown steadily, even in those categories of disease designated as severe and formerly characterized by high mortality in infancy and early childhood. Numbering an estimated 1.3 million in the United States by 2010, adults with CHD now are more numerous than children and constitute 60% of the total CHD population.
Although many ACHD patients lead lives that are functionally normal or near normal, as a group, the effects of their CHD diagnosis and the consequences of their care in early life are easily identified. In comparison with the general population, mortality is significantly higher in ACHD patients (Figure 6). Common comorbidities include heart failure, which may result from residual structural problems (eg, valvar insufficiency), the sequelae of cardiac repair (eg, ventriculotomy), or the underlying congenital lesion itself (eg, abnormal loading of systemic right ventricle), and progression to heart transplantation is increasingly common.\textsuperscript{74} Arrhythmias are prevalent, resulting from congenital abnormalities, perioperative insult, and hemodynamic pathophysiology.\textsuperscript{75} They pose a significant clinical burden resulting in symptoms and risk of cardiac death, and ablation and pacing/implantable cardioverter defibrillator therapy may be difficult to apply effectively in CHD. Not surprisingly, an increased burden of thromboembolism and stroke is observed.\textsuperscript{76} Exercise intolerance and reduced oxygen consumption is prevalent, especially in patients with complex forms of CHD,\textsuperscript{77–79} and progressive hepatic fibrosis occurs in patients with elevated systemic venous pressures.\textsuperscript{80,81} Not surprisingly, among adult
women with CHD who become pregnant, adverse cardiovascular events occurring in pregnancy and childbirth are considerably more likely during admission for delivery than the general population, particularly among those with complex CHD or pulmonary hypertension. As a result of these pathophysiologies, significant, lesion-specific effects on life expectancy can be forecast (Figure 7).

Given recent, active trends in basic and clinical research and development of new care delivery models targeted at this patient population, areas of ACHD medicine that are likely to advance quickly can be predicted. Improved understanding of the cardiomyopathy associated with surgical scarring and chronic pressure volume overload and the unique issues of ventricular performance associated with the systemic right ventricle and univentricular hearts will lead to better strategies to mitigate and prevent the development of myocardial failure. There will be greater appreciation for and therapeutic attention paid to the extracardiac consequences of chronically palliated CHD, including abnormalities of hepatic, renal, pulmonary, and lymphatic function that complicate long-term clinical outcomes or, even in some cases, result in late mortality. The ACHD population has been well characterized from a social medicine perspective, and many of the barriers and challenges facing these patients in their transition from childhood to adult life with respect to transition to adult care, general access to appropriate medical care, and educational and occupational achievement have been identified. Psychosocial morbidities in the ACHD population include an increased prevalence

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**Figure 6.** Comprehensive study of overall rates and disease-specific causes of death in adults with congenital heart disease in the Netherlands (the CONCOR study). A, Mortality rate in CONCOR patients and in the general Dutch population by decade in 2007. Sample sizes in CONCOR by age group 20 to 30 (n=1967), 30 to 40 (n=1378), 40 to 50 (n=837), 50 to 60 (n=514), 60 to 70 (n=246), and 70 to 80 (n=101). B, Proportional distribution of causes of death by defect in deceased patients (n=197). AoS/BAV indicates aortic stenosis/bicuspid aortic valve; ASD, atrial septal defect; AVSD, atrioventricular septal defect; cc-TGA, congenitally corrected transposition of the great arteries; CoA, aortic coarctation; DORV, double outlet right ventricle; Ebstein, Ebstein’s anomaly; Marfan, Marfan syndrome; PA, pulmonary atresia associated with ventricular septal defect; PS, pulmonary stenosis; TA, tricuspid atresia; TGA, transposition of the great arteries; ToF, tetralogy of Fallot; UVH/DILV, univentricular heart/double inlet left ventricle; and VSD, ventricular septal defect. Reprinted from Verheught et al with permission. Copyright © 2010, European Society of Cardiology.
Development of improved, portable ventricular assist devices should reduce associated morbidities, such as stroke, and will increasingly allow for treatment of smaller patients and for patients awaiting heart transplant to be cared for and monitored at home. Other novel approaches for myocardial failure are available, but their cost-effectiveness and specific roles have yet to be determined. An example is the use of resynchronization therapy, which has been extensively used in adults with left ventricular dysfunction but not yet systematically and prospectively studied in complex heart disease, and, as a result, it does not yet have a clearly defined role in management. We expect the next decade to bring more rigorous evaluation of resynchronization therapy and cell therapies in children with heart failure.

End-of-Life Care
In the current era, one can prolong the end of life with various advanced therapies, leaving children and families tethered to a hospital environment to receive medical and nursing support. In hospital environments and cardiovascular programs designed to provide cutting-edge technology, it is difficult to continually reassess potential for meaningful recovery in dying patients and to provide skilled and sensitive care as the goals of that care are redirected. Nonetheless, failure to recognize, reach consensus on, and respond in a compassionate manner to impending death in terminally ill children with heart disease are at present major reasons for dissatisfaction among families whose children are cared for in the cardiac intensive care unit. and ones that challenge caregivers with ethical and moral dilemmas that are stressful and difficult to resolve. As the population of chronically and terminally ill children with heart disease increases, we predict that the next decade will bring an increased emphasis on quality of life and, concomitantly, the growth and dissemination of expertise in palliative care for children with heart disease.

Evidence-Based Practice and Outcomes Research
In addition to topical areas of advance in the field, there is a revolution underway in how research in cardiovascular medicine is performed. A comprehensive discipline of evidence-based practice in pediatric cardiovascular medicine will likely mature in the next decade based on newly available sources of data, collaborative research practice, and a patient-and family-centered interdisciplinary approach to care and the evaluation and measurement of clinical outcomes. We expect to see rapid evolution of the means by which we develop and validate new knowledge, both regarding the underlying mechanisms of disease and the most effective and safe means of delivering therapy. Efforts to enhance sample size and generalizability of inferences in outcomes research in pediatric and CHD have benefited from the development of multicenter consortia and collaborative study groups such as the Society for Thoracic Surgery (STS) and European Association for Cardio-Thoracic Surgery, the Pediatric Heart...
Network (PHN), and administrative data sources, as well, such as the Pediatric Health Information System or the Kids’ Inpatient Database. Data analyses using these networks or consortia have been complemented by research performed within certain geographical regions, such as the country of Denmark and the province of Quebec in Canada, with centralized healthcare administration and excellent national databases allowing for tracking of vital statistics and health outcomes. Existing resources and deficiencies in this area are already being assessed with the formulation of practical clinical guidelines applicable to specific subspecialty areas, such as recent publications in adult congenital medicine and electrophysiology. Targeted questions in cardiac surgical practice and pharmacological treatment of CHD, Kawasaki disease, and Marfan syndrome have been addressed using high-quality randomized clinical trials under the auspices of the PHN. New approaches to investigation of clinical practice are likely to increasingly use models of collaborative, structured learning in the field, such as Standardized Clinical Assessment and Management Plans, which have proved valuable in collecting and analyzing data on common conditions in which there is significant variation of clinical practice. In addition, registries (see below) will continue to enable research on conditions that are not well suited to randomized, controlled trials.

Over the past decade, the emergence of digitally networked and interoperable clinical and research databases has dramatically increased the volume and variety of data available on pediatric cardiovascular patients, its accessibility to researchers, and our capacity for collaboration across multiple centers. Research in pediatric and congenital heart disease will increasingly be derived from the analysis of data captured in the course of clinical care, both as a matter of routine and in response to specific research and quality improvement questions. Although the challenges and opportunities afforded by this massive information stream are commonly lumped together under the rubrics of big data, quality improvement, and multicenter collaborative research, there are several different types of data and research models that will be integrated and exploited for the benefit of pediatric and congenital heart disease care and for the efficient management of healthcare systems.

Figure 8. The family of devices developed under the Pediatric Circulatory Support Program: the PediPump Ventricular Assist Device showing application for biventricular support (A), the PedialFlow Ventricular Assist System (B), the Penn State Infant VAD (C), Ension’s pCAS system with prototype controller console (D), and the infant size Jarvik 2000 showing thrombus-free bearings after 5 weeks in lamb animal model (E). VAD indicates ventricular assist device. Reprinted from Baldwin et al94 with permission of the publisher. Copyright © 2011, American Heart Association, Inc.
Real-Time Data Capture

Enormous volumes of physiological data stream through various monitors and devices used for cardiac care. In the past, these data were evanescent and difficult to pull together, but in recent years the expansion of network technology and cloud storage and the development of common protocols have resulted in a rich trove of multidimensional data sets. Such data may be used to study care processes retrospectively, for example, to assess variability in care, evaluate the evolution of adverse events, and improve resource use. Integrating real-time physiological data with outcomes data will assist in the prevention and early recognition of adverse events, facilitate the use of genetic data to allow for personalized treatments, and help understand the impact of perioperative and peri-procedural events and decision making with long-term outcomes such as late survival and quality of life. To date, studies have identified only a few modifiable factors related to critical care that clearly contribute to outcomes (see, for example, the Single Ventricle Reconstruction trial from the PHN). This reflects, in part, our present limitations in data capture and analysis. The potential for identification of such modifiable factors with better data capture is demonstrated by recent work examining the effects of technical performance in congenital heart surgeries on outcomes and costs. Streaming physiological data and improved connectivity with patient-oriented health databases will also help to extend the perception of caregivers in real time to better appreciate trends predictive of clinical decompensation. Analytic processes that may be embedded into monitoring and data capture may be simple (eg, ad hoc comparison of patient populations along a single physiological or descriptive axis). However, advances in informatics will also allow for multidimensional visualization integrating data streams relevant to ongoing care processes, and are likely to include complex predictive algorithms, based on empirical signal pattern recognition and Bayesian modeling, which forecast physiological trajectory or increased risk of adverse events.

Cardiac Registries and Databases

Sources of variability in the outcomes of CHD treatment include patient diversity associated with the occurrence and combinations of many rare and varied lesions, the technical complexity and operator dependence of treatment approaches, and approaches that vary among institutions and even between physicians within institutions. Early progress in CHD was made in patients with serious diseases for which existing treatments had limited efficacy, and, as a result, the literature highlighted outcomes of novel therapies at single centers of excellence. More generalizable patient outcomes were first gathered through regional registries of cooperating centers. The New England Regional Infant Cardiac Registry, founded in 1968 by Donald Fyler, was the first such registry. It succeeded in defining the incidence of severe CHD, possible etiologic factors, 5-year mortality, and physical and emotional assessment of survivors. The Northern Great Plains Regional Cardiac Program was founded in 1982 by James Moller to collect data from 5 centers in Minnesota, Nebraska, and Iowa. In 1990, the registry was renamed the Pediatric Cardiac Care Consortium, a collaborative multi-institutional registry of cardiac catheterizations, surgical operations, and autopsies performed for infants, children, and adults with CHD.

Led by these historic innovations, an increasing number of national databases now include information important to the care of patients with CHD, connecting investigators from institutions across North America to a greater extent than ever before. Currently active databases may derive from society-sponsored clinical data registries (eg, the STS Congenital Heart Surgery Database, the American College of Cardiology’s Improving Pediatric and Adult Congenital Treatment [IMPACT] Registry, administrative databases (eg, the Pediatric Health Information System), and research databases (eg, the NHLBI’s PHN and Pediatric Cardiac Genomics Consortium). Data can also be derived from electronic health records, industry databases for devices, genetics research registries, and consortia of centers dedicated to missions such as quality improvement (eg, the National Pediatric Cardiome – Quality Improvement Collaborative) or to specific disciplines within pediatric cardiology (PC4; the Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension [TOPP-2] registry, etc). Additional efforts in linking data across institutions comes from the Cardiovascular Research Network, a consortium linking electronic health records across healthcare systems, which is working to extract data on CHD patients using natural language text processing algorithms in unstructured electronic health records. Finally, PEDSnet, a pediatric project within the Patient Centered Outcomes Research Institute is harmonizing data across 8 pediatric academic medical centers, 2 pediatric quality improvement collaboratives, Express Scripts, and IMS Health, which aggregates claims data across payers. Simultaneously with the explosion in high-quality databases, the nomenclature historically used to describe congenital heart lesions has been harmonized by the Multi-societal Database Committee for Pediatric and Congenital Heart Disease. Patient information can now be linked, albeit with some difficulties, across databases to facilitate research on medical outcomes, quality of care, and financial costs related to CHD. Methodologies that improve our ability to link databases within the constraints of regulatory protection of patient privacy will continue to be developed. The value in leveraging information contained in these diverse databases was recently recognized by the NHLBI in its workshop, “An Integrated Network for Congenital Heart Disease Research.” Members of this workshop proposed use of unique patient identifiers, in a fashion similar to that used in research on autism. Because logistic issues may limit the feasibility of this approach, they also proposed indirect methodologies, merging local data sets using a process of deidentification and subsequent aggregation at a central data center. The availability of longitudinal patient data has historically been limited, but the future will bring patient/parent stakeholders and national organizations together to systematize the collection of long-term patient outcomes. Finally, using methodology similar to that in the Thrombus Aspiration in Myocardial Infarction (TASTE) study, we anticipate that multicenter trials of the future will rely on data already gathered in existing data registries to reduce the costs of data collection and management.
Risk Stratification in Outcomes Measurement, Quality Improvement, and Regionalization of Care

As mentioned, the development of multicenter registries for outcomes measurement was pioneered in the domain of perioperative cardiac surgical care (STS Congenital Heart Surgery Database), and this database has now been maintained actively for a sufficiently long time that historical trends can be identified. The complex relationship between procedure volume and outcomes has been identified in congenital cardiovascular procedures, and it continues to be refined (Figure 9). In addition to measurement of perioperative surgical mortality and long-term survival, the significance of comorbidities as both measurable outcomes and predictors of surgical mortality and long-term survival, the significance of comorbidities as both measurable outcomes and predictors of other outcomes is increasingly well defined. The concept of quality as a patient-centered, measurable outcome allows quantification of this variability, and although these measures remain elusive in many areas, procedural practices such as catheterization, electrophysiology, and particularly cardiovascular surgery continue to be increasingly well characterized in this regard. Reduction of practice variation has been identified, therefore, as a specific target for several collaborative quality improvement projects, such as the National Pediatric Cardiology – Quality Improvement Collaborative, the Pediatric Cardiac Critical Care Consortium, and the PHN Collaborative Learning Project.

We expect this type of activity to be driven by the increasing efforts of the STS to provide transparent, public access to congenital heart surgery outcomes at a state and national level. However, to make it possible for institutions to support initiatives aimed at measuring outcomes of cardiac surgical and interventional procedures performed on widely varying populations of patients, it is necessary that a basis for comparison of clinical performance be established and carefully validated, to give appropriate credit to providers treating the most high-risk individuals. Further development of models to adjust for differences in case mix across centers, incorporation of useful measures of morbidity in addition to mortality and accurate and standardized measures of resource use will be important components of presenting a comprehensive picture of clinical performance. Methods of risk adjustment for CHD surgery, such as Risk Adjustment in Congenital Heart Surgery-1 (RACHS-1), the Aristotle Complexity Score, and the Society of Thoracic Surgery-European Association for Cardio-Thoracic Surgery (STAT) Congenital Heart Surgery Mortality score, are highly useful in this regard but must continue to be improved. Similar concepts have been proposed for application to interventional catheterization and electrophysiological procedures.

Transparent, public availability of clinical outcomes data is an increasingly important feature of the practice of pediatric cardiovascular medicine. Building on the cooperative spirit of clinical investigators in pediatric cardiovascular research, we also anticipate the growth of learning collaboratives, such as the PHN projects on Collaborative Learning and the Residual Lesion Score. These activities will be critical in any national discussions regarding regionalization of care, a controversial topic that has already been addressed for pediatric cardiac surgical centers in countries with nationalized healthcare systems such as Sweden and the United Kingdom. Centralized planning of healthcare resources has largely been anathema to hospital institutions and advanced health services in the United States, with certain notable exceptions (eg, the United Network for Organ Sharing system for management of scarce organ transplant resources). However, association of payments with quality and outcomes is emerging in many areas of adult medicine. This approach will likely become more relevant to pediatric cardiovascular care in the United States as value-based reimbursement, reporting of risk-adjusted clinical outcomes, and risk-sharing through accountable care organizations become more common. We expect growth in the practice of referral of patients by certain payers to designated centers of excellence, and of statewide and regional efforts, as well, to coordinate care of complex CHD.

Social and Cultural Environment

In addition to the evolution of the field of pediatric and CHD in response to internal drivers, changes in the social and cultural environment are likely to affect the relationships that exist between patients, their families, and social networks and institutional and individual caregivers. Cardiovascular disease by its nature often dictates a need for long periods of outpatient care and management punctuated by dramatic interventions. In the past, patients most typically found themselves on a lifelong journey with a single institutional provider of care represented by a small group of caregivers, often in their home city or region. Access to easy air travel and digitally mediated social networks have combined with transparent access to procedure outcomes, efforts by insurers to increase value and by advanced medical centers to enhance patient volume and revenue, and self-organizing advocacy groups to rewrite the patient-provider experience in cardiovascular care, a trend that will continue in coming years. Increased involvement of the patient and family in the inpatient care process is already the expectation in many hospitals. In the future, it will be increasingly common that patients and their families will have primary relationships with other similarly affected families, mediated by networked social media and to a great extent outside the direct control of physicians and hospitals. These relationships will facilitate forms of self-advocacy that will reshape the nature of traditional care relationships, and are likely to result in new patterns of self-referral and institutional, disease- and procedure-based specialization.

Global Burden of CHD

Finally, over the next decades the advances in the care of children with cardiovascular disease must be made available to the vast number of undiagnosed and untreated or undertreated patients in less-advantaged areas of the world. As mortality attributable to infectious diseases has very gradually been reduced by advances in development, nutrition, public health practices, and vaccination, the global burden of noncommunicable diseases in children has become a target for international
Because of relatively high prevalence of CHD, its significant associated morbidity and mortality, and the availability of powerful curative and palliative therapies and procedures, provision of care in resource-constrained environments constitutes a high priority. The important prevalence of rheumatic heart disease in many developing countries alters the necessary mix of resources and therapy to address the cardiac needs of the young population. Countries such as India and China are in a rapid phase of proliferation of services capable of providing advanced cardiovascular care for children, and in each of these countries, cadres of locally and internationally trained senior physicians and surgeons are leading programs that are both providing clinical services and training younger generations of clinical providers. International support for congenital cardiac services has evolved beyond the scope of medical missions and exchange programs for training, and now includes successful multinational programs to report clinical outcomes with reference to global benchmarks and to enhance those outcomes using quality improvement practice. As this activity increases, it has also become clear that the Western model of cardiovascular care needs to be modified to provide additional value in social economies in which the healthcare budget is strictly limited. Studies of cardiovascular surgery in low- and middle-income countries highlight the enormous expense both to the system and to patients and their families with use of the technological infrastructure deployed to palliate and repair CHD in the West. The design of high-value solutions will foster unique models of care, capable of providing excellent outcomes in the developing world. This process will come full circle when Western healthcare practice recognizes and begins to incorporate practice innovations originating in other parts of the globe.

**Conclusions**

Pediatric cardiovascular medicine and surgery are the beneficiaries of a long, golden age of dramatic, creative progress in surgery, catheter intervention, myocardial preservation, and intensive care. In the 1970s and 1980s, mortality from CHD was so great that virtually every technical innovation resulted in substantial improvements in longevity and outcomes, and a generation of practitioners have been trained and have practiced in the setting of continuous, rapid evolution of their field. Advances in the coming decade will see continued dissemination of the talent and technologies necessary to treat the
common and simpler varieties of CHD, improving the reliability of surgery and intervention, mitigating the long-term morbidity in survivors, and, when possible, personalizing therapy plans to the expectations and needs of the patient and family under treatment. We also expect continued improvements in the survival of patients with rarer problems that are currently unreliably treatable using current approaches, and new, pediatric-specific technologies that will enhance the survival of patients with myocardial failure. Genetic and epigenetic information will be used increasingly frequently to individualize the care of CHD patients, to identify family members at risk, and to counsel with regard to risk of heritable disease. With tissue engineering, we will grow new valves and vascular structures using the cells of individual patients, and use cell therapies to improve myocardial function. Advances in real-time imaging, visualization, and robotics will permit increasingly accurate and less invasive approaches to cardiovascular surgery, catheter-based intervention, and treatment of arrhythmia. Neurodevelopmental disabilities will be identified earlier to allow institution of appropriate interventions and possibly reduced by mitigation of modifiable risk factors. For those who can only be palliated, behavioral interventions will improve resiliency to allow each patient to achieve his or her full potential in the face of lifelong chronic illness.

Informatics and big data will increasingly be used to establish high and reliable standards of care for patients with CHD and to provide collaborative platforms for real-time learning and rapid hypothesis testing. Properly protected data on clinical practice and outcomes will be shared in increasingly comprehensive and open registries, and clinical trials will have primary outcomes that are already gathered in these existing databases. Data mining and collaborative research techniques will be used to target patient-centered outcomes and allow for rapid deployment and testing of these new ideas. Patients will obtain healthcare information and care based on transparent access to risk-adjusted outcomes at medical centers, and care for the most complex diseases may become increasingly regionalized. Relevant, cost-effective cardiovascular care for children with CHD will be provided at high standards in countries around with world with differing levels of wealth and healthcare infrastructure. Multidisciplinary care teams for those with CHD will include specialists in genetics, ethics, quality and healthcare economics, advanced practice nursing, nutrition, and rehabilitation and palliative care. Finally, we anticipate an increasing regulatory burden and expense for the development of new therapies; advances in care increasingly will be weighed against personal and financial costs to the patient, their family, and our society.

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