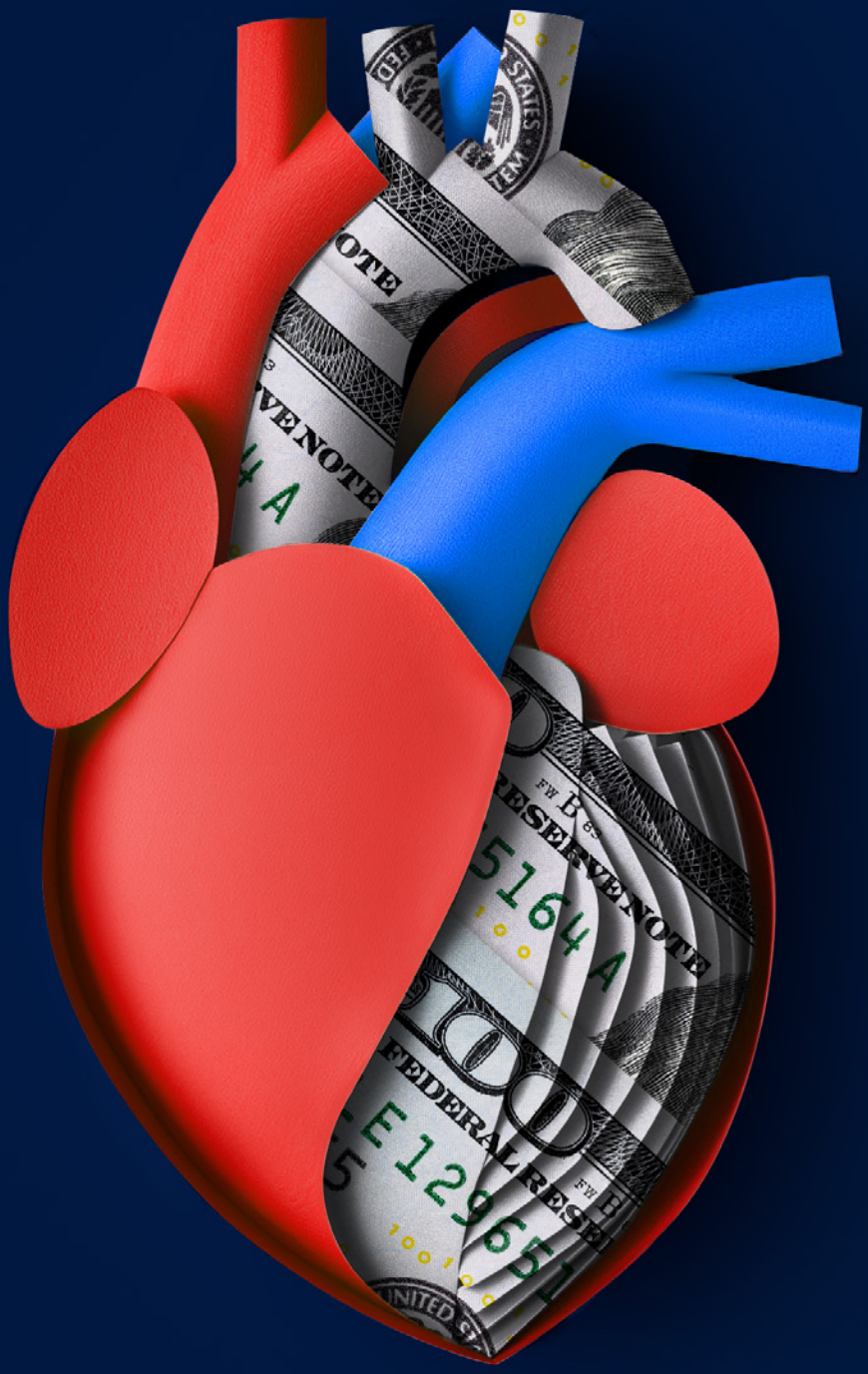

The Cost of Complex Congenital Heart Disease in the US

By Diane M Pickles and Kirstie Keller, PhD | March 2024

ADDITIONAL VENTURES

Additional Ventures thanks IQVIA for their research to develop the Cost of Complex Congenital Heart Disease in the US, led by Pedro Andreu, PhD, Principal, and N. John Atay, Associate Principal.

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In partnership with

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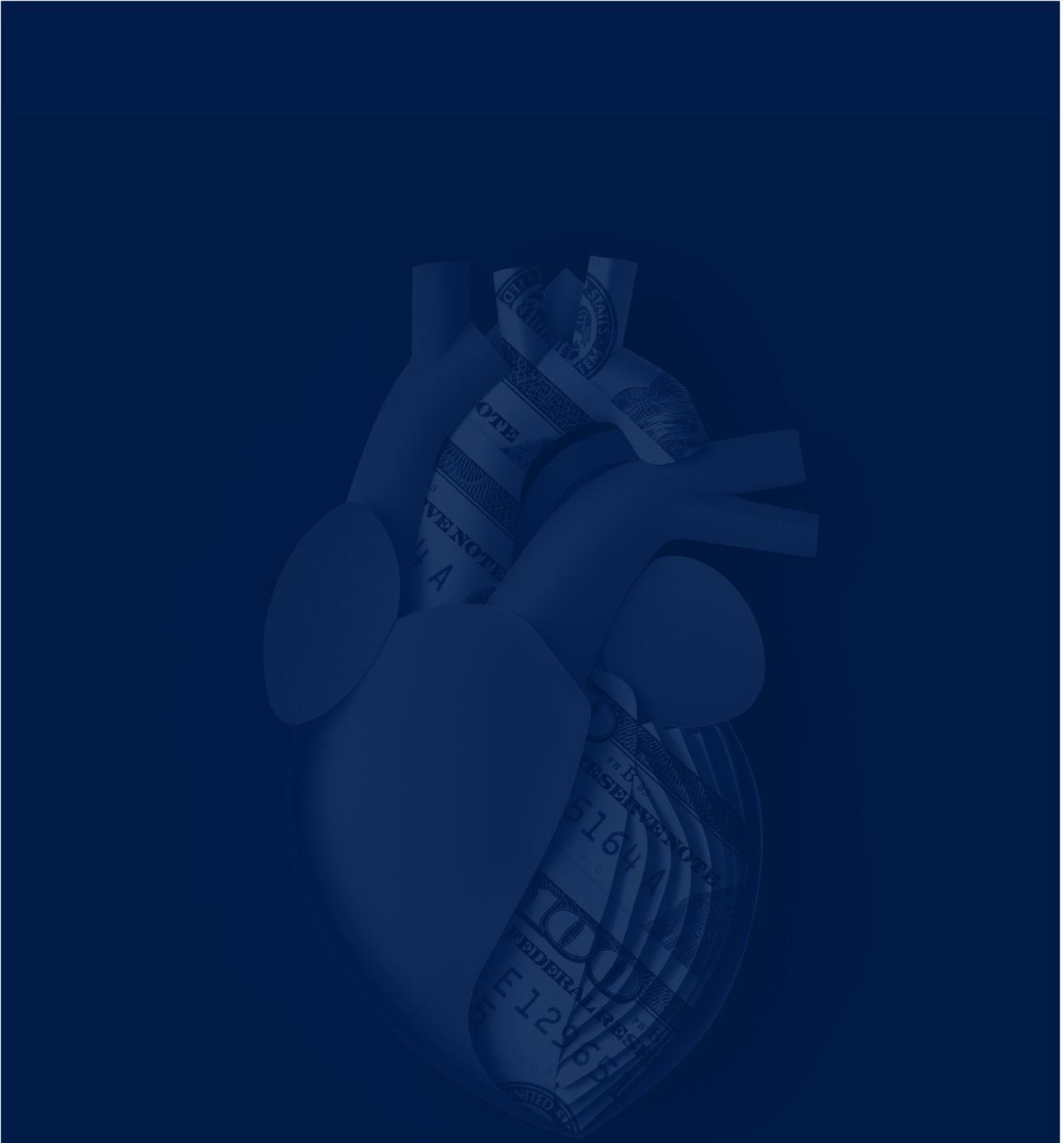
About Additional Ventures

We are a purpose-driven organization leveraging evidence-based research and deep subject matter expertise to make an outsized impact. Our relentless optimism powers bold, high-risk innovations to solve some of humanity's most complex challenges.

Our biomedical research work focuses on a rare form of congenital heart defects called single ventricle heart disease. While this field is in its infancy, with limited knowledge of cause, risk, outcomes, or treatments, we are confident that through coordinated strategic and interdisciplinary work, dynamic teaming, and flexible funding, we can illuminate a functional cure for patients and their families.



Executive Summary

Economic burden of complex congenital heart disease

In the United States, approximately one in 100 children are born with a congenital heart defect (CHD)[1], meaning that the condition occurs before or at birth and affects the structure of the heart. These defects range from simple to complex congenital heart defects (cCHDs). These cCHDs are rare, occurring in about 2.5 in 1000 children[1], and patients require intense care that includes multiple open-heart surgeries during childhood, long-term hospital stays, life-long therapeutic, physical, and/or mental health treatments, and at times mechanical support and organ transplants. In addition, approximately a third of those with cCHDs die in childhood.[2]

Here, we aimed to demonstrate the financial impact of cCHDs on the individual patient and family, the healthcare system, and the US economy. We selected six specific cCHDs and assessed the direct, indirect, and mortality costs of each disease, both individually and as a collective condition. In this study, we evaluated the following specific cCHDs with reliable primary diagnoses: Dextro-Transposition of the Great Arteries (dTGA), Hypoplastic Left Heart Syndrome (HLHS), Pulmonary Atresia with Intact Ventricular Septum (PA-IVS), Tetralogy of Fallot (ToF), Tricuspid Atresia, and Truncus Arteriosus. We found that the enormity of treatment and lifelong care is financially crippling on a per-patient level, as compared to other cardiovascular diseases. Moreover, the data demonstrate that these diseases have an outsized impact on the healthcare system, as related to prevalence. Specifically, we found that:

- The average annual cost of cCHD is nearly $50K per patient, with >45% paid solely by patients and families, which is nearly 8X more than congestive heart failure.
- The average lifetime financial burden for cCHD is $2.2M per patient, which is nearly 14X more than congestive heart failure, with the first five years of life >$650K per patient, with $190K paid directly by families.
- On average, patients lose 31 years of life, which equates to $4.5M in mortality costs.
- The annual economic burden, including mortality, for all cCHDs in the US is $74B.
- Despite their rarity, the lifetime economic burden of cCHD is disproportionately high, costing the US $3.35T in direct, indirect and mortality costs for all patients currently living with a cCHD, with direct and indirect costs 1.3X higher than a common cardiac condition.

As rare diseases, cCHDs are often overlooked in federal and philanthropic programs because their overall economic impact is thought to be dwarfed by other common mass market diseases. However, this study demonstrates that cCHDs have a disproportionate economic impact relative to prevalence, and in some cases, are more burdensome than common cardiac diseases. These results demonstrate the immediate need for increased awareness of cCHD by key policy-making groups to ultimately yield increased research funding, development of comprehensive patient and family financial support services, and improved incentives to pave new pathways for therapeutic and device development for the cCHD community.

Introduction

Congenital heart defects (CHD) are abnormalities in the structure or function of the heart that are present at birth. CHDs are the most common birth defect, affecting approximately **one in 100 live births[1]** and range greatly in severity and complexity. Indeed, some CHDs self-resolve with little or no medical intervention, while others, known as complex congenital heart defects (cCHDs), cause life-threatening complications that require lifelong medical care. Such defects are less common, affecting around **2.5 in 1,000 live births[1]**, and include a multitude of distinct conditions, such as an underdeveloped ventricle or missing valve, that ultimately lead to a dysfunctional heart.

With novel detection and surgical methodologies, most cCHDs have transitioned from universally fatal to treatable conditions with improved life expectancy and care options, yet they remain lifelong. The journey for patients with a cCHD is far from easy, often requiring **multiple open-heart surgeries beginning at birth** and ongoing medical care throughout the patient's childhood and adult life[3]. Moreover, patients face a range of additional comorbidities, which can include pulmonary vascular dysfunction, myocardial dysfunction, arrhythmias, bleeding and stroke, protein-losing enteropathy, liver disease, renal failure, neurodevelopmental defects, and psycho-social challenges, which add layers of complexity to their medical needs. Furthermore, patients with cCHDs have a significantly reduced life expectancy; those with a single ventricle heart defect, a particularly complex form of cCHD, have a five-year survival rate of 38%[4], and those who survive to adulthood can lose up to 47 years of life. At this time, **a normal duration and quality of life are impossible** for most cCHD patients, and the experience of living with such conditions is often filled with physical and emotional pain.

Beyond the medical procedures and long-term care required for cCHDs, these defects impose a considerable financial toll on patients and their families. Indeed, costs begin accruing nearly immediately after diagnosis, as patients require a minimum of one, and often multiple surgical interventions in their first years of life, giving rise to costs both from surgeries and in-patient hospitalizations. Unfortunately, given the chronic nature of cCHD and the many related co-morbidities that arise beyond the palliative surgeries, costs continue to mount. Families and adult survivors experience lifelong financial outputs, which include out-of-pocket (OOP) healthcare payments, time missed from work and school, special education, home renovations, and specialized services such as occupational therapy, physical therapy, and behavioral therapies.

Our findings demonstrate a disproportionate impact on individual patients and families as well as the US economy relative to prevalence as compared to common cardiac diseases.

While there is an obvious medical impact on patients, there is a lack of data available describing the economic impact of these diseases. This minimizes the understanding of the financial effect these diseases have on a per patient or national scale and arguably reduces awareness, research and clinical care funding, and financial support mechanisms for patients and families. Therefore, we sought to create a comprehensive resource that describes the full spectrum of costs and sheds light on how cCHDs impact not just patients, but the US economy. To do so, we examined individual cCHDs as independent case studies, and as a collective condition, and assessed the direct, indirect, and mortality costs associated with these diseases. We included six cCHDs in this study:

- Dextro-Transposition of the Great Arteries (d-TGA)
- Hypoplastic Left Heart Syndrome (HLHS)
- Pulmonary Atresia with Intact Ventricular Septum (PA-IVS)
- Tetralogy of Fallot (ToF)
- Tricuspid Atresia
- Truncus Arteriosus

Detailed information about each of the above cCHDs, including incidence, treatment pathways, and outcomes, are contained in Appendix B.

Here, we report the financial burden on both patients and families suffering from cCHDs and to the US economy. Our findings demonstrate a disproportionate impact on individual patients and families as well as the US economy relative to prevalence as compared to common cardiac diseases. These results demonstrate the immediate need for increased awareness of cCHD by key policy-making groups to ultimately yield increased research funding, development of comprehensive patient and family financial support services, and improved incentives to pave new pathways for therapeutic and device development for the cCHD community.

Methods

Inclusion Criteria

First, we compiled a list of all CHD diagnoses within the United States. We discovered a multitude of presentations, primary diagnoses, and outcomes, with the medical treatment paradigms ranging drastically depending on the degree of the condition. Therefore, an accurate and representative financial analysis of all CHDs was not possible, and we subsequently narrowed the scope of this report. We next looked exclusively at just cCHDs and their presentation, primary diagnoses, and treatment pathways. We found that given their complexity, these are often rife with inaccurate and inconsistent primary diagnoses, which could lead to inaccuracies in the findings. Additionally, cCHDs have a variety of treatment pathways, complicating the forecast of costs associated with each diagnosis. Finally, in consultation with pediatric cardiology experts, we narrowed the present study to examine only those cCHDs with consistent primary coding and defined medical treatment pathways; this limited our analysis to the following six: Dextro-Transposition of the Great Arteries (d-TGA), Hypoplastic Left Heart Syndrome (HLHS), Pulmonary Atresia with Intact Ventricular Septum (PA-IVS), Tetralogy of Fallot (ToF), Tricuspid Atresia, and Truncus Arteriosus. Several are specific types of single ventricle heart defects, an umbrella term used to indicate that only one ventricle is functional.

Evaluation of Healthcare Costs

Costs of care associated with the selected six cCHDs were explored using a non-interventional cross-sectional study design, comprising four principal phases: literature review, medical claims analysis, qualitative expert interviews, and patient and caregiver survey (more detail found in Appendix A).

In short, we reviewed hundreds of papers, assessed claims data from relevant databases, including IQVIA MIDAS, IQVIA National Sales Perspectives (NSP), and the Centers for Medicare & Medicaid Services (CMS), spoke with 30 experts (pediatric cardiologists, adult congenital heart disease cardiologists, cardiac surgeons, and hospital administrators), and conducted a survey of 219 patients and caregivers in the United States.

The overall cost burden was evaluated across three categories (Table 1).

- Direct medical costs encompassing diagnosis, interventions, procedures, medications, and follow-up care. Variances in costs and treatment modalities were examined.
- Indirect costs incurred by cCHD patients and families, including productivity losses and caregiver burden. This included assessing absenteeism, reduced work hours, missed educational opportunities, increased healthcare expenses, and reduced workforce participation.
- Mortality costs associated with premature deaths attributable to cCHD, estimated using Value of Statistical Life (VSL) metrics. Factors such as disease severity and timely interventions were considered.

Cumulative healthcare costs were calculated for each of the selected cCHDs individually as well as a collective condition and compared the data to that of other cardiac diseases and mass market diseases[5].

Table 1	Direct Costs	Indirect costs	Mortality Cost
Definition	– All direct costs related to medical care – This burden is often assumed by payers and patients	– All indirect costs attributed to a specific condition – Economic burden derived from the productivity loss of patients and caregivers	– Value of Statistical Life (VSL) adjusted to the patient life span
Summary	– Prescription drugs for diseases – Cost of secondary treatments – Medical procedure e.g. Dialysis – Hospitalization – Inpatient – Hospitalization – Outpatient – Home Healthcare – Professional services, e.g. nurse visits	– Work productivity loss · Presenteeism · Absenteeism – Activity impairment – Caregiver burden · External caregiver cost · Family member productivity loss – Home improvements – Traveling and accommodation to receive care	– The amount of money the government will be willing to pay to preserve a life for one additional year/marginal cost of avoiding death
Sources	– IQVIA MIDAS database – Academic literature review – Physician/KOL interviews – Patient surveys	– Secondary research & literature review – Physician / KOL interviews – Patient surveys – IQVIA Integrated Research	– Secondary research & publicly available data (e.g. Bureau of Labor Statistics, EPA, Census of Fatal Occupational Injuries, etc.)

Results

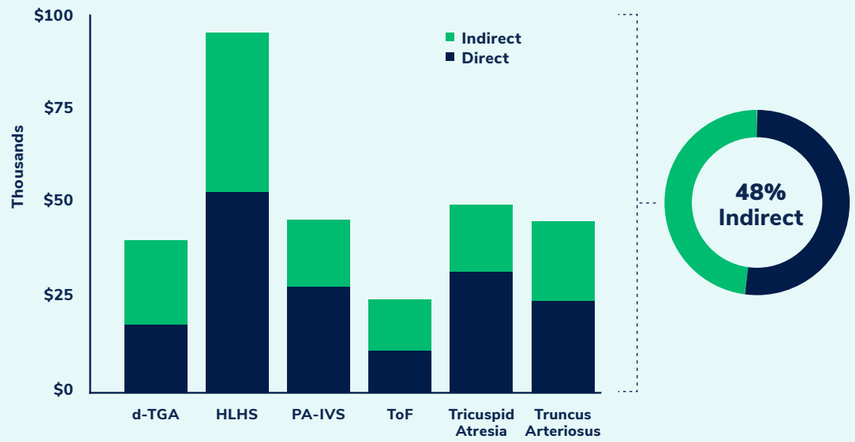
Financial burden for patients and families is disproportionately high in cCHD, as compared to other cardiac diseases

Average annual cost of cCHD is nearly $50K per patient, with ~50% paid solely by patients and families

We sought to determine how the overall costs of cCHDs on a per-patient basis compared to other diseases. First, we defined the annual costs associated with treatment and management of each of the selected cCHDs and investigated both indirect and direct costs. For the six selected cCHDs, the average direct and indirect cost per patient per year (PPPY) was found to be $49,449, with a range of $23,855 to $94,990 (Figure 1). Surprisingly, we discovered that indirect costs, which are often incurred solely by the patient and/or their family, exceeded, on average, more than 48% of the total annual burden, yielding an average of $22,900 PPPY with a range of $14,257 to $42,892 (Figure 1).

The indirect costs associated with these diseases included a broad range of expenses, including out-of-pocket copays, prescriptions, and medical equipment, as well as lost productivity from work and school. For example, approximately 10% of parents reported a change of jobs, reduced work hours, or exit from the workforce to care for their cCHD child. Among those who remained in the workforce, parents of cCHD children missed an average of 19 days of work per year, nearly a full month, to care for their cCHD child; adult patients also reported missing approximately 19 days per year to attend to their medical care. Moreover, children aged 6-18 with cCHD missed an average of 20.5 school days per year, which meets the definition of chronic absenteeism, defined as 15 or more missed school days in a year for any reason[6].

FIGURE 1
Annual Per Patient Direct and Indirect Costs of cCHD in US

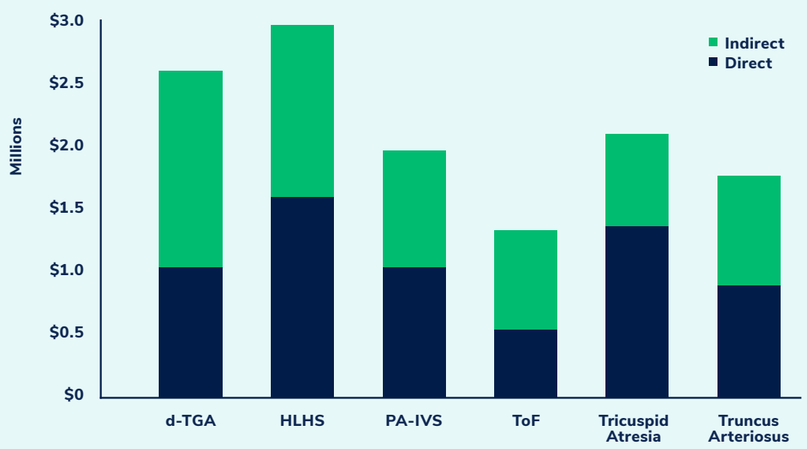


Average lifetime financial burden for cCHD is $2.1M per patient

Next, we examined the lifetime costs of these diseases, while also considering trends in spending during different periods of life. While annual costs provide general insight into the financial impact of cCHDs on patients and their families, they fail to provide a complete long-term perspective, as they do not consider the number of years a patient requires treatment and care. Given cCHD is a lifetime disease beginning before or immediately after birth, costs compound year after year throughout a patient's life. Accordingly, we sought to uncover the comprehensive financial burden to patients and families across the lifespan.

We first identified the average lifespan for each cCHD, equivalent to the number of life years requiring treatment and care (average lifespan, 46 years; range 30-65 years; Table 2). We then extrapolated annual costs over the expected lifespan of each cCHD to evaluate lifetime financial burden. We found that the average lifetime combined indirect and direct medical cost was $2,091,163 per patient, with a range of $1,312,025 to $2,849,700 per patient (Figure 2).

FIGURE 2
Lifetime Per Patient Direct and Indirect Costs of cCHD

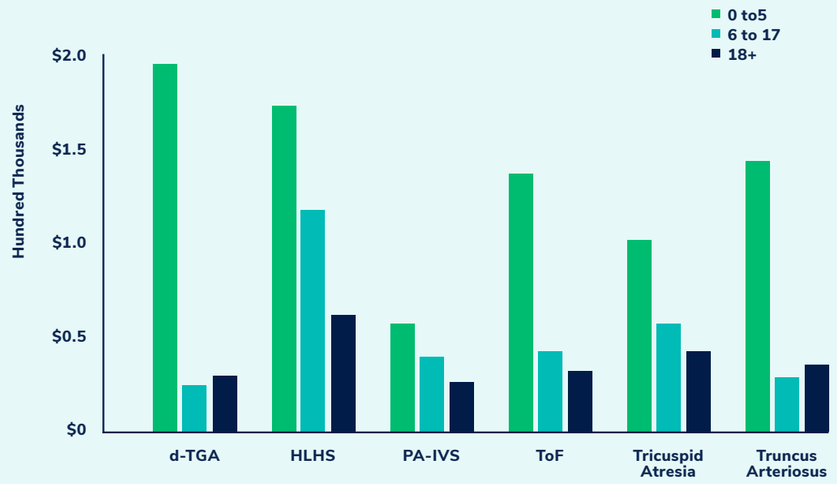


First five years of life on average cost >$650K per patient, with $190K paid directly by families

As the most complex cCHD care generally occurs during early childhood, we next sought to understand the distribution of costs over distinct age ranges: 0-5, 6-17, and 18+ years old. Unsurprisingly, we found that the economic burden is most substantial in the first five years of life, which have an average total direct and indirect cost of $130,868 per year (range $51,499 to $193,996), substantially higher than patients 6-17 and 18+ ($46,689 and $35,579 respectively). Strikingly, 31% of lifetime costs occur in the first years, averaging $654,343 with a range of $465,055 to $969,980 (Figure 3).

This unbalanced distribution is likely due to high direct medical costs from complex medical procedures and hospitalizations incurred in early childhood and is exacerbated by considerable acute indirect costs from intense caregiving demands. In this first five-year period, indirect costs average nearly $190,000 (range $100,265 - $304,285), which families pay out of pocket. The financial weight of these first five years compounded over a lifetime of additional direct and indirect costs can have a lasting impact, subjecting caregivers to a cycle of debt that cannot be overcome.

FIGURE 3
Average Cost Per Patient Across Age Ranges: 0-5, 6-17, 18+



cCHD healthcare is 8X more expensive annually and 14X more expensive over the lifetime than congestive heart failure

Finally, we compared the annual direct and indirect cost burden of each cCHD to two common cardiovascular diseases: congestive heart failure and coronary heart disease. We found that PPPY direct and indirect medical costs of cCHD were 8X more than congestive heart failure and 4X more than coronary heart disease ($49,449 vs $5,967 and $11,826, respectively; Figure 4).

While the PPPY costs revealed a disproportionate impact, cCHDs are unique in that they are lifelong diseases and carry a longer burden of care than most common cardiovascular diseases. Accordingly, our analyses indicate that on average these six cCHDs have nearly a 14-fold higher lifetime burden of medical costs than congestive heart failure, with lifetime indirect costs nearly 23X more (Figure 5).

Absent from all the above assessments is the cost of a reduced lifespan. While impossible to quantify the cost of loss for patients and their families, it is important to highlight that cCHD patients lose significantly more years of life than those with common cardiac diseases, with an average loss of 31 years (range 12 to 47 years) for cCHDs, compared to 9.4 years and 6 years for congestive heart failure and coronary heart disease respectively (Table 2).

Table 2

Life years Lost with cCHD and Mass Market Diseases

Disease	Years of Life Lost
d-TGA	12
HLHS	47
PA-IVS	36
ToF	22
Tricuspid Atresia	32
Truncus Arteriosus	37
Congestive Heart Failure	9
Coronary Heart Disease	6

FIGURE 4
Annual Per Patient Direct and Indirect Costs of cCHD versus Mass Market Diseases in US

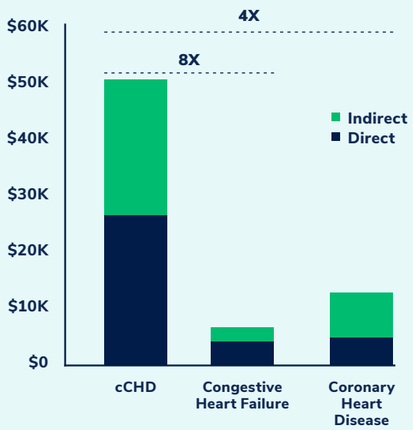
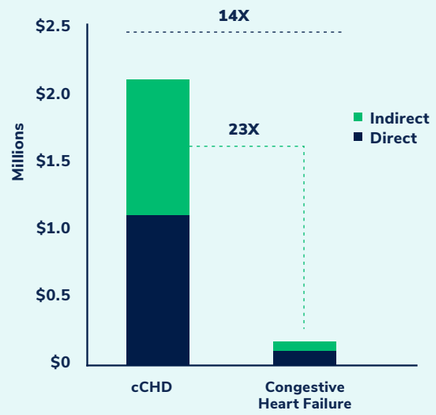


FIGURE 5
Lifetime Per Patient Direct and Indirect Costs of cCHD versus Mass Market Diseases in US



The financial weight of these first five years compounded over a lifetime of additional direct and indirect costs can have a lasting impact, subjecting caregivers to a cycle of debt that cannot be overcome.

Results

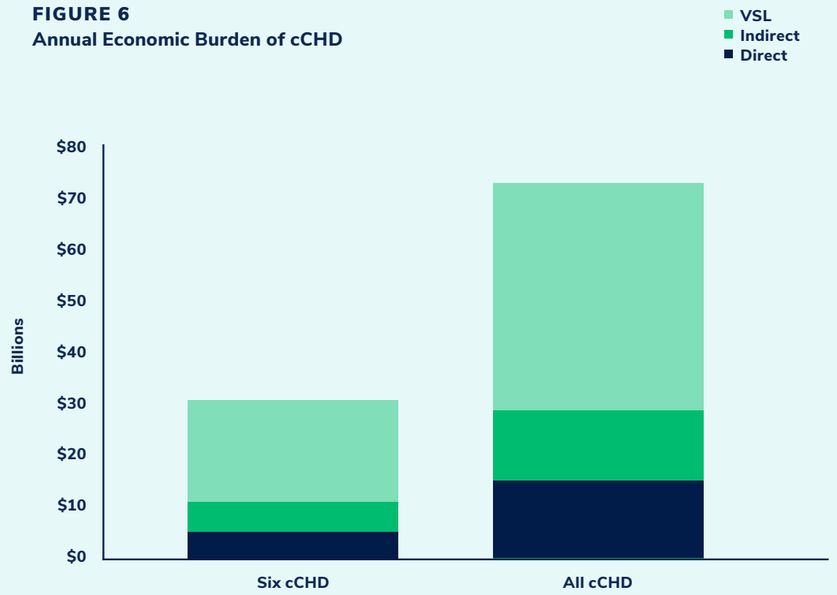
cCHDs impose a disproportionately high financial burden on the US economy

Although cCHDs are relatively rare, we found that these lifelong conditions have a substantial impact on patients and families and result in a significant loss of life years. As such, we sought to understand the impact of cCHDs on the US economy by examining the total patient burden of direct, indirect, and mortality costs and comparing against two common cardiac diseases, congestive heart failure and coronary heart disease. To understand mortality costs, we utilized the statistical value of life, which assigns an economic value per year of life lost.

Annual economic burden for all cCHDs in the US is $74B

We found that the six studied cCHDs have a combined annual economic burden of $27.5B, which is inclusive of direct, indirect, and mortality costs for all 223,000 patients in the United States. Because the included subset of cCHDs represents a range of complexities and associated healthcare costs, data included in this analysis can be reasonably extrapolated to assess costs of all cCHDs. As 25% of all CHDs are complex, and there are an estimated 2.4M patients living in the US with a CHD[7], we projected that 600,000 people are currently living with a cCHD. Thus, the extrapolated total annual economic burden of cCHD is $74B (Figure 6).

FIGURE 6
Annual Economic Burden of cCHD



We next sought to contextualize our findings by comparing against the impact of more common cardiac conditions. We found that the annual burden of congestive heart failure and coronary heart disease is $163B and $441B, respectively; however, these common cardiac diseases affect 6.2M and 18.2M patients, respectively. Thus, although congestive heart failure affects nearly 10X the population of cCHDs, the associated total annual cost is only 2X greater. Similarly, coronary heart disease is only 6X greater despite affecting 30X more patients (Figure 7).

As it is important to consider the annual economic burden of disease in the absence of mortality, we also examined the total annual economic impact of accrued direct and indirect costs. For the six cCHDs studied, the annual burden across all patients was $9.5B; collectively for all cCHDs, this total soars to $25.4B. By contrast, the total annual burden of congestive heart failure is only 1.5X more than all cCHDs, yet affects 10X more patients; coronary heart disease costs 8.5X more annually despite affecting 30X more patients (Figure 8).

FIGURE 7
Annual Total Economic Burden of cCHD and Mass Market Diseases

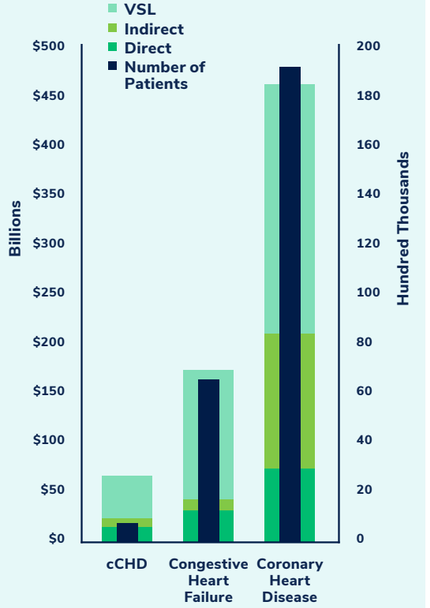
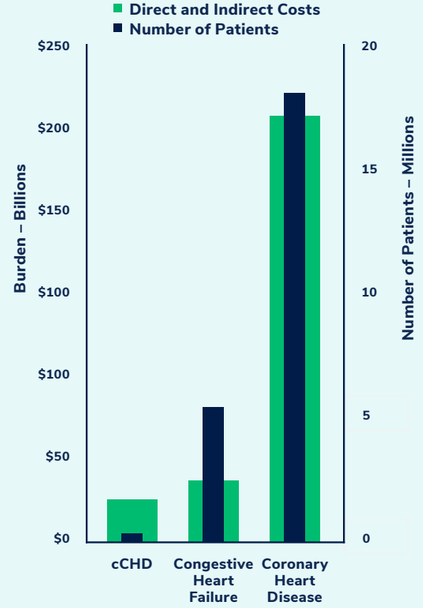


FIGURE 8
Annual Direct and Indirect Economic Burden of cCHD Compared to Mass Market Diseases



Total lifetime economic burden for cCHDs is disproportionately high, costing the US up to $3.35T

The lifelong nature of cCHDs and years lost due to disease make it critical to assess the lifetime burden for all patients in the US. We found the total lifetime economic burden of the studied cCHDs for all current patients to be $1.24T, inclusive of direct, indirect, and mortality costs; this data can be extrapolated to $3.35T for all cCHDs.

We next compared these costs to congestive heart failure, for which the total lifetime burden is $9.7T. While congestive heart failure affects 10X more patients, the total lifetime cost across all patients is only 3X higher than that of cCHDs (Figure 9). Strikingly, when mortality is excluded, the lifetime direct and indirect costs for all cCHDs are 1.3X higher than congestive heart failure ($1.23T vs $943B; Figure 10).

FIGURE 9
Lifetime Total Economic Burden of cCHD and Mass Market Diseases

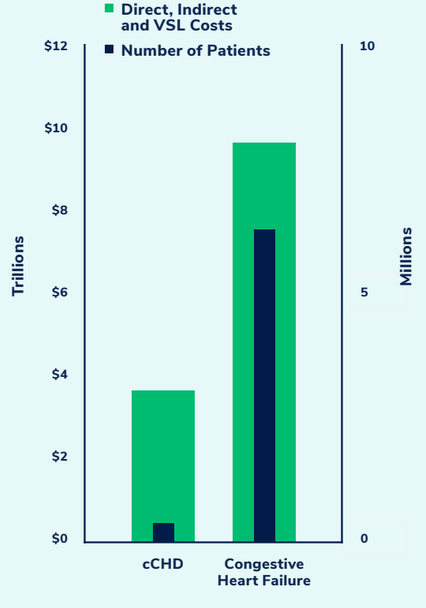
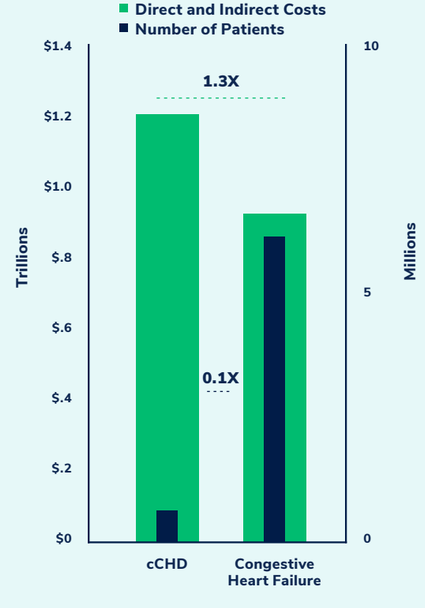


FIGURE 10
Direct and Indirect Economic Burden of cCHD and Mass Market Diseases



Discussion

Complex congenital heart diseases begin at birth and require a lifetime of care that drastically alters the quality and duration of life for affected patients. Despite their lifelong impact, the burden of cCHDs is often minimized, referred to as a set of rare, pediatric diseases that do not carry broad significance to the healthcare system or our economy, overall. While true that cCHDs are rare and require intensive caregiving early in life, the burden of disease is not restricted to childhood – patients, with their continued medical needs, are now aging into adulthood[8].

This comprehensive study has unequivocally demonstrated that the financial impact of cCHDs is in fact disproportionately high for patients and their families, as well as for the US economy, on both an annual and lifetime basis.

The present study reveals that cCHDs are exorbitantly expensive for patients and families and for the US healthcare system, frequently demanding more resources than common cardiac conditions like congestive heart failure. Currently, the level of support for cCHD research and clinical advancement, family and patient support programs, and therapeutic and device development mirrors the perceived underestimated impact and pales in comparison to true need. Indeed, there are virtually no dedicated or inclusive financial support programs available to these patients and families, and the federal and philanthropic investment in research to improve care and outcomes is inadequate to realistically bring new therapies to market.[9,10]

Notably, three important areas of analysis were beyond the scope of this research study. First, while it is well established that inequities exist for patients from racial and ethnic minorities as well as low socioeconomic status[11], we were unable to account for these factors in the present study.

Second, many adult CHD patients are lost to cardiac care for a variety of reasons[12], and this study was unable to assess the economic impact of these lapses in care. Finally, we examined the costs of a general treatment course for a typical patient with each cCHD; however, there are likely cases in which care is more complex and as a result, more expensive. For example, a significant number of patients with cCHD require a heart transplant, which carries a higher burden of costs than what was captured in the generalized costs. We encourage future research in each area to shed light on the additional burden incurred by these elements.

The findings of this study provide a robust foundation for the development of targeted healthcare policies and increased resource allocation. Understanding the high economic burden of cCHDs opens the door for the implementation of measures that enhance accessibility to specialized care, reduce financial strain on families, and prioritize research and development in the field of congenital heart diseases. We recommend the following actions, that if carried out, could significantly decrease the economic burden of cCHD and help improve lives of patients and their families:

Increased federal and philanthropic funding for cCHD research and development

Creation of comprehensive financial and support programs for caregivers and patients

Federal policy change to incentivize discovery and translation for rare and pediatric diseases

Additional research on the economic impact of health inequities and adults lost to care

This study's importance lies in its ability to catalyze a paradigm shift in the perception and management of cCHDs. By quantifying the burden across various dimensions, we empower all stakeholders to advocate for more holistic healthcare solutions, foster public awareness, and ultimately improve the lives of individuals and families grappling with the challenges posed by these complex congenital heart diseases.

Appendix A: Methods

Literature Review

The initial research phase involved an exhaustive review of existing literature, focusing on delineating the patient journey across the six specified cCHDs. Emphasis was placed on identifying gaps within the literature pertaining to costs and economic burdens associated with these conditions. Rigorous scrutiny of reputable sources, particularly high-impact journals, formed the foundation for data extraction. The review encapsulated:

- Disease comprehension, including ontology, epidemiology, unmet needs, and associated comorbidities
- Present treatment modalities, medical procedures, and any necessary reinterventions
- Patient journey, encompassing pre-natal diagnosis, pre-surgical interventions, and involved stakeholders
- Special education requisites
- Estimated treatment and surgical costs derived from CPT/DRG codes

Medical Claims Analysis

The second phase of work utilized several datasets, both publicly available and proprietary to ascertain estimated treatment and surgical costs as provided through medical claims data. The datasets utilized include:

- **IQVIA MIDAS Disease:** A proprietary platform for assessing worldwide healthcare markets using national audits conducted by IQVIA. This platform tracks products in 693 therapeutic classes and provides estimated product volumes, trends, and market share. Data is updated monthly and retains 12 years of history.
- **IQVIA National Sales Perspectives (NSP):** Measures dollar and unit sales for pharmaceutical products across multiple distribution channels, including retail, mail, and non-retail. Data is collected from a panel of wholesalers, distributors and pharmaceutical manufacturers representing 90% of the pharmaceutical market and projected to a national total.
- **Center for Medicare and Medicaid Services (CMS) – Medicare Physician Fee Schedule:** Provides more than 10,000 physician services, the associated relative value units, a fee schedule status indicator and various payment policy indicators needed for payment adjustment (i.e., payment of assistant at surgery, team surgery, bilateral surgery, etc.). The Medicare physician fee schedule pricing amounts are adjusted to reflect the variation in practice costs from area to area.

The insights gained from this phase informed subsequent investigations during the third phase and shaped the structure of the patient and caregiver survey.

Qualitative Expert Interviews

Interviews with key experts within the cCHD domain served to validate findings derived from the literature review, particularly identifying and confirming existing knowledge gaps, and the claims analysis. Engaging experts across various disciplines, including pediatric and adult congenital heart disease cardiologists, cardiac surgeons, payers, health economists, and hospital administrators, ensured a comprehensive understanding of the economic burden. Each 60-90 minute discussion was tailored to the expertise of the participants. A cohort of 30 experts was selectively engaged based on their experience, authored papers, and participation in relevant conferences. Honoraria aligned with market value were provided to respondents for their contributions.

Patient and Caregiver Survey: This critical component of the study gathered data on direct and indirect costs from 219 patients and caregivers, distributed equally across the 6 diseases. There was a similar split of male (46%) and female (54%) respondents spread across the US (East North Central 16%, East South Central 8%, Middle Atlantic 11%, Mountain 7%, New England 4%, Pacific 12%, South Atlantic 22%, West North Central 7%, and West South Central 13%).

Table 3	Truncus Arteriosus		Hypoplastic Left Heart Syndrome (HLHS)		Dextro-Transposition of the Great Arteries (d-TGA)		Tetralogy of Fallot (ToF)		Tricuspid Atresia		Pulmonary Atresia with Intact Ventricular Septum (PA-IVS)	
	Target	Completed	Target	Completed	Target	Completed	Target	Completed	Target	Completed	Target	Completed
Caregivers of patients aged 0 to 2 years	8	7	8	8	8	8	8	8	8	8	8	8
Caregivers of patients aged 3 to 5 years	8	5	8	9	8	8	8	8	8	8	8	12
Caregivers of patients aged 6 to 17 years	10	11	10	10	10	10	10	10	10	10	10	10
Patients aged 18 years and over	10	11	10	10	10	10	10	10	10	10	10	10
Total	**36**	**34**	**36**	**37**	**36**	**36**	**36**	**36**	**36**	**36**	**36**	**40**

Survey participants were sourced through CHD advocacy organizations and advocates who shared the survey on their social media channels, as well as through M3 Global Research. This organization has a panel of more than 10,000 patients across the US who have volunteered to provide insights for research. Dedicated lists of communities, including the CHD community, can be leveraged for copy testing, longitudinal attitude measuring and/or experience tracking for both qualitative and quantitative studies.

The approximately 25-minute survey aimed to collect detailed data on the indirect costs stemming from the burden of these congenital heart diseases. Strategically structured screening ensured participant eligibility and consent for anonymous data analysis and publication. Anonymity for both patients and caregivers was maintained throughout data collection. Participants were categorized into sub-groups based on age, allowing the collection of economic burden data at various stages of the cCHD patient journey. The questionnaire covered four primary sections:

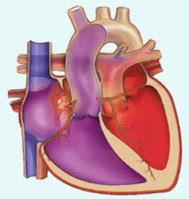
1. Specialist consultations and associated costs
2. Productivity loss
3. Costs related to external services and education
4. Additional unaddressed costs

Completion of each section facilitated progression through the subsequent segments. An honorarium was offered upon survey completion.

Comparison to mass-market diseases

As a comparator, we searched published literature for direct, indirect, and mortality costs associated with common mass-market diseases. We identified two common cardiac diseases, congestive heart failure and coronary heart disease, and gathered available cost data.[5,13,14,15] While these diseases impact much larger numbers of individuals in the US than cCHD which are rare diseases, we believed it would provide an important view of the per patient impact on the healthcare system and on patients and families.

Appendix B:
Overview of Individual Diseases



Summary of Average Costs Per Patient:	
Annual Direct Costs	$16,862
Annual Indirect Costs	$22,376
Lifetime Costs	$2.6 million

dextro-Transposition of the Great Arteries (d-TGA)[1]

Prevalence: 3.15 in 10,000 live births

Description: In a normal heart, blood is carried in a specific pattern: body-heart-lungs-heart-body. In d-TGA, the pulmonary artery and the aorta are transposed, causing this blood flow pattern to be altered. The blood flow is stuck in either 1) body-heart-body, without being routed to the lungs for oxygen, or 2) lungs-heart-lungs, without delivering oxygen to the body.

Treatment: Open-heart surgery to correct the transposition is required for all patients, usually occurring soon after birth. Additionally, many medications to control heart rate and fluid production are required. Without surgery, this condition is considered fatal.

Prognosis: Despite surgical treatment, patients are not cured and require lifelong care and follow-up. Patients with d-TGA are at higher risk for heart function problems including heart muscle decline and valve issues, heart rhythm abnormalities that may result in the need for a pacemaker, and endocarditis, an infection of the heart.

Life span: Patients with d-TGA live to approximately 65 years old, whereas the average American lives to be 77 years old.

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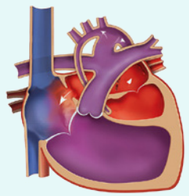
[1] Facts about d-TGA by CDC: https://www.cdc.gov/ncbddd/heartdefects/d-tga.html

Image from Transposition of the Great Arteries by Children's Hospital of Philadelphia, available at https://www.chop.edu/conditions-diseases/transposition-great-arteries



Hypoplastic Left Heart Syndrome (HLHS)[2]

Summary of Average Costs Per Patient:	
Annual Direct Costs	$52,098
Annual Indirect Costs	$42,892
Lifetime Costs	$2.9 million

Prevalence 2-3 in 10,000 live births

Description: In a normal heart, the left ventricle is responsible for pumping oxygenated blood to the body. In HLHS, the left side of the heart is underdeveloped and unable to pump oxygen-rich blood to the rest of the body. This condition is referred to as a single ventricle heart defect, an umbrella term used to describe conditions in which one ventricle is unable to properly function.

Treatment: A series of three reconstructive open-heart operations is generally required. These sequential and palliative procedures, known as the Norwood, Glenn, and Fontan, occur in the first few days of life, at about six months of age, and between 3-5 years old, respectively. Intensive care, medication, and surveillance are required during the interstage periods between surgeries, and after the Fontan. HLHS is considered universally fatal without treatment.

Prognosis: Despite surgical treatment, patients are not cured and require lifelong care and follow-up. Individuals with HLHS may need additional procedures including a heart or a heart-liver transplant. Patients experience a significant range of complications and comorbidities that include, but are not limited to, liver disease, renal failure, arrythmias, lymphatic dysfunction, protein losing enteropathy, plastic bronchitis, heart failure, stroke, myocardial dysfunction, and valve dysfunction.

Life span: Patients with HLHS live to approximately 30 years old, whereas the average American lives to be 77 years old.

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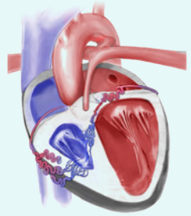
[2] Facts about Hypoplastic Left Heart Syndrome from the CDC, available at https://www.cdc.gov/ncbddd/heartdefects/hlhs.html#%3A~%3Atext%3DThe%20Centers%20for%20Disease%20Control%2Cwith%20hypoplastic%20left%20heart%20syndrome.%26text%3DIn%20other%20words%2C%20about%201%2Cwith%20hypoplastic%20left%20heart%20syndrome

Image from Hypoplastic Left Heart Syndrome (HLHS) by Children's Hospital of Philadelphia, available at https://www.chop.edu/conditions-diseases/hypoplastic-left-heart-syndrome-hlhs



Pulmonary Atresia with Intact Ventricular Septum (PA-IVS)[3]

Summary of Average Costs Per Patient:	
Annual Direct Costs	$26,763
Annual Indirect Costs	$18,550
Lifetime Costs	$1.9 million

Prevalence: 0.4 – 0.8 in 10,000 live births

Description: Pulmonary atresia is a defect in which the pulmonary valve is not correctly formed, so blood cannot flow from the heart to the lungs. In some cases, there may also be a small or missing right ventricle that cannot pump blood properly to the lungs. Additionally, the coronary arteries, which provide oxygenated blood to the heart, may not form correctly, causing the formation of abnormal connections from the right ventricle. This condition is referred to as a single ventricle heart defect, an umbrella term used to describe conditions in which one ventricle is unable to properly function.

Treatment: A series of two-to-three reconstructive open-heart operations is generally required, or, in some cases, a heart transplant. The sequential and palliative surgeries occur in the first few days of life, at about six months of age, and between 3-5 years old. Intensive care, medication, and surveillance are required during the interstage periods between surgeries, and after the final palliative procedure, called the Fontan. PA-IVS is considered universally fatal without surgical treatment.

Prognosis: Despite surgical treatment, patients are not cured and require lifelong care and follow-up. Individuals with PA-IVS may require additional procedures including a heart or a heart-liver transplant. Patients experience a significant range of complications and comorbidities that include, but are not limited to, liver disease, renal failure, arrythmias, lymphatic dysfunction, protein losing enteropathy, plastic bronchitis, heart failure, stroke, myocardial dysfunction, and valve dysfunction.

Life span: Patients with PA-IVS live to approximately 41 years old, whereas the average American lives to be 77 years old.

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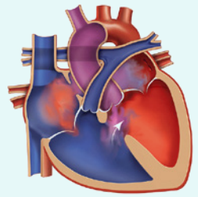
[3] Facts About Pulmonary Atresia by the CDC, available at https://www.cdc.gov/ncbddd/heartdefects/pulmonaryatresia.html

Image from Online Supplement to the Boston Children's Hospital Cardiac ICU Handbook, available at https://bchcicu.org/pa-ivs/



Tetralogy of Fallot (ToF)[4]

Summary of Average Costs Per Patient:	
Annual Direct Costs	$9,598
Annual Indirect Costs	$14,257
Lifetime Costs	$1.3 million

Prevalence: 3.97 in 10,000 live births

Description: In ToF, four related heart defects change the way blood flows to the lungs and to the heart:

1. Ventricular septal defect (VSD): In a normal heart, the ventricular septum acts as a barrier to prevent blood from the two sides of the heart from mixing. In VSD, there is a hole between the two ventricles of the heart that causes oxygenated and deoxygenated blood to mix and can result in either too much or too little blood flow to the lungs.
2. Pulmonary stenosis: The pulmonary valve and main pulmonary artery are narrowed, causing the heart to work harder to pump blood to the lungs and reducing oxygen in the blood.
3. Overriding aorta: The aorta is enlarged and is out of place, causing some of the unoxygenated blood to flow into the body, instead of the oxygen-rich blood.
4. Right ventricular hypertrophy: The wall of the right ventricle is thicker than it should be, which can block blood flow to the lungs.

Treatment: Generally, surgical repair is done soon after birth or early in infancy. Babies with ToF are typically very sick prior to surgery, and require intensive care after the repair. Without open-heart surgery, ToF is considered fatal

Prognosis: Despite surgical treatment, patients are not cured and require lifelong care and follow-up. Many individuals with ToF develop leaky valves and narrowing of the arteries over the course of their lives which can require valve replacement, or enlargement of the right heart, leading to heart rhythm issues that may require a pacemaker, and at times, may lead to sudden cardiac death.

Life span: Patients with ToF live to approximately 55 years old, whereas the average American lives to be 77 years old.

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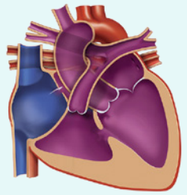
[4] Facts about Tetralogy of Fallot by CDC, available at https://www.cdc.gov/ncbddd/heartdefects/tetralogyoffallot.html#:~:text=Occurrence,born%20with%20tetralogy%20of%20Fallot.&text=In%20other%20words%2C%20about%201,born%20with%20tetratology%20of%20Fallot

Image from Children's Hospital of Philadelphia, available at https://www.chop.edu/conditions-diseases/tetralogy-fallot



Tricuspid Atresia[5]

Summary of Average Costs Per Patient:	
Annual Direct Costs	$30,939
Annual Indirect Costs	$18,060
Lifetime Costs	$2.2 million

Prevalence: 1-2 in 10,000 live births

Description: In a normal heart, blood is carried in a specific pattern: body-heart-lungs-heart-body. In tricuspid atresia, the tricuspid valve, which controls blood flow from the upper chamber of the heart (the right atrium) to the lower right chamber of the heart (the right ventricle), does not develop. This means that blood cannot be pumped to the lungs to be oxygenated. The right ventricle and pulmonary artery may also be underdeveloped. This condition is referred to as a single ventricle heart defect, an umbrella term used to describe conditions in which one ventricle is unable to properly function.

Treatment: A series of two or three reconstructive open-heart operations is generally required, with the first occurring in the first few days of life. Intensive care, medication, and surveillance are required during the interstage periods between surgeries and after the final surgery, called the Fontan. Without surgery, tricuspid atresia is considered fatal.

Prognosis: Despite surgical treatment, patients are not cured and require lifelong care and follow-up. Individuals may require additional procedures including a heart or a heart-liver transplant. Patients experience a significant range of complications and comorbidities that include, but are not limited to, liver disease, renal failure, arrythmias, lymphatic dysfunction, protein losing enteropathy, plastic bronchitis, heart failure, stroke, myocardial dysfunction, and valve dysfunction.

Life span: Patients with tricuspid atresia live to approximately 45 years old, whereas the average American lives to be 77 years old.

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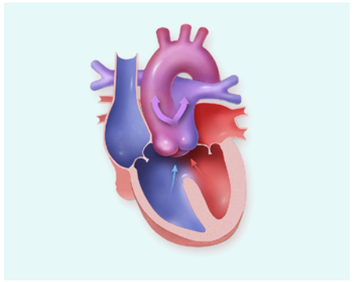
[5] Facts about Tricuspid Atresia by the CDC, available at https://www.cdc.gov/ncbddd/heartdefects/tricuspid-atresia.html

Image from Tricuspid Atresia by Children's Hospital of Philadelphia, available at https://www.chop.edu/conditions-diseases/tricuspid-atresia



Truncus Arteriosus[6]

Summary of Average Costs Per Patient:	
Annual Direct Costs	$23,030
Annual Indirect Costs	$21,270
Lifetime Costs	$1.8 million

Prevalence: 0.5-1 in 10,000 live births

Description: In a normal heart, blood is carried in a specific pattern: body-heart-lungs-body. In truncus arteriosus, the blood vessel that comes out of the heart fails to separate completely during development, which leaves the aorta and pulmonary artery connected. Additionally, there is usually a ventricular septal defect (VSD) which is a hole between the right and left ventricles. Oxygen-poor and oxygen-rich blood mix together as the blood flows to the lungs and the body, which means the heart must work harder than normal to pump. Lastly, there is only one valve, called the truncal valve, that controls blood flow out of the heart instead of having both an aortic valve and a pulmonary valve.

Treatment: Surgery is generally required in the first few months of life to correct the defect and create an artificial tube with an artificial valve (called a conduit) that enables oxygen-poor blood to flow to the lungs, and create a new aorta that enables oxygen-rich blood to flow to the body.

Prognosis: Despite surgical treatment, patients are not cured and require lifelong care and follow-up. Individuals with truncus arteriosus who have had reconstructive surgery will require a lifetime of care, and potentially, additional procedures. Of note, the conduit does not grow with the patient and may need to be replaced as the patient ages. Additionally, blockages can occur in the blood flow and the truncus valve may need repair or replacement.

Life span: Patients with truncus arteriosus live to approximately 40 years old, whereas the average American lives to be 77 years old.

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[6] Facts about Truncus Arteriosus by the CDC, available at https://www.cdc.gov/ncbddd/heartdefects/truncusarteriosus.html#%3A~%3Atext%3DWhat%20is%20Truncus%20Arteriosus%2Cthe%20aorta%20and%20pulmonary%20artery

Image from Truncus Arteriosus by Children's Hospital of Philadelphia, available at https://www.chop.edu/conditions-diseases/truncus-arteriosus

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ADDITIONAL
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