Journal of the American Heart Association

ORIGINAL RESEARCH

Adherence With Lipid Screening Guidelines in Children With Acquired and Congenital Heart Disease: An Observational Study Using Data From The MarketScan Commercial and Medicaid Databases

Justin H. Berger, MD, PhD; Jennifer A. Faerber, PhD; Feiyan Chen, PhD; Kimberly Y. Lin, MD; Julie A. Brothers, MD*; Michael L. O'Byrne, MD, MSCE*

BACKGROUND: Universal lipid screening in children provides an opportunity to mitigate the lifetime risk of atherosclerosis, particularly in children with chronic conditions that are predisposed to early atherosclerosis. In response, national guidelines recommend additional early screening in a subset of cardiac conditions. The penetration of such guidelines has not been evaluated.

METHODS AND RESULTS: We performed a retrospective study of a geographically representative sample of US children using the MarketScan Commercial and Medicaid claims databases. The study population was children with cardiac disease between ages 2 and 18 years and ≥3 years of continuous coverage from January 1, 2013, to June 30, 2018, divided into 4 major strata of heart disease. We assessed the likelihood of screening between these classifications and compared with healthy children and calculated multivariate models to identify patient factors associated with screening likelihood. Of the eligible 8.4 million children, 155 000 children had heart disease, of which 1.8% (31 216) had high-risk conditions. Only 17.5% of healthy children underwent lipid screening. High-risk children were more likely to be screened (odds ratio [OR], 2.1; 95% CI, 2.09–2.19; $P<0.001$) than standard-risk children, but that likelihood varied depending on strata of cardiac disease (22%–77%). Timing of screening also varied, with most occurring between ages 9 and 11 years. Among cardiac conditions, heart transplantation (OR, 16.8; 95% CI, 14.4–19.7) and cardiomyopathy (OR, 2.9; 95% CI, 2.8–3.1) were associated with the highest likelihood of screening.

CONCLUSIONS: Children with cardiac disease are more likely to undergo recommended lipid screening than healthy children, but at lower rates and later ages than recommended, highlighting the importance of quality improvement and advocacy for this vulnerable population.

Key Words: congenital heart disease ■ lipid screening ■ pediatrics

Atherosclerosis and associated cardiovascular disease (CVD) remain the number one cause of death in American adults. Atherosclerotic changes begin in childhood, and as a result, national guidelines from the American Academy of Pediatrics and National Heart, Lung, and Blood Institute recommend that all children should undergo lipid screening between ages 9 and 11 years and again in late adolescence/early adulthood (17–21 years).[1–3] The goal of such screening is timely identification of dyslipidemia,

Correspondence to: Justin H. Berger, MD, PhD, The Children's Hospital of Philadelphia, 3401 Civic Center Blvd, 8NW, Philadelphia, PA 19104. E-mail: bergerj@chop.edu

*J.A. Brothers and M.L. O'Byrne are co-senior authors.

Supplementary Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.024197

For Sources of Funding and Disclosures, see page 8.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Lipid screening is performed at low rates in children with congenital and acquired heart disease at the highest risk for early-onset adult cardiovascular disease.

What Are the Clinical Implications?

- Appropriate screening in the high-risk cardiac patients may allow for necessary interventions to improve long-term cardiovascular health as these children age into adulthood.

Nonstandard Abbreviations and Acronyms

KD	Kawasaki Disease
OHT	orthotopic heart transplantation
SV	single ventricle

which provides an opportunity for intervention and reduction in the lifetime risk of morbidity and mortality from CVD.

Several forms of congenital and acquired heart disease have been identified as "high risk" for early development of CVD (Table S1). Early identification and treatment of these at-risk patients would improve long-term cardiac morbidity and mortality. As a result, initial screening between 2 and 8 years of age is recommended for them. It is unknown whether lipid screening occurs routinely in each of these high-risk cardiac diseases, which is an important first step in decreasing lifelong disease burden in a vulnerable patient population. We have previously demonstrated that real-world adherence to these guidelines is limited, with just 20% of all "standard-risk" children screened appropriately.[4] Though children with chronic disease were more likely to receive screening, the rates of screening were highly variable.

A major obstacle to studying these issues is obtaining a generalizable sample of US children. Studies based on a single hospital or health system are of limited generalizability, and surveys are subject to social desirability bias. We sought to overcome this limitation by using a geographically representative sample from a claims database of commercial and public insurance recipients. We hypothesize that the likelihood of lipid screening will vary across specific anatomic/disease diagnoses, with screening rates proportional to perceived severity of illness or risk of atherosclerosis. Identifying specific groups of diagnoses in which screening is performed at higher and lower rates is an important step to improving screening rates and eventually, lifelong outcomes.

METHODS

Study Design and Data Source

We conducted a retrospective cohort study using the MarketScan Commercial and Medicaid Claims and Encounters Databases (MarketScan) (Truven Health Analytics, Ann Arbor, MI). The MarketScan database is one of the largest sources of longitudinal, deidentified healthcare reimbursement data for children ages 0 to 18 years.[5–12] The data are aggregated from US commercial and public payers, including inpatient, outpatient, emergency department, and pharmacy encounters, and constitute a convenience sample which is geographically representative. Data were directly extracted from the MarketScan database and included presence of cardiac disease as well as sex, race, ethnicity, census region, and insurance type. We identified exposures, outcomes, and covariates using billing codes. Our Institutional Review Board determined that the study was exempt from review. Our data use agreement prohibits sharing subject-level data; statistical methods are described herein, and code is available upon request. Since the data are deidentified and the study exempt from review per the Institutional Review Board, participant consent was not obtained.

Study Population and Study Data

The study period was January 1, 2013 to June 30, 2018. Eligible subjects were between ages 2 and 18 years and had at least 3 years of continuous insurance coverage. We compared healthy children (without previously described high-risk chronic medical conditions[1]) with those with a cardiac diagnosis (Figure S1). We identified specific cardiac diagnoses using *International Classification of Diseases*, *Ninth Revision* (*ICD-9*) or *Tenth Revision* (*ICD-10*) codes (Table S2).

The primary exposure was high-risk cardiac lesions predisposing to early atherosclerosis based on the 2006 American Academy of Pediatrics/American Heart Association guidelines (Table S1), including: left-sided obstruction (aortic valve disease and arch obstruction), coronary anomalies, Kawasaki Disease (KD) with coronary aneurysms, cardiac lesions requiring surgeries that include coronary artery manipulation (eg, transposition of the great arteries status post arterial switch operation, Ross procedure), cardiomyopathies, and orthotopic heart transplantation (OHT).[1] We further subdivided cardiomyopathies by phenotype (Table S3 and Figure S2).

We were also interested in the relative likelihood of screening amongst children with congenital heart

disease (CHD), so we also divided CHD into simple biventricular, complex biventricular, and single ventricle (SV) heart disease strata as defined previously.[13] Presence of a code for any of these diagnoses at any encounter was considered sufficient for inclusion. Subjects who fit criteria for more than one category were classified as follows to prevent overlap between groups (in descending priority): SV, high-risk, complex biventricular, simple biventricular. While patients with SV often have features of the high-risk category (eg, left-sided obstruction), the nature of their underlying cyanotic disease changes their risk profile for early CVD.[14,15] We did not exclude cardiac patients with concomitant non-cardiac high-risk diagnoses.

The primary outcome was a binary variable of any screening during the data period, defined as a composite of: 1) blood lipid levels testing, 2) filled prescriptions for a lipid-lowering agent, and/or 3) *ICD-9* or *ICD-10* codes for dyslipidemia.[4] Use of lipid-lowering agents or a diagnosis of dyslipidemia were included in the outcome because they imply previous screening.

During the design of the study, we considered potential covariates for lipid screening to include in our analysis. Several important clinical covariates (obesity, smoking exposure, and family history of dyslipidemia or early myocardial infarction) are not reliably coded in billing data and were not studied.[4] Socioeconomic status is limited to receipt of commercial or public insurance. Additionally, race and ethnicity data were only included in the Medicaid database and census region was available only in the commercial insurance data set. Of note, requiring continuous insurance enrollment sacrifices sample size to avoid missing data. If it introduces bias, it will likely result in a high-bound estimate of likelihood of screening (excluding those with changing insurance who are less likely to be screened).

Statistical Analysis

We summarized the characteristics of subjects with cardiac disease using percentages for categorical variables. Chi-squared tests were used to determine if the distributions of these characteristics differed between our subgroups.

The primary analysis described the percentage of any lipid screening across healthy and cardiac groups and examined if the likelihood of screening differed between high-risk and healthy children using multivariable logistic regression adjusting for sex and insurance type (Medicaid or commercial). Age was not included as a covariate in the primary analysis because of variable follow-up between subjects and imprecision introduced by the way age is recorded in the database (rounded to the nearest integer year). Two post-hoc secondary analyses were performed to evaluate whether there was effect modification between 1) sex and risk-strata and 2) insurance payer (commercial insurance or Medicaid) and risk-strata on the odds of undergoing lipid screening.

As a planned secondary analysis, we tested whether the likelihood of screening differed between high-risk lesions. The percentage of subjects screened in each subgroup were calculated and presented along with 95% CIs. Unadjusted differences in likelihood of screening were compared using Chi-squared tests. We then used multivariable logistic regression to determine if high-risk lesions were associated with likelihood of screening after adjusting for sociodemographic characteristics: age, race or ethnicity for Medicaid recipients, and census region for recipients of commercial insurance. These results are presented as adjusted odds ratios and 95% CIs.

We also studied the timing of screening in children with high-risk conditions. Specifically, we looked at whether children received early screening (ie, 2–8 years) in accordance with the published guidelines; between 9 and 11 years, when universal screening is recommended; or during adolescence (12–18 years). We calculated unadjusted prevalence of first lipid screening by year of age in non-overlapping cohorts of standard risk, all cardiac (excluding high-risk), high-risk (excluding transplant), and transplant patients. This same analysis was repeated and grouped in the 3 specified age ranges. Because the timing of screening was important, serum lipid testing was used (rather than the previous composite outcome). The maximum longitudinal follow-up time was limited to 5 years, so this represents a minimum incidence of lipid screening at a given age range. For acquired diseases (KD and OHT), we counted only time after the incident diagnosis.

Missing data for covariates was small so imputation was not performed. Race and ethnicity data were only available for patients with Medicaid; census region was available only in the commercial insurance data set. For region and race and ethnicity, the amount of missing data was <10%, so we created an "other/unknown" category for analysis. We performed all statistical analyses using SAS v9.4 (SAS Corporation, Raleigh NC) and set the threshold for statistical significance at $P<0.05$.

RESULTS

Study Population

Of the 8 599 653 subjects included in our cohort, 1.8% of children had cardiac conditions (Figure S1). The cohort was 51% male, with a mean age of 8.4±4.9 years (Table S4) and nearly evenly split between commercial insurance (51%) and Medicaid (49%, $P<0.001$). Among Medicaid recipients, 47% were White, 34% were Black, and 9% were Hispanic.

Among the children with heart disease, 20% had CHD or acquired cardiac disease placing them at increased risk of early atherosclerosis (high-risk group), 44% had simple biventricular, 31% had complex biventricular, and 5% had SV heart disease. High-risk children were more likely to be male than standard-risk (61% versus 51%, $P<0.001$). Compared with standard-risk subjects, a similar proportion of high-risk subjects received Medicaid (48% versus 49%, $P=0.003$). For those with commercial insurance, there existed statistically significant but small differences in the census region distribution of subjects, with a higher proportion of cardiac subjects in the Northeast (22%–26% versus 18%, $P<0.001$) and a smaller proportion in the West (13%–14% versus 18%, $P<0.001$). Among Medicaid recipients, cardiac subjects were less likely to be Black than standard-risk subjects (24%–28% versus 34%, $P<0.001$).

The most prevalent high-risk disease categories in this cohort comprised aortic valve and arch lesions (ie, left-sided obstructive lesions) (62%) and cardiomyopathies (21%) (Table S4). Diagnoses of transposition of the great arteries (6%), coronary anomalies (8%), and OHT (3%) were less frequent. KD had the lowest prevalence (0.9%). Among cardiomyopathies, dilated cardiomyopathy was the most prevalent phenotype (39%), followed by other—including secondary, nutritional, and metabolic etiologies (31%)—and hypertrophic (20%). Mixed (7%) and restrictive (1%) phenotypes were the least prevalent (Table S5).

Subjects with cardiac diagnoses had several noticeable differences in baseline characteristics compared with standard-risk subjects. KD subjects were younger (5.7±4.4 years versus 8.4±4.9 years, $P<0.001$), with a greater proportion of males (70% versus 51%, $P<0.001$), and a lower proportion who were Black ($P=0.04$). Structural cardiac disease (59%–65%, $P<0.001$) and cardiomyopathy (60%, $P<0.001$) were also associated with a higher likelihood of male sex. Cardiomyopathy subjects were older than the average standard-risk population (9.7±5.0 versus 8.4±4.9 years; $P<0.001$), consistent with later clinical presentation; this diagnosis was more prevalent in the Northeast and less prevalent in the South and West. Subjects with complex biventricular disease, SV, and OHT were more likely to have Medicaid insurance than standard-risk subjects (54%, 55%, and 56%, respectively versus 49%; $P<0.001$). We found no other discernable patterns among region or race or ethnicity across categories of disease.

Likelihood of Screening

Lipid screening was performed in 17.5% (95% CI, 17.48%–17.53%) of standard-risk subjects across all ages (Figure 1A). High-risk patients were screened at significantly higher rates than standard-risk patients (31.2%; 95% CI, 30.7%–31.7%; $P<0.001$). Screening rates increased among non-high risk cardiac patients based on disease complexity: simple biventricular disease, complex biventricular disease, and SV groups were screened at 18.3%, 25.0%, and 29.4%, respectively.

After adjusting for identifiable covariates including sex, race or ethnicity, region, and payer, high-risk patients were more than twice as likely to undergo lipid screening than standard-risk children (OR, 2.1; 95% CI, 2.09–2.19) (Figure 2). The increased odds of lipid screening in the adjusted multivariable model were identical to the observed data (data not shown). Complex biventricular and single ventricle patients were also more likely to be screened compared with standard risk. The increased likelihood of children with simple biventricular heart disease undergoing screening compared to standard-risk children was small but statistically significant (OR, 1.07; 95% CI, 1.05–1.09; $P<0.001$). There was no effect modification by sex or payer plus risk category on the likelihood of screening (data not shown).

We next investigated whether specific high-risk lesions were associated with different likelihoods of screening. Among the high-risk subjects, structural lesions were screened 23% to 30% of the time (Figure 1b), while cardiomyopathies (40%; 95% CI, 38%–41%) and heart transplant (77%; 95% CI, 75%–80%) were much more likely to be screened. All differences in screening between structural lesions (pairwise comparisons) were statistically significant, except for KD with aneurysm compared with either aortic valve disease ($P=0.63$) or coronary anomalies ($P=0.76$). Screening rates based on cardiomyopathy phenotypes were similar (Table S5). After adjusting for covariates, cardiomyopathy (OR, 2.9; 95% CI, 2.8–3.1) and heart transplant (OR, 16.8; 95% CI, 14.4–19.7) were still associated with greater odds of lipid screening compared with other high-risk lesions (Figure 2).

Early Screening

Lastly, we wanted to understand whether "early" screening was occurring in high-risk patients between 2 and 8 years of age as per recommendations. We graphed the unadjusted percentage of patients with a first-time lipid screen by age (Figure 3). As expected, minimal screening occurred in standard-risk patients before age 9 (4.56%; 95% CI, 4.55–4.58), when there was an increase in yearly first-time screening coincident with guideline recommendations. The yearly screening nearly doubled during the teenage years (11.8% to 20.3%). Patients with non-high risk cardiac disease and those with high-risk cardiac disease excluding transplant had higher early screening prevalence than standard-risk children; this increased substantially after age 9 and again in the teenage period. Transplant

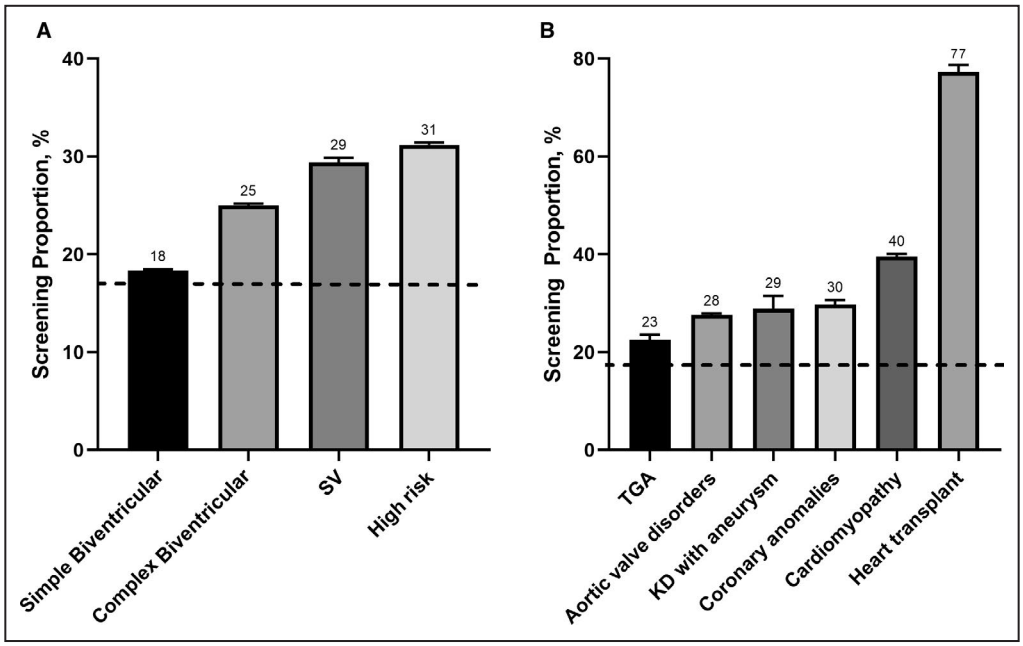


Figure 1. Proportion of lipid screening by (A) broad cardiac diagnosis and (B) high-risk subgroups. Outcome is composite of lipid testing, dyslipidemia diagnosis, or lipid-altering therapy. Dotted line represents screening rate among healthy children (mean±SD). All pairwise comparisons $P<0.001$ except for Kawasaki disease versus aortic valve and Kawasaki disease vs coronary anomalies, which were not significant. KD indicates Kawasaki disease; SV, single ventricle; and TGA, transposition of the great arteries.

patients started at a higher screening prevalence than all other categories, and this also increased with age. Taken together, these data demonstrate a low rate of early screening in standard-risk and most cardiac patients, with most screening starting after age 9 and accelerating in the teenage years.

DISCUSSION

Using a geographically representative convenience sample of US children, this retrospective observational study depicts contemporary lipid screening practice in US children with cardiac disease. In this vulnerable

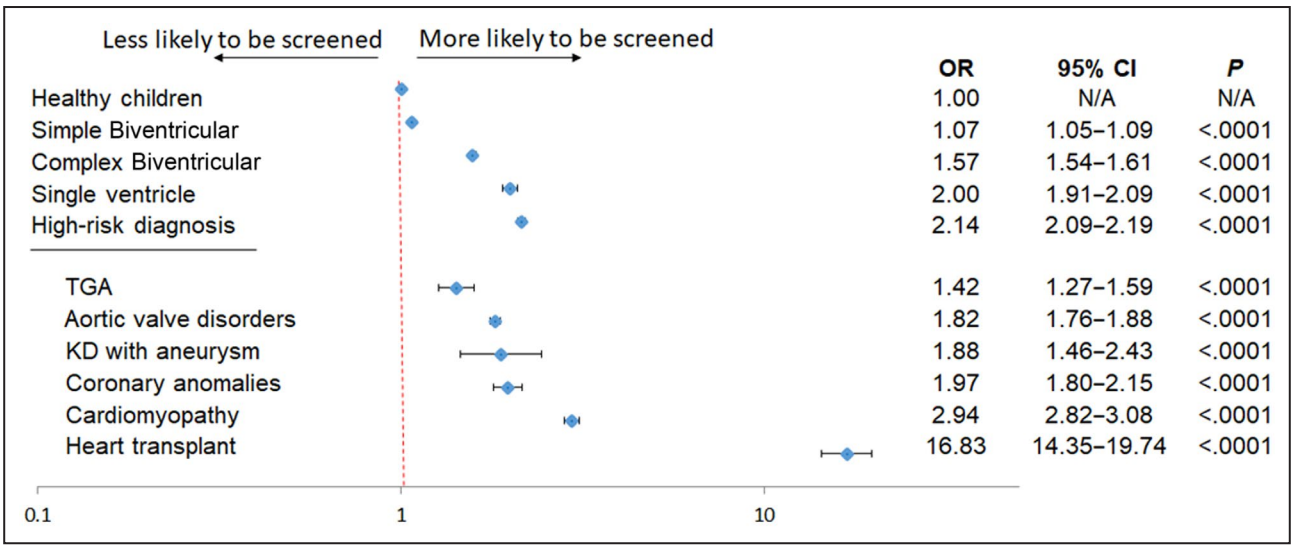
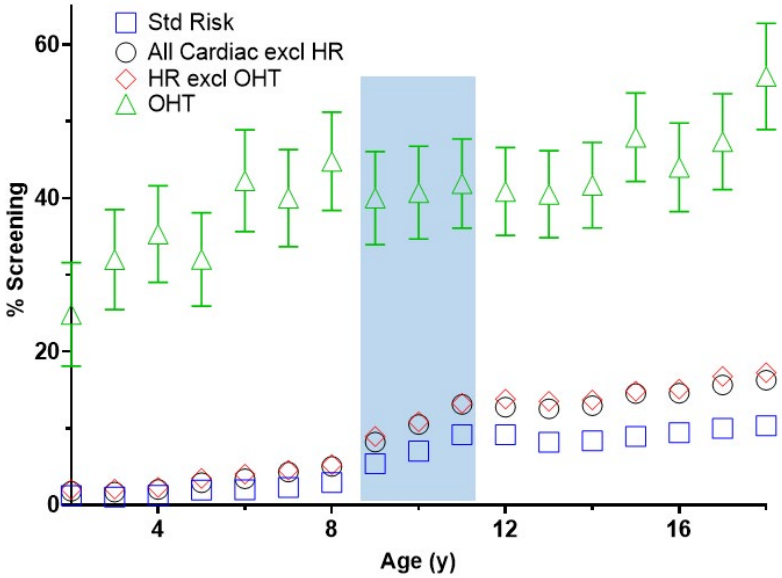


Figure 2. Likelihood of lipid screening by disease cohort.
Odds ratios as compared with standard-risk group, adjusted for sex and payer, as well as region and race and ethnicity. High-risk diagnoses represented collectively and by specific diseases. KD indicates Kawasaki disease; NA, not applicable; OR, odds ratio; and TGA, transposition of the great arteries.



	2-8y	9-11y	12-18y
Standard risk	4.56% (4.55-4.58)	11.8% (11.82-11.87)	20.3% (20.24-20.30)
All cardiac (excl. high risk)	7.0% (6.86-7.14)	18.6% (18.25-18.92)	32.5% (32.11-32.84)
High risk (excl. OHT)	8.4% (8.08-8.81)	19.0% (18.44-19.62)	34.8% (34.19-35.34)
OHT	56.7% (52.68-60.66)	51.5% (47.18-55.85)	69.2% (65.89-72.57)

Figure 3. Observed per-age and per-time period prevalence of screening.
Serial cross-sectional data presented as non-cumulative, per-year prevalence of first occurrence of lipid screening (not composite outcome) for standard-risk, all cardiac (excluding high-risk), high-risk (excluding orthotopic heart transplant), and orthotopic heart transplant patients. Blue bar represents timeframe of recommended universal screening. Error bars present on all data points even if not visible. Screening proportions by period (early, 2–8 years; universal, 9–11 years; and teenage, 12–18 years) presented as percent (95% CI). excl indicates excluding; HR, high risk; OHT,orthotopic heart transplant; and Std Risk, standard risk.

population, we found that most children do not receive lipid screening. This is despite broad recommendations that all children should receive lipid screening twice by age 21 years and special recommendations for additional early screening in this population. Because of lack of screening and subsequent intervention, this high-risk cardiac population is placed at a higher lifetime risk of developing premature CVD. Understanding these lipid screening patterns among subsets of high-risk cardiac patients will allow for targeted health policy interventions. Improved screening rates may allow for earlier lifestyle or pharmacologic interventions with the goal of improved long-term cardiovascular health.

To this end, we evaluated whether the likelihood of screening differed between classes of cardiac diagnoses. Interestingly, the likelihood of screening increased with complexity of cardiac disease. Explanations for this pattern include that these patients are more likely to undergo laboratory testing for other reasons so the threshold to send lipid screening is lower, these patients are perceived to be a "sicker" population of children with heart disease, or even because they receive additional – subspecialty cardiology – care. Ironically, cyanotic CHD had a higher-than-average level of screening, even though the disease has previously been associated with reduced likelihood of developing atherosclerosis.[14,15]

Certain types of high-risk structural heart disease had statistically significant increases in screening rates. Coronary artery-related diseases (either KD with aneurysm or anomalous coronaries) were slightly more likely to be screened than patients with transposition of the great arteries or left-sided obstruction. However, it is not clear whether those small differences are clinically meaningful. The highest rates of screening, which also started at an earlier age, were in children with cardiomyopathy and OHT. In transplant patients, this may reflect the widespread use of statins to prevent coronary graft vasculopathy and for which patients receive surveillance lipid testing. One might speculate that the

increased screening in patients with cardiomyopathy relates to "spill-over" as the teams taking care of transplant patients often take care of patients with cardiomyopathy and so may their relative comfort with ordering lipid testing. Interestingly, we found no discernible patterns of lipid testing among cardiomyopathy phenotypes.

We also performed an analysis looking at early screening, which demonstrated that few patients with structural heart disease (8%) are screened before 8 years of age. Children with heart disease who undergo lipid screening tend to do so during the 9- to 11-year window recommended for all children. The majority of children with heart disease are never lipid screened, consistent with other chronic (non-cardiac) pediatric illnesses.[4,16] This is of particular concern in a vulnerable cardiac population, where the additive effects of underlying CHD substrate coupled with early CVD could result in worse outcomes. Indeed, the current adult population with CHD has reached 3 million and is growing, as >90% of children born with CHD survive into adulthood.[17] Unfortunately, adults with CHD have an increased prevalence of metabolic syndrome and coronary artery disease compared with the general population.[18,19] Since lipid screening and effective lipid management in childhood is a proven strategy in diseases like familial hypercholesterolemia, it is reasonable to postulate that early detection would allow for interventions to mitigate the risk of early CVD in cardiac patients.[20,21]

The mechanisms underlying increased risk of atherosclerosis in children with heart disease are not fully understood but may be important to guide future interventions. In left-sided obstructive lesions, such as those with repaired coarctation of the aorta or stenotic bicuspid aortic valve, atherosclerotic changes are ascribed to chronic hypertension, resulting in left ventricular hypertrophy and demand ischemia.[1,22–26] Patients with cardiomyopathies or lesions requiring surgical intervention on the coronary arteries may be subject to similar mechanisms. Alternatively, in patients with acquired heart disease such as KD and after OHT, CVD risk is attributed to inflammation.[1] It is not possible in this current era to risk-stratify the predisposing lesion to lifetime CVD risk, but further basic and translational research into these mechanisms could identify modifiable risk factors.

Future research to address these concerns could take several forms. We must identify the barriers to cardiology-directed outpatient screening, as children with CHD tend to maintain close contact with their cardiologists; however, during longitudinal cardiac follow-up, multiple issues compete for attention, so preventative cardiology becomes deprioritized. In previous studies using medical documentation as a metric, pediatric cardiologists often fail to note obesity and recommend potential dietary and lifestyle interventions, even in patients with complex CHD.[27,28] Even when prompted through a framework of an institutional quality improvement project, only half of pediatric cardiologists provided weight-related counseling.[29] Moreover, pediatric cardiologists report that anticipatory guidance and counseling are not emphasized in their routine follow-up, despite an increasing incidence of obesity in children with CHD.[30,31] If screening in these patients generally correlates with the timing of screening in standard-risk patients (that is, during the 9- to 11-year-old window of universal screening), perhaps it is the pediatrician, rather than the cardiologist, directing this testing at present. Better understanding of why these screening recommendations were not widely adopted, as well as stronger data about the utility of pediatric screening – currently rated as insufficient by the US Preventative Services Task Force – is required.[32,33]

The subsequent phenomenon of a steadily increasing screening rate throughout the teenage years, even in standard-risk patients, also bears further study; this could reflect provider beliefs that older patients are an easier population in which to obtain laboratory tests, a more acceptable age range to consider statin therapy if needed, or an under-recognition of the need to conduct early screening in high-risk children.

More immediately, health policy initiatives should optimize our care for these patients. The electronic medical record could be used to "nudge" providers towards guideline-directed care based on underlying diagnosis, age, or comorbidities (eg, body mass index). Outpatient pediatric cardiology care has established quality metrics, which should be augmented to include preventive cardiac screening. Educational and advocacy initiatives should target both cardiologists and pediatricians for familiarity and adherence to published guidelines for patients with cardiac disease. However, the concept of a medical home for complex patients is vital. Our data does not suggest that moving lipid testing from a medical home to a subspecialist is either necessary or appropriate; we speculate increasing screening would be accomplished working together.

We acknowledge several limitations related to the design of our study and the nature of a claims data source. The study design used a composite outcome to best capture lipid screening and management, when use of a lipid modulating agent often implies lipid screening. Additionally, we restricted our study population to patients with consistent follow-up, sacrificing some sample size to minimize missing data. This also helps minimize the potential for double counting an individual patient because of insurance changes (the deidentified patient level data does not link a single individual across multiple insurers) but could result in undercounting screening. These assumptions mean that the generated estimates of screening are low-bound estimates. Subject identification depends on

accurate diagnosis coding. The identification of specific cardiac lesions is limited with billing codes, but broad categorization is less susceptible to this imprecision. Subjects all had longitudinal data for at least 3 and up to 5 years. However, the analysis of screening dates is inherently a series of overlapping individual patients and does not represent true longitudinal follow-up, limiting inference. Particularly in the youngest age range, the reported screening represents a low-bound estimate. This is unlikely to represent a substantial amount of missed screening, as barely 3 out of 10 children in this population are screened overall. Despite these limitations, we were able to analyze data from >150 000 children with cardiac disease in the first real-world sample of lipid screening in acquired and CHD.

We conclude that few children with high-risk cardiac disease are screened in either the recommended early or universal time periods. Prior studies have highlighted the potential unease of a pediatric cardiologist to act as a generalist in performing preventative health screening. However, for children with cardiac disease who frequently spend more time in their cardiologist's office than that of their pediatrician, these data highlight an important preventative gap that the pediatric cardiologist can help bridge in the lifelong cardiac health of these patients. Further study is warranted to understand the efficacy of pediatric lipid screening, practice variation, and methods to improve guideline adherence.

ARTICLE INFORMATION

Received October 11, 2021; accepted February 16, 2022.

Affiliations

Division of Cardiology (J.H.B., K.Y.L., J.A.B., M.L.O.), Data Science and Biostatistics Unit (J.A.F., F.C.), and Center for Pediatric Clinical Effectiveness (M.L.O.), The Children's Hospital of Philadelphia, Philadelphia, PA; Department of Pediatrics (J.H.B., K.Y.L., J.A.B., M.L.O.), Leonard Davis Institute for Health Economics (M.L.O.), and Center for Cardiovascular Outcomes, Quality, and Evaluative Research (M.L.O.), Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA (M.L.O.).

Acknowledgments

This research was supported by the Cardiac Center Clinical Research Core at the Children's Hospital of Philadelphia.

Sources of Funding

This research was funded by an intramural grant from The Children's Hospital of Philadelphia Cardiac Center. Dr. O'Byrne (K23 HL130420-01) and Dr. Berger (T32 HL007915) receive support from the National Institutes of Health/National Heart, Lung, and Blood Institute. The funding bodies had no part in the design or conduct of the study. The views expressed are solely those of the authors.

Disclosures

None.

Supplemental Material

Tables S1–S5
Figures S1–S2

REFERENCES

1. Kavey REW, Allada V, Daniels SR, Hayman LL, McCrindle BW, Newburger JW, Parekh RS, Steinberger J. Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American heart association expert panel on population and prevention science; the councils on cardiovascular disease in the young, epidemiology and prevention, nutrition, physical activity and metabolism, high blood pressure research, cardiovascular nursing, and the kidney in heart disease; and the interdisciplinary working group on quality of care and outcomes research: endorsed by the American academy of pediatrics. *Circulation*. 2006;114:2710–2738. doi: 10.1161/CIRCULATIONAHA.106.179568
2. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. *Pediatrics* 2011;128(Suppl 5):S213–256. doi: 10.1542/peds.2009-2107C
3. de Ferranti SD, Steinberger J, Ameduri R, Baker A, Gooding H, Kelly AS, Mietus-Snyder M, Mitsnefes MM, Peterson AL, St-Pierre J, et al. Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American heart association. *Circulation*. 2019;139:e603–e634. doi: 10.1161/CIR.0000000000000618
4. Berger JH, Chen F, Faerber JA, O'Byrne ML, Brothers JA. Adherence with lipid screening guidelines in standard- and high-risk children and adolescents. *Am Heart J*. 2020;232:39–46. doi: 10.1016/j.ahj.2020.10.058
5. Leshem E, Moritz RE, Curns AT, Zhou F, Tate JE, Lopman BA, Parashar UD. Rotavirus vaccines and health care utilization for diarrhea in the United States (2007–2011). *Pediatrics*. 2014;134:15–23. doi: 10.1542/peds.2013-3849
6. Thornhill MH, Gibson TB, Cutler E, Dayer MJ, Chu VH, Lockhart PB, O'Gara PT, Baddour LM. Antibiotic prophylaxis and incidence of endocarditis before and after the 2007 AHA recommendations. *J Am Coll Cardiol*. 2018;72:2443–2454. doi: 10.1016/j.jacc.2018.08.2178
7. Janson CM, Millenson ME, Dai D, Tan RB, Iyer VR, Vetter VL, Vogel RL, Shah MJ, O'Byrne ML. Incidence of life-threatening events in children with wolff-parkinson-white syndrome. *Circulation*. 2018;138:A17031. doi: 10.1161/circ.138.suppl_1.17031
8. Agarwal A, Thombley R, Broberg CS, Harris IS, Foster E, Mahadevan VS, John A, Vittinghoff E, Marcus GM, Dudley RA. Age- and lesion-related comorbidity burden among us adults with congenital heart disease: a population-based study. *J Am Heart Assoc*. 2019;8:e013450. doi: 10.1161/JAHA.119.013450
9. Montalbano A, Rodean J, Kangas J, Lee B, Hall M. Urgent care and emergency department visits in the pediatric medicaid population. *Pediatrics*. 2016;137: doi: 10.1542/peds.2015-3100
10. Jimenez N, Quistberg A, Vavilala MS, Jaffe KM, Rivara FP. Utilization of mental health services after mild pediatric traumatic brain injury. *Pediatrics*. 2017;139: doi: 10.1542/peds.2016-2462
11. O'Byrne ML, Faerber JA, Katcoff H, Huang J, Edelson JB, Finkelstein DM, Lemley BA, Janson CM, Avitabile CM, Glatz AC, et al. Prevalent pharmacotherapy of US Fontan survivors: A study utilizing data from the MarketScan Commercial and Medicaid claims databases. *Am Heart J*. 2021;243:158–166. doi: 10.1016/j.ahj.2021.09.012
12. O'Byrne ML, Faerber J, Katcoff H, Frank DB, Davidson A, Giglia TM, Avitabile CM. Variation in the use of pulmonary vasodilators in children and adolescents with pulmonary hypertension: a study using data from the Marketscan® Insurance Claims Database. *Pulm. Circ.* 2020;10(3):1–9. doi: 10.1177/2045894020933083
13. Burstein DS, Shamszad P, Dai D, Almond CS, Price JF, Lin KY, O'Connor MJ, Shaddy RE, Mascio CE, Rossano JW. Significant mortality, morbidity and resource utilization associated with advanced heart failure in congenital heart disease in children and young adults. *Am Heart J*. 2019;209:9–19. doi: 10.1016/j.ahj.2018.11.010
14. Fyfe A, Perloff JK, Niwa K, Child JS, Miner PD. Cyanotic congenital heart disease and coronary artery atherogenesis. *Am J Cardiol*. 2005;96:283–290. doi: 10.1016/j.amjcard.2005.03.060
15. Duffels MGJ, Mulder KM, Trip MD, de Groot E, Gort J, van Dijk APJ, Hoendermis ES, Daliento L, Zwinderman AH, Berger RMF, et al. Atherosclerosis in patients with cyanotic congenital heart disease. *Circ J*. 2010;74:1436–1441. doi: 10.1253/circj.CJ-09-0858
16. Zachariah JP, McNeal CJ, Copeland LA, Fang-Hollingsworth Y, Stock EM, Sun FF, Song JJ, Gregory ST, Tom JO, Wright EA, et al. Temporal trends in lipid screening and therapy among youth from 2002 to 2012. *J Clin Lipidol*. 2015;9:S77–87. doi: 10.1016/j.jacl.2015.06.014

17. Gilboa SM, Devine OJ, Kucik JE, Oster ME, Riehle-Colarusso T, Nembhard WN, Xu P, Correa A, Jenkins K, Marelli AJ. Congenital heart defects in the United States: estimating the magnitude of the affected population in 2010. *Circulation*. 2016;134:101–109. doi: 10.1161/CIRCULATIONAHA.115.019307
18. Deen JF, Krieger EV, Slee AE, Arslan A, Arterburn D, Stout KK, Portman MA. Metabolic syndrome in adults with congenital heart disease. *J Am Heart Assoc*. 2016;5: doi: 10.1161/JAHA.114.001132
19. Awerbach JD, Krasuski RA, Camitta MGW. Coronary disease and modifying cardiovascular risk in adult congenital heart disease patients: should general guidelines apply? *Prog Cardiovasc Dis*. 2018;61:300–307. doi: 10.1016/j.pcad.2018.07.018
20. Luirink IK, Wiegman A, Kusters DM, Hof MH, Groothoff JW, de Groot E, Kastelein JJP, Hutten BA. 20-year follow-up of statins in children with familial hypercholesterolemia. *N Engl J Med*. 2019;381:1547–1556. doi: 10.1056/NEJMoa1816454
21. Joyce N, Wellenius GA, Dore DD, Newburger JW, Zachariah JP. Patterns of lipid lowering therapy among children ages 8–20 years. *J Pediatr*. 2015;167(113–119):e111. doi: 10.1016/j.jpeds.2015.04.004
22. Roux SP, Kuhn H, Lengsfeld H, Morand OH. Effects of chronic aortic coarctation on atherosclerosis and arterial lipid accumulation in the Watanabe hereditary hyperlipidemic (WHHL) rabbit. *Atherosclerosis*. 1992;93:123–132. doi: 10.1016/0021-9150(92)90206-V
23. Verheugt CL, Uiterwaal CSPM, Grobbee DE, Mulder BJM. Long-term prognosis of congenital heart defects: a systematic review. *Int J Cardiol*. 2008;131:25–32. doi: 10.1016/j.ijcard.2008.06.023
24. Luijendijk P, Lu H, Heynneman FB, Huijgen R, de Groot EE, Vriend JWJ, Vliegen HW, Groenink M, Bouma BJ, Mulder BJM. Increased carotid intima–media thickness predicts cardiovascular events in aortic coarctation. *Int J Cardiol*. 2014;176:776–781. doi: 10.1016/j.ijcard.2014.07.090
25. Aboulhosn J, Child JS. Left ventricular outflow obstruction: subaortic stenosis, bicuspid aortic valve, supravalvar aortic stenosis, and coarctation of the aorta. *Circulation*. 2006;114:2412–2422. doi: 10.1161/CIRCULATIONAHA.105.592089
26. Collins RT. Cardiovascular disease in Williams syndrome. *Circulation*. 2013;127:2125–2134. doi: 10.1161/CIRCULATIONAHA.112.000064
27. Pinto NM, Marino BS, Wernovsky G, de Ferranti SD, Walsh AZ, Laronde M, Hyland K, Dunn SO Jr, Cohen MS. Obesity is a common comorbidity in children with congenital and acquired heart disease. *Pediatrics*. 2007;120:e1157–1164. doi: 10.1542/peds.2007-0306
28. Greco M, Sood A, Kwon S, Ariza AJ. Cardiovascular risk factor screening and management of obese patients at an outpatient pediatric cardiology center. *Springerplus*. 2016;5:1868. doi: 10.1186/s40064-016-3340-9
29. Harahsheh AS, Sabati A, Anderson J, Jenkins K, Wilhelm CM, Jedeikin R, Chowdhury D. American college of cardiology body mass index counseling quality improvement initiative. *Pediatr Cardiol*. 2021;42:1190–1199. doi: 10.1007/s00246-021-02600-6
30. Lentzner BJ, Connolly DM, Phoon CK. Do paediatric cardiologists discuss cardiovascular risk factors with patients and their families? *Cardiol Young*. 2003;13:551–558. doi: 10.1017/S104795110300115X
31. Steele JM, Preminger TJ, Erenberg FG, Wang L, Dell K, Alsaied T, Zahka KG. Obesity trends in children, adolescents, and young adults with congenital heart disease. *Congenit Heart Dis*. 2019;14:517–524. doi: 10.1111/chd.12754
32. de Ferranti SD, Sheldrick RC. USPSTF is unable to recommend for or against lipid screening to identify multifactorial dyslipidaemia in childhood: no recommendation is not without consequences. *Evid Based Med*. 2017;22:162–163. doi: 10.1136/ebmed-2016-110585
33. Grossman DC, Bibbins-Domingo K, Curry SJ, Barry MJ, Davidson KW, Doubeni CA, Epling JW, Kemper AR, Krist AH, Kurth AE, et al. Screening for obesity in children and adolescents: US preventive services task force recommendation statement. *JAMA*. 2017;317:2417–2426. doi: 10.1001/jama.2017.6803

SUPPLEMENTAL MATERIAL

Table S1. Cardiac diagnoses with increased risk of developing early CVD and major cardiovascular events.

Diagnosis
Left heart obstructive lesions (aortic valve and arch disorders)
Lesions requiring surgical relocation of the coronary arteries (e.g., transposition of the great arteries)
Anomalous coronary arteries
Kawasaki's disease (KD) with aneurysms
Cardiomyopathies
Orthotopic heart transplantation (OHT)

Data derived from Kavey et al. Circulation, 2006; 114:2710-38.

Table S2. High-risk categories and subcategories based on ICD-9/10 codes.

Cardiac Disease	Subcategory	ICD-9	ICD-10
Simple Biventricular		745.4, 745.5, 745.80, 745.90, 747.0, 747.39, 747.49, 746.83	Q21.0, Q21.1, Q21.8, Q21.9, Q25.0, Q25.6, Q26.0, Q26.1, Q26.8, Q24.3
Complex Biventricular		745.0, 745.11, 745.12, 745.2, 745.60, 745.61, 745.69, 745.7, 746.00, 746.01, 746.02, 746.09, 746.2, 746.4, 746.5, 746.6, 746.82, 746.84, 746.87, 746.89, 746.9, 747.31, 747.40, 747.41, 747.42	Q20.0, Q20.1, Q20.5, Q21.3, Q21.2, Q22.0, Q22.1, Q22.2, Q22.3, Q22.5, Q23.1, Q23.2, Q23.3, Q24.2, Q24.8, Q24.0, Q24.9, Q20.9, Q25.5, Q25.71, Q26.9, Q26.2, Q26.3, q26.4
Single Ventricle		745.3, 746.1, 746.7	Q20.4, Q22.2, Q23.4
High-Risk	TGA	745.10, 745.19	Q20.3, Q20.8
	Aortic Valve/Arch	424.1, 746.3, 746.81, 747.22, 747.1, 747.10, 747.11, 747.20, 747.21, 747.29	I35.0, I35.2, I35.8, I35.9, Q23.0, Q24.4, Q25.1, Q25.9, Q25.3, q25.21, Q25.29, Q25.41, Q25.42
	KD w/aneurysm	446.1 with 414.11	M30.3 with I25.41
	Coronary Anomaly	746.85, 414.11	Q24.5, I25.41
	Cardiomyopathy	425.1, 425.11, 425.18, 425.8, 425.4, 425.7, 425.8, 425.9	I42.1, I42.2, I43, I42.5, I42.8, I43, I42.7
	Heart Transplant	V42.1, 996.83	Z94.1, T86.20. T86.21, T86.22

Table S3. Stratification of cardiomyopathy phenotype based on ICD-9/10 codes.

Cardiac Disease	Subcategory	ICD-9	ICD-10
Cardiomyopathy	Hypertrophic	425.1, 425.11, 425.18	I42.1, I42.2
	Dilated	425.4	I42.0
	Restrictive		I42.5
	Other (nutritional, metabolic)	425.7, 425.8	I42.8, I43
	Secondary	425.9	I42.7
	Unknown/Not otherwise specified		I42.9

Table S4. Demographic variables by high-risk category.

	Standard Risk N=8,444,325	Simple BiV N=67,655		Complex BiV N=47,947		Single Ventricle N=8,510		High-Risk Diagnoses											
								TGA N=1,768		Aortic Valve N=19,494		KD w/aneurysm N=294		Coronary anomaly N=2,328		Cardiomyopathy N=6,464		Heart Transplant N=868	
Male sex	51% (4,319,922)	50% (33,598)	<0.001‡	51% (24,687)	0.14	56% (4,782)	<0.001	65% (1,141)	<0.001	62% (12,008)	<0.001	70% (206)	<0.001	59% (1,385)	<0.001	60% (3,851)	<0.001	55% (476)	0.03
Age, mean ± SD	8.4 ± 4.9	4.9 ± 4.2	<0.001	7.3 ± 5.1	<0.001	7.6 ± 4.6	<0.001	7.5 ± 4.6	<0.001	8.4 ± 5.0	0.02	5.7 ± 4.4	<0.001	8.0 ± 4.9	0.002	9.7 ± 5.0	<0.001	8.6 ± 4.9	0.11
Commercial insurance	51% (4,284,796)	43% (29,394)	<0.001	46% (21,971)	<0.001	45% (3,849)	<0.001	50% (880)	0.4	52% (10,060)	0.02	50% (148)	0.9	50% (1,157)	0.3	54% (3,477)	<0.001	44% (379)	<0.001
Census region (commercial insurance only)																			
Northeast	18% (779,529)	22% (6,405)	<0.001	26% (5,821)	<0.001	24% (917)	<0.001	18% (158)	0.02	23% (2,311)	<0.001	28% (41)	0.002	24% (282)	<0.001	34% (1,174)	<0.001	26% (98)	<0.001
Midwest	21% (906,738)	19% (5,547)		20% (4,353)		20% (758)		24% (214)		20% (2,027)		13% (19)		19% (216)		21% (715)		19% (71)	
South	43% (1,824,214)	45% (13,190)		39% (8,654)		43% (1,667)		44% (383)		42% (4,211)		34% (51)		40% (466)		34% (1,188)		42% (160)	
West	18% (763,488)	14% (4,187)		14% (3,069)		13% (486)		14% (125)		15% (1,494)		25% (37)		16% (190)		11% (384)		13% (50)	
Unknown	<1% (10,827)	<1% (65)		<1% (74)		1% (21)		0% (0)		<1% (17)		0% (0)		<1% (3)		<1% (16)		0% (0)	
Race/Ethnicity (Medicaid only)																			
White	47% (1,935,286)	46% (17,575)	<0.001	46% (11,901)	<0.001	44% (2,067)	<0.001	52% (454)	<0.001	55% (5,168)	<0.001	45% (66)	0.04	35% (412)	<0.001	44% (1,327)	<0.001	39% (192)	0.02
Black	34% (1,397,603)	28% (10,879)		28% (7,223)		27% (1,281)		18% (156)		20% (1,843)		27% (39)		39% (459)		31% (935)		25% (121)	
Hispanic	9% (365,652)	8% (2,933)		7% (1,745)		5% (211)		6% (53)		7% (674)		16% (23)		9% (107)		7% (200)		5% (26)	
Unknown	3% (128,395)	3% (1,027)		2% (629)		2% (102)		3% (27)		3% (254)		3% (5)		2% (28)		3% (80)		4% (18)	

‡ All statistical comparisons to standard risk

Table S5. Demographic variables and screening proportion by cardiomyopathy phenotype.

	Standard Risk N=8,444,325	Hypertrophic CM N=1,653	Dilated CM N=3,194	Restrictive CM N=76	Mixed CM N=607	Other/Unknown CM N=2,624
Male sex	51% (4,319,922)	63% (1,044)	59% (1,875)	59% (45)	59% (361)	58% (1,512)
Commercial insurance	51% (4,284,796)	49% (817)	55% (1,772)	41% (31)	49% (299)	59% (1,550)
Census region (commercial insurance only)						
Northeast	18% (779,529)	27% (222)	40% (710)	48% (15)	26% (78)	43% (662)
Midwest	21% (906,738)	21% (170)	19% (343)	13% (4)	24% (73)	17% (266)
South	43% (1,824,214)	37% (300)	31% (554)	32% (10)	41% (122)	29% (442)
West	18% (763,488)	15% (124)	8% (148)	3% (1)	8% (25)	12% (179)
Unknown	<1% (10,827)	<1% (1)	1% (17)	3% (1)	<1% (1)	0% (1)
Race/Ethnicity (Medicaid only)						
White	47% (1,935,286)	47% (395)	42% (598)	38% (17)	43% (133)	50% (532)
Black	34% (1,397,603)	34% (288)	32% (453)	42% (19)	29% (90)	25% (269)
Hispanic	9% (365,652)	6% (52)	5% (77)	2% (1)	8% (26)	8% (88)
Unknown	3% (128,395)	3% (21)	3% (43)	2% (1)	2% (7)	3% (32)
Screening	17.5% (1,476,817)	35% (571)	37% (1,195)	43% (33)	31% (188)	42% (1,106)

Figure S1. Flow chart of study design and participant inclusion.

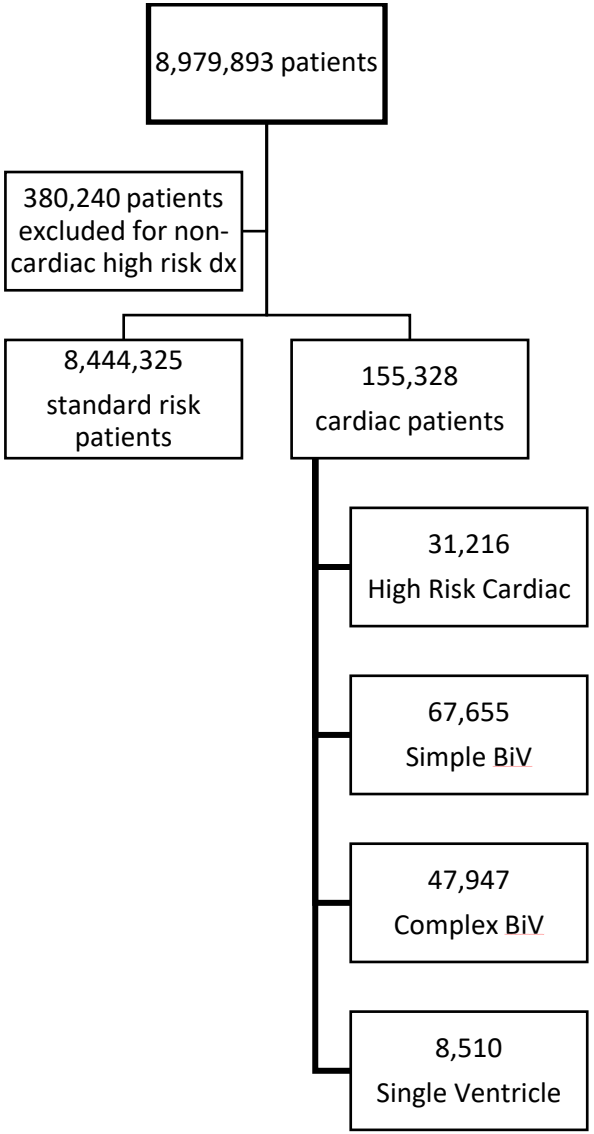
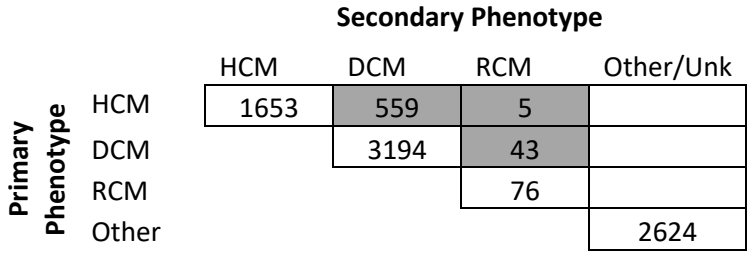


Figure S2. Breakdown of cardiomyopathy patients by phenotype.



Shaded gray boxes represent mixed phenotype patients.