Electrocardiogram Screening for Disorders That Cause Sudden Cardiac Death in Asymptomatic Children: A Meta-analysis


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Electrocardiogram Screening for Disorders That Cause Sudden Cardiac Death in Asymptomatic Children: A Meta-analysis

BACKGROUND AND OBJECTIVES: Pediatric sudden cardiac death (SCD) occurs in an estimated 0.8 to 6.2 per 100,000 children annually. Screening for cardiac disorders causing SCD in asymptomatic children has public appeal because of its apparent potential to avert tragedy; however, performance of the electrocardiogram (ECG) as a screening tool is unknown. We estimated (1) phenotypic (ECG- or echocardiogram [ECHO]-based) prevalence of selected pediatric disorders associated with SCD, and (2) sensitivity, specificity, and predictive value of ECG, alone or with ECHO.

METHODS: We systematically reviewed literature on hypertrophic cardiomyopathy (HCM), long QT syndrome (LQTS), and Wolff-Parkinson-White syndrome, the 3 most common disorders associated with SCD and detectable by ECG.

RESULTS: We identified and screened 6954 abstracts, yielding 396 articles, and extracted data from 30. Summary phenotypic prevalences per 100,000 asymptomatic children were 45 (95% confidence interval [CI]: 10–79) for HCM, 7 (95% CI: 0–14) for LQTS, and 136 (95% CI: 55–218) for Wolff-Parkinson-White. The areas under the receiver operating characteristic curves for ECG were 0.91 for detecting HCM and 0.92 for LQTS. The negative predictive value of detecting either HCM or LQTS by using ECG was high; however, the positive predictive value varied by different sensitivity and specificity cut-points and the true prevalence of the conditions.

CONCLUSIONS: Results provide an evidence base for evaluating pediatric screening for these disorders. ECG, alone or with ECHO, was a sensitive test for mass screening and negative predictive value was high, but positive predictive value and false-positive rates varied. Pediatrics 2012;129:1–12
Although sudden cardiac death (SCD) in children and adolescents (hereafter “children”) is rare (0.8–6.2 per 100,000 annual incidence), the sudden death of a child is tragic and has widespread repercussions. Concern about SCD has raised calls for screening in primary care or school-based settings for all children; others have recommended screening for subgroups of children starting stimulants or participating in competitive athletics, both of which increase heart rate and may theoretically precipitate SCD.\(^1,3,4\)

Population-based screening programs that identify children at risk for SCD have broad public appeal, as common sense suggests that presymptomatic diagnosis saves lives, and the societal cost is presumed to be the cost of the screening test itself. Japan is the sole country with published data on mass screening of school-aged children, including a targeted cardiac history and physical and electrocardiogram (ECG).\(^5\) No data regarding mass pediatric screening and associated costs are available in the United States.\(^6\)

In 2008, the American Heart Association released a statement\(^7\) broadly interpreted as recommending an ECG before initiating stimulants for children with attention-deficit/hyperactivity disorder, estimated at 4% to 12% of children.\(^8\) The American Academy of Pediatrics later released a statement, in collaboration with the American Heart Association, recommending that children with attention-deficit/hyperactivity disorder be assessed with a targeted history and cardiac examination but that further evaluation, including an ECG, be obtained only if indicated.\(^9\) A recent decision analysis recommended that children participating in competitive sports undergo mass screening.\(^5\) Several studies have described screening programs for athletes. Italy uses preparticipation screening, including ECGs, for athletes aged 12 to 35\(^1\) and some American universities use preparticipation screening and ECGs for college athletes. Because 10 million people in the United States may be classified as “young competitive athletes,”\(^10\) calls for screening have far-reaching implications.

Screening programs are most effective if (1) preclinical prevalence is sufficiently high in the screened population, (2) a highly discriminatory screening test is available, (3) the disease or disorder is serious, and (4) treatment while asymptomatic decreases morbidity and mortality more than treatment after symptoms develop.\(^11\) These criteria enable evaluation of the efficiency of ECG to detect the disorders that may cause SCD in asymptomatic children.

Several rare disorders cause pediatric SCD, but not all have ECG findings.\(^12\) The most common disorders detectable by ECG are hypertrophic cardiomyopathy (HCM), long QT syndrome (LQTS), and Wolff-Parkinson-White syndrome (WPW). Their estimated prevalence rates are low in otherwise healthy, asymptomatic children, moreover, the value of the ECG as a “highly discriminatory” test is not well established. The ECG should selectively identify disorders responsible for SCD in all affected patients (ie, sensitivity) and rule out these disorders in healthy children (ie, specificity). Together, low prevalence and imperfect sensitivity and specificity estimates could result in inefficient screening strategies with unanticipated societal and economic costs.

We undertook a systematic review and meta-analysis of the literature of these 3 disorders that cause SCD. Our first aim was to summarize how often ECG- or echocardiogram (ECHO)-based testing (phenotypic prevalence) suggests HCM, LQTS, or WPW among asymptomatic and undiagnosed children who could be identified by mass screening. We focused on phenotypic prevalence, rather than genetic prevalence, because genetic testing is currently impractical in mass screening programs and is limited to diagnosis or risk stratification. Our second aim was to examine the reported sensitivity and specificity of the ECG, alone or with ECHO, to detect these disorders and calculate predictive values. Together, this information on phenotypic (ECG- or ECHO-based) prevalence, sensitivity, specificity, and predictive value form an evidence base that will facilitate further evaluation of the efficiency and downstream implications of ECG screening programs for SCD.

**METHODS**

We focused on HCM, LQTS, and WPW because they are the most common disorders potentially detectable by ECG among children. Because ECG findings in HCM are age sensitive (ie, may not be detected until late adolescence or early adulthood) and can be nonspecific, thus requiring an ECHO for diagnostic guidance, we chose to include articles that examined test characteristics of ECG alone, ECHO alone, or ECG combined with ECHO (ECG/ECHO).

**Literature Searches**

We performed a systematic review and searched the Medline database (1950 to December 2010) for studies reporting on HCM, LQTS, WPW, and SCD or on ECG and/or ECHO detection of these disorders. We combined keywords and Medical Subject Heading terms for hypertrophic cardiomyopathy, long QT syndrome, Wolff-Parkinson-White syndrome, sudden cardiac death, echocardiography, echocardiography, sensitivity, and specificity. The search was limited to English-language publications of primary studies in humans with no geographic restrictions. Six reviewers screened titles and abstracts to identify relevant studies and then examined full-text articles for eligibility.
Eligibility Criteria
To summarize how often ECG- or ECHO-based testing (phenotypic prevalence) suggests HCM, LQTS, or WPW in asymptomatic children or young adults (3–25 years old), we included cross-sectional or cohort studies from the general population that used ECG or ECHO diagnostic criteria for each disorder consistent with clinical standards. Studies in which the mean age was >2 SDs from 25 years were excluded, including a recent study focused on neonates. We also excluded studies of highly selected subgroups that were not representative of the general population. For example, “elite” athletes who competed in competitive regional, national, or international events were excluded, but studies of normally active high school athletes were included. Studies that used sampling techniques that might result in a nonrepresentative sample (eg, convenience sampling, studies requiring informed consent from participants) were excluded. Studies assessing the frequency of genetic variations related to HCM, LQTS, or WPW were excluded, given our focus on ECG screening in asymptomatic and previously undiagnosed children. For our second aim we included studies with data on the sensitivity or specificity of ECG (with or without ECHO) to identify children who would have a diagnosis of HCM, LQTS, or WPW according to clinical criteria. Specifically, we deemed that an adequate reference (“gold”) standard for HCM is ECHO, genotyping, or a well-documented HCM diagnosis. For LQTS, we accepted as reference standard testing for pathogenic variations (eg, the KCNQ1, KCNH2, and SCN5A genes) or a combination of personal and family history, clinical follow-up, and ECG. For WPW, ECG is the reference standard, so sensitivity and specificity information were not collected. Based on these criteria, studies with incorporation bias (where the index test comprises part of the reference standard against which it is measured) were eligible. We included studies in which only those with positive ECG and/or ECHO were verified with the reference standard (verification bias, which may overestimate sensitivity and underestimate the specificity of the index test). For those studies that had multiple alternative sets of ECG and/or ECHO criteria, we selected the most widely used or most sensitive criteria to avoid duplication of information.

Data Extraction
Four reviewers extracted data with at least 2 independently extracting or reviewing each article. All 4 reviewers discussed and resolved any discrepancies by consensus. From studies informing on phenotypic (ECG- or ECHO-based) prevalence, we extracted information on study population (description, country), study design (prospective, retrospective), sampling technique (representative or not), age of the study sample, sample size, diagnostic criteria, and number of participants with each disorder. From studies on the sensitivity and specificity of ECG and/or ECHO to identify HCM or LQTS, we extracted information on study population (description, country), age of the study sample, type of test (ECG and/or ECHO), diagnostic criteria and thresholds for the test, reference standard definition, true-positive, false-negative, false-positive, true-negative, and presence of verification bias. If the study provided only sensitivity and specificity, we used this information to calculate the true-positive, false-negative, false-positive, and true-negative values.

Analysis
Because of the complexities of our methods, we briefly discuss analyses in the following paragraphs and provide detailed Supplemental Information that discusses characteristics of screening tests in general (eg, sensitivity, specificity, predictive value) and analytic methods used (eg, creation of hierarchical summary receiver operating characteristic [HSROC] curve).

Analysis of Phenotypic Prevalence
Phenotypic (ECG- or ECHO-based) prevalence (per 100 000) estimates and 95% confidence intervals (Cls) for HCM, LQTS, and WPW were calculated by using the exact binomial distribution. We obtained summary estimates of phenotypic prevalence by using random effects meta-analysis of logit-transformed phenotypic prevalence. To assess the extent to which variation in the reported outcomes may be a result of chance alone, we used Cochran Q to test for heterogeneity (significant when $P < .10$) and quantified its magnitude in terms of $I^2$, which ranges between 0% and 100% and expresses the proportion of between-study variability attributable to heterogeneity rather than chance. We considered $I^2$ values exceeding 75% suggestive of substantial heterogeneity. These calculations were performed by using Stata, version 11 (StataCorp LP, College Station, TX).

Analysis of Sensitivity and Specificity
For each disorder, we summarized the relationship between sensitivity (ie, the probability of having a positive test among those with the disorder) and specificity (ie, the probability of having a negative test among those without the disorder) of ECG and/or ECHO with an extension of the HSROC model. For each disorder and screening tool combination, we plotted the HSROC curve for individual studies and the HSROC curve for the summary of the reviewed studies. These curves allow visual comparison between individual studies and the summary curve. Points along the summary curves incorporate different diagnostic criteria and do not correspond directly to specific observed study cut points for ECG and/or ECHO. Restricting the range to that observed in the data, the area under the posterior estimate...
of the HSROC curve (AUC) calculated by numeric integration indicates test performance. An AUC of 1.0 represents a perfect test, whereas an AUC of 0.5 represents a test that performs no better than chance.

For each summary curve, we identified 2 illustrative examples to demonstrate how changes in sensitivity and specificity resulted in different predictive values, number needed to screen, false-positives, and false-negatives. We selected 2 points on the HSROC curve: (1) the point with “maximal accuracy” (ie, maximizing the sum of the sensitivity and specificity), thereby giving equal weight to ruling in people with disease (sensitivity) and ruling out those without disease (specificity); and (2) the point with “maximal specificity” where specificity was near 1 and the corresponding sensitivity, thereby giving more weight to ruling out those without the disease (specificity). We did not select a point on the curve where sensitivity was maximized because the corresponding specificity was low (0.001). By using the 2 illustrative points, we calculated 5 parameters: (1) positive predictive value (PPV, ie, the probability of having the disorder given a positive test), (2) negative predictive value (NPV, ie, the probability of not having the disorder given a negative test), (3) number needed to screen to detect 1 case, (4) number of false-positives when detecting 1 case, and (5) number of false-negatives per 100 000 children screened. To explore the effect of alternative prevalence rates, we repeated these calculations by using oft-cited prevalences of 200 per 100 000 for HCM, 50 per 100 000 for LQTS, and 200 per 100 000 for WPW (See Supplemental Information, Supplemental Figures 4-8, and Supplemental Tables 1-3 for more information on screening trade-offs in general.).

**Sensitivity Analysis**

To determine whether alternative assumptions substantially affected the meta-analysis results, we performed extensive sensitivity analyses. For key questions related to phenotypic (ECG- or ECHO-based) prevalence, we repeated the analyses excluding studies where (1) diagnostic criteria were not specified, (2) reported phenotypic prevalence exceeded the range of often-cited prevalence rates, or (3) phenotypic prevalence was based on previously diagnosed cases and not asymptomatic cases. For key questions addressing the ability of ECG- or ECHO-based testing to diagnose people with the conditions of interest, we repeated the analyses by excluding studies that did not apply the reference standard to participants with a nonsuggestive ECG and/or ECHO (ie, verification bias).

For additional sensitivity analyses, we back-calculated disease prevalence when applying a non-ECG reference standard to define disease. A positive screening ECG (eg, a result suggesting LQTS) can be either a true-positive (the person has LQTS) or a false-positive (the person does not and will not have LQTS). Thus, the frequency of “suggestive ECGs” is not the same as the prevalence of the disease. One can back-calculate the prevalence of LQTS from an acceptable alternative non-ECG reference standard to diagnose LQTS (eg, genetic testing for deleterious mutations in LQTS genes15), and from the proportion of positive ECG tests in a population. We performed such analyses only for LQTS, as an example to contextualize our discussion comments. As described in the Supplemental Information, we extended the Bayesian method of Joseph and colleagues.22

**RESULTS**

From 6954 titles and abstracts screened for eligibility, we retrieved and evaluated the full text in 396 articles, with 30 meeting eligibility criteria (Fig 1).

### Characteristics of Reviewed Studies

In the 11 primary studies1,19,23–31 that reported phenotypic (ECG- or ECHO-based) prevalence findings, study populations ranged from general to subgroups of high school athletes and military conscripts. Studies were conducted in North America, Europe, and Asia and had sample sizes ranging from 1369 to 1 336 377 (Table 1).

Twenty primary studies28,32–50 reported sensitivity and specificity estimates by using ECG to detect LQTS and/or HCM,

**FIGURE 1**

Literature search strategy.
<table>
<thead>
<tr>
<th>Author</th>
<th>Population and Source</th>
<th>Location</th>
<th>Study Design</th>
<th>Sampling Technique</th>
<th>Age, y Sample Size</th>
<th>Diagnostic Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arola (1997)23a</td>
<td>Medical chart review within hospitals</td>
<td>Finland</td>
<td>RC</td>
<td>Representative</td>
<td>Range: 0–20 1 336</td>
<td>Interventricular septum or LV wall thickness $\geq$ 2 SD of normal</td>
</tr>
<tr>
<td>Colivicchi (2004)24</td>
<td>Pre-participation athletic screening</td>
<td>Italy</td>
<td>PC</td>
<td>Representative</td>
<td>Mean=16.2 SD=2.4 756</td>
<td>LV wall thickness $\geq$ 15 mm</td>
</tr>
<tr>
<td>Corrado (1998)25</td>
<td>Pre-participation athletic screening</td>
<td>Italy</td>
<td>PC</td>
<td>Representative</td>
<td>Mean=19 SD=5 3735</td>
<td>LV wall thickness $\geq$ 15 mm</td>
</tr>
<tr>
<td>Corrado (2000)1</td>
<td>Pre-participation athletic screening</td>
<td>Italy</td>
<td>PC</td>
<td>Representative</td>
<td>Range: 12–35 42 386</td>
<td>LV wall thickness $\geq$ 15 mm</td>
</tr>
<tr>
<td>Maron (1995)19</td>
<td>Epidemiology study with subjects selected from general population</td>
<td>USA</td>
<td>PC</td>
<td>Representative</td>
<td>Range: 23–35 4111</td>
<td>LV wall thickness $\geq$ 15 mm</td>
</tr>
<tr>
<td>Maron (1999)26a</td>
<td>Diagnostic testing requested by primary physician in rural community</td>
<td>USA</td>
<td>PC</td>
<td>Representative</td>
<td>Range: 16–87 15 137</td>
<td>LV wall thickness $\geq$ 15 mm</td>
</tr>
<tr>
<td>Niimura (1989)27</td>
<td>Screening of &quot;presumably healthy&quot; nursery school and junior high school children</td>
<td>Japan</td>
<td>PC</td>
<td>Representative</td>
<td>Ranges: 3–5, 12–14 930 939</td>
<td>Not specified</td>
</tr>
<tr>
<td>Corrado (2006)1</td>
<td>Pre-participation athletic screening</td>
<td>Italy</td>
<td>PC</td>
<td>Representative</td>
<td>Mean=19 SD=2 34 910</td>
<td>LV wall thickness $\geq$ 15 mm</td>
</tr>
<tr>
<td>Maron (1999)26a</td>
<td>Epidemiology study in random sample of general population</td>
<td>China</td>
<td>PC</td>
<td>Representative</td>
<td>Range: 18–29 1 369</td>
<td>LV wall thickness $\geq$ 15 mm</td>
</tr>
<tr>
<td>Chiu (2008)30</td>
<td>Citywide survey of general population</td>
<td>Taiwan</td>
<td>PC</td>
<td>Representative</td>
<td>Range: 6–20 450 391</td>
<td>QTc $&gt;450$ ms</td>
</tr>
<tr>
<td>Corrado (2000)1</td>
<td>Pre-participation athletic screening</td>
<td>Italy</td>
<td>PC</td>
<td>Representative</td>
<td>Range: 12–35 42 386</td>
<td>Male: QTc $&gt;440$ ms, Female: QTc $&gt;460$ ms</td>
</tr>
<tr>
<td>Kobza (2009)31a</td>
<td>Screening of military recruits (mostly male) before mandatory military service</td>
<td>Switzerland</td>
<td>PC</td>
<td>Representative</td>
<td>Mean=192 SD=1.4 40 917</td>
<td>Male: QTc $&gt;450$ ms, Female: QTc $&gt;460$ ms</td>
</tr>
<tr>
<td>Niimura (1989)27</td>
<td>Screening of &quot;presumably healthy&quot; nursery school and junior high school children</td>
<td>Japan</td>
<td>PC</td>
<td>Representative</td>
<td>Ranges: 3–5, 12–14 930 939</td>
<td>Not specified</td>
</tr>
<tr>
<td>Zou (2004)29</td>
<td>Epidemiology study in random sample of general population</td>
<td>China</td>
<td>PC</td>
<td>Representative</td>
<td>Range: 18–29 1 369</td>
<td>LV wall thickness $\geq$ 15 mm</td>
</tr>
<tr>
<td>Chiu (2008)30</td>
<td>Citywide survey of general population</td>
<td>Taiwan</td>
<td>PC</td>
<td>Representative</td>
<td>Range: 6–20 450 391</td>
<td>PR interval $&lt;120$ ms, slurred upstroke of the QRS complex, QRS $&gt;120$ ms</td>
</tr>
<tr>
<td>Corrado (2000)1</td>
<td>Pre-participation athletic screening</td>
<td>Italy</td>
<td>PC</td>
<td>Representative</td>
<td>Range: 12–35 42 386</td>
<td>PR interval $&lt;0.12$ s, QRS $\geq0.12$ s</td>
</tr>
</tbody>
</table>

LQTS, n = 4

Chiu (2008)30

Corrado (2000)1

Kobza (2009)31a

Niimura (1989)27

WPW, n = 3

Chiu (2008)30

Corrado (1998)23

Corrado (2000)1

WPW (6 studies), 33,35,36,41 and ECG/ECHO (4 studies). 33

To provide clinical context for interpreting these results, we used the previously described illustrative points the maximal accuracy point and the maximal sensitivity point on the HSROC curves for HCM, the 2 previously described illustrative points the maximal specificity point on the HSROC curves for detection of HCM using ECG, ECHO, and ECG/ECHO Table 3. Regardless of whether an ECG, ECHO, or ECG/ECHO was used, both illustrative points yielded an accuracy of 91% or greater. These studies were included in sensitivity analysis only.

For HCM, the 2 previously described illustrative points. Based on the summary HSROC curves, the AUC used, both illustrative points yielded an accuracy of 91% or greater. These studies were included in sensitivity analysis only.

Inclusion of the study by ECG/ECHO (10 studies), 28,32 helped inform the upper bounds of the estimate. Although 1 of 2 studies did not specify diagnostic criteria, we included it because its exclusion had no effect on phenotypic prevalence. After adding 2 nonrepresentative studies,23-25 for sensitivity analysis, the summary HSROC curves, the AUC used, both illustrative points yielded an accuracy of 91% or greater. These studies were included in sensitivity analysis only.
<table>
<thead>
<tr>
<th>Disorder &amp; Screening Test</th>
<th>Author (year)</th>
<th>Sample</th>
<th>Location</th>
<th>Age, y</th>
<th>Screening Test Criteria</th>
<th>Definition of Reference (“Gold”) Standard</th>
<th>Verification Bias</th>
<th>Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCM, n=11 ECG, n=10</td>
<td>Autore (1988)</td>
<td>First-degree relatives of patients with HCM</td>
<td>Italy</td>
<td>Mean=36 SD=20</td>
<td>LV hypertrophy; abnormal Q waves; negative T waves; atrial fibrillation; left or right bundle branch block</td>
<td>ECHO</td>
<td>No</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>Charron (1997)</td>
<td>Genotyped probands and first-degree relatives</td>
<td>France</td>
<td>Range: 18–29</td>
<td>Q waves; LV hypertrophy; repolarization alterations; isolated left atrial enlargement; short PR interval; microvoltages; minor Q waves; bundle-branch block or hemiblock</td>
<td>Genotyping</td>
<td>No</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>Charron (1998)</td>
<td>Children of HCM genotyped families</td>
<td>France</td>
<td>&lt;18</td>
<td>Q waves; voltage; repolarization alterations; abnormal PR interval, left and/or right atrial enlargement; atrial fibrillation; abnormal QRS axis; increased QRS duration; increased ventricular activation time; T waves; R/S ratio, rSr’ aspect; bundle branch block or hemiblock; microvoltages</td>
<td>Genotyping</td>
<td>No</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>Charron (2003)</td>
<td>Genotyped probands and first-degree relatives</td>
<td>France</td>
<td>Mean=37.7 SD=17.9</td>
<td>abnormal Q waves; T-wave inversion; LV hypertrophy</td>
<td>Genotyping</td>
<td>No</td>
<td>109</td>
</tr>
<tr>
<td></td>
<td>Dipchand (1993)</td>
<td>Children with HCM and healthy controls</td>
<td>Canada</td>
<td>Median=3, Range: 0–19</td>
<td>Q waves; R waves; S waves; T waves; QTc interval; voltage</td>
<td>ECHO, LV angiography</td>
<td>Yes</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>Fragola (1993)</td>
<td>First-degree relatives of patients with HCM</td>
<td>Italy</td>
<td>Mean=34 SD=19</td>
<td>LV and RV hypertrophy; atrial enlargement; rhythm disturbances; atrioventricular and intraventricular conduction; ST-T displacement; Q waves; R waves; QRS</td>
<td>Genotyping</td>
<td>No</td>
<td>116</td>
</tr>
<tr>
<td></td>
<td>Konno (2004)</td>
<td>Genotyped relatives of patients with HCM</td>
<td>Japan</td>
<td>&lt;30</td>
<td>Q wave; LV hypertrophy; ST-segment depression; T-wave inversion</td>
<td>ECHO</td>
<td>No</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>Nistri (2003)</td>
<td>Screening of military recruits (males only)</td>
<td>Italy</td>
<td>≥17</td>
<td>LV wall thickness; Q waves; ST-T waves</td>
<td>ECHO</td>
<td>No</td>
<td>2770</td>
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<tr>
<td></td>
<td>Potter (2010)</td>
<td>Patients with HCM and healthy controls</td>
<td>UK, Sweden, US</td>
<td>Mean=48.7 SD=14.0</td>
<td>RR, PR, P-wave, QRS and QT and JT intervals; P, QRS, and T-wave amplitudes; frontal plane QRS and T-wave axes; and ST-segment levels</td>
<td>ECHO</td>
<td>Yes</td>
<td>181</td>
</tr>
<tr>
<td></td>
<td>Ryan (1995)</td>
<td>Probands and relatives</td>
<td>UK, Poland</td>
<td>Mean=47 SD=19</td>
<td>R waves; S waves; Q waves; ST-T waves</td>
<td>Genotyping or clinical diagnosis</td>
<td>No</td>
<td>506</td>
</tr>
<tr>
<td></td>
<td>Charron (1997)</td>
<td>Genotyped probands and first-degree relatives</td>
<td>France</td>
<td>Range: 18–29</td>
<td>MWT</td>
<td>Genotyping</td>
<td>No</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>Charron (1998)</td>
<td>Children of HCM genotyped families</td>
<td>France</td>
<td>&lt;18</td>
<td>MWT; intraventricular septum/posterior wall; left atrium diameter; systolic anterior motion of mitral valve; mid-systolic aortic closure; gradient &gt;30 mmHg; mitral valve regurgitation; E/A wave ratio</td>
<td>Genotyping</td>
<td>No</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>Charron (2003)</td>
<td>Genotyped probands and first-degree relatives</td>
<td>France</td>
<td>Mean=37.7 SD=17.9</td>
<td>MWT in anterior septum or posterior wall; MWT in posterior septum or free wall; systolic anterior motion of the mitral valve; redundant leaflets</td>
<td>Genotyping</td>
<td>No</td>
<td>109</td>
</tr>
<tr>
<td></td>
<td>Fragola (1993)</td>
<td>First-degree relatives of patients with HCM</td>
<td>Italy</td>
<td>Mean=34 SD=19</td>
<td>Increased interventricular septal thickness; posterior wall thickness</td>
<td>ECHO</td>
<td>No</td>
<td>122</td>
</tr>
<tr>
<td></td>
<td>Ho (2002)</td>
<td>Genotyped relatives of patients with HCM and healthy controls</td>
<td>USA</td>
<td>Mean=35.6 SD=12.6</td>
<td>LV ejection fraction; early diastolic myocardial velocities</td>
<td>Genotyping</td>
<td>No</td>
<td>72</td>
</tr>
</tbody>
</table>
NPV that was near 100%, but PPV, number needed to screen, false-positives, and false-negatives differed substantially. At the maximal accuracy point, the PPVs fell below 1% compared with PPVs from 2% to 21% at the maximal specificity point. The maximal accuracy point led to fewer false-negatives (16%) and a lower number needed to screen to detect 1 case of HCM (2600). In contrast, the maximal specificity point led to 40% to 96% false-negative rates and 4000 to 57 000 needed to screen to detect 1 case of HCM. Last, the maximal accuracy point led to more false-positives per true HCM case detected (400 vs 4–57) than the maximal specificity point.

By using the often-cited prevalence of 200 per 100 000\textsuperscript{19} (4 times our estimate) resulted in similar NPV, a fourfold increase in PPV and false-negatives per 100 000 screened, and a decrease in the number needed to screen to detect 1 case and number of false-positives when detecting 1 case.

**Long QT Syndrome**

Phenotypic (ECG-based) prevalence rates of the 3 studies reporting on LQTS ranged from 1 to 12 per 100 000 (Fig 2).\textsuperscript{1,27,30} with a summary phenotypic prevalence rate of 7 per 100 000 (95% CI: 0–14) and substantial heterogeneity ($I^2 = 93\%$, $P < .001$). Although 1 study\textsuperscript{27} did not specify diagnostic criteria, we included it because its exclusion increased phenotypic prevalence to only 9 per 100 000 and this study was based on a well-established screening program in Japan. The Kobza study\textsuperscript{31} was excluded because its prevalence rate (550 per 100 000) exceeded often-cited prevalence rates of LQTS (40–50 per 100 000).\textsuperscript{13} When incorporating Kobza, the summary prevalence increased fivefold to 38 per 100 000 (95% CI: 19–58) and heterogeneity increased ($I^2 = 99\%$, $P < .001$).\textsuperscript{42–50} The Bayesian sensitivity analysis giving the Schwartz\textsuperscript{15} prior a low weight (1/2500) resulted in similar
phenotypic prevalence of 7 per 100 000 (95% CI: 1–30), whereas giving the Schwartz prior more weight increased the phenotypic prevalence to 34 per 100 000 (95% CI: 20–54). For detecting LQTS (9 studies), Fig 3 illustrates a set of HSROC curves for ECG with a summary AUC of 0.92.

To provide clinical context, we used the summary phenotypic prevalence estimate for LQTS and 2 illustrative points (the maximal accuracy point and the maximal specificity point) on the HSROC curve for detection of LQTS by using ECG (Table 3). For both points, the NPV was near 100%. The PPV was very low (0.04% [1 in 2324]) at the maximal accuracy point, but increased slightly at the maximal specificity point (0.7% [1 in 136]). With maximal accuracy, the number needed to screen to detect 1 case of LQTS with an ECG was more than 16 000 with only 14% of those with LQTS missed (false-negatives), but more than 2000 false-positives per LQTS case detected. With maximal specificity, the number needed to screen to detect 1 case increased to 135 000 and 91% of those with LQTS would be missed, but there would be only 135 false-positives per LQTS case detected. By using the often-cited prevalence of 50 per 100 000 (7 times our estimate) resulted in a similar NPV, a sevenfold increase in PPV and false-negatives per 100 000 screened, and a decrease in number needed to screen to detect 1 case and number of false-positives when detecting 1 case.

WPW Syndrome
Three studies reported phenotypic (ECG-based) prevalence rates for WPW ranging from 68 to 222 per 100 000 with a summary phenotypic prevalence rate of 136 per 100 000 (95% CI: 55–218) (Fig 2) and substantial heterogeneity (I² = 95%, P < .001). Because ECG is considered the reference standard and no studies reported estimates of sensitivity and specificity for any other screening tests to detect WPW, we assumed that its sensitivity and specificity were one and the PPV and NPV estimates were perfect and are not discussed further. By using the often-cited prevalence estimate of 200 per 100 000 did not substantially alter the number needed to screen.

DISCUSSION
By using published literature, we report on phenotypic (ECG- or ECHO-based)
prevalence rates of HCM, LQTS, and WPW in asymptomatic children and the test characteristics of ECG and/or ECHO in detecting these disorders. Based on our prespecified inclusion/exclusion criteria and methodology, phenotypic prevalence estimates demonstrated wide variation across studies and were lower than those in neonates (eg, Schwartz et al\textsuperscript{13}) or studies examining genotypic prevalence. Consequently, we explored the effects of alternative prevalence estimates in our results. Although the AUC ranged from 0.88 to 0.92, indicating that ECG and/or ECHO are statistically acceptable screening tests for detecting the most common disorders that cause SCD, the low phenotypic prevalence substantially affected the predictive value.

Because these disorders have a very low phenotypic prevalence, choosing a point on the HSROC curve that maximizes accuracy or maximizes specificity had little impact on NPV (nearly 100% NPV for HCM and LQTS); however, the maximal specificity point resulted in improved PPV (0.74% [1 in 136] to 21%) at the cost of needing to screen more individuals to detect 1 case and missing more diseased individuals because of reduced sensitivity. With maximal accuracy, the number needed to screen to detect 1 case fell and fewer cases were missed, but at the cost of lower PPV (0.04% [1 in 2324] to 0.26% [1 in 390]) and more false-positives per case detected. These findings help define boundaries of the theoretical utility of ECG and/or ECHO as screening tests for these disorders, but are difficult to comprehend in isolation. Unlike “typical” screening programs that value sensitivity over specificity, these illustrative points demonstrate that when phenotypic prevalence is low, prioritizing specificity over sensitivity can improve PPV while not affecting the NPV (similar to HIV screening\textsuperscript{21}).

We performed calculations to understand how these estimates might apply to population-based ECG screening. First, assuming independence, the combined prevalence estimate of HCM, LQTS, and WPW from our meta-analysis is 188 per 100,000. When maximizing accuracy, the NPV approaches 100%, indicating a low false-reassurance rate. However, the PPV of using an ECG to screen for any of the 3 disorders is 1%, indicating a high false-alarm rate (99% of children with a positive ECG would not have any of the disorders). Conversely, when maximizing specificity, the PPV still approaches 100% (false-reassurance rate remains near 0%), but the PPV is 41% (false-alarm rate decreases to 59%). A sensitivity analysis using often-cited alarm rates (99% of children with a positive ECG would not have any of the disorders) showed a more favorable outlook for screening (higher PPV, fewer need to screen to detect 1 case).
detect 1 case, fewer false-positives when detecting 1 case, but more false-negatives per 100 000 screened.

Although these results suggest that ECG may be considered for mass screening from a statistical perspective and from the US Preventive Services Task Force criteria,\(^{52}\) it does not address other components of screening programs, including changes in mortality, morbidity, cost, quality of life, and functioning that need to be weighed. Because of the very low phenotypic prevalence and inherent inaccuracy in nearly all medical tests (including pediatric cardiologists reviewing ECGs\(^{53}\)), screening for rare disorders will lead to many false-positive tests that trigger additional diagnostic evaluations and, possibly, unnecessary therapies and physical activity restrictions. In addition, false-positives may lead to unwarranted child and parent anxiety; previous work suggests this anxiety may not dissipate immediately following a cardiac evaluation and may influence lifelong lifestyle decisions.\(^{54}\)

Concern has been raised about increased rates of diagnosed heart disease where diagnosis may not be helpful (resulting in diagnosis of cardiac nondisease and overtreatment\(^{55}\)). Some children may ultimately be diagnosed by other means (eg, family history, emergence of sublethal symptoms, diagnostic testing for unrelated indications) even in the absence of mass screening, and earlier diagnosis of the disorder may not provide survival benefit. Among those children detected by screening, the safety, efficacy, and acceptability of specific therapies and recommendations for prophylaxis of SCD in asymptomatic children is sometimes uncertain and often based on expert consensus as opposed to clinical evidence.\(^{5}\)

In addition, families need to be aware that a negative ECG does not definitively rule out risk for SCD. Other rare cardiac disorders cause SCD, such as anomalous origin of the coronary artery, arrhythmogenic right ventricular cardiomyopathy, catecholaminergic ventricular tachycardia, and Brugada syndrome. With the exception of Brugada syndrome, which manifests in late adolescence, these disorders are not typically diagnosed by ECG. Also, given that clinical and ECG findings may not manifest in HCM until adolescence, programs that screen young children may miss those genetically predisposed to developing HCM, which may necessitate repeat ECGs during adolescence.

This study has several limitations. First, our search was restricted to literature cataloged by Medline. Medline indexes most biomedical articles, making it unlikely that we omitted important findings. Second, our estimates may reflect publication bias, as it is conceivable that “unsuccessful” studies of diagnostic or detection interventions may not have been published. This phenomenon, if it took place, would inflate our test accuracy estimates. Third, heterogeneity existed between studies. Populations varied by age and studies varied in their screening approach and their diagnostic criteria. Fourth, our calculations omitted a targeted history and physical. Although we included medical history, physical examination, and family history in our search, we found insufficient data for further analyses. Published studies suggest that history and physical examination have low sensitivity,\(^{25}\) low PPV,\(^{56}\) and limited value from a health economics perspective.\(^{3,4}\) Fifth, we defined phenotypic prevalence based on results from ECG or ECHO (not genotyping) because these were the screening options considered in our analysis and because genotyping has only recently become available and is still evolving. In estimating the sensitivity and specificity of ECG and/or ECHO, however, we allowed genotypically identified cohorts because genetic testing will likely play a more prominent role in screening and diagnosing disorders that cause SCD. By using genotyping as the reference standard allows us to incorporate some variability in penetrance (leading to false-positives), which will likely be important for screening test interpretation. Finally, this study is limited by considering only 3 disorders, but these are the 3 most common disorders detectable by ECG and/or ECHO.

Despite these limitations, this study provides an important starting point for evaluating SCD screening programs. Screening programs may be gaining popularity because of availability bias in risk perception (ie, recent publicized events result in the overestimated likelihood of a similar event occurring). Given our results on the low phenotypic (ECG- or ECHO-based) prevalence and the variation in false-positive rate based on different sensitivities and specificities, further cost- or comparative-effectiveness analyses will be necessary to determine whether screening programs to detect SCD in asymptomatic children should be promoted as public health policy.

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10 RODDAY et al

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