Missed Diagnosis of Critical Congenital Heart Disease

Ruey-Kang R. Chang, MD, MPH; Michelle Gurvitz, MD; Sandra Rodriguez, MS

Objectives: To evaluate the rate and the clinical and demographic characteristics of missed diagnosis of critical congenital heart disease (CCHD).


Setting: California.

Participants: The study cohort consisted of 898 infants who died of CCHD at 1 to 364 days of age who either did not undergo surgery or had an unknown surgery status. From all patients who met these initial criteria, we examined (1) whether autopsies were performed and autopsy results were used to establish the cause of death, (2) whether autopsies were performed but the results were not used to establish a cause of death, and (3) whether infants with hypoplastic left heart syndrome (HLHS) were potentially receiving comfort care.

Main Outcome Measures: Missed and possibly late diagnosis of CCHD.

Results: Among 152 infants with a missed CCHD diagnosis, the median age at death was 13.5 days. More than 50% of patients with a missed CCHD diagnosis (n=78) died at home or in the hospital emergency department. The most common diagnoses were HLHS and coarctation of aorta. There were an average of 10 patients with missed CCHD diagnoses and 20 patients with late diagnoses in California per year. The total annual number of patients with missed or late diagnoses decreased in 1989-1999 and remained unchanged in 2000-2004.

Conclusions: Up to 30 infants per year died of a missed or possibly late diagnosis of CCHD in California. Most deaths due to a missed diagnosis were from HLHS and coarctation of the aorta. Because the median age at death was younger than 2 weeks, a careful cardiovascular evaluation for left heart obstructive CHD should be performed during the first postdischarge visit to a pediatrician’s office at 3 to 5 days of age.

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CONGENITAL HEART DIS-EASE (CHD) affects 8 to 12 per 1000 live-born infants and is 1 of the most common and serious types of birth defects.1 If not diagnosed early in life, many of these defects may result in life-threatening events or significant morbidity.2,3 With early diagnosis, however, most infants with CHD can benefit from successful surgical repair or palliation.4-7 Nevertheless, many infants born with CHD are discharged from the hospital nursery with their conditions undiagnosed.8 Although for more than 30 years standard practice has called for clinical examination of the cardiovascular system at the routine newborn examination, studies9,10 suggest that routine cardiovascular examination misses nearly half the newborns with significant CHD. Even with newer diagnostic techniques, CHD in many children is likely still missed in the newborn period.

Population-based data on infants who died without a timely diagnosis of CHD have been limited. This study uses statewide death registry data to attempt to identify infants with critical congenital heart disease (CCHD) who died when the CHD diagnosis was either unknown or made too late for effective surgical intervention. This study examines statewide death registry data from California for a 16-year period spanning 1989 through 2004. As set forth by the Tennessee Task Force on Screening Newborn Infants for Critical Congenital Heart Disease,11 CCHD is defined as CHD lesions that are ductal dependent or may require surgical or catheter intervention in the first month of life. The objectives of this study are 2-fold: to estimate the rate of missed or possibly late diagnoses of CCHD among infants dying within a year of birth, in California, between 1989 and 2004, and to analyze the clinical and demographic characteristics of this population.

METHODS

DATABASE

We used 1989-2004 statewide death registry data from the Death Statistics Master File at the
California Department of Health Services, Center for Health Statistics.12 The Death Statistics Master File data include state-mandated reports of all deaths to the California Department of Health Services. Data fields available in the public release of Death Statistics Master File data include date of death, date of birth, sex, race/ethnicity, operation performed before death, and underlying cause of death (in International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-9-CM; International Statistical Classification of Diseases, 10th Revision; ICD-10; International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-9-CM; and International Statistical Classification of Diseases, 10th Revision; ICD-10 codes). The death registry also identifies whether an autopsy was performed and whether the autopsy results were used to establish the cause of death or no autopsy was performed (excluding patients with HLHS who did not undergo an autopsy were enumerated in a separate group and excluded from the other categories. To avoid an overestimate of missed or late diagnosis these in-

### Table 1. Critical Congenital Heart Diseases and Corresponding ICD-9-CM and ICD-10 Codes

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Aortic stenosis</td>
<td>746.3</td>
<td>Q23.0</td>
</tr>
<tr>
<td>Coarctation of aorta (including interrupted aortic arch)</td>
<td>747.1, 717.2, 747.11</td>
<td>Q25.1, Q25.3, Q25.4</td>
</tr>
<tr>
<td>DORV and single ventricle</td>
<td>745.1, 745.3</td>
<td>Q20.1, Q20.2</td>
</tr>
<tr>
<td>Hypoplastic left heart syndrome</td>
<td>746.7</td>
<td>Q23.4, Q25.2</td>
</tr>
<tr>
<td>Pulmonary atresia</td>
<td>747.3</td>
<td>Q25.5</td>
</tr>
<tr>
<td>Tricuspid atresia</td>
<td>746.1</td>
<td>Q22.4, Q22.6</td>
</tr>
<tr>
<td>TAPVR</td>
<td>747.41</td>
<td>Q26.2, Q26.4</td>
</tr>
<tr>
<td>d-Transposition of great vessels</td>
<td>745.1</td>
<td>Q20.3</td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
<td>745.2</td>
<td>Q21.3</td>
</tr>
<tr>
<td>Truncus arteriosus</td>
<td>745.0</td>
<td>Q20.0</td>
</tr>
</tbody>
</table>

Abbreviations: DORV, double outlet right ventricle; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10, International Statistical Classification of Diseases, 10th Revision; TAPVR, total anomalous pulmonary venous return.

### PATIENT SELECTION

For the types of CHD that could result in life-threatening events without a timely diagnosis, we modified the list of CCHD diagnoses from the Tennessee taskforce.13 Table 1 lists the CHD diagnoses considered when selecting CCHD cases. The ICD-9-CM codes were used for data from years 1989 through 1998, and ICD-10 codes were used for data from years 1999 through 2004.

The study population reflects 3 case selection criteria (Figure 1): (1) the decedent was between 24 hours and 1 year old at death, (2) the recorded cause of death was CCHD from the diagnoses listed in Table 1, and (3) either no surgery was performed or the surgery status was unknown from the data set. The death registry database defines the “surgery” field as any surgery performed within 1 year before the occurrence of death. Since all of the selected patients were younger than 1 year, the “surgery” field for the initial cohort indicates any surgery ever performed in the patient’s life.

From all patients who met these initial criteria, we examined (1) whether autopsies were performed and autopsy results were used to establish the cause of death, (2) whether autopsies were performed but the results were not used to establish a cause of death, and (3) whether infants with hypoplastic left heart syndrome (HLHS) were potentially receiving comfort care.

### MISSED CCHD DIAGNOSIS

In the missed CCHD diagnosis group, autopsies were performed and autopsy results were used to establish the causes of death. The diagnosis was missed in these patients because it was assumed that no clinical cardiac diagnosis was made before the autopsy.

### PATIENTS WITH HLHS RECEIVING COMFORT CARE

To avoid an overestimate of missed or late diagnoses, the patients with HLHS who did not undergo an autopsy were enumerated in a separate group and excluded from the other categories.

### UNKNOWN

The unknown group includes all selected patients who were not in the missed CCHD diagnosis group and were not infants with HLHS receiving comfort care. In these patients, either autopsies were performed but autopsy results were not used to establish the cause of death or no autopsy was performed (excluding patients with HLHS who did not undergo an autopsy). In this group, the CCHD diagnoses were assumed to have been made before death because it was listed as the cause of death in the Master File. However, no surgery was per-
Of the 152 patients in the missed CCHD diagnosis group, 10 (6.6%) died at home and 68 (44.7%) died in the hospital. Of those, autopsy results established the cause of death as CCHD in 152 infants; these infants comprise the missed CCHD diagnosis group.

Among the 898 infants in the study cohort, HLHS was the most common cause of death (n=565 or 62.9% of the cohort). Of the 565 infants with HLHS, 118 had autopsies performed and 447 had no autopsies performed. Of the 118 patients with HLHS who had autopsies performed, the autopsy results were used to establish the cause of death as HLHS in 58; these 58 patients were a part of the missed CCHD diagnosis group. The other 60 were included in the unknown group. The 447 infants with HLHS who did not have autopsies performed were classified as patients with HLHS receiving comfort care.

The patients who were classified neither as having a missed CCHD diagnosis nor as patients with HLHS who were receiving comfort care were treated as unknown. The unknown group totaled 299 infants with CCHD who did not undergo surgery likely because of late diagnosis. The comparisons of the different CCHD diagnoses in the entire study cohort and in the unknown and missed CCHD diagnosis groups are listed in Table 2.

### Table 2. Total Number of Patients in Each Group by Diagnosis

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Study Cohort (n=898)</th>
<th>Unknown (n=299)</th>
<th>Missed CCHD Diagnosis (n=152)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic stenosis</td>
<td>31 (3.5)</td>
<td>19 (6.4)</td>
<td>12 (7.9)</td>
</tr>
<tr>
<td>Coarctation of aorta, including</td>
<td>90 (10.0)</td>
<td>49 (16.4)</td>
<td>41 (27.0)</td>
</tr>
<tr>
<td>interrupted aortic arch</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DORV and single ventricle</td>
<td>15 (1.7)</td>
<td>4 (1.3)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Hypoplastic left heart syndrome</td>
<td>565 (62.9)</td>
<td>60 (20.1)</td>
<td>58 (38.2)</td>
</tr>
<tr>
<td>Pulmonary atresia</td>
<td>30 (3.3)</td>
<td>22 (7.4)</td>
<td>8 (5.3)</td>
</tr>
<tr>
<td>Tricuspid atresia</td>
<td>9 (1.0)</td>
<td>9 (3.0)</td>
<td>0</td>
</tr>
<tr>
<td>TAPVR</td>
<td>32 (3.6)</td>
<td>23 (7.7)</td>
<td>9 (5.9)</td>
</tr>
<tr>
<td>d-Transposition of great vessels</td>
<td>37 (4.1)</td>
<td>31 (10.4)</td>
<td>6 (3.9)</td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
<td>55 (6.1)</td>
<td>50 (16.7)</td>
<td>5 (3.3)</td>
</tr>
<tr>
<td>Truncus arteriosus</td>
<td>34 (3.8)</td>
<td>22 (7.4)</td>
<td>12 (7.9)</td>
</tr>
</tbody>
</table>

Abbreviations: DORV, double outlet right ventricle; TAPVR, total anomalous pulmonary venous return.

### Table 3. Demographic Characteristics of Each Study Group

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Study Cohort (n=898)</th>
<th>Unknown (n=299)</th>
<th>Missed CCHD Diagnosis (n=152)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age at death, d</td>
<td>11</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Male, No. (%)</td>
<td>518 (57.7)</td>
<td>163 (54.5)</td>
<td>13 (8.6)</td>
</tr>
<tr>
<td>Race/ethnicity, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>399 (44.4)</td>
<td>119 (39.8)</td>
<td>64 (42.1)</td>
</tr>
<tr>
<td>Black</td>
<td>72 (8.0)</td>
<td>18 (6.0)</td>
<td>13 (8.6)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>343 (38.2)</td>
<td>130 (43.5)</td>
<td>62 (40.8)</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>82 (9.1)</td>
<td>31 (10.4)</td>
<td>12 (7.9)</td>
</tr>
<tr>
<td>American Indians</td>
<td>2 (0.2)</td>
<td>1 (0.3)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Died at home, No. (%)</td>
<td>110 (12.2)</td>
<td>29 (9.7)</td>
<td>10 (6.6)</td>
</tr>
</tbody>
</table>

*Study cohort indicates the 898 patients selected by the initial selection criteria specified in the “Patient Selection” subsection of the “Methods” section.*

**RESULTS**

A total of 898 infants (24 hours to 364 days of age at death) were identified as having a CCHD diagnosis as the cause of death, with either no surgery (n=792) or an unknown surgery status (n=106). Of these 898 infants who comprised the study cohort, 268 (29.8%) had autopsies performed. Of those, autopsy results established the cause of death as HLHS in 152 infants; these infants comprise the missed CCHD diagnosis group.

Among the 898 infants in the study cohort, HLHS was the most common cause of death (n=565 or 62.9% of the cohort). Of the 565 infants with HLHS, 118 had autopsies performed and 447 had no autopsies performed. Of the 118 patients with HLHS who had autopsies performed, the autopsy results were used to establish the cause of death as HLHS in 58; these 58 patients were a part of the missed CCHD diagnosis group. The other 60 were included in the unknown group. The 447 infants with HLHS who did not have autopsies performed were classified as patients with HLHS receiving comfort care.

The patients who were classified neither as having a missed CCHD diagnosis nor as patients with HLHS who were receiving comfort care were treated as unknown. The unknown group totaled 299 infants with CCHD who did not undergo surgery likely because of late diagnosis. The comparisons of the different CCHD diagnoses in the entire study cohort and in the unknown and missed CCHD diagnosis groups are listed in Table 2.

### MISSED CCHD DIAGNOSIS

Of the 152 patients in the missed CCHD diagnosis group, 10 (6.6%) died at home and 68 (44.7%) died in the hospital. Both HLHS (n=58) and coarctation of the aorta (n=41) accounted for roughly two-thirds of the patients with a missed CCHD diagnosis. Whereas only 58 of the original cohort of 565 selected patients with HLHS (10%) were identified as having a missed CCHD diagnosis, 41 of 90 patients with coarctation of the aorta (46%) from the original cohort had a missed diagnosis. The median age at death was 11 days for the patients with HLHS and 17 days for the patients with coarctation of the aorta. Of the 152 patients with missed CCHD diagnosis, 114 had no surgery performed; the rest (38 patients) had an unknown surgery status. Among these 38 patients, 28 died in the emergency department and 1 died on arrival to the emergency department. Nearly half these patients (17 of 38) had coarctation of the aorta (median age at death, 24 days). Seven had HLHS (median age at death, 11 days).

### INCIDENCE AND DEMOGRAPHICS

The demographic characteristics of all selected patients, the patients in the unknown group, and the patients in the missed CCHD diagnosis group are listed in Table 3. As indicated in Table 3, the median age at death was within the first 2 weeks of life regardless of what definition was used. There was a slight male predominance. Among the patients with a missed CCHD diagnosis, 42.1% were non-Hispanic white and 40.8% were Hispanic.

We calculated the incidence of missed CCHD diagnosis for each racial/ethnic group using the 152 patients from the missed CCHD diagnosis category as the numerator and the number of live births during the study period as the denominator. The overall incidence of missed CCHD diagnosis was 1.7 per 100 000 live births. By race, the incidence (per 100 000 live births) was as follows: white, 2.1; black, 2.2; Hispanic, 1.5; Asian, 1.3; and American Indian, 2.6. No statistically significant difference was found in the incidence among the racial/ethnic groups.

### TIME TRENDS

Viewed annually, the data show decreasing incidence from 1989 to 2004. The decrease occurred between 1989 and 2000.
1999, and the number of cases remained relatively constant in 2000 to 2004. The annual incidence decreased from approximately 90 missed or unknown CCHD deaths per year at the beginning of the study period to 30 per year in recent years. Figure 2 shows the number of cases for each year of the study period. The entire study period contained a total number of 152 patients with a missed CCHD diagnosis and 451 combined patients with a missed and unknown CCHD diagnosis. Thus, during the study period, the average number of missed CCHD diagnosis was approximately 30 cases per year, and the average number of both missed and unknown CCHD diagnoses was approximately 10 cases per year.

Figure 2. Time trend of the number of patients who died of critical congenital heart disease (CCHD) at 1 to 364 days of age without surgery. Study cohort consists of 898 patients who fulfilled the initial selection criteria.

Missed or late CCHD diagnoses are preventing a small but discrete population of infants from receiving the successful surgical repair or palliation now available with advances in pediatric cardiology and cardiac surgery. The problem seems centered on infants younger than 2 weeks, many of whom are discharged from hospital nurseries without a CCHD diagnosis. Applying strict selection criteria, this study demonstrates that, between 1989 and 2004 in California, an average of 10 infants per year died from missed CCHD diagnoses. Applying broader selection criteria (including the unknown category of patients), this study indicates that within the same population an average of up to 30 infants died per year in California without timely CCHD diagnosis or treatment.

These data confirm a persistent problem of missed CCHD diagnosis that the literature has identified in the United States and other developed countries, suggesting a systematic deficiency in diagnostic regimens for newborns. Diagnosing CCHD in the first few days of life is a difficult task because tremendous transitional changes occur in the cardiopulmonary physiology occur during that period. Furthermore, trends toward early hospital discharge of newborns since the early 1990s may make early diagnosis of CCHD even more challenging. Consequently, some newborns have CCHD diagnosed in various settings after nursery discharge or have missed diagnoses. The setting in which CCHD is first recognized is an important determinant for subsequent clinical outcomes. Studies have shown that prenatal diagnosis of HLHS and d-transposition of the great vessels improves clinical outcomes of cardiac surgery. Early postnatal diagnosis may improve preoperative condition, which in turn influences postoperative progress and survival after surgery.

Unfortunately, studies have shown that many infants never have their conditions diagnosed until after death. In such cases, the cause of death from CHD is not known until an autopsy is performed. In the Baltimore-Washington Infant Study, CCHD diagnoses of 76 of 800 infant deaths were unknown until autopsies were performed. In a study from the United Kingdom using data from 1985-1990, a total of 185 of 1074 infants with CHD died, and the CHD diagnoses of 56 of these 185 infants (30%) were unknown at the time of death.

In a review of 1590 infants with CHD in the United Kingdom, Wren et al found that 876 (55%) were discharged without a diagnosis. In a cohort of 7204 newborns undergoing routine neonatal examination, Ainsworth et al reported that 44% of infants with CHD had diagnoses missed by initial physical examination, including cases of complex CHD, left heart obstruction, and total anomalous pulmonary venous return. It is apparent that the detection rate by clinical examination of newborns is low for at least some forms of CHD, and doubling the number of hospital neonatal examinations (from 1 to 2) does not improve the detection of some newborn abnormalities.

These reported results support our analysis, which includes data from a more recent era in a large, diverse population. The data, in short, confirm that missed CCHD diagnosis continues to be a significant problem. The trends in this study, however, are decreasing, suggesting some improvement in early CHD detection. The time trend in Figure 2 shows a decrease in the number of missed CCHD cases during the study period. This result is inconsistent with published data from Sweden between 1993 and 2001, which suggest that missed CHD diagnosis may be increasing over time. In that study, Mellander and Sunnegardh reported that the proportion of CHD cases detected only after discharge increased from 13% in 1993-1995 and 21% in 1996-1998 to 26% in 1999-2001. The authors speculated that such an increase in undiagnosed CHD at discharge may have been related to increasing trends for early newborn discharge during the 1990s. The reasons for the divergent trends are not clear and require further investigation.

The dominant diagnoses among missed CCHD diagnoses in this study were HLHS and coarctation of the aorta. This result agrees with the study by Mellander and Sunnegardh, which indicated that current neonatal screening primarily fails in infants with ductal-dependent systemic circulation. Abu-Harb et al reviewed 120 infants with left heart obstructive lesions, including HLHS, interruption of the aortic arch, coarctation of the aorta, and aortic valve stenosis. From this cohort of 120 infants, 94 (78%) were discharged home without a diagnosis. Among those, 51 developed heart failure before 6 weeks, and another 7 died without a diagnosis.

Although many screening strategies have been studied, none have been proved effective in detecting newborn CCHD. In the past few years, researchers have con-
considered pulse oximetry as an aid to clinical examination in the detection of some forms of CCHD.\textsuperscript{25-32} In a systematic review by Knowles et al.,\textsuperscript{32} the authors reviewed current practice and all possible alternatives and concluded that “pulse oximetry is a promising alternative newborn screening strategy.” More recently, a systematic review\textsuperscript{33} of 8 clinical studies on pulse oximetry concluded that pulse oximetry screening is not sensitive enough to serve as an independent screening tool.

Although fetal echocardiography has been used as a screening tool in selected high-risk populations, the effect on missed postnatal diagnoses may be limited. Acharya et al\textsuperscript{34} found that, despite almost universal prenatal ultrasonicographic screening, and at least 1 neonatal examination before discharge, the diagnosis of major CHD is made after a relevant delay in a substantial proportion of cases. Use of a handheld echocardiogram system has been suggested by Li et al.,\textsuperscript{35} who reported that such images have sufficient quality for targeted echocardiography examinations to determine the presence, absence, or status of CHD in newborns and young children. However, the cost of a universal echocardiographic screening program is estimated to be prohibitively high.\textsuperscript{32}

A recent report\textsuperscript{36} from the United Kingdom suggested that a structured approach to CHD screening and early return for rechecking of infants with suspected CHD can be effective. Patton and Hey\textsuperscript{37} reported that, for newborns with a heart murmur at 1 day of age, reexamination at 7 to 10 days is effective in detecting a significant number of infants with a structural defect.

In this study, we found that the median age at death in the patients with missed and unknown CCHD diagnoses was younger than 2 weeks. The American Academy of Pediatrics currently recommends that every infant should have an evaluation within 3 to 5 days of birth and within 48 to 72 hours after discharge from the hospital, to include evaluation for feeding and jaundice.\textsuperscript{38} It should be emphasized in the recommendation that a careful cardiovascular evaluation be performed during this visit for detection of CCHD that was missed during the nursery examination.

The present study used statewide data from the Death Statistics Master File maintained by the California Department of Health Services. Although this is an administrative database, it is populated from data on each individual death certificate submitted to the Department of Health Services. Because most death certificates are completed by physicians or coroners, information from the death database may be more precise and accurate than other administrative databases, such as hospital discharge databases. However, limitations from the lack of clinical information and from miscoding of clinical information from the data used may affect the results of this study. For instance, if the death certificate lists a complication as the cause of death rather than the primary disease that leads to the complication and death, the cases of missed CCHD might not be identified.

The present study relied on assumptions to identify the patients with CCHD who have a missed or late diagnosis. The categorizations are based on the information available in the death database. Although clinically plausible, these assumptions have not been validated. For example, infants with tetralogy of Fallot or double outlet right ventricle (DORV) may not undergo surgery until 6 to 9 months of age.\textsuperscript{37} Therefore, infants with tetralogy of Fallot or DORV who died before planned surgery could be performed may not represent cases of late diagnosis. In this study of patients with unknown CCHD, we found that the age at death among infants with tetralogy of Fallot or DORV was mostly younger than 3 months, suggesting that the diagnosis may not have been identified previously. It is also possible that some families of infants with HLHS receiving comfort care may have requested an autopsy but not used the autopsy to establish cause of death. These patients would be included in the unknown category but are expected to be rare. It is more likely that the infants placed in the group of patients with HLHS receiving comfort care might create an underestimate of the missed or unknown groups.

In conclusion, missed CCHD diagnosis in newborns before nursery discharge continues to be a significant clinical problem. Up to 30 infants died of missed or possible late diagnoses of CCHD in California each year between 1989 and 2004. The most common missed CCHD diagnoses were the lesions of ductal-dependent systemic circulation, including HLHS and coarctation of the aorta. The median age at death in the patients with missed diagnoses was younger than 2 weeks. The American Academy of Pediatrics Recommendations for Preventive Pediatric Health Care should emphasize a careful cardiovascular evaluation for left heart obstructive CHD during the first postdischarge visit to a pediatrician’s office at 3 to 5 days of age.

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Author Contributions: Study concept and design: Chang, Gurvitz, and Rodriguez. Acquisition of data: Chang and Rodriguez. Analysis and interpretation of data: Chang, Gurvitz, and Rodriguez. Drafting of the manuscript: Chang, Gurvitz, and Rodriguez. Critical revision of the manuscript for important intellectual content: Chang, Gurvitz, and Rodriguez. Statistical analysis: Chang, Gurvitz, and Rodriguez. Administrative, technical, and material support: Chang, Gurvitz, and Rodriguez. Study supervision: Chang and Rodriguez.

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If evolution really works, how come mothers only have 2 hands?
—Milton Berle