Research Implications of Defect Classification and Coding Practices

2°ASD as an Illustration

12th Annual National Birth Defects Prevention Network Meeting
February 24, 2009
Marcia Feldkamp, PhD
What do your data look like?

Fig 32. Diagram illustrating the distortion of the information in a reporting system, from the infant to the coded data.
(A) shows the actual infant
(B) is the doctor’s picture of it and what is written down in the medical records
(C) is the content of the report form to the surveillance registry
(D) is the interpretation of that form in the registry
(E) is the coded data which is stored in a computer

Epidemiology of Human Reproduction, 1988
Birth Defect Research

- Important to think in terms of embryology
  - Pathogenesis
    - Normal processes
    - Abnormal processes
  - Timing of structural formation
- Is lumping appropriate?
Superior vena cava
Right atrium
Ostium primum
Right endocardial cushion
Inferior endocardial cushion
Ventricle
Inferior vena cava
Septum primum
Left endocardial cushion

Cross section of heart between atrium and ventricle

33 days
Superior vena cava
Septum primum
Septum secundum
Right atrium
Blood flow
Left atrium
Ostium secundum
Foramen ovale
Sectioned septum intermedium
Left ventricle
Muscular ventricular septum
Right ventricle
Inferior vena cava
Early 7th week (43 days)
Atrial Septal Defects

- An opening in the atrial septum, other than a competent foramen ovale
  - Secundum ASDs
  - Sinus venosus ASDs
  - Coronary sinus ASDs
- Classified by location relative to the fossa ovalis

(Moss and Adams, 2008)
Atrial Septal Defects

- Classified by location relative to the fossa ovalis
  - Inadequate formation of septum secundum
  - Ostium secundum too large

(Moss and Adams, 2008)
Atrial Septal Defect - Secundum

- Most common: 6-10% of all CHDs
- 1 in 1,500 live births
- Most are considered sporadic

(Moss and Adams, 2008; www.mayoclinic.org)
Atrial Septal Defect – Sinus Venosus

- 5-10% of all ASDs
- Commonly associated with an anomalous pulmonary vein connection

(Moss and Adams, 2008; www.mayoclinic.org)
Atrial Septal Defect – Coronary Sinus

- Rare
- May be associated with complete AV septal defect or heterotaxy

(Moss and Adams, 2008; www.mayoclinic.org)
ASD Codes

- Secundum ASDs - prone to misclassification

- Distinguishing a PFO vs ASD2 can be difficult for the echocardiographer/interpreter

- Many atrial level shunts are small
  - Echo obtained during first few weeks of life
  - ASDs may close spontaneously
ASD Codes

- Misclassification of secundum ASDs
  - Differential
    - Bias exposure-disease relationship
    - Unpredictable direction
  - Nondifferential
    - Bias toward the null
- Aggregating heterogeneous phenotypes that pathogenetically are likely not similar lead to missed opportunities to improve our understanding
- Homogeneous groupings important but decrease your sample size
ASD Codes

- **International Classification of Diseases 9th**
  - 745.5

- **British Pediatric Association Classification of Diseases ICD9 Modified**
  - 745.500 PDA or PFO; nonclosure of PFO, NOS (exclusions based on gestation)
  - 745.510 atrial septal defect, secundum type (ASD2)
  - 745.520 Lutembacher syndrome → out of date
  - 745.580 other specified atrial septal defect
    - Usually includes the sinus venosus, coronary sinus or vena cava atrial septal defects
  - 745.599 atrial septal defect, NOS; auricular septal defect, NOS; partial foramen ovale; PFO vs ASD
ICD9 ASD Codes

- 745.5 Ostium Secundum Type ASD
  - A combination of atrial septal defect and mitral stenosis
  - 745.5 is a specific code that can be used to specify a diagnosis
  - 745.5 contains 50 index entries
  - Also known as:
    - Defect:
      - atrium secundum
      - fossa ovalis
    - Lutembacher's syndrome (mitral stenosis w/ ASD usually 2°)
    - Patent or persistent:
      - foramen ovale
      - ostium secundum

ICD10 ASD Codes

- Q21.1 Atrial septal defect Coronary sinus defect
  Patent or persistent:
  - foramen ovale
  - ostium secundum defect (type II)
  Sinus venosus defect

http://www.who.int/classifications/apps/icd/icd10online/?gq20.htm+q211
Utah Birth Defect Network

ASDs 2003-2006
Classification of Birth Defects

Clinical geneticists consider:

- **Mechanism**
  - pure defects, sequences, developmental field defects

- **Cause**
  - chromosome abnormalities, genetic conditions, teratogens, in-utero events

- **Family history**
  - Considered familial if 1 or more parents or sibs with same defect
<table>
<thead>
<tr>
<th>Birth Defect Code</th>
<th>Birth Defect</th>
<th>Prenatally Diagnosed</th>
<th>Birth Defect Description</th>
<th>NBDPS Eligible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trisomy 21/Down syndrome with</td>
<td>Major</td>
<td>Yes</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Hirschsprung's disease, NOS</td>
<td>Major</td>
<td>No</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Simian crease / Transverse palm</td>
<td>Minor</td>
<td>No</td>
<td>Bilateral simian crease</td>
<td>No</td>
</tr>
</tbody>
</table>

**Classification**: Multiple Chromosomal

**Familial**: No

**Etiology Known**: Yes

Clinical Case Review Comments

Clinical Case Reviewer:
Utah Birth Defect Network
Classification Structure

Sentinel Defect

Multiple
- 2+ Majors
- 1+ Majors & 1 Unique Minor
- 1 Major & 1 Minor
- Presumed Provisionally Unique Syndrome

Isolated
- Pure Isolated
- Developmental Field Defect
- Sequence

Other Description
- Familial
- Not Familial

Known Etiology
- Chromosomal
- Genetic
- Teratogen

Vater
- Charge
- Murcs
- OAV
- Schisis

Created by Dr. John Carey
UBDN Reported Potential ASDs

<table>
<thead>
<tr>
<th></th>
<th>Number Reported 2003-2006</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth Certificates</td>
<td>7</td>
<td>&lt;1</td>
</tr>
<tr>
<td>NonIHC Hosp D/C</td>
<td>40</td>
<td>2</td>
</tr>
<tr>
<td>IHC Hosp D/C</td>
<td>1142</td>
<td>62</td>
</tr>
<tr>
<td>PCMC Hosp D/C</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Univ Hosp D/C</td>
<td>183</td>
<td>9</td>
</tr>
<tr>
<td>Ped Cardiology</td>
<td>354</td>
<td>19</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1855</strong></td>
<td></td>
</tr>
</tbody>
</table>

Determined to be NOT A CASE
UBDN 2003 – 2006
Reported ASDs (745.5) n=595

745.580
ASD other specific
14 (2%)

745.500
Nonclosure PFO
50 (8%)

745.590
ASD NOS
19 (3%)

745.510
ASD secundum
512 (86%)

Birth Defect Cases

Is Cause Known?

Non Syndromic

Does the case meet the definition of developmental field, sequence or isolated pure?

Yes

Isolated

No

Multiple

Syndromic
## Classification Tool in Action

**Overall Frequency and Prevalence by Classification**

<table>
<thead>
<tr>
<th>ASDs</th>
<th>2003-2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classification</td>
<td>Frequency (%)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolated</td>
<td>321 (58.9)</td>
</tr>
<tr>
<td>Multiple</td>
<td>87 (16.0)</td>
</tr>
<tr>
<td>Syndromic</td>
<td>137 (25.1)</td>
</tr>
<tr>
<td>Total</td>
<td>545</td>
</tr>
</tbody>
</table>

11.2% of all UBDN cases
# Classification Tool in Action

## Overall Frequency and Prevalence by Classification

<table>
<thead>
<tr>
<th>Classification</th>
<th>Frequency (%)</th>
<th>Prevalence (per 10,000 births)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated</td>
<td>297 (58.9)</td>
<td>14.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 in 694</td>
</tr>
<tr>
<td>Multiple</td>
<td>84 (16.0)</td>
<td>4.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 in 2439</td>
</tr>
<tr>
<td>Syndromic</td>
<td>133 (25.1)</td>
<td>6.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 in 1562</td>
</tr>
<tr>
<td>Total</td>
<td>512</td>
<td>24.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 in 404</td>
</tr>
</tbody>
</table>

10.5% of all UBDN cases

6.4% change
Birth Defect Cases
N=512

Is Cause Known?

No

Non Syndromic

Yes

Is Cause Known?

Does the case meet the definition of developmental field, sequence or isolated pure?

Isolated

Multiple

Syndromic

Causal Mechanism

Classification n=297
Cases # (%) Familial (%)

Pure

293 (99) 6 (2)

Sequences

Pierre Robin
Amniotic Band
Amn.Band & Limb-Body Wall
Limb-Body Wall
Frontonasal Dysplasia
Oligohydramnios
Urethral Obstruction
Twinning Abnormality

Developmental Field

Sirenomelia
Holoprosencephaly
Cloaca
Cantrell Pentology
Heterotaxia

4 (1) 0 (0)

Classification n=84
Cases # (%) Familial (%)

Multiple

2+ Majors 70 (83) 0 (0)
1 Major/Minors 11 (13) 0 (0)
Association 1 (1) 0 (0)
Additive 1 (1) 0 (0)
Recognizable Pattern 1 (1) 0 (0)

Classification n=133
Cases # (%) Familial (%)

Syndromic

Chromosomal 125 (94) 1 (1)
Genetic 8 (6) 1 (1)
Teratogen 0 (0) 0 (0)

ASD Secundum only (n=512)
<table>
<thead>
<tr>
<th>Classification n=297</th>
<th>Cases # (%)</th>
<th>Familial (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure Pure</td>
<td>293 (99)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Sequences</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pierre Robin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABS/LBWC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LBWC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontonasal Dysplasia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oligohydramnios</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urethral Obstruction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Twinning Abnormality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Developmental Field</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sirenomelia</td>
<td>4 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Holoprosencephaly</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cloaca</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cantrell Pentology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterotaxia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ASD Secundum only (n=512)
## Classification n=84

<table>
<thead>
<tr>
<th>Classification</th>
<th>Cases # (%)</th>
<th>Familial (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Multiple</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2+ Majors</td>
<td>70 (83)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>1Major/Minors</td>
<td>11 (13)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Association</td>
<td>1 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Additive</td>
<td>1 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Recognizable Pattern</td>
<td>1 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Syndromic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Isolated</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ASD Secundum only (n=512)
### Classification n=137

<table>
<thead>
<tr>
<th>Classification</th>
<th>Cases # (%)</th>
<th>Familial (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syndromic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chromosomal</td>
<td>125 (94)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Genetic</td>
<td>8 (6)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Teratogen</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

ASD Secundum only (n=512)
### Syndromic cases

(Known cases)

<table>
<thead>
<tr>
<th>Chromosomal n=125</th>
<th>Cases # (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trisomy21</td>
<td>86 (69)</td>
</tr>
<tr>
<td>Trisomy18</td>
<td>7 (6)</td>
</tr>
<tr>
<td>Trisomy13</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Turner</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Deletion 22q11</td>
<td>8 (6)</td>
</tr>
<tr>
<td>Prader-Willi 15q deletion</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Wolf-Hirschhorn 4p deletion</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Other conditions</td>
<td>16 (13)</td>
</tr>
<tr>
<td><strong>Total # of cases</strong></td>
<td><strong>125 (100)</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Genetic n=8</th>
<th>Cases # (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthrogryposis</td>
<td>1 (13)</td>
</tr>
<tr>
<td>Apert syndrome</td>
<td>1 (13)</td>
</tr>
<tr>
<td>CHARGE</td>
<td>1 (13)</td>
</tr>
<tr>
<td>Noonan syndrome</td>
<td>2 (25)</td>
</tr>
<tr>
<td>BWS</td>
<td>1 (13)</td>
</tr>
<tr>
<td>Cornelia de Lange</td>
<td>1 (13)</td>
</tr>
<tr>
<td>Conradi syndrome</td>
<td>1 (13)</td>
</tr>
<tr>
<td><strong>Total # of cases</strong></td>
<td><strong>8 (100)</strong></td>
</tr>
</tbody>
</table>
What if?

<table>
<thead>
<tr>
<th>Disease Misclassification</th>
<th>Disease</th>
<th>No Disease</th>
<th>OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E₁</td>
<td>E₀</td>
<td>Total</td>
</tr>
<tr>
<td>15% - E₁</td>
<td>200</td>
<td>375</td>
<td>575</td>
</tr>
<tr>
<td>15% - E₁, E₀</td>
<td>162</td>
<td>413</td>
<td>575</td>
</tr>
<tr>
<td>15% - E₀</td>
<td>125</td>
<td>450</td>
<td>575</td>
</tr>
<tr>
<td>real</td>
<td>125</td>
<td>375</td>
<td>500</td>
</tr>
</tbody>
</table>

Fixed $P_0=0.15$ and $P_1=0.25$
Why is this important?

- Effective monitoring and finding causes of birth defects are crucial but not yet achieved goals.
- Birth defect coding likely limits our ability to improve our understanding.
- Compared to traditional approaches, classification that includes cause and mechanism will hopefully advance our understanding of birth defect etiology.
- Such classification requires accurate and detailed information as well as expert clinical review.
- Surveillance system databases must be flexible in order to reclassify cases as genes are identified.
- Homogeneous case grouping is extremely important.
Challenges: Surveillance to Research

- Surveillance systems are limited to what is in the medical records
  - Not all cases ascertained – vary by phenotype
  - Stillbirth and ToP will be missed if phenotype not prenatally diagnosed or autopsy obtained
- Need additional text vs. coding
- Paradigm shift for clinicians describing the defect
- Small sample size when you create very homogeneous case groups
- Pathogenesis
  - Embryologic timing of event
- Etiology
Decisions on data collected are very important!

Fig32. Diagram illustrating the distortion of the information in a reporting system, from the infant to the coded data.

(A) shows the actual infant
(B) is the doctor’s picture of it and what is written down in the medical records
(C) is the content of the report form to the surveillance registry
(D) is the interpretation of that form in the registry
(E) is the coded data which is stored in a computer

Epidemiology of Human Reproduction, 1988
Thank You!