Newborn Screening for Fragile X Syndrome: Current Issues and Activities

Don Bailey, Ph.D.
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Age of identification for Fragile X Syndrome (1991 – 2001)

Age in Months

First Concern: 13
Delay Confirmed: 21
Special Services: 25
FXS Diagnosis: 32
What were the consequences of delayed identification?

- Parents experienced frustration with professionals and doubts about themselves
- Costs to families and the health care system for repeated visits
- Children and families did not have access to early intervention
- Families made reproductive decisions without knowledge of risk
Recent Trends in the Diagnosis of Fragile X Syndrome

![Graph showing recent trends in the diagnosis of Fragile X Syndrome.](image)
Genetic testing should be offered to identify if a newborn baby has FX shortly after birth.
What would be the benefits of newborn screening?

- Benefit to the infant is a fundamental tenet of newborn screening; historically this has been a necessary condition for screening.

- Although there is no cure for FX, children with the full mutation are likely to experience a range of impairments that could be reduced, delayed, or prevented through early intervention.
### Selected Child Characteristics

Has this child ever been diagnosed or treated for… (% Yes)

<table>
<thead>
<tr>
<th></th>
<th>Males with the Full Mutation (n = 1,167)</th>
<th>Females with the Full Mutation (n = 323)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention problems</td>
<td>78</td>
<td>62</td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>60</td>
<td>29</td>
</tr>
<tr>
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<td>35</td>
<td>13</td>
</tr>
<tr>
<td>Self-injury</td>
<td>38</td>
<td>11</td>
</tr>
<tr>
<td>Autism</td>
<td>43</td>
<td>16</td>
</tr>
<tr>
<td>Seizures</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td>Anxiety</td>
<td>63</td>
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</tr>
<tr>
<td>Depression</td>
<td>10</td>
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</tr>
<tr>
<td>Developmental Delay</td>
<td>95</td>
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</tr>
</tbody>
</table>
Technical Advance

A Rapid Polymerase Chain Reaction-Based Screening Method for Identification of All Expanded Alleles of the Fragile X (FMR1) Gene in Newborn and High-Risk Populations

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Mutations of the fragile X mental retardation 1 (FMR1) gene (OMIM *30060) are responsible for several distinct forms of clinical involvement that together constitute a significant societal health burden across the life spectrum—for child health, reproductive fitness in women, and aging. Fragile X syndrome, mostly caused by large (noncoding) CGG repeat expansions (>200 repeats; full mutation) within the FMR1 gene, is the leading heritable form of cognitive impairment¹ and the leading single-gene disorder associated with autism.² Smaller expa-
Projected Number of Children Identified:
3500 births per year

<table>
<thead>
<tr>
<th>FX Status</th>
<th>Incidence</th>
<th>Total Per Year</th>
<th>Total for 5 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>FM Male</td>
<td>1:2400-1:3500</td>
<td>0-1</td>
<td>2-3</td>
</tr>
<tr>
<td>FM Female</td>
<td>1:2400 – 1:6000</td>
<td>0-1</td>
<td>2-3</td>
</tr>
<tr>
<td>PM Male</td>
<td>1:290-1:800</td>
<td>2-5</td>
<td>9-26</td>
</tr>
<tr>
<td>PM Female</td>
<td>1:129-1:259</td>
<td>6-12</td>
<td>29-58</td>
</tr>
<tr>
<td>TOTAL</td>
<td>9-19</td>
<td></td>
<td>45-90</td>
</tr>
</tbody>
</table>
What should we be concerned about when screening identifies carriers?

- Would there be any benefit for the infant?
- Would parents want to know this information?
- Would this cause increased stress or anxiety in parents?
- Would parent-child bonding be disrupted?
- Would the child suffer any discrimination?
- Would it cause the child to worry about later life consequences?
If a genetic test showed your newborn baby was not affected but is a carrier of FX would you want to be informed at that time?

- Yes: 95%
- No: 5%
- Don't know: 0%
If genetic testing showed that your newborn baby had FX, how it would affect the bonding between you and your child?

- It would make bonding more difficult
- It would have no effect on bonding
- It would make bonding easier
- Don't know
### Selected Child Characteristics

#### Has this child ever been diagnosed or treated for... (% Yes)

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<th>Premutation Males (n = 65)</th>
<th>Premutation Females (n = 211)</th>
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<td>38</td>
<td>11</td>
<td>8</td>
<td>4</td>
</tr>
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<td>Autism</td>
<td>43</td>
<td>16</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>Seizures</td>
<td>16</td>
<td>6</td>
<td><strong>8</strong>*</td>
<td>1</td>
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<td>63</td>
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Family Adaptation to Newborn Screening For Fragile X Syndrome

• The social science equivalent of a Phase I clinical trial
• The “treatment” is disclosure of information about FX
• Two primary goals:
  – How do families adapt to this new information?
  – Are there any “adverse events”
Aim 1: Participation

- How much effort does it take to offer screening to all parents, with consent?
- What proportion of families consent to screening?
- Does this vary by ethnicity or income?
- What reasons do parents give for accepting or declining screening?
Recruitment Materials

- Posters in OBGYN offices
- Tear-off contact info
- Web site
- Brochure
- Bilingual research associates in hospital
Aim 2: Satisfaction

• Do families of identified children believe they were adequately informed about the possible results from screening?

• Are these families initially satisfied with their decision to participate?

• Do their views about screening change over time?
Aim 3: Maternal mental health outcomes

- Do mothers experience adverse mental health outcomes following a diagnosis?
- 6- and 12-month follow-up
- Matched group of parents

<table>
<thead>
<tr>
<th>- Stress</th>
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<tr>
<td>- Depression</td>
<td>- Hope</td>
</tr>
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<td>- Quality of Life</td>
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Study Design

17,000 Families Offered FXS Screening

- Accept Screening (n = 15,000)
  - Screen Positive (n = 45–90)
  - Screen Negative (n = 14,900)
- Decline Screening (n = 2,000)
  - Brief Survey to Determine Reasons for Declining

Diagnose Positive (n = 45–90)

Diagnose Negative (none expected)

Matched Comparison Group (n = 45–90)

Follow-up Interviews

4-Month Post-Diagnosis Assessment (n = 45–90)

4-Month Assessment Linked to Timing of Diagnosed Group (n = 45–90)

12-Month Post-Diagnosis Assessment (n = 45–90)
Aim 4: Parent-child relations

• Does a diagnosis of FXS or carrier status affect the quality of parent-child relations?
• Compared with matched group of families
• Videotapes of mother-child interaction and interviews to measure
  – Expressed emotion and warmth
  – Positive affect
  – Maternal responsivity
Aim 5: Ramifications for nuclear and extended family

• How do parents and extended family members respond to, share, and use information gained from a newborn diagnosis of FXS?
Hopefully this research will provide useful information about the costs and benefits of broader disclosure of genetic information.