



Lessons Learned From Newborn Screening for Fragile X Syndrome

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Major points

- Fragile X syndrome (FXS) and autism both suffer from an early diagnosis problem
- Although very different conditions, there is some overlap in phenotype
- Because FXS is a single-gene disorder with an accurate diagnostic test, a definitive early diagnosis is possible
- This will likely never be the case in autism (a single definitive biomarker), but there will be an increasing number of biomarkers identified that are associated with elevated risk for autism
- Some of the ethical, legal, and social issues that have arisen in our FX newborn screening work may have some relevance for autism

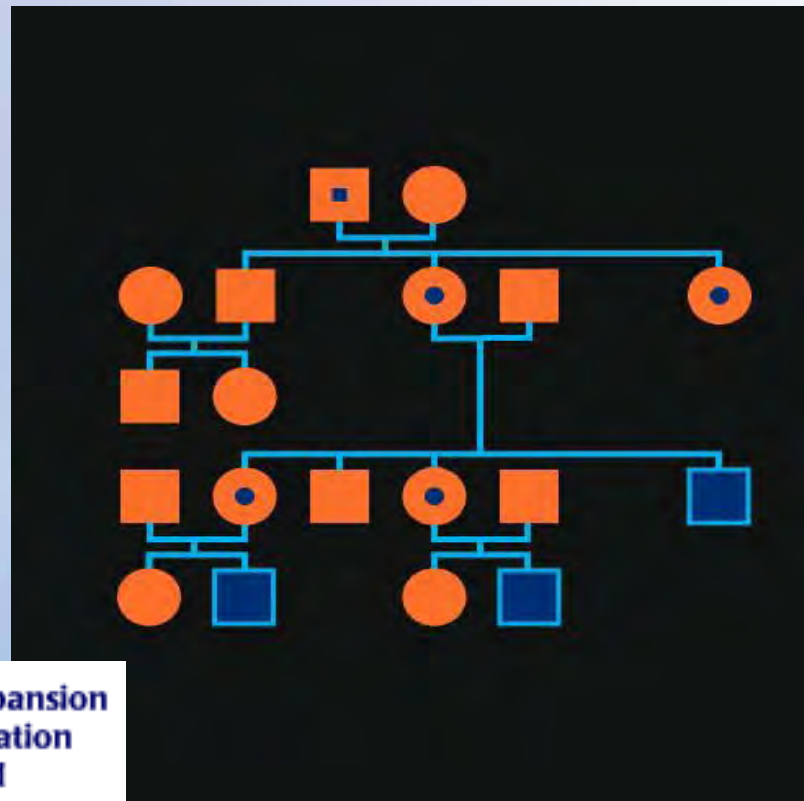
What is fragile X syndrome?

- Most common inherited form of intellectual disability (@ 1:4000)
- Males and females affected, males more severe
- Many individuals with FXS also meet the diagnostic criteria for autism (35-60%)



How is fragile X syndrome inherited?

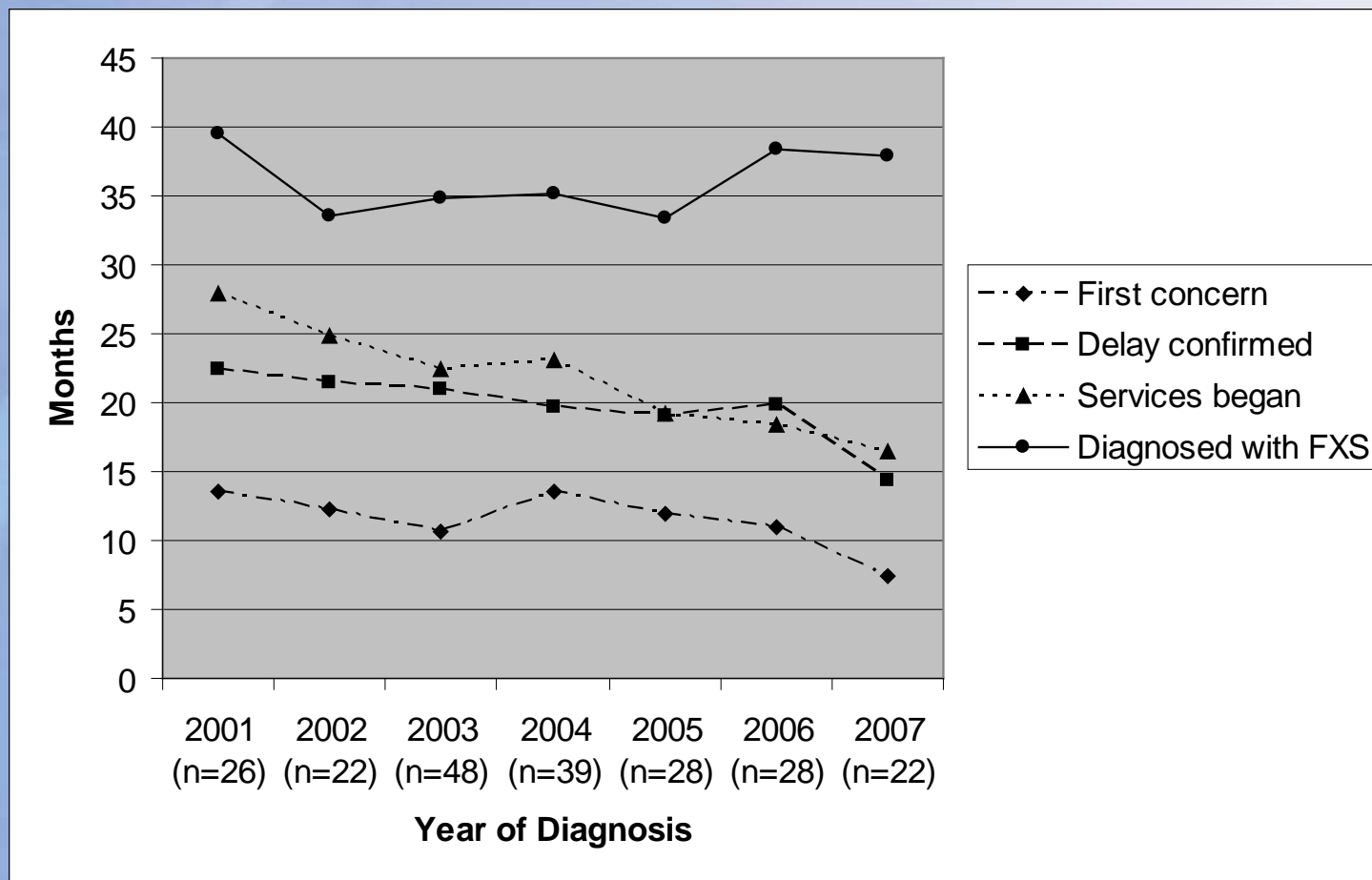
- A single-gene disorder passed down through carrier parents
- Unstable CGG triplet repeats with increasing risk of expansion in subsequent generations



Number of Repeats in Mother's Pre-mutation	Chance of Expansion to Full Mutation in Child
56 - 59	<1.0%
60 - 69	17%
70 - 79	71%
80 - 89	82%
90 -199	99%

No change in the age of diagnosis of FXS

(Bailey et al., 2009, *Pediatrics*)



Promoting earlier identification will be hard

- Lack of clear phenotype, especially in the early years
- Differences in severity between males and females
- Moving from a diagnosis of “developmental delay” or “autism” to genetic testing and the FX diagnosis

Projected best case scenario if relying on developmental screening as “point of entry”

- 9-month developmental screening identifies some males (probably a lot fewer females) with FXS as infants “at-risk” for delay
- Infants are referred for follow up developmental evaluations (1-3 months?)
- A majority (but not 100%) of males will show definite delays in a full evaluation at 12 months
- Those with significant delays would be referred for genetic testing
- Best case scenario for all of this is 16-18 months for a diagnosis of boys

So, what about newborn screening?

- All states have NBS to test babies for important but non-obvious health conditions
- Bloodspots obtained before the baby leaves the hospital
- Spots sent to a state or regional laboratory for quick analyses
- Positive results are returned for diagnostic confirmation and treatment
- States decide which conditions to screen
- Most screening is mandatory

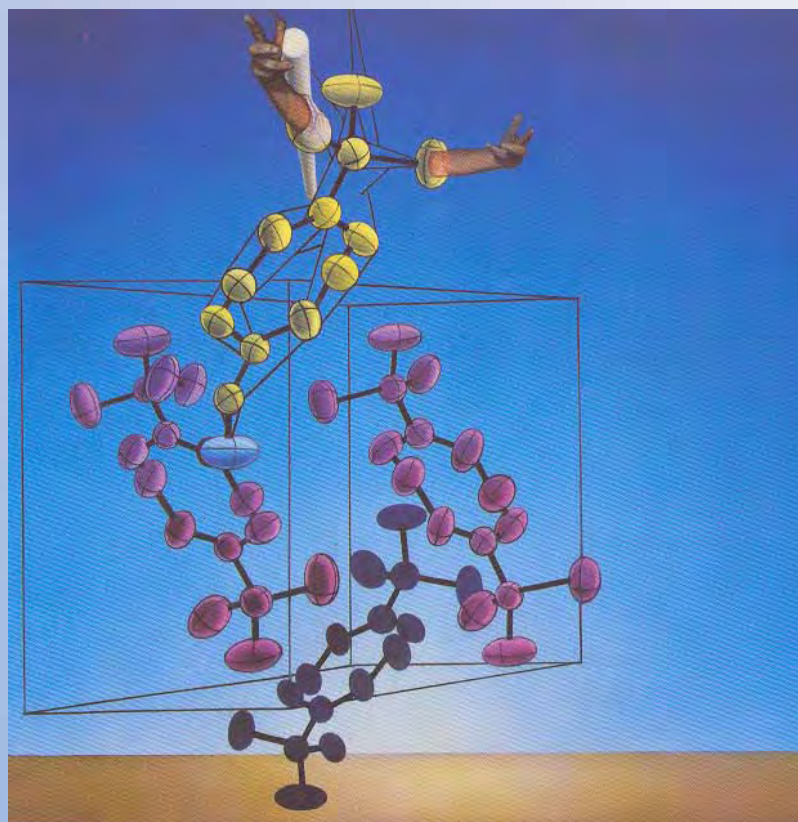
The image shows a newborn screening card with four circular blood spots on the left side. The card is yellow and contains a form with various fields for data entry. A barcode is visible at the top right. The form includes fields for baby's name, address, mother's name, birth weight, and other medical information. A prominent instruction reads: "FILL ALL 4 CIRCLES COMPLETELY. BLOOD MUST BE OBTAINED IMMEDIATELY THROUGHOUT THE FIRST 24 HOURS OF LIFE. DO NOT APPLY BLOOD TO ANY OTHER PART OF THE CARD. DO NOT USE AFTER 15000-8-85 EXPIRES 12/01/95".

FXS could be identified through newborn screening, but....

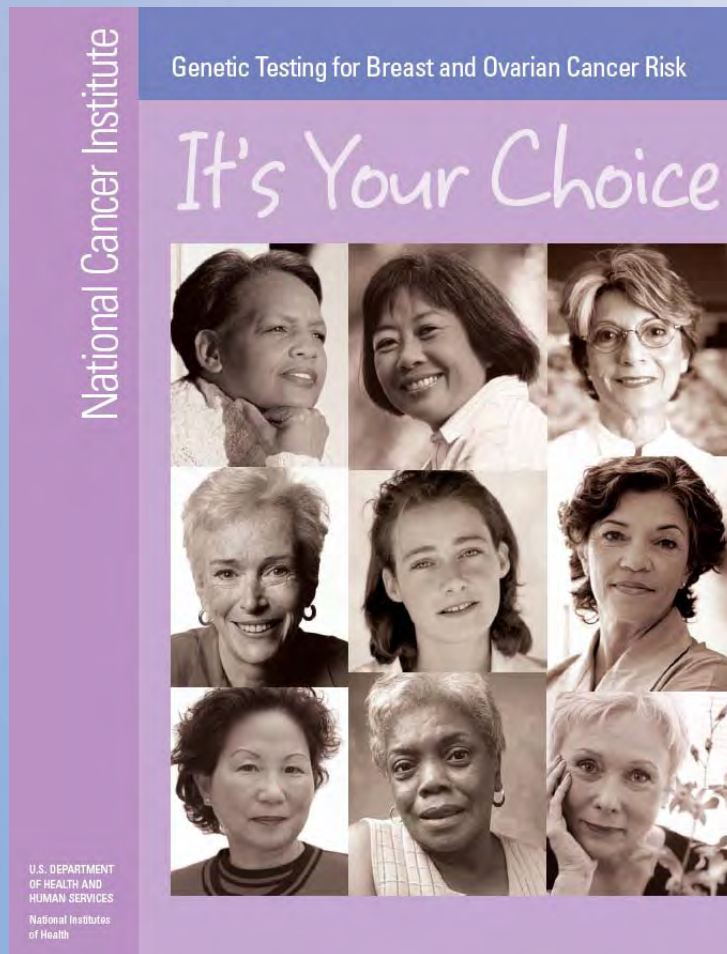
- There is no medical treatment currently available that must be provided early
- A DNA-based screening test would identify carriers
- The test is too expensive for population screening
- There are late-onset conditions associated with a subset of carriers (FX-POI and FXTAS, + ???)
- Given these concerns, FXS would not meet current NBS criteria
- BUT....
 - The test is getting cheaper
 - Parent advocates are pushing for earlier identification
 - New pharmacological treatment possibilities are on the horizon

We must envision a future of whole genome sequencing or some variation thereof at birth

- Many rare conditions will be identified
- Most will not have biomedical treatments
- Conditions will be pre-symptomatic and some will be normal
- Information may be increasingly “probabilistic” rather than certain disease – ***this will almost certainly be the case with autism***



The autism scenario might be more similar to BRACA1 or APOE genetic testing than to FX testing



Newborn screening for FXS evokes a number of ELSI concerns that may also apply to autism

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STATE-OF-THE-ART REVIEW ARTICLE

Ethical, Legal, and Social Concerns About Expanded Newborn Screening: Fragile X Syndrome as a Prototype for Emerging Issues

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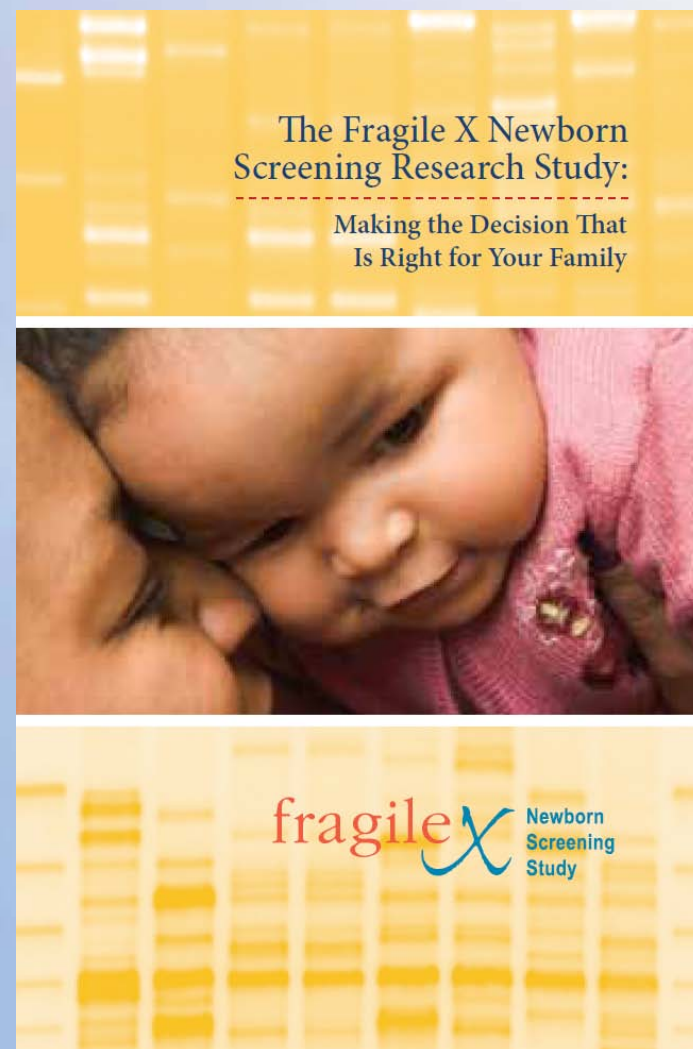
Concerns about NBS for fragile X

- Early identification of an “untreatable” condition could lead to heightened anxiety about parenting, oversensitivity to development, alterations in parenting, or disrupted bonding



Concerns about NBS for fragile X

- FX screening should be voluntary. But the consent process could overwhelm parents, burden hospitals, and reduce participation in the core screening program



Concerns about NBS for fragile X

- Screening will identify some children who are or appear to be normal, or are only mildly affected



Concerns about NBS for fragile X

- Screening could overwhelm an already limited capacity for genetic counseling and comprehensive care



Concerns about NBS for fragile X

- If carrier status (or in the case of autism, genetic risk) is disclosed, it could increase the likelihood of harm, including negative self-concept, societal stigmatization, and insurance or employment discrimination



Concerns about NBS for fragile X

- Screening would implicate or suggest risk in extended family members, raising ethical and legal issues (since they never consented to screening), creating a communication burden for parents or expanding the scope of physician responsibility



Questions asked by families of children identified with pre-symptomatic conditions

- What is my child's "condition?"
- What are the chances that my child will exhibit any aspects of the syndromes associated with his or her genetic variation?
- Should I seek preventive services or wait until a problem becomes apparent?
- How often should he or she be checked?
- Should we have more children, and would they possibly be affected?
- Should we tell other family members, friends, or teachers?
- When and what should we tell our child about his or her "condition?"

Conclusions

- Both the hopes and concerns about NBS for FXS are valid, but we do not have sufficient data to estimate the magnitude of each
- Many of these concerns could apply to autism, especially as genes or other biomarkers emerge as “predictors” of elevated autism risk
- Anticipatory research is needed to be prepared for such a scenario.



FX Screening Pilot Study

- We are currently conducting a pilot FX newborn screening project
- The screening test detects carriers and children with FXS
- Because of all of these concerns, we framed the study as the social science equivalent of a Phase 1 Clinical Trial
 - Treatment is the information
 - One goal is to determine uptake rate (do people want to know this information?)
 - A second goal is to identify any “adverse events”
 - Postpartum depression
 - Altered parent-child relationships
 - A third goal is to study early development, especially of carriers

Funding support

- NICHD (Intellectual and Developmental Disabilities Branch)
- NHGRI (Ethical, Legal, and Social Implications Program)
- CDC (National Center on Birth Defects and Developmental Disabilities)
- DHHS (Maternal and Child Health Bureau)
- U.S. Dept of Education (Office of Special Education Programs)