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Policy considerations in designing a fragile x screening program

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The success of the pilot study by Saul et al.[1] reaffirms the feasibility of Fragile X (FrX) syndrome detection in newborn males.[2–6] One unique aspect of this study is its reporting of the consent rate. Three hundred eighty five of 1844 (21%) postpartum women refused to have their newborn males screened, although reasons were not ascertained.[1]

Twenty-one percent is a high rate of refusal compared to the <3% refusal rate in Massachusetts and 10% refusal in California when tandem mass spectrometry (MS/MS) was first introduced as pilot programs.[7,8] It is also high compared to the <8% refusal rate in Wales for screening newborn males for Duchenne Muscular Dystrophy (DMD).[9] FrX screening is more similar to that of DMD screening because of the focus on male infants for a condition in which early treatment has not been shown to prevent long-term morbidity or mortality.

One possible explanation for the lower consent rate is that the decision was made to require mothers to sign a consent form approved by an institutional review board (IRB). In Massachusetts, the New England Newborn screening program provided in-service training at all birth units in more than 55 Massachusetts hospitals, offered many statewide educational programs, and redesigned lab slips to distinguish those who consented from those who did not.[7] The consent was verbal, not written, and was obtained by clinical staff. In California, when MS/MS was offered as a pilot study, the biggest obstacle was getting hospitals to offer the screening to infants. It was found that only 48% of infants were offered screening.[8] When offered, 90% of the mothers consented and 10% declined.[8] Again, consent was verbal and obtained by clinical staff. In Wales, parents were given an information sheet in the hospital but consent was not obtained until the midwife home visit at day of life 6 or 7.[9] Again the consent was verbal not written and was obtained by clinical staff.[9] Thus the study by Saul et al. may have had a lower consent rate because of the requirement for written consent and the participation of research personnel to obtain the consent.

Traditionally, newborn screening (NBS) in the United States has been mandatory. This policy has been justified on the grounds of promoting equity through universal access.[10] Although studies show that parents are more concerned about being informed about NBS programs than about whether or not they have provided explicit consent,[11,12] the American Academy of Pediatrics and the Institute of Medicine have both questioned why

NBS is exceptional. [13,14] There are many pediatric opportunities that are beneficial and yet require parental permission (e.g., immunizations). Nevertheless, as NBS expands beyond the traditional criteria for public health screening,[15] the role of consent will attain greater significance.

Putting consent issues aside, the pilot study raises a fundamental question about the goals of a screening program. The study by Saul et al..1] and most other studies use polymerase chain reaction (PCR)-based technologies.[2–6] A standard PCR protocol for amplifying the fragile X mental retardation-1 gene (FMR1) trimucleotide repeat lets the researchers distinguish between those with <45 repeats who are normal; those who have a pre-mutation (between 45 and 200 repeats), those with a full mutation (>200 repeats), and those who are in the gray area (having between 45 and 55 repeats).[16] In females, a single band on PCR testing represents either 1) a normal female with two normal FMR1 genes of similar repeat number that make them relatively indistinguishable; 2) a chromosomal abnormality (e.g., Turner syndrome or Androgen Insensitivity syndrome); or 3) a large mutation that poorly expands by PCR. An estimated one-fourth of all female samples initially screened by PCR would have a single band.[16] Southern blot testing would then be required to distinguish those with and without an abnormal FMR1 gene. Because southern blot testing is quite labor intensive, females were traditionally excluded from PCR-based FrX population screening protocols.[16] However, in 2007, Strom et al. reported on a high-throughput technique using capillary Southern analysis (CSA) for FrX detection in both males and females that minimizes the number of samples that need southern blot confirmatory testing.[16] Although Strom et al. proposed their methodology for prenatal population screening, they acknowledged its potential use in NBS.[16]

The development of the CSA technique described by Strom et al. 16] forces us to ask why research continues to focus on FrX NBS methodologies geared only to male infants? The benefits of a NBS program according to Saul et al. would be both to detect young boys who could benefit from early developmental services, and to give parents reproductive information.[1] Consider the first claim regarding developmental services. If one believes that early developmental services are beneficial, then one must ask how one can justify excluding female infants? One answer is that only half of females with full mutations will have some degree of cognitive and behavioral disability and their symptoms will often be less severe than the symptoms of their male counterparts.[16] But for those girls who are delayed, early developmental services would be helpful. A fear is that some girls will be inappropriately classified as having developmental delays. This may lead to unnecessary participation in early developmental services, but there are no data to suggest that such participation would be harmful. Inappropriate labeling by itself however can be quite harmful by causing stigma, discrimination, and lower achievement due to self-fulfilling prophecies.[17,18] Thus, from a developmental perspective it is ambiguous at best whether screening infant girls for FrX syndrome is more beneficial than harmful.

The second claim of a screening program, however, is to provide reproductive information to parents. To achieve this goal, the diagnosis of pre-mutation and full mutation girls and boys would be more useful than restricting the diagnoses to affected and carrier males. However, pediatricians and policy makers become uncomfortable when the goal of NBS is described as providing reproductive information for parents.[10,13,14] If the goal is to educate parents about their reproductive risks, then it would be preferable to screen the women or couple pre-conception and not to use children as the canaries in the coal mine. [16] This would allow women to decide prenatally (preferably pre-conception) what risks they are willing to take and how they want to manage a high-risk pregnancy before an affected child is born. While the method proposed by Saul et al. could not be applied to the prenatal period, the method by Strom et al. could.

There is precedence for routine prenatal screening for mental retardation and developmental disabilities. Until the mid-1980s, the American College of Obstetrics and Gynecology (ACOG) recommended prenatal screening for Down syndrome only for high risk women (e.g., advanced maternal age), but with the discovery that maternal serum alpha fetoprotein is decreased in women whose pregnancies are complicated by Down syndrome, routine prenatal screening of all women became the norm.[19] In fact, California requires that physicians document those who refuse.[20] ACOG's current recommendations for prenatal screening for FrX is limited to those with a family history of mental retardation or FrX. syndrome.[21] An accurate automated high throughput FrX screening program could lead ACOG to reconsider this recommendation and to propose routine prenatal FrX screening.

The major disadvantage of implementing prenatal screening for FrX rather than newborn screening is the greater disparity in access to prenatal genetic testing than to neonatal screening.[22] If diagnosis early in childhood offers significant benefits, unequal prenatal access could justify screening all newborns rather than infants identified as high risk prenatally. Supporters of NBS assert that early diagnosis is essential to procure early developmental services.[23] However, any child with developmental delays is eligible for early developmental services, and with routine developmental screening assessments, developmental delays are clinically identifiable in the first years of life.[24] Referral to early developmental services can be made even before a specific diagnosis is made. A genetic evaluation of all children with developmental disabilities is medically indicated for prognostic purposes and should be offered,[25] although uptake may not be universal because of the reproductive implications that the diagnosis may hold.

Population screening for FrX is on the horizon. The study by Saul et al. focused on NBS because of the technology used. However, the decision whether to provide prenatal and/or neonatal screening should be based on well-articulated and transparent goals. That is, values rather than technology should guide policy decisions. The lack of cure for FrX syndrome and the association of pre-mutation carrier status with reproductive risk and other adult-onset conditions means that all screening program must be accompanied by a robust informed consent process. To the extent that the study by Saul et al. is at all representative, we should anticipate that a large number of women and/or parents will refuse.

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