commentary

Policy considerations in designing a fragile X population 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 with the <3% refusal rate in Massachusetts and 10% refusal in California when tandem mass spectrometry was first introduced as pilot programs.[7,8] It is also high compared with the <8% refusal rate in Wales for screening newborn males for Duchenne Muscular Dystrophy.[9] FrX screening is more similar to that of Duchenne Muscular Dystrophy 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. 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 laboratory 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 tandem mass spectrometry 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.[1] may have had a lower consent rate because of the requirement for written consent and the participation of research personnel to obtain the consent.

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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 premutation (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.[16] reported on a high-throughput technique using capillary Southern analysis for FrX detection in both males and females that minimizes the number of samples that need southern blot confirmatory testing. Although Strom et al.[16] proposed their methodology for prenatal population screening, they acknowledged its potential use in NBS.

The development of the capillary Southern analysis 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.[1] would be both to detect young boys who could benefit from early developmental services and to give parents reproductive information. Consider the first claim regarding developmental services. If one believes that early developmental ser-

vices 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 because of 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 Saul et al.[1] is that a screening program should provide reproductive information to parents. To achieve this goal, the diagnosis of premutation and full mutation of 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 preconception and not to use children as the canaries in the coal mine.[16] This would allow women to decide prenatally (preferably preconception) what risks they are willing to take and how they want to manage a high-risk pregnancy before an affected child is born. Although the method proposed by Saul et al.[1] could not be applied to the prenatal period, the method by Strom et al.[16] 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 must 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 NBS 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 only 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 etiology is identified. A genetic evaluation of all children with developmental disabilities is medically indicated for prognostic purposes and should be offered.[25] Parents, however, need to be informed that this evaluation may provide a specific diagnosis which may have reproductive implications for them. Uptake, then, may not be universal because some parents may decide that they do not want this information or do not want it at this time.

Population screening for FrX is on the horizon. The study by Saul et al.[1] focused on NBS because of the technology used. However, values rather than technology should guide policy decisions. The decision whether to provide prenatal and/or neonatal screening should be based on well-articulated and transparent goals. The lack of cure for FrX syndrome and the association of premutation carrier status with reproductive risk and other adult-onset conditions means that all screening programs must be accompanied by a robust informed consent process. To the extent that the study by Saul et al.[1] is at all representative, we should anticipate that a large number of women and/or parents will refuse.

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References

1. Saul RA, Friez M, Eaves K, et al. Fragile X syndrome detection in newborns-pilot study. *Genet Med* 2008;10:714–719.
2. Dawson AJ, Chodirker BN, Chudley AE. Frequency of *FMR1* premutations in a consecutive newborn population by PCR screening of guthrie blood spots. *Biochem Mol Med* 1995;56:63–69.
3. Strelnikov V, Nemtsova M, Chesnokova G, Kuleshov N, Zaletayev D. A simple multiplex FRAXA, FRAXE, and FRAXF PCR assay convenient for wide screening programs. *Hum Mutat* 1999;13:166–169.
4. Rifé M, Mallolas J, Badenas C, et al. Pilot study for the neonatal screening of fragile X syndrome. *Prenat Diagn* 2002;22:459–462.
5. Rife M, Badenas C, Mallolas J, et al. Incidence of fragile X in 5,000 consecutive newborn males. *Genet Test* 2003;7:339–343.
6. Chow JC, Chen DJ, Lin CN, et al. Feasibility of blood spot PCR in large-scale screening of fragile X syndrome in southern Taiwan. *J Formos Med Assoc* 2003;102:12–16.
7. Atkinson K, Zuckerman B, Sharfstein JM, Levin D, Blatt RJ, Koh HK. A public health response to emerging technology: expansion of the Massachusetts newborn screening program. *Public Health Rep* 2001;116:122–131.
8. Feuchtbaum L, Lorey F, Faulkner L, et al. California's experience implementing a pilot newborn supplemental screening program using tandem mass spectrometry. *Pediatrics* 2006;117(5 pt 2):S261–S269.
9. Bradley DM, Parsons EP, Clarke AJ. Experience with screening newborns for Duchenne muscular dystrophy in Wales. *BMJ* 1993;306:357–360.
10. Andrews LB, Fullarton JE, Committee on Assessing Genetic Risks, Division of Health Sciences Policy, Institute of Medicine. In: Andrews L, Fullarton JE, Holtzman NA, Motulsky AG, editors. Assessing genetic risks: implications for health and social policy. Washington, DC: National Academy Press, 1994.
11. Committee for the Study of Inborn Errors of Metabolism, Division of Medical Sciences, National Research Council. Genetic screening: programs, principles, and research. Washington, DC: National Academy of Sciences, 1975.
12. Holtzman NA, Faden R, Chwalow AJ, Horn SD. Effect of informed parental consent on mothers' knowledge of newborn screening. *Pediatrics* 1983;72:807–812.

13. Campbell E, Ross LF. Incorporating newborn screening into prenatal care. *Am J Obstet Gynecol* 2004;190:876–877.
14. American Academy of Pediatrics (AAP) Committee on Bioethics. Ethical issues with genetic testing in pediatrics. *Pediatrics* 2001;107:1451–1455.
15. Wilson JMG, Jungner G. Principles and practice of screening for disease. Public health paper number 34, Geneva: World Health Organization (WHO), 1968.
16. Strom CM, Huang D, Li Y, et al. Development of a novel, accurate, automated, rapid, high-throughput technique suitable for population-based carrier screening for Fragile X syndrome. *Genet Med* 2007;9:199–207.
17. Finlay WM, Lyons E. Rejecting the label: a social constructionist analysis. *Mental Retard* 2005;43:120–134.
18. Whitmarsh I, Davis AM, Skinner D, Bailey DB Jr. A place for genetic uncertainty: parents valuing an unknown in the meaning of disease. *Social Sci Med* 2007;65:1082–1093.
19. ACOG Committee on Practice Bulletins. ACOG practice bulletin no. 77: screening for fetal chromosomal abnormalities. *Obstet Gynecol* 2007;109:217–227.
20. Cunningham GC, Tompkinison DG. Cost and effectiveness of the California triple marker prenatal screening program. *Genet Med* 1999;1:199–206.
21. American College of Obstetricians and Gynecologists Committee on Genetics. ACOG committee opinion. No. 338: screening for fragile X syndrome. *Obstet Gynecol* 2006;107:1483–1485.
22. Park JH, Vincent D, Hastings-Tolsma M. Disparity in prenatal care among women of colour in the USA. *Midwifery* 2007;23:28–37.
23. Bailey DB Jr, Beskow LM, Davis AM, Skinner D. Changing perspectives on the benefits of newborn screening. *Mental Retard Dev Disabil Res Rev* 2006;12:270–279.
24. American Academy of Pediatrics Council on Children with Disabilities, Section on Developmental Behavioral Pediatrics, Bright Futures Steering Committee, Medical Home Initiatives for Children with Special Needs Project Advisory Committee. Identifying infants and young children with developmental disorders in the medical home: an algorithm for developmental surveillance and screening. *Pediatrics* 2006; 118:405–420.
25. Moeschler JB, Shevell M. American Academy of Pediatrics Committee on Genetics. Clinical genetic evaluation of the child with mental retardation or developmental delays. *Pediatrics* 2006;117:2304–2316.