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# Newborn Screening for Fragile X Syndrome

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Newborn screening for fragile X syndrome (FXS) is technically possible, and in the relatively near future accurate and inexpensive screening technologies are likely to be available. When that happens, will America's public health system adopt newborn screening for fragile X syndrome? This article addresses this issue by first placing screening for FXS in the context of the history and current status of newborn screening policy and practice. Lack of a proven medical treatment may stand as a barrier to newborn screening, but strong arguments can be made that early intervention provides important services for identified newborns and their families. Furthermore, other arguments could be used to justify newborn screening, including informed reproductive risk, medically necessary information, and consumer demand. Fragile X syndrome is offered as a prototype for many of the issues that will face society as more genetic disorders are discovered and new technologies for screening are developed. 
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**Key Words:** newborn screening; genetic testing; fragile X; diagnosis

## NEWBORN SCREENING FOR FRAGILE X SYNDROME

Since the discovery of the FMR-1 gene in 1991, fragile X syndrome (FXS) has been the focus of considerable attention. Basic scientists are interested in the biology of FXS because research on the inheritance mechanisms, molecular consequences, and neurobiological functions affected by FXS could lead to a fundamental understanding of how normal development is disrupted and the potential for treatments such as gene therapy or targeted pharmaceutical interventions. Social scientists and parents are interested in the functional consequences of FXS on development and behavior and the educational, therapeutic, or psychosocial interventions that could maximize developmental attainments and quality of life for individuals with FXS and their families. Intriguing aspects of FXS, such as the wide variability in phenotypic expression, the unique patterns of strengths and weaknesses in cognition, language, and motor development, its high association with autism, and the role of arousal and anxiety in both the biology and behavior of FXS have led to interesting theories that are now being examined from a number of perspectives.

Clearly FXS has challenged geneticists, molecular biologists, neuroscientists, and practitioners to think differently about human function and strategies by which impaired function can be improved. Yet there is another domain in which FXS poses equally unique challenges and opportunities—the public policy arena and the public health system within which newborn screening occurs. The rapid discovery of hundreds of genetic causes of mental retardation, coupled with new technological developments that will soon make it possible to screen for many disorders as cheaply as one or two, is forcing America's public health system to reexamine processes and guidelines for decision making about newborn screening. FXS is a single-gene disorder and the most common inherited form of mental retardation and developmental disabilities, but it is not detectable at birth except through genetic testing. As such, fragile X syndrome exemplifies many of the issues that will arise in this new era of emerging genomic knowledge and technical capability. This article examines the desirability of newborn screening for FXS in the context of history, current status, and emerging trends in newborn screening. I summarize arguments in support of early identification, evaluate newborn screening as a way to promote earlier identification, and review criteria for weighing decisions about newborn screening for FXS. The article concludes with recommended research and policy initiatives needed to inform this process.

### The Early Days of Newborn Screening

Newborn screening in the United States first became a reality in the 1960s, when Robert Guthrie developed a screening test for phenylketonuria (PKU) using blood spots. PKU was the ideal disorder to serve as the initial prototype for screening because of three key features. First, when untreated, PKU has a devastating effect on development, usually resulting in severe mental retardation. Second, Guthrie had created a screening method that was accurate, inexpensive, and easily done. Finally, there was a clear and simple treatment, a dietary change that, if implemented consistently over time, could completely prevent the ill effects of PKU. The treatment resulted in an obvious and marked difference in quality of life and has saved millions of dollars that families and society would have to invest in the care of individuals with PKU-based mental retardation.

The history of PKU screening demonstrates the complexities inherent in using research findings and technological inno-

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vations to influence policy and change institutional practice. Despite possessing all of the features that would seem to make screening for PKU an easy policy decision, it took more than 10 years for the majority of states to mandate newborn screening for PKU. The history of PKU screening implementation and the subsequent creation of the current system of screening policy and practice is well documented in a report from the Newborn Screening Task Force of the American Academy of Pediatrics [AAP Newborn Screening Task Force, 2000]. A distillation of this and other reports indicates two main factors that stood as barriers to immediate implementation of PKU screening in the 1960s. First, the scientific community had not developed standards and procedures for evaluating the accuracy of screening tests or the efficacy of treatments. In fact, advocacy efforts quickly outpaced science such that research validating the PKU screening test and fully evaluating the safety and efficacy of the dietary treatment were not completed until after state laws were passed mandating screening [AAP Newborn Screening Task Force, 2000]. Second, the United States had no public health infrastructure at either the state or federal level by which newborn screening could be implemented. The relative roles of state and federal governments had not been articulated and there was no precedent for who would conduct screening, pay for it, or provide treatment.

Concerted and sustained advocacy efforts at state and national levels led to mandated newborn screening for PKU in most states by the mid-1970s. Guthrie's research and these advocacy efforts ushered in a new era of public health medicine focusing on preventing the debilitating effects of a disorder through early identification and early treatment. They set the stage for developing the current infrastructure for newborn screening in the United States and prompted numerous debates and discussions about a wide range of complex issues involving the interplay of science, ethics, human rights, public policy, and economics.

## Newborn Screening Today

Now, nearly 40 years later, the United States has made considerable progress in both infrastructure and policy decision making, both of which serve as an important background for current discussions about newborn screening for FXS.

### *Infrastructure*

As it has evolved in the United States, newborn screening decisions and practices fall under the aegis of states, rather than the federal government, and are overseen by state public health departments. The federal government's role has primarily been one of support and stimulation of program development, providing some financial assistance, overseeing laboratory certification and quality control, and stimulating the development of new laboratory procedures. But decisions regarding whether to screen, which disorders to screen, how to finance screening, and the follow-up mechanisms for treatment and support are all the responsibilities of individual states. As a result, there is considerable variability across states in all of these domains. The National Newborn Screening and Genetics Resource Center maintains an updated web site (http://genes-r-us.uthscsa.edu/resources/newborn/screenstatus.html) listing the status of newborn screening by state and by disorder. A recent examination of this report indicates that the number of disorders mandated for screening ranges from 3 to 33, with five states engaging in a universal pilot for 1 or more additional disorders. All states screen for PKU and congenital hyperthyroidism and all but one screen for galactosemia and for sickle cell disease. Beyond that, considerable variability is evident.

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Cross-state inconsistency in disorders included in newborn screening programs has caused considerable concern, and a number of organizations as well as a recent report from the U.S. General Accounting Office [2003] have advocated greater uniformity. The American Association of Pediatrics has called for a national agenda on state newborn screening programs. The March of Dimes has recommended that all states screen for at least 10 disorders: PKU, hypothyroidism, galactosemia, sickle cell anemia, congenital adrenal hyperplasia, biotinidase deficiency, maple syrup urine disease, homocystinuria, MCAD, and hearing loss. And the American College of Medical Genetics, with a contract from the Genetic Services Branch, Maternal and Child Health Bureau, HRSA, has formed an expert group to establish a set of guidelines and recommended panel of disorders for all states. All of these efforts should help standardize screening practice. However, rapid changes in technology, the continued discovery of new genetic causes of disease and disability, the natural tendency of states to make their own decisions, and the variable role of advocacy groups within each state mean that state variability in screening will likely continue for the foreseeable future.

### *Guidelines for Policy Decisions*

By what criteria should decisions about newborn screening be made? This question has been the focus of considerable discussion; however, four major task force reports [Andrews et al., 1994; Holtzman and Watson, 1997; National Research Council, 1975; World Health Organization (WHO), 1968], key publications (e.g., [Wilson and Jungner, 1968]) and distillations of these and other reports (e.g., [AAP, 2000]) have reached substantive agreement on the answer. Currently accepted guidelines rest on three fundamental criteria: (1) the disorder must be a significant public health problem that has major consequences for affected individuals; (2) there must be available an accurate, acceptable, and cost-effective procedure for screening for the disorder; and (3) a treatment must exist which, if provided early, can significantly alter the course of the disease or disorder. Other criteria, such as an adequate system for screening and follow-up and public acceptability of the process and outcomes, are also commonly used, but the three fundamental criteria typically represent the necessary conditions for making the decision to screen. It should be evident, however, that wide agreement on the criteria for screening has not resulted in a highly standardized national system.

### Challenges to Newborn Screening Policy

Several trends are now challenging the criteria by which decisions about newborn screening are made [Collins, 1999; Collins and McKusick, 2001; Khoury et al., 2003; Therrell, 2001]. First, the Human Genome Project and associated research efforts have resulted in the discovery of the genetic basis for hundreds of disorders, many of them rare. Thus the potential pool for disorders that could be evaluated for newborn screening has grown exponentially. Second, technological advances such as tandem mass spectrometry and microarray analysis mean that many disorders, perhaps hundreds, could be screened as cheaply and easily as one. Thus once a decision to use a particular technology is made, cost of screening may become irrelevant in determining whether to add disorders to a screening panel. Third, advocacy groups continue to push for newborn screening even when a known treatment is not available. Public acceptance of genetic screening appears to be high, and parents of affected children strongly endorse screening. Finally, commercialization of genetic technology is likely to result in a private market for genetic testing that will offer parents a wide range of options for testing both definitive genetic disorders as well as information about the probabilities of other health outcomes. This could result in parallel sets of screening systems (public and private) with different standards and expectations.

If cost and frequency of occurrence are no longer salient issues, by what criteria will decisions about newborn screening be made? Discussions about newborn screening for FXS highlight the debates that likely will occur in the coming decade and thus FXS stands as a prototype for weighing alternative criteria.

## DISCOVERING FRAGILE X SYNDROME: PROCESSES AND CHALLENGES

How do parents typically find out that their child has FXS? Several studies in the United States and the United Kingdom have reached similar conclusions [Bailey et al., 2000; Bailey et al., 2003; Carmichael et al., 1999]. FXS is not identifiable at birth and thus must be discerned through some other means. Some families learn about it through the diagnosis of a relative. However, most must learn about it through a long and arduous discovery process. Considerable variability is evident, but on average, someone, usually a parent, first becomes concerned about the child's development between 9 and 13 months of age. Often there ensues a series of multiple visits to a physician or other specialist to determine if development is delayed, a fact that is typically confirmed by 22–25 months of age. On average, the diagnosis of FXS does not occur until 30–35 months.

This scenario is improving as the medical community becomes more aware of FXS as a possible cause of developmental delay. However, several features of FXS and the current system of medical practice in the United States impose constraints that set boundaries on the potential for dramatic improvements in early identification through currently available processes. First, the FX phenotype is not so distinctive as to be immediately apparent. A number of checklists have been proposed to help facilitate accurate and earlier identification [Bailey et al., 2001; Butler et al., 1991; Hagerman et al., 1991; Laing et al., 1991], but variability in phenotypic expression and the lack of unique physical characteristics make the use of checklists problematic [Lachiewicz et al., 2000].

Second, research suggests that the moderate to severe levels of delay seen in older individuals with FXS only gradually become evident during the first 18 months of life. The database on the attainment of early developmental milestones is sparse [Kau, Meyer, & Kaufmann, 2002]. However, in a retrospective study based on maternal recollections of early development, Roberts, Hatton, and Bailey [2001] found that average delays in key developmental milestones such as sitting (2-month delay), crawling (3-month delay), and walking (4- to 6-month delay), although significant, are within the range in which some (although admittedly relatively few) normally developing children attain these skills. The emergence of first words, which typically occurs at an average age of 11 months but may not occur until 2 years of age in children with FXS, is a more powerful indicator, but because first word expression in normal toddlers can range as high as 17 or 18 months, it is only at this time that professionals typically begin to acknowledge that something in development indeed might be amiss.

Third, preliminary findings from our lab in a study of 9-, 12-, and 18-month-olds with FXS suggest that measurable delays and atypical patterns of behavior are clearly evident in the majority of males with FXS by 9 months of age and could be detected using currently available developmental screening tests [Mirrett et al., in press]. However, despite a recent recommendation from the American Academy of Pediatrics for pediatricians to incorporate the systematic use of developmental screening measures in pediatric practice [American Academy of Pediatrics, 2001], most pediatricians do not do this. Furthermore, many families, especially poor families, have inconsistent medical care and thus even if pediatricians used screening measures on a regular basis, many children would still not have access to this service. Finally, even if screening was a regular part of pediatric practice and widely available to all families, documenting a delay would not necessarily result in a referral for FX testing. In a recent survey of families of children with FXS [Bailey et al., 2003], we found that pediatricians rarely requested the genetic test, instead first referring the family to another specialist such as a neurologist who then requested the FX testing, further delaying the diagnosis.

### Consequences of Delayed Identification of Fragile X

Four clear consequences occur as a result of delayed identification of FXS. First, parents experience frustration with professionals and doubts about themselves in their attempts to find a professional who will acknowledge that their child's development is atypical. This can happen, for example, when pediatricians reassure parents that nothing is wrong (making some parents feel that they are not good observers of development or perhaps overly concerned about their child) or when they see that they are not able to manage their child's behavior or that development is not proceeding at a normal rate (making some parents feel incompetent in their parenting roles). Second, there are real financial costs to families, insurance companies, and the health care system for the repeated visits that often are necessary before a diagnosis is made. Bailey et al. [2003] found that over 40% of families of children with FXS reported having made 10 or more visits to a physician before a diagnosis was made.

Third, children and families do not have access to early intervention. Through Part C of the Individuals with Disabilities Education Act, all states have mandated early intervention programs for children with disabilities and their families, a program for which all children diagnosed with FXS would be immediately eligible. Without the genetic diagnosis, however, states require a documented developmental delay, as mea-

sured by standardized tests. Because this typically does not happen until the child is nearly 2 years of age, families and children with FXS are precluded access to an existing system of services that is individualized according to child and family needs. Finally, families do not have access to information about carrier status of parents and thus many will make future reproductive decisions without knowledge of the risk that a child will have FXS. Bailey et al. [2003] found that more than half of their sample of families had a second child before diagnosis of FXS in their first child. Of the 191 children born after the birth of their first child with FXS but before the diagnosis, 109 (57%) had the full mutation FXS. Thus many families had two or more children with the disorder.

## Genetic Screening Options for Fragile X Syndrome

Earlier identification of FXS could be promoted to some extent through changes in pediatric practice and the systematic use of developmental screening tests for all children. However, absent major changes in health care reimbursement policies, institutionalization of regular developmental screening in pediatric practice is not a likely scenario in the next decade. Furthermore, because so many children do not see a pediatrician or family physician on a regular basis, there would be many opportunities for children to "fall between the cracks" and never receive developmental screening.

An alternative to enhanced developmental screening and surveillance would be the systematic use of genetic testing for FXS. At least four options for genetic screening are possible [Bailey et al., 2001; Pembrey et al., 2001].

### *Population screening of women of childbearing age*

This approach would have the advantage of providing women with information about their carrier status and allow them to make a range of reproductive choices prior to pregnancy, such as not having children, donor gametes, adoption, preimplantation genetics, or selective abortion. However, there is no natural mechanism or public health policy for conducting such a program and some of these choices (e.g., selective abortion and preimplantation genetics) are controversial. Its success would depend almost entirely on a major public awareness campaign that encouraged women to ask for such a test and encouraged obstetricians to offer it. Of course, men could be screened as well, but because the expansion into the full mutation never occurs through paternal transmission, screening would tell parents only that all of their daughters would carry the premutation. Male screening only for carrier status is highly unlikely, and thus the burden for screening will inevitably fall to women.

### *Screening of pregnant women*

This option would be less expensive because it would involve fewer women. However, three factors remain problematic. As with the first option, a public health awareness campaign would still be needed and the relevant medical professional societies, such as the American Association of Obstetrics and Gynecology, would need to endorse the practice and encourage their membership to offer it to all pregnant women. Second, many pregnant women receive little or no prenatal care, especially women struggling with poverty. Finally, because the woman is already pregnant, certain reproductive decision-making options (e.g., adoption and preimplantation genetics) are no longer available, and the issue of abortion becomes salient. A possible advantage of knowing about the diagnosis prenatally is that parents could go through a period of adjustment and preparation before birth, avoiding potential trauma associated with receiving a diagnosis shortly after birth. On the other hand, for some parents this information and the uncertainty of their child's level of disability could exacerbate stress during pregnancy.

### *Newborn screening*

Newborn screening is an attractive option in that a screening program already exists in every state. It is the one option that is virtually universal, although it almost certainly would have to be voluntary and some families would surely choose not to participate. However, it provides the best opportunity for screening the maximum number of children. Newborn screening would allow immediate entry into the nation's Part C early intervention programs, providing access to both child and family services. Also, because some babies with FXS experience medical problems such as gastroesophageal reflux, failure to thrive, poor coordination of sucking, or hypotonicity, early diagnosis could help in early treatment and management of these problems before they become significant. And although it would completely eliminate reproductive options regarding the diagnosed child, it would provide information about carrier status in sufficient time that families could use it in subsequent reproductive decision making.

### *Screening at the first sign of delay*

A fourth option would be to screen for FXS at the first sign of developmental delay. This would conceivably be the least expensive approach in terms of screening cost because it would limit the testing to those children with a documented or suspected developmental delay. However, even assuming that (a) all children had access to a pediatrician, (b) pediatricians engaged in regular developmental screening, and (c) pediatricians or family physicians immediately followed up on parental concerns and referred directly for FX testing, it is still unlikely that a diagnosis would occur before 12 months of age, precluding at least a year of early intervention services and eliminating reproductive choice for those families in which a second pregnancy occurs within 12–15 months after birth.

## An Analysis of Newborn Screening for FXS

Newborn screening for FXS provides the one opportunity for nearly universal access because newborn screening programs already exist in each state. How would FXS as a candidate for newborn screening be evaluated with respect to existing decision-making standards?

### *Significant public health problem*

This standard has two key parts: (1) does the disorder occur relatively frequently in the population? and (2) does the disorder result in significant health consequences for affected individuals, regardless of frequency of occurrence? FXS is a strong candidate for newborn screening relative to both parts of this standard. Although there is controversy over the true incidence rate, a recent review estimates that at least 1:4000 males are born with the full-mutation FXS and 1:270 women may be a carrier [Crawford et al., 2001]. These numbers stand in stark contrast to the frequency of occurrence of PKU (1:15,000) or galactosemia (1:30,000), two disorders currently screened in almost every state. Furthermore, FXS exerts a clear and devastating effect on affected individuals, especially males, resulting in moderate to severe mental retardation, high levels of anxiety and arousal, and frequent instances of autism or self-injurious behavior. Thus FXS should easily meet the first standard regarding both public health and individual burden.

*Availability of an inexpensive and valid screening measure*

Fragile X syndrome does not currently meet this standard. The DNA test for FXS using PCR or Southern blot is virtually 100% accurate but is very expensive ($200–$300) relative to the costs of other newborn screening tests. In a state such as North Carolina, for example, with over 100,000 births per year, the annual cost of screening using this technique would be more than $20,000,000 to detect 12–13 males with the full mutation. However, this scenario is likely to change in the very near future. Several pilot studies have been published (e.g., [Rife, 2002; Strelnikov et al., 1999] and a number of laboratories are exploring a variety of technologies that appear promising. It is quite likely that the cost of a PCR-based automated screening could be reduced to $10–20 per child in the next 2–3 years, and other methods could even be cheaper. A factor contributing to cost will be whether to test for carrier status. And although cost is currently a factor, one likely scenario in the next decade is that technological advances will mean that screening for multiple disorders will be no more expensive than for one.

*A proven treatment*

Under current policy, it is the standard of proven treatment efficacy that could impede the adoption of newborn screening for FXS. PKU set an early standard as the ideal prototype for proven treatment efficacy, as a simple dietary intervention is highly effective in eliminating the mental retardation caused by untreated PKU. No such treatment is available for FXS. Although considerable research is now underway on the molecular processes disrupted by FXS, with the ultimate hope of powerful gene therapy or targeted pharmaceutical treatments, not a single study has been published to date on the efficacy of any biomedical or psychosocial interventions provided during the first 3 years of life. If FXS is held to a strict interpretation of the proven medical treatment standard, then newborn screening will need to wait for the completion of a randomized clinical trial providing clear evidence that treatment provided during the first 2 years of life results in more optimal outcomes than treatment provided later.

If a less strict interpretation is followed, however, *relevant evidentiary data* could be used to argue that it is *reasonable to conclude* that nonmedical treatment by early intervention programs ought to promote more optimal development in individuals with FXS. This argument rests on a wide range of supporting data. A broad and extensive literature documents that during the first 3 years of life (a) much happens in terms of learning, synaptic development, and dendritic pruning; (b) the environment, social interactions, parenting styles, and other experiences exert a direct effect on brain development and on behavioral trajectories over time [Hauser-Cram et al., 2001]; and (c) optimal environmental effects on development and behavior are dependent on the amount, quality, and timing of experiences [Bailey, 2002; Bailey et al., 1999]. Major literature reviews consistently show that high-quality early intervention efforts can have a moderate effect on the development of children with disabilities, with impressive effect sizes typically ranging from 0.40 to 0.75 [Guralnick, 1998].

With FXS, intriguing hypotheses suggest the possibility that earlier intervention might be essential. It is already clear that FMRP, the protein disrupted by FXS, is critical to normal brain development and function. Recent studies show that when expression of FMRP is reduced, abnormal morphology of cortical dendritic processes is observed, suggesting that FMRP is involved in synapse maturation and elimination [Weiler and Greenough, 1999, see Beckel-Mitchener and Greenough, this issue). If FMRP plays an important role in activity-dependent synaptic function, maturation, and plasticity during development, then it is possible that the most powerful interventions may be those that could be provided early in life during the period of rapid proliferation and pruning of neural connections.

These facts and hypotheses, coupled with the existence of a nationwide system of services readily available for infants with disabilities, a system that parents view as highly responsive and effective [Bailey et al., in press], provide a strong logical basis in support of early intervention for children with FXS. In fact, Warren [2003] has argued that FXS specifically, and mental retardation disorders more generally, have already met a proven treatment efficacy standard for newborn screening and should not be held accountable for a randomized trial of treatment efficacy prior to making a decision about newborn screening. Time will tell whether the public health system agrees with this assertion, but it is likely not to be a conclusion that is uniformly endorsed, despite the collective power of the information available.

**Alternative Criteria**

Although prevalence, the availability of a valid, affordable screening test, and proven treatment efficacy are the current "gold standards" for evaluating disorders relative to their candidacy for newborn screening, arguments are now being posed that challenge these standards. For the purpose of this discussion, we briefly review three interrelated considerations—reproductive risk, consumer demand, and medical necessity—and conclude by juxtaposing these arguments with the possibility that in the near future all criteria will become irrelevant.

*Reproductive risk*

Female carriers of FXS are at risk for having a child with the full mutation. Newborn screening would lead to the identification of parents who are carriers and knowledge of carrier status would provide information about reproductive risk that parents could use (or choose not to use) in future reproductive decision making. Research in FXS [Bailey et al., 2003; Pesso et al., 2000] shows that knowledge of carrier status of the mother or of the full mutation of a fetus has a powerful effect both on decisions such as whether to have additional children, adopt, seek donor gametes, or carry an affected fetus to full term. When interviewed, carrier parents state strongly that had they known their carrier status before giving birth, it definitely would have affected their reproductive plans [McConkie-Rosell et al., 1997].

At least two rationale for the reproductive risk argument exist. At one level, the argument rests simply on the right to know, irrespective of the reproductive choices made. At a second level, some argue that the real rationale behind the reproductive risk argument is the elimination of fragile X syndrome through selective abortion or opting out of childbearing altogether. And indeed, Wildehagen et al. [1998] conclude that screening for FXS can be highly cost-effective, but the primary determination of cost savings was the extent to which a particular screening option "will lead to the highest number of avoided fragile X syndrome patients" (p. 36).

In the United States, the reproductive risk argument will not be uniformly endorsed, as some groups such as anti-abortion or disability rights advocates are very opposed to any intentional efforts to eliminate disability through reproductive decision making. Newborn screening sidesteps these issues to some extent (because no immediate reproductive decision can be made), but only partially,

because it will inevitably influence future decisions. If reproductive decision making is to be used as a primary argument in support of newborn screening for FXS and other heritable disorders, it will need to be done carefully and inevitably there will be strong protests. A more effective and acceptable route would be to have early treatment as the primary argument, with knowledge of carrier status an important but secondary benefit.

*Consumer demand*

A closely related argument is that decisions about newborn screening should be based on consumer demand—a market-driven approach to decision making. Hiller, Landenburger, and Natowicz [1997] report that only a few states involve consumers on state advisory boards and that state decisions about newborn screening have not included significant or systematic consumer input. When consumer input has had an effect, it more likely has resulted from concerted efforts by influential advocacy groups who typically push for screening for a particular disorder within a particular state [Stockdale and Terry, 2002].

Research on consumer perspectives is limited and comes from two sources. Public opinion polls have repeatedly assessed public perceptions of genetic testing. These studies are almost never disease-specific, but they consistently show that the public thinks that genetic testing is a good idea, even though they acknowledge not knowing very much about it [Singer et al., 1998]. More traditional research studies published in peer-review journals have also been conducted, but in contrast to public opinion polls, these studies are almost always in the context of particular diseases and the respondents usually are individuals who directly or indirectly are already affected by the disorder. In general, however, these studies reinforce the conclusion from public opinion polls that the public is very supportive of genetic testing. In FXS, families report that diagnosis generally has more benefits than drawbacks [Bailey et al., 2003; Roy et al., 1995] and they endorse the need for systematic screening for adults and newborns, both for those affected by FXS and those who are carriers of the disorder [McKonkie-Rosell et al., 1999; Skinner, Sparkman, and Bailey, 2003]. Carrier testing of children is particularly controversial among professionals, and the American Academy of Pediatrics has taken a position that it does not support the current use of carrier testing or screening in children due to a lack of research on the potential negative consequences [AAP Committee on Bioethics, 2001]. However, parents of children with FXS strongly endorse carrier testing, and the discrepancy among parents', professional, and disability rights perspectives is likely to cause some tensions in upcoming debates.

Although the public strongly endorses genetic testing in general, as do affected families, research also shows that a number of concerns exist—assuring confidentiality of information, possible insurance discrimination, the potential for labeling and stigmatization of groups or individuals, external pressure to make reproductive choices, and lack of adequate information or follow-up support [Alper et al., 2002]. Despite these concerns, however, consumer confidence is high and advocacy for screening is likely to expand exponentially in the coming decade.

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*Medical necessity*

In the current health care environment, the term "medical necessity" has become a central determinant of which health care services are provided and who will pay for them. Determining whether a treatment or service is medically necessary is often a prerequisite for insurance, HMO, or Medicaid coverage.

In 1999, a task force supported by the Joseph P. Kennedy, Jr. Foundation, the Health Resources and Services Administration of DHHS, and the National Policy Center for Children with Special Health Care Needs drew on a wide variety of perspectives to create a new definition of medical necessity and guidelines for promoting access to quality care for individuals with disabilities [Ireys, Wehr et al., 1999]. The task force concluded that a covered service or item is medically necessary if it will do one or more of the following: (a) arrive at a correct medical diagnosis; (b) prevent the onset of an illness, injury, or disability in the individual or in relatives of the individual; (c) reduce, correct, or ameliorate the effects of an illness, condition, injury, or disability; or (d) assist the individual to achieve or maintain functional capacity.

Drawing on this definition, newborn screening for any disorder that causes a disability could be construed as medically necessary in that it clearly helps both parents and physicians "arrive at a correct medical diagnosis." In an era in which public health decisions are influenced in part by the managed care system, if this task force report ultimately becomes accepted as standard of care, it would have dramatic and direct implications for newborn screenings. Any screening that would lead to a definitive diagnosis of a medical condition would be considered medically necessary and thus subject to insurance reimbursement and other covered services. The impact of this task force report [Ireys et al., 1999] is not yet evident because it has no implementation authority, and continued advocacy will be required for the managed care field to endorse its recommendations.

*An alternative perspective—no criteria*

Despite efforts to construct a rational argument for newborn screening for a disorder such as fragile X syndrome, there is an alternative scenario that could dramatically affect the nation's public health system and require a major reexamination of both policy and practice. In brief, it is possible that in the next decade rapid advances in technology and consumer advocacy, fueled by media attention heralding genetic discoveries and the potential to secure information about ourselves heretofore unavailable [Conrad, 2002; Petersen, 2001], will lead to widespread and indiscriminate disclosure of genetic information without the current constraints imposed by America's public health system. If this scenario develops, efforts to construct a rational ar-

gument for newborn screening for FXS could become irrelevant, as it would become merely a part of a much larger disclosure of genetic information. It will be interesting to see whether this happens through the private market or through the public health system. Inevitably private-economy forces will push this agenda, and the public health system needs to engage in wide-ranging discussions about the ramifications of this alternative scenario. Because this trend is likely to move quickly from a limited focus on known disorders to include disclosure of genetic susceptibility for a wide range of medical conditions and possibly even behavioral traits [Alper et al., 2002], it is urgent that these discussions begin immediately.

## CONCLUSION

Newborn screening for fragile X syndrome has many arguments in its favor and has strong support among parents and advocacy groups, but (a) it does not fully meet existing criteria for newborn screening, (b) some are concerned about the negative consequences for children (e.g., stigmatization) or families (e.g., pessimism, guilt, and disrupted parent–child bonding) [Kay and Kingston, 2002], and (c) controversies still exist over issues related to reproductive decision making and screening for carrier status. As a result, routine screening for FXS will not happen in the next 3–5 years. However, this scenario may change quickly as a result of increased advocacy efforts and newer technologies making screening less expensive. Furthermore, rapid advances in genetics and genetic technology could mean that fragile X syndrome is swept up in a new and perhaps uncontrolled movement in which disclosure of more and more genetic information becomes a routine expectation.

In the meantime, several parallel efforts are needed to promote earlier identification of children with FXS, help inform decision making about fragile X screening specifically, and promote appropriate newborn screening more generally. *First*, physicians, nurses, and other health department employees continue to need support and encouragement in the systematic use of developmental screening in the context of pediatric practice. *Second*, more focused research is needed on the public reactions to a screening program for a disorder such as FXS for which there is no cure. Rather than polls or interviews, however, such a study needs to be prospective and be based on the actual implementation of a screening program, with a comprehensive assessment of family participation in and reactions to the screening, as well as a careful documentation of later consequences for families, both positive and negative. *Third*, it would be very useful to have a rigorous clinical trial documenting that early timing of psychosocial interventions for mental retardation has a more powerful effect on development and behavior than interventions provided later. Fragile X syndrome would be a good disorder to serve as a prototype for this question, although creative experimental designs will be needed to conduct a study that is both ethically defensible and scientifically rigorous. Policymakers ultimately will need to decide how many different disorders would need to be tested before the conclusion that earlier is better could be generalized to the broader set of causes of mental retardation. It is unreasonable to expect a clinical trials study for every etiology, but one or two well-controlled studies using gold-standard methods and showing clear evidence of real efficacy would be very informative and influential in subsequent policy decisions. *Fourth*, a series of forums or task force reports examining various options for screening for fragile X syndrome should be convened. Such efforts have already been completed in the United Kingdom [Murray et al., 1997, Pembrey et al., 2001] and would form a useful basis for U.S. discussions, but the two countries have such different health care systems that separate discussions are warranted. It will be important that these discussions include the most active and senior researchers in the field, key agencies responsible for various aspects of newborn screening, and a wide range of consumers. *Finally*, a broader set of discussions is needed on the larger issue of criteria for newborn screening programs in the 21st century. These discussions are urgent and should engage a wide range of constituencies to assure that America's public health system can respond in a thoughtful and proactive way to rapid changes in genetic information and technology. ■


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