Assessing the Fragile X Syndrome Newborn Screening Landscape

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abstract

BACKGROUND: Fragile X syndrome (FXS) is the most common known inherited form of intellectual disability. Early identification is an important step in linking FXS individuals with appropriate and timely medical and social services. Newborn screening (NBS) is 1 approach that has been used for other conditions to facilitate early identification.

METHODS: A literature review was conducted to identify issues, barriers, challenges, and approaches to addressing challenges related to NBS for FXS. Search terms included: fragile X syndrome, FMR1, newborn screening, screening, and genetic testing. To supplement the literature review, 9 key informant interviews were conducted. Information gathered through these interviews supplemented what was identified in the literature. Information from both the literature review and supplemental interviews was reviewed by 3 researchers who discussed and came to consensus on thematic areas and categorization of issues.

RESULTS: The barriers and challenges related to NBS for FXS identified in the literature and by experts and stakeholders are categorized into 5 thematic areas: public health burden, treatment, timing, screening/testing methodologies, and translating results. Summaries of these issues and barriers are provided, along with potential approaches to addressing them.

CONCLUSIONS: The issues and barriers described in this article highlight limited areas of knowledge that need be addressed to improve our understanding of FXS and the potential benefit of NBS. The landscape of NBS for FXS could be influenced by a series of research findings over time or a larger breakthrough that demonstrates an effective targeted treatment that has to be implemented early in life.

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Fragile X syndrome (FXS) is the most common known inherited form of intellectual disability. Individuals with 55 to 200 repeats on the *FMR1* gene are considered to have the premutation and those with >200 CGG repeats have the full mutation, also known as FXS. Due to the location of the genetic mutation being on the X chromosome,[1,2] boys can have moderate to severe developmental delays,[3] whereas girls, who have a second, potentially protective X chromosome, can present with typical development or have mild to moderate delays.[4] Although phenotypic symptoms are not obvious at birth, both animal and neuroimaging studies suggest that the effects of FXS begin in the prenatal period. The downstream result of the *FMR1* mutation responsible for FXS includes a diminished production of a protein (FMRP) believed to play a key role in early brain development and brain function.[5]

Despite indications that parents recognize delays in their infants as early as 9 months of age, the average age of diagnosis for FXS is ~36 months.[6] This timeline can be longer for girls and boys with milder symptoms. A delay in diagnosis can reduce access to early intervention, family support programs, and medical treatments.[7] Families may experience a "diagnostic odyssey," in which they take their child to see multiple providers and have a host of tests done that may not be needed. This can be stressful for families and can also lead to a significant financial burden.[8] For an inherited condition such as FXS, the delayed diagnoses of a first child may mean parents do not have important information about their reproductive risk. Approximately 29% of these parents have a second child with FXS before the first is diagnosed.[6] Additionally, increasing evidence points to a unique phenotype with increased health risks for individuals who have a premutation in the *FMR1* gene,[9] additionally complicating the cumulative risks for the family.

A variety of screening and testing strategies could be applied to FXS to promote earlier identification. These include preconception or prenatal carrier testing, prenatal fetal testing, newborn screening (NBS), systematic infant developmental screening, and genetic testing for children that present with a global developmental delay of unknown etiology. The latter is the current American Academy of Pediatrics recommendation.[10] This article focuses on large-scale NBS, which has the potential to reach the most individuals and to do so in a fair and equitable way, which can potentially reduce health disparities.[11]

Two broad factors are currently used in the decision process by the Advisory Committee on Heritable Disorders in Newborns and Children in making recommendations to the Secretary of Health and Human Services regarding a nominated condition.[12] The first is the overall net benefit of screening, the primary consideration being the health of the child, but other factors are considered, such as the certainty of evidence regarding the benefit of early identification.[12] The second factor is the capability of state NBS programs to conduct screening for the targeted condition, factoring in the feasibility of screening (including availability of a screening test and treatment options) and state readiness to implement screening.[12]

FXS was considered for possible inclusion in the recommended panel for NBS in 2003 to 2004 by an expert group led by the American College of Medical Genetics, but at that time, FXS did not satisfy the criteria for inclusion.[6] FXS received high ratings for incidence, lack of phenotypic presence at birth, and severity, but received low scores for a validated screening test, as one did not exist at the time, and treatment efficacy.

The potential benefits and concerns of NBS have been presented in the literature by researchers, policy specialists, and ethicists.[6,8,13–15] A review of potential ethical and social issues was published in response to these concerns, addressing major issues, such as (1) lack of a medical treatment; (2) carrier detection for those with a *FMR1* premutation in infants, given increased health risks associated with carriers; (3) whether knowledge of reproductive risk should be considered; and (4) the possible need for an informed consent protocol.[16] Systematic research and extensive stakeholder discussions to address these and other complex issues were recommended.

A systematic review of population screening options for FXS was published in 2010.[17] Among several screening options presented was voluntary or mandated NBS; other options included preconception carrier screening for FXS in women of reproductive age and voluntary screening of pregnant women. Authors noted ethical and policy issues focused on identification of carriers, whether premutation status ought to be reported, and, if so, how that information would be presented to providers and parents. Premutation is more common and the risks associated with premutation status reported to date are primarily adult onset and are variably penetrant.

In this article, we offer a description of the current landscape for NBS for FXS and identify prominent issues and barriers presented in the literature and described by experts in the field.

METHODS

The most pressing issues surrounding NBS for FXS and potential approaches for addressing these issues were identified through a review of the literature and

TABLE 1 Public Health Impact

Potential Approaches	Strengths and Challenges
Conduct an anonymous study by using dried blood spots approved for research use.	Strength If conducted by a large state or multiple states, it could be done in a relatively short period of time. A large sample would make it possible to stratify by sex and ethnicity. Challenges Determining a robust estimate of FXS prevalence would require hundreds of thousands samples. Cost. An anonymous study would not allow for return of results to individuals/families.
Conduct a large statewide study of NBS.	Strengths In addition to prevalence data, this study design could identify affected children, allowing for the possibility of studies to determine the efficacy of earlier identification and intervention. Could elucidate the benefits of avoiding a diagnostic odyssey. Challenges Informed consent. If the study looks at efficacy of early identification and intervention, linking follow-up support systems and intervention programs could be a challenge. Cost.

Content based on synthesis of available literature and key informant interview responses.

information provided by experts and stakeholders. A literature review was done by using PubMed and Google Scholar searches. Search terms included: fragile X syndrome, *FMR1*, newborn screening, screening, and genetic testing. The searches were limited to research focused on humans, conducted in the United States, and published in English between 2008 and 2013. Selected manuscripts published on the topic through 2015 are also referenced in the article. The same search terms were used in Google, Bing, and Yahoo search engines to locate the "gray literature," such as organization and agency Web sites and unpublished reports. Issues, barriers, challenges, and approaches to addressing the challenges were identified in the literature. Key informant interviews were conducted with experts and stakeholders, including a patient advocate, a pediatrician, a state laboratory expert, an early intervention specialist, a genetic counselor, a medical geneticist, someone who develops screening tests, clinicians serving individuals with FXS, and an FXS researcher. A limited number of interviewees were selected based on expertise in either NBS or FXS or both. A semistructured interview guide was used to focus the interview on potential issues, common barriers, unidentified or under-discussed barriers, and potential approaches to addressing the barriers identified. Because these interviews were not considered human subjects research they were exempt from institutional review board approval. Information gathered through these interviews was used to supplement what was identified in the literature. Information from both the literature review and supplemental interviews was reviewed by 3 researchers, who discussed and came to consensus on thematic areas and categorization of issues.

RESULTS

Drawing on the published literature, the gray literature, and stakeholder interviews, a variety of issues were identified and categorized into 5 thematic areas: public health burden, treatment, timing, screening/testing methodologies, and translating results. A summary of each of these themes is provided in the subsequent sections along with potential approaches to address each. Strengths and challenges of each approach are presented in table format.

1. Public health impact. The public health burden of any condition is an important consideration for non–life-threatening conditions, such as FXS. Understanding public burden of FXS requires a robust estimate of prevalence, a description of natural history, and a description of current interventions being used, preferably with outcomes data. Large population-based studies, such as those conducted within the NBS system, can provide more accurate prevalence estimates. To date, estimates of prevalence of full mutation vary, ranging from ~1:2000 to 1:9000.[18–23] Estimates of prevalence of premutation are more reliable due to larger sampling and population-based studies.[9,24] However, even with premutation studies, numbers have not been high enough to determine if the prevalence of any *FMR1* mutation varies by ethnic group, or varies among geographic regions either nationally or worldwide. Studies using anonymized dried blood spots or a statewide NBS pilot have been suggested as potential approaches to addressing the unknown public health burden. Strength and challenges of each approach are outlined in Table 1.

2. Treatments for FXS. To meet criteria for NBS, an effective treatment that needs be delivered

TABLE 2 Treatment

Potential Approaches	Strengths and Challenges
Conduct a well-designed study of the efficacy of EI for infants/children with FXS.	Strengths Could provide evidence for determining the impact of EI on developmental trajectories or behavior. Challenges There is great diversity in the nature and quality of EI programs around the country, and the often low intensity (eg, 1-h/wk home visiting) may not be sufficient to show developmental effects. Identifying an effective and accurate way to measure the impact of EI. Without NBS, it would be challenging to recruit a large enough study sample to determine if there are statistically significant differences between groups.
Conduct a study to assess the benefit of early, presymptomatic detection on outcomes in a cohort of children differing in age of diagnosis and treatment	Strengths Study the impact of early detection in the absence of NBS. Challenges This type of study would require identification through older siblings, which could limit and potentially bias the sample size.
Conduct a study of the efficacy of EI for children with symptoms that overlap with FXS (eg, ASD, sensory sensitivities, anxiety disorders, ADHD)	Strengths Could provide evidence of importance of early identification for improving outcomes of specific overlapping symptoms. Would be easier to get a sufficient sample of children than a study of FXS only. Challenges Variability in the FXS phenotype could lead to selection bias toward those exhibiting specific symptoms. If the study does not focus specifically on children with FXS, it could dilute the evidence base. The study still would not involve a birth cohort, because it is not possible to conduct NBS for the other conditions listed.
Conduct efficacy trials of new fragile X–specific medications	Strengths Can determine if a medication is proven to be effective in improving outcomes. Identifying effective medication/treatment will impact the clinical utility of an FXS diagnosis, which is a good fit for the current NBS model. Challenges Time; it could be years or possibly decades before medications are available for infants or toddlers. Does not take into consideration other types of interventions (OT, PT, behavioral therapy), either administered on their own or in conjunction with medication.

Content based on synthesis of available literature and key informant interview responses. ADHD, attention-deficit hyperactivity disorder; ASD, autism spectrum disorder; EI, early intervention; OT, occupational therapy; PT physical therapy.

early in life to prevent mortality or significant morbidity must exist. To date, there has not been a successful clinical trial for a drug specific to treating FXS, nor a published study demonstrating that medical treatments used to treat FXS symptoms or other early intervention services (eg, behavioral therapy) are more effective if administered early in infancy compared with being administered on clinical presentation. Clinicians and researchers have hypothesized that to make a difference in brain development and brain function, treatment needs to be administered early, before damage occurs. However, evidence that demonstrates the impact of earlier age at initiation of early intervention on developmental trajectories or behavior is lacking. There are a few noted challenges related to conducting a study to determine the impact of intervention in infancy versus standard early intervention services that commence on identification of a developmental delay. Potential approaches presented in the literature and offered by experts to address the issues identified are presented in Table 2.

3. Timing of screening and relaying results. Two primary issues related to the timing of screening and relaying results emerged from the literature and expert interviews. First, it was noted that some parents feel that if the condition is not life-threatening, they would prefer to have some bonding time with their child before the child is identified with a genetic disorder; the second issue noted was that DNA-based screening tests could identify premutation carriers. As noted previously, premutation carriers have a higher risk of later-onset health conditions. However, the developmental, social, and health risks for children with a premutation have not been well described. Although identification of premutation carriers provides important information to parents regarding their reproductive risk, the unknown prognosis for a child with a premutation could lead to unnecessary anxiety among parents and caregivers. Table 3 offers several potential approaches to addressing issues related to the timing and relaying of results that were suggested.
4. Screening/testing methodology. Another requirement for NBS is that there be a reliable,

TABLE 3 Timing and Relaying of Results

Potential Approaches	Strengths and Challenges
Screen for FXS at a later time in development (eg, 6 wk or 6 mo of age).	Strengths Would allocate time and resources to the most concerning conditions first, while still allowing for large-scale screening at a later date. Parents would have more bonding time with their child before finding out results. Would result in earlier identification than is currently occurring. Challenges The public health and clinical infrastructure for this type of screening would need to be developed. More families may be lost to follow-up if the time lapse between testing and receiving results is too long. If evidence were to indicate children can benefit from earlier EI, this approach would delay the implementation of beneficial services.
Through NBS, provide the *FMR1* mutation status to parents of infants with premutation or full mutation.	Strengths Would allow for earliest identification of individuals with FXS and identify individuals who may be at risk for a FXD. Provides additional information regarding familial risk. Challenges Parents might worry about their child's future health and will have to decide when and how to disclose carrier status to their children. Burden on the public health and medical systems due to the higher prevalence of carriers of the premutation (compared with the full mutation). Burden on the public health and medical systems to relay complex genetic information to a lay population.
Through NBS, provide the *FMR1* mutation status only to parents of infants who screen positive for a full mutation.	Strengths Would allow for the earliest identification of individuals with FXS without increasing the possibility of family anxiety regarding identifying carriers of the premutation. Could potentially be more in line with current state NBS programs. The burden of follow-up would be greatly reduced. Challenges Establishing a screening cut-off for a positive screen; >200 CGG repeats is the current cutoff to diagnose FXS, but findings have been reported that children in the high CGG repeat premutation range can have developmental and behavioral challenges. Families would not have information about reproductive risk. Families in which the mother is a premutation carrier could receive false assurance that they are not at risk for having a child with FXS. Ethical concerns regarding not reporting potentially medically useful information from parents.
Create a screening model in which parents could choose whether they would like to know if they are a carrier of the premutation.	Strengths Could reduce some ethical concerns. Respects parental autonomy and allows families to make decisions that are consistent with their values and preferences. Challenges The consent and decision-making process could be challenging to implement in terms of timing, cost, and responsibility. Some parents will opt not to have their child screened, and therefore some children with FXS could be missed.
Develop protocol for follow-up/ monitoring of developmental and physical health of infants (and parents) identified as carriers of the premutation.	Strengths Tracking child development could reduce parental anxiety. Children could be identified at the first signs of delay. Provides families with information regarding reproductive risk and risk for the potential later-onset health concerns. Challenges Would require building the infrastructure to conduct monitoring.

Content based on synthesis of available literature and key informant interview responses.

inexpensive method for large-scale screening. Currently, screening for FXS cannot be done by using testing platforms already being used by state NBS laboratories. There are no FDA-approved screening tests, although several methodologies have been proposed.[25–28] Factors to consider regarding screening methods are the equipment requirements, laboratory personnel needed, sensitivity, specificity and cost of the test, and cost of interpreting and following up on results. Depending on the type of screening method used, the screen may or may not identify girls with full mutation. Currently, there is no way to determine how impacted a girl with FXS would be based on molecular information. Girls can have an IQ within the normal range (>70), but some girls will experience mild to moderate cognitive impairment. It would be difficult to distinguish from an early age which girls would quality for, or benefit from, early intervention services. Table 4 summarizes potential approaches to the screening methodology issues identified.

5. Adequate capacity for follow-up. Resources needed

TABLE 4 Screening Methodology

Potential Approaches	Strengths and Challenges
Only screen boys at birth and determine a later point in early childhood for screening of girls.	Strengths Could allow for the earliest identification of those at the highest risk for developmental delay. Could reduce possible anxiety of parents of girls who may or may not be require early intervention. Challenges Because at least one-third of girls with FXS have intellectual disability and many more have learning disabilities, not screening girls would result in a large number of girls not identified that could benefit from EI before a diagnosis of developmental delay.
Wait for identification of biomarkers to determine likelihood of relative impact on girls.	Strengths Once identified, biomarkers could be assessed during diagnostic testing to inform the need for EI services. Challenges Could be years or decades before clear biomarkers are identified and validated; in the meantime, many girls in need of EI would not receive it as early as their boy counterparts.
Wait for the development of an improved and more cost-effective laboratory test.	Strengths Advances in technology suggest this is likely to occur. Once there is an FDA-approved, cost-effective test, the technical aspects of screening will be similar to other conditions for which states conduct NBS. Challenges Waiting until a laboratory test is "ready" prolongs readiness of the rest of the public health screening system.
Include FXS in a platform approach to testing that would include a number of other conditions.	Strengths The cost of screening per condition would likely be lower. The collective benefit of screening for a group of conditions could be greater. Challenges Deciding which conditions make up the platform would be a challenge. Current technology may not make a platform approach realistic or cost-effective.
Conduct a demonstration project of high-throughput FXS NBS in a state laboratory by using a technology that is potentially ready for adoption.	Strengths The demonstration could provide clear guidance as to the feasibility of the screening test in a state laboratory environment under conditions requiring high throughput. The demonstration could provide a cost estimate of large-scale screening. Challenges Cost. Confidence in the proposed technology would need to be high.

Content based on synthesis of available literature and key informant interview responses. EI, early intervention; FDA, US Food and Drug Administration.

to adequately translate results and provide follow-up services are significant. If the screening method identifies FXS and premutation carriers, it will be challenging to relay potential risks associated with premutation, given the broad spectrum of phenotypic presentation and current emphasis on adult-onset conditions. Screening could lead to cascade testing of extended family members, potentially leading to identification of a large number of carriers. Accommodating a large number of carriers could be a capacity issue for health care systems (access to medical genetics, genetic testing, and genetic counseling). Most state NBS programs currently do not have these types of resources. Given that FXS is rare, pediatricians and other professionals (eg, allied health professionals, early intervention service providers, and teachers) may not be familiar with the condition or the phenotype, which could result in variability of the information conveyed and the type of treatments provided. Education and outreach to these audiences would be a key component in any type of large-scale screening program for FXS. See Table 5 for possible solutions to resource-related issues.

DISCUSSION

The evidence is a key factor when the Advisory Committee on Heritable Disorders in Newborns and Children is considering recommending a condition for the Recommended Uniform Screening Panel or when a state is considering adding a condition to their state NBS panel. Because NBS is a public health program run by individual states, it is ultimately up to each state to determine for which conditions the state will screen. The scientific evidence must ensure that there is a sensitive and specific testing methodology available that can be administered in a large-scale screening program. Concurrently, states need to know if there is a treatment or intervention available and if evidence demonstrates that intervening early, before the onset of symptoms, results in improved outcomes.

If screening all newborns for FXS is considered in the future, the decision-making bodies will be looking for information and evidence to inform the decision-making process. The issues identified and presented in the 5 thematic areas

TABLE 5 Capacity

Potential Approaches	Strengths and Challenges
Increase training opportunities for professionals through targeted education, publications in journals, and awareness of online resources.	Strengths Universal training opportunities would provide at least some standard training to increase knowledge. Targeting multiple avenues of training is likely to capture the widest audience. This could allow for increases in the number of "frontline" professionals equipped to provide necessary support and guidance for families. Challenges Developing curriculum, resources, and training protocols that could be used across training programs. For professionals who see few, if any, individuals with FXS, it is unlikely they will seek out or receive ongoing training updates regarding advances in the field.
Expand current genetic counseling training programs across the country.	Strengths Increasing the number of genetic counselors could potentially expand available genetic counseling resources for individuals with an FXD. Challenges Infrastructure/cost. It will likely be years before the effect is noticeable.
Increase education for the general public about genetics (beginning in elementary school).	Strengths Early and ongoing awareness of genetics for the public could reduce the amount of education needed when an individual receives a diagnosis. Increased public awareness of genetics could lead to increased interest in professions related to genetics. Challenges Difficult to implement and would require national dedication to increased genetics focus in education. Would not necessarily provide greater preparation for a family whose child is diagnosed with a genetic condition, such as FXS.

Content based on literature review and key informant interview responses.

discussed in this article illustrate the complexity and breadth of potential research or program development that could generate this type of information. For example, this research or development could entail breakthrough discoveries, large-scale pilot studies, or new information on the impact of early intervention on health outcomes.

Conducting research on rare conditions in general can be challenging because it is frequently difficult to get a sufficient sample size to study prevalence or assess differences in treated versus nontreated patients.[29] A large prevalence study, as described in the Results section, could yield more reliable estimates of prevalence, allowing a better understanding of the public health burden, and could demonstrate a laboratory's capability to implement high-throughput screening for FXS. However, if conducted as an anonymous study, researchers would not be able to investigate whether intervening before clinical presentation has a different impact on health outcomes than treatment or intervention strategies administered on symptomatic presentation and clinical diagnosis.

Not unique to FXS, a major issue facing both clinical and public health communities is how to develop the evidence base for rare conditions before large-scale screening. Implementation of NBS will be difficult without sufficient evidence on analytic validity of a screening methodology and clinical validity and utility of potential screening results. To gather a sufficient evidence base, a large sample size is necessary. The clinical utility of screening considers how results impact the trajectory of care. To determine improved outcomes and inform the trajectory of care, studies of infants identified at birth or early infancy are necessary.

CONCLUSIONS

The future possibility of NBS for FXS could be influenced by a series of findings over time that, in aggregate, provide the evidence needed to be considered for the Recommended Uniform Screening Panel. A prominent singular finding could also prompt movement toward NBS for FXS, such as a breakthrough clinical trial demonstrating an effective targeted treatment when implemented early in infancy. This description of the landscape has highlighted several issues and areas in which future research could provide needed information. One area identified with limited evidence is early development in FXS and *FMR1* premutation carriers and how early identification and intervention can impact individuals with a mutation on the *FMR1* gene. Additionally, how would the impact of NBS be reliably measured in populations of individuals with FXS or fragile X-associated disorders? This assessment sheds light on challenges and opportunities inherent in implementing large-scale screening for a rare condition like FXS.

The issues and barriers identified, along with the potential approaches offered for addressing these issues, pose a promising research agenda

for the fragile X community. Some of the opportunities and challenges presented are not unique to FXS in that other rare disorders face similar difficulties gathering the evidence needed to achieve a standard of acceptance for use in decision-making. As discussed at the 2014 Centers for Disease Control and Prevention FXS stakeholder meeting, the ability to address these issues cannot fall to 1 agency or organization.[30] Addressing barriers and developing evidence will take a community of clinicians, researchers, public health professionals, educational specialists, behavioral specialists, advocates for the FXS population, and individuals with FXS and their families all coming together to move future research activities forward.

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ABBREVIATIONS

FXD: fragile X–associated disorder
FXS: fragile X syndrome
NBS: newborn screening

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