HHS Public Access

Author manuscript

Pediatrics. Author manuscript; available in PMC 2017 September 11.

Published in final edited form as:

Pediatrics. 2017 June ; 139(Suppl 3): S147–S152. doi:10.1542/peds.2016-1159B.

The Future of Fragile X Syndrome: CDC Stakeholder Meeting Summary

Catharine Riley, PhD, MPH[a], **Marsha Mailick, PhD**[b], **Elizabeth Berry-Kravis, MD, PhD**[c,d,e], and **Julie Bolen, PhD, MPH**[a]

[a]National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia

[b]Waisman Center, University of Wisconsin, Madison, Wisconsin

[c]Department of Pediatrics, Rush University Medical Center, Chicago, Illinois

[d]Department of Neurological Sciences, Rush University Medical Center, Chicago, Illinois

[e]Department of Biochemistry, Rush University Medical Center, Chicago, Illinois

Fragile X syndrome (FXS) is the most common known inherited cause of intellectual disability (ID). Males and females with FXS exhibit a wide range of intellectual ability and may experience various degrees of emotional, behavioral, sensory, learning, and social difficulties. In 1991, the gene responsible for FXS was identified on the X chromosome at q27.3 and named fragile x mental retardation 1 (*FMR1*) gene.[1] FXS and fragile X–associated disorders (FXD) are caused by a trinucleotide repeat (CGG) expansion mutation in the promoter region (exon 1) of *FMR1*. Affected individuals with the full FXS mutation have >200 repeats. When the full mutation is present, *FMR1* methylation occurs during gestation, which causes silencing of gene transcription.[2] This in turn leads to a reduction or absence of fragile X mental retardation protein (FMRP), which is needed for brain development and function. Most males with FXS have ID. A small number of males have less impaired function due to methylation patterns or mosaicism. In females, FMRP levels depend on the X activation ratio, or the percent of cells expressing the normal allele on the active X chromosome,[3] resulting in a range of normal intellectual ability to moderate ID.

Over the past 2 decades, scientists have made significant advancements in identifying and describing genetic, molecular, and cellular underpinnings of FXS, allowing for a more precise diagnosis of this condition. The present challenge is to move from accurate diagnosis

Address correspondence to Julie Bolen, PhD, MPH, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, 4770 Buford Hwy (E-88), Atlanta, GA 30341. jcr2@cdc.gov.

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

POTENTIAL CONFLICT OF INTEREST: Dr Mailick is Chair of the Scientific Advisory Board of the Developmental Disabilities Program of the John Merck Fund; Dr Berry-Kravis is a member of the Scientific and Clinical Advisory Board of the National Fragile X Foundation and is the recipient of 2 current grants “Acamprosate in Fragile X Syndrome” and “GABA-mediated Mechanisms of Altered Sensory Perception in Fragile X Syndrome” from the John Merck Fund; and Drs Riley and Bolen have indicated they have no potential conflicts of interest to disclose.

Dr Riley conceptualized and organized the stakeholder meeting, led the planning committee, and drafted and revised the manuscript; Drs Mailick and Berry-Kravis served on the planning committee and revised the manuscript; Dr Bolen contributed to the stakeholder meeting and revised the manuscript; and all authors approved final submission.

to public health action for FXS, requiring better understanding of the natural history of FXS, a clear description of how this complex condition affects individuals and their families, and identification of interventions and treatments that can lead to better outcomes. The more we know about this population across the life span, both from a clinical and parent or caregiver perspective, the better we can design treatments, services, and care. The Centers for Disease Control and Prevention (CDC) hosted a meeting in May 2014 to engage FXS stakeholders in the process of framing a public health research agenda geared toward the CDC's long-term goal of improving care and quality of life for individuals living with FXS and their families (Fig 1).

To identify needs and plan for the stakeholder meeting, the CDC supported a structured literature review for FXS and FXD, which identified what is known about conditions caused by an *FMR1* mutation (see Raspa et al [4] and Wheeler [5] et al in this supplement). Working from the results of this literature review and an environmental data scan, the CDC, with input from a planning committee, identified 6 areas where public health research and programs could potentially contribute knowledge to benefit FXS patients and their relatives: (1) epidemiology, (2) early identification and screening, (3) impact on individuals and families, (4) FXS across the life span, (5) cooccurring conditions, and (6) interventions and outcome measures. To help delineate goals, the CDC gathered a broad range of 60 experts and stakeholders to discuss the future of public health research for FXS. Attendees included researchers, clinicians, public health professionals, behavior and education specialists, patient advocates, and affected individuals and their families. Over 2 days, this group discussed each of the 6 topic areas, while describing how to address limited areas of knowledge. In particular, participants were asked to identify potential challenges in developing and implementing research and strategies needed for overcoming these limitations. To start the discussion for each topic, a summary of the literature was presented, followed by a large group discussion on the topic and then small breakout workgroups for more in-depth discussion. A summary was then presented back to the large group to provide an opportunity for all attendees to share additional discussion points.

This process (see Fig 1), from describing what is known to incorporating ideas from stakeholders about overcoming challenges, helped the CDC plan and develop public health research and programmatic activities for FXS, providing information for broader FXS clinical and public health communities regarding FXS population needs.

DISCUSSION

Epidemiology

The structured literature review presented noted the following limitations in our current knowledge base, thereby highlighting potential needs: (1) prevalence estimates for the full mutation lack precision; (2) there is no large-scale, population-based study on FXS; (3) there is a lack of complete consensus on prevalence of the premutation; (4) much is unknown about the sociodemographic characteristics of FXS and FXD populations; and (5) there are inadequate data regarding FXS and FXD variability among racial or ethnic groups.

Estimates of the prevalence of the full mutation vary, ranging from 1:2000 to 1:9000.[6-11] Although the exact prevalence of FXS is unknown, the research community currently uses estimates between 1 in 4000 to 5000 for boys and about 1 in 6000 to 8000 for girls. These estimates have been based on relatively small samples and could be biased if they exclude higher functioning boys and girls with FXS. Additionally, little is known about whether FXS is more or less prevalent in population subgroups. Prevalence of the premutation has been estimated based on population-based samples, with converging evidence that between 1 in 150 to 200 females and 1 in 300 to 450 males carry the premutation.[12-14]

Early Identification and Screening

A summary of the literature noted that the average age of a child first diagnosed with FXS is 36 months [15] and suggested that a delay in diagnosis could potentially reduce access to interventions and other support mechanisms, [16] leading to emotional stress, increased financial burden for families,[17] and delay in families receiving information about future risk. After discussing the literature more, areas for future research were identified. The first area identified was the need for the development of new models and strategies to increase frequency of genetic testing for individuals with global developmental or intellectual delay, which could result in the identification of individuals with FXS who currently are not accurately diagnosed. Another area with limited research is the development and validation of low-cost, effective approaches for population-based FXS screening. The benefits of early (ie, presymptomatic) detection and early intervention on health outcomes, compared with identification after clinical presentation, has not yet been studied. In addition, we have only a limited understanding of the benefits and risks of reporting carrier/premutation status versus only reporting full mutation status in a large-scale screening program. Attendees also noted the importance of identifying public health and medical system infrastructure needs in relation to implementing large-scale screening for FXS.

Part of enhanced infrastructure is the need to improve outreach to health care professionals, including psychologists, therapists, and educators, to promote early identification of FXS, as well as the type of data and information needed to determine if FXS is ready for newborn screening. More detail on potential research that could provide the evidence needed to assess the feasibility and utility of newborn screening for FXS can be found in a companion article by Riley and Wheeler in this supplement.[18]

Impact on Individuals and Families

A literature summary included studies on the impact of FXS on mothers, caregivers, and family units as a whole. With regard to mothers, the mental health effects of raising a child with FXS that have been reported are diverse, including increased levels of stress, depression, anger, and anxiety.

Stress, in particular, appears related to child behavior and can vary among mothers, depending on their *FMR1* mutation status.[19-21] A few studies have indicated that most mothers that participated in the studies reported average or above average levels of hope, optimism, quality of life, well-being, and adaptation, noting that social support could play a role in this positive adaption.[19,22,23] In relation to caregivers, a recent survey and subsequent

comparison of these survey data with children with autism spectrum disorder (ASD), an ID, and both ASD and ID described high caregiver burden with regard to financial impact as well as impact on employment due to increased caregiving demands.[24,25] Several studies described the possible effects of raising a child with FXS on marriages, family units, maternal interaction, and mother's religiosity.[26-32]

Because most studies have focused on mothers, little is known about how FXS affects fathers, siblings, and other caregivers. The issue of stress on caregivers and family members was discussed as an area in need of additional research to provide insight into magnitude of the issue and options for addressing stress on families. Attendees noted that family-focused interventions are not readily available. Little evidence exists regarding factors that influence family and maternal outcomes. Future research on outcomes in premutation carrier mothers could address the need to separate the impact of caring for a child with FXS from the direct effects of the premutation itself. With improved understanding of these issues, strategies could be designed to lessen the impact of FXS. Attendees also discussed the need for more outreach to families, specifically focusing on resources caregivers need to navigate complex health, social, educational, and occupational systems.

Lifespan/Transition/Aging Population

A particular area in need of additional inquiry is the impact of FXS on individuals and families across the life span and potential issues related to aging with FXS. As children with FXS grow up, they experience areas of improved functioning, but also new challenges. Some studies report an age-related decline in scores on standardized measures of cognition in individuals with FXS. Limited information is available on this phenomenon in adults with FXS, but the decline in scores does not appear to reflect a loss of skills, rather an increasing divergence in performance relative to the normative group.[33,34] FMRP levels or a codiagnosis of ASD are correlated with the magnitude of decline.[35-40] A contrasting pattern of age-related changes has been described in the areas of adaptive behavior and behavior problems; a recent longitudinal study found that adaptive behavior improves and behavior problems decline in severity during adolescence and into adulthood.[41]

Once individuals with FXS reach adulthood, they still may require considerable care, based on limited research. Little has been reported on the behavioral functioning of adults with FXS. In 1 study that examined the independence level of a large sample of adults with FXS, findings indicated that a majority of adult males with FXS (70%) lived with their parents, and 50% of adult females were living at home at the time of the survey.[42] Almost half (48%) of females were working full time compared with only 20% of males.[42] In a cross-sectional study of adult men with FXS, findings suggested that there is a pattern of age-related improvement in many ASD symptoms across adulthood.[43] However, the aging process and the impact of more frequently occurring coconditions on individuals as they age have not been adequately described. Only 1 paper has addressed this subject in a small cohort of individuals with FXS >40 years of age.[44]

Meeting attendees emphasized the need for more research and data collection that include longitudinal studies to better understand the natural history of FXS and how it impacts individuals across the life span. In particular, studies of older adolescents and adults are

needed. Literature regarding the transition out of school, employment opportunities, daily living and functional skills, behavior problems, health, and social needs of adolescents and adults is limited. Issues related to guardianship and self-advocacy have also not been adequately explored. Attendees emphasized the importance of researching the health and social needs of adolescents and adults with FXS.

Cooccurring Conditions

A range of behaviors that individuals with FXS exhibit has been described in the literature, including anxiety, aggression, self-injury, tactile defensiveness, hand flapping, poor eye contact, hyperactivity, distractibility, tantrums, perseveration, hyperarousal to sensory stimuli, and impulsivity.[45-48] Information about attention problems, anxiety, and ASD in the FXS population is more robust, compared with other behaviors and conditions that have been reported to occur in the FXS population, such as self-injury, aggression toward others, and sleep problems. Additionally, limited information is available about effective interventions and treatments for these behaviors and conditions that have been observed in the FXS population.

Meeting attendees discussed the importance of identifying and describing conditions that occur most frequently in conjunction with FXS and the need for additional research on why these behaviors and conditions occur and how they can be addressed to improve health outcomes. Additionally, there is an overall need to better characterize the health status of individuals with FXS, including the presence of health disparities, health literacy, and health care decision-making.

Interventions and Outcome Measures

Developing interventions and understanding how to best measure their impact is an area of ongoing need in the FXS population. Reliable outcome measures for clinical trials of new-generation medications have not been identified or validated, so determining clinical end points that could be used to assess change is important. One difficulty in evaluating FXS treatment effectiveness is the lack of a feasible biomarker. Many of the outcome measures in FXS are related to behavioral or cognitive changes. There are few validated outcome measures that describe rates of learning that could be used to determine medication efficacy for improving cognition. Current research suggests several promising outcome measures. Efforts to validate them in the FXS population are currently being funded by the CDC.

Attendees discussed the need to identify new ways of measuring developmental changes in individuals and populations living with FXS to address short- and long-term changes achieved through interventions and treatments. In addition to pharmacologic treatments, there is a need for large randomized controlled trials on specific behavioral or educational interventions. No large randomized controlled trial for this type of intervention has been conducted to date. Attendees also discussed the need to identify end points and quality measures that can assess learning rate, rather than cognitive achievements that may not be sensitive to change. Finally, attendees agreed on the need for biomarkers that could be used to document target engagement or to determine the level of response to specific interventions for clinical trials and other types of research.

FUTURE DIRECTIONS

Even with major advances in basic and clinical research, there is still much to learn about the impact of public health efforts on FXS and how they can improve health outcomes and quality of life for those living with it. The efforts described have helped the CDC develop a public health research agenda for FXS. Part of this research agenda is being addressed through awards that began in September 2015 under a request for applications titled “Using Longitudinal Data to Characterize the Natural History of Fragile X Syndrome to Improve Services and Outcomes.” The purpose of these awards are to conduct research on the natural history of FXS across the life span; explore effective strategies to increase participation in longitudinal studies among minority, underserved, and adult populations living with FXS; and test approaches to measure cognitive and behavioral function in the FXS population. The CDC is also collaborating with the American Academy of Pediatrics to work on improving early identification of FXS. Addressing limited areas of knowledge will be a collective effort of the research, clinical, and patient communities. Federal agencies, academic researchers, health care professionals, private corporations, and FXS patient organizations all play an important role in addressing the identified needs of individuals and families impacted by this complex condition.

Acknowledgments

We thank the CDC Stakeholder Meeting cosponsors, the John Merck Fund and National Fragile X Foundation; Planning Committee members: Don Bailey, Elizabeth Berry-Kravis, W. Ted Brown, Katie Clapp, Jeffrey Cohen, Marsha Mailick, Catharine Riley, Nancy Stockford, Mark Swanson, and Tiina Urv; Facilitator: Rebecca Reeves; and RTI International: Don Bailey, Anne Wheeler, and Melissa Raspa (background materials) and Marjorie Margolis (note taker).

The findings and conclusions in this publication are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

FUNDING: No external funding.

References

1. Verkerk AJ, Pieretti M, Sutcliffe JS, et al. Identification of a gene (FMR-1) containing a CGG repeat coincident with a breakpoint cluster region exhibiting length variation in fragile X syndrome. Cell. 1991; 65(5):905–914. [PubMed: 1710175]
2. Pieretti M, Zhang FP, Fu Y-H, et al. Absence of expression of the FMR-1 gene in fragile X syndrome. Cell. 1991; 66(4):817–822. [PubMed: 1878973]
3. Loesch DZ, Huggins RM, Hagerman RJ. Phenotypic variation and FMRP levels in fragile X. Ment Retard Dev Disabil Res Rev. 2004; 10(1):31–41. [PubMed: 14994286]
4. Raspa M, Wheeler A, Riley C. Public health literature review of fragile X syndrome. Pediatrics. 2017; 139(S3)
5. Wheeler A, Raspa M, Hagerman R, Mailick M, Riley C. Implications of the FMR1 premutation for children, adolescents, adults, and their families. Pediatrics. 2017; 139(S3)
6. Coffee B, Keith K, Albizua I, et al. Incidence of fragile X syndrome by newborn screening for methylated FMR1 DNA. Am J Hum Genet. 2009; 85(4):503–514. [PubMed: 19804849]
7. Hagerman RJ, Rivera SM, Hagerman PJ. The fragile X family of disorders: a model for autism and targeted treatments. Curr Pediatr Rev. 2008; 4(1):40–52.
8. Crawford DC, Acuña JM, Sherman SL. FMR1 and the fragile X syndrome: human genome epidemiology review. Genet Med. 2001; 3(5):359–371. [PubMed: 11545690]

9. Crawford DC, Meadows KL, Newman JL, et al. Prevalence of the fragile X syndrome in African-Americans. Am J Med Genet. 2002; 110(3):226–233. [PubMed: 12116230]
10. Jacobs PA, Bullman H, Macpherson J, et al. Population studies of the fragile X: a molecular approach. J Med Genet. 1993; 30(6):454–459. [PubMed: 8326487]
11. Pesso R, Berkenstadt M, Cuckle H, et al. Screening for fragile X syndrome in women of reproductive age. Prenat Diagn. 2000; 20(8):611–614. [PubMed: 10951469]
12. Tassone F, Iong KP, Tong TH, et al. *FMR1* CGG allele size and prevalence ascertained through newborn screening in the United States. Genome Med. 2012; 4(12):100. [PubMed: 23259642]
13. Maenner MJ, Baker MW, Broman KW, et al. FMR1 CGG expansions: prevalence and sex ratios. Am J Med Genet B Neuropsychiatr Genet. 2013; 162B(5):466–473. [PubMed: 23740716]
14. Seltzer MM, Baker MW, Hong J, Maenner M, Greenberg J, Mandel D. Prevalence of CGG expansions of the FMR1 gene in a US population-based sample. Am J Med Genet B Neuropsychiatr Genet. 2012; 159B(5):589–597. [PubMed: 22619118]
15. Bailey DB Jr, Raspa M, Bishop E, Holiday D. No change in the age of diagnosis for fragile x syndrome: fi ndings from a national parent survey. Pediatrics. 2009; 124(2):527–533. [PubMed: 19581269]
16. Bailey DB Jr, Skinner D, Warren SF. Newborn screening for developmental disabilities: reframing presumptive benefit. Am J Public Health. 2005; 95(11):1889–1893. [PubMed: 16195526]
17. Bailey DB Jr. Newborn screening for fragile X syndrome. Ment Retard Dev Disabil Res Rev. 2004; 10(1):3–10. [PubMed: 14994282]
18. Riley C, Wheeler A. Assessing the fragile X syndrome newborn screening landscape. Pediatrics. 2017; 139(S3)
19. Bailey DB Jr, Sideris J, Roberts J, Hatton D. Child and genetic variables associated with maternal adaptation to fragile X syndrome: a multidimensional analysis. Am J Med Genet A. 2008; 146A(6):720–729. [PubMed: 18266246]
20. Seltzer MM, Barker ET, Greenberg JS, Hong J, Coe C, Almeida D. Differential sensitivity to life stress in FMR1 premutation carrier mothers of children with fragile X syndrome. Health Psychol. 2012; 31(5):612–622. [PubMed: 22149120]
21. Wheeler A, Hatton D, Reichardt A, Bailey D. Correlates of maternal behaviours in mothers of children with fragile X syndrome. J Intellect Disabil Res. 2007; 51(Pt 6):447–462. [PubMed: 17493028]
22. Raspa M, Bailey DB Jr, Bann C, Bishop E. Modeling family adaptation to fragile X syndrome. Am J Intellect Dev Disabil. 2014; 119(1):33–48. [PubMed: 24450320]
23. Wheeler AC, Skinner DG, Bailey DB. Perceived quality of life in mothers of children with fragile X syndrome. Am J Ment Retard. 2008; 113(3):159–177. [PubMed: 18407719]
24. Bailey DB Jr, Raspa M, Bishop E, et al. Health and economic consequences of fragile X syndrome for caregivers. J Dev Behav Pediatr. 2012; 33(9):705–712. [PubMed: 23117595]
25. Ouyang L, Grosse SD, Riley C, et al. A comparison of family fi nancial and employment impacts of fragile X syndrome, autism spectrum disorders, and intellectual disability. Res Dev Disabil. 2014; 35(7):1518–1527. [PubMed: 24755230]
26. Baker JK, Seltzer MM, Greenberg JS. Behaviour problems, maternal internalising symptoms and family relations in families of adolescents and adults with fragile X syndrome. J Intellect Disabil Res. 2012; 56(10):984–995. [PubMed: 22676314]
27. Hall SS, Burns DD, Reiss AL. Modeling family dynamics in children with fragile x syndrome. J Abnorm Child Psychol. 2007; 35(1):29–42. [PubMed: 17165142]
28. Johnston C, Hessl D, Blasey C, et al. Factors associated with parenting stress in mothers of children with fragile X syndrome. J Dev Behav Pediatr. 2003; 24(4):267–275. [PubMed: 12915799]
29. Raspberry K, Skinner D. Enacting genetic responsibility: experiences of mothers who carry the fragile X gene. Sociol Health Illn. 2011; 33(3):420–433. [PubMed: 21054442]
30. Raspberry KA, Skinner D. Negotiating desires and options: how mothers who carry the fragile X gene experience reproductive decisions. Soc Sci Med. 2011; 72(6):992–998. [PubMed: 21333433]

31. Sterling A, Barnum L, Skinner D, Warren SF, Fleming K. Parenting young children with and without Fragile X syndrome. Am J Intellect Dev Disabil. 2012; 117(3):194–206. [PubMed: 22716262]
32. Sterling AM, Warren SF, Brady N, Fleming K. Influences on maternal responsivity in mothers of children with fragile X syndrome. Am J Intellect Dev Disabil. 2013; 118(4):310–326. [PubMed: 23937372]
33. Fisch GS, Holden JJ, Simensen R, et al. Is fragile X syndrome a pervasive developmental disability? Cognitive ability and adaptive behavior in males with the full mutation. Am J Med Genet. 1994; 51(4):346–352. [PubMed: 7942997]
34. Fisch GS, Carpenter N, Howard-Peebles PN, Holden JJ, Tarleton J, Simensen R. The course of cognitive-behavioral development in children with the FMR1 mutation, Williams-Beuren syndrome, and neurofibromatosis type 1: the effect of gender. Am J Med Genet A. 2010; 152A(6): 1498–1509. [PubMed: 20503326]
35. Borghgraef M, Swillen A, Van den Berghe H, Fryns JP. Fragile X boys: evolution of the mental age in childhood. Preliminary data on 10 prepubertal boys. Genet Couns. 1995; 6(2):97–101. [PubMed: 7546457]
36. Fisch GS, Simensen R, Tarleton J, et al. Longitudinal study of cognitive abilities and adaptive behavior levels in fragile X males: a prospective multicenter analysis. Am J Med Genet. 1996; 64(2):356–361. [PubMed: 8844080]
37. Fisch GS, Carpenter N, Holden JJ, et al. Longitudinal changes in cognitive and adaptive behavior in fragile X females: a prospective multicenter analysis. Am J Med Genet. 1999; 83(4):308–312. [PubMed: 10208167]
38. Fisch GS, Carpenter NJ, Holden JJ, et al. Longitudinal assessment of adaptive and maladaptive behaviors in fragile X males: growth, development, and profiles. Am J Med Genet. 1999; 83(4): 257–263. [PubMed: 10208158]
39. Kover ST, Pierpont EI, Kim JS, Brown WT, Abbeduto L. A neurodevelopmental perspective on the acquisition of nonverbal cognitive skills in adolescents with fragile X syndrome. Dev Neuropsychol. 2013; 38(7):445–460. [PubMed: 24138215]
40. Skinner M, Hooper S, Hatton DD, et al. Mapping nonverbal IQ in young boys with fragile X syndrome. Am J Med Genet A. 2005; 132A(1):25–32. [PubMed: 15551333]
41. Smith LE, Hong J, Greenberg JS, Mailick MR. Change in the behavioral phenotype of adolescents and adults with FXS: role of the family environment. J Autism Dev Disord. 2016; 46(5):1824–1833. [PubMed: 26861717]
42. Hartley SL, Seltzer MM, Raspa M, Olmstead M, Bishop E, Bailey DB. Exploring the adult life of men and women with fragile X syndrome: results from a national survey. Am J Intellect Dev Disabil. 2011; 116(1):16–35. [PubMed: 21291308]
43. Hartley SL, Wheeler AC, Mailick MR, et al. Autism symptoms across adulthood in men with fragile X syndrome: a cross-sectional analysis. J Autism Dev Disord. 2015; 45(11):3668–3679. [PubMed: 26123010]
44. Utari A, Adams E, Berry-Kravis E, et al. Aging in fragile X syndrome. J Neurodev Disord. 2010; 2(2):70–76. [PubMed: 20585378]
45. Bailey DB Jr, Raspa M, Olmsted M, Holiday DB. Co-occurring conditions associated with FMR1 gene variations: findings from a national parent survey. Am J Med Genet A. 2008; 146A(16): 2060–2069. [PubMed: 18570292]
46. Hagerman RJ, Berry-Kravis E, Kaufmann WE, et al. Advances in the treatment of fragile X syndrome. Pediatrics. 2009; 123(1):378–390. [PubMed: 19117905]
47. Hatton DD, Hooper SR, Bailey DB, Skinner ML, Sullivan KM, Wheeler A. Problem behavior in boys with fragile X syndrome. Am J Med Genet. 2002; 108(2):105–116. [PubMed: 11857559]
48. Symons FJ, Byiers BJ, Raspa M, Bishop E, Bailey DB. Self-injurious behavior and fragile X syndrome: findings from the national fragile X survey. Am J Intellect Dev Disabil. 2010; 115(6): 473–481. [PubMed: 20946000]

ABBREVIATIONS

ASD	autism spectrum disorder
CDC	Centers for Disease Control and Prevention
FMR1	fragile x mental retardation 1
FMRP	fragile X mental retardation protein
FXD	fragile X–associated disorder
FXS	fragile X syndrome
ID	intellectual disability

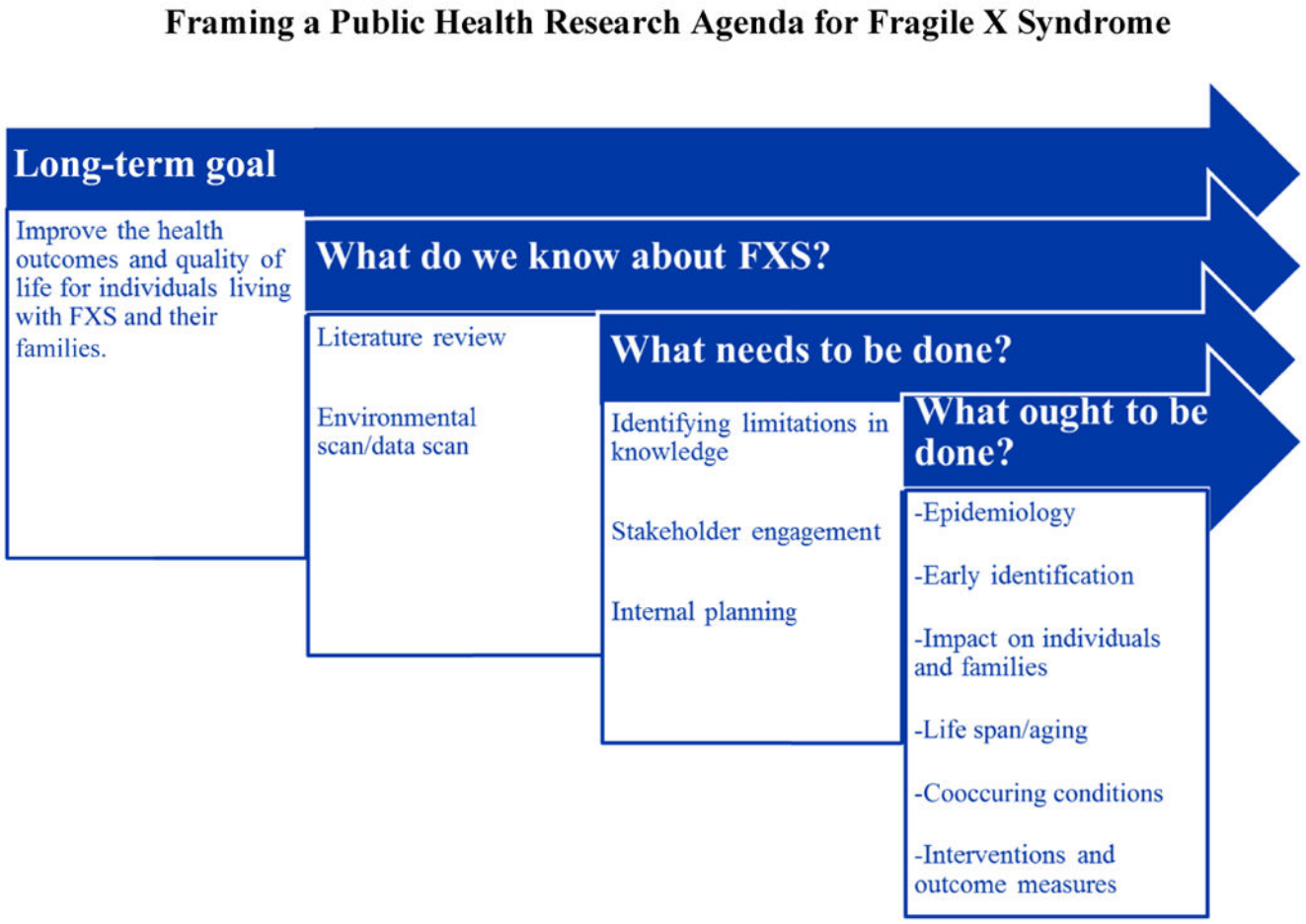

FIGURE 1.
Framing a public health research agenda for FXS.