Should we implement population screening for fragile X?

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Fragile X is the most common cause of inherited intellectual disability. Previous studies have demonstrated that caregivers of children with fragile X generally support the offer of preconception genetic screening. A study in this issue of *Genetics in Medicine*¹ demonstrates that such population screening is not associated with significant psychosocial harm and raises the question whether such screening should be offered. The classic Wilson and Jungner criteria provide a framework in which to consider the question. Fragile X is an important health problem, being the most common inherited cause of intellectual disability, and similar screening is provided for another genetic syndrome associated with intellectual disability. The utility of preconception or antenatal testing for fragile X is uncertain as there are no widely accepted and available prenatal treatments for this disorder. Nonetheless, therapeutic interventions for affected males are relatively widely available. Most premutation carriers are not clinically recognized prior to conception without DNA testing. However, the methodology for the interpretation of long-term effects of “gray zone” results and of premutation carrier status is still in its infancy. There are significant costs associated with such screening that do not translate to increases in quality- or disability-adjusted life-years (QALYs or DALYs). Consequently, resources should be prioritized to other conditions that do meet current screening criteria and for which screening has not yet been implemented.

In this issue of *Genetics in Medicine*, Metcalfe and colleagues¹ present an important study evaluating the potential harms and diagnostic yield of screening asymptomatic women for fragile X premutation status. They specifically measure the level of knowledge, indecision around choice, and decisional regret in a small minority of women who agreed to participate in the study. Fragile X is the most common cause of inherited intellectual disability. In addition, men and women with pre-expansions have a range of potential clinical phenotypes. Probably the most significant of these in women is premature ovarian failure, leading to reduced fertility. This reduced fertility has significant clinical implications at a population level for the risk of having affected children. In the work by Metcalfe and colleagues,¹ as with many such studies, there is significant difficulty in

understanding how generalizable the opinions solicited are, given the extremely low uptake rate for research.

Probably the most significant finding is that nonpregnant women who elect to be tested do not demonstrate increased anxiety or decisional regret if they find that they are at risk of an affected child. This allays often-cited fears that knowing about a risk of, or being at risk of, having a child with an “untreatable disease” is associated with a risk of psychological harm. This absence of perceived risk of harm is an important catalyst for questioning whether health systems should offer population screening for asymptomatic or presymptomatic individuals at risk of having children affected with fragile X. Conversely, the research by Metcalfe et al.¹ provides important information suggesting that discovering one’s “affected” status during pregnancy seems to be associated with an increase in anxiety and decisional regret compared with those tested outside of pregnancy or those testing negative when pregnant. These data, if confirmed in other studies or across testing for other disorders, are important because they may indicate that while (as the authors state) many programs use prenatal testing as the norm because it is “convenient,” this may actually be a harmful time to make a diagnosis for a woman who is at significant risk of having a child with a disorder for which there is no specific therapy targeted at the underlying cause. Significantly, authors of previous studies looking at families with children affected with fragile X have similarly expressed a strong preference in favor of preconception over antenatal screening.²

The World Health Organization³ notes “Although genetic services and screening programmes aim to improve the health of the population, there is growing concern that the increasing number of genetic tests becoming available at lower costs could compromise the viability of the health care system. Even though the tests themselves may be inexpensive and suitable for large-scale use, the infrastructure and human resources needed to provide appropriate education, counseling, interventions and follow-up are likely to be far more costly. When it comes to the allocation of scarce resources, economic considerations must be considered alongside “notions of justice, equity, personal freedom, political feasibility, and the constraints of current law.””

It is therefore essential that, as we consider such population screening programs, we include the whole costs of programs

along with an understanding of the personal and societal benefits. Economic analysis must go beyond the immediate costs of the genetic test and counseling, ideally including the downstream costs such as those of preimplantation genetic diagnosis (PGD) and amniocentesis of current pregnancy as well as the potential long-term costs associated with mental health services needed for the premutation carrier.

When considering population screening, the original Wilson and Jungner criteria⁴ provide a logical framework for such conversations. There is a much more limited data set for considering the implications of screening for fragile X than the more widely developed programs for antenatal screening for Down syndrome (DS). Therefore, the lessons learnt from DS screening are informative when considering population screening for fragile X.

THE CONDITION SOUGHT SHOULD BE AN IMPORTANT HEALTH PROBLEM

This is potentially the most subjective of the criteria, as it is difficult to define the medical importance of knowing the risks of having an affected child prenatally or preconception. Indeed, most publications on this issue have concentrated on reductions in societal financial costs of caring for a child with DS,⁵ rather than social or personal utility resulting from reducing the number of affected individuals born. Nonetheless, most Western societies have chosen to screen for DS. DS screening is in many ways qualitatively different from fragile X screening as it is performed on biomarkers, DNA, or cells from the fetus rather than determining that the mother is at risk, in this or future pregnancies, of having an affected child. Nonetheless the high uptake of and broad support for funding DS screening does appear to demonstrate that society values the provision of diagnostic testing for disorders that predispose children to intellectual disability, providing the option to prevent the child from being born.

THERE SHOULD BE AN ACCEPTED TREATMENT FOR PATIENTS WITH RECOGNIZED DISEASE

As touched on above, there is significant debate within wider society about what constitutes “treatment.” The most strict definitions would define treatment as interventions targeted at the underlying cause of a disorder. In the preconception/prenatal screening model, this is possible in cases such as severe urea cycle defects, where prenatal identification provides improved management in the neonatal period. In contrast to other disorders for which carrier testing is performed, such as cystic fibrosis or spina bifida, there are no perinatal therapies, such as elective C-Section or dietary changes, that can improve the long-term functioning of the child with fragile X. There is a suggestion from the literature on DS that earlier identification of children at risk for intellectual disability may, at least in the short term, improve cognitive outcomes.⁶ However, such DS data are confusing, and large randomized controlled trials (RCT) that would withhold early intervention would be considered unethical. There have not been large RCTs for therapy in fragile X.

However, there are limited case reports of apparent benefit from early pharmacologic and behavioral therapy, suggesting there may be in the future the ability to generate evidence-based interventions that benefit boys with this disorder.⁷

Instead, the common element of “therapeutic strategies” is avoiding the birth of children affected with full expansion fragile X. Clearly, in taking this approach there is a crucial difference when considering identification of individuals with the disorder during pregnancy, as distinct from identifying those who would be at risk of having an affected pregnancy. For those who are identified during a current pregnancy, there is the option to perform a diagnostic amniocentesis and if the result is positive, to terminate the pregnancy. While this option is widely available in most Western countries, it remains significantly contentious and to call it a treatment would perhaps be moving beyond the common definition of this term. For carriers identified at the preconception stage, there are several options available. The least technologically dependent options would include the choice not to have biological children, but instead to advance family plans through methods such as adoption. Such strategies are almost universally available and acceptable to communities. However, such approaches may be unacceptable to prospective parents, especially considering that they may not have affected children or even carriers. In the medical space there are options to use donor gametes, or to perform *in vitro* fertilization with subsequent PGD and implantation of embryos that are either pre-expansion or ideally within the “normal range.” However, PGD is technically difficult for fragile X,⁸ with a much lower live birth rate per cycle than PGD for other indications. In addition, the considerable cost and patchy insurance coverage make this option significantly less acceptable or available to those at risk of affected pregnancies.

FACILITIES FOR DIAGNOSIS AND TREATMENT SHOULD BE AVAILABLE

One of the significant challenges with fragile X is in the ability to define a case. It is clear that *FMR-1*-related disorders involve complex genetics with a degree of inconsistency in phenotype. For example, males have been identified with repeats within the range associated with mental retardation but with intelligence quotients above 70.⁹ Perhaps almost as important is the reality that most female “premutation carriers” will develop neurological disease involving ataxia with the risk of cognitive decline⁹ (fragile X–associated tremor/ataxia syndrome (FXTAS)) so they will be affected, but not with the phenotype in question. Conversely, not all premutations will expand in the next generation. Thus the standard confirmatory testing cannot be used to identify an individual who will have a 50% chance of having a boy affected with classic fragile X. The test will, however, identify a woman as having a very high likelihood of a progressive neurological disorder. Consequently, it is hard to definitively state that there is a reliable test for identifying women who will have an affected child. It is therefore difficult for women

to confidently choose not to have their own biological children or to undergo further procedures for a less than 25% risk of having an affected male (although ~50% chance of having a child with some disease).

Perhaps even more challenging for those considering ending a pregnancy is the inability of routine prenatal testing such as amniocentesis to predict the affected status of an at-risk child. Indeed, one paper says “Reproductive options for the couples with familial history of FXS include prenatal diagnosis followed by possible termination of an affected pregnancy. However, the decision whether or not to terminate is frequently hard and difficult, especially since the prediction of phenotype is not possible because of mosaicism in males and X-inactivation ratios in females.”⁸ Given the current shortage of genetic counselors in the United States,¹⁰ it is unclear that there is a workforce to discuss the complexities of such positive tests.

When considering whether treatment is available, as noted above, it is important to understand what is accepted as “treatment.” As noted above, termination of pregnancy remains far from either universally available or acceptable; PGD is challenging for this disorder and not routinely available; and there are no clear data suggesting that preconception counseling is useful in family planning around this condition.

THERE SHOULD BE A RECOGNIZABLE LATENT OR EARLY SYMPTOMATIC STAGE

The underlying intent of this criterion is that there must be a period in which the affected individual would not come to clinical attention but during which intervention would provide improved outcomes. Clearly there is no latent phase for postnatal therapy, although there may be delays in clinical identification and service provision. Conversely, most pre-mutation women are going to be asymptomatic and unaware of their risk of having an affected pregnancy, without molecular testing. Thus, there could be a “latent phase” between molecular diagnosis and pregnancy, allowing the possibility of preconceptual intervention.

THERE SHOULD BE A SUITABLE TEST OR EXAMINATION

As demonstrated in the study by Metcalfe et al.¹ in this issue, there is an available molecular test to identify women with premutations, which can be deployed through primary-care clinics. This screen can successfully identify women at higher risk of having a premutation. However, the predictive value for having an affected child is much lower than, for example, DNA-based noninvasive prenatal screening for trisomy 21.

For the test to be scalable, all parts of the process need to be scaled. The approach identified by Metcalfe and colleagues¹ identifies a clear need for pretest consent and counseling as well as expert return of results, and such resources are currently deployed in antenatal clinics. However, these resources need to be universally available to primary-care doctors during routine “wellness screening,” if such screening

is to be deployed before conception. There is encouraging data from this study that such counseling is scalable with an expanded genetics workforce.

THE TEST SHOULD BE ACCEPTABLE TO THE POPULATION

This is a simple blood-based test. There may be significant societal concerns about the identification of presymptomatic adults with a progressive disorder and the potential therapeutic options that such testing enables. Metcalfe et al.¹ do not provide direct information on acceptability among the target population in general. Of those who participated in the research, 70.6% nonpregnant and 58.8% pregnant women chose testing, indicating that a majority of those enrolled found the test acceptable. However, it is impossible to know why 82% of those approached did not participate in the study. They may have decided not to enroll because they did not want to be part of a research project or because they did not want genetic testing. In total, 96% of the population approached declined both enrollment and testing. A skewing toward participation for those favorable to testing, with high posttest satisfaction, has been described previously, in the context of another trinucleotide repeat disorder.¹¹ This suggests that such high test satisfaction may not be generalizable. In spite of the studies cited by the authors confirming that large portions of the population would hypothetically accept testing, there is limited empirical data to support such acceptability. Indeed, such hypothetical questions were found not to be borne out, in the case of another progressive neurodegenerative disorder (Huntington disease), when testing became available.¹² This suggests that this study does not provide evidence enabling us to conclude that fragile X testing is generally acceptable to the population.

THE NATURAL HISTORY OF THE CONDITION, INCLUDING DEVELOPMENT FROM LATENT TO DECLARED DISEASE, SHOULD BE ADEQUATELY UNDERSTOOD

There is a wealth of data on fragile X and FXTAS¹³ in women from families identified as having the disorder.⁹ However, it has been the experience of the genetics community when looking at disorders such as Pompe, medium-chain acyl-CoA dehydrogenase (MCAD), and very-long-chain acyl-CoA dehydrogenase (VLCAD), that individuals clinically ascertained may represent the more severe end of the spectrum.

We do not yet understand what factors beyond the locus affect, for example, the penetrance and age of FXTAS, which at the low end is going to be identified probably at least four times more often than fragile X (a one-in-four chance of an identified carrier's having a son with the allele, and if they do, that son will almost certainly either have FXTAS or fragile X, in addition a subset of daughters will have FXTAS or less commonly, fragile X). Perhaps more disturbing for those engaged in population screening is data from Wisconsin that suggest that ~1/150 women are in the gray zone. The data from that paper suggest that the majority of these women had

symptoms attributable to FXTAS.¹⁴ Significantly, only 1 in 5000 boys have fragile X when methylation testing is performed on newborn screening dried blood spots.¹⁵ This suggests a gross underestimate of the prevalence of FXTAS and a very low (3%) conversion rate from being in the gray zone to having an affected child.

THERE SHOULD BE AN AGREED POLICY ON WHOM TO TREAT AS PATIENTS

A public discussion is needed about disclosure to infants identified prenatally or postnatally as being at risk for FXTAS and women in the premutation range in order to determine whether they are “patients” or “patients in waiting,” and what criteria should be used to determine whether they are affected. For boys, there are guidelines for clinical care based on clinical assessment of impairment, not a specific molecular profile. Consequently, services would be expected to be provided as a child becomes symptomatic.

THE COST OF CASE FINDING (INCLUDING DIAGNOSIS AND TREATMENT OF PATIENTS DIAGNOSED) SHOULD BE ECONOMICALLY BALANCED IN RELATION TO POSSIBLE EXPENDITURE ON MEDICAL CARE AS A WHOLE

Cost-benefit analysis in which the primary benefit is in avoiding long-term care costs is fraught with both emotional and economic challenges.¹⁶ In general, in health-care economics specific measures are used to compare the value of interventions to enable rational commitment of limited health-care resources. DS antenatal screening provides the example most like the case of fragile X. Analysis of DS screening typically puts a financial figure on the costs of all the medical needs of a child born with DS. Clearly children with DS have a very different range of problems, with more frequent cardiac defects. The estimate is that the total impact on health and reduced life expectancy of DS approximates to 53.1 life years lost in a DALY framework¹⁷ (or, put another way, each child with DS has 26.9 DALYs).¹⁷ This number is within the same disability class as congenital total hearing loss and fragile X.¹⁸ Lifetime costs for a child born with DS are estimated at \$677,000 (~25,000 per DALY). It is likely that the costs for fragile X will be considerably lower, as fragile X is not associated with a high rate of cardiac defects. The total estimated prenatal screening costs in the United States for DS are \$3.4–3.8 million to detect 4,823 cases of DS, which is estimated to prevent 3,600 children with DS being born, giving a cost of approximately \$3.4 million to avoid 10,000 DALYs. Conversely, as a society we have chosen to invest in other medical interventions that prolong life at considerable expense, such as adding PCSK9 inhibitors to statins in heterozygous familial hypercholesterolemia at a cost of \$503,000 per QALY gained.¹⁹ The cost of saving one QALY through use of these drugs is comparable to the estimated lifetime costs of caring for a child with DS. This strongly suggests that in DS screening, for every dollar spent in

antenatal screening we lose DALYs and the investment in caring for children with DS provides more DALYs than other funded health interventions. Therefore, there is unlikely to ever be a DALY- or QALY-based cost argument in favor of antenatal screening for fragile X.

CONCLUSION

When considering the cost of introducing a screening program it is important to recognize the opportunity cost to other population health initiatives of prioritizing such interventions. There are several significant public health programs, such as universal neonatal screening for Pompe disease, that are expected to yield significant improvements in population health but have yet to be implemented because of a lack of public funds or available infrastructure.²⁰ Other recommended population interventions, such as cascade screening for familial hypercholesterolemia, have significantly limited uptake.²¹ Although the study published in this issue does demonstrate a lack of harm in being screened, there are many other areas in which population screening for fragile X does not yet fit within the accepted criteria for a screening test. Consequently, from a population health point of view it is difficult to recommend implementation of fragile X screening ahead of screening for other disorders for which there is currently stronger evidence of benefit.

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