Fragile X population carrier screening

To the Editor: We wish to respond to the recent *Genetics in Medicine* commentary on fragile X syndrome (FXS) population screening in which Dr Dimmock's views raise a number of important issues.[1] As authors of the article[2] to which he refers, we feel obliged to clarify some misconceptions specifically about population carrier screening for FXS.

Dr Dimmock confirms that the *FMR1* full mutation is the most common cause of inherited intellectual disability. It is also the most common single-gene cause of autism spectrum disorder and a cause of a range of physical, emotional, and behavioral disorders ranging from mild to severe and occurring in both genders across the age spectrum. Female carriers are at risk of having children with the full mutation, the vast majority of whom are significantly affected. In addition to reproductive risk of FXS, the *FMR1* premutation causes fragile X–associated tremor ataxia syndrome, a neurodegenerative disorder seen mainly in males, and fragile X–associated primary ovarian insufficiency, which causes reduced fertility in females.

We believe that there is a wealth of evidence to demonstrate that the Wilson and Jungner criteria are in fact all met for carrier testing for FXS. FXS is an important condition that is well understood; the cost-effective blood or saliva test is acceptable to the population, is highly accurate at a relatively low cost, with minimal evidence of harm, and with diagnosis and full range of treatments readily available. However, Dr Dimmock's well-meaning attempt to utilize the 50-year-old Wilson and Jungner criteria to critique reproductive carrier screening is of questionable relevance for today's technological advances and era of informed consent. Assessing FXS using more recent screening criteria developed specifically for genetic conditions[3] highlights that there is in fact quite a compelling argument for carrier screening. The reality is that offering carrier screening for common conditions such as cystic fibrosis, spinal muscular atrophy, and FXS, or much larger panels of diseases, following the provision of appropriate information is increasingly becoming the norm. While neglecting to offer the option of privately funded carrier testing to women planning a family may have been accepted in the past, unilateral decision-making by doctors today is rarely acceptable. Discussing carrier screening as part of preconception or early pregnancy consultations is now considered by many to be a duty of care.

The statement "The utility of preconception or antenatal testing for fragile X is uncertain" is manifestly incorrect. The aim of genetic carrier screening is to allow families access to the full range of reproductive options. These include not proceeding to pregnancy, adoption, donor gametes, prenatal diagnosis, preimplantation diagnosis, or early intervention. There is evidence from FXS carriers identified through both cascade testing and population screening that knowing one's carrier status empowers women and their partners to make informed choices when planning a family.

FXS carrier screening has been clearly shown to be cost-effective in multiple studies around the world. This is even more true today, with the lifetime cost of supporting a person with FXS (with normal life expectancy) estimated at up to US$3 million, and the reducing cost of testing, especially when combined with current expanded carrier test panels of 100 or more conditions.

Current American College of Obstetricians and Gynecologists guidelines recommend genetic carrier testing be offered to all women planning a family, singling out cystic fibrosis and spinal muscular atrophy, with FXS reserved for those with a positive family history. Our paper provides sound scientific data to now add FXS to the list. Many of the key concerns raised about FXS carrier screening can be addressed in the design of the carrier screening program, such as only offering FXS carrier screening to females (who are at a much lower risk than males of developing fragile X–associated tremor ataxia syndrome later in life), reporting individuals with gray zone alleles as being at "low risk" of having a child with FXS, and ensuring there is prompt access to genetic counseling for carriers.[4]

We believe rather than finding barriers to offering FXS screening, it is now time to offer testing as an option to families. Discussion about carrier screening should shift from "if" to "how." Our recent study provides evidence that carrier screening can be offered with minimal harms and emphasizes that education and genetic counseling are essential components of any such program. Offering testing involves equity and informed consent. The primary challenge is determining how to offer carrier testing panels in a way that achieves this.

DISCLOSURE

M.D. and A.A. are employees of the Victorian Clinical Genetics Services, which provides a fee-for-service carrier screening panel (Prepair) for cystic fibrosis, spinal muscular atrophy, and fragile X syndrome. It is a not-for-profit specialist laboratory and clinical genetics service, and a wholly owned subsidiary of the Murdoch Children's Research Institute. The other authors declare no conflict of interest.

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