Response to Metcalfe *et al.*

To the Editor: It is encouraging that the article by Metcalfe and colleagues[1] and my corresponding Commentary[2] have stimulated a debate about the timeliness and value of prenatal and preconception screening for fragile X. The subsequent letter by Metcalfe et al.[3] reflects the ongoing controversy.

Even using more recent screening criteria than those of Wilson and Jungner, it is not clear that a fragile X screening program would respond to a "recognized need." Although fragile X is an important condition, there is ongoing debate about the appropriateness of testing for it in children with intellectual disability or autistic disorders.[4] Furthermore, there is no specific therapeutic intervention that improves health-care outcomes. The majority of women approached in the current paper declined screening.

As identified in more detail in the original Commentary, the usual way of ascribing value in health economics is to consider what programs offer the least cost for a given improvement in health outcomes, not simply the lowest-cost option. There are no data demonstrating that screening for fragile X, or avoiding children being born with fragile X, improves societal or individual health outcomes. Instead, the advocacy for a screening program to avoid societal costs of caring for children with intellectual disability is reminiscent of the controversy surrounding cardiac repairs for children with Down syndrome.[5] It is inconceivable now that we would deny lifesaving surgery to a child with Down syndrome because it would be cheaper to let them die than pay the costs of surgery. Many would also question the ethics of screening, as they do already with Down syndrome, when the sole aim is to save costs through eliminating affected individuals before birth rather than providing later therapeutic interventions for those same individuals after birth. The implementation of pre-conception or prenatal screening should be based on improvements in maternal and child health-care outcomes, not merely on cost savings.

Furthermore, regardless of the timing of screening, it is essential to understand the natural history of the condition detected by the screening. It is clear from previous publications that the risks of having an affected child are low; conversely there are data to suggest that there is a significant risk of health or mental health consequences in premutation carriers, with one recent paper noting "we have imperfect knowledge about phenotype–genotype correlations within the carrier range, data that can only be gathered through systematic longitudinal research based on population screening of large samples."[6] This same paper also notes the considerable costs and challenges of newborn follow-up programs for the high number of carrier-positive parents.

Consequently, although there have been significant advances in our understanding of parental acceptance for both preconception and newborn screening for fragile X, there remain considerable controversies and unanswered questions about whether we should screen for fragile X. In the meantime, as noted in my Commentary, there are conditions for which we can improve health-care outcomes by screening, for which there are less significant controversies. Our public health efforts should be focused on implementing screening for these disorders ahead of considering fragile X.

DISCLOSURE

The author has received consulting fees and related expenses from Audentes Therapeutics, Biomarin, Complete Genomics, Demeter Therapeutics, and Illumina in the past 5 years. Through his previous institution, he has received restricted research grants and related travel funding from Biomarin, Genzyme Sanofi, Hyperion, Alexion, and Demeter Therapeutics.

ACKNOWLEDGMENTS

The opinions in this letter are those of the author and should not be considered to reflect the opinions of his employer.

David P. Dimmock, MBBS, MS[1]

[1]Rady Children's Institute for Genomic Medicine, San Diego, California, USA. Correspondence: David P. Dimmock (ddimmock@rchsd.org)

REFERENCES

1. Metcalfe SA, Martyn M, Ames A, et al. Informed decision making and psychosocial outcomes in pregnant and nonpregnant women offered population fragile X carrier screening. *Genet Med* 2017;19:1380–1389.
2. Dimmock DP. Should we implement population screening for fragile X? *Genet Med* 2017;19:1329–1333.
3. Metcalfe SA, Delatycki MB, Cohen J, Archibald AD, Emery JD. Fragile X population carrier screening. *Genet Med* E-pub ahead of print 7 December, 2017.
4. Mullegama SV, Klein SD, Nguyen DC, et al. Is it time to retire fragile X testing as a first-tier test for developmental delay, intellectual disability, and autism spectrum disorder? *Genet Med Pediatrics* 2017;19:1427–1428.
5. Champagne CR, Lewis M, Gilchrist DM. Should we mend their broken hearts? The history of cardiac repairs in children with Down syndrome. *Pediatrics*. 2014;134:1048–50.
6. Bailey Jr DB , Berry-Kravis E, Gane LW, et al. Fragile X newborn screening: lessons learned from a multisite screening study. *Pediatrics.* 2017;139 (suppl 3):S216–S225.

Advance online publication 14 December 2017. doi:10.1038/gim.2017.208