The paper by Bowman-Smart et al on non-invasive prenatal genetic testing (NIPT) for non-medical traits aims to set out the case for and the case against such testing. In response to their paper, this commentary adds to the range of concerns about such testing. First, however, I raise some questions of language and terminology.

Terminology

In describing the performance of some NIPT tests, the authors - like the authors of a paper they refer to (Suzumori et al 2021) - use the term “accuracy”. In the context of NIPT used as a population screening test for autosomal trisomies, this term is unhelpful and, indeed, positively misleading. Such tests, predominantly intended to identify fetuses with Down’s syndrome, will be >99% ’accurate’ even if all results are given as “low risk” without any test being performed, because the chance of trisomy 21 is small. The important measure of performance in this setting, which must be used in reporting the performance of a test and in discussing it with pregnant women, is its positive predictive value (PPV) (Nuffield Council on Bioethics 2017). In the paper discussed, the PPV is 93%, as nearly 7% of screen-positive results will be chromosomally normal. It is the term PPV that must be understood and used by professionals and whose sense must be conveyed to prospective parents, not the misleading notion of “accuracy”.

Another word to be used with care is ‘screening’, which is used to convey several different meanings in different contexts. It can refer to a population screening program, to the application of a supplementary test process to a sample taken for other reasons, or to a search for molecular genetic or chromosomal variants. The considerations that justify screening in one sense and one setting may not apply to another, and dubious arguments in favor of ‘screening’ may mislead by slipping from one sense to another. The authors make the statement that, “NIPT is a screening test, and is not diagnostic”; that is far too sweeping to be accurate as there are many types of NIPT and it is indeed diagnostic in a number of contexts.

Susceptibility not Prediction with Polygenic Testing

A third question of terminology relates to “prediction”. Polygenic tests are presented by Bowman-Smart et al as plausibly giving us predictive information: “It may also be possible to use polygenic scores … to predict a variety of non-medical traits such as cognitive

ability …". While a quiet note of caution is introduced later, the damage has been done as polygenic scores and prediction are immiscible: these terms simply do not mix. Polygenic scores give information that might modify a prior risk estimate but that is all. They may conceivably have some clinical utility in setting criteria for screening or surveillance programs, although none have so far been established. Equating polygenic scores with prediction amounts to the implicit promotion of a false genetic determinism, while leaving aside the problems of pleiotropy, complexity and inequity they acknowledge (Turley et al 2021). Furthermore, the focus on cognitive ability lends unwise support to the persistent - historical and contemporary - over-emphasis on variation in IQ within the normal range, that is of no relevance to medicine but is wide-open to abuse.

In addition, the authors fail to emphasize a crucial difference between prenatal polygenic testing and the more usual NIPT screening for chromosomal anomalies: the fact that no confirmatory test is available, either before or after the end of the pregnancy. If the pregnancy is terminated, there can be no possibility of discerning what the phenotypic outcome for such traits would have been. Accordingly, there is no possibility of learning from the events to improve testing in the future (Mertens et al 2022). Furthermore, if the pregnancy continues and a child is born, there is the potential for inappropriate influences on the child's future life through altered parental expectations (JCMG 2022) and the mechanisms of self-fulfilling prophecy.

The difficulty in conveying the biological basis of such polygenic testing is mentioned by Bowman-Smart et al but is not given its full weight. The heritability of most complex traits - the fraction of the variance in the trait that can be attributed to underlying genetic factors - is often of the order of 50%, and the fraction of this that can be accounted for by molecular investigations is usually modest (15-20%), so the polygenic scores draw on only a few of the relevant influences, the rest being excluded from analysis. When offered to most pregnant women, such tests are so likely to cause confusion that it will often be unethical to make the offer at all. A paper cited by Bowman-Smart et al acknowledges that consent will be 'challenging' but sets any reservations aside, arguing that such difficulties in comprehension apply to many other important decisions, e.g. such as those about insurance policies (Chen and Wasserman 2017). This is an inadequate response, when the context of pregnancy raises the stakes so high.

In the setting of preimplantation genetic diagnosis (PGD) there is the possibility of selection between ‘embryonic siblings’, but the basis for the use of polygenic testing is weakened because the range of difference between siblings will be much less than the range of difference between individuals in a population, as it is limited by the genotypes of the two parents so that the scope for its ‘effectiveness’ (if its claims are taken at face value) is much less. The use of polygenic tests for non-medical traits in PGD has been strongly criticized (Forzano et al 2022); how much more these arguments apply to prenatal testing!

Consistency

The core argument put forward by Bowman-Smart et al in support of polygenic testing in pregnancy is that of consistency. It is said to be necessary that prenatal selection be permitted on the basis of likely cognitive ability (within the “normal range”) given that prenatal selection against fetuses with sex chromosome anomalies is permitted in the context of fetal sex determination by NIPT on social grounds. The connection is that one factor in the decision to terminate a pregnancy in which the fetus has a SCA could be the possible reduction in the child’s IQ. When Bowman-Smart et al set out this argument, they fail to discuss another approach that would also achieve consistency. This would be to prohibit NIPT for fetal sex except for medical reasons, such as whether to perform an invasive test in a pregnancy at high risk of a severe, sex-linked condition. Of course, this approach runs counter to women’s autonomy, although the appeal to autonomy is itself weakened by the difficulty of ensuring both that consent to such NIPT is grounded in an adequate understanding of the biology and that the woman is the one who has made the decision.

However, there is a strong argument against the authors’ approach to consistency. This is that prohibiting fetal sex determination on social grounds would discourage fetal sex selection, which has been greatly facilitated by NIPT for fetal sex. The loss of autonomy is more than justified as an act of support for, and a mark of solidarity with, women in countries and communities where they are of low status and subject to disrespect, discrimination and disempowerment. Indeed, India and China have both banned pregnancy termination on the grounds of fetal sex, as they recognize the broad scale of the social problems it leads to, although they fail to enforce the ban. Not only does this counter the questioning by Bowman-Smart et al of“ whether individual decisions made in

the private sphere propagate negative attitudes on the societal sphere"; individual decisions about fetal sex are also leading to devastating social consequences. A narrow individualism is inadequate at tackling many of the major societal problems of today.

The broader argument of Chen and Wasserman (2017), supporting the removal of all barriers to parental knowledge of the fetal genome, is another internally consistent approach but one that is based on two fantasies. The first is the mistaken belief that polygenic tests can be understood sufficiently well by most people that consent to such testing in a pregnancy would be legitimate; it would be fairer to suggest that a person placing their trust in such testing must have failed to understand it. Rather, the promotion of such tests seems to be a marketing ploy on behalf of commercial genetic testing enterprises that ought to know better and probably do. Perhaps the conviction of Elizabeth Holmes for the misrepresentation of her Theranos product will have a salutary effect on misrepresentation in this field too.

The second fantasy is that prospective parents can make satisfactory decisions about hypothetical questions as to what information they would, in the abstract, want to learn during a pregnancy, i.e. outside the context of a specific high risk of which they are already aware. The offer of information that purports to be "accurate" can be all but irresistable but many may make decisions they or their children later regret.

Conclusion

The overview of the arguments for and against polygenic testing for socially valued non-disease traits in pregnancy by Bowman-Smart et al tackles an important question but fails to consider several important arguments against such testing, and the weakness of several of the arguments for it. Accordingly, the authors fail to draw appropriate conclusions about the weakness of the case for such testing. We should use the regulation of professional practice and legislation against the misrepresentation of services in marketing to discourage such developments. The most effective way to select for the non-disease traits in one's child remains the very traditional and widespread practice of taking care in selecting one's spouse or partner.

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Target Article:

Bowman-Smart et al. “Non-invasive Prenatal Testing for ‘Non-Medical ’Traits: Ensuring Consistency in Ethical Decision-Making” AJOB target article

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