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LETTER TO THE EDITOR

Clinical utility and cost of non-invasive prenatal testing

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Song et al. [1] have proposed a maternal age-stratified Down syndrome screening policy based on the incorporation of cell free (cf)DNA testing into existing conventional screening protocols, such as the Combined test. All women aged over 35 years would be offered cfDNA testing, as would younger women with screen-positive Combined test results. They claim that, in USA, such a policy would lead to a 43% increase in Down syndrome detection and a reduction in overall costs.

Unfortunately, this claim is not valid, as it is entirely dependant on the assumption of a large differential uptake of invasive prenatal diagnosis following a positive result: 75% for the Combined test and 99% for cfDNA. Using the authors' estimates of screening performance, prevalence and unit costs, if uptake was the same for both tests, the policy would increase detection by only 8% and there would not be a reduction in overall costs, rather they would actually increase.

There might well be a higher uptake of invasive prenatal diagnosis following cfDNA testing than the Combined test, but the assumed 24% differential uptake is extreme. In the only large prospective study of cfDNA screening published so far, in China, uptake was 96% (182/190) [2]. In a recent comparably sized prospective study of the Combined test, in Hong Kong, it was 93% (637/684) [3]. Until a study has been carried out to directly compare uptake following cfDNA and conventional screening in the same population, it is prudent to assume a difference of under 5%.

Additionally, there are problems with the authors' estimate of screening performance and with the calculated average cost per case detected.

The performance of a Down syndrome screening test changes with maternal age. However, on the basis of the numbers of detected cases in Table 1, it appears that the authors have assumed the same Combined test detection and false-positive rates (85% and 5.0%) for the overall population and for women aged under 35 years.

The average cost per Down syndrome case detected was calculated to include the lifetime cost of caring for a child born with the disorder, both in unscreened pregnancies and in those screened but not detected. This is not of use when planning public health policy. The Combined test is already established practice in most developed countries. Moving to a policy involving cfDNA is likely to increase overall costs, and the critical factor for health planners will not be the average cost of the existing and new policies but the ''marginal'' cost. This is the cost per additional case detected by the new approach that would otherwise not have been detected. Planners will then be able to compare this with other opportunity costs or possibly with potential savings by avoiding the lifetime cost of a Down syndrome birth.

Modelling with the same unit costs as in the paper, published Combined test parameters [4], the USA maternal age distribution in 2010 [5] and assuming no differential uptake, the marginal cost of the proposed cfDNA policy would be $1.4 million. This is about twice the author's estimate of lifetime expenses.

The authors' proposed age-specific policy is more expensive than a ''contingent'' approach whereby all women, regardless of age, have a conventional screening test and a low cut-off level is used to select 10–20% for cfDNA testing. Using the above model, selecting 15% would yield a marginal cost of $0.7 million, approximately equivalent to the authors' estimate of lifetime expenses.

Declaration of interest

H. Cuckle is a consultant to PerkinElmer Inc, Ariosa Diagnostics Inc, Natera Inc, and director of Genome Ltd; E. Pergament is a consultant to PerkinElmer Inc and Natera Inc, and director of Northwestern Reproductive Genetics Inc.

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