Extending the provision of cell-free DNA screening for trisomy 21

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It is now 12 years since the discovery that fetal cell-free DNA (cfDNA) fragments in maternal plasma can be used to detect trisomy 21. This single marker has a detection rate above 99% and a false-positive rate below 0.2%, a performance greatly exceeding conventional multiple serum and ultrasound marker screening tests. Nevertheless, there has not been a widespread replacement of conventional screening with cfDNA. Commercial providers report annual cfDNA testing totalling millions, but this covers only a few percent of pregnancies worldwide.

Initially, several objections were put forward against policy change: cfDNA studies were in highly selected pregnancies; samples required shipping to laboratories in the USA or China; efficacy in twins was uncertain; and testing was expensive. All objections were subsequently overcome, although only partially so regarding expense. The starting price of cfDNA was particularly high at first because of the heavy research investment, patent issues and use of massively parallel sequencing. Thereafter, the prices have fallen somewhat, and recent test simplifications are leading to further reductions in cost.

Healthcare planners have two financial considerations: total additional cost and the ‘marginal’ cost of detecting each affected pregnancy missed by conventional screening. These calculations must take account of local consequences: there is no saving on ultrasound if nuchal translucency (NT) scanning is retained for the detection of other abnormalities; there are no savings on biochemistry if serum markers are retained for the detection of pre-eclampsia.

Several studies have shown that routine (‘primary’) cfDNA screening has a considerable additional cost and an extremely high marginal cost unless the price of a cfDNA test can be reduced substantially. Rather than replacing conventional screening, two more affordable policies have been proposed. ‘Secondary’ cfDNA testing, whereby all women with positive conventional screening tests are offered cfDNA, is used in the current study (Guy GP et al. BJOG 2021;128:440–446). This policy minimises the hazards of invasive prenatal diagnosis and is likely to be cost saving, depending largely on the relative prices of cfDNA and invasive testing. But it has no detection advantage, as the detection of trisomy 21 is slightly reduced. A more effective policy is ‘contingent’ cfDNA screening whereby 15–25% of women with the highest risk of trisomy 21, based on conventional screening, are offered cfDNA. Both the additional and the marginal costs are much lower than for primary cfDNA screening, the false-positive rate is very low and the detection rate is higher than that obtained with conventional screening.

Policy decisions have been complicated by the additional abnormalities now included by commercial cfDNA providers. Trisomies 13 and 18 are considerably less common than trisomy 21, and are readily detectable by ultrasound, sex chromosome abnormalities and 22q deletion syndrome are more common but less severe, other copy-number variants are much less common and the detection of rare autosomal trisomies is of unproven benefit. Taken together, these additions will increase the overall false-positive rate by about 15-fold, with consequent cost implications.

Primary cfDNA screening focusing on trisomy 21 is now an affordable option for many healthcare systems and contingent screening is a reasonable alternative for most. Secondary screening has limited benefit and at best represents a temporary stage, while examining the practicalities reported in the current study, before rolling out more extensive provision.

Disclosure of interests

HSC is a paid consultant to PerkinElmer, who supply reagents and equipment used in conventional and cfDNA screening. Completed disclosure of interests form is available to view online as supporting information.