ISPD RAPID RESPONSE STATEMENT

Prenatal Detection of Down Syndrome using Massively Parallel Sequencing (MPS): a rapid response statement from a committee on behalf of the Board of the International Society for Prenatal Diagnosis, 24 October 2011

BACKGROUND

The International Society for Prenatal Diagnosis (ISPD) has provided recommendations for best practices in prenatal screening for aneuploidy (Benn *et al*., 2011). The development of non-invasive tests based on the presence of cell-free fetal nucleic acids in maternal plasma offer substantial new opportunities to improve prenatal screening. Recent studies have shown that in *high-risk* populations, massively parallel sequencing (MPS) can detect a large proportion of Down syndrome affected pregnancies with a low false-positive rate (Chiu *et al*., 2011; Ehrich *et al*., 2011; Sehnert *et al*., 2011; Palomaki *et al*., 2011; and others presented at international scientific meetings). However, this test is not fully diagnostic and therefore constitutes an advanced screening test. Accordingly, confirmation of MPS positive results through invasive testing would still be required. It is also important to recognize that for women who are screen-positive using current screening protocols, Down syndrome represents only about half of the fetal chromosomal abnormalities identified through amniocentesis and CVS.

MPS IN PRENATAL POPULATION SCREENING

Before routine MPS-based population screening for fetal Down syndrome is introduced additional trials are needed. These need to provide evidence that:

(a) There is efficacy in low risk populations

(b) The test is suitable for the diverse sub-populations such as twins and IVF donor pregnancies

(c) The test can be provided in a cost-effective, timely, and equitable manner

(d) If used in conjunction with other screening tests, the MPS result can be combined to provide a composite risk estimate.

MPS FOR INDIVIDUAL PATIENTS

Commercial MPS-based testing for prenatal detection of Down syndrome has recently been introduced in the United States and it has been advocated for women who have been determined to be at high risk based on other conventional screening tests (Palomaki *et al*., 2011). Commercial testing is also available in China and will soon be launched in Europe.

ISPD accepts that with suitable genetic counseling (see below) MPS can be helpful for women who may have been determined to be high risk by one of the previously recommended screening strategies (Benn *et al*., 2011).

ISPD does not endorse the *ad-hoc* use of MPS testing in women at lower risk, outside a formal protocol that considers the overall best combination of tests, their impact on screening performance and patient acceptability. In general, the components that are incorporated in multi-test prenatal screening protocol should be defined by the population that will most benefit, the gestational age that each test can be offered, impact on invasive testing, economics, and other practical considerations such as the availability or need for genetic counseling.

GENETIC COUNSELING

At this time, individual women who might be considering the MPS test need to receive detailed genetic counseling that explains the benefits and limitations of the test. Testing should only be provided after an informed consent. Information that must be provided to the patient includes:

(1) The test currently available in the USA is only for fetal Down syndrome which constitutes only about half of the fetal aneuploidy that would be identified through amniocentesis or CVS. In China the available test also detects Edwards syndrome.

(2) The test does not detect all cases of fetal Down syndrome.

(3) There are also occasional false-positive results and therefore women with positive MPS results need to receive confirmatory testing through an amniocentesis or CVS.

(4) Patients with positive MPS results are at very high risk of Down syndrome and for some women the extended period awaiting confirmatory invasive testing results is likely to be highly stressful.

(5) For some patients a MPS test result may not be informative.

(6) For those women who are at increased risk of a child with a prenatally diagnosable disorder with Mendelian pattern of inheritance, microdeletion syndrome, and some other conditions, amniocentesis or CVS would still be indicated.

REFERENCES

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