NON INVASIVE PRENATAL DIAGNOSIS

Study of Cell-Free Fetal DNA in maternal blood and its clinical applications in the UK National Health System

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PRENATAL TESTING

Prenatal Screening Tests

- Routinely offered to all pregnant woman.
- Determine risk of the fetus having a particular disorder or characteristic.
- **Do not give definitive answers.**
- Carry no risk of miscarriage.
- Methods of testing:
  - Blood test
  - Ultrasound scan

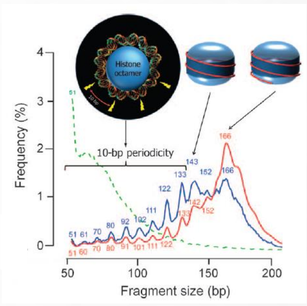
Invasive Diagnosis Tests

- Only performed in women identified as high-risk.
- Involve invasion of fetal milieu for genetic sample.
- Give definitive diagnosis.
- **1 to 2% risk of fetal loss.**
- Methods of testing:
  - Amniocentesis
  - Chorionic Villus Sample

Objective: Find reliable source of fetal genetic material that could be sampled without incurring health risk

CELL-FREE FETAL DNA

- Originates from apoptotic trophoblast cells derived from the embryo.
- Significant proportion in maternal plasma, representing 3.4-6% of total cell free DNA in maternal circulation during early and late pregnancy respectively.
- Its transfer to maternal circulation is detectable in all pregnancies. However, the percentage of cffDNA varies between individuals.
- Reliable detection from the 7th week of gestation.
- Rapidly cleared from maternal circulation, undetectable 2h after delivery due to its mean half-life of 16.3 min.
- Consists of short fragments (143bp) DNA derived from the nucleosome, smaller than those maternally derived.



CLINICAL APPLICATIONS

FETAL SEX DIAGNOSIS

Aim: to manage pregnancies at risk of **sex-linked disorders** such as **Hemophilia and Duchenne Muscular Dystrophy**, and pregnancies at risk of certain **endocrine disorders**, namely **Congenital Adrenal Hyperplasia**, by detecting cffDNA sequences of the Y chromosome.

Benefit: used as a replacement for invasive tests when the sex of the fetus indicates that the disease will not manifest, avoiding hazards of invasive procedures and needless treatments.

RhD STATUS DIAGNOSIS

Aim: to manage pregnancies where the newborn is at risk of **Haemolytic Disease** caused by the sensitisation of RhD-negative women to RhD-positive fetal cells, by detecting the presence of specific exons of the RHD gene that will predict a RhD-positive fetus.

Benefit: replaces invasive procedures which are associated to the severe risk of sensitisation and reduces the use of unnecessary anti-D therapy when there is no risk of incompatibility.

SINGLE-GENE DISORDERS DIAGNOSIS

Aim: to determine whether the fetus has inherited the wild type allele from an affected father with an **autosomal dominant condition (Achondroplasia)**, or from a father carrying a **recessive mutation** that is absent in the mother (**Cystic Fibrosis**).

Benefit: eliminates necessity for a further invasive diagnosis as this pattern will indicate an unaffected fetus.

Future development prospectives: possibility of implementation for all single-gene disorders shown by relative mutation dosage methods.

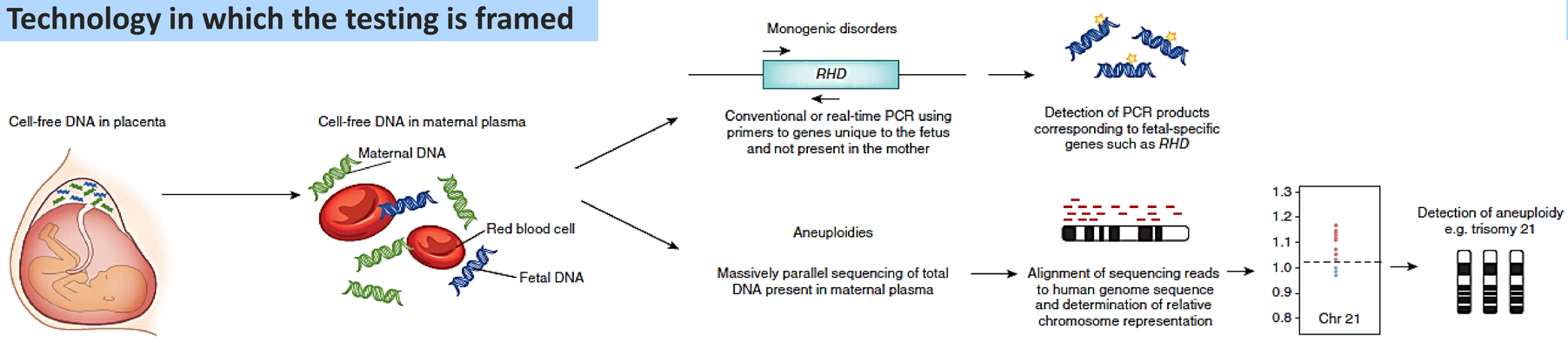
ANEUPLOIDY TESTING

Aim: to manage pregnancies at high risk of **Down's, Edward's or Pateau's syndrome** by detecting an abnormal concentration of a particular chromosome.
N.B. Only privately available .

Future development prospectives : implementation as a **second-term screening test**, only offered to women at increased risk of **trisomies 21,18 and 13**.

Future benefit: the introduction of NIPT should mean that much fewer women will need invasive diagnostic tests. However, invasive procedures will still be needed for diagnosis confirmation of positive screening tests.

Technology in which the testing is framed



Limitations

Possible sources of error:

- Early gestational age.
- Multiple pregnancies.
- Maternal obesity.
- Placental mosaicism.
- Other maternal conditions such as mosaicism.

CONCLUSIONS

Advantages

- Potential to be much more accurate than current screening approaches.
- Additional benefits such as safety, ease of performing the test, early testing and reduction of anxiety.
- Reducing number of invasive tests performed thus reducing the loss of uncomplicated pregnancies through these procedures.
- Knowing definitive information in the earlier stages of pregnancy is helpful for parents to make decisions about termination or to plan for the birth of an affected child.

Disadvantages

- NIPD carries a number of socio-ethical implications E.g.
- selective termination of foetuses according to sex
- use of technology for non-medical purposes such as paternity testing.
- diagnosis for an increasing number of minor abnormalities.
- risk of routinization and normalization of testing and abortion.
- Market and consumer needs as the driving force for the utilisation and adoption of testing rather than evidence based on clinical research therefore the standard of care determined by the wrong factors.

Opinion :
Implementation is desirable and development should be pursued. However, many factors still need to be considered E.g. standardised protocols production, lower test cost, training of health professionals, etc.

Bibliography

Bianchi DW (2012) From prenatal genomic diagnosis to fetal personalized medicine: progress and challenges. Nat Med. 18(7):1041-1051.
Lo YMD et al (2010) Maternal Plasma DNA Sequencing Reveals the Genome-Wide Genetic and Mutattional Profile of the Fetus . Sci Transl Med. 2(61):61ra91
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