NIPT in France

Challenge to a restrictive legal framework and standards of practice

Genetic testing

Article 16-10 – Preamble of the Civil Code

A person's genetic characteristics can be examined only if this is done for a medical purpose or for scientific research.

The person's explicit consent must be given in writing prior to testing, after s/he has been duly informed of the nature of the test and the purpose of testing. The consent mentions the purpose of testing. Consent is revocable without formalities and at any time.

CSP R. 1131-5

Genetic testing can only be prescribed for a minor or an adult under guardianship if the person or his or her family can personally benefit from immediate curative or preventive mesures.

Prenatal testing

French legal framework for prenatal testing highly restrictive:

- PGD and abortion after PND: restricted to diseases qualified as "particularly severe and known to be incurable at the time of diagnosis
- *Evaluation of severity is delegated exclusively to the medical profession*
  - Law in 1994 : creation of accredited pluridisciplinary centers (CPDPN) to evaluate and approve patient requests
  - PGD performed only in accredited centers

Legal framework for abortion following PND

PND (amniocentesis or chorionic villi sampling) can be provided on the basis of a woman's request

CSP Art. 2131-1

Abortion is possible <u>only if</u>:

- Disease is a "*particularly severe condition* known to be *incurable* at the time of diagnosis"
- *High probability* that the child to be born will be affected by the disease

Request for abortion must be examined and approved by pluridisciplinary team of competent professionals (CPDPN)

CSP Art. L2213-1

Legal framework for PGD

PGD is made available exceptionally if a *pluridisciplinary team of competent professionals (CPDPN) attests to :*

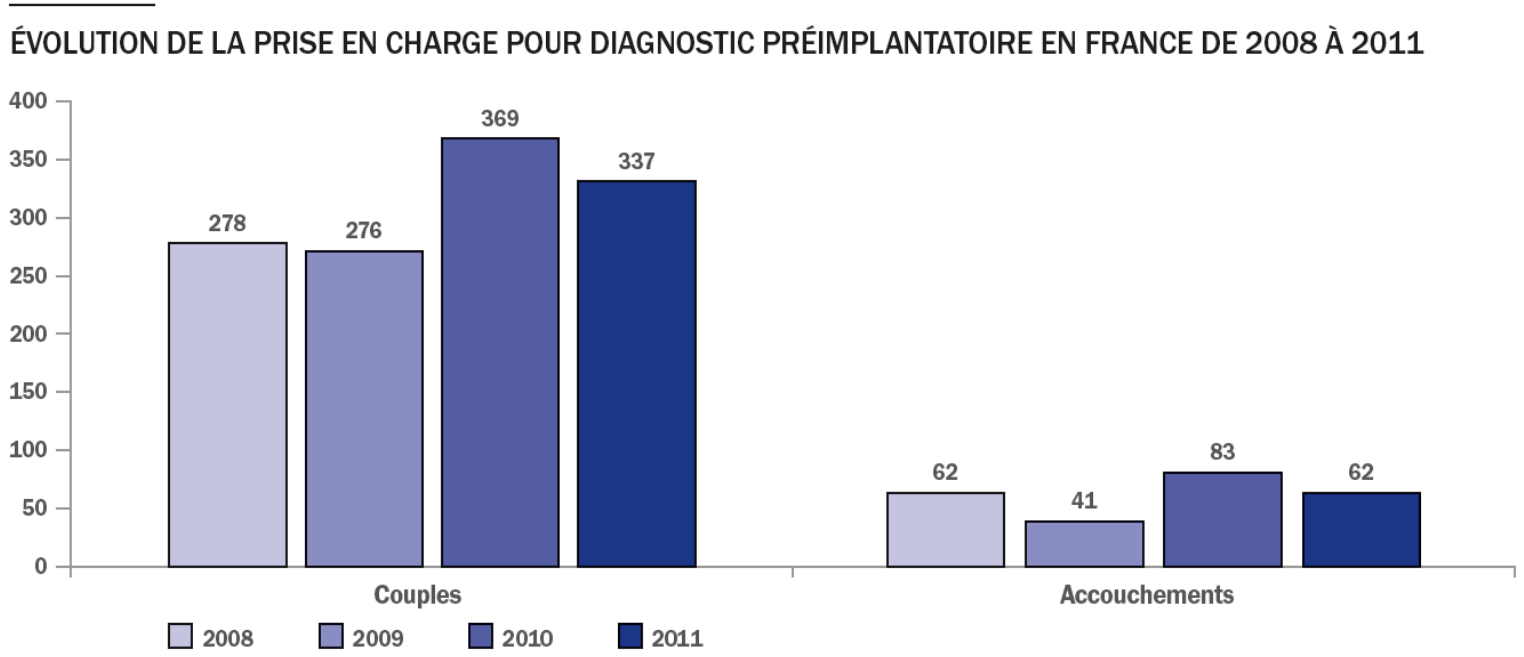
- "…high probability of conceiving a child with a *particularly severe genetic disease* known to be *incurable* at the time of diagnosis"
  - the abnormality or abnormalities responsible for the condition *have been previously identified* in one of the parents
    - a previous child was born with a genetic disease *leading to death in the first years of life* and recognized as *incurable* at the time of diagnosis

CSP art. L2131-4 and 4-1

PGD in France – 2008 to 2011

Agence de la Biomédecine - Annual Report 2012

PGD authorized in 4 centers



French National Ethics Committee (CCNE) Opinion n° 120- April 2013

Opinion 120 –

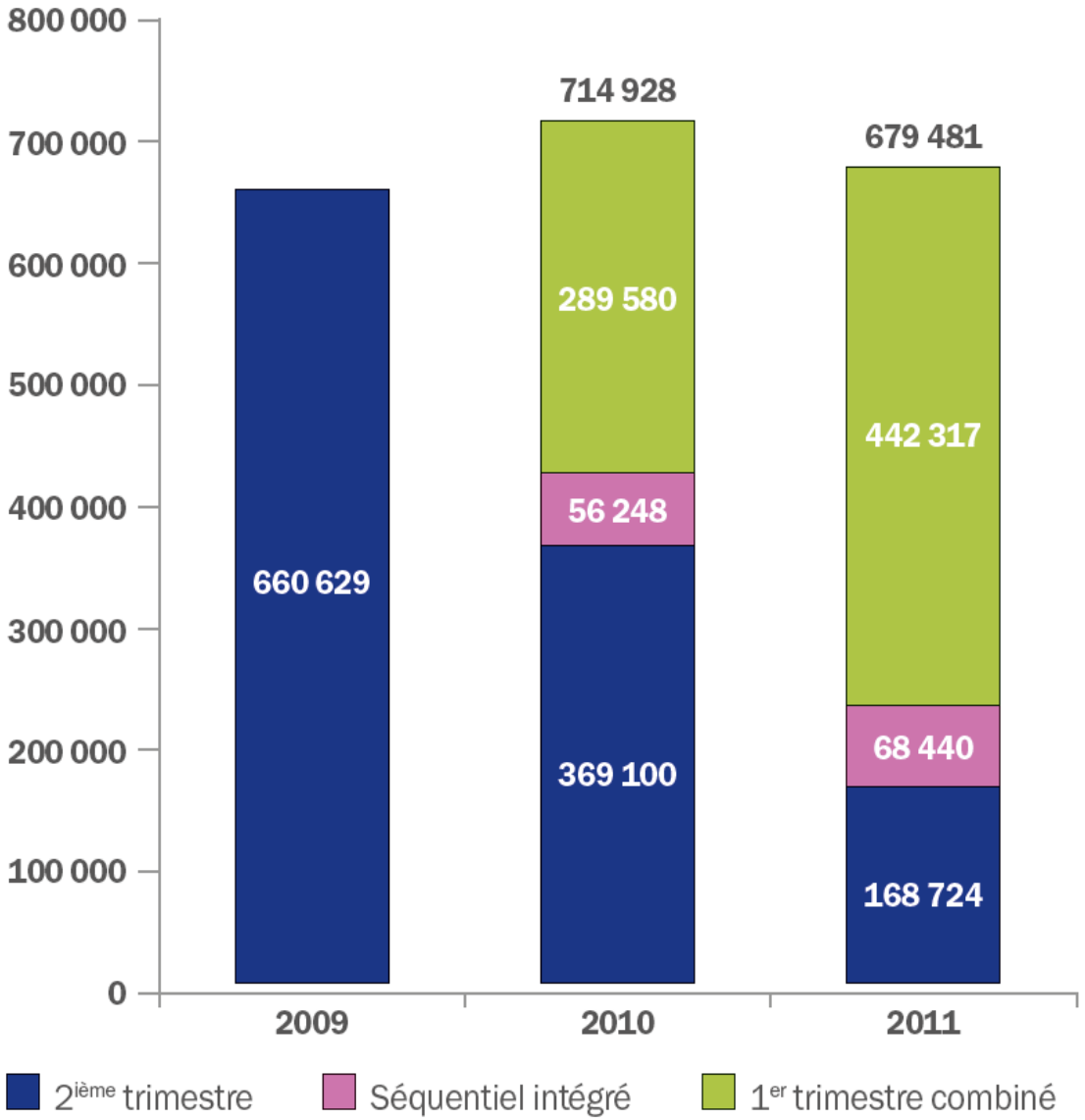
Ethical Issues in Connection with the Development of Foetal Genetic Testing on Maternal Blood

1. Evaluates and recommends NIPT for trisomy 21 screening as an improvement on combined screening strategy (offered since 2009)
2. Provides blueprint for future use of NIPT

Screening for trisomy 21

- Before NIPT:
  - 1970's : Amniocentesis (or CVS) proposed only to women over 40 (later 38)
  - 1997: following discovering of several aneuploidy markers in maternal serum, prenatal T21 screening regulated and offered to all women
  - 2007: assessment of screening strategies by the Haute Autorité de Santé (HAS)
  - 2009: combined screening stratgegy systematically proposed to all women during first trimester of pregnancy
    - Ultrasound + markers in maternal serum
    - Risk calculation takes maternal age into account

ÉVOLUTION DU DÉPISTAGE DE LA TRISOMIE 21 SUR TROIS ANS



Invasive procedures decrease

N° of cases of trisomy 21 remain stable

PND for Trisomy 21 in France in 2010

In its 2010 activity report, the *Agence de la Biomédecine* (ABM - French National Biomedical Agency) recorded 1934 diagnosed trisomy 21 cases, resulting in 1567 therapeutic terminations, 60 foetal losses, 12 stillborns, 62 live births (in 233 cases, the outcome was unreported). Furthermore, 500 trisomy 21 cases were born as a result of either choosing not to undergo the screening procedure or because of its imperfect sensitivity.

CCNE Opinion 120, p. 14

NIPT for trisomy 21

CCNE recommends introducing NIPT progressively

- Improvement on screening procedure:
  - reduces the number of invasive procedure (fœtal losses
  - avoids problem of incidental findings
- Positive results must be confirmed by amniocentesis

Can be integrated within the existing procedure without changing it

For the time being (and given the cost), proposed only to women at risk

Ongoing evaluation since November 2013 – Test by Laboratoire CERBA

- CCNE recommends reimbursement to ensure equal access (800€)

Eradicating Trisomy 21 or giving parents free choice?

Rendering screening more efficient, as proposed, would very probably have the effect of reducing the number of children born with trisomy 21. This however is not the stated object of the operation. The end purpose of this screening is to give a free choice to parents and to inform their decision regarding the continuation of the pregnancy. As a result, in the context of the decision taken many years ago by the community to offer systematically (and reimburse) screening for trisomy 21 to all expectant mothers, making such screening both more efficient and less dangerous (since it would preserve around 20,000 women every year from an invasive procedure, potentially dangerous for both mother and foetus), it can only be viewed in ethical terms as being an improvement.

CCNE Opinion 120, p. 20

Objectives and challenges in connection with the development of foetal genetic tests on maternal blood.

For the health care system

- Inform and train members of the medical professions, counsellors and practitioners, in the new genomic technologies and their interpretation.
- Inform and provide genetic counselling to all expectant mothers on the decisions they will have to take as regards screening and prenatal diagnosis.
- Develop reliable tests, reducing to a minimum false negatives and false positives, so as to arrive at an acceptable degree of *quality assurance*.
- Manage efficiently the considerable quantity of data produced by high throughput DNA sequencing, as well as the fate of such data after the prenatal period.
- Develop computing tools capable of interpreting this data to the best standard of competence so that the information it provides is medically fit for purpose.
- Obtain a reduction in the cost of tests so that they can reimbursed on a national basis and thus achieve equality of access.

For individuals and the community

- Draft information in such a way that it is readily understood by all regarding the issues arising out of testing for a great diversity of disorders, both as regards their medical management and the repercussions on those concerned and their loved ones.
- Allow for a very broad-based process of free and informed consent, but also respecting the right not to know.
- In the framework of a narrowly defined procedure, avoid incidental data which, if revealed *ex abrupto*, impinges on principles of doing-no-harm and of equity.
- Regulate or even repress access to tests available via the Internet (Direct to consumer [DTC]) and provide information on the dangers, humane in particular, of making use of them without any medical assistance or counselling.
- Ensure the quality and permanence of care and assistance to women and families who decide not to undergo these tests or to continue with pregnancy after foetal abnormality is diagnosed
- Make every effort to ensure that the 2005 law on equality of rights and opportunity, participation and citizenship of disabled people is fully applied so that disabled and chronically sick adults and children may obtain full integration, counselling and access to their rights.

CCNE is well aware that in the near future it will become easier technically, and perhaps cheaper, to carry out whole foetal genomic sequencing than to select specific regions of interest to perform targeted sequencing, as is currently the case. This would be particularly true for commercially available tests. It follows therefore, that foetal genomic testing on maternal blood for trisomy 21 immediately raises the issue of detecting a growing number of chromosomal abnormalities and mutations associated with genetic disorders some of which are relatively benign. Once whole foetal DNA sequencing becomes a practical reality (in economic terms, in particular) and its quality is clinically acceptable, the ethical issue arises of how the information it provides will be communicated to expectant mothers and/or the couple concerned. How would the current pertinent and rigorous criterion, relating to the particular severity of the disorder and the impossibility of a cure at the time of diagnosis, be observed? How would this exercise in communication be constantly updated in the light of rapid and continuing scientific progress?

In effect, we need not be concerned so much with wondering whether such procedures are going to be used, since they surely will be, but rather with how they should be used.