National Consultative Ethics Committee for Health and Life Sciences

OPINION N° 120

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

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Members of the Working Group:

Christiane BASSET
François BEAUFILS
Frédérique DREIFUSS-NETTER
Roger-Pol DROIT
Patrick GAUDRAY (rapporteur)
Claude MATUCHANSKY
Francis PUECH
Philippe ROUVILLOIS
Dominique STOPPA-LYONNET (rapporteur)
Claude SUREAU

Personalities heard:

Roger BESSIS[1]
Henri BLEHAUT[2]
Romain FAVRE[3]
Jean-Marie LE MENE[4]
Stanislas LYONNET[5]
Nicole PHILIP[6]
Géraldine VIOT[7]

[1] Sonographer, Former President of the *Collège français d'échographie fœtale.*

[2] Director of Research, Jérôme LEJEUNE Foundation.

[3] University Professor, Hospital practitioner, Coordinator of the Strasbourg *Centre pluridisciplinaire de diagnostic prénatal*.

[4] President of the Jérôme LEJEUNE Foundation.

[5] University Professor, Hospital practitioner, Department of Genetics, Necker-Enfants Malades Hospital, Inserm Université U 781, Genetics and Embryology of Congenital Malformations, Paris.

[6] University Professor, Hospital practitioner, Genetics Department, La Timone Hospital, Marseilles.

[7] Paediatrician, geneticist, University Hospital Paris Centre, Hospital Group Cochin St Vincent de Paul, Cochin Hospital 75014

Executive Summary

Recent developments in human genetics raise major ethical issues which have not failed to attract the attention of the National Consultative Ethics Committee for Health and Life Sciences (CCNE) on numerous occasions. These developments have included genetic fingerprinting, genetic testing in adult medicine, prenatal or preimplantation diagnosis and neonatal screening.

Whilst in the process of a review of ethical issues raised by the medical and societal use of high throughput human DNA sequencing techniques, CCNE received a referral from the French Ministry of Health's Direction Générale de la Santé (DGS) stating that: "…it is now possible to detect detailed foetal genetic variations using foetal genome sequencing combined with statistical and biological data processing techniques. The scientific community can now look forward to needing only a single non invasive assay to perform foetal genome sequencing and identify several thousand genetic conditions. Such biotechnological developments add fuel to concerns regarding the potential for eugenicist tendencies." Against this background, the DGS requested from CCNE "an in-depth reflection and an opinion on the ethical issues and the problems raised by the development of the technique for prenatal diagnosis of foetal genetic abnormalities based only on a sample of a pregnant woman's blood."

Despite impressive scientific breakthroughs in understanding and diagnosing certain genetic conditions, only rarely have they been followed thus far by decisive progress for their treatment and cure. Identifying them, however, does make it possible to provide expectant mothers and couples with information on their future child's chances of being affected by a disease or a disability defined as particularly severe and incurable at the time of diagnosis. The challenge now before us is how that information should be used. Taking as an example the situation regarding the foetal diagnosis of the frequent and emblematic anomaly, trisomy 21, CCNE has been considering the potential ethical issues and the risk of a perversion of societal practices were all expectant mothers offered the possibility of sequencing the entire foetal genome merely with one single sample of the mother's blood early in pregnancy (before the fourteenth week of amenorrhoea, i.e. the legal term in France for authorising voluntary termination).

The genetic data that these techniques are already challenging us with, and will doubtless be challenging us with to an even greater extent in the future, are complex, in particular as regards interpreting the probability of a disability's or disease's onset and its degree of severity. Such data must be converted into useful, rigorous, scientifically pertinent and medically useful information. CCNE insists on the need for such conversion and for its timely use.

Since 2009, expectant mothers are routinely given the opportunity of screening for trisomy 21. Combining ultrasound examination, the dosage of maternal serum markers and the woman's age, such screening could be significantly enhanced by using the foetal genomic test on maternal blood. This increased efficacy and sensitivity is perceived in some quarters as a perverse trend leading to the elimination of a greater number of foetuses carrying trisomy 21. But in fact, adding genomic screening to the tests routinely on offer would not change the existing purpose of the procedure which is to give future parents the possibility of making a free and informed decision regarding the continuation of pregnancy. The consequence would be that the almost entire

complement of the over twenty-four thousand pregnant women per year who undergo the invasive tests required to confirm a diagnosis would be spared the risk to the foetus, and in some cases to the mother, that they represent, although they return a positive result in less than ten per cent of cases.

The foetal genetic trisomy 21 test on maternal blood could be introduced gradually as a component of the current combined screening procedure, i.e. only used for women known to be "at risk", since it would not modify intrinsically the fundamental purpose of the procedure and would simply makes it possible to reduce substantially the number of invasive follow-up sampling operations which are potentially hazardous, particularly for the foetus. Subsequently, if its scientific pertinence is confirmed, the test could be proposed as a first-line screening procedure to all expectant mothers, the limits being more technical, organisational and financial than they are ethical. However, supposing that these hurdles can be successfully negotiated, such an extension would require certain conditions to be fulfilled to ensure pertinence, safety, equality of access regardless of financial resources, as well as information and counselling procedures of appropriate quality.

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. The fact that their technological and economic context is on the whole favourable (the cost of whole genomic sequencing is on a rapid and continuing downward curve) does not, however, justify indiscriminate use without due consideration for the very important ethical issues which they may raise. In this connection, CCNE wishes to highlight a social context generating currents of thought regarding the stigmatisation of disability and the economic and social burden it represents, a relative rejection of "differences", or even the claim that there is such a thing as a "right" guaranteeing a future child's good health. CCNE prefers to insist on the need to care for people suffering from disablement or disease, in particular chronic and/or degenerative disorders. Over and above overriding humane considerations, such care also implies an essential research dimension, both in biomedical terms and involving the human and social sciences.

Accepting the right to be different leads CCNE to consider, in defiance of existing concepts on the relationship between health and normality, that disability and ill-health are also "hallmarks of humanity ". Should not human normality include disability and disease?

Table of Contents

Key to Abbreviations:

ABM	*Agence de la biomédecine* (French national biomedical agency)
CCNE	*Comité consultatif national d'éthique pour les sciences de la vie et de la santé* (National Consultative Ethics Committee for Health and Life Sciences)
CNGOF	*Collège national des gynécologues et obstétriciens français (French National College of Obstetricians and Gynaecologists)*
CPDPN	*Centre pluridisciplinaire de diagnostic prénatal* (Pluridisciplinary Prenatal Diagnosis Centre)
DGS	*Direction générale de la santé* (French Ministry of Health's General Directorate for Health)
DNA	Deoxyribonucleic acid (*see* Glossary)
DTC	"Direct To Consumer". At-home testing, i.e. tests directly available to consumers, *via* the Internet in particular.
ETP	Elective Termination of Pregnancy
HAS	*Haute autorité de santé* (French National Authority for Health)
IVF	*In vitro* fertilisation
PD	Prenatal Diagnosis
PIGD	Pre-Implantation Genetic Diagnosis
RNA	Ribonucleic acid (*see* Glossary)
TTP	Therapeutic Termination of Pregnancy
WHO	World Health Organization

"The road to genomic medicine is paved with challenges and uncertainty"[8]

This Opinion refers to genetic concepts which may be difficult to follow for non specialists and, to preserve the substantive meaning of the Opinion, some technical vocabulary was inevitable. For the reader's convenience, a GLOSSARY of technical terms attempts to provide simple definitions of the main scientific and technical terms, and has been included at the end of the document.

I Introduction

Based on a simple blood sample from an expectant mother, it is now possible to sequence the foetal genome by reconstituting the foetal DNA that is present in a fragmentary form in the mother's blood[9]. Methods for foetal genome analysis on maternal blood, which are non invasive for the foetus and devoid of risk for the expectant mother, were developed years ago and are already in use for certain rare and specific cases. In 2013, they became available for general use. This major technological breakthrough came about in two successive phases: (1) the observation in 1997 that free foetal DNA was present in maternal plasma as early as the first weeks of gestation[10]; (2) the extremely rapid increase in the capacity for sequencing nucleic acids (DNA, RNA) in recent years[11].

The French General Directorate for Health (DGS)[12] referred to the National Consultative Ethics Committee for Health and Life Sciences (CCNE) and asked for *"an in-depth reflection and the submission of an opinion on the ethical issues and the problems raised by the development of the technique for prenatal diagnosis of foetal genetic anomalies based on a single sample of a pregnant woman's blood."*

CCNE also received a query on the same subject from the (National College of French Obstetricians and Gynaecologists) (CNGOF), and from the CERBA Laboratory. The questions concerned the legitimacy of such testing, and the conditions in which the possible development of foetal genetic testing on maternal blood would be used. It would seem, *a priori*, since they are non

[8] MacArthur DG, Lek M. *The road to genomic medicine is paved with challenges and uncertainty. Trends Genet.* 2012; **28**: 303-305.

[9] An alternative line of research involves the foetal cells present in maternal blood which currently developing techniques can isolate and purify. (Mouawia H, *et al*. Circulating trophoblastic cells provide genetic diagnosis in 63 fetuses at risk for cystic fibrosis or spinal muscular atrophy. *Reprod Biomed Online*. 2012; **25**: 508-520.) The DNA of these cells can also be the object of high throughput sequencing.

[10] Lo YM, *et al*. Presence of fetal DNA in maternal plasma and serum. *Lancet*. 1997; **350**: 485-487.

[11] Metzker ML. Sequencing technologies, the next generation. *Nat. Rev. Genet*. 2010; **11**: 32-46. Eisenstein M. The battle for sequencing supremacy. *Nat. Biotechnol*. 2012; **30**: 1023-1026.

[12] See the letter of referral appended to this Opinion.

invasive, take place very early in pregnancy and can analyse part or the whole of the foetal genome, that they would be easily implemented. Other points at issue are that, should such tests be used, there would be a risk that expectant mothers might take hasty decisions to terminate a pregnancy and a further risk of triggering eugenicist tendencies.

Context of the Opinion and review of earlier basis for CCNE reflection on the subject, in particular Opinion N° 107 in 2009.

CCNE has published several opinions on antenatal diagnosis. The latest, Opinion N° 107, in November 2009, considered ethical issues in connection with prenatal diagnosis and preimplantation genetic diagnosis as practised in France. The Committee came to the conclusion that, in the context of then current legislation and practices, the system was "*generally satisfactory*", taking account of the fact that it was limited to conditions of particular severity incurable at the time of diagnosis and the decision by the expectant mother or the couple concerned was based on free and informed personal choice within a medically assisted framework.

In Opinion N° 107, CCNE initiated a prospective reflection process, on the acceptability of genetic testing in the absence of any particular warning signs, such as the birth of an older sibling suffering from a serious and incurable disease. Another line of thought was concerned with ethical issues arising out of very early diagnosis based on maternal blood. CCNE also pointed out, in connection with a proposal to initiate preconceptional screening of future parents carriers for genetic abnormalities and with the question of antenatal diagnosis, that *"the central issue must always be the predictive value of such mutations in terms of severity and incurability. Today, this issue stands in the way of rapid generalisation of such tests."*

As regards more specifically foetal tests on maternal blood, CCNE, after emphasising the undeniable advantage of avoiding invasive procedures (e.g. amniocentesis, etc.) with a risk for the foetus and even for the mother, insisted on the "*risk of proceeding with elective termination at the slightest doubt (before the legal deadline) for mothers and couples who are left without benefit of counselling.*" The Committee's concern was the danger inherent to the speed of diagnosis which could eliminate the possibility of thinking the question through before taking a momentous decision.

CCNE was also concerned with the possibility of antenatal genetic diagnosis tests on maternal blood samples being open to commercial transactions, in particular on the Internet, which would make it difficult to control the procedure at all and could lead to "*a real threat of predictive "medical tourism" becoming the norm with helpless and distraught couples attempting to cope with unvalidated test procedures*." CCNE went on to say: *"Harmonising legislation on an international scale is a hazardous undertaking due to cultural particularities (see for example the differences between countries as regards paternity tests), even though we should try to move in that direction at the European level."*

The scientific and medical context

The first applications of foetal DNA testing in maternal plasma were developed early in the first decade of the twenty-first century to determine the prenatal diagnosis of foetal gender for recessive X-linked genetic disorders, for the risk of masculinisation of female foetuses in the presence of an adrenal enzymatic deficit or for diagnosing foeto-maternal rhesus factor incompatibility. In the latter two situations, prenatal diagnosis gives rise to medical treatment for the foetus. Such applications are relatively simple since they are based on the detection of short foetal DNA sequences (specific areas on the Y chromosome, mutations of the gene encoding 21-hydroxylase or specific variants of the rhesus system genes) which are not part of the expectant mother's genome. They are in frequent use in France.

High-throughput sequencing, also called "next generation sequencing", multiplies by a factor of 50,000 the capacities of classic sequencing. Combined with bioinformatic analysis, high-throughput sequencing can find foetal DNA sequences representing only some 10% of plasmatic DNA as early as the 11th week of amenorrhea. In this way, a large number of genes or other chromosomal foetal areas[13], or even the whole genome[14], can be studied.

Such analysis may be directed at (1) diagnosing abnormalities in the number of chromosomes (aneuploidy), of which trisomy 21 is the most frequent and emblematic; (2) diagnosing chromosomal microdeletions associated with clinical conditions, intellectual disability in particular; (3) diagnosing Mendelian monogenic disorders; and finally, (4) the coding regions for the foetus' 23,000 genes, or even the six billion foetal genome base pairs which can be sequenced. We are therefore dealing with a vast number of genetic variations, a large part of which we are still unable to interpret.

Very early on in pregnancy, before the fourteenth week of amenorrhea, with is the legal limit in France for requesting elective termination of pregnancy (ETP) foetal testing on maternal blood becomes possible, which is the reason why such tests are described as being "ultra-early". We must note here that the difference between elective termination of pregnancy (ETP) and therapeutic termination of pregnancy (TTP) is not limited to their timing, the former being earlier than the latter. The indications are also different as is the procedural path followed by the two kinds of termination and therefore the counselling provided for the woman concerned. To sum up, the indication for TTP is associated with the existence of a severe threat for the foetus, whereas ETP takes into account the pregnant woman's state of distress. However, if instances where testing reveals a genetic risk for the foetus within a time frame compatible with acceptance of the request for elective termination, it is clear that the mother's distress, which might not be proportionate to the severity of a risk justifying therapeutic termination, could nevertheless be in her judgment a legitimate reason to proceed with elective termination.

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[13] Lo YM, *et al*. Maternal plasma DNA sequencing reveals the genomewide genetic and mutational profile of the fetus. *Sci. Transl. Med*. 2010; **2**: 61ra91.

[14] Fan HH, *et al*. Non-invasive prenatal measurement of the fetal genome. *Nature*. 2012; **484**: 320-324. Lo YM, *et al*, Maternal plasma DNA sequencing reveals the genomewide genetic and mutational profile of the fetus. *Sci. Transl. Med*. 2010 ; **2**: 61ra91.

Prenatal genetic tests on maternal blood will inevitably be automated both as regards the procedure itself and its computed analysis, so that they may well be made available to a large number of pregnant women. They will therefore be representing major financial interests, the object of keen competition between the small number of companies developing them[15], and there will be a market for genetic testing freely accessible over the Internet. We cannot allow such test to be acceptable or otherwise purely as the result of their being marketed by these economic agents and the commercial arguments which are bound to be part of the selling process.

"Knowing" the genome and "genetic determinism".

CCNE is well aware that in the near future, it will be technically easier, and probably cheaper, to carry out whole foetal genomic sequencing than to select specific regions of interest to perform targeted sequencing, as is currently the case, in particular for commercially available tests (Prenatest®, in particular). A major ethical issue, consubstantial with the limits of knowledge that genomic sequencing can provide: to distinguish between promises and illusions, or between predicting a devastating disease and a variation with no impact on health. The fact that we can read the foetal or adult DNA sequence in no way signifies that we are able, as yet, to interpret it fully in terms of its medical implications.

While there are cases when a gene mutation leads univocally to a certain disease, the complexity of living organisms is not defined by 23,000 simple components, the genes, but by their combination and their interaction with the environment and the partly random characteristics of their expression. *"The elegant simplicity of the DNA structure revealed by Watson and Crick is still stunning. True to its promise when it was first discovered, it opened up the flood-gates to understanding heredity. But one of the most profound lessons from the ensuing decades of genome exploration must be that the linear arrangement of bases in the DNA is not an absolute set of instructions but is malleable by the cellular environment. We are just beginning to uncover some of the mechanisms that are responsible for these effects. As is the rule in biology, wherein the whole is often greater than the sum of its parts, we are realizing that the genome is far more complex than the sequence of its DNA."* [16].

Recent genetic practice refers increasingly to concepts involving risk and susceptibility, which can only be expressed as probabilities, implying that factors external to the genome, and *a fortiori* to the DNA, influence the way in which genes will be put to use by various cells and by the whole organism, especially when complex traits are involved. [17],[18]

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[15] The number of these companies is still limited at the present time because of the patents protecting the techniques used.

[16] Misteli T. The cell biology of genomes: bringing the double helix to life. *Cell*. 2013; **152** : 1209-1212.

[17] CCNE, Opinion N° 46 (2005) : "Genetics and Medicine : from prediction to prevention".

[18] *« L'intérieur et l'extérieur s'interpénètrent, et tout être vivant est à la fois le lieu et le produit de cette interaction ».* Lewontin R. *La triple hélice: les gènes, l'organisme, l'environnement.* Seuil, 2003.

For a general overview of the subject, it may also be helpful to read: Jablonka E. & Lamb M. *Evolution in four dimensions: genetic, epigenetic, behavioural, and symbolic variation in the history of life.* MIT Press, 2006.

Position of this Opinion

As a first step, it would appear necessary to consider how antenatal screening for trisomy 21 would be modified by the introduction of a foetal test on maternal blood and to discuss the specific ethical issues raised by the technical developments of this form of screening.

In the second place, CCNE wishes to extend its consideration to the full complement of genetic tests for which clinical pertinence is currently confirmed, in particular when the follow-up is medical treatment beginning in childhood or when a particular severe disease or disability is involved and it is incurable at the time of diagnosis[19].

[19] French Code of Public Health - Article L2213-1.

II Trisomy 21 foetal test on maternal blood

Trisomy 21, also known as Down's syndrome[20], is a genetic disorder associated with physically recognisable developmental abnormalities and a varying degree of intellectual disability, leading only too frequently to stigmatisation of those affected, both children and adults. Although it is still incurable, medical treatment of course, but above all access to education, the acquisition of learning skills and counselling greatly improve the quality of life of sufferers and provide them with a life expectancy which is almost on a par with that of the general population.

Trisomy 21 is a special case compared to other genetic diseases and disabilities because:

1. It is a frequent disability, since its incidence in the absence of prenatal screening was evaluated at one of every 770 births in the early 1990s[21]. Incidence at birth has diminished as a result of systematic offers for prenatal screening. Today, it is estimated at one out of every 2000 births in France.
2. It was the first constitutional aneuploidy to be identified[22]. In the majority of cases it appears *de novo*, i.e. not inherited from parents.
3. There is an extra copy of an entire chromosome representing therefore, a third copy (instead of the usual two) of over 250 genes, making it difficult to identify those involved in the physiopathology of the disease.
4. At this point in France, it is the only disability or genetic disease for which prenatal screening is proposed to all expectant mothers (around 800,000 annually). There are several detectable risk markers present in a pregnant woman's serum or by ultrasound foetal screening so that it is possible to determine a group of women "at risk" to whom is proposed an invasive foetal genetic test (karyotype based on chorionic villous or sampling amniotic fluid). Although these tests do represent a risk for the continuation of gestation or even, exceptionally, for the mother herself, they are quite frequently used: 10% of pregnant women in 2009.
5. Trisomy 21 is classified as a severe and incurable disability and therefore qualifies for the possibility of therapeutic termination of pregnancy (TTP). Systematic screening

[20] The clinical disease was described for the first time in 1866 by John Langdon Down, i.e. almost a century before the underlying chromosomal abnormality that is its cause was discovered. The impairments caused by trisomy 21 affect patients to a greater or lesser degree as regards frequency and severity: a varying degree of intellectual disability, dysmorphia, retarded growth, less than average size, general hypotonia and malformation of various organs (heart, digestive tract, kidneys, bones).

[21] Although prevalence of trisomy 21 is estimated at one out of 770 births, it is much higher at conception (1/345) but may lead to spontaneous abortion.

[22] Lejeune J, Gautier M, Turpin R. *Étude des chromosomes somatiques de neuf enfants mongoliens.* (Study of somatic chromosomes of nine Down's syndrome children) *C R Acad Sci Paris*. 1959; **248**: 1721-1722 et *Bull Acad Med*. 1959; **143**: 256-265.

offers, accepted in 85% of cases, lead to therapeutic termination in 95% of positively diagnosed cases[23].

The medical and technical dimension

Since the mid 1970s, a number of western countries have set up various policies for prenatal screening of trisomy 21, in particular for groups of women recognised as being statistically at risk, above all because of their age (40 years old or older, later 38 years or more)[24]. These policies evolved following the discovery of several aneuploidy markers (for trisomy 21 in particular) in maternal blood and the identification of ultrasound imagery signs which made it possible to develop new and more efficient screening strategies. Since 1997, prenatal trisomy 21 screening has been regulated in France and became available to all pregnant women. In 2007, the *Haute Autorité de Santé* (HAS - French National Authority for Health) circulated a report on the assessment of strategies for trisomy 21 screening, and in 2009 the French Ministry of Health published an official order to set out: *"rules of good practice as regards screening and prenatal diagnosis using maternal serum markers for trisomy 21"*. This systematic screening offer is currently based on a strategy combining the maternal blood assay of serum markers[25] and an ultrasound scan of nuchal translucency, performed in the first trimester of pregnancy. The interpretation of results furthermore takes the mother's age into account.

Once the screening process is completed, a risk factor is calculated. Depending on its value, invasive sampling may be suggested to arrive at a karyotype analysis and provide an almost certain diagnosis. With a low risk threshold motivating the suggestion to diagnose, and with higher screening sensitivity (i.e. the number of false negative results is low), but with lower specificity (i.e. the number of false positive results of screening is high) the greater the number of invasive tests will be performed, although most of them will diagnose an absence of trisomy. Conversely, the higher the risk threshold triggering a suggestion to diagnose, the higher will be the number of false negatives, but the number of false positive screening results will be lower. The specialists chose a compromise figure for the risk value threshold of at least 1/250 before an invasive diagnostic procedure for confirmation is suggested. For this risk value, the rate of false negatives is around 20%, leading to excluding from screening one trisomic foetus in five, and approximately 3% of pregnant women (i.e. some 24,000 women) will be targeted for an invasive procedure. In over 9 cases out of 10, trisomy 21 will be excluded (i.e. a false positive

[23] Source: Agence de la Biomédecine (ABM) (French national biomedical agency), 2010

[24] The recent situation in 14 European countries is presented in: Eurocat (European surveillance of congenital anomalies) special report on Prenatal screening policies in Europe, 2010 (http://www.eurocat.ulster.ac.uk).

[25] The serum markers assayed between the 11th and 13th week of amenorrhea as part of the combined screening procedure are the free beta fraction of the human chorionic gonadotropin hormone (beta hCG) and the Pregnancy Associated Plasma Protein A (PAPP-A).

The combination of alpha-protein, human chorionic gonadotropin and oestriol levels, expressed as multiples of the median (MoM), evaluates the risks based on a blood sample taken between 14 and 16 weeks of amenorrhea as part of a sequential screening procedure.

rate of over 90% in relation to the women to whom the invasive procedure was suggested, and a 2.8% false positive rate in relation to the total number of pregnant women)[26].

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.

1 - Risk of foetal loss.

When the results of screening indicate a 1/250 risk at least of trisomy 21, the expectant mother is given the possibility of agreeing to an invasive diagnosis based on the foetal karyotype. Choriocentesis or amniocentesis is used to sample foetal cells. The risk of miscarriage brought about by these sampling procedures is estimated at 1/300 to 1/100. "Combined" screening in the first trimester of pregnancy has resulted in a marked reduction of the number of foetal sampling procedures and thereby, in the risk of foetal loss. This number of sampling procedures has dropped from 10% of pregnant women before 2009, to about 3% currently, i.e. a yearly drop from 80,000 to 24,000 out of the 800,000 pregnancies[27]. Had the 24,000 annual karyotype analyses to diagnose trisomy 21 been continued, 80 to 240 foetal losses due to foetal sampling would have occurred.

The latest trisomy 21 diagnostic test procedures using foetal DNA circulating in maternal blood are based on an analysis of specific sequences of chromosome 21 and of other chromosomes as controls. The quantitative ratio between the foetal DNA of chromosome 21 and the DNA of each of the other chromosomes is 1.5 in the event of trisomy 21 and 1 in the absence of trisomy 21. The nature and extent of sequenced control chromosomes vary from one kind of test to another. However, the studies published on various foetal tests available for trisomy 21 are all coherent: they are almost perfect as regards their sensitivity (≥ 99% of samples that can be interpreted). It should be noted, however, that 5% of samples cannot be interpreted for technical reasons. Moreover, the number of false positives is very small but not zero: it is estimated to be 1/500[28]. Because of these false positives, the professional view is that they must validate positive results by means of a karyotype based on a foetal sample, i.e. an invasive procedure. As a result, the foetal test on maternal blood is not seen at this point as a diagnostic test, in other words as a confirmation of disease, but rather as a screening test, leading to inclusion in an "at risk" group.

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[26] Weingertner AS, *et al*. *Dépistage combiné de la trisomie 21 au premier trimestre : à propos de cinq ans d'expérience prospective multicentrique.* (Combined trisomy 21 screening during the first trimester: five years of multicentric prospective experience) *J. Gynec. Obst. Biol. Reprod*. 2010; **39**: 353-361.

[27] All these estimates are based, for the sake of convenience, on 800,000 pregnancies per year. They do not take into account the fact that not all pregnant women decide to go through with screening or diagnosing trisomy 21.

[28] The false positive rate is the number of foetuses counted as positive for trisomy 21 who are in fact not affected. The 1/500 ratio (or 0.2%) was observed in an "at risk" population of women [Bianchi DW. From prenatal genomic diagnosis to fetal personalized medicine: progress and challenges. *Nature Med*. 2012; **18**: 1041-1051]. It could be similar in the general population.

The excellent sensitivity of the foetal test on maternal blood would mean that if it were used for women considered to be at risk (> 1/250, for example), there would be a reduction in the number of invasive procedures. This test would therefore prevent a great many foetal losses and furthermore would be danger-free for the pregnant women concerned[29]. Furthermore, in the event that the trisomy 21 diagnosis is confirmed, since the test on maternal blood is done at a very early gestational age and can be validated very swiftly, the formal diagnostic (using the classic foetal karyotype procedure) could be brought at a much earlier point in pregnancy so that therapeutic termination could be asked for and accepted at a much earlier time in the pregnancy and would be less traumatic both physically and psychologically.

If the foetal test on maternal blood was suggested at the outset and to all the 800,000 women expecting a child annually, this could compensate for the lack of sensitivity (81%) of the combined screening protocol in the first trimester of pregnancy. The results would be that all trisomy 21 foetuses would be diagnosed for women who had chosen to be screened, i.e. around 2,400, and therefore divide by ten the number of invasive and potentially dangerous samplings. In view of on-going technical advances, the samplings might well cease to be essential when the use of maternal blood tests brings the number of false positives down to almost zero.

2 - Incidental data associated with classic foetal karyotype analysis.

For the detection of trisomy 21, necessary confirmation of diagnosis is still given today by a karyotype of foetal cells based on chorionic villus or amniotic sampling. While it is a technical reference, karyotype analysis does raise some ethical issues, in particular because as it can analyse all the chromosomes, it opens the door to the possible detection of other abnormalities or chromosomal alterations which were not the original object of the research and which may, or may not, be “of particular clinical severity”. Apart from the diagnosis of the severe 13 and 18 trisomies which are frequently, but in a less sensitive form, associated with a modification of the same serum markers as those for trisomy 21, these abnormalities may be clinically less severe, or even much less severe, such as those involving the number of sex chromosomes, the Klinefelter syndrome for instance, where two X chromosomes are associated to a Y chromosome with an effect on the fertility of the person concerned. As these “incidental” abnormalities were not the initial object of investigation and are identified fortuitously, expectant mothers or couples are unprepared or uninformed when are told about them. Furthermore, they are already vulnerable because the whole trisomy 21 screening process itself generates anxiety.

Although a very different systematic genetic screening was being discussed at the time, both as regards when it was performed (post-natal screening) and the kind of disorder (cystic fibrosis), CCNE has already examined the issue of incidental discoveries from two angles: that of the direct interest for the patient being screened and that of the equity between the small number of those screened at the end of a multi-phased procedure and the great majority of

[29] Apart from foetal loss, chorionic villous and amniotic fluid sampling can be the cause of rare maternal morbidity, such as septicaemia, pulmonary embolism and haemorrhage.

those who are not. CCNE urged the greatest caution regarding the dissemination of information which was not sought after initially and which, therefore, had not been the subject of prior free and informed consent: "*Scientific and technological breakthroughs could lead to founding the choice of our behaviour, not on ethical reflection but on obtaining automatically generated data through the use of new techniques when they are neither expected nor planned for. In-depth prospective examination by professionals and society as a whole is therefore needed to determine appropriate access to genetic test results and data so that their contribution to health and personal dignity is optimal and their unconsidered use does not contradict the ethical dimensions of medicine"* [30].

Learning about an abnormality in the prenatal period puts future parents in a very singular position; they are stunned and unable to reason, they become conscious of anticipated responsibility for an unrepresented being. They project themselves into their child's future and may be unable to accept the idea that the child will have to cope with a disability of some kind (sterility with Klinefelter's syndrome; sterility and short stature with Turner's syndrome[31]). In the circumstances, they may find it difficult to take in the "reassuring" arguments put forward by members of the medical professions.

On the contrary, because of its specificity in recognising trisomy 21, the foetal genetic test on maternal blood targets a specific abnormality being researched on the basis of a risk calculated following warning signs. As a result, this test reduces by over 90% the absolute number of classic foetal karyotyping based on chorionic villus or amniocentesis sampling, and therefore reduces the absolute frequency of the risk of fortuitous discovery of incidental chromosomal abnormalities, of varying clinical severity as discussed in the examples above. Nevertheless, the technical limit imposed by the strict targeting of a specific disability, in this instance trisomy 21, does not put to rest the ethical debate. In fact, this is a limitation put on the transmission of information which may be perceived as an obstruction to the process of informed consent. How will the ethical problem be solved once genome analysis on maternal blood is extended to other targets, or even to the entire genome?

3 - Technical and economic feasibility

It is absolutely essential to reflect on the feasibility of foetal testing for trisomy 21 on maternal blood. At this time, technical feasibility is constrained by the existence of patents which are the subject of court proceedings so that the number of companies offering the product is limited. In Europe, a commercial corporation called LifeCodexx is marketing one of these, called PrenaTest®, at a unit price of €1250. Maternal blood, sampled by the physician monitoring the mother during pregnancy, is analysed by LifeCodexx's diagnostic laboratory

[30] CCNE, Opinion N° 97 (2007): Ethical issues arising out of the delivery of neonatal genetic information after screening for genetic disorders (the examples of cystic fibrosis and sickle-cell disease).

[31] A syndrome affecting women discovered by Henry Turner in 1938, combining short stature, dysfunctional ovaries, sterility and sometimes heart disease. In most cases, the syndrome is linked to the absence of an X chromosome (monosomy X).

(Konstanz, Germany) who return the results within two weeks[32]. Considering the probable extension of this test to the rest of Europe (Germany, Austria, Lichtenstein and Switzerland have already authorised it for use on their national territory) and, *a fortiori*, if the offer is made to all pregnant women, it will become necessary to revise existing procedures. Getting this test started up requires the creation of platforms equipped with very high-throughput sequencers, with the requisite computing capability and capable of coping with an inrush of samples and returning results within a short space of time. These platforms, be they or not connected to hospital services, must satisfy quality controls and be approved by the competent authorities[33]. Collecting the blood samples, rapid plasma isolation, transport to a diagnostic platform, will require seamless and faultless organisation. Limiting the number of samples that cannot be interpreted will also be a major issue. Currently, it is 5%, that is 1,200 for every 24,000 tests if combined screening remains the norm, and would 40,000 if all pregnant women were offered the test. In any event, specifications would have to be drawn up and pilot experiments be conducted before the testing is scaled up to full strength.

In economic terms, running this genetic test on maternal blood samples, to begin with on the 24,000 women at risk identified through the first trimester combined tests, is in itself a challenge[34]. To scale up to the annual complement of 800,000 pregnant women would be a further challenge. The cost of diagnosing trisomy 21 by karyotyping, taking into account only the 24,000 women screened as a result of the first trimester combined protocol is estimated at this point at €12 M[35]. If the maternal blood test was done only for women at risk, this would cost at the unit price given of €1250, two and a half times this amount, i.e. around €30 M.

If the maternal blood test was, at the outset, done annually for the 800,000 pregnant women on the same unit cost basis, the cost would be considerable, approximately 1 billion Euros. Apart even from the constant reduction in the individual cost of such a test, as is currently observed, its extension to all pregnant women would reduce even further the unit price, although at this point it is not possible to be more precise.

Nevertheless, this cost is bound to have an impact of health care expenditures. CCNE's Opinion N° 101[36], already underscored that "*Disregarding the finite nature of available*

[32] Currently, a Belgian firm called Belge Gendia, European representative of Natera™, is proposing a test which can evaluate five chromosomes (13, 18, 21, X & Y) on a sample of 20 ml of maternal blood for €850. At this time, the analysis is carried out in the firm's Californian laboratory.

[33] If the platforms were funded by industry, their cost would be included in the tests' unit price. Depending on the results of the current legal "sparring" regarding the property and exploitation of patents, they could also be run at the expense of the community, the cost of which would not be included in the unit price of the test, or they could be funded by the community, so that testing could be done without buying the test kits from industry. The answers to these questions will, quite obviously, condition the economic feasibility of the entire operation and therefore the acceptability of such tests.

[34] This number of 24,000 women represents the goal for the complete implementation of the current screening protocol; an objective that is in the course of being achieved. It was still 45,000 in 2011.

[35] Not forgetting that a karyotype procedure costs €250, to which should be added about as much for the cost of sampling.

[36] CCNE, Opinion N° 101 (2007): "Health, ethics and money: ethical issues as a result of budgetary constraints on public health expenditure in hospitals".

resources would necessarily lead to restricting access to health care. For some patient populations access would then be a question of chance or discrimination, with major ethical consequences." Opinion N° 101 argued in favour of choices being made deliberately rather than being forced by circumstances and for avoidance of the two major risks arising out of authoritarian limitations on financial resources: loss of accountability on the part of social actors and impaired access to health care. Priorities must therefore be collectively recognised if choices are not to be arbitrarily imposed.

The Ethical Dimension

Trisomy 21 is a special case in the array of prenatal care, since it is the only disability or serious disease which leads systematically to an offer of prenatal screening which, despite imperfect sensitivity, leads to a significant number of therapeutic terminations. Actually, it is society's choice to implement this screening protocol which raises a fundamental ethical issue[37], in particular because of the large number of foetuses affected and the very high preponderance of therapeutic termination when the foetus is affected.

In the presence of this situation and of this apprehension, one cannot but remark on the very great deficiencies of French research on disabilities in general and on trisomy 21 in particular[38]. CCNE therefore wishes to reiterate a significant message expressed in its Opinion N° 107, to the effect that the "*...authorities [should] promote and finance research...*" which is known to be insufficient in this country. Attention should also be drawn to the persistence in our country (despite de 2005 law on equality of rights and of opportunity, participation and citizenship of disabled people, and despite France's ratification of the UN December 2006 Convention on the rights of disabled people) of a major flaw in the assistance to, and social inclusion of, children and adults suffering from a disability. In its Opinion N° 101, CCNE strongly emphasised this point: "*A society which is incapable of recognising the dignity and pain of those who are most vulnerable and most in need, be they children, adolescents, or adults, and which cuts them off from the community, because of that extreme vulnerability, is a society which is losing its humanity*." [39].

And yet, the introduction of new methods, just as reliable but less invasive than karyotyping based on chorionic villus or amniocentesis sampling, does not intrinsically modify the substance of current procedure. It should even be perceived as progress as regards currently available screening offers since, in particular, it would limit harmful side effects.

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[37] "*...CCNE cannot approve a public health programme for the mass systematic detection of trisomy 21, whether by direct means or biological blood tests. However, the Committee would not have any objection to a programme designed to narrow down the medical indications of cytogenetic diagnosis of foetal trisomy 21 so that women who so wish may use biological blood tests.*" CCNE, Opinion N° 37 (1993). Opinion on the detection of the risk of foetal trisomy 21 by blood tests in pregnant women.

[38] There is a clear lack of scientific research on trisomy 21, in particular in France where under half a dozen research teams are working on this subject.

[39] CCNE, Opinion N°102 (2007) : "*On the situation of autistic children and adults in France*".

There might be cause for doubts as to possible unintended adverse consequences in the event that the foetal trisomy 21 test on maternal blood would be offered to all pregnant women as a component or complement of today's combined screening procedure. The offer of screening made to all pregnant women would not change, as would not probably change either the proportion of women who accept the procedure (currently 85%). What would change, however, would be the efficacy of this first screening step, from 99% for the genetic maternal blood test as compared to approximately 80% for today's combined screening procedure.

The introduction of a reliable molecular test is therefore a step forward for expectant mothers[40]. While there does not seem to be any reason *a priori* for coming to any other conclusion on the subject, the practical aspects of its implementation raise questions concerning: (1) the actual conditions of making a choice or taking a decision for pregnant women, in particular the quality of information provided and the time lapse allowed for taking a decision; and (2) the risk of trivialising the decision, or even presenting it as routine owing to the apparently anodyne and easy use of this test, considered in some quarters as being the first steps on a slippery slope.

1 - The contraction of time between screening and diagnosis in future and the difficulties of providing information

Following the French National Authority for Health's (HAS) report in 2007 on screening for trisomy 21 and its recommendation that adequate information be given to all the women involved, information on diagnosing foetal trisomy 21 and the possibility of therapeutic termination is now communicated on three separate occasions: at the time when screening is offered to the 800,000 women who become pregnant every year, but particularly when the almost 24,000 women who are at risk are approached with an offer of an invasive diagnostic procedure, and finally when the almost 2,000 women for whom the results of the test are positive are apprised of the fact. Despite all the efforts currently deployed to ensure free and informed decision, there can be reasonable doubt that all the women fully understand the situation and therefore that their consent is truly informed. The efforts on the part of professionals — the CNGOF in particular — to clarify the information deserves a mention. CNGOF recently published a leaflet, in cooperation with the National Committee for Obstetrical and Foetal Ultrasonography, DGS and ABM. Furthermore, certain regional branches of the *Ordre des Médecins* (French Medical Association) are circulating a similar document.

The value of information resides not only on its quality and the ease of access to the documents delivering that information, but also on the quality and the length of time spent by professionals in explaining it orally. It also depends on the amount of time the person receiving the information can devote to assimilating and absorbing it. The ethical issue here is linked to the formidable and rapid development of techniques leading to "the time contraction" between a test being offered and its implementation, one the one hand, and between the

[40] "*New possibilities offered by judicious and sober use of prenatal diagnosis can only be of benefit to patients, their families, and the population as a whole.*" CCNE, Opinion N° 5 (1985): "Opinion on problems raised by prenatal and perinatal diagnosis."

performance of the test and the results becoming available, on the other hand. The problem is compounded by the price-per-activity system which favours the time spent on the performance of technical actions at the expense of time spent on being receptive and dialogue.

It is of course clear that however excellent it may be, the information supplied to pregnant women or to expecting couples is injected with an element of "urgency" when it is imparted to people who are directly and immediately concerned; it may be received with a certain bias. Moreover, it is part of a societal context where a number of the messages received are tainted with the notion of stigmatisation of disabilities and the burden they represent in economic and social terms, of a certain degree of rejection of whatever may be different, or even the "right" of a future child to be born healthy. The information given at this point, therefore, cannot be a substitute for information given at a much earlier time, either before the couple has even conceived, or even better, as part of the school curriculum via teaching of the basics of genetics and of an effort on the part of society to accept differences more readily[41].

2 - Do the ease and speed with which they are done, and the absence of risk of these new non invasive tests for trisomy 21, raise any new ethical issues?

As a part of the current procedure for trisomy 21 foetal screening, and while both screening and diagnosis are an offer which pregnant women are under no obligation to accept, there could be indirect pressure due to a negative collective perception of trisomy 21 and, more generally, of disability, and by the major shortcomings in the integration and assistance our society[42] provides to its disabled citizens, particularly in an increasingly insistent context of trying to "save on health expenditure".

In the circumstances, the apparent ease of implementation of foetal trisomy 21 screening tests based on maternal blood, leading to technical improvement of the screening procedure (easier, more effective and fewer side effects), added to an overall simplification due to being done very early in the course of gestation, are seen in some quarters — even though they approve of replacing amniocentesis with a test on maternal blood — as a further step in the direction of trivialisation and the risk of "hunting down" trisomy 21. They interpret this as a risk of drifting into a form of eugenics.

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.

[41] CCNE, Opinion N° 109 (2010): "Society and the communication of scientific and medical information: ethical issues".

[42] See CCNE's Opinion N° 102 (2007), quoted above.

But there still remains a potential ethical issue: the way in which society will integrate and assist those dwindling numbers of people born with this disability. How will the community regard those parents who chose to give birth to children with trisomy 21? Nor should such considerations lead to instigating a sense of guilt in those parents who preferred to avoid, for themselves and for their families, the burden of educating a trisomic child and of providing for his or her future.

III Extending, or even generalising the offer of antenatal screening for disabilities and genetic disorders by sequencing foetal DNA present in the blood of pregnant women

As mentioned above, the expected advances brought about by high throughput sequencing techniques and reduction of costs will eventually lead to offering maternal blood screening or even trisomy 21 foetal diagnosis in a single procedure to all expectant mothers. Going a step further than focusing on chromosome 21, full foetal genome examination will soon be possible.

The possibility of partial or entire genome sequencing for all expectant mothers will then inevitably lead to considering whether the diagnosis of other gene or chromosome based disabilities or genetic diseases should also be on offer[43].

Prenatal diagnosis of certain particularly severe disabilities and diseases, incurable at the time they are revealed (including particularly grave mental disability), would become possible, whereas today they can only be identified after the child is born because of the absence of any ultrasound warning signs and of any family history. Prenatal diagnosis of a recessive Mendelian inheritance, which is currently impossible at this time in a majority of cases until a first affected child is born, would on the contrary become possible at the time of the mother's first pregnancy. Would it then be legitimate to refrain from offering

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.

[43] A major ethical concern raised by these techniques is the role of prediction in medical practice. The subject was previously discussed by CCNE in Opinion N° 46 (1995): "Genetics and medicine: from prediction to prevention". The involvement of genetics in predictive medicine will be examined in a forthcoming Opinion by the Committee.

such prenatal diagnosis when the diseases predicted are of "particular severity and currently incurable", i.e. when they conform with today's criteria for allowing therapeutic termination?

In a future which is certainly close, it is highly likely that it will be easier to sequence the entire foetal genome than to select areas of particular interest for targeted sequencing. Be that as it may, does the fact that it is technically possible to sequence the entire foetal genome justify its complete interpretation and/or the communication of all the data that was obtained?

If prenatal diagnosis conducted in the absence of any ultrasonic warning sign or of any family history of disease were to be accepted as the norm, it would lead to major upheaval concerning requests for prenatal diagnosis. There would be problems to be solved: technical, large-scale feasibility and the quality of prediction. And above all, there would be conditions to be met: a personal decision taken by the expectant mother or the couple and not a public health policy to be imposed on everyone; continuing research on genetic disorders and on the integration of disabled or sick children and adults into the community.

Medical and technical dimension

1 - Is it advisable to move on from prenatal diagnosis on the basis of warning signs to proposing prenatal diagnosis to all expectant mothers?

In the event that foetal tests for disabilities and disorders, which are listed as giving rise to acceptance of requests for therapeutic termination, became the norm, the prevailing system for requesting prenatal diagnostic tests and therapeutic termination would be totally transformed. At the present time in France, close on 3,000 prenatal diagnoses for Mendelian disorders[44], for over 220 different diseases, are carried out every year and lead to the discovery of over 500 cases of foetal impairment. These are genetic diseases listed by the *Centres pluridisciplinaires de diagnostic prénatal* (CPDPN - Pluridisciplinary Prenatal Diagnosis Centres) as severe and incurable at the time of diagnosis. The acceptability of therapeutic termination of pregnancy is examined on a case-by-case and family-by-family basis by the CPDPNs.

Article L. 2131 of the Code of Public Health is concerned with prenatal diagnosis in order to detect *in utero*, in the embryo or foetus, a disorder of particular severity. It provides every expectant mother, once she has had the benefit of reliable and clear information from her medical advisers, in terms appropriate to her particular circumstances, with the "*possibility of requesting further biological and medical imaging tests to ascertain the risk for the embryo or the foetus of being affected by a disorder which could modify the progress or the medical supervision of her pregnancy*". It also mentions that there is a need to "*evaluate the risk for the unborn child of being born with a particularly severe disorder, taking into account family history or medical findings during gestation*".

It is at this point that the question of the existence of a documented risk, and therefore of warning signs, arises. These may be in part the result of a chance discovery of signs of foetal

[44] As defined by the *Agence de la Biomédecine*, Mendelian disorders are genetic diseases caused by a single mutation (monogenic or single-gene disorder), excluding *inter alia* chromosomal disorders such as trisomy 21.

malformation detected by, for instance, ultrasonography. Trisomy 21 stands out as an exception in this respect, since warning signs are only evidenced once the first screening steps for the disorder have been taken, this screening being systematically proposed to all expectant mothers.

Apart from the very special case of trisomy 21, these warning signs include the existence of a genetic disorder in a member of the family, either one of the two parents or a sibling. The medical and psychological burden, and more generally the impact on the whole family of a severe and incurable genetic disorder, particularly when the first born is affected, is extremely weighty and may be experienced as an "unfair" ('why us?), while a simple and physically non invasive genetic test could have detected it.

Up to now, a technical constraint was the barrier opposing possible excesses or misuse, since chromosomal or genetic disorders were detectable after the warning signs. However, with the development of foetal genetic tests on maternal blood, based on high throughput foetal DNA sequencing, the technical and medical limits and impossibilities are no longer unbreakable obstructions[45]. Is it not a contradiction of the 'do no harm' principle that a sick child must be born before its younger siblings can be born free of disease? Is it not contrary to the principle of equity if not all expectant mothers or couples can benefit from this technique? And yet, it must also be emphasised that the possibility of giving birth to a child exempt from all and every genetic "abnormality" is no more than an illusion, which is reinforced in the public belief by technical progress in DNA analysis.

2 - From sequencing the whole genome to a selective analysis?

Besides the mutations for which the clinical transcription is both well known and frequent, there are a great number of uninterpretable modifications in the sequences of our genome, in particular when they are situated elsewhere than on our 23,000 genes. We have no knowledge of their impact on an individual's health. Worse still, a certain number of modifications in sequences, in particular chromosomal deletions, sometimes very large ones when measured against the scale of a gene, easily detectable today by DNA chips, may be inappropriately interpreted, in particular as associated with a disability.

Furthermore, a complete analysis of the foetal genome would lead to identifying genetic susceptibility to adult-onset diseases. In a majority of cases, this would be a prediction of a small increase in the probability of being affected by multifactorial disorders (diabetes for example) of variable severity. Such predictions could have a particularly stressful effect on the expectant mother or the couple. Furthermore, if it were a Mendelian, monogenic, dominant inheritance disease, this would indicate that in a large number of cases, one of the two parents

[45] It must be said however that these limits and impossibilities have not entirely vanished. From a strictly technical point of view, recent progress to which this Opinion refers demonstrates that such obstacles can be overcome. Nevertheless, the cost generated by DNA foetal sequencing alone plus that of its computed analysis and therefore its interpretation, are still very high. In so far as the French health care system is based on national solidarity, the degree of priority that can be granted to the financing of such tests is a matter for national evaluation.

would be at risk of becoming affected themselves. While this could be a useful item of knowledge for the parent concerned and for both parents in the event of their conceiving other children, it must be noted that such information is not the primary purpose of foetal testing on maternal blood.

In the circumstances, in view of the possible detection of modifications in DNA sequences that could not be interpreted, or would be misinterpreted, or would not concern only the foetus, the question arises of a selective reading of the foetal genome. An ethical issue is connected to the possibility that the identification in the foetus of gene sequences associated with a severe and currently incurable disease might well overstep the mark by answering queries that were left unasked, such as the example in the trisomy 21 diagnosis of the "fortuitous" discovery of "incidental" chromosomal abnormalities. In the case of extensive DNA sequencing, the very notion of "incidental abnormality" becomes meaningless since, in the long run, the complete set of genetic characteristics determined by that single sequence would itself become "incidental" to the answer given to the questions which would have been the justification for the foetal DNA analysis.

3 - Difficulties to overcome

Were the principle of complete sequencing and analysis of foetal DNA on the basis of a maternal blood sample to be adopted, a significant number of problems would need to be solved.

a. As in the trisomy 21 test, the number of false positives would have to be as low as possible, even lower than for trisomy 21. In this event, it would no longer be one test, but rather dozens or even hundreds of tests that would be supported by one single maternal blood sample: the risk being that the number of false positives would increase in proportion to the number of tests carried out, i.e. the number of chromosomal areas or of genes under examination. We would need to avoid creating an absurd situation where a large number of expectant mothers would have to undergo an invasive test so as to verify a result provided by maternal blood analysis. Ideally, it should be possible to validate a positive result with a second blood sample, not through invasive sampling.

b. Setting up structures qualified to provide test results of the high quality required for a large number of blood samples would be quite a challenge, be they operated by the test providing industry or by the community. They would naturally be the same structures as those testing for trisomy 21. The set up should be gradual as outlined above for trisomy 21.

c. Other difficulties are connected to the quality of the prediction and, therefore, of striving for ever-increasing reliability and precision between an identified genetic abnormality (genotype) and its clinical expression (phenotype) and to the evaluation of the probability of the disease or disability appearing in the event of such genetic abnormalities existing. It was mentioned above that in some cases, deletions of several million nucleotides do not necessarily give rise to clinical expression. They, or their mirror image, i.e. some

duplications, are no more than variations of the norm, revealing the genetic diversity of human beings. International consortia are working on mapping them for large numbers of people and discovering their clinical expression. For prenatal diagnostic purposes, only deletions or duplications of chromosomal areas for which there is a known association with a serious clinical expression should be undertaken. For very many Mendelian disorders, the gene (or genes) concerned have been identified. Their harmful mutations are associated with the onset of a disease, but with variable frequency however, which raises the issue of the threshold for considering the risk to be significant. There may also exist for these same genes variations, or rather variants for which we are unaware of their effect on the onset of the disease. Further research is needed to decide whether the variants are, or are not, harmful. There are international consortia of laboratories who are working on this subject for each of various diseases. Furthermore, the Human Variome Project[46], grouping many consortia, aims to establish a catalogue of variations of the human genome.

d. Finally, for a number of Mendelian disorders which can already today be the object of prenatal diagnosis, there are variations in penetrance and expressivity which are not dependent on the nature of the mutation in the gene involved. Such variations are due to modifying factors, genetic or non genetic in origin, environmental in particular. It would be essential to try and identify them, since it would make it easier to evaluate the probability of disease onset and the degree of its severity, thereby improving the quality of genetic counselling. It would also help to gain a better understanding of the disease's physiopathology and open up new therapeutic avenues.

For recessive diseases, there are suggestions that an alternative to foetal testing on maternal blood could be **preconceptional testing**. The idea would be that before conceiving, or before any plan to bear children, genetic tests would be initiated to check whether both members of the couple are carriers for a harmful mutation of the same gene, one involved in a serious and currently incurable disease, giving rise to the option of therapeutic termination of the pregnancy. In this way, the identification of risk would be shifted from the foetus to its future parents. This identification of couples at risk of giving birth to a child affected by a serious genetic disease, although it is already in use in certain countries for certain diseases, raises extensive and delicate ethical issues, in particular because it amounts to establishing a kind of "genetic risk identity card" with the dual danger of interference into plans for union between people who intend to have children and of classifying or categorising such people so that they could be subjected to discrimination or stigmatisation. This situation would raise ethical issues which are included in the general context of those raised by access to complete genome sequencing, at whatever age. The subject therefore requires a specific analysis which CCNE has begun to work on in view of a forthcoming Opinion.

[46] www.humanvariomeproject.org

The ethical dimension

1 – A large number of ethical issues.

The development of foetal genetic testing on maternal blood raises the following ethical issues:

a. Genetic counselling would be all the more difficult because expectant mothers or couples would have no experience of the disease and the number of them needing counsel would be greater. It would be essential that all the conditions which make it possible for expectant mothers and couples to take an informed decision are in fact present. The terms and conditions in which the information on an identified disease is given to them would have to conform to the description given in CCNE's Opinion N°107. The expectant mothers and the couples would have to benefit from the assistance of trained multidisciplinary genetic counselling teams, including in particular psychologists, with the option of calling on the expertise of a doctor specialising in the disease which had been identified. More general information to be provided to young couples, before they consider starting a family, should be encouraged.

b. The risk that anxious expectant mothers or couples might have a "pangenomic" foetal genetic test done, *via* the Internet, should concern us. In fact, results of such tests, delivered without either explanation or counsel, might lead the women or couples concerned to decide on termination of the pregnancy without the benefit of advice, providing the woman was within the legal limit of 14 weeks of amenorrhea during which elective termination is authorised. The availability of such tests forces us to be specially watchful, particularly when they are capable of detecting pathogenic mutations of Mendelian disorders which, for the time being, do not qualify for the acceptance of a request for prenatal diagnosis, or of common variants associated with an increase of a risk of multifactorial disorders, or finally, of variants of unknown biological and clinical significance. Such watchfulness cannot just be supported by the sum of prohibitions, the contours of which set the limits of their effectiveness, in particular when the prohibitions are national[47]. Even now, it is challenged by the existence of tests directly available to consumers (so called "direct to consumer" - DTC), *via* the Internet in particular. And yet, after an initial phase of enthusiasm, it would seem that the direct access to these "consumers" of the commercial companies dealing in genetic diagnosis is impeded by the fact that such consumers are also, and above all, patients. These firms, whose initial claim was their direct relationship with the population at large, seem to have understood and accepted that they cannot neglect the important part played by doctors and the one to one patient-doctor dialogue, which is of such value for essential genetic counselling; this privileged relationship gives meaning to the course chosen and helps to make the

[47] Unanimously and universally accepted regulation, conforming with the founding principles of equity governing the French health care system, seems to be unrealistic at the present time. But perhaps international ethical standards, in particular as regards personal medical genomics, is an issue that should be addressed.

messages and information derived from the analysis of the DNA sequence more acceptable[48].

c. Continuing research on all of the diseases which are the subject of prenatal diagnosis is essential. It would be proof of society's commitment to caring for the sick and of the fact that termination of pregnancy is not an end in itself, but rather a last resort. As mentioned above, research on the causes of modified penetrance and expressivity would be important because it could open up new therapeutic avenues. If, thanks to such research, a disease was no longer "incurable at the time of diagnosis" and therefore was no longer the trigger for accepting a request for prenatal diagnosis, there would be reason for both families and their doctors to be greatly pleased.

d. Acceptance, assistance and care provided by the community for those, children or adults, who are disabled or in poor health, are also essential in this instance. As stated above, it would prove that termination of pregnancy is not an end in itself. There is a special effort to be made on behalf of mentally retarded adults since it is well known that assistance and their inclusion in French society is deeply deficient. If an expectant mother or a couple know that their child will be welcomed into the community, this may well modify their decision regarding the continuation or otherwise of pregnancy.

e. It would not be acceptable, particularly from an ethical standpoint, to consider the issue of foetal genetic tests on samples of maternal blood in isolation without including in the analysis the more general subjects of sickness, disability and "being different". Similarly, the subject cannot be limited to its technical, economic and medical aspects, to the exclusion of the social and political dimensions.

f. As referred to above, systematic screening for trisomy 21 as it is currently on offer, still requires confirmation of the diagnosis through an analysis of the karyotype of foetal cells by chorionic villous and amniotic fluid sampling. Karyotype analysis raises ethical issues because since it makes it possible to analyse all the chromosomes, it opens the door to the possible detection of numerous abnormalities or chromosomal modifications which were not the object of the initial research and may not be of "particularly severe clinical consequence", such as for example the Klinefelter and Turner syndromes mentioned above. These "incidental" abnormalities, identified by chance, are announced to expectant mothers and couples who had no prior information regarding this research. These couples are, furthermore, in a vulnerable frame of mind due to the whole stressful trisomy 21 screening process. Were an offer of complete foetal DNA sequencing and of communicating all the results to the expectant mother and her partner to be made, the same kind of ethical issue would arise but expanded on a scale far beyond any comparison with the situation as it is at this point.

   At the opposite end of the dilemma, in the presence of a risk of disease or disability "incurable at the time of diagnosis and of particular severity", but with a low probability of onset, how would it be possible to differentiate responsibly between severity and

[48] Allison M. Direct-to-consumer genomics reinvents itself. *Nat Biotech*. 2012; **30**: 1027- 1029.

probability of onset? At what point would the probability be considered too low for it to be worth diagnosing and therefore taken into consideration in the case of a request for therapeutic termination?

g. Since it would be totally unreasonable to encourage the public in the illusion that it would ever be possible to achieve total prevention of genetic disabilities and disorders, one of the main issues that arise out of the very existence and development of these tests is that of the acceptance and assistance provided to the disabled and the sick. From this standpoint, antenatal detection of genic or chromosomal abnormalities can be viewed as a preliminary — at least in some cases — to early provision of care and as a kind of preparation for accepting a child who is different, when such acceptance is tolerable for the child's parents.

h. We should also reflect on the illusion that any and every disability and genetic disorder can be eradicated, an illusion that transpires in the fascination regarding technology, genetic technology in particular[49], which is perceived to be omnipotent. This illusion can only be dispelled if to the fullest extent possible the public can acquire some knowledge of genetic sciences and become aware of the boundaries of such sciences[50]. CCNE's Opinion N° 109, insisted more generally on the need for disseminating and sharing knowledge *via* institutional and pedagogical channels, in particular in genetics and genomics. This was seen as a priority[51].

2 - Is there a risk of straying into a form of "eugenics"?

In the text of his referral, the Director General for Health remarked that *"...it is now possible to detect detailed foetal genetic variations using foetal genome sequencing combined with statistical and biological data processing techniques. The scientific community can now look forward to needing only a single non invasive assay to perform foetal genome sequencing and identify several thousand genetic conditions.*

Such biotechnological developments add fuel to concerns regarding the potential for eugenicist tendencies."

The "potential for eugenicist tendencies" mentioned here, refers to the sinister eugenicist practices set up at the end of the 19th century and the first half of the 20th in democracies like the United States and Sweden, in the form of campaigns for the forced sterilisation of tens of thousands of people, with the aim of "improving" the "quality" and hereditary characteristics of the population. In the name of a scientifically preposterous and morally despicable interpretation of Darwin's evolutionary theory, biology and medicine put themselves in the

[49] "We are all young barbarians still enthralled by our new toys." Antoine de Saint-Exupéry. *Wind, Sand and Stars* (1939).

[50] "*What really needs to be done is help couples to acquire genetic knowledge, to become aware of the limitations of such knowledge, of the risks of excessive diagnosis and, at an absurd extreme, of the risk of never conceiving a child. It must be remembered that no human being is born genetically exempt of the risk of developing a serious disease at some point in his or her life.* CCNE, Opinion N° 107 (2009): "Opinion on ethical issues in connection with antenatal diagnosis: Prenatal diagnosis (PND) and Preimplantation Genetic Diagnosis (PGD).

[51] CCNE, Opinion N° 109 (2010) : "Society and the communication of scientific and medical information: ethical issues".

service of a brutal ideology of stigmatisation, discrimination and violence practised by States on the most vulnerable members of the community: people suffering from mental, motor and sensory impairment, single mothers, the unemployed, alcoholics, etc. The tragic consequences of these ideologies and practices were analysed in the evolutionist Stephen Jay Gould's book "The Mismeasure of Man" [52].

In terms of barbarity, Nazism added a radical dimension to the word "eugenics" moving on from massive forced sterilisation policy to laws on "racial purity", to murdering disabled children and adults, and finally to genocide. It was when Nazi doctors were tried in Nuremberg, in 1947, that the Nuremberg Code emerged, setting out the principles underlying modern biomedical ethics, in particular the principle of free and informed consent.

In today's world, any attempt by a State to adopt eugenicist policies is very widely[53], or even universally condemned and prohibited and viewed as a violation of fundamental human rights[54]. And even more forcibly than prohibition, messages conveyed by society may be the source of unanimous rejection of these practices.

These eugenicist policies, founded on violence against individuals and a denial of their fundamental rights, bear no resemblance to the offer made to expectant mothers of being informed of the possibility of undergoing, should they so wish, a test that can detect possible risks of disability or serious and incurable disease that their foetus may be exposed to. But, as mentioned above, care must be taken to ensure that this individual decision is truly freely taken. It must not, therefore, be influenced by pressure from society, however indirect that pressure may be, which could be the outcome of: (i) the expression of a collective negative perception regarding the birth of a disabled or sick child, (ii) concern regarding the economic cost of supportive solidarity which might have to be borne, and (iii) the major shortcomings of our society as regards the care and counsel to be provided for disabled children and adults.

It would seem essential, therefore, to muster up and comply with the conditions enabling couples to benefit from true freedom of choice and take an independent and informed decision. As a complement, collective efforts to engage in research as well as provide assistance, counselling and care must continue so that the systematic offer to diagnose — responding to the necessary requirement for equality of access to screening — in no way suggests to expectant mothers, couples, and more generally to society as a whole that there is any encouragement or instruction contained in public health policies or in the wishes of the community to the effect that only children who are exempt from any genetic abnormality which might lead to a disorder or disability can be allowed to see the light of day.

[52] Gould SJ. *The Mismeasure of Man*.

[53] See, for example, the European Union's Charter of Fundamental Rights proclaimed on December 7th, 2000.

[54] But this condemnation and this prohibition were powerless to prevent massive forced sterilisation campaigns from continuing to occur until the final years of the 20th century, as in Alberto Fujimori's Peru.

3 - How should the foetal genome be interpreted and what should be communicated?

With the intent of limiting any risk of stigmatisation and discrimination and of preserving the singularity of each family's circumstances, legislators did not adopt the principle of an *a priori* list of diseases for which a therapeutic termination request would be acceptable. And yet there is an ethical tension between the absence of such a list and the specific reference to trisomy 21 qualifying for prenatal diagnostic screening or even therapeutic termination. Is this attitude still appropriate in view of the considerable quantity of information that can be generated by the analysis of foetal DNA at an early point of prenatal existence?

With the possibility of sequencing the foetal genome present in maternal blood, numerous ethical issues emerge which, to some extent, replicate those raised more generally by the medical and societal applications of high-throughput human genome analysis techniques. CCNE is working on an Opinion on the subject. Nevertheless, there are specific aspects to foetal testing the implications of which require examination.

The first of these implications is that the information originating in a DNA sequence, whose interpretation evolves on a daily basis, will be delivered during a short period of time, i.e. the first weeks of pregnancy. Once the DNA sequence established, although its technical reliability is sufficient to enable clinical use[55] to be made of it at the time of diagnosis, interpretation of this sequence will gradually increase in precision as time goes by which raises the issue, once the child is born, of the updating of the information given to parents, then to the child and later to the adult the child may become. Should all the raw data be kept? In what form? Under whose responsibility? And when, how and to whom should it be communicated if the case arises?

The second implication is that prenatal medicine, predictive in this case, which would generalise the possibility, in principle on an equality footing for everyone, of reading the DNA sequence of very many, perhaps even of all foetuses, would currently be an exception in a society which not only does not offer this access to everyone, to adults in particular, and even prohibits access to most people. But should this lead us to not searching out in the foetus possible "particularly serious" diseases and genetic disabilities which could lead eventually to prevention and therapy?

Finally, the third implication stems for the impossibility of curing at the present time most of the genetic impairments as is also the case for most of the diseases that DNA sequencing is so far capable of predicting.

The fundamental choice which the woman or the couple concerned must make is that of continuing or terminating the pregnancy. Furthermore, the decision must be taken during a very short and particular window of time, a time of urgency. How can help in taking this decision be fully effective, but also fully neutral? Quite obviously, there is no absolute and categorical answer to such a question, nor is there a simple one, but four possible courses of action raise issues which deserve careful consideration:

[55] This is referred to as "clinical quality".

a. Use the total sequencing of foetal DNA circulating in maternal blood as simply a substitute for genetic and chromosomal tests currently authorised, reading and communicating only the results which correspond to these tests.

   In the same way as the law prohibits and punishes, except in some specific cases, the use of genetic tests for adults which are in fact less sophisticated than those we are discussing (paternity tests, genetic tests *via* the Internet) it would be theoretically possible to entertain the idea of sequencing circulating foetal DNA (when in the near future the cost will probably be lower than that of genetic testing today) solely as a technical substitute for the genetic and chromosomal tests that are currently authorised, to leave unchanged current practices for indications and free and informed consent, and only communicate after sequencing the results that would have been obtained with today's targeted genetic tests[56]. But while there is such a thing as the right not to know, is it acceptable to deny knowledge?

b. Communicate all the data acquired to the expectant mother and the couple

   At the other end of the spectrum, would it be reasonable to let them face on their own the immense quantity of data contained in a total genomic DNA sequence? No one on this earth is in possession of the computing tools required to interpret such a sequence, so that even the most distinguished specialists could not extract from it any useful or usable medical information. To obtain such information from raw data, very high-technological equipment and therefore one or several mediators are needed. Such intermediaries could be participating in a voluntarist public health scheme, aware of the need to provide compassionate counsel to couples taking delicate or difficult decisions. Otherwise, "mediation" can only be left in the hands of commercial undertakings who, in one way or another, will be motivated by considerations other than benevolence, autonomy or equity. There is reason to question, for instance, the current choice made by a commercial company to seek out aneuploidy in five chromosomes and give the same status to trisomy 21, 13 and 18 and to trisomy of the sex chromosomes.

c. Targeting, before medical intervention, the complete genome sequence.

   By attaching an interpretation to a DNA sequence (specialists call this genome annotation), one enters an area where there is great dependence on the state of the art which evolves very swiftly.

   Be it by deliberately refraining from reading certain DNA sequences, or by determination of them all and then choosing the areas which are of clinical interest, the question arises of what areas to choose and the reason for choosing them. Should sequencing target a

[56] In any case, such prohibition would be largely ineffective at a point in time when the circulation of biological samples for DNA sequencing is difficult to control and when offers across national borders are proliferating *via* the Internet™. Furthermore, circumventing this prohibition would probably not be accessible to everyone for financial reasons so that there would be a violation of the principles of equity which are the foundation of ethical thinking and the practice of medicine in this country.

particular disorder or disorders (but in that case how many and which?) or should the parents' wishes be taken into consideration although as things stand at present, we know that they are not sufficiently well informed of all the disorders their future child may be exposed to?

Setting up a procedure for the establishment and constant review of a set of genetic and chromosomal diseases and disabilities could be considered. In such circumstances, implementing a selective DNA sequencing procedure would need to meet two essential conditions:

1. Interdisciplinary thought given to the procedure. The contribution, in particular of non medical professionals, is of paramount importance on this sensitive subject that the public is having difficulty in accepting. While the criterion of being incurable can be defined medically and can be revised as and when therapeutic advances are made, that of 'particular gravity' incorporates non medical considerations which must take on board the individual circumstances of a family and of the ongoing pregnancy[57].

2. Procedures to be very open to change so as to ensure that listing a given abnormality into the regulatory framework does not prevent the detection and information process from being suitably adaptable to the rapid and constant developments of scientific knowledge.

But this targeting procedure, even if the conditions outlined above, which are not going to be easily attainable, were to be achieved, would lead to considerable upheaval in the practice of medicine because an *a priori* selection of the DNA sequence to be targeted before the couple's medical advisor has any say on the matter, deprives the doctor who is the direct counterpart in the dialogue with the expectant mother or the couple, of any power of judgment and any possibility of responding in detail to the numerous questions that the results of the procedure are bound to prompt. The doctor would be disempowered at a time when he or she would still be responsible for providing not only pregnancy follow up but also the follow up of the child's life after birth.

d. Communicating the result of targeted reading of global sequencing but leaving the responsibility of selection to the doctor proving genetic counselling.

Even in a context as highly technological and complex as the one we are discussing, clinical medical practice can muster incomparable clinical expertise in one-to-one dialogue with patients. It could therefore be a possibility to arrange that, on the basis of a "pre-

[57] As an example, in some rare cases, requests for termination of pregnancy for a foetus carrying a predisposition for breast and ovarian cancers have been accepted. These cases involved a severe familial context, in which there was a link not only to mutation of the BRCA1 gene, but also to still unidentified modifying genetic factors as shown by the severity of the family's medical case history. It would ill advised, however, to take into account the presence of all the BRCA1 and BRCA2 gene mutations, since such mutations concern approximately one individual out of every 400 in France. Furthermore, while on average the risk of breast cancer is high, there is a variability of risk in the population at large, linked to modifying genetic factors currently in the process of being identified. This example is an illustration of the need for caution in disorders with variable penetrance and expressivity.

interpreted" DNA sequence, i.e. containing information meaningful to specialists only, clinical geneticists avail themselves of the entire complement of information before targeting *a posteriori* the information that the people they are counselling should, or should not, be provided with. This would be a highly dynamic approach since it would take care of the very swiftly evolving nature of human genomic knowledge. It would also be very flexible since it would retain the human dimension of the relationship between doctors and patients as well as the latter's right to know, or not to know, in the process of a private dialogue respecting the principle of free and informed decision.

But this approach is fraught with problems that need solving. The first of these is that it could only be implemented if a sufficient number of doctors providing genetic counselling can acquire and keep up to par advanced high level genomic expertise. All such doctors, moreover, would have to join proficiency networks so as to avail themselves of collective expertise with which to review on a continuing basis the information they could see as important and pertinent for transmission to the people they are counselling. They would then be in a context which is similar to medical imagery, foetal imagery in particular, in that the doctor providing genetic counsel would be challenged by the same kind of responsibility issues as those ultrasonographers have to contend with[58].

[58] They are accountable in both ethical and medical terms, and there are also some legal responsibilities, so that they are the object of a large number of complaints, some of which in court.

IV Suggestions and possible lines of thought

Although there is no question of allowing technology to dictate our conduct, we cannot today totally ignore the fact that at this point the tools of human genomics are evolving very speedily. This is particular true for new foetal genetic tests on samples of maternal blood based on high-throughput DNA sequencing methods.

These tools exist and will probably be put to use if that is not already the case. Our concern therefore should be rather how we consider they should be used and regulated rather than speculating that they might not be used. To be able to do something which still seems today to be a technological breakthrough and furthermore, do it in rather favourable economic conditions since costs are on a continuous and steep downward curve, does not mean that we can feel authorised to apply that technology irresponsibly and without any consideration of its ethical implications.

Accepting the need for time to know and to inform

The "genetic revolution" brought about by the new possibilities for DNA sequencing, human sequencing in particular, should not lead us into forgetting that our knowledge is still of a very highly probabilistic nature and that it is progressing ahead of its possible medical application. What we can deduce from a DNA sequence is, *inter alia*, that in a gene sequence there exist certain mutations which, if they are inherited from each of the two parents, will very probably lead to a certain disease, cystic fibrosis for example. What we frequently are not able to deduce, is the clinical severity of the disorder brought about by the genetic abnormality concerned.

The sum of genetic data with which we are confronted — and will be ever increasingly confronted — must be transposed into information that is medically pertinent and useful. The immense majority, or rather the almost total number of genetic variations (mutations, deletions, sequence duplications) are no more than a reflection of the diversity and singularity of human beings which are brought about, with each passing generation, by the mechanisms for diversification and genetic intermingling owed to sexual reproduction. The complexity of such data requires that information be faultless and scientifically pertinent. To deliver that information is the prime duty of genetic counselling and its influence on the choices and decisions of expectant mothers and couples must be emphasized. The issue of information is therefore central to CCNE's thinking and the need for the process to be implemented is one of our prime recommendations.

Propose trisomy 21 screening using foetal DNA sequencing on maternal blood

The above analysis of the trisomy 21 testing example based on foetal DNA sequencing on maternal blood leads to the conclusion that it would constitute ethical progress compared to current procedures for providing systematic trisomy 21 screening, which are valued as a symbol in this country.

The genetic foetal test for trisomy 21 using a maternal blood sample cannot, as yet, become a diagnostic test in replacement of karyotypes of foetal cells. It adds up to a technical improvement in screening as it is implemented in France at this point (easier to do and less side effects). CCNE considers that this method, which does not modify intrinsically the substance of the existing procedure, would be of considerable importance from the point of view of doing no harm (diminishing the number of invasive and potentially dangerous samplings). This would be no more than an improvement and should be associated with the test being paid for out of national solidarity resources — providing its cost becomes acceptable.

As regards the possibility of the test being implemented gradually as a first screening step for all expectant mothers, the limitations are technical (a percentage of results cannot be interpreted), and also more organisational and economic than they are ethical (the cost is currently very high). This is so because: (a) the offer to screen made to all pregnant women and its voluntary character would not be a modification to current procedures; (b) the test's efficacy would give all expectant mothers on an equal footing the chance to be informed, if of course they so wished, of their foetus' status regarding trisomy 21. However, if technical, organisational and costs problems were to be solved, such an extension would require that a set of conditions guarantee the pertinence, safety and equality of access regardless of financial circumstances, as well as the quality of information and counselling provided.

Counselling to accompany the extension of prescriptions for foetal genetic testing on maternal blood

Scientific and technical advances are putting us in a position where a given test, corresponding to a specific genetic disability or disorder, can no longer be considered independently from a number of other tests, or even from the decoding of our entire genetic inheritance. It is therefore probable that the emblematic and exceptional dimension of trisomy 21 will fade in comparison with an increasing number of chromosomal abnormalities and mutations associated with genetic diseases and disabilities which are going to be identified, some of which are of extreme severity.

With a view to arriving at an effective regulatory system, one which would be respectful of individuals and in particular of their autonomy, it would be necessary to either do selective DNA sequencing, whereas technical developments are moving more into the direction of global sequencing, or else a whole reading but selective and adapted communication. Apart from what we are still unable to interpret in the succession of DNA bases, and what cannot be interpreted in terms of health, sickness or disability, there is also the quantity of knowledge which is probably not pivotal for taking a decision to continue with pregnancy or terminate it.

CCNE believes that the whole foetal DNA determination, once this becomes a practical possibility (practical economically, in particular) and can be done according to recognised clinical standards, should be passed on selectively, using pertinent and strict criteria. First and foremost among them should be how severe and incurable is the disease at the time of diagnosis. The ethical issues mentioned above would still need addressing, in particular:

- Faced with the possibility of "a particularly serious and incurable disease at the time of diagnosis" disability or disorder, but with a low probability of occurrence, how should gravity and probability of occurrence be discriminated? At what point would this probability be considered too small for it to be taken into consideration when a request for therapeutic termination is submitted, and how could a threshold be set?

Once the DNA sequence is established, its interpretation will become increasingly precise as time goes by, which leaves open the question of updating the information after the child's birth and communicating it to parents, then to the child himself and the adult that the child may grow up to be. Should the raw data be kept? If so in what form? Under whose responsibility? And when, how and to whom should it be communicated if the case arises?

Making the most of what genomics is or will be contributing to therapy

The management of people who are disabled or sick, in particular with chronic and/or progressive diseases, contains a preponderant human dimension in which not just the technicalities of medicine and clinical medical practice are involved, but also the community as a whole. Also included in the health care provided is an important research component, biomedical research of course, but also in the human and social sciences.

Such research, on the whole, tends to be largely neglected, in particular because each of the genetic diseases involved is individually not very frequent and therefore, from the perspective of research end results, its individual "value" seems limited. And yet, better understanding of each of the diseases contributes to the body of knowledge regarding their mechanisms and the regulation of vital functions and their development, paving the way in the long run for therapeutical progress. Research in the human and social sciences should make a contribution to discovering the best approach to enable each of the people concerned, in their own particular circumstances, to gain access to benefits owed to them and to be assisted in the most appropriate way.

Comparing health and absence of disorders connected to genetic abnormalities

Although in today's society, some schools of thought champion an evolution in the direction of an illusory absence of any form of genetic abnormality, or even towards the absurd notion of genetic "perfection", which is reminiscent of the tragic eugenic follies of earlier times, this is not something which weighs on the minds of women and couples expecting a child. Future parents do not seek a perfect child; they want a child in good health and, for many parents, this means a child who is not irremediably doomed from birth to living with a disability or an incurable and particularly serious disease.

When in 2012 CCNE held its annual open discussion days, with a debate focusing on standards, normality and normativity as regards health, it turned out to be difficult to define health standards. Medically and scientifically, the expression of standards corresponds to a

statistical distribution as a starting point from which a variation can be defined, on the condition that the variation results in suffering or an alteration of capabilities and autonomy[59].

Socially, the conditions, the circumstances and their quality of life within the community need to be considered and appraised for people suffering from chronic disorders or disabilities. The UN Convention of December 2006 on the rights of disabled people, ratified by France, considers that infirmity is not solely the result of physiological impairment but also of the hurdles that society puts in the way of the exercise of their rights, capabilities and autonomy. For example, when motor handicapped individuals can neither find somewhere to live, nor move from one place to another, nor go to work because all of these places are inaccessible, it is because of this inaccessibility that they are unhappy, not because they have to use a wheelchair. When children suffering from intellectual, emotional or relational disabilities are denied their right to be educated, their disability is aggravated by this lack of schooling. Even when certain infirmities do not seem to induce physical or emotional harm to the disabled person concerned (as is the case for a number of children and adults with trisomy 21) their place within the community and the way in which they are regarded by society makes them very vulnerable and may be cause for distress.

In 1946[60], the World Health Organization (WHO) produced a broadly based and demanding definition of what is meant by health, with the object of promoting the role of public health as an element essential to good health and of the responsibility of politicians for implementing it. This is an illustration of the difficulty of definition compared to description. It would seem, in this day and age, that one way of conceptualising health would be to insist on the human capacity for adaptation and resilience, as well as society's duty to provide means of access, autonomously, to the best possible "physical, mental and social state"[61].

In such a context, could we not consider, in defiance of our concept of the relationship between health and normality, that disabilities and disorders are also "*characteristic of the way in which members of the human species function. Human normality encompasses — or could encompass — disability and disease*[62]."

[59] See, for example, Georges Canguilhem. *Le normal et le pathologique*. PUF, 2009.

[60] "Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity." Preamble to the Constitution of the World Health Organization as adopted by the International Health Conference, New York, 19-22 June, 1946.

[61] Huber M., *et al*. How should we define health? *Brit. Med. J.* 2011; **343**: d4163.

[62] Weale A, Journées annuelles d'éthique, Paris, January 2012.

Glossary:

Allele

Each of the alternative forms of a gene (from the Greek 'allel-': each other) which contribute to the determination of phenotypes. For each gene we inherit one paternal and one maternal allele which may — or may not — be identical. When they are not identical, one allele may be expressed and not the other, thus determining a trait. The allele expressing itself is known as dominant, the other is called recessive.

Aneuploidy

Abnormal number of chromosomes (see trisomy).

CGH-array

Comparative genomic hybridization, CGH array, or DNA chips. The method consists in attaching (hybridising) fluorescently labelled (e.g. in green) DNA probes representing the entire reference genome to the fluorescently labelled (e.g. in red) genomic DNA under examination,. Deletion of a chromosomal area will appear in green, the duplication in red, while a normal area will be orange. Latest generation DNA chips are even more selective. Very numerous nucleotide probes are dispersed over the genome. When DNA probes represent the whole human genome, the test is described as pangenomic.

As a prenatal test, CGH array requires an invasive foetal sample. It is only useful if there are ultrasound warning signs or as a validation of foetal tests on maternal blood samples. CGH array will no longer be needed as maternal blood based tests become increasingly reliable.

Chromatin

DNA is not present in the nucleus of a cell as an individual molecule. It combines with RNA and proteins to form the chromatin which constitutes the chromosomes. Chromatin has a structural purpose which is to compact DNA so that it can be packed into a cell nucleus. (In humans, each cell contains two meters of DNA). Its other role is functional, to enable and regulate the expression of genes contained in the DNA.

Chromosome

A distinct chromatinian entity visible through an optical microscope at the time of cellular division. Humans have 23 pairs of chromosomes (inherited from their father and mother), one of these pairs being the sex chromosomes (X and Y). Women have two X chromosomes whereas men have one X chromosome and one Y chromosome. Chromosome imagery during cellular division constitutes the karyotype from which certain abnormalities leading to genetic diseases can be detected, in particular in prenatal diagnostic tests.

Chromosomal alteration or abnormality

Alteration or abnormality can only be defined in comparison to a state described as "normal". The good stability of the chromosomal formula and of the global chromosomal structure can only be defined globally when the chromosomes are observed with a microscope (traditional karyotype). It is then possible to discover chromosomal alterations compared to a normal karyotype.

But modern techniques for chromosomal analysis, and ultimately the DNA sequence residing in these chromosomes, show that on a molecular scale, there is a great deal of

variability from one person to another in various parts of the genome. Defining "normality" therefore becomes a scientific impossibility since there is no hard and fast standard. Strictly speaking, it is not therefore possible to describe any genetic variation as being an alteration or an abnormality. Nevertheless, everyday language which ratifies a commonly accepted definition of disease, genetic disease in particular, leads to defining certain genetic variations as deleterious mutations.

Chromosomal deletion

A chromosomal deletion is the loss of chromosomal DNA which may be of extremely varying size. In some cases, only a single base is lost and, in others, a large area. A microdeletion is when the loss is so small that it is almost beyond the scope of detection of traditional chromosomal analysis techniques (traditional cytogenetics). Today, molecular techniques, including CGH-array, can detect them relatively easily.

De novo

Not inherited from either parent. See "neomutation"

Dominant

Each of us carries two different alleles (inherited from each of our two parents) of the same gene for a given trait. In the case of hereditary disease, an alteration on one only of the two alleles can lead to the expression of a dominantly inherited disease.

DNA

A molecule composed of four kinds of "building blocks" or separate molecular bases: *adenine, thymine, cytosine, guanine*, symbolised by their initials A, T, C, G. In a human genome, some six billion of these bases make up the set of 46 molecules constituting each of our chromosomes. The double helix structure of the DNA molecule was discovered by James D. Watson and Francis H.C. Crick in 1953.

Epigenetics

Functional changes in the genome which may be inherited but do not lead to changes in the DNA sequence. The study of the way in which the "message" carried by DNA is expressed in the phenotype traits that can be observed. Of particular interest, the link existing functionally between the genome and the environment and the possible connection between nature and nurture.

At the molecular level, epigenetics studies chemical DNA modifications, modifications of the chromatin proteins as well as the expression of small RNA regulators.

Eugenics

Based on genetic determinism and the vindication it provides for social stereotypes, eugenic ideas advocated selecting, even forcibly, individuals allegedly the most "fit" to produce the social elite. The term eugenics was coined by Francis Galton in the 19th century and is a social current by a community seeking to control its genetic heritage by regulating the right to reproduce, encouraging people with desirable traits to have children and restraining the reproductive rights of those seen as undesirable (sometimes by exterminating them).

At the turn of the 20th century, well known biologists, such as Julian Huxley (1887 - 1975), Alexis Carrel (1873 - 1944) and Charles Richet (1850 - 1935), both of the latter Nobel Prize

winners for Physiology or Medicine, recommended the selection of "*less defective human races, so that human beings could have greater muscular strength, be handsomer, more intelligent, have better memories, more strength of character and also live longer and in better health. Our lack of concern is extraordinary! Our disregard of the future is criminal*" [63].

François Jacob asserted that "equality is not a biological concept. (...) As though equality had not been invented precisely because human beings are not identical" [64]. Eugenics seeks to present social standards in the disguise of supposedly natural, genetic standards.

Exome

The exome is the part of the genome the sequence of which is transcribed in proteins, and is the most directly and medically connected to the phenotype and to genetic diseases. The human exome constitutes about 1.5% of its DNA. Several commercial companies are offering to sequence and analyse an individual's exome to look for the variations thought be causing genetic diseases.

Founder Effect

Some rare mutations are transmitted mainly within a single family or a group of people in which there is frequent inbreeding. The mutations are inherited from a common ancestor. This is called the founder effect.

Gene

The Danish botanist Wilhelm Johannsen coined the word in 1909 to describe what parents pass on to their offspring and which expresses a particular trait of their phenotype.

Oswald Avery, Colin MacLeod and Maclyn McCarty demonstrated in 1944 that the gene's primary support is DNA.

The gene is therefore, formally, a unit of information which biology, in attempting to provide it with a single molecular base, has complicated its definition to an almost impossible degree[65].

Mammals, humans in particular, inherit two copies of each gene (one from the mother and one from the father) which may not be strictly identical, in which case this is described as two alternative allele forms, two alleles of the gene concerned.

Genetic Code

From a strictly scientific point of view, the genetic code is the almost universal code which leads from the four-letter DNA alphabet (ATCG) to the twenty-letter amino acids alphabet which are the basic building blocks constituting the proteins. This code was deciphered in the 1960s by Har Gobind Khorana.

Molecular biologists speaking on the subjects of the genome and heredity have too often used metaphors related to data processing techniques in particular: genetics is presented in terms of "programmes", based on "coding" and including "locks", "sequences" and

[63] Charles Richet, Nobel Prize for Physiology or Medicine in 1913. "*La sélection humaine*", Paris, Félix Alcan, 1913 (re-edited in 1922)

[64] François Jacob, Nobel Prize for Physiology or Medicine in 1965, "*Le jeu des possibles*", 1981

[65] *Dix-huit facettes d'un même concept : qu'est-ce qu'un gène ?* (Eighteen facets of the same concept: what is a gene? *La Recherche*, December 2001.

"letters", giving the impression of a determination coded by an unalterable alphabet, and therefore of genetic determinism.

Genetic Counselling

The purpose of genetic counselling is to communicate to patients, parents and relatives the information which will enable them to make informed decisions when coping with:

- a diagnosis of congenital and hereditary disease affecting a patient (by defining the mutation involved, for example)
- an evaluation of the risk of becoming diseased for presymptomatic patients who are carriers of a harmful mutation, but so far clinically healthy (susceptibility genes, for example)
- the management of an overt genetic disease or prevention in the event of susceptibility to an as yet latent disease
- an evaluation of the risks of giving birth to children who are carriers of a genetic disease (prenatal diagnosis), and decisions to be made concerning the affected foetus (termination of pregnancy or anticipation of neonatal care)
- existing measures to avoid the conception or implantation of embryos carrying serious genetic disorders which remain incurable at the time of diagnosis

Genetic testing must be performed in concurrence with genetic counselling provided by fully qualified professional counsellors.

Genetics

The science of heredity, genetics studies the transmission of phenotype traits in individuals belonging to the same species and the relationship between phenotype and genotype. The Czech monk, Gregor Mendel, studying the heredity of simple characteristics (in plants), in the 1860s, went on to laying down the rules governing this Mendelian or formal inheritance. However, the term "genetics" was coined in 1905 by the biologist William Bateson (1861 - 1926).

Genome

All of the genetic information for an organism. The complex structure and molecular organisation which specifies this information.

The human diploid genome is composed of 6 billion base pairs distributed over 23 pairs of chromosomes. Only 1% of the human genome, i.e. 60 million base pairs, constitute the protein-coding share of the 23,000 pairs of genes. All the coding regions of the 23,000 genes constitute the exome. Intense efforts are under way to identify the roles of the rest of the 99% of the human genome; in particular, this is the project undertaken by the international consortium ENCODE (Encyclopaedia of DNA elements). A part of these non coding regions plays a major role in gene regulation and expression.

Genotype

All of the specific allele makeup of an individual, or the genetic constitution of an individual (animal, plant, microbe). In contrast to the phenotype which are the traits expressed in that individual making that organism identifiable.

Heterozygote

An individual carrying two different alleles (one inherited from each parent) of the same gene for a given character.

In the case of hereditary disease, the presence of an alteration on only one of the two alleles can give rise to the disease's expression if it is inherited in a dominant manner. If, however, the disease is recessive, the heterozygote carrier of the mutation is referred to as a healthy carrier who does not express the disease.

Homozygote

An individual carrying an identical pair of alleles (inherited from both parents) for a specific trait. In the case of a recessive genetic disorders, only homozygous individuals for that mutation will be ill.

Karyotyping

Karyotyping is an analysis of an individual's chromosomes, that is the number and microscopic appearance of chromosomes present in the cells. In human beings, the normal full chromosomal set corresponds to 23 pairs of chromosomes, of which one pair are the sex chromosomes.

Mendelian genetic diseases

Mendelian genetic diseases are inherited diseases which are passed on to offspring following Mendelian patterns of inheritance. Their genetic determinism is simple and regulated by a single gene. Transmission is monogenic. There are two main types of inheritance: recessive and dominant.

Mutation

A variation of the DNA sequence at a particular point of an individual's genome. This may be a point mutation, meaning that it affects only one of the three billion DNA bases, or else may involve regions of varying sizes on the genome (deletions, duplications, translocations, etc.). This variation, be it on a single gene or otherwise, may or may not modify a phenotypic trait in the individual expressing it. In common parlance, scientifically inaccurate, a mutation is said to be the cause of a genetic disease. In fact, the modification may have beneficial or adverse effects. When it is (or seems to be) neutral, it is referred to as a polymorphism.

Individually, mutations are rare and occur randomly, but when they are not eliminated by negative selection or genetic drift, they may accumulate in a population and contribute to its genetic diversity. In this way, they are the drivers of evolution.

Neo-mutation (*de novo*)

A mutation in a given gene may occur accidentally in the gametes of one parent or very early on after the zygote is formed. It is not therefore inherited from the parents. Neo-mutations or *de novo* mutations are mainly found for dominant diseases. As an example, over a third of cases of people affected by type 1 neurofibromatosis (von Recklinghausen disease) are caused by a neo-mutation.

Pangenomic

Meaning the study of the genome in its entirety; this dimension takes into account observations which were not the *a priori* research objective, such as what are referred to as "incidental alterations".

Penetrance

Frequency with which the carrier of an allele expresses the trait associated with that allele.

The penetrance of a genetic disease is the frequency with which this disease appears in the population of individuals carrying an adverse mutation. Penetrance is a function of a combination of factors, both genetic and environmental, which in most cases remains to be elucidated.

Phenotype

All the observable characteristics of an individual, as opposed to the underlying genetic composition (genotype). The phenotype includes morphological or physiological traits, or even behavioural characteristics. The relationship between phenotype and genotype is not univocal since, for example, total phenotypical identity is not present in two identical twins (monozygotic).

Recessive

Each of us carries two different alleles (one inherited from each parent) of the same gene for a given trait. In the case of recessive hereditary disease, for the disease to be expressed, a mutation inactivating the gene must be inherited from both parents.

Sequence, sequencing DNA

Today, we are able to determine (to sequence) the four "building blocks" or molecular bases which appear in sequence along the DNA molecules present in the genome.

The DNA sequence in the human genome was first determined in the early years of this century. This first sequencing effort represented 13 years of work and cost around 3 billion dollars. In 2007, the DNAs of two well known scientists were sequenced in just a few months at a cost for each of them of under a million dollars, i.e. three thousand times less than the first sequencing effort. Today, the same procedure can be completed in two hours for less than €1,000 and we are told that by 2018, a few seconds and €100 will be the norm.

Leaving figures aside, the most modern genomic techniques provide a huge amount of data of which only a small part can be interpreted at this time. The question therefore arises of the nature of the real and useful information, in other words the usable information, that this technique provides. We are very far from understanding the meaning of the message although we are able to read the letters.

Single allele inheritance

When a mutation occurs on only one of the two alleles of a gene in the individual's genome. When this mutation is recessive, it is not expressed when only one allele is affected: the individual is a healthy carrier.

Trisomy

A particular example of aneuploidy in which an entire chromosome is present in three copies instead of two in each cell of an organism. Trisomy in certain chromosomes is not compatible with survival. In other cases, such as trisomy in chromosome 21, known as trisomy 21, foetal life can and does, in a large proportion of instances, continue until birth

and beyond. Trisomies 13 and 18 have a severely deleterious effect on foetal development and give rise to a high risk of spontaneous miscarriage.

Abnormalities in development and associated symptoms, in particular as regards learning and intellectual disability, is expressed to varying degrees in different cases and in a manner which, to date, cannot be predicted.

X-linked recessive disease (linked to the X chromosome)

A genetic disease caused by the presence of a mutation on both alleles of a gene located on the X chromosome in females or on the allele of the same gene in males (boys only have one X chromosome). As a result of this mode of inheritance, females are rarely affected themselves but pass the disease on to their sons in one case out of two.

ANNEXE 1

Liberté • Égalité • Fraternité
RÉPUBLIQUE FRANÇAISE

MINISTERE DES AFFAIRES SOCIALES ET DE LA SANTE

Direction générale de la Santé

Sous-direction Politique des pratiques et des produits de santé
Bureau Eléments et produits du corps humain
Suzanne SCHEIDEGGER
suzanne.scheidegger@sante.gouv.fr

Paris, le 31 JUIL 2012

Monsieur le Président,

Actuellement, les examens de génétique moléculaire connaissent des développements technologiques extrêmement rapides, ce qui renouvelle les questions éthiques posées dans ce domaine. A cet égard, le diagnostic prénatal « microinvasif » de certaines aneuploïdies (notamment trisomie 21) à partir de l'ADN fœtal circulant dans le sang maternel ouvre de nouvelles perspectives mais est aussi source de questionnements.

Certes, ce diagnostic, qui permet d'éviter un geste invasif chez les femmes enceintes dont le fœtus est à risque accru de trisomie 21[1], est encore dans le domaine de la recherche clinique en France et dans les pays européens voisins mais les publications internationales confirmant la performance du test diagnostique se multiplient. Ce test serait disponible hors recherche aux Etats-Unis depuis fin 2011.

Plus encore, des chercheurs[2] sont parvenus à séquencer le génome d'un foetus lors de la grossesse à partir d'échantillons de sang de la mère et de salive du père (travaux[3] publiés dans la revue médicale américaine Science Translational Medicine datée du 6 juin 2012). Le séquençage du génome du foetus couplé à des techniques statistiques et de biologie informatique a permis de détecter les variations génétiques du fœtus de façon détaillée. Pour la communauté scientifique, ces travaux ouvrent la voie au séquençage du génome du fœtus et à l'identification de plusieurs milliers de troubles génétiques au moyen d'un seul test non invasif.

De telles avancées biotechnologiques alimentent les questions tenant au risque possible de dérive eugéniste.

Face aux développements scientifiques et technologiques, ce sont les principes fondateurs de la bioéthique, édictés dès 1994, réaffirmés dans les lois de bioéthique du 6 août 2004 puis, plus récemment, du 7 juillet 2011 qui permettent de délimiter ce qui est éthiquement acceptable de ce qui ne l'est pas.

Monsieur le Professeur GRIMFELD
Comité Consultatif National d'Ethique
35 rue Saint Dominique
75 700 PARIS

[1] Dans les publications et les essais en cours, il apparaît que le test n'est jamais proposé en première intention mais s'adresse aux femmes qui, à l'issue du dépistage, sont placés dans le groupe à risque accru de trisomie 21 pour le fœtus .
[2] Jacob Kitzman et Matthew Snyder, de l'Université de Washington à Seattle
[3] Joints à cet envoi

14, avenue Duquesne – 75350 Paris 07 SP – Tél. 01 40 56 60 00

ANNEXE 1 (continued)

Dans ce cadre, je souhaiterais que le CCNE mène une réflexion approfondie et rende un avis sur les problèmes éthiques et les questions que soulève le développement de cette technique de diagnostic prénatal des anomalies génétiques du fœtus à partir d'un simple prélèvement sanguin de la femme enceinte. Compte tenu de la rapidité des évolutions dans ce domaine, il me semble souhaitable que l'avis du CCNE soit rendu avant la fin de l'année 2012.

Je vous prie de bien vouloir agréer, Monsieur le Président, l'expression de ma considération distinguée.

Le Directeur Général de la Santé,

Dr Jean-Yves GRALL

Copie : Madame Emmanuelle Prada-Bordenave, Directrice générale de l'Agence de la biomédecine

ANNEX 1 (continued)

Translation of a letter dated July 31st 2012, from the Ministry of Social Affairs and Health, General Directorate for Health, sub-Directorate for health care practices and products, Components and products of the Human Body Section, addressed to Professor GRIMFELD, President of the National Consultative Ethics Committee.

"Molecular genetic tests are currently in a phase of very rapid development, so that related ethical issues need reviewing. In this connection, the "micro-invasive" prenatal diagnosis for certain aneuploidies (trisomy 21 in particular) based on foetal DNA circulating in maternal blood opens up new possibilities but also raises some issues.

It is true that this diagnostic test, thanks to which expectant mothers carrying a foetus that may be at a higher risk than others of presenting with trisomy 21[1] may be spared an invasive procedure, is still in the clinical research phase in France and neighbouring countries. An increasing number of international scientific publications, however, are confirming the reliability of the test. It also appears that in the United States, the test has emerged from research and has been available since the end of 2011.

Moreover, researchers[2] have sequenced the genome of a foetus during pregnancy based on maternal blood samples and paternal saliva (published[3] in an American medical journal, Science Translational Medicine on June 6th 2012). It is now possible to detect detailed foetal genetic variations using foetal genome sequencing combined with statistical and biological data processing techniques. The scientific community can now look forward to needing only a single non invasive assay to perform foetal genome sequencing and identify several thousand genetic conditions.

Such biotechnological developments add fuel to concerns regarding the potential for eugenicist tendencies.

In the presence of these scientific and technological developments, the founding bioethical principles, laid down in 1994, reconfirmed in the August 6th 2004 bioethical laws and, more recently, on July 7th, 2011, will determine that which is ethically acceptable and that which is not.

ANNEX 1 (continued)

On the basis of the above, I am requesting CCNE to proceed with and in-depth reflection and the submission of an opinion on the ethical issues and the problems raised by the development of the technique for prenatal diagnosis of foetal genetic anomalies based on a single sample of a pregnant woman's blood. Since developments are progressing apace in this respect, it would be desirable for CCNE's opinion to be ready by the end of 2012."

Signed by the Director General for Health

Dr. Jean-Yves GRALL

Copy to: Madame Emmanuelle Prada-Bordenave,

Director General, Agence de la Biomédecine.

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[1] As reported in publications and ongoing studies, it would appear that this is never a first line test and is only offered to women who, after screening, are classified as being in a group with a higher risk for foetal trisomy 21.

[2] Jacob Kitzman and Matthew Snyder, Washington University, Seattle

[3] Attached to this letter.

35, rue Saint Dominique – 75700 PARIS Cedex 07

Tel. +(33) 142 756 642

http://www.comite-ethique.fr

The mission of the National Consultative Ethics Committee for Health and Life Sciences is to give opinions on the ethical and societal issues raised by the advancement of knowledge in biology, medicine and health.

Law dated August 6th, 2004