National Consultative Ethics Committee for Health and Life Sciences

**OPINION N° 124**

# Ethical Reflection on Developments in Genetic Testing in Connection with Very High Throughput Human DNA Sequencing

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* This Opinion is dedicated to the memory of Philippe Rouvillois

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## Foreword

In April 2013, CCNE published an Opinion (N° 120) on "Ethical Issues in Connection with the Development of Foetal Genetic Testing on Maternal Blood". The Committee emphasised at the time that this would be the first step in a more extensive appraisal of the whole subject of wider use of high throughput DNA sequencing and its medical and societal implications.

In that Opinion, CCNE observed[1] that in the near future it could become technically easier, and probably cheaper, to do so-called whole[2] genome sequencing than to select short regions of interest for targeted sequencing. At this time, such developments could, and in fact should, be the subject of a progress report. Identifying a mutation or another genomic anomaly (of a chromosome for instance) causing a disease is a necessary scientific and medical first step so that the expectations of families falling victim to a genetic disease can be satisfied ('naming the disease' is part of the therapeutic process[3]). It is also the gateway to perceiving, in the medium or the longer term, possibilities for treatment or even the cure of diagnosed genetic diseases or disabilities.

Genomics in this era of very high throughput DNA sequencing plays a role in the creation of gigantic health related data bases ('big data') raising considerable ethical challenges, particularly as regards the right to privacy. Furthermore, growing knowledge and understanding of the genome pave the way for increasingly specific and sophisticated procedures involving human DNA[4], which cannot fail to raise vast ethical issues both as regards somatic cells (cellular gene therapy) and reproductive or embryonic cells (germ cell gene therapy). CCNE has already started on a review of these two subjects but wished to devote this Opinion to consideration of genetic testing developments made possible by very high throughput DNA sequencing.

Technical progress already achieved or currently in the making in the field of human genomics stands at the meeting point between fundamental research and clinical medicine, so that it has an impact on many aspects of the lives of individuals, families and communities. CCNE proposes to devote some preliminary thinking on the conditions to be observed for a regulatory system to be both effective and respectful of individual rights.

[1] There was no intention of moral judgement in this observation.

[2] In fact, the whole DNA of an individual is rarely sequenced except for research applications. The 'whole genome' wording is used in reference to sequencing very large areas of the genome on a non selective basis.

[3] Audition of Prof. Arnold Munnich, 12/05/2014.

[4] Sometimes referred to as 'correcting'.

## I/ Why a new Opinion?

The improvement of human health is a goal that the vast majority considers to be legitimate and "*No one can deny that in the course of our history, Science has been the source of progress and has contributed to improving human well-being*."[5]. Genetic testing, be it for medical or non medical purposes, and progress in genetic research now open onto a broad vista of knowledge and major hopes for improving medical performance, in for example, therapy optimisation, preventive medicine or even health economics.

Prevention, and even prediction, have always aroused interest, but the real sea-change is that we now have instruments which can achieve these aims. This is a field in which *"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*[6]*."* Such advances can therefore create problems rather than be source of progress[7]. Genetics has become a science fraught with danger (human manipulation, eugenics, etc.) but also the source of a multitude of hopes (reducing the burden of genetic diseases and disabilities).

Fast evolving technical progress, rather than the novelty of the subject, is the reason for further reflection and society's deep concern. The technique in question, 'very high throughput sequencing', allows for automated parallel nucleotide DNA (genome) sequencing, but also of RNA, and several of its characteristics raise ethical issues: it is fast and therefore less and less costly, it can therefore be global, it generates massive quantities of data whose interpretation, in particular in terms of medical impact, is facilitated by its application to cohorts numbering thousands of individuals. Dauntingly vast computing resources, but also statistical and mathematical resources are required for the management, storage and particularly interpretation of such data. The provisioning of such resources is a real challenge in itself and in terms of the power issues, in particular economic ones, which it raises.

This type of 'global' sequencing could, in the very near future, become more accessible even for the analysis of a particular gene. Considering the evolution of the cost of sequencing since the

[5] CCNE, Opinion N° 109 (2010): *Society and the Communication of Scientific and Medical Information: Ethical Issues.*

[6] 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)*.

[7] "*There is one quality more important than* ***know-how*** *[…]. This is* ***know-what*** *by which we determine not only how to accomplish our purposes, but what our purposes are to be*". Wiener N. *Cybernetics and Society*, 1954.

first 'full[8]' human DNA sequencing published twelve years ago, three successive phases can be observed. The first of these, in the period of time up to 2007 or 2008, follows a curve similar to what is commonly known as 'Moore's law' [9]; the second phase, covering 2008 to 2012, corresponds to a technical leap forward combined with a cost factor reduction of about 2000; the third phase, since 2012, represents a certain amount of stabilisation of developments in sequencing costs. The time elapsing since the first phase, together with this form of stabilisation of the 'state of the art', can be used to make an assessment, a practical feedback appraisal of what sequencing can actually achieve. The scientific discoveries thus accessed are in constant evolution. **Perhaps the time when every individual's genome will be a routine item of his or her medical record, regularly reviewed, is not so far away.**

Beyond the change in scale and the predominance of personal data management which may be at risk of being no longer under the control of the individual concerned, it is the nature of the data obtained through such sequencing — all of which was not arrived at following the individual's own request — and uncertainty regarding its significance for the health of the individual that confront us with the true boundaries of knowledge. It follows that it is the issue of the feedback to the individual, regardless of whether the data was, or was not, procured in a medical context, and also the data's degree of uncertainty, that now arise. **Furthermore, these technical developments may move us from a time when the main object of genetics was to explain diseases to a situation where genetics are focusing on the prediction of disease, with the attendant risk of personal liberties being restricted in the event that public health policies are headed in an interventionist direction[10].**

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[8] "The human genome sequence accessible in databases today is as complete as current techniques permit." states the Génoscope, underlining that the concept of completion depends entirely on the state of technology at a given point in time.

(http://www.genoscope.cns.fr/spip/Le-projet-Genome-humain.html?artsuite=1#FAQ2),

[9] Initially, the (empirical) law expressed by Gordon Moore in 1965, predicted that the complexity of semiconductors doubled every year at constant cost. This 'law' was updated on several occasions and was generalised to mean that a phenomenon (speed, capacity, cost reduction, etc.) doubled every eighteen months, a value that is not given in any of Moore's own presentations.

[10] Qualitative/quantitative leaps as initiated by current genomics:

- Passing from measuring a single parameter belonging to an individual to measuring all the parameters; passing from a small number of specific genetic markers, selected and interpretable by a physician (to document a medical diagnostic hypothesis) to non targeted full genome sequencing, without any *a priori.*
- Shifting from analysis targeting a disease (in response to a symptom) to analysis targeting an individual in good health, unsupported by a diagnostic hypothesis, to screen for a risk run by individuals with the purpose of improving their well-being (preventing disease). In which case there is a risk of leaving behind a medical framework where the individual is taking an initiative and is in control to one where society is imposing a norm.
- Risk of misuse on human beings of what amounts to a 'purely technological exercise'
- Shift to bioinformatic management which must integrate a discussion of the protection of privacy (anonymisation). The massive quantity of data produced by today's sequencing techniques is no longer

It is with these issues in mind that CCNE decided to turn once again, without any *a priori*, to a general reflection on ethics regarding a set of concerns that UNESCO summed up in 2002 in what appeared on the surface to be a simple question: "Bioethics: The ethics of genetics"[11], although it contains a thorny query which cannot and must not be ignored: **how far is too far?**

manageable by traditional and individual publishing and archiving methods. Bioinformatics and data banks are an additional threat on privacy and data protection.

[11]UNESCO Courier, May 2002. It is worth noting that the primary purpose of this publication is to promote UNESCO ideals and serve as a platform for dialogue between different cultures.

# II/ How does the current context modify ethical reflection on human genomics?

## A- The scientific context

We have known for seventy years that DNA is the main carrier of hereditary traits and in 2003 the first *whole* human DNA (nuclear) sequence was established. Techniques for achieving this results have evolved in almost unimaginable proportions so that only ten years later, we had DNA sequences for several thousand people[12], the whole procedure can be done in a few hours at a cost of little more than a thousand Euros[13], and we can sequence foetal DNA using a maternal blood sample[14].

**DNA:**

Molecule made up of an assembly of four kinds of 'bricks' or distinct molecular bases: adenine, thymine, cytosine, guanine, symbolised by their initials A, T, C, G. A human genome contains some six billion of these bases divided into 46 sub-units constituting each one of our chromosomes.

In 1944, Oswald Avery, Colin MacLeod and Maclyn McCarty demonstrated that DNA is the primary carrier of heredity. The 'double helix' structure was discovered by James D. Watson and Francis H.C. Crick in 1953.

**Genome:**

A genome is an individual's entire complement of genetic information. The structure and complex molecular organisation specifying this information. It is estimated that 1.5% of the human genome is made up of the parts coding for proteins (exome) of our 23,000 genes. Intensive research is ongoing to identify the role of the remaining 98.5% of the human genome; this is in particular the project of the international consortium ENCODE (*Encyclopedia of DNA elements*).

Some of the non coding regions play a major role in regulating the gene's expression. Others contribute to genome plasticity (mobile genetic components) and probably to its evolution.

We are now beginning to be capable of 'reading' the letters of the 'DNA alphabet' contained in the genome. This is referred to as sequence acquisition which appears to be at this point the simple and relatively inexpensive part of sequencing. This does not mean that we understand the message; but we are gradually gathering more 'knowledge' about it. Using the same metaphor, DNA is just a sequence of letters but we still need to discover the words (genes), the meaning of the words and sentences reflecting the various ways in which cells and organs, and even whole organisms, use them. To be precise, it is rather more the products of genes than the genes themselves that construct the meaning of sentences and therefore the function. The choice of words depends on very complex not entirely genetic interactions in a normal individual. In most of the more frequent diseases, they are disordered whereas genetic 'monogenic' complaints due to the absence or replacement of letters in a single gene, are often severe and are rare or even very rare.

[12] *The 1000 Genomes Project Consortium. A global reference for human genetic variation. 2015. Nature; 526: 68-74. The UK10K Consortium. The UK10K project identifies rare variants in health and disease. 2015. Nature; 526: 82-90.*

[13] In those ten years, the cost of sequencing and the time required for doing so was divided by two million.

[14] CCNE, Opinion N° 120.

### 1- Genetics, between science and practice

The success of genome technology, anticipating the interpretation of individual genomes, paves the way for so-called 'predictive' medicine. Does it not act as an incentive to force the pace, to ignore the vast and still unresolved areas of uncertainty, or even to neglect genetics as a science, as a scientific theory of heredity?

> *"Although we lack curiosity about the past, we avidly question those who promise to reveal a glimpse of the future"*
> Pierre-Louis Moreau de Maupertuis (1698-1759), *in* Vénus physique, 1745.

Rather than just a tool, genetics is a fundamental science studying the vertical transmission of characteristics, the components of a phenotype[15]. It branches out into several disciplines:

- Population genetics seeking to elucidate the forces and interactions active within the biological diversity of populations and species; it is based on mathematical and statistical models.
- Quantitative genetics seeking to explain variations in quantitative hereditary characteristics (size, for example).
- Development genetics concerned with the development of an organism from a fertilised egg. It uses many species as models, such as mice, drosophila, nematodes *Caenorhabditis elegans*, zebrafish and, in plant research, thale cress (*Arabidopsis thaliana*).
- Evolutionary genetics concerned with genes playing an important role in genome plasticity and adaptivity to environmental modifications.
- Genomic genetics concerned with the spatial organisation of genomes and its relationship with the use made of it by cells (biological function).
- Medical genetics studying the hereditary transmission of genetic human disorders, with a view to prevention and treatment (applied).

In medical genetics, the transmissible characteristics are generally diseases, disabilities, variations by comparison to a health-related reference, or even to a state of normality which is often difficult to define. In practice, it is based on genetic testing, sometimes misguidedly described as a genetic diagnosis[16]. Its purpose varies with the hereditary trait concerned (in particular depending on the severity of the associated pathology), on whether the origin is monogenic or multigenic, on the mode of transmission (recessive or dominant), on the penetrance of muta-

[15] A phenotype is the composite of an individual's observable characteristics in contrast with the underlying genetic composition (genotype). A phenotype is related to morphological or physiological, or even behavioural traits. The relationship between phenotype and genotype is not unequivocal since there is no total phenotypical identity between two identical (monozygotic) twins.

[16] S*tricto sensu* the expression 'genetic diagnosis' should only be used in the case of monogenic diseases so that a disease can be characterised by the identification of a mutation.

tions[17] or their correlation to different forms of the disease ('genotype/phenotype' relationship), etc.

For certain genetic disorders and diseases, genetic analysis gives access to effective therapy or preventive treatment. It is therefore medically appropriate. But this is not always the case and we may well wonder whether there is any point in knowing about a genetic prediction or risk when there is no possible therapy.

It is important to remember that prediction, particularly in medical matters, designates "the anticipation of events which are only probable and recognised as such" so that it not by any means stating that something is actually going to happen[18,19]. That being so, should we not be speaking about probabilistic medicine to which a preventive purpose is attached?

### 2- Biological complexity and genetic determinism

At a time when biological development was beginning to move away from molecular reductionism in the direction of biological complexity, CCNE spoke a word of warning: "The myth of the gene as the stuff of which life itself is programmed, is such that of it is born the illusion that perfect knowledge of the genome of an individual will lead to an understanding of the reality and fate of that individual. Metaphors such as the book of life which would give access to the essential human being if only one could decipher the genetic alphabet and syntax, refer to that notion. Such a concept is scientifically unacceptable and ethically dangerous[20]. And yet, technical wizardry in the field of genetic tests, generating an illusion of simplicity, using the language of codes and predisposition, seems to drive us from reductionism[21] to a certain degree of determinism, as though our genes were 'all-powerful' and cut us off from the relationship we maintain with our

[17] The penetrance of a genetic disease is the frequency with which the carrier of a gene mutation expresses the disease. It is due to a combination of genetic and environmental factors.

[18] CCNE, Opinion N° 95 (1995): Ethical Issues Raised by Prediction Based on Detection of Early Behavioural Disorders in Children: *The history of science teaches us that attempting to reduce to a single criterion the determination of someone's future is doomed to failure. A single-dimensioned template for analysis is a "Mis-measure" of man.* (Stephen Jay Gould. The Mismeasure of Man, 1981).

[19] Weil-Dubuc Paul-Loup, *"Dépasser l'incertitude" Le pari hasardeux de la médecine prédictive*" (Beyond uncertainty. The hazardous wager of predictive medicine). in *Esprit*, 2014/7 July, p. 20-29.

[20] CCNE, Opinion N°46 (1995): Opinion and Recommendations on "Genetics and Medicine: from Prediction to Prevention."

[21] Reductionism denounced by François Jacob in his preface to the French edition of Evelyn Fox Keller's book "The Century of the Gene", Gallimard, 2003 *"Perhaps, over the course of time, has there been too much emphasis on attributing too many properties, capacities and capabilities to genes. It would seem that the part that it was given to play should be reassigned to several cellular actors. In fact, in the previous century, biological research has been essentially analytical. The gene and then the genome are evidence of the success of reductionism. But it would seem that the time has come to change this attitude. It is no longer possible to burden the gene alone with all the properties that it was initially thought to be in possession of. Biological research and interest are now focusing on the interaction between different cellular components. This does not detract, however, from the genetic determinism affecting individuals."*

environment, our education, all the history that made us human[22]. The genome is not the arbiter of our fate and knowledge of the genome is not yet of very much use to us for the treatment of the complex and multifactorial diseases which make up the major part of the public health burden of an ageing population.

Biological complexity cannot, any more than can genetic determinism, accommodate the notion that a standard genome could be defined. To suppose the existence of a 'normal genome', set once and for all in some way when humans evolved and distanced themselves from non human primates, and that it should be preserved, is illusory. To speak of 'normal' genes and 'mutant' genes is an aberration since all of our genes, products of evolution, are by definition mutant genes. Some mutations are rare and some are frequent and we should speak of **variants**, some of which are the cause of disease and others are not.

### 3- The limits of genomics: the contribution of epigenetics

"*In human diseases, the genome and epigenome operate together. Tackling disease using information on the genome alone has been like trying to work with one hand tied behind the back.*"[23].

High throughput sequencing techniques are beginning to apply to the analysis of epigenomes, this 'second dimension of genomic sequencing'. While full genome or exome sequencing of an individual provides information on the general programme of cell arrangement, it does not predict the actual execution of this programme in each cell with the passage of time and as a function of environmental signals, thus leading to the **phenotype**. The epigenome regulates the diversity of cell and tissue phenotypes and the preservation of their specific identity.

The epigenome encompasses a whole series of modifications structuring DNA organisation and the proteins surrounding it in the nucleus. This organisation dictates how genes are used (or not used) by cells[24].

The specific property of these modifications is that, contrary to genome sequences (invariant), they are dynamic, plastic and potentially reversible by the passage of time and the environment. These epigenetic variations can be transmitted by a cell to its descendants, and therefore during the lifetime of an individual. Recent research suggests that they can be transmitted in germ

[22] "*Le déterminisme génétique consiste à soutenir que l'état futur d'un organisme est prédictible sur la base de sa composition génétique. C'est impossible en l'absence de spécification d'un environnement*". (Genetic determinism consists in asserting that the future state of an organism is predictable on the basis of its genetic composition. This is an impossibility in the absence of a specified environment). Jean Gayon. *"Prédire ou Expliquer ?" Sciences et Avenir Hors-Série, L'empire des gènes - 2003*.

[23] Editorial of *Nature*; 518, 273 (19 February 2015).

[24] When a cell uses a gene, the gene is transcribed into RNA which is in its turn translated into a protein.

cells, therefore by individuals to their descendants, which opens the door to the possibility of a degree of *heredity of acquired characteristics* over several generations[25].

As yet, however, we are unable to perform a global analysis of the epigenome[26], except for specific indications (cancers, some childhood pathologies). But possibly in the future such analysis could help to define — more precisely than with only a genetic sequence — susceptibility *via*, for example, indicators of an environmental risk of exposure (nutrition, climate, toxic substances, etc.) and therefore identify with greater certainty high-risk individuals who might benefit from preventive measures.

#### 4- From genotype to phenotype with regard to health and welfare

Apart from monogenic disorders, genome sequencing alone is not very helpful to predict a risk since, in complex diseases, the genetic contribution is small and above all, difficult to evaluate. It now appears that genomic analysis alone, without the benefit of high quality phenotypic analysis, is not very useful to understand the development of a disease affecting an individual. Information acquired through 'phenotype' analysis is at least as important as the genomic contribution and it is the cross-matching of both types of data — genomic and phenotypic — which best describes the physiological status of an 'individual'**. Major international cohorts aim to provide this kind of genotype/phenotype correlation.**

**Epigenetics, the epigenome**

Epigenomes regroup the regulatory mechanisms with which the genotype (genome sequence) leads to phenotypic diversity and cell function in an organism. In an organism, the 200 or more types of different cells all have the same genome and the same genes, but they do not all do the same thing. A selection of which genes will be used (or will not be used) is made by a cell/tissue at any particular time, or even in response to an environmental modification. Such regulation is implemented via epigenetic markers of various kinds :

- Chemical modifications of the DNA itself (methylation)
- Modifications to the proteins around which DNA winds (histones), the structure of chromatin
- Regulators (proteins, RNA) binding to DNA and modifying the use or otherwise of genes.

High throughput techniques now can make it possible to define precisely thousands of parameters in parallel. Today, these are the individual bases of a DNA sequence or of an RNA sequence regulating gene expression, but tomorrow they will be the epigenetic modifications or metabo-

[25] Well documented in plants, transgenerational epigenetic-related transmission of characteristics is the subject of scientific debate for mammals, and for humans in particular. A recent review of the subject was published under the title: "Nongenetic inheritance and transgenerational epigenetics". Szyf M. 2015. *Trends Mol Med*, ; **2** : 134-144.

[26] 'Methylome' analysis (identification of all the CpG sequences of DNA carrying a methyl group) is already in clinical use.

lites or proteins in a blood or urine sample[27]. We could therefore avail ourselves of a set of parameters characterising the global physiological status of an individual at a given point in time in a given environment.

Phenotypes differ from genetic data in that they reflect the actual status of an individual (as opposed to what can be deduced from a gene sequence) and that they are dynamic (varying with time and the environment) and therefore reversible, whereas genomes are relatively 'immutable' throughout life.

To the above can be associated 'microbiome' sequencing, all the genomes of the multiple bacteria colonising our bodies and which have a considerable influence on our physiological status. This also is eminently variable. It would therefore be possible to move on from biology restricted to the study of one or several genes and of a few biochemical parameters to a more global biology embracing in a more integrated way the study of a network of molecules with an effect on the complexity of individuals and therefore of their diseases. Combining genome analysis (evaluating a risk) and the collective measure of actual phenotypic data (transcriptome, proteome, metabolome) at a given time could make it possible — in line with risk evaluation — to monitor the emergence of a disorder, its progression and its treatment taking into account the complexities of individual environments.

**Microbiota or microbiome**

The intestinal microbiome is now under study as an organ in its own right (in particular, 'faecal transplantation procedures' are becoming a possibility) engaging in complex interaction with its host organism (the immune system, for instance). It is thought to be involved in some human pathologies such as obesity, diabetes, Crohn's disease, and also in behavioural eating disorders, or even depression. Certain studies indicate that there could be a 'bacterial signature' associated with a number of diseases, liver conditions in particular ranging from cirrhosis to cancer. The composition and complexity of the microbiota is being approached by large scale sequencing of the 'metagenome' (the collection of genomic sequences contained in a given biotope, regardless of species) since a number of bacteria entering into its composition cannot be isolated and cultured *in vitro.*

While these large scale genotype/phenotype correlations are already technically feasible, they still belong to the realm of research. They are expected to open up the possibility of identifying the cause of pathologies with a genetic component and, as a first step, to identify the biomarkers with which they correlate. It is also expected that they will be able to define the environmental, epigenetic portion so as to pave the way for therapeutic approaches targeting dysfunctions

[27] The term transcriptome is used to designate the full set of RNA in a cell or a sample (RNA is transcribed by DNA). By analogy, the determination of the proteins expressed in a sample is called the proteome. The microbiome designates the determination of the DNA sequence of all the bacteria residing in a stool sample (therefore in the gut). The metabolome refers to the full set of small molecules synthesised by an organism. The metabolome provides, at a given time, an image of the metabolic status of an individual which is the result of both genetic and environmental contributions. Such a profile could very well be used in a personalised medicine approach or for purposes of public health.

themselves instead of their *per se* genetic cause alone[28].

But, along the same lines as genetic testing, they may be reason to leave aside a medical strategy responding to a symptom (a disease) in favour of anticipation of a medical risk (predicted by the genome), the monitoring of the emergence of its clinical expression (phenotypic analysis) and the offer (which could even become coercive) of public health measures.

### 5- What data and what risks?

How do the new sequencing techniques modify the issues raised by genetic studies? What new data and new risks do they harbour?

The genome with its 4 base coding system is particularly suitable for automated digital analysis and bioinformatics which have stormed in to biology and medicine and represent a very significant development, have played a major role in the advent of high throughput sequencing (precision, speed, cost reduction). This sequencing technique is not confined to human genomic DNA, it also applies to RNA[29], to the DNA of the intestinal[30] commensal bacteria, or to certain epigenetic DNA modifications. It opens up a whole new horizon of ethical issues:

*a- A change of scale in time and in quantity.*

Up to the present time, genetic studies were mostly limited to seeking out in a patient's DNA a small number of distinctive genetic markers (< 10) chosen because of their suspected implication in a medical diagnostic hypothesis. The remainder of the DNA sequence being left 'unread'.

So-called next generation sequencing or very high throughput sequencing is used to acquire, simultaneously and in a short time, the sequence of hundreds of genes, or even to acquire the full exome or genome sequence[31]. It is essential to distinguish here between three phases: **acquisition**, **assembly**, **annotation/interpretation** of the sequence[32]. Annotation and interpre-

[28] An example: the respiratory consequences of oxidative particulate pollution in children suffering from cystic fibrosis (genotype delta F508 homozygote) would differ depending on whether they are, or are not, carriers of a mutation sensitising them to oxidative stress.

[29] The RNA uses a 4-letter alphabet complementing the DNA alphabet.

[30] We are host to a very large number of bacteria on and inside our body (over ten times more than human cells) in particular in the gut, and we are beginning to discover that they play a role which goes far beyond purely digestive functions.

[31] Genes coding proteins only represent a small fraction of the genome, i.e. 1 to 2%. The exome designates the sequence of 20 to 25,000 genes coding for proteins. The function of the majority of the three billion bases making up the genome is still largely unknown.

[32] **Sequence acquisition:** the DNA of cells (blood cells in particular) is purified and cut into small fragments. The next step, using different methods depending on the machine used and the company concerned, is to determine automatically the sequence of these small DNA fragments. The major technical advance in the last few years is that it is now possible to analyse simultaneously the sequence of millions of fragments (*massive parallel sequencing*) belonging to the genomes of several individuals (each individu-

tation are complex and costly procedures and therefore rarely performed for full genomes. For diagnostic purposes, only a few dozen or hundreds of genes are analysed: those which are suspected of implication and searched out for that reason. However, much of this 'raw' sequence acquisition data will most likely be saved[33]. It can be annotated again at any time and its interpretation could progress to keep abreast with scientific breakthroughs[34]. This research is linked to the clinical approach and guarantees the dynamic analysis and interpretation of the entire genome or exome. There is a high probability of identifying variants which are not linked to the disease giving rise to the genetic study, and their interpretation may be uncertain. The management of these 'incidental or secondary findings'[35] is one of the major ethical issues raised by these new technologies.

This incidental findings issue, as also that of the evolutionary nature of scientific knowledge, are particularly worthy of attention in the case of prenatal studies now that geneticists have this new capacity of being able to sequence the genome of a foetus from a sample of maternal blood. This issue was considered by CCNE in its Opinion N° 120.

*b- The uncertainties of sequencing: the challenges of quality and interpretation.*

Very high throughput genome (or exome) sequencing seeks to identify variants whose causal link with the expression of a disease (the variant will, or will not, have pathological consequences) can be predicted. Certainty is therefore essential and this is currently the main limitation, for at least two reasons:

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al being recognised by a specific bar code) which reduces considerably the time needed (and the cost) of sequencing.

**Assembly:** this phase consists in aligning small segments of raw sequences to determine their succession and reconstruct the individual's genome. You could compare this phase with putting together a puzzle. The work is done by computers.

**Annotation/interpretation:** This phase consists in seeking out the pertinent information in the sequence. There are usually two steps in this part of the procedure: automatic annotation (bioinformatics) and manual annotation (tedious verifications). For clinical purposes, the procedure calls for locating the differences between the sequence obtained and a reference sequence and determining the significance of such differences.

[33] This is currently under discussion since in some quarters it is felt that sequencing data should not be kept beyond the time frame of the specific analysis or study for which it was acquired. *"Use it or lose it" as an alternative approach to protect genetic privacy in personalized medicine*. Wagner JK, Mozersky JT, Myeritz RE. 2014. *Urol. Oncol.*; **32**: 98-101.

[34] Genetic variants of unknown/uncertain significance (VUS) may be associated with certain genetic diseases. The possibility of classifying them as 'neutral mutations' or pathogenic ones depends on the number of genetic analyses that have been performed on the gene concerned (size of patient cohorts) and therefore on how much knowledge exists on their significant association with a disease.

[35] The expression 'incidental data' which continues to be the subject of scientific debate, should only be used for truly fortuitous discoveries, while the expression 'secondary findings' should be used for deliberate research for pathogenic variants which do not correspond to the primary indication of the genetic testing but the understanding of which is conducive to treatment or preventive measures (Hehir-Kwa JY *et al. Towards a European consensus for reporting incidental findings during clinical NGS testing. 2015. Eur J Hum Genet;23(12):1601-6).*

- While the acquisition of the 'raw' DNA sequence of a genome does not take very long and is relatively cheap, it contains a large number of errors; a reasonably good quality sequence will have to be verified about thirty times and if very high quality is required (as with a clinical quality exome), the number of verifications will be in the region of one or two hundred times[36].There are hundreds or thousands of individual variants in each genome; how then can they be made significant in terms of health and disease? Defining the absence of consequence of a variant or its statistical association relationship, or even its link of causality with a future risk or phenotype (a disease) is risky. Establishing a statistically significant link and steering clear of false positives involves an analysis of very large cohorts[37] of several thousand individuals whose phenotype is known (whether they are or are not suffering from a particular disease), whose full genome has been sequenced and analysed, in order to catalogue the variations and their link with any particular pathology. While causality can be demonstrated in many cases of rare monogenic[38] diseases, the link is not so clear for a number of complex multifactorial diseases and those are the conditions which raise major public health issues and for which preventive action would be desirable. Because of these weak correlations and in order to achieve this objective, it is necessary to accumulate data and therefore the voluntary participation of informed individuals consenting to participate in multidisciplinary international studies[39].

*c- The challenge of data management.*

The acquisition of sequences corresponding to full genomes generate enormous quantities of data whose interpretation and automatic computerised processing cannot be managed by traditional and individual methods. The results obtained are now numbered in terabytes so that unprecedented data processing power is required as is the design of appropriate software.

The question of what should be kept and for how long is becoming a crucial problem and this is also true of links to personal and phenotypic data. We are entering an era of databases[40], where the internationalisation of storage and access adds to the risk of privacy erosion and to the diffi-

[36] This is called redundancy or depth or coverage.
[37] For example the 1000 *Genomes Project* and the *Exome Variant Server*.
[38] To keep it simple linguistically, monogenic disease is the expression used to qualify a genetic condition the cause of which depends on the existence of a single gene mutation. Frequently, expressivity and penetrance of the disease depend on other genetic factors or other factors besides this simple mutation.
[39] This participation is often described in research as a **partnership**.
[40] *dbGaP, The database of Genotypes and Phenotypes (dbGaP)* was developed by the NIH (USA) to archive and distribute the results genotype-phenotype correlation financed by NIH. The database is managed by NIH; the 1000 Genomes Project has a database open to public access. (http://www.1000genomes.org/data- #DataAccess)

culty of data protection[41]. The risk seems even greater in the very buoyant field of data sharing over the internet and social networks. Protecting personal and public data versus restricted access to databases which are no longer confined to national frontiers is currently one of the main areas of ethical issues to be considered[42], with certain currents of opinion to the effect that "… *the ethics norms that govern clinical research are not suited for the wide range of data privacy and consent issues in today's social networks and bioinformatics systems*" [43].

Reflection on the management of large bodies of data ('big data') is increasingly conspicuous on the international scene. The Council of Europe, for example, is reflecting on ethical issues arising out of 'big data' connected medicine, this subject extending far beyond the confines of genetic data derived from very high throughput human DNA sequencing. One of the characteristics of this trend is that the main operators are big concerns (Google, Amazon, Facebook and Apple, for example) who have no traditional history of working with physicians and biologists. Another characteristic is that the resources required to process and store such data is such that it preselects a small number of corporations who are equipped for the task, thus creating both a concentration of power nearing seemingly hegemonic proportions and a form of appropriation of this data which is in fact in contradiction with the basis and the justification for this analysis of massive quantities of health related data, i.e. the unrestricted sharing of information and its free access. This is very central to CCNE's concerns and it will be the subject of further independent study by the Committee on the ethical issues arising out of using such data, beyond the genetic issues which are the subject of this Opinion.

### 6- Fields of application

Genetic studies are generally undertaken for medical purposes and, less frequently, outside the scope of medical use for forensic or criminological pursuits (*DNA forensics*) or, more recently, as part of what goes under the name of 'recreational genetics'. In a medical context, genetic analysis seeks to identify the cause of a disease or the genetic profile to which it is attached, the causal link not always being easy to find. In other contexts, it is the individual's *identity*, or history or origin which is the subject of genomic research. DNA being heredity's major carrier, DNA sequencing provides particular information (biological) relating to family history (paternity/filiation/genealogy) and geography (geographical origins, ancestors, migration, etc.).

#### *a- Medical approach*

[41] In certain cases, for instance *The Personal Genome Project (PGP),* participants accept the risk of identification through genetic and personal data becoming public (http://www. personalgenomes.org/data/PGP12.05/)

[42] *"Use it or lose it" as an alternative approach to protect genetic privacy in personalized medicine*. Wagner JK, Mozersky JT, Myeritz RE. 2014. *Urol. Oncol.*; **32**: 98-101.

[43] Knoppers BM. "Consent to personal genomics and privacy". 2010. *EMBO rep.*; **11**: 416-419.

Moving from genetics focusing on disease to genetics focusing on health, defined as being a complete state of physical, mental and social well-being[44], places human genomics in a new context. This is no longer a simple change in scale, albeit a major change in scale, and it leads to a not unreasonable expectation of medicine targeting the genome, or 'precision' medicine, still frequently and loosely designated by the name 'personalised medicine'.

There must be a clear distinction between **constitutional** genetic modifications, those which were present in the one-celled egg — or zygote — and will therefore be found in every cell of the body, and '**somatic'** modifications which are acquired by a few cells during the course of the life of an organism, such as for instance in cancer genesis.

The first category of modifications are present in the gametes and often inherited from ancestors (they may also be acquired *de novo*) and are transmitted to descendants. They therefore involve the family.

- In this constitutional genetic context, genetic studies have led to considerable advances: the number of Mendelian diseases which could be attributed to certain mutations of a single gene, numbered a total of 5 in 1982, 150 in 1990 and nearly 3,000 in 2011. In the particular case of neonatology, this may concern etiological research in the presence of a clinical symptomatology without any specific diagnosis (malformation, mental retardation), which is only successful in a quarter of cases. Or it may be a process of systematic neonate DNA analysis, in the absence of any specific warning sign, so as to reveal genetic defects and in the event of positive responses, to organise possible preventive measures. Clinical validity and usefulness, in particular for systematic studies, are debated on a case-by-case basis and may raise ethical issues; conservation of sequences and their possible re-examination throughout the subject's life can have a serious impact on public health, particularly if a large number of people can be 'genetically' monitored. Some thinkers foresee a time when every human being's genome will be sequenced at birth so as to prepare for a more 'informed' treatment of the individual's future health. As regards prenatal diagnosis, CCNE has already discussed the development of so-called non invasive tests (Opinion N° 120) and observed that issues of the same nature arise with pre-conceptional analysis (see below, paragraph III-2-5).
- There is also another group of constitutional variations: that of complex multifactorial diseases (metabolic diseases, including diabetes, cancers[45], cardiovascular diseases, psychiatric

[44] The 1946 definition of health by WHO, see infra paragraph IV-1.3.

[45] Many susceptibility-to-cancer factors have been identified through the use of association studies. The added risk contributed by these factors taken individually is small. Interactions between factors are largely unknown. For the time being, susceptibility factors do not have any clinical application. A distinction must be made between the susceptibility factors and genetic factors associated with a high cancer risk

disorders, etc.) for which multiple genetic variations increase the risk of disease onset although they are neither individually necessary nor sufficient, the actual clinical expression of the disease being the consequence of environmental factors, including the lifestyle of the individual concerned. In this context, uncertainty is the rule and the interpretation of these variations — of which there are a large number — is all the more risky as one moves away from a given clinical context. In such circumstances we may in the future be able to discuss so-called *preventive* medicine, or the application of 'systemic biology'.

So-called '**somatic**' modifications on the other hand, are specific to a tissue, absent from gametes and not transmissible to descendants. Mostly they are related to oncology. When analysing a tumour, for example, the procedure seeks to define a 'signature' specific to a specific cancer; the analysis also focuses on the genetic heterogeneity from one patient to another, which helps to gain a better understanding of the tumorous process and also as a guide to define therapy targeted to the genetic profile of patients' tumours. The next step in the process is to seek out the therapeutic molecules targeting a particular anomaly and identify patients likely to respond to them.

The overlap between the exploitation of research activities (or of one such activity) without immediate benefit to the patient and the clinical use that can be made of this data is immediately obvious. This is one of the ambiguities of today's genetic analyses.

There is also a clinical application dimension to the genetic tests on offer on line on the Internet. Generally, a genetic profile is based on almost a million SNPs[46], but full genome sequencing could be put on offer. Results of such studies encourage consumers to adapt their lifestyle to genetic susceptibilities that have been identified and possibly initiate medical monitoring[47]. The main issues concern accuracy (quality control and redundancy), the validity and clinical usefulness of data, the need for genetic counselling or the possibility of abusive exploitation of personal data[48].

governed by Mendelian transmission. Clinically, genetic tests are performed. Mutations for genes BRCA1 and BRCA2, associated with a high risk of breast and ovarian cancers are emblematic of these predisposing factors.

[46] SNP: pronounced snip is a *single nucleotide polymorphism*, i.e. a genetic marker made up of the variation of a single base (letter) at a given point on the DNA. Frequent SNP occurrence detection is very widely in use at present.

[47] "Knowing that my personal risk of contracting diabetes is 20, 30 or 40% higher than average — meaning that my risk in absolute terms is 1.2 to 1.4% instead of the usual 1% — is that really what you can call an essential item of information which is likely to make we want to adopt a healthier diet?" (B Jordan, MS 2010). This market is evaluated as worth $250 million in 2018.

[48] 23andMe have recently sold their genetic database (Parkinson's disease) to Genentech for $60 million.

*b- Non medical use*

In parallel with highly regulated genetic studies when they are part of a medical activity, there is open access genetic testing (DTC, direct to consumer) which is flourishing alongside a number of non medical applications in a totally unregulated sector, obeying the laws of 'electronic commerce', making use of new information technology *via* the Internet[49]. This trend, particularly vigorous in the United States, follows the current thinking regarding the individual empowerment without interference from the medical professions and without community support. The main motivation in the United States for those paying for such testing is to know more about their ancestry "Bring your ancestry to life" says the 23andMe website, and trace your "lineage" through genetic links. In the genealogical indication — unlike medical prediction — results are robust, but they use other markers. Advertising for these studies is aimed directly at the consumer, and the sale of tests and communication of results is addressed directly to the consumer. Usually, members of the medical professions do not play any role. This does lead to health-related, economic and social risks and raises ethical issues.

Another use for DNA is what English-language literature calls *forensic DNA phenotyping*, i.e. the production of a phenotype based on DNA analysis (DNA profile). Currently, conventional genetic fingerprinting for criminological purposes are produced using non coding sequences and do not contribute any personal information. It would therefore be a major change in procedure if genetic variations giving indications on hair or eye colours, stature or other visible characteristics were used[50].

**Predisposed to violence?**

The late 19th century theories on 'born criminals' have triggered controversy and debate between studies claiming to support the notion of innate behaviour and those giving preference to psychological and sociological crime factors. The studies favouring innateness have served to support 'genetic defence' theories for criminal accountability or screening programmes for a potential 'crime gene' which apart from having doubtful pertinence and limited efficacy, would represent a major risk of stigmatisation and exclusion.

In an Opinion on *Ethical Issues Raised by Prediction Based on Detection of Early Behavioural Disorders in Children* (Opinion N° 95, January 2007), CCNE was concerned about the danger of a postulate giving prominence "*to the innate (genetic factors, cerebral predisposition, etc.) at the expense of the acquired (economic, social, cultural, educational and family-related environmental factors, etc. It suggests a linear and reductive approach of human behaviours and thus raises several epistemological and ethical problems."*

[49] "The market for these analyses is dominated by four players, all in the United States: *23andMe*, focusing on medical aspects, claims it has four hundred thousand clients; the *Genographic Project*, launched by the *National Geographic* magazine is concerned with population genetics and client ancestor profiles, of which there over six hundred thousand to date; the remaining two players, *Ancestry.com* and *Family Tree DNA*, identify themselves mainly as assistance for genealogical research and claim respectively a hundred and twenty thousand and six hundred thousand clients". (B Jordan. 2013. Med Sci (Paris); 29 : 1167–1170). The market is estimated as being worth US$250 million by 2018.

[50] As regards criminal investigation, based on genetic material found on the crime scene, information can be extracted on the physical appearance of the unknown person (sex, eye, hair and skin colour, etc.). The

Nor should it be forgotten that the advent of new sequencing techniques could modify the scope of behavioural genetics, particularly as regards criminal investigation (see box).

## B- The legal context[51]

At this time, two categories of rules apply:

1° French rules, most of them stemming from the 1994 bioethics laws[52] on the principle of limiting the use of genetic tests to medical and scientific research[53] purposes alone and on the organisation of the identification of genetic diseases for predictive[54] purposes as well as for antenatal[55] diagnosis, but also from law n° 2002-303 dated March 4, 2002 which recognised the principle of non discrimination based on genetic characteristics et prohibited the use of genetic test results in matters relating to insurance policies and employment contracts, and finally law n° 78-17 dated January 6, 1978 on Information Technology, Data Files and Civil Liberties which provided for protection of genetic data under the heading of health-related data;

2° European rules: those of the Convention for the Protection of Human Rights and Fundamental Freedoms dated November 4, 1950 and those of the Convention on Human Rights and Biomedicine, known as the Oviedo Convention[56], dated April 4, 1997[57], which sets out "*common general*

Criminal Chamber of the Court of Cassation (French Supreme Court of Appeal), on 25 June 2014 (see Bulletin des arrêts de la Cour de cassation, chambre criminelle 2014, n° 166 - Criminal Chamber records) approved a decision by the Examining Chamber to order an expert examination of the DNA sampled on the person of the victim of violent rape with the aim of revealing the morphological characteristics of the perpetrator and facilitate his identification.

[51] An analysis of this legal context as regards i) examination of genetic characteristics, ii) antenatal diagnosis and iii) the protection of personal data, is provided in annex V-1 (*Analysis of the legal context*).

[52] Laws n°94-548 dated July 1, 1994, n°94-653 and n°94-654 dated July 29, 1994, incorporating modifications successively made by laws n° 2004-800 dated August 6, 2004 and n° 2011-814 dated July 7, 2011, both concerned with bioethics.

[53] Article 16-4 of the *Code civil*: "...a person's genetic characteristics can only be examined for medical purposes or for scientific research."

[54] Articles L. 1131-1 to L. 1131-7, L. 1132-1 to L. 1132-7, L. 1133-1 to L. 1132-10 of the French Code of Public Health.

[55] Articles L. 2131-1 to L. 2131-5 of the French Code of Public Health.

[56] Convention on Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine http://coe.int/Treaty/fr/Treaties/Html/164.htm

[57] Ratified by France in 2012 (Article 1 of law n° 2011-814 dated July 7, 2011 on bioethics: "is authorised the ratification of the Council of Europe Convention for the Protection of Human Rights and the dignity of the human being with regard to the applications of biology and medicine*: Convention on Human Rights and Biomedicine, signed in Oviedo on April 4, 1997* " and Decree n° 2012-855 of July 5, 2012) and, therefore applicable in French law, by virtue of article 55 of the Constitution of October 4, *1958: "duly ratified or approved treaties or agreements once published have authority superior to that of laws ...".*

*standards for the protection of the dignity of the human person in relation to biomedical sciences"*[58].

To understand their significance, the mutual influence on each other of these two categories of rules must be kept in mind. On the one hand, the adoption in 1994 of the laws on bioethics stating "the general principles underpinning the legal status of the human body in order to ensure the dignity of human beings and the protection of the integrity of the genetic heritage[59], and thereby of the human species" and setting out "*a legal framework for the use made of genetic tests and of genetic identification tests, so as to protect the fundamental rights of individuals*" put France in a position where the it could play a leading role in the drafting of the Oviedo Convention; but on the other hand, precisely because the use of genetic testing was specifically linked to the "prohibition of discrimination[60]" referred to in Article 14 of the European Convention on Human Rights, French legislators were led to proposing two new rules under the heading of "prohibition of discrimination". [61] The first of these inserting into the *Code Civil* a general principle to the effect that "no one could be the object of discrimination because of genetic characteristics"; the second rule sought to modify the *Code Pénal*[62] on repression of the infraction of discrimination[63] by extending the definition to cover genetic characteristics. However, these dispositions are not related to the law on bioethics n° 2004-800 dated August 6, 2004. They are attached to law n° 2002-303 dated March 4, 2002 on the rights of patients and the quality of the public health system, following an amendment proposed by Alain Claeys based on the fact that "discrimination by generic heritage is not radically different from discrimination based on race[64].

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[58] Explanatory report, Dec. 1996, § 4, http://conventions.coe.int/Treaty/FR/Reports/Html/164.htm. The additional protocol concerning genetic testing for health purposes of May 7, 2008(http://conventions.coe.int/Treaty/FR/Treaties/Html/203.htm) is not applicable in France since it has not yet, unlike the Oviedo Convention, been ratified by France.

[59] Article 16-4 of the Code civil: "... *No one is permitted to violate the integrity of the human species. Any eugenic practice with a view to organising a selection of persons is prohibited*."

[60] Based on "..."sex, race, colour, language, religion, political or other opinion, national or social origin, association with a national minority, property, birth or other status"

[61] Article 1 of the draft law on bioethics, AN n° 3166, 25 June 2001, 61-62. It noted in its considerations the risk of increased discriminatory use of the results of genetic tests by insurers or in employment contracts, *"predisposition to pathologies which could be the subject of revelation being increasing numerous by reason of progress in genetic testing and the arrival of offers for testing accessible without medical prescription or implementation by health care professionals".*

[62] Articles 225-1 to 225-4 of the *Code pénal*.

[63] The draft law also extended the prohibition of discrimination in recruitment, sanctions and dismissals as laid out in article L.122-45 of the *Code du Travail* (now Article L. 1132-1) to discrimination based on genetic characteristics.

[64] A. Claeys, *JO* Débats AN 3 Oct. 2001, 5432: Amendment n°99, reproducing Article 1 of the draft law on bioethics. He was referring to the European Convention on Human Rights, without explicitly saying so.

Finally, should be added to the above the rules set out by the Charter of Fundamental Rights of the European Union proclaimed on 7 December 2000 and later made binding by integration into the Treaty of Lisbon. The consecration of the Charter of Fundamental Rights expresses the European Union's determination to ensure respect for these rights which thereafter became enshrined in Union law "*in accordance with the general principles common to the laws of the Member States*". Under the heading of "*Protection of personal data, Article 8 states that "1. Everyone has the right to the protection of personal data concerning him or her. 2. Such data must be processed fairly for specified purposes and on the basis of the consent of the person concerned or some other legitimate basis laid down by law. Everyone has the right of access to data which has been collected concerning him or her, and the right to have it rectified. 3. Compliance with these rules shall be subject to control by an independent authority*". And, under the heading of Non-discrimination, Article 21 prohibits "*any discrimination based on any ground such as sex, race, colour, ethnic or social origin, genetic features,...."* [65].

## C- The socio-economic context

### 1- New types of demands

Theoretically, precision medicine based on genomics is in no way antinomic to individual claims for autonomy, insofar as people all wish for themselves or their loved ones the benefit of the best medicine, based on the highest technological quality and the most accurate information. The demand "*...is supported by personalised patient information discovered thanks to formidable scientific progress. It marks the end of mass medicine and the beginning of almost bespoken medicine; the replacement of so-called blockbuster medication catering for a specific pathology regardless of the heterogeneity of patient-specific pathological characteristics by 'stratified' medication, with indication and dosage designed to fit specific patient metabolism or to be more precise, to fit a sub-group of patients."* [66] .

It should not, however, be referred to as 'personalised' medicine if that is supposed to mean "a medicine which is closer to the patient, more intimate"; on the contrary, it "disincarnates the individual as it codes for individual particularities" and enters the patient into a narrative that is not limited to that individual's own person, but includes his or her ancestors and descendants. In this respect, a person's autonomy may be destabilised insofar as the sharing of personal information may become an obligation and new items of information may need to be taken into

[65] Charter of Fundamental Rights of the European Union, http://www.europarl.europa.eu/charter/pdf/text_fr.pdf

[66] « *La médecine personnalisée : un facteur de refonte des lois bioéthiques* ? », Sophie Paricard Université Toulouse 1- Capitole Institut de droit privé CUFR J - F Champollion, Albi.

consideration to make future personal decisions regarding behaviour and lifestyle, despite doubts about the information and the difficulty of its interpretation.

It is true that, despite this uncertainty and the difficulty in interpreting genetic data, the unvarying nature of people's DNA sequence throughout their whole life may give them the impression that such a sequence represents a firm rock foundation for their personality, even though it is equally true that human beings cannot be reduced to their sole biology and even less to their genetic makeup. And yet, as part of a person's self, sharing their genetic portion can be, and is in fact claimed as a right, at a time when social networks on the Internet are significantly modifying the boundaries of 'privacy' [67], so that what certain currents of opinion describe as 'recreational genomics', essentially representing access to the discovery of one's origins, family ties and genealogy, is publicly available on forums; in this way, the notion of 'family reunion' seems close, in this respect, to that of 'friend' on certain social networks.

Nevertheless, the rigorous parting of ways between recreational and medical aspects is not so easy to order. There is a degree of ambivalence insofar as recreational activities may be very rapidly challenged by more or less significant genetic discoveries, with varying measures of medical predictive potential.

**2- Increasing merchandisation of technology**

Although at this point we have only a partial view of the way in which genetic factors influence the risk of what we call common ailments, we are already seeing massive financial investment in molecular genomic centres which are infrastructures aiming to improve the efficiency and above all the quality of their clients' DNA acquisition and sequencing and clinical characteristics. There is fierce competition to be in the best position for playing a key role in the development of new medical approaches based on genomics and thereby benefiting from the huge financial returns generated by, for instance, a totally new therapy.

*"Internationally, estimates put forward by Illumina for the clinical oncology NGS market total some ten billion dollars distributed over clinical and companion diagnostics (eight billion), one billion for genetic predisposition testing and half a billion for follow-up (detection of residual disease). Non invasive prenatal diagnosis adds up to one billion, preimplantation diagnosis to a little less, with paediatric diagnosis profiling, HLA typing and preconception diagnosis following far behind. These values seem to be very high, but they are sales evaluated from Illumina's viewpoint, including the sales of machines added to the supply of reagents and certain in-house testing. Another estimate by DeciBio is for a much smaller amount, about one billion dollars in all, with oncology and non in-*

[67] The *Facebook* network, for example, is associated with the largest global database of faces, to which its participants contribute although they are not always fully aware that they are doing so.

*vasive prenatal diagnosis as the main resources. There is a large margin of uncertainty."*[68]

### 3- Archiving and merchandising individual data

The challenge of archiving and bioinformatics posed by the sequencing technologies also has an economic dimension. Bioinformatics burst into biology and medicine and this was yet another very significant mutation. Engineers and information technology experts have had to hone their technical skills since the true challenge is the interpretation, as much as the acquisition, of sequencing data based on ever more sophisticated and powerful algorithms. It is for this reason that new players in this field, who are specialists in the computerised analysis of large quantities of data — the big data — are people trained for activities which are not those usually required in biology and genetics. The example of the IT giant Google is particularly illuminating in this respect as is the fact that it has invested in the creation of one of the more emblematic genetic analysis companies in direct contact with consumers, 23andMe. This concentration of genetic and personal data analysis and storage facilitates the appropriation of such data, and therefore the merchandising of it, as was recently the case when 23andMe sold off the personal data and samples for re-sequencing of a cohort of 14,000 people in a study concerning Parkinson's disease to a biotechnology company called Genentech for several dozen million dollars.

### 4- The link between public research and marketable innovation

Since the beginning of the new century, there has been a transfer of public research to private research *via* the proliferation of biotechnology or 'genomic' companies, specialising in the discovery of human genes and *de facto* in fundamental research, so that they are selling scientific knowledge rather than products. As a result, the very status of scientific knowledge has changed. Granting property rights to scientific knowledge produced by fundamental research may not only slow down its dissemination, as is the case for patents law which applies to the invention of new applications[69]. There may well be a risk that the actual tempo of the acquisition of knowledge relating to the genome, and consequently of the flow of innovation arising out of its applications, is slowed down as well.[70] In fact, be the research public or private, the important point is whether or not it respects the criteria for investment in the production of knowledge in the best general interest and in large-scale dissemination of exploitable research

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[68] Jordan B. In *médecine/sciences*, Chroniques génomiques May 2014

[69] Grossman G, Helpman E. 1991. *Innovation and growth in the global economy, Cambridge (Mass.), MIT Press.*

[70] Orsi F et Moatti JP. « *D'un droit de propriété intellectuelle sur le vivant aux firmes de génomique : vers une marchandisation de la connaissance scientifique sur le génome humain* », in *Economie & prévision*, 2001/4 no 150, p. 123-138. Cf. Cassier M. « *L'expansion du capitalisme dans le domaine du vivant : droits de propriété intellectuelle et marchés de la science, de la matière biologique et de la santé* », in *Actuel Marx*, 2003/2 n° 34, p. 63-80.

results[71].

### 5- Repercussions on medical management

It is symptomatic that in our country, where public expenditure for health is among the world's highest, less than 3% of it is devoted to the prevention of disease. In this context, is there any sense in highlighting the predictive applications of human DNA sequencing?

If it is no longer questionable, or even becomes fully established, that a given mutation is associated with a significant risk of developing a given disease, should we wait for the clinical diagnosis to be formulated or should society step in with preventive action that could delay the onset of clinical symptoms?

This raises a substantial issue: defining disease. Today, it is defined clinically and, despite some diagnostic imperfection, this is very well suited to 'traditional' medicine. For quite a while, we have seen prediction making inroads into the clinical scene. This is the case, for example, when some anomalous clinical or biological parameters, such as arterial hypertension or hypercholesterolemia are seen as diseases whereas they are no more than the predictive constituent of disease.

Perhaps genomics, confronting us as it does rather abruptly with the concept of predisposition, contributes to a very reductive view of the vast stretch between genomic and clinical? Can we accept the concept that ill health begins with predisposition? This is the question which led Jean Dausset into creating the concept of predictive medicine. The possibility of a predisposition leading to a prediction, could give rise to 'preventive' medical management, which would easily enough become coercive[72].

Up to now, very high throughput DNA sequencing was most often used for clinical purposes on targeted areas of the genome, in particular in prenatal medicine or oncology as well as to identify pathogenic agents. This use of targeted testing will continue to grow, but the full potential of the kind of medicine that is erroneously designated as 'personalised' and which should more properly be described as being 'precision genomic medicine for individual use', is based on the routine application of techniques pertaining not only to the sequencing of full genomes, or exomes, in particular for oncology, but also on the integration of a number of other biological markers, in particular those produced by the so-called 'omic' techniques and the entirety of health-related data. It is hoped that this block of information could establish a connection between

[71] Cook-Deegan R. and Dedeurwaerdere T. « Biens communs scientifiques » et recherche en sciences de la vie : structure, fonction et valeur de l'accès à la diversité génétique », in *Revue internationale des sciences sociales* , 2006/2 n° 188, p. 317-338.

[72] Such constraints are unlikely to be acceptable in a country like France, in which over 30% of its citizens smoke (32.4%), where one smoker out of two will die of a tobacco-related illness and where quite a number of patients do not comply with medical prescription.

DNA sequences (the genotype) and the phenotype, and therefore between an individual genome and the dynamics of its expression so as, in particular, to gain a better understanding of the transition from good health to bad, and so improve the medical management[73] of poor health.

[73] Chen R. (2012). *Personal Omics profiling reveals dynamic molecular and medical phenotypes. Cell*; 148: 1293-1307.

## III / The future of genetic information[74] in an era of very high throughput DNA sequencing

At this time when CCNE is reopening the ethical debate on the medical and societal implications of very high throughput human DNA sequencing — a debate which is situated at the centre of all the genetic scientific and technical developments and which was already the subject of its Opinion N° 120 — the point to be made from the outset is that there is a certain amount of intercommunication between information and the exploitation of storable and usable DNA sequencing data. This is probably a major ethical upheaval: from the start, from the genetic data acquisition phase onwards, individuals are at the heart of this process of implication and participation although they may not necessarily be aware of it.

### A- At the boundary between research and medicine, constructing a science on uncertainty

Impressive developments in DNA sequencing capacity and applying them to activities such as identification, genealogy and even more significantly to precision medicine and public health, should not make us forget that **the greatest challenges of modern genetics are related to knowledge and therefore to research.** Nor should they prevent us from seeing that new genomic acquisitions (human genomics particularly) are opening a path to the now non speculative possibility of modifying DNA sequences.

#### 1- The theory of uncertainty and risk.

Contrary to the impression gained from media and commercial sources, the determination or analysis of DNA sequencing data provides information fraught with uncertainty[75]. The first level of uncertainty is irreducible; it is due to the natural variability of random phenomena. The second level, which would best be described as 'non-knowledge' rather than uncertainty *stricto sensu*, is the result of gaps in knowledge which could be narrowed by making more of an effort (acquiring data, research, asking experts, accelerating trials, etc.) [76].

Do the uncertainty and the risk match? For there to be a risk, there must be something unknown about an item or its outcome; there must therefore be some uncertainty — but for this to be a risk for those concerned, they need to know about it: either that the uncertainty is 'real',

[74] Such information, the outcome of various genetic studies, in particular in the framework of research activities, corresponds to a highly mobile scientific, medical and social object as it keeps pace with the rapidly progressing genetic sciences.

[75] O'Rawe JA, Ferson S, Lyon GJ. *Accounting for uncertainty in DNA sequencing data. Trends in Genetics. 2015; 31: 61-66.*

[76] Felipe Aguirre F., Sallak M., Schön W. *Incertitudes aléatoires et épistémiques, comment les distinguer et les manipuler dans les études de fiabilité ? 10ème Congrès International Pluridisciplinaire en Qualité et Sûreté de Fonctionnement: QUALITA 2013*

meaning that the knowledge available is insufficient to dispel it; or that they can or must have access to a significant numerical representation of that uncertainty[77].

Two attitudes in the presence of uncertainty have been defined. On the one hand, consent to transcend uncertainty, epistemic uncertainty, explaining uncertainty as a temporary incompetence, as a temporary stage of knowledge. On the other hand, an attitude tolerating uncertainty, ontological uncertainty, explaining definitive uncertainty by the irreducible unpredictability of reality[78].

To try and reconcile mathematical and sociological theory, uncertainty can be made available in various versions ranked according to its plausibility (radical uncertainty, conflictual uncertainty, consensual uncertainty), its reductiveness (possibility of reducing uncertainty with the aid of targeted research, its observability (consisting in determining if a vigilance operation is able to detect and observe the phenomenon being researched), and its reversibility (more or less credible possibility of reverting to the previous state in the event of unforeseen impact detection). Risks, however, are listed according to severity, acceptability and irreversibility[79].

Scientific uncertainty, however, should never be deemed equivalent to 'manufactured uncertainty' [80] born of the expression of opinions questioning the validity of the scientific approach.

**2- How can medical practice be constructed in the presence of, or even based on, scientific uncertainty?**

One of the major changes in medical practice is that this is no longer the business of individual clinicians; it has been taken over by pluridisciplinary communities mobilising a large number of modes of decision and forms of expertise[81].

Medical practice must cope with a double challenge when faced with uncertainty: (1) prior thought by physicians on the legitimacy of a request for very high throughput DNA sequencing; (2) subsequent to the provision of raw uninterpreted results, thought on whether they should, or should not, take into account data obtained through therapeutic action (expressing a prognosis, adjusting treatment, etc.) insofar as such data presents a degree of uncertainty.

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[77] Hansson SO. « *Les incertitudes de la société du savoir* », in *Revue internationale des sciences sociales*, 2002/1 n° 171, p. 43-51.

[78] Weil-Dubuc PL. « *Dépasser l'incertitude* » Le pari hasardeux de la médecine prédictive, in *Esprit*, 2014/7 July, p. 20-29.

[79] Chevassus-au-Louis B. L'analyse des risques - L'expert, le décideur et le citoyen, Quae éditions, 2007.

[80] Henry C. « *Incertitude scientifique et incertitude fabriquée* » D'une approche rationnelle aux dénis de science, in *Revue économique*, 2013/4 Vol. 64, p. 589-598.

[81] Bourret P. et Rabeharisoa V. « *Décision et jugement médicaux en situation de forte incertitude : l'exemple de deux pratiques cliniques à l'épreuve de la génétique* », in *Sciences sociales et santé*, 2008/1 Vol. 26, p. 33-66.

Genetic data produces information of different kinds and pertinence. In some cases, the information was wanted. It is to obtain it that the test was prescribed or requested. Some information is pertinent but was not asked for (incidental and/or secondary). There is information which is available but for which pertinence and clinical usefulness have not yet been established although that may happen in the future. High throughput screening which reads an entire genome will necessarily produce a mass of non targeted data. Furthermore, some of this data is not strictly individual. It affects families and can therefore also be of use to the patient's family. We should not forget the 'information illusion'[82] created by the predictive potential of genetics.

Processing this information — most of which is uncertain both as regards significance and therefore consequences for the individuals concerned — in an ethical manner, requires that it be differentiated and classified and that any related issues of consent be identified. Patients may then consent to one part without necessarily being obliged to consent to another. Full analysis of a genome requires justification for its necessity (need to solve a clinical problem) and its proportionality (balance between advantages and drawbacks for a patient). When full sequencing is authorised, strict protocol must guide decisions to be taken regarding unsolicited discoveries[83].

**"Genetics and Medicine: from Prediction to Prevention"**

CCNE Opinion N° 46 - 30 October 1995

*Genetic tests give information on the identity of persons and emphasise their diversity which contributes to the rich nature of humankind. To use such information for the purpose of selection or of discrimination in social or economic terms, be that in the realm of public health policies, employment, or insurance systems, would be crossing a boundary of the most extreme gravity and would question those principles of equality of rights, dignity and solidarity for all human beings upon which society as we know it is based. The CCNE insists on the necessity of observing those fundamental principles whatever aims may be pursued by genetic testing. Human Rights are at stake.*

The Presidential Commission for the Study of Bioethical Issues in the United States and the European Society of Human Genetics emphasised the need to initiate a shared decision process with patients regarding the confines within which genetic testing results would be communicated and the procedures to be observed in the event of incidental findings. Physicians must respect a patient's preference not to be made aware of incidental or secondary findings, in coherence with their professional duty to assist.

[82] Gargiulo M., Durr A. « *Anticiper le handicap. Les risques psychologiques des tests génétiques* », in *Esprit*, 2014/7 Juillet, p. 52-65.

[83] Cambon-Thomsen A., « *Chapitre 8. Acteurs et outils de la prédiction génétique : l'éthique au cœur de la gouvernance », in Journal International de Bioéthique*, 2014/2 Vol. 25, p. 159-168.

## B- The genome: where personal privacy, the heritage and common property converge

It is now clear that when the bulk of the data from DNA sequencing is available — not just the status of a few targeted genes — an individual's identity can be discovered. Despite a certain degree of genomic plasticity (somatic mutations detectable during carcinogenesis, for example) such data is largely invariant, so that it can be used in forensic medicine. It does not, however, determine a person. Rather it represents a set of possibilities of being, unique to an individual, and as such relates to that individual's private life as much as to his or her identity. And yet, these possibilities are shared by others who, particularly within a family, have received them and transmit them as so many components of their heritage. UNESCO's Universal Declaration on the Human Genome and Human Rights states in Article 1 of the human genome that "*In a symbolic sense, it is the heritage of humanity*"[84] and is therefore common property.

### 1- Can sequencing data be made anonymous?

A recent article highlighted the fact that a person who has anonymously donated DNA sequencing data, in particular for research, can be identified with the help of easily accessible research on the Internet.[85] This experiment illustrates what the theory and practice of forensic medicine implies: DNA sequencing is unique to an individual and could therefore identify that individual if sequencing and personal data were accessible, although the risk of this occurring is still very low at this point in time. Databases are filling up, day after day, with huge quantities of sequences. To have these sequences available is essential if we are to make progress on their interpretation and therefore on our fundamental knowledge of the genome and the link between genome variation and health risks. In most case, individual contributions are voluntary and are not seen *a priori* as a threat to anonymity, even though there may be some ambiguity between research and clinical use as regards 'free and informed' consent. But it should be noted that a similar situation exists in the use made of social networks on the Internet, which collect impressive quantities of personal data, photographic data in particular. In the same way as concealing one's name behind a pseudonym or an avatar is no guarantee of anonymity, the relative efficacy if not downright fragility of DNA sequencing anonymisation is anything but infallible protection of private data.

With regard to genetic data, DNA sequencing components do not always contain biological information of any great intrinsic significance. There has to be the possibility of combining them with medical or non medical phenotypic data. This is where the threat to anonymity is the

[84] "The human genome underlies the fundamental unity of all members of the human family, as well as the recognition of their inherent dignity and diversity. In a symbolic sense, it is the heritage of humanity". Universal Declaration on the Human Genome and Human Rights (1997), Article 1.

[85] Gymrek M. *et al*. (2013). *Identifying Personal Genomes by Surname Inference*. *Science*; *339: 321-324*.

greatest. Scientists and physicians working on research are well able to anonymise health data and therefore of managing associations between personal data (sex, age, geographic location, etc.) and medical data. Creating a link between such information and that derived from genomic analysis, which is not in essence anonymous, is obviously a risk to the integrity of anonymity. It would not even be unthinkable to suppose that a link between such information and the existence of a biological sample stored in a biobank[86], whose DNA could be sequenced at any time[87], is also a threat to anonymity[88].

Currently, the dispersion of data files, despite their constantly growing numbers, seems to protect against this threat. They are, however, increasingly easy to interconnect, in particular with the help of the computerised technology being developed and now capable of managing massive quantities of data ('big data'), so that genetic 'correlations' are increasingly easy to establish.

In view of these difficulties some scientists and some legal experts believe that, rather than trying to prevent information from circulating, we should concentrate on educating DNA donors (sick or in good health) included or not in a cohort, who are willing to have their DNA sequenced, and work on legislation protecting sequencing data from inappropriate use, as well as on the supervision of such uses.

**2- Do the technical advances in genetics leave enough scope for freedom and/or autonomy?**

Back in 1995, CCNE pointed out the special role played by genetic analysis in its relationship with individuals and their private lives: "*...a genetic test implies entry into the intimacy of an individual, of his body, and the significance he attaches to it in relation to his psychic identity. Furthermore, almost constitutional frailties may be revealed, of an innate and non accidental nature, the interpretation of which for the representation of self and the consequences for present and future life may be of major importance" [89].* The Committee's presentation of the rules and references was the following: "*In medical genetics, some of the ordinary rules of medical ethics also apply. But in view of the specific nature of this domain, it is immediately clear that there are particular demands in its application, for instance as regards conventional rules of beneficial behaviour, autonomy of the patient (consent and confidentiality), and justice (fair distribution of risks and benefits, costs and advantages).*"

[86] CCNE, Opinion N° 77: Ethical Issues Raised by Collections of Biological Material and Associated Information Data: "Biobanks, "Biolibraries" (2003)

[87] This raises the issue of the nature and scope of further consent and the choice which it should make available, of requesting or not the destruction of DNA once the test prescribed is done.

[88] This matter is at the heart of ethical concerns regarding the merchandising of data files and biological samples, as practised by 23andMe, for example (*vide supra*).

[89] CCNE, Opinion N°46 (1995) on "Genetics and Medicine: from Prediction to Prevention".

In its Opinion N° 120, CCNE underlined that in the field of prenatal genetic tests, "*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 […] 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 […]can be allowed to see the light of day.*" These considerations were examined in a report on: *Prenatal Diagnosis, Medical Termination of Pregnancy, Preimplantation Diagnosis and Hereditary Forms of Cancer*[90]. It is through an analysis of the social and cultural conditions underlying the implementation of the new genetic analysis technologies that can be discovered the scars left by direct and indirect pressure applied to a couple's decision, and therefore the disrespect of their autonomy.

**3- From diagnosis to screening, from the individual to the community**

In neonatology, geneticists are mainly concerned with diagnosis. It is contained in the singular dialogue between physicians (in fact the pluridisciplinary medical team) and 'their' patient, represented by the parents. When measuring up to the clinical manifestations of a developmental problem which was not anticipated during pregnancy, it is important to be able to identify the causal genetic defect — or defects. Despite massive progress in the analysis and understanding of the genome, this is only possible in a small minority of cases. Dealing with this challenge is an 'ethical imperative' and a response to the legitimate expectations of parents called upon to care for a disabled child. For Arnold Munnich, for whom the primary obligation is to name the disease and identify the molecular foundations, "*... the true ethical challenge is: how can I assure my patients that all that science is aware of has been investigated in their particular case? That none of them have suffered any 'loss of opportunity'? This is a taxing technical and economic problem in view of the fact that a severe disorder, such as mental retardation, autism, epilepsy, may be due to the effects of several hundred genes known and classified by science, but still untested in our current health care system.* [91]

And yet, rather like a person looking for missing keys under a good light rather than where they were actually mislaid, it is easier for us to investigate genomic areas and genes for which we already know the predictive nature of their mutations and to propose that they be systematically

[90] Report written at the request of the *Agence de Biomédecine* (Biomedicine Agency) and the *Institut National du Cancer* (National Cancer Institute) 2007

[91] « La génétique est-elle inhumaine ?», in *Esprit*, 2014/7 Juillet, p. 66-74.

analysed, as is the case in the prenatal context[92]. This is screening which, unlike diagnosis, has a demographic and collective dimension and is a public health concern.

Today, neonatal screening is systematic for five diseases: cystic fibrosis, phenylketonuria, hypothyroidism, congenital adrenal hyperplasia and sickle-cell anaemia (for at-risk groups). This is biological — not genetic — screening (genetic screening is now available for cystic fibrosis), whose sole objective is the direct and immediate benefit of a child suffering from one of these conditions; its justification is that it affords the possibility of providing early specific treatment or appropriate management.

Should screening become genetic or pangenomic, as is already under consideration in the United States for 56 genes, it would raise the issue of the child's or future adult's freedom. This was the subject of CCNE's Opinion N° 97, concerning the screening of heterozygote[93] carriers of cystic fibrosis: "*CCNE recommends above all that the benefit of screening should have practical consequences for the person being screened. Although there seems to be such a benefit following systematic neonatal screening for homozygous forms — a status heralding disease in the future — this should not pave the way for heterozygote screening. As screening for the disease (homozygote or double heterozygote status) leads necessarily to detecting healthy carriers (heterozygote status), CCNE recommends that systematic disclosure of the healthy carrier status of a new-born not be encouraged, since this is of no direct benefit to the child concerned. There is no cause to confine a human being to his or her genetic status with the risk it entails of sacralising the gene.*"

With the possibility of everyone having their genome sequenced at birth appears the supplementary risk that the sequence could be analysed again and again throughout life, with as a consequence a constant flow of new information, potentially undesirable, being supplied or even foisted onto the person concerned.

#### 4- Preconception screening, between individual liberty and social constraint

Preconception screening opens the way for couples to access data on hereditary pathologies before they conceive. In this country, preconception screening currently concerns couples presenting the risk of a monogenic hereditary disease. It takes place as part of a genetic counselling

[92] Issues related to prenatal diagnosis and screening were examined in detail in two recent Opinions published by CCNE, N° 107 (2009) "*On Ethical Issues in Connection with Antenatal Diagnosis: Prenatal Diagnosis (PND) and Preimplantation Genetic Diagnosis (PGD)",* and N° 120 (2013) on "*Ethical Issues in Connection with the Development of Foetal Genetic Testing on Maternal Blood",* to which the reader may wish to refer.

[93] A heterozygous individual carries two different copies of a given gene for a particular trait, inherited from each parent. This is referred to as carrying two different alleles. In the case of a 'recessive' genetic disease, the heterozygous carrier of a mutation is referred to as a healthy carrier and does not express the disease.

process when there is an index case in the family. It therefore concerns, *a priori*, couples in which both parents might be a heterozygous carrier of a predisposition for a severe pathology, but in the future it could extend to the population at large, i.e. to people who are not, *a priori*, at risk.

This possibility was raised in Opinion N° 120: "*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.*"

**Generalised preconception diagnosis and direct access testing (DAT)**

- 'Amby Screen' screens for 75 paediatric recessive or x-linked diseases.
- '23andMe' provide a more extended test schedule, including, besides the genotyping of mutations causing monogenic diseases, testing for polymorphisms associated with 'multifactorial' diseases as well as a pharmacogenetic profile.
- 'GenePeeks' whose slogan claims that protecting our children is in our DNA, has on offer a DNA analysis for prospective mothers so as to find a genetically compatible gamete (sperm) donor for them thus preventing their future child from being affected by one of the serious genetic conditions on a list drawn up by GenePeeks themselves.

Why, some people ask, reject what technology can do to 'improve' our condition?

This is already being done in some countries: the *Genzyme Genetics* company is providing a test for 98 of the most frequent mutations of the CFTR gene, some of which predispose for cystic fibrosis (one at-risk couple in 1,400). This preconception screening procedure for heterozygous people has been systematic for a long time in populations where there is a marked prevalence for certain inherited conditions. In 2004, Saudi Arabia made the test mandatory to detect the transmission of sickle-cell anaemia and thalassemia. In Cyprus and Sardinia, preconception screening for β thalassemia has had the effect of dramatically reducing the number of cases. In Israel, systematic screening is recommended for eight diseases for which heterozygous frequency is greater than 1/60 and it performed free of charge for four of them (cystic fibrosis, Tay-Sachs disease, familial dysautonomia, thalassemia); it is generally encouraged for diseases whose heterozygous frequency is over 1/110 (Nieman Pick disease, glycogen storage diseases,

etc.). In the United States, heterozygote screening is recommended for frequent conditions such as cystic fibrosis or spinal muscular atrophy, as well as Tay-Sachs in the Ashkenazi community.

Preconception screening in targeted populations could well be considered progress[94], particularly when such screening applies to incurable and exceptionally severe illness. And yet, this benevolence in favour of some people highlights a form of injustice for populations where prevalence of a given disease is lower and does not therefore qualify for the free provision of screening. It would seem, therefore, that the concern is more in terms of insurance than for ethical motives. This is the reason why some geneticists suggest that such testing should be done not only for high risk populations, possibly with already one child affected, but for the population at large with an analysis of pathologies on a specific list drawn up after careful reflection integrating ethical principles of pertinence, usefulness, interpretability, reliability, etc.

In the United States again, the *GenePeeks* Corporation has on offer, for women choosing *in vitro* fertilisation with donor sperm, a service functionally equivalent to preconception screening, so that they may have a child only with donors supplying genetically compatible gametes. More generally, those involved with gamete storage in this respect, seek to reconcile essential (genetic) security of the donation with respect for donors, and above all to refrain from reducing the ethical component to no more than a benefit-to-risk ratio evaluation.[95]

In the present context, therefore, it is no longer the possibility of offering preconception testing that needs to be discussed, since it is already on offer, but rather how it is provided. Who for? For what medical conditions? With what prognosis (severity)? For which possibilities of management or treatment? With what timeline?

**5- Will predictive genomics generate behavioural accountability?**

Back in 1995, CCNE noted:

*"On the one hand, ignorance is seldom a freedom promoting factor, and knowledge of susceptibility to avoidable ailments bestows upon an individual the responsibility of drawing the consequences of this knowledge. After all, it is universally accepted that acceptance of one's fate is a key to true exercise of one's freedom since otherwise there is nothing more than wishful thinking. Nonetheless, the significance of the exercise of freedom by a person whose genetic predisposition leaves no choice but a life in the grip of terrible constraints or preventive mutilation or risk of incurable dis-*

[94] For some, this is even referred to as an 'ethical imperative'.

[95] Dondorp W. *et al*. (2014). ESHRE Task Force on Ethics and Law 21: genetic screening of gamete donors: ethical issues. Hum Reprod; **29**:1353-1359.

*ease, is open to question"* [96]. At the time, predictive medicine was relatively powerless so that the comment seemed to apply mainly to personal autonomy and freedom.

Predictive medicine starts with the calculation of the 'risk surplus' of contracting a disease compared to the population at large and is therefore based on a probabilistic type of analysis. It therefore situates a person beyond the individual level, within society. Is the individual accountable to society?

Be they common ailments, relatively treatable such as diabetes, hypertension and cardiovascular diseases, or progressive and so far inevitable such as Alzheimer's and Parkinson's, the cost for society of such conditions which could become 'predictable' in the near future is considerable. But as regards the first group, there are preventive measures considered by some (increasingly numerous) to be dependent on lifestyle and which could have a considerable impact on national health care expenditure, in particular if DNA sequencing came to be in general use and therefore made it possible to start 'prevention' at a young age, or even at birth. Monitoring compliance with 'healthy lifestyle' rules is likely, furthermore, to become ever easier thanks to connected medical care and devices[97].

*"Although France is strongly attached to principles of non discrimination and mutualisation of risks, the emergence of predictive medicine could be disruptive. Having detailed knowledge of individual risks, if that turned out to be possible, could lead to a breakdown, or at least to dilution of solidarity and of the mutualised coverage of the health risk"*[98]. The example from the United States, not as yet reaching France, of accountability being reinforced by a private health care system which is not supportive of tobacco addiction, brings us to a situation midway between praise, or even reward, for virtuous behaviour and that of demonising or even penalising risky behaviour. In this way, there could be a blurring of the traditional distinction between a risk incurred born of a not as yet controllable heredity and a risk chosen by the adoption of a lifestyle.

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[96] CCNE, Opinion N°46 (1995): Opinion and Recommendations on "Genetics and Medicine: from Prediction to Prevention".

[97] Two articles are evidence of the (economic) interest the insurance industry is taking in connected devices for a personalised evaluation of health risks (« *Notre enjeu est de rendre les assurés acteurs de leur propre santé avec un prérequis : proagir et prévenir* » [CNP-assurances]) ("Our challenge is to get policy holders to take charge of their own health, with one proviso: they must be proactive and preventive). And they are already in use:

http://www.lemonde.fr/economie/article/2015/06/15/les-objets-connectes-transforment-le-secteur-de-l-assurance_4654485_3234.html#

http://www.insurancespeaker-solucom.fr/2014/02/objets-connectes-quels-enjeux-pour-lassurance-de-personnes/

[98] Reynaudi M. et Sauneron S. (2012). *Médecine prédictive : les balbutiements d'un concept aux enjeux considérables, (*Predictive medicine: the infancy of a concept with considerable implications). La note d'analyse, n° 289, Centre d'analyse stratégique.

## C. The genome at the boundary between information and consent

As mentioned above, very high throughput DNA sequencing analysis is situated at the dividing line between clinical and research activities. In differing degrees, modern societies have at some point considered the issue of the frontier between research and clinical practice. Ethical concerns regarding certain research practices, clinical in particular, with human subjects, led to turning this frontier into an impassable barrier: research — which may entail for an individual some form of risk without any personal benefit, for the greater good of the community — has to be held up for judgment according to standards of good practices and conformity with intangible ethical principles; while clinical and therapeutic practices are perceived as intrinsically good. And yet, the emergence of a so-called knowledge based society together with slogans about getting closer to patients ("*from bench to bedside*") put about as part of the promotion of 'translational' research, have begun to chip away at this dividing line: "(*Clinical*) *Practice cannot be what it is, and cannot be of the highest quality that morally it must be, independently of its intimate connection to ongoing, systematic learning."*[99]

### 1- The ethical challenges of genetic data

DNA is often described at the 'information molecule', and while we have observed that it is not the sole custodian of the molecular bases of life and its regulatory mechanisms, it is one of its mainstays. The information contained in DNA is not immediately apparent. Just reading a sequence is not sufficient to understand its message; a lengthy process of comprehension[100] and appropriation is required to achieve this goal and it is very tempting to cut a few corners.

DNA is a subject that fascinates. As mentioned above, there is a tendency to endow it with extravagant powers with, as a result, attempts at making it responsible for embarrassing social behaviours. It has become commonplace to quote DNA in vain to qualify the essence of something that no one wants to qualify differently any longer, in a metaphoric sense, such as 'the company DNA', or more ambiguously, 'DNA of a population'. The media (television, radio, cinema, advertising) disseminating information should fight shy of these linguistic deviations and try to contribute, each in their own sphere, to respecting the scientific reality of the information that DNA provides us with and, more importantly, the information it will be able to provide in the future.

The first and main challenge of genetic information is certainly due to the evolutionary nature of the body of knowledge provided by very high throughput sequencing since the time of the earli-

[99] Kass NE, *et al.* (2013). The Research-Treatment Distinction: A Problematic Approach for Determining Which Activities Should Have Ethical Oversight. Ethical Oversight of Learning Health Care Systems, Hastings Center Report Special Report; **43**: S4-S15.

[100] Doolittle WF *et al*. (2013). Sixty years of genome biology. *Genome Biology*; **14**:113-120.

est decoding of human DNA sequences, barely more than ten years ago. This is true of the knowledge itself and of its applications, medical applications in particular. Information exploration is now an integral part of progress in genomics[101].

Another challenge presented by this genetic information is that it is expected to be a normative basis for health and behaviour although there is not anywhere in the world a human community which voluntarily defines or accepts such a norm.

Some insignificant variants and other more predictive ones will be identified, in particular based on the analysis of large cohorts, which define genetic events as being 'at-risk' rather than as a hypothetical standard of normality or abnormality, so that data significance is moved away from the individual towards population, away from individual use towards usefulness for public health.

Finally, in the face of a floodtide of genetic information, one risk for our future is that — apart from its trivialisation — is that it tends to become insistent, and even invasive beyond the questions that we are actually asking of it. Such is the danger of tests that break out of their targeted objective, that technology inserts into a global approach, of so-called 'full genome' sequencing.

**2- Misuse of genetic information and consequential risks**

The world over, whole population or very large cohort DNA sequencing initiatives are being launched, based on various demands ranging from pure cognitive research to short term clinical exploitation. A non exhaustive list could include:

- The 100,000 genomes project in the United Kingdom (http://www.genomicsengland.co.uk/the-100000-genomes-project/).
- The *FarGen* project aiming to sequence full genomes of the whole population of the Faroe Islands (50,000 people) (http://www.fargen.fo/en).
- The recently launched "*Precision Medicine*" project, initiated by President Barak Obama with the intention of constituting a million person cohort contributing genetic and medical genetic data (http://www.nih.gov/precisionmedicine/).
- The "personal genome" project (PGP) which created as early as 2005 a free-access scientific resource collecting genetic, environmental and health data supplied by a global network of volunteers (http://www.personalgenomes.org).

The terms of reference of these studies raise questions in our minds regarding the implicit choices from which they originate. For example, one might wonder about the motive for the

[101] Gallezot Gabriel, « Exploration informationnelle et construction de connaissances en génomique », in *Les Cahiers du numérique*, 2002/3 Vol. 3, p. 121-136.

constitution of a national cohort like the one in the Faroe Islands and about the biological significance of a geographic boundary. At the other end of the scale, there could be cause for misgivings regarding the criteria for the selection of participants in projects such as the ones launched in the United Kingdom or the United States, in particular as regards the categorisation of populations and respect for rules for not discriminating on the basis of genetic criteria (the 'Oviedo' Convention, or '*Genetic Information Non-discrimination Act*' in the United States.

These undertakings, which are already known to be feasible, certainly do make a contribution to science. But incidentally, they also contribute to the trivialisation we referred to above. Trivialisation and generalisation are, wherever they occur, factors for deviation, for what ethical bodies like to refer to as 'the slippery slope' in the direction of a society which would be making prevention compulsory and would categorise and discriminate for the sake of scientific logic. These projects, in their breadth of vision and their determination to encompass society as as a whole are perhaps leading us from the outset beyond the frontiers between research and medicine, to a territory possibly redefining what we consider to be that of privacy? They make such data available to society, for public uses in particular in the realm of public health and for private uses — insurers and employers readily come to mind — and they are evidence of a relatively easy path to generalisation.

**3- Psychological risks**

Psychological risks should not be dismissed as minimal and could explain the demand for the right 'not to know'. The communication of the results of genetic testing, a case in point for instance the outcome of testing for biological paternity, or the possibility of a medical risk becoming known, leads the person concerned to mourn in advance a future which had hitherto formed one of life's premises. "*The prediction contained in the test results shortens considerably the temporality separating a state of health from a state of disease* […] *In this way, such a presymptomatic test may telescope time: the future becomes the present.*" [102] There is also an after effect as the traumatic impact of the communication triggers awareness of other past events: "*The pointer of time is reversed, travelling from the present to the past, revealing past events in a new light invested with new meanings, discovered retrospectively* […] *The past becomes of paramount importance in the manner of experiencing the here and now which the revelation forces upon the subject. Reliving history, the subject will be reflecting on real or imagined past events, interconnecting them, giving them a different meaning. The traumatic potential of the communication is all the greater when its impact strikes an unprepared psyche.*[103]

[102] Gargiulo M and Durr A. *« Anticiper le handicap. Les risques psychologiques des tests génétiques* ». In *Esprit*, 2014/7 July, p. 52-65.
[103] Gargiulo M and Durr A. Ibidem.

In such circumstances, a psychological counselling session is particularly useful to help the person concerned to prepare for and anticipate the test results and thus minimise their traumatic effect which is particularly aggravated by a state of emotional unpreparedness. Such counselling provides the patient with the tools for appropriating the contents of this new knowledge and in particular the various kinds of uncertainty it contains. "*Healthy anticipation is conditioned by acceptance of the unpredictable! Moderate and adaptive anticipation is in no way an exact (fanciful!) prediction of the future. On the contrary, it is related to a process of symbolisation of the diversity and complexity of possible scenarios*"[104].

**4- What forms of consent? For what purposes?**

Since the adoption of the Nuremberg Code, free and informed consent is the foundation for medical and biomedical ethics. Full awareness, true and sincere information are its prerequisites. But as we have seen, the evolutionary nature of the interpretation and comprehension of the genome sequence makes it necessary to consider that it is only when information is anchored in a time frame can it be deemed true, sincere and welcome and that, therefore, free and informed consent also has only a limited lease of life. When people participate in research programmes such as those mentioned above, they are required to give general and unlimited consent which, in itself, raises a time limit issue, but seems to be the only course of action if research is to be made possible. Reflection and debate are ongoing on the subject of broad or restricted consent, which will probably lead to rethinking the whole question of free and informed consent (see *infra*). Moreover, should consent be seen as within the competence of strictly personal autonomy? What of the consent of the next of kin?

Do we own the information contained in our genome?

In the case of more targeted research projects, as may be the case in an oncological context, complete genome sequencing techniques may simply be faciliatory, or be a necessity if the object is to compare the tumoral and the constitutional genomes. What type of consent can be given in such a case? Article L.1122-1 of the French Code of Public Health provides an exhaustive list of the information that must be given to the person participating in research, including *inter alia* the objectives, the length of time spent on the research, the impossibility of participating simultaneously in another research project[105].

[104] Missonnier S. (2006). Périnatalité prénatale, incertitude et anticipation. *Adolescence* ; **1** : 207-224.

[105] Article L1122-1-1 *"No biomedical research may be practised involving individuals without their free and informed consent, secured after the information listed under article L. 1121-1 has been provided to them. Consent is delivered in writing or, if that is not possible, witnessed by a third party. The latter must be entirely independent of the investigator and the instigator."*

As in all cases of genetic study originating in clinical patient investigation, even though consent is obtained on the basis of true, sincere and welcome information, can we consider that consent was actually voluntary? When people are in a state of medical frailty, are they in a position where they can give free and informed consent committing themselves for the future? Should they be asked to consider receiving an inflow of information at a future time once the interpretation of their DNA sequencing has made further progress, or to consent to the conservation of their DNA and further study of the sequence, or to accept the sharing of their data, etc.

**The HeLa cells: an emblematic case of human genetic material conservation.**

In 1951 American researchers sampled cells from the cervical cancer tumour of a young impoverished black woman without her knowledge or consent. These were the first human cells that researchers were able to keep alive permanently. They were used to elucidate certain molecular and genetic mechanisms of carcinogenesis as well as for countless other biological research projects. They were used in the production of biological products, such as Salk's polio vaccine.
When they discovered incidentally the existence of these cells, members of the patient's family were dismayed by the fact that they had never been informed of the situation nor been given any explanation. Publication of the DNA sequence of the HeLa cells genome, probably considered by researchers to be common property, raised the issue of public dissemination of private genetic data. Negotiations between the NIH management and members of the family led to rules being established for sharing the HeLa cells genome sequencing*. On this occasion, Francis Collins, Director, US National Institutes of Health, remarked that the situation created by the DNA sequencing of the HeLa cells demonstrated that ethical policy was several years or maybe several decades lagging behind science and that it was time to update it.

*Hudson KL., Collins FS. (2013) Biospecimen policy: Family matters. *Nature*; **500**: 141-142

A specific case, although at first sight it does seem to be no more than an exacerbation of issues previously raised, is that of the 'free and informed consent' of children, sometimes even of neonates or during foetal existence. The primary value of information supplied is its usefulness for those concerned. As we have discussed above, this usefulness is sometimes only assumed, since it is based on probabilities, on the risk of onset of a disease or of an inherited disability, or an anomaly for which the causal link with the phenotype is unknown. Here again, it is the permanency of the media used to store the genetic information in a database and the evolutionary nature of the knowledge to which it gives access which raise issues. Can the burden of such information be imposed on a future adult who might have preferred to claim the right not to know?

### 5- The right to know, the right not to know

The generalisation of genetic data raises the issues of wanting to know, needing to know, or even having the right to know, but also what is left of the right not to know[106,107].

[106] There are cases where prevention and treatment overlap: up to quite recently, the issues arising out of the BRCA1/2 tests were purely preventive, but lately, with the advent of specific treatment for cancers appearing in a BRCA-/- context (PARP inhibitors), there are also therapeutic issues. When someone tests positive for a disease, surely the right not to know is questionable?

[107] Weil-Dubuc PL. (2013). Les servitudes du droit de savoir. Autour du diagnostic présymptomatique. Publié dans laviedesidees.fr.

In 2013, the American College of Medical Genetics and Genomics (ACMG) published recommendations for reporting of incidental findings in the event of full genome analysis[108]. Some fifty genetic anomalies were listed which warranted, according to this recommendation, an obligation to inform those concerned or the patients, regardless of whether they had or had not requested that information and irrespective of their age. This step goes a long way in the direction of an obligation to know, to giving up the right to ignorance. The arguments following the report's publication led to the recommendations being withdrawn[109]. Being made aware of incidental findings is therefore no longer an obligation; it is still an option.

In France, since the adoption of the law dated July 7, 2011 (article L. 1131-1-2 of the French Code of Public Health, it is mandatory to inform the next of kin if a serious genetic (hereditary) disease is diagnosed. This obligation does not solve the ethical problem of disclosing the risk of disease to blood relations who had not requested the information[110]. This is an example of how difficult it is to find the right balance between personal autonomy, respect for that autonomy and the duty of solidarity which is also expressed in the warning given and the prevention of a genetic risk or danger.

[108] Green RC, et al. (2013). *ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. Genet Med.; **15**: 565–574.*

[109] *Burke W, et al. (2013*). *Recommendations for returning genomic incidental findings? We need to talk! Genet Med.*; **15**:854-859.

[110] These questions highlight the fact that our genetic heritage, the DNA sequence that identifies us as individuals, does not belong to the individual; it is shared with the individual's family. It was inherited and will be passed on to future generations but we have no control over what is transmitted nor over the 'normality' of what is transmitted.

## IV / Main issues arising out of this reflection

Rapidly progressing technology in genetics inspired in CCNE the need to continue its consideration of the subject in the light of the generalisation of high throughput DNA sequencing and its impact on medicine and society. This technological progress with faster, cheaper and more reliable analyses has become feasible thanks to considerable investment in cognitive research, particularly by the public sector, together with technological breakthroughs brought about by the activities of the private sector. This represents an unprecedented opportunity for accelerating and augmenting our grasp of the living world and for improving the help we are able to give to those who are victims of its dysfunctions.

As a result, what seemed to be no more than a technical process, i.e. full genome analysis, could challenge well-established practices or concepts, both medical and social, or could enter into conflict with national or international rules and regulations based on accepted values, thus opening a vast area of ethical debate.

Some of these developments aim primarily at improving people's health and will probably achieve their goal. They also meet a legitimate need for autonomy; attempts to curb their progress to protect people are doomed to failure. And yet, certain relatively foreseeable social developments and risks arising out of genomic analysis should be the subject of the community's consideration without further delay in order to avoid or minimise them, or take compensatory measures.

CCNE would like such consideration to be given to the important subjects for which the 'genetic revolution', as it is sometimes called, plays a major role: medical practices, free and informed consent, privacy. We may indeed be faced with a genetic revolution, but this is a change of scale rather than a hitherto unknown set of circumstances.

Questions such as "How should the right not to know be respected?" or "What should be done about incidental findings" are by no means new. Medical imaging (for example emergency abdominal CT scans leading to a large number of "incidentaloma"[111] findings) and biological tests have been raising identical problems for quite some time. Similarly, the question of personal information and whether it concerns other members of the family is not a new one. It already existed when members of the medical professions needed to ask about family history.

Nor is the difficulty of making personal genetic data anonymous a new and singular problem, even though it is even more critical. Nevertheless, although the change in scale does not make

[111] Kelly ME, et al. Incidental findings detected on emergency abdominal CT scans: a 1-year review. Abdom Imaging. 2015; Jan 10.

any previously unheard of contribution to the issue, it does magnify existing problems concerning how this should be done and the ethical obligation to find out whether the new techniques are of benefit to the majority without encroaching on the rights of individuals.

Before even entering into any discussion of these issues, it should be noted that if the procedure was to be generalised, we could neither carry out the genomic analysis nor provide personal genetic counselling for lack of the necessary financial and human resources. Furthermore, the facilities to store the massive amount of data generated for an appropriately protracted period of time would not be available.

## A. The place of genetics in the evolution of medical practices

### 1- Place and role of genetics under consideration

It would be difficult, and perhaps even impossible, to try and evaluate the percentage of a person's fate that can be attributed to the sole genetic or inherited component. No one could deny at this stage that a living organism's complexity and future does not rest solely upon a sequence of 23,000 simple elements, the genes, but rather on successive stages leading up to the use made of them by the cells. These stages are influenced by the environment in the broadest sense of the word and sometimes controlled by the random fluctuations on which human diversity is constructed. While a DNA sequence can be precisely determined — which is not the case for the other factors involved — its expression contains a measure of unpredictability representing an essential dimension of its analysis.

Although there has long been a confusion between the innate and the genome, recent research now suggests that there could be, as has already been demonstrated for plant life, a certain degree of inheritable acquired traits, inscribed in the epigenome. The extreme complexity of the arrangement and activity of DNA sequences revealed by full analysis techniques no longer coincide with traditional representations of the 'genetics alone' variety. Genetic variations may, for instance, not be expressed as symptoms, or else may be so in some individuals and not in others. There is therefore no such thing as the concept of 'a normal genome', in the meaning of 'an ideal genome'.

### 2- Precision medicine[112]

Progress in genomics is contributing to make medicine move towards a more precise definition of certain therapeutic options and introducing, within certain limits, closer clinical adjustment to a person's genetic characteristics. For the time being, this approach is still limited and sporadic, but it is full of promise. One step at a time, correlations established between certain pathologies, or subgroups of pathologies and their genetic counterparts are making it possible to diagnose or predict the onset of certain diseases and, in some cases, to treat them. The abundance of information generated by the full genome analysis is such that knowledge of the existence of genetic variants necessarily precedes knowledge of their import.

In view of the risk that information that has not as yet been validated or whose meaning is still unknown is delivered nonetheless, the first duty of geneticists (practitioners and researchers alike) is to avoid making erroneous predictions. Reinforcing the validation process of the pertinence and safety of the use made of knowledge generated by genome analysis is of primary importance, not forgetting to integrate developments in medical evidence based mathematical standards (*evidence based medicine*).

Another point is that it must be noted that precision medicine leads to a subdivision of frequent diseases, for example cardiovascular disorders or diabetes, into subgroups of rare diseases better described in molecular terms, so as to be able to prescribe appropriate treatment. These developments require specific therapeutic strategies of the same kind as those currently existing for rare diseases, or in the case of frequent diseases in patients from poor countries who are unable to buy these medications[113]. So, as attempts at 'personalised' or 'precision' medicine are made, are we not calling into question the current model for the elaboration, production and marketing of medications based on the so-called 'blockbuster' drugs? The pharmaceutical industry is currently adapting to a market for targeted, but frequently very costly drugs (for example Nivolumab for metastatic melanoma et non small cell lung cancer) whose impact on the health care budget and therefore on the French sickness insurance system raises major national solidarity issues[114].

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[112] Claeys A, Vialatte JS, Office parlementaire des choix scientifiques et techniques. Les progrès de la génétique : vers une médecine de précision ? Les enjeux scientifiques, technologiques, sociaux et éthiques de la médecine personnalisée. Office parlementaire des choix scientifiques et techniques, 2014, rapport accessible à http://www.senat.fr/rap/r13-306/r13-306_mono.html

[113] Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products: *"As a result of the high cost of research and development, the pharmaceuticals industry is reluctant to develop medicinal products intended for the treatment of rare conditions, as well as those called 'orphan medicinal products', for which the market is smaller."*

[114] Claeys A, Vialatte JS. 2014, opus quoted supra.

### 3- A different relationship with disease

Human health and its definition, unchanged since the World Health Organization expressed it in 1946[115], is a vast subject for debate. It is confronted by medicine based on scientific evidence to which, as we have seen, genetic data and particularly that generated by large-scale and high-throughput DNA sequencing, provides apparent objectivity. And yet this does not contradict an understanding of disease as "*life at a different pace*" even though it seems to call into question the primacy of clinical practice, referred to by G. Canguilhem in the following terms: "*...clinical practice is not, and never will be, a science (...) Life standards are not dictated by science".*

Can genetics 'define' symptom free disease, before the onset of symptoms?

There is a real risk that clinical practice, of which precision medicine is now becoming a key element, could inspire practitioners at some time in the future to be content with managing a person's genetic profile. This would be a form of depersonalisation of the doctor to patient relationship. This risk would have to be compensated by medical training which included a holistic conceptualisation of the individual, aiming to care for the human being and not just for a pathology, and certainly not simply for a genome.

### 4 -A different relationship with the prevention of disease

The new technologies could also accelerate developments in the practice of preventive medicine. But here again, this is not a new departure. The results of measuring arterial blood pressure or blood lipids, cholesterols in particular, do not reveal a disease but rather the risk of disease onset, such as cerebrovascular accidents or myocardial infarction. A generalisation of predictive genetic tests is helping to increase the distance between a predisposition revealed and its possible clinical expression and, if necessary, to anticipate such expression. But does it also make a decisive contribution to preventive medicine, be it for individuals or for the public health system? [116]

From the point of view of public health, empowering individuals and encouraging risk-reducing lifestyles, thus lessening the likelihood of pathological outcomes, is of value. But individualising preventive strategies according to the genetic characteristics of people who are more or less likely to develop some medical condition or another involves a risk of social inclination to discriminate or encroach on individual liberties, particularly in a context where reducing health

[115] "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.

[116] Etienne JC, Corne C. Les enjeux de la prévention en matière de santé. 2012. Avis du Conseil économique, social et environnemental.

care expenditure is widely viewed as inevitable. Exploiting this data in terms of risk, with an eye on public health policy, on a country-wide scale, does not signify that it brings with it direct individual benefit in terms of prevention and therefore of health. What information does the 'full' genome today, and the 'full' phenotype tomorrow, provide for the individual?

**5- The physician's place and role**

In Opinion N° 120, CCNE had already looked into the new impediments to medical practice in the presence of the very great degree of technicality in DNA sequencing, sequencing interpretation and, above all, the massive amount of information it generates: *"...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*." What is true for a prenatal diagnosis, is even more applicable to all the facets of 'genetic medicine'.

As discussed above, the evolutionary nature of the information provided by large scale DNA sequencing puts physicians in a special position where they must answer to their patients but also to scientific progress, where they are both clinicians and partners in research. One important consequence of the diversity and complexity of medical data is the risk that physicians become 'incapable' of understanding the data they receive and therefore unable to report and explain them to their patients.

Genetic data being a subject for research, this means that it opens up horizons at least as much as it provides answers, thus creating a certain amount of perplexity: we are not sure where all this is taking us. Our thinking on the subject should therefore enable us to single out the issues to which physicians obviously, but also educators and teachers, society and legislators should devote attention, although we are still unsure of the exact perimeter of these new areas. Taking into account the great number of players, some of whom are offering purely commercial services, how do we determine who will be answerable and how reliable and comprehensible information should be delivered, although this is essential in order to obtain a person's consent? How can we ensure that the use made of genetic data serves no other purpose than the one for which it was collected? How and by whom should the individual be informed of the genetic data collected and even more important, of its interpretation and of the uncertainties attached to this interpretation?

Nor must we forget that the broader-based and the less specific is an analysis, the more frequently will unexpected data emerge, the meaning of which may not be altogether clear. What

then shall we be able to do so that those concerned are not left to their own devices when confronted with frightening data and alarming uncertainty? How much attention should be given to psychological counselling as a component of medical practice, in particular for genetic subjects?

## B. Reflection needed on respect and protection of privacy

The change of scale as regards the instruments required for the acquisition and analysis of genetic data, the quantities of data it will generate, their multiple and varied uses and the numbers and variety of operators who will be exploiting them will have such consequences on the concept of privacy that we must review our thinking on this subject.

### 1-Legal protection for personal data

Once again, we have to point out that, in the main, the management of genetic data (DNA sequences) is part of a more general picture, that of personal data, health data in particular, which is stored in huge quantities and constantly shared, be it in the form of identifiers and banking particulars for example, or medical files, among others those stored by the French public health care system, although the special case of the 'shared medical record' is one particularly sensitive aspect of the problem[117]. Because of the duty of confidentiality, no health care professional can publish information concerning a third party, even when the person concerned has already published the information.

Since personal medical data is already protected, there is no overriding reason why human genome sequencing should be made an exception to the general principles applicable to medical care as defined in articles 6 and 7 of the law dated January 6, 1978:

- Purpose (legitimate and specific);
- Proportionality (recording only pertinent and necessary information);
- Pertinence of data (appropriate, pertinent and not superfluous in the light of stated objectives);
- Limited duration (data stored in keeping with stated treatment objectives);
- Safety and confidentiality (authorised staff, steps taken to safeguard data, preventing unauthorised access);
- Transparency (information provided to those concerned);
- Respect for personal rights (informing those concerned and the right to object; rights of access and correction for those concerned; express agreement and resulting right to oppose re-

[117] *Cf.* CCNE, Opinion N° 104 : The "Personal Medical Record" and computerisation of health-related data (2008).

cording - except if recording is mandatory; the right to oblivion; prohibition of 'profiling' according to ethnic, religious or sexual orientation criteria; penalties in the event of a breach).

**2- Limitations on the use made of personal data**

Choosing, for whatever reason, to have your genome sequenced[118], and being obliged to do so, for yourself or for the sake of your child, are two very different things. The dividing line is drawn by answering the question 'Who decides and how?' As regards the protection of privacy, an increasing number of people wish to be 'transparent'. But to be willing to make one's genetic data public is not equivalent to giving up the right to refuse to do so, even though, and possibly even more so, if there is a form of social pressure, or even a fashionable trend that this is the way to go for those who wish to have a responsible attitude towards their own health and wish to do their bit in the name of improving public health. Holding a genetic ID card seems to be gratifying and harmless, but in the same way as social networks have blurred the distinction between public and private, a day may come when the holder regrets having published information based on data that can be interpreted, and even interpreted again at a later date and whose nuisance potential was not suspected initially.

Protection of privacy protects individuals from unwarranted revelations, sources of knowledge by the public of facts of a private nature and incursions on their dignity or liberty[119]. The right to data self-determination, a concept defined by the German Constitutional Court in 1983, should be promoted; it is not a right of ownership in the traditional meaning of the term, but a personal right to "guarantee in principle the capacity of an individual to decide on the communication and use made of personal data". Using the concept of ownership rights would turn individuals into managers of a heritage whereas the right to self-determination is a reminder that they must retain the ability to make decisions on their own behalf. It would be necessary to organise a '*droit d'alerte*' (whistleblower protection) for data protection based on the same principles as those of the law dated December 6, 2013, which is a general '*droit d'alerte'* for all crimes or offences. For instance, collective measures for the protection of personal data[120] should be set up and it would also be important to reinforce the capability for individuals to control and use their own person-

[118] Kuwait, for instance, was the first country to require all its residents to have on record identity documentation based on DNA testing, on a compulsory basis. Such a decision would be illegal in Europe and contrary to the decisions of the European Court of Human Rights (CEDH). (sources: http://www.rfi.fr/moyen-orient/20150714-koweit-impose-fichage-adn-ensemble-population-test/)

[119] Halpérin JL, « Protection de la vie privée et *privacy* : deux traditions juridiques différentes ? », *Les Nouveaux Cahiers du Conseil constitutionnel* 2015/3 (N° 48), p. 59-68 ; Whitman J, "*The Two Western Cultures of Privacy: Dignity v. Liberty"*, *The Yale Law Journal*, 2004, 113, p. 1151-1221; Rosen J, *The Unwanted Gaze: The Destruction of Privacy in America*, New York, Vintage Books, 2000; Post RC, "*Three Concepts of Privacy", Georgetown Law Journal, 2001, 89, p. 2087*,*2098.*

[120] Report by the *Conseil d'État* (Council of State, highest French administrative jurisdiction): *Le numérique et les droits fondamentaux*, La Documentation française, Paris, 2014.

al data, defining a chain of accountability starting with data collecting organisms through to final users, attaching metadata to personal data indicating the purposes for which the data was collected and thereby, defining restrictions on its use[121], etc. [122]

### 3- The public health/privacy relationship

Ethics requires us to raise the issue of the impact that sequencing technology has already had on individuals and society. This is all the more important if it becomes possible to sequence not just a genome, but also to have access to all the parameters defining an individual's phenotype, thus anticipating and influencing future developments.

One of the main and specific characteristics of genetic information is that such data is not solely 'personal' and private in the usual meaning of the words. It is personal of course, but it also identifies and is shared by a kinship group[123]. How, therefore, can procedures designed for an individual be used to manage what relates to several people?

There is a need to distinguish between the case where a listing is of a purely private nature and could lead to commercial uses and the case where it responds to an *a priori* legitimate public health objective for the benefit of the community.

Privacy infringements through the creation of genetic characteristics data bases are not, obviously, only dangerous in themselves, but also because of the uses that could be made of them. To some extent, a data market already exists. Nor should the possibility be overlooked of their being put to use in certain parts of the world by repressive political regimes.

Were improvements to public health by the use of collections of personal genetic data to be the only criteria, privacy protection could be seriously at risk and all the more so since epigenetics, that is personal history and behaviour, need to be known in order to arrive at a fair interpretation of genetic data. If that were so, under the guise of advancing the cause of public health, there could be serious intrusions upon personal privacy so as to arrive at a more accurate behavioural characterisation. It becomes clear that a contract of reciprocity between an individu-

[121] Cf. the draft *Consumer Privacy Bill of Rights Act,* 2015.

[122] Moreover, the various parties concerned, in particular technical operators, should certainly be invited to set up *privacy friendly* technology (favouring the protection of privacy and personal data) by introducing the concept of privacy protection from the outset (*privacy by design*), by designating dedicated personnel for data protection within organisms collecting such personal data, by creating a right to be delisted based on the right to oppose the processing of an individual's own personal data, by inversing '*public by default'* to '*private by default*', etc.

[123] This situation is representative of others: (i) the parents of underage children holding the rights belonging to their offspring, following constant legislation; (ii) ascendants and collaterals of people to be listed in the French automated national genetic prints DNA database (FNAEG - Fichier National Automatisé des Empreintes Génétiques).

al's privacy and the furtherance of public health must always be drawn up so as to define clearly the limitations and privileges of personal capacity rights.

#### 4- Modifications to information and consent procedures

Consent is obviously required for the storage of, and access to, genetic data. It cannot, however, have the same impact as in cases where data is collected for a specific purpose since it is assumed that interpretation of the genome is work in progress and could reveal, at a later time, information that the researchers had not expected at the time the data was collected.

The requirement for free and informed consent — to use the traditional wording which is sometimes criticised because it would be more in keeping with the principle of autonomy to use the word 'choice' — is the cornerstone of medical and bioethical law. The arrival on the scene of full genome analysis, its ties with research and the evolutionary nature of the knowledge to which it provides access, calls into question the effectiveness, not to say the very existence, of the information/consent relationship.

To which must be added that the existence of unexpected data could render the 'right not to know' meaningless although good practices seek to perpetuate it, in particular for severe late-onset pathologies. Getting one's DNA sequenced may be tantamount to imposing the unexpected on others, blood relatives in particular. The system needs to be entirely reviewed, both to adapt it to the probabilistic nature of some of the information as well as to take into account the fact that all discoveries and their interpretation cannot be anticipated at the time of testing.

Those whose task it is to legislate on public health matters should address their thoughts to how individual access to quality medical genetic information should be organised, to adapting free and informed consent procedures to the possibility of incidental discoveries, and to diagnostic developments in the prenatal and perinatal periods. The possibilities for prevention, diagnosis and treatment flowing from access to the human genome deserve to be implemented without obstruction as long as they are based on scientifically validated techniques and are able to distinguish between that which is within the purview of genetics, of heredity in the broadest meaning of the word, and that which falls within the scope of the environment or of individual factors. It will be up to lawmakers, working in close cooperation with all concerned, physicians and researchers obviously, but also more generally with citizens themselves, with all the stakeholders, to develop safeguards and control procedures to make them compatible with the founding principles of our country's medical practices in genetics. Clearly, such a review will not yield results before quite some time[124]. There is, however, an essential *need* for it to be open and accessible

[124] Law and technology do not follow the same timetable.

to all as part of a democratic debate which the Committee highly recommends.

**5- Reconciling shared data and privacy**

Confronted with public heath issues, individuals may choose to revise their criteria for the rigorous protection of their privacy, in particular by deciding to reveal information on their personal health, which is what they do already on certain forums and social networks. Let us not forget that some medical data, genetic data particularly, also concerns next of kin and is situated at the outer confines of what can be considered to be **individual** data. If there is no contract stipulating reciprocal rights between the individual concerned and the organism charged with collecting the personal data, the potential for damage to the individual's privacy is too serious for it to remain unobstructed. Inversely, a form of reciprocity could be drawn up by the authorities regarding the individual's right to transparency and to be fully informed of any use made by the authorities of personal data and the way in which they intend to protect the data and control its use. The right of the individual to demand the removal of stored data would also be protected by such an agreement. Nevertheless, it would be difficult to maintain respect for the agreement over time in view of the evolutionary nature of the data, although the more the data evolved, the greater would be the need for the information it contains.

Identifiable genetic information is permanent. It can be stored electronically, used over and over again, added to at any point in the life of individuals concerned, as a result of which they may be confronted with critical problems in their relations with the public (health) institution or the private company (commercial) storing the data or the community (political) wanting to use the date. This dependence on time and the multiplicity of players is representative of the difference between genetic information and other medical data. The latter is only significant at the time it is imparted and within the confines of the doctor/patient dialogue.

In view of the fallacious nature of the 'anonymiszation' of personal and genomic data in open-access databanks, can the community guarantee that the DNA I am trusting it with will stay unidentifiable? At the other end of the scale, should not individuals consent to take the risk that their private data does not remain anonymous, for example in the context of the analysis of a cohort's data, if out of the genome sequencing of a very broad selection of the population an item of knowledge emerged which solved a public health problem or identified a risk factor, from which they themselves might also derive benefit? But, in such cases, is 'sharing' the right word to describe the process? Is this not more in the nature of a gift of information to those for whom it might be beneficial?

We are therefore entering the subject of respect for privacy from the point of view of self-determination rather than of ownership. The principle of non-appropriation of genetic data supposes the existence of a free access policy coupled with pooling such benefits as might be

forthcoming (intellectually, medically and financially), and is akin to the notion of public good. Free access, and therefore the pooling, of data are now decisive constituents of scientific progress, leading to some new practices in scientific research, in particular outside the sphere of academic research. The concept of 'publicness'[125] was coined to bear witness to the collective value of self-revelation: creating a climate of trust and common knowledge so as to improve the chances for individual emancipation. The concept is therefore 'targeted', it is a 'service' to the public, it is not identical to generalised transparency; it seeks to serve a more inclusive definition of the common good. Two points, however, need to be kept in mind.

While sharing may be considered as one way of conducting personal privacy, meaning that sharing is a free choice and not an obligation, it is still true that it must also be possible to *reverse* the process of sharing, meaning that contents that people no longer want to share could be withdrawn or deleted. However, apart from research and public health applications, current regulations seem to be rather inefficient in preventing information willingly shared at some point from being shared forever. Finally, in a world where the pooling of personal data may be considered as pertaining to the common good, then the common good cannot, whatever the circumstances, be incompatible with the right to privacy[126]. If an individual has decided to share freely personal data, this does not signify that he or she has relinquished any right to privacy or that third parties have any claim to violate that right.

[125] There is no satisfactory translation in French for the English word 'publicness'. There have been suggestions that another newly minted word, 'publitude' in French, could be used to designate an attitude of transparency, of public sharing of personal data, a new standard launched by the Internet giants with the slogan: 'If you have nothing to hide you have nothing to fear'.

[126] It would be well to consecrate the notion that genome-related data is the 'common property', of several 'co-owners', the use of which can only be decided jointly by all concerned.

## C. The risk that genetics could 'take over' the preventive component of public health

We have analysed the role and the implications of modern genomic developments as regards prediction and prevention in personal and public health, in particular those connected to large-scale high-throughput DNA sequencing.

This role is both the cause and the consequence of using a very powerful technology capable of increasing the knowledge we already have or wish to acquire about our heredity and, more generally, of our physiology, before its biotechnological or medical application. In view of the emphasis on medical applications, CCNE must stress that it is now well established that major health determinants, and therefore the major determinants of public health prediction are related to lifestyle, most particularly in the social and economic conditions affecting people's lives. [127,128]

To be sure, where individual health is involved and, in a given environmental context, the predictive value of certain genetic determinants based on rigorous scientific facts, can be significant and pave the way for preventive measures, some of which may be effective. Is there not a danger that genetics may take over the already limited attention granted to prevention in public health policies? [129]

Investigating the actual portent of defects in our genes and DNA sequences and how they could affect life expectancy is a legitimate enterprise, as long as we remember that life expectancy depends primarily on social, non-genetic determinants, such as for example the environment. Social and economic determinants have a major impact on the health of people living in the poorest countries (in particular access to safe drinking water, decent sanitation, sufficient food supplies, medication, etc.). These social and economic determinants also play a major role in the health of the population of our own country, where three million children are living below the poverty line and where an ever increasing number of people in precarious living conditions often cannot afford to see a doctor except belatedly in the accident and emergency department of a hospital; our country in which we can observe great disparities in life expectancy depending on dietary habits generating obesity or the consumption of tobacco and alcohol, but also dispari-

[127] "Closing the gap in a generation. Health equity through action on the social determinants of health." Final Report of the Commission on Social Determinants of Health. World Health Organization 2009. ISBN 978 92 4 256370 2.

[128] Marmot M. 2010. "*Fair society, healthy lives". Strategic review of health inequalities in England post-2010.*

[129] It is worth noting that only 2.24% of current health expenditure was spent on prevention in France in 2014.
http://www.irdes.fr/enseignement/chiffres-et-graphiques/depenses-de-sante/depense-courante-de-sante.html

ties due to people's professions or where they live.

Should we not also investigate the nature of the scientific, political and mainly economic forces moving relentlessly in the direction of an increasingly technical management of health care? Genetic testing is only the tip of the iceberg, currently conspicuous because of the prodigious speed of its development.

Human genomic research will only be a major asset for improving human health if it does not supplant clinical medicine and public health policy[130], both of which are inseparable from health care.

[130] *Public health* policy can help to modify the social and economic determinants of health whereas clinical medicine is, more often than not, ineffective in this respect.

# V / Annexes

## A. Analysis of the legal context

### 1- Examination of genetic characteristics

The two subjects: genetic testing for medical purposes one the one hand and forbidding discriminatory use of the results on the other, will be considered separately.

*a- Genetic testing for medical purposes*

This examination consists in analysing a person's inherited genetic traits or those acquired at an early stage of prenatal development. *The purpose of the analysis is to "either make, confirm or refute a genetic diagnosis, or to search for the characteristics of one or several genes that could cause disease in a person or in potentially concerned members of that person's family, or to adjust medical treatment to match a person's genetic traits"* [131] . The rules applicable are not those normally regulating the decisions that a sick person who has requested the advice of a physician might ordinarily be taking: they are based on the full information provided by the physician[132] as a result of a global analysis of a person's state of health, so that an informed decision can be made, i.e. accepting or rejecting the physician's proposals[133]. Nor are the rules those applicable to biomedical[134] tests. Instead, they are specific to bioethical[135] medical practices which are particular in that they are controlled, unlike 'normal' medical practices for which it is sufficient for people to consider themselves sick for them to be given the health care appropriate to their state of health[136]. Such practices are regulated, both as regards the request formulated by the person concerned and the practitioner's response, to which

[131] Article R. 1131-1 of the French Code of Public Health.

[132] The delivery of which is one of the rights of a person in ill health: article L. 1111-2 of French Code of Public Health.

[133] Article L. 1111-4 al. 1 of the French Code of Public Health: "... patients make decisions regarding their own health together with the member of the medical professions, *taking into account the information and advice the latter provides*."

[134] Articles L. 6211-1 and L. 6211-2 of the French Code of Public Health.

[135] Which, according to the explanatory statement of the bioethics draft law, should be understood as being "...ethical and societal issues related to medical innovation involving manipulation of living material": Draft law on bioethics, prec., 4.

[136] As demonstrated by Canguilhem, a physician responds to a request, that of people consulting him because they feel unwell and call on his competent care; therefore, says Canguilhem, "*it is first and foremost because people feel sick that medicine exists*", to which he adds: "*it is always by relevance to the sick person, through clinical practice, that there is justification for the qualifier "pathological".* G. Canguilhem, *Le normal et le pathologique*, PUF, coll. Galien, 1966, 156.

should be added that the law specifies the qualifications and training the physician must have, while the institutions carrying out the tests must be specifically approved for the purpose[137].

As a result, specific rules are prescribed for genetic testing[138], as is also the case for other practices, because in this genetic context, we are dealing with *medicine for the identification of a disorder rather than medicine for a patient,* a disorder which, being genetic, suggests that a biological future is written into the depths of a gene the subject carries. Moreover, evidence of the disease only implies, except in some rare cases, a probability of onset of a disease that often can neither be treated nor prevented. *Uncertainty* therefore is characteristic of this type of situation. Finally, the person carrying the harmful gene is of course directly concerned, but so are others: descendants to whom the gene may be transmitted and members of the family. As a result, rules governing the examination of genetic traits are different because there is the intention that genetic tests should not be dealt with as would be an 'ordinary' biomedical test and because this test may have consequences affecting other people than the person submitting to the test.

The law puts *two constraints on the physician* as regards *securing consent* and providing *information*; but in both cases they differ from those applicable to patients as set out in the March 4, 2002 law on patients' rights. The law distinguishes between the decision taken by the patient and the possible *provision* of the care required by the patient's condition. Information, which has been one of the recognised rights of patients[139] since the adoption of law N° 2002-303 dated March 4, 2002, has an essential role to play here, that of giving patients the possibility of making an informed decision regarding their own health. The information must include the state of health, possible treatment, its usefulness and needfulness, frequent or serious risks that are normally foreseeable and other possible solutions. Expression of the patient's wishes are the consequences of the information provided and may be acceptance or rejection of the treatment and care proposed. Later, if the medical care on offer is accepted, no medical act or treatment required for its implementation may be performed

[137] For example, in the particular case of genetic testing, they can only be done in the biomedical laboratories specifically authorised to do so (Article L. 1131-2-1 par. 1 of the French Code of Public Health. The test may be carried out only by practitioners who have been authorised to do so by the *Agence de la Biomédecine* (Article L. 1131-3 of the French Code of Public Health). Furthermore, depending on whether patients themselves are showing symptoms of a genetic condition or are patients without symptoms but with a family history of disease, prescription is dispensed individually or also individually but by a physician working in a "multidisciplinary team of medical practitioners combining both clinical and genetic qualifications (Article R. 1131-5 of the French Code of Public Health).

[138] In this context, Elsa Supiot points out the lawmaker's decision to formulate a 'genetic exception'. E. Supiot, *Les tests génétiques, contribution à une étude juridique*, thesis Paris I, 2013, p. 10 and s. Presses Universitaires d'Aix-Marseille (PUAM), 2014, 40 and s.

[139] "Everyone is entitled to information on the state of his or her health": article L. 1111-2 par. 1 of the French Code of Public Health.

without the patient's "*free and informed consent*" which "*may be withdrawn at any point*" [140]: physicians cannot treat patients without their agreement[141].

For genetic testing, *the Code Civil*[142] *contains a general principle*, to the effect that *physicians must obtain* the subject's *express consent before the test*, prior consent being an essential condition for the test to take place. Moreover, patient consent must be given formally in writing. However, it would seem that this is intended by legislators to provide the person securing consent with reasonably uncontroversial proof rather than to safeguard patient rights.

There are also *rules organising the practice of genetic testing as referred to in the French Code of Public Health*. First of all, the general rule in the *Code Civil* on this subject, the obligation on the physician to secure prior consent is reiterated, taking into consideration that since the adoption of the August 6, 2004 Law on Bioethics, this rule is no longer set out and is simply brought up by reference to the *Code Civil*[143]. Then, as a second step, rules relating to information are set out as two obligations, one on the prescribing physician to inform the subject, before the test, of the risks that silence on the subject's part would entail for members of the family in the event that a serious genetic anomaly were to be diagnosed; and the other obligation on the person submitting to the test to inform the family of the results of the test[144]. But it should be made clear that these two obligations only concern the circumstances where the anomaly can be alleviated preventively or by treatment. These obligations are evidence of the familial specificity of these diseases, since, as CCNE remarked in its Opinion n° 76[145] "*...the results of a genetic test are not the sole concern of the proband. They also affect the whole family, ascendants, descendants, collaterals, and possibly spouse*." It would seem that the information to be provided to the family is so essential that it obscures the information which one would expect to see communicated to the test subject, but which is not referred to in the law, so that one needs to consult the regulatory arrangements in order to discover the exact

[140] Article L. 1111-4 par. 4 of the French Code of Public Health.

[141] These two rules — information and consent — are only cumulative when the decision implies medical intervention or the administration of treatment.

[142] Article 16-10 par. 2 of the French *Code Civil*.

[143] This rule was repeated in Article L. 1131-1 para.1 of the French Code of Public Health, but was no longer to be found in the version of the August 6, 2004 Law on bioethics; it now only states that testing a person's genetic traits is regulated both by the Code Civil and by the articles of the Code of Public Health referring to it. As it stands, it becomes difficult to understand the paragraph 2 which follows and which provides for exceptions to this general rule, without explanation.

[144] Either in person or through the prescribing physician.

[145] CCNE, Opinion n°76, *Regarding the obligation to disclose genetic information of concern to the family in the event of medical necessity*, April 24, 2003.

contents of the information received[146]. Nevertheless, communication of genetic information to relatives seems to be so justifiable that, even though they never asked for the information, the issue is ignored of finding out whether they want or do not want to know[147]. And yet, the subject of the test may refuse to know the results while authorising the prescribing physician to inform other members of the family, thus effectively forcing the information on to them[148].

Once the genetic testing is completed, *communication of the results*[149] is dealt with according to rules specific to genetic tests instead of the general rules regulating biomedical test results. Whereas the latter are communicated to both the prescriber and to the patient[150], with genetic tests it is the prescribing physician who communicates the results to the person concerned and possibly to members of the family[151].

Following the example of Article 12 of the Oviedo Convention, these rules only concern genetic testing for health purposes: "*Tests which are predictive of genetic diseases or which serve either to identify the subject as a carrier of a gene responsible for a disease or to detect a genetic predisposition or susceptibility to a disease may be performed only for health purposes or for scientific research linked to health purposes*, and subject to appropriate genetic counselling." But ten years after being adopted, the Additional Protocol on Genetic Testing, dated May 7, 2008, observed "...*an increase in the*

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146 Article R. 1131-4 para. 1 of the French Code of Public Health: "... *the person is informed of the characteristics of the medical condition being researched, of the means of detecting it, of the degree of reliability attached to test results and also of possibilities for prevention and cure. The person is further informed of the condition's particular mode of genetic transmission and of possible consequences for other members of the person's family."* The only clear and precise indication of the contents of the information to be imparted is given in the rules of good practice applicable to the examination of a person's genetic traits for medical reasons as set out in the 27 May 2013 Decree.

147 Article L. 1131-1-2 para. 1 of the French Code of Public Health: "... *if the person has expressed in writing a wish not to be informed of the diagnosis, he or she may authorise the prescribing physician to inform those concerned in compliance with provisions in the paragraph 4".*

148 The December 8, 2014 Decree defining the rules of good practice for informing relatives on the results of genetic testing for medical purposes, does not consider this issue at all. It focuses entirely on defining a severe medical condition caused by genetic anomalies, or a preventive measure or a cure for that condition. It also devotes attention to the physician's obligation to provide information on the risk of loss of opportunity to seek medical help incurred by potentially concerned members of the family due to the subject's refusal to pass on the information to them. Finally, it calls attention to the subject's obligation to inform his or her family of the results of diagnostic testing for genetic anomalies which could lead to the onset of a serious condition when preventive measures or care can be helpful: December 8, 2014 Decree, official publication n° 0293, *JO*, text N° 63.

149 Article L. 6211-6 of the French Code of Public Health: "*...a biomedical test of a person's genetic traits [...] is governed by the articles of this document as well as to those comprising chapter 1 of title III of book 1 of the first part".*

150 Based on Article L.1111-2 of the Code of Public Health stating that : ""*a member of the medical professions within the context of his or her qualifications will communicate the information."*

151 Article R. 1131-19 para. 2 of the Code of Public Health: "*...or, as the case may be, to persons listed under the second paragraph of Article L. 1131, as part of an individual medical interview."*

*number of genetic tests sold through the internet by companies outside the established healthcare system*" and stated in the Preamble to the Protocol that it was "*Aware also of the concerns that exist regarding possible improper use of genetic testing, in particular of the information generated thereby*". But since these rules only refer to medical practices, they do not apply to genetic tests sold by commercial firms on the Internet and performed in a non medical context. The Additional Protocol could go no further than to state that clinical utility of a genetic test shall be an essential criterion for deciding to offer this test to a person or a group of persons[152].

Similarly, French legislators, noting the disturbing development of genetic tests on offer via the Internet, a subject for concern in view of their uneven quality and the fact that results are imparted without any medical assistance[153], proposed that requesting genetic testing without medical prescription should be a punishable offence[154]. But this seems to be a weak obstacle in so far as prosecution would only be possible if such behaviour was known. As for the Council of Europe, it published a brochure for the information of the public[155] in 2012, warning against directly available genetic tests.

*b- Disallowing the use of genetic test results which could lead to discrimination*

A reminder of the discussion leading to rules now applicable in this respect may be useful. In 1994, the use of genetic testing was recognised as legitimate for medical purposes exclusively, ruling out the possibility of requests from insurers using them for selection and therefore to discrimination in insurability depending on personal biological characteristics. Bowing to this rule, the *Fédération française des sociétés d'assurances* (French federation of insurance companies) accepted a five-year moratorium in 1994. However, in a prospective study published by their review and authored by François Ewald and Jean-Pierre Moreau[156] they put forward the theory that a radical change of scene had been brought about by the possibility of prediction generated by genetics since "*ill health which used to be a fatality has become an individual future*"; so that "*equality in health formerly attached to total ignorance in the face of disease"* is disrupted since it is now possible to know the likelihood of good or bad health, so that each person is now individually responsible for his or her own health

[152] Article 6 of the Additional Protocol to the Convention on Genetic Testing for Health Purposes, May 7, 2008, referred to above.

[153] Rapp. AN, n° 3403, May 11, 2011, 26, J. Leonetti.

[154] Article L1133-4-1 of the Code of Public Health, reproducing Article 226-28-1 of the Criminal Code stating that "a person requesting examination of his or her genetic characteristics or those of a third party […] except in the circumstances provided for by law, incurs a fine of €3,750".

[155] *Genetic Tests for Health Purposes,*
Council of Europe, 2012, http://www.coe.int/t/dg3/healthbioethic/Source/fr_geneticTests_hd.pdf

[156] F. Ewald, J-P Moreau, *Génétique médicale, confidentialité et assurance,* Revue Risques, n°18, 1994.

capital. Consequently, concealing information about poor health harms other insured people who are made to bear an unfair share of the burden and, at the same time, not being allowed to communicate information about good health is harmful to the person concerned who is unable to negotiate a more favourable insurance premium.

It was decided, firstly in the draft law on bioethics in 2001 and later in draft legislation on patients' rights and the quality of the health system, to extend the discrimination[157] infraction to genetic characteristics. But it must be added that discrimination based on the state of health, "*when relating to death prevention and coverage, risk of disabling personal injury or of work incapacity or disability*" [158] are not punishable so that insurers can legally refuse would-be policy holders by reason of their state of health. This exception is due to the fact that an insurance policy is a 'contract in good faith' so that a person seeking insurance is bound to "respond truthfully to questions asked by insurers […] *regarding the circumstances enabling the company to evaluate the risks it is underwriting"* [159].

However, information requested by an insurance company only applies to what is *known with certainty at the time the statement is made.* For this reason two further rules were adopted: on the one hand, insurers cannot make use of genetic information that candidates for insurance may have spontaneously contributed, nor may they ask them if they have undergone genetic testing or ask them to communicate results of genetic testing and finally they cannot require candidates to undergo genetic testing[160]; on the other hand, discrimination based on "*predictive genetic test results with the object of investigating the existence of an as yet undeclared disorder* or *for genetic predisposition to a disease"* is punishable as an infraction to laws on discrimination[161]. *The element of uncertainty concerning onset of the disease* is the reason why health data relating to genetic factors must not be demanded by insurers.

**2- Prenatal diagnosis**

A prenatal diagnosis is *genetic*; it applies predictive medicine to foetuses and embryos, but with the possible consequence of voluntary termination of pregnancy for medical reasons, hence the gradual-

[157] Article 225-1 of the *Code Pénal* (criminal code)

[158] Article 225-3 of the *Code Pénal*.(criminal code)

[159] Article L. 113-2-2° of the *code des assurances* (insurance code)

[160] Article L. 1141-1 of the Code of Public Health. The same rule is reiterated in the *code des assurances* (Article L. 133-1 of the *code des assurances),* as also in the *code de la sécurité sociale (French social security code)* as applicable to pension funds (Article L. 932-39 du *code de la sécurité sociale*), and in the *code de la mutualité* for mutual health insurance systems as define by that code (Article L. 112-4 of the *code de la mutualité*).

[161] Article 225-3 1° of the *Code Pénal*. (criminal code)

ly acceptable possibility of using embryonic cells for diagnosis before the embryo is implanted in the womb.

*Prenatal diagnosis* began in 1972 with amniocentesis to diagnose prenatally a chromosomal anomaly: trisomy 21. This technique was quoted in support of the authorisation for voluntary termination of pregnancy for therapeutic reasons (*interruption volontaire de grossesse pour motif thérapeutique - ITG*) as allowed by the January 17, 1975 law N° 75-17. The rationale on which this was based was that parents who already have one disabled child fear the birth of another and only accept to continue with pregnancy after test results confirm that their unborn child will be normal. The law accepts the possibility of therapeutic termination if the foetus is very seriously impaired and cannot be treated, the object being to allow parents to entertain the hope of giving birth later to other healthy children. Originally, investigation for certain foetal pathologies was undertaken in response to the problem posed by the absence of any known therapy: if diagnosis reveals a particularly severe condition with no known cure, parents were given the option of resorting to what was then called 'voluntary termination for therapeutic reasons' , later replaced by the wording 'voluntary termination for medical reasons' (*interruption volontaire de grossesse pour motif médical - IMG*).

Historically, it was the foetal karyotype test for chromosomal anomalies, trisomy 21 in particular, which introduced the prenatal diagnosis into medical practice; there was general agreement regarding the severity and the consistency of mental retardation as well as on the frequency of occurrence within the population. These practices therefore developed in a *genetic* context. Foetal karyotyping, aiming initially at trisomy 21 (Down's syndrome), can also evidence any other type of chromosomal anomaly, so that very soon the problem arose for trisomies 13 or 18, both of which give rise to very severe clinical expression, more often than not lethal, either during pregnancy or during the first year of the child's life.

With the development of molecular biology in the early eighties it became possible to identify genes directly. Gradually, an ever growing number of pathologies were covered. Initially, molecular biology was used to solve a specific problem: diagnosing prenatally a limited group of disorders. Later, its scope extended to cover any disease with a genetic component, which raises in particular the issue of predicting the adult onset of a disease with no known cure. As time went by, prenatal diagnosis became increasingly extensive so that there was a risk of more frequent foetal selection and, by way of consequence, fears that a new form of eugenics would emerge. This would no longer be government policy but instead correspond to individual preferences, with the result that society would become intolerant of disability, and thus it *"...could, unwittingly, lead to discrimination as to who will be born*" as CCNE feared CCNE in its Opinion n° 107 in October 2009 on "*ethical issues in connection with antenatal diagnosis: Prenatal Diagnosis (PND) and Preimplantation Genetic Diagnosis (PGD)".*

Prenatal diagnosis was initially regulated by the provisions of the law N° 94-654 dated July 29, 1994 and was defined as follows: "*it describes medical practices aiming to detect in utero in the embryo or foetus a particularly severe affection. It must be preceded by medical consultation appropriate to the disorder under research.*" This is a broad definition, but under this law, the rules applicable only apply to biomedical tests with a view to discovering a specific condition when there is reason to suspect a particularly severe anomaly.

Over the past twenty years, we have evolved from diagnosis for couples who already had a child with Down's syndrome to diagnosis proposed to certain categories of women (initially those over 38 years old) and finally to screening, as in the case of prenatal screening for cystic fibrosis which was referred to CCNE[162] in 2003, with the Committee opting in favour of generalised screening. Systematic neonatal screening has been practised in France since 2002 to ensure that any medical condition is treated at the earliest possible time. Prenatal screening, however, is still excluded.

Moreover, insofar as *obstetrical and foetal ultrasound* has become the primary diagnostic tool and provides foetal imagery so detailed that it can be used to screen for certain malformations and developmental damage at ever earlier stages of gestation, the July 7, 2011 law n° 2011-814 has extended to this practice the rules initially only applicable to genetic diagnosis.

*Preimplantation genetic diagnosis*, using embryo cells *in vitro* so as to implant in the maternal uterus only those embryos which are not carriers of a particularly severe incurable genetic disease, was authorised by law n° 94-654 dated 29th July 1994, but only as an exception[163]. An August 6th 2004 law later authorised another kind of biological diagnosis using cells sampled from the embryo in vitro, PGD/HLA tissue typing, so as to implant into the mother's womb an embryo which is not just free of the particularly severe genetic disorder in question but also has an immune system compatible with an affected older sibling so that the latter can benefit from placenta blood or bone marrow haematopoietic stem cell transplant.

The legislators' decision is unambiguous: there is no intention of analysing the full embryonic or foetal genome to detect all anomalies and even less any predisposition. Legislators did not endorse CCNE's suggestion, set out in Opinion N° 107, that in the case of a preimplantation diagnosis of the embryo *in vitro*, a karyotyping procedure would be advisable in order to detect possible trisomies, instead of waiting to then do a prenatal diagnosis of the pregnant woman.

[162] CCNE, Opinion n° 83, *Generalised prenatal screening for cystic fibrosis*, December 18, 2003.
[163] Article L. 2131-4 of the Code of Public Health.

In conclusion, it can be noted that, according to a study made by the Council of Europe, French law is evolving in harmony with a general trend of authorising prenatal diagnosis for medical purposes, with certain variations in national legislation from one country to another[164].

### 3- Protection of personal data

Rules protecting personal data have evolved with technological developments. Beginning with the French law n° 78-17 of 6th January 1978 on Information Technology, Data Files and Civil Liberty, they mainly applied to manual and computerised data banks set up by government departments[165]. With particular emphasis on the defence of public liberties, its first article proclaims that: *information technology must be at the service of each and every citizen. […]. It must not be a threat to human identity, to human rights, to privacy, nor to individual and public liberties.* But very soon after its adoption, the predominant issues debated were those arising out of the development of databases created by private enterprise.

The increase in both national and international flows of personal data transiting through automated processing led to extending protection, beyond national frontiers, to the circulation of personal data throughout Europe. This was the objective pursued by Convention n° 108 for the Protection of Individuals with regard to Automatic Processing of Personal Data, dated January 28th 1981[166] which sought to "*extend the safeguards for everyone's rights and fundamental freedoms, and in particular the right to the respect for privacy,* with regard to automatic processing of personal data relating to him". It moreover created a specific form of treatment for "*special categories of data*", data concerning health in particular, which "may not be processed automatically unless domestic law provides appropriate safeguards".

Later, the adoption of Directive 95/46/EC of October 24th 1995, on the protection of individuals with regard to the processing of personal data and on the free movement of such data, sought to harmonise the regulations of member states as regards personal data so as *provide an equivalent and high*

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[164] This 2010 study showed that prenatal diagnosis is largely acceptable (explicitly or implicitly) in the countries responding to the questionnaire, with the exception of Ireland. Preimplantation diagnosis is expressly provided for in almost half of the responding States and is totally prohibited in four delegations of the Steering Committee on Bioethics (CDBI)

http://www.coe.int/t/dg3/healthbioethic/Source/INF_2010_6_dpidpn_fr.pdf

[165] Following on from the SAFARI project (*Système automatisé pour les Fichiers Administratifs et le Répertoire des Individus* - Automated administrative identification system) put forward by *INSEE* (French national statistics bureau) in 1971.

[166] Adopted by the Council of Europe.

*level of protection*[167] *throughout the Member States*[168]. This directive was transposed into French legislation very belatedly by law n° 2004-801 of August 6th 2004[169], as France feared a decline in individual liberty and protection of privacy. This is in fact the case in particular for health related data for which processing is prohibited but which can be overturned by explicit consent on the part of the person concerned.

However the legal framework was set up in 1995 at a time when use of the Internet was in its infancy. The rapid development of technologies facilitation the acquisition and sharing of data in a global context led the European Union to prefer "...*a comprehensive, coherent, modern, high-level framework able to protect effectively individuals' fundamental rights, in particular privacy, with regard to any processing of personal data of individuals within and beyond the EU […] in order to face the numerous challenges facing data protection, such as those caused by globalisation, technological development, enhanced online activity, uses related to more and more activities...* [170]. These circumstances explain the choice made to edict a ruling rather than a directive so as to harmonise the rules applicable within the European Union "...*ensuring coherence and high standards of data protection in the new setting offered by the entry into force […] of the now binding Charter of Fundamental Rights..."* [171].

According to the European Charter of Fundamental Rights, the protection of individuals with regard to the processing of personal data is a *fundamental right*, with a reference to which begins the draft ruling submitted to the European Parliament and the Council[172]. Similarly, in Opinion N° 3/2015[173],

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[167] For "*...the level of protection of the rights and freedoms of individuals with regard to the processing of such data (*to*) be equivalent in all Member States"* there was a need to "*remove the obstacles to flows of personal data*" (8th *Recital,* Directive 95/46/EC, October 24th 1995.

[168] Hence the statement that *"Whereas the principles of the protection of the rights and freedoms of individuals, notably the right to privacy, which are contained in this Directive, give substance to and amplify those contained in the Council of Europe Convention of 28 January 1981".* 11th Recital of Directive 95/46/EC of 24 October 1995.

[169] Law on the protection of individuals with regard to the processing of personal data with modification to law N° 78-17 of January 6th 1978 on Information Technology, Data Files and Civil Liberty.

[170] European Parliament resolution of 6 July 2011 on a comprehensive approach on personal data protection in the European Union (2011/2025(INI)), http://www.europarl.europa.eu/sides/getDoc.do?pubRef=-//EP//TEXT+TA+P7-TA-2011-0323+0+DOC+XML+V0//FR&language=FR

[171] *Ibid.*

[172] On 24th June 2015, the European Parliament, the Council and the European Commission entered into co-decision negotiations with regard to the proposal for a general regulation on data protection, a procedure known as an informal 'trilogue'. The basis for the negotiation is the Commission's proposals of January 2012, the Parliament's legislative resolution of 12th March 2014 and the Council's General Approach adopted on 15th June 2015. The three institutions are committed to dealing with the general regulation as part of the wider reform package on data protection which includes the proposed directive for police and judicial activities. This process should be completed by the end of 2015.

the European Data Protection Supervisor (EDPS) notes that these principles are a reference point, but even more significantly he asserts that *respect for human dignity* is the basis for any processing of personal data, considering future European rules on personal information as a tool to "*safeguard individuals' fundamental rights and freedoms in the data-driven society of the future*". This reference to human dignity is consequential since the explanations to the Charter of Fundamental Rights took care to state that the "dignity of the human person is not only a fundamental right in itself but constitutes *the real basis of fundamental rights*".

In a constantly evolving context, reporting on the rules applicable to processing health related and genetic data is no easy task: on the one hand, the future Regulation is still in draft form with remaining differences of opinion on certain essential points with regard to privacy; on the other, the CJEU ruling in the *Schrems v Data Protection Commissioner Case of October 6, 2015*[174], emphasising the issue of the transfer of personal data to a third country outside the EU which may, in principle, take place only if that third country ensures an adequate level of protection of the data, will no doubt have an impact on the final discussions of the draft Regulation. The issue called into question is the European Commission Decision n° 2000/520/EC of 26 July 2000 regarding the adequacy of protection of the data provided by the US Department of Commerce "Safe Harbour" principles. The decision considered that the United States, third country, provided an adequate level of protection for European citizens' data under the Safe Harbour principles and therefore authorised transfers from member states to companies established in the United States who are committed to respecting the 'Safe Harbour' principles[175].

But in 2013, Edward Snowden's revelations revealed the existence of large scale data collection programmes from digital data companies such as Google, Facebook, Amazon, Twitter, Apple who were granting privileged access of the data they were storing to American intelligence agencies. An Aus-

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[173] Opinion 3/2015, *Europe's big opportunity, EDPS Recommendations on the EU's options for data protection reform,* 28 July 2015, 13,
https://secure.edps.europa.eu/EDPSWEB/webdav/site/mySite/shared/Documents/Consultation/Opinions/2015/15-07-27_GDPR_Recommendations_EN.pdf

[174] CJUE C-362 14 Schrems v Data Protection Commissioner 6 Oct. 2015, http://curia.europa.eu/juris/liste.jsf?num=C-362/14 et Conclusions Y. Bot, 23 Sept. 2015, http://curia.europa.eu/juris/document/document.jsf?text=&docid=168421&pageIndex=0&doclang=FR&mode=lst&dir=&occ=first&part=1&cid=326249

[175] The French law on Information Technology, Data Files and Civil Liberty in a similar fashion states that "The data controller may not transfer personal data to a State that is not a Member of the European Union if this State does not provide a sufficient level of protection of individual privacy, liberties and fundamental rights with regard to the actual or possible processing of their personal data" (Article 68); but it adds "However, the data controller may transfer the personal data to a State not satisfying the conditions provided for in Article 68 if the data subject *has expressly consented to their transfer*...".

trian citizen, Max Schrems, on Facebook since 2008, knew that, as was the case for other members residing in the European Union, his personal data was being transferred from Facebook's Irish entity to servers in the United States where it is processed. Considering that his data was not adequately protected in the United States, he filed a complaint with the Irish Data Protection Commissioner who rejected it on the grounds that the Commission had found, in decision n° 2000/520/EC, that the United States provided adequate protection to transferred personal data. Max Schrems then filed an application for judicial review in the Irish High Court which then referred the case to the CJEU to judge whether the Commissioner was or was not bound by decision 2000/520.

The Court invalidated the decision on the grounds that American companies receiving this data could not deny access to the US authorities by reason of national security requirements, public interest and law enforcement so that they were obliged to bypass the 'safe harbour' rules of protection and give access to personal data. In consequence, regulations allowing the US authorities generalised access to electronic communications must be viewed *as encroaching on the essential content of the fundamental right to protection of privacy*. The Court was also of the opinion that the European Commission approval of the decision in 2000 did not prevent the protection authority of a member State from examining an individual's request with regard to the protection of personal rights and liberties which had been transferred from a member State to a third country when the individual concerned claimed that the laws and practices in force in that third country did not ensure a level of protection of fundamental rights equivalent to that guaranteed within the European Union.

Although some of these rules are still being debated and others are invalidated, the data emerging from clinical medical practices and genetic research is currently regulated by the French law on Information Technology, Data Files and Civil Liberty; this refers to medical and genetic data and also data related to biomedical samples. The law prohibits the collection or processing of health related data[176], of which genetic data[177] is an integral part; but as an exception to this principle, it allows for the possibility of processing if the person concerned has given express consent[178]; similarly, processing based on genetic data cannot be used without authorisation but this is not required if physicians or biologists are doing the processing and it is necessary for medical prevention, medical diag-

[176] Article 8 of law n° 78-17 of 6 January 1978 modified and emerging from Directive 95/46/EC of 24 October 1995.

[177] Defined as follows by the Commission's Proposal for a Regulation of January 2012:"*'genetic data' means all data, of whatever type, concerning the characteristics of an individual which are inherited or acquired during early prenatal development".*

[178] Rule in Directive 95/46/EC of 24 October 1995 and repeated by the Commission's Proposal for a Regulation of January 2012, which unlike the Directive explicitly refers to genetic data.

nosis or the administration of health care or treatment[179]. In the context of genetic research, express consent by the person concerned is required[180], be it applicable to samples or genetic data and the research must respond to a specific medical or scientific objective.

In a global genetic research context, attention must be paid to the development of pooled medical and genetic data, a recent example of which is the Global Alliance[181] for Genomics and Health - GA4GH: a non-profit association gathering together health care providers, research institutions, patients' rights advocacy organisations and companies specialising in life sciences and information technology. Its main objective is to accelerate medical progress by encouraging generalised access to genomic and clinical data. In order to achieve these aims, it insists on the need to define a common framework of harmonised technical, operational and ethical international standards to enable safe and responsible inter-operability of genomic research platforms. The "*Framework for Responsible Sharing of Genomic and Health-Related Data" [182]* highlights the fundamental principles that must be respected, in particular guarantees to respect privacy, data protection and confidentiality. Although it directs attention to the need to "*Comply with applicable privacy and data protection regulations at every stage of data sharing, and be in a position to provide assurances to citizens that confidentiality and privacy are appropriately protected when data are collected, stored, processed, and exchanged"*[183]*,* in the list of "*Ethical and Legal Codes and Policies Guiding Data Sharing Behavior*" given in the annex to this document, none of the European legal rules on the protection of personal data are anywhere to be found, while those concerning biomedical research are itemized.

One issue that is even more difficult to deal with, however, is the association of *'big data' with biomedical research:* this is data from various genetic studies and medical diagnoses, therefore sensitive data which is protected by law as mentioned above, but also data obtained in various contexts and used without being absolutely sure that the individuals involved are aware of this, the data involved

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[179] Article 25 I. 2° of law n° 78-17 of 6 January 1978, modified.

[180] Article 56 para. 2 of law n° 78-17 of 6 January 1978, modified: "*in the event of research requiring the use of identifying biological samples, informed and express consent* from individuals concerned must be obtained previously to data processing." Law n° 2012-300 of 5 March 2012, related to research involving the human person, which is as yet not in force, provides that "by derogation to Article 16-10 of the *Code Civil,* first paragraph of Article L. 1131-1, the examination of a person's genetic characteristics for the purpose of scientific research *may be performed using that person's body components sampled for other purposes, on the condition that the person,* having been informed of the research project*, has made no objection".*

[181] https://genomicsandhealth.org/about-global-alliance and *Partage mondial des données génomiques et cliniques: une première étape pour la Global Alliance*, Inca, 5 March 2013, http://www.e-cancer.fr/Actualites-et-evenements/Actualites/Partage-mondial-des-donnees-genomiques-et-cliniques-une-premiere-etape-pour-la-Global-Alliance

[182] *Framework for Responsible Sharing of Genomic and Health-Related Data*
http://genomicsandhealth.org/files/public/Framework%20%28French%20translation%29.pdf

[183] Ibid., 6.

being of a personal nature but not health related. Although currently the subject often gives rise to confident speculation that this avalanche of data will be the new Eldorado for medical research[184], it cannot be denied that reflection on the legal rules for the protection of personal data extracted in extremely varied circumstances (medical and non medical) is still embryonic.

[184] C. Noiville, E. Supiot, *Big pharma, big data et recherche génétique en santé*, Review of contracts, 15 June 2015, n°2, 352.

## B- CCNE Opinions pertinent to genetic testing and its applications

Genetics, as it applies to humans, for which recent progress raises major ethical issues, has been the subject of CCNE's attention on frequent occasions and on a number of subjects: genetic fingerprinting, genetic testing for medical purposes for adults or tests for prenatal, neonatal or preimplantation diagnosis.

Twenty-two Opinions were written to address various scientific and societal issues and the challenges they raised. They can grouped into several categories:

- The level of certainty or uncertainty delivered by genetic science? Within what boundaries do sequencing techniques give access to scientific knowledge,... And to clinical gain? What predictive and preventive medicine can be defined in consequence ?
- The dangers of commoditising genetic data
- The rights and duties connected to genetic information
- The protection of genetic data and of biometric data banks
- Reflection on filiation (origins, anonymity and filiation confidentiality) now that genetic traceability is a reality
- Birth as a medically assisted event: the role of predictive medicine in life choices.

**LIST OF OPINIONS**

- OPINION N° 5 *Opinion on problems raised by prenatal and perinatal diagnosis. Report*. (May 1985)

  Focusing on prenatal diagnosis, this Opinion points out the considerable future possibilities offered by these techniques, but also to the marked discrepancy between diagnostic capability (at a time prior to DNA sequencing) and therapeutic solutions. The report examines some of the issues with regard to predictive medicine.

- OPINION N° 9 *Opinion on problems arising because of the development of methods using human cells and their derivatives.* (February 1987)

  This Opinion is concerned with donations of products of human origin and the use made of them, in particular as regards not directly medical uses. It excludes purely economic uses made of such samples.

- OPINION N° 17 *Opinion concerning the dissemination of DNA analysis identification techniques (genetic fingerprinting).* (December 1989)

CCNE proposed that strictly limited use should be made of genetic testing to ensure that citizens' civil identity did not become a marketable object or be used as means of pressure on an individual (emphasis on free will and risks of discrimination). CCNE called attention to the dangers of storing results provided by identification techniques using DNA analysis.

- OPINION N° 19 *Opinion on embryo research aiming to achieve pre-transfer genetic diagnosis for which a moratorium was declared in 1986.* (June 1990)

  Focusing on prenatal diagnosis, in particular for pre-implantation purposes, CCNE was very guarded on PID.

- OPINION N° 25 *Opinion regarding the application of genetic testing to individual studies, family studies and population studies* (June 1991).

  The extraordinary expansion of knowledge as a result of the swift development of genetic testing is an invitation to consider issues with regard to applications, apparently beneficial for individuals and for public health but also with potentially negative effects. CCNE insisted on the quality of the information which is the essential medium for all genetic testing applications. It also analysed issues related to 'DNA banks', cell 'banks' and computerised data.

- OPINION N° 27 *Opinion that the human genome should not be used for commercial purposes.* (December 1991)

  While considering the possibility of products or processes derived from genome sequencing being patented, if specific conditions are met, CCNE stood firm on the principle that genes cannot be patented. The Committee insisted that any knowledge concerning the genome must be made open to the entire community.

- OPINION N° 30 *Ethical issues raised by mandatory genetic testing for female participants in the Albertville games*. (January 1992)

  This very focused Opinion concluded negatively on the use of biological determination (genetic) gender testing as a method to detect potential fraud in competitive sport.

- OPINION N°33 *Opinion concerning the identification of patients suffering from glaucoma in France and on chromosomal location of the causative gene or genes.* (January 1993)

  Opinion on a research protocol challenging the principles set out in Opinion N° 25. It recalled the need to protect the confidentiality of genetic information, privacy and medical confidentiality.

- OPINION N° 46 *Opinion and recommendations on "Genetics and medicine: from prediction to prevention"* (October 1995)

*Opinion recalling that "The basic principle of predictive medicine is to forecast the appearance of certain diseases before their symptoms are expressed. However, there are grave uncertainties about the value of the predictions and whether it is truly possible to prevent the conditions, and also whether this form of prevention is truly beneficial to individuals and to society."* The Opinion put emphasis on the right not to know.

- OPINION N°57 *Technical progress, health and societal models: the ethical dimension of collective choices* (March 1998)

  CCNE considered the *ethical dimension of collective health policies, identification of priorities and procedures for settling inevitable conflict between certain individual aspirations and collective necessities,* in the context of very rapidly evolving medical technology and its now dominant position in medicine. The Opinion analysed the question of health confronted by the concept of economic containment.

- OPINION N° 76 *Regarding the obligation to disclose genetic information of concern to the family in the event of medical necessity* (April 2003)

  CCNE analysed the ethical issues with regard to informing relatives while strictly observing medical confidentiality. The Committee considered that *"It would be counter productive if the very notion of genetic screening were to create a priori reluctance for those who might feel threatened by compulsory disclosure of their biological privacy*."

- OPINION N° 77 *Ethical issues raised by collections of biological material and associated information data : " biobanks", " biolibraries."* (March 2003)

  This Opinion carried out an in-depth review of collections of biological objects and their conservation in conjunction with personal data, medical data in particular, associating them with the individuals providing the donations. Should the wording 'biobanks' or 'biolibraries' be used? CCNE recalled that conservation activity was not tantamount to acquisition or appropriation of the elements collected and the resulting information data. It emphasised that the value of a collection is far greater than the sum of each of its components and that there was a need to reflect on the notion of solidarity and on the accountability of the national community in a situation where large banks or networks were set up on a population-wide scale. CCNE is purposely using in this context the wording "sharing the advantages or the benefit" rather than "sharing the profits". It called for regulated transparency.

- OPINION N° 90 *Access to origins, anonymity and confidentiality of filiation*. (November 2005)

The Opinion considered filiation as related to procreation in an era of 'biological traceability' and the risk of reducing human beings to the manner in which they were conceived.

- OPINION N° 95 *Ethical issues raised by prediction based on detection of early behavioural disorders in children.* (January 2007)

  CCNE was concerned with regard to the ethical implications of prediction, following a report by INSERM (French National Institute for Medical Research) on the detection of certain behavioural disorders in very young children, with a view to improving screening, prevention and management of such childhood disorders. The Committee pointed out the latent confusion between risk factors and causality.

- OPINION N° 97 *Ethical issues arising out of the delivery of neonatal genetic information after screening for genetic disorders* (May 2007)

  Thoughts on the delivery to parents of genetic information concerning their newborn child when screening for cystic fibrosis reveals a heterozygote status. The Opinion addressed the subject of non information and the right 'not to know'. After a prospective analysis, the Committee called for taking into account the ethical consequences of current technological developments in genetic testing. It warned of the danger that 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*."

- OPINION N°98 *Biometrics, identifying data and human rights*. (April 2007)

  In this opinion which has a broader impact than pure genetic identification, CCNE was *concerned by the tendency to generalise the collection of biometric data and the ensuing risks to individual liberties.* Such risks are aggravated by the possibility of exchanging stored data which could well be misappropriated for illicit purposes. The Committee called for public debate on this fundamental issue.

- OPINION N° 100 *Migration, filiation and identification by genetic testing*. (October 2007)

  A short and critical Opinion on certain moves calling for the use of modern genetic identification methods to limit the immigration of family members joining their relatives. CCNE recalled a number of fundamental principles on filiation and the inalienable right to the protection of genetic privacy.

- OPINION N° 104 *The "Personal Medical Record" and computerisation of health-related data.* (May 2008)

While it recognised the medical value of being able to share information without difficulty, in particular for the management of serious and/or chronic disease, CCNE pointed out the danger of computerised (not 'paperless') data for medical confidentiality, the right 'not to know', the right to 'oblivion' and, more generally personal privacy.

- OPINION N° 107 *Opinion on ethical issues in connection with antenatal diagnosis: Prenatal Diagnosis (PND) and Preimplantation Genetic Diagnosis (PGD).* (October 2009)

  In this Opinion, CCNE considered ethical issues in connection with antenatal diagnosis and preimplantation diagnosis such as they are practised in France. It came to the conclusion that in the current state of law and practices, limited as they were to particularly severe and incurable diseases at the time they were diagnosed, based on free and informed personal consent, with a framework of medical assistance, the expectant mother or the couple's decision under the current system was "*generally satisfactory*". CCNE also recalled, from the perspective common to proposing preconceptional screening for future parents carriers for the genetic anomalies in question and to antenatal diagnosis, *"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."*

  CCNE was also concerned about allowing these antenatal tests to be marketed, particularly on the Internet, since they would become difficult to control and could lead to "*predictive medical tourism" becoming the norm with helpless and distraught couples attempting to cope with unvalidated test procedures*".

- OPINION N° 109 *Society and the communication of scientific and medical information: ethical issues.* (February 2010)

  This Opinion was not dealing specifically with genetic data, particularly not with personal data. But it emphasised the need for everyone to appropriate some part of scientific culture and the efforts that society was entitled to require from scientists and technicians whose work has an ever swifter and stronger impact on the lives of citizens. The right to information, therefore, is part and parcel of duty to inform.

- OPINION N°117 *Use of stem cells derived from umbilical cord blood, the umbilical cord itself and the placenta; their storage in biobanks. Ethical issues.* (February 2012)

  This Opinion was concerned with biobanks and the use made of them and with the identification of stored samples.

- OPINION N°120 *Ethical issues in Connection with the development of foetal genetic testing on maternal blood.* (April 2013)

  CCNE considered developments in human genomic tools which do not always lead to therapeutic progress. They do inform parents on their future child's chances of being affected by a particularly severe genetic disease or disability and are therefore helpful in providing improved gestation management. They raise a large number of ethical issues however which society must address.

  CCNE's thinking was that the ongoing and very rapid developments of human genomic technology can not be disregarded.

## C- The international dimension

In his 2015 State of the Union Address, the President of the United States confirmed his support for American science and research, in particular for 'precision medicine': "*Tonight, I'm launching a new precision medicine initiative to bring us closer to curing diseases like cancer and diabetes—and to give all of us access to the personalized information we need to keep ourselves and our families healthier.*" [185] This promising systemic medicine is strongly supported by American public opinion. The precision medicine concept put forward by President Obama is similar to '4P' medicine: predictive, personalised, pre-emptive/preventive and participative[186]. It is a step forward from a purely genetic contribution, albeit a foundational one, to medical science. This was expressed in October 2012, by the American Presidential Commission for the Study of Bioethical Issues reporting on "...*whole genome sequence data*" and their "*enormous promise to advance clinical care and general health*." It allowed that "While many of the potential benefits arising from whole genome sequencing will accrue to the broader public, the risks associated [...] will be borne disproportionately by the individuals whose data are being shared".[187]

Many international forums and ethics committees have reflected on the future — which is sometimes described as inescapable — of human genetics now that very high throughput DNA sequencing is upon us. Neither a complete list of such studies nor an exhaustive analysis of them has a place in this document. Closer to us are the six reports written by the British Human Genetics Commission[188], the Nuffield Council on Bioethics report published in 2010 on medical profiling[189], or the Opinion by the *Deutscher Ethikrat* on the future of genetic diagnosis, in which the German Committee under-

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185 "*Tonight, I'm launching a new precision medicine initiative to bring us closer to curing diseases like cancer and diabetes—and to give all of us access to the personalized information we need to keep ourselves and our families healthier.*"

186 Elias Zerhouni. *Les grandes tendances de l'innovation médicale au XXIème siècle*. Inaugural lesson at the Collège de France. 18 May 2011

187 *Presidential Commission for the Study of Bioethical Issues, Washington, D.C. Privacy and Progress in Whole Genome Sequencing.* October 2012 (http://www.bioethics.gov).

188 The *Human Genetics Commission's final report* », April 2012 :

- Nothing to Hide, Nothing to Fear? Balancing Individual Rights and the Public Interest in the Governance and Use of the National DNA Database (November 2009)
- A Common Framework of Principles for Direct-to-Consumer Genetic Testing Services (August 2010)
- Intellectual Property and DNA Diagnostics: A Report of a Seminar on the Impact of DNA Patents on Diagnostic Innovation (October 2010)
- Increasing Options, Informing Choice: A Report on Preconception Genetic Testing and Screening (April 2011)
- The Concept of Genetic Discrimination: A Seminar Report and Reflections and Recommendations (April 2011)
- Incidental Findings Arising from Clinical Genetic Testing: An Expert Workshop (April 2012)

189 *Medical profiling and online medicine. The ethics of "personalised healthcare" in a consumer age*. Nuffield Council on Bioethics, October 2010.

lines the need to refrain from reducing the definition of 'quality of life' to a collection of medical or genetic data[190].

**Increasing options, informing choice: A report on preconception genetic testing and screening**

The Human Genetics Commission – April 2011

*Having considered the issues associated with preconception genetic testing, in our view, there are no specific ethical, legal or social principles that would make preconception genetic testing within the framework of a population screening programme unacceptable. Indeed, there are good reasons why earlier testing is favoured over later testing, as it facilitates wider patient choice and improved access to information supporting reproductive decision-making.*

In view of certain opinions reflecting a degree of fascination for technical and scientific advances in modern human genomics (see one example in the box on this page[191]) there are recurrent issues concerning the integration of global genome sequencing into clinical medicine as well as on the conservation of access to, and the use made of, sequencing data for research purposes. With the ambition of making science and health policies sufficiently flexible and astute for them not to inhibit the capacity for adapting to an evolving technology and social standards for privacy, a number of ethics committees, in particular in the English speaking world, are seeking to draft recommendations with the aim of providing a framework and a set of good practices and thereby the means with which to manage science and technology as they apply to health policies, both public and individual. A remaining doubt, however, is whether such ambitions are altogether realistic.

As they apply to whole populations, in particular as regards health (predictive medicine) the rules for good practices and the legislation in individual countries still no doubt have meaning, but are they still useful at a time when the frontiers — geographic or time-related — of genetics have long ago collapsed ?

One particular case is that of research in human genetics which requires the creation of international cohorts in order to differentiate a 'normal' variant from a 'pathological' one, and thereby understand the concept of individual variability as compared to a norm, often very difficult to define (let us remember that the very concept of 'normal' DNA is an absurdity). We are referring here to projects like the "*Personal Genome Project*" (PGP) whose purpose is to arrive at sequencing data on genomic,

190 *Die Zukunft der genetischen Diagnostik – von der Forschung in die klinische Anwendung. Deutscher Ethikrat, 2013.*

191 "*Increasing options, informing choice: A report on preconception genetic testing and screening": Having considered the issues associated with preconception genetic testing, in our view, there are no specific ethical, legal or social principles that would make preconception genetic testing within the framework of a population screening program unacceptable. Indeed, there are good reasons why earlier testing is favored over later testing, as it facilitates wider patient choice and improved access to information supporting reproductive decision-making.*

environmental and human traits, or the "Global Alliance for Genomic and Health" whose aim is, rather than generating sequences, to define the regulation and safe pooling of data at a global level.

These scientific resources emanate from data supplied by volunteers who authorised the sequencing of their genomes and who are informed of the ethical, legal and technical aspects of the research in which they accepted to participate.

The "Global Alliance for Genomics and Health" Working Group on Regulation and Ethics (chaired by Bartha Knoppers, McGill University, Montreal, Canada) has set itself the objective of elaborating an international Code of Conduct for the pooling of genomic and clinical data. The code is intended to define a set of ethical principles to research and share genomic and clinical data with special emphasis on key issues such as free and informed consent, confidentiality, feedback to patients and participants in research, data conservation and access. It defines protection against those who seek to make improper use of this data which was contributed voluntarily for the public good[192].

[192] Record of partners' meeting to set consortium objectives for 2014.