National Consultative Ethics Committee for Health and Life Sciences

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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)

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On January 10, 2006, Professor Farriaux referred to CCNE on the question of whether genetic information should be provided to parents concerning their newborn child when the neonatal systematic generalised screening test for cystic fibrosis (in effect since 2002) reveals heterozygote[1] status, which has no consequences for the child's health, in the double heterozygote (composite heterozygosis) or the homozygote[2] form.
Screening at birth for cystic fibrosis was initiated because of the severity of the disease which is generally expressed in the form of respiratory failure leading to very high mortality at an early age. Although the disease is expressed in a great diversity of ways and the average life expectancy of sufferers has increased considerably in the last few years, it is still one of the most frequent and critical of hereditary diseases.
Cystic fibrosis is a genetic disease, due to the transmission from both father and mother of certain specific sequences (called "mutations") of the *CFTR* gene *(cystic fibrosis transmembrane conductance regulator).* This genetic disease is what is known as "recessive", which means that the risk of developing cystic fibrosis only exists if both copies (the two alleles) of the gene, inherited from both father and mother, carry the mutations.
The *CFTR* gene varies considerably in the human population: there are over 1,500 different alleles which, when both copies are present, can represent a risk of developing cystic fibrosis.
One person in 30 in the French population, has a single mutant *CFTR* gene (and is therefore a "heterozygote" for the *CFTR* gene, or "healthy carrier") which has no negative impact on his or her own health. The only use that carriers can have for this genetic information is if they wish to have a child. If both parents are "healthy carriers" of a *CFTR* gene mutation, there is a 25% probability that a child of theirs will inherit both mutations and will therefore be at risk to a certain degree (depending on the nature of the mutations) of developing the disease. There is a 25% probability that the child inherits neither of the two mutations. And there is a 50% probability that the child inherits only one of the two mutations and will therefore be "heterozygous", i.e. a "healthy carrier", with no consequences on the child's own health. What should be done as regards providing information when a newborn is, by chance, identified as a healthy carrier as a result of systematic neonatal screening for the disease?
This is the subject of the referral.

The referral also concerns the discovery of heterozygosis following neonatal screening for sickle-cell disease in children whose parents originate from various parts of the world where prevalence of the disease is high.
In fact the two situations are very different. Heterozygous status for one of the alleles involved in cystic fibrosis is not a state of disease; it is a healthy carrier status and there are no ill-effects on the child's health. But for the gene linked to sickle-cell disease, the heterozygous status involves a single mutant allele and can have pathological consequences. There is therefore a

[1] Heterozygosis: presence of one copy (one allele) of a mutant gene inherited from father or mother.
[2] Double or compound heterozygosis: presence of two different mutant alleles, one from the mother, the other from the father. Homozygosis: presence of two identical mutant alleles from both mother and father.

need to advise on care required to prevent the onset of complications (no underwater diving, vaccination against pneumococcus).
As a result, a reply to the question about information to be given on heterozygosis for sickle-cell disease is relatively straightforward, but the situation is more complex for cystic fibrosis.

In effect, telling parents that their newborn was discovered to be heterozygous (a healthy carrier) when screened for cystic fibrosis has no implications for the child's own health, but it does tell them that at least one of the two biological parents is a healthy carrier.

This information, which is the result of discovery as part of systematic screening of newborns for a disease of which they are free, is in fact meant to enlighten parents and possibly also members of their family on their own genetic status, which has no consequence on their own health, but provides information on the probability of their conceiving at some future time a child who could suffer from this disease. Such genetic counselling may in this case — but only rarely — lead to the discovery that a couple is at risk of giving birth to a child with cystic fibrosis when each of the prospective parents is heterozygous. The benefit for the couple would then be that they could turn to prenatal or preimplantation diagnosis to ensure the birth of an unaffected child. In even rarer cases, the information could also be useful to facilitate diagnosis for certain members of the family suffering from mild or late-onset cystic fibrosis, not previously discovered.

The situation is therefore very singular in that the result of a genetic test reveals a healthy carrier status which, it must be emphasised, has no repercussions on the child's own health. At present, this is made known to parents without their having explicitly requested the information and without any prior attempt to secure free and informed consent, since screening for the disease in a newborn was the only consent requested.

I – Sickle-cell disease

Whereas cystic fibrosis affects the whole population, sickle-cell disease predominantly affects people originating from Africa or India.
Screening therefore is neither systematic nor generalised. It is only offered to families from regions where prevalence of the disease is widespread*. The point of screening is to reveal the existence of a disease affecting hæmoglobin, even when the patient is a heterozygote. The notion of "healthy carrier" therefore does not apply. This heterozygote status is therefore entirely different from the heterozygote status in cystic fibrosis. With sickle-cell disease, there is a specific need to provide medical treatment for the heterozygous child.

* In France's overseas departments and territories (DOM TOM) sickle-cell disease heterozygosis involves 10% of children, and homozygosis under 1%. In Sub-Saharan Africa, heterozygosis prevalence for the disease varies from 12 to 40% (Congo) and the homozygosis count is approximately 2%.

Unlike cystic fibrosis, where over 1,500 different alleles may be involved, in sickle-cell disease only one allele plays a role. But the presence of that single allele has various consequences on the patient's health depending on the genetic or the external environment. In India, for example, homozygotes for the sickle-cell disease allele are only mildly affected.
At the Robert Debré Hospital, every year the same number of children are born with cystic fibrosis or homozygous sickle-cell disease, but obviously with a very different high-risk population ratio.
Diagnosis is not based on genetic testing, but on a simple biochemical hæmoglobin test: a form of electrophoresis, isoelectrofocalisation, which detects the hetero- or homozygous status. Detection is simple so that there is no need for a whole succession of tests. Also, the test is binary, positive or negative, with neither false negatives nor false positives; all homozygotes and heterozygotes are detected. Results are supplied to the family in the best interests of the child and because of the direct consequences of the disorder, even though the heterozygous status is much less severe than the homozygous condition.
No particular ethical issues are involved, except that information supplied is sometimes a little short on the usefulness and modalities of the test and on the possible question of targeting screening according to the family's geographic background.

II – Cystic fibrosis

Genetic and epidemiological data

Every year, 800,000 newborns are tested at birth to detect phenylketonuria (since 1972), congenital hypothyroidism (since 1978), congenital adrenal hyperplasia (since 1995) and cystic fibrosis (since 2002). Screening for phenylketonuria, congenital hypothyroidism and congenital adrenal hyperplasia, which are biochemical tests, not genetic ones, is entirely justified by the specific healthcare provided to treat the condition. This is not the case with cystic fibrosis. Biochemical and later, genetic screening is useful for the early management of pulmonary and digestive symptoms in specialised care centres. But so far, there is no possibility of providing specific medical remedy for the disorder.

Some 110 newborns (one out of 8,000) are discovered in France every year to be carrying a mutation in both of the two alleles of the *CFTR* gene (double heterozygotes or homozygotes) and are therefore likely to develop a potentially serious disease, cystic fibrosis. One newborn in 30 is a healthy carrier — approximately 26,000 per year being the usual prevalence in France — with a single heterozygosis. There are some 2 million healthy carriers in France.
As regards the bearers of two mutated alleles, who may develop the disease (110 newborns annually), mutations have been classified into six categories: three for which the early onset in infancy of serious forms of the disease is very probable, and three categories for which the onset of disease is highly likely to be mild and/or late, in adulthood. But mutations alone are insufficient to predict the expression of the disease: "modifying" genes (and

environmental factors) may, for people carrying the same *CFTR* allele mutations, have an influence on the onset and development of the condition. For certain *CFTR* alleles, even double heterozygotes may not develop the disease. The most frequent mutation in France is *F508del.* The presence of two alleles with the *F508del* mutation generally correlates with early onset of a serious form of cystic fibrosis.
Only 30 mutations of the *CFTR* gene out of the 1,500 which are presently known, are screened at birth. The 30 mutations are present in 86% of cases, which signifies that 14% of cases involving other known mutations are not currently detected by the genetic test.
As we have already noted, for two heterozygote parents, the probability of producing a homozygote child is 1 out of 4; the probability of a child who is a healthy carrier of the heterozygote trait is 1 in 2 and the probability of a child who is free of any heterozygote status for the disease is again 1 in 4. At the time when the child is found to be a healthy heterozygote carrier (which means that at least one biological parent is also a healthy carrier), the probability that the parents give birth to a sick child (and identically the probability that the child in question, once adult, gives birth to a sick child) is 1/120, i.e. 0.8%, compared to the probability in the population at large which stands at 0.02%. In other words, the probability for the parents of a healthy carrier child (and also for the child once adult) of giving birth to a child who is at no risk whatsoever of falling prey to cystic fibrosis, is over 99.98%. Although the risk is multiplied by 40 in the event of detected heterozygosis, the risk is still very low in absolute values.

The vast majority of heterozygotes will not be discovered because the genetic test will be only be performed in approximately 5,500 out of 800,000 newborns (see screening below). Some 400 healthy carrier newborns will be identified, out of a total of 26,000 unidentified newborn healthy carriers, i.e. approximately 1.5%. In other words, 98.5% of newborn heterozygote healthy carriers are not detected and neither their parents nor their families will have information giving them access to genetic counselling regarding their risk of giving birth in future to a child suffering from cystic fibrosis.

The Law

Article R.1131-5 of the decree dated June 23, 2000, states: "When the subject [of genetic testing] is a minor, it can only be prescribed if the minor can benefit personally or if preventive or curative measures can be provided for his or her family".

As it is now formulated, if there is no possibility of direct benefit for their own health, the law prohibits any genetic testing in children unless care or prevention to improve the health of a family member can ensue.

However possible interpretations of the wording "preventive measures can be provided for his or her family" are ambiguous.

Legislators may consider that prevention means the prevention of a disease as is only rarely the case for genetic disorders, one example being phenylketonuria, for which prevention inhibiting the development of disease is now possible. If that were the accepted definition of prevention, carrying out genetic tests in the event of mutations involving cystic fibrosis would be prohibited, as would consent given to testing and information on results as regards the healthy carrier status of a newborn. In this case, the only useful purpose of such information and of genetic counselling for the parents of the child who has been screened or for the members of the family would not be related to preventive measures regarding the development of disease in a future child, but the possible decision to avoid giving birth at some future time to a child who could develop the disease.
Or else, legislators wished to include in the notion of prevention the genetic counselling which could be given to parents and members of the family if they decided to avoid giving birth to a sick child. This definition would allow for the communication to parents of information on the healthy carrier status of their newborn infant, on the condition that prior and specific free and informed consent had been secured and that there was a family history of the disease or that symptoms of the genetic disease were apparent. This position would be the result of a broad reading of the law on bioethics dated August 6, 2004 which states in article L1131-1: "In the case of a severe genetic anomaly being diagnosed when testing a person's genetic characteristics, the physician must inform that person or that person's legal representative of *the risks that his or her silence would represent for those members of the family who could be concerned*, on the condition that prevention or treatment could be offered to them." In the case of screening for cystic fibrosis, the symptom which would authorise practising the test leading to the discovery of healthy carrier status, is a positive reaction to the biochemical trypsin test, i.e. for newborn healthy carriers, the false positive result to testing for the disease.

Leaving aside such ambiguities, protecting the child's interests must surely be viewed as the most important of ethical concerns. There is a risk that a healthy carrier child could become *de facto* the instrument or the "messenger bearing ill tidings", since parents are warned that they must have recourse to precautionary diagnostic procedures for any future pregnancy. The paradox is that the announcement of a favourable test result, favourable for the present, as regards screening for the disease — the child is in fact unaffected by cystic fibrosis — goes hand in hand with the revelation of results which represent a worry for the future. Parents are learning that there is a risk, a minimal risk, of giving birth in future to a sick child.

It is true that there is a discrepancy between genetic tests for which consent is required since they carry predictive information and so-called phenotypic test (that is those establishing morphological or biological characteristics) which can be performed without prior consent even when they reveal a genetic disease. The difference however is that by nature, phenotypic tests

when they are positive, do not necessarily give information about a disease, but on a particular characteristic of physical functions. Genetic tests, however, evidence a particular gene sequence which may have absolutely no functional expression.
It may be considered that the radical difference as regards consent between a genetic and a phenotypic test is linked to some form of "sacralization" of genes and to a very common, albeit erroneous, belief in absolute genetic determination. However, the difference could also be understood — although this is unfortunately only seldom the case — as protection of an individual against exaggerated interpretations of genetic test results for which the functional consequences are frequently far from obvious.

Screening
Systematic *neonatal* screening for cystic fibrosis was generalised in France in 2002. The end purpose was to organise early medical management at birth so that, in the absence of a cure, a child's life expectancy and condition can be eased significantly.
The first screening step is a biochemical test (dosage of a pancreatic enzyme, immunoreactive trypsin — IRT) using a blood sample in the first three days following birth. Detection of an abnormal level of IRT (more than 65 mg/l) in some 5,500 newborns out of 800,000, i.e. 0.68%, leads to performing a genetic diagnosis based on screening for mutated alleles, after one or both parents have consented (kit for 30 mutations). The results of such tests are sometimes difficult to interpret.

In effect, the molecular biology test can detect:
1 - Children carrying a mutation for both alleles of the *CFTR* gene (approximately 110 newborns, i.e. 2% of positive results for the biochemical test). The diagnosis will be confirmed by a sweat test[3]. Most of these children will develop the disease.
2 - Heterozygote children, that is healthy carriers of a single mutant allele (approximately 440 newborns, i.e. 8% of the positive biochemical test results and 1.5% of the total number of heterozygote newborns). These children will take a sweat test which will produce abnormal results in 40 cases.

Some 5,000 newborns, that is 9 out of 10 of the positive biochemical screenings are "hypertrypsinaemic" although they do not carry the mutation. Around 450 of them whose IRT* dosage was over 100mg/l on their 3rd day of life will be tested again in their third week for a new IRT dosage. If the results are still positive (around 40 cases), these children will be given a sweat test which will turn out to be abnormal in about 15 cases.

In total, some 190 children, including the 110 carrying a double mutation, will be diagnosed positively for cystic fibrosis, confirmed by the sweat test, with a very high risk of developing the disease.

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[3] Sweat is collected after an electrode stimulating perspiration is placed on the forearm. This painless investigation takes 5 minutes. The sodium content of the sweat is measured (normally less than 40 mmol/l) and in the presence of cystic fibrosis is abnormally high.
* Immunoreactive trypsin

As regards the 440 newborns who were found by screening to be healthy heterozygote carriers, the information will be communicated to parents so that they can obtain genetic counselling regarding their own status and the risk they would run of giving birth in future to a child carrying a double mutation. Out of these 440 couples, around 15 will both be healthy carriers and therefore at risk of giving birth to a child with the disease. It is also worth noting that among the 5,000 children with a high trypsin count but without any mutation detected by the genetic test, around 6 couples of parents will nevertheless be in the same situation, but will not be gaining access to genetic counselling so that they could believe that they do not run the risk of giving birth in future to a sick child. Moreover, the 440 newborns who are screened as healthy carriers only represent 1.5% of the 26,000 heterozygote newborn healthy carriers who were not detected because their trypsin test produced normal results. This means that some 900 couples, with both parents healthy carriers at risk of giving birth to a sick child in the future, will not have access to genetic counselling and could believe that they are not at risk.

III - Ethical issues arising out of screening for cystic fibrosis

1 – The end purpose of screening

Whereas hypothyroidism and phenylketonuria can be effectively and immediately treated following neonatal screening, the actual benefit that is derived by children screening positively for cystic fibrosis is more difficult to evaluate. It would appear from international statistics that early diagnosis as soon as the first clinical symptoms become evident and the quality of therapeutic management and monitoring are the best criteria for quality and length of life, more so than neonatal genetic diagnosis as such. The worth of screening depends therefore on certain appropriate medical measures being applied. The end purpose of screening is not, for the time being, detecting a healthy carrier status, but the detection of an important risk of onset of a potentially serious disease, so as to avoid serial misdiagnosis and facilitate early therapeutic management. But the detection techniques for the genetic mutations being screened cannot avoid detecting healthy carriers. Due to the way in which the various steps of the screening procedure are organised, parents are only informed after the sweat test has been performed (i.e. after the molecular test which is performed if the biochemical test results are positive) because the child is a healthy carrier. This presupposes psychological readiness on the part of healthcare providers to supply the information and encourage parental reflection on the subject during the interim period.

2 – Problems concerning free and informed consent

Understandably, this series of urgent tests, biochemical to begin with and in case of doubtful results, genetic and then again biochemical, together with asking parents to bring their newborn child in several times engenders considerable anxiety. It must also be underlined that over 95% of children

undergoing such tests turn out to be unaffected. It would seem that current evaluation regarding the psychological consequences of this systematic neonatal screening procedure is likely to give a more precise appreciation of the degree of caution that should be exercised for its implementation.
With neonatal screening for heterozygosis, screening can be offered to parents before a new pregnancy and genetic information can be provided to the entire family who could then also receive genetic counselling if needs be. But this is a special situation in which screening of the newborn is used to initiate screening of the family. The child's own health does not benefit in any way and the process has been described as "reverse cascade screening". The newborn's only benefit would appear in the form of genetic counselling when becoming adult in the interest of his or her future children. Should information concerning a child, which will be not be useful until that child is adult, be sought and communicated to the child's parents because it could become useful later as regards their own future children?

Consent to neonatal screening and the conditions in which it is performed raise some new issues. Genetic screening must be preceded by free and informed consent, confirmed in writing.
This written consent is currently requested, before the biochemical test, from all parents of the 800,000 newborns. In fact, only 5,500 of them (0.6%) will undergo the genetic test (if the biochemical test turns out to be positive). For 99.4% of parents who have signed a consent form, their child will not need genetic testing. In the circumstances, does the consent procedure still make much sense? In fact, it seems clear that information will be all the more summary and reflection all the more removed from reality as the probability dwindles of the test taking place, although the complex genetic information imparted before and after testing is sometimes difficult for parents to understand.

Moreover, consent should really be given in two separate stages. The first concerns the diagnosis of a disease, cystic fibrosis, in a newborn. The second stage would concern parents' agreement to genetic information, obtained following diagnosis of a newborn who is not affected by the disease, which could be of interest as regards a future child, be communicated to them. Prior information on these two radically different situations involves a significant effort of communication.

The ambiguity stems from the fact that in practice the screening test for the disease involves, for technical reasons and unavoidably, detection of the heterozygote mutation (i.e. identification of the healthy carrier status). This is not therefore a chance discovery where an urgent solution needs to be found to an unexpected ethical problem. There would be no way of *not* knowing that once the screening process began, discovery would be systematic. The frequency of positive results is also known from the outset.

If the screened newborn is indeed heterozygous, a great deal of effort will be needed to avoid causing parents excessive anxiety, which will add significantly to the genetic counselling burden. If parents are not called in,

because the biochemical test was negative (which is the case for some 26,000 heterozygote newborns), the absence of result could give them the impression that their child does not carry the mutation and that therefore they are at no risk as regards their future offspring. In fact, their child could be a healthy carrier without triggering positive results in the biochemical test. In Opinion n° 83 CCNE insisted on the difficulty of providing easily understandable genetic information. Paradoxically, the benefit that parents could derive regarding their own status from information concerning their newborn, is in fact limited. A negative result is absolutely no indication that parents themselves are not healthy carriers. In other words, although the absence of mutation in the newborn represents information on the newborn's own status as a future parent (albeit imperfectly since 15 to 20% of mutations are not detected for the time being), the absence of mutation is only, as regards parental status, simply an expression of the probability that they do not both carry mutations, but it is in no way a certainty. A couple of healthy carrier parents has a one-in-four probability of giving birth at a later time to a child who does not carry the mutation and a one-in-four probability of giving birth to a sick child.

3 – The concept of heterozygosis

There is a constant risk of confusion between "abnormal" and "heterozygote", and so creating a special status and missing the fact that all human beings are heterozygote for most of their genes and that the diversity of alleles (mutations) is one of the "normal" characteristics of the human and of all other living species. If this polymorphism did not exist, sexual reproduction would not have the effect of mingling diversity and emerging novelty which are its essential features. In other words, the medical problem is not genetic diversity — there is no such thing as a "normal" gene and a "mutant" form of gene; all genes have mutated over the course of time — but that certain particular forms of mutation are associated, in certain cases, to the frequent appearance of a disease (diseases involving monogenic Mendelian highly penetrant transmission).
Nor should it be overlooked that heterozygosis for one gene, when it does not itself lead to the onset of disease (which is the case for almost all recessive genetic diseases) may not only have a neutral effect on health; in certain environments it can be an advantage. For the allele involved in sickle-cell disease, heterozygosis provides protection against certain forms of malaria. The possibly beneficial effect of an allele which is present but does not by itself cause any disease is not something that can be predicted.

4 – The problem of non-information

As far as the newborn is concerned, keeping the information secret for some twenty years and only then revealing the truth in the event that the child grown adult requests it, borders on the absurd by reason of the time that has elapsed, the risk of losing records and above all — particularly for cystic fibrosis — the small number of heterozygotes that are revealed by the

screening process and the fact that scientific progress is likely to produce new generations of diagnostic tools and treatments for prevention and cure.
However, leaving a family in ignorance raises an ethical issue as regards the possibility of screening for the mutation in both parents with, in the event of a positive result (which will not be the case in over 99% of cases) could lead to prenatal or pre-implantation diagnosis.
Should a choice be made between ignorance and anxiety, choosing the least of two evils; should questions be asked regarding how and when access to such information can become possible and on the meaning of screening as it is practised at the present time?

IV – The contradictions

Screening must be for a purpose; if society considers that cystic fibrosis must be systematically screened for at birth but that only results contributing direct benefit for that child's health must be communicated, surely the only coherent course of action is to refrain from disclosing heterogygote status or to only tell the future adult if he or she requests it?
Ambiguity in this situation stems from the fact that, in practical terms, performing the test for which legal and informed consent has been secured (screening for the disease) for technical reasons inevitably involves the detection of the heterozygous mutation (identification as a healthy carrier) for which no legal authorisation has been given, nor as a result, any request for informed consent. This is not therefore a chance discovery for which an urgent solution would need to be found for an unexpected ethical problem. There would be no way of *not* knowing, once the screening process began, that discovery would be systematic. The frequency of positive results is also known from the outset.
Should a family be told, to serve their future plans to have more children, the results of a test which was performed and for which consent was sought from parents regarding the diagnosis of a disease? Can the discovery of a result obtained without consent be seen as retroactive authorisation to communicate the results although no informed consent was given? What is at stake in this case is the very principle of informed consent. In other words, does everything that becomes possible become by the same token retrospectively desirable or authorised?

Another ethical issue is related to equity. Discovery that a newborn is a healthy carrier is the result of systematic screening for the disease. Although the word 'systematic' is ambiguous in this case — the biochemical test is systematic, but the genetic test is theoretically the object of an informed consent procedure, and not of systematic practice, in the event that the biochemical test is positive — as it implies that the same potential benefit is extended to all those involved, both children and their families. In fact, the detection of heterozygosis only concerns some 1.5% of newborn healthy carriers, and therefore 1.5% of families in which at least one of the two parents is a healthy carrier. In the circumstances, 98.5% of the 26,000 newborn healthy carriers, and therefore of the healthy carrier parents are not detected so that they cannot, in any event, be informed. Furthermore,

revealing the heterozygote status only to certain parents could give them the impression that absence of information or information regarding a normal biochemical test result signifies that their child is not heterozygous, which is not only inaccurate, but is inaccurate in a majority of cases.

Is it acceptable to communicate information to families concerning newborns, obtained inadvertently through systematic screening, despite the absence of consent and simply because the information was sufficiently important? Or is it possible to consider that the information is not sufficiently important or that its communication would represent too many drawbacks so that it should not lead to testing parents for genetic mutation when they request it in the absence of a positive test result on their newborn child? This is a confrontation between the principles of autonomy (the child's), of benevolence (possible information concerning the future fate of as yet unborn children) and of justice (allocation of financial resources which could be used otherwise, for example to improve medical care for sick children).

Screening blood-related couples could seem more constructive than screening a non-related couple since there is a greater probability that one spouse will be carrying a given gene already carried by the other spouse. However such situations are so rare that the better course would be to recommend prenuptial screening in these cases.

V – What can be done about these contradictions?

How can children best be protected from excessive and fruitless pressure regarding their genetic status?

By modifying the law? If it is thought that the law should be modified as regards genetic testing of children, does it simply need to be made more explicit?
Should the law be more restrictive or should there be greater latitude for authorising genetic testing for children when there is no direct benefit for their own health but there is a possibility of benefit for their parents' future children?
Is this not a risk of instrumentalising children who would become the object, subject and a source of anxiety of which they are the cause, but which is not related to their own health?
Does the inclination to instrumentalise, the compulsion to make full use of the results of tests simply because they are available — whatever the cost — represent the ultimate form of obsession with genetic screening of a society which considers that what matters is to obtain results where and when possible regardless of consequences? Even though the way they are obtained puts an unnecessary burden of anxiety, guilt or even stigmatisation on a child?

By replacing the genetic test with biochemical testing? Replacing genetic tests with biochemical testing revealing, instead of the presence of

genetic sequences which may have no consequences for health, the existence of specific physical functions which suggest the risk of development of the disease, would raise fewer ethical issues since the focus would be more on the sick than on healthy carriers. This strategy would put screening for cystic fibrosis in the same category as screening for sickle-cell disease or phenylketonuria.

By biochemical screening only in the third week? Waiting three weeks would mean that only readings of over 100 micrograms per litre of immunoreactive trypsin would be considered. In this way, only a small number of heterozygotes would be involved and sick double heterozygotes would not be left undetected. The drawback — which it should be possible to overcome — is that children would have to be called back after 21 days instead of going through the whole screening procedures while they are still in the maternity ward. But, apart from some exceptional circumstances, there is no need for emergency testing. This procedure would tend to give predominance to biochemical evaluation over genetic testing.

By giving parents immediate access on request to results existing in a biobank? This biobank which would be managed according to the new biobank status, i.e. by a curator who would be the guardian of results. Results would not be given out simply because they exist, but disclosed in response to a specific request. The immediate advantage of such a procedure would be prior comprehension of the consequences of the result. However, although such a procedure would be an instrument of real information and consent, it would still represent a form of *a posteriori* consent to obtaining information for which no *a priori* consent before the genetic test would have been given, unless the law were to be changed. Does not the principle of free and informed consent become devoid of meaning if it turns into a retroactive procedure when systematic screening is involved?

By dissociating newborn screening for the disease from genetic counselling given to parents with a view to a parental project in the future?

In that case, would it not be preferable to authorise screening of future parents if they request it, rather than transform their newborn child into an instrument to provide information which concerns not their own health but that of their descendants and the descendants of their grand children — even if it could seem to be an encouragement to individual prenuptial screening with all the possible consequences regarding the choice of a potential spouse?

In this case, the child serves as a marker for the family. However, most parents who could possibly benefit are excluded *de facto* by screening which only concerns one per cent of their number.

CCNE considers that the various ethical difficulties could be solved by a procedure of consent and access to information dissociating the disclosure of the parental genetic status from disclosure of the heterozygote status of the child. This would be a sensible step in that it would reconcile confidentiality regarding the child's genetic characteristics without prejudice to his or her

health, with the information (within the framework of a free and informed consent procedure) delivered to parents on the possibility of requesting a test to assess their risk of giving birth, at some future date, to a child who could develop a serious and as yet incurable disease.
CCNE considers that this approach would only be meaningful if the information delivered to parents before they consent to neonatal screening for cystic fibrosis contained the explanation that, should their newborn be a healthy carrier, this would not be revealed before a time set aside for reflection had elapsed. Parents would furthermore need to be told that a negative result for their newborn does not exclude the possibility that both of them could be healthy carriers and therefore at risk of giving birth to a sick child at some future time.

Recommendations

1 – For cystic fibrosis

Since genetic results are an inevitable outcome of screening for homozygote forms which simultaneously reveals heterozygote status,

1.1. 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.

1.2. As screening for the disease (homozygote or double homozygote status) leads necessarily to detecting healthy carriers (heterozygote status), CCNE recommends that systematic disclosure of the healthy carrier status of a newborn 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. CCNE therefore recommends that information delivered to parents before they consent should include an explanation that healthy carrier status may be evidenced in their newborn child, but will not be communicated automatically before time is allowed for further information and reflection, for the reasons stated above.

1.3. CCNE recommends that this non disclosure to parents of heterozygous status be associated with information in the consent form to the effect that results of the test will be consigned to a biobank and may be communicated to them by the biobank if they specifically request it after the consequences have been made clear to them. CCNE also recommends the clarification of the status of biobanks created to contain these systematic samples by the creation of a code of transparent good practices. The special case of blood-related parents would be better served by prenuptial screening than by screening on the occasion of the birth of a child.

1.4. CCNE underlines de dangers of any systematic generalised screening policy for healthy carriers, but suggests, as already proposed in Opinion n°

83, that a limited prospective study should be undertaken on the psychological, social and medical consequences on future parents of an opportunity to apply for and be given the results of a test of their possible healthy carrier status, within the framework of a truly free and informed consent procedure. CCNE considers that research on these lines, addressing the various ethical issues, might not solve these issues but could provide information which is more related to collective psychology than to medicine. This could pave the way for reflection on the most appropriate access to genetic test results for future parents who would want to apply for them.

1.5. CCNE suggest that the contrast between biochemical and genetic testing be made less sharp. The existence of a wide range of different situations argues against a limitation of ethical reflection to genetic testing alone. However, with cystic fibrosis, biochemical anomalies are more likely to evidence particular bodily functions suggesting a risk of developing the disease. Research to develop new and more reliable biochemical tests should be highly encouraged since proteomic science is progressing by leaps and bounds to offer new possibilities of identifying proteins from extremely small samples. This strategy would put screening for cystic fibrosis on a par with screening for sickle-cell disease or phenylketonuria.

2 – For sickle-cell disease

CCNE recommends that present screening practices be continued but that precise information regarding their true significance and the benefits of the electrophoretic test should be associated with the procedure.

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In conclusion, CCNE recommends that all at-birth or before-birth systematic screening policies, be only implemented after the most thorough evaluation of all their consequences, in particular collateral effects, so as to avoid any features which could give rise to ethical difficulties. Screening for cystic fibrosis is emblematic of an approach leading *a posteriori* to recognising ethical issues which were predictable *a priori (*and for that matter inevitable) but had not been considered.

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Prospective thinking

CCNE also wishes its Opinion to extend beyond the initial parameters of the referral. The Committee observes that in practice, the offer of neonatal

screening tests on healthy children for serious diseases tends to drift in the direction of a broader set of problems, i.e. to disclosure of information arrived at fortuitously by the tests regarding the possible risk for a tiny minority of parents concerned to conceive at some future time a child who might develop a particular disease. The probable generalisation in the near future and the sharp reduction in the cost of genetic testing based on global chromosomal analysis of most — or even all— genes, will increase this offer considerably and generalise immoderately the discovery of heterozygosis, or of genetic particularities which have no direct effect on the health, and therefore are of no direct benefit for the person, the fœtus, or even the embryo. As a consequence there would be subordination of ethical reflection to technological development: the data generated automatically and increasingly by tests, including prenatal or pre-implantation diagnosis, will not be safe from disclosure to those entitled by law to receive it, outside the context of any form of ethical reflection and even if such disclosure is more of a handicap than an advantage for them.

Consent of what kind, to obtain which information, to which test and who should be tested?

Today's society lives in a paradox. It is extremely cautious, it is even reluctant, as regards the generalisation of systematic access by future parents to genetic analysis before a child is conceived and during pregnancy. Yet, at the same time, it encourages such analysis if a genetic test reveals by chance (as is the case in neonatal screening for cystic fibrosis) that there is a risk, even a minimal risk, of giving birth in future to a sick child. Encouraging 1.5% of parents who have given birth to a healthy carrier child (and who have an over 99% probability of giving birth to another disease-free child) to practice this test while remaining reluctant to give other parents access to the same test if they so wish, creates a situation in which the best course is guided by technology and not by authentic reflection on the freedom of future parents to decide if and when such a test should be performed. To allow technical development to deprive parents of their freedom of choice by presenting them with a *fait accompli* seems to be the antithesis of action based on ethical reflection.

Dissociating, to the fullest extent possible, the moment when information is given concerning the state of health of a newborn from the time when information is given concerning the possible health of future children.

Developing assistance for children suffering from incurable genetic diseases and physical or mental handicap.

There can be no true free and informed consent to genetic or chromosal tests, as is the present case for the detection of trisomy caused syndromes in future children unless, in return, society guarantees that it will do its utmost to alleviate pain, take care of and assist children suffering from incurable disease or serious disablement. Such is the condition for parents to be able to choose whether they want the child to be born or not.

The problem with routine screening for trisomy in pregnant women is not so much one of access to information on available test procedures but more the pressure of systematic screening on free and informed consent: the decision not to test is in fact assimilated to "refusal" and may give the impression that the decision to terminate the pregnancy or not is based on an erroneous interpretation of results.

Despite recent laws, there are cruel deficiencies in our country in the management of severely disabled children. There should therefore be no dissociation between reflection on the antenatal use of genetic testing and awareness of the urgent need for improving assistance to those suffering from incurable genetic diseases or physical and mental disorders.

Becoming aware of the ethical consequences of current technological developments.

In the case of neonatal screening for cystic fibrosis, the insidious progression from screening for a disease to screening for the status of healthy carrier is linked to the research technique in use. It screens for the presence of two mutated alleles of the *CFTR* gene (signing the risk of development of the disease status) but also evidences necessarily the presence of a single allele (healthy carrier status) since evidencing two alleles necessarily involves the individual identification of each one of them. The progression simply extends the number of units observed (1 or 2) of certain alleles of the same gene. Although the problem seems complex, it is paradoxically simple compared to the ethical problems which may be raised in the near future by extremely rapid developments in genetic analysis techniques, their availability, their considerably reduced cost and the simplification of methods allowing for multiple tests using a single cell.

Already, it is easy enough to sequence most if not all genes, to add an analysis of the whole chromosomal structure (caryotyping) and, using RNA chips, to study the manner in which these genes are used by the sampled cell or cells.

If such techniques become routine newborn screening for genetic diseases, a significant part of the results obtained from them will not be interpretable in medical terms. In that event, should all the accumulated information be communicated to families, running the risk of worrying and overwhelming them with meaningless and useless data, no doubt faithfully depicting a newborn's singularity, but of no benefit for the child's health? In such circumstances, would the notion of free and informed consent to genetic analysis make any sense at all if this is in fact consent to receiving any kind of information even if it cannot be interpreted in medical terms? Or should on the contrary parents be kept in ignorance of results that are unconnected with the health of their child? Or, as is currently thought appropriate in some circles, should those who perform the tests "mask" the major part of results so as to read and communicate only the data which can

be interpreted and which corresponds to the diseases for which screening was offered?

As methods now exist, using an ordinary blood sample, for isolating fœtal cells circulating in the bloodstream of a woman in early pregnancy and for analysing the properties of the genome in a single cell, such global genetic analyses will now be available not only when a pre-implantation diagnosis (PGD) is performed prior to the implantation of an embryo, but also in the mother during pregnancy. The anxiety caused in such circumstances by the indiscriminate disclosure of a mass of data is easy to imagine, particularly if the consequences on health can only be imperfectly interpreted or not at all.

In other words, communication of the results of neonatal screening for cystic fibrosis obtained by an old and relatively limited technique of genetic analysis already raises ethical issues which were not even anticipated although they were predictable. It requires therefore no great leap of imagination to discern the more devastating dimensions of the ethical difficulties arising out of the use, without prior thought, of much more efficient testing techniques, if the only guide of conduct is that anything which technology is capable of blindly revealing must necessarily be taken into account and communicated.

The scope for ethically acceptable free and informed consent lies between absence of access to available information and the obligation of access to non pertinent unrequested information — between the right to know and the right not to know.

This issue is also related to the status of access to personal medical data. Is its true purpose to inform patients, to protect the medical profession from legal proceedings or simply a concession to the contemporary obsession with knowing everything that is to be known — even if that knowledge is unusable and traumatising?

Scientific and technological breakthroughs could lead to founding the choice of our behaviour, not on ethical reflection but on obtaining automatically generated data through the use of new techniques when they are neither expected nor planned for. In-depth prospective examination by professionals and society as a whole is therefore needed to determine appropriate access to genetic test results and data so that their contribution to health and personal dignity is optimal and their unconsidered use does not contradict the ethical dimensions of medicine.

January 11, 2007

Contribution by a member of the Committee

The prospective conclusions added to CCNE's Opinion on "Ethical issues arising out of the delivery of neonatal genetic information after screening for genetic disorders" call for some comment.

The Opinion rightly draws attention to the need for ethical reflection before any application of any progress made on the study of the genome through screening and/or diagnosis. However, some of the Committee's conclusions reflect a slightly partisan view. The Opinion expresses concern regarding the risk of "pressure" contrary to free and informed consent in the event of "systematic screening for trisomy 21". Implicitly it establishes a link between screening, termination of pregnancy on the one hand, and insufficient assistance for disablement in our society on the other. Certain facts must be recalled. Screening for trisomy 21 by maternal serum markers is systematically proposed (but is not itself systematic). Screening modalities are supervised by the *Agence de Biomédecine* and multidisciplinary assistance is provided for women so that at each step in the decision process (offer of screening, screening, diagnostic phase if necessary, etc.) both explanation and counselling are available. In fact, some 20% of women do not request trisomy 21 screening. It is also disquieting to observe that women in more deprived social and economic circumstances are less inclined to ask for prenatal diagnosis of trisomy 21 and more often than not, choose to continue their pregnancy when the trisomy diagnosis is arrived at[4]. Finally, the simultaneous setting up of screening (1997) and of measures — still far from being sufficient, admittedly — to help the disabled contradicts the notion of a link between encouragement to terminate pregnancies for medical reasons and lack of assistance for handicapped patients.

The Opinion expresses concern over a potentially ill-considered use of genomic tools following the extremely rapid progress of this technology and its reduced cost. Obviously the matter must not be left unattended, but it would appear that extensive use (screening) is not likely to be possible in the short or medium term. Costs are still currently in the region of tens or even hundreds of thousands of euros per person and will still cost tens of thousands of euros in the near future...
So although there is legitimate reason for concern in the long term, it must be remembered that the limits of predictive medicine already exist: are only justified tests producing results which can lead to useful medical intervention. Systematic study of the genome of an embryo, a newborn or a person of any age does not fit in with this definition.
In our view, it would be more useful to reflect on the conditions for protecting individuals against the dissemination of genetic characteristics in the social environment (insurance companies, employers, banks, etc.).

[4] Khoshnood B et al. Am J. public Health 2006, 96, 2139-2144. Etude française concernant les femmes résidant à Paris et la petite couronne (French study on women residing in Paris and the immediate suburbs (period 1983-2002).

Should more attention be given to ethical reflection on genetic tests? It is worth remembering that screening during pregnancy leading to the detection of an anomaly followed by medical termination is in the immense majority of cases non genetic[5] (> 90%). Difficult situations also arise in these cases. Individual multidisciplinary counselling for couples in the throes of such harrowing circumstances, sometimes very borderline, would seem to be the most appropriate response.

CCNE is acting well within its purview by drawing attention to ethical issues arising out of the development of new methods of acquiring biological information related to (or unrelated to) genomics and to their use in particular during pregnancy and at birth. However, considerations of an overly theoretical, solemn and dramatic nature could give the impression that the Committee is detached from the reality of current, and perhaps future, practice of fœtal medicine.

[5] Study by the *Club francophone de médecine fœtale* 2004-2005