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**New ethical stakes raised since the French nationwide cystic fibrosis newborn screening program was initiated**

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***Introduction***

Pre-implantation genetic diagnosis on embryonic stem cells, prenatal screening, genetic predisposition testing for chronic or incurable diseases, tandem mass spectrometry scanning techniques aimed at detecting congenital metabolic diseases as early as possible...These *innovative biomedical technologies*, defined as novel configuration (material, scientific, institutional, epistemological) characterised by new entities (biomarkers, cellular genetic signature, genetic mutations), are currently centre stage in a heated controversy. The genesis, exploration and representation of these new technologies stem from the combination of scientific research in biological and molecular processes and the pathological signs of disease. Taking all aspects into consideration, the debate raises a number of questions not only concerning aspects such as reliability, safety, cost effectiveness, potential benefits and possible risks but also the impact of genetic testing on deep-rooted cultural or religious beliefs concerning the sanctity of human life and what defines a human being, corporal integrity and the frontiers separating life from death. The debate which is supported by professionals inevitably imposes itself and evolves by drawing in patient users<sup>1</sup>.

The biological and chemical analyses used in mass neonatal screening are a product of these biotechnical innovations that generate uncertainty<sup>2</sup>. Among these, the neonatal screening test

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<sup>1</sup> Akrich M., Méadel C. et Rabeharisoa V. (2009), *Se mobiliser pour la santé. Des associations de patients témoignent*, Paris, Les Presses de l'École des Mines ; Castel P., (2006), « Les recommandations de bonnes pratiques comme objet heuristique pour la sociologie de la médecine », *Sciences sociales et Santé*, Vol. 24, n°2, p. 105-112.

<sup>2</sup> Callon M., Lascoumes P., Barthe Y., (2001), *Agir dans un monde incertain. Essai sur la démocratie technique*. Paris, Le Seuil.

for cystic fibrosis is particularly worth investigating. The nationwide implementation and standardisation of the screening programme is the result of numerous debates concerning its effectiveness in terms of public policy (benefits against disadvantages), its scientific validity (the role of government in endorsing scientific proof in biomedicine) and the way therapeutic approach and foetal selection are articulated (life science policy)<sup>3</sup>. Furthermore, the Systematic Cystic Fibrosis Neonatal Screening Programme (CF NBS) set up by the public health authorities in 2002 made France one of the pioneers in nationwide screening and resulted in the creation of Resource and Expertise Centres for Cystic Fibrosis (Centres de Ressources et de Compétences de la Mucoviscidose: CRCM) from its inception. CF centres are charged with managing the CF diagnosis announcement and second tier sweat test on the one hand, and coordinating the patient care path on the other. Health professionals are thus exposed to decision-making processes concerning both diagnostics and prognostics. In a mass screening context these three determining practices affect (a) the diagnosis through the choice of terms used to express the presence of an incurable disease that inevitably projects an idea of the type of life the patient can be expected to lead and (b), the prognosis, in predicting clinical symptoms, outcomes and causes and the effects of living with this orphan disease in society.

Supported by empirical survey results, this presentation aims at investigating the controversies animating the CF NBS debate on the one hand, and the ethical and social implications of using innovative biomedical technology<sup>4</sup> on the other.

## **1. Neonatal screening for cystic fibrosis: a controversial technical and scientific object**

In order to understand the contemporary societal and ethical issues raised by neonatal screening, it is useful to retrace its genealogy not only in terms of its technological development but also in terms of public policy and its underlying trends revealed through the introduction of a mass screening programme. Particularly interesting is the establishment of scientific and medical protocols involving a continuous alternation between *biomedical* conventions concerning the *entities* (genetic mutations, biomarkers) involved in both pathological change and normal physiological variations, and the *systems* that establish, temporarily standardise and partially regulate recommended practice and the clinical procedures in diagnosis and prognosis, all of which taking place within multi-trade, multidisciplinary entities within institutions.

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<sup>3</sup> Vailly J., (2007), « Dépister les nouveau-nés. Évolutions, débats et consensus », *Médecine /Sciences*, Vol. 23, n°3, p. 323-326. Vailly, J. (2006). Genetic screening as a technique of government: the case of neonatal screening for cystic fibrosis in France. *Social Sciences & Medecine*; 63, 3092-101; Vailly J. (2008), "The expansion of abnormality and the biomedical norm: neonatal screening, prenatal diagnosis and cystic fibrosis in France", *Social Science & Medicine*, Vol. 66, n°12, p. 2532-2543.

<sup>4</sup> This communication is based on a research programme bringing together health professionals (doctors, nurses, geneticists, psychologists...), sociologists and statisticians. The study entitled 'Factors favouring or limiting the implementation of practice recommendations for CF diagnosis announcement following neonatal screening' (Facteurs favorisant ou limitant la mise en œuvre des recommandations d'annonce du diagnostic de la mucoviscidose suite à un dépistage neonatal), jointly financed by the association 'Vaincre La Mucoviscidose' and the 'Fondation de France', was launched in February 2008. It was conducted in two phases: 1. questionnaires in the 34 CRCM in France, 2. individual interviews and *focus group* sessions in 15 CRCM.

Neonatal screening is a mass screening, secondary prevention policy aimed at detecting one or several often congenital disorders in all neonates in a given country. To be eligible for neonatal screening, a disease should meet a number of criteria approved by the World Health Organisation; criteria taken from the taxonomy established in 1968 by Wilson and Jungner<sup>5</sup>. More specifically, the disease should constitute a serious health problem with an early symptomatic stage, be sufficiently prevalent (over 1/20 000 births), and accessible to efficient treatment in its pre-clinical phase. It should be detectable by means of a rapid, cost effective test with a low false-positive incidence (to avoid unnecessary parental stress and high resource consumption) and a false-negative rate that is virtually nil and applicable on a large scale (over 800, 000 births per year in France). The screening process should be acceptable to parents and, in the event of a positive result, include a rapid second-tier DNA mutation analysis to identify the genetic anomaly responsible, as is the case for cystic fibrosis screening. Positive results should systematically lead to the immediate provision of adequate follow-up care so as to improve prognostics and finally, all instituted screening programmes should be regularly evaluated.

As a congenital autosomal-recessive disorder with a relatively high rate of prevalence (1/4500 births), cystic fibrosis is one of the five rare diseases systematically screened from birth<sup>6</sup> since 2002. The screening test measures the dose of immunoreactive trypsinogen (IRT)<sup>7</sup> present in

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<sup>5</sup> 1- the condition sought should be an important public health problem; 2- it should present a recognised latent or early symptomatic phase prior to or at the onset of clinical symptoms; 3- the natural history of the condition should be adequately understood; 4- there should be an accepted preventive or curative treatment available; 4- a reliable early detection test should be available at its latent phase; 5- the test should be acceptable to the population in general and subject to the consent of the person being tested, or the parents in the case of a child, who should equally be clearly informed as to the nature of the test, the meaning of the results and therapeutic possibilities; 6- the screened patient must have the possibility of being examined, treated and benefit from follow-up care in high performance medical structures; 7- the screening programme must be a continuing process; 8- the cost of screening should be moderate and not exceed the cost of treatment: J.M.G. Wilson, G. Jungner, (1968), "Principles and practice of screening for disease", Geneva, WHO.

<sup>6</sup> The five diseases screened for include: hyperphenylalaninemia and congenital hypothyroidism since 1978, congenital adrenal hyperplasia since 1996, drepanocytosis among children potentially at risk (African and West Indian) and cystic fibrosis since 2002.

<sup>7</sup> The screening test takes place 3 or 4 days after the baby's birth by measuring immunoreactive trypsinogen in serum. A few drops of blood are taken from the baby's heel and collected on filter paper. A second blood sample is used for genetic testing: it enables confirming the diagnosis and determining the form of cystic fibrosis present. In the case of elevated IRT values ( $> 65\mu\text{g/L}$ ), the diagnosis is validated by a search for mutations on the '*cystic fibrosis transmembrane conductance regulator channel*' (CFTR) gene. In the attempt to establish a genotype/phenotype correlation, mutations are grouped into six classes according to the anomaly produced on the CFTR gene. The mutation is said to be serious if no functional CFTR protein is produced (classes I, II, III), moderate or '*mild*' in other cases (classes IV, V, VI). This search for genetic mutations examines a total of 30 mutations covering 90% of those observed in France using genetic test kits, the most frequent (66%) being the *F508del* mutation. In the case of a positive diagnosis, the infant is referred to a CF Centre, responsible for administering the sweat test instituted in 1952, which tests the phenotypic expression of the disease. If the test is positive (sweat chloride concentration level

the blood plasma. The singularity of neonatal cystic fibrosis screening (CF NBS) resides in its infringement of the Wilson and Jungner criterion stipulating that ‘an accepted curative treatment’ should be available: to date, cystic fibrosis remains incurable.

### ***1.1. The protagonists and mediating objects in the controversy***

Among the principal protagonists animating the CF NBS controversy, we identify:

- A fringe of doctor geneticists against mass screening in general;
- The High Authority for Public Health (Haute Autorité de Santé, HAS), mandated to evaluate the CF NBS programme after five years operation; somewhat critical;
- the National Ethics Advisory Committee (Comité Consultatif National d’Ethique, (CCNE)<sup>8</sup>, equally critical,
- the French Association for the Screening and Prevention of Infant Handicaps (Association Française pour le Dépistage et la Prévention des Handicaps de l’Enfant, AFDPHE), responsible for neonatal screening in general and the experimental NBS programme initiative launched in 1989; favourable;
- the CF NBS pioneers (located in regional NSCF program first launched in Brittany in 1988), favourable;
- paediatricians, geneticists, biologists, for the most part working in CRCM: favourable;
- and finally, associations engaged in supporting patients, families, medical research and therapeutic education such as the association ‘Vaincre La Mucoviscidose’ (Overcoming Cystic Fibrosis), a French pressure group with considerable influence on the public authorities, favourable;

The controversy has set the stage for a variety of protagonists. The mediation objects, presented below, play a preponderant role in the debate and in mediating the facts by means of:

- scientific publications detailing NBS evaluation results; they contribute in advances founded on *matters of fact* and explain *matters of concern*<sup>9</sup>;
- expert mechanisms created by authorities such as the HAS and the CCNE for the benefit of professionals and networks;
- certification and labelling protocols for approved centres;
- research dissemination conferences animated by eminent specialists on behalf of the AFDPHE and the CRCM focused on legitimising NBS;
- media communications, conferences, ethical debates (forums, hearings, conferences, and public awareness campaigns such as the ‘Virades de l’espoir’.

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above 60 mmol/L), global multidisciplinary care is provided from the outset of the diagnosis associating a specialised paediatrician, paediatric nurse, physiotherapist, nutritionist, psychologist and a geneticist biologist.

<sup>8</sup> Situated in the bioethical domain, the National Ethical Advisory Committee puts forward opinions that, even if they have no mandatory value, contribute to the normative framework governing medical practice. According to the Law of August 6th, 2004, ‘The mission of the National Ethical Advisory Committee for life sciences and health is to put forward opinions on ethical and societal issues raised by knowledge advances in the fields of biology, medicine and health.’

<sup>9</sup> Latour B., (2005), *Reassembling the social. An introduction to Actor-Network Theory*, Oxford, OUP.

## 1.2. *The different standpoints expressed*

The *opponents* are up in arms against screening tests in general and recommend the interruption of the neonatal cystic fibrosis screening programme<sup>10</sup>. Their arguments are based on the uncertain balance between the benefits and risks associated with screening. The lack of scientific proof that CF NBS screening is beneficial to patients from a medical point of view is an area of considerable tension. In other words, given the ‘*absence of proven benefits, of cohorts monitored in parallel for pulmonary disorders*’ (doctor), any experienced GP would rapidly recognise the disease in a new-born patient by signs of hypotrophy and repetitious respiratory infections. Furthermore, given the low specificity of the biological marker, thereby generating false positive results, not all infants carrying the gene mutation are seriously affected (the repercussions of the various mutations on the phenotype are variable and unpredictable) and no curative treatment is currently available. Finally the CF diagnosis announcement is a source of considerable stress for the parents and the prognosis remains deeply uncertain. Note that the same arguments succeeded in terminating the experimental NBS programme launched in 1989 by the AFDPHE.

CF NBS *supporters*, including the biomedical teams<sup>11</sup> that pioneered NBS in Brittany and subsequently joined by CRCM professionals, argue that the benefits of screening largely outweigh the disadvantages. The arguments put forward include:

- neonates referred to specialised CF centres benefit from an increased life expectancy due to early follow-up care, a reduced risk of complications due to preventive care and rapidly treated infections, respiratory physiotherapy and measures for healthy living;
- the secondary detection of CF heterozygote carrier status (healthy carrier that can transmit the disease to descendents) in both parents enabling them to opt for prenatal screening in subsequent pregnancies;
- the implementation of extended family studies to detect heterozygote carriers permitting them to make informed reproductive choices.

CF NBS supporters equally intend to take maximum advantage of the national political consensus between the actors concerned and the international position held by France as pioneer in the field by mobilising themselves to promulgate it in other countries.

NBS practitioners criticize the paradoxical ‘chicken and egg’ arguments put forward by opponents to neonatal screening: ‘*why the need for screening when there are specialised care centres and all that’s needed is to send patients for treatment as soon as the clinical symptoms appear and the disease progresses?*’. These pioneers remember a by-gone age in which GP isolation and mono-disciplinary practice was coupled with insufficient resources and a patient’s visit to the paediatrician resulted in a morbid announcement. Under the

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<sup>10</sup> This summary stems from reading specialised publications on the subject. We have not had any direct contact with NBS opponents.

<sup>11</sup> Vailly J., (2004), « Une politique de dépistage *a priori*. Le dépistage néonatal de la mucoviscidose en Bretagne », *Sciences Sociales et Santé*, Vol. 22, n°4, p. 35-60. The author shows to what extent regional policy in Brittany based on various arguments that are more based on intimate conviction than solid scientific proof (NBS offers the possibility of proposing a prenatal diagnosis to parents with a first sick child, Brittany has the highest incidence of CF and finally a strong presumption as to the therapeutic benefits of early detection and treatment and its organisation) has elevated CF to the ranks of social problem on the political agenda.

impulse of NBS, the establishment of specialised health centres and standard protocols has structured the sector in such a way as to facilitate health professionals' management of CF diagnosis announcement and the continuity of care in greater serenity.

At this stage, the controversy is polarised between:

- *supporters of a biology and medicine of principles* whose sole reflective contribution is the interruption of NBS. The aim of instituting CF NBS was ultimately the 'individual, direct, and immediate interest of the sick child'<sup>12</sup>. By this very fact, concrete situations and their resulting dilemmas are dealt with at CRCM level and rely on the experience of health professionals in CF diagnosis announcement;
- *CRCM centre practitioners are involved in the diagnosis*, the future life of affected cohorts and relationships with the families, whilst at the same time admitting the consequences, limitations and side-effects of screening technology. In their opinion, expressed by one of the pioneers in the field, the question needs reformulating; it is no longer a question of 'should we screen?' but 'how should we screen?'<sup>13</sup>. Certain practitioners request an evaluation of NBS practices enabling an assessment of their effectiveness. These practitioners are not only faced with the realities of CF announcement dilemmas, but also the equivocal nature of certain results and the fact that screening neither provides foolproof diagnostic certitudes nor absolute knowledge of subsequent clinical manifestations.

These two groups actively participated in creating a social problem assisted by two public authorities that, in adding focus on the ethical and social elements, maintained the dynamics of the controversy. The HAS report<sup>14</sup>, an evaluation of the NBS programme after five years operation, highlighted several areas for improvement thereby adding fuel to the controversy. Experienced practitioners reacted keenly, estimating that the report was riddled with '*blatant errors*': '*the comments made by the HAS were erroneous concerning a number of precise points. Having said that, it had the effect of re-launching the debate, provoking reactions among people and providing them with the occasion to refine their arguments*', '*it appears that the HAS, in the way it formulates its criticisms, demonstrates that opponents to screening still exist, that's obvious*' (Doctors). Finally, the CCNE proved to be even more dubitative as to the utility of CF NBS: '*From the information we have available at international level, it would appear that early diagnosis from appearance of the first clinical symptoms, the quality of therapeutic care and continuous surveillance are better criteria for quality and life expectancy than neonatal genetic screening as such*'<sup>15</sup>.

## 2. Bioethical stakes raised by CF NBS: genetics and prediction

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<sup>12</sup> Ardaillou R., Le Gall J.-Y., (2007), « Le dépistage néonatal généralisé par des tests d'analyse biologique », *Gynécologie Obstétrique & Fertilité*, 35 367–374 ; Comité Consultatif National d'Éthique (CCNE), « *Avis 97 : Questions éthiques posées par la délivrance de l'information génétique néonatale à l'occasion du dépistage de maladies génétiques (exemples de la mucoviscidose et de la drépanocytose)* », duplicated, p. 7.

<sup>13</sup> Farrell P.M., (2004), "Cystic fibrosis newborn screening: shifting the key question from "should we screen" to "how should we screen?", *Pediatrics*, n°113, p. 1811-1813.

<sup>14</sup> « Le dépistage néonatal systématique de la mucoviscidose en France : état des lieux et perspectives après 5 ans de fonctionnement », Rapport de la HAS, janvier 2009.

<sup>15</sup> Voir CCNE, *In Avis 97, op. cit*, page 10.

The existence of this perpetual controversy surrounding NBS is explained by the fact that cystic fibrosis is not included in the list of diseases screened at birth in all countries. Even though a recent study, after evaluating the risks and benefits, concluded that CF NBS was justified<sup>16</sup>, we note that the introduction of molecular biology methods in a neonatal screening strategy unavoidably raises a certain number of bioethical issues. NBS, a tool among others in the realm of medical genetics, is not a standard biological examination. Consequently, in its definition, indications, analyses and the announcement of results, it should be governed by principles that fall within legal and ethical frameworks. One of the side effects of introducing molecular biology in neonatal screening induces the random detection of false positives, false negatives<sup>17</sup> and borderline or dilemma cases<sup>18</sup>. In this sense, scientific and technical advances in medicine and biology create the conditions for uncertainty<sup>19</sup>.

### ***2.1. The question of false positives and false negatives: from identifying a patient to identifying genetic status***

The disadvantage of all screening tests is that they institute a new status; the false positive status that unnecessarily alarms parents whereas the infant is not affected, and the false negative status that neglects affected neonates.

The ultimate aim of screening is to identify newborn infants with cystic fibrosis, not to identify heterozygote carriers<sup>20</sup>. Inevitably, screening detects healthy newborn heterozygote carriers that tend to have an elevated IRT level, though not exhaustively. Since the mass implementation of CF NBS, and in order to limit the number of false positives referred to CRCM, the protocol has been modified on three occasions by increasing the IRT cut-off level<sup>21</sup>. The aim of these successive modifications was both to relieve CF centres and highly trained teams from carrying out superfluous tests, but more especially to reduce the number of referrals and unnecessary stress for the parents.

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<sup>16</sup> Grosse S.D., Boyle C.A., Botkin J.R., Comeau A.M., Kharrazi M., Rosenfeld M., *et al.*, (2004), "Newborn screening for cystic fibrosis: evaluation of benefits and risks and recommendations for state newborn screening programs", *MMWR Recomm Rep*.

<sup>17</sup> False negatives are CF carriers that most frequently have two dominant or recessive gene types for a certain trait (homozygotes), affected by cystic fibrosis (the sweat test is negative but the individuals are affected by the disorder, the physical manifestations appearing later) that did not benefit from the screening test. False positives, heterozygotes, are healthy CF carriers (their test is positive with one or no gene variations, but with 'resistant', 'intermediary', or 'mild' expressions of the disease); these individuals are not affected by the disorder.

<sup>18</sup> Detecting 'borderline' cases (a dominant '*mild variant*' associated with a classic variant, elevation of Trypsinogen levels, no elevation of Tst, no apparent symptoms but differed symptoms), but for which the phenotypic expression remains unpredictable, that is to say the nature, severity and onset of the illness.

<sup>19</sup> Fox R., (1988), *L'incertitude médicale*, Paris, L'Harmattan ; Fox R., 1999, "Medical uncertainty revisited", In Albrecht G., Fitzpatrick R., Scrimshaw S., eds, *The handbook of Social Studies in health and medicine*, London, Sage.

<sup>20</sup> Roussey M., *Réflexions à propos de l'avis n° 97, concernant : 'Question éthique posée par la délivrance de l'information génétique néonatale à l'occasion du dépistage de maladies génétiques (exemple de la mucoviscidose et de la drépanocytose)'*. Duplicated copy of the document supplied by M. Roussey in person, p. 6 and 7.

<sup>21</sup> The implementation of the 3rd protocol in November 2004 permitting a reduction in the rate of false positives that was initially high.

The problem of false positives can be summarised as follows: how should one regulate questions asked by parents who come for a test with an unaffected infant? Should the heterozygote carrier status be disclosed and what are the potential repercussions? To the first question, it emerges that parental stress is not apparent. To the second question, the ethical problem is more complex. It concerns healthy heterozygote carriers that are nevertheless susceptible of transmitting the genetic mutation to their descendents (the search for genetic mutations effectively detect a large number of carriers of a single type of mutation). The CCNE recommends that the systematic disclosure of CF heterozygote carrier status in neonates should not be encouraged since it is not in the immediate interest of the infant<sup>22</sup> and confines the individual within a genetic status. It adds that the information delivered prior to obtaining parental consent should clearly state that although the screening test may detect a heterozygote carrier status, the information will only be disclosed after a counselling session and serious thought as to the consequences. The CCNE also recommends that the results are stocked in a 'Biobank' permitting consent for disclosure to be obtained when the child reaches adulthood. Similarly, the HAS report 'recommends evaluating the long-term interest of the early detection of CF carrier status in healthy neonates'<sup>23</sup>.

Nevertheless, knowing that these heterozygote infants and their parents are referred to a CF centre to undergo a sweat test, it appears difficult to withhold the information from birth. Similarly, the parents of children identified as heterozygote carriers would be in their rights to question their own heterozygosity particularly if they intend to have other children. Finally 'in practice, a GP is bound to respect the confidentiality of a child's genetic status but if one applies the laws of bioethics, the GP is obliged to disclose the information to the family'.<sup>24</sup> If the parents effectively sign their written consent on the back of the sampling paper authorising a DNA mutation analysis in the case of elevated IRT, (in theory after having read the explanatory documents provided by the AFDPE in conformity with bioethical law), a consultant's decision to disclose a neonate's heterozygosity remains exigent. With the increasingly litigious nature of the patient-physician relationship, the risk of not disclosing an infant's heterozygosity is that parents who subsequently give birth to an affected child may engage in legal proceedings. In such a case of averred risk, the consultant would be held personally responsible for having withheld such crucial information.

The question of false positives brings us back to the fact that not all heterozygote neonates will be detected which creates inequalities; those with an elevated IRT level will be detected and those whose IRT level is below the cut-off level will not. 'In other words, 98,5% of healthy CF heterozygote carriers are not detected and neither the child's parents or other family members will have access to information allowing them to benefit from genetic counselling on the risks of giving birth to a child affected with cystic fibrosis in the future'<sup>25</sup>. On this point, the editorial of an academic journal<sup>26</sup> advances that 'the practical consequences' of CF NBS, is 'the multiplication of parent needs for genetic counselling and the search for defective DNA in the families thus identified.' Genetic counselling, however, gives rise to ethical interrogations situated further forward in the action chain of critical

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<sup>22</sup> Avis n° 97 du CCNE, p. 16.

<sup>23</sup> HAS Report, *op. cit.*, p. 137.

<sup>24</sup> Roussey M., *op.cit*, p. 4.

<sup>25</sup> Avis n°97 du CCNE, p. 6.

<sup>26</sup> Sarles J., Dagorn J.-C., (2006), « Dépistage néonatal de la mucoviscidose », *Pathologie Biologie*, Vol. 54, n°5, p. 263-265.

moments in the life process reaching back from neonatal to prenatal and, let's say it, eugenics. Future parents are effectively able to request prenatal screening to discover whether or not a foetus is affected. The practice of supplying both genetic and clinical information with NBS results thus pushes health professionals beyond the strict framework of technical diagnosis and prognosis to the restitution of the information to the families.

## ***2.2. The question of borderline cases: predictive medicine brought into question***

Another serious difficulty can be characterised by the detection of 'borderline', 'resistant' 'atypical' or 'equivocal' forms of cystic fibrosis, or in other words, either very mild or more serious forms of the disease. The CF NBS results are positive but the intermediary result from the sweat test does not confirm the diagnosis; subjects carry gene mutations for which the clinical outcome has not been clearly determined. For these neonates, for whom the phenotypic expression of these forms of CF is usually fairly mild, the question remains open concerning the diagnosis announcement, the need for family genetic counselling and the continuity of medical and nursing care. Implicitly, it is the very definition of the disorder that creates the problem.

The very definition of cystic fibrosis creates problems in certain cases especially as it was modified on the institution of the neonatal screening programme<sup>27</sup>. This can result in cases of overprovision of medical care, the risk of confinement and chronic interventionism. In attributing a genetic status and/or assignation to a medical category, the provision of care can be unduly heavy and constraining; in which case it should be carefully considered. *'It's in situations where we have a lot of doubts, and worries because... Well, doubts concerning what we ought to do because standard cystic fibrosis monitoring... the preventive care is very heavy, the treatment is very heavy... it can have serious consequences for an individual that may never develop the illness or develop it in a very mild form'* (Doctor). The screening and diagnosis of cystic fibrosis in such infants is a problem that is currently the subject of heated debate, presented under two different aspects: nosology and definition.

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<sup>27</sup> Before the screening era, a CF diagnosis was assumed when an element or symptom evoking cystic fibrosis was associated with a positive sweat chloride concentration test (sweat chloride level is equal to or above 60 mmol/L). In the screening context, a CF diagnosis can be made if an elevated Immunoreactive Trypsin (IRT) above the cut-off level is associated with and the presence of two CFTR gene mutations or a positive sweat test with a sweat chloride concentration level equal to or above 60 mmol/L. With this new definition, it is thus possible (and not infrequent) to find children diagnosed with cystic fibrosis whereas their sweat test is normal and there are no clinical symptoms evoking CF during the initial examination. This is the case for infants screened on the basis of a positive IRT test and a 508delF/R117H genotype (7% of screened neonates) for whom the sweat test is rarely positive but more often intermediary and occasionally, but not infrequently, totally normal. The changes in the IRT cut-off level and flow chart have not significantly increased the number of false negatives. According to the professionals interviewed they were aware from the introduction of the screening programme that "false negatives", even on combining "IRT and gene analysis" and that the IRT cut-off levels were chosen to keep the percentage at below 5%. It is thus imperative to discover these false negatives in order to correctly evaluate the pertinence of the CF NBS screening programme. Patients suffering from cystic fibrosis diagnosed on clinical symptoms outside the screening programme are detected by means of an annual questionnaire sent to CF centres by the ADFPHE. Health professionals do not know the exact causes of this false negative rate: technical error or below cut-off IRT levels.

The work of nosology consists in defining a change in phenotype over time and to classify its clinical forms in at least two categories: “Cystic Fibrosis” and “CFTR Related Disorders”, to enable the provision of appropriate follow-up care. The majority of reported cases, after several years monitoring, show a normal clinical status or very mild symptoms. Only in time can the delayed apparition of clinical symptoms be attributed to a defective CFTR gene. This nosological question is complex in that it can lead to the arbitrary classification of a variable spectrum of clinical situations from normality to severe disorder according to the level of functional CFTR protein (and other associated genetic or environmental factors). Early detection in such individuals is in fact an undesirable side-effect of the screening process. As the disease can manifest itself later in life, it remains uncertain whether health professionals should announce the diagnosis at birth.

The second problem relates to the terminology currently in use. Specialised health professionals disagree as to what the term cystic fibrosis and its derivatives should or should not include. Their use of language reveals a degree of hesitation as to the definition of ‘form’, ‘borderline’, ‘moderate’ ‘attenuated’, ‘mild’ ‘resistant’, ‘intermediary’, ‘equivocal’ and ‘atypical’. Certain will use oppositions such as ‘severe mutation vs. light mutation’ thus taking up terms used in the genetics field. The reason for these performative idioms<sup>28</sup> is on the one hand an attempt to classify other forms of CF in relation to ‘classic cystic fibrosis’, which supposes that a naming convention has defined what the term ‘classic’ refers to, whilst maintaining the inverted commas as a precaution signifying that there remains some uncertainty regarding available knowledge. These specialists each have different vested interests and vie with each other to propose, or better still impose, one terminology rather than another (*CFTR Related Disorders* was proposed in replacement of “borderline form”). Behind these conflicts, there is the question of clinical properties, differences and uncertainties. For medical practice, the critical question concerns the sequence of events that structure the interactions between the medical teams the infants and their families and the considerable stakes underlying the provision of care including the diagnosis announcement, follow-up care, family genetic counselling and costs.

The distinction between preventive and predictive medicine arises with the appearance of these technological innovations and advances in molecular biology<sup>29</sup>. Forms defined as borderline are a sign of entry into predictive medicine<sup>30</sup>, also known as ‘probabilistic

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<sup>28</sup> The notion of ‘performativity’ borrowed from the pragmatics of language, highlights the fact that the sciences in general, and social sciences in particular, as is the case examined here, are not limited to representing the world: they bring it into being, provoke it and thereby to a certain extent and in certain conditions, create it. See Callon M., 2007, «What does it mean to say that economics is performative?», in MacKensie D., Muniesa F., Siu L. (ed.), *Do economists make markets? On the performativity of economics*, Princeton, Princeton University Press, p.311-357 ; traduction : Muniesa F., Callon, M., 2009, «La performativité des sciences économiques», in STEINER P., VATIN F. (ed.), *Traité de sociologie économique*, Paris, PUF,

<sup>29</sup> See Dausset J., (1985/86), « Qu’est ce que la médecine prédictive ? », *Les Cahiers du MURS*, n°4 ; Aymé S. (coord.), (2001), « Médecine prédictive : mythe et réalité », *Adsp*, n° 34.

<sup>30</sup> Definition: detection in an apparently healthy individual in whom the disease is latent but susceptible of pathogenesis. It predicts disease severity with probability, according to whether the dominant genetic characteristic is recessive or multifactorial, whereas there are little or no curative or preventive measures available. Voir Dausset J., (1985/86), *op. cit.*

medicine', where there is no precise knowledge regarding the clinical outcome of borderline forms of CF, the ideal treatment to be delivered or the type of genetic counselling required. There is no certainty as to the legitimacy of diagnosing such cases as there is no proven correlation between genotype and phenotype and consequently no certainty that the disease will manifest itself. Predictive medicine thus generates anxiety without procuring any benefits for the patient, especially in the case of a foetus where parents may prefer to terminate the pregnancy. CF NBS thus generates potential patients that ignore their potential status: biology and medicine define the disease rather than the experience lived by the subject.

### *Conclusions*

There are two facets to the controversy concerning the ethics of CF NBS. Firstly, as a technology and a tool for public policy, screening has radically transformed the physician-family relationship in that it touches the most intimate spheres of a human being and in so doing, inevitably rekindles anxieties. Secondly, in opening up the field of possibilities through continuous technological advances, it has also created new uncertainties.

On the other hand, during the course of these analyses, it is obvious that the actors involved are deeply concerned about the collateral effects of screening; that is, the detection of heterozygote neonates and borderline forms of the disease. Yet, it turns out that equivocal forms of CF extend beyond these recognised forms and thereby question clinical practice in all its dimensions: diagnostic classification, the prognostic outcomes for this cohort of CF detected neonates, the surveillance and therapeutic approach and a better organized, more adapted form of genetic counselling for the families. The health professionals' limits in the face of these difficult situations correspond to the limits of the existing consensus concerning these patients and, by extension, to the limits of the medical professions' arguments and attitudes throughout the CF announcement and treatment process.

Two lessons emerge from this. In the first place, this technology presents itself as a social construct, or in other words, as the result of an incessant interplay between scientific, technical, political and ethical domains to which are added the interactions between the actors involved. Far from being limited to the biomedical arena, these interactions evolve in those arenas where the sphere of experimentation converges with medicine and through the intervention of the media and events that bring together health professionals and patient associations. In that sense, they constitute an "enrichment of democracy"<sup>31</sup> implicating a constant realignment of laboratory advances and clinical practice around biomedical entities, health professionals and patients.

In the second place, bioethical stakes are closely correlated to the dynamics that create, rekindle or modify controversies. This is all the more flagrant in the case of cystic fibrosis in that it concerns a chronic disease that will shroud the entire life of both patients and their families. It is undeniable that the questions surrounding mass screening and its foreseeable and, more particularly, unforeseeable side-effects have reached an unprecedented scale; from the disputes concerning the definition and classification of the disease to the progression from neonatal to prenatal screening. Even more so, given the accumulation of effects induced by NBS, a fundamental question remains unanswered: is the aim of CF NBS to enable better access to care, to provide patients with more effective treatment or is its ultimate aim to eradicate the disease?

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<sup>31</sup> Callon, Lascoumes et Barthe, p. 49.