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The Reconfiguration of the Relationship to Care for a Rare Disease: Neonatal Expended Screening in a Socio-material Perspective

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Abstract

Neonatal screening (NBS) is a mass screening, secondary prevention policy aimed at detecting one or several often congenital disorders in all neonates in a given country. The French CF NBS programme is completely functional since the middle of 2003. Drawing its inspiration from the socio-material approach, this article advances a description and analysis of the interactions between the biomedical technologies used in neonatal cystic fibrosis screening and the resulting changes in clinical practice, the bioethical debate, and finally in the interstice between voluntary individual consent to screening and the management of a population's health. The analysis grid focuses on four dimensions: institutional, techno-scientific, regulatory and socio-professional. Backed-up by a field survey conducted in the specialised healthcare centres, this study explores two major aspects of the repercussions of NBS: first, the genesis and institutionalisation of this public policy and the impact of a more flexible form of Evidence Based Medicine (EBM), and the sustained controversy on the neonatal screening programme uniting the community of cystic fibrosis paediatrics. This study suggests that institutional stability remains fragile and in this respect constitutes a paradoxical form of production with incompleteness and uncertainty as constituting factors.

Keywords: neonatal cystic fibrosis screening; socio-material approach; dispute; biomedical exploration.

Introduction

Neonatal cystic fibrosis screening (CF NBS) has been a subject of debate in the majority of Western countries since the Crossley discovery of an early biological marker: immunoreactive trypsinogen (IRT). On the basis of criteria established by Wilson and Jungner in 1968, the incidence rate and gravity of this disease ranked it as a serious candidate for a global screening programme. Despite the advances in medicine that increased the life expectancy of CF patients, the absence of a curative treatment and the low specificity of the biological marker used in the diagnosis largely contributed in curbing the widespread use of this screening test. Reservations were finally overcome with new advances in both domains: with the introduction of systematic neonatal cystic fibrosis screening (CF NBS) instituted by the public health authorities since 2002, France became the first country in the world to adopt 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. These specialised centres for the treatment of cystic fibrosis exist in numerous countries such as Belgium, the United States and Canada and were strongly supported by national associations for the fight against cystic fibrosis with considerable financial resources on the one hand, and public health policy relating to chronic diseases on the other. CF centres in France 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.

The aim of this article is to explain some repercussions of Systematic Neonatal Screening for Cystic Fibrosis (CF NBS) instituted by the French public authorities in 2002 on the diagnosis announcement process within a specialised community: the Resource and Expertise Centres for Cystic Fibrosis (RECCF). More specifically, it will be approached from two angles: the generalised screening programme as a public health policy and a biomedical technology, and the changes induced by this instrumentation of quality of life management introduced at the frontiers of voluntary individual consent to screening and population health management. In such a tight combination of individualising procedures (the consent of each individual) and globalising techniques (the screening of populations), what exactly happens in the interstice?

We will proceed in four phases beginning with an outline of the conceptual framework underpinning the *socio-material configurations* approach (1). We will then briefly discuss our methods (2) before exploring the technoscientific aspects of screening and its impacts by recounting its materiality, the significant moments in its historiography, the latest developments it has induced and the controversies it generates and fuels (3). We illustrate our argument by documenting the driving forces behind the production of institutional arrangements and their stabilisation to allow collective action (4). We end with a discussion of potential questions and consequences of emerging socio-material configuration that singularises the development of neonatal screening.

A socio-material perspective in technology, organization, and constitutive entanglement

Driven by the advances in molecular biology, the development of genetic testing, initially reserved for the diagnosis of certain rare hereditary diseases, is growing rapidly. Since the deciphering of the human genome, almost 3000 genes involved in the manifestation of genetic diseases have been identified; 2000 have been located or cloned (Ameisen, 2008)). Used in the diagnosis of hereditary diseases, genetic testing also permits the early, ‘tailored’ treatment of certain chronic genetic pathologies thereby updating the concept of preventive medicine.

The rapid development of mass screening should be simultaneously understood in terms of past efforts, marked by a proliferation of public health policies founded on prevention, and in terms of 'biomedicalisation' (Clarke et alli, 2003, Keating and Cambrosio, 2003). Attempts to describe these new combinations of medicine, biology, genetics, chemistry and the statistics of incidence or life expectancy has given rise to varied terminology. Terms such as 'genetisation', 'biologisation', 'molecularisation', or 'biomedicalisation' used in reference to medicine are thus a perfect illustration of the fundamental movement traversing society (Clarke, Shim, Shostak, Nelson, 2009).

This proliferation of terms and the rhetoric associated with this powerful movement is problematic for two reasons. The first concerns the considerable risk of seeing the quasi disappearance of the patient, the health professional and the art of clinical practice on the one hand, and on the other the scientistic and reductionist rhetoric it has introduced in the health domain (Freese, Shostak, 2009, Freese, 2008). A second reason is more directly related to the heterogeneity of the biomedical domain that covers a series of questions: what if the answers or explanations provided by the recognised advances in genetics, molecular biology, chemistry and statistics in fact generated new questions? What if medical practices within the biomedical field included and redefined the lines of research in life sciences, extending them beyond the naturally restrictive hypothesises of laboratory research (Rabeharisoa, V. & Bourret P. (2009)? How does one explain the trajectories of subjects affected by these biomedical practices and uncertain explorations (Hedgecoe, 2006, 2010) expressed as 'techno-scientific identities' (Clarke et ali, 2003)?

In answer to these questions, over the past decade, some social scientists have elucidated the notion of uncertainty accompanying the rapid development, dissemination and metamorphosis of biomedical innovation: 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 (Keating and Cambrosio, 2003, Tournay, 2007). 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 term systematic genetic screening is defined as the search for certain genetic diseases at birth, either in the population as a whole or solely in families considered at risk (Allen and Farrell (1996). Depending on the disease being screened, biochemical tests (phenylketonuria), genetic tests (hemochromatosis) or both types of tests (cystic fibrosis, drepanocytosis) are carried out. Furthermore, each disease requires a specific analytical strategy and cystic fibrosis is revelatory in this respect. The neonatal screening test 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) (Vailly, 2006, 2007, 2008). Among the rare, orphan diseases, cystic fibrosis occupies a singular position by its relative frequency and complexity. Among the serious autosomal recessive diseases, it registers the highest

prevalence in European populations (a rate of prevalence of 1/4600 neonates in France) and its clinical expression and prognostics are extremely varied. Cystic fibrosis is a potentially lethal disease characterised by a variable and progressive clinical expression for which individual prognostics are difficult to determine at the time of diagnosis. To date, there is no curative treatment for cystic fibrosis. Care is essentially focused on preventing infection or the treatment of clinical symptoms: respiratory, digestive and nutritional. The singularity and gravity of the disease make it one of the most dreaded for the patient, the family, relatives and health professionals[i].

A significant body of research is based on the notion of socio-material configuration which defines the way in which the different actors produce the inter-relational interactions between the human, the organisational and technology. The last two decades have produced a number of particularly stimulating conceptual advances permitting the emergence of a sociological representation of techno-science: the most convincing examples being actor-networks (Callon 1986; Latour 1992, 2005), object-centered sociality (Knorr Cetina 1997), and material agencies (Barad, 2003, Leonardi and Barley. 2008, 2010). More specifically, the concept of *socio-materiality* (Mol, 2002, Suchman, 2007) for these authors signifies the interactivity of the social and the material in the constitution of everyday organisational and professional life, forming heterogeneous couplings, ground-breaking amalgamations that associate and dissociate depending on conditions and circumstances and, in this theatre of perpetual metamorphosis, give rise to unprecedented configurations and reconfigurations (Orlikowski and Scott 2008).

These concepts challenge and transcend the great canonical division between the human and the material by considering them as symmetrical. Our analysis is characterised by its focus on the entanglement of these two levels in the sense that social relationships and materialities are mutually constitutive in the formation of human agents. The material properties of artefacts (bodies, clothing, accessories, protocols, equipment, labels, instruments, software and software packages) actively participate in the constitution of actor cooperation and entity coordination and represent an infinite number of potential points of contact that can materialise in space and time. In the case of CF NBS, it concerns the formalisation of protocols and practice guidelines so as to render them applicable and thus easier to use (in the form of algorithms for example) and their dissemination within the medical community. An ideal-typical example of a diagnostic algorithm is the national protocol concerning sweat test referrals for diagnosis confirmation (Sermet-Gaudelus, et al. (2010). This constitutive entanglement allows us to trace the socio-material configuration regimen for a given artefact, in this present case the point of intersection between CF NBS and CF diagnosis, molecular biology and medicine and the rationalisation of knowledge and professional practices in biomedical and clinical innovation.

While mass screening program is both technologically monitored and legitimated by the assumption that it's a progress in health care process of this rare sickness, literature lacks with empirical studies in hospital teams. Little is known about how this technology alters professionals' axiological tensions, scientists and physicians controversies, neonatal screening practices for CF.

For this article, we opted for a methodological standpoint centred on *socio-material configurations*. The chosen approach aims at reconstituting a joint evolution of *institutional* (screening and healthcare establishments), *techno-scientific* (markers, instrumentation, knowledge), *regulatory* (elaboration and normalisation of diagnostic and care practices) and *socio- professional* (actors' trajectories and aspirations) dimensions. Clinical paediatrics has evolved from the individual clinician face to face with his patient to a collective endeavour

associating multidisciplinary specialists engaged in multiple activities from research to consultation and the regulation of practices. Bourret (2005) rightly named this particular working configuration as 'biomedical collectives'.

This standpoint appears all the more pertinent in that it applies to unstable objects, unknown entities and uncertain situations as we shall discover with this genetic disease. Our reasoning is as follows: cystic fibrosis, a serious, life-threatening hereditary disease that challenges the boundaries between science and medicine, provokes bioethical controversies within the community and produces innovative institutional arrangements by the sole fact that it generates problematic clinical situations and permanently renewed uncertainties. We argue that the re-working of institutional arrangements in this respect constitutes a paradoxical form of production with incompleteness and uncertainty as constituting factors (1) between investing in a new framework for the understanding of a complex genetic, orphan, multivisceral, chronic, life-threatening disease 'model' and the reduction of tensions inherent to techno-scientific advances in screening and the clinical exploration of unstable biomedical entities: (2) between the structuring of a multidisciplinary care network for this orphan disease and the reconfiguration of neonatal or even prenatal diagnostics after extending the idea of medical abnormality detected in two specific situations, carriers of borderline forms of CF and heterozygote carriers.

Method

This article is based on a research programme bringing together health professionals (physicians, coordinating nurses (CN), geneticists, psychologists…), sociologists and statisticians. The study entitled 'Factors favouring or limiting the implementation of practice recommendations for CF diagnosis announcement following neonatal screening' jointly financed by the French association 'Vaincre La Mucoviscidose' [ii]and the 'Fondation de France'[iii], was launched in February 2008. These guidelines, on the initiative of 'Vaincre La Mucoviscidose'[iv] were elaborated by a multidisciplinary working group bringing together professionals and parents and focus on five central themes: who should announce the diagnosis? Who should accompany the announcer? To whom should the announcement be communicated? How should the announcement procedure be conducted? What information should be disclosed during the announcement? In order to study health professionals' attitudes and their relationships with the cystic fibrosis diagnosis announcement recommendations, we chose to carry out our investigations in CF Centres in two phases: a quantitative phase that consisted in distributing a questionnaire to all CF Centres in France; a qualitative phase involving one-to-one interviews and focus group sessions among CF unit staff.

The study was thus conducted in several phases:

{1}It began with a questionnaire survey among 37 CF centres. Among these, 33 completed the questionnaire. The published report was able to outline a table of announcement practices based on a typology using three ideal-typical CF centre categories: (10 historical centres, 10 low-practice centres with limited resources, 14 high practice centres with considerable resources) (Cam, Faquet, 2008). This typology was used to constitute our qualitative sample in the aim of collecting diverse opinions through one-to-one interviews and *focus groups* for the qualitative study (Langeard and Minguet, 2009). If the constructed RECCF typology was effective in the analysis their relationship with the guidelines and the spread of 'good practices' in the announcement process, it proved to be ineffective in terms of grasping the medical experience related to screening tests and its integration in the diagnostic cycle. Consequently, it was not used in the analysis and interpretation of results.

{2} One-to-one interviews and focus group sessions were then conducted in the aim of examining and documenting work practices within the different professional segments (mainly physicians, coordinator nurses, and psychologists) confronted with the crucial stage in the cystic fibrosis diagnosis announcement to the neonate's parents. The focus groups aimed at confronting health professionals' view points and replacing them in an organisational context. Among the 34 teams that completed the questionnaire, 15 Centres, respecting the RECCF typology representativity ratio, were approached for the qualitative phase (5 historical centres out of 10, 4 low-practice centres with limited resources out of 10 and 6 high practice centres with considerable resources out of 14). In total 24 physicians, 14 coordinator nurses, 4 psychologists and 2 physiotherapists were interviewed. Interview guidelines focused on professional pathway, role description and function within the RECCF and the different phases of the announcement procedure in view of the guidelines. Only extracts from the interviews with physicians (mentioned Paediatric clinician n° X) are included in this article. The analysis of thematic content concerned the following themes: the singularity of the disease and its announcement, the diagnosis announcement framework and the way it is treated in RECCFs, the announcement as part of the patient's trajectory and how it is treated, the institutionalization of the disease by the public authorities and its repercussions on professional practice, and the controversies and ethical questions posed by CF NBS.

{3}The study is backed-up by documentary research and the systematic exploitation of sociological and management publications as well as professional and academic publications (medical, biological) specialised in cystic fibrosis and the field of recommendations. To this literature can be added bioethical, media and legal publications on this topic since the 1990's.

The genealogy of CF NBS: a history of continuous alternation between biomedical entities and the joint exploration of pathology and normality, deviation and conformity.

It is important to look back at the genealogy of screening, its equipment and more especially, the 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. n the first place, the genealogy of a technology imposes a coordinated exploration of the constitutive waiving (or deviation) from the rules that have governed the approval of cystic fibrosis as a candidate for neonatal screening. The implementation of a generalised, national screening programme also supposes a solid scientific base as shown by J, Vailly in his anthropology of the politics of life (2011). The decision to generalise CF NBS and establish a regime of truth results in this case from the entanglement of strong conviction and evidence based medicine (Evidence-Based Medicine) in a more flexible form.

A joint exploration of rule waiving and tolerance to deviations

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: 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. Adapted to neonatal screening, one should retain that 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 prognosis and finally, all instituted screening programmes should be regularly evaluated.

A national screening programme was organised from 1978 with the agreement of the CNAMTS, the National Health Insurance Fund for Salaried Workers and the French Association for the Screening and Prevention of Handicaps in Children (AFDPHE) with three aims: equal access to screening and therapeutic treatment for all neonates; screening test efficiency with maximal detection of sensitivity and specificity; utility, or in other words that CF NBS should be directly beneficial to the neonate. The French CF NBS programme is completely functional since the middle of 2003.

Five diseases are currently included in the national neonatal screening programme: hyperphenylalaninemia and congenital hypothyroidism since 1978, congenital adrenal hyperplasia since 1996, drepanocytosis among children potentially at risk (African and West Indian) first introduced in the French West Indies and Guyana then in metropolitan France, and cystic fibrosis since 2002. Neonatal screening for toxoplasmosis is not included as it is only justified under specific circumstances and is not part of the AFDPHE mass screening programme[v]. Cystic fibrosis is a congenital autosomal-recessive disorder with a relatively high rate of prevalence (1/4600 births). The screening test measures the dose of immunoreactive trypsinogen in blood serum. The screening test is performed 3 or 4 days after birth and measures the IRT (immunoreactive trypsine) level in the blood. A few drops of blood, are collected from the baby's heel on Guthrie paper. A second sample is used for DNA analysis in order to confirm the diagnosis and determine the form of cystic fibrosis present. In the case of elevated IRT values (> 65µg/L), the diagnosis is validated by a search for mutations on the '*cystic fibrosis transmembrane conductance regulator channel*' (*CFTR*) gene. This search examines approximately 30 potential mutations covering 90% of those most frequently observed in France, the most frequent (70%) being the *F508del* mutation. A sweat test is then prescribed to verify the disease's phenotypic expression (mutation penetration). A sweat chloride concentration level higher than 60 mmol / L is considered abnormal. In the case of a positive diagnosis, the infant is referred to a Resource and Expertise Centre for Cystic Fibrosis (Centre de Resources et de Compétences pour la Mucoviscidose: CRCM) for the provision of global multidisciplinary care associating a specialised paediatrician, paediatric nurse, physiotherapist, nutritionist, psychologist and a geneticist biologist. The aim is thus to ensure the parents are informed, to provide advice for healthy living, avoid infections and regularly monitor the child.

The search for mutations on the *CFTR* gene permits diagnosis confirmation following a positive sweat test (ST) and provides information on possible clinico-genetic correlations. To facilitate genotype-phenotype correlations, mutations are grouped into six classes according to the type of abnormalities in the CFTR protein. These classes are defined according to data obtained by the *in vitro* study of CFTR mutants. The deterioration is considered severe if no functional CFTR protein is produced (classes I, II, III), and moderate or '*mild'* otherwise (classes IV, V, VI). In the case of compound heterozygosity, the mild mutations are dominant with respect to severe mutations. The discovery of the *CFTR* gene has thus permitted the diagnosis of cystic fibrosis with mild, late onset clinical symptoms even after negative sweat test results. Authentic cases of cystic fibrosis with negative sweat tests have already been described and can now be confirmed with the advent of molecular biology.

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 Trypsine (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 dissemination of CF NBS has not been homogeneous and has been implemented with variations according to country, region or province. Cases of noncompliance with the Wilson and Jungner criteria cited above have appeared as a result of technological advances and medical benefits that have successfully enrolled others to the cause. In effect, neonatal screening for cystic fibrosis (CF NBS) fails to comply with the Wilson and Jungner criterion stating that neonatal screening should lead to an effective curative treatment. It implies that treatment would permit affected neonates to be brought back to normal health, yet to date there exists no specific curative treatment for cystic fibrosis even if the utility of screening is increasingly based on solid medical arguments (if one adheres to professional literature written by reputed experts in cystic fibrosis). These experts are all globally favourable to the principal of mass screening, but somewhat sensitive to its quality, technological advances and the new diagnostic and prognostic dilemmas generated by its implementation (Munck, Dhont, Sahler, and al. (2008).

The bioethical questions regarding CF NBS and its validity

The CF NBS debate remains heated on both sides of the Atlantic, both in America and northern Europe. This is confirmed by the quantity and profundity of publications in specialised paediatric journals reviewing the Wilson and Jungner criteria and the emergence of new screening criteria over the past forty years (see the in-depth evaluation by Andermann A, et alii, 2008), and the time and efforts invested in creating a new set of recommendations and guidelines aimed at optimising procedures (Comeau, et al. 2007). The course followed by this literature testifies to the work of convergence and aggregation achieved through the intermediary of consensus conferences (Farrell PM et alii, 2008). Concerning the benefits of neonatal screening for CF patients, if it appears impossible today to conduct a scientifically rigorous study proving that early diagnosis increases patients' life expectancy, an improvement in nutritional and respiratory states can be confirmed, at least in the first ten years of a child's life. It also demonstrates that neonatal screening eliminates trial and error diagnoses, costly for the health system and highly stress provoking for the families, and favours the optimal organisation of care for all those affected. As for the biological marker used in screening, its sensitivity has been considerably improved by associating it with a DNA analysis to search for mutations on the cystic fibrosis gene (*CFTR*). Introducing molecular biology techniques in a neonatal screening strategy, however, gives rise to a certain number of problems.

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; critical;
- the National Ethics Advisory Committee [vi] (Comité Consultatif National d'Ethique, (CCNE), 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 mediatising 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* (Latour, 2005),
- 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'.

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. 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'* (Pae: 7), 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 terminated the experimental NBS programme launched in 1989 by the AFDPHE.

CF NBS *supporters*, including the biomedical teams that pioneered NBS in Normandy en 1985 (Travert and Wursteisen, 1999), in Brittany in 1988 (Vailly, 2004) 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?'* (focus group 4). These pioneers remember a by-gone age in where 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 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' (Ardaillou and Le Gall, 2007). 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. Pioneers in the field expressed the opinion that the dispute seemed to be out of touch. 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 fool-proof 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 (2009), 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'* (Pae: 11). 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'* (CCNE, *In* Avis 97, *op. cit*, page 10).

Table: Those critical of and in favour of CF NBS in France

Actors	Reasons for taking a stand against screening
Critical * a minority of geneticists * High Authority for Health (HAS) * National Consultative Ethics Committee (CCNE)	* the programme's lack of stability and assurance in terms of balance between advantages/disadvantages. * the lack of scientific proof from a medical point of view concerning the benefits for the patient * the screening test used is insufficiently specific and generates false-positives. The diagnosis announcement is a source of anxiety for the parents and prognostics remain deeply uncertain.
Favourable	

* the French Association for the Diagnosis and Prevention of Child Handicap (AFDPHE) * the CF NBS pioneers in Brittany, favourable *paediatricians, geneticists, biologists, for the most part working in RECCF *Vaincre La Mucoviscidose, and patient associations	* the benefits of early treatment in a specialised centre favouring the extension of life expectancy through continuous monitoring and the prevention of complications by the rapid treatment of infections, respiratory physiotherapy and lifestyle management * the secondary diagnosis of heterozygosity (healthy carrier that can transmit the disease) in both parents permitting access to prenatal diagnosis in subsequent pregnancies * the setting up of an extended family enquiry to search for potential heterozygote carriers so that they can be informed. * permits taking advantage of the national political consensus between the actors concerned and the pioneer position held by France on the international NBS scene to disseminate the technology in other countries * the distribution of activities and burdens, between professionals within certified, durable RECCF * an increase in collective skills for the RECF teams delivering an early, global care supply

It has created dissent among health professionals with the eruption of heated disputes between biologists, geneticists and paediatricians, between field clinicians and research laboratory staff. Beyond the scientific arguments and competing hypotheses concerning mass neonatal screening, we note an invisible though sensitive split between those upholding elevated meta-principles, those using persuasive arguments to justify treatment practices, and those lobbying to obtain perennial financing for clinical research and the creation multi-disciplinary structures. These different groups are manifest around organisations and networks, both national and international, but equally invisible in the form of pressure groups advocating the perpetuation or abandonment CF NBS. A paediatric clinician, considered as an expert and entrepreneur in the field, summarises this complex situation:

> "As a professional involved in patient care, the implementation and generalisation of systematic neonatal cystic fibrosis screening in France and advances in screening methods that I sincerely hope for, I am aware of existing ambiguities. I am a firm believer in the benefits of neonatal screening but I'm also aware that this belief is not based on indisputable scientific proof concerning the extent and nature of the value it adds. I am equally fully aware that professionals, including clinicians and researchers by necessity always develop rational arguments that, not surprisingly, are in perfect coherence with inexpressible desires strongly related to their professional interests" (Extract from correspondence with the authors).

On one hand, the scientific discovery of biomedical entities (*CFTR* genes), incorporated into systematic screening equipment and policies, provides new opportunities for clinical practice. On the other hand, CF delimitations and nosological categories, redefined following advances made by specialists in contact with patients and their families, have fuelled the debate regarding the causes of CF and possible curative treatments. *In fine,* they have contributed in opening up new avenues of questioning for molecular biological research, genetics and also clinical medicine.

The interviews carried out for this research clearly demonstrated that, in broaching the diagnosis announcement procedure and its associated torments, health professionals questioned the validity of NBS and were aware of the controversies. Within the restricted sphere of cystic fibrosis, and although present in the minds of the professionals concerned, this question of validity appears to be in the process of being resolved. A panel of practitioners concluded that research on CF NBS had established that the benefits outweighed the risks and more especially, that screening programmes should be organised and controlled, implicitly suggesting the need for medical management (Grosse, Boyle, et alii, 2004). One of the pioneering practitioners in the field, highly reputed in North American academia, emphasised the importance of shifting the focus from endless debates on 'should we screen?' to 'how should we screen' (Farrell, 2004). He insisted that it was high time to become proactive by renewing the focus on prevention as rapidly as possible in order to provide a more appropriate and individualised therapeutic approach: "This new era is also characterized by the predominantly ambulatory care, rather than recurrent hospitalizations, and a fundamentally pre-emptive philosophy in which we strive to prevent both malnutrition and chronic infections through routine clinical management. I want to emphasize that this does not necessarily mean more treatment but, rather, more appropriate treatment and potentially less of a therapeutic burden for children and their parents" (Farrell, et al., 2007). The same author suggested that, both beyond and in addition to the clinical argument, the debate should be oriented towards fundamental human rights as one of the corner-stones of current and future good biomedical practice in an attempt to ease the tensions surrounding the diagnosis 'odyssey' for parents and health professionals alike (Farrell, 2008).

The incorporation of systematic screening technologies in the global care of the pathology has resulted in a paradigmatic shift in therapeutic strategy from the primary care of sick individuals to the preventive care of pre-symptomatic individuals (Farrell, 2008). The indirect consequence is that the nature and configuration of clinical practice is profoundly affected; nosology and etiology, transformed by biomedical presuppositions, instrumentation and biomedical entities, can no longer provide stable systems of reference. The diagnosis and treatment of rare diseases is singular in that the entities represented have an uncertain topology. How can objectivity be maintained in a diagnosis announcement based on two legitimate sources of proof; the clinical examination of an asymptomatic patient and the difference between the patients' situation and biomedical data? The combination of screening technologies in full expansion and clinical practice guidelines for disease progression totally reconfigure the probative process on which the diagnosis is based. Finally, this probative process is further altered in the case of borderline forms of CF characterised by equivocal results, uncertain clinical judgments, the search for mutations and complex prognostics.

We have thus presented a first review of a particular regime of conciliation (a) between the expanding field of biomedicine and the space in which it is spreading, and also (b) between the entry into mass genetics and the question of individual consent to genetic testing and population management. For its advocators, the first step in the process of legitimising screening can be described as a '*credibility-investment*' in the sense understood by B, Latour and S, Woolgar (1979). The interest in the screening controversy (and the paradox is only on the surface) lies in giving strength to the terms and convictions. Along the way, it provides the dynamics on which to base public policy and technology dissemination. It serves to justify drawing positively screened neonates and their families out towards certified specialist centres (the RECCF) for an early, global care regimen (Vailly, 2011), and its justification in terms of its structuring and inscription in the institutional hospital environment. In a certain manner, this novel configuration has created a breach in professional bureaucracy by experimenting

new statuses and organisational arrangements focused on a serious medical condition. It has introduced original methods simultaneously founded on multidisciplinarity, steering between healthcare entities and external entities in networking mode. In fact, it is the actors themselves that construct legitimacy for a new form of clinical experience that distances them from curative care and transforms them into co-managers of affected children and their parents' life stories (Langeard & Minguet et alii, 2011, p. 92).

Factors contributing to the stabilisation of institutional arrangements

The driving forces behind the production of institutional arrangements and their stabilisation to allow collective action can be reconstituted in the light of the four dimensions used in the analysis grid, and the theoretical perspective put forward. New screening technologies transform the clinical process design. Modified work practices affecting diagnostics, prognostics and therapeutic strategies do not only have a mediating effect on clinical activities they also have an impact on organisational realities. The sequence of activities, the temporal and spatial redefinitions (for example, emergency criteria use of premises and coordination between the networks' internal and external services) and norms generated are all products of this socio-material configuration. But, the central role of controversy, the questioning of probative system and the unstable status of mutations and biomedical entities are notably absent of the socio-material configuration perspective in the shaping of norms and collective action (Orlikowski and Scott 2008, Leonardi and Barley. 2008, 2010).

Table 2: dimensions of the socio-material configuration and problematic situations

Situations **Dimensions**	**Screening programme**	**Screening controversies**
Institutional	Multidisciplinary coordination	Insufficient proof mechanisms
Techno-scientific	Reshaping the diagnostic sequence	Prevention for pre-symptomatic individuals
Regulatory	Extension of abnormality Early treatment regimens	Borderline forms and heterozygosity Clinical practices guidelines
Socio-professional	Reworking of paediatric work	Conciliation between macro (quantitative development of neonatal screening) and micro (individual consent)

The hospital and specialised care network (the institutional dimension) are the setting for the multiplication of points of contact between professions, internal and external resources, established principles and problematic situations. Our study conducted among healthcare teams reveal new professional practices demanding transversal, flexible, multidisciplinary approaches that inevitably come up against the compartmentalized forms of hospital bureaucracy. A public health policy such as this and its instrumentation was legitimized because it followed the lines of local clinical practice and contributed to allowing the

existence of minority identities (as orphan sickness patients), revealing a medical speciality and bringing together a hybrid interdisciplinary community structure combining health care members, patients and their families, and patient associations. Since their legalisation and institutionalisation within the general hospital, the challenge facing these specialised centres resides in the recognition of specialist care for this chronic disease (among others) and the implementation of various integrating mechanisms at internal level (to obtain human and material resources) and external level (regarding anxious and insistent requests from patients and associations). The profession thus no longer hesitates in attributing itself the title of French 'model' in the interdisciplinary organisation of care for chronic and/or rare diseases and the introduction of schemes to improve the quality of care.

At techno-scientific level (the second dimension), screening has introduced scientific knowledge (genetics, molecular biology, prevalence and life expectancy statistics) equipment (neonatal screening tests, traceability, genetic mutation kits), and norms (cut-off values) that have contributed to the reinforcement, standardization and approval of procedures and temporal scansions. At organisational level, screening results profoundly affect the flow and temporality of the diagnosis announcement process given the neonate's genetic status. To summarise: (1) generalised screening gives rise to diagnostic uncertainty, (2) encourages the development of early treatment regimens and the reorganisation of the care supply, (3) contributes in the revision of paediatric professionalism by legitimizing their role as co-managers of patients and families life histories as part of the therapeutic agreement. As an indirect consequence, the side effects of detecting genetic anomalies contribute to the emergence of previously unknown health statuses. We observed its significant progression in relation to borderline and moderate forms of CF through the interconnection between screening and the discovery of enigmatic cases. The following examples illustrate the multiplication of categories to describe states between 'healthy' and 'sick'; 'healthy carrier', 'healthy but suspect carrier', healthy but suspect', 'sick but probably from a mild form', or even 'healthy carrier' likely to become 'sick'. We will describe the multiplication and variability of terms to define clinical states as denominating. Opening up the field of possibilities generates definitional, classificatory and *in fine*, decisional disputes that in turn multiply the number of clinical states situated between the normal and the pathological. An increasing number of phenotypically healthy, asymptomatic individuals find themselves transformed into persons 'genetically at risk' or 'future patients' (Rose, 2009) or "patients in waiting"(Timmermans and Buchbinder, 2010), with the risk of creating a sort of asymptomatic heterozygotic patient register.

The third 'regulatory' dimension reveals a new form of articulation between neonatal screening and diagnostic procedures simultaneously instituted on the expansion of medical normality/abnormality criteria and consequently leading to the creation of norms. Healthcare teams independently produce new norms for borderline or moderate forms of the disease associated with 'over-diagnosis' at birth for example. The same teams are challenged by the 'labelling' of positively screened neonates and the concordance of nosographical definitions with the treatment/non-treatment of the same infants. With respect to the framework of reference and established protocols, acceptable arrangements are suspended with the emergence of problematic situations and ethical questions surrounding screening, and also the prolongation of life expectancy (the price to pay for the success of early treatment of patients and disease progression).

A second aspect of the stabilisation process is the production, dissemination and use of "good practice" clinical guidelines. In the case of cystic fibrosis, the physicians and professionals and patient parents have put considerable investment into the production and

diffusion of a body of diagnosis announcement procedure recommendations. The generalisation of CF NBS to the whole of France in 2002 was accompanied by recommendations regarding the provision of follow-up care for the affected child in specialised CF centres. It is in this very context of mass CF NBS that we were able to consider that clearly outlined and systematised diagnosis announcement procedures could represent a therapeutic advantage. The diagnosis announcement confirms the child's entry into the disease; it marks an alteration in the child's status hitherto identified as a 'sick child' in the eyes of the child concerned, in the eyes of the family and society in general. In other words, if the diagnosis announcement recommendations are embedded in a therapeutic project with a family and social dimension, but also in a broader more extensive context that constitutes the structuring elements of the provision of care for this rare chronic disease in the French context, the screening test and confirmatory diagnosis 'equip' the announcement procedure.

In the case of the RECCF teams, it clearly emerges that these standards of 'good practice' have become opportunities for collective action (Langeard and Minguet, 2009). Our study shows that, in a context of uncertainty characterised by the absence of strict scientific norms and reduced or random clinical practices, the actors elaborate their own cognitive criteria. These recommandations were for the large part established by the CF Centres in collaboration with the central authorities and built up into a common base so as to bring different professional segments into convergence. It should be noted that this is already the case in the field of oncology (Castel, 2009), and insurance medicine in the Netherlands (Berg, Horstman, Plass, Van Heusden, 2000). Faced with diagnostic typology and prognostic uncertainty, health professionals react by partly relying on announcement recommendations. They seek to domesticate rather than avoid these uncertainties by creating imperative knowledge from their own clinical practice together with formal reflexivity (staffing) and informal exchanges concerning experiences to evaluate and validate. There are situations, however, in which standardising practice proves difficult to achieve because it is dealing with a new domain with imprecise diagnosis and prognostic techniques and more especially, in health situations whose singularity place them beyond any thought of total objectivity. The qualification of uncertainties, in part generated during the course of clinical activities, becomes a central object for professionals working with these genetic practices. As a result, the framing, the content, and the modalities of medical work are all transformed.

The fourth 'socio-professional' dimension is characterised by the reworking of skills, engagements and the fundamental bases of paediatric work. This is what we have referred to as the system of conciliation between macro (quantitative development of neonatal screening) and micro (individual consent) levels that govern the socio-professional space and the clinical microsystems in RECCF. 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.

In our study, these doubts and concerns over the balance between costs and benefits and the revisable relationship between risk and benefits and by extension the dilemmas addressed to public health policy makers, are recurrent and preponderant. We are faced with an

interaction between economic factors (rationalisation, restriction, profitability) and non-economic factors (coordination organised between structures, inter-disciplinary cooperation within CF Centre teams, educational therapy to enable families to alter their views and practices in the face of CF). The question of CF NBS and diagnosis announcement recommendations aimed at improving the provision of care is situated at the crossroads between (1) the market and the cost of treatment, or the physical price, (2) the professional skills and responsibilities concerning the work of the medical teams, or the price of a high level commitment to a worthwhile cause (3) personal values and morals associated with childhood, or the symbolic price.

To conclude

The chosen example of CF NBS raises other issues in addition to simply reconciling biomedical research and evidence-based medicine for a rare disease, an area in which presuppositions (on the benefits of all screening and genetic testing), convictions (the benefits of early treatment) and values (related to subjects' autonomy and the place of health, the quality of life in rich countries) are intertwined. We chose the socio-materiality approach as one in a palette of analytical formulas that allow us to advance in the study of these social laboratories and institutional arrangements.

The common dimension between these theoretical perspectives drawn up at the beginning of this article, is the rejection of the deterministic techno-scientific scenario and clinical medicine aligned with biomedical standards, or drawn into the genetic reductionism movement. The socio-material configuration that singularises the rapid development of neonatal screening, inseparable from the advances in paediatric work, is far removed not only from the reductionist version of genetics but also from an inflexible version of technology in the detection of genetic mutations or the identification of patients within a population and all it implies in terms of suspected threats to subjects' quality of life and autonomy (e.g Rabeharisoa, and Bourret, 2009). All these uncertainties find their reflection in disease and life perspectives and also, as is the case for this rare, life-threatening disease, the creation of subjects characterised by singular states and denominations. This form of medical work not only taxes the process of defining what can be classified as disease and abnormality but also health and normality. This singular work borrows from various sources of knowledge and equipment provided by genetics, molecular biology, statistics and longitudinal observation in the way of 'exploratory medicine' as highlighted by Rabeharisoa (2006).

Two lessons emerge from this. In the first place, this technology presents itself as a social construct; that is to say as the result of incessant configurations between scientific, technical, political and ethical dimensions in which the interactions between actors within and outside the biomedical arena are paramount. These interactions occur in socialising arenas bringing together the world of experimental research and healthcare teams, through media intervention and professional meetings where patient associations and health professionals mingle. In this sense, they constitute an 'enrichment of democracy' (Callon, Lascoumes, & Barthe, 2009).

In the second place, the bioethical stakes involved are closely linked with the dynamics that generate, revive or even modify the controversies. This is all the more striking in the case of cystic fibrosis, a serious, chronic pathology that shrouds the patient and his family for an entire lifetime. From disputes regarding disease definitions and categorisations to diagnostic uncertainty and the question of prenatal diagnosis through prenatal screening, there is no doubt that the massive development of mass screening and its' expected and unexpected side-effects are considerable. The configuration analysed above is seen as a project aimed at amalgamating biology and medicine. It is necessarily incomplete and in continuous

development, implying a constant realignment with laboratory advances and clinical practice around biomedical entities, health professionals and patients (Cambrosio et al., 2006). Even more so, in view of the numerous effects resulting from CF NBS, a cardinal question remains unanswered: is the aim of NBS to provide better access to care, to improve the quality of patient care or to eradicate the disease?

NOTES

[i] We thus estimate that at the age of 20, a patient has spent, on average, 2 years at the physiotherapist and devotes 3 hours per day on therapy. One can add to this the regular hospital consultations for monitoring and prevention purposes. One can imagine that such obligations in terms of treatment can be extremely difficult for persons suffering from CF held to respect the constraints of school, sports, professional or private life: CCNE, 2007.

[ii] "Vaincre la Mucoviscidose" is a non-profit organization created in 1965 by parents of children with CF. The foundation follows 4 goals : Cure CF by helping and financing research in France and all around Europe, Treat right now by improving health care, Improve quality of life in order to make a life with CF more acceptable and bearable, Alert on the gravity of CF by communicating toward the public in general and towards parents and family affected with CF.

[iii] Fondation de France is a private-law body, founded to encourage the development of philanthropy, helping vulnerable individuals, nurturing the mind, acting for the environment. Fondation de France is mainly known for housing and managing funds and foundations, and collecting resources to support social innovation.

[iv] "Recommandations pour l'annonce du diagnostic de mucoviscidose après dépistage neonatal", (Guidelines for cystic fibrosis diagnosis announcement following neonatal screening), diffused in 2003 under the aegis of 'Vaincre la Mucoviscidose', [http://www.vaincrelamuco.org/ewb_pages/a/annonce-diagnostic.php].

[v] In 2010, 853345 neonates have been screened in France. The screening tests allowed to detect 940 sick children. Source/ AFDPHE.

[vi] 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.'

REFERENCES

Allen, D.B., and Farrell, PM. (1996). 'Newborn screening: Principles and Practice', *Advances in Pediatrics,* 43: pp. 231-270.

Ameisen, J.C. et al., (2008), *Tests génétiques : questions scientifiques, médicales et sociétales*, Éditions de l'Inserm, 351 pages.

Andermann, A. Blancquaert, I. Beauchamp, S. and V. Déry (2008), 'Revisiting Wilson and Jungner in the genomic age: a review of screening criteria over the past 40 years', *Bull World Health Organ.*86(4), pp. 317-9.

Ardaillou, R., and Le Gall J.-Y. (2007), 'Le dépistage néonatal généralisé par des tests d'analyse biologique', *Gynécologie Obstétrique & Fertilité*, 35, pp. 367–374.

Barad, K. (2003), 'Posthumanist Performativity: Toward an Understanding of How Matter Comes to Matter', *Signs: Journal of Women in Culture and Society*, 28(3), pp. 801-831.

Berg M., Horstman K., Plass S., Van Heusden M., (2000), 'Guidelines, professionals and the production of objectivity: standardization and the professionalism of insurance medicine', *Sociology of Health & Illness*, 22, pp. 765-791.

Bourret, P. (2005), 'BRCA Patients and Clinical Collectives: New Configurations of Action in Cancer Genetics Practices', *Social Studies of Science*, 35(1), pp. 41-68.

Cam, P. and C. Faquet (2008), Les pratiques d'annonce du diagnostic de mucoviscidose. Rapport commenté de l'enquête par questionnaire réalisée auprès des Centres de Ressources et de Compétences de la Mucoviscidose (CRCM), Available at http://www.centre-reference-muco-nantes.fr/downloads/AnnDiag/AnnDiag_Rapport1.pdf.

Callon, M. (1986), 'Some elements of a sociology of translation: Domestication of the scallops and the fishermen of Saint Brieuc Bay', in J. Law (ed.) *Power, action and belief: A new sociology of knowledge?*, pp. 196–233. London: Routledge.

Callon, M. Lascoumes, P. and Y. Barthe (2009), *Acting in an Uncertain World. An Essay on Technical Democracy*, Cambridge: MIT Press.

Cambrosio, A., Keating, P., Schlich, T., & Weisz, G. (2006). 'Regulatory objectivity and the generation and management of evidence in medicine', Social Science & Medicine, 63(1), pp. 189- 199.

Castel, P., (2009). 'What's Behind a Guideline? Authority, Competition and Collaboration in the French Oncology Sector', *Social Studies of Science*, 39(5), 743-764.

Clarke, A. Shim, K. Shostak, S. and A. Nelson (2009) Biomedicalizing Genetic Health, Diseases and Identities. In P. Atkinson, P. Glasner and M. Lock, (eds) *Handbook of Genetics and Society: Mapping the New Genomic Era*. London: Routledge, pp. 21-40.

Clarke, A. Shim, K. Mamo, L. Fosket, J. and J. Fisman (2003). 'Biomedicalization: Technoscientific transformations of health, illness, and US medecine', *American Sociological Review*, 68, 2, pp. 161-185.

Comeau, AM. Accurso, FJ. White, TB. and al. (2007), 'Guidelines of implementation of cystic fibrosis newborn screening programs: cystic fibrosis foundation workshop report', *Pediatrics*, 119, pp. 495–518.

Farrell, PM. Rosenstein, BJ. White, TB. Accurso, FJ. Castellani, C. Cutting, GR. Durie, PR. Legrys, VA. Massie, J. Parad, RB. Rock, MJ. and PW3rd Campbell (2008), 'Guidelines for diagnosis of cystic fibrosis in newborns through older adults: Cystic Fibrosis Foundation consensus report', *Journal of Pediatics.*,153(2), pp. 4-14.

Farrell, P.M. (2004), 'Cystic fibrosis newborn screening: shifting the key question from "should we screen" to "how should we screen?', *Pediatrics,* 113, pp. 1811-1813.

Farrell, P.M. (2008), 'Is newborn screening for cystic fibrosis a basic human right?', *Journal of Cystic Fibrosis,* 7(3), pp. 262-265.

Farrell, P. M. (2007), 'The Meaning of "Early" Diagnosis in a New Era of Cystic Fibrosis Care', *Pediatrics,* 119(1): pp. 156 – 157.

Freese, J. and S. Shostak (2009), 'Genetics and Social Inquiry', *Annual Review of Sociology, 35*, pp. 107–28.

Freese, J. (2008), 'Genetics and the Social Science Explanation of Individual Outcomes', *American Journal of Sociology, 114*, pp. 1- 35.

Grosse, SD. Boyle, CA. Botkin, JR. and al. (2004), 'Newborn screening for cystic fibrosis: evaluation of benefits and risks and recommendations for state newborn screening programs', *MMWR Recomm Rep.*; 53(RR-13): pp. 1–36.

Hedgecoe, A. (2010), 'Bioethics and the Reinforcement of Socio-technical Expectations', *Social Studies of Science,* Vol. 40, No. 2, pp. 163-186.

Hedgecoe, A. (2006), 'Pharmacogenetics as Alien Science: Alzheimer's, core sets, and expectations', *Social Studies of Science,* 36(5), pp. 723-752.

Keating, P. and Cambrosio, A. (2003), *Biomedical Platforms: Realigning the Normal and the Pathological in Late-Twentieth Century Medicine,* Cambridge, MA: MIT Press.

Knorr Cetina, K. (1997), 'Sociality with objects: Social relations in postsocial knowledge societies', *Theory, Culture & Society,* 14/4: pp. 1–30.

Langeard, C and G. Minguet (2009), Recommandations pour l'annonce du diagnostic de la mucoviscidose. Rapport commenté de l'enquête dans les CRCM. Available at http://www.centre-reference-muco-nantes.fr/downloads/AnnDiag/AnnDiag_Synthese_Result_Oct2010.pdf.

Langeard, C Minguet, G Guéganton, L Cam, P Faquet, C Lombrail, P and G. Rault (2011), 'L'expérience professionnelle du médecin hospitalier à l'épreuve du dépistage : le cas de l'annonce du diagnostic de la mucoviscidose', *Revue Française des Affaires Sociales*, n°2-3, pp. 80 -102.

Latour, B. (1994), 'On technical mediation: Philosophy, sociology, geneaology', *Common Knowledge,* 3/2, pp. 29–64.

Latour, B. (2005), *Reassembling the social: An introduction to actor–network theory.* Oxford: Oxford University Press.

Latour, B, and S. Woolgar (1979), *Laboratory Life: The Social Construction of Scientific Facts*, London, Beverly Hills, Sage Publications.

Leonardi, P.M. and S.R. Barley (2008), 'Materiality and change: Challenges to building better theory about technology and organizing', *Information and Organization*, 18(3), pp. 159-176.

Mol, A. (2002), *The body multiple: Ontology in medical practice.* Durham, NC: Duke University Press.

Munck, A. Dhont, JL. Sahler, C. and al. (2008), 'Implementation of the French nationwide cystic fibrosis newborn screening program', *Journal of Pediatrics*, 153, pp. 228-33.

Orlikowski, W.J. and S.V. Scott (2008), 'Sociomateriality: Challenging the separation of technology, work and organization', *The Academy of Management Annals*, 2(1), pp. 433-474.

Rabeharisoa, V. and P. Bourret (2009), 'Staging and Weighting Evidence in Biomedicine: Comparing Two Clinical Practices in Cancer Genetics and Psychiatric Genetics', *Social Studies of Science*, 39(6), pp. 91-715.

Rose N (2009) Normality and pathology in a biomedical age. *Sociological Review* 57(Suppl. 2) 66-83.

Sermet-Gaudelus, I. Munck, A. Rota, M. and al. (2010), 'Recommandations françaises pour la réalisation et l'interprétation du test de la sueur dans le cadre du dépistage néonatal de la mucoviscidose', *Archives de pédiatrie*, 17(9), pp. 1349-1358.

Suchman, L.A. (2007), *Human–machine reconfigurations: Plans and situated actions.* Cambridge: Cambridge University Press.

Timmermans, S. and Buchbinder M (2010) 'Patients-in-waiting: Living between sickness and health in the genomics era'. *Journal of Health and Social Behavior* 51(4): 408-23.

Vailly, J. (2004), « Une politique de dépistage *a priori*. Le dépistage néonatal de la mucoviscidose en Bretagne », *Sciences Sociales et Santé*, 22(4), pp. 35-60.

Vailly, J. (2008), 'The expansion of abnormality and the biomedical norm: neonatal screening, prenatal diagnosis and cystic fibrosis in France', *Social Science & Medicine*, 66(12), pp. 2532-2543.

Vailly J., (2007), 'Dépister les nouveau-nés. Évolutions, débats et consensus', *Médecine /Sciences*, 23(3), pp. 323-326.

Vailly, J. (2006), 'Genetic screening as a technique of government: the case of neonatal screening for cystic fibrosis in France', *Social science and medicine*, 63(12), pp. 3092-3101.

Vailly, J. (2011), *Naissance d'une politique de la génétique*. Paris, Puf.

Wilson, J.M.G. and F. Jungner (1968), 'Principles and practice of screening for disease', *Public Health Papers*, Geneva: World Health Organization, 34.

Institutional reports

Comité Consultatif National d'Éthique (CCNE), (2007), *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*, 7 pages.

Haute Autorité de Santé (HAS) (2009), *Le dépistage néonatal systématique de la mucoviscidose en France : état des lieux et perspectives après 5 ans de fonctionnement*, 174 pages.