

Elsevier Editorial System(tm) for Social Science & Medicine
Manuscript Draft

Manuscript Number:

Title: Diagnosis Challenged by Genetics: The Case of Cystic Fibrosis in France.

Article Type: Special Issue: Sociology of Diagnosis

Section/Category: Medical Sociology

Keywords: diagnosis; cystic fibrosis; neonatal screening; France; announcement; uncertainty; ethical dilemmas; processes

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Manuscript Region of Origin: FRANCE

Diagnosis Challenged by Genetics: The Case of Cystic Fibrosis in France.

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Abstract

In what way and to what extent can a disease diagnosis be transformed by biomedical technology such as the systematic screening of cystic fibrosis in neonates? This question is explored by means of a case study investigating the diagnostic processes and practices for a rare, lethal, genetically transmitted congenital disease whose clinical expressions and prognostic significance are varied and complex. Since 2002, the Public Authorities instituted a systematic Neonatal Cystic Fibrosis Screening Programme (CF NBS) in France.

In this new context, our research contribution aims to identify and describe changes in CF diagnosis and diagnosis announcement practices occasioned by the introduction of mass screening. The diagnosis is considered as a process; a sequence of events leading from presumption to proof that is progressively established during the course of the announcement process. In the case of cystic fibrosis, however, screening can reveal ‘intermediary’ or borderline’ cases that generate diagnostic uncertainty either because tests fail to provide categorical proof of the disease, or because its clinical form does not correspond to existing medical delimitations. Cases such as these result in a diagnostic dilemma since its prognostic significance for the patient is totally ignored. In this respect, CF NBS leads to the question of predictive medicine in the form of prenatal and pre-implantation diagnosis, a question that raises numerous ethical controversies. Our conclusions reveal three concurrent trends: parents, neonates and health professionals now share the principle of diagnostic uncertainty; changes in the information content resulting from the screening test not only restructures the diagnosis announcement consultation but also the way the disease is experienced; advances in the field of genetics contributing to early diagnosis raises new questions as to the ultimate aim of screening relative to the disease. Results are based on a research programme conducted in two phases: a questionnaire survey among the 37 specialised CF Centres in France followed by 28 one-to-one interviews and 8 *focus group* sessions within 15 CF Centres. In total, 34 completed questionnaires were collected and 24 physicians, 14 coordinating nurses (CN), 4 psychologists and 2 physiotherapists were interviewed.

Keywords : diagnosis; cystic fibrosis; neonatal screening; France ; announcement; uncertainty; ethical dilemmas; processes.

Introduction

Among the rare, ‘orphan’ diseases as designated by medical terminology, cystic fibrosis is in a singular position due to its relative frequency and complexity. It is the chronic autosomal-recessive disease with the highest rate of incidence (1/2500 neonates) in populations of European origin and its clinical expressions and outcomes are extremely diverse and complex. At individual level, it is therefore extremely difficult to predict the course or outcome of the disease at diagnosis. In 2010, curative treatments for cystic fibrosis have yet to be found; existing treatments are symptomatic or preventive and essentially involve respiratory, digestive and nutritional care. Since 2002, however, the French public authorities instituted the systematic neonatal screening of cystic fibrosis (CF NBS) (Vailly, 2006). An understanding of the cystic fibrosis diagnosis process requires an analysis of its close correlation with screening, defended since the 1980’s by biomedical actors in Brittany (Vailly, 2004) who argue in favour of early CF diagnosis associated with early preventive care in a specialised medical centre. As a result, regional policy in Brittany, supported by various arguments based on the intimate conviction of the actors involved rather than on concrete scientific proof, elevated cystic fibrosis to the ranks of a social problem on the political agenda (*Ibid.*).

CF NBS as a biomedical technology: regulations and their effects on the diagnosis

Mass CF NBS, as an *innovative biomedical technology*, defined as novel configuration (material, scientific, institutional, epistemological) characterised by new entities (biomarkers, cellular genetic signature, genetic mutations) whose genesis, exploration and representation stem from the combination of scientific research in biological and molecular processes and the pathological signs of disease, has become the source of numerous controversies. In the first place, the screening eligibility criteria established by Wilson and Jungner (1968) are not entirely respected since, in the case of cystic fibrosis there is no ‘accepted curative treatment’. Secondly, CF NBS generates uncertainty (Fox, 2000, Callon, Lascoumes, Barthe, 2001) and in so doing raises a number of questions in the bioethical domain. The institution and standardisation of the screening programme equally raises a number of questions concerning its effectiveness as a public health policy (benefits against risks), its scientific validity (the role of endorsing scientific proof in biomedicine) and the way therapeutic approach and foetal selection are articulated (life science policy), (Vailly, 2007, 2008).

The implementation of CF NBS in France resulted in the progressive establishment of Resource and Expertise Centres for Cystic Fibrosis (Centres de Ressources et de Compétences de la Mucoviscidose), charged with managing the diagnosis announcement following the screening test, effectuating the second tier diagnostic test known as the ‘sweat test’ and coordinating patient care. 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 Centre health professionals were thus suddenly exposed to decision-making processes concerning both diagnostics and prognostics. These decisive factors affect: (a) the diagnosis as the choice of terms used to express the presence of an incurable disease inevitably projects an idea of the type of life the patient can be expected to lead and (b), the

1 prognosis, in predicting clinical symptoms, outcomes and causes and the effects of living with
2 this orphan disease in society.

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4 Depending on the case at hand, the diagnosis announcement is accompanied by prognostic
5 considerations that will forge the state of uncertainty with which patients and their families
6 will have to evolve throughout their lives. In terms of probabilistic reasoning, this new mode
7 of managing the diagnosis announcement inaugurates a major change in medical conduct and
8 the provision of care. In sharing the premise of uncertainty with patients, parents and
9 extended families, cystic fibrosis specialists now openly recognize the limits of a medical
10 practice exclusively and conventionally based on the concept of eradication. This has equally
11 been observed in other medical domains. In her monograph of an intensive care unit for
12 neonates, Jessica Mesman explores the changes taking place at the ‘interface of diagnostics
13 and prognostics, of actors and technology’ and the way they combine and cooperate. She
14 argues that ethical borderlines are fluctuating and that new technological developments
15 inevitably give rise to new uncertainties embarking patients, families and health professionals
16 on a trajectory that is all but linear (Mesman, 2008). This observed shift in the founding
17 principles of medicine can be seen in other studies conducted on a variety of specialities such
18 as oncology (Ménoret, 2007), oncogenetics (Bourret, 2005), or even psychiatric genetics
19 (Rabeharisoa & Bourret, 2009). The analysis of predictive medicine highlights how genetics
20 has impacted the development of medical uncertainty and contributed in redefining the notion
21 of ‘patient’.
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27 The dynamics of this medical innovation consists in combining biology and medicine into a
28 hybridised form known as ‘biomedicalisation’ (Clarke et al, 2003). This concept conceals five
29 key underlying processes: (1) the politico-economic restructuring of the vast medical
30 continent; (2) the focus on health in itself and the development of biomedicine for risk
31 reduction and opportunistic disease prevention; (3) the progressive combination of science
32 and technology in biomedicine; (4) the changes in the way biomedical knowledge is
33 produced, delivered and consumed in the management of medical information; (5) a status
34 shift from individual identity to entity bearing new properties (molecularisation, implantation
35 among others) that all contribute in accessing new collective identities. The singularity of
36 biomedicalisation is its propensity to generate new medical norms and practices such as
37 prediction at the expense of prevention (prevention has become widespread with vaccination
38 or screening programmes whereas prediction remains at individual level), or even the
39 dissemination of procedures measuring relative risk factors (diagnosis based on the quantified
40 probability of disease). Besides positing the dissolution of the patient identity through the
41 process of geneticisation and probabilisation we equally suggest that the techno-sciences and
42 their equipment not only create, structure and constrain current health situations, but equally
43 transform them. As we will demonstrate below, CF NBS provides a good example of this
44 process in that it allows to us to trace the development and transformations constituting the
45 social world of cystic fibrosis.
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51 More centrally, biomedical screening technology with its effects on crucial activities such as
52 diagnostics, etiology, treatment, prognostics and finally the medical counsel given to families,
53 has become embedded in professional, institutional spaces. This translates into the
54 development of multiple points of convergence in the form of material infrastructures and
55 knowledge centres or ‘biomedical platforms’ (Keating and Cambrosio; 2003) composed of
56 norms, categories, classifications and conventions proper to a variety of social universes.
57 These authors use the term ‘regulatory objectivity’ to describe these mediatory and regulatory
58 mechanisms in which are formed novel hybrid combinations between medicine and biology,
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1 between normal physiological and pathological processes, between clinical practice and
2 research.

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4 When individuals make an appointment to consult a physician or a hospital specialist, they
5 voluntarily engage themselves on a trajectory leading to illness, or at the very least an
6 evaluation of their state of health. This process implies the existence of nosological categories
7 to permit the identification and naming of diseases. These categories, based on clinical
8 symptoms and cell morphology are now equally defined according to molecular markers. The
9 fundamental process of validating, adapting, redefining and disseminating the various
10 components underlying diagnostic categories for the benefit of health professionals is
11 regulated by approved institutional mechanisms known as consensus conferences. Their work
12 gives rise to 'mandatory clinical recommendations' or 'codes of good practice' (Castel,
13 Merle, 2002, Castel, 2009, Weisz, and ali, 2007).
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17 Over the last decades, new biomedical entities known as cell surface markers, have gained
18 increasing importance in the diagnosis, prognosis and treatment of a variety of diseases
19 (Cambrosio, Keating, Schlich, & Weisz, 2009). The first problem posed by introducing
20 molecular biology in the determination of cystic fibrosis was the choice of mutations to be
21 tested in view of finding a common denominator (Sarles & Dagorn, 2006). To this question of
22 strategy can be added a number of societal issues such as, obtaining informed parental
23 consent, the detection of healthy heterozygote carriers and extremely mild forms of the
24 disease, diagnostic uncertainty due to results that are difficult to interpret and the introduction
25 of genetic analysis techniques that considerably increase costs.
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28 *Method*

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31 This article is based on a research programme bringing together health professionals
32 (physicians, coordinating nurses (CN), geneticists, psychologists...), sociologists and
33 statisticians. The study entitled 'Factors favouring or limiting the implementation of practice
34 recommendations for CF diagnosis announcement following neonatal screening' jointly
35 financed by the French association 'Vaincre La Mucoviscidose' and the 'Fondation de
36 France', was launched in February 2008. It deals with health professionals' management of
37 the diagnosis announcement of a singular disease, cystic fibrosis and more specifically, the
38 correlation between advances in neonatal screening and the structuring of the diagnosis
39 announcement process. The neonatal screening test for cystic fibrosis is particularly worth
40 investigating in that it is a genetic disease detected in the first months of life and as a result,
41 poses the problem of determining how the disease's life cycle will evolve through time. It
42 raises the question of how to announce the diagnosis; a violent announcement at emotional
43 and relational level for all the actors, set within a singular framework. It is always a rare,
44 exceptional situation set in a medical context constrained by normalization criteria and
45 mechanisms, restructuring and the standardisation of the care supply. We show how during
46 the initial consultation, health professionals exposed to announcing the diagnosis to parents
47 and neonates attempt to render the uncertainty surrounding the future expression of the
48 disease acceptable in relation to this early diagnosis.
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55 **Insert 1: context and data**

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58 In order to study health professionals' attitudes and their relationships with the cystic
59 fibrosis diagnosis announcement recommendations, we chose to carry out our investigations
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1 in CF Centres in two phases: a quantitative phase that consisted in distributing a questionnaire
2 to all CF Centres in France; a qualitative phase involving one-to-one interviews and focus
3 group sessions among CF unit staff.

4 The study was thus conducted in several phases:

5 {1} It began with a questionnaire survey among 37 CF centres. Among these, 33 completed
6 the questionnaire. The published report was able to outline a table of announcement practices
7 based on a typology using three ideal-typical CF centre categories: (10 historical centres, 10
8 low-practice centres with limited resources, 14 high practice centres with considerable
9 resources) (Cam, Faquet, 2008).

10 {2} One-to-one interviews and focus group sessions were then conducted in the aim of
11 examining and documenting work practices within the different professional segments
12 (mainly physicians and coordinating nurses, and psychologists) confronted with the crucial
13 stage in the cystic fibrosis diagnosis announcement to the neonate's parents. Of the 37 CF
14 Centre teams in activity, 15 teams were approached. The same CF Centre typology was used
15 to ensure coherence and because it proved its validity in the correlation analysis between CF
16 Centre type and announcement recommendation protocol (Langeard, Minguet, 2009).

17 {3} The study is backed-up by documentary research and the systematic exploitation of
18 sociological and management publications as well as professional and academic publications
19 (medical, biological) specialised in cystic fibrosis and the field of recommendations. To this
20 literature can be added bioethical, media and legal publications on this topic since the 1990's.
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27 *The cystic fibrosis diagnosis embedded in the announcement procedure*

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29 In this article, the diagnosis is apprehended from the announcement procedure angle
30 (Figure 1) presented in four dimensions:

31 {1} *the seven phases of the procedure*

32 {2} *the crucial activities of coordination and cooperation* in situ (between the protagonists
33 concerned, hospital and external services, health professionals, families, parents associated to
34 the seven key phases.

35 {3} *the key actors* involved in each phase.

36 {4} *a list of critical points* that are not to be omitted if the consultation dynamics are not to be
37 penalised.

38 The announcement procedure is thus standardised in the form of clearly defined phases and
39 an emphasis on the proofs that enable to identify, diagnose, reveal and treat the disease.
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44 This analysis will first attempt to shed light on the way widespread CF NBS has modified the
45 diagnosis and announcement procedure. In the first place, neonatal screening generates
46 considerable upheaval in the organisation of medical professional practice in that presumptive
47 diagnosis precedes any medical examination. In other words, screening has supplanted
48 diagnoses established on the basis of clinical symptoms, difficult in the case of CF due to its
49 highly polymorphous symptomatology. More specifically, diagnosis is envisaged as an
50 integral process from presumption to proof, progressively established during the course of the
51 announcement process (part 1). Secondly, there are cases where the screening process
52 produces 'intermediary' or 'borderline' cases characterised by diagnostic uncertainty either
53 because the proof element is inconclusive, or because its clinical form does not correspond to
54 existing medical delimitations (part 2). This raises a diagnostic dilemma in that its prognostic
55 significance in terms of patient outcome is ignored. Cases of this kind question the validity of
56 predictive medicine as applied in prenatal and pre-implantation diagnostics; a question that
57 raises numerous ethical controversies (part 3). We will conclude with the proposition that an
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analysis of genetic disease diagnostics cannot overlook the need for serious reflexion on the principle of diagnostic uncertainty associated with screening technology, and all the more with mass-screening.

1. How the value of the diagnosis evolves during the course of the announcement process: from presumption to proof

1.1. Screening methodology (Figure 2)

Today, CF NBS is systematically carried on all neonates in France. It is effectuated on a few drops of dried blood taken on the third day of life. If the 'trypsinogen' enzyme rate falls above a pre-defined threshold, the same sample will be sent to a laboratory of molecular biology to detect CF related gene mutations (the screening test detects the 30 most frequent mutations and allows 87% of mutations to be detected). The diagnosis is then confirmed by a further biological test known as the 'sweat test' that measures chloride concentration in a sweat sample. A higher sweat chloride concentration rate than 60 mmol/l confirms the diagnosis of CF; at between 40 and 60 mmol/l it suggests the presence of CF and is thus repeated at regular intervals to eliminate doubt given the therapeutic and psychological consequences involved. In 90% of cases, molecular biology will either reveal an identical mutation on each allele (homozygote) or two different mutations (compound heterozygote). The aim of systematic cystic fibrosis screening aims at providing every positively diagnosed neonate with immediate access to care in line with a national care protocol.

The CF screening methodology has generated numerous diagnostic upheavals. It involves two successive analyses of dried blood samples effectuated on Guthrie paper at three days old: the immunoreactive trypsinogen (IRT) values and, providing the parents' informed consent has been obtained at maternity, a DNA analysis to search for the thirty most frequent gene mutations responsible for cystic fibrosis. Once the analysis effectuated, the Regional Association that centralises the results contacts a specialised CF Centre in three clearly defined situations:

1. The neonate has two gene mutations: CF diagnosis is confirmed by the sweat test. The two parents are then invited to discuss the affection and the provision of care.
2. The neonate presents one identified mutation: there is either a second mutation (not tested for by the detection kit) and the sweat test is abnormal leading to a positive CF diagnosis (1/11 risk), or the neonate is either a healthy heterozygote carrier in which case the sweat test will be normal. A supportive interview with the parents explains that their child is not ill but informs them of the interest in seeking genetic counselling.
3. The neonate has no detected gene mutations but the IRT value controlled again at 21 days remains above the cut-off value (40 $\mu\text{g/l}$): although the CF risk factor is low, a sweat test is requested.

In these three situations, the CF Centre specialist will convoke the family.

1.2. The organisational and professional consequences of presumptive diagnosis

Although the screening test results have no diagnostic value, they give rise to a high rate of presumption founded on the high probability of detecting cystic fibrosis. In effect, on receiving the results of the screening test, physicians identify two medical conditions prior to effectuating the sweat test that will confirm or invalidate the presumptive diagnosis following

1 the screening test. On the one side, the homozygotes carrying two identical gene mutations
2 generally associated with the rapid development of a serious form of cystic fibrosis, and on
3 the other, the heterozygotes whose medical status is considerably less serious.

4 The patient's previously designated medical status (homozygote/heterozygote) determines the
5 way in which the different phases of the announcement procedure will be apprehended and
6 deployed (Figure 1). Physicians tend to adjust their tone according to the patient's status, in
7 other words, according to diagnostic certainty or uncertainty. If it concerns "*heterozygotes, or*
8 *in other words 'possible false-positives', in that case our tone is much lighter...at least, more*
9 *optimistic...*" explains one physician. This is confirmed by another physician: "*If I'm sure it's*
10 *a case of cystic fibrosis, I'm not going to tell them 'There's nothing to worry about, we're just*
11 *going to verify'. I'm going to say, 'listen, I've got a result that needs confirming. I'll explain*
12 *everything tomorrow' [...]* But, on the other hand, if ever the IRT level is low and that there is
13 *only one mutation, I will be reassuring...*" The time lapse between the telephone call to the
14 parents and the first consultation is determined according to the patient's medical status that
15 in turn determines the degree of urgency. "*For those with heterozygote status, we say: 'We*
16 *don't need to see you this time, we'll see you next time'. But for those that are affected, we*
17 *imperatively have to make them come'. 'In the case of homozygotes, where we are certain*
18 *they are affected, we need to see them in priority. After that, come those with one mutation, or*
19 *10% risk and then those that have an elevated trypsinogen level at three weeks but the*
20 *probability of cystic fibrosis is very low, so they are...after that we organise ourselves*
21 *accordingly. The specialists fit them in according to their availability, but we try and see*
22 *those with the highest probability of having CF in priority.*" From the reception of the
23 screening test results, to the information content leading to presumption, will accordingly be
24 attached an optimistic/pessimistic discourse, a classification of sick/possibly sick patients and
25 a degree of urgency according to medical status. The time lapse between the telephone call
26 and the first consultation is more strictly controlled if the screening test results indicate a
27 positive diagnosis. When the initial diagnosis is less certain, the time lapse is less critical. For
28 all the CF Centres, the reception of the results determines how the phases of the
29 announcement process will be coordinated.

30 The communication of information has a significant impact on professional practice in a
31 context where physicians are more and more frequently faced with 'layman interference'
32 (Orfali, 2002). In effect, how does one conform to practice recommendations and retain
33 information during the call when parents introduce questions concerning the disease? This is
34 expressed by one paediatrician: "*When the parents ask me 'Is it to do with cystic fibrosis? I*
35 *say 'yes', I'm not going to say 'no' and then the next day tell them it's cystic fibrosis, if I've*
36 *already 'lied' on the telephone, the contact is bad from the beginning.*" Avoiding questions
37 is, for certain paediatricians, synonymous with lying and calls their credibility and
38 trustworthiness into question when trying to establish a relationship with the parents. In doing
39 so, they describe their attitude as '*hypocritical*' and feel they are '*deceiving*' the parents who
40 can always sense when a physician is hiding something. These protective strategies are
41 difficult for health professionals to come to terms with as they call into question both
42 individual identity (the lie) and professional identity.

43 Even if the sweat test is currently the most reliable indicator in diagnosing CF, a prior clinical
44 examination can be effectuated as a point of entry into the diagnosis announcement if the
45 patient is homozygotic; the aim of the clinical examination being to detect clinical symptoms
46 that will confirm the diagnosis. It should nevertheless be pointed out that almost half the
47 neonates show no clinical to symptoms to confirm or invalidate the diagnosis when the sweat
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1 test is performed. Given the stress and anxiety this causes the parents, one could legitimately
2 question the diagnosis announcement procedure itself:

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4 *“One can imagine that announcing a cystic fibrosis diagnosis to a patient is currently*
5 *extremely difficult. Before, the patients had symptoms. We could thus put a name on the*
6 *observed symptoms. This is no longer the case. We are going to snatch someone out of*
7 *their everyday life, someone that that isn’t asking for or expecting anything, and we’re*
8 *going to...I would say...crucify him. It’s difficult to handle. And then afterwards we know*
9 *that everything we’re going to say is going to be branded with a hot iron”* (Physician).
10

11 Here, medical action is confronted with its own powerlessness *“because effectively, the*
12 *patient gives no outward signs of illness...When you’re the physician who tells the parents of*
13 *a sick child that you have discovered the cause of the illness, you’re like the messiah... Even*
14 *if the diagnosis we announce is serious, we remain the person that discovered why their child*
15 *is sick. As a result, the rest follows smoothly. In the present case, you’re like the ‘thunderbolt’*
16 *that strikes in a situation where everything was fine, where everything was perfect, where they*
17 *have a healthy beautiful baby, with no signs of sickness, they’re happy having a little baby*
18 *and someone comes along and says: ‘well no, actually, it’s not as rosy as all that’. And you’re*
19 *not doing them a favour because they hadn’t asked anyone for anything. As a result, it’s not*
20 *always easy,”* emphasises another physician. The physician charged with announcing the
21 diagnosis is considered as a *‘bird of ill omen’* to take up the expression used by a number of
22 interviewees. The diagnosis announcement reveals the medical profession’s unaccustomed
23 powerlessness to possibly cure or repair; it transforms the physician into a bird of ill omen
24 that, far from being in a position to cure, is duty bound to announce a catastrophe to a family
25 whose child is well in 48% of cases. This bearer of bad tidings is more or less held
26 responsible, as explains this psychologist:
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29 *“All the announcements provoke pain, we are aware of the pain we’re inflicting on*
30 *people. We have the feeling that we’re aiming a bazooka at them and destroying their*
31 *lives in a sense. It’s terrible, they have an imaginary child on which they projected a host*
32 *of fabulous things and we come along and completely destroy the child they imagined, so*
33 *it’s a bit difficult and we are aware of the pain we’re inflicting.”*
34

35 In this context, the utility of a diagnostic test that scientifically proves the screening results
36 and lends credibility to the diagnosis for both parents and physicians can easily be understood
37 since, *“if the sweat test is positive, the disease is admitted, the patient effectively carries the*
38 *disease stigmata [...] it provides the determining factor in a certain sense”* explains a
39 physician. In effect, the sweat test provides tangible results: when a chloride concentration
40 rate above 60 mmol/L is found on several successive tests whereas the normal rate is fixed at
41 below 30 mmol/L. *‘It is either normal or abnormal, the parents need to see it written in black*
42 *and white’*, observes a physician.
43

44 In the end, the presumptive diagnosis following a screening test not only has an impact on the
45 organisation of cooperation and coordination activities associated with the key phases of the
46 announcement process *in situ* (between the protagonists concerned, hospital and external
47 services, health professionals, parents) it also has an effect at professional level in terms of
48 communication between the physician and the family.
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2. In the absence of clear-cut results: diagnosis is challenged by uncertainty

Revealing the diagnosis poses a problem when there is uncertainty, either because the confirmatory test is not conclusive (in this case the sweat test) or because the clinical form of the disease does not correspond to medical delimitations¹. Following the first consultation at the CF Centre, the physician charged with the diagnosis announcement completes an identification form on which three possible conclusions concerning the neonate's health status appear: healthy, affected and non-conclusive results in the case of an uncertain diagnosis. The latter case refers to the detection of forms of CF defined as 'borderline', 'resistant', 'atypical', or 'equivocal'. What action should be taken in cases where a mutation is detected but not identified by the screening test and where physicians have no indication as to its deleteriousness? Or again, when identical mutations on two alleles (homozygotes) are accompanied by negative or intermediary results on the sweat test? These are cases where the screening test results are positive but the neonate carries gene mutations for which the clinical outcome has not been defined and the sweat test is inconclusive. This raises a diagnostic dilemma in that the outcome for these patients is extremely difficult to predict. To this initial difficulty can be added the recurrent question relative to disease terminology, definition and nosology: can cystic fibrosis legitimately be diagnosed in these 'borderline' cases? Outside the definitional battle concerning the delimitations of cystic fibrosis, it has given rise to an ethical reflexion on the dividing line between preventive and predictive medicine.

2.1. When diagnostics are confronted with intermediary and borderline cases

The CF NBS strategy has considerably improved screening performance but has raised new diagnostic difficulties. If screening technology is presented as a compromise solution to a crucial problem, its use generates inevitable side-effects. On the one hand it produces its expected effects and perceived benefit/risk equilibrium, but on the other this technology/solution generates unexpected side-effects and as a result, the questions, problems and actors involved are drawn into a new, redefined perimeter. There are cases where the results are difficult to interpret because the confirmatory test falls outside the approved diagnostic classifications for the disease and the diagnosis remains uncertain. It thus happens that despite the detection of two identical mutations, the sweat test remains inconclusive either because the results are negative (less than 30 mmol/L) or intermediary (between 30 and 60 mmol/L). In either case, the diagnosis remains uncertain requiring the sweat test to be repeated. During this period of diagnostic medicine aimed at validating the clinical indications of disease, should the child nevertheless be positively diagnosed and treatment embarked-on?

“These are forms for which biologically speaking we have proof...where we have two mutations. We have two mutations, but a sweat test that is either normal or uncertain and no clinical symptoms, asymptomatic. Thus, these are situations where we have a lot of doubts and anxiety as to what we should do because beginning the standard treatment for cystic fibrosis...which is a heavy treatment programme... on an individual that may never develop the illness or else a very mild form of CF, is not devoid of side-effects’ (Physician).

¹ 24 centres note difficulties regarding the diagnostic procedure for cystic fibrosis. 6 centres consider that the difficulties are important if not extremely important. The difficulties essentially concern the management of 'borderline' forms of cystic fibrosis, the detection of heterozygote carriers and neonates carrying the R117H mutation with uncertain or intermediary results on the sweat test. (High Authority for Public Health report, 2009)

1 In the absence of a positive diagnosis, medical surveillance is recommended and further DNA
2 analyses to search for rarer mutations. Throughout this period, the family is maintained in a
3 state of uncertainty which is why the diagnosis announcement for cystic fibrosis from NBS
4 results is far more complex than it is for other rare diseases such as congenital
5 hypothyroidism or phenylketonuria, equally subject to NBS.
6

7 The phenotypic expression of ‘borderline’ forms of CF is unknown, that is to say the nature,
8 extent and the moment in time the disease will clinically manifest itself. It is impossible to
9 predict if it will develop into a standard form of cystic fibrosis or whether the complications
10 associated with the disease will become manifest in these children or not (certain borderline
11 forms are relatively asymptomatic). As stipulated by this physician: “*Neonatal screening has
12 led us to discover enigmatic cases, but as do all new techniques. We discovered things and
13 didn’t know whether or not they signified real problems, whether they should be announced
14 or not. We discovered minor anomalies, anomalies that we thought minor and subsequently
15 turned out to be serious. In other cases we discovered anomalies that we thought were serious
16 and that finally had no serious consequences. That is to say that technological progress is not
17 just progress.*” In other words, the repercussions of the different mutations on the phenotype
18 are variable and unpredictable. More specifically, there are ‘mild’ mutations associated with a
19 good prognostic factor and requiring reduced treatment (Roussey, Le Bihannic, Scotet,
20 Audrezet, Blayau, Dagorne, David, Deneuille, Giniès, Laurans, Moisan-Petit, Rault,
21 Vigneron, Ferec, 2007).
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27 The uncertainty surrounding the diagnosis and the evolution of the disease can provoke
28 anxiety and incomprehension among the parents and the children that can persist over the
29 long term. The impossibility of providing a clear-cut diagnosis at neonatal stage can be
30 damaging to the patient’s identity:
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34 *“I currently have patients who were affected when they were children and to whom I
35 have difficulty saying: ‘Now listen...’ I have to bring them progressively round to
36 dropping their cystic fibrosis status by telling them: “Right, now listen, we gave it
37 100%, it was better for you, etc”. They are no longer under treatment and there is no
38 sign of cystic fibrosis. We have better knowledge of these borderline forms now. And
39 maybe if we occasionally continue to benefit from providing a service that is maybe not
40 a great deal of use, we risk penalising them when they are adults. If the individual
41 wants to be a company director or have credit facilities he won’t be able to. When the
42 child was 10 years old, I said to the parents: “I think we’re in the clear now, it’s not a
43 real case of cystic fibrosis so we’re going to stop the treatment because it’s no longer
44 necessary. We have biological proof that treatment is no longer necessary” (Physician).
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47 Clinical medicine leads the medical profession to be involved in this situation, the down-to-
48 earth reality of which is to remain in a state of uncertainty for an indeterminate length of time:
49 “*This neonatal screening poses a problem in the interpretation of borderline cases. It’s a
50 problem that concerns us all but we still haven’t found a solution*” (physician). What attitude
51 should health professionals adopt when faced with announcing the diagnosis to parents?
52 Would a coherent, standardised procedure applicable to the whole French territory be
53 conceivable? In general, it appears that in the case of these ‘borderline’ and ‘intermediary’
54 cases, a common, standardised protocol is lacking: should they be considered as being
55 singular cases for which adapted medical surveillance programmes are specifically created, or
56 should these cases be considered as one of many forms of cystic fibrosis and, as one physician
57 reveals, be used as a competitive measure to increase one’s active patient file: “*There’s
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1 *currently a sort of race going on: “how about that, I’ve got X number of patients on my active*
2 *list!” Therefore, patients with an intermediary form that is not an averred case of cystic*
3 *fibrosis will nevertheless be considered as having cystic fibrosis.’*

4
5 At this stage, the critical question concerns the sequence of events that structure the
6 interactions between the medical teams, the infants and their families and the considerable
7 stakes underlying the provision of care including the diagnosis announcement, follow-up care,
8 family genetic counselling and costs. For the medical teams concerned, being confronted with
9 these ‘borderline’ forms is ‘*the most unpleasant hypothesis*’ because ‘*uncertainty*’ prevails:
10 ‘*we can neither validate nor invalidate the diagnosis*’.

11 12 13 2.2. *When disease is the outcome of a definitional battle*

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16 There are several reasons for launching the debate on ‘borderline’ forms of CF. The primary
17 reason is that, in certain cases, the problem stems from the modifications to the definition of
18 cystic fibrosis introduced at the beginnings of the mass neonatal screening programme.
19 Before the screening era, CF could be diagnosed if an element or symptom evoking cystic
20 fibrosis was associated with a positive sweat test (sweat chloride concentration level equal or
21 above 60 mmol/L). In the screening context, the diagnosis is validated if the immunoreactive
22 trypsinogen (IRT) value is above the cut-off level and is associated with the presence of two
23 mutations on the CFTR gene or a positive sweat test indicating a chloride concentration level
24 equal to or above 60 mmol/L (whether the neonate’s initial medical examination reveals
25 clinical symptoms evoking CF or not).

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29 With this new definition, it is thus possible (and not infrequent) to find neonates with a
30 normal sweat test and no clinical symptoms evoking CF during the initial examination
31 nevertheless being diagnosed with cystic fibrosis. This is the case for screened infants with a
32 positive IRT test and the delta508/R117H genotype (7% of screened neonates) for whom the
33 sweat test is rarely positive, more often intermediary (between 40 and 60 mmol/L inclusive)
34 and occasionally, but not infrequently, totally normal (less than 40 or even 30 or 20 mmol/L).
35 The screening and diagnosis of cystic fibrosis in such infants is a problem that is currently the
36 subject of heated debate, presented under two different aspects: nosology and definition. In
37 effect, some borderline cases or anomalies are not among the most frequent which often
38 entails completing the initial analyses with more exhaustive tests to detect the mutations
39 responsible. If the classic form of cystic fibrosis (delta F508) causes both pancreatic
40 insufficiency and respiratory disorders in patients, other milder forms exist (the most
41 frequently detected being the R117H mutation) that do not cause pancreatic insufficiency and
42 in which the overall clinical expression is less serious. Other forms are associated with a
43 variable phenotypic expression for which the underlying mechanisms are not yet understood.
44 The problem posed by these cases is the type of treatment and follow-up care that should be
45 provided for these children.
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51 The work of nosology consists in defining phenotypic evolution through time and classifying
52 clinical forms of CF into at least two categories: “Cystic Fibrosis” and “CFTR Related
53 Disorders”, to enable the provision of appropriate follow-up care. The majority of reported
54 cases, after several years monitoring, show a normal clinical status or very mild symptoms.
55 Only in time can the delayed apparition of clinical symptoms be attributed to a defective
56 CFTR gene. This nosological question is complex in that it can lead to the arbitrary
57 classification of a variable spectrum of clinical situations from normality to severe disorder
58 according to the level of functional CFTR protein (and other associated genetic or
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1 environmental factors). Early detection in these cases is in fact an undesirable side-effect of
2 the screening process. The aim of CF NBS is to detect neonates for whom early diagnosis and
3 treatment at nutritional and/or respiratory level will be of immediate benefit. Outside certain
4 exceptions, this is not the case for children in the 'borderline' category. As the disease
5 invariably manifests itself later in life, it remains uncertain whether health professionals
6 should announce the diagnosis at birth.

7
8 The second reason for launching the debate concerns the terminology currently in use.
9 Specialists in the field of cystic fibrosis, both practitioners and researchers, disagree as to
10 what the term cystic fibrosis and its derivatives should or should not include. Whether in
11 professional medical literature or during the course of our interviews, their use of language
12 reveals a degree of hesitation as to the definition of 'form', 'borderline', 'moderate'
13 'attenuated', 'mild' 'resistant', 'intermediary', 'equivocal' and 'atypical'. Certain will use
14 oppositions such as 'severe mutation vs. light mutation' thus taking up terms used in the
15 genetics field. The reason for these performative idioms ² is on the one hand an attempt to
16 classify other forms of CF in relation to 'classic cystic fibrosis', which supposes that a naming
17 convention has defined what the term 'classic' refers to, whilst maintaining the inverted
18 commas as a precaution signifying that there remains some uncertainty regarding available
19 knowledge. These specialists each have different vested interests and vie with each other to
20 propose, or better still impose, one terminology rather than another:

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25 *"The term CFTR Related Disorders was proposed to replace the term 'borderline form'.
26 I like neither the term 'borderline form' nor CFTR Related Disorders, an English term
27 which is difficult to announce to French-speaking parents and which presupposes the
28 existence of a 'disorder' that has not yet been proved (outside the occasional elevated
29 but not abnormal chloride concentration in the sweat test). I proposed the term
30 Cyfitrose which, in my opinion, is simpler and more pertinent as it is possible, or more
31 likely probable, that a high percentage of these individuals (I do not use the term
32 'patient') will never develop any clinical symptoms or disorders even later in life. To
33 date, this proposal has not been adopted"* (Physician).

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37 *"One thing I don't like at all concerning the terminology is that it implies that the
38 patient risks developing cystic fibrosis. No, for this individual, we don't know what the
39 phenotypic expression will be. The genotype remains extremely modest. We can, in
40 some rare cases, see the development of mild or more serious forms of the illness...this
41 is being scrutinised at European level. We can call it 'atypical cystic fibrosis', we can
42 call it 'mild cystic fibrosis'...which in my opinion is incorrect because a mild form can
43 develop into a more serious form...you can't call it 'cystic fibrosis risk factor'...I hate
44 that. I prefer referring to it as 'an atypical expression of cystic fibrosis'... we don't
45 know how it will develop...whether it will remain mild... Being at risk from cystic
46 fibrosis suggests that it can be prevented. You can't be at risk from cystic fibrosis
47 because you can't do anything to prevent it"* (Physician).

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52 To summarise, these clinical forms that generate erratic diagnostic and prognostic uncertainty
53 render nosological delimitation of cystic fibrosis difficult and consequently, what it may
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57 ² The notion of 'performativity' borrowed from the pragmatics of language, highlights the fact
58 that the sciences in general, and social sciences in particular, as is the case examined here, are
59 not limited to representing the world: they bring it into being, provoke it and thereby to a
60 certain extent and in certain conditions, create it. See Callon M., 2007, and Barad, 2003.

1 entail in terms of social responsibility and psychological and economic costs. For these
2 identified patients, possibly expressing singular forms of cystic fibrosis, the aim of clinical
3 research is to enable specialists to agree on a national, standardised care programme including
4 the medical announcement, follow-up care and also family genetic counselling.
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7 **3. Diagnosis challenged by bioethical stakes**

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10 A final impact of NBS on the diagnosis of cystic fibrosis concerns the provision of care at
11 family level. Whereas the intermediary and borderline cases question the validity of predictive
12 medicine, genetic counselling implies access to information that could lead to prenatal and
13 pre-implantation diagnostics that both raise bioethical questions.
14

15 *3.1. A move towards predictive medicine?*

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18 The distinction between preventive and predictive medicine emerges as a result of these
19 technological innovations and advances in molecular biology. In a first situation, mild
20 mutation, apparently dominant in relation to a classic mutation, requires further analysis to
21 determine whether it will develop into a classic form of cystic fibrosis. A second situation
22 involves an anomaly on the CFTR gene which will ultimately become pathogenetic; the
23 clinical symptoms are likely to appear in later life. The first is a case of preventive medicine
24 seeking to avoid, or at the least delay, the classic complications related to the disease by the
25 early provision of adapted care. The second is more a case of predictive medicine³ that calls
26 into question the legitimacy of diagnosing CF at birth.
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30 *“It’s inherent to the practice of screening. We’re no longer in the realm of preventive*
31 *medicine here we’re talking about predictive medicine. It’s not the same as if we were*
32 *determining a patient’s predisposition for high blood pressure, etc. So it’s not easy*
33 *for the patient, the families or the professionals when we come across cases like this.*
34 *For example, we only have one mutation, the infant is referred to the CF centre, we*
35 *administer the sweat test and ‘bingo’ we have an intermediary result. So, is it CF or*
36 *not? We then scan the gene, we discover that there’s a form...a second, moderate*
37 *mutation. Thus, there are two mutations and an intermediary result on the sweat test.*
38 *It’s extremely difficult to explain to the families: ‘We have detected cystic fibrosis, but*
39 *it isn’t cystic fibrosis, so we’re going to monitor it as if it was CF, but rest assured, it’s*
40 *not like cystic fibrosis...’ (Physician).
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45 There is no certainty that the detected neonate will ultimately develop the disease given the
46 absence of a genotype-phenotype correlation. In this space, the participants (especially
47 practicing physicians and researchers) find themselves having to deploy strategies involving
48 new research to simultaneously produce new knowledge, refine their arguments and acquire
49 new clinical, therapeutic and announcement possibilities for this chronic disease. In the
50 balance between prevention and prediction, scientific advances and technological
51 developments tend to reinforce the belief in predictive possibilities. The limits of genetics
52 become apparent and occasion redeployment in favour of molecular biology where
53 observation is once again envisaged. It is at this point that we identify the connection
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57 ³ Definition: detection in an apparently healthy individual in whom the disease is latent but susceptible of
58 pathogenesis. It predicts disease severity with probability, according to whether the dominant genetic
59 characteristic is recessive or multifactorial, whereas there are little or no curative or preventive measures
60 available (Dausset, 2001, Aymé, 2001).
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1 between neonatal screening, the categorisation of cystic fibrosis and the contents of the
2 diagnostic announcement.

3
4 The reasoning then concerns the clear distinction between screening and diagnosis, screening
5 being revelatory but *'is not a diagnosis'* insists one physician. In this respect, *'the real*
6 *problem, that should not be forgotten, is that screening remains just that, screening. This*
7 *means that at the end of the screening test we have to say either yes it is, or no, it isn't. We*
8 *can't tell families maybe it is, or maybe it isn't. It's not acceptable. We can't say that. So,*
9 *after the screening test we have to be clear-cut: it's 'yes' or it's 'no' even if we make a*
10 *mistake, but it has to be either 'yes' or 'no' and we have to assume the decision''.*

13 3.2. The question of prenatal or pre-implantation diagnosis

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16 A prenatal diagnosis is available for heterozygote couples identified after the birth of a child
17 affected with CF, signifying a 1/4 risk of transmitting an autosomal-recessive affection in
18 future pregnancies. It can also be proposed to parents if CF is diagnosed during the course of
19 a pregnancy; a diagnosis that can be evoked during the course of an ultrasound scan where
20 hyperechoic fetal bowel or meconium peritonitis is detected.

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23 Prenatal diagnosis can be effectuated by chorial villosity biopsy from 12 weeks amenorrhea
24 or by amniocentesis from 15 weeks amenorrhea. The identification of a foetus with cystic
25 fibrosis can justify a medical interruption of pregnancy. In certain mild cases of the disease,
26 prenatal diagnosis is difficult, yet geneticists are more and more frequently solicited by low-
27 risk couples, notably the brothers and sisters of parents with an affected child. Furthermore,
28 the National Ethics Advisory Committee (Comité Consultatif National d'Ethique⁴; CCNE) is
29 opposed to widespread prenatal screening (CCNE, 2003). It underlined that prenatal screening
30 was perfectly justified in a family context where a risk factor was averred, when one of the
31 parents carries the genetic mutation responsible for cystic fibrosis, but not for the population
32 as a whole.

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36 Pre-implantation genetic diagnosis allows the selective transfer of embryos free of a given
37 genetic anomaly. This heavy technique avoids the need for prenatal diagnosis and the medical
38 interruption of pregnancy. It involves a complex procedure effectuated in few highly
39 specialised Centres and is strictly regulated. It is authorised in France under exceptional
40 conditions since the Law of July 29th 1994. A screening test for the Delta F508 mutation in
41 the spouse of a carrier is eventually proposed by the CCNE because if both parents are
42 carriers, the Delta F508 mutation carries a 25% risk of producing a homozygote.

46 Conclusions

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48 This investigation into professional management practices integrated into the CF diagnosis
49 announcement to parents and the neonate brings to light the process of coordinating and
50 rationalising the diagnosis. What this first contribution reveals is that, for the large part, this
51 delicate medical activity has become organised, standardised, approved and virtually
52 rationalised. One can understand this in a context where the discomfort provoked by such a
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56 ⁴ Situated in the bioethical domain, the National Ethical Advisory Committee puts forward opinions that, even if
57 they have no mandatory value, contribute to the normative framework governing medical practice. According to
58 the Law of August 6th, 2004, 'The mission of the National Ethical Advisory Committee for life sciences and
59 health is to put forward opinions on ethical and societal issues raised by knowledge advances in the fields of
60 biology, medicine and health.'

1 violent, managed by CF Centre teams with limited experience in the matter (at the time the
2 research was carried out) given their relatively recent creation. Yet, our results clearly
3 establish the co-evolution of three organisational dimensions: organisational (precise
4 coordination of the CF diagnosis announcement), techno-scientific (biological markers,
5 instrumentation, knowledge) and regulatory (elaborating and normalising standard diagnosis
6 and care practices) achieved by bringing together screening technology on the one hand, and
7 the diagnosis announcement on the other.
8

9
10 Along the way, biomedical advances together with the professional knowledge acquired
11 through the reflexive staffing of CF Centre teams have revealed unknown factors and
12 generated uncertainty. In medical language, this uncertainty is formulated with sobriety: NBS
13 strategy has considerably improved screening performance but has equally revealed new
14 difficulties for the teams and for the patients as they experience a diagnostic “odyssey”. The
15 patients and their parents are led into sharing the factor of uncertainty with the medical teams;
16 a factor that permeates the tonality and interpretation of results. From presumption and
17 suspicion to proof, from certainty to the presentation of results that do not authorise a clear-
18 cut conclusion, their expression can be as unequivocal as equivocal placed as they are under
19 the seal of uncertainty. This critical dilemma surrounding information content and
20 communication procedures is one of the key corroborating factors in understanding the
21 diagnostic process and its announcement. This change in information and interactive content
22 that in three decades has shifted from ‘lethal announcement’ to ‘explained announcement’ and
23 currently to an ‘uncertain announcement’ is equally performative in that, not only does it
24 modify medical communication and care practices, but also the way the disease is
25 experienced and anticipated.
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30 What this research equally reveals is situated in the domain of philosophical, social and
31 political questioning. The ethical controversy surrounding CF NBS has two facets: firstly, as a
32 technology and a tool for public policy, screening has radically transformed the physician-
33 family relationship in that it touches the most intimate spheres of a human being and in so
34 doing, inevitably rekindles anxieties. Secondly, in opening up the field of possibilities through
35 continuous technological advances, it has also created new uncertainties. This situation is
36 rendered more complex by the coexistence of typical cases with foreseeable outcomes, and
37 hybrid cases such as the false-positives, false-negatives and ‘borderline’ forms. The
38 borderline forms of cystic fibrosis fall outside its current delimitations and thereby questions
39 clinical practice in all its dimensions: diagnostic classification, the prognostic outcomes for
40 this cohort of CF detected neonates, the surveillance and therapeutic approach and a better
41 organized, more adapted form of genetic counselling for the families. These enigmatic cases
42 confronting physicians, screening technology and knowledge advances combine to instil
43 doubts and discomfort and thereby impede the satisfactory resolution of conflicts in that the
44 problems raised involve social, political and human choices on the part of patients, families,
45 and therapists. It remains difficult to respond to the new challenges launched by the advances
46 described above for the sole reason that the foundations on which these choices are based are
47 in total incongruity with the situations that emerge in that they cannot be fitted into the
48 existing categories of thought. The health professionals’ limits in the face of these difficult
49 situations correspond to the limits of the existing consensus concerning these patients and, by
50 extension, to the limits of the homogenisation of the medical professions’ arguments and
51 attitudes throughout the CF announcement and treatment process.
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58 It is for this reason that ‘maximalist ethics’ based on the application of universal precepts
59 albeit a change in context, is seemingly being replaced by ‘pragmatic ethics’ inspired by the
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1 fact that medical professionals and teams are duty bound to make decisions and take action
2 when innovative techniques create novel situations that call existing categories of thought and
3 established references into question. We are then confronted with the emergence of team-
4 specific local codes of practice (Timmermans & Berg M., 1997), as evoked by this physician:
5 “*Intermediary forms are definitely uncomfortable to deal with because it varies from one CF*
6 *Centre to the next. No one is quite sure how they should be treated.*”
7

8 From the disputes concerning the definitions and classifications of the disease to the
9 uncertainty caused by borderline forms, from questions regarding prenatal diagnosis in
10 relation to neonatal screening, there is no doubt that the debate surrounding CF NBS and its
11 side-effects has reached an unprecedented scale. Genetic analysis, molecular tools, in
12 modifying the diagnostic process has altered the physician-patient relationship. The search for
13 appropriate treatment is no longer the primary aim in medical practice and the ethical
14 implications underlying this new perspective are paramount. Predicting disease is only
15 meaningful if preventive or curative treatment programmes are available. Failing that,
16 predictive medicine will simply become a source of anxiety extending into an uncertain
17 future. Moreover, does it not equally include the risk of physicians reducing an individual’s
18 identity to a health status, confined within a simplistic, predetermined fate? Even more so,
19 given the accumulation of effects induced by NBS, a fundamental question remains
20 unanswered: is the aim of CF NBS to enable better access to care, to provide patients with
21 more effective treatment or is its ultimate aim to eradicate the disease?
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RECEPTION OF CF NBS RÉSULTS

Figure 1. ANNOUNCEMENT PROCEDURE

POST-ANNOUNCEMENT

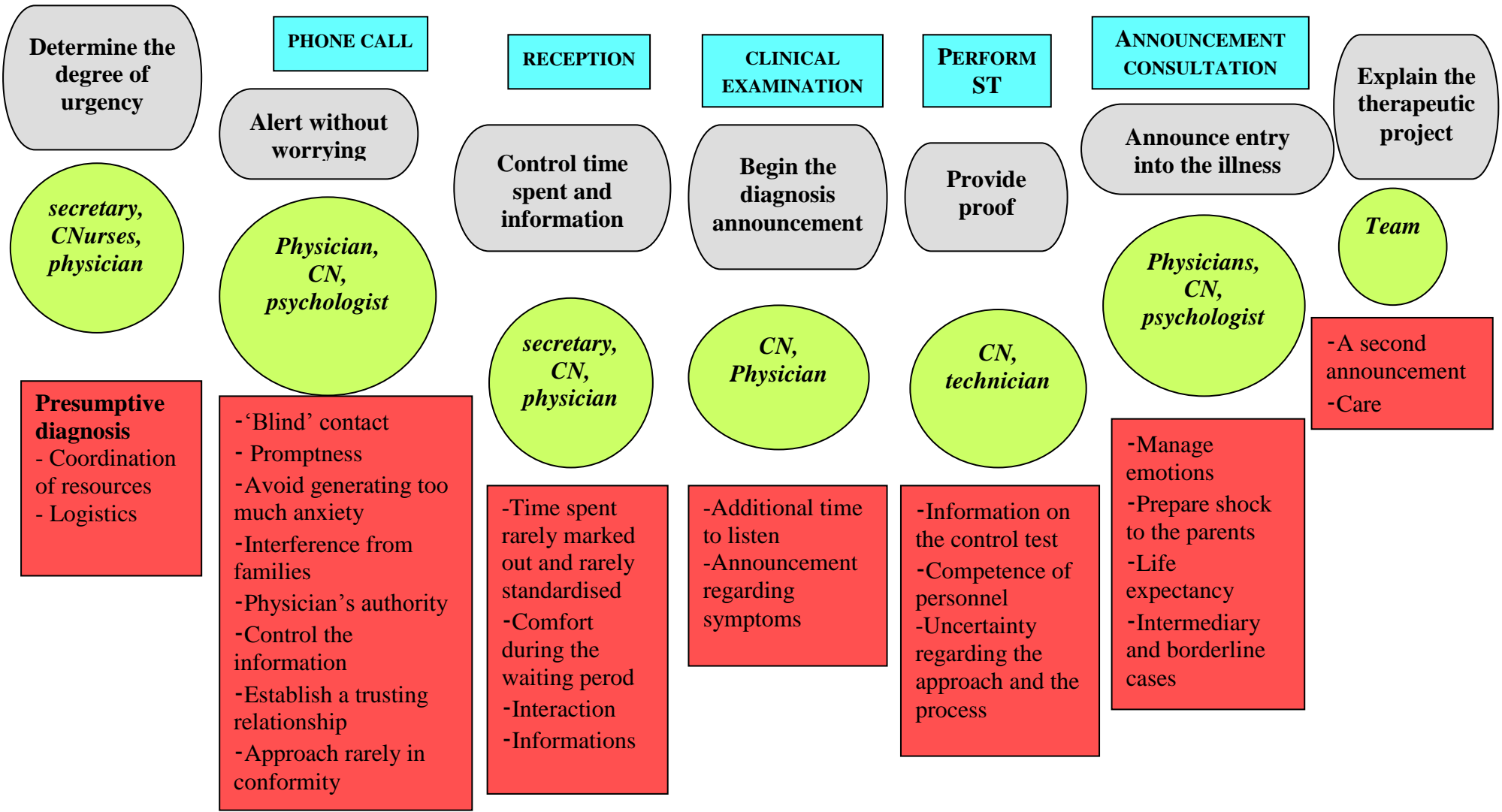


Figure 1 : Algorithme du dépistage néonatal de la mucoviscidose

