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French and Portuguese patients' organizations' engagement in
research

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The dynamics of causes and conditions. The rareness of diseases in French and Portuguese patients' organizations' engagement in research

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Abstract

Many actors in the field of rare diseases point to the role played by the notion of 'rareness' in the emergence and development of what we refer to as the 'hybrid collective model' (HCM) of collaboration between patients and experts. The HCM features two main characteristics: (i) the constitution of communities which bring together families and researchers as actors in the 'war on disease'; and (ii) organized cooperation between experts and patients' organizations in the production of knowledge on diseases. This article seeks to highlight the reflexive work carried out by French and Portuguese patients' organizations on the notion of rareness and its relation with the HCM. A systematic survey and fieldwork conducted in both countries have shown that such relation is neither systematic nor univocal. Some patients' organizations point to the limits or the lack of relevance of rareness as a category for grounding their action. These criticisms have led us to envisage a more general dynamic: the choice of the HCM as a mode of involvement in a politics of singularization-generalization of causes and conditions. We suggest some possible consequences of this singularization-generalization dynamic in the conclusion.

Keywords

Patients' organizations, rare diseases, France, Portugal, hybrid collective model, delegation model, singularization-generalization

Introduction

Several studies on patients' organizations have documented the emergence of new forms of intervention in biological and therapeutic research by patients and their families (Barbot 2002; Brown et al. 2004; Dodier 2003; Dumit 2006; Epstein 1996; Novas 2005; Rabeharisoa & Callon 1999; Rapp et al. 2001; Silverman 2011). These new forms of intervention, in which patients collaborate closely with researchers, clinicians and industries, have two main characteristics: (i) the constitution of communities bringing together families and researchers as actors in the 'war on disease'; and (ii) organized cooperation between experts and patients' organizations in the production of knowledge on the diseases concerning them, which in some cases, can engender patients' active participation in research work. Based on our own work on these new forms of patients' organizations' engagement in research (Rabeharisoa 2003; Rabeharisoa & Callon 2004), we coin the term 'Hybrid Collective Model' (HCM), in contrast with the 'Delegation Model' (DM) in which patients take care of the emotional and social aspects of diseases and delegate what they consider to be strictly medical problems to experts.

The mechanisms that lead certain patients' organizations to adopt the HCM remain largely unexplored. The marginalization of certain diseases is one of the mechanisms most frequently identified. This process, which sometimes goes as far as exclusion, is said to be largely due to the characteristics of the pathologies concerned. *Rareness* is a characteristic frequently referred to both by patients' organizations and by social scientists who study these organizations (Boon & Broekgaarden 2010; Crompton 2001; Panofsky 2011; von Gizycki R.,

1987). The aim of this article is to discuss the validity of this explanation and to further our understanding of the role of rareness.

We begin by drawing on the existing literature to examine the relationships that have developed, at particular times and in particular countries, between rareness and the emergence of the HCM (section 1). We then show that patients' organizations themselves have emphasized the ambiguous nature of these relations. Our findings from systematic surveys that we have undertaken on French (section 2) and Portuguese (section 3) patients' organizations, complemented by field observations and interviews with members of these organizations, with researchers and with clinicians in both countries, show that certain non-rare disease patients' organizations appropriate the HCM. But, and more significantly, our investigations show that certain rare disease patients' organizations privilege other forms of engagement in research than the HCM, and/or introduce other criteria than rareness to characterize their conditions. This reflexive analysis undertaken by patients' organizations on the notion of rareness, which manifests itself not only in their discourses but also in their practices, highlights the existence of a tension, at the heart of their action, between a logic of singularization (aimed at defining what makes the specificity of a condition and of the problems encountered by patients), and a logic of generalization (aimed at demonstrating how a singular condition has much in common with many others) (section 4). The existence and management of this tension enable us to suggest why rareness has played a crucial role in the emergence of the HCM in certain cases, whereas it has not in others.

1. Exploring rareness and shaping a new model of engagement in research: the role of patients' organizations

1.1. From orphan drugs to rareness and to the invention of the HCM

The social science literature reviewed above shows that the organizations of patients and their families concerned with rare diseases have played a relevant part in the invention and development of the HCM, and that they frequently refer to the rareness of their conditions in order to justify such a model. The movement started in the 1980s in the USA, when Abbey Meyers, the mother of a child with a rare disease, discovered that there was no indicated medicine for her child who had Tourette syndrome. Apart from purely economic considerations, as rare diseases often correspond to markets which are too small to be profitable, the absence of medication was a consequence of the system regulating clinical trials. This system prohibited the testing of molecules on populations considered to be vulnerable (children, pregnant women, people with dementia), or too limited in size (people with 'rare diseases') for the 'gold standard' of clinical trials to be applied to them (Marks 1997). This regulation prevented not only the development of therapeutic research on innovative molecules, but also a possible extension of indications of existing medicines to 'under-served populations' (Epstein 2007). The pharmaceutical industry coined the term 'orphan drugs' (No authors 1968; Lyle 1975) for such products that were unable to attain viability and an economic existence. In order to raise awareness of the large numbers of people who were being deprived of medicines, Abbey Meyers undertook action to unite the 'rare diseases' patients' organizations in the USA, which coalesced as National Organization for Rare Disorders (NORD). The organization's main objective was to secure an amendment of the American legislation on clinical trials. This led to negotiations on the prevalence threshold below which diseases would be considered rare and industry would benefit from special arrangements for clinical trials, along with economic incentives to develop medicines.

In 1983, the threshold, set by the American Orphan Drug Act, defined as rare a disease affecting less than one person in 2,000 in a particular area or country. Thus defined, rareness became a compound concept that US patients' organizations helped to shape in direct relation to industry and the legislator. By becoming synonymous with situations of potential exclusion, rareness appeared as the cause of discrimination against patients, and thereby became a political issue. It was in the name of equity and social justice that actions aimed at reconfiguring relations between health and markets were undertaken.

Inspired by the North Americans, the European organization for rare diseases (EURORDIS), created in 1997 by four French 'rare diseases' organizations, including the AFM¹ – a pioneer in the field of rare disease patients' organizations in France – adopted a discourse that directly linked orphan drugs to rare diseases as a means to demand a European regulation similar to that of the USA. The European regulation was promulgated in 1999, setting the same prevalence threshold as in the USA (Crompton 2007; Huyard 2011/2). EURORDIS was also influential in structuring the collective mobilization of rare disease patients' organizations in Europe. In both France and Portugal, EURORDIS facilitated the creation of national alliances on rare diseases, grouping together patients' organizations. These alliances mobilized to develop actions based on the principles of equity and social justice, and protested against the fact that the rareness of diseases was all too often equivalent of patients' exclusion. The strength of these alliances was based on what we call a 'politics of numbers', summed up in their slogan 'Rare diseases are rare but rare disease patients are many', a motto designed to show that these pathologies are a major problem for public health.

¹ *Association Française contre les Myopathies* – French patients' organization against myopathies.

From the point of view of certain ‘rare disease’ patients’ organizations and alliances, this public health problem was largely a result of the lack of both academic and industrial investment in research, what Hess (2007) and Frickel et al. (2010) have since called areas of ‘undone science’. It was with an aim to fill this knowledge gap that they advocated patients’ active engagement in research, as well as the creation of communities of patients and researchers united around a single objective: war on disease. The convergence between the notion of rareness and the HCM was promoted by certain influential actors, which made it a key element in their strategy². This model is now considered by certain leaders of patients’ organizations, researchers and clinicians that we met as a form of relevant action to fight against rare diseases.

The history briefly outlined above shows that rareness has been explored, defined, and mobilized by certain patients’ organizations to highlight and explain the situation of exclusion in which people with rare diseases find themselves. It has served to legitimize political demands, in the name of equity and social justice. Instituted in the form of a threshold, rareness took on new meaning related to the absence of investments in research and

² In France, for example, the AFM, created in 1958, was actively involved in research to put an end to what it called “the vicious circle of ignorance and indifference” (Paterson & Barral 1994; Rabeharisoa & Callon 1999; Rabeharisoa & Callon 2004). It was instrumental in the invention of the HCM, which it consolidated throughout the 1980s and 1990s, and in the creation of the French *Alliance Maladies Rares* and of EURORDIS. It contributed to developing strong ties, both in France and in other European countries, between the cause of rare diseases and the establishment of the HCM.

therapeutic innovation. The HCM is both an organizational and a political response to this situation, deemed to be unacceptable by rare disease organizations.

1.2. What is rareness the cause of? From rareness to the 'rare diseases concept'

The link that was established at *particular* times and in *particular* countries by *particular* organizations, between the rareness of conditions on the one hand and, the invention and implementation of a model of engagement enabling patients to solve the problems that they encounter on the other, has gradually been reassessed by the patients' organizations themselves. The interviews that we conducted with members and representatives of these organizations in France and Portugal showed that they actively engage in a reflexive analysis of what rareness actually encompasses. Emphasizing the abstract nature of the threshold of rareness, they begin their analysis from the difficulties encountered by patients in their daily lives.

This reflexive analysis was notably formalized by EURORDIS when it decided to lobby for a European global strategy on rare diseases in the mid-2000s. Realizing that the epidemiological definition of rareness and the 'politics of numbers' it implied should be complemented with a substantive appraisal of common problems that patients and families with rare diseases face, EURORDIS and its member organizations elaborated the 'rare diseases concept'. This concept, delineated in a statement published in 2005³, highlighted a number of traits shared by diseases considered to be rare and which make certain conditions

³ EURORDIS, "Rare Diseases: Understanding this Public Health Priority", November 2005, 14 p. http://www.eurordis.org/sites/default/files/publications/princeps_document-EN.pdf

an unsettled public health problem: (i) rare diseases are complex and usually come with multiple and severe impairments and disabilities which impact on patients' and families' quality of life; (ii) diagnosis is often difficult to establish, which results in a search for diagnosis for patients and families; (iii) for many rare diseases, there is no cure; (iv) there are so few specialists – if any – that expertise is not accessible to everyone, everywhere and all the time; (v) knowledge and information on certain diseases is embryonic, if not lacking; and (vi) due to their complexity, many rare diseases raise challenging scientific questions that are still to be solved.

The new depiction of rare diseases not only lists commonalities between these conditions. It also echoes the variety of problems that patients and their families struggle with in their daily lives, and suggests the diversity of actions that should be undertaken to overcome their problems. Particularly, EURORDIS used this 'rare disease concept' to call for a European recommendation for National Plans for Rare Diseases which articulate research, clinical medicine and social support for patients and their families. From the point of view of national alliances on rare diseases, the concept implies that their social and political advocacy mission may no longer stand without *research* advocacy (Dresser 2001). This is what the French alliance reports on its website: "The Alliance has worked with the AFM on the creation of the Institute for Rare Diseases whose mission is to promote, develop and coordinate research on these rare diseases"⁴. On Rare Disease Day 2011, co-organized by EURORDIS and the national alliances, the FEDRA (*Federação de Doenças Raras de Portugal*) announced that: "Promoting investigation, creation of databanks and solid political intervention will allow a

⁴ www.alliance-maladies-rares.org/

better future for these patients, so many times forgotten and marginalized”⁵. However, the variety of situations experienced by patients, captured by the ‘rare diseases concept’, suggests that the articulation between research advocacy and social-political advocacy should be tailored to the specificity of the condition at stake. In particular, the ‘rare diseases concept’ helps patients’ organizations to clarify the causes for which their action should, or should not be geared towards the adoption of the HCM. This manifests itself not only in organizations’ pronouncements, but also in their practices, as we will now demonstrate.

2. French patients’ organizations’ response to the issue of rareness

2.1. French patients’ organizations’ adoption and problematization of the HCM

In what ways have French patients’ organizations translated the notion of rareness and their reflection on it into practice, especially in their forms of engagement in research? To answer this question we undertook a longitudinal survey in France – in 2006 and 2009 – with the following objectives: (i) to draw up a typology of the modalities of French patients’ organizations’ engagement in research; and (ii) to compare the forms of intervention of ‘rare disease’ and ‘non-rare disease’ organizations in research.

Considering our objectives, we limited these surveys to those organizations – both ‘rare disease’ or ‘non-rare disease’ – whose discourse and practices reflected an interest in research⁶. By ‘research’ we mean not only laboratory work but also any activity aimed at

⁵ <http://www.fedra.pt/>

⁶ The survey population was identified by crossing different sources (directories, membership lists of umbrella organizations, lists of participants to workgroups, conferences,

collecting, disseminating and comparing knowledge and information in the biomedical field as well as the more general health field. In 2006 we counted 497 organizations that met these criteria, 281 of which were 'rare disease' organizations and 216 'non-rare disease' organizations. This population has grown significantly in the following years: in 2009 it consisted of 650 organizations, 328 of which were 'rare disease' and 322 'non-rare disease'.

A self-administered questionnaire was sent out in 2006 and in 2009 to these organizations, to collect data on the following: (i) their organizational characteristics; (ii) the actions that they undertook in the field of research; and (iii) the relations that they maintained with one another and with academic teams. A total of 215 organizations responded to the 2006 survey, 143 of which were 'rare disease' and 72 'non-rare disease'. In 2009, 293 organizations responded, 187 of which were 'rare disease' and 106 'non-rare disease'. In the following

lists of associations registered by the *Journal Officiel*, websearch, etc.). The main directory was *Annuaire des associations de santé*®, which was created in 1996 and regularly updated (until 2008) by B. Tricot Consultant SARL, and listed all French non-profit organizations active in the field of medicine, disability and health (approximately 7000 at the time of our 2006 survey, of which about 2,000 patients' organizations). To identify the 'rare disease' patient organizations within this population, we used data from Orphanet, a web portal on rare diseases created by INSERM (the French research institute on medicine and health) and present today throughout the world, as well as the list of organizations that are members of the French Alliance for Rare Diseases.

paragraphs we outline the main findings of this research, to show how the organizations have adopted and adapted the HCM in different ways.⁷

Our results show, first, the diversity of the organizations' modes of engagement in research. Some go as far as to establish tight research cooperation with academic teams, while others are content with circulating scientific and medical information to make it available to patients and their families, or else to supply the specialists with questions and data, without ever organizing a full-blown collaboration between patients and professionals. In the former case one can talk of a form of involvement that is very close to the spirit of the HCM; in the latter, we witness instead the implementation of a model of delegation. Our results also show that this diversity of modes of engagement concerns both 'rare disease' and 'non-rare disease' organizations, even though the proportion of organizations that adopt the HCM is higher in the case of 'rare disease' than in that of 'non-rare disease' (however, the gap between them narrowed between 2006 and 2009). There is therefore not necessarily a relation between the rareness of conditions and the HCM.

This finding does not exclude the fact that rareness may have served as an incentive for certain 'rare disease' patients' organizations to implement the HCM, if only because of the structuring nature of the AFM's form of activism, which many organizations see as a reference point. What these results suggest is that the 'rare diseases concept', because it fully acknowledges the difficulties experienced by patients suffering from very different conditions,

⁷ The full results of these two surveys are available upon request to our team (MAPO Report – *Mapping and Analyzing Patients' organization Movements on Rare Diseases*, and EPOKS Report – *European Patients' organizations in Knowledge Society*, Centre de sociologie de l'innovation, Mines-ParisTech).

is probably more relevant than the *epidemiological* notion of rareness in accounting for the diversity of patients' organizations' modes of engagement in research. The interviews that we conducted with members of certain organizations enabled us to show this with more clarity.

2.2. *The 'rare diseases concept' and the variety of patients' organizations' profiles*

Between 2009 and 2011, we conducted interviews and carried out ethnographic observations⁸ in eleven 'rare disease' organizations (cf. Appendix 1).

We selected these organizations according to three criteria. Firstly, we chose organizations concerned with pathologies that differ with regard to both their prevalence and their characteristics. Two of them are actually concerned with diseases of which only certain forms are rare (the *Association Lupus France* – the Association on Lupus, and the *Association des personnes de petite taille* – the Little People Association), and one of them is concerned with diseases that are similar and of which some are rare and others not (the *Federation de recherche sur le cerveau* – the Federation for Brain Research). Secondly, we focused on organizations that were created at the time of the structuring of the French associative milieu on rare diseases in the late 1990s and early 2000s, and excluded large pioneering organizations like the AFM. Thirdly, we used the findings of our surveys to sort contrasting organizations with regard their modes of engagement in research and the types of knowledge they target.

Our interviews and observations enabled us to distinguish four different engagement profiles, and in each case, to identify the reasons why the organizations concerned adopted

⁸ Participation to meetings and conferences organized with or by patient organizations, written material analysis (newsletters, information leaflets, minutes, websites, reports, etc.)

them. They correspond to forms of intervention that the organizations considered relevant at some point in their struggle against their diseases, and are therefore not mutually exclusive.

- The first form of intervention aims at cognitively equipping patients so that they can deal with the problems they encounter. Teaching patients to be experts of their own diseases (Epstein 1995), capable of talking to doctors on an equal footing, of judging the validity of a therapy, and of anticipating the evolution of their pathologies or the side-effects of treatments, is an objective frequently mentioned by these patients' organizations.

The *Association Wegener Infos et autres vascularites* (the Association on Wegener's granulomatosis and other vasculitis), the *Association Lupus France*, the *Association de l'Ostéogénèse Imparfait* (the Association on Osteogenesis Imperfecta), to cite but a few examples, regularly update their websites with knowledge on the aetiology, pathological mechanisms, clinical descriptions, and treatments of their diseases, in formats resembling scientific publications (bibliographies, abstracts and/or full-texts of articles, synthesis written by specialists, links to scientific and medical references, white papers, information on research projects under way, etc.). Even if the organization chooses to delegate research to the specialists, without becoming involved in defining research orientations, it does nevertheless participate actively in the dissemination of the results and ensures that this knowledge is understood and used by patients.

This form of intervention corresponds to the scarcity and dispersion of knowledge and information available on rare diseases. More significantly, patients' organizations that develop this mode of engagement said to be preoccupied with the low numbers of clinicians who can accurately diagnose their diseases and offer care to patients.

- The second form of intervention consists of financial or logistical support for research teams. The patients' organizations do not intervene directly in defining the project

orientations or in running the operations, but neither do they simply transfer money without any concern for the content of research. Their financial support is the result of a process of identification and enrolment of research teams, involving multiple interactions with a view to aligning interests. Moreover, to avoid being dispossessed of their ability to make decisions and monitor the researchers' use of the resources they allocate to them, these organizations set up monitoring procedures that cause them to take an interest in the research subjects (Rabeharisoa 2003). This is what the vice-chairman of the *HPN France - Aplasie Médullaire* (the French organization on paroxysmal nocturnal hemoglobinuria and bone marrow depression) was referring to when he stated that: “The patients are attached to their doctors [at Saint-Louis hospital in Paris] and to their molecules”.

This mode of engagement stems from three observations: (i) the complexity of rare diseases and the need for longstanding investments in research; (ii) the existence of academic teams ready to investigate the conditions with which the patients' organizations are concerned; (iii) the need for ensuring that supported teams explore the biological pathways and entities that the patients' organizations deem important for a better understanding of their pathologies.

- The ‘rare disease’ patients’ organizations' third form of engagement consists of bringing to the fore questions on which no research has as yet been undertaken. Often these are topics relating to the day-to-day preoccupations and experiences of patients, and which are situated on the periphery of biomedicine. The formulation of these questions is partly enabled by the efforts that have been devoted to clinical and therapeutic research. The results obtained have had the effect not of healing patients (cure remains rare), but of gradually adjusting the care they receive. The natural history of rare diseases has thus been altered. Some of them became chronic illnesses that generated unexpected problems.

That is why SolHand *Solidarité Handicap – Autour des Maladies Rares* (Association on disabilities induced by rare diseases), created in 2007, has chosen to distance itself from biomedicine and to focus rather on issues that its chairwoman qualifies as medico-social, ranging from assistive technologies to rare diseases patients' inclusion in the job market. In the conferences that she organizes, she privileges speakers who are rehabilitation therapists and researchers in human and social sciences.

This form of engagement aims at mobilizing researchers and professionals in the production of knowledge focused on solutions to problems that patients encounter in their daily lives, notably medico-social problems related to multidimensional impairments and disabilities induced by rare diseases.

- The fourth form of intervention concerns patients' organizations' participation in the production of scientific and medical knowledge. The organizations contribute to therapeutic research and are involved in the definition and evaluation of clinical practices.

Some organizations undertake studies on their members to collect data on their experiences and to compare it to scientific knowledge. That is for example the case of an organization created in 2008 for Tarlov's Syndrome (whose main manifestations are cysts on the sacrum), which launched a survey in 2009 on 173 patients identified via the French Alliance for Rare Diseases. At the time of our interview, its objective was to transmit the results of this survey to a researcher-clinician that it had contacted via the French Alliance, so that this 'anecdotal evidence' (Moore & Stilgoe 2009) could be studied more closely.

If we look at the therapies, we note that certain organizations, even small and with limited financial means, actively involve themselves in designing clinical trials, liaise with the regulatory authorities, and recruit patients. That is for instance the case of the *Association San Filippo* that gathers families concerned with this serious and debilitating lysosomal syndrome,

which entails a dramatically reduced life expectancy. It eventually imposed itself as a *de facto* co-promoter of one clinical trial.

Clinical practices are also activities in which certain ‘rare disease’ patients’ organizations are proactive. For example, *Generation 22*, concerned with the 22q11 deletion syndrome, a complex syndrome involving heterogeneous disorders with multiple manifestations, participated in setting up the PNDS⁹. It monitored the implementation of this plan by organizing visits to the centres of reference for diagnosis and care on rare diseases¹⁰, during which the families related their experiences and concerns, mainly with regard to paramedical care (speech therapy, psychological help).

The patients’ organizations that adopt this fourth mode of engagement enter the black box of complex biological pathways that are still unknown and remain to be explored. They thus contribute to a collective exploration close to the HCM that may result in the requalification and reclassification of their diseases.

By and large, our interviews and observations all confirm the diversity of rare disease patients’ organizations’ modes of engagement in research. This diversity – which, in various ways, combines the translation of information, the monitoring of research, the formulation of questions and the production of knowledge – includes the HCM but leaves room for intermediate forms of involvement between this model and what we have called the DM. Moreover, patients’ organizations provide evidence on the relevance of the ‘rare disease

⁹ *Plan national de diagnostic et de soins* = National Plan for Diagnosis and Care.

¹⁰ These centres of reference were created in the frame of the French National Plan on Rare Diseases in the mid-2000s.

concept' for justifying their choices. The criteria underlying their actions are indeed those put to the fore by this concept: complexity of diseases and of their consequences, scarcity of expertise on diagnosis and care, lack of knowledge, etc. In the same movement, additional criteria such as the chronic nature of conditions and disability also emerge. Thus, depending on their conditions and according to their priorities at a certain moment, patients' organizations privilege certain forms of engagement over others.

In the following section, we continue to document this reflexive analysis undertaken by patients' organizations, by shifting our focus to the Portuguese case. This will enable us to further clarify the mechanisms that relate the issue of rareness to the implementation of the HCM.

3. Rareness put to the test by Portuguese patients' organizations

In contrast to the French context, the issue of rareness was brought to Portugal from the outside and by EURORDIS. This top-down movement was a subject of debate among Portuguese patients' organizations, which have highlighted the contingent and questionable nature of the notion of rareness. The controversy has resulted, in particular, in the creation of two rare disease umbrella organizations, FEDRA (*Federação de Doenças Raras de Portugal* - Portuguese rare diseases federation) and APADR (*Aliança Portuguesa das Associações de Doenças Raras* - Portuguese alliance of rare diseases associations), with contrasting approaches. Before examining this aspect further, we examine the choices made by Portuguese 'rare disease' and 'non-rare disease' patients' organizations with regard to their engagement in research.

We undertook a quantitative survey and a qualitative fieldwork in Portugal concurrently with the French survey, and using the same approach. Given the small number of patients'

organizations formally active in Portugal¹¹ (113), all of them, whether they showed an interest in research or not, were included in the survey¹². Of the 34 answers received, 10 were from organizations that belonged to one of the two Portuguese alliances of rare diseases and/or said they were concerned with rare diseases (Nunes et al 2007).

The majority of Portuguese organizations of patients and their families are support groups (25 out of the 34 respondents), whose main aim is to provide psychological support and practical assistance to patients. A significant number of them nevertheless show an interest in research¹³: most of these organizations are concerned with rare diseases, although the nature and intensity of their engagement in research does not differ from those of ‘non rare disease’ organizations. The survey yielded two significant findings. First, those Portuguese organizations that explicitly refer to rareness often choose forms of engagement half way between the HCM and the DM. Second, those that develop the HCM have an approach aimed

¹¹ In Portugal, contrary to the French case, there is no mandatory legal registry for patients’ organizations. They are usually public utility organizations, private social solidarity institutions, or other kinds of associations and foundations.

¹² The data collected in 2006 and 2009 show no noteworthy differences, probably because Portuguese civil society organizations developed much later than in France, after the transition to democracy in 1974. We have therefore mainly used data from 2009-2010.

¹³ In our survey, 11 organizations said they had a scientific committee or the intention to create one; 6 had raised funds for research; 14 had participated in research programmes; 5 had participated in clinical trials; and 19 had mobilized the public authorities for the development of research on their diseases.

at mainstreaming rare diseases, and at including them in more general categories of conditions and problems.

3.1. Portuguese 'rare disease' patients' organizations: between the DM and the HCM

Interviews with members of the ten 'rare disease' organizations in Portugal (cf. Appendix 2) revealed that they were often formed by doctors who had patients with these diseases. These organizations were created as therapeutic groups before being transformed into self-help/mutual aid groups supported by the medical teams that had contributed to their creation. This associative profile has had particular effects on the content, form and scope of the knowledge-related activities in which Portuguese 'rare disease' organizations engage. These activities have two distinct forms.

- All Portuguese 'rare disease' patients' organizations give high priority to the collection and dissemination of knowledge on diseases. These are the main means for raising awareness of the existence and seriousness of their pathologies, not only among medical and health professionals but also the general public. To this end, conventional tools are used: brochures sent to specialists, training activities for health professionals, participation in conferences, and dissemination of information in schools.

The experts involved in the Committee for the National Rare Diseases Plan we brought together in a focus group considered that 'stating the fact of rare diseases' is an important dimension of political advocacy – which, in their opinion, is one of the patients' organizations' main missions. Patients' organizations, on the other hand, value the help and the scientific authority offered by the experts from whom they seek advice in drafting their scientific and medical documents. This distribution of tasks and competencies is apparent in the status attributed to the patients' experiences. The specialists and professionals regard patient's experience as a form of knowledge that is different and complementary to scientific

and medical knowledge. It helps them to understand the psychological and social impacts of diseases on the lives of the patients whom they see in consultations. Patients' organizations' point of view is not very different: most of them consider that the patient's experience is always singular and enables doctors to provide personalized care. Yet, even though testimonies circulate between patients and their families, no organization has, on its own initiative, undertaken a survey on its members with a view to producing and publicizing what is known as 'experiential knowledge' (Borkman 1976).

- A second type of knowledge-related activity of Portuguese 'rare disease' organizations is their participation in projects or surveys launched by research institutions, and in clinical trials promoted by industry. In all cases, the organizations are more reactive than proactive. They respond to appeals made to them without intervening directly in the design and running of operations. The APPDH (*Associação Portuguesa de Pais e Doentes com Hemoglobinopatias* - Portuguese association of parents of patients with hemoglobinopathies), for example, participates in a project on patients' compliance with treatments and the control of pain in blood-related pathologies, in the framework of a programme launched and supported by the Portuguese national institute for health, involving various large hospitals in the country.

To sum up, one could say that the Portuguese 'rare disease' patients' organizations, along with the specialists who collaborate with them, constitute communities in which a strict division of roles and missions is observed. The social and political advocacy is handled by the former, while the research activities fall within the province of the latter. Thus, it is neither a pure DM, which excludes the idea of community, nor a pure HCM, which includes the constitution of a community but one with hybridization of competencies and prerogatives. The choice of this middle way shows that, in the case of Portugal where rareness as an issue arrived with EURORDIS, the notion of rareness is not necessarily linked to the HCM. More

interestingly, we are going to see that when certain Portuguese organizations adopt this model, they clearly reject rareness as a criterion justifying their choice.

3.2. Adopting the HCM and moving beyond the reference to rareness

The Portuguese case illuminates a debate, which is not as explicit in France, on the role that the notion of rareness ought to play in shaping the action of patients' organizations. This debate is triggered by the intervention of EURODIS in Portugal. It is expressed in two different situations: (i) first, on the occasion of the constitution of the two rare disease alliances, and with regard to the types of activity that ought to be promoted; and (ii) second, at the point at which certain rare disease organizations have to decide whether to join these alliances or not.

- In Portugal, the notion of rareness first appeared in the public sphere in 2006, when an organization called *Rarissimas* started to informally bring together the patients and families concerned with rare diseases. Its aim was to reveal the difficulties these people experienced in daily life, so that they could secure access to appropriate care. The arrival of EURORDIS in the country, in 2007, contributed to the formalization of this associative mobilization that very quickly split into two branches. *Rarissimas* and a few other organizations grouped together in FEDRA, while others formed a second alliance, APADR. The personal conflicts that led to this schism stemmed from disagreement over the meaning of associative action on rare diseases. FEDRA, which was mainly concerned with the management of life with a rare disease, invested in building a home for patients and their families who needed specific help and care. APADR, on the other hand, wanted to put the EURORDIS programme into action, concerning the structuring of research, the creation of centres of reference for diagnosis and care, the establishment of patient registries, and more generally the implementation of the

Plan for Rare Diseases, the principle of which had been endorsed by the Portuguese government in 2008.

FEDRA's approach clearly indicates that rareness does not automatically imply a proactive engagement in research, notably the choice of the HCM. The case of organizations that join APADR and that subscribe to EURORDIS' politics favouring the HCM, is even more telling on the compounded relation between this model and the rareness of diseases.

- Certain member organizations of APADR do not (exclusively) deal with rare diseases, but they apply the 'rare diseases concept' to non-rare conditions in order to enable the latter to benefit from the innovative structures and forms of coordination that this concept promotes (such as the centres of reference for diagnosis and care and multidisciplinary consultations). This is illustrated by the case of the APH (*Associação Portuguesa de Pessoas com Hemofilia e outras Coagulopatias*), the Portuguese organization for haemophilia and other congenital coagulopathies. As a founding member of APADR, this powerful organization, created in 1976, was clearly inspired by the European guidelines to strengthen its support for therapeutic research in a framework of collaboration with a pharmaceutical company, Baxter and Bayer, and to propose the creation of patient registries and of multidisciplinary consultations, not only for rare diseases but also for non-rare blood-related diseases. To justify its action, APH explained that what matters is the complexity and the chronic nature of these pathologies. We thus see emerging causes that help to understand why non-rare disease organizations adopt the HCM.

- A second form of rare disease mainstreaming is defended by patients' organizations that consider the HCM to be relevant but openly challenge rareness as a criterion to justify it. This is for example the position of the *Associação dos Doentes com Lupus*, the Portuguese organization concerned with lupus. The organization stands as one exception in the

Portuguese patient organization landscape by its adopting the HCM. A number of reasons are put forward by the organization for its choice: firstly, the uncertainty of knowledge about lupus, including its prevalence as an autoimmune disease, some forms of which are considered to be rare; secondly, the complexity of the disease; thirdly, difficulties of the diagnostic work; and finally, the fledgling nature of the treatment. The organization's chairwoman voiced the fact that it is not rareness that organizes patients' experiences, but certain characteristics that diseases conventionally defined as rare share with other pathologies considered as non-rare¹⁴. The organization goes further than this, explicitly excluding rareness as a criterion for grouping patients and as a relevant characteristic for action. From its point of view, the most important things are the chronic nature and the complexity of the condition and its consequences – medical, emotional, social and professional – for patients. The organization includes rare diseases in the broader category of chronic illnesses and wants them to be treated as such. Although defending the HCM in all its actions, it forms alliances with organizations or federations of patients' organizations concerned with chronic diseases, but keeps its distance vis-à-vis APADR, and refuses to join EURORDIS.

To sum up, the Portuguese experience confirms that rare disease patients' organizations are not necessarily oriented towards the HCM, and that this model does attract interest from non-rare disease organizations. Moreover, the case of the Portuguese organization on lupus shows that the choice of the HCM may come with a critique of the notion of rareness. Although this notion triggers a collective awareness of the existence of rare diseases in Portugal and of the

¹⁴ Huyard (2009) came up with similar findings on rare disease patients' experience in France.

importance of research to obtain better knowledge on complex pathologies, whether rare or not, it neither explains the reasons why certain patients' organizations engage in research, nor does it justify the modes of engagement they choose.

4. Rareness and the dynamics of singularization-generalization

The analysis of the French and Portuguese patients' organizations highlights the role they play in the definition of the conditions that they deal with. It also shows their ability to develop and implement certain forms of engagement in research, and to explain why their conditions justify certain modes of intervention. Emphasizing the problems that patients experience in their daily life (getting a diagnosis, identifying specialists etc.), some of them have put the focus on notions such as complexity, uncertainty, or the chronic nature of conditions rather than on their rareness. The (observable) relations that *particular* organizations develop between *particular* conditions and *particular* forms of engagement in research should thus be interpreted as the outcome of reflexive work carried out by these organizations (in relation to other actors such as public authorities, research institutions and industry). To understand the dynamics of these reconfigurations of causes and conditions, we consider, from a perspective similar to that of Dewey (1938), this reflexive work of patients' organizations as an inquiry aimed at problematizing their conditions, while developing forms of action that provide (provisional) solutions to their problems.

To study this dynamic of problematization, we introduce the two notions of singularization and generalization and explore their essential tension. Singularization corresponds to a set of discourses and practices deployed by actors to investigate the more or less specific character of their problems, and whose definition cannot be separated from their own history (Moreira in press). Generalization denotes the reverse process, by which, to build collective causes, actors explore proximities between their singular situations. As we will see, this process of

singularization-generalization illuminates patients' organizations' rationale for adopting and adapting the HCM, whether they are concerned with rare diseases or not. For the sake of demonstration, we will focus on a few French and Portuguese organizations that have explicitly embraced this process either in their pronouncements or in their actions.

4.1 Singularization

To illustrate the singularization undertaken by patients' organizations, the case of *HPN France – Aplasie médullaire* provides a notable example; its creation in 2003 was the outcome of reflection on the necessary singularization of two rare blood diseases - paroxysmal nocturnal hemoglobinopathy and bone marrow depression -, as compared to more common diseases. The organization split off from an older association that provided financial help and psychological support to families of patients hospitalized in the haematology ward at Saint-Louis hospital in Paris for a bone marrow transplant or a plasmapheresis. These treatments have been applied for many years to rare and non-rare blood diseases, especially leukaemia. *HPN France – Aplasie médullaire* had been founded by three adults with these two rare blood diseases, with the aim of finding less invasive treatments, better adapted to the specificities of their pathologies. During our interview, the organization's vice-chairman clearly described this singularization strategy underlying its action.

Defining the organization's field of competencies, he noted that the organization was meant for “young adults suffering from acquired rare blood diseases for which there exist therapeutics”. It was precisely in order to single out these diseases that the organization actively contributed to the constitution of a French registry of patients concerned with these pathologies. The organization deliberately excluded patients suffering from related diseases (for instance leukaemia, myelodysplasia, or Fanconi's disease) that did not correspond to the criteria that it had defined. It was this same singularization strategy that led the *HPN France –*

Aplasia médullaire to maintain exclusive relations with the ward at Saint-Louis hospital, which in turn contributed to an increasingly sound understanding of these diseases and facilitated therapeutic research. When an American firm contacted the ward a few years ago to test a new class of immunosuppressants called .imab, on PNH, the organization readily agreed. The head of the ward noted that, owing to this collaboration, “It took only five years between the screening of molecules, the proof of concept, the phase 3 clinical trials and the launching of the drug on the market”. Interestingly, the rareness of these diseases¹⁵, a characteristic that distinguishes them from common blood diseases and which the organization brought to light, is now tending to become an inherent feature of their singularity. The organization has therefore taken the decision not to join any ‘rare disease’ coalition, whether French or European (EURORDIS), to avoid being ‘drowning by numbers’, as its vice-chairman put it.

We also found this stubborn willingness to capture singularities and to draw boundaries in some of the other organizations in our surveys. This singularization process does not concern rare disease patients’ organizations only, far from it. APH, the Portuguese organization for haemophilia and other congenital coagulopathies, is a telling example. APH was initially formed around haemophilia. Thanks to the emergence of the issue of rareness in Portugal, APH progressively opened its doors to patients suffering from certain rare blood diseases. As stated earlier, this extension however came with collaborations with specialists and industry that the organization was not used to in the past, with an aim at delineating the specificities of the conditions that today constitute its portfolio. Still another phenomenon illustrates this

¹⁵ 500 people have been diagnosed with PNH in France, and the prevalence of bone marrow depression is 1/500,000 in Europe.

process of singularization: over the past few years, organizations have been created around singular or atypical forms of common pathologies, like certain child cancers or early-onset Alzheimer's disease among young adults. Close to 6% of our French population surveyed in 2006, and 11% in 2009, are organizations of this nature.

The process of singularization, the logic of which is to produce relevant differences, has obvious links with the notion of rareness, since it tends almost inevitably towards the constitution of strictly delimited populations. But whereas rareness implies a stabilization of the definition of the pathology – if only for it to be measured – singularization, as a process of investigation intended to define pathologies and conditions better, suggests a dynamic of constant movement. At the heart of this process, collaborative research plays an essential part, notably when diseases are complex and evolving. Patients indeed not only formulate the problems they encounter; they also test solutions to their problems, thus contributing to the transformation of their conditions and their re-specification thereof, as manifested by the ‘chronicization’ of certain rare diseases that we mentioned above.

4.2 Generalization

The logic of investigation, which as we have just seen, lies at the heart of the process of singularization, simultaneously induces mechanisms of generalization, two main forms of which our fieldwork highlighted. These two mechanisms are very different from the ‘politics of numbers’ – that is the addition of diseases and patients –, in so far as they are based, precisely, on the question of commonalities between the entities and the individuals that are to be aggregated.

- One form of generalization, which we could qualify as epistemic, has progressively transformed researchers' and firms' approach to so-called rare diseases. At a public hearing organized in 2011 by the French Parliamentary Office for Scientific and Technological

Choices on monogenic rare diseases, two researcher-clinicians vehemently argued that, because they display extremely specific phenomena, these diseases enable them to explore fundamental elements of normal functioning and dysfunctioning of certain biological pathways. They could also serve as ‘disease-tests’, even ‘disease-models’, for the study of these pathways. This form of generalization, which takes a strong interest in particular cases as they afford access to realities that traditional nosological classifications tend to hide and to mix up, is made easier with the patients' close collaboration and the constitution of hybrid collectives in which the patients are both the objects and the subjects of research. The patients' organizations see this status of patients transformed into ‘models for experimentation’ as a matter that needs to be treated with caution, as the chairman of the *Association Ostéogénèse Imparfait*e pointed out: “You can't deny the fact that our patients are guinea pigs” – albeit voluntary ones who participate in their own investigation (as the case of *HPN France – Aplasie médullaire* shows) and therefore have a high scientific value. Because it carries the ferment of a possible generalization based on the ubiquity of certain biological mechanisms – ubiquity that researchers would like to prove –, singularization is also becoming attractive from an economic point of view with the upsurge of new regimes of innovation (Callon 2007). Pharmaceutical firms, which for a long time gambled on the development of blockbusters, are increasingly focusing on markets that are differentiated yet based on shared technologies and knowledge (Crompton 2007).

- The second form of translation of the specific into the general that can be observed has gradually altered the self-description of the patients concerned and their families. The case of *Génération 22* is interesting in this respect. The organization was formed in 1998 by the mother of a then young adolescent, born in 1983, who was diagnosed in 1996 with 22q11 deletion syndrome, a syndrome characterized by multiple organic, mental and psychiatric disorders. The manifestation and severity of disorders vary from one patient to another. The

syndrome was not previously unknown but was diagnosed in patients scattered between different medical consultations, based on the most visible signs. In the literature, there are at least three labels and descriptions of the syndrome: DiGeorge syndrome, VCFS (velo-cardio-facial syndrome), and Shprintzen syndrome. The former chairwoman chose to name her organization after the deletion, discovered in 1991, because the main problem for the families is the complex and multiple combinations between heterogeneous disorders that accompany this deletion. The organization thus embraces what Rabinow (1999; Gibbon & Novas 2008) calls 'biosociality'.

Complexity, multiplicity and heterogeneity are the keywords of this strategy that leads *Génération 22* today to join collectives of researchers and patients' organizations working on chromosomal syndromes with psychiatric symptoms. From its point of view, these alliances could lead to a revision of the prevalence of this syndrome, currently estimated at between 1/4,000 and 1/3,000. In particular, the organization believes that adults suffering from schizophrenia, a co-morbidity of the syndrome, could carry the 22q11 micro-deletion, which would have the effect of making the syndrome a borderline case in respect of rareness¹⁶. It

¹⁶ This attention to certain bio-entities brings to the fore the reconfiguration of nosological categories (Hedgecoe 2003; Rabeharisoa & Bourret 2009) as a new basis for translating specific concerns into general issues. When these entities are associated with genetic material, the re-classification resembles what Navon (2011) proposes to call 'genetic designation'. But other entities may be concerned. The French Federation for Brain Research (*Fédération de Recherche sur le Cerveau*), for example, brings together organizations concerned with Alzheimer's disease, strokes and epilepsy, as well as less common neurodegenerative diseases

would therefore like to foster relations with organizations that deal with schizophrenia, to undertake work that could result in the production of generality on the basis of scattered observations focused on singularities. Such an inquiry closely relates to the HCM. It cannot but be collective, for the production of knowledge on complex and intersecting conditions involves an increasing number of bio-entities, patients and specialists from various backgrounds. Patients' organizations are key actors in the mobilization and coordination of these multiple biosocial networks that entails what we call 'politics of recombinant science'.

This 'politics of recombinant science' and the process of generalization that it induces however are not exclusively arranged around bio-entities. The Portuguese organization on lupus for instance, points to what its chairwoman considers as critical social issues like depression that patients, who are mostly women, undergo over many years and that leads them to be stigmatized as "lazy" and "self-victimized" individuals. ALF, the French association on lupus, voices similar concerns. In 2009, it participated in a conference with other rare autoimmune patients' organizations, and raised questions they share, including depression and pregnancy, for which it called for cooperation between biomedical researchers and scientists in human and social sciences. This preoccupation is also to be found in *SolHand*, which focuses on the emotional, psychological and social impacts of rare diseases.

To sum up, we can reasonably argue that the process of singularization-generalization is driven by a form of collective inquiry seeking differences and similarities, and requiring close collaboration between patients and specialists, in the spirit of the HCM. This explains why

such as Huntington's disease or multi-systematized amyotrophy, around the exploration of the brain.

rareness, which designates a sort of frozen moment in this process, has been able to be (and still is) associated with the HCM, and at the same time why this association between the two may well vanish in the long run for certain conditions.

Conclusion

Our article sought to test a hypothesis, made by a number of patients' organizations, as well as by certain social scientists who study them, which posits that the rareness of diseases has led patients' organizations to become proactively involved in research. Based on the inter- and intra-national disparities we observed in France and Portugal, we considered the diversity of ways in which patients' organizations take part in research, and the role of the notion of rareness in their choice of a given mode of involvement over another. Before synthesizing the results of our analysis, we would like to revisit the methodology underpinning our surveys.

The aim of these surveys was not to compare national situations in order to see how contrasting contexts could explain different modes of involvement. The objective was more fundamentally to capture the intense reflexive work that patients' organizations carried out on the notion of rareness and on the links between this notion and the modes of action they chose to follow. This reflexive work led these organizations to think about the problems posed by their diseases, in other words to specify their conditions and the causes they wished to defend. It is this dynamic of causes and conditions, which our surveys highlighted as crucial to patients' organizations' activism, that we described and analyzed.

The first set of results from our surveys concerned the ubiquity of the notion of rareness and, as such, its 'evidential' status in the choices made by patients' organizations regarding given forms of involvement in research. We have shown that many rare disease patients' organizations opted for other forms of involvement in research than the HCM, which

supposedly prevails because of the rareness of their diseases. We also highlighted the fact that, conversely, some non-rare disease patients' organizations did adopt the HCM, thereby calling into question the relevance of the link between the rareness of diseases and the proactive involvement of patients in research. Finally, we gave examples of patients' organizations which, although they chose the HCM, explicitly denied rareness any role in their choice.

The second point that emerged from the surveys is that patients' organizations do not simply put the explanatory power of the notion of rareness into perspective; they also, and more significantly, elaborate new ways of characterizing diseases. The chronic and evolving nature of diseases, the complexity of clinical manifestations, areas of ignorance that they struggle to overcome, the search for diagnoses, and specialists' lack of competence, are raised by patients' organizations to justify their chosen modes of intervention in research. The abstract and formal notion of rareness is thus called into question by patients' reflection on the problems they encounter in their daily lives.

To account for both the historical role of the notion of rareness in the emergence of the HCM and the gradual shift, within certain organizations, towards other justifications for choosing this model, we examined the tension between singularization and generalization. We argued that these two notions emerge as the rationale underpinning the enactment of the HCM by some organizations, albeit not in a consciously expressed form. As we have suggested, the collective investigation organized and structured by the HCM seeks to identify diseases and the associated issues more and more specifically and precisely, while also facilitating and stimulating the connexions with other diseases, thereby giving the questions raised a more general reach. Rareness can be – and often is – associated with the tension between singularization and generalization, of which it is a product rather than a starting point. The distinction is no longer between non-rare and rare diseases, but between organizations that choose to undertake this process of singularization-generalization and those which, for good

reasons, prefer to think of the diseases they deal with as stabilized frameworks, and to develop their action without changing these frameworks.

In proposing that the singularization-generalization of causes and conditions is core to patients' activism, we must then identify the drivers of this dynamic, as well as its consequences. As we have shown, rareness is one of those drivers, which owes its strength to its capacity to make patients major political actors (of what we have called the 'politics of numbers') and scientific actors in their own right (of what we have called the 'politics of recombinant science'). The dynamic of singularization-generalization takes this in a direction that is likely to echo a more general movement, which simultaneously affects political and economic life. Singularization, a process very different from individualization (Rosanvallon, 2011), can be viable and sustainable only if it simultaneously contributes to the construction of common causes. The same dynamic is witnessed in economic markets and innovation regimes they promote (Callon 2007). By granting particular attention to this dialectic of singularization-generalization, patients' organizations would be in a position to participate in (and to benefit from) a more general trend affecting political and economic activities.

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Appendix 1: French patients' organizations included in the fieldwork

<i>NAME</i>	<i>CREATED IN</i>	<i>CONCERNED CONDITIONS</i>
Alliance San Filippo	2006	San Filippo syndrome
Association HPN France - Aplasie Médullaire	2004	Paroxysmal nocturnal hemoglobinuria, and bone marrow depression
Association Wegener Infos et autres Vascularites	2006	Wegener granulomatosis, and other vasculitis
Association Fénix - Maladies rares autrement	2003	vasculitis
AOI. Association Ostéogénèse Imparfait	1985	Osteogenesis imperfecta
ALF. Association Lupus France	1999	Lupus
Association des personnes de petite taille	1976	Dwarfism
Association internationale des malades souffrant de kystes méningés de Tarlov et apparentés	2008	Tarlov meningeal cysts and related conditions
Génération 22 - Association de personnes atteintes de micro-délétion 22q11 et leurs familles	1998	22q11 deletion syndrome
SolHand. Solidarité Handicap - Autour des maladies rares	2007	Rare disabilities and diseases
FRC. Fédération de Recherche sur le Cerveau	2000	Alzheimer disease, Parkinson disease, stroke, epilepsy.

Appendix 2: Portuguese patients' organizations included in the fieldwork

<i>NAME</i>	<i>CREATED IN</i>	<i>CONCERNED CONDITIONS</i>
APART. Associação de Pais e Amigos de Portadores do Síndrome de Rubinstein-Taybi	2003	Rubinstein-Taybi Syndrome
APH. Associação Portuguesa de Hemofilia e de Outras Coagulopatias Congénitas	1976	Haemophilia and other congenital coagulopathies
Associação dos Doentes com Lupus	1992	Lupus

APN. Associação Portuguesa de Doentes Neuromusculares	1992	Neuromuscular diseases
APPDH. Associação Portuguesa de Pais e Doentes com Hemoglobinopatias	1992	Heamoglobinopathies
APADR. Aliança Portuguesa de Associações das Doenças Raras	2009	Rare diseases
RESPIRA. Associação Portuguesa de Pessoas com DPOC e outras Doenças Respiratórias Crónicas	2007	Chronic obstructive lung disease and other chronic respiratory diseases
APAHE. Associação Portuguesa de Ataxias Hereditárias	2006	Hereditary ataxias
RARISSIMAS. Associação Nacional de Deficiências Mentais e Raras	2003	Rare and mental disorders
FEDRA. Federação de Doenças Raras de Portugal	2008	Rare diseases