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Living with the rare late-onset genetic disease CADASIL: Improvising "tactics" to appropriate biomedical knowledge and technology

Madeleine Akrich *, Florence Paterson, Vololona Rabeharisoa

Centre de sociologie de l'innovation, UMR CNRS i3, Mines Paris, PSL University, Paris, France

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ABSTRACT

This study focuses on cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), a rare late-onset neurodegenerative disease of genetic origin. For CADASIL—and for other late-onset genetic conditions—genetic testing can predict whether an individual will develop the disease, even in the absence of symptoms. Multiple bodies of research in the social studies of medicine and in science and technology examine how individuals with genetic risks and diseases live through the in-between situation of being simultaneously healthy and on the cusp of ill-health. Drawing on data from interviews with 30 individuals concerned with CADASIL, we show that they do not allow themselves to be reduced to their genetic status. On the contrary, they appropriate the possibilities offered by biomedical knowledge and technology (genetic testing and reproductive technologies) to, as much as possible, control the way the disease manifests in their lives. We explore three pivotal moments or situations in the lives of these individuals: facing the possibility of genetic testing, dealing with the disease and its surveillance after the diagnosis, and becoming a parent with or without the assistance of reproductive technologies. In contrast to criticisms of *geneticization*, we examine how, at each of these stages, these individuals develop "tactics"—in the sense employed by de Certeau (1990)—with respect to genetics to keep the disease at arm's length and live as *good* a life as possible.

1. Introduction

Over the last few decades, the field of rare genetic diseases has undergone profound changes induced by a twofold shift. First, rare genetic disorders—as a disease category—are presently a mainstream target of contemporary biomedical research and healthcare in many Western and Northern countries and have been declared a public health priority in France since the 2000s—thanks to collective mobilization through patient organizations, the biomedical milieu, and public authorities (Huyard, 2011). Second, biomedical research findings have changed the designation of these diseases (Hedgecoe, 2003; Navon, 2011) by recharacterizing them as genetic mutations, such that what were once considered defects of nature that medical specialists could hardly grasp have been redesignated as genuine pathologies, i.e., entities that lend themselves to diagnosis, clinical description, and—in some cases—care. Consequently, the experience of individuals potentially affected by such a disease has been altered, as they are now exposed to information indicating that they may have a genetic mutation that they may transmit to their offspring. In addition, they are presented with the option of undergoing genetic testing in the absence of any symptoms; however, once done with the test, they may find themselves in the paradoxical situation of knowing that they carry a mutation that causes a disease while also presently being in good health.

This study explores the experience of individuals with or at risk of a rare late-onset genetic disease, cerebral autosomal dominant arteriopathy with subcortical infarcts, and leukoencephalopathy (CADASIL) in the French context. CADASIL is responsible for the slow and progressive accumulation of cerebral ischemic insults that lead to disabling cognitive and motor symptoms at a late age. To date, there is no available cure for CADASIL, although clinical and therapeutic research programs that may lead to preventive treatments are underway in France and other countries. CADASIL is an autosomal dominant genetic disease, which means that individuals carrying the genetic mutation will develop the disease, and their offspring has a 50% probability of inheriting the mutation. Thus, from a medical point of view, someone who carries the genetic mutation will be sick in the—more or less—distant future. Interestingly, our fieldwork reveals that a proportion of our interviewees who carry the mutation do not consider themselves ill, regardless of

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* Corresponding author.
E-mail address: madeleine.akrich@minesparis.psl.eu (M. Akrich).

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whether they report symptoms or not. However, it can hardly be said that they are in denial of the disease, as they have a sound knowledge of the condition, and some of them are enrolled in a longitudinal cohort study conducted by the French reference center on CADASIL. This observation is the common thread in our inquiry into the experience of individuals with CADASIL, with a focus on the following questions: (i) What place does the disease occupy in their lives?, and (ii) How is it that some individuals who carry the mutation and engage with biomedicine assert that they are not ill—a category of interviewees that we thus propose to refer to as *not-ill carriers* (NICs)?

The concept of *geneticization*, first coined by Lippmann (1991), does not fully resolve the aforementioned conundrum. Lippman tirelessly warned against genetic reductionism of diseases and of life writ large. Although it is tempting to think that NICs are resisting genetic reductionism, we contend otherwise, as NICs—and most of the participants in our study—keep the disease at arm's length in their lives, and they do so in part by embracing knowledge of genetics. To deepen our understanding of this situation, we opt to follow the "after geneticization" perspective advanced by Arribas-Ayllon (2016), who criticizes the exaggerations of the essentializing effects of genetics knowledge and highlights the multiplicity of genetics concepts and genetics technologies. The concept of *geneticization* denounces the supposed reductionism and determinism associated with the development of genetics, while the *after geneticization* approach reintroduces the sense of symmetry between genetics and society. In this research, we take Arribas-Ayllon's analysis a step further by showing that individuals with genetic conditions are able to appropriate genetics knowledge and technology and shape their use of these elements to suit their aspirations and needs. The main point we want to emphasize is how individuals with CADASIL rely, at *certain* points, on *certain* opportunities offered by biomedicine in ways that allow them to live a meaningful life from their perspective, i.e., a life that is not reduced to a gene-driven disease.

The history of the very first CADASIL family in France illustrates our main point. The following is mainly based on interviews with a member of the family and the neurologist who discovered the disease. Research into what was then an unknown pathology, which would later be identified as CADASIL, began in 1976 at Lariboisière Hospital in Paris, impelled by the persistence of the then-young neurologist, Marie-Germaine Bousser. Indeed, Marie-Germaine Bousser challenged the Binswanger's disease diagnosis made by her senior colleagues for a patient because the patient did not have arterial hypertension, which is the cause of brain damage in Binswanger's disease. In 1987, the patient's daughter, accompanied by her brother, consulted with Marie-Germaine Bousser because the siblings were experiencing symptoms similar to their father's symptoms. Magnetic resonance imaging (MRI) scans—an emerging technology at the time—performed on all three patients revealed similar abnormalities. At the prompting of Marie-Germaine Bousser, who wanted to investigate a hypothesis of familial clustering of the disease, the first patient (i.e., the father) contacted his other family members one by one and convinced many of them to make the trip to Paris for an MRI scan and a blood test. Thanks to their often-enthusiastic participation, the mutation of the NOTCH3 gene responsible for the disease that would come to be known as CADASIL was identified in 1996 by the team at Lariboisière Hospital, which subsequently became the French reference center for rare vascular diseases of the central nervous system and the retina (CERVCO), including CADASIL as one of its most important targets.

Interestingly, when the first patient's daughter and cousin organized a family gathering in 2008, to which they invited the neurologist Marie-Germaine Bousser, many of their relatives did not attend, although 130 people attended the event. As the cousin explained to us:

> *"I know some people didn't come because they were too afraid to meet [the neurologist]—of her asking them questions about their health—though that was not why she was coming. She was just coming to take part in a family event."*

The people who did not show up expressed a desire not to have biomedicine intrude uncontrollably into their lives. Some may have participated in the initial study, but once the gene was identified—and even once they were done with the diagnosis—they wanted to be able to shape as much as possible—that is, as much as the disease allowed—the in-between situation in which they found themselves.

This episode in the history of this family is illustrative of the research question we address in this study: Why and how do individuals with CADASIL seize *certain* opportunities offered by biomedicine at *certain* points in their lives? In fleshing out our analysis, we borrow the term "tactics," as used by de Certeau (1990). This term connotes the ways in which lay people uses and tinkers with technology for the purpose of "inventing" their daily lives. In our case study, we explore what these tactics are and how they affect the lives of individuals with or at risk of CADASIL.

To answer these questions, we first outline the theoretical background that underpins our study—that is, bodies of research in the social studies of medicine and in science and technology that provide analyses of the multifaceted social dimension of new genetics, such as its impact on the identities of patients and individuals at risk, the management of their situations, as well as their relations within families with a familial predisposition to genetic diseases. We then present our research methods and materials. The paper progresses on to three empirical sections corresponding to three points/situations in the lives of individuals with CADASIL during which the issue of their relationship with biomedicine is at stake in one or more of the following ways: facing the possibility of genetic testing, dealing with the disease and its surveillance after the diagnosis, and becoming a parent with or without reproductive technologies. Finally, we discuss our main findings regarding the tactics individuals with CADASIL employ to appropriate biomedicine. Then, we conclude with two prospective lines of research in the social studies of new genetics.

2. Theoretical background: living with a rare genetic disease

New genetics, which refers to the incorporation of genetics into medical knowledge and practice, has been topical since the late twentieth century to date. In its early days, new genetics triggered criticisms of *geneticization*, i.e., the reduction of people's identities, diseases, and lives to a few genes (Lippmann, 1991). Instead of this general criticism of genetics, Arribas-Ayllon (2016) proposes what he calls an *after geneticization* perspective—that is, in-depth studies of the actual changes brought on by new genetics, including nosography (Hedgecoe, 2003; Navon, 2011), clinical practices in the spheres of various disease conditions (Rabeharisoa and Bourret, 2009; Latimer, 2013), and the contribution of patient organizations to biomedical research (Novas, 2006; Rabeharisoa and Callon, 2004).

Several studies have focused on issues closer to the patient's experience, especially with respect to genetic testing offered to people with a family history of genetic disease—often diseases for which there are no curative treatments. Medical professionals and ethicists have progressively put together a series of procedures for framing this new clinical exercise that has practitioners encountering individuals who are *at risk* but not necessarily ill. This translates to the protocolization of genetic testing, which includes multidisciplinary consultations with geneticists, organ specialists, psychologists, and nurses repeated over a certain period, for individuals at risk of a genetic disease to take their time to weigh the advantages and disadvantages of genetic testing—notably because once a person's genetics status is released, they are no longer in a position to unknown that information—and for medical professionals to take stock of the fears and expectations of these individuals (Williams et al., 1999; Evers-Kiebooms et al., 2000; Hess et al., 2009). Genetic testing protocols for Huntington's disease (HD) are the first to have been established and have served as the *princeps* protocol for late-onset genetic diseases with 100% penetrance for which there is no available cure and, subsequently, for multifactorial diseases with a genetic dimension

(Williams et al., 1999; Hess et al., 2009). In France—and very likely in other countries as well—the genetic testing protocols for CADASIL are inspired by the protocols for HD (Reyes et al., 2012).

The cost-benefit perspective on genetic testing surmises that improved genetic literacy, open interaction with professionals and family members, and time for reflection before deciding will result in choosing the most optimal option for the individuals concerned: to either opt in or opt out of genetic testing. This cost-benefit approach is grounded in the rationale that the individual at risk of a genetic disease will at some point make an informed decision. This approach has proved fruitful to some extent. For instance, before genetic testing was available for HD, 56%–75% of the at-risk population expressed interest in taking the test; however, once the test was available, only 2.5%–20% of these individuals underwent genetic testing (Jacobs and Deatrick, 1999). The follow-through figures for CADASIL genetic testing are similar (Reyes et al., 2012). Social scientists propose a slightly different approach. For instance, Cox (2003) has debunked the concept of rational decisions made on predefined criteria and has shown that the protracted introspection in people have engaged—sometimes paved with prevarications—has ultimately led them to choose genetic testing. Following in the footsteps of Cox, we highlight one additional element in this reflexive process: the multiple contingent routes via which the disease makes itself evident in people's lives. How the disease presents in the lives of individuals, sometimes unexpectedly, is a determinant in the equation of whether they opt in for or choose not to undergo genetic testing.

Once genetic testing has been performed, and if the results come back positive, there is then the question of what it is like to live with a genetic mutation. A constellation of notions such as *perpetual patients* (Finkler, 2000), *partial patients* (Greaves, 2000), and *presymptomatic individual* (Konrad, 2003) have been introduced to denote the situation of carriers who fall somewhere in between health and ill-health. In the same vein, Timmermans and Buchbinder (2010) have coined the umbrella concept "patient-in-waiting," which aptly captures the blurring of the clinical category of *diagnosis*, the proliferation of *proto-diseases* (Rosenberg, 2009), and the rise of *secondary prevention* through genetic screening, all of which are phenomena accompanying the new era of *surveillance medicine* (Armstrong, 1995). Interestingly, the concept of *patient-in-waiting* has been referenced by some medical professionals who have reflected upon "what it is to be affected, yet currently well; diagnosed, yet still not diseased" (Kwon and Steiner, 2011) and on the accompanying clinical activity. Our study allows us to enrich this body of research. Carriers of the genetic mutation involved in CADASIL whom we interviewed turn to biomedicine at *certain* points and in ways that permit them to live as "good" a life as possible in an "extended present" (Geelen et al., 2015). Those we refer to NICs s even explicitly refuse to be labeled *patients-in-waiting*.

The aforementioned notions point to one crucial issue in the lives of individuals who engage with new genetics at *certain* points: that of temporality. This issue takes on salient importance when it comes to dilemmas regarding reproduction. Rare genetic diseases such as CADASIL are hereditary and impact families' lives. There is an extensive literature under the umbrella of *family studies* on how new genetics transforms relations within families through the following lenses: by positioning carriers of a genetic mutation as "moral pioneers" (Rapp, 1987; Cox and Burgess, 2000; Hallowell et al., 2003) responsible for disclosing their genetics status to their relatives, by reflecting on "risky relations" within families (Featherstone et al., 2005; Dimond et al., 2022), and by redesigning kinship (Franklin, 2003). Reproduction features as a highly sensitive issue, with the looming conundrum of transmission. Our fieldwork contributes fresh data and analyses on this issue. Similar to their handling of other related issues, some individuals concerned with CADASIL attempt to dissociate reproduction and heredity by either engaging with or refusing specific biomedical interventions at *certain* points in their lives. Nevertheless, distancing oneself from the "risky family" one belongs to, either with or without biomedical interventions, is a critical issue for individuals with CADASIL, as highlighted by the history of the first family diagnosed with the condition—which we mentioned in the introduction.

In a word, social studies of new genetics have shown that new genetics constitutes a watershed in the emergence of predictive and preventive medicine and the accompanying ethical and social problems. Our study contributes to the literature on this subject by examining the lives of people with—or at risk of—CADASIL, in an era where new genetics are part and parcel of the field of rare genetic diseases, preventive treatments are within reach (according to researchers and clinicians), and individuals concerned with CADASIL are more familiar with genetic parlance than they were a few decades ago. This encouraged us to expand upon the *after geneticization* perspective (Arribas-Ayllon, 2016) to explore the affordances of genetics knowledge, genetics technologies, and the *tactics* (de Certeau, 1990) that individuals at risk of or afflicted by CADASIL formulate to appropriate this knowledge and technology.

3. Methods and materials

This research draws on 30 semi-structured interviews with individuals concerned with CADASIL, which were conducted between February 2018 and February 2020 as part of a large clinical research project conducted by the Department of Neurology at Lariboisière Hospital in Paris.

Interviewees from different regions of France were recruited on a voluntary basis via the website and newsletter of the patient organization, CADASIL France, as well as through a presentation of the study at two of its annual meetings and through documents displayed in the waiting room at Lariboisière Hospital. Information about the study indicated that it was possible to schedule an interview anonymously by contacting us directly and without providing any identifying details. Additional interviewees came to us after they were referred to the study. Thus, in contrast to similar studies in the literature (Akrich et al., 2024), our recruitment protocol was not limited to the specialized medical consultation at Lariboisière Hospital but included a broader outreach through the website of CADASIL France; hence the enrollment of at-risk individuals who had not yet engaged in the genetic testing protocol at the time of their interview.

The interviewee population includes the following categories: (i) carriers of the genetic mutation with clear symptoms of the disease who consider themselves ill (N = 11), (ii) carriers of the genetic mutation with no or mild symptoms of the disease who do not consider themselves ill (N = 6), (iii) at-risk individuals on account of a known history of the disease in their family but who have not been diagnosed as at the time of interview (N = 4) [4], and (iv) spouses or partners of individuals with CADASIL (N = 9) (See Table 1).

Table 1
– Interviewee population: disease status, age, and gender.

Disease status	
Carriers of the genetic mutation with clear symptoms of CADASIL who consider themselves ill	11
Carriers of the genetic mutation who report no symptoms, mild symptoms, or non-conclusive symptoms of CADASIL and do not consider themselves ill	6
At-risk individuals who have not undergone genetic testing	4
Non-genetic relatives (spouse or partner)	9
Age	
70 years or older	7
60–69 years	7
50–59 years	7
40–49 years	4
30–39 years	3
20–29 years	1
Under 20 years	1
Gender	
Female	22
Male	8
Total	**30**

Notably, some carriers of the genetic mutation do not consider themselves ill. Rather than labeling them *carriers*, we designate them as NICs where relevant in the subsequent subsections.

Interviews were conducted either at our office or at the interviewees' homeplaces, depending on their choice. The interviews were planned as long sessions lasting an average of 2 h, with the objective of reconstructing the interviewee's detailed history of CADASIL and genetic testing, the impact on their daily lives and how situations were envisioned and handled within their families, and, if relevant, their involvement in the creation and activities of CADASIL France. The final part of the interview focused on the interviewee's position on prospective clinical trials. The interviews were transcribed by the authors, who then proceeded to the reading and coding of the interviews using the grounded theory methodology (Glaser and Strauss, 1967).

4. Facing the possibility of genetic testing

The question of how individuals engage with genetic testing is pertinent here. Along with aspects regarding whether they are caught up in this possibility or retain some form of control over the decision. To answer these questions, it is worth examining the processes that lead these individuals to submit being tested and the tactics they devise along the way.

A distinction should be made between individuals with a family history of the disease and those who had been unaware that there is a familial recurrence of the disease in their family. The latter experienced disturbances in their bodies and sought medical attention in the hope of getting treatment. They recounted that they did not anticipate the consequences of the diagnosis they received, especially the aspect of the discovery pertaining to the hereditary nature of the condition. Their encounters with genetic testing were simultaneously desired and tempestuous.

However, knowledge of a family history of the disease does not necessarily lead to seeking timely diagnosis. The CERVCO Reference Center recommends not rushing into genetic testing and proposes a multistep process similar to the staggered process employed in HD genetic testing to give room for individuals to contemplate the implications of knowing whether they have the disease or not and the impact it would have on their lives. Consequently, a significant proportion of at-risk individuals tend to delay getting a diagnosis until they begin to experience what they perceive as overt symptoms of the disease (Akrich et al., 2024). The in-depth interviews we conducted allowed us to explore this issue in depth. Often, these individuals get tested several years or even decades after discovering that they are at risk, and the point at which they undergo testing is linked both to the evolution of the disease and to the evolution of the meaning they ascribe to the disease in their lives.

Some of these individuals suffer from a range of disorders for which they do not find solutions and eventually turn to genetic testing once the family disease is known, even if their disorders are not considered by health professionals as CADASIL-typical. For both Sylvain, who has had to deal with a series of psychological and physical disorders since childhood, to which he attributes a series of personal and professional setbacks, and Tania, who develops "mood disorders that turn [her] marital and professional life into jeopardy," going through the diagnostic process was driven in part by a desire to make sense of painful experiences.

In other cases, until an event or a person prompts the individual to make a connection, the knowledge of the disease in the family remains something abstract that is not integrated as a concern for themselves. When his older brother revealed the existence of the disease after he was diagnosed, Frédéric did not fully grasp the implications. Eight years later, Frédéric sought medical help for severe migraines. Concern grew when the radiologist awkwardly told him that his MRI scan showed "the image of an 80-year-old's brain" though he was 30 years younger. At first, he did not make the connection to his brother's disease and suspected it was Alzheimer's until his mother-in-law pointed out the similarities. He decided to get tested, relieved to see that his brother was living well with the disease. Another interviewee, Lionel, had been suffering from severe migraines for a long time. When his wife, a medical doctor, had him examined by colleagues at the hospital, they were unable to interpret the abnormalities found on the MRI scans. Twenty years later, his wife incidentally learned of the familial recurrence of the disease in his family and, in a state of extreme anxiety, urged her husband to seek a diagnosis. Having no symptoms other than migraines, Lionel treated the issue with nonchalance but finally relented after a period described by his wife as "locked-in denial" that caused marital tension.

In other cases, the individuals progressively mature to the point where they decide to undergo genetic testing. They do not ignore the risks or symptoms, but they make the decision to handle the issues by blocking them out of their lives for as long as possible and prioritizing other aspects of their lives. When she first learned of the disease, Gabrielle said she wanted to get to know her status. She began the diagnostic process, then decided to opt out: "I didn't want to be in the shoes of an ill person." However, some fifteen years later, she realized that the idea of illness had become an obsession:

> *"I spent my time—between the moment we received this information and a few months ago when I took the test—with this in the back of my mind like a sword of Damocles or unresolved questions about what I could interpret as symptoms. And that's why I ended up doing it, because it weighed on me to always wonder and not know."*

Another interviewee, Betty, deliberately kept the disease at the margins of her life for over twenty years; so much so that when she suffered mild aphasia during her pregnancy, she let the doctors suspect multiple sclerosis, even though she had made the connection with CADASIL herself. More than ten years later, anticipating the possibility of treatment, she began the diagnostic process:

> *"I actually thought that maybe they had made progress, maybe there was a drug, so maybe it was a good idea for me to do the diagnosis, so that if they ever found a drug, they would give it to me, and I wouldn't be at a loss. I wouldn't be ten years late."*

In both cases, the move toward greater proximity to the biomedical world is linked to the acceptance of the idea that they had the disease already, either because it was anticipated or because it was at the back of their minds.

The various examples presented here show the extent to which the decision to get tested and follow through with the diagnosis cannot be understood as the product of a rational pondering of the disadvantages and advantages of each option. This is not to say that people do not bear these arguments in mind but that the arguments are not the decisive factors. In this respect, our argument is more in keeping with that of Cox (2003) who emphasizes the slow process that leads to a decision, which is perceived as obvious at the moment the decision is made. Nevertheless, in our case study, the disease itself, whether through its physical or psychological manifestations, appears to play an important role in shaping how people engage in genetic testing, as the shift toward diagnosis is the culmination of a process that brings the disease into people's lives. As long as the disease remains more or less silent, most participants have developed and maintain tactics for delaying genetic testing—which would make the existence of the disease harder to ignore, as well as make it tougher to keep the prospect of the disease presenting at the periphery of their minds.

5. Dealing with the disease and its surveillance after diagnosis

Given the above, testing positive rarely comes as a surprise; the diagnosis of CADASIL is not so much a "biographical disruption" (Bury, 1982) as an event for which affected individuals have been somehow prepared. This does not mean that they are fearless regarding the

disease—ten of our interviewees used the expression, *"having a sword of Damocles" hanging over their head*—but that the possibility of having the disease was already part of their history. For these individuals, CADASIL is a "biographically anticipated illness" (Pound et al., 1998; Williams, 2000) in that they have progressively integrated the possibility of having the disease. These raises the following questions: What then does the diagnosis do to these people? and how do they live with it?

Our empirical material allows us to propose that individuals with CADASIL are actively refraining from being labeled "patients-in-waiting" (Timmermans and Buchbinder, 2010), as indicated by the effort they invest into keeping the disease at arm's length after receiving a diagnosis—as does their pondering of biomedical knowledge, surveillance, and interventions. Their efforts manifest in various tactics, three of which are particularly telling: (i) developing a reflexive attitude toward biomedical knowledge and surveillance, (ii) using their diagnosis to make the disease *present-absent*, and (iii) placing themselves beyond the reach of their relatives' medical gaze.

5.1. Developing a reflexive attitude toward biomedical knowledge and surveillance

Morgane is one of those individuals whom we refer to as NICs. She is in her thirties. Her father died of CADASIL. Her diagnosis was made quite unexpectedly while she was hospitalized after an assault and mentioned to the medical team that there is a history of CADASIL in her family. After an MRI scan that revealed abnormalities, she underwent genetic testing and the results turned out to be positive. Asked about changes that the diagnosis has brought into her life, she states, "My life has not changed. I am not ill." This somehow articulates Canguilhem's (1991) distinction between "having a disease" and "being sick". Her only worry is becoming like her father, whose dying had been terrible. Thus, despite being asymptomatic, she volunteers to participate in a longitudinal cohort study on CADASIL at Lariboisière Hospital, which offers regular check-ups, including cognitive tests. While relativizing the meaning of the tests, Morgane says, "They are rather difficult. I suspect that even 'normal' people may not pass."

Like Morgane, Lionel is part of the cohort and has quite a critical view of the "math" exercises that are part of the cognitive tests:

> *"I don't want to seem pretentious, but I am at ease with numbers. The tests are not specific enough. On the day I would not be able to handle numbers anymore, that would be a major evolution [of the disease]."*

He wonders how to distinguish the effects of age from those of disease. As does Serge, a retired engineer, who is involved in the patient organization, CADASIL France. Serge staves off physical and cognitive decline by practicing sports on a regular basis and learning a new language.

These three cases show how keeping the disease at arm's length comes with a reflexive attitude toward biomedical knowledge and surveillance, which mirrors the attitude of those who, conversely, are always wondering whether this or that sensation could be a symptom of the disease. Carriers of the genetic mutation, notably those we refer to as NICs, are well aware that CADASIL is heterogeneous. They clearly relativize some symptoms, such as memory loss, that may be related to multiple phenomena—notably aging. Furthermore, although enrolled in medical surveillance protocol, they are cautious about the results of their tests, such that they compare their unique situation or experience with those of their sick relatives. This latter point reminds what Snell and Ilpo (2020) have observed with people who have gene-driven cardiovascular diseases in their families: carriers tend to refer to their sick relatives to assess their own situation and ponder biomedical knowledge and surveillance accordingly to keep the disease at arm's length.

5.2. Using the diagnosis to make the disease "present-absent"

We mentioned earlier the case of people who manifested a series of health problems intimately intertwined with personal issues and for whom CADASIL was an "illness you have to fight to get" (Dumit, 2006). The diagnosis helps these individuals make sense of a chaotic existence, and sometimes it also helps them sort out what they deem priorities in their life.

Mirko recounted memories of married life, which was filled with endless arguments with his ex-wife, and acknowledged that he was often violent. Diagnosed with CADASIL, he parallels his behavior with the disease, although without the certainties though, and tends to indulge himself. He has met someone who, according to him, is ready to accept him along his disease: "We are very happy together, and she told me 'I will never let you down. Even if something happens tomorrow, I will always be by your side'."

Dalia has had multiple health problems, including depression and bipolar disorder, that have led her to three suicide attempts. It was a stroke that triggered her diagnosis. Interestingly though, her main concern is not CADASIL but bipolar disorder, recognized as a possible consequence of CADASIL, that disturbs her professional and personal life. Her diagnosis of CADASIL consolidated the diagnosis of bipolar disorder by giving it a biological basis; it permits her to focus on bipolar disorder, which she calls a "mild bipolar depression," and to get good care for.

Peggy's situation is somewhat similar to Dalia's, as she also has had an impressive list of health problems, ranging from painful menstruation to breast cancer. She is the daughter of an eminent professor of medicine who died of strokes, and she learned about CADASIL from an internist she met in one of her numerous medical consultations. She recounts her tense relationship with medical doctors and specialists she has consulted, who, according to her, were patronizing and brushed away her multiple problems, arguing that they are not linked to CADASIL. The hard-won diagnosis does not particularly bother her; rather, it provides the ammunition she needs against those who claim she is "completely mad."

The diagnosis does not only help people objectify behavioral disorders, but it is a means for certain people to privilege certain priorities or live an "extended present," as Geelen et al. (2015) put it. Sylvain has had recurrent behavioral problems in his youth, notably at his workplace, and has been told by his parents that he has been "pretending" to be sick. After CADASIL was diagnosed, he made the decision to live as good a life as possible, devoting himself to what pleases him the most: sculpture. Frédéric has passed an agreement with his partner: to live apart and see each other occasionally to share only "good moments."

The situations we described show how some people strive to make the disease "present-absent." Diagnosis helps to sort things out: the disease is there, and it takes its share of the troubles observed, but alongside it, there is a "good life" that can unfold *hic et nunc* all the more.

5.3. Placing oneself beyond the medical gaze of relatives

The individuals concerned about CADASIL, whom we interviewed, fully understand that the disease does not have a rosy outlook. This is notably the case for relatives who manifest much anxiety for the future. Relatives may even create toxic relationships within the family. This was the case with Vanessa's family. Vanessa, whose husband died of CADASIL, recounted that her husband's brother-in-law forced family members to undergo genetic testing when he discovered that his wife was sick. He claimed to them that he had "euthanized" his wife, making them accomplices in an act that filled them with dread.

Delphine's case is less dramatic than Vanessa's but is illustrative of how some family members may bring the disease back into the lives of their sick relatives. Her father was diagnosed with CADASIL and a bipolar disorder, and her own genetic test turned out to be positive. Her mother, a psychiatrist by occupation, considers that her daughter must keep her updated with the disease: "I feel so much like I'm constantly under my mother's surveillance," echoing the burden of mutual observations within "risky families." (Featherstone et al., 2005). Delphine

goes on to add,

> *"What I blame my mother for is that when she talks about me with her friends, she talks about CADASIL. I said to her yesterday, 'But why don't you talk about other things? Why don't you talk about the good things in my life?'"*

Pregnant at the time of interview, she underwent prenatal diagnosis to know whether her fetus carries the mutation or not. To place herself beyond the reach of her mother's medical gaze, she did not inform her about this biomedical intervention.

Our interviews show that after diagnosis, people continue to keep the disease at arm's length in a way that allows them to live as normal a life as possible. This does not imply that they deny the disease and the devastation that it may bring—many of them have witnessed the lives of relatives living with CADASIL—but for the time being, they do not wish to live like "patients-in-waiting" (Timmermans and Buchbinder, 2010). Interestingly, they rely on biomedicine, each in their own way, in their quest for a good life here and now. In contrast to reductionism and determinism associated with geneticization, it is noteworthy that the tactics people use to appropriate biomedical knowledge, surveillance, and interventions are not alien to their efforts to put the disease in what they deem is its proper place.

6. Becoming a parent with or without reproductive technologies

The hereditary nature of CADASIL was highlighted as a sensitive issue by some of our interviewees, as it is an autosomal dominant genetic disease. This section explores how their concern with inheritance further translates into other tactics for keeping the disease at arm's length. We focus on singular accounts of parents and grandparents that illustrate different ways of dealing—or not dealing—with genetic testing or the diagnostic tests offered by reproductive medicine, namely prenatal diagnosis (PND) and preimplantation genetic diagnosis (PGD).

6.1. CADASIL: a distant prospect

Having the project to become a parent is a time when the place of the disease in one's life is put to the test, as it poses the question of whether one should be tested to make a fully informed choice. A number of people actively choose not to investigate their status, demonstrating that hereditary risk is not in itself permanently problematic (Cox and McKellin, 1999). Speaking about her and her spouse, Gabrielle had the following to say:

> *"It wasn't an issue for us because despite everything, this disease—I was still young—was a distant prospect. (…) Today I tell myself that in the end I'm glad I didn't do it [genetic testing] at the time because maybe I wouldn't have had a third child."*

Furthermore, in reference to the aspect of the disease being a distant prospect, Gemma explicitly counters the biomedical problematization of reproduction with an alternative mode of questioning:

> *"I was wondering whether I should take the test to see if I have it [the mutation] or not because I could potentially pass it on, it's not just my life that is at stake. My thinking about it was, 'How old am I? I'm 30. I have lived well up to this point,' I mean, it's not a disease that strikes when you are 10 or 20, but when you are an adult and even later in general. So, I said to myself, 'Is this really the right question to ask?'"*

Being an NIC does not necessarily bring a drastically different outlook on childbearing plans. Morgane and her partner are considering conceiving "normally," meaning without the preventive techniques presented to her during genetic counseling. Rather than a far-off perspective, the couple's thoughts and plans are focused on the present experience:

> *"For the time being, she sees that I'm living well, and so are my brothers (…), she told me that there is still a large chunk of life that we are living well, and that, with regard to research, no one knows whether or not there will later be a treatment."*

6.2. Facing an unbearable prospect

For some people, however, the idea of *transmitting* the disease is unbearable. Fleur takes this stance particularly far away. She has undergone a PGD to enable her to conceive a child who is unaffected by the disease, without disclosing her genetics status. She has resorted to biomedical resources as a way of literally shielding the family she and her partner are about to start from the disease—her case highlights the fact that keeping the disease at bay takes a lot of effort.

For Delphine, involving reproductive medicine is a matter of course: even before learning the details from the geneticist, she and her partner had opted for PND, considering that the procedure allowed them to hope "conceiving naturally":

> *"Right now, we're starting to talk about the unnatural aspect of it, and that's no fun, that's for sure. If I have to terminate the pregnancy, it will be very hard, but it will be even harder if I do nothing. I don't want to think that I'm going to pass this disease on to my children, so the decision for us is very clear: we won't keep a child who's carrying CADASIL."*

The procedure also contributes to making the announcement of the pregnancy as "ordinary" and as happy a family event as possible, and an important rite of passage within kinship networks (Atkinson et al., 2013). Delphine says:

> *"I will be the first in the family to have a child (…) I want it to be a happy event, when I tell everyone, I want it to be 'yes, we are going to keep the child, we have done the test'."*

The involvement of biomedical intervention (PND) thus appears here as a means of preserving the arrival of a child as a "natural" physical and social event and preventing any other form of biomedicalization related to the disease in the child's future.

6.3. The contrasting views of grandparents-to-be and parents-to-be

The views of grandparents-to-be often contrast those of parents-to-be: the future grandparents we interviewed tended to favor biomedical approaches to reproduction. Lehmann et al. (2011), who researched the experiences of X-linked carrier grandmothers, suggest that this attitude may be the result of their recurrent feelings of guilt and responsibility in transmitting the disease. Our findings suggest that parents of young adults expect their children to undergo genetic testing or to use diagnostic tests offered by reproductive medicine. Incorporating biographical and temporal considerations, parents describe the uncomfortable dilemma they face between their view that their adult children should decide for themselves, so as parents they must be careful not to be too insistent, and their conviction that genetic testing is essential to prevent the birth of children carrying the mutation.

For Dalia, who is convinced that "testing a fetus for this" is currently not feasible, anticipation is key; there is a right time for genetic testing, and even a pressing need when it comes to one of her two daughters. She seems puzzled by the lack of a clear-cut answer from either of them regarding what appears to be a recurring topic of discussion:

> *"The youngest, I am going to wait a bit, until next year, and then I will talk to her again because by then she will be settled in her job, and so on. The eldest, I think I really need to talk it over with her, because now she is in a relationship with her boyfriend, so I think it's time to talk to them."*

In the same vein, Laetitia gives a reflexive account expressing both her inability to do much and her disagreement with the ways of her son and his partner:

"His girlfriend wants to have a child before she is 30; she knows there is this disease. (..) I don't think anyone has the right to wait for the last moment to get tested. I didn't tell her because I know how my children are; they will tell me it's none of your business. (…) Since they have come of age, I tell myself that their lives are their own, but at the same time I think it's a pity not to do it [genetic testing], because if they give birth to a child who is a carrier of this, well who has this, it's a pity. If I had known [about CADASIL], I don't think I would have had children."

What emerges from these accounts – and is also found in the different approaches to genetic testing linked to the parental plans mentioned above – is the discrepancy between these (future) grandparents' medicalized and anticipatory approach and their children's apparent indecisiveness or avoidance of these issues. Interpreting this difference is complex: beyond possible ethical considerations, children may also want to avoid their parents' meddling in these matters by not sharing their questions or choices, as Delphine's case illustrates. We can also assume, supported by the preceding developments, that parents and children may be in different temporalities regarding the disease, while for the parents it is undeniably present, for the children it remains on a distant horizon.

7. Discussion

Our research examines how individuals concerned about CADASIL appropriate genetics knowledge and engage with the following biomedical practices: genetic testing, longitudinal cohort studies, and reproductive technologies. The *after geneticization* perspective (Arribas-Ayllon, 2016) we have adopted has been informed by our empirical material, which shows how patients, at-risk individuals, and their relatives turn to biomedical practices in pragmatic and situation-specific ways to master their lives with the (risk of) disease. We borrow the term "tactics" from de Certeau (1990) to denote the multiple arrangements they put together with biomedicine for inventing as good and ordinary a life as possible with CADASIL. To describe and analyze these tactics, it would therefore be inaccurate to talk about the "geneticization" of life, but rather of appropriation of genetics knowledge and biomedical practices into life. This has allowed us to make a few contributions at the intersection of social studies of new genetics and science and technology studies.

First, many research studies have investigated the process through which individuals concerned about genetic diseases come to undergo genetic testing at some point. In contrast to the rational decision-making process through which people are supposed to ponder the pros and cons of genetic testing, which has led to the setting of protocols in many countries (Evers-Kiebooms et al., 2000; Fortea et al., 2011), social scientists have analyzed the long reflexive path through which individuals with CADASIL eventually come to undergo genetic testing. Cox (2003) has demonstrated that the concepts of rational decision-making backed upon clear-cut criteria does not capture the complex and hesitant process that individuals with CADASIL go through. This processual approach is not alien to genetic testing protocol, although it somehow extends and diversifies the modalities and times to decision. Our contribution to this processual understanding of genetic testing is slightly different. Indeed, our empirical material has shown that the ways the disease itself manifests or is enacted, sometimes unexpectedly, throughout people's lives play a decisive role in their undergoing genetic testing. Somehow then, it is the singular articulation of the disease to people's lives that results in their undergoing genetic testing. As the disease gradually takes hold in people's lives, not least because they start to show symptoms or because the situation of their sick relatives deteriorates, they turn from being "concerned" people to being "affected" people for whom genetic testing takes on a tangible meaning. This may explain why, in the case of CADASIL at least, the distant perspective of preventive treatments is not a determinant criterion in people's approach to genetic testing (Akrich et al., 2024). At a more general level, this suggests that individuals at risk of CADASIL seldom come to presymptomatic genetic testing before some symptoms manifest, though mild and uncertain.

Second, there is an extensive body of research on what it is to live as a carrier of a genetic mutation and yet not be sick. This situation challenges traditional clinical work organized around the nexus of diagnosis and care. It is also unsettling for people who know that they will surely be affected by the disease at some point but do not know when and how. This situation is all the more critical in that there is no treatment available, either curative or preventive. The image of the "sword of Damocles" used by many individuals at risk of CADASIL translates this liminal position on the frontier of health and illness. This has prompted the setting of surveillance programs for at-risk individuals, whom Timmermans and Buchbinder (2010) refer to as "patients-in-waiting." Genetic screening and related surveillance programs have been blamed for the pervasive biomedicalization of life. Our fieldwork sheds a different light on people's enrolling in biomedical surveillance. As with genetic testing, they put together tactics where biomedical knowledge and surveillance are part and parcel of their efforts to keep the disease at arm's length, i.e., not to be invaded by the disease and go on with as good and ordinary a life, *hic et nunc*, as possible. This does not imply that they deny the disease, as their relatives sometimes suggest, but that they proactively refuse to be in a position of "patients-in-waiting." Interestingly, as Timmermans and Buchbinder (2010) have shown, it is their relatives who occupy this position, fearing the future and the upcoming impact of the disease on family lives. The *presentism* of individuals at risk of CADASIL—or, more precisely, their reworking of the temporality of life—is one issue that our research helps bring to the fore.

Third, this issue of temporality is very much at the core of reproductive issues, which at-risk individuals work through. Our empirical material provides examples of tactics that include—or do not include—biomedical interventions through which these individuals strive to disentangle reproduction and heredity and/or to keep parental projects within the scope of *natural* and ordinary events in life. This is not meant to understate the invasiveness of reproductive technologies, which many rich and detailed research works have documented, but to point to the affordances of those technologies which at-risk individuals appropriate as part and parcel of their pursuit of a life as "good" as possible.

To recap, when examining the lives of individuals concerned about rare late-onset genetic diseases such as CADASIL, we can fairly say that the topics of "geneticization" and "biomedicalization" fail to account for the appropriation of genetics knowledge and biomedical interventions into their daily lives with the (risk of) diseases. The term "tactics" is used in our study as a vehicle to introduce this multifaceted, sometimes contentious organizing of one's life with biomedical technology.

8. Conclusion

In conclusion, we propose two prospective lines of research. At a time when new genetics is no longer that new—it is now institutionalized in biomedical research and healthcare policies, and genetic literacy is likely higher than it was a few decades ago, if only because new genetics is heavily popularized—it is worth renewing research into the normativity it carries. By this, we refer to the shifting attention from broad criticism and/or celebration of the era of new genetics to its multiple unfoldings in local situations. We propose that what is deemed a *good* life and what this entails for individuals with genetic diseases remain empirical questions. Social research on new genetics and science and technology research have a lot to offer from this perspective. For instance, people's situated resistance to certain biomedical technologies at certain points in their lives would provide interesting insights into this normativity question. The case of Fleur, which we mentioned earlier, is very intriguing: she has accepted sophisticated and complex reproductive technology to make sure that her baby-to-be will not carry the mutation, whereas refusing to engage in genetic testing for herself to avoid knowing about her own genetic status. What is a "good" life for

her is enacted as a completely different thing than a "good" life for her child.

A second line of research concerns the family as a genetically defined unit. In addition to existing research on this topic, we think that one issue is worth exploring. Throughout our fieldwork, we have witnessed how new genetics puts intergenerational relations to the test: parents and children often disagree on the importance that should be placed on genetic kinship and the relevant reproductive technologies. These tensions are interesting to dig further to extend "family studies" into inquiries into how new genetics impact different generations of individuals with CADASIL.

CRediT authorship contribution statement

Madeleine Akrich: Writing – original draft, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Florence Paterson:** Writing – original draft, Formal analysis, Data curation, Conceptualization. **Vololona Rabeharisoa:** Writing – original draft, Project administration, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Ethical approval statement

This research work received ethical clearance (Opinion number 18-485 dated May 15, 2018) from the IRB of INSERM's Ethics Evaluation Committee (CEEI) (IRB00003888, IORG0003254, FWA00005831). INSERM is the French Institute for Medical Research. Transcripts of all interviews were anonymized and stored in a locked, dedicated desk space. In this paper, the interviewees have been assigned pseudonyms.

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Declaration of competing interest

The authors report no potential competing interests.

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Data availability

The authors do not have permission to share data.

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