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At-risk individuals and presymptomatic diagnosis for late-onset neurodegenerative disease

PERSPECTIVES FOR THE POTENTIAL DEVELOPMENT OF CLINICAL TRIALS

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ABSTRACT

CADASIL is an adult-onset genetic neurodegenerative disease, associated with recurrent strokes (cerebral infarcts) susceptible to generate disabling cognitive and motor related disorders, especially after the age of 50. Although there is currently no cure, the prospect opened up by research into new therapies raises the issue of the participation of asymptomatic carriers of the genetic mutation in the planned clinical trials. Inclusion in the trials will likely presuppose that they accept presymptomatic diagnosis. Our focus is on this at-risk population, described in the literature as being in majority unwilling to know their genetic status. On the basis of findings from a questionnaire survey of people concerned by CADASIL (N=359), carried out as part of the TRT-cSDV project coordinated by the CERVCO, we discuss both what underlies at-risk people's choices to whether or not undergo genetic testing, and what might constitute, in the course of the experience of living with the risk of developing the disease, the tipping point leading people who initially were not interested in presymptomatic diagnosis to finally resort to it. We suggest that, far from being a straightforward and unambiguous journey, the decision process leading to the choices to keep ignoring their genetic status or be diagnosed has mainly to do with the desire to distance themselves from the disease to prevent it from taking over their life, but also with an entanglement between progression in age and the disease making its presence felt, and also their relationship to uncertainty, that bringing the prospect of therapy for CADASIL a step closer may possibly change.

KEYWORDS

Presymptomatic diagnosis; genetic testing; CADASIL; decision making; at-risk populations; family disease.

Introduction

CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy) is a genetic neurodegenerative disease, identified in 1991. As its name indicates, it is transmitted as an autosomal dominant trait with complete penetrance, which means that any offspring of a carrier of the mutated gene has a 50% probability of being a carrier and that the carriers will all present clinical manifestations. CADASIL is an adult-onset disease whose first symptoms (generally migraine with or without aura) usually appear between the ages of 20 and 40. However, the most disabling symptoms resulting from the recurrent strokes (cerebral infarcts) associated with the disease, namely the gradual onset of cognitive disorders (concentration and memory impairment and loss of other cognitive skills, dementia) and walking and balance difficulties, most commonly do not appear until the age of 50, or even later.

To date, there is no treatment for this disease. The presymptomatic diagnosis allowing at-risk individuals to know whether they are carriers of the genetic mutation is based on protocols inspired by those used for Huntington's disease, another late-onset genetic neurodegenerative disorder. The protocol used in France, at the CADASIL reference center, is consistent with what is observed internationally (Crook et al., 2022): it provides for various specialized consultations (geneticist, neurologist, psychologist...) and a delay before the decision is made whether or not to proceed with the diagnosis, so that each person has the opportunity to reflect on what knowing their status could mean for them. As a result of this policy, the use of presymptomatic diagnosis has been very limited: a study carried out in France in 2012 showed that only a third of people who consulted with the intention of undergoing a presymptomatic diagnosis actually went through with it (Reyes et al., 2012), which is in line with the findings of several similar studies carried out since the widespread introduction of this type of testing (Evers-Kiebooms et al., 2000; Fortea et al., 2011; Williams et al., 1999).

However, the development of research into these diseases and the prospect of clinical trials on potential treatments are now raising concerns among researchers and clinicians about the adequacy of the current presymptomatic diagnosis protocol, because to be effective, potential treatments will likely be given before the onset of lesions caused by small cerebral infarcts, and therefore before the development of symptoms. In order to adjust the pre-symptomatic diagnosis protocols accordingly, better understanding is needed of the people who may potentially be eligible, and this importantly means both people who have considered such diagnosis and decided not to proceed after following the protocol, and those who are not considering it, at least not to the point of seeking advice about it. Understanding the reasons behind these choices is crucial, as is gaining an insight into what may be the tipping point that leads people who initially were not interested in diagnosis to finally resort to it. These were two of the main topics discussed in this paper, based on the findings of the questionnaire survey we carried out of people dealing with CADASIL. Before delving any further, let's look at some insights that can be drawn from previous surveys of concerned populations regarding presymptomatic diagnosis.`

In addition to the literature on the general ethical principles that should guide practitioners in this unprecedented situation where an individual can learn whether he or she has a disease

even before its onset, a number of studies have focused on genetic counselling protocols for people at risk for a genetic disease. Surveys have been carried out, often by healthcare professionals, to investigate people at risk, their socio-economic characteristics, their family situation, their motivations and their expectations. One of the main results of these studies was to show that in the case of late-onset diseases a small proportion of people at risk actually undergo genetic testing (Crook et al., 2021; Evers-Kiebooms et al., 2000; Fortea et al., 2011; Jacobs & Deatrick, 1999; Williams et al., 1999). They are more likely to turn to genetic testing when treatment is available, although not systematically (Leite et al., 2017; Medlej-Hashim & Mégarbané, 2005; Paneque et al., 2019).

A number of these studies have focused on describing people's motivations for opting or not for presymptomatic diagnosis in the case of late-onset neurodegenerative diseases, and among them some have only studied the motivations of those who actually underwent screening (Cox, 2003; Leite et al., 2017; Ramond et al., 2019); others have looked upstream of the decision, focusing on people who consulted regardless of their final decision (Cox & McKellin, 1999; Ibisler et al., 2017; Reyes et al., 2012); and others have investigated related issues such as the comparative evolution of people who have and have not undergone screening (Cohn-Hokke et al., 2018) or the propensity of Huntington's gene carriers to recommend or not testing to relatives (Pierron et al., 2021).

Different methods were used in these studies: file review, questionnaires, interviews. However, most shared a recruitment method involving a close link to a hospital department: respondents had at least contacted this unit in view of a presymptomatic diagnosis. This introduces an obvious bias since it excludes people who have decided from the outset not to seek such a diagnosis.

Two articles are exceptions to this rule. The first (Tillerås et al., 2020) is a secondary analysis of interviews of 33 people at risk of developing Huntington's disease, of whom 19 were tested, on the experience of growing up in a family affected by Huntington's disease. Recruitment was carried out by a variety of methods: snowballing from contacts at the Norwegian National Association for Huntington's Disease, through advisors at the Norwegian reference center, and via websites and social media. But, apart from the idea that there are family norms regarding the use of genetic testing, the decision to either proceed or not is not a central issue of the article.

The article by Pierron et al. (2021) combined two modes of recruitment, based on the one hand on the file of people who had attended a consultation at the Pitié Salpétrière, a reference center for Huntington's disease, and on the other, via calls for participation posted on the websites of patient associations. However, the focus lies on the issue of intra-family transmission of information in a context of low uptake of testing for Huntington's disease.

Overall, the views of people who opt out of the genetic testing that would allow them to find out if they are carriers of a mutation that causes a neurodegenerative disease are poorly documented, except when they consult with the intention of having a presymptomatic diagnosis and subsequently abandon the idea. Given both the importance of this population - since testing uptake is in the minority - and its crucial importance for the potential development of clinical trials, we carried out a survey designed, inter alia, to gather the views of this population.

Methods

The questionnaire survey was made available online and sent by post; respondents were recruited by three means:

- A paper copy was sent:
  - to all patients treated for CADASIL at CERVCO, or who consulted CERVCO for a genetic diagnosis (430);
  - 190 members of the CADASIL France patient association.
- An e-mail was sent to 263 CADASIL France members and contacts.
- A link to the online version of the questionnaire was posted on the CADASIL France website, along with a short explanatory article.

People who had received the paper questionnaire had the option of responding directly online.

The survey was aimed at three categories of people:

- People carrying the CADASIL mutation, whether or not there is a known family history of the disease;
- Relatives of these people who are not affected by the disease;
- People at risk for CADASIL who do not know their carrier status.

It was preceded by a qualitative interview survey of 30 people: 18 carriers of the CADASIL mutation, 8 relatives of carriers, 4 people at risk for CADASIL. This survey enabled us to gather the experience of the people concerned, and gain a better understanding of the place of the disease and/or diagnosis in their lives. It led to the identification of relevant themes for the questionnaire survey. A first version of this questionnaire was discussed and amended by members of the CADASIL France Board of Directors, as well as by the TRT_cSVD project coordinators. Responses were collected between March 20 and December 1, 2021.

Given the variety of respondent profiles, we had to design specific versions of the questionnaire: the questionnaires for carriers and relatives of carriers have 95% of questions in common; on the other hand, the questionnaire for people at risk has only 30% of questions in common with the other two questionnaires.

The questionnaires, each comprising around 40 questions, cover the following topics in addition to basic socio-demographic data:

- Diagnostic pathway (for carriers and their relatives) / Reasons for seeking diagnosis or for delaying diagnosis (at-risk individuals)
- Sources of information about the disease
- Discussions about the disease
- Resources considered important in relation to the disease
- Current and future concerns (for carriers and their families)
- Position on clinical trials.

The main focus of this article is on the case of at-risk population, who currently has no knowledge of their carrier status. We draw on data collected from the diagnosed respondents mostly as a counterpoint to this case and as a means to shed light on interpretation.

The respondents

We received 359 exploitable questionnaires, of which 15 were returned partially completed. The respondents population includes:

- 197 mutation carriers
- 81 close relatives
- 81 people at risk.

This represents a significant response rate: in fact, 855 online and paper questionnaires were sent by e-mail or post, with a probable overlap between the association's files and those of the reference center[1].

Table 1 presents the main characteristics of the respondent population. The population of mutation carriers was divided into two subgroups, the subgroup of carriers with no known family history of CADASIL, and the subgroup of carriers with a family history of the disease. Similarly, the at-risk population was divided into two subgroups: those who had consulted for CADASIL disease and those who had not, the latter subpopulation being very poorly represented in studies of presymptomatic diagnosis, as we saw earlier.

As in virtually all surveys of this type, women are over-represented (69% among carriers, 77.5% among those at risk). Carriers with no known family history of CADASIL are the oldest (median age: 60-69), which is congruent with the fact that they are diagnosed only when significant symptoms appear. Those at risk are the youngest (median age: 40-49), while the median age of carriers with a known family history of CADASIL is 50-59, suggesting that age may be an important factor leading to a diagnosis.

People at risk are less likely to be in couples than carriers, but this is an effect of age differences: the difference disappears when considering only people aged over 30. Furthermore, carriers are slightly more likely to have children than at-risk people, even when considering only people over 40, which is consistent with the fact that the potential for disease transmission is a major concern (Ibisler et al., 2017; Pierron et al., 2021).

Nearly all respondents with a known family history of CADASIL have first-hand experience of the disease through close contact with someone with the condition: greater or lesser proximity to the disease therefore plays no role in the choice of being diagnosed or not.

Finally, as in most surveys of this type, there is an over-representation of higher socio-professional categories, which is expressed in a similar way in both carriers and at-risk individuals.

To sum up, people at risk differ from carriers essentially in age, and in a slight tendency, not very significant given the numbers involved, to be more likely to be childless.

[1] The Ethics Evaluation Committee of Inserm, the Institutional Review Board (IRB00003888, IORG0003254, FWA00005831) of the French Institute of Medical Research and Health reviewed and approved the questionnaire survey and its protocol, conducted as part of research project TRT-cSVD. Opinion number 18-485bis dated July 7, 2020.

TABLE 1: DESCRIPTION OF THE POPULATION OF RESPONDENTS

	Carriers with no known family history of CADASIL	Carriers with a known family history of CADASIL	**Total carriers**	At-risk persons who consulted	At-risk persons who did not consult	**Total at-risk persons**
N	81	114	**197**	29	51	**81**
Gender						
Female	58 (72%)	76 (67%)	**135 (69%)**	25 (86%)	37 (73%)	**62 (77,5%)**
Male	23 (28%)	38 (33%)	**62 (31%)**	4 (14%)	14 (27%)	**18 (22,5%)**
Median age category						
	60-69	50-59	**50-59**	40-49	40-49	**40-49**
Way of living						
In couple	56 (69%)	68 (60%)	**126 (64%)**	15 (52%)	30 (59%)	**45 (56%)**
Alone	19 (23%)	29 (26%)	**48 (24%)**	8 (28%)	10 (20%)	**18 (23%)**
With other family members	6 (7%)	16 (14%)	**22 (11%)**	6 (22%)	11 (22%)	**17 (21%)**
With other people		1 (1%)	**1 (1%)**		1 (2%)	**1 (1%)**
Have children						
No	13 (16%)	18 (16%)	**31 (16%)**	10 (34%)	19 (37%)	**29 (36%)**
Yes	68 (84%)	96 (84%)	**166 (84%)**	19 (66%)	33 (63%)	**52 (64%)**
Yes (people over 40)			**86%**			**73 %**
In close contact with someone with the disease (before diagnosis)						
No		10 (9%)		2 (7%)	5 (10%)	**7 (9%)**
Yes		104 (91%)		26 (93%)	45 (90%)	**71 (91%)**
Occupation (before retirement, if applicable)						
Farmers and manual workers	6 (8%)	7 (6%)	**13 (7%)**	1 (4%)	2 (4%)	**3 (4%)**
Employees	28 (35%)	35 (32%)	**63 (33%)**	19 (48%)	13 (26%)	**26 (34%)**
Intermediate professions	8 (10%)	13 (12%)	**21 (11%)**	2 (7%)	8 (16%)	**10 (13%)**
Executives and higher intellectual professions		38 (34%)	**63 (33%)**	9 (33%)	15 (30%)	**24 (31%)**
Craftsmen, shopkeepers and company managers	5 (7%)	12 (11%)	**17 (9%)**		5 (10%)	**5 (6%)**
No professional activity	7 (9%)	6 (5%)	**13 (7%)**	2 (7%)	7 (14%)	**9 (12%)**

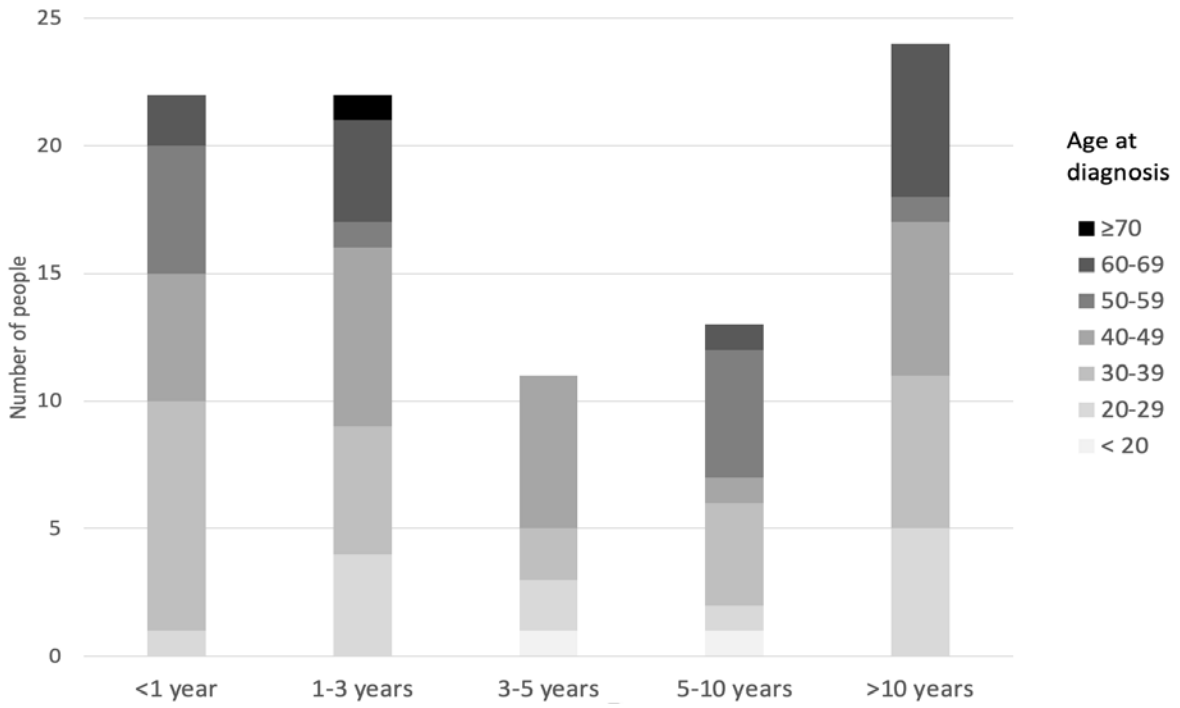
In the results presented hereafter, the total number of responses may vary according to the variables analyzed, as some respondents have chosen to not answer certain questions.

Results

Circumstances of diagnosis in mutation carriers with a known family history of CADASIL

People who were aware of a family history of the disease display a wide range of behaviors in relation to the diagnosis. This U-shaped curve shows two opposite behaviors: on the one hand, a certain number of people rush to make a diagnosis as soon as they find out about the disease in the family, on the other hand, people wait quite a long time before embarking on the diagnosis procedure.

GRAPH 1: TIME BETWEEN AWARENESS OF RISK AND DIAGNOSIS



The median year of diagnosis is 2013 for those who were diagnosed within 3 years of becoming aware of their own risk, and 2012 for those who waited more than three years before being diagnosed. In other words, there is no significant difference between the two populations in terms of the age of diagnosis in relation to the date of the survey. However, those who were diagnosed rapidly were older at the time of diagnosis (mean 44 years, median 44 years) than those who waited longer (mean 41 years, median 40 years).

A comparison between these two populations in terms of symptoms experienced at the time of the survey shows that those who waited more than three years have fewer disabling symptoms than those who were diagnosed within three years of learning of the existence of a family history of the disease.

TABLE 2: SYMPTOMS AND TIME BETWEEN AWARENESS OF RISK AND DIAGNOSIS

	Carriers diagnosed within 3 years after learning about a family history of CADASIL (N=44)	Carriers diagnosed more than 3 years after learning about a family history of CADASIL (N=49)
No clear CADASIL-related symptoms	20%	27%
CADASIL-related but not disabling symptoms	39%	59%
CADASIL-related disabling symptoms	41%	14%
Total	**100%**	**100%**

Situation of people at risk

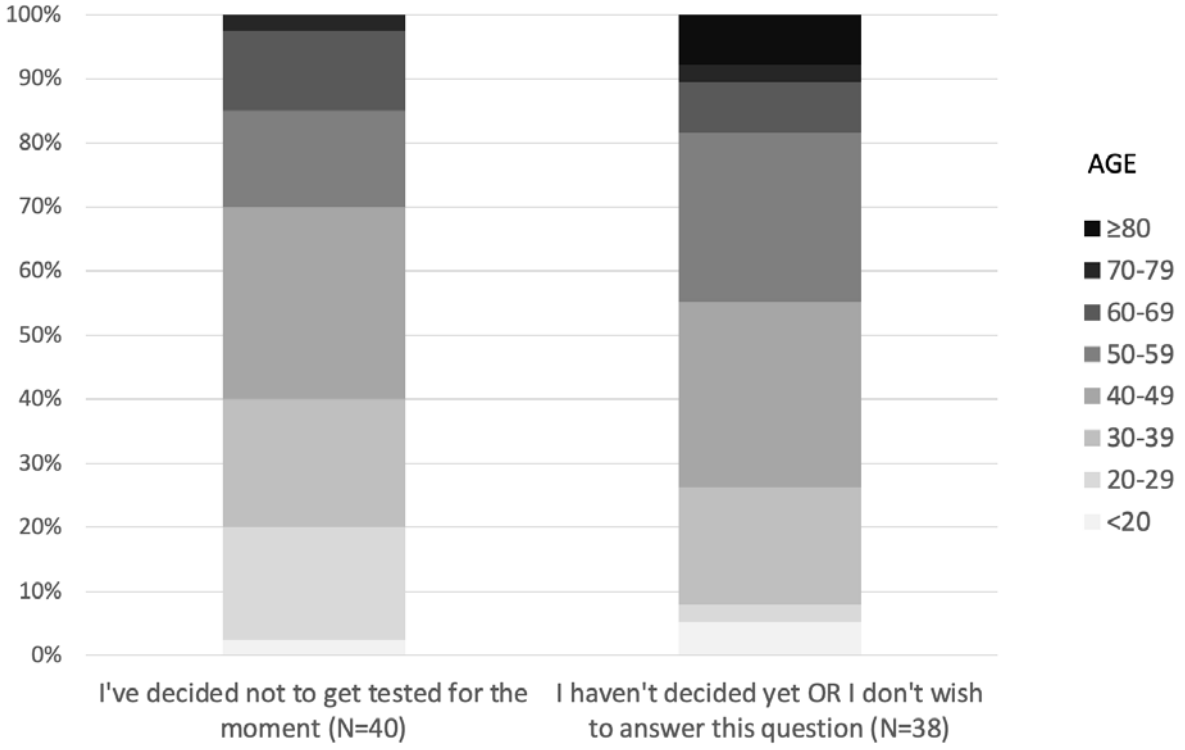
Half of the people at risk stated that they had decided not to undergo genetic testing for the time being, 38% say they have not yet decided, and 10% do not wish to answer the question.

TABLE 3: CONSIDERATION OF GENETIC TESTING

How would you describe your position	N	%
I have decided to undergo genetic testing	2	2%
I have decided not to undergo genetic testing for the moment	40	49%
I haven't decided anything yet	31	38%
I don't wish to answer this question	10	10%
Total	**81**	**100%**

Those who have decided not to undergo genetic testing for the time being are younger on average than those who are undecided and those who do not wish to answer the question.

GRAPH2: AGE AND POSITION IN RELATION TO THE TEST



Half of the respondents reported experiencing disorders possibly related to CADASIL; this is also the case of 40% of those who have decided not to undergo genetic testing, and 56% of those who are undecided on the issue (the difference is non-significant, given the numbers involved).

TABLE 4: CONSIDERATION OF GENETIC TESTING
AND DISORDERS LIKELY RELATED TO CADASIL EXPERIENCED BY PEOPLE AT RISK

	No disorders usually associated with CADASIL	Disorders possibly related to CADASIL (migraines, fatigue, etc.)	Total
I have decided to undergo genetic testing (N=2)		100%	**100%**
I have decided not to undergo genetic testing for the moment (N=40)	60%	40%	**100%**
I haven't decided anything yet (N=32)	44%	56%	**100%**

A third of the respondents had consulted a specialist, 57% of them at the reference center. However, this does not affect the distribution of diagnostic choices.

TABLE 5: CONSIDERATION OF GENETIC TESTING AND CONSULTATION WITH A SPECIALIST

How would you describe your situation?	Did not consult a specialist N=48	Did consult a specialist N=23
I have decided not to undergo genetic testing for the moment	56%	57%
I have not decided anything yet	44%	43%
Total	**100%**	**100%**

Motivations for undergoing genetic testing or not

We then asked the respondents what reasons would make them decide to undergo genetic testing. They were presented with a list of six motives:

- The onset of mild symptoms
- The onset of severe symptoms
- The illness of a relative
- A parental project
- Pressure from relatives
- The prospect of a clinical trial for drugs

The events that might lead them to make such a decision are mainly the onset of symptoms (68%), whether mild or severe.

A parental project appears to be a significative incentive: 40% of the people of reproductive age with no children say that they would choose to be diagnosed should they have a parental project.

The prospect of a clinical trial also appears to be a moderate incentive (37%).

The answers show a certain independence from what is played out in the family: the illness of a close relative is one of the less frequently cited motivations (33%), pressure from relatives is declared as a very weak incentive (5%).

TABLE 6: INCENTIVES THAT WOULD ENCOURAGE PEOPLE AT RISK TO UNDERGO GENETIC TEST

Which of the following might lead you to undergo genetic testing? N=81	Yes	No	*Total*
The onset of symptoms	**68%**	**32%**	*100%*
A parental project (*respondents under age 50; n=48)* ***of which respondents under age 50 with no children (N=20)***	19% **40%**	81% **60%**	*100%* ***100%***
The prospect of a clinical trial (for drugs)	39%	61%	*100%*
The illness of a relative	35%	65%	*100%*
Pressure from relatives	5%	95%	*100%*

Conversely, we asked respondents what would keep them from getting diagnosed: fear that the disease will become too invasive in their life is by far the main motivation for not being diagnosed.

TABLE 7: CONSIDERATIONS THAT WOULD KEEP PEOPLE AT RISK FROM UNDERGOING A GENETIC TEST

Which of the following would keep you from undergoing genetic test? N=70	Yes	No	Total
Fear that the disease may become too invasive in your life	66%	34%	100%
The consequences on your professional activity	26%	74%	100%
Consequences on social relationships	23%	77%	100%
A real estate project	19%	81%	100%
Pressure from family and friends	4%	96%	100%
A parental project	1%	99%	100%

Information about the disease

Information on CADASIL is concentrated on three French websites: CERVCO, the reference center for this disease; Orphanet, a portal and information server dedicated to rare diseases and orphan drugs; and the CADASIL France patient association.

25% of mutation carriers and 17% of people at risk have not consulted any of these sites. 35% of carriers and 21% of people at risk consulted all three sites. At-risk individuals consulted the association's website to a very large extent, and the medical websites to a lesser extent. It should be noted that the fact of not consulting any sites is not linked to age or socio-professional category.

TABLE 8: SOURCES OF INFORMATION FOR CARRIERS AND PERSONS AT RISK

Percentage of respondents who sought information:	Carriers of the mutation (N=197)	People at risk (N=81)
On the CERVCO website	65%	38%
On the Orphanet website	49%	27%
On the CADASIL France website	73%	77%

TABLE 9: NUMBER OF CONSULTED WEBSITE FOR CARRIERS AND PERSONS AT RISK

Percentage of respondents who sought information:	Carriers of the mutation (N=197)	People at risk (N=81)
On the three websites	35%	21%
On two out of three websites	20%	21%
On one out of three websites	20%	41%
Did not consult any of the three websites	25%	17%
Total	100%	100%

Position on clinical trials

The responses of people at risk regarding clinical trials are similar to those of carriers and are characterized by a high rate (73%, compared to 87% for mutation carriers) of people expressing their willingness to participate in a clinical trial.

TABLE 10: PROSPECTIVE PARTICIPATION IN CLINICAL TRIALS OF CARRIERS OF THE MUTATION AND PEOPLE AT RISK

Would you be willing to participate in a clinical trial for a drug that prevents the progression of the disease?	**Mutation carriers (N=192)**	**People at risk (N=67)**
Yes	56%	46%
Depends on the risk of side effects	30%	24%
Depends on the length of the trial	1%	3%
No	5%	7%
I don't know	8%	19%
Total	**100%**	**100%**

However, these results should be compared to the responses to a previous question : as noted above, 61% of respondents said that the prospect of a clinical trial would not motivate them to get tested. When looking at the group of these individuals – not motivated to get tested by the prospect of clinical trials – it appears that their responses to the question about their willingness to participate in a clinical trial split up as follows:

TABLE 11: POSSIBLE PARTICIPATION IN CLINICAL TRIALS OF PEOPLE AT RISK WHO SAY THE PROSPECT OF A CLINICAL TRIAL WOULD NOT BE A MOTIVATION TO UNDERGO TESTING

Would you be willing to undergo genetic testing to participate in a clinical trial for a drug that prevents the progression of the disease?	People at risk (N=68)
No	10%
Depends on the length of the trial	3%
Depends on the risk of side effects	36%
Yes	28%
I don't know	23%
Total	**100%**

Thus 67% of those who did not consider the prospect of a clinical trial as a motivation to undertake genetic testing would in fact be willing to participate in a clinical trial.

Conversely, the 29 respondents who stated that they were willing to undergo genetic testing in the prospect of a clinical trial also answered that they were willing to participate in a clinical trial, 2 said they were willing to participate depending on the side effects, and 1 said he/she would be willing to participate depending on the duration of the trial, which amounts to nearly 80% of these 29 people.

Discussion

The onset of symptoms, a trigger for diagnosis

As mentioned in the introduction, a number of studies have focused on identifying the motivations of people requesting presymptomatic testing for late-onset neurodegenerative diseases, the most studied of which is undoubtedly Huntington's disease. Most of these studies are based on the implementation of a protocol for presymptomatic testing. These studies, some of which date back to the 90s, highlight a small number of main motivations. As early as 1991, (Meissen et al.1991) described the desire to reduce uncertainty and anxiety and being in a better position to and make decisions and plan their life and career as two strong motivations; more recent studies reach similar conclusions (Leite et al., 2017; Ramond et al., 2019; Reyes et al., 2012; Scuffham & Macmillan, 2014; Williams et al., 1999). That said, these studies focus on the motivations of all individuals, and do not differentiate between those who ultimately make the decision to undergo genetic testing and those who opt out. They also point out that, regarding most socio-demographic criteria, there is no significant difference between people who go through with the process and those who drop out, whose proportion can be very high. One of the blind spots in these studies is that they hardly ever question the role played by the protocol and its concrete implementation in the choices made by the people concerned: only Ramond et al. (2019), who found a much lower drop-out rate in their Huntington cohort than in most published cohorts, raise the question of the role of protocol duration in the drop-out rate.

In any case, the analysis stumbles over what we might call the trigger for the decision in favor of testing. In the population we have studied, we have seen that the delay between learning of a risk and the test is highly variable. We observe 1) that people who underwent genetic testing shortly after were slightly older at the time of diagnosis than those who waited longer (44 years / 41 years); 2) that the distribution of diagnosis dates is equivalent in both groups and 3) that the proportion of people with disabling symptoms is 41% (n=44) in the first group, versus 14% (n=49) in the second group, but that, overall, the proportion of people experiencing symptoms, disabling or not, is similar in both groups (80% / 73%). We therefore hypothesize that the perception of symptoms could be one of the triggers for the decision to diagnose. This hypothesis is supported by the article by Ramond et al. (2019), which shows that 1) three times fewer people with symptoms (motor and cognitive) of Huntington's disease - identified by the consulting physicians - withdrew from the testing protocol than those without symptoms, and 2) 91% of people who thought they had symptoms turned out to be carriers of the disease gene. As the authors put it, "[patient] clinical impressions should indeed not be taken lightly". In other words, the notion of presymptomatic testing is a little misleading: people faced with a genetic disease such as Huntington's or CADASIL are fairly well informed, notably via the internet (Kanga-Parabia et al., 2018), and able to identify certain symptoms, which potentially encourages them to get tested.

In the at-risk group, half the respondents (49%) state that they had decided not to get tested for the time being, while 38% report that they had not yet made a decision. How can this result be interpreted? Cox's (2003) enlightening way of approaching the issue consists in addressing the "meaning and experience of making the decision" of requesting predictive genetic testing. This approach is at odds with many analyses of clinical ethics, which tend to focus on the question of *why* (what are the reasons for the decision) rather than on *how* people reach the decision, thus constructing a model of "rational decision-making which assumes that the decision-maker will weigh the existing options and arrive at the most rational decision" (p. 274), feeding the "predominant clinical 'discourse of potential benefits'". Some of the narratives Cox has collected unfold a landscape in which decisions are made or imposed rather than issued as a result of a deliberative weighing up of pros and cons. In one of the three types of narrative she identifies, the person "evolves towards" the decision to carry out a test: decision-making is progressive, and in the narrative it implies a conscious recognition that there is a decision to be made, and that requesting a test is not self-evident. People move from moments of opposition or ambivalence towards the test to others where the consequences are weighed up, for themselves and for others, and where a provisional positioning is gradually replaced by the feeling of being ready to proceed with the test. People who say they "haven't made a decision yet" seem to us, at least for some of them, to be early in this process.

We also observe that the average age in this group is slightly higher than in the group of those who said they have decided not to take the test (46.5 / 43.5), and that the proportion of those experiencing disorders possibly linked to CADASIL is slightly higher (56% / 40%).

Taken together, the available evidence supports our hypothesis that the onset of symptoms is an event likely to trigger the diagnostic process.

This is further confirmed by the answers to the question of what might prompt them get tested, since the onset of symptoms is considered by far the most important reason, with 68% of positive responses.

Then come, with more or less the same intensity

- a parental project for people who have no children (40%), a point emphasized by many authors (Crook et al., 2021; Ibisler et al., 2017; Pierron et al., 2021; Ramond et al., 2019; Tillerås et al., 2020);
- the prospect of clinical trials (39%) ;
- and the illness of a relative (35%), which, like the symptoms, contributes to making the disease an inescapable reality.

Pressure from loved ones is considered to have virtually no impact on the decision, which is in line with what Ibisler et al. (2017) suggest in the case of Huntington's disease.

Conversely, the concern about the disease taking over their life is by far the most significant factor holding back people at risk from getting tested (66% of the respondents): Gargiulo et al. (2017) emphasize the burden of self-observation in the lives of those diagnosed even if they state that the onset of Huntington's disease does not seem to be triggered by a newfound awareness of their carrier status,.

People at risk but not in denial

Is this desire to "distance oneself" from the disease akin to denial, as suggested by Evers-Kiebooms et al. (2000) who identify among the untested people those "with avoiding behavior regarding the disease, the risk and the test" (p. 833)?

The results of our survey do not validate this hypothesis, in line with Geelen et al. (2015), although we may wonder whether people in denial would have responded to the questionnaire: with a methodology using a questionnaire survey, it is virtually impossible to access the population of those who would be in such a situation.

Nevertheless, we observe that 56% to 57% of respondents - whether they have decided not to be tested for the time being or have not yet decided - have consulted a specialist regarding CADASIL.

Secondly, we can see that many of them have sought information about the issue, since 83% of those at risk have consulted at least one of the three recognized CADASIL websites, and 21% have consulted all three, compared with 35% of carriers. They differ from carriers in that they are significantly less likely to consult websites run by medical organizations (CADASIL reference center, Orphanet): 56% have not consulted any of these sites, versus 36% of carriers. Conversely, just as many undiagnosed people as carriers consulted the patient association website.

In addition, 91% say they have been in close contact with a person with CADASIL disease.

Presymptomatic diagnosis for clinical trials

Existing work discussing the reasons justifying the use of biomarkers to identify presymptomatic carriers of a disease in view to clinical trials mainly focus, and for many years, on populations at risk of Alzheimer's disease, as in this area, research and development of potential tests and treatments for other diseases such as Huntington's disease or CADASIL are still at an early stage. After briefly re-examining the question of the legitimacy of Alzheimer's disease screening in the absence of available treatment, Calzà et al. (2015) focus their

argument on the expected benefits of such screening, including the potential for biomarker research and improved secondary or tertiary prevention or the possibility of identifying non-neurological factors which could be treated. Carrillo et al. (2013) argue along the same lines: while they note that screening for Alzheimer's disease does not meet all the criteria set out by the WHO, they argue that the possibility of carrying out secondary prevention trials is sufficient justification for performing screening. These articles do not deny the uncertainties regarding biomarkers in the pre-clinical stages of disease, nor the potential difficulties in designing secondary prevention trials based on these biomarkers. However, they are optimistic about their potential, and reduce questions on the ethics of presymptomatic diagnosis to general analyses of the potential collective benefits of clinical trials versus individual risks.

The question of benefits for the individual is nevertheless reiterated by several authors. Favoring a strategy of presymptomatic diagnosis, some argue that a person's moral right to know his or her status with a view to preventive treatment could be interpreted as an attempt to translate collective benefits to the individual level (Dubois et al., 2016). Others question the legitimacy of revealing a person's presymptomatic status when knowledge about the long-term implications is uncertain, and consider the trade-off between the individual risks (associated with such revelation for the purposes of participating in clinical trials) and the collective benefits expected from the trials as a new ethical dilemma (Gauthier et al., 2023; Léger & Ouango, 2009). In these studies, the issue relates therefore much more to the attitude that researchers and physicians should have than to the standpoint of the primary stakeholders, namely the patients.

In our survey, most people, whether they be at risk or a mutation carrier, express their willingness to participate in a clinical trial. Nevertheless, 31% of mutation carriers and 27% of at-risk individuals conditioned their participation on a review of the trial's characteristics in terms of potential side effects and duration.

That said, how should we interpret the fact that 67% of the respondents who did not consider the prospect of a clinical trial as a motivation to undertake genetic testing still claim that they would be willing to participate in a clinical trial?

There are several possible hypotheses:

- In the question about their participation in a clinical trial, there is no mention of genetic testing; as a result, the barrier of having to project oneself into making the decision of being diagnosed is lifted, with respondents' implicit assumption being that they are being asked to place themselves in an imaginary situation in which they have been diagnosed and are carriers of the mutation.
- The "prospect" of a clinical trial refers to a less tangible situation than actually participating in a clinical trial, which implies its very existence and therefore justifies a more wait-and-see stance.
- Intentions in this area are quite volatile and, as illustrated by the case of Huntington's disease diagnosis, are likely to vary considerably from the moment people simply anticipate a future possibility to the moment they are faced with a straightforward choice.

Overall, however, we can say that both mutation carriers and people at risk are a priori relatively open to the possibility of participating in clinical trials.

Conclusion

The aim of this article is to clarify the circumstances that are likely to lead people at risk of CADASIL to be diagnosed, in order to provide food for thought on the question of their participation in possible clinical trials. With regard to the existing literature on these issues, our approach is distinctive in that, through to diversified recruitment methods, we were able to collect responses from people at risk who had visited a specialist CADASIL consultation - or even initiated the process of pre-symptomatic diagnosis - as well as people who had never consulted in the first place. Virtually almost all studies of this type are carried out as part of a pre-symptomatic diagnosis protocol, and therefore do not have access to such a wide range of people, with such diverse CADASIL-related experiences..

It may be noted that there is no substantial difference between those who had already been diagnosed and those who had not; in particular, they all sought information about the disease, even if they have not seen a specialist. In both cases, the potential or actual move towards diagnosis appears to be linked to the development of symptoms possibly related to CADASIL. This is not to say that the motivations observed in previous studies are non-existent: on the contrary, they are widely shared, as evidenced in our survey by the fact that they were reported by both those who went through with the genetic testing protocol and those who opted out. Similarly, the perceived risks are common to both populations. People at risk do not engage in the kind of reasoning discussed in articles on clinical ethics that consists in weighting expected benefits against plausible risks: the answers they gave to questions about what would act as an incentive or prevent them from undergoing genetic testing show that they are acutely aware of what the diagnosis may bring and compromise. As Cox (2003) suggests, before deciding whether or not to be diagnosed, people are ambivalent, in a kind of unresolved tension. This tension does not dissipate because, at some point, the balance has stabilized on the side of benefit, but rather because getting tested imposed itself on them, through their bodily perceptions in particular. From this point of view it seems only partially accurate to describe the diagnosis as presymptomatic. It's as if people at risk put off the shift from indeterminate to *patient-in-waiting* (Timmermans & Buchbinder, 2010) until the disease makes its presence felt, even if discreetly: from that tipping point onwards, other uncertainties - about how the disease develops or what it's like to be ill - take the place of uncertainty about status (Hess et al., 2009; Pihet, 2017).

The picture we have sketched here is obviously not intended to provide an all-encompassing description of these experiences, in so far as questionnaire-based studies tend to obscure subtle variations. There will always be some examples, as evidenced by our qualitative survey, of people for whom not finding out their status as soon as they learn of the existence of this family disease is inconceivable, or conversely, people who may go so far as to enter into complex MAP protocols in order to keep their status unknown for as long as possible, without risking having a child affected by the disease. The latter case is actually not inconsistent with our analysis.

What we describe would at first sight seem to jeopardize the recruitment of asymptomatic people for clinical trials, as this would require them to engage in early diagnosis. Responses to questions on this topic are more ambiguous, showing a potential interest in participating in such trials. This interest is, however, unstable: more precisely, the apparent inconsistencies

between the answers to two questions on this topic seem to us to refer to the difficulty for the people concerned of thinking this pivotal moment of diagnosis as externally driven and reverting to forms of reasoning that weigh benefits for oneself and others against personal risks. That said, because the prospect of treatment transforms the disease itself and with it the meaning of diagnosis, a likely scenario would suggest that that many people would accept a proposal to participate in clinical trials.

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