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### ► To cite this version:

Madeleine Akrich, Florence Paterson, Vololona Rabeharisoa. Social and ethical issues regarding presymptomatic diagnosis A LITERATURE REVIEW. 2020. hal-03040870

**HAL Id: hal-03040870**

**<https://minesparis-psl.hal.science/hal-03040870>**

Preprint submitted on 4 Dec 2020

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# Social and ethical issues regarding presymptomatic diagnosis

## A LITERATURE REVIEW

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**Working Paper 20-CSI-02\_EN**  
**Mai 2020**

Pour citer ce papier / How to cite this paper : Akrich M., Paterson F. & Rabeharisoa V. (2020). Enjeux sociaux et éthiques du diagnostic présymptomatique. Synthèse de la littérature. i3 Working Papers Series, 20-CSI-02\_EN.

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## ABSTRACT

Why research the genetic status of members of a family affected by a hereditary disease and reveal this information to them, particularly when there is no treatment available? On what basis does the individual at risk make the decision of whether or not to find out their genetic status and whether or not to inform their relatives? What are the effects of the presymptomatic diagnosis on those who chose to undergo it? How and to what extent does it change their lives, if at all? These three questions are the starting point for the present overview of the literature on the social and ethical issues of presymptomatic diagnosis. The analysis is based on a corpus of 57 articles and 7 reports gathered from Scopus, Cairn and the websites of various institutions, and identifies two main approaches.

The first approach is to consider the decision as a rational process in which the associated risks and benefits are weighed. In a certain way, these risks and benefits have an objective existence, even if they must be assessed subjectively by each individual. In this context, the practitioner is, a priori, as well placed as the individual themselves to determine the "right decision", either with them, or possibly in their place. A second approach is to consider that the decision is only one point in a long process which gradually leads people to both incorporate and come to terms with what the illness means in their lives, and how the presymptomatic diagnosis can influence the course of their lives. In this approach, a shared journey is forged between caregivers and the individual, the aim being to explore together the significance the diagnosis can have for them.

The issue of clinical trials as a potential motivation for receiving a presymptomatic diagnosis complicates the analysis by revealing long-term collective benefits, in contrast with immediate individual risks. Should this element be considered, and if so how, should this be within the options presented to the individual with a view to a possible presymptomatic diagnosis? The protocols discussed in this review provide useful benchmarks for ethical framing both by and in practice: the relatively long time frame of the procedure, the process of collective exploration of what the decision may imply, and the non-interference of researchers are arguably the main features to retain.

## KEY WORDS

presymptomatic diagnosis • ethics • social issues • genetic counseling • genetic illness

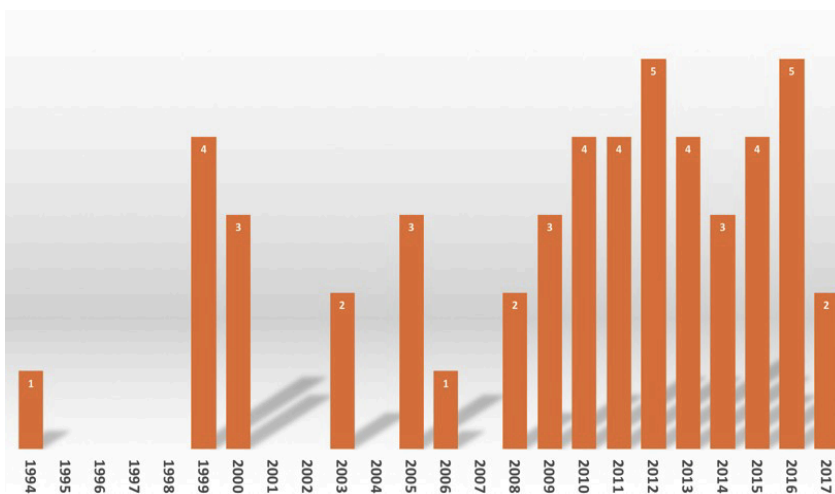
# INTRODUCTION

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This review of the literature on the social and ethical issues of presymptomatic diagnosis adopts, as a starting point, the three important questions which arise with this type of diagnosis: 1) Why research the genetic status of family members affected by a hereditary disease, and reveal this information to them, particularly when there is no treatment available? 2) On what basis does the individual at risk make the decision of whether or not to find out their genetic status, and whether or not to inform their relatives? and 3) What are the effects of the presymptomatic diagnosis on those who choose to do it? How and to what extent does it change their lives, if at all?

To answer these questions, the present authors developed a corpus of 57 articles and 7 reports collected from the Scopus and Cairn bibliographical databases, as well as from the websites of several institutions. In terms of temporal distribution, we can observe an increasing interest in these issues as diagnostic technologies develop: most of the earlier papers focused on Huntington's disease, one of the first incurable late-onset genetic diseases for which a genetic test was developed. From the 2000s onwards, there has been an increased focus on rare genetic diseases and on certain forms of common diseases for which genetic factors have been identified. More recently, Alzheimer's disease has provoked increased debate along these lines, also similar to the context of CADASIL disease, where some people express the desire to develop treatments supposed to prevent the development of the disease long

before the first symptoms appear.



The authors of these various documents have varied disciplinary backgrounds: around half are social scientists and ethicists, and the other half belong to medical disciplines such as genetics, psychology and psychiatry. Two thirds of these documents are produced

by researchers belonging to the same discipline, but only 10% combine social sciences and medical sciences broadly.

This paper identifies three main themes which form the structure of the discussion herein:

- Research examining ethics from a theoretical stance, mainly considering the principles of clinical ethics, and setting out acceptable conduct in the field of presymptomatic diagnosis. This paper examines the way in which these papers formulate recommendations for professionals, and how the emergence of secondary prevention trials is changing the consensus outlook and provoking new subjects for debate.

- Research which draws on the authors' experience as practitioners, in order to develop proposals which are significantly different from previous ones. First, this paper explores how some authors question the existing framework, in light of predictive medicine, and develop restrictive recommendations regarding the use of presymptomatic diagnosis. It then presents analyses of the protocols proposed by some teams to manage the issue of presymptomatic diagnosis and examines how, in practice, they address the theoretical questions evoked in clinical ethics.
- Studies which anchor their arguments in empirical research with the individuals concerned and identify ethical issues based on the experience of these people: rather than pre-defining which values are important, such as autonomy, for example, these studies attempt to describe the actual practical effects which the presymptomatic diagnosis produces in people's lives.

## I/ PRESYMPTOMATIC DIAGNOSIS THROUGH THE PRISM OF CLINICAL ETHICS

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An initial set of studies aimed to provide professionals, particularly clinicians, with information on the questions which may arise, and the various aspects they must consider in developing their proposals to patients. These studies were based on three main principles of **clinical ethics**:

- (i) the principle of autonomy, i.e., the ability of each person to determine what is good for them, which presupposes fair information is provided about the options available;
- (ii) the principles of beneficence and non-maleficence, which purport that proposed actions must enhance the well-being of the individual and not harm them in any way; and
- (iii) the principle of confidentiality, which implies the non-disclosure of medical information to third parties.

It should be noted that the stance taken to uphold the principles of beneficence and non-maleficence is different to that for the principle of autonomy, as in the first case, the assessor is the patient, whereas in the second, health professionals are implicitly designated as assessment authorities. Since these two stances have no explicit reason to converge, a potential ethical dilemma arises, almost by design.

### I.1/ Medical benefits versus psychological and social risks

Ethical analysis consists of reviewing the various options available to doctors - whether or not to propose a genetic test or biomarker research, whether or not to transmit the results of these tests to the individual, etc. - by anticipating the effects of each option on the patient and their relatives, and assessing the relative weight of the associated benefits and risks of each. The

effects of divulging the individual's genetic status to them include, on the upside, the possibility of implementing treatment or preventive measures, and on the downside, psychological effects (anxiety, depression, etc.) which such an announcement is likely to provoke, as well as social and economic effects (discrimination, insurance eviction, impact on their work, etc.).

In situations marked by significant uncertainty about the development of the disease and/or lack of treatment, most authors agree that it is not appropriate to prescribe screening or diagnostic tests at the presymptomatic stage (Dubois et al., 2016; Gauthier et al., 2013; Hedgecoe, 2006), concluding that the risks outweigh the benefits.

## I.2/ Significance in terms of autonomy?

However, this position conflicts with the principle of autonomy, as doctors make the decision in the place of the individual, and this is therefore contested by some authors (Gauthier et al., 2013); Borillo (2012) even considered that "*the restriction of personal access to one's own genetic data is akin to state control*".

However, some authors question whether individuals can really exercise such autonomy (Hess, Preloran, & Browner, 2009). Dierickx (2012) doubts whether patient consent is informed by sufficient information which is neither excessive nor manipulative. He moreover considers that an individual's freedom to consent (or not consent) is restricted in various ways. Indeed, the very fact of offering the possibility of screening presents constraints. When asked, individuals are reluctant to refuse: pressure from insurance companies and from doctors who are afraid of the possibility of legal proceedings may push people to accept to undergo the test. These authors highlight "*the moral hypertrophy of responsibility*" – the individual becomes responsible for what happens to them – which may be a result of applying the principle of autonomy. Such accountability is effectively the basis of recent developments in the law according to Gaboriau (2016).

For Bortolotti and Widdows (2011), aligned with the arguments set out by Husted (2014), there are in fact two contrasting notions of autonomy:

- a "*thin conception of autonomy*", which is based on the premise that knowledge is a higher state than uncertainty and enables informed decision-making, whereas refusal to know amounts to renouncing one's autonomy in terms of the ability to make informed and reasonable decisions about one's own life;
- a "*thick conception of autonomy*" which forms the premise of the right not to know - autonomy is thus protected by the refusal to know, which leaves the future open, instead of potentially locking people into the disease. We note that this "thick conception of autonomy" potentially resolves an ethical dilemma: not proposing presymptomatic diagnosis to patients in the name of the principle of beneficence and non-maleficence is in this way no longer incompatible with preserving their autonomy.

It can be seen from the above that, with the exception of the particular case of minors (ESHG, 2009), the individuals considered in these approaches are undifferentiated and somewhat

universal patients. The factors considered in this reasoning relate exclusively to the disease: the predictive value of the tests, the existence of symptoms and treatments, etc. The aim is to develop general ethical benchmarks for professionals by assessing the implications of the diagnosis in terms of ethical principles, based on an examination of the characteristics of the disease as assessed by medicine.

### I.3/ The development of secondary prevention: collective benefits versus individual risks

These analyses have, however, changed in recent years due to the emergence of a "secondary prevention" perspective: the term 'secondary prevention' refers to measures or treatments designed to prevent the development of a disease in a person at risk, which risk may be genetic.

Much of the debate on these issues has revolved around research on biomarkers, i.e. measurable biological characteristics which are purported to indicate the progress of an otherwise imperceptible disease. Alzheimer's disease is an exemplary case of this research, motivated in large part by the relative failure of anti-cholinesterase molecules. This, according to the researchers, could be attributed to the fact that treatments were administered at a stage when the disease was already advanced and impairments were irreversible. Research on biomarkers aims to highlight this silent presence of the disease. This research has led to a new understanding of the natural history of the disease comprising consecutive stages: asymptomatic, pre-clinical and clinical. The hope is that, by intervening at an early stage, it will be possible to prevent or delay the onset of the disease.

In order for preventive clinical trials to be conducted, it is necessary for individuals potentially at risk to undergo a presymptomatic diagnosis, that their status be revealed to them, and that these individuals not yet strictly speaking ill agree to test products, the effectiveness and side effects of which are as yet unknown. Articles about these trials only marginally address the ethical issues they raise: Frisoni & Visser (2015), who report controversies between researchers and regulators over the meaning of biomarkers and their potential use, do not mention ethical issues at all. 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<sup>1</sup>, 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 benefits versus risks: they argue

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<sup>1</sup> Tertiary prevention is the prevention of complications following a disease.



that the benefits largely outweigh the risks, which are barely mentioned. It should be noted, however, that unlike the research on clinical ethics presented at the beginning of this paper, this latter work introduces a major difference: it balances the potential collective benefits of clinical trials - the hypothetical discovery of treatments in secondary prevention - against 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 of this status is uncertain, and they 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., 2013; Léger & Ouango, 2009). A seminar organized in 2017 by *l'Espace Ethique d'Ile de France* (Espace Ethique d'Ile de France, 2017) raised these questions: as, on an individual level, the worst-case scenario will not definitely occur, why should a person take a presymptomatic test which risks placing them on a disease trajectory? In-keeping with this hypothesis, one philosopher reported a study in which 78% of individuals having undergone a presymptomatic diagnosis believed that they had symptoms of the disease and that these symptoms were perceptible.

The increasing overlap between clinical work and research projects raises further questions. Eustache (2012) notes that the growing body of research on the pre-clinical stages of Alzheimer's disease raises the question of what difference it makes, in the practice of neuropsychologists, to have to now care for people who are not ill. Other authors question the acceptable limits of intrusion into people's lives for the purpose of research. For example, is it possible to communicate genetic information to the family, which they have not requested, but which was nevertheless produced during a search for the cause of death in a young person? Can we ask to take samples from relatives for genetic analyses, collect information on the presence of the disease in their family, etc.? (Hall & Burton, 2010).

Clinical ethics has provided an almost unequivocal answer to the ultimate question raised by presymptomatic diagnosis: given its potential negative effects, it is only justified in cases where treatments exist. This position nevertheless gives precedence to the principle of beneficence over that of patient autonomy.

The prospect of secondary prevention trials has revived the debate: do the possible collective long-term benefits (development of a preventive treatment) outweigh the negative effects for the individual? This seems to be the view shared by most authors.

# III/ ALTERNATIVE APPROACHES TO CLINICAL ETHICS

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Alternative approaches to clinical ethics have been developed to address these issues. This paper first presents analyses which start not with an assessment of the benefits and risks of the procedure, but rather with a vision of what the limits of medicine should be. Thus, a point of view which remained internal to medicine - in the sense that it did not call into question the legitimacy of the horizon towards which the presymptomatic diagnosis tends, i.e. predictive medicine - is confronted with a perspective which is based on criticism of this medicine. In a second part, this paper focuses on the practices associated with presymptomatic diagnosis and the way in which protocols established by some medical teams have shaped a form of ethics in practice.

## II.1/ Prediction is not medicine

One argument is to discredit the ambition of predictive medicine with which presymptomatic diagnosis is commonly associated. Several authors (Munnich, et al., 2014; Sicard, 2005) agree that presymptomatic diagnosis, or the biological or genetic test carried out as part of a medical consultation, does not predict anything: assuming that it can identify a genetic mutation or biomarker, this discovery does not allow determination with certainty of the time and form in which the disease will manifest itself or evolve over time. Even in the case of Huntington's disease, considered a "disease model" for the development of the presymptomatic diagnosis as it is a disease with complete penetrance, Sicard points out that we know neither when the disease will manifest nor its severity, thus echoing the idea of the "normativity of life" developed by the philosopher of medicine Canguilhem (1966). The radical nature of this criticism must be considered: according to these authors, it is impossible to accurately predict how a disease will develop because of the indisputable uncertainty as to how it will evolve in any individual patient (see also Munnich, 2000). To disregard this warning is a moral error for Munnich, who considers that in such cases "Prediction is a form of curse".

Only genetic tests associated with precise objectives are acceptable for Munnich et al. (2014), such as those used for pre-conception diagnoses for parents who already have a child with an identified mutation, or those used routinely in the case of genetic or chromosomal diseases for which preventive treatments exist: it thus dissociates the genetic test from the illusory purpose of prediction, in order to re-link it to preventive medicine, practiced in specific situations and with specific clinical objectives.

Sicard (2005) is more circumspect about this association with preventive medicine: he considers that (primary) prevention has been diverted from its original purpose, which was to make people aware of the potentially deleterious effects of their lifestyles and thus encourage them to change their habits. He argues that the geneticization of diseases and medicine leads to a disempowerment of individuals with regards to their health. Following the work of Lippman (1993), many authors have seized upon this notion of geneticization to warn against "genetic reductionism", reinforced, according to some, by the rapid growth of an industry

which is keen to market tests of all kinds with no proven benefits to patients. Supporting the idea that genetics should not be seen to confiscate the future, some authors, including Novas and Rose (2000), completely turn the perspective on its head, making it a vector of a transformation of identities and relationships between people: they argue that the presymptomatic diagnosis (they studied Huntington's disease) should be seen as an opportunity for individual and family reflection on the different future scenarios available to the individuals concerned, to weigh up those options which they consider desirable and undesirable.

In total contrast with this vision, Weil-Dubuc (2013) considers that the rationale developed around the possibility of accessing knowledge through presymptomatic diagnosis traps the individual, rather than liberating them. The right to know poorly disguises an obligation to know: once we know we can know, it is difficult (as others have highlighted) to evade what is considered a duty of responsibility. However, the knowledge produced by the diagnosis itself is not only uncertain knowledge but is also knowledge which generates uncertainty around the concerns it imposes on the individuals: *"Predictive medicine provides uncertain information to questions we haven't asked"*. This perception is all the more violent for individuals concerned because it is purely intellectual knowledge which does not manifest itself by any *"sign accessible to the perceptive field"* (Dürr et al., 2010). As argued by Munnich (2016) in a shock statement for which he is renowned: *"Genes don't hurt. What hurts are the consequences of a faulty gene"*.

How, therefore, can the violence of this knowledge be stopped, and freedom restored? For Weil-Dubuc, critical work must be undertaken to both demystify the knowledge produced by the presymptomatic diagnosis and to reveal its limitations. This includes revealing the motives of those behind the injunction: some motives may be acceptable, such as the desire to develop research; and some are less defensible, such as the interests of pharmaceutical, insurance and banking companies. In addition to the right to know, he argues for the right to be critical of knowledge, and invites political and medical authorities to be pedagogical in order *"(...) that predictive knowledge be demystified and not presented in itself as a certain response to a question for all time, but as an uncertain answer to a question invented and provoked by a provisional and culturally-constructed desire to know"*.

What are the limits we must place on the power of medicine? The perspectives developed herein consider that the questions surrounding the presymptomatic diagnosis are poorly formulated due to their initial framing: by taking the existence and legitimacy of predictive medicine for granted, we overlook the fundamental and irreducible uncertainty inherent to the development of a genetic disease. Some argue that this uncertainty, which can thrust people into an existential crisis, prohibits medicine from going beyond its field of competence, prevention and treatment.

## II.2/ Ethics in practice – the protocols

How does this translate in reality? How are the issues of information, consent, autonomy, the right to know and the right not to know dealt with in situ? How do health professionals deal, in practice, with the problems highlighted in previous theoretical analyses?

### A/ A new medical practice: can we talk about patients? Can we talk about care?

Some of the texts examined are based on the observation that carrying out presymptomatic tests forges a new clinical relationship and warn of its complexity. This novelty questions both medical practices and the identity of those who consult. According to some, *“receiving ‘patients’ who have no medical complaints is both a novelty in medicine, and a feature of presymptomatic genetic consultations”* (Héron & Gargiulo, 2012). In these conditions, which term should be used to describe these people who come for consultation? Some prefer to employ the term ‘patient’ rather than ‘sick person’, as it describes the relationship forged between healthcare specialist and the individual without prejudging their health status (Jaunait, 2007). Others consider that the term ‘patient’ over-implies a request for medical care, and they prefer to use the term ‘individual’ (HDSA, 2016).

The situation seems no less complex when we explore the skills and knowledge applied within the context of test protocols. Test practices profoundly influence the work of clinicians (Dürr et al., 2010; Héron et Gargiulo, 2012). Dürr et al. describe how the emergence of uncertainty dominates these novel situations: *“Indeed, the traditional medical relationship is completely overwhelmed by these new practices, as the doctor does not know what is best for the person who is not yet ill but comes to consult them about their genetic status”*. The uncertainty of a situation in which the determination of what is “good for the patient” is beyond the area of expertise of the physician provokes debate on how to redefine his/her positioning; it also fosters the development of collegial and multidisciplinary accompaniment (Benjamin et al., 1994) bringing together, among others, psychologists and psychiatrists, or even general practitioners called upon to advise at-risk individuals (Evers-Kiebooms et al., 2000). The aim of this accompaniment is to provide the person who is considering undergoing a test with optimal conditions in which to progress towards what they decide will be best for them, hence the methods - rather unusual in medicine - used to assess the quality of the proposed treatment: *“Medical teams in charge of these people always consider abandonment of the test as proof of the success of preparation work.”* (Dürr et al., 2010).

### B/ Protocols as an ethical framework

Several research teams have published the protocols they implement for carrying out presymptomatic tests. These protocols are based on the recommendations of expert groups, but also on multidisciplinary programs set up specifically to address the subject, involving clinicians and researchers from different medical fields, as well as ethicists, sociologists and anthropologists (Benjamin et al., 1994; Fortea et al., 2011). In addition, the teams’ experience with people in consultation, as well as various qualitative surveys carried out among people considering undertaking these tests, play an important role.

Two temporal characteristics are consistent across their protocols: the need to take time (Danion-Grilliat, 2012; Fortea et al., 2011) and that of dissociating the information phase from

the subsequent phases of the protocol over time. The information provided is both understood as the transmission of genetic knowledge on the disease, the test and its results, and also - and above all – as a reflection on the impact the test is likely to have on the individual's future life, and on that of their family and friends (Dürr et al., 2009; Evers-Kiebooms et al., 2000). The aim of the system in place is to invite the individual to project themselves into the future with the hypothetical result of the test, whatever it may be, and to anticipate the psychological, social and family consequences deemed important by most authors.

This is followed by a phase of examinations, including a psychological assessment, on the basis of which a collegial discussion takes place, that leads to an opinion then communicated to the individual (Fortea et al., 2011) before they make the decision to undergo the test or not.

In the protocol outlined by Benjamin et al. (1994), a preparation session prior to disclosure of the test result is planned. The patient may decline to be informed of the test result following this session. The counselor themselves is unaware of the test result to avoid bias. In general, follow-up sessions are planned after the test, with the aim of providing short- and long-term emotional and social support (Evers-Kiebooms, 2000).

Protocols generally advise that someone (who is not a person at risk themselves) should accompany the individual concerned. This person may be present throughout the process, or only at the time of communication of the result.

This analysis of protocols offers a physiognomy of ethics in practice which does not overlap with the analyses based on clinical ethics presented above:

- The protagonists of the presymptomatic diagnosis are arranged differently: on the professional side, one deals with a multidisciplinary collective and not an individual; on the patient side, likewise, the person can face the process by being accompanied for all or part of the journey.
- The notion of autonomy is complicated to deal with: the long-term perspective of the process gives way to a maturation of the decision on the part of the person concerned, away from professionals; the possibility of interrupting the process at any moment avoids them being unwillingly coerced one way or another. At the same time, there is no point at which the professionals withdraw, as they are committed to an in-depth exchange with the patient and may even express their opinion on the appropriateness of the test.
- As for the notion of beneficence and non-maleficence, these are always assessed dynamically for each situation, through exchanges between professionals and patients.

Faced with the challenges presented by presymptomatic diagnosis, some practitioners have sought to establish protocols which consider the uncertainty caregivers feel in determining what is "good for the patient". Four points can be noted: (i) the decision to undertake a presymptomatic test is a process that has to **take time** and that supposes dissociating the information phase from subsequent phases over time; (ii) it is a twofold **collective** process involving doctors working in a multidisciplinary team, and patients with the recommended presence of a companion at their side during the process; (iii) it is a process which requires **elaboration**: individuals are invited to project themselves into the future and to imagine what the consequences of the test could be for them, as there are no straightforward answers to this question, the response must be formulated individually; (iv) it is a process which does not stop with the decision and the potential undergoing of the test, since individuals are offered an accompaniment and support over the long term.

## III/ PRESYMPTOMATIC DIAGNOSIS FROM THE PERSPECTIVE OF THOSE CONCERNED

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A number of studies have sought to capture the views of the people concerned by the presymptomatic diagnosis: the scope of this paper is limited to a review of the literature examining individuals' motivations for choosing or not to undergo the test and the effects these decisions have on them. At the outset, a significant "bias" in these field inquiries should be noted: for reasons of access to people to interview, many researchers have focused on people who have decided to undergo genetic testing. Indeed, it is quite complicated, other than through family networks, to reach people who may be at risk, but who have refused genetic testing. Such contact could also raise ethical issues and put the researcher in a difficult situation (Callon & Rabearisoa, 2004): as seen above, there is a certain violence in reminding people of the potential availability of knowledge, itself the bearer of an obligation of sorts. Thus, in most of these studies, researchers, whether medical doctors or sociologists, meet patients in the course of their work within centers specializing in genetics, and ask them about the reasons for their request to undergo a test.

### III.1/ Motivations captured in the moment

A first type of investigation focuses on the individual's decision to undergo the test. These have led to results which partially overlap with the considerations of clinical ethics: consequently, around the time that the test was developed, Williams et al. (1999) interviewed

17 presymptomatic adults who each had a family history of Huntington's disease. Their work revealed that people reported that they underwent the test to reduce their uncertainty - including being able to attribute an explanation to the "symptoms" they were experiencing - to plan their lives and to know if their children were at risk. They were, however, concerned that this information may be disclosed and used by insurance companies or employers for discriminatory purposes. In a more original way, they highlighted their findings that individuals concerned anticipate changes in their relationships with their families, since the results, whatever they may be, would affect certain relatives.

Much more recently, Leite et al. (2017), clinicians of the Center for Predictive and Preventive Genetics within the Institute for Molecular and Cell Biology in Porto, interviewed 217 people about their motivations in seeking to undergo a presymptomatic diagnosis. These people were at risk of developing amyloid neuropathy, Huntington's disease, or Mashado-Joseph's disease - three late-onset autosomal diseases, with serious and lethal consequences, and for which no treatment currently exists - or haemochromatosis, which is a recessive autosomal genetic disease, for which treatments for certain manifestations exist. In response to the question: "what led you to undergo the predictive test?" (p. 130), seven categories of reasons were identified, the most frequent of which have been specified above (organizing one's life, whether this involves taking preventive measures or planning procreation; knowing the risks of transmission; reducing uncertainty; etc.). Among other reasons evoked, we can observe the importance of the individual's entourage, the members of which can influence them, directly or indirectly, to have the test; the desire to refine the diagnosis of another pathology by being able to attribute ambiguous symptoms to identified causes; and finally, in the case of haemochromatosis, to gain access to treatment (obligation to register to plan a liver transplant, etc.).

### III.2/ From one uncertainty to another

These studies, which are based on a kind of freeze-frame focused on the moment of the decision, do not follow patients over the long term and therefore it is not possible to say whether people's expectations are met. Some studies, in-keeping with the findings of Weil-Dubuc (2013), suggest that removing the uncertainty anticipated by test candidates often results in the emergence of new uncertainties. Hess, Preloran and Browner (2009) show that, while conducting genetic tests on people with possible symptoms of Huntington's disease, or ataxia in families with no history of these diseases, puts an end to the uncertainty about the pathology from which they suffer if the results are positive, it also opens up another area of uncertainty about their personal and family future. The article by Kwon and Steiner (2011) explores the single case study of a young man with late-onset Pompe disease: regularly monitored so that the optimal time to start treatment can be identified, he experiences this monitoring - which makes him, according to the authors, a *patient-in-waiting* (Timmermans & Buchbinder, 2010) - as a burden difficult to bear. Other uncertainties, about when the disease will develop and what the experience of the illness is like (Pihet, 2017), are therefore replacing the original uncertainty about one's disease status. Ultimately, the presymptomatic diagnosis leads, in a certain number of cases, to an ontological insecurity which overwhelms the present and sometimes paralyses the individual's ability to live in any other way.

### III.3/ A process developed over time

Other studies have adopted an alternative perspective and are rather focused on the dynamics of whether or not genetic testing is part of the process, in order to understand how this potential approach transforms people's lived experiences.

Studies carried out by Cox (2003), Cox & McKellin (1999) and Geelen et al. (2015) are characterized by their follow-up of individuals or families over several years. The interviews they conducted are long and relatively open. Cox (2003) developed an argument around the differences in methods observed: she noted that the ways in which people recount their stories and the reasons which led them to request genetic testing are diverse. Telling the story of how that decision was made is a process of framing the decision as a decision, because "*the stories we tell ourselves and others about our experiences play an important role in producing as well as describing these experiences*" (p. 260). Each unique context in which the story is told produces a slightly different narrative, which incorporates the present situation, including the interaction between the listener and the teller. However, many investigations and investigators focus on the 'why' (the reasons for the decision) rather than on how people came to make their decision, developing a model of "*rational decision-making which assumes that the decision-maker will weigh up the existing options and arrive at the most rational decision*" (p. 274) thus supporting the "*predominant clinical 'discourse of potential benefits*".

Cox's analysis stands in opposition not only to clinical ethics analyses, but also to attempts to model the decision of which economists are so fond: one example of this is the model developed by Pélissier et al. (2016) which proposes to determine the preferences of an individual based on their consent to pay for the information, in other words, narrowing on a single assessment modality to gauge the way in which individuals approach the situation.

For some, the accounts collected by Cox unfold a landscape in which decisions happen to be rather than being made through a process of deliberation in which the pros and cons are weighed. She identifies three main types of narrative:

1) The candidate "moves towards" the decision to undergo a test: their decision-making is progressive and, in the narrative, involves the conscious recognition that there is a decision to be made and that asking for a test is not the only obvious solution. The narrators go through moments of opposition or ambivalence about the test, towards subsequent moments where the consequences, both for themselves and others, are weighed up and where an initial position is gradually replaced by a sense of feeling ready to undergo the test. They have all experienced the death of a close family member either due to the illness directly or due to its advanced stages. They all describe the fear of becoming extremely ill themselves, or even suspecting having symptoms of the illness already. This deep-seated fear is confronted with the expression of rational ideas which provide explanations for their desire to undergo the test and, in so doing, to exercise some control over their future. Each stage of reflection is developed from, and informed by, what has happened in previous stages.

2) The candidate "has to know", the decision is an obvious one: the author expresses surprise at the absence of a narrative about the decision-making in some interviews, as if the question did not occur to the interviewee. These narratives focused on the immediacy of undergoing



the test, without describing decision-making as a progression with a beginning and an end. All of these candidates were relatively late in discovering the family history of the disease. None of them had experienced a prolonged fear of developing signs of the disease and all were very motivated to talk to other family members about their decision to seek a test, wanting to inform them and set an example for them to follow, feeling responsible for their children and future generations. In their accounts, taking the test was associated with a rather strong sense of empowerment, and has nothing to do with passively following their doctor's recommendations.

3) The candidate "makes the decision" at a pivotal moment after which they take on a different view of the situation: this type of narrative shares some features with the other two, without corresponding entirely with either. The triggering event is, in four out of five cases, the discovery of the existence of a test and, for the remaining fifth, their awareness of being in a state of indecision which they can no longer tolerate.

### III.4/ The importance of temporality

Beyond the different approaches to the decision, Cox & McKellin (1999) demonstrate how the ways in which the individual perceives the risk, and thus the way in which they receive information about the risk, correspond to defined periods in time: many people remember how, during their adolescence, they did not feel particularly concerned and had received information from their parents with a sense of detachment, all the more so as this information was received against a background of vague and timeless knowledge, Huntington's disease being "*this 'thing' that is 'in' the family*". Several aspects help to understand why at certain times the risk becomes more present: when a parent or brother or sister is diagnosed, when the threat comes closer in their space -from distant cousins to people closer to them, when certain decisions are envisaged (e.g. pregnancy), or when the age of onset of the disease, as reported by the family history, is approaching.

This means that neither social scientists nor clinicians should assume that, for the individual, hereditary risk is itself perceived as being problematic: it may or may not be, depending on circumstances which change throughout their lives.

The article underlines a second point in relation to what the diagnosis does; from the individuals' perspective, for as long as they have not taken the test, they feel they are somehow not ill. And yet they aren't not ill either, as demonstrated by the reactions of those who, in the end, learn that they are not carriers: they are so used to the idea that this thing is there, inside them, that they need a certain amount of time to realize that finally it's not the case.

Geelen, Hoyweghen and Horstman (2015) highlight another kind of relationship between presymptomatic diagnosis and temporality: they focus on families in which hypertrophic cardiomyopathies are found, a disease which may be genetic with variable expression, the potentially serious consequences of which could be limited by close monitoring and preventive measures. The article shows that, from one person to another, genetic information takes on very different meanings, particularly in terms of how the future is perceived and how this perception relates to the present: for some, the idea that diagnosis can control one's future is evident, while others categorically reject this idea, insisting either on the limited

expression of the disease in the family or on the importance of other risk factors such as stress. The perspective adopted by this research stream leads to a very different vision from that developed by clinical ethics or surveys on motivations: instead of a list of disease-related elements that are likely to be associated with benefits or risks, we are faced with individuals undergoing a unique process of their own, having a relationship with the disease built up over time through family experience, and a certain way of managing this relationship which evolves over time and which may or may not lead them to seek a genetic test.

The descriptions persons concerned may make of their perception of the presymptomatic diagnosis depend on the methods used to produce these. One stream of research focuses on the moment of the decision, which they portray as a singular moment where, like approaches in clinical ethics, they weigh up arguments against one another: unsurprisingly, these arguments are similar to those put forward in clinical ethics. Other research focuses on the dynamics involved in the diagnostic process: like protocols studied previously, these emphasize the importance of temporality – people's assessment of the risks associated with the disease and the potential benefits of a diagnosis vary over time and are affected by events such as the illness of a loved one or their desire to start a family. Moreover, they describe the process of presymptomatic diagnosis not as a decision to be made, but as an element in the course of their life which, especially in the case of diseases with incomplete penetrance, is not necessarily as decisive as one may think. Finally, several studies demonstrate how post hoc, the presymptomatic diagnosis, far from putting an end to uncertainty, rather transforms its nature and creates a new sense of ontological insecurity.

## CONCLUSION

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This review aimed to highlight the existence of very different ways of approaching the question of presymptomatic diagnosis. By exaggerating the contrasts, we can conclude that there are two main competing approaches.

One approach considers the decision as a rational process wherein the associated risks and benefits are weighed, risks and benefits which have a kind of objective existence even if they are assessed in a specific way for and by each person concerned. In this scenario, the practitioner is a priori as well placed as the person themselves to determine the "right decision", with them, or possibly in their place.

A second approach is to consider that the decision is only one point in a long process which gradually leads people to both incorporate and come to terms with what the illness means in their lives and how the presymptomatic diagnosis can change the course of their lives. In this approach, a shared path is forged between health professionals and the individual, in order to explore what the diagnosis means to them together.

Interestingly, methods which aim to investigate individuals' perceptions invariably present the same dichotomy: depending on whether the researchers are aligned with one or other of the

above approaches, they will favor either a search for motivations determined post hoc, but supposed to give a rational account of a decision made, i.e. an attempt to reconstruct the (possibly ongoing) process, and which, at a given moment, may have converged towards a particular decision. Patients grouped in this way present rather different profiles. While both methods provide interesting elements, it is advisable to be cautious about the anticipatory capacity provided by the former: in the same way that statements of intent made out of context can be very misleading - there is been a considerable gap between reported intentions to undergo presymptomatic diagnosis of Huntington's disease prior to the development of a test, and the performance of tests once treatment became available (Jacobs & Deatrick, 1999) – post hoc rationalizations may not be very relevant to the process which led to the observed result. Indeed, research conducted according to the second approach highlights the fact that the decision of whether or not to receive the diagnosis is the result of a personal journey, in which the experience of a loved ones' illness, temporality, the development of a life project, an encounter with the care system, etc., are likely to play a predominant role.

The issue of clinical trials as a potential motivation for undergoing a presymptomatic diagnosis introduces an additional complicating factor: whereas until that point, attention could be focused on the individual risks and benefits, or on the significance of this act and the transformations it can introduce into the lives of the individual and their entourage, the prospect of clinical trials presents a horizon which goes beyond the individual. It is not possible to determine whether this perspective is likely to induce potential candidates to seek presymptomatic diagnosis. Rather, the question is whether and how this can be incorporated into options proposed to the individual. In this perspective, the discussion on protocols presented herein provides useful benchmarks for ethical framing both by and in practice: the relatively long duration of the procedure, the process of collective exploration of what the decision may imply, and the non-interference by researchers are arguably the main features to retain.

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