

# MOTIVATION TO PERFORM PRESYMPTOMATIC TESTING IN PORTUGUESE SUBJECTS AT-RISK FOR LATE-ONSET GENETIC DISEASES

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## RESUMEN

El papel del psicólogo clínico en el contexto del consejo genético incluye brindar apoyo a los sujetos en riesgo en el proceso de toma de decisiones, independientemente de la decisión adoptada por el sujeto (conociendo o no el resultado de las pruebas genéticas).

El estudio que se informa aborda la motivación para realizar las *pruebas pre-sintomáticas (PPS)* de *sujetos en situación de riesgo* para tres enfermedades: *polineuropatía amiloide familiar (PAF)*, la *enfermedad de Huntington (EH)* y la *enfermedad de Machado-Joseph (EMJ)* y comparar con la motivación para realizar las PPS para hemocromatosis (HH).

La muestra consistió en 213 sujetos portugueses que tenían riesgo genético para contraer las tres enfermedades y 31 sujetos en situación de riesgo genético para contraer hemocromatosis. Ellos fueron evaluados con una entrevista para obtener datos sociodemográficos y debían responder a una pregunta sobre la motivación para llevar a cabo las pruebas pre-sintomáticas.

Se obtuvieron siete categorías principales y las siguientes son las más significativas para PAF, EH y EMJ: razones relacionadas con el futuro, razones relacionadas con los demás y razo-

nes relacionadas con la curiosidad y la necesidad de conocer. Para hemocromatosis, las más importantes resultaron ser razones relacionadas con los demás y las relacionadas con las características de la enfermedad.

La motivación para realizar el test pre-sintomático (PST) de la PAF, EH y EMJ es externa y sin relación con la enfermedad, mientras que la motivación de los sujetos en situación de riesgo para la HH está relacionada con la enfermedad. Las razones relacionadas con los demás es una motivación común en ambos grupos. A los sujetos también les preocupa la posibilidad de transmitir la enfermedad a sus hijos.

*Palabras clave:* Pruebas pre-sintomáticas (PPS); Enfermedad genética; Sujetos en situación de riesgo; Polineuropatía amiloide familiar (PAF) TTR V30M; Enfermedad de Huntington (EH); Enfermedad de Machado-Joseph (EMJ).

## ABSTRACT

The role of the clinical psychologist in the context of genetic counseling includes support for the process of decision-making for *subjects at-risk*, regardless of the decision that was made. For this,

it is important to know the motivations behind these decisions. What may be considered advantageous and justifiable reasons to perform the PST for *genetic diseases* from the medical and public point of view, i.e., planning for the future, helping in the choice of a profession, family planning, improving quality of life and contributing to health, may not be recognized as such by the individual seeking the PST.

This study addresses the *motivation to perform the presymptomatic testing* (PST) of subjects at-risk for three diseases, *Familial Amyloid Polyneuropathy (FAP)*, *Huntington's disease (HD)*, and *Machado-Joseph disease (MJD)*, compared with the motivation to perform the PST for Hemochromatosis (HH).

FAP, HD and MJD are three genetic (monogenic) autosomal dominant late-onset diseases (LON-Ds) with no cure. FAP is a progressive sensorimotor and autonomic neuropathy of adulthood. HD is characterized by a triad of clinical symptoms of chorea (motor, cognitive and psychiatric symptoms), emotional distress and cognitive decline. MJD is characterized by slowly progressive clumsiness in the arms and legs, a staggering lurching gait, sometimes mistaken for drunkenness, difficulty with speech and swallowing, involuntary eye movements, and may be accompanied by double vision or bulging eyes, and lower limb spasticity. HH is a disease in which too much iron accumulates in parenchymal organs, leading to iron overload and subsequent organ toxicity and failure.

The study participants consisted in 213 subjects at genetic risk for FAP, HD, and MJD and 31 subjects at genetic risk for HH, that were assessed through an interview to obtain sociodemographic data and the answer to one question about motivation to perform PST: "Which were the reasons that led you to perform the predictive test?" This study was carried out in Center for Predictive and Preventive Genetics (CGPP), Institute for Molecular and Cell Biology (IBMC), Porto (Portugal). This research used a mixed-method, since qualitative and quantitative techniques of data analysis were used.

Before deciding to seek genetic counseling and to know their genetic status, subjects at-risk have naturally considered their motives and it was probably the pro-counseling reasons the ones dictating the motivation to perform the PST. This

may suggest that in fact there is a prior self-selection to the test, i.e. only those considering to have emotional skills to go through the process, performing the test.

Seven major categories were obtained. The most significant ones for FAP, HD and MJD were reasons related to the future, reasons related to others and reasons related to curiosity and to the need to know. For HH, the most important ones were reasons related to others and reasons related to the characteristics of the disease.

The motivation of subjects at-risk to perform the PST for FAP, HD and MJD is external and unrelated to the disease, while the motivation of subjects at-risk to perform the PST for HH is related to the disease. Reasons related to others are a common motivation: as subjects at-risk for FAP, HD and MJD, subjects at-risk for HH also chose reasons related to others as one of the most important motivations to carry out the PST. These subjects also care about the fact that they can transmit the disease to their children and care about other family members which are already ill. The category reasons related to others includes sub-categories that identify the person and the situation that led to the decision to perform a PST. Subjects at-risk are also concerned about the fact that they have to decide whether or not to have children and its economic implications.

*Key words:* Motivation to perform the PST; Genetic diseases; Subjects at-risk; Familial Amyloid Polyneuropathy (FAP); TTR; V30M; Huntington's disease (HD); Machado-Joseph disease (MJD).

## INTRODUCTION

The subset of psychological issues and processes that are most salient within the clinical genetics context has evolved and it must take into consideration the potential costs but also the benefits since psychologists can play a critical role, assisting patients, families, physicians, and policymakers as they grapple with the complex task of integrating genetic information into their profes-

sional practice and everyday lives (Lerman, Croyle, Tercyak, & Hamann, 2002). The role of the clinical psychologist in the context of genetic counseling includes support for the process of decision-making for subjects at-risk, regardless of the decision that was made. For this, it is important to know the motivations behind these decisions. This study will enable to know the reasons why subjects at-risk for Familial Amyloid Polyneuropathy (FAP), Huntington's Disease (HD), and Machado-Joseph Disease (MJD) want to perform the PST and compare the results with the motivations of the subjects at-risk for Hereditary Hemochromatosis (HH) which also wish to carry the presymptomatic testing (PST).

## THE STUDIED DISEASES

FAP, HD and MJD are three genetic (monogenic) autosomal dominant late-onset diseases (LONDS) with no cure.

FAP, also known by Transthyretin (TTR) Amyloid Neuropathy or even Transthyretin (TTR) Amyloid Polyneuropathy (since the three terms are considered synonyms) is a progressive sensorimotor and autonomic neuropathy of adulthood (Adams, 2013) and is caused by mutations in the TTR gene (18q12.1). FAP is a rare and fatal systemic disease resulting from autosomal dominant inherited single-point mutations (Coutinho et al., 2013). FAP is presented in many different forms, with considerable phenotypic variation across individuals and geographic locations. Diagnosis can be challenging and treatment often requires a multidisciplinary approach. Physicians likely to diagnose and treat patients with this disease include neurologists, cardiologists, gastroenterologists, ophthalmologists, and other specialists (Ando et al., 2013). The age of onset varies between the 20s and the 90s (Seca, Ferreira, & Coelho, 2014). Lemos and colleagues (2014) consider that early-onset ( $\leq 40$  years) and later-onset ( $\geq 50$  years) cases of TTR-FAP V30M are not different entities, often coexisting in the same family, and showing antic-

ipation, with earlier age-at-onset in younger generations, usually associated with more severe phenotype. Acknowledgment of anticipation may have important clinical implications in genetic counselling of offspring and in follow-up of mutation carriers (Lemos et al., 2014). The largest cluster of individuals with TTR-FAP caused by the Val30Met mutation is found in northern Portugal, particularly in Póvoa de Varzim and Vila do Conde, where the incidence is estimated to be one in 538 individuals (Conceição & De Carvalho, 2007), i.e., one in every 1,000 individuals has the disease, and one in every 538 are carriers of the mutated gene.

HD is an adult-onset, fatal genetic disease with psychosocial implications (Kessler & Bloch, 1989), since it is a disease in which nerve cells degenerate. It is characterized by a triad of clinical symptoms of chorea (motor, cognitive and psychiatric symptoms), emotional distress and cognitive decline (Lee, Hwang, Ryu, Kowall, & Ryu, 2014). The gene responsible for HD is located near the terminus of the short arm of chromosome 4 and the defect causes a part of DNA, called a CAG repeat, to occur many more times than it is supposed to (Kirkwood, Siemers, Hodes, Conneally, Christian, & Foroud, 2000). There are basically two forms of HD but the adult-onset HD is the most common one (Ross et al., 2014). There is no cure for HD (van Dellen, Blakemore, Deacon, York, & Hannan, 2000). There is currently no known way to stop the disease from getting worse. The goal of treatment is to slow the symptoms and help the person to function for as long as possible.

MJD, also called *spinocerebellar ataxia Type 3* (SCA3), is one of approximately 30 recognized, dominantly inherited forms of ataxia. *Ataxia* is a common used term meaning lack of muscle control or coordination (Bettencourt & Lima, 2011). MJD is characterized by slowly progressive clumsiness in the arms and legs, a staggering lurching gait, sometimes mistaken for drunkenness, difficulty with speech and swallowing, involuntary eye movements, and may be accompanied by double vision or bulging eyes, and lower limb spasticity (D'Abreu et al., 2010).

Some individuals develop dystonia symptoms, sustained muscle contractions that cause twisting of the body and limbs, repetitive movements, and abnormal postures, or symptoms similar to those of Parkinson's disease (D'Abreu et al., 2010). Persons with MJD have the same disease gene mutation, a DNA repeat expansion in the ATXN3 gene (Bettencourt & Lima, 2011). MJD is considered to be incurable (Rolim, Zagalo-Cardoso, Paúl, Sequeiros, & Fleming, 2006), but some symptoms of the disease can still be treated. Levodopa therapy (van Alfen et al., 2001), used in treating individuals with Parkinson's disease, can ease parkinsonian features, stiffness and slowness of movements, often accompanied by a tremor, for many years.

HH is a disease in which too much iron accumulates in parenchymal organs, leading to iron overload and subsequent organ toxicity and failure (Fleming & Sly, 2002). The gradual accumulation of iron can severely affect most of body's organs, but especially the liver, pancreas and heart (Eng, Taylor, Reyes, Raaka, Berger, & Kowdley, 2005). The excess of iron in the liver can cause an enlarged liver, liver failure, liver cancer, or cirrhosis. The excess of iron in the pancreas can lead to diabetes and in the heart it can cause irregular heartbeats called *arrhythmias* and heart failure (Philippot, 2002). The two existing types of HH are primary and secondary. Primary HH is caused by a defect in the genes that control the amount of iron absorbed from food (Yen, Fanher, & Bowlus, 2004). Secondary HH usually is the result of another disease or condition that causes iron overload. Primary HH is also a genetic disease and the treatment is commonly through phlebotomy for removal of excess iron store (Salgia & Brown, 2015).

#### MOTIVATION TO PERFORM THE PST FOR GENETIC DISEASES

What may be considered advantageous and justifiable reasons to perform the PST for genetic diseases from the medical and public point of view, i.e., planning for the future,

helping in the choice of a profession, family planning, improving quality of life and contributing to health, may not be recognized as such by the individual seeking the PST (Fleming & Lopes, 2000).

Several studies regarding the motivation to perform PST for neurogenetic diseases and the underlying decision-making process have been carried out. According to Schuler-Faccini, Osorio, Romariz, Paneque, Sequeiros, and Jardim (2014), the decision to undergo PST for late-onset neurological diseases is mainly a question of awareness and accessibility. Rodrigues and colleagues (2012) concluded that this decision seems to be genuinely autonomous, since after genetic counseling half of the individuals who asked for PST decided in favour of it and half decided against it. Meissen, Mastromauro, Kieley, McNamara, and Myers (1991) found that the reasons to perform the test are related with the reduction of anxiety and the uncertainty associated with being at-risk, and enhanced planning and decision making. The emotional aspects and the perception of personal risk, i.e., the subjective risk, seem to further influence the decision of performing the genetic test rather than the knowledge relating the precise genetic risk (Zagalo-Cardoso & Rolim, 2005). The socio-emotional skills, understood as a set of knowledges, skills and attitudes necessary to understand, express and manage emotional phenomena (Mikulic, Crespi, & Radusky, 2015) are crucial in the decision to undergo the PST.

For Lucas (1998), the most common reason for undertaking the testing for HD was to make plans for the future; the wish to know before a future planned marriage, or remarriage; the wish to know before starting a family, or having further children; to make career decisions; to inform one's children of their risk status, and to alleviate the dissonance caused by not knowing one's HD status. The *intolerance of uncertainty* is defined as a characteristic arrangement resulting from a set of negative thoughts about uncertainty (Brenlla & Rodríguez de Behrends, 2015). According to Meiser and Dunn (2000), between 40 and 79% of people at-risk of devel-

oping HD reported the intention to use the test and found different age-related motives for HD testing: one being a reproductive risk decision and another one the intention to clarify the risk for their children. On the other hand, Wahlin and colleagues (2000) found that subjects at-risk for HD showed high suicidal ideation and self-injurious behavior and 30.8% of the HD carriers reported suicide or suicide attempts in the family, whereas the corresponding figure for HD non-carriers was 14.3%. These data raise greater concern about the subjects at-risk for HD seeking genetic counseling.

At-risk symptomatic adult family members of FAP may seek testing in order to make personal decisions regarding reproduction, financial matters, and career planning. Others may have different motivations including simply the *need to know* (Sekijima, Yoshida, Tokuda, & Ikeda, 2001). In FAP context, the adherence to the test has been clearly influenced by the possibility of performing the liver transplant, a therapeutic modality that allows to halt the progression of the disease. Many subjects at-risk point as the main reason for performing the genetic test the possibility of being able to make an early registration regarding the waiting list for transplantation, in case the test result is positive (Zagalo-Cardoso & Rolim, 2005).

Rolim and colleagues (2006) concluded that the decision to undergo the PST for MJD generates emotional distress and involves major personal issues, with the potential for short- to long-term psychological consequences for the individual and the family. However, the same authors agreed that having PST for MJD included a reduction in the level of uncertainty and the chance to plan their future, with regard to procreation and to the disease itself; the possibility of informing the offspring about the risk of developing the disease or even the chance of beginning a medical treatment, not yet available, to prevent its development and / or to delay its course. Cruz-Mariño and colleagues (2013) refer as main reasons to perform the PST for SCA2 the risk assessment in the subjects' at-risk descendants, and the physical

and psychological preparation to cope with the disease and to plan the future. The authors did not include subjects at-risk for MJD, but for SCA2, a genetically different condition, nonetheless their clinical distinction with MJD / SCA3 may at times be difficult to make.

## OBJECTIVE

The aim of this research was to know the motivation to perform the PST of subjects at-risk for FAP, HD, and MJD, and then to compare the results obtained with the motivations to perform the PST that subjects at-risk for HH have.

## METHODOLOGY

### PARTICIPANTS

The study participants consisted of two groups: individuals with *a priori* genetic risk of 50% for FAP, HD, or MJD diseases, although asymptomatic, aged over 17 years and subjects at-risk for HH, the group to which the results will be compared with, whose risk differs from case to case, also aged over 17 years. The subjects which were 17 years-old at the time the research was done were allowed to participate in the study, as long as they would already have 18 years-old at the time they received the test result. Many subjects at-risk are emigrants, enjoying their vacations in and taking that time to perform the PST. They would be told about the genetic status later.

The first group, the clinical one, consisted of 213 subjects at genetic risk: 174 subjects at-risk for FAP, 34 subjects at-risk for HD and only 5 subjects at-risk to MJD. Age ( $t = 36.328$ ;  $df = 212$ ;  $p = .000$ ), gender ( $t = 41.720$ ;  $df = 212$ ;  $p = .000$ ), nationality ( $t = 62.619$ ;  $df = 212$ ;  $p = .000$ ), education ( $t = 42.219$ ;  $df = 212$ ;  $p = .000$ ), and disease ( $t = 52.433$ ;  $df = 212$ ;  $p = .000$ ), were distinguishable from a statistical point of view, where  $t$  is the *Student t* Distribution,  $df$  is the

Degrees of Freedom and  $p$  is the  $p$  value. The second group, acting as the comparison group, consisted of 31 subjects at genetic risk for HH. Age ( $t = 17.499$ ;  $df = 30$ ;  $p = .000$ ), gender ( $t = 23.242$ ;  $df = 30$ ;  $p = .000$ ), and education ( $t = 13.493$ ;  $df = 30$ ;  $p = .000$ ), were distinguishable from a statistical point of view. Regarding nationality, all these 31 subjects are Portuguese (see Table 1).

Subjects at-risk for HH were chosen to incorporate the comparison group because these subjects were also at-risk for a genetic disease, although with a different risk and less severe and limited disease. HH presents possible treatment and patients may live a long time with the disease, unlike the other three diseases, FAP, HD, and MJD.

None of the subjects at-risk, either belonging to the clinical or the comparison group, had previously done the PST. Inclusion criteria in the counseling program were the following: being at-risk for diseases for which a direct relative has a molecular diagnosis (1); being adulthood (2); and expressing the desire to perform the PST, even when counseling was suggested by the family doctor (3).

## MEASURES

All the individuals at genetic risk for FAP, HD, MJD and HH were assessed through an interview, to which the participants answered orally, in order to obtain socio-demographic data and the answer to an open-ended question relating the motivation to perform de PST: "Which were the reasons that led you to perform the predictive test?"

## PROCEDURES

This study took place in Centre for Preventive and Predictive Genetics (CGPP), which is an integrated research centre at the Institute for Molecular and Cell Biology (IBMC) (Porto - Portugal). In this research centre, genetic counseling is available for LOND's, mostly, FAP, HD and MJD. This

study has been reviewed and approved by the IBMC ethics committee. All subjects at-risk attending consultations for genetic counseling in the CGPP, in order to know their genetic risk for FAP, HD and MJD, or HH, were contacted to participate in the study. Those who agreed to do it, were interviewed by the authors before the first consultation of the genetic counseling program. The intention was to understand the motivations that drive the subjects at-risk to perform the PST, aiming to know their genetic status for diseases for which they are at-risk for. All subjects were informed about the nature of the research, the aims of the study and the type of treatment to give to the data. The confidentiality of the data was guaranteed and the informed consent to voluntary collaborate in the research was obtained. This study took place between 2013 and 2015.

## DATA ANALYSIS

This study used a mixed-method, since qualitative and quantitative techniques of data analysis were used. Initially, an analysis of the responses of the participants was carried out through the data analysis software package NVivo (QSR I, 2012). After the data collection, the authors have separated the answers according to the disease being studied. Based on the Grounded Theory Methodology (Glaser & Strauss, 1967), response patterns have emerged and categories and, in some cases, sub-categories, have been established. As a result, a set of general categories and another set of specific categories were created. Then, the frequencies of categories were assessed to obtain a hierarchy of importance, since the most frequently reported categories would be the most representative and significant ones.

## RESULTS

The open-ended question "Which were the reasons that led you to perform the predictive test?" has provided clear answers and

has also revealed prior reflection regarding the same question. Seven categories have emerged: reasons related to the future, reasons related to others, reasons related to curiosity and the need to know, reasons related to the characteristics of the disease, reasons related to metaphors about the disease, reasons related to other diseases, and reasons related to other reasons.

The motivations for subjects at-risk to perform the PST related to the *future* include planning the future, for example, marrying, having children, making decisions regarding professional life and financial issues, etc., and how these subjects will in the future deal and manage the disease - for example, whether to seek professional assistance or preferring to be cared for by their families, etc.

Motivations resulting from *others* relate to concerns felt in relation to family members who are already ill, such as the parents, uncles, cousins, brothers, etc., and those that may get ill, especially sons and nephews, in addition to others who will be affected by the fact that the subject at-risk is likely to have the disease, namely, spouses or companions. The motivations that arise from the *curiosity and the need to know* consist mainly in issues related to stress management by reducing uncertainty and own curiosity about the genetic status-carrier or non-carrier. The specific characteristics of the disease itself also constitute reasons for carrying out PST, e.g., symptoms that are perceived in the other can be experienced by the subjects at-risk, and often these subjects reported having symptoms that are actually not confirmed, or they would not be in the PST protocol. The *metaphors* that subjects at-risk have about the diseases for which they are at-risk originate the conducting of the PST, since what they know about the disease makes the subjects at-risk preoccupied and anxious. The *reasons related to other diseases* to perform the PST are connected with the fact that subjects at-risk want to understand the symptoms that have been associated with the disease for which they are at-risk for or previous diseases, because this ambivalence intensifies the uncertainty and anxiety. Finally,

all isolated and specific motivations of each case were categorized in *other reasons*.

From the above reported seven categories, three can be considered significant for subjects at-risk for FAP, HD and MJD: *Reasons related to the future*, *Reasons related to others*, *Reasons related to curiosity and the need to know*, while the motivation of the subjects at-risk for HH is *Related to the characteristics of the disease*. *Reasons related to others* are a common motivation to all diseases (see Table 2).

With regard to the first category, *Reasons related to the future*, the subjects at-risk for neurodegenerative diseases are the ones who mainly seek more PST for reasons connected with the future: 80% for the subjects at-risk for MJD, 66.7% for the subjects at-risk for FAP and 58.8% for the subjects at-risk for HD. Subjects at-risk for HH present a lower value, 19.4%. Overall, the main reasons that lead people to want to perform PST, when considering the future, are: (a) *to take preventive measures* (44 references) (e.g., “I want to perform the PST because I want to prevent the disease”); (b) *to be pregnant, to have children* (e.g., “I want to perform the PST because I want to have children but I do not want them to have the disease”); (c) *to organize life, to make decisions, to choose* (36 references each) (e.g., “I want to know if I have the disease or not because I would like to invest in a business and I do not know if I should do it if I have the disease”).

When analysing each disease separately, it is possible to conclude that priorities described above coincide for subjects at-risk for FAP. The same applies to the subjects at-risk for HD, which, in addition to these aspects, also seek to have a more peaceful life and therefore want to know the result of the PST. Subjects at-risk of MJD take special care in organizing life, while subjects at-risk for HH seek essentially to take preventive measures.

Regarding the second category, *Reasons related to others*, most of the subjects at-risk for HH searched genetic counseling because of another person, and the same happens with subjects at-risk for FAP. Subjects at-risk for HD and for MJD were influenced by third

parties to seek genetic counseling in order to carry out the PST, but fewer in number than the former. It is important to distinguish in this category between wishing to take the PST because subjects at-risk felt they were driven to it by someone else, and to want to perform the PST because somebody else is pressing them to do it. Therefore, this particular category was also divided into other subcategories given its complexity: *Because of someone else* (e.g., “I would like to know because of my son / daughter”), *Instigated by others* (e.g., “My family doctor told me to perform the PST”), *Because someone has the disease* (e.g., “I want to perform the PST because my aunt has the disease and I want to know if I also have it”), and *Because someone died with the disease* (e.g., “My mother died of the disease and I want to know if I will also have it”) (see Table 3). In the subcategory *Because of someone else*, sons / daughters and brothers / sisters emerge as the key drivers behind the completion of PST. With regard to the subcategory *Instigated by others*, and in relation to the subjects at-risk for FAP, brothers / sisters are mainly the ones who play the instigator role. In relation to the subjects at-risk for HH, mainly doctors (13 references) act as instigators. For the subcategory *Because someone has the disease*, and with regard to the subjects at-risk for FAP, brothers / sisters and the mother emerge as patients, while the subjects at-risk for HH refer, above all, parents and children, source of concern. Finally, and regarding the subcategory *Because someone died with the disease*, the subjects at-risk for FAP mainly refer parents, while subjects at-risk for HH refer above all the brothers/sisters. Of all the subcategories indicated, the first three are the ones most referred by the subjects at-risk.

Regarding the third category, *Reasons related to curiosity and the need to know*, the subjects at-risk who felt more need to know their genetic status were the subjects at-risk for MJD, followed by subjects at-risk for HD (e.g., “I need to know because I cannot stand uncertainty”), then by subjects at-risk for FAP, and finally, by subjects at-risk for HH (see Table 2).

Concerning the fourth category, *Reasons related to the characteristics of the disease* (see Table 2), subjects at-risk for HH particularly reported the characteristics of the disease as a reason to perform the PST (e.g., “I want to perform the PST because I have many digestive problems and I have to know whether or not it has to do with the disease”), oppositely to the subjects at-risk for other diseases under consideration, who reported very few features about the disease. While the few subjects at-risk for FAP limited the reference to the disease to the fact of being hereditary and that is considered reason enough to perform the PST, subjects at-risk for HH have seen in the characteristics of the disease different important reasons to perform the PST: iron overload, liver problems, and digestive problems.

As for the fifth category, *Reasons related to metaphors* (see Table 2), low numbers have been reported: only 5.9% of the subjects at-risk for HD, and 1.1% of the subjects at-risk for FAP. Although these numbers may be considered insignificant in quantitative terms, they are related to negative aspects like nightmare, inheritance, fear and uncertainty (e.g., “This disease is hell and so I have to know whether or not I have it”).

Regarding the sixth category (Table 2), *Reasons related to references to Other diseases*, only subjects at-risk for HH (6.5%) and subjects at-risk for HD (5.9%) made references to other diseases. Epilepsy and depression (e.g., “I was always depressed and as my mother was also depressive and had the disease, I need to know whether or not I have it”) appear related to HD, while cirrhosis and kidney problems appear related to HH.

Finally, in relation to the seventh category (Table 2), *Other reasons*, only subjects at-risk for HD (23.5%) and FAP (8.0%) seem to be able to find other reasons to perform the PST, at the time of the application of the PST protocol. Of all the reasons that have been presented by the subjects at-risk, and that were considered valid to be referred in this text, the ones appearing to be more consensus are the ones presented in the response *be-*

*cause they have symptoms and in the response the disease must end.*

In conclusion, it is possible to state that some subjects at-risk want to perform the PST because they think they have symptoms or because they are looking for them and, therefore, that is a valid reason for them. However, the results clearly indicated that most individuals are asymptomatic. It is also important to highlight that many subjects cherish the idea that it is in their hands to end the disease, and they take this task seriously, seeking to influence others to do the same.

## DISCUSSION

Before deciding to seek genetic counseling and to know their genetic status, subjects at-risk have naturally considered their motives and it was probably the pro-counseling reasons the ones dictating the motivation to perform the PST. This may suggest that in fact there is a prior self-selection to the test, i.e. only those considering to have emotional skills (Mikulic et al., 2015) to go through the process, performing the test.

The question “Which were the reasons that led you to perform the predictive test?” gives place to seven categories, suggesting that all the responses obtained are homogeneous because the reasons why subjects at-risk perform the PST do not diverge significantly. From these seven categories that have been considered regarding the motivation to perform the PST, there are three that seem to be most relevant: *Reasons related to the future*, *Reasons related to others*, and *Reasons related to curiosity and the need to know*. These motivations do not differ from the ones found by other authors (Fleming & Lopes, 2000; Lucas, 1998; Meissen et al., 1991; Meiser & Dunn, 2000; Rolim et al., 2006; Sekijima et al., 2001).

Regarding the category *Reasons related to the future*, some expected subcategories were found: *to take preventive measures*; *to be pregnant, to have children*; *to organize life, to make decisions, to choose*. The concern with future is deeply related to the possibility

of becoming physically dependent and to die, in case the subjects at-risk are carriers. This scenario triggers in subjects at-risk subsequent concerns about others, namely their children. Because this research relates the period before genetic counseling, it is important to refer that, regarding preventive measures, many subjects at-risk wrongly believe to be possible to prevent the disease or delay its onset. To become pregnant or not is one of the hardest decisions to make when the subject at-risk thinks he/she might be a carrier of the disease, particularly when referring to the subjects at-risk who do not have children yet. The threatened maternity or paternity is one of the most distressing situations for these subjects. When they decide to have children, they have yet to make another decision: whether or not to perform prenatal testing (Bouchghoul et al., 2016), and this option may only be considered feasible if the person is willing to terminate the pregnancy in the case of the *fetus* is a carrier of the mutated gene. Although all of these options are considered and assessed step by step, the reality is that subjects at-risk admit they feel overwhelmed because they must take a significant number of important decisions in a short space of time (Bouchghoul et al., 2016). Ethical (Kromberg & Wessels, 2013), legal (Freckelton, 2010, 2014), financial, logistical and material aspects become the centre of general decisions related to life organization as a whole, depending on what is expected to happen to the subjects at-risk (Kromberg & Wessels, 2013).

The category *Reasons related to others* clearly includes subcategories that identify the person and the situation that led to the decision to perform a PST (Cox, 2003). Subjects at-risk are concerned about the fact that they have to decide whether or not to have children because they will be a concern for a parent who is not sure if it will be possible to economically support them. Oppositely, the same subjects at-risk may decide that children will act as a source of support at an advanced stage of the disease. When subjects at-risk already have children and seek for genetic counseling, their concerns are focused on

their future (Zagalo-Cardoso & Rolim, 2005), because they feel that a time may come in which they will no longer be able to give them appropriate support. Subjects at-risk with children also express the hope that a cure for the disease will already be possible at the age of the onset of the symptoms, if the children are carriers (Rolim et al., 2006). Subjects at-risk do not care only about their descendants. They also express significant concern with relatives who are already carriers and who depend on their care, as the case of parents, brothers/sisters, uncles/aunts, cousins, etc. They fear that they will not be able to provide such care in a short period of time, given the perspective that their own health will get worse and may incapacitate them (Cox, 2003).

Regarding the category, *Reasons related to curiosity and the need to know*, the subjects at-risk who felt more deeply the need to know their genetic status were the subjects at-risk for MJD, followed by subjects at-risk for HD, then by subjects at-risk for FAP and, finally, by subjects at-risk for HH. These findings are in accordance with most studies about the motivation behind PST (Lucas, 1998; Meissen et al., 1991; Meiser & Dunn, 2000; Sekijima et al., 2001). The acquisition of knowledge regarding the genetic status of subjects is a way to reduce anxiety and to be able to plan life based on that same knowledge (Cruz-Mariño et al., 2013; Rolim et al., 2006). Accordingly, there is also no known evidence that this knowledge may significantly increase the burden among those who are carriers of the disease's gene, although Wahlin and colleagues (2000) have found high levels of suicidal ideation among individuals at-risk for HD. In general, the subjects at-risk who seek genetic counseling because they feel the need to know their genetic status consider that they have the capacity to deal with the PST outcome, whatever it is. However, some subjects at-risk have not previously reflected on the implications resulting from the knowledge of their genetic status. Therefore, this task of explaining to subjects at-risk the practical implications of the PST outcome is one of the

most important ones to be carried out in the genetic counseling process, before the disclosure of the results. In the specific case of FAP, many subjects at-risk feel the need to know their genetic status because they are aware of the existence of two treatments that may prevent or slow the progression of the disease: liver transplantation and the Tafamidis Medicine. However, many of these subjects at-risk confuse treatment with healing. This distinction is crucially important and it must be considered another fundamental task of the genetic counseling process for this specific disease.

As in the case of the subjects at-risk for FAP, HD and MJD, the subjects at-risk for HH also chose *Reasons related to others* as one of the most important motivations to carry out the PST in the genetic counseling. These subjects at-risk also care about the fact that they can transmit the disease to their children and care about other family members which are already ill. However, the future is not one of the primary reasons for performing the test, unlike subjects at-risk for FAP, MJD and HD, since there is treatment for HH. Accordingly, there is a future, which will be more or less affected by the disease. Again, and unlikely to what happens with the subjects at-risk for FAP, HD and MJD, subjects at-risk for HH choose the *Reasons related to the characteristics of the disease* as one of the main motivations to perform the PST, because the symptoms of the disease may significantly disappear or decrease depending on the available treatment, which may result in a possible cure.

## CONCLUSIONS

Seven categories have emerged from the responses given to the question aiming to evaluate the motivations behind PST "Which were the reasons that led you to perform the predictive test?" However, the most important ones are: *Reasons related to the future*, *Reasons related to others*, and *Reasons related to curiosity and the need to know*. This allows to conclude that the main reasons why the Portuguese subjects at-risk perform the

PST for FAP, HD and MJD are the *Future*, *Others*, and *Curiosity*. Subjects at-risk for HH indicated that the main reasons to perform the PST are *Reasons related to others* and *Reasons related to the characteristics of the disease*.

#### PRACTICE IMPLICATIONS

A better understanding of the motivations leading the subjects at-risk for FAP, HD and MJD to know their genetic status will allow to adapt the genetic counseling protocol in order to meet the needs of these individuals. Questions relating to the future, significant others and the need to know should become part of genetic counseling protocols. Guimarães, Sequeiros, Skirton, and Paneque (2013) reported that subjects at-risk who underwent the PST for LOND's addressed the appropriateness and adaptation of the protocol and highlighted the need for a greater flexibility of genetic counseling protocols according to the counsellee's personal expectations and needs. A personalized adaptation of the PST protocol

can lead the subjects at-risk to redefine the underlying motivations for its completion.

#### STUDY LIMITATIONS

The limitations of the present study are mainly related to the small number of subjects at-risk for MJD. However, there is another important limitation that has to do with the fact that the subjects at-risk were questioned on their motivations in a single moment, before the PST, and not during or after the PST.

#### COMPLIANCE WITH ETHICAL STANDARDS, HUMAN STUDIES AND INFORMED CONSENT

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

TABLE 1  
CHARACTERIZATION OF THE STUDY PARTICIPANTS

Variables	At-risk group for FAP, HD or MJD (n = 213)	At-risk group for HH (n = 31)
<i>Gender</i>		
Female		7 (22.6%)
Male		24 (77.4%)
<i>Age</i>		
Minimum	17	18
Maximum	79	68
<i>M</i>	29.1	42.7
<i>Place of birth</i>		
Portuguese	199 (93.4%)	31 (100%)
Foreign	14 (6.6%)	0 (0%)
<i>Education</i>		
Illiterate	2 (.9%)	0 (0%)
Basic	88 (41.3%)	16 (51.6%)
9th grade	5 (23.9%)	5 (16.1%)
12th grade	52 (24.4%)	3 (9.7%)
University	20 (9.4%)	7 (22.6%)
Post-university	0 (0%)	0 (0%)
<i>Disease</i>		
FAP	174 (81.7%)	
HD	34 (16.0%)	
MJD	5 (2.3%)	
HH		31(100%)

N = 244

TABLE 2  
CATEGORIES RESULTING FROM INTERVIEWS

"Which were the reasons that led you to perform the predictive test?"	FAP		HD		MJD		HH	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
1.- The future	116	64.8	20	58.8	4	80	6	19.4
2.- Others	107	61.5	14	41.2	1	20	22	71.0
3.- Curiosity and the need to know	57	31.8	14	41.2	4	80	5	16.1
4.- The characteristics of the disease	5	2.9	1	2.9	0	0	20	64.5
5.- Metaphors	2	1.1	2	5.9	0	0	0	0.0
6.- Other diseases	0	0.0	2	5.9	0	0	2	6.5
7.- Other reasons	14	8.0	8	23.5	0	0	1	3.2
Total	179	100	34	100	5	100	30	100

TABLE 3  
SUMMARY OF THE SUBCATEGORIES UNDER THE 2<sup>ND</sup> CATEGORY (REASONS RELATED TO OTHERS)

Category	Subcategories	<i>n</i>
Reasons related to others (144)	(1) Because of someone else	43
	(2) Instigated by others	49
	(3) Because someone has the disease	40
	(4) Because someone died with the disease	12

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