

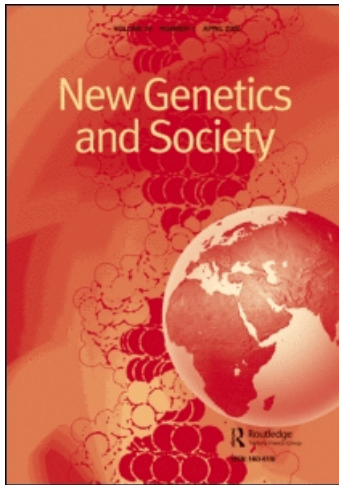
This article was downloaded by: [CDL Journals Account]

On: 25 February 2009

Access details: Access Details: [subscription number 785022369]

Publisher Routledge

Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



New Genetics and Society

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title-content=t713439262>

Diagnostic genetic testing for a fatal illness: the experience of patients with movement disorders

Pascale G. Hess ^a; H. Mabel Preloran ^a; C. H. Browner ^a

^a Center for Culture and Health, Semel Institute for Neuroscience and Human Behavior, University of California at Los Angeles, USA

Online Publication Date: 01 March 2009

To cite this Article Hess, Pascale G., Preloran, H. Mabel and Browner, C. H.(2009)'Diagnostic genetic testing for a fatal illness: the experience of patients with movement disorders',*New Genetics and Society*,28:1,3 — 18

To link to this Article: DOI: 10.1080/14636770802670225

URL: <http://dx.doi.org/10.1080/14636770802670225>

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: <http://www.informaworld.com/terms-and-conditions-of-access.pdf>

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

Diagnostic genetic testing for a fatal illness: the experience of patients with movement disorders

Pascale G. Hess*, H. Mabel Preloran and C.H. Browner

Center for Culture and Health, Semel Institute for Neuroscience and Human Behavior, University of California at Los Angeles, USA

While neurologists encountered the social and ethical concerns associated with diagnosing incurable genetic diseases long before direct DNA testing became available, the increased availability of these tests has magnified these concerns. Most research has focused on the implications of testing asymptomatic individuals; research on the experience of patients with symptoms of heritable conditions is lacking, leaving an ambiguity about their needs with regard to genetic counseling, whether it involves professional counselors or physicians. Here, we investigate the meaning that patients with chorea and ataxia symptoms ascribe to potential or actual DNA testing and explore how patients diagnosed with Huntington's disease or genetic ataxia experience the social, economic and familial implications of a genetic diagnosis. Data come from 27 neurology consultations and 27 in-depth interviews with patients. We found that most view an actual or potential genetic diagnosis as providing relief from uncertainty about their health status. While for some a genetic test can be very similar to other types of procedures aimed at confirming or ruling out a diagnosis, for others (e.g. early symptomatic patients), the implications of diagnostic genetic testing are similar and sometimes amplified when compared with those of predictive testing. Through a case study approach, we identify several expectations and adverse reactions. These include unrealistic hopes that a test will yield a diagnosis leading to treatment, uncertainty about the meaning and reliability of a positive test, and distress upon learning that one has a lethal genetic condition that has already progressed. Even if molecular genetic testing is similar in many respects to prior diagnostic procedures, the many ethical and social issues that have been identified in the context of predictive testing also apply to diagnostic testing. At the same time, concerns specific to symptomatic patients should be considered.

Keywords: diagnostic genetic testing; movement disorders; biomedical ethics

Introduction

The development of molecular genetics has made possible the use of DNA tests to detect gene mutations responsible for a number of late-onset neurodegenerative

*Corresponding author. Email: phess@ucla.edu

conditions. These tests can be used to predict the future health status of individuals at risk before they develop a condition (predictive or presymptomatic testing). Identical genetic tests are also used to identify a condition in patients showing signs of the disease (diagnostic testing).

Numerous studies conducted in Europe, North America and Australia have addressed the social, economic and psychological impacts of testing asymptomatic individuals for severe late-onset genetic conditions – in particular familial cancers and HD (see Meiser and Dunn 2001, Taylor 2004 for reviews). International protocols have been designed by health professionals and support groups to establish counseling standards. For example, the reference guideline for the molecular genetic predictive test in Huntington's disease (IHA and WFN 1994) serves as a model for other dominantly inherited diseases (Paulson 2002). This guideline outlines the potential harms associated with presymptomatic testing such as coercion by family members and discrimination by insurers and employers. It recommends truly informed consent, pre- and post-test genetic education as well as psychosocial support. Consequently, presymptomatic testing is usually carried out in specialized medical centers where teams of geneticists, genetic counselors and psychologists collaborate.

In contrast, diagnostic DNA testing is typically offered by non-geneticist clinicians in traditional healthcare settings. Authors have stressed the need to provide symptomatic patients with genetic counseling (Tan and Ashizawa 2001, Gasser *et al.* 2002, Paulson 2002, Nance *et al.* 2003). Yet there is no research on physicians' counseling strategies and practices for referring patients with HD or inherited ataxia to genetic counselors or geneticists. Further, there is a lack of systematic qualitative research on the experience of clinically affected individuals undergoing testing for lethal neurogenetic disorders, and no consensual protocol exists to respond to their specific needs.

The contrast between the defined status of asymptomatic individuals regarding genetic counseling and the undetermined one of symptomatic patients may be explained in part by several contextual clinical factors. First, traditional means of clinical assessment, such as physical examinations or brain scans, were used to diagnose Mendelian neurological disorders long before DNA testing became available. In contrast, predicting with certainty the appearance of a disease decades before its onset introduced an unprecedented approach that was made possible by the recent development of molecular genetics (Bird and Bennet 1995). Hence, protocols and careful assessments of the implications were needed to define when and how presymptomatic testing should be implemented. Second, symptomatic persons may not have a known family history of the illness or may have affected but undiagnosed relatives. DNA testing may help identify a disease in such individuals (Bird 1999, Paulson 2002) while a negative test encourages further evaluation for other causes of the syndrome (Bird 1998). Therefore, diagnostic testing may be clinically useful even if the conditions are not curable. In contrast, a person who chooses to undergo predictive testing does so because she

knows she is at risk of carrying a mutation for a disease already identified in the family. If the disease is non-preventable and incurable, presymptomatic testing does not bring any clinical benefit and for that reason raises specific ethical dilemmas when compared to diagnostic testing.

The information resulting from a DNA test for such devastating disorders as HD or genetic ataxias, however, is equally sensitive, whether the test is used to predict or to diagnose the conditions. In particular, its familial ramifications are the same. The predictive aspect of the information yielded by a positive test characterizes both situations since, in most cases, it means that premature death is inevitable. Further, many of the concerns associated with predictive testing, such as confidentiality, privacy and potential discrimination are likely to hold true with diagnostic testing. To our knowledge, no published studies have evaluated the extent to which these concerns may be affected by the symptomatic status of the person being tested.

Few studies have addressed the attitudes of adult neurogenetic patients towards diagnostic genetic testing for lethal neurogenetic conditions. Through a case study approach, Paulson and Prior (1997) identified contrasting responses to a positive test for HD in American patients; some expressed relief from uncertainty while others denied the diagnosis. Jankovic (1995) reports that, although a few patients among 35 participants expressed some distress after a positive test for HD, coping strategies and depression levels appeared to be unaffected by DNA confirmation of the diagnosis. Finally, an exploration of ethical dilemmas associated with diagnostic genetic testing for several variously severe neurogenetic conditions found that adult Finn patients had generally fewer ethical concerns than did clinicians (Nyrhinen *et al.* 2004).

While few published studies are concerned with neurogenetic patients, a growing body of studies conducted in Europe, North America and Australia addresses affected patients' views on and responses to genetic testing for other life-threatening conditions, mostly familial cancers (see e.g. Kinney *et al.* 2000, Hallowell 2004, Schlich-Bakker *et al.* 2006). Unlike HD and genetic ataxias, familial cancers can in principle respond to treatment or be prevented. Further, the purpose of the DNA test is to identify causative factors and estimate the risk of future recurrences rather than to diagnose or confirm the conditions. These fundamental differences lead to very different levels of ethical implications (Burke *et al.* 2001). Undoubtedly, they also shape prevailing attitudes towards genetic testing. For example, the gap between the power of genetic tests as diagnostic tools and the absence of effective therapeutic options likely generates more implications for HD and ataxia patients. For that reason, it is critical to redress the paucity of research involving patients with untreatable disorders, in particular neurogenetic patients.

To help close this gap, this paper explores the expectations, experience, and responses of symptomatic adults recently diagnosed with or undergoing DNA testing for HD and genetic ataxia. Our goal as social scientists is not to formulate specific recommendations, but to identify concerns, expectations and needs to

better define the ethical features of diagnostic testing. Our findings, however, might help clinicians, researchers and support groups in their efforts to clarify the status of such patients with respect to genetic counseling.

Background

HD and inherited spinocerebellar ataxia

Chorea (non-rhythmic involuntary movements) and ataxia (lack of coordination and disturbed gait) can lead to the respective diagnoses of HD and genetic ataxia. HD is a single disease whereas genetic ataxias represent a class of similar conditions. Both disorders are progressive and usually lethal. Rate of progression and life expectancy vary with each ataxia subtype. In patients with HD, death typically occurs 15–20 years after the appearance of motor symptoms. Speech problems and cognitive and/or psychiatric disorders are common in both conditions. Mental disturbances associated with HD, however, are more severe than with hereditary ataxias (Leroi *et al.* 2002) leading to differences in their respective needs for psychological and social support (Tan and Ashizawa 2001). To date, no therapy can prevent or slow the progression of HD and most genetic ataxias. Palliative treatment, however, can alleviate some symptoms.

Inheritance patterns and clinical use of DNA tests

HD and many genetic ataxias are caused by a defect referred to as “repeat expansion” on a single gene. This means that the gene contains too many copies of one of its sequence of nucleotides. HD and the majority of genetic ataxias are autosomal dominant, which signifies that one copy of the dysfunctional gene is sufficient to produce symptoms. Offspring have a 50% chance of inheriting the mutation. In HD and many genetic ataxias, penetrance is usually high, meaning that almost everyone with the repeat expansion will develop the disease at some point in their life. The disorders can sometimes become more severe and have an earlier onset with each generation – a phenomenon called anticipation. Because of anticipation, the early death of a parent, false paternity or new mutations, the absence of a family history of the conditions is not uncommon (Bird 1999, Tan and Ashizawa 2001).

Testing for HD and ataxia can improve the diagnosis process. A positive test establishes an exact diagnosis while a negative one may lead the physician to consider possible non-genetic causes of the clinical syndromes, such as other treatable diseases (e.g. metabolic disorders) or environmental factors (e.g. neurotoxins) (Bird 1998). To date there are dozens of identified ataxias resulting from distinct mutations (Paulson 2002, Bird 2007). As there is a great amount of symptom overlap between them, direct DNA testing can be the only way to determine which one a patient suffers from. However, since DNA testing is available only for a fraction of all ataxia subtypes, a negative result does not necessarily exclude a genetic origin (Tan and Ashizawa 2001, Paulson 2002).

Data collection and study participants

The present paper is based on 27 interviews with patients. Preliminary observations of the clinical encounters between the patients and a neurologist provided background information on the diagnosis process.

This study is part of a wider research project on the use of genetics in neurologists' clinical practice, which includes participants not only with chorea and ataxia, but also with various other movement disorders. For the present analysis, we chose to focus specifically on the perspectives of patients with chorea and ataxia because genetic information and DNA testing were more often associated with these conditions than with any others in the larger sample.

Participants were recruited in neurology clinics located in Southern California. The sample consisted of 27 patients (14 females and 13 males). Fourteen patients had symptoms suggestive of HD, and 13 had signs of ataxia. Twenty patients had children. Because the symptoms are late-onset, the vast majority of patients had passed the age of reproduction (age range from 37 to 86, 57 mean age). Nine were still working, five were retired, 11 had to quit their job because of their conditions, and two were homemakers. A DNA test was ordered following the consultation in 16 cases, while 10 participants had previously received a test result (ordered by a primary care physician or another neurologist) and sought the consultation to inquire about possible treatments. One participant was diagnosed following a neurological examination and a brain scan.

The study was approved by the relevant IRB committees. Written informed consent was obtained from each patient. Strict confidentiality was maintained through pseudonyms and identification numbers. Participants were told they were free to withdraw at any time and to decline to respond to any question. Interviews were conducted no later than 15 days after the initial clinical evaluation. Since the issue has previously received little attention, an exploratory qualitative method was found to be the most appropriate. The semi-structured interview guides were designed to allow participants to express themselves in their own terms on a wide range of issues, such as their functional impairments, their understanding of the DNA test, and what they perceived to be the familial and economic implications of their diagnosis. The transcribed interviews and observational data were subjected to content analyses in order to identify patterns and key topics constant across sub-groups of respondents. Conjointly, we used a case study approach to discern the way genetic information was appraised in relation to particular medical and life circumstances, such as a participant's work status and stage of the disease.

Limitations

Because of its small size, our sample probably reflects only partially the range of perspectives on a potential or actual neurogenetic diagnosis; in particular we could not assess the impact of cultural variations. For the same reason, we may have overemphasized some concerns at the expense of others. For example, we

did not encounter any patients who refused or did not want to be informed of a diagnosis, responses that have been reported elsewhere (Bloch *et al.* 1993, Paulson and Prior 1997). Further, the proportion of HD patients with no known affected relatives commonly reported in the medical literature (see e.g. Creighton *et al.* 2003) suggests that these patients are over-represented in our sample. This may be because most participants were recruited in neurogenetic clinics to which patients for whom the diagnosis is the most problematic are typically referred. For the same reason, it is possible that patients who have been undiagnosed for years might also be over-represented in our sample. In addition, our cross-sectional perspective did not allow capture of possible evolutions of views and attitudes through time, and owing to differences between countries, we cannot generalize our findings to all patients undergoing genetic testing for HD and ataxia.

Findings

Before signing the informed consent form, five patients in our sample did not distinguish a DNA test from other types of clinical assessment, or a genetic diagnosis from some other outcome. Those who had already been tested were unaware that they had undergone genetic testing. While other patients were often self-referred, all these participants came to the consultation following a referral by a prior physician. For patients who knew what a genetic test is, having or not a diagnosed relative appeared to determine for a large part the nature of their motivations towards testing. Fourteen patients were unaware of the existence of the disease in their family or had affected but undiagnosed relatives. For most of them, the decision to undergo testing was primarily a medical one driven by the need to find a diagnosis and a treatment. In contrast, for patients who were aware of the disease in their family ($N = 8$), the decision to undergo testing was similar to that of asymptomatic persons (Burke *et al.* 2001, Taylor 2004) as it related more to familial and personal issues, such as life-planning and concerns about their children's genetic risk, rather than medical ones.

Overall, participants' comments suggested that their responses to a positive test were influenced by personal and medical factors, such as their work status, their level of family support and personal preparation before taking the test, the stage of the disease, and whether they had children.

Looking for a diagnosis

Because of frequent symptom overlaps among various neurodegenerative disorders, diagnostic difficulties are commonly mentioned in the medical literature (see e.g. Bird and Bennett 1995, Bird 1999, Tan and Ashizawa 2001). The average length of time patients said they had been symptomatic was four years for those who had relatives that had been previously diagnosed and 12 years for participants who did not have any diagnosed relatives. Among the latter group,

most had had their symptoms previously attributed to other neurological conditions (e.g. multiple sclerosis, Parkinson's disease). Such patients typically welcomed a DNA test and said that they would prefer a genetic diagnosis to none at all.

As noted above, no therapy can prevent or slow the progression of HD and most genetic ataxias. Although the majority of undiagnosed participants said they believed neurogenetic diseases are incurable, many assumed that a treatment could slow or even stop the degenerative process. In addition to the prospect of treatments specifically tailored to their illness, many referred to the burden of suffering from a degenerative condition with no medical identity.

Margaret's account is typical of the wearisome medical itineraries and persistent uncertainty described by patients. Margaret is a 65-year-old retired accountant who does not have children. Margaret reported that her symptoms – vertigo, walking and speech difficulties – started three years before we met her and their progression is accelerating. She reflects on her past medical experiences:

When I began to have these symptoms, I started to go from one doctor to the other looking for an answer. I think I saw six, eight doctors . . . I lost track. You go from one place to the next and it seems that you're always in the same place. Dr X said it could be hereditary ataxia . . . cerebellum . . . or something like that. I said, "fine at least it has a name". But doctor Y wasn't sure. I am tired of hearing "it is possible," "we have to see". I would like to hear something more real.

Self-referred, Margaret found the name of her latest neurologist on the Internet. Disappointed that a genetic test was not ordered by a prior physician, she came to the consultation hoping that this time it would be offered to her. When the neurologist mentioned a test for ataxia and the need for written consent, Margaret said she wanted to take the test right away and declared enthusiastically: "I would like so much to know for sure what is going on with me that I will sign anything."

While others have found that a genetic disease is perceived as uncontrollable and that a positive DNA test may result in resignation (see e.g. Senior *et al.* 1999), for most undiagnosed participants, identifying the condition, even if genetic, represented the first step towards gaining some control over their illness. None received precise information on the disease for which they were about to be tested which prevented them from assimilating the full implications of a positive DNA test.

Some participants appeared to favor a genetic etiology over a non-genetic one because they perceived the former as more definitive. Thomas, a 58-year-old engineer, exemplifies the dynamic of such expectations. Thomas, who had been experiencing speech, gait and walking problems for 10 years, had several children and grandchildren, and no affected relatives. In addition to a genetic mutation, the physician mentioned several possible non-genetic causes for his symptoms. Thomas said he favored a genetic test over other types of clinical assessment offered by the neurologist because he perceived the former as more accurate. As he said, "a genetic test tests for A and it's A". There is an apparent paradox in

this patient's expectation, knowing that a non-genetic diagnosis would likely lead to a cure and would not have any familial implications. This paradox disappears when we see that it is not because of its genetic nature that these persons looked forward to a genetic diagnosis. Rather, the length of time they had been ill generated strong desires for an accurate and definitive diagnosis, and the information yielded by a genetic test was perceived to fulfill such expectations better than other types of diagnostic procedures. We need to stress, however, that a minority of participants who had been searching for a diagnosis for a long time indeed feared a positive genetic test. For one, the test result was particularly poignant: he was relieved to have tested negative for HD but later found he probably had another fatal neurogenetic disorder. This patient, as well as others with ataxia symptoms, did not seem to be aware that ruling out one inherited condition did not necessarily mean that their illness was not caused by a mutation. As Thomas' comments suggest, for some patients the aura of the "new" genetics may mask the limits of its clinical implications.

Facing an unexpected incurable illness

We observed a discrepancy between the hopefulness of patients not yet diagnosed and the discouragement of those whose disease was already identified because the diagnosis came with the information that the condition is incurable.

As noted above, symptomatic patients with genetic diseases do not always have a family history. Hence, a specific consequence of diagnostic testing compared with predictive testing is that it can lead patients to be suddenly confronted with an unexpected familial disease.

Susan is a 49-year-old office worker, with two adult children and two grandchildren. Her father died at age 70 after being diagnosed with Parkinson's disease. She said she had been experiencing worsening balance problems, tremors and memory impairment for 15 years. She received a positive test for HD a few months before we met her.

When the physicians offered the test, I was so anxious to find out what was wrong with me I didn't care what the answer was. I wanted to know I wasn't crazy. So, I was happy to find out that it was because I was sick. At first, I wanted my children tested, but when my son thought about getting it done, I panicked and realized I didn't want to know if my children have it, but I feel I gave it to them . . . Now, I need to plan. I need to move because I can't afford to stay where I am and I wonder if I will be able to be in a house alone and take care of myself.

The test result represented for Susan a sudden transition from years of uncertainties about the cause of her illness to a state of certitude in a predetermined future. From a clinical perspective, however, many questions remain: Have Susan's children inherited the mutation? How will the symptoms progress? How long before they become seriously disabling? Susan anticipates the worst out of a range of possible outcomes: "I feel I gave the disease to [my children] . . . Neurologists

just do not want to bombard me with the reality". Probably, Susan's apprehension that the worst will happen is mediated not only by a lack of information, but also by the heavy burden of having to cope at once with the unforeseen diagnosis, its familial implications, and her worsening symptoms.

For our sample participants, receiving an unforeseen genetic diagnosis and being informed that no efficient treatment exists pressed them to face at once a myriad of issues for which they were not prepared: guilt and worries about their children's genetic status, uncertainty about the prognosis, a pressing need to plan for the future as the disease had already progressed, and questions about the exact meaning of the test. Some of these concerns are also encountered in the narratives of presymptomatic individuals whose genetic status was confirmed (see e.g. Sobel and Brookes 2003). Without minimizing the hardship of asymptomatic individuals who undergo genetic testing, we emphasize that being symptomatic already and totally unprepared for such a diagnosis may induce additional stresses, as Susan's account of her experience suggests.

A DNA test for HD or genetic ataxia does not simply provide a yes/no answer, but also indicates the number of repeats. As Susan is pressured to plan her future, like other participants, she wondered about the relation between this number and her prognosis. Her quest led to more uncertainties:

Dr X and Y said since my number was low, it means my case is mild, and somebody else said that doesn't matter, the number means absolutely nothing. I've had everybody in the world give me a different answer to that question. I called the lab that did the testing to find out if that number meant anything and they said no, and I think they know better than the doctors. I think the neurologists just do not want to bombard me with the reality.

When repeats are in the lower range, their number may suggest but cannot predict how symptoms will progress in a given individual. The apparently contradictory information given to Susan reinforces her fears for the worst. Like the majority of participants, Susan was not referred to a genetic counselor. Even if miscommunication in genetic counseling sessions frequently occurs (see e.g. Browner *et al.* 2003), genetic counselors are the best trained to explain complex genetic concepts in language understandable to those being counseled. By clarifying the opaque relationship between repeats and prognosis, a genetic counseling session could have alleviated Susan's apprehension.

Inheriting the familial disease (confirmatory genetic testing)

Among the eight participants who said they had family members diagnosed with HD or genetic ataxia, seven were aware that the condition was incurable. Although all eight patients had witnessed the devastation of the illness in their relatives, four appeared relatively accepting of their actual or anticipated diagnosis whereas four were extremely distressed. Both groups had common characteristics: participants showing a relative serenity had all been symptomatic for more than five years,

had no children or had lost contact with them, and were retired or searching for disability benefits. Among participants expressing marked distress, one had suggestive but unconfirmed symptoms and three said they had been symptomatic for less than two years. All were still working, and all except one had children. The two examples below illustrate how these personal circumstances may impact on responses to a positive test.

“The right time”

Dennis is a mechanical manager who tested positive for HD a few weeks before we met him. He had lost contact with his only child who lives with his ex-wife in another state. Dennis’ brother had been diagnosed with HD and his mother had died of the condition. Dennis had experienced tremors and lack of balance for about 10 years. With his current wife, Patricia, he sought the consultation to inquire about treatment options, the possibility of participating in a clinical trial, and to document an application for disability benefits. Because his symptoms had worsened, Dennis was laid off from his job and quit driving about a year before taking the test. The couple had not attended any genetic counseling sessions but had discussed the pros and cons of genetic testing with members of a HD support group that they had joined many years ago. Patricia appeared to be very educated about HD and lent strong support to her husband. Dennis’ choice to undergo genetic testing resulted from a mature decision and he seemed relatively untroubled by the result:

It was just the time in my life that I needed the answer. One year earlier, I was afraid of losing my job if they found out I had the illness; now I don’t have a job to lose. I didn’t want to do anything until I couldn’t handle the illness. Then, I wanted to know for sure and I didn’t get depressed when getting the result.

When it is too early

Unlike Dennis, Ana appeared devastated after she learned that she carried the HD gene. Ana, whose father died of HD when she was a child, was a 37-year-old mother of two young children. She tested positive for the disease shortly before we met her. Recently divorced, she worked as an office assistant in a large company. She said that her decision to get tested was prompted by a television show where “somebody with Huntington’s disease became mad, and killed the whole family”. Fearing that the same might happen to her, she suddenly decided to ask her primary care physician to order the test. As with most participants previously tested, Ana had not been referred to a genetic counselor or received any professional psychological support before taking the test. She sought the neurology consultation to inquire about the exact meaning of the test result as she had a slight hope that one negative and one positive gene may mean that she was not a carrier.

Ana said that she experienced memory and concentration difficulties. She insisted the test result meant that these problems were symptoms of the disease although the neurologist could not establish a definitive link. She also mentioned that the diagnosis brought her some relief as she said it alleviated her feeling of uncertainty and proved to others that her cognitive problems were signs of the illness and not the result of a supposed weakness of her character. As she perceived herself as already symptomatic, the positive DNA test had for her two other powerful meanings: first, what she had feared for years was indeed the case, she was a carrier for the mutation; second, the symptoms she was experiencing were those of HD and therefore the illness had already started its irreversible progression. She said she regretted having taken the test without prior insurance planning and feared that her children might carry the mutation. She also anticipated losses in her near future: not being able to sustain a parental role and losing her job as a result of her declining memory and concentration.

As noted above, for participants who had relatives already diagnosed, the decision to undergo testing was essentially personal rather than medical. Ana's and Dennis' different itineraries and divergent reactions suggest that the decision-making process may have an important impact on patients' responses to a positive test. As his symptoms progressively worsened, Dennis came to recognize that he had HD before taking the test. More than an answer about whether he had the illness, the test was for him the concluding step of a progressive process of acceptance. In contrast, Ana made the decision to take the test abruptly, without any prior emotional and financial preparation and, since she had been symptomatic – or perceived so – only for a short period of time, she did not have the opportunity to adjust gradually to the possibility of the diagnosis. These observations agree with the conclusions of previous studies involving HD patients: depression levels appear to be unaffected by DNA confirmation of an established diagnosis (Jankovic 1995). In persons diagnosed following a neurological examination, vulnerability is especially high in those presenting early signs of the disease (Lam *et al.* 1988, Paulsen *et al.* 2005), while individuals with more pronounced symptoms are more likely to have made adjustments to the disease and therefore are better equipped to cope with a definitive diagnosis (Bloch *et al.* 1993).

Ana's account also illustrates that a positive genetic test can validate people's belief that they are already ill even if clinicians cannot confirm that the symptoms they are experiencing are an expression of the disease. One specific implication of DNA testing compared to other diagnostic procedures is that it enables clinicians to make a diagnosis at a much earlier stage in the illness (Appollonio *et al.* 1997). At the same time, there is a gray area in which the distinction between a non-symptomatic carrier and a symptomatic patient can be called into question. In the case of HD, psychiatric and cognitive disturbances can be the first signs of the condition but, as in the case of Ana, are not specific enough to determine whether an individual is already sick (Squitieri *et al.* 2001). Such disturbances could result as well from being at risk and from the adverse effects that social

and psychological hardships associated with a family history of HD may have on mental health (Decruyenaere *et al.* 1999). It has been noted that individuals who seek predictive testing while not recognizing that they are already showing signs of the disease should receive special attention (IHA and WFN 1994, Nance and Ludowese 1994). This could be equally crucial for individuals who perceive that the illness has already started its progression, whether or not the clinicians believe that is the case. For them also, the information yielded by a positive test concerns their current situation rather than an undetermined future.

A genetic test? What is it?

Among the five patients who did not distinguish between a genetic test and other types of blood analyses, four appeared to be extremely disadvantaged economically, had little or no familial support, and said they had been raised in chaotic families. The psychopathologies associated with HD and genetic ataxia can sometimes result in significant impairment in social and occupational functioning, especially in the case of HD (Leroi *et al.* 2002). Having witnessed the disease in a relative, the premature loss of a parent because of the illness, or stigmatization undoubtedly heightens psychological disturbances. The disease becomes the starting point of an intergenerational spiral of misfortune that can result in extreme social and economic hardship. The need to provide social support may prevail over the need to inform these patients about genetics. However, the fact that some participants in our study did not have any knowledge of the nature of genetic testing raises concerns about the informed consent process. Further, providing information on the genetic aspect of their illness might help these persons understand the root of their and their relatives' chaotic life history, which could perhaps lessen feelings of guilt and shame.

Discussion and conclusion

The ethical, legal and social implications of presymptomatic testing can be broadly categorized according to the accuracy with which a test predicts a particular clinical outcome and the availability of effective treatment. Tests with high clinical validity for incurable conditions, such as HD and ataxia, raise major ethical dilemmas and require adequate counseling to ensure autonomous decisions (Burke *et al.* 2001). In addition to the test's clinical validity and the disease's potential for treatment, our findings suggest that two additional factors need to be considered in the context of testing symptomatic persons. These include whether or not a patient is aware of the condition in the family and the stage of the disease.

In the case of individuals with a known family history of an incurable disease, diagnostic testing is similar to presymptomatic testing for the absence of substantial clinical benefits and the centrality of the patients' personal decision. However, in patients with advanced symptoms, the use of DNA tests to confirm a diagnosis

may be less ethically problematic than presymptomatic testing for two reasons. First, these patients may have adjusted to the possibility of their diagnosis. Second, the potential for discrimination entailed by a positive test is likely to be limited for persons with advanced symptoms. Participants who were noticeably disabled did not seem to be concerned about communicating the test result to their medical insurance company or the social security administration. On the contrary, most were looking forward for their information being released so they could be covered for the right treatment (even if only symptomatic), see the right doctor, or be recognized as disabled by social security. As several participants suggested, having a name for one's condition may facilitate medical and disability insurance claims.

In contrast to individuals with advanced symptoms, for early-symptomatic patients aware of the disease in their family, the ethical and social implications of DNA testing appeared to be similar, if not greater, compared to those of predictive testing for three main reasons. First, the boundary between an asymptomatic person and a symptomatic patient is blurred. Second, persons with mild symptoms have to deal at once with the information that they carry the mutation and their emerging illness. Third, in countries without adequate protection against genetic discrimination, the economic ramifications of a positive result are the same for asymptomatic people and for mildly affected patients. As in the case of healthy carriers, privacy is a critical concern for these persons since a positive genetic test may affect their ability to keep a job and to obtain health or life insurance while not yet being eligible for disability benefits.

Our data indicate that patients with no known diagnosed relatives may be more likely to be in a later stage of the disease. When DNA testing is the only means to establish a diagnosis in such patients, it may be less ethically problematic than pre-symptomatic testing; patients' decision processes, without being irrelevant, might not be as central. For participants looking for a diagnosis, the decision to be tested was generally viewed as unproblematic. Those who had already received a result said they did not regret knowing their genetic status, despite their distress about the incurability and gravity of the diseases. On the contrary, a substantial number said they were relieved to have a definitive answer and a name for their progressive symptoms. As noted above, both HD and ataxia have a high potential for stigmatization because of speech and cognitive problems. As observed elsewhere (Meiser *et al.* 2005, Sankar *et al.* 2006), reassuring oneself and asserting to others that symptoms were signs of the disease and not one's fault was a common thread throughout the interviews. Mutation analyses have contributed to the differentiation of a number of neurogenetic diseases (Bird 1999, Gasser *et al.* 2002). Without the possibility of direct genetic tests, some of the participants who were finally diagnosed may have lived years with a stigmatizing disease with no clear clinical identity. Compared to asymptomatic or symptomatic persons with a family history, these patients however are more likely to have unrealistic expectations about treatment outcome and to be unprepared for the diagnosis. For these reasons, they may be especially vulnerable to distress once the diagnosis is established.

Genetic counselors have reported that symptomatic patients tested for ataxia and HD did not receive any genetic information before being tested and lacked knowledge on the genetic aspect of their illness (Ehr 2006). Our observations mirror these findings. Although eight patients were referred to social workers, only one had seen a genetic counselor prior to the consultation and only one was referred to a genetic counseling session following the consultation we observed. Apart from the few patients totally unfamiliar with genetics, several were uncertain about the exact significance of their test result. Variable expressions within a family were also topics of confusion, as exemplified by a patient whose daughter had died of a more rapidly progressing form of ataxia than hers. Patients with no family history wondered why they had or may have a genetic disease and no affected relatives. When applicable, an explanation of genetic concepts relevant to their diagnosis, such as repeat expansion, anticipation, or new mutation, would have greatly helped these patients understand their diseases and their family members' genetic risk.

Like healthy at-risk individuals, we suggest that patients already symptomatic might benefit from psychosocial support and information on genetics before and after the diagnosis is established, especially those whose disability is still mild and those who do not have any previous knowledge of the disease for which they are tested. Further, the genetic tests for HD and ataxia have specific features compared to other diagnostic procedures. They may allow earlier diagnosis and provide a measure of the extent to which the gene has mutated. Our observations suggest that these particularities have specific implications for patients. However, the points of convergence noted earlier between some of our findings and previous studies involving patients diagnosed following a neurological examination indicate that the implications of a genetic diagnosis are not fundamentally different, whether a direct DNA test or other clinical assessments are used. This reminds us that DNA tests should not be regarded as exceptional (Wertz 1992, Green and Botkin 2003), and highlights the need to apply the concerns associated with such tests to all kinds of approaches aimed at identifying or confirming a genetic disease.

Acknowledgements

Research was supported in part by NIH grant 1 RO1 HG003228-01, Carole H. Browner, Principal Investigator and by the UCLA Center for Culture and Health. We would like to thank the physicians who agreed to participate in this study, which would not have been possible without their generous collaboration. We also wish to express special gratitude to the patients and their relatives who took the time to tell us about their difficult experiences. We are grateful to Warren Thomson of the UCLA Center for Culture and Health and to Maria Christina Casado, Jennifer Musto, and Marissa Strickland for their outstanding assistance.

References

- Appollonio, I., *et al.*, 1997. Which diagnostic procedures in the elderly? The case of late-onset Huntington's disease. *Journal of Geriatric Psychiatry and Neurology*, 10 (1), 39–46.
- Bird, T.D., 1998. Genetic testing. *Western Journal of Medicine*, 168 (4), 265.

- Bird, T.D., 1999. Risks and benefits of DNA testing for neurogenetic disorders. *Seminars in Neurology*, 19 (3), 253–259.
- Bird, T.D., 2007. Hereditary ataxia overview [online]. Available from: <http://www.geneclinics.org/profiles/ataxias/details.html> [Accessed 2 July 2007].
- Bird, T.D. and Bennett, R.L., 1995. Why do DNA testing? Practical and ethical implications of new neurogenetic tests. *Annals of Neurology*, 38 (2), 141–146.
- Bloch, M., et al., 1993. Diagnosis of Huntington disease – a model for the stages of psychological response based on experience of a predictive testing program. *American Journal of Medical Genetics*, 47 (3), 368–374.
- Browner, C.H., et al., 2003. Genetic counseling gone awry: miscommunication between prenatal genetic service providers and Mexican-origin clients. *Social Science & Medicine*, 56 (9), 1933–1946.
- Burke, W., Pinsky, L., and Press, A., 2001. Categorizing genetic tests to identify their ethical, legal, and social implications. *American Journal of Medical Genetics*, 106 (3), 233–240.
- Creighton, S., et al., 2003. Predictive, pre-natal and diagnostic genetic testing for Huntington's disease: the experience in Canada from 1987 to 2000. *Clinical Genetics*, 63 (6), 462–475.
- Decruyenaere, M., et al., 1999. Psychological functioning before predictive testing for Huntington's disease: the role of the parental disease, risk perception, and subjective proximity of the disease. *Journal of Medical Genetics*, 36 (12), 897–905.
- Ehr, J., 2006. Effects of presymptomatic genetic testing for adult-onset genetic neurodegenerative conditions without pre-test genetic counseling: a study of genetic counselors' experiences with patients referred after testing and clinical laboratory protocols. Thesis submitted for the degree of Master of Science in Genetic Counseling. University of California Irvine.
- Gasser, T., et al., 2002. Molecular diagnosis of inherited movement disorders. Movement Disorders Society task force on molecular diagnosis. *Movement Disorders*, 18, 4–18.
- Green, M. and Botkin, J., 2003. "Genetic exceptionalism" in medicine: clarifying the differences between genetic and non-genetic tests. *Annals of Internal Medicine*, 138 (7), 571–576.
- Hallowell, N., 2004. Accommodating risk: responses to BRCA1/2 genetic testing of women who have had cancer. *Social Science & Medicine*, 59 (3), 553–565.
- IHA and WFN (International Huntington Association and World Federation of Neurology), 1994. Guidelines for the molecular genetics predictive test in Huntington's disease. *Neurology*, 44, 1533–1536.
- Jankovic, J., 1995. Emotional and functional impact of DNA testing on patients with symptoms of Huntington's disease. *Journal of Medical Genetics*, 32 (7), 516–518.
- Kinney, A.Y., et al., 2000. Attitudes toward genetic testing in patients with colorectal cancer. *Cancer Practice*, 8 (4), 178–186.
- Lam, R.W., et al., 1988. Psychiatry morbidity associated with early clinical diagnosis of Huntington disease in a predictive testing program. *Journal of Clinical Psychiatry*, 49 (11), 444–447.
- Leroi, I., et al., 2002. Psychopathology in patients with degenerative cerebellar diseases: a comparison to Huntington's disease. *American Journal of Psychiatry*, 159 (8), 1306–1314.
- Meiser, B. and Dunn, S., 2001. Psychological effect of genetic testing for Huntington's disease: an update of the literature. *Western Journal of Medicine*, 174 (5), 336–340.
- Meiser, B., et al., 2005. Implications of genetic risk information in families with a high density of bipolar disorder: an exploratory study. *Social Science & Medicine*, 60 (1), 109–118.
- Nance, M. and Ludowese, C., 1994. Diagnosis of Huntington disease: model for a predictive testing program based on understanding the stages of the disease. *American Journal of Medical Genetics*, 52 (1), 118–119.
- Nance, M., Bird, T., and Pulst, S.M., 2003. Ethical issues in genetic testing for movement disorders. In: S.M. Pulst, ed. *Genetics of movement disorders*. San Diego: Academic Press, 541–550.

- Nyrhinen, T., Leino-Kilpi, H., and Hietala, M., 2004. Ethical issues in the diagnostic genetic testing process. *New Genetics and Society*, 23 (1), 73–87.
- Paulsen, J., et al., 2005. Critical periods of suicide risk in Huntington's disease. *American Journal of Psychiatry*, 162 (4), 725–731.
- Paulson, G. and Prior, T., 1997. Issues related to DNA testing for Huntington's disease in symptomatic patients. *Seminars in Neurology*, 17 (3), 235–238.
- Paulson, H.L., 2002. Diagnostic testing in neurogenetics: principles, limitations, and ethical considerations. *Neurologic Clinics*, 20 (3), 627–643.
- Sankar, P., et al., 2006. What is in a cause? Exploring the relationship between genetic cause and felt stigma. *Genetics in Medicine*, 8, 33–42.
- Schlich-Bakker, K.J., ten Kroode, H., and Ausems, M., 2006. A literature review of the psychological impact of genetic testing on breast cancer patients. *Patient Education and Counseling*, 62 (1), 13–20.
- Senior, V., Marteau, T., and Peters, T.J., 1999. Will genetic testing for predisposition for-disease result in fatalism? A qualitative study of parents' responses to neonatal screening for familial hypercholesterolaemia. *Social Science & Medicine*, 48 (12), 1857–1860.
- Sobel, S. and Brookes, C., 2003. Ambiguous loss and disenfranchised grief: the impact of DNA predictive testing on the family as a system. *Family Process*, 42 (1), 47–57.
- Squitieri, F., et al., 2001. Onset and pre-onset studies to define the Huntington's disease natural history. *Brain Research Bulletin*, 56 (3–4), 233–238.
- Tan, E.K. and Ashizawa, T., 2001. Genetic testing in spinocerebellar ataxias: defining a clinical role. *Archives of Neurology*, 58, 191–195.
- Taylor, S.D., 2004. Predictive genetic test decisions for Huntington's disease: context, appraisal, and new moral imperatives. *Social Science & Medicine*, 58 (1), 137–149.
- Wertz, D.C., 1992. Ethical and legal implications of the new genetics: issues for discussion. *Social Science & Medicine*, 35 (4), 495–505.