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Ethical Considerations of Genetic Presymptomatic Testing for Huntington's Disease

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The aim of this literature review was to determine if there is adequate ethical justification for presymptomatic genetic testing on potential Huntington's disease patients. Huntington's disease is a neurological genetic disorder characterized by midlife onset which consists of cognitive, physical, and emotional deterioration. Although genetic testing has traditionally been guided by the principle of autonomy, severe psychological consequences such as depression, anxiety, survival guilt, and suicide have complicated the ethical issue of providing a presymptomatic yet definitive diagnosis for an incurable disease. An analysis of available articles yielded inconclusive findings, namely due to insufficient evidence, self-selection bias of test participants, or lack of a longitudinal design. Additional results indicated psychological distress is not solely associated with test result, but rather with individual characteristics including, but not limited to, psychological history, test motivation, level of preparation, social support, and age. In the interest of upholding the principles of autonomy, beneficence, nonmaleficence, and justice, it is recommended that medical professionals follow strict protocol, provide extensive counseling, and employ vigilance when assessing at-risk individuals for HD presymptomatic test eligibility to ensure psychological well-being.

Huntington's Disease (HD), also called Huntington's chorea, was first documented in 1872 by American physician George Huntington (Skirton, 2005). HD causes deterioration of cognitive, physical, and emotional abilities leading to serious incapacitation and eventual death some 15 to 20 years after the onset of symptoms (Bombard et al., 2007). The cognitive symptoms of HD include difficulties with problem solving and planning, impaired short-term memory, and ultimately dementia; physical symptoms include jerky involuntary movements called chorea, slurred speech, difficulty swallowing, and abnormal walking; and emotional symptoms consist of depression, mood changes, aggression, and impulsiveness (Dawson, Krisitijanson, Toye, & Flett, 2004). The most common age of onset for HD is between 30 and 45 years old, with symptoms usually beginning around 40 years old, yet symptoms can start as early as childhood or as late as the eighth decade of life (Keenan, Miedzybrodzka, Van Teijlingen, Mckee, & Simpson, 2007; Timman, Bonke, Stijjnen, Tibben, & Maat-Kievit, 2008). It is one of the most devastating diseases, not only because of its constant degenerative deterioration, but also because of the emotional and psychological impact it has on individuals and their families (Dawson et al., 2004).

Individuals suffering from HD have a mutant gene IT-15 on the short arm of chromosome four, which codes for the protein huntingtin (Htt) (van Duijn, Kingma, & van der Mast, 2007). Specifically, the affected allele contains repeats of 36 or more of the CAG trinucleotide, whereas unaffected individuals have 35 or less (Walker, 2007). While the exact mechanism of the disease is not fully understood, it has been proposed that the polyglutamine tail caused by the CAG repeats aggregate and impede the function of other proteins, neuronal signaling, and the cells' ability to break down the huntingtin, thereby producing symptoms of the disease (Walker, 2007).

As of 2008, there were an estimated 30,000 cases of HD in the United States, with about 150,000 individuals at risk of inheriting HD from a parent (National Center for Biotechnology Information, 2008). Children who have a parent with HD genetically have a 50% risk of developing the disease (Skirton, 2005). HD is not gender specific, it affects both genders equally, and if a child inherits the huntingtin-mutated gene, he/she will eventually develop the disease (Cox & Mckellin, 1999). Individuals cannot be a carrier without developing the disease and it does not skip generations (Dawson et al., 2004).

Currently, there are no available treatments to reverse or stop the progression of HD, however, presymptomatic genetic testing has been available since 1993 (Pakenham, Goodwin, & Macmillan, 2004). Individuals who are aware of the disease being present in their family may choose to have presymptomatic testing to determine their mutation status before they show

onset of symptoms (Hamilton, Bowers, & Williams, 2005). There are benefits of presymptomatic testing, which include relief of uncertainty, knowing the potential risk for offspring, and ability to plan for the future. There are also psychological risks that can follow presymptomatic testing, including anxiety, depression, stress, guilt, and thoughts of suicide (Soldan, Street, Gray, Binedell, & Harper, 2000). HD falls into a category that has a highly valid genetic test but no effective treatment, producing concerns related to potential discrimination and psychological distress (Burke, Pinsky, & Press, 2001). This implies an ethical dilemma in balancing the risks of testing as contrasted with potential benefits.

Whether analyzing HD or any other illness, treatment alternatives always involve ethical principles commonly identified by various health care ethics experts (Beauchamp & Childress, 2001). Normally four ethical principles are used as moral measures: autonomy, beneficence, nonmaleficence, and justice (Hursthouse, 2003).

- Autonomy

The word *autonomy* refers to the ability to decide for one's self. Autonomy as a concept means that the person is self-ruling, free to make his or her own decisions. In a health care setting, it is often unclear whether the patient possesses the conditions for autonomy or not. Two important conditions must be met for autonomy: competence and noncoercion (American Medical Association, 2001).

- Beneficence

Beneficence means to do well and to provide a benefit. It is the practice of doing a kindness or good thing and implies more than just avoiding doing harm. This ethical principle of having to engage in altruistic or beneficent acts means that one is obligated to take proactive and direct steps to help others (Morrison, 2006).

- Nonmaleficence

Nonmaleficence means to not do wrong toward another. Medical ethicists and physician educators have long established the dictum of, first, do no harm. This is not an easy rule to follow due to the debate concerning the meaning of the word *harm*. It is no simple matter because much of health care involves pain, discomfort, inconvenience, expense, and perhaps even disfigurement and disability (Summers, 1989). Harm could mean physical failure, emotional distress, and/or financial loss. Furthermore, harm might

also be negligence, lack of due diligence, or violations of patient autonomy (Betancourt, Green, & Carillo, 2002).

- Justice

Justice is more than just fairness. It also includes elements of righteousness, equity, and lawfulness. A just person is fair, lawful, reasonable, correct, and honest. In general, to know something is just is to have a good reason to think that it is morally correct and proper. The term is often used to mean fairness in treatment; it is both procedural and distributive. Procedural justice is defined as due process and being equal under the law. Distributive justice involves determining how to divide up burdens and benefits (Arthur & Shaw, 1979).

The purpose of the following research study was to ascertain if there is clinical support for presymptomatic genetic testing on potential Huntington's disease patients in light of ethical considerations.

METHODS

The research was conducted to complete a comprehensive literature review on the psychological and ethical implications of genetic testing for HD. The research strategy was limited to selecting articles from reputable journals in which online access was available from electronic databases. All researched topics were related to psychological and ethical implications of presymptomatic genetic testing of HD in the potentially affected populations. The research strategy yielded journal articles of high impact and an analysis of findings from the literature was performed. The studies were investigated to determine their pertinent findings and ethical conclusion, whether stated or implied by the article's general perspective.

Search Strategy

When completing the online research, the following terms were combined using the Boolean "OR": *Huntington's disease, Huntington's chorea, presymptomatic testing,* and *ethics*. All pertinent articles came from four electronic databases: EbscoHost, Psyc-Info, Springer, and PubMed. Reference lists from retrieved articles were utilized to identify other relevant research articles.

Inclusion, Exclusion, and Assessment

There was abundant information available regarding the disease; however, the review was restricted to literature including information about the psychological and ethical effects of presymptomatic genetic testing in HD. Reviews and primary research articles were included in this study. All selected articles were in English. No articles were excluded due to the age of the article, but unpublished works were excluded from this study.

RESULTS

After reviewing research information available from the electronic databases, 20 specific articles were selected for an analysis in this study. Numerous articles covering topics in HD such as biological genetic research, genealogy of the disease, medical and nursing care, and palliative treatment did not address the research criteria and were excluded from this review. The 20 selected studies included an array of relevant national and international research. Table 1 illustrates the key issues, findings, and viewpoints related to the psychological and ethical implications of HD testing.

DISCUSSION

In general, earlier published articles speculated on the ethical principles of HD testing, yet more recent articles were found to examine the psychological effects associated with testing. The passage of time has allowed more researchers to shift their focus from a hypothetical ethical issue to one based on clinical evidence and long-term analysis. This shift of focus highlights the medical community's desire to describe the fundamental principles of medical ethics as they realistically apply to HD testing.

Overall, five studies indicated HD testing was ethical and advantageous to at-risk individuals. However, the validity of these findings could be questioned due to the impact of inherent biases related to self-selection and participants' state of denial (Meiser & Dunn, 2000; Robins Wahlin, 2007). Furthermore, many of the 20 researchers could not indicate the long-term effects of their findings due to the lack of a longitudinal design. Longitudinal studies were completed by Tibben, Duivenvoorden, Niermeijer, Van Der Vlis, Roos, and Verghage (1994), Williams, Schutte, Evers, and Holkup (2000), Almqvist, Brinkman, Hayden, Wiggins, and the Canadian Collaborative Study of Predictive Testing (2003), and Decruyenaere, Evers-Kiebooms, Cloostermans, et al. (2003). These studies did show a unique progression of psychological effects over a period of several years, with most negative effects decreasing in the long term. However, individual characteristics such

TABLE 1 Results of Studies Related to HD Testing, Psychological Health, and Ethical Issues

Author(s)	Year	Type of Study	Psychological/Ethical Keywords	Key Findings	Ethical Viewpoint/Conclusion
Craufurd & Harris	1986	Qualitative	• Burden of knowledge • Misuse of information	Testing for Huntington's disease is unique due to poor prognosis and lack of treatment; conflict of interest related to other family members and outside entities	Inconclusive: controlled clinical trials are needed
Huggins et al.	1990	Qualitative: Case studies	• Autonomy • Beneficence • Nonmaleficence • Confidentiality • Justice	In general, autonomy takes precedence; exceptions: confidentiality and beneficence may supersede autonomy in some cases	Inconclusive: dependent on pre-test assessment and other ethical and legal principles
Terrenoire	1992	Qualitative: Literature review	• Social ethics • Autonomy	Both personal and community interests need to be considered; no consensus among medical community	Inconclusive: long-term analysis needed
Wexler	1992	Qualitative	• Denial • Survival guilty • Depression • Anxiety	Specific testing protocols need to be enforced; intensive counseling may be better alternative to testing in certain cases	Inconclusive: special training, screening, and precautions are needed
European Community Huntington's Disease Collaborative Study Group	1993	Qualitative	• Autonomy • Confidentiality	Identified potential testing problems relating to referrals, family members, and result disclosure	Ethical: when protocol is established and followed
Tibben et al.	1994	Qualitative: Longitudinal	• Stress • Survival guilt	Initial post-test emotions were negative but returned to baseline, pretest levels six months after diagnosis	Ethical: no major long-term negative effects
Binedell & Soldan	1997	Qualitative: In-depth interviews	• Coping ability	At-risk individuals who chose not to be HD tested more often believe they are carriers than those who choose to be tested	Inconclusive: self-selection may eliminate those unfit for HD testing
Meiser & Dunn	2000	Qualitative: Literature review	• Depression • Anxiety • Adjustment • Ego strength	Difference between carriers and noncarriers in short-term psychological distress, not long-term	Inconclusive; self-selection of at-risk individuals may lead to biased studies

Williams, Schutte, Evers, & Holkup	2000	Qualitative: Longitudinal	• Doubt • Survival guilt • Redefinition	At-risk individuals testing negative for HD experienced paradoxical emotions prior to period of redefinition of self	Ethical: due to long-term benefit
Burgess	2001	Qualitative	• Autonomy • Informed consent	Clinicians find it difficult to justify withholding HD test due to its accuracy; autonomy may be overemphasized when there is no proven clinical benefit	Inconclusive: social and psychological effects have not been accurately described or predicted
Chapman	2002	Qualitative: In-depth interviews	• Adaptability	Younger participants adapted well in short-term; reportedly could appreciate life and make responsible reproductive decisions	Ethical: benefits outweigh harms
Witjes-Ané, Zwinderman, Tibben, van Ommen,& Roos	2002	Quantitative	• Self-esteem • Depression • Aggression • Compulsions • Anxiety	Carriers: complained more of low self-esteem, depression, aggression, and compulsions than noncarriers; noncarriers: young experienced more anxiety than old; history of depression associated with behavioral complaints	Inconclusive: long-term analysis needed
Almqvist et al.	2003	Qualitative: Longitudinal	• Suicide • Depression • Coping ability	Psychological distress decreased after five years; history of psychological distress more predictive of adverse event than actual test result	Inconclusive: dependent on pre-test psychological history
Decruyenaere, et al.	2003	Qualitative: Longitudinal	• Anxiety • Depression • Intrusion • Avoidance	Ego strength and test motivation were key indicators of psychological distress while actual test result was not	Inconclusive: dependent on pre-test psychological history and test motivation
Taylor	2004	Qualitative: In-depth interviews	• Perception	At-risk individuals viewed test decision as autonomic; decision was made based on test-value perception and ability to handle long-term and short-term effects	Ethical; maintains autonomic principle
Larsson, Luszcz, Bui, & Wahlin	2006	Qualitative	• Suicide • Depression • Compulsions • Self-esteem	Carriers reported more sadness, aggressive behavior, compulsions, and low self-esteem than noncarriers	Inconclusive: further study needed

(Continued on next page)

TABLE 1 Results of Studies Related to HD Testing, Psychological Health, and Ethical Issues *(Continued)*

Author(s)	Year	Type of Study	Psychological/Ethical Keywords	Key Findings	Ethical Viewpoint/Conclusion
Robins Wahlin	2007	Qualitative: Literature review	• Coping ability • Denial • Suicidal ideation • Depression	Negative effects may be underestimated due to denial and self-selection	Inconclusive; precedent needed for who or what determines an individual's readiness to be tested
Duncan et al.	2008	Qualitative: In-depth interviews	• Anxiety • Stress • Regret • Guilt	Young individuals experienced both harms and benefits related to gene-positive status, gene-negative status, and the HD testing experience	Inconclusive: long-term analysis needed
Lickleder, Wolff, & Barth	2008	Qualitative	• Depression	Depression affected both carriers and noncarriers in short term; post-test psychosocial intervention may decrease depressive symptoms and improve social support	Inconclusive: long-term analysis needed
Quaid et al.	2008	Qualitative	• Self preservation • Fear of discrimination • Anxiety	Risk concealment is never-ending process; genetic testing may be problematic for those experiencing anxiety with at-risk status	Inconclusive: examined those who chose not to be tested

as mental health status and level of preparation were shown to have as much of, if not more than, an effect on study participants' well-being as actual test results.

The majority of the research reveals that solutions to the ethical dilemma surrounding HD testing are both inconclusive and multifaceted. While the decision to be tested has historically been viewed as strictly autonomic, certain findings indicate a need for intervention for those deemed unprepared to handle the test implications, based on factors such as psychological history or test motivation. Huggins, Bloch, Kanani, Quarrell, and Theilman (1990) addressed the predicament of unanimously adhering to the principles of autonomy, beneficence, nonmaleficence, and justice when they often contradict each other with respect to HD testing. With no real medical benefit of knowing one's fate with respect to HD, autonomy has been given precedence. It is unclear under what exact circumstances a medical professional's duty to do what is right and to do no harm can override the autonomous rights of the individual. Most of the findings uncovered in this study suggest the principles must be weighed on a case-by-case basis due to the effects of a great many variables. From the early stages of research to present research, studies have stressed the important role that strict protocol, pretest assessments, long-term psychological counseling, and social support play in every case of HD genetic testing. It will be a steep challenge for future researchers to definitively prove the advantages and disadvantages of presymptomatic genetic testing over the lifespan, and to complete clear recommendations on whether or not an at-risk individual should be tested depending on the known outcomes.

Many researchers pointed out the importance of using HD genetic testing for presymptomatic individuals only, but not as a diagnostic tool for those who have already developed the disease. For presymptomatic individuals, the test outcome can give them a sense of control over their lives, allow them to plan for their future, and provide assistance with making responsible reproductive decisions (Chapman, 2002). Yet the issue is complicated by the somewhat ambiguous nature of the term *presymptomatic* and the progressive nature of the disease. The criteria for diagnosis are typically based on the physical symptoms, yet numerous patients demonstrate cognitive or behavioral changes, including difficulty in concentrating, memory lapse, and mood swings, prior to the movement disorder onset (Aubeeluck & Buchaman, 2007).

Further research is needed to determine why so many potential HD carriers are not getting tested. A survey in 2004 found that approximately 66% to 79% of individuals who were at risk for Huntington's disease could have the presymptomatic genetic testing completed, while research has shown that only 5% to 15% of those have actually been tested (Pakenham et al., 2004). Binedell and Soldan (1997) indicated these individuals chose not to

be tested due to their lack of coping ability, yet insufficient information or other factors may also contribute.

Other avenues of research continue to emerge that could significantly affect the current views on HD genetic testing. Of particular interest is the clinical research surrounding potential treatment for the cognitive, psychiatric, or neurological symptoms of HD through use of surgeries or various medications, including tetrabenazine (Adam & Jankovic, 2008; Kenney, Hunter, Davidson, & Jankovic, 2007). Obviously, any further advances and opportunities for what was once thought to be an incurable and untreatable disease would alter the fundamentals of the ethical dilemma.

CONCLUSION

Despite being thoroughly analyzed for nearly two decades, there remains no definitive consensus on the ethical viability of HD presymptomatic testing. Many studies pertaining to the issue result in inconclusive findings, namely due to the inability to accurately measure the positive effects related to reproductive planning, life planning, and relief of uncertainty against negative effects experienced through pre- and post-testing for both carriers and noncarriers of the Huntington's gene.

Medical professionals and at-risk individuals should take a serious look at their options and scientific recommendations regarding testing in order to preserve the best mental health possible for all affected parties. Even though a significant amount of helpful information was found reflecting the psychological implications of HD presymptomatic testing, further longitudinal studies should be conducted in order to better understand the long-term effects. Since there is currently no cure or reliable treatment for Huntington's disease, these psychological implications of presymptomatic testing are the primary criteria for judging whether HD testing maintains the medical ethical principles of autonomy, beneficence, nonmaleficence, and justice.

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