Ethics and Genetics in Huntington's Disease

Cara Garcia, Harmony Getts, and Adam Grimsley

University of Mary Graduate Nursing Program

NUR 510 Healthcare Across the Population

Dr. Joan Doerner

September 25th, 2022

Ethics and Genetics in Huntington's Disease

For those with cause to fear the conferring of a heritable disease upon an unborn child, the decision to engage in fetal genetic testing may be agonizing. In the case of Huntington's disease (HD), the prognosis adds to the burden of genetic testing considerations. Very often, at least one of the parents facing this struggle has witnessed the progression of HD in a loved one; they have seen the suffering first-hand. This paper will examine the characteristics and progression of Huntington's disease; genetic risk and ethical dilemmas of fetal genetic testing; quality of life, planning, and hope.

HD is an inherited disorder caused by the mutation of a protein called huntingtin. The defect in the mutation causes DNA building blocks to duplicate with much greater frequency than they typically do, which causes neurons to die throughout the brain. Neuronal death causes a person to lose control of voluntary movements. Individuals with HD experience changes in conduct, comprehension, decision-making abilities, and feelings and perceptions. The disease negatively impacts speech and makes eating and swallowing difficult (National Institute of Neurological Disorders and Stroke, n.d.).

The symptoms of HD vary for each person. However, once a person starts to experience motor symptoms, the disease can be divided into three stages: early, middle, and late (Huntington's Disease Society of America [HDSA], n.d.). Though they may experience minor involuntary movements and subtle coordination losses, a person in the early stage of HD commonly retains their normal functional abilities; they may continue to work, drive, and live independently (HDSA, n.d.). As the disease progresses to the middle stage, a person can still perform tasks such as eating and dressing but may need assistance with activities of daily living. Difficulty with voluntary motor skills increases and the loss of organized thinking manifests during the middle stage (HDSA, n.d.). Once an individual enters the late stage of HD, they will need assistance with all activities of daily living. While they can still comprehend some things, they are usually bedridden and nonverbal (HDSA, n.d.).

The genetic nature of HD has led to a breakthrough in genetic risk potentiation. HD is an autosomal dominant inherited disease, meaning that a single copy of the altered gene will cause HD. The actual cause of disease inheritance is in a trinucleotide repeat caused by Cytosine-Adenine-Guanine (CAG) in the first exon of genes on chromosome 4p16.3 (Myers, 2014). The risk level of HD inheritance is related to the number of CAG repeats. The estimated number of repeats for a genetically "normal" individual is 10-26 times. If the expression of CAG repeats is 40 or greater, the result is offspring with the most significant chance of HD. Brocklebank et al. (2009) explain that CAG repeats between 27 and 35 are sparse in population testing and do not seem to result in HD onset. However, males with this range may pass on their abnormally high CAG count, resulting in the expression of illness in their offspring, at least in mathematical simulations.

The best guidelines are that CAG in range 27-35 has a shallow chance of passing HD to offspring in a fully penetrant range (Brocklebank et al., 2009). CAG repeats of 36-39 have reduced penetrance, meaning some will not develop HD while others may (Myers, 2014). Like 27-35, 36-39 show poor penetrance, and because of the small to no observable HD cases, it is difficult to estimate risk percentage. Souza and Clarke (2022) estimate a 3% chance of offspring showing HD symptoms at 27-35 and a 6% chance in CAG repeats of 36-39. However, this number is minimally supported and highly hypothetical as insufficient research is done on this CAG range. Because the penetrance at the CAG range of greater than 40 is complete, those offspring that inherit the gene will eventually develop the disease during their lifetime (Myers, 2014).

Arguments for and against genetic testing flourish in this golden era of DNA analysis. Medical ethics tasks providers with facilitating discussions and offering options without making decisions for the family. Berlinger (2015) explains that providers who feel uncomfortable supporting a medical decision they disagree with must take appropriate steps to transition care to a provider capable of letting the family decide. The decision to undergo fetal genetic testing is formidable and may be complicated by

questions regarding when personhood begins. From many sacred and philosophical points of view, human life begins at conception, while secular and bioethical viewpoints often simplify the lifespan to mean birth through death (Kurjak & Barisic, 2021). Macha and McDonough (2012) clarify that, unlike prenatal screening, prenatal testing can cause fetal injury or demise, making informed consent crucial.

Often viewed as unethical, preimplantation genetic testing involves performing invitro fertilization and subsequent embryonic rejection if genetic testing reveals HD in the embryo (Van Rij et al., 2012). Direct prenatal testing comes with ethical issues as well. Discovering an unborn child is an HD carrier can have life-altering repercussions. Unless pregnancy interruption is a consideration, making that discovery is only beneficial if something positive comes from knowing. Parents facing HD must consider how they will cope and help their child cope with the disease.

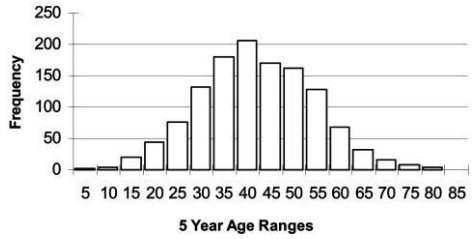
Petzke et al. (2022) found that counseling to improve resilience and reduce guilt should be part of a couple's care plan. Roman et al. (2018) discovered that for HD patients who regularly focused on the distressing aspects of the disease, an increased risk of suicidal ideation was noted. Parents must be aware of this and should plan to provide counseling. In conjunction with reducing negative perseverations, coping can be improved by learning strong self-management skills and engaging in discussions on feelings (Hubers et al., 2016).

As the quality of life is a significant concern, fear related to progressive functional decline, married with the knowledge that there is no cure for HD, may cause parents to consider pregnancy interruption if the fetus is a carrier. While fear is understandable, the concept of quality of life is highly subjective. To say that a prognosis of HD is tantamount to a reduced quality of life is one-sided. George Washington was 44 years old on July 4, 1776, and the leader of the American Army that gained the United States its independence. Martin Luther King Jr., a civil rights leader, was 39 years old at his death, having started numerous movements responsible for racial justice. Jesus Christ, the man responsible for

the world's largest religion, died at 33-36 years of age. All three of these men have one thing in common; they all did something remarkable by middle age. That is the same time on average that HD strikes.

Table 1

The Average age of HD onset



Note: Myers (2014) shows the typical onset of HD

Although the average age of onset is around 40 years, HD can enter early-stage onset by 2 years of age or as late as 80 (Myers, 2014). The quality of life for people diagnosed with HD remains high and correlates with "normal" quality of life before symptom onset. During the early to the early-intermediate stage, lasting 3-13 years, activities of daily living are possible with little assistance. Nearing the early-advanced to advanced stage, around 21-26 years, total care is needed, with many body systems starting to fail (Mozersky et al., 2017). Along with a variable onset, once symptoms start, survival averaged 17-20 years, with later onset correlating with slower disease progression. The average age of 40 years prior to symptoms, along with the two decades before death, seems to support the conclusion of quality of life remaining high for many years after diagnosis of HD.

There is hope for individuals with HD. Organizations like Huntington's Disease Society of America, The Huntington Study Group, The Hereditary Disease Foundation, and the Cure Huntington's Disease Initiative Foundation work continuously to improve patients' lives with HD. Presenting yearly to share research updates on HD and new protocols for disease management help keep all organizations

and HD patients up to date (Yohrling & Vetter, 2017). There is always a chance that this disease can be cured. The high certainty of disease causation increases the possibility of a cure (Gorantla at el., 2021).

A ray of hope showing promising results in HD treatment is stem cell research; pluripotent stem cells, embryonic stem cells, neural stem cells, adipose stem cells, and mesenchymal stem cells have all been studied to some extent (Gorantla at el., 2021). The most recent and notable studies with embryonic stem cells enriched with dopamine and phosphoproteins in mice resulted in glutaminergic and dopaminergic correction of motor deficits (Gorantla at el., 2021). The current regimen for HD focuses on symptom management.

Mozersky et al. (2017) warn that genetic testing alone is dangerous and must be accompanied by in-depth education, genetic counseling, and thorough informed consent. Further, parents that feel compelled to learn of a child's status should use the information to plan for counseling and resilience strengthening for the family. Preimplantation genetic testing is unethical in that it leads to embryonic rejection. Direct fetal genetic testing for HD would be an unethical choice without solid consideration of the following:

1) Fetal testing during pregnancy cannot be accomplished without risk to the fetus.
2) There are psychological repercussions to knowing the child's carrier status; awareness is not beneficial unless interventions to strengthen coping skills are utilized.
3) Fetal testing offers no guarantee that an unaffected child will live a long and healthy life.
4) The unknown future and medical technology are evolving with radiant speed.

While Huntington's is a terrible disease, hope exists for patients and families. Many resources are available to aid in coping. It is the responsibility of the parent to do all they can to protect their child. If a parent carefully considers all these facts and still chooses direct testing, the decision must be respected.

References

Berliner, J. (2015). *Ethical Dilemmas in Genetics and Genetic Counseling.* Oxford University Press.

Brocklebank, D., Gayán, J., Andresen, J. M., Roberts, S. A., Young, A. B., Snodgrass, S. R., Penney, J. B., Ramos-Arroyo, M. A., Cha, J. J., Rosas, H. D., Hersch, S. M., Feigin, A., Cherny, S. S., Wexler, N. S., Housman, D. E., & Cardon, L. R. (2009). Repeat instability in the 27-39 CAG range of the HD gene in the Venezuelan kindreds: Counseling implications. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *150B*(3), 425–429. https://doi.org/10.1002/ajmg.b.30826

Gorantla, V., Bhat, A., Ghosh, A., Bolla, S., Bhojaraj, S., Mohan, S., Veeraraghavan, V., Chidambaram, S., Essa, M., & Qoronfleh, M. (2021). Stem cells therapy: A ray of hope for Huntington disease. *International Journal of Nutrition, Pharmacology, Neurological Diseases*, 11(2), 95–104. https://doi-org.ezproxy.umary.edu/10.4103/ijnpnd.ijnpnd_107_20

Hubers, A. A. M., Hamming, A., Giltay, E. J., von Faber, M., Roos, R. A. C., van der Mast, R. C., & van Duijn, E. (2016). Suicidality in Huntington's disease: A qualitative study on coping styles and support strategies. *Journal of Huntington's Disease,* 5(2), 185–198. https://doi-org.ezproxy.umary.edu/10.3233/JHD-160188

Huntington's Disease Society of America. (n.d.). *Huntington's disease stages*. https://hdsa.org/what-is-hd/huntingtons-disease-stages/

Kurjak, A., & Spalldi Barišić, L. (2021). Controversies on the beginning of human life – Science and religion are closer and closer. *Psychiatria Danubina,* 33(Suppl 3), S257–S279. https://pubmed.ncbi.nlm.nih.gov/34010252/

Macha, K., & McDonough, J. P. (2012). *Epidemiology for advanced nursing practice.* Jones & Bartlett Learning.

Mozersky, J., Ravitsky, V., Rapp, R., Michie, M., Chandrasekharan, S., & Allyse, M. (2017). Toward an

ethically sensitive implementation of noninvasive prenatal screening in the global context. *Hastings Center Report,* 47(2), 41–49. https://doi-org.ezproxy.umary.edu/10.1002/hast.690

Myers, R. H. (2014). Huntington's disease genetics. *NeuroRX*, *1*(2), 255–262. https://doi.org/10.1602/neurorx.1.2.255

National Institute of Neurological Disorders and Stroke. (n.d.). *Huntington's disease*. https://www.ninds.nih.gov/health-information/disorders/huntingtons-disease

Petzke, T. M., Rodriguez-Girondo, M., & van der Meer, L. B. (2022). The Hold me Tight Program for couples facing Huntington's disease. *Journal of Huntington's Disease*, 11(2), 203–215. https://doi-org.ezproxy.umary.edu/10.3233/JHD-210516

Roman, O. C., Stovall, J., & Claassen, D. O. (2018). Perseveration and suicide in Huntington's disease. *Journal of Huntington's Disease,* 7(2), 185–187. https://doi-org.ezproxy.umary.edu/10.3233/JHD-170249

Souza, J. D., & Clarke, A. (2022). G03 the psychosocial implications of receiving an intermediate allele or reduced penetrance allele predictive test result for Huntington's disease. *G: Genetic Testing and Counselling*. https://doi.org/10.1136/jnnp-2022-ehdn.164

Yohrling, G. J., & Vetter, L. A. (2017). Stewarding hope: The evolving landscape of Huntington's disease science communications. *Journal of Huntington's Disease*, 6(1), 33–35. https://doi-org.ezproxy.umary.edu/10.3233/JHD-160230

Van Rij, M. C., De Rademaeker, M., Moutou, C., Dreesen, J. C., De Rycke, M., Liebaers, I., Geraedts, J. P., De Die-Smulders, C. E., & Viville, S. (2012). Preimplantation genetic diagnosis (PGD) for Huntington's disease: the experience of three European centres. *European Journal of Human Genetics,* 20(4), 368–375. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3306852/