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Adolescent Perspectives on Genetic Testing for Huntington's Disease

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ABSTRACT

In 2015, the American Society of Human Genetics (ASHG) released a position statement which recommended minors to defer genetic testing for adult-onset conditions until adulthood. In the 2016 DNA Day Essay Contest, high school students were asked to research an adult-onset genetic disorder and use it to formulate a stance on whether they agreed or disagreed with the position statement. Phase two of this study focused on the essays written about Huntington's Disease (HD). Within the HD essays, 57% chose to defer, 35% chose not to defer, and 8% did not clearly state an opinion. Essays were analyzed using a codebook that was established in Phase one and the top codes were further analyzed for themes. The top codes that were thematically analyzed were "Psychological Risks to Minor", "No Medical Benefit/Not Preventable", "Necessary to Plan/Prepare", and "Genetic Testing Variability and Uncertain Predictability." Although many of the essays agreed to defer testing, many students cited similar reasons, regardless of their stance.

Keywords: predictive testing, presymptomatic testing, minors, adolescents, adult onset, ethics, perspectives, attitudes, genetic testing, Huntington's Disease

BACKGROUND

Genetic testing in the pediatric setting is a rare occurrence outside of newborn screening. Generally, genetic testing of minors is only done for diagnostic or immediate medical purposes; otherwise, most professional organizations recommend that minors postpone testing until adulthood. There are arguments in the literature both supporting and discouraging the testing of minors for adult-onset conditions, such as Huntington's Disease.

Current Guidelines for the Genetic Testing of Minors

A number of North American societies for genetics professionals, including the National Society of Genetic Counseling (NSGC), the American Society of Human Genetics (ASHG), and the American College of Medical Genetics and Genomics (ACMG) have guidelines for genetic testing of minors. With regards to predictive testing of minors for adult-onset conditions, the professional organizations all acknowledge potential concerns, such as possible stigma, discrimination, loss of autonomy, or anxiety; however, they vary slightly in their recommendations. The American Academy of Pediatrics (AAP), ACMG, and ASHG take a strong stand on the deferral of testing with the exception of medical necessity during adolescence, while NSGC is less cut and dried in their recommendation. If a minor is undergoing sequencing, a lab may feel an obligation to analyze and interpret the genomic data for pathogenic variants for the 59 medically-actionable genes recommended by the ACMG, which are responsible for 24 conditions, some of which are adult-onset (Kalia et al., 2017). As a result, there was a tension between two ACMG-supported guidelines—minors should postpone predictive testing for adult-onset conditions and the requirement to return secondary findings on a sequencing result regardless of age (Clayton et al., 2014). However, the ACMG has updated their recommendations to give parents the opportunity to opt-out of secondary findings for their children, if they wished to do so (Kalia et al., 2017). NSGC recommends that, if possible, testing be deferred until a time at which the individual who is being tested has the capacity to understand the weight and process the decision to be tested. This recommendation does not bar the testing of an adolescent or other minors if conditions warrant it ("National Society of Genetic Counselors: Position Statement: Genetic Testing of Minors for Adult-Onset Conditions," 2017). Although ASHG recommends deferring testing for adult-onset conditions until adulthood, they

recognize the potential for earlier testing in the context of relieving psychosocial distress and making life-planning decisions (Botkin et al., 2015). While the professional organization guidelines provide a guide for healthcare professionals, it is based on limited data summarizing clinical experience and there remains questions to be answered that will require continued reevaluation with the growth of genetic testing.

Consent vs. Assent

In most settings, the legal age for decision making is 18 years old. However, legal and ethical policy guidelines encourage caregivers to help minors take on a greater role in decision-making regarding their health when they are competent to do so (Botkin et al., 2015). Competence has been defined by three main capacities: "(1) to process and communication, (2) to reason and deliberate, (3) to develop and sustain moral values" (Botkin et al., 2015). The capacity of a child to give consent vs. assent is driven by their cognitive ability. In the United States, children can begin being involved in decision-making by age 7 and thus can provide "assent" to participate in research from that time on (Botkin et al., 2015). Assent only requires a basic understanding of risk and benefit, while consent requires the ability to make independent decisions. Consent becomes possible around the time of adolescence when minors have begun to connect the present with the future and understand the long-term effects of decision-making to some degree. This is thought to be around age 12-14. In adolescence, experts argue, minors are still very malleable and can be influenced by a variety of factors including self-image, family pressures, and stigmatization. (Botkin et al., 2015). The AAP statement on testing of minors asserts that for predictive testing, the assent of the child should be sought and stresses that the results of the test are ultimately theirs (Clayton, 2015).

Risks of Testing Minors for Adult-Onset Conditions

In the bioethics literature, there are three main arguments against testing minors for adult-onset conditions: lack of respect for the child's autonomy and their right not to know, concerns about breaching the child's confidentiality, and the potential psychological harm (Aatre & Day, 2011; Duncan et al., 2008; Malpas, 2008; Mand, Gillam, Delatycki, & Duncan, 2012). Among the possible harms that have been discussed are distress, anxiety, and depression with the return of a positive result (Aatre & Day, 2011; Bradbury et al., 2016). Some experts have raised the possibility of vulnerable child syndrome and survivor guilt (Aatre & Day, 2011; Bradbury et al., 2016; Mand et al., 2012). Overall, potential adverse emotional outcomes include altered self-esteem, feelings of blame, stigma, discrimination, and difficulty forming or maintaining relationships with family and peers (Aatre & Day, 2011; Bloch & Hayden, 1990; Bradbury et al., 2016; Mand et al., 2012; Wade, Wilfond, & Mcbride, 2010). All of these feelings might reasonably be expected to tie into the child's maturity level but, to contrary, Duncan et al. found that many of the harms described by adolescents were not much different than those experienced by adults (2008).

Benefits of Testing Minors for Adult-Onset Conditions

Counter arguments have been made to refute the idea that testing minors for adult-onset conditions is problematic. Parents, it has been pointed out, can be expected to act in their child's best interests (Mand et al., 2012; Rhodes, 2006). Furthermore, adolescents are often more than capable of making decisions regarding their own health (Borry, Goffin, NYS, & Dierickx, 2008). Rhodes goes on to argue that the issue of confidentiality is moot because parents already bear the responsibility of their child and make medical decisions on their behalf (2006).

As for psychological harm, Rhodes found in a 2006 study that after a brief period of adjustment to the information, there was little to no harm (Rhodes, 2006). The argument for testing assumes that testing may be beneficial because it promotes knowledge and a sense of control and empowerment in the individual and, in turn, offers them a realistic expectation of their prognosis with the condition (Malpas, 2008; Mand et al., 2012). In some studies, children who have been tested have been found to have higher self-esteem in the context of both positive and negative results (Aatre & Day, 2011; Mand et al., 2012; Rhodes, 2006). Bradbury et al. found that girls with a positive *BRCA1* or *BRCA2* result and family history had higher self-esteem than those without the family history; this was found to be correlated with lower maternal anxiety, strong communication within family, and having prior exposure to the condition (2016).

Huntington's Disease

Huntington's Disease is an adult-onset neurodegenerative disorder that has an autosomal dominant pattern of inheritance. Individuals who carry an expansion of 36 or more CAG trinucleotide repeats in one of their *HTT* genes will inevitably develop severe and progressive motor, cognitive, and psychiatric disturbances. Currently, there are no effective treatments for HD and the median survival time is 15-18 years after onset, which typically occurs during the 3rd or 4th decade of life. To date, care remains mainly supportive (Warby, Graham, & Hayden, 1993). Genetic testing for HD is extremely accurate. Pre-symptomatic testing is accompanied in most medical centers by a team-based, pre-test protocol including psychiatric and neurologic evaluations and genetic counseling. It is generally not easily available to minors (Huntington's Disease Society of America, 2016; MacLeod et al., 2013).

One study that included 480 adults who had not previously been clinically diagnosed with HD but had either a positive genetic test or family history of the disease found that almost

half (46 %) of respondents reported genetic discrimination or stigma based on their genetic status and/or family history of HD (Erwin et al., 2010). The highest proportion of discrimination and/or stigma was described as related to insurance and relationships (Erwin et al., 2010). Within this study, they discussed how it is currently not understood to what extent genetic stigma and/or discrimination has an impact on daily life decisions. As such, there is little understanding of the potential impact that genetic stigma and discrimination could have on minors.

The Need for Adolescent Opinions

Currently, literature on the impact of predictive testing of minors for adult-onset conditions is very limited and consists mainly of research and opinion provided by healthcare providers and bioethicists. The perspective of the minors themselves is absent from the debate. This study is part of an ongoing analysis of the essays from the ASHG 2016 International DNA Day essay competition, which provide a unique opportunity to hear from adolescents on their opinions on genetic testing of minors for adult-onset conditions. The present study focuses on a subgroup of those essays which discuss Huntington's Disease.

MATERIALS AND METHODS

In Phase one of this study, a mixed-methods approach was developed to analyze essays written by high school students submitted to ASHG's annual 2016 International DNA Day Essay Contest. The essay prompt for 2016 was as follows:

> *"Choose a genetic test that is currently available for a condition or disease that does not cause symptoms until adulthood (i.e., an adult-onset condition such as hereditary breast cancer). Describe how the test works and how certain the test results are. Then, either defend or refute the recommendation below from ASHG's recent position statement on pediatric genetic testing. "Adolescents should be*

encouraged to defer predictive or pre-dispositional testing for adult-onset conditions until adulthood because of the complexity of the potential impact of the information at formative life stages."

The high school students were informed that their submissions might be used for research. Phase one of this project received an exemption from the Sarah Lawrence College Institutional Review Board (IRB) in April 2016 and Phase two received an exemption from the same body in October 2017. Approval was also sought and received from the Geisinger Health System IRB in March 2016.

All essays were initially categorized based upon demographic information (grade, gender, country), which disease the individual chose to write about, and whether they chose to agree with the ASHG statement (defer testing), disagree (not defer testing), or did not clearly state at opinion (other). A code book was developed with the intention of investigating reasons why minors would defer or not defer genetic testing for adult-onset diseases. The final code book consisted of 25 universal codes that were used to analyze the essays in the qualitative analysis program Atlas.ti (www.atlasti.com).

Code	**Description**
Psychological benefits to minor	Benefits of knowing or not knowing their own genetic information
Psychological risks to minor	Risks of knowing or not knowing their own genetic information
Genetic testing accuracy and predictability	High accuracy of genetic testing due to detection rate, reliability, validity, predictability, technological accuracy
Genetic testing variability and uncertain predictability	Limitations of genetic testing due to low detection rate, reliability, validity, predictability, technological accuracy (low genotype to phenotype predictability)
Factual genetic/disorder information	Facts about genetics/the disorder that they chose to write about

Incorrect facts	Any facts that are used in the essay that are incorrect
Risks to family	Possible negative effects of knowing or not knowing the genetic information would have on family members
Benefits to family	Possible negative effects of knowing or not knowing the genetic information would have on family members
Personal experience with the condition	Mention of personal experiences with the disorder described (themselves or family members) that influences their opinion on testing or not testing
Personal experience with genetic testing	Mention of personal experiences with genetic testing described (themselves or family members) that influences their opinion on testing or not testing
Medical benefit/prevention	Possibility of medical prevention or benefit that comes with testing for the condition
No medical benefit/prevention	Lack of medical prevention or benefit that comes with testing for the condition
Disrupts formative years	The right to be a child/have a normal adolescence.
Social risks	Negative changes in any social relations such as friends, colleagues, and schoolmates
Social benefits	Positive changes in any social relations such as friends, colleagues, and schoolmates
Mature and capable	Minor's ability to adapt, handle, fully process the information
Immature and incapable	Neurological, emotional, and/or social immaturity
Potential discrimination	Any discrimination in career, insurance, social, stigma.
Necessary to plan/prepare	Genetic testing is necessary to plan for future as a minor
Unnecessary to plan/prepare	Genetic testing is unnecessary to plan for future as a minor (at this time)
Advancements in science	Altruism or altruistic intent/contribute to research
Case-by-case	Suggestion to take each genetic testing case individually (indicating that there are some instances when it is and is not appropriate)
Loss of autonomy	Child's inability to provide informed consent. Should not be pressured, voluntary.

Individual's choice	The opinion of the minor should be upheld over anyone else
Family/parent's choice	The opinion of the minor/s family/parents should be upheld over anyone else

Of the 1241 essays submitted, 77 were discarded as unfit for coding, including those that did not address the prompt or focused on a different topic, were illegible or unintelligible, did not state an opinion, or misinterpreted the question or ASHG policy.

In order for the coders in Phase one of the project to reach inter-rater reliability (IRR), five essays were coded by each coder separately, and then compared. This process was repeated until an IRR $\geq$ 75% was reached, and then the remaining HBOC, AD, and Lynch Syndrome essays were divided evenly between the four group members for coding.

The most common disorders discussed in these essays were Huntington Disease (HD), Alzheimer's Disease (AD), and Hereditary Breast and Ovarian Cancer (HBOC). In Phase one, all essays with an HBOC or Alzheimer's Disease theme were coded, analyzed, and discussed. All essays discussing Lynch syndrome (13 in total) were also thematically coded but not included in the final analysis.

The focus of Phase two of the study was the coding and analysis of themes emerging in the essays written about HD. An IRR of 82.9% was established between four new coders in the same manner as described above. In addition, five previously coded essays from the Phase one data set were blindly coded by each new group member and subsequently compared to one another as well as the previous codes in order to establish if IRR between the Phase one and Phase two coders. A collective IRR (between the coders from Phase one and two combined) of 76.5% was established.

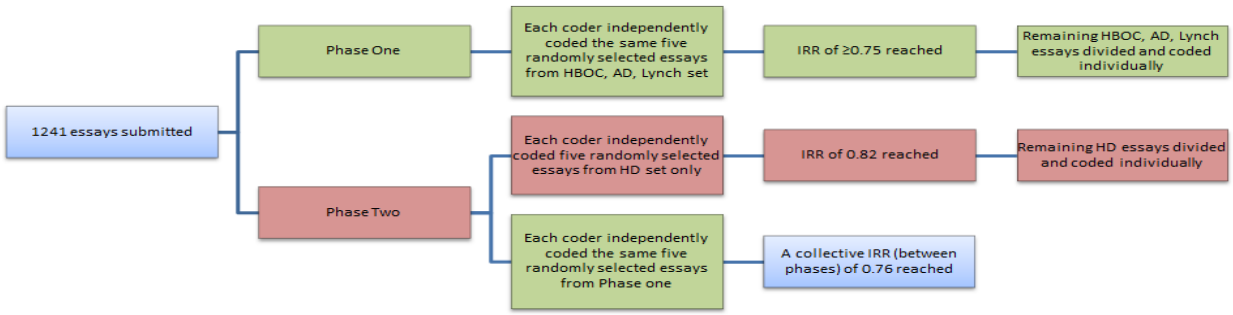

Figure 1. The process of reaching inter-rater reliability (IRR) between coders in Phase one and two

A total of 467 HD essays were equally divided among the four group members for coding. The Phase one universal codebook was adopted in full with no changes to the 25 codes. All essays had been previously uploaded to Atlas.ti and were coded using this program.

Upon completion of initial coding of the HD essays, data was downloaded from Atlas.ti to Excel spreadsheets. Included in these data sets were totals of top codes used as well as a list of the exact quotes used for these codes. Top five codes used were established to be: "Factual Genetic/Disorder Information", "Necessary to Plan/Prepare", "Genetic Testing Variability and Uncertain Predictability", "No Medical Benefit", and "Psychological Risks to Minor." All five of these codes, except for "Factual Genetic/Disorder Information", were further analyzed for themes by reading through the quotes pulled from the respective essays. "Factual Genetic/Disorder Information" was excluded from the additional analysis for themes because this information was required to be included in the essays and offered no further insight into their reasoning behind whether they agreed or disagreed with the ASHG recommendation. Each of the

other main codes were analyzed further for specific themes. Themes were counted and organized into tables of their own. All final counts accounted for the number of unique essays that used a particular theme within a code. For example, one essay might have used one code three times, but only addressed two themes. This essay would be counted twice in the tables, one for each theme. The essay was the unit of analysis, and the number of themes per essay was quantified to illustrate any thematic similarities or differences between defer and non-defer arguments.

RESULTS

Of the 1241 student essays submitted to the 2016 ASHG DNA Day Essay Contest, 467 essays were about Huntington's Disease. Out of these 467 essays, 266 chose to "Defer" testing, 163 essays chose to "Not Defer" testing, and 38 essays cited "Other" or "None" on testing opinion. Table I illustrates how the Huntington's Disease essays were broken down by testing choice. Table II shows the demographics of the 429 "Defer" and "Not Defer" essays, broken down by gender and grade level.

Testing Choice	Number of Essays	% of Total Essays
Defer	266	57%
Not Defer	163	35%
Other/None	38	8%

Table I. Testing choices of the 467 Huntington's Disease essays

Demographics	% that Deferred	% that Not Deferred
Female	64%	36%
Male	58%	42%
9th Grade	63%	37%
10th Grade	58%	42%

11th Grade	69%	31%
12th Grade	59%	41%

Table II. Demographics of the 429 Huntington's Disease essays that chose to "Defer" and "Not Defer" testing

Table III describes the top five codes utilized in the Huntington's Disease essays and the number of quotes associated with each code.

Code	**Number of Quotes**
Factual Genetic/Disorder Information	817
Psychological Risks to Minor	526
No Medical Benefit or Prevention	341
Necessary to Plan and Prepare	340
Genetic Testing Variability & Uncertain Predictability	191

Table III. Top five codes used in the Huntington's Disease essays

Psychological Risk to Minor

The code "Psychological Risk to Minor" was used 526 times in essays. This code was defined in the codebook as statements that describe an increase in the adolescent's anxiety, depression, apathy, fear, helplessness, devastation, or loss of self-esteem, as well as statements about risky behavior, self-harm and suicide. This code was used to describe any psychological consequences that may arise due to the decision to pursue or to not pursue genetic testing for Huntington's Disease. The themes present within this code were *General psychological risk to minor, Anxiety, Depression, Self-harm/suicide, Harm self-esteem, Harm development, Substance abuse, Survivor's guilt, Hopelessness,* and *Helplessness.* "Psychological Risk to Minor" was split into the following four testing scenarios: (1) pursuing genetic testing and receiving a positive result, (2) pursuing genetic testing and receiving a negative result, (3) pursuing genetic testing in general, and (4) not pursuing genetic testing. These scenarios were then subdivided into essays

that chose to defer or not defer testing. The frequency of use for each theme is displayed in Table IV.

Psychological risk to a minor when receiving a positive genetic testing results for Huntington's Disease was the most commonly discussed scenario, showing up 389 (74.0%) times. Of the 389 essays which discussed this topic, 331 (85.1%) of these essays chose to defer testing, while 38 (9.8%) chose to not defer, and 20 (5.1%) did not clearly specify. Of the essays which chose to defer, the most common themes were *Psychological risk to minors in general* (31.7%), risk for *Depression* (21.1%), and the risk for *Anxiety* (19.3%).

The second most common scenario was the psychological risk to a minor when pursuing genetic testing for Huntington's Disease in general, without specifying the outcome of the results. This was discussed 113 (21.5%) times. Out of the 119 times this topic was discussed 92 (77.3%) chose to defer, 17 (14.3%) chose to not defer and 4 (3.4%) did not specify.

All but one essay which discussed negative test results and chose to defer (91.7%) used the theme *Survivor's guilt.*

Overall, the three most commonly used themes were *Psychological risk to minor in general* (47.8%), risk for *Anxiety* (20.7%), and risk for *Depression* (12.0%).

Theme	**Positive Test Results**			**Negative Test Results**			**Testing in General**			**Not Testing**			**Total**
	Defer	**Not Defer**	**Other /None**	**Defer**	**Not Defer**	**Other /None**	**Defer**	**Not Defer**	**Other /None**	**Defer**	**Not Defer**	**Other /None**	
General	105 (31.7 %)	7 (18.4 %)	6 (30.0 %)	0	0	0	44 (47.8 %)	8 (47.1%)	2 (50.0 %)	1 (50.0 %)	5 (50.0 %)	0	**178 (33.8 %)**
Anxiety	64 (19.3 %)	10 (26.3 %)	4 (20.0 %)	1 (8.3%)	0	0	19 (20.7 %)	3 (17.6%)	1 (25.0 %)	1 (50.0 %)	2 (20.0 %)	0	**105 (20.0 %)**

Depression	70 (21.1 %)	11 (29.0 %)	4 (20.0 %)	0	0	0	11 (12.0 %)	3 (17.6%)	0	0	2 (20.0 %)	0	**101 (19.2 %)**
Self-Harm / Suicide	31 (9.4%)	4 (10.5 %)	4 (20.0 %)	0	0	0	4 (4.3%)	2 (11.8%)	0	0	0	0	**45 (8.6%)**
Harm Self Esteem	17 (5.1%)	2 (5.3%)	1 (5.0%)	0	0	0	4 (4.3%)	1 (5.9%)	1 (25.0 %)	0	1 (10.0 %)	0	**27 (5.1%)**
Harm Development	17 (5.1%)	0	0	0	0	0	3 (3.3%)	0	0	0	0	0	**20 (3.8%)**
Substance Abuse	14 (4.2%)	0	0	0	0	0	6 (6.5%)	0	0	0	0	0	**20 (3.8%)**
Survivor's Guilt	1 (0.3%)	2 (5.3%)	1 (5.0%)	11 (91.7 %)	0	0	0	0	0	0	0	0	**15 (2.9%)**
Hopelessness	9 (2.7%)	1 (2.6%)	0	0	0	0	1 (1.1%)	0	0	0	0	0	**11 (2.1%)**
Helplessness	3 (0.9%)	1 (2.6%)	0	0	0	0	0	0	0	0	0	0	**4 (0.8%)**
Total	**331**	**38**	**20**	**12**	**0**	**0**	**92**	**17**	**4**	**2**	**10**	**0**	**526**

Table IV. Psychological Risk to Minors and its Themes

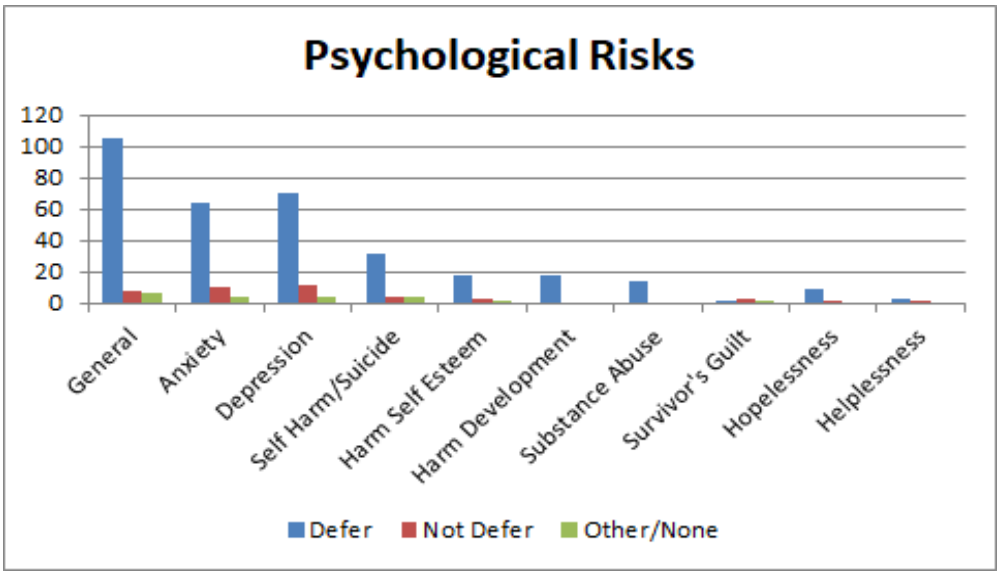

Figure 2. Psychological Risks and its Themes

No Medical Benefit/Not Preventable

The code "No Medical Benefit/Not Preventable" was defined within the codebook as a discussion of the lack of benefit or prevention. This code was used with statements that describe no treatments or prevention to stop the development of the disease or to cure the disease and the lack of available screening to minors. The essays that were coded as "No Medical Benefit/Not Preventable," were then subcoded for themes. The themes included *Ineligible for clinical trials, Limited treatment options, No changes in medical intervention as child, No cure, No indication of disease course, No indication of disease onset, No prevention, No treatment, Treatment side effects,* and *Treatment can't slow down /stop illness*. Among the essays coded, the themes *No cure* and *No treatment* were most common (Table V).

The theme *No Cure* was the most common theme in both the "Defer" and "Not Defer" essays. In the "Defer" essays, the *No cure* theme was used 42% of the time and in the "Not Defer" essays, it was used 60% of the time. *No treatment* was the second most common theme under the code "No Medical Benefit/Prevention." In the "Defer" essays, the *No treatment* theme was used 19% of the time and in the "Not Defer" essays it was used 11% of the time.

Theme	Defer	Not Defer	Other/None	Total
Ineligible for clinical trials	3 *(1.8%)*	0	0	**3 (1.2%)**
Limited treatment options	3 (*1.8%*)	2 *(3.5%)*	0	**5 (2.0%)**
No changes in medical intervention as child	1 *(0.5%)*	0	0	**1 (0.4%)**
No cure	72 *(42%)*	34 *(60%)*	9 *(45%)*	**115 (46.5%)**
No indication of disease course	5 *(2.9%)*	0	0	**5 (2.0%)**

No indication of disease onset	6 *(3.5%)*	1 *(1.8%)*	0	**7 (2.8%)**
No prevention	23 *(14%)*	5 *(9%)*	1 *(5%)*	**29 (11.7%)**
No treatment	33 *(19%)*	6 *(11%)*	5 *(25%)*	**44 (17.8%)**
Treatment side effects	1 *(0.5%)*	1 *(1.8%)*	0	**2 (0.8%)**
Treatments can't slow down/ stop illness	23 *(14%)*	8 *(14%)*	5 *(25%)*	**36 (14.5%)**
Total	***170***	***57***	***20***	***247***

Table V. No Medical Benefit and its Themes

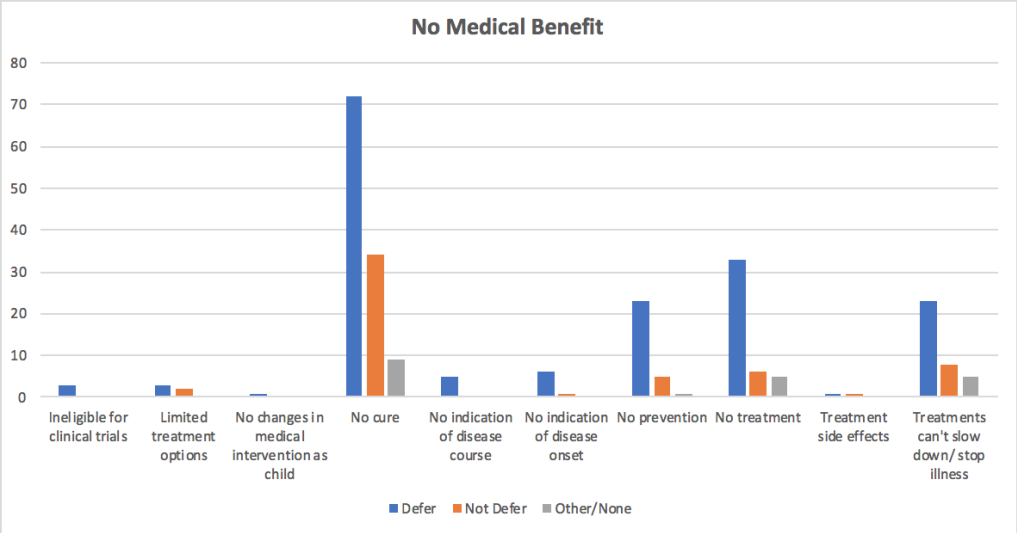

Figure 3. No Medical Benefit and its Themes

Necessary to Plan/Prepare

The code "Necessary to Plan/Prepare" was defined within the original codebook as "genetic testing is necessary to plan for future as a minor." This code was used with statements that describe the necessity of obtaining their genetic information in order to adequately plan and prepare for future aspects of one's life. The quotes that were coded as "Necessary to Plan/Prepare," were then analyzed for themes. The themes that emerged from this code included: *Making proper financial/emotional arrangements before getting sick, Family*

planning/reproductive purposes, General planning/preparing for one's future, and Accomplish goals/have meaningful life before disease onset.

The two most common themes for this code are *Making proper financial/emotional arrangements before sick* and *Family planning/reproductive purposes.* These themes accounted for 40% and 38%, respectively, of the 255 essays in which this code was used (including defer, not defer, and other/none). The majority of essays expressing the *Making proper financial/emotional arrangements before sick* theme were "Not Defer" essays (72 versus 20 "Defer" essays). This was similar for the *Family planning/reproductive purposes* theme, where 67 were "Not Defer" and 24 were "Defer". The vast majority of essays using the code "Necessary to Plan/Prepare" were "Not Defer" essays (181 of 255 or 70.9%), regardless of the theme (Table VI).

Theme	**Defer**	**Not Defer**	**Other/None**	**Total**
Making proper financial/emotional arrangements before sick	20 (34.5%)	76 (42.0%)	6 (37.5%)	**102 (40%)**
Family planning/reproductive purposes	24 (41.4%)	67 (37.0%)	5 (31.3%)	**96 (38%)**
General planning/preparing for one's future	9 (15.5%)	18 (9.9%)	3 (18.8%)	**30 (12%)**
Accomplish goals/meaningful life before disease onset	5 (8.6%)	20 (11.0%)	2 (12.5%)	**27 (11%)**
Total	**58**	**181**	**16**	**255**

Table VI. Necessary to Plan/Prepare and its Themes

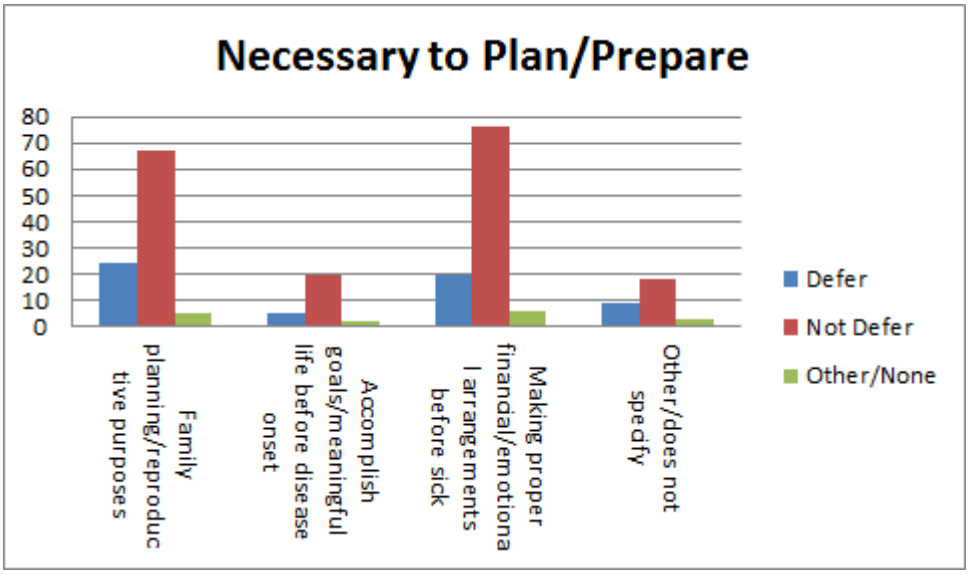

Figure 4. Necessary to Plan/Prepare and its Themes

Genetic Testing Variability and Uncertain Predictability

The code "Genetic Testing Variability and Uncertain Predictability" was defined in the original codebook as: "Limitations of genetic testing; detection rate, reliability, validity, predictability, technological limitations (unclear genotype to phenotype correlation)." This code was used with statements that described the genetic testing for Huntington's Disease as uncertain, inaccurate, or unable to predict the onset or symptoms of the condition. The themes within this "Genetic Testing Variability and Uncertain Predictability" code were *Intermediate range of repeats*, *Not 100% accurate/certain*, *Uncertain predictability of symptoms*, and *Inconclusive results*.

The most common theme was *Uncertain predictability of symptoms*, which made up about 46% of all the essays that used "Genetic Testing Variability and Uncertain Predictability" code. The same theme was also the most prevalent in both the "Defer" and "Not Defer" essays with 45% and 50% of the essays, respectively. In the "Other/None" essays, the most common theme used was *Not 100% accurate/certain*, accounting for 57% of those essays. Table VII lists

the proportion of “Defer”, “Not Defer”, and “Other/None” essays that fall under the various themes.

Theme	Defer	Not Defer	Other/None	All
Intermediate range of repeats	32 (26%)	17 (31%)	1 (14%)	**50 (27%)**
Not 100% accurate/certain	36 (29%)	9 (17%)	4 (57%)	**49 (26.5%)**
Uncertain predictability of symptoms	56 (45%)	27 (50%)	2 (29%)	**85 (46%)**
Inconclusive results	0	1 (2%)	0	**1 (0.5%)**
Total	**124**	**54**	**7**	**185**

Table VII. Genetic Testing Variability and Uncertain Predictability and its Themes

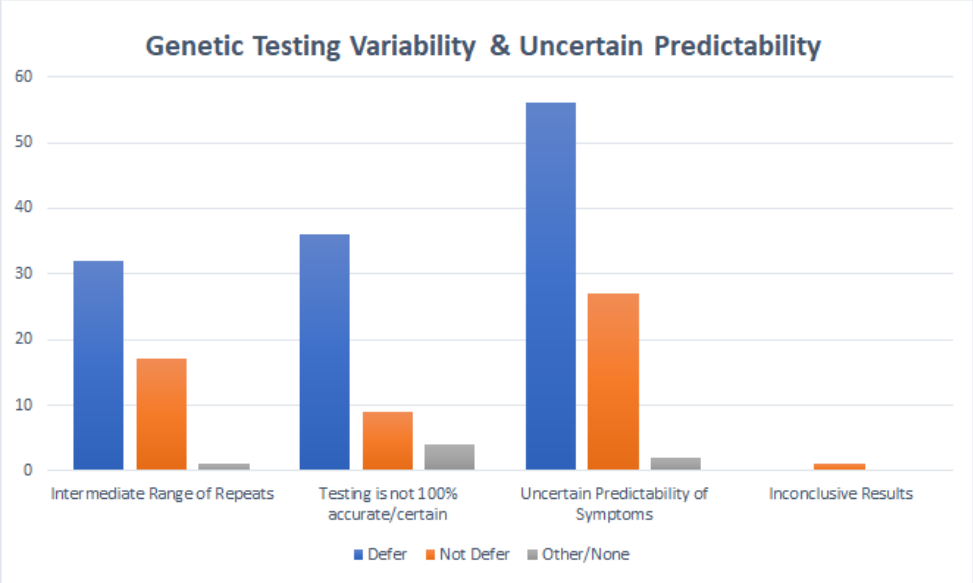

Figure 5. Genetic Testing Variability and Uncertain Predictability and its Themes

DISCUSSION

Psychological Risk to Minor

Limited research so far has not found an increase in psychological risk with testing; however, this was the second most discussed theme in the essays discussing HD in this study

(Wade, Wilfond & McBride, 2010). Overall, students appear to use potential psychological risks as a key deciding factor in their argument whether to defer or not defer testing.

Some students had concerns regarding the potential psychological risk, as demonstrated by one student who stated, "*The results of testing positive could have major effects on the emotional stability of the adolescent*" (Essay 667, Defer), but did not delve into the specifics. Other students went further in elaborating details of psychological harm. For example, one student stated, "*Knowing one's test results at a young age can result in anxiety, behavioral issues, depression, lessened self-esteem and independenc*e" (Essay 1236, Defer). Most students used the natural history, clinical features and the lack of treatment for HD to identify causes for the psychological risk. Students referred to HD resulting in early death as an argument both for and against testing. As stated by a few students, "*the prospect of a confirmed early death could have enormous psychological ramifications on individuals positive for HD*" (Essay 456, Defer), most often noted as an increase in anxiety and depression, and "*would have a devastating effect on [a person's] quality of life*" (Essay 204, Defer).

Students who argued for not deferring testing often also recognized the psychological risks that could arise due to a positive result, "*The simple knowledge that the disease will one day be active can hugely impact one's life and bring forth many emotional consequences. Learning about it at a young age may cause huge amounts of fear, anxiety, depression, stress*" (Essay 1202, Not Defer). Individuals who chose to not defer testing, while they cited psychological risks associated with testing, many also considered the potential benefits.

Although a majority of essays discussing psychological risk to minors pursuing genetic testing for HD had stated concerns with receiving a positive HD test result, some students also dove into the possible psychological implications of receiving a negative test result and the risks

associated with not pursuing testing. Students were able to dissect the complexities associated with both testing and not testing for a degenerative neurological disorder. All but one student who discussed psychological risk in respect to receiving a negative test result brought up the possibility of survivor's guilt. One student described survivor's guilt as "*feel guilty for escaping the disease that other members of the family suffer from*" (Essay 956, Not Defer). Another student demonstrated the complexities of their thoughts by contrasting these potential risks. "*The result of the HD test may be enough to push the patient into depression and place a heavy burden on them. After disclosure of the results, people were found more likely to succumb to depression and hopelessness. Those who believed that their results were going to be normal experienced many difficulties after knowing their result was positive. Alternatively, those who found that their result was negative also experienced survivor's guilt if a relative's result happened to be positive*" (Essay 879, Defer).

Anxiety and *Depression* were present in both arguments made for and against deferring genetic testing. These themes were brought up in the context of eventually knowing one will develop HD status from a positive test result as demonstrated by the following statement, "*Realistically, the frustration and helplessness derived from the idea that the deterioration of their lives is inevitable would likely lead to depression and anxiety*" (Essay 1153, Defer). *Anxiety* was also brought up in the context of not knowing what the future holds by not pursuing genetic testing, "*deferring a genetic test for an adolescent suspected of carrying a disease places uncertainty on that individual, which results in negative emotional effects such as excessive worrying and anxiety*" (Essay 1094, Not Defer). Many students acknowledged that regardless of if they agreed or disagreed with ASHG's position statement, there were potential psychological consequences.

No Medical Benefit/Not Preventable

The most common theme used in all HD essays was *No cure*. The discussion found in essays where students argued to not defer testing for HD commonly discussed potential treatment, "*There is no cure for Huntington's Disease (HD) but there are treatments to reduce its symptoms*" (Essay 636, Not Defer). In the "Not Defer" essays, students often discussed the lack of cure, but then commented on the availability of treatments. "*Even though a cure has yet to be discovered, there are steps that can be taken to slow down the progression of the disease*" (Essay 1146, Not Defer). This was in contrast to the discussion found in essays where students argued to defer testing, the *No cure* theme was often used in the context of death, "*HD is fatal, and there is no cure*" (Essay 585, Defer). In some of the cases, there appears to be a lack of knowledge about the availability of treatment, "*As this is a fatal disease with no cure, receiving a positive test is sometimes seen as a death sentence*" (Essay 387, Defer). Even in situations where the students acknowledged the availability of medical treatment, the fatality of the condition was discussed in essays where the student encouraged deferral, "*There are some medications for Huntington's disease, but, ultimately, none of the medications can completely prevent the symptoms or the imminent death caused by the disease*" (Essay 498, Defer). This contrast in the way in which the *No cure* theme was used in "Defer" and "Not Defer" essays suggests that there are some students who felt that the therapies were good enough to warrant testing, while others were either unaware of therapies and/or felt that the current treatment is insufficient at this time for them to pursue genetic testing.

Another common theme within the code, "No Medical Benefit/Not Preventable," was *Treatments can't slow down/stop illness*. This was the second most common theme in essays that chose to not defer testing for HD, whereas it was fourth most common theme in essays that chose

to defer testing for HD. In the "Not Defer" essays, the theme *Treatments can't slow down/stop illness* was used in a much more hopeful manner, "*No treatments of our generation are able to alter or slow the effects of Huntington's disease*" (Essay 897, Not Defer). This student was discussing the lack of treatment, in the context of the current "generation," which implied that there might be changes in the future generations. Another "Not Defer" essay said, "*as of now, there is no treatment that can alter the course of Huntington's disease*" (Essay 806, Not Defer). Several of the students referenced the treatments in the context of current time, implying that there is hope for future improvements to treatment, "*As of today, there are no treatments that have the capability of curing the fatal disease*" (Essay 367, Not Defer). This may represent how some students showed dispositional optimism with regards to the future of medicine, while others focused more on the risks. Some research has found that individuals who are high in optimism are actually more knowledgeable about risk factors than those who had less optimism (Carver et al., 2014). A student who chose to defer testing wrote, "*Maybe someday, when there are treatments for HD, adolescents should be tested in hopes of being able to fight the disease before it attacks. But currently, there are none*" (Essay 1226, Defer). Interestingly, this student who wrote in favor of the deferral of testing, recognized that there is some hope from improvements in treatment, but they feel that testing should be deferred until such time. In comparison, in the essays that chose to defer testing, many of the students used this code in conjunction with the psychological risk to minors, "*However, since there is currently no way to prevent, cure, or slow the progression of this disease, testing a child may cause more harm than good, for both the child and the parents*" (Essay 480, Defer). Another student wrote, "*determining early in life that the child will develop HD later on does not benefit them in any way since there is no treatment that can reduce the risk or change a child's outcome of*

developing HD" (Essay 841, Defer). Students who wrote in favor of deferring testing often wrote about how there is no benefit, but rather a risk to the child, since there is currently no treatment available.

Necessary to Plan/Prepare

The variety in themes that emerged under the "Necessary to Plan/Prepare" code illustrated the depth of insight these minors have with regards to their future. The majority of writers who discussed this concept chose to argue in favor of not deferring testing until adulthood, suggesting that they think the information gained through genetic testing for HD is valuable during their teen years. This is a time in their life where they are already planning for things, such as starting a family and accomplishing long term goals. Even though these minors are children in the eyes of some, they are already beginning to speculate what a future family might look like for them and how to best plan for the genetic health of that family, "*Also, having the understanding of the possibility of developing a hereditary disease would prepare adolescents ahead of time of the risk of passing on the faulty HD gene to their own offspring. This prior knowledge could assist adolescents, later in life, when making decisions concerning conception*" (Essay 705, Not Defer).

In addition to family planning, minors expressed the desire to adapt their life goals and financial situation to best suit their future health. Even students who argued overall to defer testing still acknowledged its potential benefits in adolescence, "*a negative result would provide reassurance, whereas a positive result would allow for more realistic goals*" (Essay 450, Defer). Another writer stated, "*Adolescence is in fact a superior time to discover such as disease because more time is available for planning, whether social, personal, or especially financial*" (Essay 609, Not Defer).

Genetic Testing Variability and Uncertain Predictability

It is well-known in the medical community that the genetic test for HD is highly accurate, and a positive result almost certainly means that an individual will develop symptoms of HD in the future. Despite this inevitability, the test cannot predict when the symptoms will begin. Interestingly, roughly half of the "Defer" and "Not Defer" essays that used the code "Genetic Testing Variability and Uncertain Predictability" discussed *Uncertain predictability of symptoms*. Most of the time, the students talked about how the test cannot predict the age of onset, the severity of the symptoms, or the progression of the disease, "*However, genetic testing cannot determine when the symptoms will develop in their intensity and severity*" (Essay 378, Not Defer). No one identified this as the main reason why they chose to "Defer" or "Not Defer." It was mainly used as factual information to describe the genetic test for HD.

The theme *Intermediate range of repeats*, similar to *Uncertain predictability of symptoms*, was mainly used to describe the genetic test for HD and what it entailed. In this theme, individuals talked about how the 36 to 39 repeat range was considered the gray area, where it is unknown if someone would be affected in the future. Quotes from this theme often also cited the unpredictability of the symptoms, but more in terms of whether or not someone would truly be affected, rather than the uncertainty of the onset of symptoms, "*There is some uncertainty with the HD DNA testing; for example, some individuals with CAG repeats from 36-39 never develop symptoms for HD, while others develop symptoms*" (Essay 1074, Defer). Only about half the essays that used this theme also mentioned that getting this uncertain result is rare and only happens in about 1% of cases. Interestingly, a couple of essays used this uncertain result to determine that the test is not accurate, "*Some people with counts between thirty-five and forty have developed Huntington's and others have not, so such a count is considered an*

inconclusive result. This gray area means that the test is not entirely accurate" (Essay 1201, Defer). They interpreted test accuracy in terms of sensitivity rather than as a measure of the test correctly calling the number of repeats.

Of the essays that used the code "Genetic Testing Variability and Uncertain Predictability," about 29% of the "Defer" essays and 17% of the "Not Defer" essays cited the theme *Not 100% accurate/certain*. Although the genetic test for HD is highly accurate, many essays focused on the fact that the test is not 100% accurate, citing human and technical errors that may occur, "*This genetic test for HD is 98-99% accurate, leaving one or two percent chance of inaccuracy only due to the possible, unavoidable errors that may occur in laboratory procedures*" (Essay 552, Defer). There might be confusion about the definition of accuracy because some essays described how the test is not accurate because it is not truly predictive and only provides an increased risk of developing HD, "*Several genetic tests can only give a possibility for a condition and not full certainty, making them unreliable*" (Essay 322, Defer). Many of the "Defer" essays that had the theme *Not 100% accurate/certain* used it as one of their reasons to defer testing, "*Another example of unnecessary stress due to premature testing is worrying despite the possibility that one will not develop Huntington's at all. Even though the test is reliable, it is not 100 percent accurate*" (Essay 364, Defer).

Limitations

The ASHG DNA Day essays used in this study were a convenience sample which had a few limitations. While many of the essays were submitted from the United States, it is unclear whether essays were self-submitted or a teacher assigned this to the entire class and hand-selected the best ones to submit. As discussed in Phase one of this study, there were disparities in the demographics of this data. Females represented 67% of the submissions and although 87% of

submissions were from the United States, not all states were represented equally and some were not represented at all; thus, this was not representative of all adolescents.

CONCLUSIONS

Adolescents were split as to whether or not genetic testing for HD should be deferred until adulthood, with a majority favoring deferral. Although they were required to argue for or against deferring genetic testing for HD until adulthood, most students discussed similar points, regardless of their stance. Many were able to consider their lifestyle, values, and goals in their decision-making, but there were occasions when they misunderstood or were not fully aware of specific information, such as medical management and test accuracy. This exemplifies the importance of genetic counseling in the pre-test protocol to make sure that adolescents are well-informed and mentally prepared to receive genetic testing results. Although many professional organizations recommend the deferral of genetic testing for adult-onset conditions until adulthood, there is some flexibility in the timing of testing minors on a case-by-case basis. In order to provide assent for testing, adolescent perspectives must be considered to determine whether the benefits of testing truly outweigh the risks.

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