

High School
Human Genome Program
Ethics

Presymptomatic Testing for Huntington's Disease

Robert W. Hansen, M.S., Pharm.D.

Sharon J. Durfy, Ph.D.

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Introduction

Welcome to the High School Human Genome Program's Huntington's Disease Ethics Module. As you may be aware, the High School Human Genome Program includes both scientific and ethics components, paralleling the organization and efforts of the national Human Genome Project.

In this ethics unit, ethical issues associated with predictive testing for Huntington's disease are examined. Students are asked to pretend they are one of five siblings in a hypothetical case, each of whom are deciding whether or not to have presymptomatic testing for Huntington's disease. As much as is possible, the issues represented by the case scenario, and the materials provided are true-to-life, that is, they reflect the current state of scientific and clinical understanding of Huntington's disease and represent the types of dilemmas faced by individuals considering presymptomatic testing.

However, the main point of this exercise is not to have students engage in an approximation of genetic counseling. Rather, the goal is to have students use the provided ethical decision making model and supporting materials to arrive at a personal stance regarding the dilemmas presented in this case, and to be able to justify their stance.

This ethics package contains a hypothetical case, background materials and figures on molecular, genetic, clinical, and ethical aspects of Huntington's disease and predictive testing, the ethical decision making model, positive and negative laboratory reports for each character in the case, and exercises in pedigree construction and determining trinucleotide repeat length (the basis of the predictive test). We have also included a description of how these materials were used in four Seattle classrooms during the fall and winter of 1994-1995, and teacher and student comments and reports about the use of these materials. Finally, we have included a resource list of places teachers and students can go for more information about Huntington's or genetics and genetic testing in general.

We hope you have success with this High School Human Genome Program Ethics Module, and that you enjoy using it. This ethics module is a work in progress, and we welcome any comments, questions and ideas you may have. We'd love to hear first hand about your experiences with it. Please contact us.

Sharon J. Durfy, Ph.D. Research
Assistant Professor, Department of
Medical History and Ethics,
Box 357120, University of Washington,
Seattle, WA 98195-7120
sjdurfy@u.washington.edu

Robert W. Hansen, M.S., Pharm.D.,
Clinical Research Associate
Immunex Corporation
51 University Street
Seattle, WA 98101-2936

Using These Materials in the Classroom

BACKGROUND

The High School Human Genome Program includes both scientific and ethics components. The ethics component is valuable because it fosters a discussion of the ethical questions arising from genetic research, complements the scientific component of the program, and results in a format that parallels the organization of the national Human Genome Project. The potential for research in genetics and genetic testing to ultimately affect all persons in society underscores the value of having students who are involved in the study of genetics consider the ethical issues that are associated genetic technology. The ethics module presented here challenges students to consider their personal stance regarding presymptomatic genetic testing for HD. This module provides students with an ethical decision making model that they can use as a guide when considering the social and ethical implications of undergoing a genetic test.

This exercise examines the issues surrounding predictive testing for HD and asks students to decide whether or not, as a particular character in a scenario, they would choose to be tested for HD. Students work through a decision making model, justify their decisions, and have the opportunity to receive mock lab results. Various materials have also been included in this module to support the decision making process. As much as possible, the case scenario and the supporting materials are true-to-life. That is, they reflect the current state of scientific and clinical understanding of HD as well as the types of dilemmas that individuals face when considering presymptomatic testing for HD. The supporting materials include modified versions of documents and reports that are used in the University of Washington Genetics Clinic. However, the main point of this exercise is not to have the students engage in an approximation of genetic counseling. Indeed, the core component of this exercise, the ethical decision making model and process, is not included in genetic counseling sessions and could be applied to many types of ethical questions, not merely those genetic in nature. The goal of this exercise is to have individual students use the decision making model to arrive at a personal stance regarding a dilemma presented in the case, and to be able to justify this position. It would be possible to meet this goal without providing the hypothetical test results to students. We chose to provide test results to students in order to model the entire testing process and to reflect the true-to-life necessity of living with the results of a decision about an ethical question.

The ethics portion of the curriculum was tested during 1994-1995 in four schools in the Seattle area. A formal evaluation of the ethics materials is currently ongoing and will be made available shortly. In 1994-1995, class sizes ranged from seven to thirty students and class periods ranged from 55 to 110 minutes. Because of the great variability in class size and length of class period, the ethics unit was designed to be adapted to each individual class. Thus, participating teachers were given a great deal of flexibility in presenting the

materials and the decision making model in a way that would suit the particular characteristics and needs of their classes. Despite these variations, however, there are three core components to the unit that were presented to all of the classes. These core components included: (1) an introduction to the genetics and clinical aspects of HD, (2) an introduction to ethics and ethical decision making, and (3) the testing decision and receiving of test results. See the accompanying figure for a schematic representation of these core components. This figure represents these components in a linear fashion, however, in our experience, teachers presented the materials in many diverse ways.

CORE I: Genetics and Clinical Aspects of Huntington's Disease

The first component of the ethics unit is intended to facilitate a coherent and logical transition from the laboratory sequencing activities of the science unit to the classroom discussion of the ethical issues arising from biotechnology. One important way of making this transition is to have the students consider how the technology they use in the laboratory portion of the science unit might impact the lives of people (including the students themselves) outside of the laboratory. To bridge the gap between the specifics of DNA strands and nucleotide base pairings on the one hand, and questions about the use of genetic information by individuals and society on the other hand, genetic screening was chosen. In particular, HD was chosen as an appropriate model because the HD gene has been identified and the mutation has been characterized. Also, there has been a significant amount of attention paid to the ethical aspects of testing presymptomatically for HD. Furthermore, many resources exist for teachers in this area, including an abundance of literature and videos that teachers can incorporate into their presentation of the ethics unit.

The first component of the ethics unit involves presenting students with information about the genetics of HD and its clinical course either through an assigned reading of the background materials, through classroom lectures, or both. At this point several videos of various lengths can be shown to enhance student understanding of the disease itself and how people who carry the HD gene mutation are affected by both the disease and having to decide whether to be tested presymptomatically for their HD status. After this process, students are presented with a hypothetical case of a family affected by HD and asked to draw the family's pedigree using the format for pedigree construction that was provided to them. Finally, students are asked to assume the role of one of the characters in the case scenario and to consider whether they would want to be "tested" for the HD gene mutation. Students are told that as part of the unit they will have to come to a decision about whether to be tested and that they will have an opportunity as part of the unit to receive mock lab results for the characters whose roles they were assuming.

In our experience, students who experienced the entire unit found that receiving mock test results was a very stimulating and valuable experience. A large number of students suggested that they would like more time to consider the individual characters whose roles they were assuming. One suggestion made was that students be assigned a role at

the beginning of the unit so as to allow more time to fully understand the character they were portraying. Students can be assigned roles early on in the discussion (immediately after reading the case scenario) and then can write a personality profile of the character assigned to them. These approaches allow students to further identify with the characters in the case and provides students with more "factual" information about the characters than the case itself could provide.

CORE II: Ethics and Ethical Decision Making

The second component of the unit involves a general discussion of the ethical issues that are manifested in the case. Each of the five characters can be examined to clarify the ethical conflicts or problems that are associated with their decisions whether to be tested for the HD gene mutation. Students are asked to consider how they make such difficult decisions in their everyday lives and how they justify these decisions. In our experience, many students had a difficult time clearly articulating their method of arriving at and justifying decisions involving ethical issues. Many relied on their moral intuitions about what was right or appropriate and others relied on a personal value system. Next, students are introduced to the Hastings Center model for ethical decision making which is intended to provide a logical framework for arriving at ethically justified solutions to ethical problems. Students are asked to consider the most important ethical issue that influences their characters' decision to be tested presymptomatically for the HD gene mutation. They are then encouraged to use the model when considering whether, as the character in the case, they would want to undergo testing. To demonstrate how the model is used, we suggest working through the ethical issue(s) faced by one of the siblings in the case as an example. Depending on class size, the model can be demonstrated to the entire class or within small groups. If small groups are used, students can be asked to report to the class how they had resolved the dilemma and to defend their decisions against counter arguments raised by other groups. Once students are familiar with the issues raised by the case and the model for ethical decision making, they then use the model to help them determine whether they, as characters in the scenario, should undergo testing.

CORE III: The Testing Decision and Receiving Test Results

In preparation for the third component, students are given a list of questions that are routinely discussed with individuals who undergo the genetic counseling process associated with the presymptomatic testing for a genetic disorder. Reviewing these questions insures that the students have fully considered all of the issues surrounding the decision to be tested, as well as the consequences of that decision. There are several ways to structure the class to consider these questions- for example, in groups by character or in family groups. Students are also given a copy of an informed consent form and asked to read and sign it prior to receiving mock test results. This provides an opportunity to discuss the purpose of an informed consent procedure and mirrors the process that actually occurs in real testing situations.

The third component of the unit consists of having the students determine whether they want to receive the results of their characters' genetic test, to justify their decisions using the principles or values identified during the decision making process, and in that way resolve for themselves the corresponding ethical issues. Our teachers provided mock test results to either individual students or small groups by taking them aside or to an adjoining office to receive their test results. Before giving results, students are first asked if they have any final questions about any feature of the testing process or HD itself. Students are then asked if they have considered the discussion questions and how they think they would react to receiving results indicating the presence or absence of the HD gene mutation. Once any questions are answered a brief overview of informed consent can be given and students who choose to receive mock test results are asked to sign their consent forms if they have not already done so. Students who choose not to receive test results can be excused from the rest of the exercise and told that they can receive their results in the future if they so desire. Students who feel pressure to receive test results (either as characters in the case scenario or as students undergoing the educational exercise) can also be excused from the exercise at this point. Students who decide to receive their results are given copies of the mock lab report. The three sections of the lab report are explained to the students and any further questions can be answered. In our discussions with students, an attempt was made to reinforce the fact that for the purpose of this exercise, these reports, like actual medical reports, are confidential and that students need not reveal their characters' status to any other students if they did not desire to do so. While it may seem silly to take the reporting of mock test results so seriously, we found that students who were presented with test results in this manner were deeply impacted by the exercise and enlightened by its realism.

We made an effort at the end of the ethics unit (which in our experience ranged from three to five days) to discuss as a group the experience of having to decide whether to be tested for HD and how receiving test results impacted students' views about having access to this kind of technology. At this point in the exercise students were very eager to discuss how they felt and the implications of policy decisions surrounding access to this technology. Our students suggested that more time be spent discussing the results of the testing process. This is a good point in the exercise to introduce students to existing resources where they can receive more information about other genetic conditions that might interest them.

Flowsheet: Core Components of the HD Ethics Module

CORE 1: Genetics and Clinical Aspects of Huntington's Disease

Introduction to High School Sequencing Project's Ethics Module



Presentation of Background Information on HD and Video



Presentation of Klein Family Case Scenario



Pre Ethics Unit Exercise (Initial Assessment)



Pedigree Construction: Exercise



Assignment of Roles to Students

CORE 2: Ethics and Ethical Decision Making

Introduction to Bioethics



Distribution of Discussion Questions & Informed Consent Forms



Student Assignment: Make and Justify Testing Decision

CORE 3: The Testing Decision and Receiving Test Results

Determining Repeat Length: Exercise



Presentation of Test Results



Class Discussion of Results



Administration of Post-unit Evaluation

Ethics Unit Assessment

GENERAL DESCRIPTION

In developing this ethics unit, one of the goals was to equip students with a method for arriving at reasoned and justifiable conclusions and to make sound decisions based on those conclusions. To assess whether the ethics unit is successful in achieving this goal and to evaluate the strengths and weaknesses of the ethics unit as an educational tool we have developed two exercises. The purpose of these exercises is to examine how students reason through a case scenario before they participate in the ethics unit and to compare these results to students' reasoning abilities immediately after their participation in the ethics unit. By determining students' baseline reasoning abilities and comparing them to their level of reasoning immediately after completion of the ethics unit, we can assess whether the unit was effective in improving students' capacity to reason through ethical cases.

During the 1995-1996 school year, we collected data on students' reasoning abilities prior to and immediately after their completion of the ethics unit. Analysis of this data is currently underway and we hope to submit the data for publication in the near future. In this section we provide the evaluation tools that we used in our data collection, in case some teachers wish to use these exercises with their students. The first is an assessment that is designed to be administered to the students after the background materials on HD have been presented but before the decision making model is discussed (see core components figure in the previous section). Students are asked to refer to characters in the Klein family case scenario in answering three questions about the case and are given twenty minutes to answer these questions. The second assessment is designed to be administered to students immediately upon completion of the entire ethics unit. Students read a second brief HD case and are asked to answer three questions about this case, again in a twenty minute time period.

**High School Human Genome Program Ethics Unit
INITIAL ASSESSMENT**

Directions: Please refer to the Huntington's disease case in your packet to answer the following questions. You will have approximately 20 minutes to complete this exercise.

In the case, Sara and Lauren Klein are monozygotic (identical) twin sisters who are considering whether to be tested presymptomatically for the gene mutation that is associated with Huntington's disease. Please answer the following questions, which deal with the twin sisters' decisions regarding whether to undergo genetic testing. If you need extra room, use the back of the page.

1. What, if any, ethical issue(s) are involved in the twin sisters' decisions regarding whether to undergo presymptomatic testing?

2. (a) What is/are the ethical principle(s) or values involved in the sisters' decisions? (b) List all of the possible solutions or alternative approaches that Sara and Lauren might choose.

3. If you were Sara or Lauren, what would you choose to do and how would you justify your decision?

High School Human Genome Program Ethics Unit
FOLLOW-UP ASSESSMENT

Directions: Please read the following case scenario and answer the following questions. If you need extra room, use the back of the page. You will have approximately 20 minutes to complete this exercise.

Pam Morris is a genetic counselor affiliated with the Union University Medical Center. Pam was recently contacted by Krista Klein-Hunter about presymptomatic testing for Huntington's disease. Krista's father, Jack Klein, died of Huntington's disease three years ago. Krista is pregnant and wants to discuss her options with regard to presymptomatic testing and the potential impact testing may have on her life. Pam met with Krista and her husband, Tim, to discuss the testing process and experience. Before he died, Jack Klein's blood was stored in a DNA/blood bank in case it would be of use to his children. Ruth Klein has indicated she would be happy to provide a blood sample should any of her children choose to be tested. If she decides to proceed, Pam expects that using DNA from both parents will generate a very clear picture of whether or not Krista has inherited the HD gene mutation.

After considerable deliberation, Krista decides to be tested and a blood sample is taken. The testing laboratory received blood samples and signed consent forms from Krista, blood from her mother, and the banked blood from her father and initiated testing. Some time later Pam was contacted by a laboratory staff member, who asked if there could have been a sample mix up during the blood collection. The results indicated that Krista had not inherited an HD gene mutation, but the results suggested the reason for this was nonpaternity for Krista's sample, that is, that she was not the biological daughter of Jack Klein. How should Pam handle this information?

1. What, if any, ethical issue(s) are involved in this case?

2. (a) What is/are the ethical principle(s) or values involved in this case? (b) List all of the possible solutions or alternative approaches that Pam might choose.

3. If you were Pam, what would you choose to do and how would you justify your decision?

Bioethics and Ethical Decision Making: Tips for the Teacher

INTRODUCTION TO BIOETHICS

Many of the advances made in the medical sciences have greatly influenced how medicine is practiced. Often this has occurred through the development of technology. Examples of such technological applications of biomedical advances include the development of mechanical ventilation, hemodialysis, organ transplantation, and more recently testing for genetic disease. While these technologies were designed to be beneficial, they also have raised a number of profoundly difficult questions. For instance, under what circumstances, if any, can life-sustaining technologies be removed? Who should benefit from these technologies when they are limited by cost or demand? Because tests are now available for a number of genetic disorders, should they be widely used?

Questions of this sort are particularly difficult to answer because they force us to examine the principles and values that guide our lives and our society. In addition, these questions challenge us to justify the values and principles we hold in light of new and changing circumstances. Since the 1960s a discipline has developed which attempts to understand and examine the moral questions associated with the biological sciences and health care in general. This discipline, called biomedical ethics or bioethics, has developed in large part as a consequence of the advances in medical science and technology, as well as the unique moral problems that have resulted from these recent advances.

In an effort to more fully understand what bioethics is, it may be instructive to distinguish between two terms that are commonly used interchangeably. "Morality" is used to refer to a set of social conventions about what is right and wrong human conduct. Thus, morality usually refers to practices, actions, or customs that are widely shared by a stable community or group. "Ethics" refers to the field or discipline that examines the reasoning and rationale behind such customs or practices. As a result, ethics is concerned not only with actions but also with theory and with the examination of the nature and function of morality. In addition, ethics takes on a formal or logical structure that attempts to achieve a perspective that is more universal and more detached or objective than the perspective that is found at the level of morals.

Bioethics, therefore, is concerned with the scholarly examination and study of the legitimacy and appropriateness of certain actions or forms of conduct that are unique to the biomedical sciences. Bioethics uses ethical principles, theories, and paradigm cases of appropriate behavior in developing guides to action within the realms of medicine and health care. As medicine and health care change and challenge our commonly held conceptions of what should or should not be done in meeting society's health needs, bioethics seeks to provide a structure for examining and evaluating our moral judgments in light of these challenging new situations.

Why should bioethics be studied as a unique discipline? In his *Morality and the Good Life*, Solomon outlines several reasons why ethics should be studied (Solomon 1992). Following this example, there are at least four good reasons for studying bioethics:

1. The advent of life-sustaining technology has fundamentally changed the choices people must make regarding their health care. Furthermore, the medical decisions we make may impact a great number of other individuals. Therefore, when choosing among possible courses of action, we should be prepared to justify and defend the choices we make. Bioethics provides us with the means by which we can come to better decisions and to justify those decisions.
2. The social conventions about what is right or wrong human conduct are continually changing, especially with respect to medicine. Not long ago, for example, medicine was very paternalistic. Patients rarely questioned the judgment of their physicians and did not participate in the medical decision making process. Often physicians made decisions for patients without seeking input from the patient about his or her own preferences. Thus, practices that were widely accepted years ago are seen as morally inappropriate today. Bioethics allows us to understand the changes that have taken place and to examine the stable values that underlie these changes.
3. Ours is an ethically pluralistic society. Many different values, rules, and cultural traditions exist within our society. Certain bioethical issues, such as abortion and euthanasia, serve to point out the pluralism in society. Bioethics attempts to understand the nature of these differences and to provide a forum where different moral judgments can be evaluated.
4. Sometimes ethical values and principles conflict. For example, an individual's right of privacy may conflict with another individual's right to be informed. When confronted with such conflicts a re-evaluation of the priority of values and principles must occur. Bioethics provides a means by which these values and principles can be balanced against one another in the context of medicine and health care.

References

Solomon RC. *Morality and the Good Life: An Introduction to Ethics Through Classical Sources*. New York, NY: McGraw-Hill, Inc., 1992.

THE USE OF AN ETHICAL DECISION MAKING MODEL

Introduction

Teaching bioethics to high school students can be a challenge for a variety of reasons. First, bioethical issues are complex matters that raise very serious questions about our personal freedoms, our obligations to others, our values, and the consequences of our actions. The difficulty of bioethical dilemmas and the tendency of one ethical question to give rise to several other ethical questions are factors that add to the challenge of ethics instruction. Second, because of this complexity, high school teachers may feel uncomfortable or may avoid introducing bioethics into their classes. Finally, teaching bioethics can be challenging given that not all students share our enthusiasm for it and may find its complex nature frustrating.

The Case-Study Approach

One approach to teaching bioethics that teachers of applied ethics have found useful is the case-study approach. This method involves working through a bioethical case drawn from real life situations using a model for ethical decision making as a guide. This two-pronged approach (case scenario and decision making model) addresses the aforementioned concerns in the following ways. First, the case scenario limits the philosophical complexity of the issues raised by providing facts and details relevant to the decision at hand. Oftentimes, a case will deal with a very specific bioethical issue and in doing so avoids other serious, but unrelated concerns. Second, since case scenarios do not deal exclusively with abstract philosophical questions, they generally are more interesting to students. Thus, case studies tend to be more stimulating and relevant to a larger number of students. Finally, incorporating a systematic process of ethical decision making provides teachers with a way of thoroughly examining these very complicated bioethical issues. Such a model provides a framework for reasoning through a case to a morally justified conclusion. Having such a system may allow otherwise reluctant teachers to introduce bioethics instruction into their classes.

The Hastings Center Model

The ethical decision making model used in this unit was developed at the Hastings Center (Campbell et al. 1990). It is a six-step process that involves: (1) identifying the ethical questions raised in the case, (2) gathering and assessing all the facts that are relevant to the decision, (3) identifying who has a stake in the decision, (4) identifying all the values that play a role in the decision, (5) identifying possible solutions and (6) choosing the better solutions for this particular case, justifying them, and responding to possible criticisms. To further explain the process and to relate how it has been used in the classroom with this unit, each of the six steps will be briefly discussed.

Step 1: Identifying the Ethical Questions Raised in the Case

The first step involves identification of the ethical problems the case raises. Once the problems have been identified, one must decide which problem is to be considered. In other words, what is the ethical question the actor in the case must decide? Clearly, many different kinds of questions are raised in bioethical cases. Some are ethical questions, while others are legal, medical, social, or psychological questions. Each of these types of questions requires a different type of analysis, however. Thus, in identifying the ethical question to be analyzed one must make certain that it is a bona fide ethical question. This is not always an easy task. Certain key terms may suggest, however, when a question is an ethical question. These terms include: "right" (in terms of entitlement), "responsibility", "duty", "ought", and "should". A common element to ethical questions is that they raise concerns about what is appropriate conduct in a given situation and/or directly refer to the rights or interests of others.

Step 2: Gathering and Assessing all Relevant Facts

The second step in the decision making process involves assessing the facts that are available to the decision-makers. At this step it is important to address the non-ethical issues raised within the case. For example, one may need to know the legal constraints of the decision. Furthermore, the likely legal, medical, or social consequences of a proposed course of action must also be considered. In addition to the facts that are readily available, a decision-maker should also consider what factual information is not presented in the case but that is important to the decision and how this information can be obtained.

Step 3: Identifying the Stakeholders

Step 4: Identifying the Values That Play a Role in the Decision

The third and fourth steps involve identifying the stakeholders and identifying the values at stake in the decision. Stakeholders include those individuals who will be affected by the decisions to be made. Stakeholders could include individual people (both existing and future), collections of people, like societies or organizations, non-human beings, and entities, such as the environment. Values are concepts, goals, or standards that are important to consider when choosing between competing courses of action. These include, but are not limited to, beneficence, justice, autonomy, truth telling, and caring within interpersonal relationships. While each of these values should be considered in every case, they will vary in their importance depending upon the circumstances and facts of the case at hand. Often it will not be difficult to discern values that are in conflict.

Step 5: Identifying Possible Solutions

The fifth step is to develop and assess the options that are available to resolve the conflict, that is, to answer the question, "What could be done?" Students are asked to be

as creative as possible in coming up with a list alternative solutions to the problem, even if these include options that are obviously ethically unacceptable. (Demonstrating why an option is unacceptable or unjustified can be a very valuable exercise.)

Step 6: Choosing the Better Solutions and Justifying Them

The sixth step is to consider what should be done. At this point one identifies those options that are ethically acceptable by eliminating the unacceptable or unjustified options from the list of possible solutions. It may be that a range of actions is acceptable. In that case, those options that are preferable can be identified and justified in terms of the values that these options support.

It is useful, in conclusion, for the student to consider the decision making process as a whole. Was the process fair? Were the interests of all the stakeholders represented or considered? In many cases the solution that results from the stepwise application of a decision making model is the same as one's initial or intuitive belief about what should have been done in the case. In these cases, therefore, the value of the decision making model is not found in the solution that came as a result of using the model, rather it is in the thoughtful justification for the proposed solution that the model provides.

References

Campbell C, Donnelly S, Jennings B, and Nolan K. *New Choices, New Responsibilities: Ethical Issues in the Life Sciences*. Briarcliff Manor, N.Y.: Hastings Center, 1990.

Template for Decision Making

<i>Identify the ethical question(s) raised by the case</i>	<i>List all the relevant facts of the case</i>	<i>Identify the stakeholders and values that play a role in the decision.</i>	<i>List several possible solutions to resolve the conflict. (What <u>could</u> you do?)</i>	<i>Choose the better solution(s) and justify them. (What <u>should</u> you do?)</i>

CONDUCTING DISCUSSIONS OF ETHICAL ISSUES

1. Listen carefully to what students are saying when they argue a particular issue. Be patient and allow students to express their views fully.
2. Take notice of the words that students use in arguing their positions. Often the choice of words will reveal a bias or an unquestioned assumption.
3. Ask clarifying questions. Many students will express important ideas that are rough or unclear. Asking students to define their terms or to reword their statements may help students hone their ideas.
4. Make distinctions that will further the analysis. For example, if students are discussing duties, ask them what kinds of duties they want to include or emphasize in their arguments. Are they referring to legal duties, professional responsibilities, or ethical obligations? To whom is the duty owed? To oneself or to others?
5. Look for logical inconsistencies or fallacies in the students' arguments. Do the premises of the argument support the conclusion? Do they support any other conclusions? Are the premises true? Are there unquestioned or hidden assumptions that influence the argument? Are the students committing the "naturalistic fallacy", i.e. using statements of fact to justify or support their moral judgements? This is also called the fact/value distinction and requires a leap in logic from "IS" statements to "ought" statements.
6. Ask yourself whether a student's comment is supportive of an ethical theory, e.g. utilitarianism or rule-based theories. Challenge them to consider the shortcomings of that theory and how an alternate theory might address the issue.
7. Challenge students to take an opposing view or to be critical of their own view. Ask them to consider the weaknesses of their arguments. How confident are they in their decisions? What, if anything, makes them uneasy about their views?
8. Ask students to justify their views or the statements they make. If the response is "I just feel that way" or "I just know it's right", ask them to explain why. Many times students will refer to principles or values to justify their views, and these provide more justificatory power than do feelings or intuitions. If no principle or value emerges, challenge students to consider whether their emotive responses or intuition are wrong.
9. Provide balance. Play the devil's advocate. Don't let the argument be decided by the strength of a student's personality or by the loudness of an argument.

10. Check whether to see if this is a redundant view. Has it been represented already in the discussion? Keep the analysis as simple as possible.
11. Be on the lookout for frustration. If you sense a student is becoming frustrated, ask him or her to express this frustration. Many times this will lead to interesting and important ideas.
12. Stick to the case. While departing from the case may be useful sometimes, letting the discussion go to far afield can be dangerous. You may create a discussion that is difficult to direct. Stick to the facts of the case. Many of the facts will limit the number of issues that need to be considered.

GIVING RESULTS: TIPS FOR TEACHERS

One of the valuable features of the High School Human Genome Program is its integrated science and ethics components. Students have the opportunity to participate directly in the scientific process and to reflect on how science and technology can impact their lives. The main purpose of asking students to decide, as one of the Klein siblings, whether or not to have presymptomatic testing for the HD gene mutation is to give students some insight into how these important decisions can be made. In addition, allowing students to choose whether to receive mock lab results provides them with an opportunity to go beyond intellectualizing the exercise and to internalize the experience. Our hope is to foster in students a greater understanding of the very difficult decisions that real people face when incorporating advances in genetics into their lives and how individuals cope with the consequences of their decisions.

Our experiences testing these materials in the classroom have shown us that some of the students were profoundly affected by the receipt of the mock lab results. In fact, a number of students expressed their surprise at how this role play exercise could move them so deeply. Because of the intensity of some students' reactions and the concern that receiving mock lab results might be troubling to a few students, we have developed the following tips for teachers. Of course, individual teachers who are familiar with their students are in the best possible position to determine how mock laboratory results should be presented to students and should use their professional judgement when doing so. The following are some suggestions from our classroom experience.

- **When giving mock results, plan your schedule to include a debriefing session for students to discuss their feelings about receiving their results.** Several students suggested more time be spent on follow-up discussions of this sort. You may want to ask students if they were surprised by their reactions to receiving results. Did they react the way they had expected? Do they regret receiving the results? Very often students will have further questions about HD or other genetic conditions at this point. Teachers should be prepared to refer students to additional resources for information or support. (See Resources section.)
- **When giving mock lab results and during the follow-up discussion, consider involving school counselors or other appropriate professionals when available.** In addition to fostering interdisciplinary collaboration, these individuals may be able to provide additional support to students and may serve as an additional resource to students who have questions.
- **Emphasize to students that they can opt out of the unit at any time.** There are several points during the unit where students are able to discontinue their participation if they feel uncomfortable. One point is before the unit is begun when teachers may initially ask if there are any students who feel uncomfortable discussing HD or other genetic disorders. This provides an opportunity to identify

students who may feel uneasy going through before the unit begins. After the decision making model students are asked to consider whether they would like to receive mock lab results. Anyone who feels strongly about not receiving these results can choose not to at this point. When students are to receive their mock results, they should be asked if anyone has changed their mind. Another point occurs when students are asked to sign the informed consent form.

- **Students who choose not to receive results can be given an opportunity to discuss or share their decisions.** It may be of great interest to others to hear why these students chose not to receive mock results.
- **Results can be provided in many ways, such as individually, in small groups, or to the class as a whole.** One possibility is to give results to a group of students, all of whom are playing the same character and all of whom request the hypothetical test result. For example, all those students playing the role of Krista can be given the same result in a group. Using this approach, a hypothetical test result indicating the presence of a HD gene mutation would not be identified with an individual student, but rather with the character in the scenario.

Finally, teachers can choose not to give mock lab results. In this case the exercise would end after the discussion of the decision making model. Students could be asked to hypothetically consider whether they would want to be tested for the HD gene mutation, as a particular character in the case, and could work through the decision making process and justification, but not be provided results. This option maintains the central component of the ethics unit -- the decision making model -- while de-emphasizing the receipt of results.

Classroom Materials I. Genetics & Clinical Aspects of HD

HUNTINGTON'S DISEASE CASE

James Klein is 17 years old and has just graduated from high school. Along with several of his friends, James will be entering college in the fall. Because he is so anxious to start college, the summer has been going very slowly for James. This weekend should be different, however, because James' older cousin, Jon, will be coming with his parents to visit the Klein family for the Fourth of July.

James' mom, Ruth, is particularly excited because several other relatives and all of her children will be home for the holiday weekend. Sara and Lauren, James' 21 year old twin sisters, will be coming home from their junior year in college. Another of James' sisters, Krista, who is 24 and works for a bank in another state, will be home with her husband, Tim Hunter. Krista is particularly eager to see her family because she and Tim plan on surprising them with the news of Krista's pregnancy. The oldest of the Klein children is Paul, who is 27 years old. He and his wife, Joan, will drive in from a neighboring town with their two children, Andrew and Grace.

The only member of the Klein family that will be missing is Ruth's husband, Jack. That is because Jack Klein died three years ago, when he was 47, from Huntington's disease (HD). At that time James was a freshman in high school and Sara and Lauren were freshmen in college. Like his father before him, Jack's symptoms declined from initial difficulty with coordination to finally requiring institutionalized care until his death from the disease.

In the last two weeks, Ruth finished all the necessary preparations for the holiday weekend. All of the Klein children have arrived home and are eagerly awaiting the arrival of their Aunt Susan, her husband, Steven, and their only child, Jon. Susan is their father's only sibling and she too has HD. A few years ago, Susan was having difficulty walking and because of the HD slurred her words slightly. Now, because of her loss of coordination, she is most comfortable using a wheel chair. Susan can still talk clearly enough to be understood by her close friends and family, although strangers would have a more difficult time understanding her.

Over the weekend, everyone had a chance to catch up on family news and to reminisce about their lives. The conversation eventually turned to how HD had affected the Klein family. When he was alive Jack had faced the disease with a positive attitude and a strong sense of humor. Remembering Jack's attitude toward the disease made it easier for the family members to discuss HD. Ruth asked Susan about her health and how HD had affected her family. Susan said that for her the hardest part of having the disease was knowing that she could have passed on the HD gene mutation to her son, Jon. For years,

her greatest fear was that he would test positive for the HD gene mutation and would ultimately develop the disease.

That is why she was so relieved when Jon was tested for the HD mutation two months ago, when he turned 18 years old, and found that he did not carry the mutation for HD. Jon admitted that the decision to be tested was the hardest he had ever had to make, but that he was very glad that he had chosen to be tested. The Klein children could relate to the difficulty Jon experienced in deciding whether to be tested. They knew that they each had a 50-50 chance of having inherited the single, dominant gene mutation for HD from their father, but so far none of them had been tested. Silently, they wondered if HD would affect anyone in their family.

Testing to determine whether the HD gene mutation is present, and thus whether symptoms of HD will arise at some point in the future, raises very complex issues. Therefore, the decision whether to be tested is left to each individual at risk for HD. Ruth Klein believes that her children should decide for themselves whether to be tested for the genetic change causing HD. A year ago, James and Ruth checked with their local genetics clinic about possibly testing James for the HD gene mutation. At the time, James was unsure whether he wanted to be tested, and after his father's death, he certainly didn't want to cause his mother any more pain. Ruth and James discovered that their local genetics clinic only recommends testing for people aged 18 and over. However, James will be turning 18 soon. He has often wondered how knowledge of his genetic status for HD would impact his plans for the future.

The question of whether to be tested for HD is a very difficult challenge for Sara and Lauren as well. They are monozygotic (identical) twins and, as a result, carry the same genes. Consequently, if Lauren were to be tested for the HD gene mutation, she would, in effect, also be choosing to have Sara tested, since their genes are the same. They have never directly discussed the issue with each other. Thus, Sara doesn't know for sure whether Lauren wants to be tested, and Lauren isn't certain about how Sara feels about being tested.

Krista and Tim also are thinking about HD testing. They know that fetal cells could be obtained from the amniotic fluid and tested to see whether the gene mutation for HD is present or absent in their fetus. Because the pregnancy is in its earliest stages, the fetus could be tested now and the pregnancy terminated if the fetus was found to carry the HD gene mutation. On the other hand, they don't know whether they should take the low risk of miscarriage associated with undergoing amniocentesis (approximately 1%) if the fetus does not have the HD gene mutation.

The couple has already talked to a genetic counselor about the possibility of testing their fetus for the HD gene. Krista has not been tested for the HD mutation yet, and is not sure whether she wants to know if she has it. Of course, if Krista does not have the HD mutation the fetus will not be at risk for HD. If she does carry the mutation, the fetus' risk

of having the HD gene is 50%. The genetic counselor explained that without knowing Krista's genetic status, the chances of the fetus carrying the HD gene are 25%, or one in four--Krista's risk of 50% (1/2) multiplied by the 50% (1/2) chance that a parent will pass on any gene to their offspring. If the fetus was tested and found to have the gene mutation, Krista would then know that she must have passed on the HD gene mutation and that she will therefore develop HD in the future.

Krista and Tim are currently trying to understand all these numbers and are discussing several options, including testing to determine Krista's HD status, testing the fetus only, or proceeding with the pregnancy and their lives without any genetic testing. If they choose to undergo testing, they wonder how information about Krista's status might impact their lives and what they would do if their fetus was found to carry the mutation for HD.

Paul is also worried about the impact that knowing his genetic status might have on the welfare of his family. Paul works as a paramedic for the Fire and Rescue Department in his town. He has not told his boss or his coworkers that he is at risk for HD because he is afraid that he might be forced to leave the job he loves. Paul is approaching the same age at which his father began to show symptoms. Every time he trips or drops something, Paul worries that he may be in the earliest stages of the disease. Recently, he also made a few errors in judgment while at work. The last time he was called to a rescue, for example, he made a wrong turn onto a one-way street, delaying the arrival of the ambulance at the scene by several minutes.

Even if these events are not early signs of HD, Paul is still worried that the Fire Department will find out about his 50% risk and will relieve him of his duties. This would mean a loss of his livelihood, his health and life insurance plans, and would affect his retirement benefits. Paul doesn't know if anyone else would hire him if he were found to carry the HD mutation, and is worried he wouldn't be able to get health insurance for himself or his family. His greatest fear is to have to go on public assistance.

Each of the Klein children are trying to decide whether or not to be tested presymptomatically for the HD gene mutation. In this exercise, you will play the role of one of the Klein children, and decide as that character whether or not you would want presymptomatic HD testing. There are many pieces of information that the Klein children need in order to make their decisions. You will find some of this information in the Background Materials.

HUNTINGTON'S DISEASE BACKGROUND INFORMATION

Clinical

Huntington's disease (HD) is an inherited neurological disorder which usually appears in mid life. In HD, nerve cells in a region of the brain called the basal ganglia die over a period of time (Quarrell 1991). These cells are involved in coordination, thought, and cognitive abilities. People with Huntington disease have chorea (involuntary movements; the disease used to be called Huntington's chorea), including involuntary jerking of the arms and/or legs and facial twitching or grimacing (Quarrell and Harper 1991). These movements are minor to begin with but progressively worsen to an incapacitating condition. People with HD also experience cognitive loss (although they retain awareness of their condition), difficulties in judgement, problems with speech, and often may have mood or behavior disturbances, including changes in work performance, emotional outbursts, and frequent depression (Martin and Gusella 1986). For most people, symptoms begin in their 30's to 40's, although onset of symptoms is variable, ranging from 2 to 75 years, and death usually occurs 10 to 20 years after symptoms begin (Harper 1991). There is no treatment to prevent the onset of symptoms or to alter the course of the disease. Medications may help symptoms but don't stop the progression of the disease.

Genetic

HD is a genetic disease that affects about one in 10,000 - 20,000 people (Harper 1991). It is an autosomal dominant condition, autosomal meaning that it is not linked to a sex chromosome (males and females are affected in equal numbers) and dominant meaning that only one gene change, or mutation, from one parent is required for disease symptoms to ultimately arise. A person whose parent has HD has a 50-50 chance to develop the condition themselves, and a 50-50 chance that they will pass on the disease mutation (if they have it) to their children. This does not mean that half of all the children of a parent with HD will have HD; rather, the chance of a each child inheriting an HD gene mutation is 50% with each conception. Thus, it is possible in some families that all children will inherit the HD mutation, and in other families that no children will inherit the HD mutation. The pattern of autosomal dominant inheritance is shown in Figure 1.

In 1983, the HD gene was localized or "mapped" to the tip of the short arm of chromosome 4 (Gusella et al. 1983), see Figure 2. The actual HD gene was isolated in 1993 (Huntington's Disease Collaborative Research Group 1993). The gene transcript is 10,366 nucleotide bases long, and encodes a protein, called huntingtin, that is 3,144 amino acids in length (Huntington's Disease Collaborative Research Group, 1993). One of the genes present in people with HD has a different structure than the genes carried by

people who do not have HD. Near the beginning of the HD gene, the DNA sequence contains a number of trinucleotide repeats, that is, three nucleotide bases that are repeated over and over again. In the HD gene, these bases are cytosine (C), adenine (A) and guanine (G) and they are repeated in the pattern CAGCAGCAGCAG and so on (Huntington's Disease Collaborative Research Group, 1993). CAG codes for the amino acid glutamine. People with HD have an HD gene that has more of these repeats than usual (although the absolute number varies from individual to individual). As a result, the HD gene in people with HD is longer than it is in people who don't have HD, and the protein produced by this gene is also larger than usual, with many copies of the amino acid glutamine. The biological significance of the extra copies of this trinucleotide repeat is not known, although researchers think that it may result in an effect on mRNA or protein functioning (Huntington's Disease Collaborative Research Group, 1993). (See Figure 2). Although the gene has been identified, and the protein sequence determined, the mode by which this gene and its protein are involved in the degeneration of the basal ganglia seen in HD is still unknown. Recently, however, researchers have shown that the protein glyceraldehyde-3-phosphate dehydrogenase (GAPDH) interacts with huntingtin (Barinaga et al. 1996). GAPDH is a key enzyme in glycolysis, the process by which cells convert the sugar glucose to energy. It is possible that the larger huntingtin protein may interfere with energy production in the brain by interfering with GAPDH, although this still remains to be demonstrated. Other research has implicated huntingtin in the cell death pathway. Cleavage of huntingtin in vitro by proteases involved in cell death has recently been demonstrated, and the rate of cleavage increases with an increasing number of trinucleotide repeats (Goldberg et al. 1996).

Understanding the structure of the HD gene allows a test to be developed to distinguish between genes that ultimately will cause symptoms of HD and those that will not. People who have or ultimately will develop HD almost always have over 39 copies of this trinucleotide repeat. People who do not and will not develop HD have 34 or less copies of this triplet sequence (Duyao et al. 1993; Kremer et al. 1994). This is illustrated in Figure 3. In this figure, you will note a very small degree of overlap in the middle, that is, a very few rare instances in which the gene with the HD mutation is smaller than expected and/or the non-HD gene is larger than expected. Examples of elderly individuals with repeats in this range who have not developed signs of HD have recently been reported, as have examples of individuals who have developed HD (Rubinsztein et al. 1996). In this intermediate range, it is not possible to make a distinction between a gene with a mutation that ultimately will cause HD and a non-HD gene.

Testing

a: the genetic test

With the discovery of the HD gene and understanding of the trinucleotide repeat differences, it is now technically possible to look directly at anyone's DNA to determine if they have a HD gene mutation. A HD DNA test can be used to test people who are showing symptoms or people who are not showing symptoms but are at risk for inheriting the HD gene mutation from one of their parents. This latter form of testing is called "predictive" or "presymptomatic", since people who are not yet showing symptoms are tested to provide them with information about whether they will have HD at some (unknown) time in the future. Prenatal diagnosis can also be performed.

The HD gene test determines the number of copies of the trinucleotide repeat on both chromosomes of the individual who requests testing. A blood sample is obtained, DNA is isolated from the white blood cells, and a technique called polymerase chain reaction (PCR) is used to synthesize millions of copies of the region of the HD gene that may or may not contain extra copies of the trinucleotide repeat (see Figure 4; for a description of the PCR process, see Marx 1988; Guyer and Koshland 1989; Mullis 1990; Erlich et al. 1991). The products of the PCR are separated by gel electrophoresis and the sizes of the DNA fragments synthesized are compared to a set of size standards. In this way, the size of the beginning of the HD gene and the number of trinucleotide repeats are determined. For sample data and calculation of trinucleotide repeat sizes, see the Classroom Exercise, "Determining Repeat Length." In actual practice at one lab that provides HD testing as a clinical service, the sensitivity of the test is 98-99% (sensitivity refers to the probability that the test will be positive in someone who will manifest the condition), and the specificity of the test is 99.8% (specificity refers to the probability that the test will be negative in someone who will not manifest the condition) (J. Tait, personal communication, November 1994).

Thus, a test to look at the HD gene will reveal whether or not an individual can expect to develop HD in the future, but will not provide information on when this will happen, what the exact symptoms will be, or the rate of decline. For a general history of the test development and associated issues, see the attached article about Nancy Wexler (Murray 1994).

b: the testing process

The test for HD, like other medical tests, has risks as well as benefits. Because there is no cure for HD, and no treatment to slow the course of the symptoms, there are no medical benefits to HD presymptomatic testing. However, there are risks and benefits associated with the HD test (and with most genetic tests) that are personal, psychological and social in nature.

Predictive testing for Huntington's disease can potentially have a dramatic impact on the life of the person being tested and their family members. Possible risks include depression, anxiety, suicide, feelings of despair and hopelessness, changes in self perception and altered family dynamics and relationships. Possible benefits include relief of anxiety, decreased depression and improved psychological well being (Wiggins et al. 1992). One study has suggested that many of these risks and benefits may be experienced regardless of the outcome of the test (Wiggins et al. 1992). In addition, people undergoing testing may reexamine and/or alter various aspects of their lives. For personal accounts of the testing process, see the attached articles (Ager 1988; Spaulding 1991; Hayes 1992; Harville 1994). For case examples of the experiences of some people who have gone through the testing experience, see the attached articles by Bloch et al. and Huggins et al. (Bloch et al. 1991; Huggins et al. 1991). At a societal level, people at risk for HD have experienced stigmatization and discrimination, including, for example, insurance and employment discrimination, and difficulties in the adoption process (Billings et al. 1992). Detection of the HD gene in a person at risk may result in difficulties with health care benefits, life and disability insurance coverage for themselves and possibly for their family.

Because of these risks and the impact of predictive testing for HD, a great value is placed on the individual's right to decide to be tested or not. In order to preserve each individual's right to make an autonomous decision, and because the impact of testing on children and their familial relationships is unknown, HD predictive testing generally is provided only for people over 18 years of age (Benjamin et al. 1994). However, prenatal testing is offered under certain circumstances (Benjamin et al. 1994).

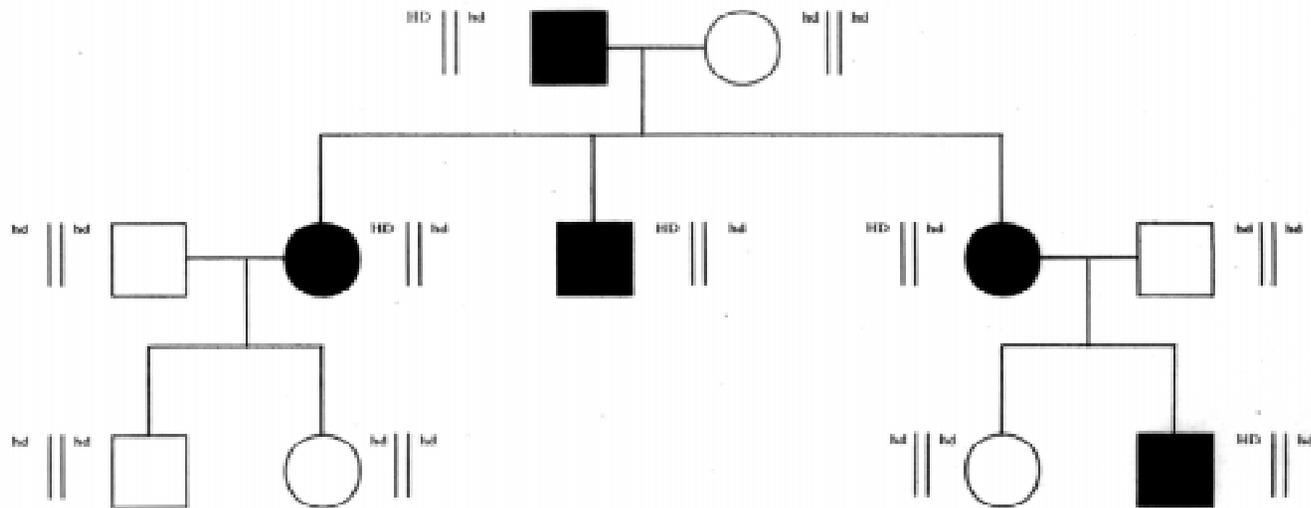
Because of the complex nature of the issues and risks surrounding testing for HD, testing occurs within the context of a larger counseling and information exchange process. Counseling and information about predictive testing for Huntington's disease is provided by specially trained medical geneticists and/or genetic counselors. "Genetic counseling is a communication process which deals with the human problems associated with the occurrence, or the risk of occurrence, of a genetic disorder in a family. This process involves an attempt by one or more appropriately trained persons to help the individual or family to (1) comprehend the medical facts, including the diagnosis, probable course of the disorder, and the available management; (2) appreciate the way heredity contributes to the disorder, and the risk of recurrence in specified relatives; (3) understand the alternatives for dealing with the risk of recurrence; (4) choose the course of action which seems to them appropriate in view of their risk their family goals and their ethical and religious standards, and to act in accordance with that decision; and (5) to make the best possible adjustment to the disorder in an affected family member and/or to the risk of recurrence of that disorder." (Epstein et al. 1975).

People who wish predictive testing for HD attend a number of individual counseling sessions at a genetics clinic prior to finding out their HD status. It is recommended that persons considering testing bring a support person with them to the counseling sessions.

In these sessions, a genetics counselor and/or medical geneticist convey information about the test itself, the various implications of being tested are discussed, and a blood sample is drawn. Some questions that people are asked to consider prior to testing for HD appear in “Discussion Questions” in the Classroom Materials. (Bennett et al. 1993). People who choose to be tested are asked to sign an informed consent document that reiterates the risks associated with testing and describes the testing process itself (for a sample informed consent document, see “Informed Consent Form” in the Classroom Materials). After DNA is isolated from the blood sample(s) and tested, results are provided at a subsequent counseling session. Follow up contact between the genetics clinic and the person tested occurs, which may include phone calls by the genetic counselor to the person tested, additional counseling appointments, or other options, depending on the needs of each individual. (Quaid 1992; Bennett et al. 1993; Benjamin et al. 1994).

The decision to be tested or not to be tested is viewed as a highly personal matter, and thus genetics professionals do not advise a person about whether or not they ought to be tested. In genetic counseling, this is called a "nondirective" counseling approach, and is an approach used for counseling related to most genetic tests. In addition, the person choosing to be tested has the opportunity to change their mind about receiving test results at any point in the process. To date, many fewer people than are eligible (that is, they are members of families with HD) have been tested to determine their HD status. The reasons why many people choose not to be tested are still under examination. One study found that some factors important to people who chose not to be tested included: 1. worries about the risk to their children if they discovered they carried the HD gene; 2. the lack of a cure for HD; 3. concerns about losing health insurance if they were found to carry the HD gene; 4. prohibitive financial costs of testing; and 5. the inability to "undo" the knowledge once the test results were known (Quaid and Morris 1993). (Note: Financial costs of testing have decreased substantially with identification of the HD gene and the ability to directly examine this gene for mutations vs. linkage analysis and family studies and are currently about \$1000 or less per person requesting the test.) For personal accounts of the decision to not have HD presymptomatic testing see Wexler 1994.

Figure 1: Autosomal Dominant Inheritance



Legend

| = chromosome 4

HD = Huntington's disease gene mutation

hd = "normal" gene

Figure 2: The HD Gene

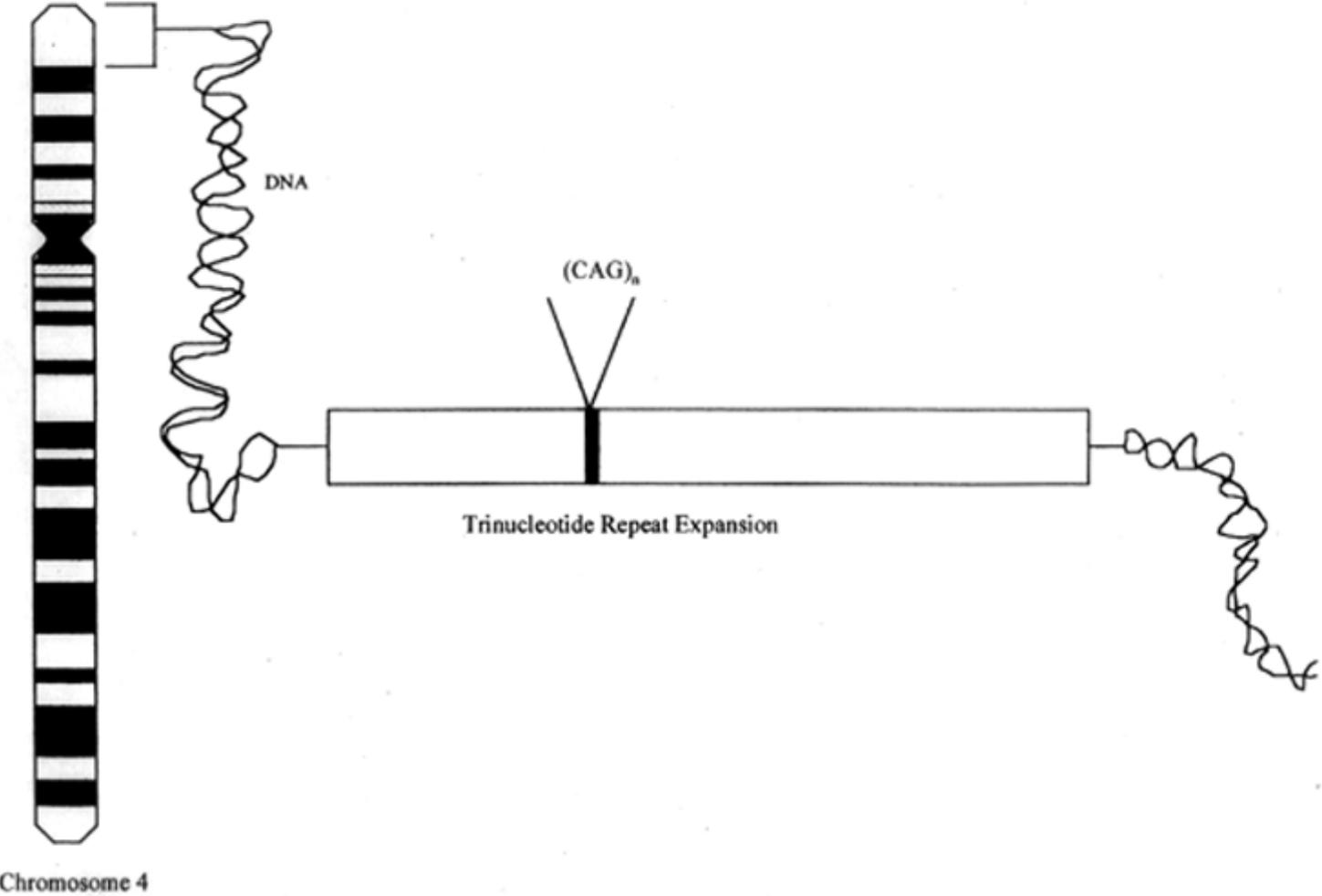
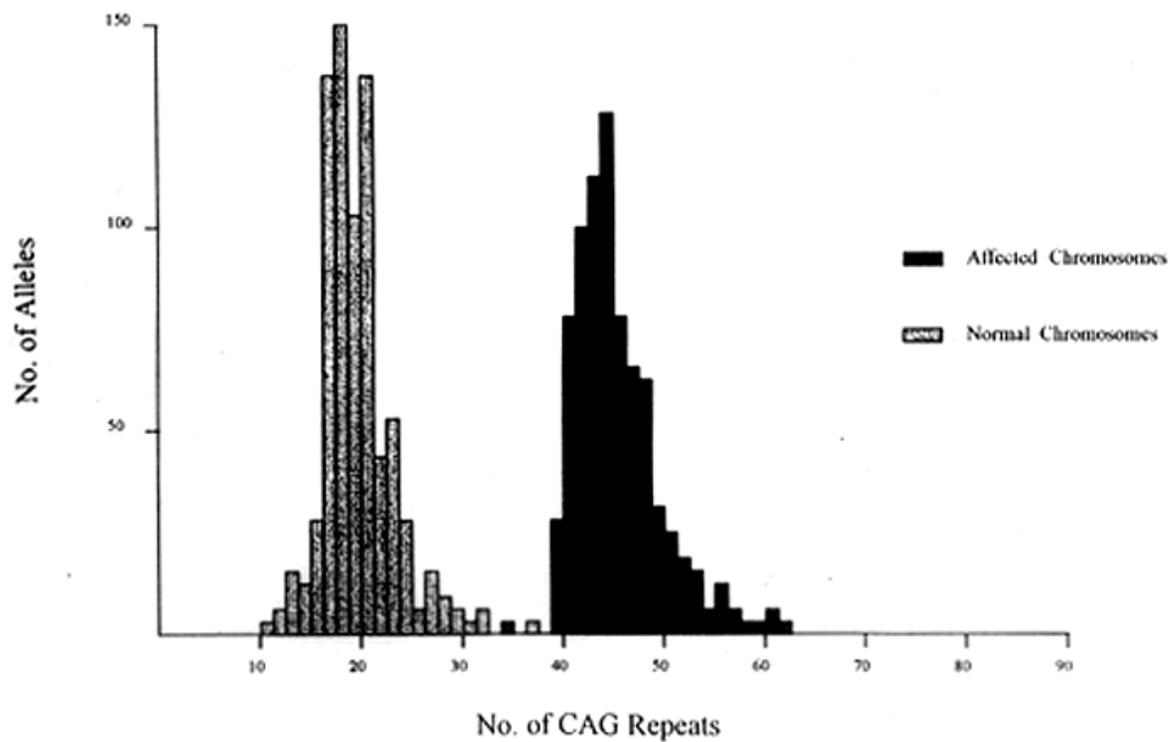
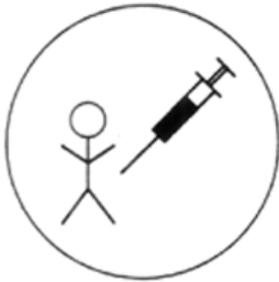


Figure 3: Distribution of CAG Repeats on Different Chromosomes*

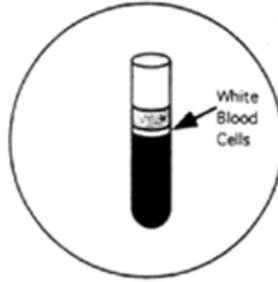


*data from: Kremer, B. et al. "A worldwide study of the Huntington's disease mutation," N Engl J Med 330: 1401-1406, 1994

Figure 4: The HD Gene Test



1) A blood sample is obtained.

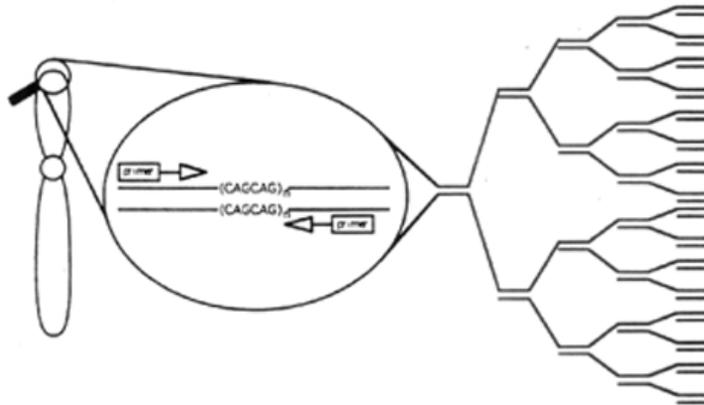


2) White blood cells are separated from the sample.

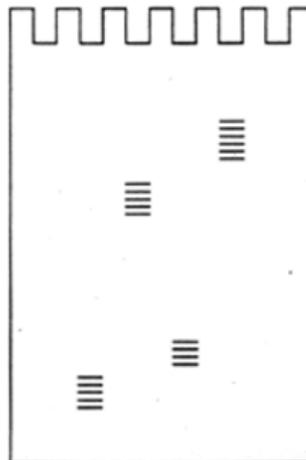


3) DNA is isolated from the white blood cells.

4) PCR is used to synthesize millions of copies of a region of the HD gene that contains the trinucleotide repeat expansion.



5) The samples are run on a gel to determine the size of the fragments.



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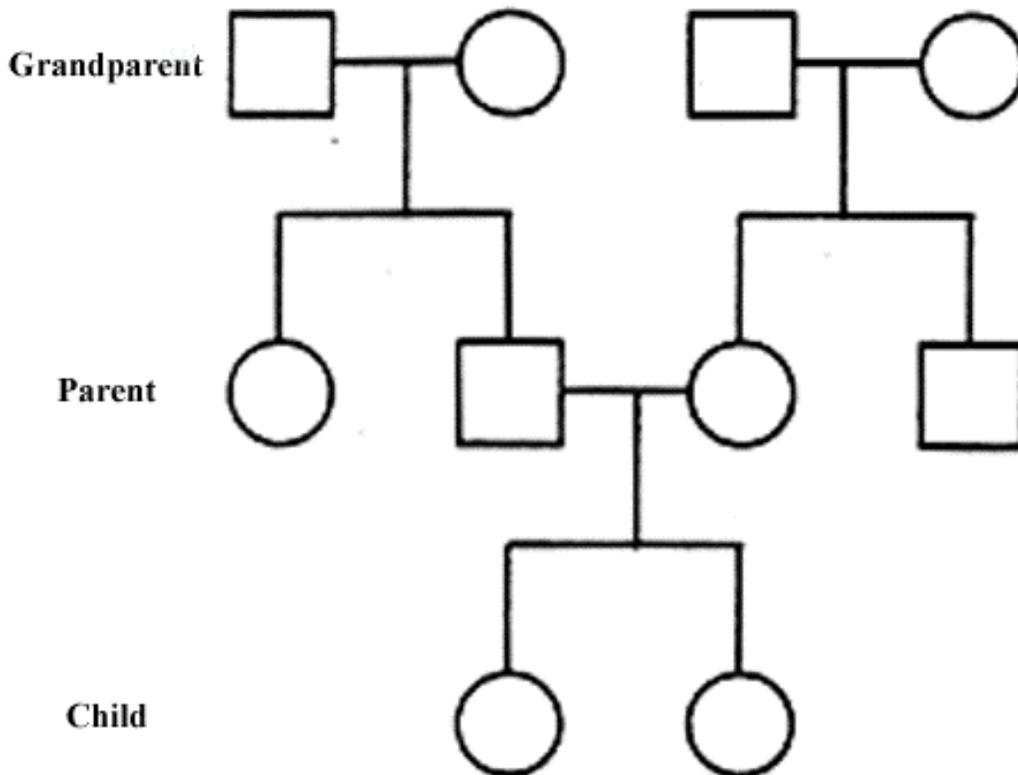
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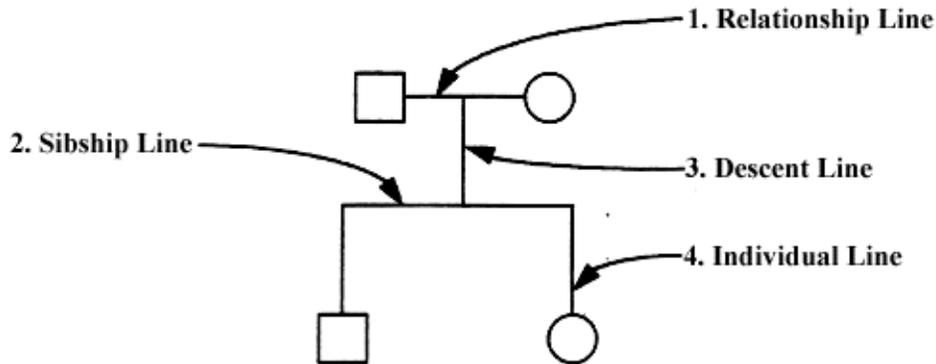
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Constructing A Pedigree: Exercise

A pedigree is a family tree that is used to illustrate the history of a genetic trait within an extended family. It allows the reader to easily trace a particular trait or condition through several generations within a common line of ancestors. Below is an example of an extended nuclear family pedigree.



In genetics pedigrees, men are represented by squares and women are symbolized by circles. When two individuals marry, their symbols are connected by a short horizontal line called the relationship line (line 1 in the figure below). When couple bear children, a line is drawn downward from the relationship line to another line, called the sibship line (line 2), which runs parallel to the relationship line. The line connecting the relationship line to the sibship line is called a descent line (line 3). Individual children are represented by squares or circles depending on the sex of the child. The symbol representing the individual children are then connected to the sibship line by short vertical lines called individual lines (line 4).



The easiest way to construct a pedigree is to begin with the oldest known family member. Draw the symbol for this person. Is he or she married? If so, add the spouse to the pedigree using a relationship line. Does this couple have children? If so, draw a descent line from the relationship line that connects the original couple. At the end of the descent line, draw a sibship line. Then add the symbols for each of the couple's children from left to right, starting with the oldest child and proceeding to the youngest child. If any of these children in the second generation are married, add their spouses to the pedigree using the appropriate symbol and a relationship line. If this couple has children they can be added to the pedigree using a descent line, a sibship line, and the appropriate symbols. Continue the process of adding the spouses and children to the pedigree until all pertinent relatives or descendants are included.

In genetics pedigrees, transmission of a genetic condition from generation to generation is indicated by the shading of individual symbols. For example, if Huntington's disease (HD) is found in a family, the symbols of the individuals who are affected by the condition are shaded. Unaffected individuals are represented by open, or unshaded, symbols. Family members who are deceased are represented by drawing a diagonal line through that person's symbols in the pedigree. These, and other standard symbols used in pedigree construction are shown in the following key, or legend. Use the information contained in the legend to draw a genetic pedigree of the Klein family.

Once you have completed the exercise, you may check your results with the actual Klein Family Pedigree.

Pedigree Legend:

○ Female, Unaffected

□ Male, Unaffected

● Female, Affected

■ Male, Affected

⊘ Deceased, Unaffected

●⊘ Deceased, Affected

◇_P Pregnancy



Identical (Monozygotic) Twins



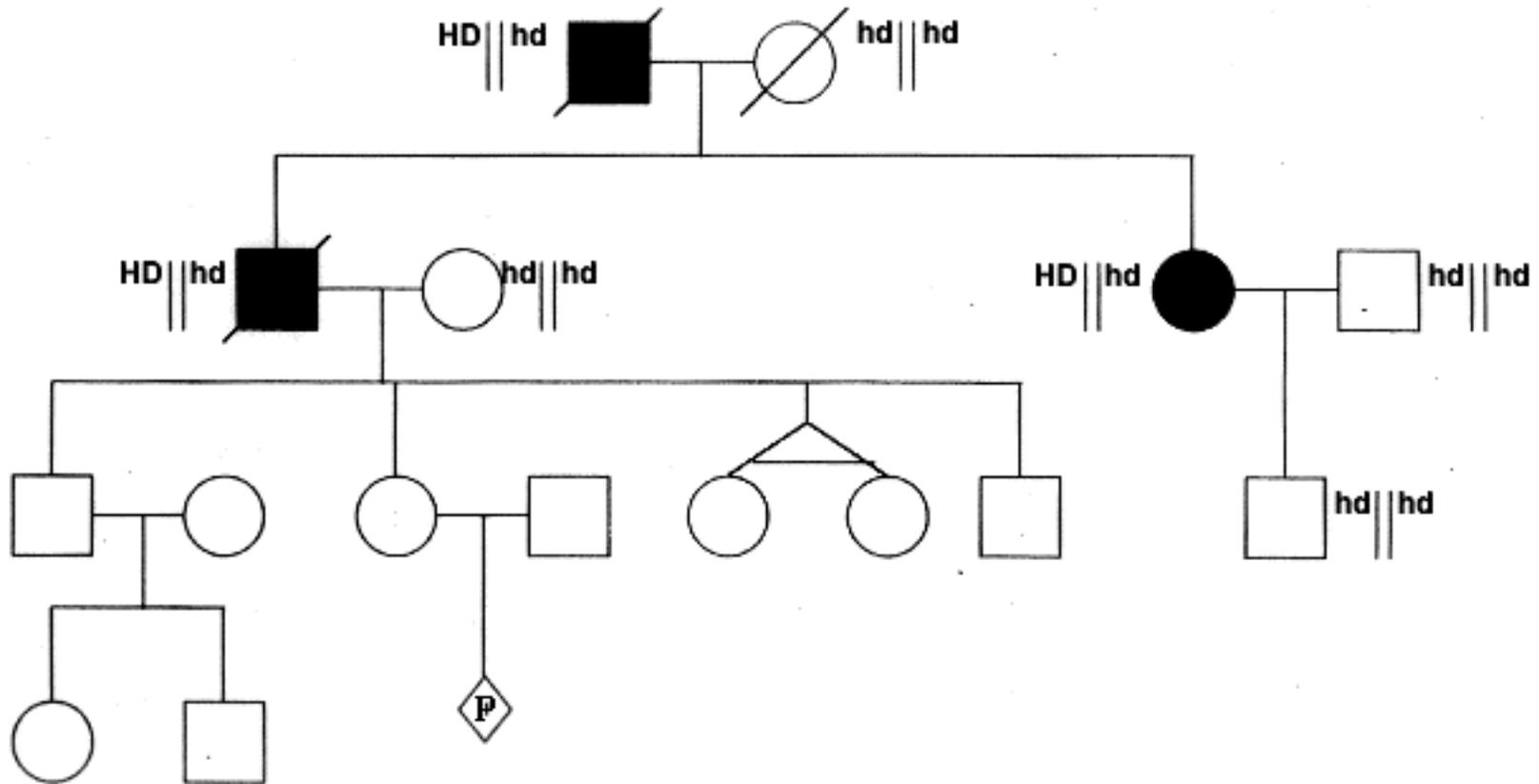
Fraternal (Dizygotic) Twins



Relationship Ended

*Adapted from Bennett et al. Recommendations for standardized human pedigree nomenclature. Am J Hum Gen 56: 745-752. 1995.

Klein Family Pedigree



Classroom Materials II: Bioethics and Ethical Decision Making

Template for Decision Making

<i>Identify the ethical question(s) raised by the case</i>	<i>List all the relevant facts of the case</i>	<i>Identify the stakeholders and values that play a role in the decision.</i>	<i>List several possible solutions to resolve the conflict. (What <u>could</u> you do?)</i>	<i>Choose the better solution(s) and justify them. (What <u>should</u> you do?)</i>

DISCUSSION QUESTIONS*

Table 1. Discussion Questions for Clients Considering Predictive Testing for Huntington's Disease

What has been your experience living with people in your family with Huntington's disease?

What is the single most important reason for wanting to know if you have inherited the HD allele?

Why have you chosen to consider predictive testing at this time vs. earlier or later than now?

What decisions in your life have you made that you would have made differently if you had not been at risk for HD?

Do you believe you have inherited the HD allele? What does your spouse/partner think?

What does your family think?

What effects do you think being given an increased risk would have on your:

Personal life?

Significant other?

Decision to have children/more children?

Children if you have any?

Parent(s) including your affected parent if living?

Siblings who are at risk/siblings who are affected?

Friends?

Other relatives including those affected or at risk?

Career plans/present and future?

Colleagues at work?

Financial planning?

Medical and life insurance?

Choices in how you would spend the next 10-20 years?

What about a decreased risk? What about and uninformative risk?

If the DNA testing discloses non-paternity, do you want to know this information if it does not alter your final test results?

Who will you tell that you are participating in predictive testing? Who will you tell of your results (e.g. family members, friends, colleagues at work)?

How have you coped at difficult points in your life in the past? Who do you turn to for support? How do you ask for help when you need it?

Have you ever been depressed? How did you get yourself out of depression/ Have you ever considered suicide? If so, what or who helped prevent you from taking this action?

Is there anyone pressuring you to find out your status? Explain.

What will you do the day you are given your results if you are given an increased risk? A decreased risk? An uninformative result? What will you do the next week? The next month? The next year? (e.g. take the day off work, go out to dinner, stay home).

*From: Bennett et al. "Offering predictive testing for Huntington disease in a medical genetics clinic: practical applications," J Genet Counsel 2: 123-137, 1993

Classroom Materials III: The Testing Decision and Receiving Results

DETERMINING REPEAT LENGTH: EXERCISE

This exercise is designed to provide a bridge between basic science and technology (DNA synthesis and gel electrophoresis) and the applications of that technology (genetic testing). The purpose of this exercise is to size HD and non-HD alleles using an actual protocol used by the HD clinical testing laboratory at the University of Washington Medical Center. You may want to refer back to Huntington’s Disease Background Information to remind yourself of how this ladder of bands was generated.

Materials needed: Autoradiogram (Figure x), metric ruler, 2-cycle semilog graph paper.

Step 1: Constructing a Standard Curve

Using a metric ruler, measure the distance in centimeters from the reference point on the autoradiogram (142 bp) to the following points of the sequencing ladder size control:

	Distance from 142 bp:
155 bp	
169 bp	
178 bp	
190 bp	
211 bp	
227 bp	
253 bp	

Plot the distance from 142 bp in centimeters (X axis) versus the number of base pairs (Y axis) on 2-cycle semilog graph paper.

For each of the five patients on the autoradiogram,

Step 2: Choose the HD Band to be Sized

Normal Range (143-212 bp): Choose the uppermost DARKEST band, which is usually the second band from the top of a series of bands.

Abnormal Range (236-308 bp): Bands within this range are usually slightly lighter than bands that fall within the normal range. Choose the HIGHEST, clearly discernible band of the ladder that falls within this region of the gel.

Step 3: Determine the Size of the Chosen Band

Measure the distance in centimeters from the reference point (142 bp) that the band you selected in Step 2 has migrated.

Migration distance of selected band = _____ cm

On the X-axis of the graph of sizing standards that you created in Step 1 find the migration distance of the band you selected in Step 2. From this point on the X-axis read up to the standard curve. From this point on the standard curve read over to the Y-axis. This is the size in bp of the band you selected in Step 2.

Size of selected band = _____ bp

Step 4: Calculate the Number of CAG Repeats

Use the following equation to calculate the number of copies of the CAG repeats that your selected band represents (Note: The piece of DNA that you are sizing includes a constant region of 110 bp which must be subtracted in the final calculation):

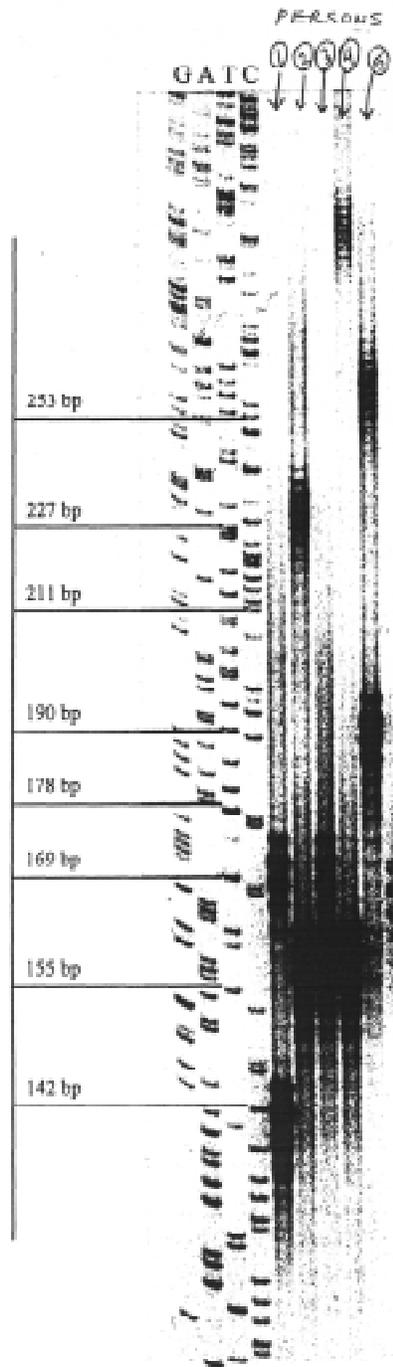
$$\# \text{ of CAG repeats} = \frac{\text{Size of selected band (bp)} - 110}{3}$$

Step 5: Compare this number to the following reference ranges:

Normal range: 10-34 CAGs

Intermediate range: 35-38 CAGs

Abnormal range: ≥ 39 CAGs



Semi-Log Graph of CAG Repeats

Huntington's Disease DNA Screen

Department of Genetic Medicine
Union University Medical Center

Send Report To:

Method: The region of the HD gene containing the CAG repeat was amplified and its size measured on a denaturing 6% polyacrylamide gel against M13mp18(-20) as standard as described by Goldberg YP et al. *Hum Molec Genet* 1993; 2: 635-636.

Reference range:

Number of CAG Repeats in the Upper Allele	% of Normal	% of HD Patients	Interpretation
≤34	100	0	Normal
≥39	0	100	Abnormal
	n=125	n=125	

Clinical History: Prenatal testing for 12 week old fetus. Mother is a 24 year old whose father died at age 47 of HD. Test required to determine HD gene mutation status of fetus.

Results:

Name	DOB	Hosp#	Drawn	Recvd	Spec Type	# of CAG Repeats	
						Upper allele	Lower allele
Klein-Hunter, Fetus	1/00	123461	7/7/99	7/8/99	Amniotic Fluid	48	25

Interpretation: The testing of fetal cells indicates that the fetus has one normal-sized and one expanded allele in the CAG repeat region of the HD (IT15) gene. Presence of an expanded allele, together with the family history, indicates the fetus will develop Huntington's disease at some time in the future. Genetic counseling is recommended for any relatives of the patient who might be prompted to consider DNA testing for HD due to the presence of a detectable mutation in this patient.

Comments: Expansion of a CAG repeat in the HD (IT15) gene is present in almost all cases (95-98%) of Huntington's disease, and is essentially absent in normal controls (*Cell* 1993; 72:971-983; *Lancet* 1993; 342: 954-958). Presence of more than approximately 39 CAG repeats is thus strong evidence that a patient has the Huntington's disease gene mutation. The number of CAG repeats does not reliably predict the age of onset, the rate of disease progress, or the severity of symptoms for an individual patient.

Laboratory Supervisor

Laboratory Director

PT.NO. 123461

NAME Klein-Hunter, Fetus

D.O.B. 1/00

Union University Medical Center
LAB REPORT

Report Date 8/13/99 #1

Huntington's Disease DNA Screen

Department of Genetic Medicine
Union University Medical Center

Send Report To:

Method: The region of the HD gene containing the CAG repeat was amplified and its size measured on a denaturing 6% polyacrylamide gel against M13mp18(-20) as standard as described by Goldberg YP et al. *Hum Molec Genet* 1993; 2: 635-636.

Reference range:

Number of CAG Repeats in the Upper Allele	% of Normal	% of HD Patients	Interpretation
≤34	100	0	Normal
≥39	0	100	Abnormal
	n=125	n=125	

Clinical History: Prenatal testing for 12 week old fetus. Mother is a 24 year old whose father died at age 47 of HD. Test required to determine HD gene mutation status of fetus.

Results:

Name	DOB	Hosp#	Drawn	Recvd	Spec Type	# of CAG Repeats	
						Upper allele	Lower allele
Klein-Hunter, Fetus	1/00	123461	7/7/99	7/8/99	Amniotic Fluid	32	25

Interpretation: The testing of fetal cells indicates that the fetus has two normal sized alleles in the CAG repeat region of the HD (IT15) gene. Absence of an expanded allele indicates the fetus will not develop Huntington's disease. Genetic counseling is recommended for any relatives of the patient who might be prompted to consider DNA testing for HD due to the presence of a detectable mutation in this patient.

Comments: Expansion of a CAG repeat in the HD (IT15) gene is present in almost all cases (95-98%) of Huntington's disease, and is essentially absent in normal controls (*Cell* 1993; 72:971-983; *Lancet* 1993; 342: 954-958). Presence of less than approximately 34 CAG repeats is thus strong evidence that a patient does not have the Huntington's disease gene mutation.

Laboratory Supervisor

Laboratory Director

PT.NO. 123461

NAME Klein-Hunter, Fetus

D.O.B. 1/00

Union University Medical Center
LAB REPORT

Report Date 8/13/99+ #2

Huntington's Disease DNA Screen

Department of Genetic Medicine
Union University Medical Center

Send Report To:

Method: The region of the HD gene containing the CAG repeat was amplified and its size measured on a denaturing 6% polyacrylamide gel against M13mp18(-20) as standard as described by Goldberg YP et al. *Hum Molec Genet* 1993; 2: 635-636.

Reference range:

Number of CAG Repeats in the Upper Allele	% of Normal	% of HD Patients	Interpretation
≤34	100	0	Normal
≥39	0	100	Abnormal
	n=125	n=125	

Clinical History: Presymptomatic testing for 18 year old male. Father died at age 47. Test requested to determine HD gene mutation status.

Results:

<u>Name</u>	<u>DOB</u>	<u>Hosp#</u>	<u>Drawn</u>	<u>Recvd</u>	<u>Spec Type</u>	<u># of CAG Repeats</u>	
						<u>Upper allele</u>	<u>Lower allele</u>
Klein, James	10/4/81	123460	10/7/99	10/8/99	Blood	32	28

Interpretation: The patient has two normal sized alleles in the CAG repeat region of the HD (IT15) gene. Absence of an expanded allele indicates the patient will not develop Huntington's disease. Genetic counseling is recommended for any relatives of the patient who might be prompted to consider DNA testing for HD due to the presence of a detectable mutation in this patient.

Comments: Expansion of a CAG repeat in the HD (IT15) gene is present in almost all cases (95-98%) of Huntington's disease, and is essentially absent in normal controls (*Cell* 1993; 72:971-983; *Lancet* 1993; 342: 954-958). Presence of less than approximately 34 CAG repeats is thus strong evidence that a patient does not have the Huntington's disease gene mutation.

Laboratory Supervisor

Laboratory Director

PT.NO. 123460

NAME Klein, James
D.O.B 10/4/81

Union University Medical Center
LAB REPORT

Report Date: 11/13/99 #3

Huntington's Disease DNA Screen

Department of Genetic Medicine
Union University Medical Center

Send Report To:

Method: The region of the HD gene containing the CAG repeat was amplified and its size measured on a denaturing 6% polyacrylamide gel against M13mp18(-20) as standard as described by Goldberg YP et al. *Hum Molec Genet* 1993; 2: 635-636.

Reference range:

Number of CAG Repeats in the Upper Allele	% of Normal	% of HD Patients	Interpretation
≤34	100	0	Normal
≥39	0	100	Abnormal
	n=125	n=125	

Clinical History: Presymptomatic testing for 18 year old male. Father died at age 47. Test requested to determine HD gene mutation status.

Results:

Name	DOB	Hosp#	Drawn	Recvd	Spec Type	# of CAG Repeats	
						Upper allele	Lower allele
Klein, James	10/4/81	123460	10/7/99	10/8/99	Blood	48	28

Interpretation: The patient has one normal-sized and one expanded allele in the CAG repeat region of the HD (IT15) gene. Presence of an expanded allele, together with the family history, indicates the patient will develop Huntington's disease at some time in the future. Genetic counseling is recommended for any relatives of the patient who might be prompted to consider DNA testing for HD due to the presence of a detectable mutation in this patient.

Comments: Expansion of a CAG repeat in the HD (IT15) gene is present in almost all cases (95-98%) of Huntington's disease, and is essentially absent in normal controls (*Cell* 1993; 72:971-983; *Lancet* 1993; 342: 954-958). Presence of more than approximately 39 CAG repeats is thus strong evidence that a patient has the Huntington's disease gene mutation. The number of CAG repeats does not reliably predict the age of onset, the rate of disease progress, or the severity of symptoms for an individual patient.

Laboratory Supervisor

Laboratory Director

PT.NO. 123460

NAME Klein, James

DOB 10/4/81

Union University Medical Center

LAB REPORT

Report Date 11/13/99 #4

Huntington's Disease DNA Screen

Department of Genetic Medicine
Union University Medical Center

Send Report To:

Method: The region of the HD gene containing the CAG repeat was amplified and its size measured on a denaturing 6% polyacrylamide gel against M13mp18(-20) as standard as described by Goldberg YP et al. *Hum Molec Genet* 1993; 2: 635-636.

Reference range:

Number of CAG Repeats in the Upper Allele	% of Normal	% of HD Patients	Interpretation
≤34	100	0	Normal
≥39	0	100	Abnormal
	n=125	n=125	

Clinical History: Presymptomatic testing for 24 year old female. Father died at age 47. Test requested to determine HD gene mutation status.

Results:

Name	DOB	Hosp#	Drawn	Recvd	Spec Type	# of CAG Repeats	
						Upper allele	Lower allele
Klein-Hunter, Krista	6/17/75	123457	7/7/99	7/8/99	Blood	32	22

Interpretation: The patient has two normal sized alleles in the CAG repeat region of the HD (IT15) gene. Absence of an expanded allele indicates the patient will not develop Huntington's disease. Genetic counseling is recommended for any relatives of the patient who might be prompted to consider DNA testing for HD due to the presence of a detectable mutation in this patient.

Comments: Expansion of a CAG repeat in the HD (IT15) gene is present in almost all cases (95-98%) of Huntington's disease, and is essentially absent in normal controls (*Cell* 1993; 72:971-983; *Lancet* 1993; 342: 954-958). Presence of less than approximately 34 CAG repeats is thus strong evidence that a patient does not have the Huntington's disease gene mutation.

Laboratory Supervisor

Laboratory Director

PT.NO. 123457

NAME Klein-Hunter, Krista

D.O.B. 6/17/75

Union University Medical Center
LAB REPORT

Report Date 8/13/99 #5

Huntington's Disease DNA Screen

Department of Genetic Medicine
Union University Medical Center

Send Report To:

Method: The region of the HD gene containing the CAG repeat was amplified and its size measured on a denaturing 6% polyacrylamide gel against M13mp18(-20) as standard as described by Goldberg YP et al. *Hum Molec Genet* 1993; 2: 635-636.

Reference range:

Number of CAG Repeats in the Upper Allele	% of Normal	% of HD Patients	Interpretation
≤34	100	0	Normal
≥39	0	100	Abnormal
	n=125	n=125	

Clinical History: Presymptomatic testing for 24 year old female. Father died at age 47. Test requested to determine HD gene mutation status.

Results:

Name	DOB	Hosp#	Drawn	Recvd	Spec Type	# of CAG Repeats	
						Upper allele	Lower allele
Klein-Hunter, Krista	6/17/75	123457	7/7/99	7/8/99	Blood	48	22

Interpretation: The patient has one normal-sized and one expanded allele in the CAG repeat region of the HD (IT15) gene. Presence of an expanded allele, together with the family history, indicates the patient will develop Huntington's disease at some time in the future. Genetic counseling is recommended for any relatives of the patient who might be prompted to consider DNA testing for HD due to the presence of a detectable mutation in this patient.

Comments: Expansion of a CAG repeat in the HD (IT15) gene is present in almost all cases (95-98%) of Huntington's disease, and is essentially absent in normal controls (*Cell* 1993; 72:971-983; *Lancet* 1993; 342: 954-958). Presence of more than approximately 39 CAG repeats is thus strong evidence that a patient has the Huntington's disease gene mutation. The number of CAG repeats does not reliably predict the age of onset, the rate of disease progress, or the severity of symptoms for an individual patient.

Laboratory Supervisor

Laboratory Director

PT.NO. 123457

NAME Klein-Hunter, Krista
D.O.B. 6/17/75

Union University Medical Center
LAB REPORT

Report Date 8/13/99 #6

Huntington's Disease DNA Screen

Department of Genetic Medicine
Union University Medical Center

Send Report To:

Method: The region of the HD gene containing the CAG repeat was amplified and its size measured on a denaturing 6% polyacrylamide gel against M13mp18(-20) as standard as described by Goldberg YP et al. *Hum Molec Genet* 1993; 2: 635-636.

Reference range:

Number of CAG Repeats in the Upper Allele	% of Normal	% of HD Patients	Interpretation
≤34	100	0	Normal
≥39	0	100	Abnormal
	n=125	n=125	

Clinical History: Presymptomatic testing for 21 year old female. Father died at age 47. Test requested to determine HD gene mutation status.

Results:

Name	DOB	Hosp#	Drawn	Recvd	Spec Type	# of CAG Repeats	
						Upper allele	Lower allele
Klein, Lauren	12/1/78	123459	2/7/00	2/8/00	Blood	32	22

Interpretation: The patient has two normal sized alleles in the CAG repeat region of the HD (IT15) gene. Absence of an expanded allele indicates the patient will not develop Huntington's disease. Genetic counseling is recommended for any relatives of the patient who might be prompted to consider DNA testing for HD due to the presence of a detectable mutation in this patient.

Comments: Expansion of a CAG repeat in the HD (IT15) gene is present in almost all cases (95-98%) of Huntington's disease, and is essentially absent in normal controls (*Cell* 1993; 72:971-983; *Lancet* 1993; 342: 954-958). Presence of less than approximately 34 CAG repeats is thus strong evidence that a patient does not have the Huntington's disease gene mutation.

Laboratory Supervisor

Laboratory Director

PT.NO. 123459

NAME Klein, Lauren
D.O.B. 12/1/78

Union University Medical Center
LAB REPORT

Report Date 3/13/00 #7

Huntington's Disease DNA Screen

Department of Genetic Medicine
Union University Medical Center

Send Report To:

Method: The region of the HD gene containing the CAG repeat was amplified and its size measured on a denaturing 6% polyacrylamide gel against M13mp18(-20) as standard as described by Goldberg YP et al. *Hum Molec Genet* 1993; 2: 635-636.

Reference range:

Number of CAG Repeats in the Upper Allele	% of Normal	% of HD Patients	Interpretation
≤34	100	0	Normal
≥39	0	100	Abnormal
	n=125	n=125	

Clinical History: Presymptomatic testing for 21 year old female. Father died at age 47. Test requested to determine HD gene mutation status.

Results:

Name	DOB	Hosp#	Drawn	Recvd	Spec Type	# of CAG Repeats	
						Upper allele	Lower allele
Klein, Lauren	12/1/78	123459	2/7/00	2/8/00	Blood	48	28

Interpretation: The patient has one normal-sized and one expanded allele in the CAG repeat region of the HD (IT15) gene. Presence of an expanded allele, together with the family history, indicates the patient will develop Huntington's disease at some time in the future. Genetic counseling is recommended for any relatives of the patient who might be prompted to consider DNA testing for HD due to the presence of a detectable mutation in this patient.

Comments: Expansion of a CAG repeat in the HD (IT15) gene is present in almost all cases (95-98%) of Huntington's disease, and is essentially absent in normal controls (*Cell* 1993; 72:971-983; *Lancet* 1993; 342: 954-958). Presence of more than approximately 39 CAG repeats is thus strong evidence that a patient has the Huntington's disease gene mutation. The number of CAG repeats does not reliably predict the age of onset, the rate of disease progress, or the severity of symptoms for an individual patient.

Laboratory Supervisor

Laboratory Director

PT.NO. 123459

NAME Klein, Lauren
D.O.B. 12/1/78

Union University Medical Center
LAB REPORT

Report Date 3/13/00 #8

Huntington's Disease DNA Screen

Department of Genetic Medicine
Union University Medical Center

Send Report To:

Method: The region of the HD gene containing the CAG repeat was amplified and its size measured on a denaturing 6% polyacrylamide gel against M13mp18(-20) as standard as described by Goldberg YP et al. *Hum Molec Genet* 1993; 2: 635-636.

Reference range:

Number of CAG Repeats in the Upper Allele	% of Normal	% of HD Patients	Interpretation
≤34	100	0	Normal
≥39	0	100	Abnormal
	n=125	n=125	

Clinical History: Presymptomatic testing for 27 year old male. Father died at age 47. Test requested to determine HD gene mutation status.

Results:

Name	DOB	Hosp#	Drawn	Recvd	Spec Type	# of CAG Repeats	
						Upper allele	Lower allele
Klein, Paul	3/24/72	123456	8/10/99	8/11/99	Blood	32	28

Interpretation: The patient has two normal sized alleles in the CAG repeat region of the HD (IT15) gene. Absence of an expanded allele indicates the patient will not develop Huntington's disease. Genetic counseling is recommended for any relatives of the patient who might be prompted to consider DNA testing for HD due to the presence of a detectable mutation in this patient.

Comments: Expansion of a CAG repeat in the HD (IT15) gene is present in almost all cases (95-98%) of Huntington's disease, and is essentially absent in normal controls (*Cell* 1993; 72:971-983; *Lancet* 1993; 342: 954-958). Presence of less than approximately 34 CAG repeats is thus strong evidence that a patient does not have the Huntington's disease gene mutation.

Laboratory Supervisor

Laboratory Director

PT.NO. 123456

NAME Klein, Paul
D.O.B. 3/24/72

Union University Medical Center
LAB REPORT

Report Date 9/1/99 #9

Huntington's Disease DNA Screen

Department of Genetic Medicine
Union University Medical Center

Send Report To:

Method: The region of the HD gene containing the CAG repeat was amplified and its size measured on a denaturing 6% polyacrylamide gel against M13mp18(-20) as standard as described by Goldberg YP et al. *Hum Molec Genet* 1993; 2: 635-636.

Reference range:

Number of CAG Repeats in the Upper Allele	% of Normal	% of HD Patients	Interpretation
≤34	100	0	Normal
≥39	0	100	Abnormal
	n=125	n=125	

Clinical History: Presymptomatic testing for 27 year old male. Father died at age 47. Test requested to determine HD gene mutation status.

Results:

Name	DOB	Hosp#	Drawn	Recvd	Spec Type	# of CAG Repeats	
						Upper allele	Lower allele
Klein, Paul	3/24/72	123456	8/10/99	8/11/99	Blood	48	22

Interpretation: The patient has one normal-sized and one expanded allele in the CAG repeat region of the HD (IT15) gene. Presence of an expanded allele, together with the family history, indicates the patient will develop Huntington's disease at some time in the future. Genetic counseling is recommended for any relatives of the patient who might be prompted to consider DNA testing for HD due to the presence of a detectable mutation in this patient.

Comments: Expansion of a CAG repeat in the HD (IT15) gene is present in almost all cases (95-98%) of Huntington's disease, and is essentially absent in normal controls (*Cell* 1993; 72:971-983; *Lancet* 1993; 342: 954-958). Presence of more than approximately 39 CAG repeats is thus strong evidence that a patient has the Huntington's disease gene mutation. The number of CAG repeats does not reliably predict the age of onset, the rate of disease progress, or the severity of symptoms for an individual patient.

Laboratory Supervisor

Laboratory Director

PT.NO. 123456

NAME Klein, Paul

D.O.B. 3/24/72

Union University Medical Center

LAB REPORT

Report Date 9/1/99 #9

Huntington's Disease DNA Screen

Department of Genetic Medicine
Union University Medical Center

Send Report To:

Method: The region of the HD gene containing the CAG repeat was amplified and its size measured on a denaturing 6% polyacrylamide gel against M13mp18(-20) as standard as described by Goldberg YP et al. *Hum Molec Genet* 1993; 2: 635-636.

Reference range:

Number of CAG Repeats in the Upper Allele	% of Normal	% of HD Patients	Interpretation
≤34	100	0	Normal
≥39	0	100	Abnormal
	n=125	n=125	

Clinical History: Presymptomatic testing for 21 year old female. Father died at age 47. Test requested to determine HD gene mutation status.

Results:

Name	DOB	Hosp#	Drawn	Recvd	Spec Type	# of CAG Repeats	
						Upper allele	Lower allele
Klein, Sara	12/1/78	123458	2/7/00	2/8/00	Blood	48	28

Interpretation: The patient has one normal-sized and one expanded allele in the CAG repeat region of the HD (IT15) gene. Presence of an expanded allele, together with the family history, indicates the patient will develop Huntington's disease at some time in the future. Genetic counseling is recommended for any relatives of the patient who might be prompted to consider DNA testing for HD due to the presence of a detectable mutation in this patient.

Comments: Expansion of a CAG repeat in the HD (IT15) gene is present in almost all cases (95-98%) of Huntington's disease, and is essentially absent in normal controls (*Cell* 1993; 72:971-983; *Lancet* 1993; 342: 954-958). Presence of more than approximately 39 CAG repeats is thus strong evidence that a patient has the Huntington's disease gene mutation. The number of CAG repeats does not reliably predict the age of onset, the rate of disease progress, or the severity of symptoms for an individual patient.

Laboratory Supervisor

Laboratory Director

PT.NO. 123458

NAME Klein, Sara
D.O.B. 12/1/78

Union University Medical Center
LAB REPORT

Report Date 3/13/00 #11

Huntington's Disease DNA Screen

Department of Genetic Medicine
Union University Medical Center

Send Report To:

Method: The region of the HD gene containing the CAG repeat was amplified and its size measured on a denaturing 6% polyacrylamide gel against M13mp18(-20) as standard as described by Goldberg YP et al. *Hum Molec Genet* 1993; 2: 635-636.

Reference range:

Number of CAG Repeats in the Upper Allele	% of Normal	% of HD Patients	Interpretation
≤34	100	0	Normal
≥39	0	100	Abnormal
	n=125	n=125	

Clinical History: Presymptomatic testing for 21 year old female. Father died at age 47. Test requested to determine HD gene mutation status.

Results:

Name	DOB	Hosp#	Drawn	Recvd	Spec Type	# of CAG Repeats	
						Upper allele	Lower allele
Klein, Sara	12/1/78	123458	2/7/00	2/8/00	Blood	32	22

Interpretation: The patient has two normal sized alleles in the CAG repeat region of the HD (IT15) gene. Absence of an expanded allele indicates the patient will not develop Huntington's disease. Genetic counseling is recommended for any relatives of the patient who might be prompted to consider DNA testing for HD due to the presence of a detectable mutation in this patient.

Comments: Expansion of a CAG repeat in the HD (IT15) gene is present in almost all cases (95-98%) of Huntington's disease, and is essentially absent in normal controls (*Cell* 1993; 72:971-983; *Lancet* 1993; 342: 954-958). Presence of less than approximately 34 CAG repeats is thus strong evidence that a patient does not have the Huntington's disease gene mutation.

Laboratory Supervisor

Laboratory Director

PT.NO. 123458

NAME Klein, Sara
D.O.B. 12/1/78

Union University Medical Center
LAB REPORT

Report Date 3/13/00 #12

Resource List

A resource for further information about Huntington's disease is:

Huntington Disease Society of America (HDSA)
140 W. 22nd Street, 6th Floor
New York, NY 10011-2420
(212) 242-1968

Debbie Korevaar, President
Huntington Disease Society of America, Northwest Chapter
(206) 747-4882

The following organizations can provide information about other Huntington's disease and other genetic conditions:

The National Society of Genetic Counselors
233 Canterbury Drive
Wallingford, PA 19086-6617
(610) 872-7608

Alliance of Genetic Support Groups
35 Wisconsin Circle, Suite 440
Chevy Chase, MD 20815
(1-800) 336-GENE
(301) 652-5553

National Organization for Rare Disorders (NORD)
P.O. Box 8923, 100 Rt. 37
New Fairfield, CT 06812-1783
(203) 746-6518

The Pacific Northwest Regional Genetics Group (PacNoRGG)
CDRC, Clinical Services Building
901 E. 18th Ave.
Eugene, OR 97403-5254
(503) 346-2610

In addition, your library is a good place to find many books and articles with information about genetic conditions, including Huntington's disease.

Teacher and Student Comments from the 1994-95 Pilot

CLASSROOM EXPERIENCES

The ethics portion of the curriculum was originally field tested during 1994-1995 in four schools in the Seattle area. Class sizes ranged from seven to thirty students and class periods ranged from 55 to 110 minutes. In the following section you will find descriptions of how the materials were used in the classroom by the teachers who conducted this field testing. In addition, we have included some student responses to the decision making model and ethics materials.

During 1996, a more formal evaluation of the ethics materials was conducted as previously described in the section titled Ethics Unit Evaluation. We have collected data on students' reasoning abilities prior and immediately after their completion of the ethics unit. Preliminary results and analyses are in preparation and are soon to be submitted for publication. As these results are available, they will be appended to this curriculum unit package.

I. Ethics lesson using Huntington Disease materials, taught by Robert Hansen and Barbara Schulz, Shorewood High School

December 12 -16, 1994, the Biology III class at Shorewood High School used the ethics materials developed by Dr. Sharon Durfy for use in the high school setting. Dr. Robert Hansen assisted in the instruction and class discussions. This dialogue is meant as notes from the class proceedings for use by anyone wishing to try this series of lessons with their classes. There was considerable discussion on each of the questions listed here. No pejoratives were used by those teaching in response to student comments.

Shorewood High School operates on 100 minute class periods that meet twice per week on alternating days followed by a 50 minute class period on Friday. This class met on Tuesday, Thursday, and Friday.

Day 1: Students were given the scenario about the family with Huntington's disease. They read the scenario and were asked to work in groups of three or four to discuss the issues presented and to construct a pedigree for the family. Students spent about 30 minutes reading and talking about family members presented. I then spent about 15 minutes explaining pedigrees and answering questions about how the pedigree should be constructed. Students then worked for about 10 - 25 minutes longer on the pedigree. I then held a brief discussion about Huntington's disease and told students about Dr. Nancy Wexler. The class then viewed two videos. The first video is an interview of Dr. Wexler, her sister, and her father done for the 60 Minutes television show. This was followed by discussion and student questions. Dr. Wexler's research was explained and clips of the 10,000 member family living on Lake Mericebo in Venezuela were shown. The class then viewed the first part of the NOVA special on Huntington's disease in which Nancy Wexler and her research were highlighted. The class was emotionally involved with the video and the realities of Huntington's disease began to set in. On a personal note, I think that viewing this video is essential in allowing students to focus on the realities of Huntington's disease. Without this video, the genetic disorder is just another paragraph from the book.

Day 2: The class reviewed ideas from the previous class and viewed the remainder of the NOVA video. The following is a list of questions asked by Robert Hansen of the class. I served as a moderator giving all students an opportunity to express their views while not allowing any one student to dominate the conversation. (Students appreciated this and said so after class. Apparently a few students tend to dominate class discussions in other classes.) The questions and discussion relate to both the scenario and the videos that were very graphic showing all stages of Huntington's disease.

Questions relating to the scenario:

- Should one be tested for a genetic disorder?
- How does one decide?
- How much influence should a parent have over their child in the testing issue?
- How much should such a child be influenced by parent pressure?
- How would you live differently if you knew that you would get the Huntington's disease?
- Do you have a responsibility to inform family members?

The above questions raised the conflict. The next set of questions followed, serving to define ethics.

- What are the issues?
- What makes them ethical issues?
- What are words like "should"?
- Robert: Ethics questions beliefs and morals: beliefs that conflict; values that conflict.
- How do we apply moral values to technology?
- How do we decide who gets the technology?
- How do we decide personal interest? Medical vs. ethical issues?
- Should we use this technology to make humans "better"?
- Are we then trying to make the perfect human? Isn't that eugenics? Hitler?
- How do we develop ways to decide?
- Do we develop rules and guidelines?
- What are ways for analysis of burdens (risks) vs. benefits?
- The "slippery slope" argument – once you start, how do you stop?
- Philosophy discussions are necessary to get ideas out – to resolve conflict.
- How do we hold discussions? Justify your view, listen to others; try to "prove" the others wrong and your ideas correct.
- Formal decision making process; the law – morality and the law are not the same. All that is legal is not moral.

We now need some decision making models for students to try. Is this the next step?

II. Huntington's Disease Bioethics Unit Taught By Peggy Skinner, The Bush School

This unit was taught in two classes, and advanced biology class (11 - 12th graders with at least three years of science background) and a biotechnology class (10 - 12 grade with multiple levels of science background). The classes are quite small with most subjects taught with extensive lab or discussion format. It is fairly rare for subjects to be presented in a strict lecture. Each of the classes spent between four and five days developing the ideas presented in the curriculum. The material was based on the Weinstein model for ethical decision making. Robert Hansen was present for most of the sessions.

Day 1 (What's the Question?): The Klein family scenario and pedigree in class for biotechnology and as homework for the advanced biology class. Students in class worked in small groups to read through the material and to complete the family tree. Since there was a broad range of background, the students worked at very different rates and frustration levels. By the end of the class, they put the pedigree and discussed more detail with the pedigree and family in their 45 minute class.

***Without additional background, the students were asked who should be tested. This was to set the stage for them recognizing that difficult decisions may need framework.

Day 2 (Information): Students were given more information about the disease. We viewed the Nancy Wexler interview and discussed the background material (given as a Xerox) about the trait. The biotechnology class went on to view the NOVA program as well. (optional Day)

Day 3 (Values/Conflict and Options): With Robert, the students discussed the nature of an ethical question. One class used their 90 minute lab period for this discussion, one class used a 60 minute class period, but were not able to cover the material. With a focus on just one of the five individuals in the family, the students worked through the ethical decision making model.

Some highlights of the discussion with Krista following the framework:

Questions: What makes this an ethical question?

"Should" makes it ethical.

Outcomes might conflict.

Concerned with the interests, beliefs and rights of the individuals.

Facts: What do you want to know?

- Length of pregnancy.
- Risks involved in testing.
- Risk of having a child.
- Religion/social/group background of individuals.
- Acceptance of father's disease in the community and family.
- Fetus rights independent of parental rights.

Values/Conflict: What factors might be in conflict?

- Abortion and respect for life
- Individual's right to decide
- Quality of couple's relationship
- View of death
- Fear of death and getting to the essence of life

Options: What could be done?

- Abortion
- Testing
- Suicide
- Defer choice to someone else
- Choose not to decide
- Test after fetus is aborted

After this discussion, the students were assigned one of the five family members. They were to complete this decision making model with their character and come to class the next day with an answer to the question, "What should be done?"

Day 4 (What should be done?) Students worked in small groups of the same character to resolve what should be done using their own arguments to reach consensus. They presented their arguments to the class. If they chose to be tested, they signed the consent forms and received their results in a separate room. Many of the students chose not to be tested. The results were explained to those student groups who needed help.

III. Bioethics Lesson Taught by Ed Hopfner, Nathan Hale High School

This activity took place at Nathan Hale HS with a genetics class composed of approximately 18 students, with 55 minute periods.

On Friday, the students looked at gels from the DNA synthesis lab and discussed their results. They then viewed a videotape about the human genome project, which included information about testing for Huntington's and sickle cell, along with a little molecular biology. They were told they would be discussing ethical issues related to genetic testing and were given (the old version of) the 'case study' to read. They were asked to develop a pedigree for the family.

On Monday, the students were introduced to Robert and to the program. We watched the 60 minutes video and then looked at the pedigree (which only took a few minutes with pedigrees before). The students were reminded that HD was an autosomal dominant disease. They then looked at each character's situation, raised some of the medical and ethical questions that character might have, and then discussed the differences between these two types of questions. They were asked to generate a specific question for their character for the following day.

Tuesday, we went over specific medical questions. Sharon Durfy was present and able to answer some (but not all) of them. Students were asked to focus on ethical questions and come up with at least one for the character for Wednesday.

Wednesday, we went through the list of questions and then chose one of them ("Should the twins be tested, if one wants to and the other one doesn't?") to focus on. We used the model and got through most of it before the end of the period.

On Thursday, we finished going through the model (deciding on a hierarchy of options, beginning with the most preferable). We then had Sharon answer more questions and talk about the process of having the test done, including the extensive counseling. As luck would have it, she also had a copy of a case in the literature where twins had the same dilemma as our class (and came up with essentially the same resolution). The students were given a copy of the informed consent form and a list of questions that might be asked in an interview.

On Friday, after a brief introduction, we then viewed the Hayden videotape (Dr. H and the first 3 interviewees). The students were allowed to choose whether or not to be 'tested'. Robert provided results for their 'character' in UW Medical Center envelopes.

Some thoughts: I would probably sequence this a little differently. I like the context in which the NOVA videotape puts the disease, along with the bit about molecular biology (and chance to differentiate between tests 6 years ago and now), and would show it at the beginning, in its entirety if possible, and probably skip the 60 minute segment. I agree

that getting students interested in people with this disease is essential. I personally should have emphasized more that we were going to be working on a decision-making process.

Overall, I found this very worthwhile, though some of my less-involved students had hoped for more activity (such as role-playing). Sharon and Robert discussed the possibility of a genetic counselor being involved in the role-play and able to 'really' answer questions. One student felt we needed debriefing after the test results were given, even though the test results weren't valid. When the first student to open his envelope started whooping "I'm OK" and she found herself positive for HD just afterwards, she got a little depressed. It would have been good to discuss peoples' reactions.

Some (abbreviated) student comments:

- “it was interesting, it was kind of hard (to get involved) because it didn't affect anyone (one student suggested having a patient with HD speak with us)”
- “it could have been more active, we could learn more role-playing and describe why we want our character to be tested or not”
- “it was interesting, but got kind of boring, we never got (were given) an answer”
- “it made me realize the significance of what we're studying- this is not just a lab, it actually affects people's lives”
- “it really made you think about the effects of genetic advances on our lives. I had never thought of the question we discussed.”
- “we repeated everything, many parts were boring (this is from a student who complains about almost everything).”
- “I liked discussing moral and medical aspects of the disease, it was interesting receiving results of a real person.”

IV. Ethics Unit Taught By Sharon Masse, Garfield High School

DAYS 1 & 2

1. Explain the decision making process on the 1st day. What information does a genetic counselor gather and why.

2. Questions to deal with:

What issues arise?

Who has ownership of the information and why?

Under what circumstances would a patient not be given information?

Who else gets the information and how might the patient control or circumvent this?

Explain policies on confidential information

How easy is it for others in the hospital to gain access to your information?

3. Show the videos from B.C. but must be of better quality.

4. Students need more time knowing their assigned person to gain ownership.

- We counted off randomly 1-5 and then assigned family members.
- Students might write out a personality profile of their person as a homework assignment discussing facts about their person, values and possible opinions that person holds.
- This also provided working groups to do the CAG repeat activity while other groups were getting results.
- Give students the consent form and additional questions to consider the day before the results are to be given to them.

DAY 3:

5. Regarding the Autoradiogram activity:

- Different semi-log paper or renumber 10-13
- Explain how gene is cut out of the chromosome to be run.
- Why calculate repeat when you can see which alleles are normal or HD?
- Why run 1 row vs. 4 to actually see the CAG repeats?

6. Giving out the results to the students:

- Find another adult to counsel students.
- Robert and I counseled one group of students at a time (all the Kristas, etc)
- We need a list of information that each counselor should present to each counseling group before they decide to receive their results. This time was really effective, some of my students really thought they were going to be tested and receive their results.
- We need to develop a result for Krista's fetus, as well as the one for Krista, some students wanted only that information.
- Robert developed two sets of results for each of the family members so that when the results were distributed to those that wanted to know, some were affected and others weren't.
- Post result information list is important to have.
- POWERFUL ACTIVITY!!!

DAY 4:

7. Follow-up after everyone received their results:

- We really ran out of time here and then spring vacation hit.
- The first day after vacation, most students needed the entire period to finish the activity.

V. Huntington's Disease - A Student Report

One can still live a happy life with Huntington's and it is, therefore, not vital that the Klein children (now grownups) get tested or that they get their children tested. It should be a personal choice and no "higher" authority should have the right to affect that choice. In my opinion, the only person who should seriously consider getting tested is Paul, the paramedic. Again it is his choice, but his ability to perform in an emergency situation affects the welfare of the community. If he were to have a lapse while giving CPR and a person died, then that person's family could sue the Fire and Rescue Department for a few million dollars. This event would mean trouble for Paul and his family, and for the taxpayers. You cannot force a person to take a test because of his or her occupation, but I wish there was a way to convince people to do so. If Paul tested positive, I would hope that because he loves his job so much and cares about the community, he would take an alternative position. He could become an assistant maybe. He would still be making a difference, but he wouldn't be putting others at risk. In regards to the other Klein children's occupations and lifestyles, they do not affect the welfare of the community. Therefore, it is not necessary to be tested. It's just a matter of how they want to live their lives.