Bioethics of Genetic Testing - Leaving a Legacy **Name: _____**

Part I: Something to Think About

"Whew!" Hannah sighed in relief as she slid into her seat just as the bell rang for sixth period genetics class. One more tardy and she would get detention for sure.

Mrs. Davis immediately welcomed the class and asked everyone to take a moment to consider the question she had displayed on the board.

Hannah read the question to herself, "Should someone with a family history of a genetic disorder seek genetic testing for the condition?" Hannah immediately felt a little uneasy.

"Okay, everyone. We have been discussing bioethics. Mark, please describe what we mean by that term," Mrs. Davis asked.

"It is kind of like what we should or should not do or what might be right or wrong but related to biology," Mark said. We had completed an exercise the day before identifying the difference between bioethical questions and scenarios versus other types of questions and situations, so Mark pretty much summed up what the rest of us took away from that activity.

"That is a good way to think about it and if you remember from yesterday, many of our ethical questions were asking, 'Should we do something.' We have to make decisions regarding biological issues based on an analysis of the effects or impacts. So, before we start that thinking process, let's see where everyone stands right now. I have a piece of tape on the floor. This end of the tape is a 'Yes' for choosing to have the genetic test and that end of the tape is a 'No.' There are 10 separate marks on the tape. Go stand at the mark that represents what you would choose to do if the first mark is a definite yes and the last mark is a definite no," Mrs. Davis instructed the class.

Hannah did not know what to do. This question was definitely affecting her on a personal level. Her older sister, Rachel, had just been diagnosed with breast cancer at the age of 30. Her mom, Deborah, was diagnosed with breast cancer when she was 42, only five years after Hannah had been born. Her other sister, Sarah, is 25 and does not have breast cancer thus far. They had all watched what their mom had gone through during her treatments. Knowing that Rachel is now facing the same battle was definitely taking its toll and what about Sarah and herself? Hannah went to stand at number 5. While she kind of wanted to know if she could develop cancer, she was also only 18 and she did not know if she wanted to constantly be wondering about when it might develop.

"Okay, class. Now that we see where we initially stand, let's think about the ethical considerations of genetic testing. Take a few moments and complete the graphic organizer and then we will share some of the advantages and disadvantages of genetic testing. Feel free to use your device to obtain information about both perspectives, the impact of choosing to get tested and the impact of electing not to get tested," Mrs. Davis instructed.

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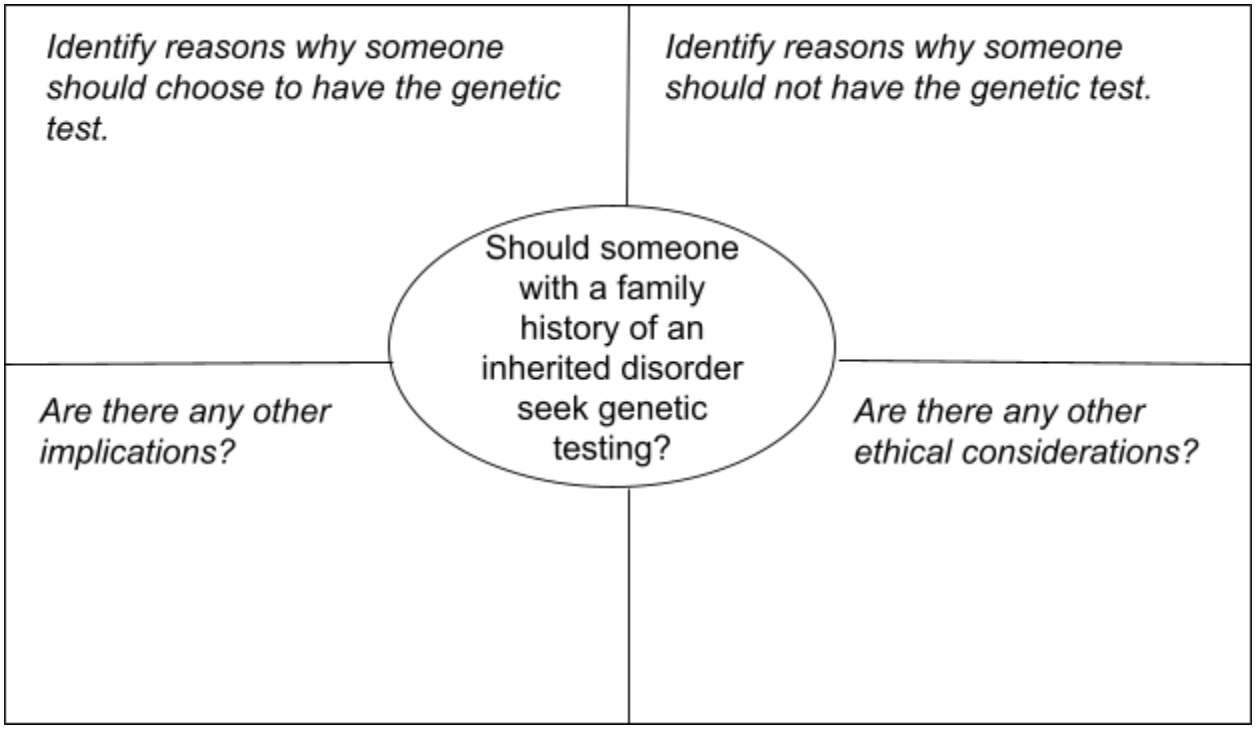
Critical Analysis: Imagine you are in Hannah's class. **Obtain and evaluate information** or think of your own reasons for choosing whether or not to undergo genetic testing.



Mrs. Davis gave her students some time to think about the bioethical question individually, in small groups and then as a class. Hannah listened intently as students shared lots of reasons for each perspective. As the class was ending Mrs. Davis asked if anyone had any questions.

Hannah raised her hand. "Yes, Hannah," Mrs. Davis acknowledged.

"Mrs. Davis, isn't there a genetic test for breast cancer?" Hannah asked.

"Yes. There are a number of genetic tests and options for identifying different alleles that could increase a person's chances of developing breast cancer," Mrs. Davis replied just as the bell rang.

Hannah knew the answer before she asked it, but the class definitely had given her a lot to think about.

Part II: Finding Answers

"Good afternoon, Hannah, Sarah, Rachel and Mrs. Alterman. My name is Dr. Chaney. I am a genetic counselor. It looks like you are interested in learning more about genetic testing for breast cancer. Is that correct?"

"Yes," Mrs. Alterman replied. "I am a breast cancer survivor and, Rachel, has recently been diagnosed with breast cancer. Hannah has expressed interest in finding out if she is at risk, along with her sister, Sarah."

"Well, you are taking the right first step. When a family history has been determined, it is good to see a genetic counselor to learn more about what might be causing the cancer and to determine if family members are good candidates for genetic testing. The next step is for us to gather some more information about your family history and to conduct a physical examination. Let's continue to collect family history. I am going to make some notes and construct at least a three-generation pedigree to help us see any patterns of breast cancer in your family. We can then conduct physical exams on Sarah and Hannah just as a precautionary screening. Can I ask you a few questions?"

Everyone nodded in agreement.

Critical Analysis: Imagine you are Dr. Chaney and **evaluate** the responses to the following questions. **Use the information** to **construct a model pedigree** of the occurrence of breast cancer in the space provided.

Alterman Family History Notes

Question 1: Do you have any other family members who have been diagnosed with breast cancer? And if so, can you give me their age of onset or when they were diagnosed?

Answer 1: Mrs. Alterman replied, "Yes. My father, Nathanael Goldberg, was also diagnosed in his forties. No one in my mother's family was diagnosed. My husband's family has no history of breast cancer." Rachel noted that there is no history of breast cancer in her husband's family either. Rachel has a daughter who is five and a son who is three. Sarah and Hannah are not married.

Note: Deborah was diagnosed when she was 42. Rachel was recently diagnosed at the age of 30. Sarah is 25 and has not been diagnosed. Hannah is 18 and has not been diagnosed.

Question 2: Has anyone in your family ever been diagnosed with ovarian cancer?

Question 2: No

*Question 3: Sometimes there are population specific mutations known as **"founder"** mutations that tend to affect certain populations in higher frequency than others. Is there anything unique you can tell me about your ancestry?*

Answer 3: Our family is Jewish, specifically Ashkenazi or eastern European.

Based on this information, **develop a model of a pedigree** illustrating all four generations below.

Based on the pattern in the pedigree, do you think it is likely that breast cancer is inherited in this family? If yes, **predict** the mode of inheritance.

Given the family history, use a Punnett Square to **predict** the likelihood of Hannah or Sarah inheriting breast cancer. What is the likelihood that Rachel's children could have inherited breast cancer?

Part II: Finding Answers (continued)

"The good news is that the physical examinations show no signs of breast cancer in Hannah or Sarah right now," Dr. Chaney explained. "However, your family history reveals a lot of information that we should discuss."

"When an individual cannot be identified clinically as having breast cancer but there is a family history of the condition, another option is genetic testing using genomic biomarkers. You may have heard of BRCA1 and BRCA2 which are tumor suppressor genes that normally help to repair damaged DNA and help to prevent cancer. The problem is when mutations occur in these genes and other genes that have been identified to be linked to breast cancer. BRCA1 and BRCA 2 account for 13% of breast cancer biomarkers. They are known as highly penetrant because they predict a high likelihood of disease when identified through genetic testing. Fifty percent of biomarkers are unexplained and there are many others that have been identified as well. It is important to also note that only 10% of breast cancers may be hereditary. There are lots of other factors that play a role as well. As a genetic counselor, I have to weigh all this information before determining whether family members are good candidates for biomarker testing.

In your family's case, it appears that all of you are candidates for BRCA2 biomarker testing. Narrowing down to this particular biomarker is cheaper and quicker than DNA sequencing. We would be looking at a very specific region of the DNA on chromosome 13 rather than the entire genome. Mutations in BRCA2 are more likely when both males and females are affected whereas identifying BRCA1 mutations tends to be used when families have incidents of both breast and ovarian cancer.

That is a lot of information to process. Do you have any questions?" Dr. Chaney asked.

"Why did you ask about our ancestry?" Hannah inquired.

"Excellent question. Sometimes, throughout history groups of individuals from an initially larger population found communities that are smaller. Incidences of certain genes tend to increase in those smaller populations and then individuals pass those genes or mutations of those genes to others in the population. Two founder mutations in BRCA1 and one in BRCA 2 have been identified. The penetrance or likelihood of disease tends to be higher in the BRCA1 founder mutations than those of the BRCA2. These mutations have been well documented and it is believed that 3% of individuals in this population carry a founder mutation. It increases your family's likelihood of testing positive for a BRCA2 mutated allele." Dr. Chaney explained.

"Since Rachel and I have been diagnosed and may carry the allele, what does that mean for Sarah, Hannah and even Rachel's children?" Deborah asked.

"Mutations in BRCA1 and BRCA2 have been identified as Autosomal Dominant. They are autosomal because each gene is not found on a sex chromosome. BRCA1 is on chromosome 17 and BRCA2 is on chromosome 13. It is considered dominant, meaning you only need to have one of the mutated alleles to increase your chances of developing breast cancer. Individuals with only one of the mutated alleles for BRCA2 have an estimated 49% chance of developing breast cancer. Those at greatest risk have an 83% chance of breast cancer by age 80. There are just many factors involved that determine the degree of risk. Unfortunately, your family has a number of those risk factors," Dr. Chaney continued to explain.

"Should we get tested?" Hannah asked.

"Ultimately, that decision is up to each of you. Your family history shows that you are candidates for BRCA2 testing. You meet a number of the criteria:

- You have a history of breast cancer in your family.
- Men in your family have had breast cancer; in this case, one.
- Your family is of Ashkenazi (Eastern European) Jewish descent.
- Usually, we say three or more women have had breast cancer, particularly those diagnosed prior to age 50 but you have two.

Since both your mom and one of your sisters have already been diagnosed, we can test them and Sarah and you. It is always better to have someone who is diagnosed tested because if

they test positive for the biomarker, the test is more valid because they have been confirmed to have the disease. Then we can compare the pattern in their DNA to yours and to Sarah's to see if you two have that marker as well. We do not advise testing children under the age of 18 because there are really no effective preventive measures in children so young and they are not old enough to provide informed consent. Each individual should decide how much information they want to know about their lifetime cancer risk. By the time they could develop cancer, new treatments may be available and there is no need to add that level of anxiety.

People who test positive have the benefit of exploring better preventative strategies, implementing strategies to decrease the risk, and exploring other targeting therapies. At the same time, a positive test can increase anxiety. A positive test means you are at higher risk for developing breast cancer. A negative test does not mean you will not develop breast cancer; it means the risk may be more similar to the general population.

I am going to provide you with some materials about the benefits and risks associated with biomarker testing. I want you all to read over the materials and make a list of questions that we can discuss at our next meeting. After we discuss all your questions, I will go over the informed consent document. We do not want you to agree to testing until you feel you understand all the benefits and risks.

Critical Analysis: After reading Dr. Chaney's explanation, answer the following questions.

1. Provide evidence for why the BRCA2 biomarker test is the best choice for the Alterman family. Why would Hannah's niece and nephew not be included in the test?

2. What is a founder mutation? Why does this type of mutation support that the Altermans are good candidates for biomarker testing?

3. The BRCA2 gene is 70,000 bases and includes 27 exons or coding regions. Most mutations in this gene result from premature truncations due to a nonsense or frameshift mutation. Explain what is meant when a gene is truncated. How could either a nonsense or frameshift mutation cause a gene to be truncated?

4. The BRCA2 founder mutation in Ashkenazi (eastern European) Jewish ancestry is noted as 6174delT. Describe how you think that mutation affected the original DNA sequence.

5. Based on the information provided, who do you think should be tested and why?

Part III: Deciding Yes to the Marker Test

As a Molecular Genetics Technologist, you will be performing the genetic marker test today for the Alterman family. All four women decided to be tested and signed an informed consent document. Blood samples were taken from each woman, DNA was extracted from the white blood cells, and the DNA was amplified using Polymerase Chain Reaction. The samples were then prepared using a restriction digest using the biomarker and a restriction enzyme to cut the DNA into different fragment sizes.

Below are the protocols used by this lab for running the DNA samples using gel electrophoresis. Since you are new to your position, follow the directions below exactly and listen to further instructions provided by your supervisor.

Procedure:

1. First practice using the adjustable micropipette to load some dye into the practice gels before loading your DNA samples into the wells of the actual gel in the electrophoresis chamber. A tip should ALWAYS be on the micropipette when you are transferring liquids. When everyone has practiced a few times, move on to the actual lab. Use the same tip when you are practicing.

2. Your gel chamber should be set up so that it contains the gel and buffer solution covering the gel. You should be able to see the wells in the gel.

3. Once you are ready to perform the genetic test, you will load the following samples into the gel in this order. Make sure you load 10 microliters of sample into each well. **Make sure you change tips between samples.** Turn the low intensity blue light on by pressing the small lightbulb on the carriage/chamber to help visualize the wells when loading.

    a. Lane 1: MiniOne Universal DNA Marker
    b. Lane 2: Sarah
    c. Lane 3: Rachel
    d. Lane 4: Deborah
    e. Lane 5: Hannah
    f. Lane 6: Negative Control

4. Once you have all the DNA samples loaded, place the photo hood (orange and black cover) securely on top of the gel chamber.

5. Press the power button and make sure there is a solid green light to show that it is on and working.

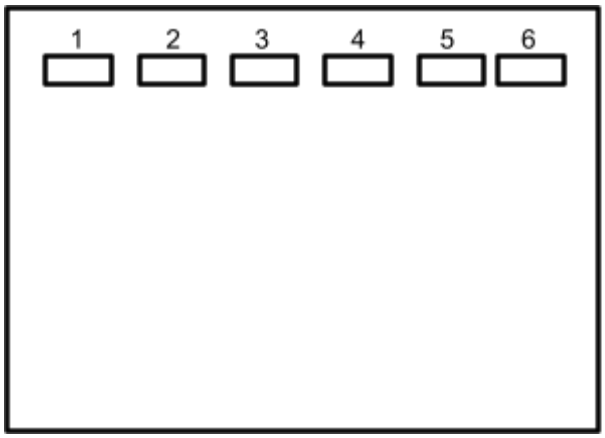
6. Check the migration of the bands every 5 minutes. You can place your phone on top of

the circle in the photo hood to take pictures or even take a time-lapse video.

7. Allow the gel to run about 20 minutes or until DNA separation is sufficient. After the run is complete, turn off the power by pressing the power button. Use the low intensity for viewing during the run. Light will weaken the fluorescent DNA signal.

8. Record your results on the diagram below. Be sure to write the name of the individual whose sample you place in each well on each line. Hannah's mom, Deborah, has had breast cancer and her sister, Rachel, has been diagnosed with breast cancer. Compare the banding patterns and see if there is a band Deborah and Rachel have in common. Write the approximate base pair size based on the marker bands for any common bands on the line beside their names. Do Sarah and Hannah share any bands with Deborah and Rachel? If so, write the size in base pairs beside their name.

Gel Analysis: Sketch your results on the gel template below: Identify the size of any common bands between Deborah and Rachel who have been diagnosed with breast cancer and Sarah and Hannah who do not know if they will develop breast cancer..



Lane 1: _____

Lane 2: _____

Lane 3: _____

Lane 4: _____

Lane 5: _____

Lane 6: _____

Analysis:

1. Describe how a genetic biomarker test works.

2. Why is it important to test a patient who has been diagnosed with breast cancer like Deborah and Rachel?

3. Explain why a negative control is used. What is the purpose of a negative control?

4. Describe how the process of gel electrophoresis works.

5. Describe how this form of biotechnology helps us to utilize DNA evidence to better inform patients about their chances of developing an inherited form of breast cancer.

Part IV: Learning What the Test Means

Analyzing and Interpreting Data

DNA Sample	Fragment	Fragment length in base pairs (bp)	Allele Present
Sarah Alterman	Fragment 1	1050	8
	Fragment 2	700	6
Rachel Alterman Epstein	Fragment 1	600	5
	Fragment 2	400	3
Deborah Goldberg Alterman	Fragment 1	700	6
	Fragment 2	400	3
Hannah Alterman	Fragment 1	1050	8
	Fragment 2	400	3

Based on the banding pattern results from the gel you ran and the information provided above, pretend you are Dr. Chaney. How would you explain the results to Mrs. Alterman and her daughters?

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Part V: Leaving a Legacy

After learning about her family's test results, Hannah became very interested in learning more about breast cancer research and particularly new methods for testing. Although she still did not know her own fate, she used the information to become informed about risk-reducing strategies and measures that were options for her, Sarah and her niece and nephew. She had always been interested in biology but her family's experience led her to declare her major in molecular biology as she headed off to college. She was determined to become a part of the solution as she aimed for a career in cancer research.

Analysis and Extension:

1. Why do you think Hannah's experience has motivated her to pursue a molecular biology degree and a possible career in cancer research?

2. Watch the short video clip below about Nancy Wexler and her experience both personally and professionally with Huntington's disease. **Obtain and evaluate additional information** about Dr. Wexler and her lifelong work and battle with Huntington's disease. Why do you think she considers this work and this disease her family's legacy?

(Huntington's Disease and Nancy Wexler - https://www.youtube.com/watch?v=Yf8gh4oDAXk)

3. Science should be objective, but that does not mean it is not sometimes personal. How do both Hannah's and Dr. Wexler's experiences show how one's personal experiences can be impacted by their understanding of science?

4. **Extension:** Research other forms of testing for breast cancer like Next Generation Sequencing and Liquid Biopsies. What innovative measures are being used to help with testing and treatments?

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Teacher Notes:

To begin this interrupted case study, you could choose to engage your students in the same activities that the class in the case study is participating in during Part I.

Sources:

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