Breast Cancer In-Class Worksheet

Introduction to Cancer

1) Provide a definition of cancer.

2) What are different stages of cancer growth?

3) What is apoptosis, and why is it an important defense mechanism against the development of cancer?

4) Explain ***why*** breast tissue is particularly susceptible to cancer.
Then… using this logic, propose other tissues in the human body that might be particularly susceptible to cancer, and which tissues would be less susceptible.

5) Describe and illustrate the following processes:
    a) DNA Replication.

    b) Transcription.

    c) Translation.

6) **Investigate:** From an evolutionary perspective, what is a "conserved trait"? Do some internet sleuthing and identify a few traits that are conserved in humans.

7) ***Discuss in your table groups!***
Think about the following characteristics, try to come up with one or more proximate and ultimate explanations for each

Characteristic	**Proximate explanation(s)** (HOW does the trait work?)	**Ultimate explanation(s)** (WHY does the trait exist?)
Black and yellow coloration in poison dart frogs		
Crying in human babies		

Cancer in humans		

8) ***Discuss in your table groups!***
Pick a human health condition or human disease (other than cancer). Without any further exploration try your best to theorize both a proximate and ultimate explanation for the condition:

Health condition:

Proximate explanation:

Ultimate explanation:

9) Cancer is the cost of multicellularity. Explain both the advantage and the potential costs of being made up of billions of cells.

Breast Cancer In-Class Worksheet

Cancer Genetics 1

1) Four overarching aspects associated with the process of evolution are: (i) the potential for individuals of a species to increase in number; (ii) heritable genetic variation; (iii) competition; (iv) "survival of the fittest".
   Use these ideas to explain how cancerous cells can evolve within a population of seemingly "normal" cells.

2) When a person reaches the age of 60, the DNA within most cells in their body have accumulated MANY mutations. Although cancer is certainly more common among people in their 60s, why isn't ***everyone*** at that age suffering from cancer, given all the mutations within their cells?

3) Cancers, like breast cancer, arise from a combination of genetic mutations within cells that that (i) increase the rate of cell proliferation (open throttles) and/or (ii) interfere with DNA synthesis and repair (brakes fail). This module presents a few genes whose mutant alleles are associated with breast cancer.
   Explain the terms ***proto-oncogene*** and ***tumor suppressor gene*** and give an example of each.

4) The *TP53* gene is called the "guardian of the genome", variants of which are associated with many kinds of cancer, including breast cancer. The protein product of the TP53 gene is part of the apparatus that repairs DNA. It also initiates apoptosis, cell self-destruction, preventing DNA damaged cells from reproducing.
   What is the relationship between apoptosis and cancer?

5) Elephants, despite being huge (many cells!) and long-lived (possible chance for mutations!) rarely develop cancer. This resistance is likely due their 20+ copies of the *TP53* gene.
   (i) Why would multiple copies of the TP53 gene act as a cancer deterrent?

6) Let's say that Dr. White quits his job and opens an elephant zoo. His favorite elephant is a salty bad tempered bull elephant named *Zeus*. As time passes, Zeus develops a tumor on his leg.

   This doesn't seem right!!! Elephants are supposed to be immune to cancer!!

   Dr. White decides to have a tissue sample from Zeus's tumor genetically tested. He discovers that 14 out of Zeus's 20 TP53 genes have nonsense genetic mutations in them.

   - How would the presence of these mutations in Zeus's tumor cells impact Zeus's susceptibility to cancer?

   - Are there any other genetic reasons that could be responsible for Zeus's tumor?

   - Are there any non-genetic factors that could contribute to the development of Zeus's tumor?

7) Zeus has fathered seven elephant calves. Describe the state of the TP53 gene in Zeus's seven beautiful elephant children. In what circumstances would they inherit "bad copies" of the TP53 gene, and in what circumstances would they inherit only "good copies" of the TP53 gene?

The following question will help begin to guide the development of your independent project.

Pick a human health condition.

Do some investigation online about the genetic underpinnings of this condition, and try to answer the following questions:

a.) Is there a specific allele and/or mutation that has been implicated in causing this condition? If possible, describe the exact way the nucleotides differ in the implicated gene.

b.) What is the evidence that this gene influences your chosen health condition? You will need to cite at least one source to answer this question.

Have questions? Email: pwhite@msu.edu

Breast Cancer In-Class Worksheet

BRCA and HER2

1) Describe the association between HER2 variants and cancer rates.

2) What does HER2 stand for? What does the HER2 protein do?

3) Describe the association between BRCA1 / BRCA2 variant and cancer rates.

4) What does BRCA stand for? What do the BRCA1 and BRCA2 proteins do?

5) Do some internet searching and come up with a **list of cancers** that have been associated with mutations in either BRCA1 or BRCA2.

6) Does a BRCA1 or BRCA2 mutation mean that you are likely to develop cancer? Why or why not?

Go to the University of Utah BRCA database,
found at; https://arup.utah.edu/database/BRCA/

7) Go to the BRCA1 landing page.

(i) How many variants of BRCA1 have been identified, and what percentage are pathogenic?

Go to the BRCA1 database

(ii) Choose a pathogenic variant that arises from an insertion or a deletion in an exon.

What is the nucleotide change?

Does the mutation result in a nonsense or missense change to the protein?

Click on the link that takes you to the abstract of the paper that describes the variant.
Summarize the findings of the research, below:

8) Go to the BRCA2 landing page.

(i) How many variants of BRCA2 have been identified, and what percentage are pathogenic?

Go to the BRCA2 database

(ii) Choose a pathogenic variant that arises from an insertion or a deletion in an exon.

What is the nucleotide change?

Does the mutation result in a nonsense or missense change to the protein?

Click on the link that takes you to the abstract of the paper that describes the variant. Summarize the findings of the research, below:

9) Dr. White had his DNA tested by a company called “23 and Me”. The company sequences various genes and reports back on the presence or absence of certain alleles. Here is the report that Dr. White received regarding his BRCA1 and BRCA2 alleles:

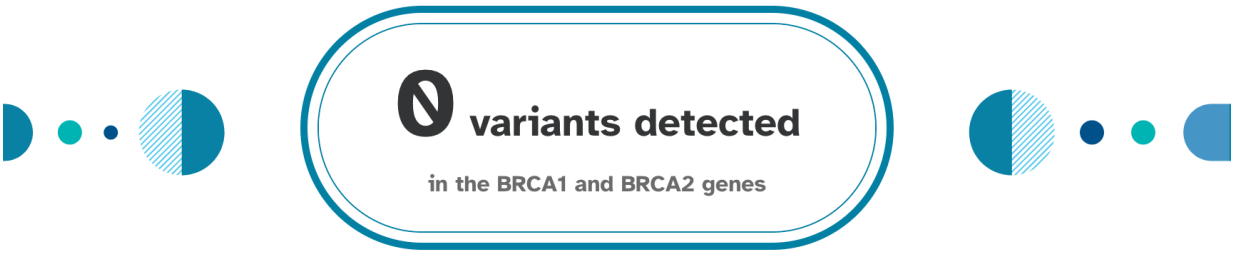
BRCA1/BRCA2 (Selected Variants)

Specific genetic variants in the BRCA1 and BRCA2 genes are associated with an increased risk of developing certain cancers, including breast cancer (in women and men) and ovarian cancer. These variants may also be associated with an increased risk for prostate cancer and certain other cancers. This test includes three genetic variants in the BRCA1 and BRCA2 genes that are most common in people of Ashkenazi Jewish descent.

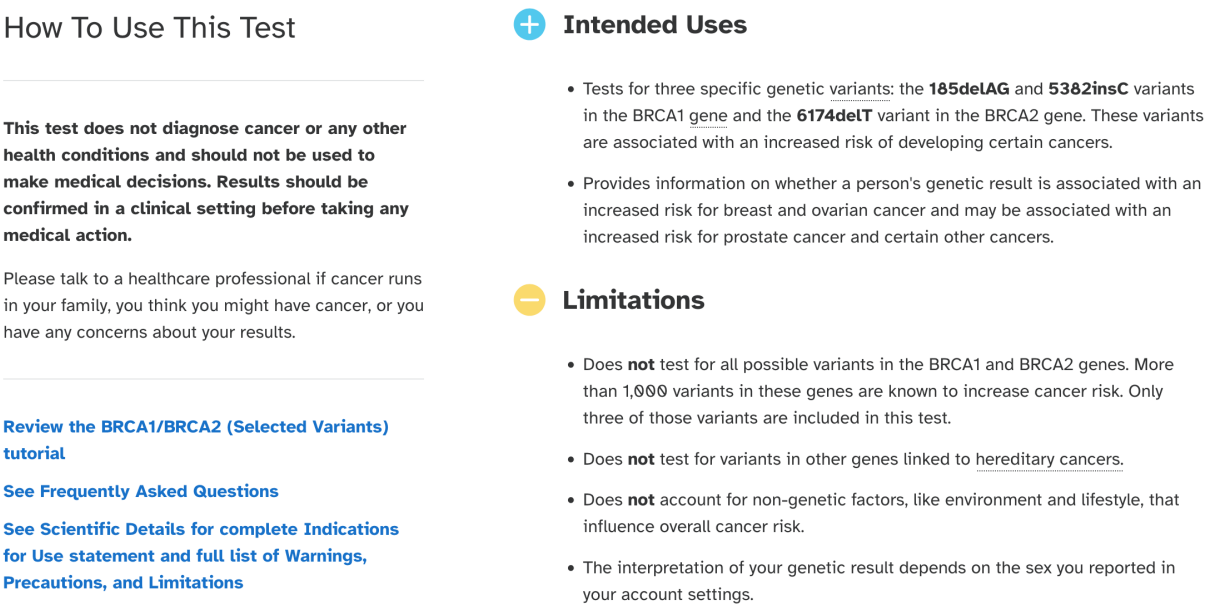
Overview | Scientific Details | Frequently Asked Questions

Peter, you do not have the three genetic variants we tested.

However, more than 1,000 variants in the BRCA1 and BRCA2 genes are known to increase cancer risk, so you could still have a variant not included in this test. In addition, most cases of male breast cancer and prostate cancer are not caused by inherited variants, so men without a variant are still at risk of developing these cancers. It's important to continue with any cancer screenings your healthcare provider recommends.



These worksheets can be modified, as desired, for your own purposes
Have questions? Email: pwhite@msu.edu



How To Use This Test

This test does not diagnose cancer or any other health conditions and should not be used to make medical decisions. Results should be confirmed in a clinical setting before taking any medical action.

Please talk to a healthcare professional if cancer runs in your family, you think you might have cancer, or you have any concerns about your results.

Review the BRCA1/BRCA2 (Selected Variants) tutorial

See Frequently Asked Questions

See Scientific Details for complete Indications for Use statement and full list of Warnings, Precautions, and Limitations

Intended Uses

- Tests for three specific genetic variants: the **185delAG** and **5382insC** variants in the BRCA1 gene and the **6174delT** variant in the BRCA2 gene. These variants are associated with an increased risk of developing certain cancers.
- Provides information on whether a person's genetic result is associated with an increased risk for breast and ovarian cancer and may be associated with an increased risk for prostate cancer and certain other cancers.

Limitations

- Does **not** test for all possible variants in the BRCA1 and BRCA2 genes. More than 1,000 variants in these genes are known to increase cancer risk. Only three of those variants are included in this test.
- Does **not** test for variants in other genes linked to hereditary cancers.
- Does **not** account for non-genetic factors, like environment and lifestyle, that influence overall cancer risk.
- The interpretation of your genetic result depends on the sex you reported in your account settings.

What are the three variants that *23 and Me* test for? And, what kinds of mutations occur to produce those variants?

10) What is the lifetime risk of developing breast cancer for a nonbinary person, a transgender man, a cisgender man, a cisgender woman, a transgender woman? (express these as a percent… it may take some internet exploring to try to determine these rates… try to find research articles to back up your numbers).

11) Use google Scholar, or a similar search engine, and determine how much a cisgender woman's risk for breast cancer would have increased with the presence of each of the variant alleles that *23 and Me* included in their test.

12) Can you find any information on the internet regarding the presence/absence of these variant alleles and the risk of breast cancer for (i) transgender women, (ii) cisgender men, (iii) transgender men, and/or (iv) nonbinary folx? (If not, why not?)

13) Let's say that Dr. White's three children were cisgender women. Would their lifetime risk of cancer be reduced if they did not have any of the three variant alleles tested for by *23andMe*? Why or why not.

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Breast Cancer In-Class Worksheet

Cell Biology – Breast cancer

For the following questions, **investigate** the functions of each protein. It may be helpful to refer to the breast cancer unit on www.evo-ed.org to get started.

1) a.) What does the HER2 protein do, and how does it relate to cell division?

   b.) How might an overexpressed and/or more functional HER2 protein lead to an increased risk of cancer?

2) Most mutations in coding regions typically reduce the function of a protein, or eliminate altogether. If a somatic mutation arises that reduces the function of the HER2 protein, or a similar protein that stimulates cellular replication (i.e. proto-oncogene), would this be a problem for the organism? Why or why not?

3) What are the G1-, G2-, and M-checkpoints? How does a cell "pass" each checkpoint?

4) a.) What does the p53 protein do, and how does it relate to cell apoptosis?

   b.) How might a non-functional p53 protein lead to an increased risk of cancer?

5) a.) What do the BRCA proteins do, and how do they relate to DNA replication?

   b.) How might non-functional BRCA proteins lead to an increased risk of cancer?

The following question will help continue to guide the development of your project. Work with the human health condition you picked for your project.

Do some research online about the cellular underpinnings of this condition, and try to answer the following questions:

a.) Is there a specific protein involved in the expression of your chosen health condition (what kind of protein is it? (E.g. enzyme, hormone, receptor etc).

b.) How does this protein affect cellular processes in a "healthy" state? What about when it is not functioning as it should?

Have questions? Email: pwhite@msu.edu

Breast Cancer In-Class Worksheet

Evolution (Trade-offs and Mismatches) – Breast cancer

1. From a humanity-wide perspective, describe why cancer cannot actually "be cured". In other words, why does it seem likely that humans will always be impacted by cancer?

2. What is an antagonistic pleiotropy? **Investigate** to find an example of an antagonistic pleiotropy that is not related to humans, or cancer.

3. Antagonistic pleiotropy (a trade-off) is one possible explanation for why breast cancer persists in human populations. Discuss scenarios where (i) a population bottleneck/founder event, (ii) kin selection, and (iii) mutation load might be responsible for breast cancer maintenance in human populations. Along with each scenario that you describe, see if you can find any supporting evidence on **Google Scholar**.

4. What is an environmental mismatch? Explain some examples of mismatches in human populations.

The following question will help continue to guide the development of your project. Work with the human health condition you picked for your project.

Do some research online about the cellular underpinnings of your chosen condition, and try to answer the following questions:

- Can evolutionary principles explain why humans remain vulnerable to the health condition you are working on? If so, explain the principle (i.e. is it a trade-off, mismatch, bottleneck, etc) and how it relates to your health condition.

Have questions? Email: pwhite@msu.edu

Breast Cancer In-Class Worksheet

Traditional Treatments

1) What are the three traditional treatments for cancer? How do they each work to combat cancer?

2) Why are multiple types of treatments often used instead of just one?

3) Would it matter if 100 cancerous cells were “missed” by the cancer treatments? What if only 10 cells were “missed”? What if only a single cell was “missed”?

4) Draw two rungs of a DNA ladder where interstrand cross-linking has occurred.
(You will need help from the internet on this one.)

5) When interstrand cross linking occurs, which specific proteins would this interfere with when it comes to DNA replication?

6) Is ESR1 a tumor suppressor gene, or a proto-oncogene?

7) How does ESR1 relate to the onset of cancer?

8) Go to the GenBank website from the National Center for Biotechnology Information here: https://www.ncbi.nlm.nih.gov/genbank/

   This website has a database of most genes that have been sequenced.

   In the nucleotide search box at the top, type in “*ESR1 homo sapiens complete cds*”

   Navigate to search result #14; this will open up a page that shows the complete sequence for the ESR1 gene.

   The answers for the following set of questions can be found on the ESR1 NCBI page that you’ve just opened. **In some cases, you will need to scroll down quite far to find the answer(s).**

(i) How many nucleotides are listed for the ESR1 gene?
(ii) How many amino acids are in the protein?

(iii) How many exons and how many introns does ESR1 have?

(iv) At what nucleotide position does the **mRNA** start?

(v) At what nucleotide positions is the start codon found?

(vi) At what nucleotide positions is the stop codon found?

(vii) At what nucleotide positions would you look for the tata box?
Why can you not find one

(viii) At what positions can you find the polyadenylation sequence?

9) With regards to your semester-project, what gene or genes are related to the health condition you are investigating?

Gene: _____

Go back to the genbank search page, and type in **the name of your gene** followed by "*homo sapiens complete cds*"

(i) How many nucleotides are listed for your gene?

(ii) How many amino acids are in the protein

(iii) How many exons and how many introns does your gene have?

(iv) At what nucleotide position does the **mRNA** start?

(v) At what nucleotide positions is the start codon found?

(vi) At what nucleotide positions is the stop codon found?

(vii) Is there a tata box? If so, what are the positions?

(viii) At what positions can you find the polyadenylation sequence?

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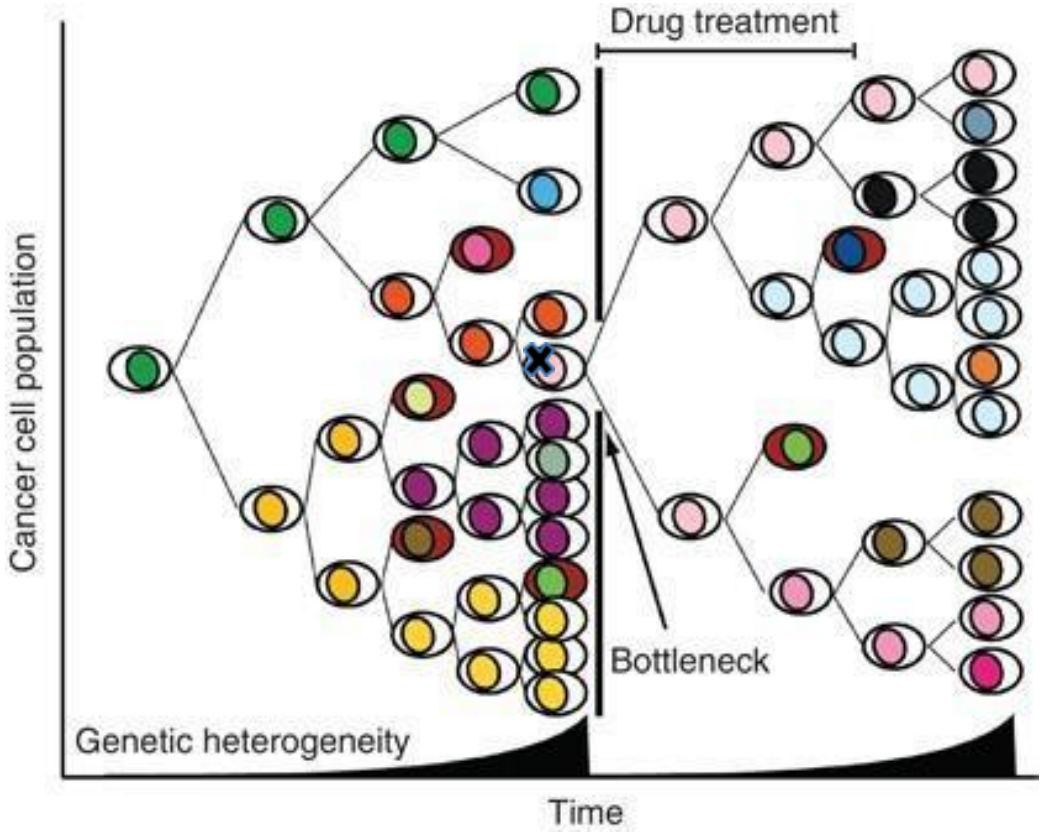
Breast Cancer In-Class Worksheet

Cancer Recurrence and Adaptive Therapy

1) Why does cancer return sometimes, even after treatment?

2) In situations where cancer returns, why is it often more aggressive and harder to treat?

3) Consider the following diagram and answer the questions, below.



- What is meant by “genetic heterogeneity” in the context of the cells shown?

- Does the vertical black line represent radiation or chemotherapy? Explain your answer.

- The X-marked nucleus cell represents a line of cells resistant to treatment. We can assume that its progeny cells will also be resistant to this particular treatment and more virulent. Propose a way to administer therapy to prevent this from happening.

Synthesis Questions

4) Think about how you might determine whether or not a particular allele is associated with increased rates of cancer. Use bullet points to describe a study you could run to determine if a new allele of the proto-onco gene ESR1 is associated with higher cancer rates.

5) The genes that we explored in the breast cancer unit were either proto-oncogenes or tumor suppressor genes. Theoretically, can a gene be ***both*** a proto-oncene **and** a tumor suppressor gene?
   - If so, what would the protein product have to be capable of doing?
   - If not, why not?

6) A breast cancer patient has variant BRCA alleles that they inherited from both parents. The tumor is surgically removed and after radiation and chemotherapy, it has been determined that ***100% of the cancerous cells were successfully removed***.
   Five years later, doctors discover a new occurrence of invasive ductal carcinoma. You have heard that recurring cancers can be much harder to treat and often metastasize.
   - In the case of this patient, would the new cancerous growth be more difficult to treat than the original tumor? Justify your answer, using your knowledge of cancer treatment and how/why cancers form.

7) What are the pros and cons of adaptive cancer treatment *versus* traditional cancer treatment?

Project Question

8) The following question will help continue to guide the development of your project. Work with the human health condition you picked for your project.
   Do some research online about the treatment options available for this condition, and try to answer the following questions:

   a.) What are two traditional treatment options for the health condition? Describe the procedure associated with each treatment, and the typical outcome following that treatment.

   Treatment option 1:

   Treatment option 2:

   b.) Is there any way that an evolutionary perspective can inform potential treatment options for this condition?