Updated 01/24/2024

TEACHING THE GENOME GENERATION

Module on Cancer Genetics

The Jackson Laboratory

Leading the search for tomorrow's cures

NIH National Institutes of Health
Turning Discovery Into Health

SEPA SCIENCE EDUCATION PARTNERSHIP AWARD

SUPPORTED BY THE NATIONAL INSTITUTES OF HEALTH

Contents

Cancer Genetics Module Overview

Introduction & Theme

Newborn Genetic Sequencing in the Future

Decades into the future, genomic sequencing will likely be a routine part of healthcare. Knowledge of gene variants associated with disease risk or outcomes can help individuals make decisions about not only their healthcare, but also their overall lifestyle.

Imagine it is some time in the future and for the last 40 years, whole genome sequencing has been the standard of care. While still in the delivery room, a few of the newborn baby's cells are collected for DNA analysis. Parents who opt for this testing will receive an electronic *Newborn Genomics Report* (NGR) detailing the gene variants associated with a range of diseases or conditions that were detected. The report also includes lifetime risk for developing specific diseases, as well as a description of the lifestyle factors that could increase or decrease the risk for disease and, additionally, any genomic-based treatments developed to treat disease based on the presence of a specific gene variant. The NGR is updated periodically as new information becomes available and treatments are developed. The NGR is part of the baby's official medical record.

Cancer Genomics

Cancer is a genetic disease. Changes in DNA sequence in specific genes contribute to the onset and development of cancer. Cancer is a disease that results when cells in the body grow out of control and form a mass called a tumor. Only about 5–10% of cancer cases are **hereditary** and associated with an inherited gene variant, and therefore, most cancers are **sporadic** and arise from DNA sequence changes that occurs in body cells. Sequence changes are called mutations and mutations create gene variants. Changes in DNA sequence arise from errors in DNA replication or from environmental exposure such as to UV radiation or carcinogens like those found in cigarette smoke. Not all gene variants lead to cancer, but those in a set of important genes are more frequently associated with cancer.

Minute to Understanding

What are DNA variants?
What is cancer?

Learning Outcomes

The following enduring understandings are emphasized in this module:

- Risk for cancer increases with age
- Cancer is a multifactorial disease with genetic, environmental, and other influences
- Only germline gene variants are inherited, and somatic variants are not
- The decision to receive genetic testing is personal and potentially impacts the lives of an individual and their family members

Lesson Descriptions & Learning Objectives

Activity: Exploring Hereditary Cancer on the cBioPortal: This activity guides students through data within a study on the cBioPortal. A short reading will introduce the students to a clinician who will see a young patient recently diagnosed with skin cancer. Students will calculate and analyze the range and median age of diagnosis for individuals with potentially inherited gene variants and discuss concepts such as germline inheritance, predisposition for cancer, and how genetics could influence age of diagnosis.

Skills	Computation; quantitation; data analysis & interpretation
Concepts	Gene variants associated with cancer risk; germline inheritance; genetic predisposition
Learning Objectives	Interpret the age of diagnosis histogram and calculate a median age of diagnosis within a single cancer study on the cBioPortal
	Sort a study on the cBioPortal by gene variant
	Explain why the age of diagnosis can be impacted by inherited gene variants associated with hereditary cancer syndromes
	Discuss the factors that impact age of cancer diagnosis

Extension: Interaction between genes & environment: In this extension activity, first students solve genetic inheritance problems to learn about penetrance, and then interpret a graph illustrating how geography can influence the penetrance of a gene variant associated with cancer risk. This is followed by a discussion of environmental factors contributing to cancer risk.

Skills	problem solving; graphical analysis & interpretation
Concepts	cancer risk; penetrance; interaction of genes and environment
Learning Objectives	Describe the concept of penetrance and how it applies to cancer risk
	Discuss the factors that impact age of cancer diagnosis

Application: Inquiry Project Exploring Hereditary Cancer on the cBioPortal: In this independent project, students formulate a hypothesis and use the cBioPortal to find data to support the association of specific gene variants with the development of cancer.

Skills	Computation; quantitation; data analysis & interpretation
Concepts	Gene variants associated with cancer risk; germline inheritance; genetic predisposition
Learning Objectives	Interpret the age of diagnosis histogram and calculate a median age of diagnosis within a single cancer study on the cBioPortal
	Sort a study on the cBioPortal by gene variant
	Explain why the age of diagnosis can be impacted by inherited gene variants associated with hereditary cancer syndromes
	Discuss the factors that impact age of cancer diagnosis

Activity: Identifying Hereditary Cancer using BLAST: This activity guides students through three scenarios in which they use BLAST to compare gene sequences for melanoma patient and their relatives to uncover if they carry a gene variant associated with hereditary skin cancer.

Skills	Data analysis & interpretation; problem solving; pattern recognition
Concepts	Gene variants associated with cancer risk; germline inheritance; genetic predisposition
Learning Objectives	Align two or more DNA sequences in BLAST
	Identify mismatches in aligned DNA sequences
	Determine presence of germline gene variants by interpreting DNA sequence alignment
	Use principles of genetic inheritance to conclude if an individual is at risk for hereditary cancer syndrome

Ethics of Genetic Testing in Cancer, Part 1: In this bioethics exploration, students address questions focused on the ethical implications of genetic testing. Students will discuss the concept of genetic destiny and will weigh the advantages and disadvantages of having genetic knowledge associated with increased cancer risk.

Skills	Formulating and articulating opinion
Concepts	Genetic testing; interaction of genes and environment
Learning Objectives	Discuss the advantages and disadvantages of uncovering gene variants associated with hereditary cancer using genetic testing for a healthy individual
	Reflect on genetic testing for cancer and how it is a very personal decision

Ethics of Genetic Testing in Cancer, Part 2: In this bioethics exploration, students address questions focused on the ethical implications of genetic testing. Students will discuss how they would feel about family members potentially receiving sensitive genetic information and whether they should share it. Students will think about the issue of consent within a family and consent regarding medical decisions for minors.

Skills	Formulating and articulating opinion
Concepts	Genetic testing; consent
Learning Objectives	Explain how one family member revealing genetic testing results could affect another family member's knowledge of cancer risk
	Discuss the role of consent when considering hereditary cancer, genetic testing, and respecting family members' wishes
	Describe how parents or guardians provide medical consent for children and how this can impact the entire life of a child

Lessons & Activities

Activity: Exploring Hereditary Cancer on the cBioPortal

Introduction

Dr. Myra Ortiz sat down at her office desk early one morning. Her computer screen automatically brought up today's schedule and her virtual assistant prompted her, "Do you want to review the files and histories for the patients you will see today?" The doctor agreed and her assistant brought up the first patient, Monica age 25.

"Another young one," Dr. Ortiz thought to herself. As a doctor who treats cancer patients, also called an oncologist, she specializes in melanoma, a type of skin cancer. Dr. Ortiz typically saw middle-aged patients, but every so often came across younger patients in their second or third decade of life. Cases presenting at this age can, but not always, have an inherited gene variant increasing risk for cancer. The doctor asked her virtual assistant to find Monica's Newborn Genomic Report (NGR). The assistant successfully located the NGR and Dr. Ortiz searched the report for cancer risk. Sure enough, Monica has a variant in the *CDKN2A* gene, which increases her risk for hereditary melanoma. "Ah yes, *CDKN2A*," Dr. Ortiz thought about the function of this gene. *CDKN2A* codes for a protein that acts as a guardian for the cell and prevents cells from growing out of control when something goes wrong. However, when one copy of this protein is not functioning properly, the risk for cancer increases.

After reviewing the rest of the day's patients and histories, Dr. Ortiz stood up, took a deep breath, and walked into the clinic.

Quick Knowledge Check:

a. How old is Monica and what type of cancer does she have?

b. What is an oncologist?

c. Which gene appeared on Monica's newborn genomic report as a variant increasing her risk for cancer?

d. What does this gene normally do in the cell?

Activity: Exploring Hereditary Cancer on the cBioPortal

Is Dr. Ortiz's patient Monica an outlier? Cancer is typically a disease of the aged. As people grow, they accumulate variants (mutations) in their DNA and therefore, advanced age is considered one of the most significant risk factors for cancer diagnosis.

1. Have a look at this graph from the National Cancer Institute's SEER database[1] (see **Figure 1**).

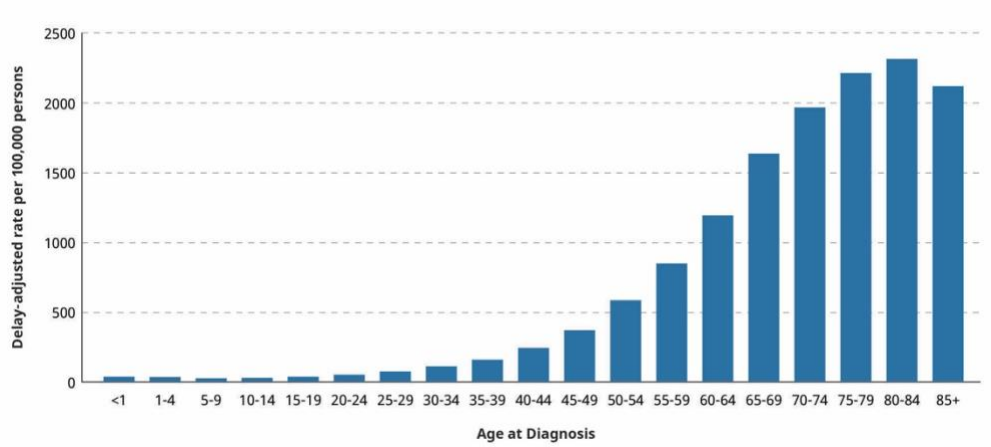


Figure 1. Cancer diagnosis increases as a function of age. New diagnoses of all types of cancer broken down into age groups. The data was collected by National Cancer Institute from 2013-17 for all races and both assigned sexes.

a) What do you notice about the shape of the graph?

b) At what age do you notice a steep increase in cancer diagnoses?

c) Use this graph to estimate the median age of cancer diagnosis.

Now let's explore the average age of diagnosis for patients with melanoma, which is the type of cancer Monica has.

2. Navigate to the cBioPortal and find the Metastatic Melanoma (DFCI, Science 2015) study. First, find the "Age of Diagnosis" histogram.

> *See cBioPortal Tutorial Series: Introduction & homepage navigation; Navigating a single study; Locating demographic data; Calculating age of diagnosis range; Calculating median age of diagnosis*

a) *Use the median feature to calculate the range and median age of diagnosis for patients in this metastatic melanoma study.*
   i. *What are the ages of the oldest and youngest patient in this study?*
   ii. *What is diagnosis age range?*
   iii. *What is the median age of diagnosis?*

b) *Is this median higher or lower than the one for the overall median age of diagnosis for all cancers that you estimated in question 1c?*

c) *What factors do you think contribute to the age of diagnosis for melanoma, a type of skin cancer?*

Note: Part c can be used as a discussion topic either as a whole or small group discussion or written reflection to introduce the concept of the interaction of genes and environment.

Monica has a *CDKN2A* gene variant. While *CDKN2A* variants are rare in the overall population, 20-40% of individuals with hereditary melanoma have an inherited *CDKN2A* gene variant. As Dr. Ortiz described, *CDKN2A* codes for factors that act as guardians in the cell, which are also called tumor suppressors. Tumor suppressors prevent cells from growing out of control. Let's investigate *CDKN2A* within this melanoma study.

See cBioPortal Tutorial Series: Locating gene variants within a single study; Sorting a study by gene name

3. Locate the list of "Mutated Genes" on the study main page. Use the search bar at the bottom of the list to find mutations in the gene *CDKN2A*.

   a. *How many mutations were identified in* CDKN2A *in this study?*

   b. *How many patients in this study have mutations in* CDKN2A*?*

   c. *How do you account for this discrepancy?*

4. Sort the study data to display only the patients who have mutations in *CDKN2A*, which has variants that can be inherited. Find the "Mutated Genes" table and scroll or search to find the *CDKN2A* gene. Check the box under "#" and click "Select samples" to display the data for only the patients with this mutation.

5. Once the data is sorted, locate the "Age of Diagnosis" histogram.

a. *What do you notice about the shape of the histogram?*

b. *What is the range of age of diagnosis for this group of patients?*

c. *What is the median age of diagnosis for patients with* CDKN2A *mutations?*

d. *Is the median age of diagnosis for patients with* CDKN2A *mutations different than the median age for the entire study (see Question 2)?*

e. *Is the median age for people with* CDKN2A *variants surprising to you? Why or why not?*

6. Still focusing on the *CDKN2A* sorted data, click the "Clinical Data" tab at the top of the study page. Then find the patients Pat 110 and Pat127. Without clicking on the patient ID numbers, find the "Age at Diagnosis" listed for each patient.

See cBioPortal Tutorial Series: Locating individual patient data

a. *How old were each of these patients when they received their melanoma diagnoses?*

b. *What factors do you think contribute to someone getting melanoma earlier in life versus later in life?*

c. *If both individuals have melanoma resulting from inherited mutations in* CDKN2A*, how can you explain this age difference?*

Note: Part c can be used as a discussion topic either as a whole or small group discussion or written reflection to continue the dialogue around the concept of the interaction of genes and environment.

d. *Challenge: Reflect on your answer to question 6c in connection with the shape of the histogram you observed in question 5a. Formulate a hypothesis that could be tested to explain the observed distribution of the age of diagnosis histogram. This question (part d) can be used as a "design an experiment" exercise, completed in groups or individually, in which students start with a hypothesis and propose how to test their hypothesis.*

See NGSS alignments for this activity

Reference

National Cancer Institute. Age and Cancer Risk. March 5, 2021. https://www.cancer.gov/about-cancer/causes-prevention/risk/age

Extension: Interaction between genes & environment

When studying genetics, we learn that if an individual has one dominant allele associated with a specific trait, that individual will likely have that trait. In the activity Exploring Hereditary Cancer, we learned that inheriting one variant allele of the gene *CDKN2A* is associated with risk for a type of skin cancer called melanoma. Having one variant allele of *CDKN2A* is considered dominant.

Use the above information to solve the following genetic problems:

1. *If a person with one copy of variant of* CDKN2A *has children with a person with no variants of* CDKN2A*, what percentage of their children are likely to be at risk for melanoma?*

2. *Challenge: If one of the children (unknown* CDKN2A *status) from question 1 has children with someone who does not any variants of* CDKN2A*, what percentage of their children will likely inherit the variant?*

While certain *CDKN2A* variants are associated with melanoma, the variant allele simply leads to "risk" for melanoma and not everyone with variant *CDKN2A* will ultimately develop this disease. Cancer is a disease controlled by many factors, therefore, fewer than 100% of people with a variant in *CDKN2A* will develop the disease. This percentage is referred to as "penetrance." If a particular allele has 0.5 or 50% penetrance for a disease, someone with the allele has a 50% chance of developing the disease.

Use the above information to solve this genetic problem:

3. *If variant CDKN2A has a 50% penetrance for melanoma, let's re-solve question 1 above. If a person with one variant allele of* CDKN2A *has children with a person with no* CDKN2A *variants, what percentage of their children will likely develop melanoma?*

As it turns out, the penetrance of *CDKN2A* gene variants varies within a population. An analysis of 80 families with *CDKN2A* variants living across the world, yielded data that indicates that there are other factors, such as the environment, playing into melanoma risk and affecting the penetrance of *CDKN2A* gene variants (Bishop *et al*., see **Figure 1**).

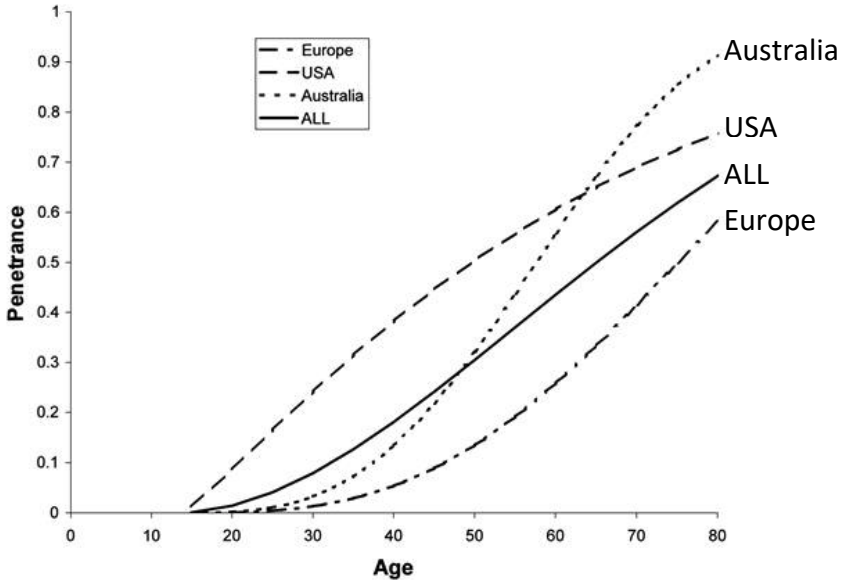


Figure 1. Penetrance of *CDKN2A* gene variants vary by geographic location. Researchers estimated the penetrance values for melanoma incidence associated with *CDKN2A* gene variants by age for a total number of families in the study (ALL); families living in Australia (Australia); families living in France, Italy, the Netherlands, and the United Kingdom (Europe); or families living in the United States (USA) (Bishop *et al*., 2002).

Use the graph to answer the following questions:

4. *On this graph, what are the independent and dependent variables?*

5. *Estimate the penetrance values of* CDKN2A *gene variants resulting in melanoma for the following geographic locations at age 60 (an age close to the median age for melanoma diagnoses):*

    i. *All locations*
    ii. *Australia*
    iii. *Europe*
    iv. *US*

6. *An individual with an inherited CDKN2A gene variants is most likely to get melanoma in which geographic region at age:*

    a. *30*
    b. *50*
    c. *70*

7. *During their entire lifetime (>60 years), in which geographic region are individuals carrying mutations in CDKN2A most likely to get melanoma? Least likely?*

8. *What factors do you think explain the observed discrepancy in penetrance based on geographic location?*

    Note: Question 8 can be used as a discussion topic for a whole or small group discussion or a written reflection.

See NGSS alignments for this extension

Reference

Bishop DT *et al*. 2002. Geographical variation in the penetrance of *CDKN2A* mutations for melanoma. *J Natl Cancer Inst.,* 94(12): 894-903.

Application: Inquiry Project Exploring Hereditary Cancer on the cBioPortal

Note: This is an outline for an inquiry project the students could do after completing Activity 1 using the cBioPortal to emphasize the connection between diagnosis age and inherited gene variants. This could be used as a short, additional in-class exercise or as an out-of-class assignment that could be expanded to include a write-up.

Implementation suggestions:
Short version: Using class time, students can investigate their hypothesis using the cBioPortal. This can be completed individually or in small groups and students could assemble a summary slide of their hypothesis and data to show to the class to briefly report out their findings (e.g. calculated medians) and conclude if their hypothesis was supported or not.

Project with write-up: Students can complete this out of class as a larger assignment. In addition to conducting research on the cBioPortal, students can write a report to describe the process, their findings, and conclusions. This write-up could include some or all of the following sections: an introduction to the hereditary cancer and the gene under investigation as well as a written hypothesis statement; a short method describing the study on the cBioPortal and which data were collected or used; a summary of the findings including a table or figure displaying the data (e.g. range and median age of diagnosis); and a written conclusion if the data supported the hypothesis or not.

Now it's your turn to investigate inherited gene variants using the cBioPortal. We learned inherited variants in *CDKN2A* are associated with hereditary melanoma. There are other genes that scientists and clinicians have identified to be associated with hereditary cancers (see **Table 1**).

Table 1. Gene variants associated with inherited cancers of different types

Gene Name	Cancer Type
APC	Stomach, Colon
BRCA1	Breast, Ovarian
BRCA2	Breast, Ovarian
MLH1	Colon
MSH2	Colon
MSH6	Colon
NF2	Brain
PALB2	Breast
PMS2	Colon
PTEN	Breast, Thyroid, Endometrial
SMAD4	Colon
WT1	Kidney

Select a gene and cancer type from this list to investigate. Then use the method you used in this activity to evaluate one or more cancer studies on the cBioPortal and your gene of interest.

a) First, write a hypothesis for the study or group of studies you would like to explore regarding a selected gene.
b) Use the cBioPortal to gather data to test your hypothesis. HINT: Think about age of diagnosis.
c) Draw conclusions about the data you gathered and determine if the data supports your hypothesis or not.

See NGSS alignments for this application

Activity: Identifying Hereditary Cancer using BLAST

Introduction

Vacations at the beach, sometimes forgetting to wear sunscreen, nursing sunburns with soothing aloe vera—Patrice's brain spun with memories of all the events over the last sixty-eight years that could have contributed to her melanoma diagnosis. She immersed herself in the literature, reading articles such as "*What is melanoma?"* and *"Surviving skin cancer."* One figure stuck with her: *5-10% of melanomas are hereditary.* Patrice remembers her mother never leaving the house without her large sunhat after Patrice's grandfather had passed away from skin cancer. Patrice wondered if she inherited a gene variant associated with hereditary melanoma, such as *MC1R*, *CDKN2A*, or *BRCA2* as the literature detailed. Nervously awaiting her genetic testing results, Patrice remembered her two daughters received genomic sequencing at birth. Maybe their newborn reports would be telling. She immediately called them and asked them to look at their NGRs. Neither had gene variants associated with melanoma. Maybe it was a coincidence that she and her grandfather both developed melanoma. *Maybe*.

Quick Knowledge Check:

1. How old is Patrice?

2. What type of cancer does Patrice have?

3. Who else in Patrice's family had this same type of cancer?

4. What do you think the word "hereditary" means when it is used to describe cancer?

Activity: Identifying Hereditary Cancer using BLAST

To determine if the variants identified in a tumor are inherited, it is important to investigate the same genes in other body tissues. Why?

Note: This opening question can be used for a whole group discussion or pre-write or to initiate a review of big-picture concepts such as, genomes and chromosomes, genomic testing, etc.

In this activity, you will analyze DNA sequences for a gene associated with increased risk for skin cancer, *CDKN2A*. For each section of the activity below, genomic sequencing revealed that none of the individuals has two copies of variant *CDKN2A*; all individuals with *CDKN2A* variants only have one copy variant copy. Therefore, all sequence comparisons will consider only one allele for each individual.

This link contains the DNA sequences required for this activity.

See BLAST Tutorial Series: Comparing two or more DNA sequences

Patrice

Patrice, age 68, received genetic testing on both her tumor tissue as well as the DNA isolated from a check swab. You will use BLAST to compare DNA sequences, specifically sequences of the *CDKN2A* gene. Variants in *CDKN2A* are associated with hereditary melanoma.

1. Locate the DNA sequences for Patrice.
2. Then navigate to the Nucleotide BLAST website and select the option to "align two or more sequences."
3. In the top box labeled, "Enter Query Sequence" paste the "CDKN2A Reference Sequence." Copy the entire text of the sequence as it is written in the sequences file including the description line beginning with ">."
4. In the box under "Enter Subject Sequence" paste the two sequences: Patrice's tumor tissue and Patrice's cheek swab.
5. Run the BLAST alignment and once the results load, use the "Alignments" tab and "Pairwise with dots for identities" view to compare the two sequences to the reference sequence.
    a) *Did you detect a variant in the tumor compared to the reference sequence?*

    b) *If yes, describe the sequence difference.*

    c) *Did you detect a variant in the cheek swab compared to the reference sequence?*

d) *If yes, describe the sequence difference.*
e) *Does Patrice likely have an inherited variant in* CDKN2A*? Explain your reasoning.*

To confirm your idea, let's compare the *CDKN2A* genes sequenced from cheek swabs of Patrice's living relatives, none of whom have melanoma. Edit your BLAST search to align the different sequences provided for Patrice's relatives which include her three sisters and one brother.

6. To do this, clear the "Enter Subject Sequence" box and copy and paste each relative's cheek swab sequence into the box. These sequences can be pasted in succession with a return between them. Remember to include the description line starting with ">" for each sequence.

    a) *What did you discover from comparing the relatives' sequences? Do any of them have a variant in* CDKN2A*?*

    b) *If yes, is the variant the same as the one identified in Patrice?*

    c) *Is this consistent with your answer to question 5e? Explain.*

Patrice reflects on the results of the genetic testing for herself and her family members. Her extended family is not overly close and her only memory of cancer in the family is her maternal grandfather who died of skin cancer when Patrice was very young. Neither of her parents had cancer before they both passed away over 10 years ago.

7. Consider all the information you have about Patrice and her family members:
    a) *Draw a pedigree or family tree indicating the inheritance pattern of heredity melanoma and CDKN2A variants in this family.*

    b) *Patrice's daughter is worried about her children potentially getting melanoma, are they at greater risk for melanoma?*

Monica

Patrice meets Monica in a skin cancer support group that she attends every week. Like Patrice, Monica also has melanoma, but is very young, only twenty-five-year-old. As a much younger individual, Monica received genetic testing at birth, which revealed a variant in the gene *CDKN2A*. Despite this information being included in her report, she was caught off guard with her diagnosis. She lives in a northern US state with long winters and has had very few sunburns in her life. She just did not expect to develop cancer at age 25. Concerned for her family members, Monica alerts her relatives about this variant and suggests that they consider genetic testing as several of them did not receive newborn genomic sequencing. A few of her relatives decide to get tested. Let's compare the *CDKN2A* genes sequenced from cheek swabs of her relatives, including her mother, brother, and paternal aunt, to the *CDKN2A* reference sequence.

1. Locate the DNA sequences for Monica.
2. Then navigate to the Nucleotide BLAST website and select the option to "align two or more sequences."
3. In the top box labeled, "Enter Query Sequence" paste the "CDKN2A Reference Sequence." Copy the entire text of the sequence as it is written in the sequences file including the description line beginning with ">."
4. To identify which variant Monica has, copy and paste her tumor tissue and cheek swab sequences into the "Enter Subject Sequence." These sequences can be pasted in succession with a return between them. Remember to include the description line starting with ">" for each sequence. Run BLAST.
    a) *Describe the variant you observe in Monica's cells.*

5. Now edit your BLAST search to align the different sequences provided for Monica's relatives. To do this, clear the "Enter Subject Sequence" box and copy and paste each relative's cheek swab sequence into the box. These sequences can be pasted in succession with a return between them. Remember to include the description line starting with ">" for each sequence.
    a) What did you discover from comparing the relatives' sequences? Do any of them have a variant in CDKN2A*?*

    b) What other information would you like to have to increase your confidence that Monica inherited the CDKN2A variant? Are there any individuals or data points that are missing?

    c) Assuming that Monica has an inherited variant in CDKN2A, describe how it is possible that her aunt does not have the variant.

Note: Part c can be used for a whole group or small group discussion or writing exercise

Carlo

Another active member of the skin cancer support group is Carlo. Like Patrice, he did not receive genetic testing at birth seventy-six years ago and therefore, does not know if he has any gene variants associated with increased risk for melanoma. Carlo undergoes genetic testing on his tumor tissue as well as on a cheek swab.

1. Locate the DNA sequences for Carlo.
2. Then navigate to the Nucleotide BLAST website and select the option to "align two or more sequences."
3. In the top box labeled, "Enter Query Sequence" paste the "CDKN2A Reference Sequence." Copy the entire text of the sequence as it is written in the sequences file including the description line beginning with ">."
4. In the box under "Enter Subject Sequence" paste the two sequences: Carlo's tumor tissue and his cheek swab.
5. Run the BLAST alignment and once the results load, use the "Alignments" tab and "Pairwise with dots for identities" view to compare the two sequences to the reference sequence.
    a) *Did you detect a variant in the tumor compared to the reference sequence?*

    b) *If yes, describe the sequence difference.*

    c) *Did you detect a variant in the cheek swab compared to the reference sequence?*

    d) *If yes, describe the sequence difference.*

    e) *Does Carlo likely have an inherited variant in* CDKN2A*? Explain your reasoning.*

    f) *Carlo has three sons all who have not had genetic testing. Should Carlo tell his sons to get tested?*

After informing his relatives about the results of his genetic testing, one of Carlo's sons mentions that his ten-year old son (Carlo's grandson) has a *CDKN2A* variant on his newborn genomic report.

6. Edit your BLAST search to align the cheek swab from Carlo's grandson to the reference sequence. To do this, clear the "Enter Subject Sequence" box and copy and paste the cheek swab sequence into the box. Remember to include the description line starting with ">."

    a) *Describe the variant present in the* CDKN2A *sequence from the cheek tissue of Pat110's grandson.*

    b) *Describe how it is possible that Carlo's grandson has a* CDKN2A *variant in his cheek tissue.*

See NGSS alignments for this activity

Ethics of Genetic Testing in Cancer, Part 1

Are genetics everything?

a. Monica is only 25 years old and was diagnosed with a disease that is more common to older adults. Monica may think back to all the times she forgot to wear sunscreen and feel like this was her fault. What could Dr. Ortiz tell Monica to help her cope with her diagnosis?

b. Imagine a person has a family history of skin cancer. Should this person get screened for germline/inherited gene variants associated with increased risk for skin cancer? Why or why not? What factors would contribute to their decision?

c. Simply having one gene variant associated with risk does not guarantee a cancer diagnosis. If a person found out they had a gene variant that confers risk for skin cancer, should they change their behavior to lower the risk? If yes, how?

For more ethics discussion ideas, explore ethics of personal genetics – pgEd lesson plan on personal genetics

See NGSS alignments for the ethics lessons

Ethics of Genetic Testing in Cancer, Part 2

Medical consent and respecting other's medical decisions

There are times when a family member does not agree with medical decisions another family member has made. If one family member uncovers genetic information about themselves, it could have significant implications for other members of the family. Not everyone will actively consent to being informed of genetic data that is shared within a family. Additionally, babies receiving newborn sequencing cannot consent to this.

1. Imagine a young adult in her early 20s decides to get genetic testing because her maternal grandmother and maternal uncle both had breast cancer. She finds out that she carries a gene variant putting her at high risk for breast and ovarian cancer. She is now able to get a higher level of preventative care so that doctors could identify cancer at an earlier stage. Her mother, who is in her 40s, does not want to know if she carries a high-risk gene variant. Because it is highly likely the young adult inherited the gene variant from her mother, should she tell her mother about the gene variant even if she doesn't want to know? What factors play into her decision?

2. Parents are given power to make medical decisions for their minor children. Parents face such decisions on a regular basis, from selecting medications, signing off on surgery, or deciding whether to vaccinate their children. Is it ethical that parents make the decision to get their baby sequenced when the baby cannot consent to this and yet it has implications affecting their entire life?

For more ethics discussion ideas, explore ethics of personal genetics – pgEd lesson plan on personal genetics

See NGSS alignments for the ethics lessons

Implementation Strategies

To accommodate different learners, it is possible to adapt the lessons in this module by process, product, or content. Process adaptations focus on the tasks the students use to master the material; product adaptations center around the ways in which students will demonstrate their learning; and content adaptations focus on the specific knowledge or skills needed to master the material.

Process Adaptations

Adjust the activities in this module:

- Modify activity length
    - *Exploring Hereditary Cancer with the cBioPortal,* stop the activity after:
        - Analyzing Study Age at Diagnosis (Step 2)
        - Locating Mutated Genes (Step 3)
        - Analyzing *CDKN2A+* Age at Diagnosis (Step 5)
    - *Identifying Hereditary Cancer Using BLAST*:
        - Stop the activity after aligning Patrice's tumor and cheek tissue
        - Stop the activity after aligning Patrice and her relatives' sequences
        - Assign just one case (Patrice, Monica, or Carlo)

- Alter the level of teacher support
    - Lead an interactive demonstration of the cBioPortal or BLAST
    - Provide scaffolds such as word banks, illustrations, and partial answers with blacks to fill in when answering questions
    - Guide students in completing the activity in chunks during class
    - Assign elements of the activity as homework

- Use different modes of student engagement
    - Large group discussion
    - Partner or small group conversations
    - Divide up the questions or cases by group (jigsaw)
    - Independent work

Product Adaptations

Students can demonstrate their learning through:

- Written responses
    - Short answers to questions
    - Essay or report
    - Posts on an online discussion board

- Presenting their findings:
  - Synchronous: during class
  - Asynchronous: slide deck or video
- Documenting their progress on the cBioPortal or BLAST:
  - Screen prints
  - Screen recording
- Participation in discussions:
  - Contributions during class
  - Reporting back on partner or small-group conversations

Content Adaptations

The lessons can focus more particularly on certain content. Possible content foci are listed under each student learning objective:

Exploring Hereditary Cancer with the cBioPortal:

- *Interpret the age of diagnosis histogram and calculate a median age of diagnosis within a single study on the cBioPortal.*
  - Define the concept of a median.
  - Practice calculating a median.
  - Interpret a data visualization.
- *Sort a study on the cBioPortal by gene variant.*
  - Describe the outcome of sorting, as demonstrated by the teacher.
  - Collaborate with peers to sort the study.
  - Sort the study independently.
- *Explain why the age of diagnosis can be impacted by inherited gene variants associated with hereditary cancer syndromes.*
  - Define the concept of inheritance with regards to a disease phenotype.
  - Describe the concept of genetic variation.
  - Make inferences about hereditary versus sporadic cancers.
- *Discuss the factors that impact age of cancer diagnosis.*
  - Identify risk factors for cancer.
  - Research social, economic, and environmental influences on cancer diagnosis.
  - Construct an explanation for observed patterns in age of cancer diagnosis data.

Identifying Hereditary Cancer Using BLAST:

- *Align two or more DNA sequences in BLAST.*
  - Input data correctly in a computational system to produce a desired output.
  - Navigate multiple applications using foundational commands such as copy/paste.
- *Identify mismatches in aligned DNA sequences.*
  - Practice orienting to a data visualization.
  - Describe one's interpretation of the data.

- *Determine presence of germline variants by interpreting DNA sequence alignment.*
    - Define germline.
    - Compare and contrast data appropriately based on category.
- *Use principles of genetic inheritance to conclude if an individual is at risk for a hereditary cancer syndrome.*
    - Construct and/or annotate a pedigree.
    - Interpret a pedigree to infer patterns of inheritance.

Sample Adaptations

Exploring Hereditary Cancer with the cBioPortal

Adaptation 1

This 40-minute lesson plan includes the following adaptations:

- Process: The length of the activity is modified to fit in one 40-minute class period.
- Content: Some steps are modified to highlight and define the concept of a median.

Download: Sample Lesson 1

Adaptation 2 with Bioethics

This two-day lesson plan includes the following adaptations:

- Product: Students produce written work to document their learning.
- Content: Bioethics content is integrated into the lesson.

Download: Sample Lesson 2

Identifying Hereditary Cancer Using BLAST

Adaptation 1

This lesson plan includes the following adaptations:

- Process: Completed in two 40-minute class periods with no homework, focused on one case study.
- Content: Students focus on annotating a pedigree to illustrate patterns of inheritance for Patrice and her family.

Download: Sample Lesson 1

Adaptation 2 including Bioethics

- Product: Students will produce notes for an in-class or asynchronous debate.
- Content: Students will particularly focus on the bioethical implications of genetic testing.

Download: Sample Lesson 2

NGSS Alignments

Activity or Lesson	Disciplinary Core Ideas	Cross Cutting Concepts	Science & Engineering Practices
Activity: Exploring hereditary cancer on the cBioPortal	Mutation & Variation	Cause & Effect; Patterns	Analyzing & interpreting data; Using mathematical & computation thinking
Extension: Interaction between genes & environment	Mutation & Variation	Cause & Effect; Patterns	Analyzing & interpreting data; Using mathematical & computation thinking; Constructing explanations and designing solutions
Application: Inquiry project exploring hereditary cancer on the cBioPortal	Mutation & Variation	Cause & Effect; Patterns	Asking questions; Planning & carrying out investigations; Analyzing & interpreting data; Using mathematical & computation thinking; Obtaining, Evaluating, & Communicating information
Activity: Identifying hereditary cancer using BLAST	Basic Inheritance; Mutations & Variation	Patterns	Analyzing & interpreting data; Using mathematical & computation thinking; Constructing explanations and designing solutions
Ethics of Genetic Testing in Cancer, Part 1 & Part 2		Cause & Effect	Engaging in argument from evidence

Supporting Materials

A. cBioPortal Tutorials

1. Written Tutorials
2. Video Tutorials
    a. Introduction & homepage navigation
    b. Searching for a gene of interest
    c. Navigating a single study
    d. Locating demographic data
    e. Calculating range of diagnosis age
    f. Calculating median diagnosis age
    g. Locating gene variants within a study
    h. Storing a single study by gene
    i. Locating individual patient data

B. BLAST Tutorials

1. Written Tutorials
2. Video Tutorials
    a. Comparing two or more DNA sequences

C. Minute to Understanding Videos

1. What are DNA variants?
2. What is cancer?

D. LabXchange

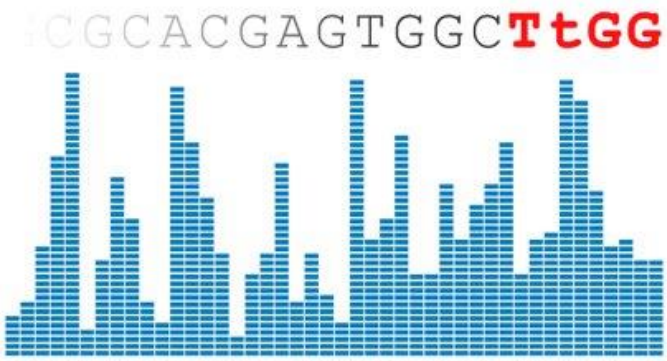
The TtGG Cancer Genetics module is also available as a pathway on LabXchange. Using this platform, it is possible to assign, combine, and remix parts of this module to create a unique, contextualized learning experience for students. LabXchange also hosts a range of other TtGG content including laboratory simulations and scrollables.

Cancer Genetics Pathway on LabXchange
Other TtGG content on LabXchange

E. Answer Keys

Download this teacher guide including activity and question answer keys.

Virtual Teacher Professional Development Course



TtGG™ Cancer Genetics Curriculum

Teacher Professional Development Course

The TtGG team has created a virtual MiniCourse on the Cancer Genetics module curriculum. This MinCourse is self-paced, takes 1.5-2 hours to complete, is completely FREE, and is designed for educators who are interested in implementing the TtGG™ Cancer Genetics curriculum with their students. The course provides interactive demonstrations of the databases used in the Cancer Genetics lessons and describes creative ways to integrate these lessons into courses for learners with varying abilities.

At the end of the MiniCourse, you will be able to:

- Identify the key features of the cBioPortal and BLAST, and navigate the database components relevant to the *Exploring Hereditary Cancer* and *Identifying Hereditary Cancer* activities;
- Outline the *Exploring Hereditary Cancer* and *Identifying Hereditary Cancer* activity and determine the appropriate resources used to complete each activity;
- Match Next Generation Science Standards (NGSS) to unit learning activities;
- Determine implementation strategies for adapting the module activities for various classroom scenarios.

Register here for free!

Feedback

Did you use the cancer genetics content in your class(es)? If so, we'd love to hear how it went. Use the following form to provide the TtGG team with feedback:

Cancer Genetics Feedback Form

Questions? Email ttgg@jax.org