OVERVIEW OF CANCER DISCOVERY ACTIVITIES

This educator guide provides support for **two Cancer Discovery activities**, both based on a Howard Hughes Medical Institute 2013 Holiday Lectures on Science video featuring researcher Dr. Charles L. Sawyers. Students begin by watching the online video clip, *Cancer as a Genetic Disease* *(http://www.hhmi.org/biointeractive/cancer-genetic-disease-video-highlights)*, and completing the accompanying *Video Worksheet*. After that assignment, instructors can decide which of the two activities (or both!) to use in class.

Activity 1: Classifying Cancer Genes

In Activity 1, students identify the locations on chromosomes of genes involved in cancer, or "cancer genes." By using the set of 139 *Cancer Gene Cards* and associated chromosome posters, students discover the following:

- About 140 human genes are currently known to be involved in cancer.
- Cancer genes are located throughout the human genome.
- The proportion of oncogenes versus tumor suppressor genes is roughly equal.
- The main cellular processes affected by mutations in cancer genes are cell survival, cell fate, and genome maintenance.
- One way to visualize genetic data is to map genes onto chromosomes.

Activity 2: Examining Cancer Patient Data

In Activity 2, students explore the genetic basis of cancer by examining cards that list genetic mutations found in the DNA of actual cancer patients. Small-group work spurs discussion about the genes that are mutated in different types of cancers and the cellular processes that the affected genes control. Students are asked to identify patterns and trends in the data.

Using the *Cancer Patient Cards*, students discover the following:

- Cancer is typically caused by mutations in several genes (i.e., two to eight genes for each cancer).
- Patients with cancer have different combinations of mutated genes.
- Mutations in the same genes can be involved in the development of different types of cancers (i.e., breast cancer or lung cancer).
- Mutations in different genes can cause the same type of cancer.

KEY CONCEPTS AND LEARNING OBJECTIVES

- Cancer is a disease of unregulated cell growth and division that interferes with the normal functions of the body (Activity 1 and 2).
- Cancer is caused by mutations in genes that normally play important functions in cells—in cell growth and division, cell fate (differentiation), and genome maintenance (Activity 1 and 2).
- By analyzing the genome sequences of many different kinds of cancer, researchers have thus far identified about 140 genes that, when mutated, contribute to the development of different cancers. These genes are distributed throughout the genome (Activity 1 and 2).
- Cancer genes can be classified as either tumor suppressor genes or proto-oncogenes/oncogenes (Activity 1 and 2).

- Tumor suppressor genes act like "brakes" that inhibit cell growth and division. When mutated, they can lose their braking function, which results in uncontrolled cell growth and division (Activity 1 and 2).
- Proto-oncogenes normally stimulate cell growth and division in a carefully controlled way. Mutated versions of proto-oncogenes, called oncogenes, act like "accelerators," causing cells to grow and multiply uncontrollably (Activity 1 and 2).
- Not all cancers of the same type have the same combination of mutated genes (Activity 2).
- Certain genes are involved in multiple types of cancer (Activity 2).

After completing these activities, students will be able to

- visualize genetic data (Activity 1);
- describe the differences between proto-oncogenes, oncogenes, and tumor suppressor genes in their own words and using examples (Activity 1 and 2);
- use online databases to determine information about the genes listed in the cancer cards (Activity 1 and 2);
- connect the information in the video clip to the data contained in the *Cancer Patient Cards*, the *Cancer Gene Cards*, or both (Activity 1 and 2); and
- summarize what they have learned and what surprised them, and formulate one outstanding question (Activity 1 and 2).

CURRICULUM CONNECTIONS

Curriculum	Standards
NGSS (April 2013)	HS-LS1-1, HS-LS1-2, HS-LS1-4
AP Biology (2012–13)	2.A.3, 2.E.1, 3.A.2, 3.B.2, 3.D.3, 3.D.4, 4.A.3, and SP 5, 6
IB Biology (2016)	3.1, 3.2, 3.4, and Aims 7, 8

KEY TERMS

cancer, cell cycle, cell death, cell fate, differentiation, mutation, oncogene, proto-oncogene, tumor suppressor gene

TIME REQUIREMENTS

Each activity is designed to be completed within one 50-minute class period, provided that the *Cancer as a Genetic Disease* video clip (8:30 minutes) and the accompanying *Video Worksheet* are assigned beforehand as homework. See **Figure 1** for a flowchart outlining the activities.

SUGGESTED AUDIENCE

Both cancer discovery activities are appropriate for first-year high school biology (honors or regular), AP and IB Biology, and other biology-related electives (i.e., Genetics, Anatomy and Physiology). Activity 2 is also appropriate for an undergraduate freshman biology class.

PRIOR KNOWLEDGE

In order to get the most out of these activities, students should be familiar with the following terms and concepts: the cell cycle and its regulation; genes and mutations; oncogenes and tumor suppressor genes; dominant and recessive genes.
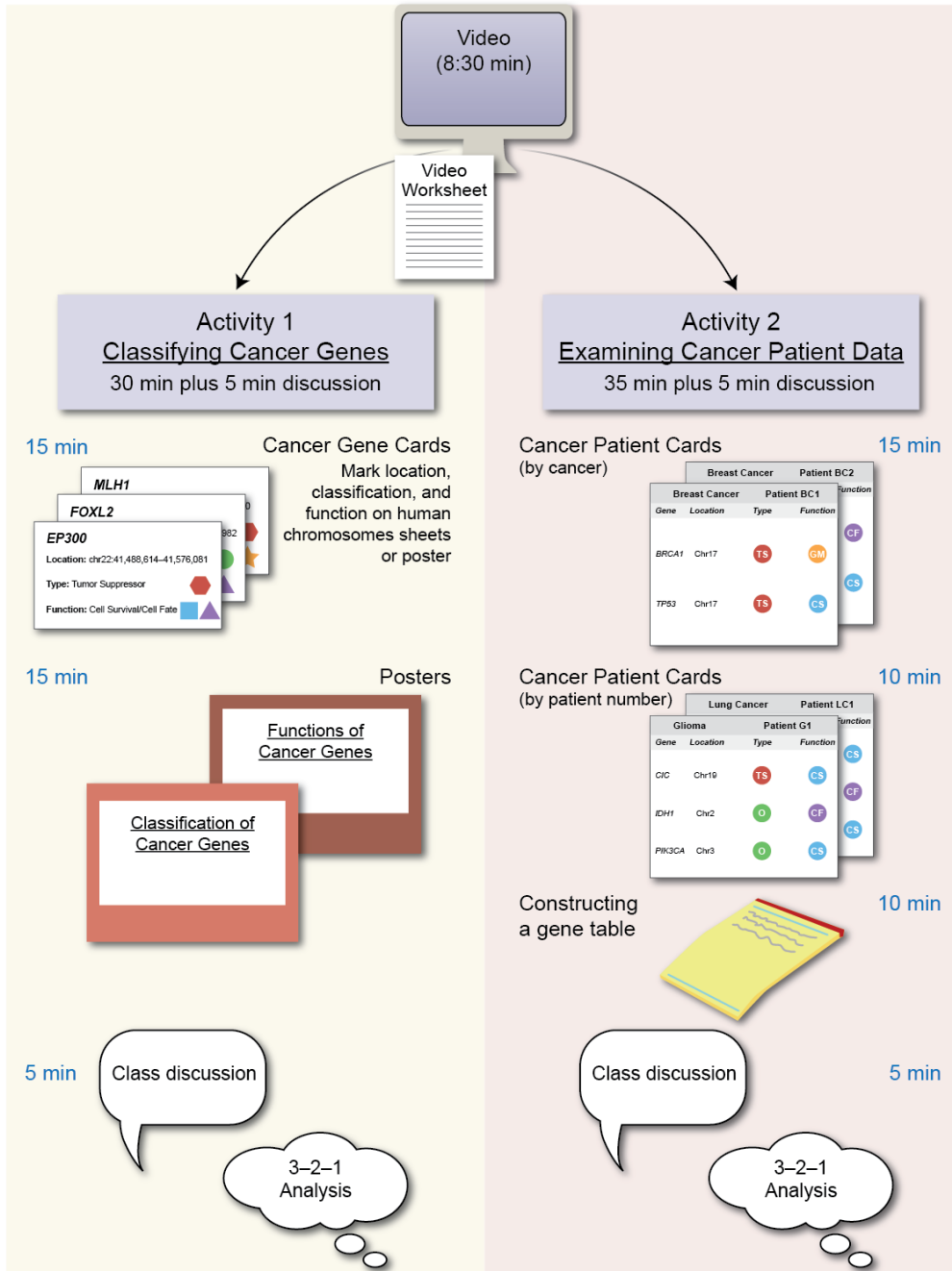
Figure 1. Planning flowchart for the two Cancer Discovery activities. Instructors may assign one activity or both. Both activities are based on a video clip that can be assigned as homework in advance of the in-class activity. *Activity 1* requires roughly 35 minutes of class time and *Activity 2* roughly 30 minutes. Both activities suggest a concluding class discussion (about 5 minutes) and a 3-2-1 analysis as a follow-up homework assignment.

BACKGROUND

Cancer consists of a group of diseases caused by mutations in the DNA of cells. Some mutations are inherited, but most occur during a person's lifetime as a result of random errors in replication. Environmental factors that damage DNA, such as smoking and sunlight, can also cause mutations to occur.

As a single cell in the body accumulates mutations, one of those mutations could provide a survival or a growth advantage to the cell, causing the cell to divide at a faster-than-normal pace or to not die. The resulting daughter cells with that mutation, which are dividing quickly, are more likely to accumulate additional mutations. Additional mutations that affect cell division may cause those cells to divide even faster. Eventually, a cell may acquire enough mutations that it starts to grow and divide uncontrollably (**Figure 2**).
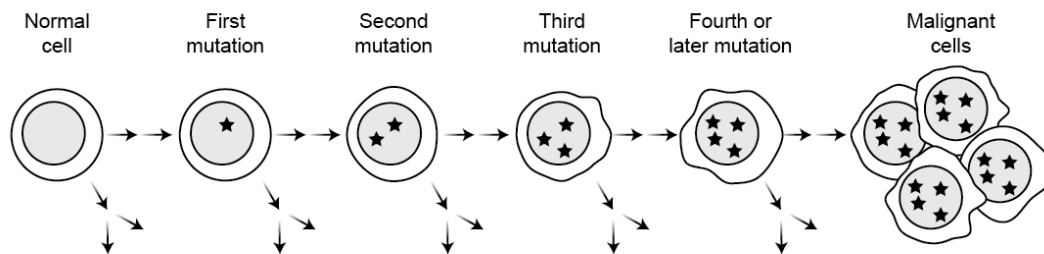

Figure 2. Schematic of cancer development. Cells accumulate mutations as they divide. Mutations that are most advantageous for cell growth and survival are passed on to daughter cells, which, in turn, acquire further mutations and may eventually become malignant cancer cells. (The arrows represent multiple cell divisions.)

Scientists have thus far identified about 140 different genes that, when mutated, can lead to the development of cancer. Most cancers contain mutations in two to eight of these genes. The 140 or so genes that drive the development of cancer fall into two categories that describe their effects on cell division. One category consists of **oncogenes**, which are mutated genes whose protein products cause cells to divide faster. The normal versions of oncogenes are called proto-oncogenes; they code for proteins that stimulate normal growth and division. The second category consists of **tumor suppressor genes**, which encode proteins that normally put the brakes on cell division and, when mutated, have the effect of taking the brakes off.

Oncogenes and tumor suppressor genes affect several different cellular processes, which can be grouped into **cell growth and survival** (genes involved in the cell cycle), **cell fate** (genes involved in cellular differentiation), and **genome maintenance** (mostly DNA repair genes).

QUESTIONS AND DISCUSSION POINTS

Some possible discussion questions and answers follow.

1. Are cancer genes only present in people who have cancer?

The genes on the Cancer Patient Cards and Cancer Gene Cards are normal genes that are part of the genomes of all people. People with cancer have mutations in subsets of these genes. When these genes are mutated, they can contribute to cancer. The normal versions of the genes produce proteins that have important functions in cells.

2. Does everyone who inherits a mutation in *BRCA1* eventually get breast cancer?

The *BRCA1* gene is a tumor suppressor gene, which means that both copies of the gene (or alleles) have to be inactivated for cancer to develop. People who inherit a mutation in one allele have a much higher risk of developing cancer, because they start with only one working copy of the gene in all their cells. If an additional mutation occurs on the other allele in one cell, it may lead to cancer. The cancer cards also show that patients with *BRCA1* mutations may have other types of cancer (i.e., glioma or hepatic cancer) than breast cancer. The type of cancer that develops depends on which cell type in the body first gets two inactivating (or loss-of-function) mutations in the *BRCA1* gene.

3. Do mutated tumor suppressor genes and oncogene carry different types of mutations? As explained in the answer above, tumor suppressor genes have to have two loss-of-function mutations for cancer to develop. Oncogenes carry mutations that increase the activity of the gene and its gene product to stimulate the growth and survival of cells. Because these are gain-of-function mutations, a single mutation in one allele of the gene is sufficient to contribute to cancer.

4. In the video clip, some tumors had hundreds or even thousands of mutations. Why do these cancer cards only list three to six mutations?

The cards only list the mutations that may cause a cancer to develop; these are so-called driver mutations. Cancers often have additional mutations that occur as a cancer progresses, but these mutations do not drive the disease. They are referred to as passenger mutations. Cancers with hundreds of mutations mostly have passenger mutations (see **Figure 3**).

5. What is the difference between driver and passenger mutations? How do you know which is which?

Mutations occur at random as a cell divides or as a result of environmental factors. Driver mutations provide survival and growth advantages to a cell; cells with these mutations are more likely to divide and survive, and the mutations are maintained in the population of cells in the final cancer.

A cell that acquires a driver mutation may also have some other mutations that do not provide a growth advantage. Although there is no selection for these passenger mutations, these will be carried along as a cell with driver mutations divides and multiplies. Passenger mutations will therefore also be present in cells of the final cancer.

A key challenge for researchers is to distinguish driver from passenger mutations. By analyzing thousands of cancer genomes, researchers can determine which genes are most frequently mutated in different cancers and thus likely to be involved in cancer development.

6. How does smoking cause cancer? The chemicals in cigarettes (e.g., tar, arsenic, benzene) cause mutations to occur. As more and more mutations accumulate in different cells, it is more likely that some of these mutations will cause cancer.

7. Although cancer can strike at any age, why are older people more likely to have cancer?

Cancer becomes more likely as we age and as damage to our DNA builds up. Advancing age is a high risk factor for cancer, with persons over 65 year of age accounting for 60 percent of newly diagnosed malignancies and 70 percent of all cancer deaths (see Berger *et al*.).
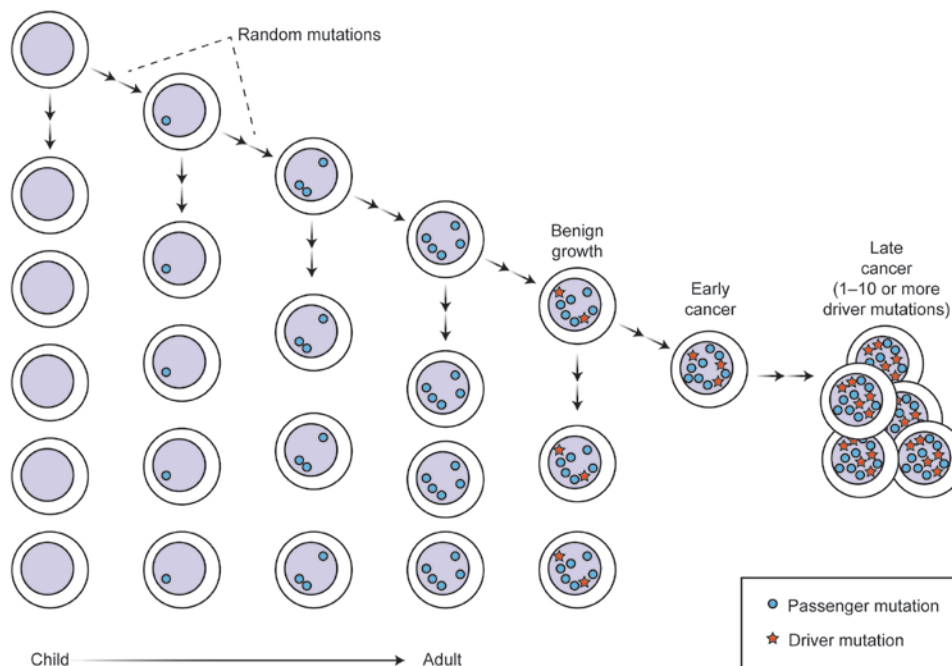

Figure 3. Driver versus passenger mutations in cancer. A single fertilized egg gives rise to the thousands of cells in the body. In this figure, we see the lineage of cell division from a fertilized egg to a single cell within a cancer. Mutations may occur in a normal cell as a result of cell division and the effects of environmental and lifestyle factors, such as smoking or sunlight. Once the first cancer-causing, or driver, mutations occur, defects in cellular processes—for example, in DNA repair—may cause more mutations to occur.

OPTIONAL RESEARCH PROJECT

Ask students to research one or more of the genes on their cancer card. Suggested websites for their research include the National Institutes of Health's (NIH's) Genetics Home Reference website, the Online Mendelian Inheritance in Man (OMIM) online catalog, the PubMed website, and the COSMIC database. Suggested questions for students to research include:

- What is the normal function of the gene? (Include whether it is a proto-oncogene or tumor suppressor gene.)
- Specifically, what does the mutated version of the gene do that contributes to cancer?
- In what other type(s) of cancer is the gene mutated?
- Are the mutations loss-of-function or gain-of-function types?

The product of this research extension project could be a scientific article, a miniposter, a pamphlet, or a concept map. An example of a concept map and a rubric for scoring the research project are provided at the end of this document.

RELATED BIOINTERACTIVE RESOURCES

1. Medicine in the Genomic Era, 2013 Holiday Lectures on Science Series, **Lecture 2: Cancer as a Genetic Disease**, by Dr. Charles Sawyers

Dr. Sawyers presents an overview of cancer biology and describes how understanding the molecular mechanisms involved in a type of cancer, chronic myeloid leukemia, resulted in the development of Gleevec, one of the first targeted cancer drugs.

2. Medicine in the Genomic Era, 2013 Holiday Lectures on Science Series, **Lecture 4: From Cancer Genomics to Cancer Drugs**, by Dr. Charles Sawyers

Cancers can now be classified not only by the type of tissue and cell that they affect, but also by the genes that are mutated. As Dr. Charles Sawyers reveals in this lecture, both types of classification are necessary for devising new targeted therapies.

3. Learning from Patients: The Science of Medicine, 2003 Holiday Lectures on Science Series, **Lecture 1: Research Mechanics: Putting the Brakes on Cancer**, by Dr. Bert Vogelstein

Cancers are caused by an accumulation of mutations that alter the activity of genes involved in controlling cell birth, growth, and death. Dr. Vogelstein explains that all cancers stem from alterations that allow cell division to outstrip cell demise.

4. Learning from Patients: The Science of Medicine, 2003 Holiday Lectures on Science Series, **Lecture 2: Chaos to Cure: Bringing Basic Research to Patients**, by Dr. Bert Vogelstein

The identification of hundreds of genes involved in the formation and spread of cancer is leading to promising new methods for diagnosis, prevention, and treatment. Dr. Vogelstein reviews some of these methods, including one that his own lab is working on.

5. Click and Learn: **The p53 Gene and Cancer**

In this Click and Learn activity, students learn what *p53* does and how interfering with its function can lead to cancer.

6. Animation: **Angiogenesis**

This animation illustrates what happens in a tumor, from cells dividing at an abnormally high rate, to the recruitment of blood vessels, and finally metastasis.

7. Animation: **VEGF (Vascular Endothelial Growth Factor)**

This animation explains how cancers release VEGF to stimulate the growth of blood vessels and increase blood supply, thus supporting their further growth**.**

8. Animation: **Mismatch Repair**

This animation shows how DNA polymerase's proofreading system works during DNA replication.

9. Animation: **Using p53 to Fight Cancer**

This animation illustrates a new, experimental cancer treatment that takes advantage of the fact that many cancer cells have a mutant and inactive form of the protein p53.

10. Animation: **CML and Gleevec**

Through this animation, students learn that chronic myeloid leukemia (CML) is caused by a mutation that leads to an abnormal protein that is always active and stimulates cell growth. The drug Gleevec has a shape that fits into the active site of the abnormal protein and stops its function.

11. Animation: **Gleevec**

This animation shows how the drug Gleevec has been designed to disrupt the growth of cancer cells by blocking a binding site of an abnormal protein found only in tumor cells and not in normal cells.

12. Animation: **Genetic Mutations and Disease**

This poster for the 2013 Holiday Lectures on Science series, Medicine in the Genomic Era, illustrates the difference between germline and somatic cell mutations.

13. Animation: **The Evolution of Cancer**

This article summarizes how cancers grow and spread by a process akin to evolution.

14. Animation: **Understanding Cancer Diversity**

In this article, students learn how cancer occurs when a cell acquires the ability to reproduce aggressively and invade other tissues.

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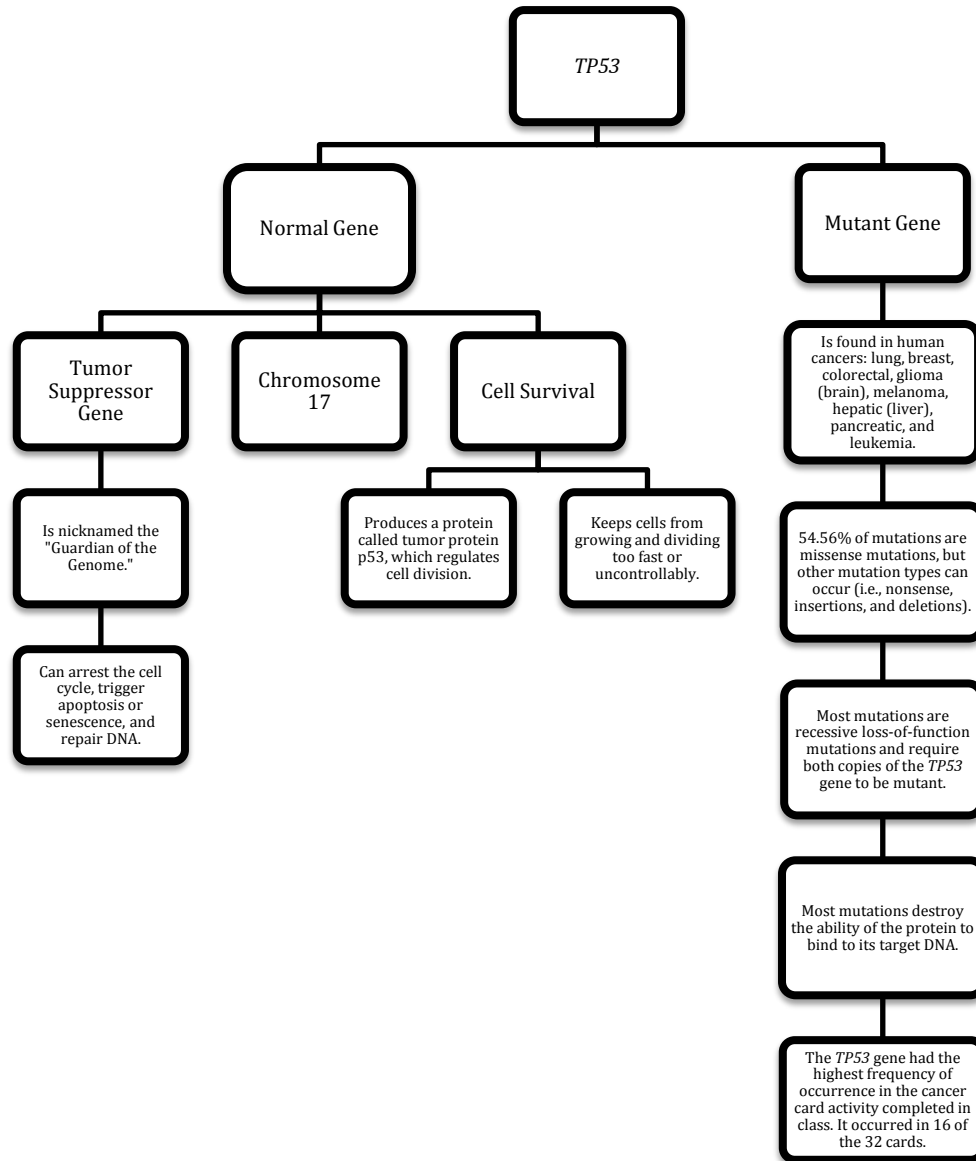
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SUGGESTED RUBRIC FOR 3-2-1 ANALYSIS

	Below Expectations	Meets Expectations	Exceeds Expectations
Knowledge	Items are missing or incomplete. Items do not reflect original ideas. Items do not reflect an understanding of the concepts and learning objectives.	All items are complete. All items reflect original ideas. Items reflect an understanding of the concepts and learning objectives.	All items are complete. All items reflect original ideas and are of high quality. Items reflect a much deeper understanding and application of the key concepts and learning objectives.
Thinking/Reasoning	Items do not reflect deeper thinking or further application of the key concepts and learning objectives.	Items reflect solid thinking about the key concepts and learning objectives.	Items reflect solid thinking about the key concepts and learning objectives and suggest applications or questions beyond the key concepts of the activity.
Clarity/Presentation	Submission was poorly written and unclear.	Submission was clearly organized and well written.	Submission was clearly organized, well written, and included additional images, ideas, or suggestions that went beyond the assignment.

STUDENT RESEARCH PROJECT: EXAMPLE CONCEPT MAP

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                          TP53
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           Normal Gene            Mutant Gene
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TP53

Normal Gene
- **Tumor Suppressor Gene**
  - Is nicknamed the "Guardian of the Genome."
  - Can arrest the cell cycle, trigger apoptosis or senescence, and repair DNA.
- **Chromosome 17**
- **Cell Survival**
  - Produces a protein called tumor protein p53, which regulates cell division.
  - Keeps cells from growing and dividing too fast or uncontrollably.

Mutant Gene
- Is found in human cancers: lung, breast, colorectal, glioma (brain), melanoma, hepatic (liver), pancreatic, and leukemia.
- 54.56% of mutations are missense mutations, but other mutation types can occur (i.e., nonsense, insertions, and deletions).
- Most mutations are recessive loss-of-function mutations and require both copies of the *TP53* gene to be mutant.
- Most mutations destroy the ability of the protein to bind to its target DNA.
- The *TP53* gene had the highest frequency of occurrence in the cancer card activity completed in class. It occurred in 16 of the 32 cards.