7 Who Should Pay?
Funding Research on Rare Genetic Diseases

Introduction

Students learn about Leigh's disease, a rare form of **Subacute Necrotizing Encephalomyelopathy (SNEM)** that can be caused by a deficiency in the cytochrome c oxidase complex (**Complex IV**). Deficiencies in the large, 13-subunit cytochrome c oxidase complex can result from defects in one of several proteins, including cytochrome c oxidase subunit 1, the protein encoded by the DNA barcoding gene, and examined in *Lesson Five*. Without the COI protein, cells are unable harness usable energy from **glucose**. This is a jigsaw exercise. Students are assigned or choose one of four stakeholder parties. They meet in "like" interest groups to become more familiar with that stakeholder's position and concerns. Afterwards, they meet in "mixed" groups with a representative from each of the stakeholder groups. Students identify areas of agreement and disagreement, and propose a compromise to recommend to Congress regarding funding for rare disease research. In ***Lesson Seven***, students also learn how ***pediatric neurologists*** might use bioinformatics tools in their career.

Class Time

1 class period of 50 minutes.

Prior Knowledge Needed

- DNA contains the genetic information that encodes traits.
- Basic introduction to bioethical principles is helpful.
- Cellular components, including DNA and mitochondria.

Common Misconceptions

- There is an unlimited amount of money available to fund research for all genetic diseases.
- Because pharmaceutical companies are very profitable, they should fund the development of drugs for all diseases instead of having taxpayer money fund research.

Learning Objectives

At the end of this lesson, students will know that:

- Rare genetic diseases affect a limited number of people but can cause great suffering.
- Much research in this country is funded by the public (i.e., taxpayer money).
- Not all research can be funded; there is a limited amount of money (resources) that must be allocated based on our values.
- Congress often hears testimony from many different stakeholders about important issues before making decisions about what to fund and what bills to pass.
- Knowledge of ethical principles can provide a structure for making complex decisions. The bioethical principles used in this lesson are:
  a. Respect for Persons (respecting the inherent worth of an individual and his or her autonomy)
  b. Maximize Benefits/Minimize Harms (beneficence/nonmaleficence)
  c. Justice (being fair)

At the end of this lesson, students will be able to:

- Identify stakeholder positions for different people concerned about funding research on rare genetic diseases.
- Identify ethical issues involved in funding research on rare genetic diseases.
- Apply their understanding of bioethical principles to the issue of allocating limited resources.
- Explain why someone would or would not support research on rare genetic diseases.

Key Concepts

- Rare genetic disorders like Subacute Necrotizing Encephalomyelopathy (SNEM) and Leigh's disease affect very few individuals but cause great suffering.
- Genetic research is a long process involving time, people, and financial resources.
- There are limited resources available to address a number of different research projects.
- Choices must be made to maximize the use of resources, to enhance the public good, and to limit harms.

Materials

Materials	Quantity
Copies of Student Handout—*Careers in the Spotlight* (handed out in *Lesson One*)	1 per student
Copies of Student Handout—*Issues in Funding Research on Rare Genetic Diseases*	1 per student
Copies of Student Handout—*Group 1: Testimony of Sally Meyers, Mother of Alex Meyers*	1 per 4 students (i.e., 25% of students are assigned Group 1)
Copies of Student Handout—*Group 2: Testimony of John Herring, Research Scientist*	1 per 4 students (i.e., 25% of students are assigned Group 2)
Copies of Student Handout—*Group 3: Testimony of Karen Holman, Pharmaceutical Representative*	1 per 4 students (i.e., 25% of students are assigned Group 3)
Copies of Student Handout—*Group 4: Testimony of Harry Tullman, Heart Disease Research Advocate*	1 per 4 students (i.e., 25% of students are assigned Group 4)
Teacher Answer Key—*Issues in Funding Research on Rare Genetic Diseases*	1
Teacher Answer Key—*The Process of Genetic Research* (found in *Lesson One*)	1

Computer Equipment, Files, Software, and Media
Computer and projector to display PowerPoint slides. ***Alternative:*** Print PowerPoint slides onto transparencies and display with overhead projector.
Lesson Seven PowerPoint Slides—*Who Should Pay: Funding Research on Rare Genetic Diseases.* Available for download at: http://www.nwabr.org/curriculum/advanced-bioinformatics-genetic-research.
A student version of lesson materials (minus *Teacher Answer Keys*) is available from NWABR's Student Resource Center at: http://www.nwabr.org/students/student-resource-center/instructional-materials/advanced-bioinformatics-genetic-research.
Computer lab with internet access and a word processing program such as Microsoft® Notepad or Word for answering homework questions.

Teacher Preparation

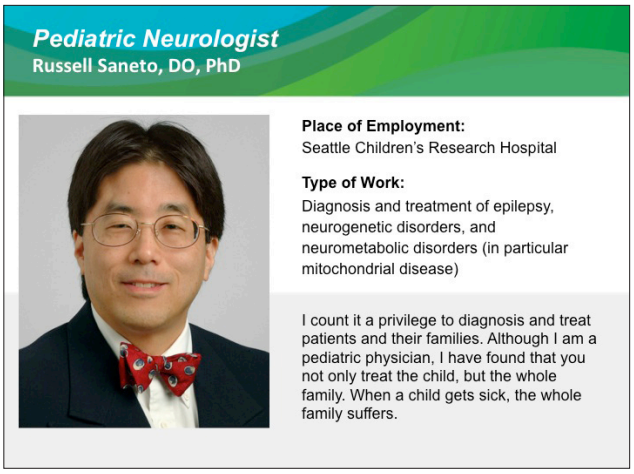
- Load the classroom computer with the *Lesson Seven* PowerPoint slides.
- Make copies of the Student Handouts. The Student Handouts *Group 1: Testimony of Sally Meyers, Mother of Alex Meyers*; *Group 2: Testimony of John Herring, Research Scientist*; *Group 3: Testimony of Karen Holman, Pharmaceutical Representative*; and *Group 4: Testimony of Harry Tullman, Heart Disease Research Advocate* are designed to be re-used as class sets.
- Students will be meeting in "like" groups of about six students per group (*Part II*), and "mixed" groups of about four students per group (*Part III*). Teachers may wish to reserve nearby meeting areas so that small groups can spread out and have quiet spaces to meet and talk.

Procedure

Warm Up

1. As students enter the classroom, display the PowerPoint slides for *Lesson Seven*, beginning with ***Slide #1***. This slide highlights pediatric neurologist Russell Saneto, DO, PhD.

2. Have students retrieve Student Handout—*Careers in the Spotlight*, which they were given during *Lesson One*.



Funding Research: ***Slide #1***

3. Students should think about, and write down, what kind of work a pediatric neurologist might do (*Pediatric Neurologist Question #1*). This will be revisited at the end of the lesson, including how a pediatric neurologist might use bioinformatics in his or her job.

4. Tell students to keep their *Careers in the Spotlight* handout available for future lessons.

PART I: Subacute Necrotizing Encephalomyelopathy (SNEM) and Leigh's Disease

5. Explain to students the ***aim of this lesson***. Some teachers may find it useful to write the aim on the board.

   Lesson Aim: Explore the ethical issues involved in funding research on rare genetic diseases.

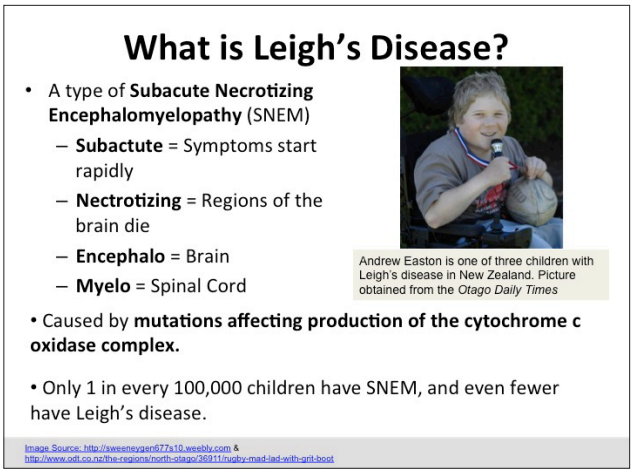
   Teachers may also wish to discuss the *Learning Objectives* of the lesson, which are listed at the beginning of this lesson plan.

6. Show ***Slide #2*** and introduce the students to Adam Kinnear, who is the only child in the United Kingdom (as of 2008) who has a rare genetic disease called Leigh's disease. Adam has difficulty swallowing or moving, and his parents do not know how long he will live. His father organized a bike ride with his friends to raise money for research on Leigh's disease, as shown in the photograph.

Funding Research: ***Slide #2***

Subacute Necrotizing Encephalomyelopathy (SNEM):
A rare metabolic disorder that affects the brain and spinal cord.

7. Show ***Slide #3***, "What is Leigh's Disease?" Explain that the disease is a form of **Subacute Necrotizing Encephalomyelopathy** (pronounced sub-A-cute neck-ROH-tizing en-CEPH-a-lop-a-theey), or SNEM for short. We can understand what that means by looking at what each part of the disease name means:
   - ***Subacute*** means that the disease comes on somewhat rapidly.
   - ***Necrotizing*** means that regions of the brain die, in this case from lack of energy (ATP).
   - An ***encephalomyelopathy*** is a disease that involves the brain and the spinal cord ("encephalo" means brain, "myelo"means "marrow" or "of the spinal cord," "pathy" means "disease of").



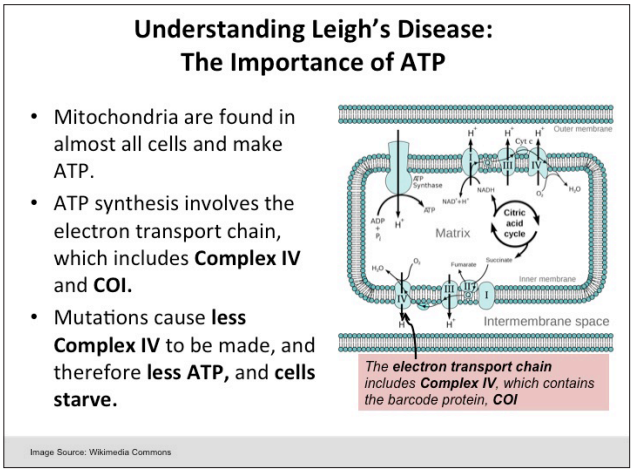
Funding Research: ***Slide #3***

8. Explain that Leigh's disease is caused by mutations that affect production of the cytochrome c oxidase complex (**Complex IV** of the electron transport chain). This complex includes the COI protein, encoded by the *COI* gene, the gene we use for DNA barcoding. This disease is very rare, affecting only 1 in every 100,000 children, including Adam Kinnear and Andrew Easton (pictured in ***Slide #3***). Andrew is one of three children in New Zealand to have Leigh's disease.

Complex IV: One of the protein complexes found in the mitochondria. Complex IV contains cytochrome c oxidase and is involved in the production of ATP (adenosine triphosphate).

9. Show ***Slide #4***, "Understanding Leigh's Disease: The Importance of ATP." Remind students that mitochondria are found in almost all cells, metabolizing the sugar and fats we eat to make ATP (adenosine triphosphate), which all cells use to power life. The electron transport chain is found in the inner membrane of the mitochondria (shown in the diagram in ***Slide #4***). Mutations that inhibit or prevent production of Complex IV result in less ATP produced, and the cells essentially starve.

[Note: While all cells in the body are impacted by the reduced production of ATP (including the muscles used in moving and swallowing, as mentioned in Step #6), the brain and spinal cord are particularly sensitive to low ATP levels, which can cause severe mental impairment.]

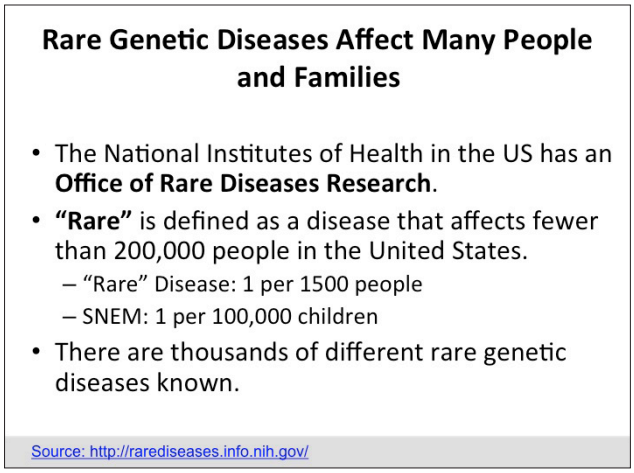


Funding Research: ***Slide #4***

10. Show ***Slide #5***, "Rare Genetic Diseases Affect Many People and Families." Share with students the following information:

    The National Institutes of Health in the United States has a special office called the Office of Rare Diseases Research, which focuses only on rare diseases. They define "rare" as any disease that affects less than 200,000 people in the US (or about 1 in every 1500 people). SNEM affects about 1 in every 100,000 children. There are thousands of different rare diseases known, many of them genetic, with each one affecting people and their families. While each disease affects only a small number of people, together these different diseases affect millions of people. In contrast, a common disease like heart disease causes 1 in every 5 deaths in the United States.

Funding Research: ***Slide #5***



11. Ask students, "Who do you think funds research on diseases like Leigh's disease and heart disease in the United States?" Some students may say "the government" or "companies." Explain to students that most scientific research in the United States is funded by:

    - ***Government grants*** of taxpayer money to scientists at universities, non-profit institutions, and small businesses. These grants usually come from the National Institutes of Health (NIH) or the National Science Foundation (NSF).
    - ***Pharmaceutical or biotech companies***. These for-profit companies have investors who pay for research and drug development, and then share the profits generated by that research (such as treatments for disease).
    - ***Private foundations*** like the Howard Hughes Medical Institute, the Gates Foundation, and the American Heart Association fund specific areas of research related to the mission of their group.

12. On the board, write these two questions:

    - Should Congress fund research into rare genetic diseases, like Leigh's disease?
    - How should Congress decide what research to fund?

13. Tell students that today they will be learning more about the various **stakeholders** involved in research on rare genetic diseases, such as Leigh's disease. Stakeholders are people who are directly affected by a particular situation or ethical decision. Congress often hears testimony from various stakeholders when they are developing a new law (legislation) or determining how much funding to provide for a particular situation or project (like research into Leigh's disease or heart disease). Today, students will explore different stakeholders' positions regarding funding for research on rare genetic diseases. First they will learn about the different stakeholder positions and then they will try to find a compromise that benefits everyone involved.

Stakeholder: Any person, institution or entity that is interested in, invested in or will be affected by the outcome of an ethical decision.

14. Ask students to brainstorm about people or groups that have an interest in how research on rare genetic diseases is funded. Write the heading "Stakeholders" on the board and list their ideas underneath. ***Prompt students to include in their list***:
    - Families of those with Leigh's disease
    - Research scientists studying Leigh's disease
    - Pharmaceutical companies
    - People researching diseases other than Leigh's disease that need taxpayer funding
15. After students have generated a list, circle the four they will be exploring (listed above).

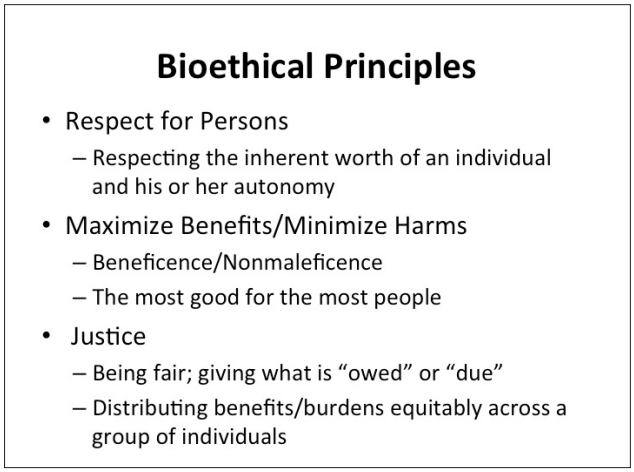
PART II: Exploring One Position – Meeting in "Like" Groups

16. Tell students that they will be assigned to represent one of the stakeholders and learn about that person's perspective. Later, they will meet in mixed-stakeholder groups to learn about other perspectives.
17. Pass out Student Handout—*Issues in Funding Research on Rare Genetic Diseases* to each student.
18. Assign a number (1-4) to each student and pass out the corresponding stakeholder Student Handout to each student: Student Handouts—*Group 1, Group 2, Group 3,* and *Group 4*. ***Alternatively, each handout could be passed out as homework to be completed the night before***.
19. Give students about 10 minutes to read through the stakeholder handout, and fill out *Part I* of Student Handout—*Issues in Funding Research on Rare Genetic Diseases*.
20. Assign different sections of the room to each group of stakeholders: parents, researchers, pharmaceutical companies, and directors of a heart disease organization. Have students move about the room, finding other students within their stakeholder group.
21. Once students are in their stakeholder groups, ask them to fill out *Part II* of Student Handout—*Issues in Funding Research on Rare Genetic Diseases*, identifying the position of each stakeholder, and the three most important things that stakeholder should share with Congress.

PART III: Finding a Compromise – Meeting in "Mixed" Groups

22. After students become "experts" in their stakeholder's position, review with students some of the bioethical principles to consider when trying to reach consensus or compromise on a difficult issue. ***Slide #6*** lists these principles:
    - ***Respect for Persons:*** Respecting the inherent worth of an individual and his or her autonomy.
    - ***Maximize Benefits/Minimize Harms:*** Beneficence/nonmaleficence.
    - ***Justice:*** Being fair, giving what is "owed" or "due." Distributing the benefits and burdens equitably across groups of individuals.

Funding Research: ***Slide #6***



23. Students are then rearranged into new "mixed" groups so that each new group has at least one representative from each of the four different stakeholder positions, 1-4. Assign an area of the room where each numbered group can gather. Two students can represent the same stakeholder in the same group if there is an odd number of students.

24. Each student should share, in turn, the position of his stakeholder and the three most important things he has learned about that stakeholder's position.

25. Students should record the information from their peers on Student Handout—*Issues in Funding Research on Rare Genetic Diseases*.

26. After each stakeholder has presented her position, the group should move to *Part III: Guidelines for Funding*. As a group, they should decide on at least four factors Congress should consider when funding scientific research on human diseases. Assigning a dollar value to funding or a percentage of the total research money spent for Leigh's disease may be helpful for some classes.

27. After students have agreed on several guidelines, they should indicate which principle(s) apply to each guideline.

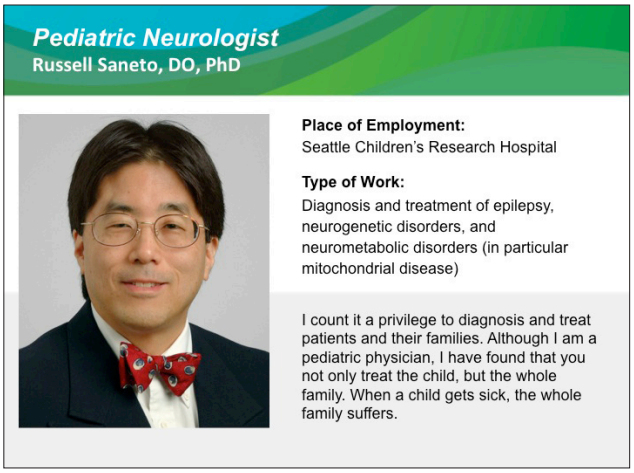
28. Finally, students should prioritize the guidelines ***individually***—which should be most important for Congress to consider when making funding decisions for research on rare genetic diseases and which should be least important. Students should also explain the reasoning they used in ranking their guidelines.

Closure

29. Conclude the lesson by highlighting the fact that there are no easy decisions when allocating limited resources (i.e., limited public money for research). In the case of research on rare genetic diseases, the number of people affected may be limited, but the suffering of those people is great. Research into the causes and cures of one disease or condition can increase our understanding of basic biology, and ultimately lead to other seemingly unrelated discoveries.

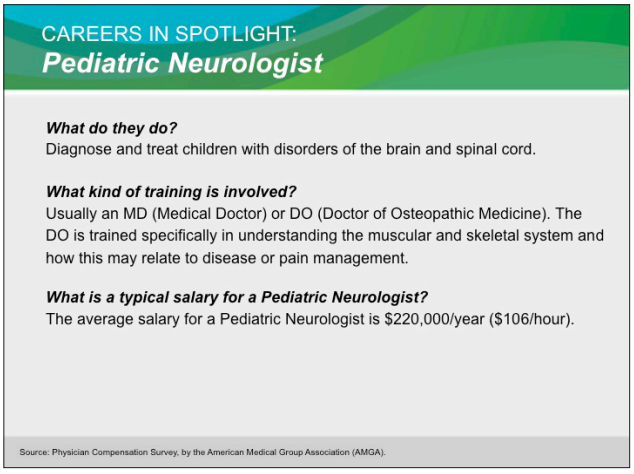
30. Explain that the bioethical principles of Respect for Persons, Maximize Benefits/Minimize Harms, and Justice can inform our decisions about difficult issues. Members of Congress must weigh the needs of many different people and groups when deciding how to allocate public money for different projects and causes.

31. Lastly, show ***Slide #7***, which returns to the picture of the pediatric neurologist from ***Slide #1***.



Funding Research: ***Slide #7***

32. Show ***Slide #8***, which provides job information for a pediatric neurologist. Review this information with students.



Funding Research: ***Slide #8***

33. Ask students, "What more do we know about pediatric neurologists after today's lesson?" Point out that pediatric neurologists often rely on genetic tests, which are developed by researchers using bioinformatics. In addition, the knowledge Dr. Saneto has gained about how to diagnose and treat pediatric neurological conditions has come from research into the function of mitochondria, and research on rare genetic diseases like Leigh's disease.

34. Ask students to answer *Pediatric Neurologist Question #2* on their *Careers in the Spotlight* Handout, which has students explain how this lesson has changed their understanding of the kind of work a pediatric neurologist does.

35. Ask students to also answer *Pediatric Neurologist Question #3* on their *Careers in the Spotlight* Handout, which has students explain how a pediatric neurologist might use bioinformatics in his or her work.

36. Tell students to keep their *Careers in the Spotlight* Handout available for future lessons.

Homework

As homework, ask students to write about the things they learned in *Lesson Seven* in their lab notebook, on another sheet of paper, or in a word processing program like Microsoft® Notepad or Word which they then provide to the teacher as a printout or via email. This can serve as an entry ticket for the following class. Have them complete these prompts:

a. Today I learned that…

b. An important idea to think about is…

c. Something that I don't completely understand yet is…

d. Something that I'm really confident that I understand is….

Teacher Background: Causes and Inheritance of Leigh's Disease

Leigh's disease is a form of Subacute Necrotizing Encephalomyelopathy (SNEM). Leigh's disease is quite heterogeneous, and can arise via different modes of inheritance: X-linked recessive, mitochondrial, and autosomal recessive. All forms of Leigh's disease have a negative impact on mitochondrial function and reduce the production of ATP, resulting in the Leigh's disease phenotype. While the *COI* gene is found in the mitochondrial genome, many of the genes that encode Complex IV proteins are located on chromosomes in the nucleus. When the mutation causing Leigh's disease is in a nuclear gene, the resulting inheritance pattern is either X-linked recessive (if the mutated gene is located on the X chromosome) or autosomal recessive (if the mutated gene is located on one of the somatic chromosomes). When the mutation is in a gene encoded by the mitochondrial genome, the inheritance pattern is mitochondrial, or maternal, as mitochondria are passed from mother to offspring in the egg.

The type of Leigh's disease highlighted in this lesson is X-linked recessive and involves a deficiency in Complex IV of the electron transport chain. Complex IV includes the large multi-subunit cytochrome c oxidase complex. The protein encoded by the barcoding gene, *COI*, is one of these subunits (cytochrome c oxidase subunit 1). As students saw in *Lesson Five*, the cytochrome c oxidase protein contains 13 subunits, and many different proteins are required to help these subunits assemble into a single complex. The mutations that cause Leigh's disease are not found in the *COI* gene itself; they can be found in genes that encode other proteins within the complex, or in genes that encode the proteins that help the cytochrome c oxidase complex assemble in the inner mitochondrial membrane. As noted above, some of these genes are found in the nuclear genome, while others are found in the mitochondrial genome. The most common causes of Leigh's disease are mutations in the *SURF1* gene, which is located on chromosome 9 and codes for a protein that helps the cytochrome c oxidase complex assemble. Other common causes are mutations in the mitochondrial-encoded cytochrome c oxidase subunit 3 (*CO3*) gene. Mutations in the nuclear-encoded *TACOI* (translational activator of mitochondrially encoded cytochrome c oxidase I) also reduce production of COI and lead to late-onset Leigh's disease.

Glossary

Complex IV: One of the protein complexes found in the mitochondria. Complex IV contains cytochrome c oxidase and is involved in the production of ATP (adenosine triphosphate).

Efficacy/effectiveness: The ability to produce the desired effect; the ability to successfully treat what you want to treat.

Fatty acids: Molecules containing carbon and hydrogen, often obtained from food, and used by living organisms for energy production.

Glucose: A simple sugar usually obtained from food that living organisms use for energy production.

***In vitro*:** Means "in the glass" and is used to refer to experiments that are performed in the laboratory (such as in a test tube) and not in living organisms.

Metabolic: Describes the chemical reactions that happen in living organisms to sustain life.

Phases: In clinical trials to test medicine for use in people or animals, phases are the different steps of testing that must be done: Phase 1 tests safety in a small number of people or animals (usually 20-100); Phase 2 tests effectiveness in a small number of people or animals (usually 100-500); and Phase 3 tests effectiveness and safety in a large group of people or animals (usually hundreds or thousands of subjects).

Stakeholder: Any person, institution or entity that is interested in, invested in or will be affected by the outcome of an ethical decision.

Subacute Necrotizing Encephalomyelopathy (SNEM): A rare metabolic disorder that affects the brain and spinal cord.

Toxicity: The degree to which something is poisonous.

Resources

Dr. Russell Saneto's Homepage:
http://www.seattlechildrens.org/medical-staff/russell-p-saneto/.

The United Mitochondrial Disease Foundation has information about a variety of mitochondrial diseases:
http://www.umdf.org/site/c.otJVJ7MMIqE/b.5472191/k.BDB0/Home.htm.

The Mitochondrial Research Guild: A Special Interest Guild at Seattle Children's Hospital:
http://www.nwmito-research.org/doctors.jsp.

"What is a Doctor of Osteopathic Medicine (DO)?" from the American Osteopathic Association:
https://www.osteopathic.org/osteopathic-health/about-dos/what-is-a-do/Pages/default.aspx.

For more information about Leigh's disease, visit:

- The National Institute of Neurological Disorders and Stroke, Leigh's Disease Information Page:
  http://www.ninds.nih.gov/disorders/leighsdisease/leighsdisease.htm.
- Gene Reviews: Mitochondrial DNA-Associated Leigh Syndrome and NARP:
  http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=narp.
- Online Inheritance in Man (OMIM) at the NCBI, "Leigh Syndrome (LS)":
  http://www.ncbi.nlm.nih.gov/omim/256000.

Credit

Faughy, K. "Rare strain of Leigh's Syndrome makes little Adam one in a million." *The Evening Gazette*. July 8, 2008. Gazette Media Company Limited.

Rae, S. "Rugby-mad lad with grit to boot." *Otago Daily Times*. December 20, 2008. Allied Press Limited.

Sweeney, Clayton. *Subacute Necrotizing Encephalomyelopathy and MT-COI*. University of Wisconsin-Madison. Spring 2010.

Saneto, Russell. Personal Interview. 22 July 2010.

The authors wish to thank Wikimedia Commons for the images contained in this lesson.

Name _____ Date _____ Period _____

7 Issues in Funding Research on Rare Genetic Diseases

PART I: Understanding Your Stakeholder's Position

A stakeholder is any person, institution or entity that is interested in, invested in or will be affected by the outcome of an ethical decision. These include individual people, special interest groups, companies, or even local, state or federal governments. After reading through your stakeholder's position statement, meet with the other members of your group to discuss each position.

1. My stakeholder is: _____

2. Why is your stakeholder testifying before Congress today? What is his/her position on the issue of public funding for research on rare genetic diseases?

3. What evidence did s/he present in support of his/her position? What are the three most important things you think Congress should know about his/her position?

   a.

   b.

   c.

4. Do you believe that your stakeholder presented a good case for his/her position? Why or why not?

5. What questions would you like to ask your stakeholder? What else would you like to know about funding for research on rare genetic diseases in general or about your stakeholder's position in particular?

PART II: Understanding the Positions of Others Stakeholders

As you listen to the testimony of other stakeholders, take notes about his/her position in the sections below.

Stakeholder #2:

6. Who is this stakeholder? _____

7. What is his/her position?

8. Why does this person have this position? What evidence did s/he present in support of his/her position?

9. How does this position compare to the position of your stakeholder? Is it compatible or not?

10. What question(s) would you like to ask this stakeholder?

Stakeholder #3:

11. Who is this stakeholder? _____

12. What is his/her position?

13. Why does this person have this position? What evidence did s/he present in support of his/her position?

14. How does this position compare to the position of your stakeholder? Is it compatible or not?

15. What question(s) would you like to ask this stakeholder?

Stakeholder #4:

16. Who is this stakeholder? _____

17. What is his/her position?

18. Why does this person have this position? What evidence did s/he present in support of his/her position?

19. How does this position compare to the position of your stakeholder? Is it compatible or not?

20. What question(s) would you like to ask this stakeholder?

PART III: Can You Reach a Compromise? Congressional Guidelines for Public Funding of Research on Rare Genetic Diseases

Congress votes every day on funding and laws that affect many different areas of our lives. When deciding which diseases should receive public funding for research, what factors should be considered? With your group, you should decide on at least four criteria that should be considered when making decisions. ***After you have at least four guidelines, record which of the ethical principles apply best to each one. Individually, rank each guideline: #1 means you think it is the most important criteria, and #4 means you think it is the least important criteria.***

21. First decide on the guidelines as a group:

Guideline / Criteria	Ethical Principle(s)	Rank
1.		
2.		
3.		
4.		

22. Explain why you ranked the guidelines the way you did.

7 Group 1:

Testimony before Congress Regarding Funding by the National Institutes of Health for Research on Rare Genetic Diseases

Sally Meyers
Mother of Alex Meyers

Subacute Necrotizing Encephalomyelopathy (SNEM): A rare metabolic disorder that affects the brain and spinal cord.

My name is Sally Meyers and my son, Alex, suffers from Leigh's disease, a form of **Subacute Necrotizing Encephalomyelopathy** or SNEM. This disease is very rare, with fewer than 10,000 children in America being affected.

When Alex was only a few months old, his father Brian and I noticed that he slept a lot more than the other babies we knew. At first we thought we were lucky that he was sleeping through the night at such a young age. But before long, we noticed that he rarely cried, and he had a hard time nursing because he couldn't suckle. He couldn't hold his head up, and he started to lose weight. When the doctors became worried, too, they began genetic testing for all kinds of different diseases. As his condition worsened, he became irritable and started having seizures. I have never been as scared as I was the first time I saw my baby boy have a seizure.

Doctors did many types of medical imaging scans, took muscle and skin biopsies, and interviewed Brian and me and our families about any history of genetic diseases. After many different genetic tests, we finally received the diagnosis of Leigh's disease.

Now Alex is two years old. He has a hard time moving, and he has very little strength. He can't eat solid foods, and we have to help him with his eating. A high-fat, low-carbohydrate diet and treatment with B vitamins helps some people with SNEM, but there is no cure. The doctors have warned us about his developmental delays – he will not run and play like other children, and he probably won't grow up to have children of his own. Many children with Leigh's disease die within a year of diagnosis, so we are grateful that Alex is still with us. The doctors have told us that he may not live past the age of three, but a very small number of children with this disease have lived to be 10 years or older, so we still hope and pray every day.

There are multiple forms of SNEM and Leigh's disease. Some are passed on from both parents, but the form of Leigh's disease my son has is only inherited from the mother, and I have passed on this condition to my son. I am a carrier of Leigh's disease, but I have no symptoms. The **mutations** are found in the energy-producing parts of my cells called the mitochondria, and I could pass these mutations on to other children Brian and I have. Brian has been tested for this condition as well, but he does not carry any mutations.

I urge you to support increased public funding for research into Subacute Necrotizing Encephalomyelopathy and Leigh's disease. This may be a rare condition, but it is painful for the children who have it, and for the families who watch them suffer. How can we put a price on the life of a child? Increased funding for this condition could lead to more effective treatments and someday, may lead to a cure.

7 Group 2:
Testimony before Congress Regarding Funding by the National Institutes of Health for Research on Rare Genetic Diseases

John Herring, PhD
Research Scientist Studying Mitochondria

My name is Dr. John Herring, and I am a cellular biologist. I study the function of the mitochondria at the non-profit research institute, the Institute for Mitochondrial Function and Disease. My research is funded by a taxpayer research grant from the National Institutes of Health. I am here today to explain what causes **Subacute Necrotizing Encephalomyelopathy** (SNEM) and Leigh's disease, and why these diseases are so devastating to the people who suffer from them. I also urge you to increase public funding for research into SNEM and Leigh's disease.

Subacute Necrotizing Encephalomyelopathy (SNEM): A rare metabolic disorder that affects the brain and spinal cord.

Fatty acids: Molecules containing carbon and hydrogen, often obtained from food, and used by living organisms for energy production.

Glucose: A simple sugar usually obtained from food that living organisms use for energy production.

Most of our 25,000 or so genes are encoded by DNA found in the nucleus. However, the mitochondria have DNA as well, and in humans the mitochondrial DNA encodes almost 40 genes, most of which are involved in the electron transport chain. The mitochondria are the powerhouses of the cell. They convert **fatty acids** and **glucose** into adenosine triphosphate (ATP) which is used by the body to drive almost all of the cell's basic functions. The number of mitochondria in each cell varies depending upon the cell type. Those cells that need lots of energy, like muscles or the brain, have many mitochondria, while cells that need little energy may contain only a few.

Leigh's disease was named for Dr. Denis Leigh who first described this condition in a 7 month old infant in 1951. We now know that Leigh's disease comes in many different forms, but all forms of Leigh's disease involve malfunctions of the mitochondria and reduced ATP production. The type of Leigh's disease affecting Mrs. Meyer's son involves a deficiency in Complex IV of the electron transport chain. Complex IV includes the large multi-subunit cytochrome c oxidase complex. The protein encoded by the barcoding gene, *COI*, is one subunit of that complex (cytochrome c oxidase subunit 1). In tissues that use lots of energy, like muscles and the brain, mitochondrial defects are quite severe. As cells are slowly starved of ATP, this causes symptoms such as low energy, heart problems, liver and lung problems, developmental delays, and mental retardation. Because the mitochondria are so vital to the everyday function of the body, symptoms often occur during infancy, and it is very rare that someone can survive to adulthood with this condition.

Leigh's disease is diagnosed clinically based on behavioral symptoms, abnormalities in biochemistry because the baby cannot metabolize his or her food well, medical imaging scans of the brain, genetic tests, and for families with a history of this condition, prenatal screening can be done as well. However, there is no cure for Leigh's disease, and the chance for survival is very minimal. By modifying diet and supplementing with B vitamins, which are vital to the function of electron transport, symptoms can be moderated, but not prevented.

By increasing funding to study diseases like SNEM and Leigh's disease, we not only increase the chances that we will discover a drug treatment or a cure, but we also learn more about how mitochondria function. Because the mitochondria are vital to all cells, this research can benefit everyone by improving our knowledge of energy metabolism and cellular function, as well as helping people who suffer from other diseases involving the mitochondria, like diabetes and Alzheimer's disease.

7 Group 3:

Testimony before Congress Regarding Funding by the National Institutes of Health for Research on Rare Genetic Diseases

Karen Holman
Representative, Pharmaceutical Association of America

My name is Karen Holman, and I am a representative of the Pharmaceutical Association of America. It is with great sadness that I hear about children like Alex Meyers with a very rare and untreatable disease. I am often asked why pharmaceutical companies have not developed drugs to treat conditions like **SNEM** and Leigh's disease. I am here today to try to explain why.

The process of drug development is a long one. First, basic research must be done to identify the cause of the condition, and create a compound or drug that is an effective treatment. This is often the part of the process that takes the longest and is the most difficult to predict, because no one knows when the next experiment will reveal a potential treatment or cure for a condition. This could take months, years, or decades.

Once scientists have a potential drug, they must determine both the safety and the **efficacy** of the new drug (in other words, how well it works at treating what you want it to treat) through a series of ***in vitro*** tests, which are tests performed in test tubes and in cells grown in the lab. Many research scientists and laboratory technicians apply the drug to isolated cells in a variety of conditions. If the drug appears to work, then it is given to laboratory animals such as mice to test for **toxicity** and drug side effects, as well as effectiveness at treating the condition in animals. Only if it appears safe and effective is it considered for human trials.

Efficacy/effectiveness: The ability to produce the desired effect; the ability to successfully treat what you want to treat.

In vitro: Means "in the glass" and is used to refer to experiments that are performed in the laboratory (such as in a test tube) and not in living organisms.

Phases: In clinical trials to test medicine for use in people or animals, phases are the different steps of testing that must be done.

Subacute Necrotizing Encephalomyelopathy (SNEM): A rare metabolic disorder that affects the brain and spinal cord.

Toxicity: The degree to which something is poisonous.

Once approved for testing in humans, all drugs undergo three levels or **phases** of clinical trials. In Phase 1, 20-100 healthy volunteers take a small dose of the drug to test for safety and side effects. If the drug passes Phase 1, then Phase 2 trials begin with a few hundred volunteers to test how effective the drug is at treating the condition, and to monitor for any rare side effects or safety concerns. If the drug also passes Phase 2, it can continue into Phase 3, where thousands of volunteers are recruited for a thorough study of the effectiveness of the drug. Only after completing successful Phase 3 clinical trials can the company then apply for approval from the Food and Drug Administration (FDA) to market the drug to people.

While there is some debate among experts as to the true cost of bringing a new drug to patients, conservative estimates are that it costs between $500 million and $2 billion dollars. The cost estimate of successful drug development also includes the cost of research that fails to result in new products. Only between 1 in 1,000 and 1 in 5,000 new chemical compounds become new drugs, and this process takes an average of eight and a half years. For a condition as rare as Leigh's disease, affecting only about 10,000 people per year in the United States, if a drug were made available, the cost of the drug would be quite high. In order to make back within a year just the $500 million spent in the drug development process, each family would pay approximately $4,000 per month for treatment. That cost is simply too high to justify for such a small group of people. Any research into Leigh's disease should be funded by the United States taxpayers, not the pharmaceutical industry. If taxpayer money were to fund this research process, the cost of drugs for families suffering from rare genetic conditions like Leigh's disease would be much less.

7 Group 4:
Testimony before Congress Regarding Funding by the National Institutes of Health for Research on Rare Genetic Diseases

Harry Tullman, MD
Director, Americans for Healthy Hearts

Subacute Necrotizing Encephalomyelopathy (SNEM): A rare metabolic disorder that affects the brain and spinal cord.

My name is Dr. Harry Tullman and I am the Director of the non-profit organization, Americans for Healthy Hearts. Our mission is to promote understanding about heart disease, including how to prevent heart disease from developing, and how to recognize the signs of a heart attack. I understand the pain and loss that can come from rare genetic diseases; however, many more Americans suffer from heart disease than from rare conditions like Leigh's disease. According to the American Heart Association, heart disease—also called cardiovascular disease—is the number one killer in America today, causing 1 in every 5 deaths. Every 34 seconds, someone in America dies from heart disease. According to the World Health Organization, 30% of deaths worldwide are from some form of heart disease. It is the number one killer for both men and women.

There is only a limited amount of taxpayer money that the National Institutes of Health can spend each year on biomedical research. This year, we ask that you take the money requested by those supporting research into Leigh's disease and **SNEM**, and instead spend that money on heart disease research. We know a great deal about how to treat heart disease, but there is still a great deal we need to learn.

Genetic research in the past two decades has shown that there is an association between certain genes and a person's risk of developing heart disease, but we do not currently have a genetic test for heart disease risk. If we had such a test, we could determine which people are at increased risk before they develop symptoms, help them manage their lifestyles—including things that can increase your risk of heart attack, like lack of exercise and a high fat diet—and monitor them closely for early signs of disease. This would be similar to the monitoring we now do for people who test positive for *BRCA1* or *BRCA2* mutations associated with breast cancer; with increased and more frequent testing, we can try to catch disease in its earliest possible stage, improving the chances for successful treatment.

Many people can recover from a heart attack—if they get treatment fast enough. But there is still much we have to learn, and much research that must be done. We have drugs to treat people with heart disease, but they are not 100% effective. There may be better ways to treat heart disease—or to prevent it from developing in the first place—that we will only learn through further scientific research.

Rare genetic diseases affect only a limited number of families, while heart disease affects so many. I believe for-profit companies, like pharmaceutical companies, make large profits on other drugs. These profits could be used to fund research for very rare genetic conditions.

7 Issues in Funding Research on Rare Genetic Diseases Teacher Answer Key

PART I & II: Understanding Your Stakeholder's Position & the Positions of Others

A **stakeholder** is any person, institution or entity that is interested in, invested in or will be affected by the outcome of an ethical decision. These include individual people, special interest groups, companies, or even local, state or federal governments. After reading through your stakeholder's position statement, meet with the other members of your group to discuss each position.

Stakeholder #1: Group 1

1. My stakeholder is:

Sally Meyers, mother of a child with Leigh's disease.

2. Why is your stakeholder testifying before Congress today? What is his/her position on the issue of public funding for research on rare genetic diseases?

Mrs. Meyers is testifying before Congress today to urge increased funding for research on rare genetic diseases. Her position is that public funding for research on rare genetic diseases should be increased.

3. What evidence did s/he present in support of his/her position? What are the three most important things you think Congress should know about his/her position?

Ms. Meyers described the pain her son Alex suffers, and the pain she and her husband suffer because there is no cure for SNEM or Leigh's disease. Also, there is no effective treatment for the disease now, and she believes that should change.

4. Do you believe that your stakeholder presented a good case for his/her position? Why or why not?

Student answers will vary, and will be subjective. Some students may find her case compelling, others may not.

5. What questions would you like to ask your stakeholder? What else would you like to know about funding for research on rare genetic diseases in general or about your stakeholder's position in particular?

Student answers will vary. They may want to know more about how effective the current treatments for SNEM are, and how much this research may cost.

Stakeholder #2: Group 2

1. My stakeholder is:

Dr. John Herring, a research scientist studying mitochondria.

2. Why is your stakeholder testifying before Congress today? What is his/her position on the issue of public funding for rare genetic diseases?

Dr. Herring is testifying before Congress today to urge increased funding for research on rare genetic diseases. His position is that public funding for research on rare genetic diseases should be increased, and that this will not only help people with SNEM and Leigh's disease, but may also benefit others by increasing our basic understanding of the function of the mitochondria, including increasing our understanding of conditions like diabetes and Alzheimer's disease.

3. What evidence did s/he present in support of his/her position? What are the three most important things you think Congress should know about his/her position?

Dr. Herring talked about the vital function of the mitochondria in producing ATP (energy) for all cells in the body. Dr. Herring also described the causes and symptoms of SNEM and Leigh's disease, which confirmed the suffering these diseases cause to children and their families. In addition, Dr. Herring believes that research on SNEM and the mitochondria could benefit people with other common diseases that may involve mitochondrial dysfunction, including diabetes and Alzheimer's disease.

4. Do you believe that your stakeholder presented a good case for his/her position? Why or why not?

Student answers will vary, and will be subjective. Some students may find his case compelling, others may not.

5. What questions would you like to ask your stakeholder? What else would you like to know about funding for research on rare genetic diseases in general or about your stakeholder's position in particular?

Student answers will vary. They may want to know more about how effective the current treatments for SNEM are, and how much this research may cost. They may also want to know about the benefits of mitochondrial research to treat other conditions such as diabetes and Alzheimer's, and how that can help the wider community and those who do not suffer from rare genetic diseases.

Stakeholder #3: Group 3

1. My stakeholder is:

Karen Holman, Pharmaceutical Association of America.

2. Why is your stakeholder testifying before Congress today? What is his/her position on the issue of public funding for rare genetic diseases?

Ms. Holman is testifying before Congress today to explain the high cost of developing new drugs. Her position is that pharmaceutical companies cannot afford to perform this research because they would have to pass their costs on to families with rare diseases, and the cost of those medications would be too high for individual families to pay. She believes that any research into rare genetic diseases should be paid for by taxpayers.

3. What evidence did s/he present in support of his/her position? What are the three most important things you think Congress should know about his/her position?

Ms. Holman described how long and involved the drug development process is, with new treatments taking many years to make it from the lab to use in patients. She also explained that bringing one new drug treatment to patients can cost between $500 million and $2 billion. If a new drug to treat Leigh's disease cost that much, families would have to pay $4,000/month for pharmaceutical companies to make back in the first year the money they spent on developing the drug.

4. Do you believe that your stakeholder presented a good case for his/her position? Why or why not?

Student answers will vary, and will be subjective. Some students may find her case compelling, others may not.

5. What questions would you like to ask your stakeholder? What else would you like to know about funding for research on rare genetic diseases in general or about your stakeholder's position in particular?

Student answers will vary. They may want to know more about how much profit the average pharmaceutical company makes on different drugs (over and above the cost of drug development), and who keeps those profits (the pharmaceutical researchers, the company president, and/or the people who own stock in the company (stockholders)).

Stakeholder #4: Group 4

1. My stakeholder is:

Dr. Harry Tullman, Director, Americans for Healthy Hearts.

2. Why is your stakeholder testifying before Congress today? What is his/her position on the issue of public funding for rare genetic diseases?

Dr. Tullman is testifying before Congress today against increased funding for research on rare genetic diseases. His position is that the amount of public funding for research should be proportional to the number of people suffering from the disease, and that funding for conditions that are very rare will take taxpayer money away from research into diseases like heart disease that affect hundreds of thousands of people each year.

3. What evidence did s/he present in support of his/her position? What are the three most important things you think Congress should know about his/her position?

Dr. Tullman discussed the fact that heart disease is the leading cause of death in America, accounting for 1 in 5 fatalities. While there are some treatments available, there is still much to learn, including developing genetic tests for heart disease risk, and developing better drug treatments. He believes that the amount of money spent on researching rare diseases should be proportional to the number of people who suffer from that disease.

4. Do you believe that your stakeholder presented a good case for his/her position? Why or why not?

Student answers will vary, and will be subjective. Some students may find his case compelling, others may not.

5. What questions would you like to ask your stakeholder? What else would you like to know about funding for research on rare genetic diseases in general or about your stakeholder's position in particular?

Student answers will vary. They may want to know more about how much money is currently spent on heart disease research compared to research on rare genetic diseases, and how much of this research is funded by the public (taxpayers) versus private industry like pharmaceutical companies.

PART III: Can You Reach a Compromise? Congressional Guidelines for Public Funding of Research on Rare Genetic Diseases

Congress votes every day on funding and laws that affect many different areas of our lives. When deciding which diseases should receive public funding for research, what factors should be considered? With your group, you should decide on at least four criteria that should be considered when making decisions. ***After you have at least four guidelines, record which of the principles apply best to each one. Individually, rank each guideline: #1 means you think it is the most important criteria, and #4 means you think it is the least important criteria.***

21. First decide on the guidelines as a group:

Answers will vary. Potential responses include:

Guideline / Criteria	Ethical Principle(s)	Rank
1. How many people are affected by the disease?	Maximize Benefits; Justice	
2. How debilitating is the disease?	Minimize Harms; Respect for Persons	
3. Are there currently treatments for the disease?	Maximize Benefits; Justice	
4. Are there currently any preventative measures (like lifestyle changes) for the disease?	Maximize Benefits; Justice; Respect for Persons	
5. How much potential is there for research breakthroughs to successfully treat or cure the disease?	Maximize Benefits	
6. Will research into the disease benefit our understanding of basic biology or other, unrelated diseases?	Maximize Benefits	

22. Explain why you ranked the guidelines the way you did.

Answers will vary, but students should provide an explanation of why they ranked each guideline as they did.