Exploring Precision Medicine

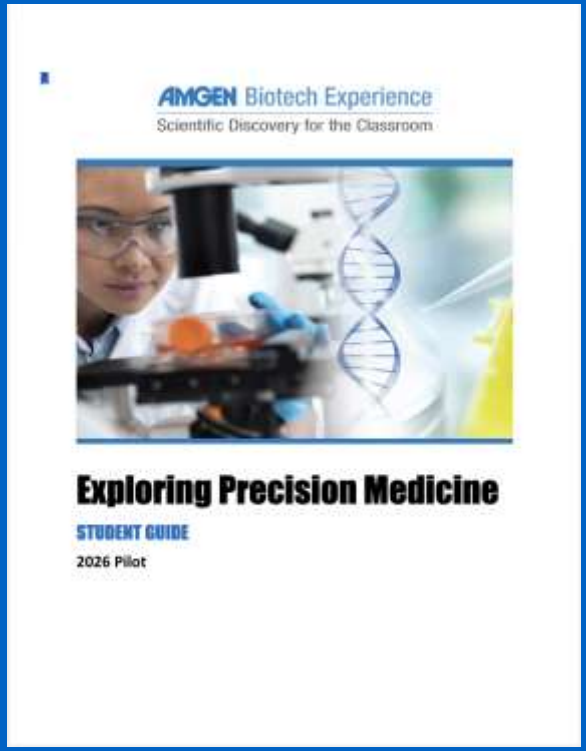
- Chapter 1: What's the Right Medicine?
- Chapter 2: Is My Sense of Taste Controlled by my Genes?
- Chapter 3: Exploring Our DNA
- Chapter 4: How Is DNA Sequenced, and What Can We Learn?
- Chapter 5: Restriction Enzyme Digestion of TAS2R38 PCR Products
- Chapter 6: Gel Electrophoresis and Genotyping
- Chapter 7: SNPs and Drug Metabolism

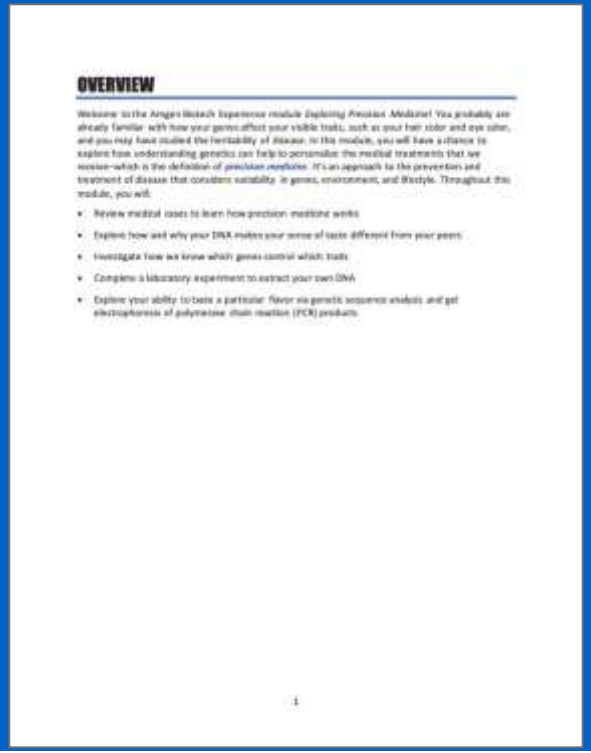
Chapter 1: What's the right medicine?

How and why are people different?

Are there differences you can’t see?

Read the Overview





Video and discussion: What is precision medicine?

VIDEO LINK

Are all medicines equally effective for everyone?

Read the Introduction to Chapter 1, then complete RM 1.1

INTRODUCTION

What are traits? People often talk about personality traits, such as being funny, thoughtful, or quiet. In genetics, *traits* refer to characteristics of living organisms that can be described, quantified, or measured. *Genotype* is the genetic makeup of an individual, and *phenotype* is the set of observable characteristics of an individual based on how their genotype is expressed. While an individual's genetic makeup is the set of instructions on which their phenotype is based, environmental factors also influence their phenotype. For example, skin temperature affects the fur color of Siamese cats.

What determines our traits? For the activities in this chapter, you will think about the factors that control traits and discuss your ideas with your teammates.

First, you will start to explore traits by filling out a reproducible master that challenges you to consider the influence of genetics and environment on particular traits.

Next, you will read an article from a webpage and answer some questions to think about the ways in which a patient's race and socioeconomic background might be important for individualized treatment.

Lastly, you will explore the case of a patient whose doctor proposes genotyping to reduce potential negative side effects from their necessary medication and review the science that makes this approach possible.

ACTIVITY: Genetics vs. Environment

Has anyone ever told you that you share facial features with a related family member? How about their personality? To what extent are your personal characteristics the result of your DNA versus your upbringing and lifestyle? Challenge yourself to consider the impact of genetics versus the environment on a number of human traits. Read and complete **What Controls Traits? (RM 1.1)**. Be prepared to discuss your answers with the class.

READING: Diversity and Inclusion in Clinical Trials

Read the article "Diversity and Inclusion in Clinical Trials" from the U.S. National Institute of Health's (NIH) National Institute on Minority Health and Health Disparities (NIMHD) to learn more about how medications have traditionally been tested and why and how that approach has changed in recent decades.

As you read, answer the following questions, either in your science notebook or on **Including Diverse Populations in Medical Studies (RM 1.2)**:

1. Why are clinical trials important?
2. What are some factors that can influence an individual's risk of developing a disease?
3. What group was studied almost exclusively in past clinical trials, and why is that problematic?

1

Reproducible Master 1.1

WHAT CONTROLS TRAITS?

1. Read through the following list of traits:

Eye color	Height	Enjoyment of hip-hop music
Hair length	Foot size	Hair color
Skin color	Religiosity	Ability to speak Spanish and Arabic
Affinity for cats	Scar on abdomen	

2. Use the table below to sort these traits into categories based on how you believe they are controlled: by genetics only, by the environment only, or by both genetics and the environment.

Controlled by genetics only	Controlled by the environment only	Controlled by both

3. Read over the traits in all three columns. Write a rule (or group of rules) for determining what influences a trait.

Discussion: RM 1.1

- Which traits were controlled only by genetics?
- What traits were controlled solely by the environment?
- Were any traits influenced by both genetics and environment?

What influences a trait? Can you think of rules?

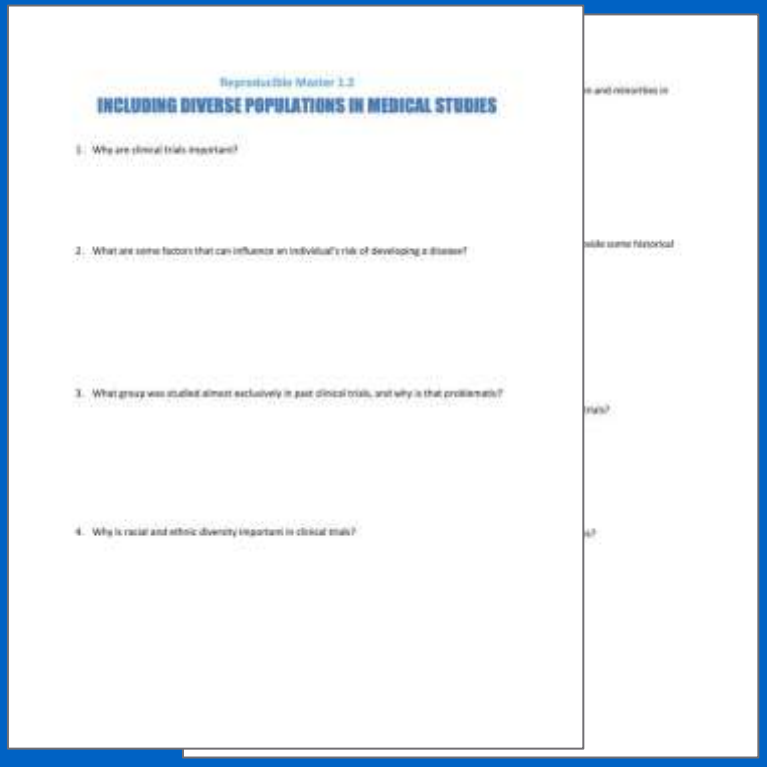
- How the body looks and works: most likely **genetic**
- How people behave: most likely **environmental** (due to experiences)
- Inherited traits can be influenced by the environment
  - Adult height has a genetic component (birth parents' heights) and an environmental component (nutrition, infections, etc.)

Can you think of traits people might have that are related to their health?

Trait related to health	Controlled by genetics only	Controlled by the environment only	Controlled by both

Read “Diversity and Inclusion in Clinical Trials”

Answer the questions on RM 1.2.


Reproducible Master 1.2

INCLUDING DIVERSE POPULATIONS IN MEDICAL STUDIES

1. Why are clinical trials important?

2. What are some factors that can influence an individual's risk of developing a disease?

3. What group was studied almost exclusively in past clinical trials, and why is that problematic?

4. Why is racial and ethnic diversity important in clinical trials?

Discussion: “Including Diverse Populations in Medical Studies”

- Why are clinical trials important?
- What are some factors that can influence an individual’s risk of developing a disease?
- What group was studied almost exclusively in past clinical trials, and why is that problematic?

Discussion: “Including Diverse Populations in Medical Studies” (continued)

- Why is racial and ethnic diversity important in clinical trials?
- What steps has the NIH been taking to increase the percentage of women and minorities in clinical trials?
  - How effective have these changes been so far?
- Describe some barriers to participation in clinical trials by minorities.
  - Provide some historical examples that might explain some of these barriers.

Discussion: “Including Diverse Populations in Medical Studies,” continued

- What other forms of diversity might be important to consider in clinical trials?
- What are the dangers of combining data for large categories of minorities?

Exploring Precision Medicine: Activities

AMGEN Biotech Experience
Scientific Discovery for the Classroom

Sample Our Own DNA

Take a sample of cheek cells, isolate DNA, and amplify a short sequence of the bitter taste gene.

Sequence Analysis

Use bioinformatics software to explore the bitter taste gene and how genotypes can be distinguished.

Restriction Enzyme Digest

Use restriction enzyme digestion to prepare to determine our bitter taste genotypes.

Gel Electrophoresis

Use gel electrophoresis to determine our bitter taste genotypes.

Investigate Genetics of Drug Metabolism

Investigate the genetics of drug metabolism and consider how genotyping can aid medical treatment.

Medical Mystery

Explore the idea that people respond differently to medications and consider the possible reasons.

Is Taste Genetic?

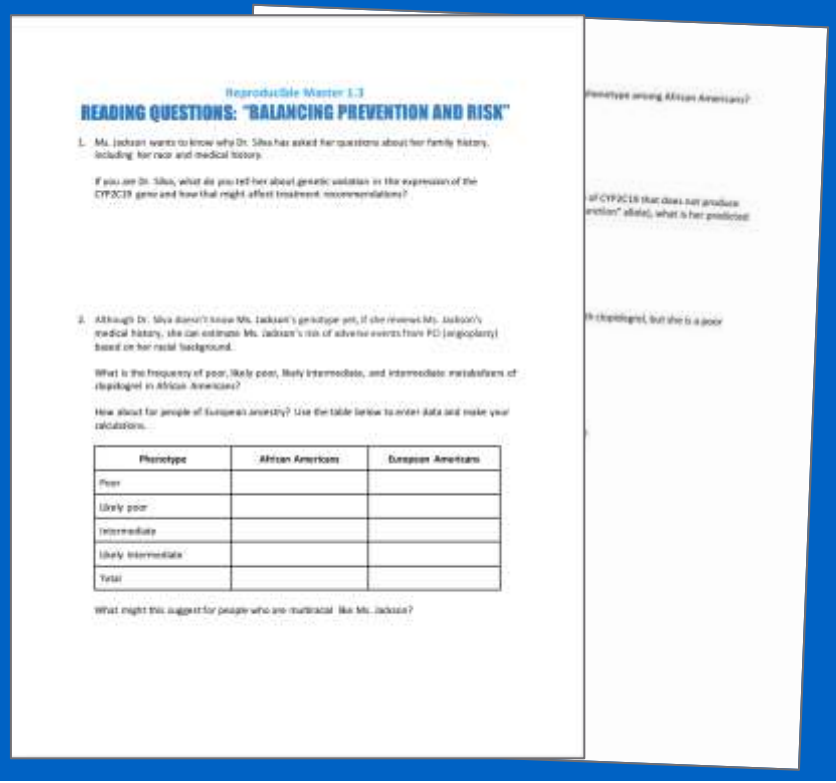
Begin to explore a trait (taste) and investigate whether people experience it differently.

UNDERSTANDING PRECISION MEDICINE

In this module, we explore the genetics of the ability to taste bitter substances. It turns out that even small differences in our DNA—our genotype—can lead to major differences in traits—our phenotype. All of our genes have such individual differences, and some lead to changes in medically important traits. Advances in DNA sequencing and bioinformatics have made it much easier to discover these differences. Similarly, understanding how each of us metabolizes medications differently allows doctors to practice precision medicine—medicine based on each individual's genotype.

Reading: “Balancing Prevention and Risk”

Use the data tables after the reading to answer the questions on RM 1.3



Reproducible Master 1.3

READING QUESTIONS: "BALANCING PREVENTION AND RISK"

1. Ms. Jackson wants to know why Dr. Silva has asked her questions about her family history, including her race and medical history.

   If you are Dr. Silva, what do you tell her about genetic variation in the expression of the CYP2C19 gene and how that might affect treatment recommendations?

2. Although Dr. Silva doesn't know Ms. Jackson's genotype yet, if she reviews Ms. Jackson's medical history, she can estimate Ms. Jackson's risk of adverse events from PCI (angioplasty) based on her racial background.

   What is the frequency of poor, likely poor, likely intermediate, and intermediate metabolizers of clopidogrel in African Americans?

   How about for people of European ancestry? Use the table below to enter data and make your calculations.

Phenotype	African Americans	European Americans
Poor		
Likely poor		
Intermediate		
Likely intermediate		
Total		

   What might this suggest for people who are multiracial like Ms. Jackson?

Review: Renee Jackson's medical history

Age: 64

Race: Mixed-race (Black and White).

Family history: Her father (Black) had heart disease and diabetes, and his ancestry was West African. Her mom (White) had high cholesterol and metabolic syndrome, and her ancestry was European (British Isles).

Health conditions: Metabolic syndrome, arthritis, glaucoma, angina, high cholesterol

Clopidogrel Mechanism of Action

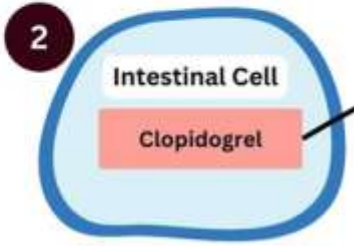
1 INGESTION
Patient ingests clopidogrel.

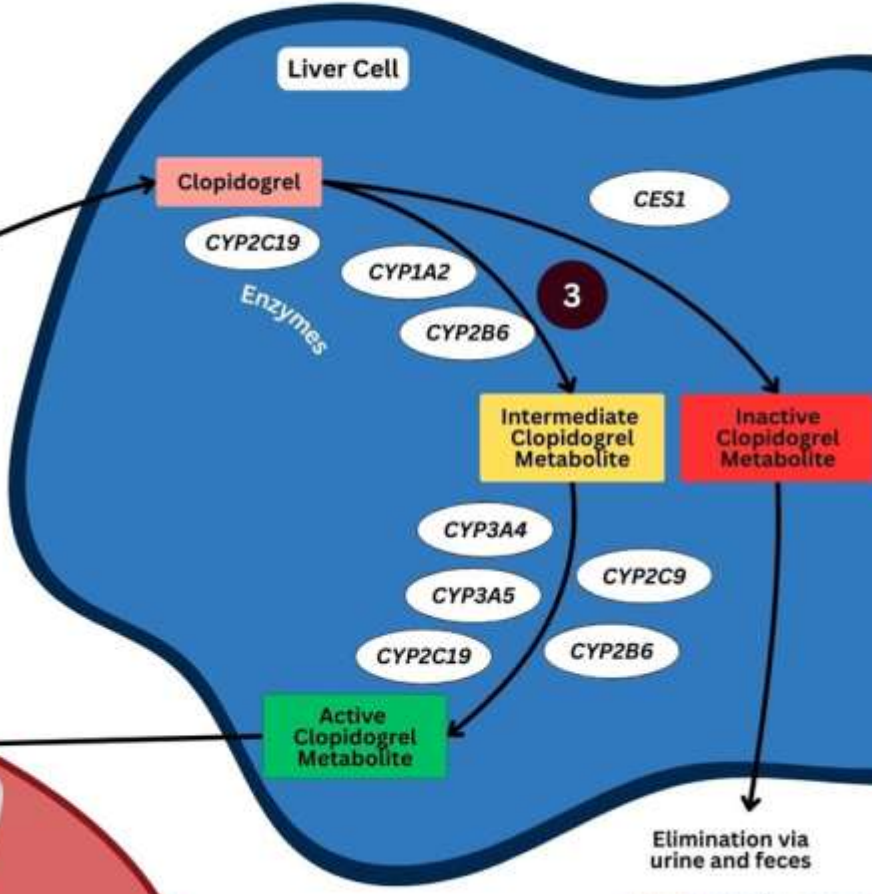
2 ABSORPTION
Clopidogrel is absorbed into the bloodstream through the stomach and intestines.

3 METABOLISM
Clopidogrel is converted into its active form (metabolite) by a series of enzymes in the liver, especially *CYP2C19*.

The inactive metabolites are excreted in the urine and feces.

4 BINDING
The active metabolite binds to and blocks this receptor on platelets circulating in the bloodstream and prevents clotting.





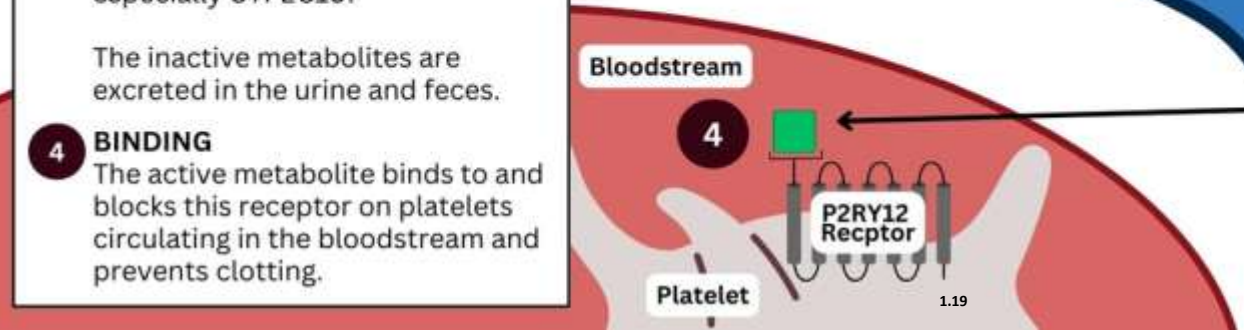


*Diagram is not drawn to scale

Discussion: “Balancing Prevention and Risk”

- Ms. Jackson wants to know why Dr. Silva has asked her questions about her family history, including her race and medical history.
- If you are Dr. Silva, what do you tell her about genetic variation in the expression of the CYP2C19 gene and how that might affect treatment recommendations?

Discussion: “Balancing Prevention and Risk,” continued

- Although Dr. Silva doesn’t know Ms. Jackson’s genotype yet, if she reviews her medical history, she can estimate Ms. Jackson’s risk of adverse events from PCI (angioplasty) based on her racial background.
- What is the frequency of likely intermediate, intermediate, likely poor, and poor metabolizers of clopidogrel in African Americans?
- How about for people of European ancestry (this includes White Americans)?

Discussion: “Balancing Prevention and Risk,” continued

Phenotype frequency: metabolism of clopidogrel

Phenotype	African-Americans	Europeans
Likely intermediate	0.02779	0.00112
Intermediate	0.31399	0.26109
Likely poor	0.00709	0.00020
Poor	0.04051	0.02388
Total		

Due to the higher likelihood of poor/intermediate metabolizer alleles in African Americans, Ms. Jackson may be at higher risk of adverse outcomes than if both her parents were of White background.

Discussion: “Balancing Prevention and Risk,” continued

- What is the most common (highest frequency) CYP2C19 phenotype among African Americans?
- How about people of European ancestry?
- What does this suggest for people who are multiracial like Ms. Jackson?

Discussion: “Balancing Prevention and Risk,” continued

- If Ms. Jackson is **heterozygous** for an allele of CYP2C19 that does not produce any functional protein the gene encodes (a so-called “no function” allele), what is her predicted phenotype?
- What if she is **homozygous** for that no-function allele?
- What might happen to Ms. Jackson if Dr. Silva treats her with clopidogrel, but she is a poor metabolizer?
- What options does Dr. Silva have for alternative treatments?