# CHAPTER 1:
# What's the Right Medicine?

# 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. Traits may be inherited or learned. ***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 worksheet 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 questions on **Including Diverse Populations in Medical Studies (RM 1.2)**.

## ARTICLE:

# Diversity and Inclusion in Clinical Trials

Our health is a combination of physical and mental well-being, which is affected by our behavior, biology, environment, societal policies, and importantly, our lived experiences. The lived experiences of people in the United States vary based on their race and ethnicity, socioeconomic status (SES), geographic location, sexual orientation, gender identity, and other sociodemographic characteristics.

Lived experiences also need to be understood in the context of the individual and structural social determinants of health.

How and where we live, learn, work and play, and our access to high quality health care, healthy foods, and quality education can enhance our health outcomes.

Similarly, negative experiences and exposures, such as pollution, violence, and structural racism and discrimination, can negatively affect our health.

***Our health status reflects the interwoven effects of such factors.***

A clinical trial is a type of clinical research that evaluates the effects of intervention(s), including drugs, devices, surgeries, diets, behavioral approaches, and lifestyle interventions, on health-related biomedical or behavioral outcomes.

To account for the diverse lived experiences and exposures of various populations, clinical research should be appropriately inclusive of racial and ethnic minority groups, as well as other populations experiencing health disparities, including sexual and gender minority or socioeconomically disadvantaged populations.

## Why Are Clinical Trials Important?

Clinical trials can:

- Determine if a new intervention is safe, works better, and/or has fewer side effects than an existing treatment or intervention.
- Examine ways to detect a disease early, when it is potentially more treatable, or ways to prevent a health problem altogether.
- Evaluate ways to improve the quality of life of people who have an illness or chronic medical condition.
- Include testing of behavioral, social, environmental, and structural interventions.

Participating in clinical trials is voluntary. People volunteer to participate in clinical trials for a variety of reasons.

- One of the most common reasons is altruism—the opportunity to contribute to science and the common good and/or help those with similar health issues.

- People may volunteer when it allows them to receive an experimental intervention for life-threatening or disabling disease where no standard treatments are available or were already tried without success.
- New interventions (e.g., weight loss or tobacco cessation interventions) that haven't yet been approved by the U.S. Food and Drug Administration (FDA) may be tested for common conditions to understand if the intervention might help a condition in situations where current treatments or interventions don't exist, don't work well, or have unwanted side effects, or provide symptomatic relief, but offer no cure.

## The Importance of Diversity & Inclusion in Clinical Trials

People may experience the same disease differently. It's essential that clinical trials include people with a variety of lived experiences and living conditions, as well as characteristics like race and ethnicity, age, sex, and sexual orientation, so that all communities can benefit from scientific advances.

Factors that can influence the risk and likelihood of developing a disease, experiencing a long-term health outcome, and responding to treatment include (but are not limited to):

- Age
- Biological sex
- Pregnancy status
- Life experiences (negatives, such as psychosocial stress and lack of basic resources, or positives, such as educational and employment opportunities)
- Unhealthy behaviors (e.g., substance use, sedentary lifestyle, overeating, risky sexual activity)
- Health-promoting behaviors (e.g., adequate sleep, obtaining recommended preventive services, physical activity, healthy eating)
- Environmental conditions (e.g., pollution, access to health care or healthy foods, neighborhood segregation)
- Genetic variation and geographic ancestry
- Underlying medical problems or presence of comorbidities (i.e., additional diseases or conditions)

Historically, clinical trials did not always recruit participants who represented the individuals most affected by a particular disease, condition, or behavior. Often, these clinical trials relied almost exclusively on White male study participants. This shortcoming has created gaps in our understanding of diseases and conditions, preventive factors, and treatment effectiveness across populations. These gaps in knowledge can impede the quality of health care decision making, ability to counsel people on ways to reduce their risk, optimal treatment responses, and even the development of more effective medications or interventions.

Clinicians and researchers should carefully consider the inclusion or exclusion criteria for their clinical trials. For example, a clinical trial excluding participants with high blood pressure or other comorbidities may end up excluding many people over 65 years old, who are more likely to have these conditions. The trial may then underrepresent certain groups in the study and make the results less applicable to groups who may benefit the most from the findings.

## Real-World Examples of the Need for Inclusion in Clinical Trials

### Understanding COVID-19 Disparities

During the early stages of the pandemic, Coronavirus disease 2019 (COVID-19) disproportionately affected racial and ethnic minority populations, including African American, Hispanic/Latino, American Indian/Alaska Native, and Native Hawaiian and Pacific Islander population groups, with increased cases, hospitalizations and deaths.

It was critical that COVID-19 vaccine trials included sufficient representation across population groups to better understand vaccine effectiveness in populations who vary on environmental exposures and other lived experiences. By using inclusive recruitment practices in COVID-19 clinical trials, researchers have been able to show that vaccine safety and efficacy are similar across all racial and ethnic populations. Engaging diverse populations in planning and implementing such trials can also help increase public confidence that the vaccine is safe and effective.

### Understanding Asthma Disparities

Asthma disparities are intricately linked with the environment. Living in a city may increase exposure to air pollution and risk for developing asthma. Exposure to tobacco smoke, chronic social stress, or unhealthy diets may also influence asthma risk or severity. Thus, it is vital for clinicians and researchers to consider where patients live, what they eat, and how they feel—as well as characteristics like race, ethnicity, socioeconomic status, and age—to get a more thorough understanding of their patients' experience with asthma symptoms and identify the best preventative strategies or treatment options.

## Inclusive Participation in Clinical Trials Benefits Scientific Discovery

NIH is committed to inclusivity in clinical trial research. It is essential to have a wide range of people from different communities participate in clinical trials to reduce biases, promote social justice and health equity, and produce more innovative science. Below is a list of topics and examples to illustrate the important role of inclusive participation in clinical trial research.

### Countering Mistrust in Clinical Research

Historical atrocities and incidents have engendered mistrust in clinical research and medical institutions.

Investigators conducting the U.S. Public Health Service Syphilis Study at Tuskegee between 1932 and 1972 did not explain the study's risks and obtain formal agreements (called informed consent) from the African American men who were its participants. The researchers wanted to study the effects of untreated syphilis and withheld penicillin treatment when it became available in 1945, which would have helped the 399 study participants with the disease. Only when news leaked of the study in 1972 did their unethical and discriminatory behavior come to light. Their actions caused preventable illness and death in study participants and their families.

In 2003, members of the Havasupai Tribe in Northern Arizona learned that DNA samples given in the early 1990s for a diabetes research study were later being used for additional research on ethnic migration, schizophrenia, and other unrelated genetic studies. The informed consent form from the original study did not ask participants for their permission to use these samples for these other

analyses. The researchers failed to obtain their consent for use of their data and specimens for other research purposes.

The failings of the Syphilis Study at Tuskegee contributed to the creation of the Belmont Report in 1976, which addresses ethical issues in research with human participants. It outlines basic ethical principles and essential guidelines to protect human research participants and ensure safety in clinical trial research.

Today, Institutional Review Boards are responsible for reviewing all studies involving humans for compliance with these guidelines and reports of any study protocol violations. In recent years, people from racial and ethnic minority communities and other populations experiencing health disparities have become more willing to participate in clinical research. Developing trust with communities who have been marginalized is best achieved through meaningful partnerships between researchers and community members in planning and carrying out studies with their input.

## Inclusion of Women and People from Racial and Ethnic Minority Groups in Clinical Trials

The NIH Revitalization Act of 1993 was signed into law, authorizing NIH to continue its mission and importantly establishing guidelines for the inclusion of women and persons from racial and ethnic minority populations in clinical research. The goal of this law, and other guidelines, is for clinical trial participants to adequately reflect the diversity of the real-world population, so that researchers can determine whether the variables being studied affect women or members of any racial and ethnic population group. This helps ensure that research findings are generalizable to the entire population.

NIH efforts toward research inclusion remain at the forefront of clinical research policy. Recent activities include the publicly available NIH Research, Conditions and Disease Categorization Inclusion Statistics Report, which provides data on human research participation in NIH clinical research studies by race, ethnicity, and sex/gender. Additionally, in 2017, NIH updated its policy on the inclusion of women and people from racial and ethnic minority populations with a requirement that "recipients conducting applicable NIH-defined Phase III clinical trials ensure results of valid analyses by sex/gender, race, and/or ethnicity are submitted to Clinicaltrials.gov." See NIH Inclusion Outreach Toolkit: How to Engage, Recruit, and Retain Women in Clinical Research for more information.

## Inclusion of Sexual and Gender Minority Populations

Until recently, health care systems and epidemiological surveys often didn’t ask sexual orientation and gender identity questions to consider inclusion of sexual and gender minority (SGM) persons. This has made it difficult to know if individuals within SGM populations are represented in clinical research studies in significant numbers to make results representative for them. This lack of knowledge can influence patient-clinician communication and can result in fewer health screening or treatment opportunities.

## Inclusion by Socioeconomic Status (SES)

An individual’s SES is a major predictor of health outcomes, because it can impact access to health care, nutritious foods, prescription medications, and other resources for healthy living. Yet, SES measures (i.e., education and income level) are not collected routinely and reported in clinical trials.

In an analysis of all randomized clinical trials published in 2015 and 2019 in the Journal of the American Medical Association, The Lancet, and the New England Journal of Medicine, study

investigators reported that less than 15% of studies reported on the SES of trial participants. Lack of data collection and reporting on SES measures make it difficult to generalize research findings to all SES groups or to tailor interventions (e.g., new medications or other treatment interventions) to people with lower SES who may not be able to access or maximize the benefits of clinical trial outcomes. In addition, limited access to socioeconomic resources may pose a barrier to participation in clinical trials.

To ensure the inclusion and representation of participants across different SES levels in clinical trials, researchers should use appropriate data collection and reporting protocols. For example, NIMHD supported a social determinants of health collection in the PhenX Toolkit that includes established instruments for conducting research with human participants, such as clinical trials.

Researchers should also design their studies and provide resources to make it easier for people with lower SES to participate in clinical trials, such as offering convenient locations and hours of operation, childcare services, and transportation vouchers.

## Data Collection and Reporting: Unmasking Hidden Truths

When scientists combine information from individual research participants, this is called data aggregation. Data aggregation is an important part of the research process that protects the anonymity of research volunteers and strengthens the statistical analysis of the study. However, aggregation of demographic data, including race and ethnicity, can also mask important differences in health risks or outcomes for specific subpopulations.

For example, many prior studies on the health of Asian Americans have not always examined differences by nationality. A recent study found that among Filipino, Vietnamese, Chinese, Japanese, and Korean American adults living in California, categorizing all participants as "Asian American" masked at least one health disparity for each subpopulation.

Clinicians and researchers must take care to define as best as possible the clinical trial sample in their studies and consider whether their findings can be generalized across population groups, including consideration for differences in lived experiences.

**Source:** NIH National Institute on Minority Health and Health Disparities (NIMHD), https://www.nimhd.nih.gov/ (accessed December 2024; hyperlinks removed)

# READING: Applying Personalized Medicine

No two patients are alike, which makes the practice of medicine challenging. For example, no two surgeries are the same due to people's individual variations. Also, in many cases, an effective dosing of medication depends on an individual's genetic makeup and lifestyle.

When caring for a patient, a medical professional must come up with a diagnosis, determine appropriate treatments, properly administer medication or therapy, monitor the patient's progress, and adjust the course of treatment as needed—and each step must take the patient's medical history into account while respecting the patient's wishes.

It is crucial to provide patients with the right medication at the right dosage, but this is not as simple as it seems, as you have learned from reading the NIMHD article on diversity in clinical research. Numerous factors, including life stage, pre-existing conditions, and genetics, can result in patients responding quite differently to the same medication. Depending on the medication, some people may need larger or more frequent doses, and others, less frequent or smaller doses.

The enormous variety of medications currently on the market creates a large pool of options from which physicians and pharmacists can choose. However, this adds another layer of troubleshooting when prescribing medications. Sometimes even very subtle differences between multiple formulations of a single drug—such as generic versus brand name—can influence a patient's better response to one form over another.

So, how do practitioners know which medication to use? They rely on guidelines from groups of medical professionals who conduct clinical research trials to determine optimal treatments.

Below, read about a patient who needs a lifesaving medication and learn how their doctor treats them based on their genetics. Then, answer the questions on **Reading Questions: Balancing Prevention and Risk (RM 1.3).**

# READING: Balancing Prevention and Risk

Renee Jackson is a 64-year-old grandma and recreational pickleball player. Recently, she began having perplexing episodes of chest pain, even when at rest and not exercising. She let her primary care physician know and was diagnosed with ***angina*** (one cause of chest pain) and told to monitor her symptoms.

At a recent tournament, she had to stop playing mid-match due to severe chest pain and shortness of breath and was rushed to the nearest emergency department. Thankfully, they determined that she had not had a heart attack, but that several of her coronary arteries were almost completely blocked. That set the stage for small blood clots to form in her arteries, reducing blood flow and causing her symptoms, termed ***unstable angina***.

Ms. Jackson will need a ***percutaneous coronary intervention (PCI)***, also known as an angioplasty, to clear the blockages and to insert ***stents***, which are tiny, expanding metal cage-like structures that prop arteries open. These devices will work to reduce her chest pain. She will also need to make

some medication and lifestyle changes to manage her coronary artery disease to prevent her arteries from being blocked in the future.

Ms. Jackson has an appointment with her interventional cardiologist, Naomi Silva, for a pre-procedure consultation.

Dr. Silva tells Ms. Jackson that she wants to pre-treat her with ***antiplatelet therapy*** (medication that prevents blood clotting), since potential clotting from the procedure might lead to an increased risk of heart attack and stroke. Usually, she would prescribe the medication clopidogrel (brand name Plavix), which reduces blood clots by stopping platelets from clumping.

However, she tells Ms. Jackson that her health insurance has approved a genetic test to determine whether she is a carrier of an abnormal allele, or variant, of the CYP2C19 gene, which encodes a ***cytochrome P450*** enzyme. ***Enzymes*** are proteins that catalyze chemical reactions without being used up or altered themselves, so they can be reused repeatedly. Cytochrome P450 enzymes are expressed in the liver, where they carry out oxidation and reduction reactions on substrates that include medications.

An ***allele*** is one of two or more alternative forms of a gene. Some alleles alter the form or function of the protein the gene encodes. Mutant alleles of CYP2C19 could put Ms. Jackson at additional risk for complications if Dr. Silva prescribes clopidogrel. If Ms. Jackson carries one or more of these alleles, she can still have the PCI, but will be prescribed a different antiplatelet medication instead, to minimize her risk of heart attack or stroke from the angioplasty.

Dr. Silva asks Ms. Jackson if she would be willing to share her self-identified race, in addition to providing details of her medical history.

Ms. Jackson understands that she needs to have the procedure as soon as possible but is worried about it and the possibility of complications. She's also concerned about the cardiologist's request to learn about her racial background. She has questions for the doctor before she consents to genetic testing.

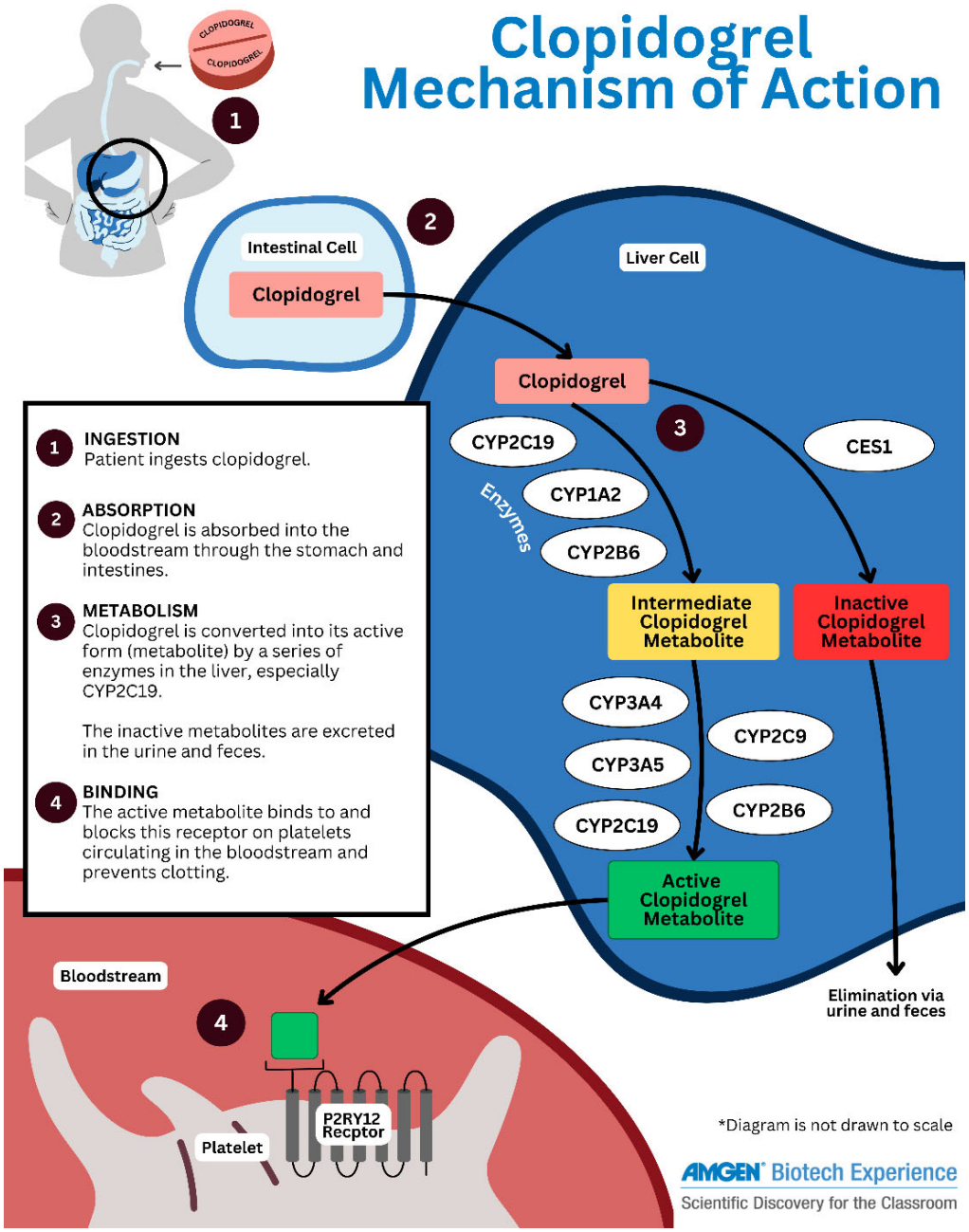
What should Dr. Silva tell her?

## BACKGROUND INFORMATION

See **Figure 1.1** below to learn about the crucial role of the cytochrome P450 enzyme family in drug metabolism, and review Ms. Jackson's medical and family history. Then, view the video *Simple Genetic Test Shows Promise for Better Outcomes in Heart Stent Patients* to learn what researchers found about the effect genetic variation in CYP2C19 has on metabolism of antiplatelet medication.

Next, use the two tables from the Clinical Pharmacogenetics Implementation Consortium guidelines for the use of clopidogrel versus other antiplatelet agents to treat cardiovascular conditions, along with a table of phenotype frequency below, to answer the questions on **RM 1.3**.

**Figure 1.1: Clopidogrel mechanism of action**




**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 mother (White) had high cholesterol and metabolic syndrome, and her ancestry was European (British Isles).

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

**Table 1.1: Assignment of predicted CYP2C19 phenotype based on genotype**

| Predicted phenotype | Genotype | Examples of *CYP2C19* diplotypes[a] |
|---|---|---|
| CYP2C19 ultrarapid metabolizer | An individual carrying two increased function alleles | **17/*17* |
| CYP2C19 rapid metabolizer | An individual carrying one normal function allele and one increased function allele | **1/*17* |
| CYP2C19 normal metabolizer | An individual carrying two normal function alleles | **1/*1* |
| CYP2C19 likely intermediate metabolizer[b] | An individual carrying one normal function allele and one decreased function allele or one increased function allele and one decreased function allele or two decreased function alleles | **1/*9, *9/*17, *9/*9* |
| CYP2C19 intermediate metabolizer | An individual carrying one normal function allele and one no function allele or one increased function allele and one no function allele | **1/*2, *1/*3, *2/*17, *3/*17* |
| CYP2C19 likely poor metabolizer[b] | An individual carrying one decreased function allele and one no function allele | **2/*9, *3/*9* |
| CYP2C19 poor metabolizer | An individual carrying two no function alleles | **2/*2, *3/*3, *2/*3* |
| Indeterminate metabolizer | An individual carrying one or two uncertain function alleles | **1/*12, *2/*12, *12/*14* |

[a] Please refer to the *CYP2C19* Diplotype-Phenotype Table online for a complete list. For allele functions and population-specific allele and phenotype frequencies, please refer to the *CYP2C19* Allele Functionality Table and the *CYP2C19* Allele Frequency Table online.[8,9]
[b] There are limited data to characterize the function of decreased function alleles.

**Table 1.2: Antiplatelet therapy recommendations based on CYP2C19 phenotype when considering clopidogrel for cardiovascular indications**

| CYP2C19 phenotype[a] | Implications for phenotypic measures | Therapeutic recommendation | Classification of recommendation[b] - ACS and/or PCI[c] | Classification of recommendation[b] - non-ACS, non-PCI cardiovascular indications[d] |
|---|---|---|---|---|
| CYP2C19 ultrarapid metabolizer | Increased clopidogrel active metabolite formation; lower on-treatment platelet reactivity; no association with higher bleeding risk | If considering clopidogrel, use at standard dose (75 mg/day) | Strong | No recommendation |
| CYP2C19 rapid metabolizer | Normal or increased clopidogrel active metabolite formation; normal or lower on-treatment platelet reactivity; no association with higher bleeding risk | If considering clopidogrel, use at standard dose (75 mg/day) | Strong | No recommendation |
| CYP2C19 normal metabolizer | Normal clopidogrel active metabolite formation; normal on-treatment platelet reactivity | If considering clopidogrel, use at standard dose (75 mg/day) | Strong | Strong |
| CYP2C19 likely intermediate metabolizer | Reduced clopidogrel active metabolite formation; increased on-treatment platelet reactivity; increased risk for adverse cardiac and cerebrovascular events | Avoid standard dose clopidogrel (75 mg) if possible. Use prasugrel or ticagrelor at standard dose if no contraindication | Strong[e] | No recommendation[e] |
| CYP2C19 intermediate metabolizer | Reduced clopidogrel active metabolite formation; increased on-treatment platelet reactivity; increased risk for adverse cardiac and cerebrovascular events | Avoid standard dose (75 mg) clopidogrel if possible. Use prasugrel or ticagrelor at standard dose if no contraindication | Strong | No recommendation |
| CYP2C19 likely poor metabolizer | Significantly reduced clopidogrel active metabolite formation; increased on-treatment platelet reactivity; increased risk for adverse cardiac and cerebrovascular events | Avoid clopidogrel if possible. Use prasugrel or ticagrelor at standard dose if no contraindication | Strong[e] | Moderate[e] |
| CYP2C19 poor metabolizer | Significantly reduced clopidogrel active metabolite formation; increased on-treatment platelet reactivity; increased risk for adverse cardiac and cerebrovascular events | Avoid clopidogrel if possible. Use prasugrel or ticagrelor at standard dose if no contraindication | Strong | Moderate |

ACE, acute coronary syndrome; PCI, percutaneous coronary intervention.

[a] The online *CYP2C19* Allele Frequency Table provides phenotype frequencies for major race/ethnic groups, and the online *CYP2C19* Diplotype-Phenotype Table provides a complete list of possible diplotypes and phenotype assignments.[8,9]

[b] Rating scheme described in the **Supplementary Material** online.

[c] ACS and/or PCI includes patients undergoing PCI for an ACS or non-ACS (elective) indication.

[d] Non-ACS, non-PCI cardiovascular indications include peripheral arterial disease and stable coronary artery disease following a recent myocardial infarction outside the setting of PCI.

[e] The strength of recommendation for the "likely" phenotypes are the same as their respective confirmed phenotypes. "Likely" indicates the uncertainty in the phenotype assignment, but it is reasonable to apply the recommendation for the confirmed phenotype to the corresponding "likely" phenotype.

Tables 1.1 and 1.2 reproduced with permission from "Clinical Pharmacogenetics Implementation Consortium Guideline for *CYP2C19* Genotype and Clopidogrel Therapy: 2022 Update (January 2022)."

**Table 1.3: Frequencies of CYP2C19 phenotypes in biogeographical groups***

| Phenotype | African American/Afro-Caribbean | American* | Central/South Asian | East Asian | European* | Latino | Near Eastern | Oceanian | Sub-Saharan African |
|---|---|---|---|---|---|---|---|---|---|
| Ultrarapid Metabolizer | 0.04294 | 0.00741 | 0.02916 | 0.00042 | 0.04641 | 0.02774 | 0.03664 | 0.00325 | 0.03005 |
| Rapid Metabolizer | 0.23738 | 0.13638 | 0.18567 | 0.02534 | 0.27118 | 0.24136 | 0.25737 | 0.02133 | 0.21081 |
| Normal Metabolizer | 0.32806 | 0.62756 | 0.29553 | 0.38055 | 0.39612 | 0.52498 | 0.45192 | 0.03501 | 0.36977 |
| Likely Intermediate Metabolizer | 0.02779 | 0 | 0 | 0.00077 | 0.00112 | 0.00371 | 0 | 0 | 0.04286 |
| Intermediate Metabolizer | 0.31399 | 0.21383 | 0.40807 | 0.45928 | 0.26109 | 0.19036 | 0.23548 | 0.36903 | 0.29946 |
| Likely Poor Metabolizer | 0.00709 | 0 | 0 | 0.00043 | 0.0002 | 0.00044 | 0 | 0 | 0.01033 |
| Poor Metabolizer | 0.04051 | 0.01482 | 0.08157 | 0.12979 | 0.02388 | 0.01141 | 0.01858 | 0.57139 | 0.03671 |
| Indeterminate | 0.00224 | 0 | 0 | 0.00341 | 0 | 0 | 0 | 0 | 0 |

Table 1.3 adapted and reproduced with permission from "Supplement to: Clinical Pharmacogenetics Implementation Consortium Guidelines for *CYP2C19* Genotype and Clopidogrel Therapy: 2022 Update (January 2022)."

*In this table, the "American" biogeographical group refers to people of Indigenous ancestry, such as Native Americans and Indigenous people of Mexico. White Americans are included in the "European" group.

# OPTIONAL READING: How Your Genes Influence What Medicines Are Right for You

If your teacher has assigned the optional reading "How Your Genes Influence What Medicines Are Right for You" by Julie A. Johnson (2015), you can access it at the link in the Student Resources document.