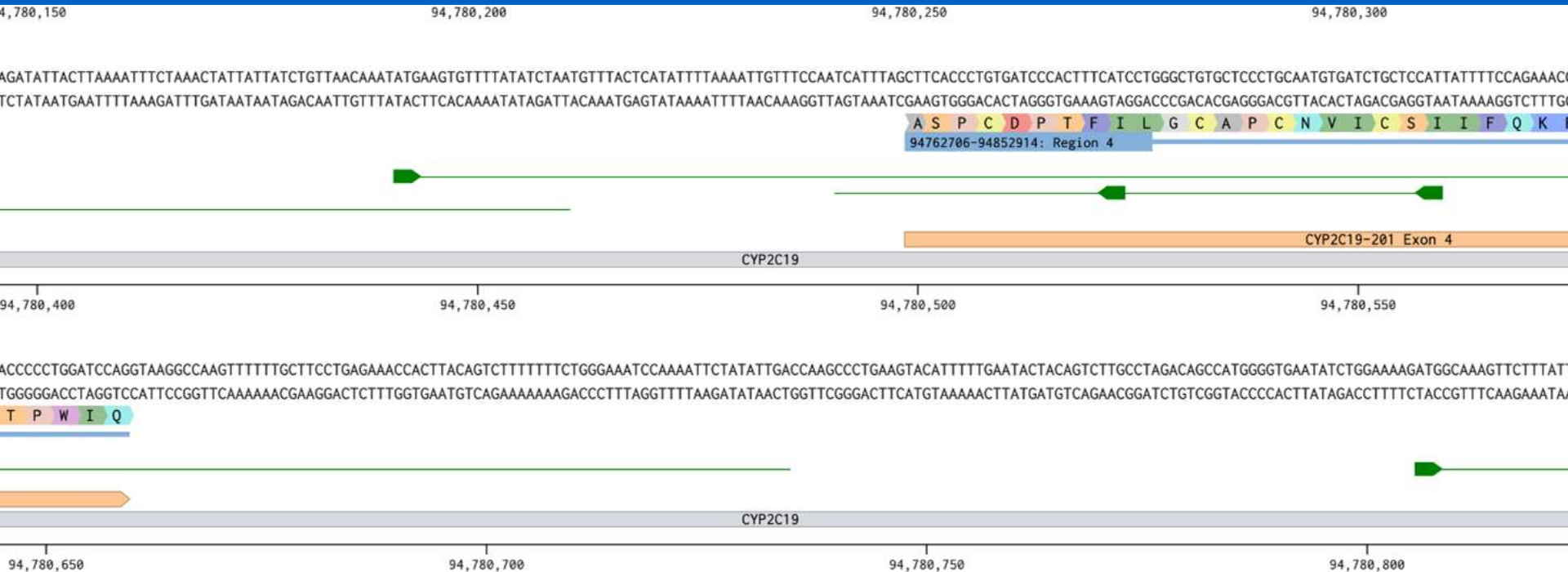


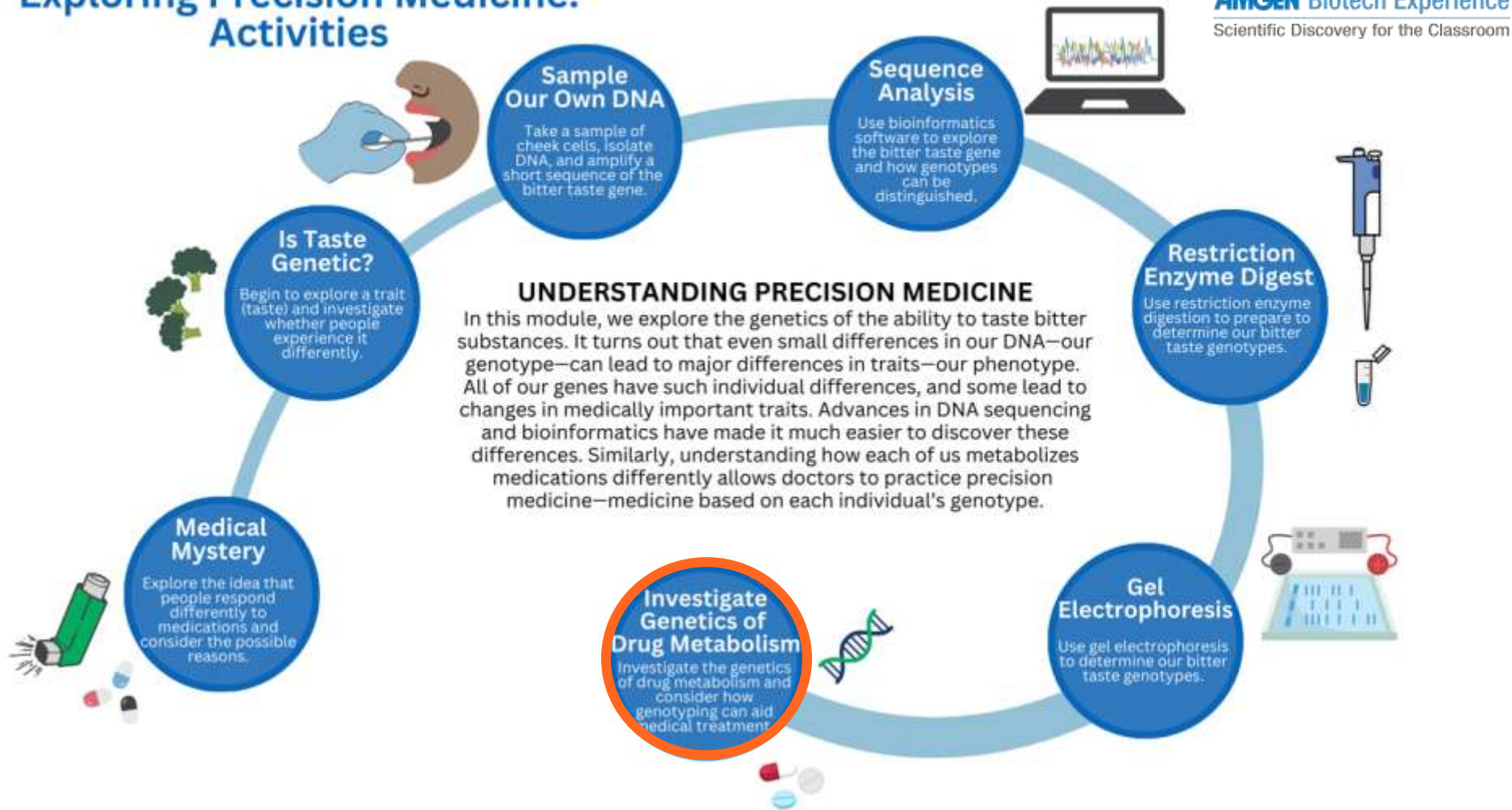
Exploring Precision Medicine

- 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 7: SNPs and drug metabolism



Exploring Precision Medicine: Activities



Why did we explore the TAS2R38 gene?

- **We followed steps also used in precision medicine:**
 - Observe phenotype
 - Extract DNA
 - Explore genotype
- **We did our own genotyping:**
 - PCR
 - Restriction enzyme digestion
 - Gel electrophoresis

Review: What's the relationship between SNPs and phenotype?

- Phenotype = genotype + environment
- SNPs = genomic variation
- Most variants are “silent”
- Some variants change traits
- Traits may affect health

Review: Patient case, Ms. Renee Jackson

- **Family background: one White parent, one Black parent**
 - Why would patient race be informative? Pros/cons?
- **Has blocked arteries**
 - Needs Percutaneous Coronary Intervention (“angioplasty”)
- **Needs genotyping of CYP2C19**
- **Can’t metabolize clopidogrel? Will need a different medication**



RM 7.1: Pharmacogenomics and clopidogrel

1. What is Ms. Jackson's genotype at the CYP2C19*2 locus?

CYP2C19*1/CYP2C19*2 (*1 is the designation for the "wild type" allele).

2. Is she heterozygous or homozygous at this locus? How do you know? How can you tell the PCR and restriction digests were carried out correctly?

She's heterozygous. Her restriction digest yielded 3 bands: two from the wild-type allele (*1), one from the *2 allele.

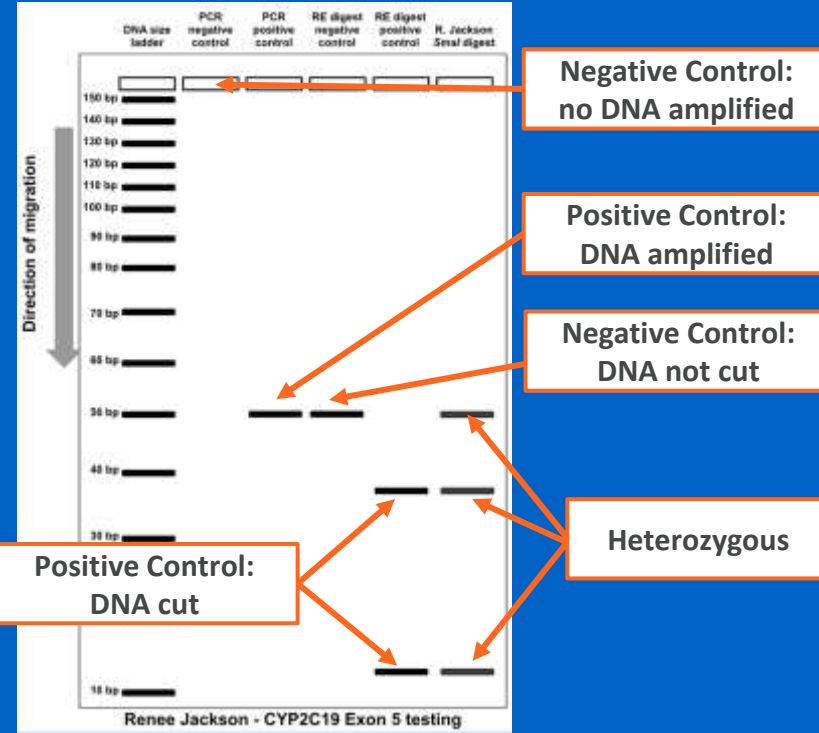
PCR worked: DNA was amplified.

Digest worked: Wild-type genomic DNA was cut.

3. Review the tables in Chapter 1 to determine the optimal treatment for Ms. Jackson prior to her angioplasty. How should Dr. Silva treat her, and why?

She should not take clopidogrel. It won't prevent clotting well enough!

Dr. Silva needs to prescribe an alternative antiplatelet medicine.



RM 7.1 (continued)

- **Direct genomic sequencing vs. PCR/restriction fragment length polymorphism (“PCR-RFLP”) for genotyping—which one’s better? Pros and cons?**
 - Sequencing:
 - Definitive answer
 - Takes longer
 - More expensive
 - PCR-RFLP:
 - Quicker
 - Less expensive
 - May be inconclusive if restriction digest is incomplete

RM 7.1 (continued)

- **Should every patient have medical genetic testing?**
 - **Pros:**
 - Better treatment of conditions with a genetic component
 - **Cons:**
 - Potential violations of privacy
 - Patients may end up on more medications
 - More expensive for health insurers and providers
 - Doctors need more training
 - Less research on treating multiple conditions simultaneously

**Do we know everything about the human genome,
now that it's been sequenced?**

Sequencing every patient's DNA: pros and cons?

RM 7.1 (continued)

- **PharmGKB: What other medications' metabolism is affected by the CYP2C19*2 mutation?**
 - Proton pump inhibitors, psychiatric medications, blood clotting medications, sedatives, opioids, etc.
- **Why is the availability of so many classes of drugs affected?**
 - Because the class of cytochrome P450 enzymes is involved in metabolizing most medications



Clopidogrel Mechanism of Action

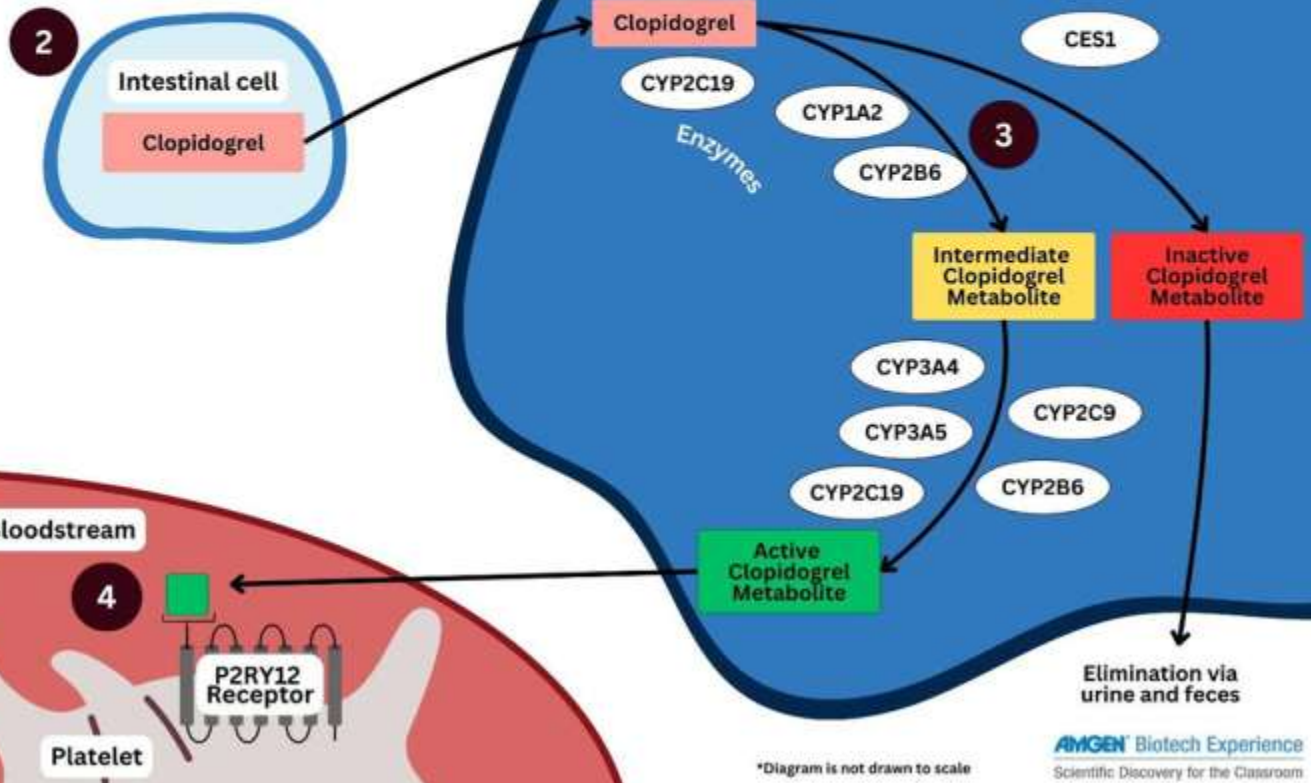
1 INGESTION
Patient ingests clopidogrel.

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

Medication metabolism phenotypes



Poor metabolizer (PM)

- Reduced activity of the enzyme responsible for metabolizing a particular drug
- Slower or inadequate metabolism of the drug
- Increased risk of adverse drug reactions and toxicity



Intermediate metabolizer (IM)

- Reduced but not absent activity of the enzyme responsible for metabolizing a particular drug
- Slower metabolism of the drug compared to normal metabolizers



Normal metabolizer (NM)

- Normal enzyme activity and can metabolize drugs at a normal rate



Ultrarapid metabolizer (UM)

- Increased activity of the enzyme responsible for metabolizing a particular drug
- Faster metabolism of the drug compared to normal metabolizers
- Reduced effectiveness of the drug
- Increased risk of adverse drug reactions due to accumulation of toxic metabolites