Safety in Polypharmacy Training Course

## Session 3

# Drug-Gene & Drug-Drug-Gene Interactions

Written version of the video scripts

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PATIENT ENGAGEMENT IS IN OUR DNA

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# VIDEO #1 — Your DNA Decoded: Genetics Foundations for Drug Safety

**Estimated Duration:** 6-7 minutes
**Target Audience:** Broad: patients, caregivers, and clinicians

## 1. Introduction

Have you ever wondered why the same medication works perfectly for one person but causes terrible side effects in another? Or why your doctor might say, "We need to try a different drug for you"? The answer might be hiding inside every single cell of your body. In your DNA!

Welcome to Session 3 of the SafePolyMed series. Over the next three videos, we are going to explore how your genes influence the way drugs work in your body. And trust me, even if you think genetics is complicated, by the end of this video, you will have a solid foundation. Let's start with the basics.

## 2. Main content

### Why Genetics Matters for Patient Advocates

Before we dive into the science, let's talk about why this matters for you. Whether you are a patient, a caregiver, or a patient advocate, understanding genetics is becoming essential. It helps you understand clinical trial data and why some trials select patients based on genetic markers. It helps you advocate for access to treatments that depend on genetic testing. It prepares you for future developments like CRISPR gene editing. And it helps you understand the limitations of polypharmacy, because your genetic makeup adds another layer of complexity to how multiple drugs interact in your body.

### DNA - Deoxyribonucleic acid

Let's start at the very beginning. DNA, or deoxyribonucleic acid, is the molecule inside nearly every cell of your body that contains your genetic instructions. It is structured as a double-stranded helix, like a twisted ladder. The steps of that ladder are made of four chemical letters:

A, T, C, and G. Which stands for Adenine, Thymine, Cytosine and Guanine. They are arranged in pairs, with A always pairing with T, and C always pairing with G.

## DNA, Genes, Chromosomes: The Building Blocks

The specific sections of this DNA that code for specific functions are called genes. Think of genes as individual recipes in a cookbook. They tell your cells how to make the proteins that build and run your body, from your hair colour to how your liver processes a drug.

Then those genes are organised into compact structures called chromosomes. Humans have 23 pairs of them, 46 chromosomes in total, with one set of 23 chromosomes inherited from each parent. And the complete collection of all your DNA across all your chromosomes is called your genome. So, your unique version of this genome is your genotype.

## Genotype vs. Phenotype: Instructions vs. Results

Now, here's an important distinction. Your genotype is your full set of genetic instructions, the complete cookbook. But your phenotype is what actually shows up: your appearance, how your body functions, how you behave. It's the finished dish, so to speak.

And here's the key: your phenotype is not determined by your genes alone. It results from the interaction of your genotype with your environment. Things like your diet, exercise, pollution exposure, medications, stress, and infections, ALL influence which genes get expressed and how strongly. So, two people with the same gene might end up with different outcomes because they live in different environments.

## MicroRNA: The Fine-Tuning Knobs

There is one more piece of the puzzle worth knowing about: microRNAs. These are tiny single-stranded, non-coding RNA molecules. They don't make proteins themselves, but they regulate how much of a gene gets expressed. Think of them as the volume knobs on your genetic stereo. They are part of the reason why even identical twins can respond differently to the same drug.

The discovery of microRNAs was considered so significant that the researchers behind it were awarded the 2024 Nobel Prize in Physiology or Medicine.

### Gene Expression & Environment

So, it is important to know that when you think of gene expression consider that it is not static, it changes over time. Genomes are designed to promote adaptation to the environment.

A fascinating example comes from a research on caloric restriction in mice. When mice were fed significantly restricted diets, not only did they live longer and look healthier, but the expression of genes related to metabolism, inflammation, and stress response actually changed. The environment literally altered which genes were turned on or off.

Here is another example you might relate to: lactose intolerance. Most humans lose the ability to digest lactose after childhood, because the gene for producing the enzyme lactase gets switched off. But Europeans, whose ancestors relied heavily on dairy, carry a mutation that keeps this gene active into adulthood. East Asians and West Africans, who historically did not depend on dairy, typically become lactose intolerant. Same gene, different environments and evolutionary pressures, and you see completely different outcomes.

### Epigenetics

This brings us now to epigenetics, the study of how age and environmental factors cause changes in the way genes are switched on or off, without changing the actual DNA sequence. It's like a layer of instructions on top of your genetic code that determines how that code is used. Epigenetics is what tells a liver cell to do liver things and a brain cell to do brain things, even though they have the same DNA.

And here is why this matters for polypharmacy: both genetic and epigenetic differences can affect how you respond to a drug. Even identical twins might need different doses of the same medication because of epigenetic differences that have accumulated over their lifetimes.

## 3. Key takeaways

So, here's what you now know: your DNA is the instruction manual for your body, but it's not the whole story. You learned about the genome, that DNA fragments that code for a certain function are called genes, and genes are organised in chromosomes. The difference between Genotype and Phenotype, and what can determine your phenotype. That the epigenetic information layers on top of our genetic code and determines how that genetic code is used.

And all, your environment, your lifestyle, and even your epigenetics all play a role in how you respond to medications.

In our next video, we will explore what happens when those instructions contain errors, called mutations, and how they directly impact drug safety. Stay with us. See you in the next one!

# VIDEO #2 — When Genes Mutate: Variations, Genomics & Ethical Frontiers

**Estimated Duration:** 7-8 minutes
**Target Audience:** Broad: patients, caregivers, and clinicians

## 1. Introduction

What if a single "typo" in your DNA could change the way a drug works in your body?

What if that same typo could make a life-saving medication either useless or dangerous?

That's what mutations can do.

In this video, we are going to explore the different types of genetic mutations, how they affect drug response, and what happens when we sequence the human genome, including some surprising ethical dilemmas that nobody expected.

## 2. Main content

### Genetic Variations and Drug Response

In the last video, we compared your DNA to a cookbook. Genetic variations are like small typos in those recipes. Everyone has some variations, they are what make each of us unique. But just as a typo in a recipe can change how a dish turns out, genetic variations can change how your body reacts to drugs.

There are several types of gene mutations, grouped by how they change the DNA code. Like point mutations that swap one letter for another, and can be further identified as a substitution, which can be sometimes harmless, sometimes disease-causing. So, they can be what is called a silent mutation that changes a letter but does not change the resulting protein at all, or a missense mutation that changes one letter that results in a different amino acid in the protein. Let's think of sickle cell anaemia, caused by this exact type of mutation; or a nonsense mutation which accidentally introduces a "stop" signal, cutting the protein short.

Then there are mutations by insertion or deletion, such as a frameshift mutation, which adds or removes letters in a way that throws off the entire reading frame, it's like shifting all the words in a sentence by one letter, and there might be a change of the amino acid.

But beyond individual genes, there are also chromosome-level mutations, these are large-scale changes of whole chunks of your DNA, like duplications: A section of a chromosome is copied, creating extra genetic material; deletions: A piece of a chromosome breaks off and is lost; inversions: A segment breaks off, turns upside down, and reattaches; or translocations: A piece of one chromosome breaks off and attaches to a different, non-homologous chromosome. And these changes affect many genes at the same time.

Another type of variation is the CNV or copy number variation, which are changes in the number of copies of a particular gene or region of the genome. And these can be linked to conditions ranging from autism to certain cancers.

But let's be clear, mutations are not always bad. They can be harmless, beneficial, or drive evolution. They occur spontaneously through natural DNA replication errors, or they can be induced by environmental factors like UV radiation, chemicals, or viruses.

### Epistasis: When One Gene Hides Another

Now, there is also a fascinating concept worth learning about, called Epistasis, where one gene's effects can mask or modify the effects of another gene. The best example here is sickle cell disease.

Sickle cell disease is caused by a single missense mutation in the HBB gene, and this mutation results in the production of haemoglobin S - HbS. If you inherit two copies of this mutation, one from each parent, you develop the disease: your red blood cells become crescent-shaped, get stuck in blood vessels, and cause severe pain and organ damage.

But here's where epistasis comes in. Some individuals also carry an HPFH mutation, hereditary persistence of foetal haemoglobin. Normally, foetal haemoglobin is replaced by adult haemoglobin shortly after birth. But people with the HPFH mutation continue producing foetal haemoglobin throughout their lives. This foetal haemoglobin protects them from the effects of the sickle cell mutation, leading to much milder symptoms or even no symptoms at all, even though they genetically have sickle cell disease. So, HPFH mutations are in epistasis with HbS, Haemoglobin S.

This discovery was so powerful that it became the basis for gene therapy approaches to sickle cell disease: using CRISPR to reactivate foetal haemoglobin production in patients.

## From Genetics to Genomics

Now let's zoom out from individual genes to the big picture: genomics. This is the study of entire genomes; all of your DNA.

Here a fun fact! The term genomics is thought to have been coined in 1986 by Dr. Tom Roderick a geneticist at the Jackson Laboratory in Bar Harbor, Maine, over beers at a meeting on the mapping of the human genome and the naming of a new academic journal.

So, in genomics there are two main approaches. Whole genome sequencing, that looks at all 20,000 genes plus the regions between them. While targeted gene sequencing, or genetic testing, examines a specific panel of 100 to 500 genes that are most relevant to a particular condition. Both use a technology called Next Generation Sequencing, or NGS.

And here an important distinction to consider: genetic testing is typically used to find inherited mutations in healthy cells, while genomic sequencing can be used to find mutations in unhealthy cells, like cancer cells.

Once sequencing is complete, you have a massive amount of data. In fact, genomic data storage is estimated to account for about 2% of all data storage worldwide.

## Incidental Findings and the Right to (Not) Know

Now, with the power of genome sequencing comes a profound ethical challenge: what do you do when you are looking for one thing and find something else entirely?

These are called incidental findings, genetic discoveries unrelated to the original reason for testing. You might sequence a child's genome to diagnose a kidney problem and discover they carry a predisposition for cancer, Alzheimer's, or Huntington's disease.

The key ethical questions include: How do you respect patient autonomy through consent? How do you balance harm and benefit, considering potential stigmatisation? How do you protect confidentiality, knowing that relatives share DNA? And how do you manage incidental findings that may not be clinically actionable, meaning there is nothing you can do about them yet?

In practice, patients are asked before testing whether they want to be informed about incidental findings. Some patient communities, like those affected by Huntington's disease, strongly support not disclosing non-actionable findings. The logic behind it is this: if there is no treatment available, knowing you will develop the disease may cause more harm than good through anxiety and potential impacts on insurance and employment. But when findings are actionable, like a BRCA1 mutation that increases breast cancer risk, there is an ethical obligation to inform the patient.

As it was shared in the live sessions, the ideal approach combines disclosure with professional genetic counselling to help patients understand, process, and make decisions about their results.

## 3. Key takeaways

Now you have learned that mutations are typos in your DNA and they can change how drugs work in your body, making them more effective, less effective, or even dangerous. You learned about Epistasis and Genomics. We acknowledged that genome sequencing is giving us unprecedented insight into individual differences. But with that power comes real ethical responsibilities and challenges.

In our final video of this session, we will explore the cutting edge: pharmacogenomics, how gene editing is transforming medicine, and real-world examples of drug-gene interactions that are already changing clinical practice today. See you in the next one!

# VIDEO #3 — Pharmacogenomics, Gene Editing & the Future of Personalised Medicine

**Estimated Duration:** 7-8 minutes

**Target Audience:** Broad: patients, caregivers, and clinicians

## 1. Introduction

Imagine a world where, before you take a single pill, your doctor already knows exactly how your body will process it. Not a guess based on your age or weight, but a precise prediction based on your DNA. That world isn't science fiction anymore. It's called pharmacogenomics, and it's already changing medicine today.

In this final video of Session 3, we are bringing everything together: how your genes determine whether you are a fast or slow drug metaboliser, real cases where genetic testing prevented life-threatening drug reactions, and how gene editing technologies like CRISPR could one day eliminate some genetic diseases altogether.

## 2. Main content

### The Four Metaboliser Types: Which One Are You?

In Session 2, we learned about CYP450 enzymes in the liver that break down drugs. Now we add the genetics layer. Your genes determine how active those enzymes are, and that places you into one of four categories that exist. The four metaboliser types.

Extensive metabolisers, these are the "average" population. Drugs work as intended for this group. It is what most drugs are designed for.

Intermediate metabolisers, these process drugs more slowly than normal. They might experience more side effects or reduced effectiveness.

Poor metabolisers, these have genetic variants that make their enzymes barely functional. Drugs can build up in their body, causing toxicity, because the drug is not being cleared.

And ultra-rapid metabolisers are the opposite: their enzymes work so fast that drugs are eliminated before they can do their job, potentially requiring higher doses.

Here's the striking part: most people have no idea which type they are. And yet, this information could completely change the safety and effectiveness of their medication.

## Pharmacogenomics & DDGIs

This is the field of pharmacogenomics, the branch of pharmacology that studies how your individual genetic inheritance affects the way your body responds to drugs. It combines traditional pharmaceutical sciences such as biochemistry with annotated knowledge of genes, proteins, and single nucleotide polymorphisms. Its goal is elegantly simple! get the right drug, at the right dose, to the right person. Maximum effectiveness, minimum side effects!

But here's where it gets complex in the context of polypharmacy. When a patient is taking multiple medications and they have a genetic variant affecting a key metabolising enzyme, you don't just get a drug-drug interaction or a drug-gene interaction, you get a drug-drug-gene interaction, or DDGI.

Let's look at an example. Let's imagine a psychiatric patient with COPD, chronic obstructive pulmonary disease, who is being treated with a PDE4 inhibitor like Roflumilast for the lung inflammation, plus an SSRI antidepressant like Fluvoxamine. Both drugs are processed by CYP enzymes in the liver. Now, if that patient has a genetic variant that reduces CYP1A2 activity, the Fluvoxamine further slows down the metabolism of Roflumilast. The result is excessive drug levels in the blood, causing both physical side effects like nausea and weight loss, and psychiatric risks like agitation and depression, imagine this in a patient who already has a mental health condition.

This is the triple collision of a DDGI: the gene variant, the first drug, and the second drug all converging to create a dangerous situation. Genetic testing could have predicted this and prompted a dosage adjustment or an alternative therapy.

## Gene Editing

Now let's have a look at what might be the most revolutionary development in medicine: gene editing! This is where scientists make precise changes to an organism's DNA, like editing text in a document, as gene editing allows genetic material to be added, removed, or altered at specific locations in the genome. It is a molecular system that uses a "highlighter" to find the

target DNA and uses a "scissors" to cut it. Then the cell's own repair machinery fixes the gap. The most well-known tool used by scientists to perform this, is CRISPR, Clustered Regularly Interspaced Short Palindromic Repeats, it locates genetic errors that cause disease and either correct the sequence or replace it with a new one provided by scientists.

The goal is extraordinary: to correct faulty genes that cause diseases, add new functions, or remove harmful DNA sequences. It is already being explored in clinical trials for sickle cell disease, cystic fibrosis, haemophilia, and even more complex conditions like cancer, heart disease, and HIV.

We saw earlier how sickle cell disease can be masked by persistent foetal haemoglobin. Gene therapy using CRISPR is now being used to reactivate foetal haemoglobin production in patients with sickle cell disease. It is not science fiction, it's happening in hospitals right now!

## Real-World Examples: Genetic Testing Saving Lives

So, let's close with three concrete examples where genetic testing directly impacts drug safety.

First: thiopurine drugs, used to treat leukaemia and autoimmune diseases. The enzyme TPMT, thiopurine methyltransferase, breaks them down. Patients with genetic variants causing low TPMT activity cannot metabolise these drugs properly, leading to dangerous drug buildup and bone marrow suppression. Genetic testing before treatment can identify these patients and allow physicians to adjust the dose accordingly.

Second: clopidogrel, the antiplatelet drug we discussed in Session 2. The enzyme CYP2C19 converts it into its active form. Patients with certain variants in this gene are poor metabolisers, which means they have reduced ability to activate the drug clopidogrel. So, blood clot prevention fails, and the risk of heart attacks and strokes increases. These patients need an alternative medication.

In a real case, a 60-year old patient with coronary artery disease was tested after a stent procedure, found to be a poor CYP2C19 metaboliser, and was switched to a different drug, with no further cardiovascular events.

Third: fluorouracil, or 5-FU, a chemotherapy drug used in colorectal and breast cancer. The enzyme DPD breaks it down. Patients with mutations in the DPYD gene that reduces or eliminates the activity of DPD cannot effectively break down 5-FU, meaning 5-FU builds up to life-threatening levels, causing severe, life-threatening toxicities, including extreme

gastrointestinal side effects, bone marrow suppression, and neurological symptoms. Today, patients are routinely tested for DPD deficiency before receiving 5-FU. It is now standard practice.

## 3. Key takeaways

Here is the big takeaway from this entire session: your genes are not just about how you look like. They directly influence how every drug in your medicine cabinet works inside you.

Pharmacogenomics is already making polypharmacy safer by identifying who will benefit from a drug and who might be harmed by it.

As a patient or caregiver, ask your healthcare team: has genetic testing been considered for my medications?

As a patient advocate, push for pharmacogenomic testing to become part of routine clinical care. The technology is here! The evidence is here! It's about access and awareness now.

> **You have completed Session 3!**

In our next session, we will explore vulnerability factors in polypharmacy: the individual, social, and systemic risks that make some patients more vulnerable than others. See you in Session 4!

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