A Textbook of

Clinical Pharmacy

for Pharmacy Students

Lesson 10:

Pharmacogenomics and Clinical Pharmacy

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Lesson 10: Pharmacogenomics and Clinical Pharmacy

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10.1 Pharmacogenomics and Clinical Pharmacy

Pharmacogenomics extends the traditional goals of clinical pharmacy by using genetic information to explain **why patients with similar clinical characteristics can show markedly different responses to the same medicine**, and to use that information prospectively to individualize pharmacotherapy. In this context, pharmacogenetics is often used to describe the study of variability in drug response attributable to single genes or a small number of variants, whereas pharmacogenomics is a broader term encompassing the contribution of multiple genes and genome-wide variation to drug pharmacokinetics and pharmacodynamics.

From a clinical pharmacy perspective, pharmacogenomic information offers an additional explanatory layer on top of established determinants such as age, renal and hepatic function, comorbidities, concomitant medicines and adherence patterns, rather than replacing them.[1] Genetic variation can influence absorption and distribution, metabolism and elimination, interaction with drug targets, and the risk of idiosyncratic immune-mediated reactions, so that two patients with similar creatinine clearance and comorbidities may nonetheless require different starting doses, titration speeds or even different drugs to achieve comparable benefit–risk profiles.[2]

The clinical impact of incorporating pharmacogenomic concepts into pharmacotherapy is already evident in several therapeutic areas where robust evidence and guidelines exist. For example, genotype-guided strategies have been associated with improved effectiveness of antiplatelet and antidepressant therapy, reduced toxicity with certain anticoagulants, antineoplastic agents and statins, and fewer unplanned health-care utilizations in older adults

[1] Elewa H, Awaisu A. Pharmacogenomics in Pharmacy Practice: Current Perspectives. Integr Pharm Res Pract. 2019;8:97-104.
[2] Hayashi M, Hamdy DA, Mahmoud SH. Applications for pharmacogenomics in pharmacy practice: A scoping review. Res Social Adm Pharm. 2022;18(7):3094-3118.

exposed to multiple medicines. As implementation broadens, pharmacogenomics is expected to support safer and more effective use across cardiovascular, psychiatric, oncologic, gastroenterological, and pain management indications, while also creating new opportunities for clinical pharmacists to design, interpret and apply testing within routine medication review and precision pharmacotherapy services.

Pharmacogenetics and pharmacogenomics

Pharmacogenetics has been classically defined as the study of variability in drug response due to heredity, with a predominant focus on single genes that influence the pharmacokinetics or pharmacodynamics of specific medicines. In other words, pharmacogenetics is concerned with how particular genetic variants in one gene (for example, a drug-metabolizing enzyme or a drug target) explain interindividual differences in efficacy or toxicity for a given drug, often yielding "one gene–one drug" relationships that can be translated into concrete clinical recommendations.

Pharmacogenomics is described as a broader, genome-wide extension of pharmacogenetics that "encompasses all genes in the genome that may determine drug response" and addresses the simultaneous impact of multiple variants and pathways. Rather than restricting itself to single-gene traits, pharmacogenomics integrates variation across many pharmacokinetic and pharmacodynamic genes, sometimes together with transcriptomic or other "omics" data, to understand and predict complex drug-response phenotypes at the systems level and to guide individualized pharmacotherapy.

Some controversy exists around these two terms and their differences. Respected researchers declared that the term pharmacogenomics results from "the fashion for adding the suffix '… omics' to areas of research" and both terms can be used interchangeably. In this course, we use the term pharmacogenomics because this is how the EU Directive 2024/782 described this area.

- Pirmohamed M. Pharmacogenetics and pharmacogenomics. Br J Clin Pharmacol. 2001;52(4):345-347.

10.1.1 Genetic Variants that Influence Pharmacotherapy

Genetic variants that influence pharmacotherapy can be usefully structured by the **type of gene involved** (metabolizing enzymes, transporters, drug targets, immune-response genes) and by **the way they alter pharmacokinetics or pharmacodynamics**, with each class linked to characteristic clinical phenotypes (e.g. poor vs ultra-rapid metabolism, high vs low sensitivity, intolerant vs tolerant).[3]

[3] Ahmed S, Zhou Z, Zhou J, Chen SQ. Pharmacogenomics of Drug Metabolizing Enzymes and Transporters: Relevance to Precision Medicine. Genomics Proteomics Bioinformatics. 2016;14(5):298-313.

Genetic Variants by genomic mechanism (variant level)

At the most basic level, clinically relevant pharmacogenomic markers fall into a few mechanistic categories, regardless of the gene they affect. Common mechanisms are:

- **Single-nucleotide polymorphisms** (SNIPs): These variants consist of a change in a single base pair in the DNA sequence, which can alter an amino acid (missense), introduce a premature stop codon (nonsense), or affect splicing or regulatory regions, thereby decreasing, abolishing, or occasionally increasing the activity of the encoded protein. In pharmacogenes, SNIPs are the dominant mechanism underlying many classic metabolizer phenotypes and HLA-defined hypersensitivity risks (for example CYP2D6, CYP2C19, CYP2C9, VKORC1, and several HLA alleles).
- **Small insertions/deletions and regulatory length variants**: Small insertions or deletions of a few base pairs, variable number tandem repeats, and promoter-region length variants change the amount of transcript produced rather than the protein's structure, leading to under-expression or over-expression of the gene product. In pharmacogenomics, such variants typically manifest as low- or high-expression alleles that modify enzyme or transporter abundance, as described for some CYP2C19 promoter variants that increase expression or low-expression VKORC1 haplotypes that enhance warfarin sensitivity.
- **Copy-number variants**: Copy-number variants involve whole-gene deletions, duplications, or multiplications, which markedly reduce (deletions) or increase (duplications/multiplications) the total amount of enzyme or transporter produced. A canonical pharmacogenomic example is CYP2D6, where gene deletions generate poor metabolizer phenotypes and duplications (for example 1xN, 2xN) create ultrarapid metabolizers with correspondingly low or high exposure to CYP2D6 substrates at standard doses.

Genetic Variants by functional gene class

A clinically oriented classification that maps directly onto clinical decisions is **by what the gene does in the pharmacokinetic/pharmacodynamic** pathway. Four broad classes cover most actionable pharmacogenes:

Drug-metabolizing enzymes (PK genes)

These genes **encode Phase I and Phase II enzymes** that determine how quickly a drug is activated/inactivated and cleared. Typical examples are CYP2D6, CYP2C19, CYP2C9, CYP3A5, TPMT, NUDT15, DPYD and UGT1A1. For many of these, clinical laboratories and guidelines translate genotype into standardized phenotypes: poor, intermediate, normal (or extensive), rapid and ultra-rapid metabolizers, based on the combined activity of both alleles.

From a clinical pharmacist perspective, two key patterns are:

- Active drugs inactivated by metabolism (e.g. many SSRIs, tricyclics, warfarin, some beta-blockers): poor metabolizers have higher exposure and toxicity risk, whereas rapid/ultra-rapid metabolizers have lower exposure and risk of non-response or therapeutic failure at standard doses.
- Prodrugs activated by metabolism (e.g. codeine via CYP2D6, clopidogrel via CYP2C19): poor metabolizers may show lack of effect (e.g. poor analgesia or reduced antiplatelet activity), while rapid/ultra-rapid metabolizers may have exaggerated effect or toxicity.

CYP2D6, CYP2C19 and CYP2C9 are prototypical for illustrating this class: CYP2D6 copy-number and loss-of-function alleles stratify patients into poor through ultra-rapid metabolizers affecting tricyclics, SSRIs and some opioids; CYP2C19 loss- and gain-of-function alleles define poor to ultra-rapid metabolizers relevant for clopidogrel and proton-pump inhibitors; CYP2C9 reduced-function alleles (*2, *3) explain lower warfarin dose requirements and increased bleeding risk at standard dosing.

Drug transporters (PK distribution/clearance genes)

Transporter genes **encode influx and efflux proteins in gut, liver, kidney and blood–tissue barriers**, modulating absorption, hepatic uptake, biliary excretion and tissue penetration. Common clinically relevant examples include SLCO1B1 (hepatic uptake transporter OATP1B1), ABCB1 (P-glycoprotein) and several others depending on therapeutic area.

Variants that reduce transporter function usually increase systemic exposure of susceptible drugs but may reduce hepatic or target-organ uptake. For instance, reduced-function SLCO1B1 haplotypes lead to higher circulating statin concentrations and increased risk of dose-dependent muscle toxicity, which underpins recommendations to avoid high-dose simvastatin or choose alternative statins in high-risk genotypes. In contrast, increased efflux activity at the blood–brain barrier (e.g. some ABCB1 variants) has been associated in some studies with reduced CNS drug penetration and potential non-response, although evidence is more heterogeneous than for metabolizing enzymes.

Drug targets and pharmacodynamic signaling genes

This class includes **genes encoding the molecular target of the drug** (receptors, enzymes, ion channels) **or key downstream signaling components** that determine sensitivity at a given concentration. Classic pharmacodynamic pharmacogenes include VKORC1 (warfarin target), ADRB1 (beta-1 receptor), SLC6A4 and HTR2A (for SSRI response), and various oncologic targets or repair enzymes for cytotoxics (e.g. TYMS, ERCC1).

For VKORC1, haplotypes associated with lower expression or higher target sensitivity yield a “high-sensitivity” phenotype: patients require substantially lower warfarin maintenance doses and have higher bleeding risk if dosed empirically. The reciprocal “low-sensitivity” phenotypes need higher initial and maintenance doses to achieve therapeutic anticoagulation. In psychiatry and cardiology, variants in transporters or receptors (e.g. SLC6A4, ADRB1, ADRB2) can shift the dose–response curve, contributing to non-response or heightened adverse-effect burden at usual doses, although the strength of evidence and guideline support varies by gene and drug.

Immune-response genes (idiosyncratic toxicity)

Immune-mediated adverse drug reactions are strongly influenced by HLA and other immune-response genes, which define an “intolerant” pharmacodynamic phenotype rather than a change in usual PK parameters. HLA-B*57:01 with abacavir hypersensitivity, HLA-B*15:02 and HLA-A*31:01 with carbamazepine-induced Stevens–Johnson syndrome/toxic epidermal necrolysis, and HLA alleles associated with certain antibiotic or allopurinol reactions are canonical examples.

Genetic Variants clinical phenotype and use consequences

A succinct framework for a cross-classification by **clinical phenotype** and **typical clinical pharmacist action**, independent of the specific gene is:

1. **Altered metabolism phenotypes** (poor, intermediate, normal, rapid, ultra-rapid metabolizers): primarily CYPs, DPYD, TPMT, NUDT15, UGT1A1; typical actions are dose reduction or drug avoidance for poor metabolizers with toxicity risk, and dose escalation or alternative drug selection for rapid/ultra-rapid metabolizers with non-response risk.

2. **Altered distribution/clearance phenotypes** (low- vs normal-function transporters): mainly SLCO1B1 and some ABC transporters; actions include dose limitation or drug substitution to mitigate exposure-related toxicity (e.g. simvastatin myopathy risk in SLCO1B1 low-function carriers).

3. **Altered sensitivity phenotypes at the target** (high-sensitivity vs low-sensitivity): e.g. VKORC1 for warfarin, some receptor polymorphisms; actions are to choose lower or higher starting doses and tighter monitoring to achieve the same PD effect.

4. **Intolerant vs tolerant immune phenotypes** (HLA-associated severe hypersensitivity): e.g. HLA-B*57:01-positive vs negative for abacavir; actions focus on pre-emptive genotyping and complete avoidance of the culprit drug in high-risk genotypes.

10.2 Pharmacogenomics and Optimization of Pharmacokinetic Processes

10.2.1 CYP-mediated Metabolism and Genotype-Guided Use

For many commonly used drugs, cytochrome P450 polymorphisms explain several-fold differences in clearance and thus in steady-state concentrations achieved with standard dosing. Translating CYP genotype into metabolizer phenotype (poor, intermediate, normal, rapid, ultra-rapid) allows individualization of both the initial dose and the selection of alternative drugs when the predicted exposure would fall clearly outside the therapeutic range.

A first set of clinically instructive examples are **CYP2D6 and antidepressants or opioids**. CYP2D6 poor metabolizers have markedly reduced conversion of prodrugs such as codeine or tramadol into their active metabolites and therefore show reduced or absent analgesic response, whereas ultra-rapid metabolizers may generate excessive active metabolite and be at higher risk of opioid toxicity at standard doses. Guidelines consequently recommend avoiding codeine and tramadol in CYP2D6 poor and ultra-rapid metabolizers, and instead using opioids not substantially affected by CYP2D6 or non-opioid analgesics. For tricyclic antidepressants and some SSRIs, CYP2D6 and CYP2C19 poor metabolizers exhibit higher plasma concentrations and increased risk of adverse effects, while ultra-rapid metabolizers may not achieve effective concentrations.

A second prototypical CYP is **CYP2C19**, which illustrates both inactivation of active drugs and bioactivation of prodrugs. CYP2C19 metabolizes several proton pump inhibitors (PPIs), so poor metabolizers tend to have higher exposure and more pronounced acid suppression, whereas rapid or ultra-rapid metabolizers can have lower PPI exposure and reduced acid suppression, potentially requiring higher doses or an alternative PPI with less CYP2C19 dependence in rapid metabolizers. In contrast, clopidogrel is a prodrug requiring CYP2C19 for conversion into its active thiol metabolite. CYP2C19 intermediate and poor metabolizers show reduced active metabolite formation, diminished platelet inhibition and increased rates of major cardiovascular events, so current guidance supports either alternative antiplatelet therapy (e.g. prasugrel,

ticagrelor where indicated) or carefully adapted dosing strategies instead of standard clopidogrel dosing in these patients.

CYP2C9 provides a third illustrative metabolic example, particularly for drugs with narrow therapeutic indices. CYP2C9*2 and *3 alleles encode enzymes with reduced activity, leading to slower clearance of S-warfarin and other substrates such as some antiepileptics, and thus higher exposure at a given dose. In warfarin therapy, carriers of reduced-function CYP2C9 alleles require lower maintenance doses, longer time to reach steady-state and are more prone to early over-anticoagulation and bleeding if treated with standard empiric doses. Warfarin dosing algorithms that incorporate both CYP2C9 and VKORC1 genotypes can reduce out-of-range INRs and bleeding risk by recommending lower starting doses and slower titration in genetically sensitive patients.

10.2.2 Transport, Distribution and Exposure at the Site of Action

Transporter polymorphisms modify drug disposition by altering the rate at which drugs enter or leave hepatocytes, myocytes, the central nervous system or other tissues, which in turn changes the balance between systemic and tissue-specific exposure. From a clinical pharmacist perspective, such variants are most relevant when they affect drugs with narrow therapeutic windows or when toxicity is driven by high plasma or tissue levels rather than by on-target pharmacodynamic sensitivity alone.[4]

SLCO1B1, encoding the hepatic uptake transporter OATP1B1, is the best-established example in routine cardiovascular pharmacotherapy. Reduced-function SLCO1B1 variants decrease hepatic uptake of several statins, resulting in higher circulating statin concentrations and substantially increased risk of statin-induced myopathy, particularly with high-dose simvastatin and, to a lesser extent, some other statins. Genotype-guided strategies therefore recommend avoiding high-dose simvastatin in SLCO1B1 low-function phenotypes and preferentially using statins with lower dependence on SLCO1B1 (e.g. pravastatin, fluvastatin) or lower starting doses with cautious titration and closer monitoring for muscle symptoms and creatine kinase in these patients.[5]

P-glycoprotein (ABCB1) is another transporter that can influence distribution across the gut and the blood–brain barrier for several cardiovascular and central nervous system drugs, although the evidence base is more heterogeneous than for SLCO1B1. ABCB1 polymorphisms have been associated in some studies with altered oral bioavailability or CNS penetration of digoxin, certain antiepileptics, antidepressants and antipsychotics, which may contribute to interindividual variability in both efficacy and neurotoxicity; however, current guidelines rarely recommend specific dose adjustments based solely on ABCB1 genotype, and any genotype-informed modification of starting dose or monitoring usually needs to be integrated with clinical response and comorbidities rather than applied as rigid rules.

[4] Ahmed S, Zhou Z, Zhou J, Chen SQ. Pharmacogenomics of Drug Metabolizing Enzymes and Transporters: Relevance to Precision Medicine. Genomics Proteomics Bioinformatics. 2016;14(5):298-313.
[5] Xiang Q, Chen SQ, Ma LY, et al. Association between SLCO1B1 T521C polymorphism and risk of statin-induced myopathy: a meta-analysis. Pharmacogenomics J. 2018;18(6):721-729.

10.3 Pharmacogenomics and Pharmacodynamic Targets

Pharmacogenomic variation in pharmacodynamic targets and immune pathways identifies patients who are intrinsically more sensitive, resistant or intolerant to particular drugs, leading to genotype-specific recommendations to avoid certain agents, choose alternatives, or modify dosing and monitoring intensity.

10.3.1 VKORC1 and Vitamin K Antagonists

VKORC1 encodes the vitamin K epoxide reductase complex subunit 1, the molecular target of warfarin and other vitamin K antagonists, and common promoter and intronic polymorphisms modulate VKORC1 expression and warfarin sensitivity. Haplotypes associated with lower VKORC1 expression confer a high-sensitivity phenotype, in which standard empiric starting doses yield excessive suppression of vitamin K recycling, lower dose requirements and increased risk of over-anticoagulation and bleeding. Conversely, VKORC1 variants associated with higher expression or lower sensitivity require higher maintenance doses to reach the same INR.[6]

Clinical algorithms and implementation guidelines combine VKORC1 with CYP2C9 and clinical factors to refine initial warfarin dosing and titration, typically recommending lower starting doses and slower up-titration in VKORC1 high-sensitivity genotypes and, in some settings, higher starting doses in low-sensitivity genotypes, with the overarching goal of minimizing early supratherapeutic INRs and bleeding while achieving therapeutic anticoagulation more predictably.

10.3.2 HLA-associated Hypersensitivity and Drug Avoidance

HLA polymorphisms exemplify pharmacogenomic markers of qualitative intolerance, where the primary recommendation is to avoid the problem drug altogether in carriers because of the high risk of severe immune-mediated reactions. The association between HLA-B*57:01 and abacavir hypersensitivity is the most widely implemented: prospective HLA-B*57:01 screening before starting abacavir almost eliminates immunologically confirmed hypersensitivity and markedly reduces clinically suspected reactions, and current guidelines therefore recommend that abacavir is not prescribed to HLA-B*57:01-positive patients and is considered only in HLA-B*57:01-negative individuals. In fact, testing for HLA-B*57:01 is mandatory in European Union before prescribing abacavir, as described in the Summary of Product Characteristics (SmPC).

Similarly, HLA-B*15:02 is strongly associated with carbamazepine-induced Stevens–Johnson syndrome/toxic epidermal necrolysis in several Asian and some other populations, and carriers of HLA-B*15:02 are considered at unacceptably high risk for severe cutaneous reactions when exposed to carbamazepine; screening is recommended in high-prevalence populations, and alternative antiepileptics should be used in carriers. Other HLA alleles, such as HLA-A*31:01 for carbamazepine and HLA markers for allopurinol, show similarly large effect sizes and underpin recommendations to avoid the suspect drug in carriers and to select safer alternatives, while non-carriers can generally receive the drug with routine monitoring.[7]

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[6] Johnson JA, Cavallari LH. Warfarin pharmacogenetics. Trends Cardiovasc Med. 2015;25(1):33-41.
[7] Bellón T, Ramírez E, Borobia AM, et al. The HLA-B*15:02 allele in a Spanish Romani patient with carbamazepine-induced Stevens-Johnson syndrome. Pharmacogenomics. 2016;17(6):541-545.

10.3.3 Receptor and transporter polymorphisms in psychiatric and cardiovascular therapy

Variants in receptors, transporters and other signaling components can alter the pharmacodynamic response to cardiovascular or psychiatric drugs at a given plasma concentration, often **shifting the dose–response curve rather than changing systemic exposure**. For example, polymorphisms in the serotonin transporter gene promoter (5-HTTLPR in SLC6A4) and certain serotonin receptor genes (such as HTR2A) have been associated in several studies with differential response and tolerability to SSRI antidepressants, although the strength and consistency of associations vary and guideline recommendations are more cautious than for PK genes or HLA markers. In cardiology, ADRB1 and ADRB2 variants have been investigated in relation to beta-blocker response in heart failure and hypertension, with some data suggesting genotype-specific differences in blood pressure or heart rate responses and outcomes, but routine genotype-guided prescribing has not yet been widely adopted because of heterogeneous evidence.

In contrast to high-penetrance VKORC1 or HLA effects, these receptor and transporter polymorphisms often have more modest effect sizes, so they are better viewed as one component in a broader precision-medicine assessment rather than as stand-alone determinants of drug choice.

10.4 Pharmacogenomic Information in Official Drug Labeling

For many medicines, pharmacogenomic information is now included in official drug labeling, but **the depth and practical usefulness of this information vary substantially between products and regulatory regions**. In the **United States**, the Food and Drug Administration maintains a public "Table of Pharmacogenomic Biomarkers in Drug Labeling", which lists drugs whose prescribing information mentions genomic biomarkers and may describe variability in exposure or response, risk of adverse events, genotype-specific dosing, or required testing; however, even within this table, some labels provide only descriptive statements while others include clear actionable recommendations.[8] Similar heterogeneity is observed in European Union Summary of Product Characteristics (SmPCs), where pharmacogenomic content is scattered across sections (e.g. pharmacokinetics, special warnings, posology) and often lacks explicit, implementable advice.[9]

Comparative analyses show that **official labels frequently lag behind or diverge from independent pharmacogenomic guidelines**. For a set of drugs with well-established gene–drug interactions and high-level recommendations from consortia such as CPIC and DPWG, only about half of the corresponding US labels or EU SmPCs contain any actionable pharmacogenomic information, and concordance between FDA, EMA and guideline recommendations is limited. In several cases, labels acknowledge that variants in genes such as CYP2C9, CYP2C19 or VKORC1 influence exposure or dose requirements but stop short of providing specific genotype-based dosing algorithms, whereas specialist guidelines offer concrete dose ranges, alternative drugs, or decision trees. This discrepancy means that reliance

[8] Kim JA, Ceccarelli R, Lu CY. Pharmacogenomic Biomarkers in US FDA-Approved Drug Labels (2000-2020). J Pers Med. 2021;11(3):179.

[9] Reis-Pardal J, Rodrigues A, Rodrigues E, Fernandez-Llimos F. Comparing cytochrome P450 pharmacogenetic information available on United States drug labels and European Union Summaries of Product Characteristics. Pharmacogenomics J. 2017;17(6):488-493.

on the package insert alone can underestimate the clinical relevance of certain gene–drug pairs or fail to highlight when testing is strongly recommended, particularly for high-risk combinations such as warfarin with VKORC1/CYP2C9, clopidogrel with CYP2C19, or abacavir with HLA-B*57:01.[10]

From a clinical pharmacy perspective, **official labeling remains a necessary but not sufficient information source for pharmacogenomic decisions**. Pharmacists should be aware that US prescribing information and EU SmPCs may omit pharmacogenomic recommendations that are considered standard in independent guidelines, may provide only qualitative statements ("exposure may be increased") without concrete dose adjustments, and may differ between regulatory jurisdictions for the same drug. Integrating label information with up-to-date, evidence-based pharmacogenomic resources (such as CPIC, DPWG and curated databases) enables pharmacists to move beyond the limitations of the official documents, supporting more consistent genotype-guided therapy while still complying with the legal framework of product labeling in their jurisdiction.

10.5 Complementing official information with other sources (ClinPGx)

The SmPC is the legally binding, product-specific document that you must respect, but it is not designed to give a complete, up-to-date pharmacogenomic implementation guide. ClinPGx, in contrast, aggregates and curates pharmacogenomic knowledge across drugs, genes and guidelines (CPIC, DPWG, etc.), and annotates drug labels with a standardized "PGx level" and explicit genotype-based recommendations. **A major recommendation** is starting from the SmPC to see what regulators explicitly acknowledge, then use ClinPGx to (a) interpret that information in the context of a specific genotype and (b) check whether stronger or more detailed guidance exists than what the SmPC states.

Here is a process to follow the sequence of information that can be obtained from ClinPGx[11] using amitriptyline as an example. The specific SmPC used as a start point is the Portuguese RCM of "ADT 10, 25, 75 mg comprimidos revestidos".

First, it is essential to extract explicitly all pharmacogenomically relevant information from the SmPC. In this amitriptyline SmPC, the key sentences are in section 4.2, which states that known CYP2D6 or CYP2C19 poor metabolizers may have higher plasma concentrations of amitriptyline and nortriptyline and that a 50% reduction of the recommended initial dose should be considered in these patients. Section 4.5 explains that amitriptyline is primarily metabolized by CYP2D6 and CYP2C19, that these isoenzymes are polymorphic in the population. Section 5.2 confirms that amitriptyline metabolism occurs mainly via CYP2C19- and CYP3A4-mediated demethylation and CYP2D6-mediated hydroxylation, that metabolism is subject to genetic polymorphism (CYP2D6 and CYP2C19), and notes that therapeutic plasma concentrations for amitriptyline plus nortriptyline are about 80-200 ng/ml, whereas levels above 300-400 ng/ml are associated with an increased risk of conduction disturbances. Together, these statements define the regulatory pharmacogenomic "signal": CYP2D6 and CYP2C19 genotype influences exposure, poor metabolizers and strong CYP2D6 inhibitor co-treatment increase

[10] Shekhani R, Steinacher L, Swen JJ, et al. Evaluation of Current Regulation and Guidelines of Pharmacogenomic Drug Labels: Opportunities for Improvements. Clin Pharmacol Ther. 2020;107(5):1240-1255.
[11] https://www.clinpgx.org

concentrations, and in such situations a dose reduction and/or plasma level monitoring should be considered.

From this signal, the pharmacist formulates a focused pharmacogenomic question to take to ClinPGx. For amitriptyline, a clinically relevant question is: "In a patient who fulfils an indication in the SmPC, how should the dose and monitoring of amitriptyline be adapted according to CYP2D6 and CYP2C19 genotype (for example poor, intermediate, or ultrarapid metabolizer), and how does this relate to the 50% dose reduction suggested for known poor metabolizers in the SmPC?" ClinPGx is then used not as a replacement for the SmPC, but as a structured evidence layer that answers this specific question in a standardized way across genes, drugs and guidelines.

ClinPGx is organized into several complementary sections, each curated with a specific purpose: to describe what regulatory labels say, to summarize variant–drug associations, and to link to guideline-level recommendations and other evidence. Understanding the scope and limitations of each section is a prerequisite for using the database rationally in clinical pharmacy.

Prescribing information: In ClinPGx, "prescribing information" refers to curated, genotype-specific guidance on how to adjust treatment for certain medications based on a person's genetic information. For each drug with pharmacogenomic guidance, this section aggregates recommendations from clinical pharmacogenomics guidelines (primarily CPIC and DPWG) and from labels that contain explicit, variant-specific prescribing advice, and presents them in a concise, clinician-oriented format that focuses on what action (dose change, alternative drug, enhanced monitoring) should be taken for each metabolizer phenotype or genotype group. In practical terms, this is the part of ClinPGx that answers the question "Given this genotype or phenotype, how should I prescribe or adjust this drug?" and it is therefore the closest analogue, within ClinPGx, to a genotype-stratified dosing table or decision aid. In this section, the **Clinical Guideline Annotations** is of special interest to investigate specific allele variants in a patient, by selecting the Annotation corresponding to a specific gene in a specific source, the clinical pharmacists can introduce the phenotype map of the patient and obtain tailored recommendations.

Drug label annotations: Drug label annotations in ClinPGx capture and standardise the pharmacogenomic content of official product information from regulatory authorities such as FDA and EMA. For each drug–label pair, ClinPGx provides a brief text summary of the pharmacogenomic statements in the label, an excerpt of the exact wording (especially where genotype-specific dosing or contraindications are described), a list of any specific genes or variants mentioned, and a set of "PGx level" tags that classify the label as "testing required", "testing recommended", "actionable PGx", "informative PGx", or "criteria not met", along with additional tags such as "Dosing Info", "Alternate Drug", "Prescribing Info", "Indication", or "On FDA Biomarker List". This section therefore answers the question "What does the current approved label say about pharmacogenomics for this drug, and how strong or explicit is that label-based guidance?".

Summary annotations: Summary annotations (also called clinical annotations) are ClinPGx's synthesis of variant–drug relationships at the clinical level, built on top of the individual variant annotations. Each summary annotation corresponds to a specific variant–drug or gene–drug pair and contains a structured description of the association between genotype (or diplotype) and a clinical phenotype such as efficacy, toxicity, dose requirement, pharmacokinetics, or other drug response outcomes, and it specifies the direction of effect (for example "decreased response"

or “increased toxicity”) relative to a reference genotype. All relevant variant annotations, whether supportive or not, are listed beneath the summary, and a Level of Evidence (assigned according to the ClinPGx clinical-annotation scoring system) quantifies the overall strength and reliability of the association, allowing users to distinguish robust, guideline-level relationships from preliminary or conflicting findings.

Variant annotations: Variant annotations are the most granular curation unit in ClinPGx and record single findings from individual published studies. Each variant annotation is essentially one sentence linking a specific variant (for example rsID or star allele), a drug, and an outcome, summarizing the result of a single comparison in a single paper (for instance “carriers of allele X had higher clearance and lower exposure to drug Y than non-carriers”, or “no association was found between variant Z and adverse event W”), along with bibliographic details and basic study characteristics. A single article may therefore give rise to multiple variant annotations if it assesses several variants, drugs, or phenotypes, and these variant annotations are then grouped and synthesized into the higher-level summary annotations described above, providing the evidentiary substrate for clinical interpretation.

At this point, the clinical pharmacist can integrate SmPC and ClinPGx information into a concrete prescribing and monitoring plan for a given patient. If a patient meeting an ADT indication (for example major depressive disorder or neuropathic pain) is known to be a CYP2D6 or CYP2C19 poor metabolizer, the SmPC already recommends a 50% reduction in the initial dose and acknowledges the higher expected plasma concentrations of amitriptyline and nortriptyline. ClinPGx refines this by specifying, for the exact genotype, the expected change in exposure, the recommended percentage dose reduction at initiation, how aggressively to titrate, and whether an alternative antidepressant with lower dependence on CYP2D6 should be preferred in high-risk patients. For ultrarapid metabolizers, where the SmPC is silent, ClinPGx-linked guidelines may suggest that standard doses could produce subtherapeutic concentrations and recommend higher target doses or, in some cases, an alternative drug, again combined with plasma level monitoring. This enables the pharmacist to move from a generic “consider 50% dose reduction in poor metabolizers” wording to a fully individualized regimen that incorporates genotype, co-medications inhibiting CYP2D6, age, hepatic function, and target plasma concentration range.