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Biochemical Mechanisms in Drug Metabolism: Implications for Personalized Pharmacotherapy in Pharmacy Practice

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Abstract

Background: Drug metabolism is a complex biochemical process, where cytochrome P450 enzymes (CYPs) play a crucial role in the biotransformation of medications. Variations in these enzymes can influence the pharmacokinetics and pharmacodynamics of drugs, leading to inter-individual differences in drug response. Personalized pharmacotherapy aims to tailor drug treatment based on individual genetic and metabolic profiles to optimize therapeutic outcomes and minimize adverse effects.

Aim: This paper explores the biochemical mechanisms involved in drug metabolism, focusing on the role of cytochromes in drug biotransformation. It also examines how personalized medicine and pharmacometabolomics can enhance drug efficacy and safety in clinical practice.

Methods: A comprehensive review of the literature was conducted to assess the biochemical mechanisms involved in cytochrome-mediated drug metabolism. Studies on cytochrome P450 enzymes and their genetic polymorphisms were analyzed to understand their role in personalized pharmacotherapy. Additionally, the potential applications of pharmacometabolomics in drug therapy optimization were explored.

Results: Cytochrome P450 enzymes are responsible for the oxidative metabolism of many drugs, and variations in their genes can significantly affect drug metabolism rates. For instance, some individuals are slow metabolizers of certain drugs due to genetic variations in CYP genes, leading to an increased risk of toxicity, while others are fast metabolizers, which may result in suboptimal drug efficacy. Pharmacometabolomics, the study of metabolic profiles, can offer insights into these variations, allowing for more precise and individualized treatment strategies. Emerging technologies in genomics and metabolomics offer the potential to predict patient responses to drugs, paving the way for personalized pharmacotherapy.

Conclusion: Personalized pharmacotherapy, empowered by pharmacometabolomics and cytochrome analysis, offers significant promise in optimizing drug therapy. Understanding individual metabolic profiles and cytochrome variations enables clinicians to tailor drug treatments, improving therapeutic outcomes and minimizing adverse effects. The integration of these technologies into pharmacy practice can revolutionize the way medications are prescribed, ensuring more effective and safer treatments for patients.

Keywords: Cytochrome P450, drug metabolism, personalized medicine, pharmacometabolomics, pharmacotherapy, genetic variations, pharmacy practice, drug efficacy, drug safety.

1. Introduction

Once drug molecules enter the body, they undergo chemical changes known as drug metabolism [1]. The therapeutic efficacy of medications is usually diminished by this metabolic process [2]. The majority of medications change from lipophilic to hydrophilic forms during drug biotransformation, which increases their water solubility and makes it

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easier for them to be eliminated through bile or urine [3]. Given that many medications have lipophilic qualities that might prolong their retention in the body and perhaps lead to toxicity, this change is a crucial step in drug metabolism [4,5]. Phase I and phase II reactions are the two primary steps of drug metabolism [6]. Cytochrome P450 (CYP) enzymes mediate the common routes in drug metabolism. Through oxidation, reduction, or hydrolysis, phase I processes add reactive or polar functional groups (-OH, -COOH, -NH2, -SH, etc.), which makes medications better suited for further processing as opposed to quick excretion. Various transferase enzymes, including glutathione S-transferases, uridine diphosphate (UDP)-glucuronosyltransferases, and sulfotransferases, aid in the conjugation of modified medicines with polar molecules during phase II processes [7]. Before conjugated medications are detected and removed from cells by efflux transporters, they may go through additional changes. However, depending on certain structural components in these chemicals, these metabolic processes might occasionally result in reactive metabolites that are harmful to the body. This phenomenon is called drug bioactivation.

The term "drug metabolism" describes the enzymatic breakdown of medications that is made possible by specific metabolic processes [8]. More than 90% of documented enzymatic drug responses are caused by cytochrome P450 enzymes (CYPs) [3]. Although other organs like the kidneys, placenta, adrenal glands, gastrointestinal tract, and skin also contribute to drug metabolism [10], CYPs are the most common drug-metabolizing enzymes and are mostly found in the liver [9]. Approximately 80% of clinical medicines are metabolized by members of the CYP1, CYP2, and CYP3 families, which comprise the 57 functional human CYP isoforms [11]. Drug efficacy, safety, bioavailability, and resistance in metabolic organs and target sites are all impacted by CYP-mediated drug metabolism, which also transforms lipophilic molecules into hydrophilic forms for simpler excretion [12]. In addition to environmental determinants including gender, age, nutritional state, and disease conditions, CYPs are very diverse biochemical catalysts that contribute to individual medication response variability due to genetic and epigenetic variances [13]. Notably, concurrent medications and circulating metabolites can either inhibit or activate CYPs, which can change the effectiveness of treatment through drug-drug interactions (DDI), drug-gene interactions (DGI), and combination drug-drug-gene interactions (DDGI) [14]. Crucially, the most common, important, and varied enzymes in clinical drug metabolism are CYPs [15]. Although early CYP research used animal models, the main goal of this review was to clarify human enzymatic systems that are pertinent to observed changes. Since the initial discovery of CYP in the early 1980s, structural knowledge has improved our comprehension of CYP dynamics and how different-sized and structurally diverse substrates are accommodated by their active sites.

Human Cytochromes:

Human cytochrome P450 enzymes (CYPs) are essential for drug metabolism and digest about 75% of medications. At least 57 CYPs, arranged into 18 families and 43 subfamilies, are encoded by the human genome. These enzymes are essential for preserving human health in general, especially when it comes to the metabolism of pharmaceuticals. Individual differences in medication reactions are a noteworthy feature of CYPs in drug metabolism. The rate at which medicines are metabolized varies from person to person [16,17]. The expression of CYPs, especially in the liver and intestines, is frequently connected to these metabolic variations [18]. It is thought that exogenous and endogenous substance metabolism are impacted by the expression and functional activity of CYPs, which are influenced by external factors such food, past drug exposure, and alcohol and tobacco use. The function of CYPs in the metabolism of anticancer drugs is another important field of research. In addition to cancer cells and cell lines, CYPs have been found in tumors [19,20]. CYPs from the CYP1, CYP2, and CYP3 families metabolize a variety of anticancer medications, such as thalidomide by CYP2C9 and CYP2C19, paclitaxel by CYP2C8, flavonoids by CYP1b1, tamoxifen by CYP2D6, docetaxel and cyclophosphamide by CYP3A4/5, and CYP2C8 [21,22]. As a result, CYP expression in tumor cells plays a critical role in assessing how well anticancer treatments work. It has been observed that, in contrast to nearby normal tissues, CYP expression in tumor cells is frequently abnormal [23]. The activation of anticancer drugs in tumor cells can be diminished by low CYP expression and activity, which may be caused by metabolic reprogramming and changed cellular circumstances. On the other hand, excessive CYP expression in tumor cells may cause anticancer medications to detoxify quickly, which could worsen treatment resistance, tumor recurrence, and prognosis [24,25]. Because of their aberrant expression in tumor cells, CYPs are now increasingly considered as possible therapeutic targets and biomarkers for the treatment of cancer [26,27]. CYP1B1 is a viable target for new oncological therapeutics because it has been linked to tumor growth and treatment resistance [28,29,30]. The creation of CYP1B1 inhibitors is regarded as a cutting-edge method of treating

cancer and is thought to be a crucial tactic for defeating resistance in different tumor cell lines [31]. Other CYPs have also surfaced as possible therapeutic targets, including CYP2J2 for breast cancer [32] and CYP2W1 for colon cancer [33]. It has been demonstrated that CYP targeting in preclinical and clinical trials is a successful tactic for enhancing chemoprevention and chemotherapy results.

Structure of Cytochrome:

A single heme prosthetic group is found in the active region of cytochrome P450 enzymes (CYPs), which are hemoproteins with 400–500 amino acids [34]. The Protein Data Bank (PDB) currently contains 104 distinct CYP structures, demonstrating the general structural conservatism of these enzymes. Subfamilies share about 55% of their sequences with each other, whereas members of the CYP family share about 40% [35]. Although several enzymes, including CYP450nor [36], prostacyclin synthase [37], and allene oxide synthase [38], have CYP-like folds but do not catalyze conventional CYP reactions, no nonheme proteins with CYP-like folds have been found to date. A cysteine thiolate ligand situated in a distinctive FXXGXXXCXG motif in their amino acid sequence coordinates the heme–iron center found in the active site of every CYP. CYPs usually share four β-sheets and twelve common helices (A-L) in their tertiary structures. Even while the general folds are preserved, distinct CYPs differ in the exact location of structural components. For example, areas near the heme, especially helices I and L, which have direct interactions with the heme, are more preserved. Furthermore, a section of helix I close to the heme and the β-bulge segment, which contains the cysteine ligand, are essential for oxygen activation in CYPs. The ability of CYPs to adapt to substrates of different sizes and shapes is one of their most notable characteristics. Certain CYPs that firmly attach to their substrates provide the majority of information on CYP–substrate interactions. The main entry point for many CYPs is the intersection of helices F and G, where substrates usually enter the active site. It is thought that substrate specificity is influenced by structural changes in these helices, especially the F and G helices [39]. Cytochrome P450epoK and CYP101 demonstrate extremes in substrate shape and size. In contrast to CYP101, the B' helix in cytochrome P450epoK is notably rotated 90°, opening the substrate-binding pockets and accommodating the distinct sections of the substrates [40].

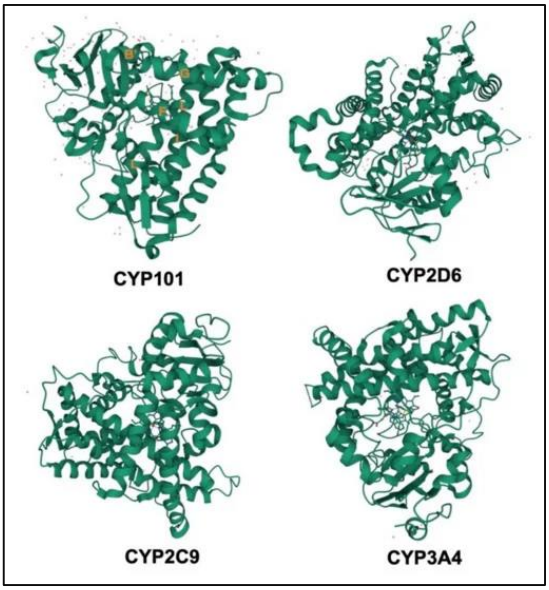

Figure 1: Chemical Structure of Cytochromes.

Characteristics of Cytochromes:

The major drug-metabolizing cytochrome P450 (CYP) isoforms belong to the CYP1, CYP2, and CYP3 families, which account for approximately 80% of the metabolism of clinical drugs. Among these, CYP3A4 and CYP2D6 are the most significant contributors, responsible for more than 50% of CYP-mediated drug metabolism [11]. **CYP1 family**: The CYP1 subfamily includes CYP1A1 and CYP1A2. CYP1A1 is mainly expressed in the lungs, unlike most other drug-metabolizing CYPs that are expressed in the liver. CYP1A2, however, is exclusively expressed in the human liver. Both isoforms play critical roles in the bioactivation of carcinogens, particularly aromatic and heterocyclic amines. CYP1A1 is known to be induced by cocarcinogens, and high CYP1A2 activity has been linked to an increased risk of colon cancer, particularly in the presence of high N-acetyltransferase activity and consumption of charbroiled meats [41][42][43]. **CYP2 family**: The CYP2 family is the largest, with isoforms such as CYP2D6 and CYP2C9 being the most influential in drug metabolism. These isoforms have distinct active sites, and there is minimal overlap in their substrate specificity. CYP2D6 primarily metabolizes basic molecules, while CYP2C9 prefers slightly acidic compounds. Genetic variability in CYP2D6 results in considerable clinical issues, including variations in drug metabolism rates among individuals. An interesting clinical issue regarding CYP2C9 involves the drug tienilic acid, which can act as a mechanism-based inactivator of CYP2C9, leading to liver injury in some patients. CYP2C9 also has associations with liver–kidney microsomal antibodies in patients treated with tienilic acid [44]. Except for CYP2J2, which is primarily found in the cardiovascular

system, all CYP2 isoforms are predominantly expressed in the human liver. CYP2J2 is associated with diseases such as hypoxia, cardiotoxicity, and coronary artery disease. The common inducers for most CYP2 isoforms include Rifampicin and Artemisinin, with each isoform also having well-known inhibitors useful for selective in vitro studies [45][46]. **CYP3 family**: The CYP3A subfamily, particularly CYP3A4 and CYP3A5, plays a critical role in drug metabolism and is responsible for the metabolism of over 30% of currently used drugs. These isoforms are the most abundant in the human body and have overlapping substrate specificities, with CYP3A4 being able to accommodate a diverse range of structures. This broad substrate specificity and the ability to metabolize multiple drugs at once make CYP3A4 an important enzyme in drug discovery and development. Transgenic 'humanized' mice expressing CYP3A4 have been developed to improve predictability in drug development [45][46].

Cytochrome Variations:

Both genetic and environmental factors have a substantial impact on the diversity in CYP-mediated drug metabolism. Over the past 20 years, genetic variations in CYP genes have been thoroughly investigated as a major cause of individual variability [22,48]. Numerous allelic variants of CYP genes are involved in these genetic differences, and their frequencies vary among populations [49, 50]. More than 350 polymorphic CYP alleles have been listed by the Human CYP Allele Nomenclature Committee (retrieved on September 15, 2021; http://www.pharmvar.org/, Version 5.1.3, last updated November 6, 2021). Interestingly, with 63, 28, and 22 alleles, respectively, the CYP2D6, CYP2B6, and CYP2A6 genes have the most allelic variants [48]. The most common mutant isoform is CYP2D6, which metabolizes around 25% of clinical medications; its polymorphisms affect how over half of these medications are metabolized [51]. Studies have indicated that CYP gene genetic polymorphisms mainly present as gain-of-function or loss-of-function variants [52]. By altering gene splicing or expression, loss-of-function variations usually decrease enzyme activity, which lowers drug clearance and raises plasma concentrations [53]. Conversely, gain-of-function variants might increase enzyme activity, increase drug clearance and decreasing plasma concentrations. These variants can result from gene duplication or mutations in promoters or coding areas [54].

Four identified phenotypes are also produced by CYP-mediated metabolism: ultra-rapid metabolizers (UM), extensive metabolizers (EM), intermediate metabolizers (IM), and poor metabolizers (PM). Drug reactions are influenced by these characteristics, which are associated with genetic differences [55]. Due to decreased enzyme activity, PMs—who are usually homozygous for functional variations or gene deletions—experience negative medication responses at conventional dosages [56]. EMs have two fully functioning alleles, but IMs, who are heterozygous for particular allelic variations, show intermediate enzyme activity [44]. Higher drug dosages are frequently needed to have therapeutic benefits in UMs because they have two or more active gene copies [44]. CYP gene genetic variations are essential for maximizing medication effectiveness and reducing side effects [48]. CYP variability is influenced by both genetic and epigenetic factors, including DNA methylation, which controls CYP gene expression through interactions with transcription factors or promoters [49,57]. By blocking transcription factor binding, DNA methylation can inhibit gene expression [59]. Certain methylation sites have been found in genes such as CYP1A1, CYP1B1, CYP2W1, CYP2C19, and CYP2D6 [60,61]. Additionally, by targeting the 3′-UTR region of mRNAs, noncoding RNAs, such as miRNAs, may modify CYP expression; longer sections have a higher potential for control [63,64]. CYP gene expression may also be impacted by variations in miRNA binding sites or precursor regions.

CYP activity and drug metabolism are also impacted by environmental factors, both extrinsic (nutrition, smoking) and intrinsic (age, disease) [48]. CYPs, especially those in the CYP2 family, play a major role in the metabolism of central nervous system (CNS)-acting medications, which are used to treat disorders like schizophrenia, depression, and anxiety [66]. The pharmacokinetics of CNS medications are impacted by age-related changes in CYP activity, such as the progressive rise in CYP2D6 expression from birth to age 65 [67]. Drug metabolism can be hampered by disease states that change CYP expression, such as cancer and liver disorders [71,72,73]. Variability in medication responsiveness is also influenced by CYP expression alterations brought on by inflammation and infection [76]. CYP activity is also influenced by lifestyle factors such as food and smoking. CYP2D6, CYP2E1, and CYP2B6 levels are generally greater in smokers than in nonsmokers [69,79]. CYP activity can also be controlled by diet; for example, unsaturated fatty acids can increase CYP expression, while protein, vitamin, and mineral deficits can decrease CYP function [80–83]. While foods like spinach and turnips can stimulate CYP3A, grapefruit juice, which is high in bioflavonoids, can block it and change how drugs are metabolized [84,85]. Drug-drug interactions (DDIs) are facilitated by the active and allosteric sites of CYPs, which have the

ability to bind drugs as inducers or inhibitors [86]. Drug metabolism is increased, and drug responses are impacted by CYP induction, which is frequently mediated by transcriptional and epigenetic pathways [87,88]. By attaching to DNA response elements, a number of nuclear receptors, such as AhR, PXR, and CAR, control CYP induction [95,98]. On the other hand, one of the main mechanisms of metabolism-based DDIs, CYP inhibition, can raise drug plasma levels, which may have negative effects [88,100]. Both reversible and irreversible CYP inhibition are possible; reversible inhibition involves competition for active sites, whereas irreversible inhibition involves covalent interaction with the enzyme and results in a long-lasting suppression of enzyme activity [101,107]. Because both types of inhibition can change how drugs are metabolized, it is crucial to take CYP activity into account while developing new drugs and conducting clinical procedures.

Personalized Medicine:

Precision medicine seeks to provide the best possible care with the fewest possible side effects. This objective is difficult to achieve, nevertheless, because patients react differently to medication treatments [101]. According to reports, there were 100,000 associated deaths and 2 million adverse drug reactions (ADRs) in the US each year in 1998 [102]. The frequency of ADR incidents grew steadily between 1999 and 2006 [103]. The idea of tailoring medicine and reducing side effects by utilizing big data and pharmacogenetics simultaneously gained popularity. The study of how genetic factors affect a person's response to drugs is known as pharmacogenetics and pharmacogenomics (PGx) [104-107]. The practical influence of PGx on patient care has not yet reached the level that the pharmaceutical and regulatory sectors had hoped for, despite the fact that it has identified several genetic connections to metabolism and response. As of September 3, 2019, 270 FDA-approved medications or treatments were linked to 385 drug label warnings [108]. However, most intra- and inter-patient variability in pharmacokinetics and pharmacodynamics that affect therapy results is rarely explained by PGx. One major drawback is that contextual factors—such as age, food, polypharmacy, gut microbiota, physical activity, occupation, stress, alcohol use, and health status—can have a big influence on how a patient reacts to medicine and are not taken into consideration by genetics alone. According to current estimates, only 20–40% of individual differences in medication metabolism and response can be attributed to hereditary variables [109]. This suggests that non-genetic factors account for 60–80% of the response.

"The prediction of the outcome (e.g., efficacy or toxicity) of a drug or xenobiotic intervention in an individual, based on a mathematical model of 'preintervention' metabolite signatures" is the definition of pharmacometabonomics, which was first described in 2006 [110]. The Consortium for Metabonomic Toxicology (COMET) research at Imperial College London, in partnership with a number of pharmaceutical corporations, played a major role in the development of this discipline by conducting drug testing in animal models [111,112]. Pharmacometabolomics (PMx), on the other hand, is described as "an improved comprehension of the mechanisms for drug or xenobiotic effects and the ability to predict individual variation in drug response phenotypes, based on both baseline metabolic profiles prior to treatment and longitudinal metabolomic profiles after drug exposure" [113]. In order to gain insight into treatment outcomes, the first PMx study was conducted in 2007 and examined lipid profiles in individuals with schizophrenia both before and after they were treated with three antipsychotics [114]. Together, the Pharmacometabolomics Research Network [115] and the Pharmacogenomics Research Network [116] made pharmacometabolomics a major area of study. Together, 17 academic teams produced insightful information about how people react to important drugs for cardiovascular and neuropsychiatric disorders, such as antidepressants, antihypertensive statins, and antiplatelet treatments [117,118]. The network showed how metabolomics data could enhance knowledge of pharmacokinetics (statins and methylphenidate, for example) [119,120], therapeutic efficacy, ethnic variability (atenolol responses, for example) [121], and adverse drug reactions, including statin-induced diabetes [122]. The idea that metabolomics could aid precision medicine was influenced by the vast amount of information gathered from pharmacogenomics and pharmacometabolomics research [117,118].

Building models to forecast specific medication reactions in clinical practice is the goal of both pharmacometabonomics and pharmacometabolomics. Numerous reviews of pharmacometabolomics research [17,18,25,26] and pharmacometabonomics research [123,124] have been published. Finding biomarkers or metabolic patterns connected to drug metabolism, as well as identifying responders, non-responders, or people having negative drug reactions, are the main goals of the majority of PMx investigations. Baseline or treatment samples can be included in PMx models since samples can be taken before, during, or after drug administration. This method makes it possible to find biomarkers or mechanisms linked to medications that might not have effects right away but could still have negative effects months or years after they are first administered. Examples of these include cancer medications that raise the risk of cardiotoxicity over time [127] and idiosyncratic drug-induced liver injury (DILI), which develops

gradually and only affects a small percentage of patients [128]. More often than not, samples collected during therapy may yield more pertinent metabolite information (such as glutathione levels in oxidative stress) that can more precisely forecast patient reactions than pre-dose samples. Provisional biomarkers that may eventually be categorized as pharmacodynamic response, prognostic, efficacious, safe, or monitoring biomarkers can be found using samples obtained during or after therapy. An outline of current approaches and potential uses for clinical PMx research is provided in this review.

A person's metabolic profile can be influenced by a variety of factors, including genetics, epigenetics, sex, gut microbiota, nutrition, age, occupation, health condition, and other environmental factors [125,126,129]. Drug response is known to be influenced by heredity, but many of these characteristics can alter over time or during therapy, influencing how a person responds to drugs. The idea that a person's metabolic profile dictates how they react to a medicine is at the heart of pharmacometabolomics. Endogenous metabolic products, food metabolites, gut microbial byproducts, medications, drug metabolites, and other environmental xenobiotics are among the metabolites that can be identified using untargeted biofluid profiling. Therefore, information on a patient's health, nutritional state, gut bacteria composition, and disease-affected metabolic pathways—all of which impact treatment responses—can be gleaned from their metabolome. The term "metabotype" refers to the grouping of an individual's overall metabolic profile, such as those who respond poorly or well to particular drugs [30]. As a result, metabolic profiling before to, during, or following drug delivery can offer biomarkers, patterns, or mechanistic information related to a patient's reaction to a certain medication. Clinical professionals may gain important insights about a patient's therapeutic response by metabolic profile pertaining to energy status, lipids, vitamins, gut microbial metabolites, environmental exposures, and pre-treatment drug use. These biomarkers may be categorized as biomarkers relevant to upcoming clinical trials and patient studies if they are validated across a range of patient demographics. Clinical discovery of metabolic signatures with potential utility for comprehending illness subtypes and associated patient responses is made possible by early PMx research.

Any quantitative trait that suggests biological, pathogenic, or therapeutic processes—including reactions to exposure or intervention—is referred to as a biomarker. Unless it satisfies specific requirements, a biomarker is more than just an analyte (FDA analytical advice). A biomarker must be analytically reproducible by definition. Biomarkers can be used by clinicians to identify patient drug response patterns. Under the 21st Century Cures Act, the FDA may qualify individual biomarkers or groups of biomarkers with adequate supporting data [131]. Prior to the 21st Century Cures Act, Leptak and associates described the biomarker qualifying procedure [132], and the FDA is presently creating new guidelines. A letter of intent (LOI) outlining the biomarker's intended context of use (COU) and whether it comes from an animal model or clinical result is the first step in the submission process, but specifics may change. Before submitting the LOI, the FDA may be consulted [133]. The two parts of the COU—the BEST biomarker category and the anticipated application in drug development—describe how the biomarker will be used in drug development [134]. A Qualification Plan (QP) detailing the information required to qualify the biomarker for the COU can be provided if the FDA accepts the LOI. The biomarker and its suggested COU are finally supported by thorough evidence in a full qualification package (FQP) [135].

Pharmacometabolomic:

To enhance drug response prediction, pharmacometabolomics (PMx) examines how metabolism and pharmacology interact. This field distinguishes between two kinds of metabotypes: the treatment metabotype, which is acquired during the dosing period, and the baseline metabotype, which is collected from pre-treatment samples. Similar to how pharmacogenomics is used to predict treatment results, researchers frequently restrict the term "pharmacometabolomics" to baseline metabolic profiles [110]. To evaluate a patient's response to treatment, a more thorough method in PMx uses both baseline and longitudinal metabolic data [113,118]. These metabotypes are influenced by a person's genetics, food, microbiome makeup, and exposure to different environmental factors like stress, medicines, and nutrients. Insights on disease subtypes and pre-treatment metabolic factors, including sulfur pool status or nutrient levels, can be gained from baseline and treatment metabotypes, which can also show differences in drug response within and across patients. Drug reactions can be directly impacted by the baseline metabotype, especially when metabolic markers of safety or effectiveness appear rapidly. Researchers can evaluate a drug's effect on metabolic pathways, especially those linked to adverse effects, by comparing treatment metabotypes with baseline data. The treatment metabotype might be a more useful indicator for predictive PMx research than baseline metabotypes since medications might change the gut microbiota or epigenetic processes before noticeable effects appear. Pharmacometabolomics also provides a useful tool for evaluating differences in therapeutic

outcomes or side effects, mapping the impact of medications on metabolism, and discovering pathways implicated in drug responses. The groundwork for this new field can be laid by combining baseline data with treatment fingerprints to help elucidate the mechanisms underlying individual variations in medication responses. Numerous medication classes, such as antidepressants, statins, mood stabilizers, antihypertensives, and antiplatelets, have undergone clinical PMx trials, demonstrating the dynamic nature of the metabolome in contrast to the static genome.

Drug interactions are complicated and can occur during concurrent drug usage or at separate times and involve other medications (polypharmacy), vitamins, botanicals, and environmental exposures. These interactions fall into one of two categories: pharmacokinetic (PK), which deals with modifications to drug absorption, distribution, metabolism, or excretion (ADME), frequently impacted by interactions with enzymes that break down drugs, or pharmacodynamic (PD), in which the biological effects of the drug are changed by outside influences, which may have additive or opposing effects on the activities for which the drug is intended. New drug–exposome interactions, many of which are still unknown but could have a major impact on drug metabolism, could be discovered by PMx as analytical tool advancements increase. The stomach and intestine are important sites for drug–exposome interactions, even though the liver is the main site of drug metabolism . As an illustration, consider the medication warfarin, which has a history of food-drug interactions that can significantly impact both its safety and effectiveness. Samples are collected at baseline, during therapy, and occasionally after treatment as part of the standard PMx protocol (**Figure 2**). Although urine, feces, saliva, and breath can all be utilized, blood is the most frequently used sample. Data reliability is ensured by processing samples in accordance with established protocols to reduce degradation. Reducing experimental variation is essential for producing high-dimensional data in metabolomics research, and this methodical technique helps achieve this goal. Following processing, the data is examined to find metabolites, which are further utilized to create patient response prediction models that classify people according to how they react metabolically to treatment.

Adopting strict procedures is necessary to avoid making erroneous biomarker discoveries when modeling PMx data. Clarifying the molecular mechanisms involved can be aided by the discovery of biomarkers associated with medication response. Data from baseline samples, treatment samples, or the noted changes between these time periods can be used to create PMx models. The majority of untargeted PMx studies are exploratory in nature, producing ideas that need to be confirmed by more study. These models can be used to anticipate unfavorable reactions, such as identifying patients who may have few side effects or who metabolize drugs slowly or quickly, or they can be used to classify patients according to their drug metabolism rates. The biomarkers found may be used as early predictors of treatment outcomes, such as efficacy or safety biomarkers, when treatment samples are incorporated into PMx models before the emergence of clinical signals of efficacy or safety. As is the case with drugs that decrease cholesterol, certain metabolites identified in these investigations may be useful pharmacodynamic indicators for determining therapeutic dosages. Clinical trials that include baseline and treatment data may eventually find provisional biomarkers in phase II trials. These biomarkers might then be tested in phase III trials to improve drug development procedures.

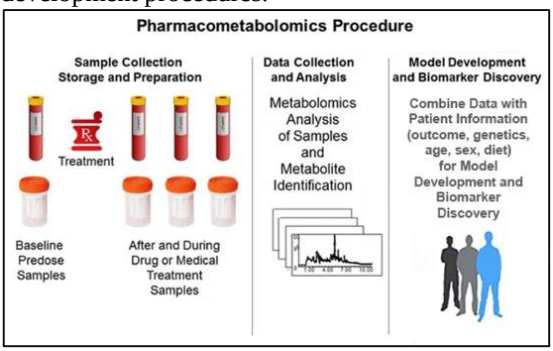

Figure 2: Pharmacometabolomics Procedures.

Drug dosage selection and pharmacokinetic/pharmacodynamic analysis can benefit from the discovery of biomarkers, which can occur during preclinical or clinical studies. By providing preliminary biomarkers that facilitate improved dose selection and safety evaluation, PMx may improve drug development. PMx may aid in capturing biomarkers linked to pharmacokinetic and pharmacodynamic events, as well as off-target effects that may contribute to adverse reactions and overall drug response, since drug pharmacology is dependent on factors like target exposure and drug binding, which are influenced by both genotype and phenotype. Multiple time periods are necessary to correctly analyze intra-patient variability, which is likely caused by dynamic gene-environment interactions and cannot be entirely explained by genetic information alone. Tacrolimus, whose variability is linked to poor kidney transplant outcomes, and raltegravir, whose plasma level variability correlates with treatment efficacy regardless of particular genetic markers, are two examples of substantial intra-patient variability. Following the completion of PMx investigations, the metabolomics data should be posted for public access and future research in clinical trials and

public databases such COMETS, Metabolomics Workbench, and MetaboLights. 179 of the 974 metabolomics studies that were mentioned in Clinical Trials as of September 2019 had to do with medication interventions, such as midazolam, cholecalciferol, and metformin. There are four primary categories of PMx experiments: (2.1) studies based on metabolomics data obtained prior to or during drug treatment; (2.2) studies combining pharmacogenomics and metabolomics (PGx); (2.3) studies combining data from gut microbiota and metagenomics; and (2.4) multi-omics studies combining proteomics, genomics, epigenomics, metabolomics, metagenomics, and other "omics" in a specific clinical or operational context.

Conclusion:

This review highlights the critical role of cytochrome P450 enzymes in drug metabolism and their impact on personalized pharmacotherapy. Cytochrome P450 enzymes are pivotal in the oxidative metabolism of numerous drugs, and genetic variations in these enzymes can lead to significant differences in how individuals respond to medications. These variations can influence drug efficacy, toxicity, and the risk of adverse drug reactions, underscoring the importance of considering cytochrome polymorphisms in clinical decision-making. Personalized medicine aims to tailor treatments based on individual genetic and metabolic profiles, ensuring optimal therapeutic outcomes. The advent of pharmacometabolomics has further advanced this concept by allowing the assessment of metabolic profiles to predict how patients will metabolize drugs. By integrating this technology with genomic data, clinicians can gain valuable insights into the metabolic pathways involved in drug processing, leading to more accurate drug prescriptions and reduced risk of adverse effects. Pharmacometabolomics, through the analysis of metabolite levels and metabolic networks, can provide a deeper understanding of the biochemical mechanisms that govern drug metabolism. For example, variations in cytochrome P450 activity can be used as biomarkers to predict a patient's response to specific drugs. This can be particularly important in drugs with narrow therapeutic windows or those with a high risk of side effects, such as anticancer agents and immunosuppressants. Incorporating pharmacometabolomics into pharmacy practice can enhance the precision of drug therapy, particularly in populations that experience variable drug responses due to genetic and environmental factors. The use of pharmacometabolomics could pave the way for more personalized treatment regimens, improving patient outcomes, reducing adverse drug reactions, and minimizing healthcare costs. However, further research and clinical trials are needed to fully realize the potential of pharmacometabolomics in routine clinical practice. Ultimately, the integration of pharmacogenomics and pharmacometabolomics could transform how drugs are prescribed, moving towards more personalized and precise pharmacotherapy.

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