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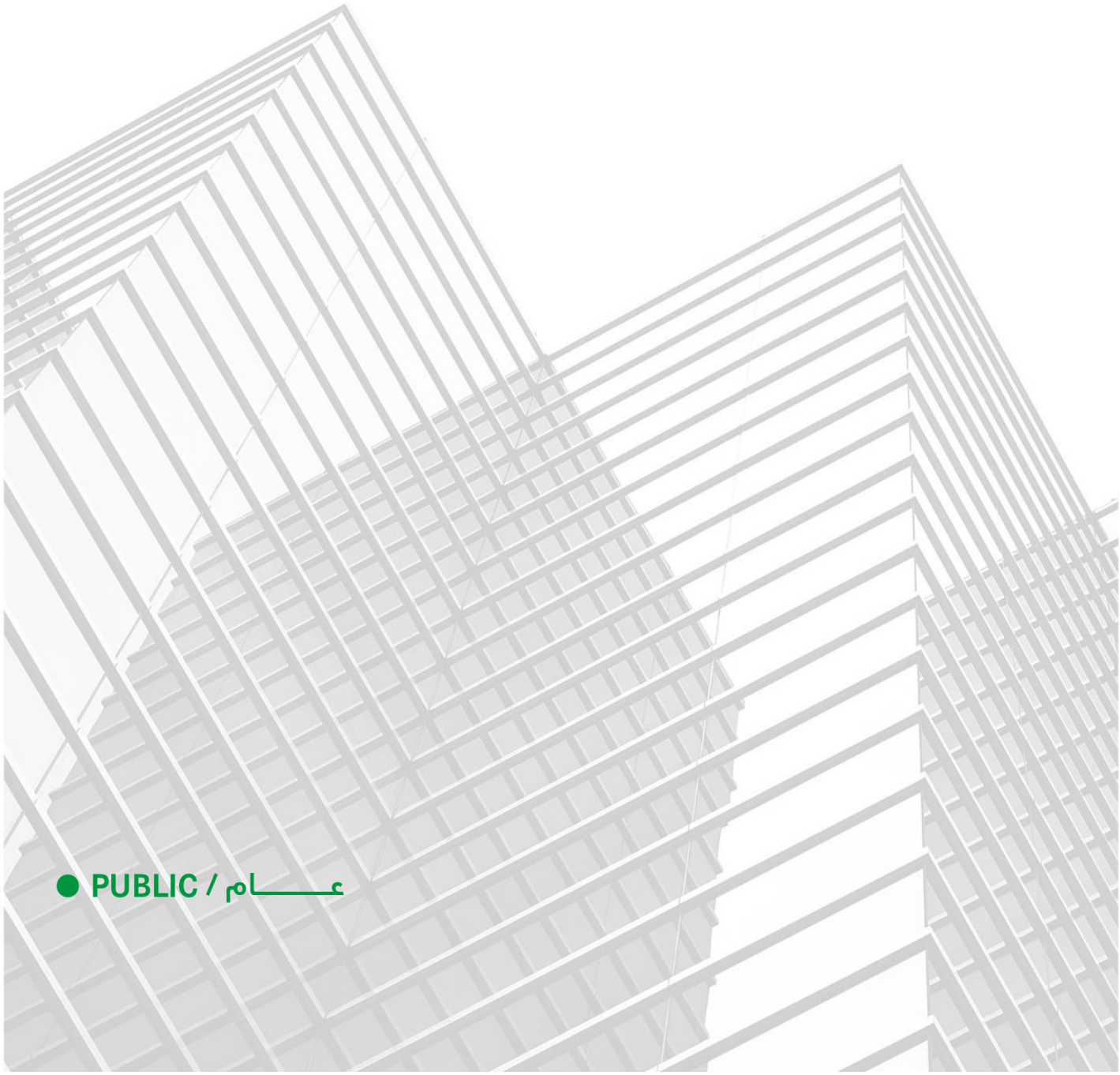
DEPARTMENT OF HEALTH

PHARMACOGENOMICS (PGx) GUIDELINE



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1.Guideline Purpose and Brief

The purpose of the pharmacogenomic guideline is to give a comprehensive overview of pharmacogenes, pharmacogenetic approaches, types of testing and applications, aiding in guiding healthcare professionals to provide personalized medicine by optimizing treatment efficacy and minimizing adverse reactions based on individual genetic profiles. The pharmacogenomic guideline scope encompasses an introduction of pharmacogenomic and polymorphism. It includes an evaluation of factors influencing phenoconversion, incorporating epigenetic modifications, environmental influences, and gene-gene interactions. This guideline scope also addresses common pharmacogenomic applications, such as drug metabolism, response prediction, and adverse reactions, while illustrating emerging technologies like next-generation sequencing and microarray analysis. Additionally, the scope presents several key pharmacogenes, including those involved in drug metabolism, targets, and transport, and highlights several trusted references and guidelines that healthcare professionals can use to interpret or intervene based on pharmacogenomic test results. Considerations and guidance for pharmacogenomic research and technology assessment are clarified as well in this document.

2. Definitions

No.	Term / Abbreviation	Definition
2.1	**ABC**	ATP-binding cassette: genes that plays a role in the resistance of malignant cells to anticancer agents.
2.2	**CYP**	The cytochromes P450 (CYP450 and CYP are used interchangeably) are a superfamily of hemoproteins that consist of a set of isozymes that are intimately involved in the oxidative metabolism of drugs in the liver. CYP 450 are so-called due to their maximum absorbance at 450 nm, ie, “Pigment–450 nm,” when bound to carbon monoxide. P450s are also divided into families, each of which is based solely on amino acid sequence homology. Examples of CYP 450 families and subfamilies includes but not limited to: 2D6, 2C19 and 3A4.
2.3	**DNA**	Deoxyribonucleic acid is the molecule that carries genetic information for the development and functioning of an organism.
2.4	**Exome**	protein-coding portion of a genome
2.5	**Genome**	The entire set of DNA instructions found in a cell. In humans, the genome consists of 23 pairs of chromosomes located in the cell’s nucleus, as well as a small chromosome in the cell’s mitochondria. A genome contains all the information needed for an individual to develop and function.
2.6	**Genotype**	The genetic constitution of an organism. Also known as the scoring of the type of variant present at a given location (i.e., a locus) in the genome.

2.7	**HLA**	Human Leukocyte Antigen: A type of molecule found on the surface of most cells in the body. Human leukocyte antigens play an important part in the body's immune response to foreign substances.
2.8	**Micro-array**	A general laboratory approach that involves binding an array of thousands to millions of known nucleic acid fragments to a solid surface, referred to as a "chip." The chip is then bathed with DNA or RNA isolated from a study sample (such as cells or tissue). Complementary base pairing between the sample and the chip-immobilized fragments produces light through fluorescence that can be detected using a specialized machine. Microarray technology can be used for a variety of purposes in research and clinical studies, such as measuring gene expression and detecting specific DNA sequences (e.g., single-nucleotide polymorphisms).
2.9	**PhamGKB**	The Pharmacogenomics Knowledgebase is an NIH-funded resource that provides information about how human genetic variation affects response to medications.
2.10	**Phenotype**	An individual's observable traits
2.11	**proteomics**	The study of the interactions, function, composition, and structures of proteins and their cellular activities
2.12	**SNP**	Single Nucleotide Polymorphism: Genomic variant at a single base position in the DNA.
2.13	**TPMT**	Thiopurine methyltransferase is an enzyme that breaks down (metabolizes) a class of drugs called thiopurines.
2.14	**UGT**	UDP-glucuronosyltransferases: belong to a superfamily of microsomal enzymes responsible for glucuronidation of numerous endogenous and exogenous compounds including bilirubin, hormones, various drugs as
2.15	**xenobiotics**	Chemical compounds which are not endogenously produced and therefore foreign to a given biological system.

Abbreviations

No.	Term / Abbreviation	Definition
2.16	**EMs**	extensive metabolizers
2.17	**IMs**	intermediate metabolizers
2.18	**kB**	Kilobyte- unit of measurement
2.19	**PGx**	Pharmacogenomics
2.20	**PMs**	poor metabolizers
2.21	**SNV**	Single nucleotide variant
2.22	**UMs**	ultrarapid metabolizers
2.23	**VIPs**	Very Important Pharmacogenes.

3.Guideline Content

3.1. Pharmacogenomics and important concepts

Pharmacogenomics is the branch of science concerned with the identification of the genetic attributes of an individual that lead to variable responses to drugs. The goal of pharmacogenomics has been the development of prediction models to forecast debilitating adverse events in specific individuals and, more recently, across populations based on similarities in age, gender, or more commonly, race or ethnicity, as contrasted with the rest of the population. In recent practice, pharmacogenomic tools coupled with proteomics and other advanced molecular diagnostics are emerging as the cornerstone of individualized patient therapy, especially when differential genetic responses to xenobiotics are considered across specific ethnicities. The ultimate promise of pharmacogenomics is the possibility that knowledge of the patient's DNA sequence might be used to increase the number of patients who respond to a therapeutic regimen with a decrease in the incidence of adverse drug reaction or failure to respond to therapy[1]. It is essential to read this document in conjunction with other relevant genomic and precision medicine DoH-published documents, as well as DOH data and patient privacy.

3.2. Polymorphism

Polymorphism refers to the presence of two or more variant forms of a specific DNA sequence that can occur among different individuals or populations. The most common type of polymorphism involves variation at a SNP. Other polymorphisms can be much larger, involving longer stretches of DNA.[2] Therefore, by identifying polymorphism through PGx testing, healthcare providers can tailor treatment plans to maximize effectiveness and minimize risks for each patient based on their genetic profile. This personalized approach to medication management enhances patient outcome and safety.

3.3. Phenoconversion

Phenoconversion describes the mismatch between the genotype-based prediction of drug metabolism and the true capacity of an individual to metabolize drugs (phenotype) due to the presence of non-genetic factors. Phenoconversion may be a consequence of the use of concomitant medication or presence of comorbidities, such as inflammation.[3] For instance, enzyme inducers can increase enzymatic activity beyond what a genetic test might indicate, which indicates the

importance of considering the effects of drug-drug interactions before making any clinical decision. There are many available tools that help with identifying drug-drug/gene interaction, the patient activity score, and the phenotype. One of those free tools that have been used widely is Sequence2Script. Sequence2script is an online free tool that creates a report that outlines medication and dosing recommendations based on a patient's known genotypes. The recommendations made by this tool are based on expert, peer-reviewed guidelines developed by the Clinical Pharmacogenetics Implementation Consortium (CPIC®), the Dutch Pharmacogenetics Working Group (DPWG), and US Food & Drug Administration (FDA). However, this tool is not a substitute for good clinical practice but is instead intended to be a companion tool for medication selection and dosing decisions [4].

3.4. Phenotype categories

There are four different PGx phenotypes categories including: poor metabolizers (PMs) lack a working enzyme; intermediate metabolizers (IMs) are heterogeneous for one working, wild-type allele and one mutant allele (or two reduced-function alleles); extensive metabolizers (EMs) have two normally functioning alleles; and ultrarapid metabolizers (UMs) have more than one functioning copy of a certain enzyme.[1]

3.5. Pharmacogenes[5]

Pharmacogenes either play a role in drug transport (e.g. SLCO1B1), the metabolism of many drugs (e.g. CYP2D6), polymorphic drug target and disposition genes, or contain variants which potentially contribute to a severe drug response (e.g. HLA-B) which are discussed in more details in the following section. Furthermore, PharmGKB provides a summary of the Very Important Pharmacogenes (VIPs). The summaries present an overview of 69 VIPs, and they are divided into three tiers as shown in the figure 1 below:

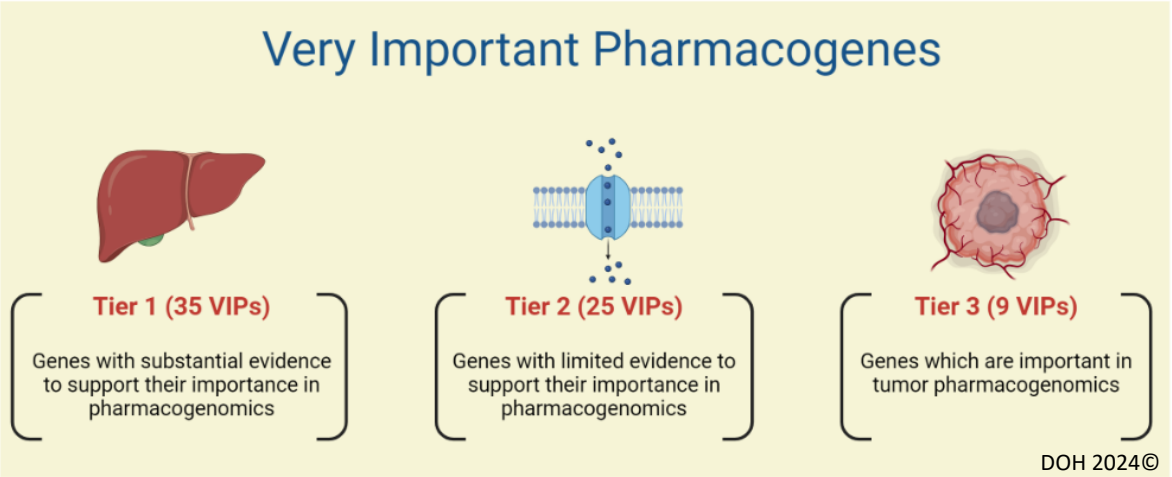

Figure1: Very important pharmacogenes. More details are shown in Appendix 1 table 1,2 &3 respectively [6].

3.5.1. Drug Transporters[5]:

Drug transporters are cell surface proteins that transport biotics and xenobiotics from one side of the cell membrane to the other. They are found at all barriers between tissues, vasculature, and excretory pathways, and are important in the absorption, distribution, and excretion of drugs. Because of the different substrates of each transporter, their distribution throughout the body determines which chemicals can reach certain sites in the body and the concentrations at each site. Some transporters are influx transporters, meaning they control the movement of compounds into a cell. Others are efflux transporters, meaning they control the movement of compounds out of a cell. The two major families are the solute carrier (SLC) transporters and the ATP-binding cassette (ABC) transporters. Variation in these genes can both increase and decrease transporter function. Variability in genes can affect both the influx and efflux of compounds, and as a result can increase or decrease concentrations of that compound within and outside of a cell. Due to the necessity for a drug concentration to reach a sufficiently high level at the site of action to be therapeutically active, while simultaneously acknowledging that higher concentrations increase the risk of toxicities, alterations in transporter function can significantly affect both the efficacy and toxicity profiles of a drug. Consequently, these variations can explain the interindividual differences in drug dosage and response. Examples of drug transporters include Influx transporters: SLCO1B1 and Efflux transporters: ABCB1, ABCC2 and ABCG2.

3.5.2. Drug Metabolizing Enzymes[5]:

Drug metabolizing enzymes control the chemical conversions of chemotherapeutics that ultimately enable their degradation and excretion from the body. They are found throughout all tissues but most predominantly in the liver, which is the main detoxifying organ of the body. Metabolism can inactivate compounds and can activate compounds into therapeutically active or toxic metabolites depending on the metabolic pathways. There are two main categories of metabolizing enzymes: the phase 1 metabolism, which is dominated by the cytochrome p450 enzymes (CYP450) that add or subtract hydrogens to change the charge of a compound, and the phase 2 metabolism enzymes, which conjugate chemical groups to the compound to change its polarity. These reactions facilitate the excretion of the compound into the bile or the urine. Examples of drug metabolizing enzymes include Phase 1 metabolizing enzymes: CYP2C9, CYP2D6, CYP2C19, CYP3A5 and Phase 2 metabolizing enzymes: TPMT, UGT1A. Moreover, Phase 1 metabolism includes reduction and hydrolysis pathways as well; therefore, understanding how genetic variations and gene encoding affect hydrolysis and reduction pathways is crucial in pharmacogenomics and can influence an individual response to drug metabolism.

3.5.3 Major histocompatibility complex genes[5]:

The Human Leukocyte Antigen (HLA) alleles are also called the major histocompatibility complex (MHC) which are important for initiating an immune response against foreign invaders. They are cell-surface proteins that bind pieces of proteins from pathogens and present them to T cells for recognition of a target and to activate an immune response. Some HLA alleles are associated with increased risk for an allergic response to certain medications, which can result in a hypersensitivity reaction like Stevens-Johnson Syndrome or toxic epidermal necrolysis. The exact mechanism for this response is unknown, though it may be through changing the presentation of self-peptides by binding directly to the binding groove of the MHC complex. Signs of a drug hypersensitivity reaction due to HLAs include that a second exposure to the same drug elicits a more rapid and severe response, similarly to how other allergic reactions behave. There are 3 classes of HLAs, the most associated with hypersensitivity reactions are class 2 alleles. Each human cell expresses six MHC class I alleles (one HLA-A, -B, and -C allele from each parent) and six to eight MHC class II alleles (one HLA-DP and -DQ, and one or two HLA-DR from each parent, and combinations of these). The MHC variation in the human population is high, at least 350 alleles for HLA-A genes, 620 alleles for HLA-B, 400 alleles for DR, and 90 alleles for DQ.

3.5.4 Drug targets[5]:

Drug targets are the molecules or pathways that a drug is designed to affect delivery therapy. Variation in genes involved in these pathways can affect how well a drug works by altering the amount of the target protein or by delivering therapy only to specific genetic variants. For example, the drug warfarin inhibits the vitamin K recycling needed for anti-coagulation by blocking the protein that controls the recycling (VKORC1). As a result, genetic variation that increases or decreases the amount of VKORC1 can affect the dose of warfarin needed. As another example, genetic variation in the cystic fibrosis transmembrane conductance regulator gene causes cystic fibrosis, but different variants cause the disease through different mechanisms. The drug ivacaftor is shown to be an effective treatment only in a subclass of those causative variants because the way it works is fixing the specific mechanism of cystic fibrosis transmembrane conductance regulator gene function.

3.6 Pharmacogenomic testing approaches:

PGx testing can be done preemptively or reactively. Preemptive testing can be conducted before a disease is symptomatic and a drug with PGx information is prescribed. The results can then be integrated into patients' health records, making this information available at the point of care. Reactive testing, on the other hand, is conducted for patients who will start a drug therapy or have failed all known therapies or to better understand the inadequate response and the side effects. Reactive testing requires prescriber knowledge about drug/gene interaction to determine which test to order and will help maximize treatment effectiveness upon receiving the PGx test results[7]. PGx testing approaches are shown in figure 2 below. It is important to get the patient's consent and explain the benefits, as well as the reasons why this test should be ordered. This ensures that the patient understands the potential impact on their treatment plan and healthcare outcomes.

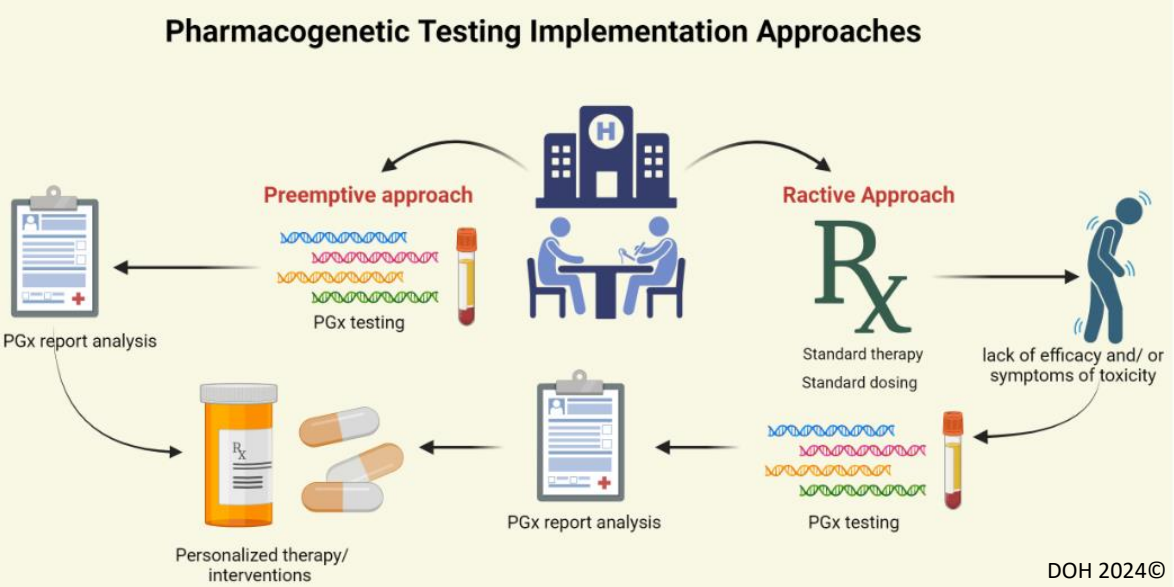

Figure 2: Pharmacogenetic Testing Implementation Approaches [8]

3.7 Type of testing [8]

There are three categories of PGx tests: single gene tests, multi-gene tests, and combinatorial tests. Single gene tests focus on one or multiple genetic variants, also referred to as alleles, within a single gene, which are linked to the effectiveness or tolerance of specific drugs or drug groups. For instance, examples include CYP2C19 for escitalopram, CYP2D6 for risperidone, or HLA-B*15:02 for carbamazepine. Multi-gene tests, alternatively known as "panel tests," analyze genetic variants across several genes. These tests may incorporate genes most relevant to medications used within a particular therapeutic domain, such as pain management, cardiovascular health, or mental health. Both commercial and noncommercial laboratories commonly offer this type of testing. Lastly, combinatorial tests represent a specialized form of multi-gene panel tests, employing proprietary algorithms to interpret test results and provide prescribing recommendations. Although some combinatorial PGx tests yield positive clinical outcomes, there can be disparities between their drug selection and dosing recommendations compared to those derived from established PGx-based prescribing guidelines (e.g., CPIC, DPWG) or PGx information outlined on drug labels (e.g., FDA).

3.8 Common PGx technologies [9]

3.8.1 Single nucleotide variant (SNV) panel

SNV panel testing is the most used technology in PGx practice, either through commercially available micro-array platforms or with custom arrays. The arrays typically contain a preselected set of SNVs, which, depending on the array and platform, can range from a few variants in a single gene to thousands of variants genome wide. Commercially available PGx arrays typically contain variants that are linked to drug response in PGx guidelines or on PharmGKB. The evidence underlying the selected variants can vary, from small arrays containing only the most strongly associated variants, to very large arrays containing all variants potentially or theoretically associated with drug response—for example, including all known drug-related genes. Almost all available arrays use PCR, sequencing by synthesis and nanospheres or beads, combined with a form of fluorescence or chemiluminescence detection to identify which variant is present at the site of interest. Another technology is the use of mass spectrometry, relying on differences in mass between wildtype and mutant nucleotides. The pre-selection of variants and the relatively low amount of data to process allow for a quick result at low costs.

3.8.2 Next Generation Sequencing (NGS) Technologies

While SNV panels only cover a limited set of selected variants, NGS data can cover full exome or genome through parallel sequencing to sequence a sample all at once unlike traditional sanger sequencing that sequence one section at a time. NGS offers ultra-high throughput, scalability, and speed. NGS applications can be roughly categorized into three approaches:

3.8.2.1. Whole exome sequencing (WES) focuses on sequencing the coding regions of the genome, covering approximately 1–2% of the entire genome.

3.8.2.2. Whole genome sequencing (WGS) which is aimed at sequencing the entire genome, both coding and non-coding regions.

3.8.2.3. Targeted sequencing of a region or panel of genes of interest.

NGS technology allows for high throughput and parallel sequencing of single DNA molecules and can be performed at relatively low costs. This approach is often referred to “short read” as it involved massive parallel sequencing of short reads. However, the large amount of data makes processing more challenging.

3.8.3 Long-Read Sequencing

Long-read sequencing technologies have emerged on the playing field and are slowly gaining ground over the short-read approaches in the field of research. Both Pacific Bioscience (PacBio) technology as well as Oxford Nanopore Technologies (ONT) are becoming an integrated part of genetic approaches. PacBio uses SMRT (single molecule real-time)-sequencing to be able to sequence reads up to 45 kB. SMRT cells make use of microwells, each of which contains one single strand of DNA which is then sequenced by assembly and recorded in real time. Oxford Nanopore Technologies uses nanopores through which the DNA strand is pulled, the disruption in the current is specific to a codon, allowing for the full assembly of the DNA sequence. Long read sequencing is advantageous as these technologies can overcome issues encountered with short reads, such as genome wide repeats and structural variant detection. By correcting randomly distributed errors in single cell sequencing, the consensus reads can obtain very high accuracy. While an abundance of data can be generated by long-read sequencing, the processing is significantly more intensive compared to SNV panels and NGS. Common PGx technologies are summarized in the figure 3 below:

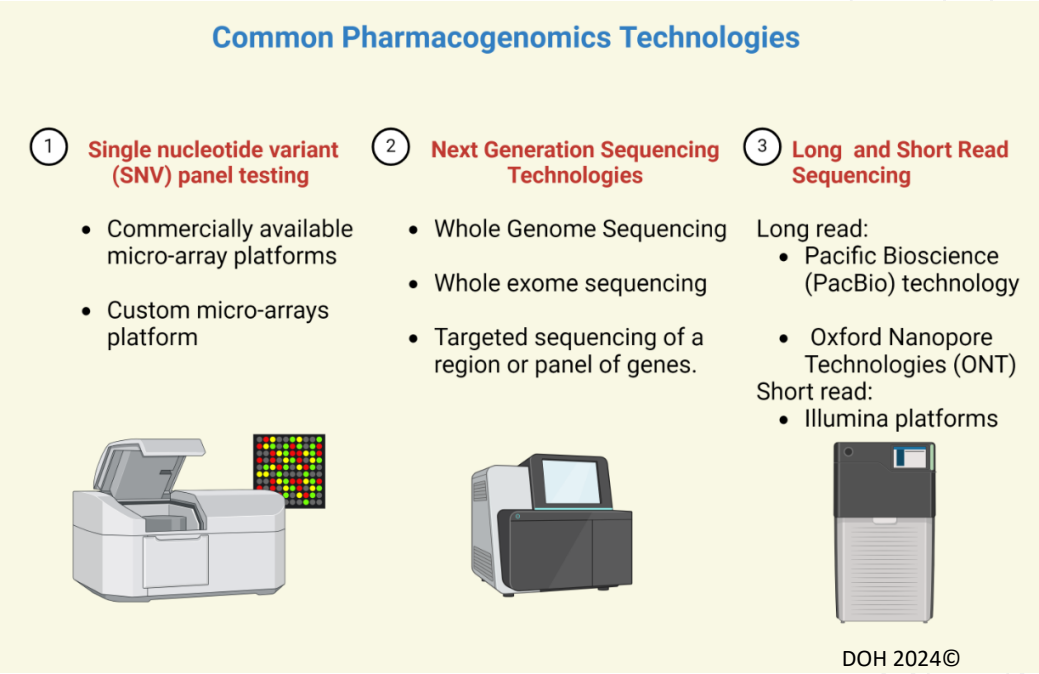

Figure 3: Common PGx technologies

3.9. Pharmacogenomics guidelines and resources

Important pharmacogenomics guidelines and resources includes but not limited to:

3.9.1 Clinical Pharmacogenetics Implementation Consortium (CPIC)[10]:

CIPIC is a consortium that focuses on implementing pharmacogenetic testing into clinical practice. It provides guidelines and recommendations for the implementation of pharmacogenetic testing. CIPIC offers guidance on how to interpret genetic test results, recommend appropriate medications, and adjust dosages based on an individual's genetic makeup, thus optimizing drug therapy in clinical settings.

3.9.2 Pharmacogenomics Knowledge Base (PharmGKB)[11]:

PharmGKB is a comprehensive database that collects, curates, and disseminates information about the impact of human genetic variations on drug responses. It includes data on genes, drugs, phenotypes, and clinical annotations. PharmGKB is a valuable resource for researchers, clinicians, and patients to access information about pharmacogenomics, aiding in the interpretation of genetic test results and guiding personalized drug therapy decisions.

3.9.3 Dutch Working Pharmacogenomic Group (DWPG)[12]:

DWP group focuses on pharmacogenomics research and implementation within the Dutch healthcare system. It collaborates with healthcare professionals, researchers, and policymakers to promote the integration of pharmacogenomic testing into clinical practice. The Dutch Working Pharmacogenomic Group contributes to the development of pharmacogenetic guidelines and protocols, facilitates research initiatives, and supports the adoption of pharmacogenomic testing to improve patient care in the Netherlands.

3.9.4 Pharmacogene Variation Consortium (PharmVar)[13]:

PharmVar is a database that catalogs genetic variations in pharmacogenes, providing standardized nomenclature and annotations for these variants. PharmVar assists in the interpretation of genetic test results by providing information about specific genetic variants and their potential impact on drug response, aiding in the selection of appropriate medications and dosages for individual patients.

3.9.5 Single Nucleotide Polymorphism Database (dbSNP)[14]:

dbSNP is a public database maintained by the National Center for Biotechnology Information (NCBI), containing information about genetic variations, including SNPs, insertions, deletions, and other types of variations. dbSNP serves as a central repository for genetic variations, including those relevant to pharmacogenomics. Researchers and clinicians can query dbSNP to identify known genetic variants associated with drug response and metabolism.

3.9.6 Genetic Testing Registry (GTR)[15]:

GTR is a public database that provides information about genetic tests and laboratories offering genetic testing services. It includes details about the purpose of the test, the genes analyzed, and the clinical validity and utility of the test. GTR facilitates access to information about pharmacogenetic tests available for clinical use, helping clinicians and patients identify appropriate testing options and laboratories for assessing individual drug response characteristics.

3.10 Drug labels containing pharmacogenetic information and its source [16.]

Drug label annotation for pharmacogenetics involves integrating genetic data into drug labels to assist healthcare providers in prescribing medications tailored to individual patients' genetic characteristics. Pharmacogenetic information on drug labels may identify genetic variants influencing drug response, metabolism, or susceptibility to adverse effects, aiding clinicians in adjusting dosages or selecting alternative treatments. Annotations in drug labels also highlight pharmacogenetic factors relevant to drug interactions, aiding clinicians in selecting appropriate medications or adjusting dosages to avoid adverse outcomes. Guidance on incorporating pharmacogenetic testing into clinical decision-making may be provided in drug labels as well, including recommendations for pre-emptive testing to identify patients at risk of adverse reactions based on genotype. Drug label sources encompass approvals from regulatory bodies like the FDA, European Medicines Agency (EMA), Health Canada (Santé Canada) (HCSC), Swissmedic, and Pharmaceuticals and Medical Devices Agency (Japan) (PMDA). Pharmacogenetic information is classified into several categories based on the label's recommendations, such as:

- Testing Required: Indicates that genetic testing or related studies should be conducted before using the drug.
- Testing Recommended: Suggests considering genetic testing before drug administration.

- Actionable PGx: Provides information on genetic variants affecting drug efficacy, dosage, metabolism, or toxicity, without specifying testing requirements.
- Informative PGx: Indicates that genetic variants have no clinically significant impact on drug efficacy, dosage, metabolism, or toxicity.

3.11 Ethical Consideration in Pharmacogenomics [17]

Pharmacogenomic research and implementation are governed by the same principles of bioethics as other human subject research and clinical decisions. These principles include respect for autonomy, beneficence, non-maleficence, and justice.

3.11.1. Autonomy: Patients should have the right to make informed decisions regarding pharmacogenomic testing and its implications for their treatment. This includes providing comprehensive information about the benefits, risks, and limitations of genetic testing, as well as respecting their choices regarding the use of genetic information in their healthcare.

3.11.2. Beneficence: Healthcare providers should strive to use pharmacogenomic information to optimize patient outcomes and medication efficacy. This involves identifying genetic variants that influence drug response and tailoring treatment regimens to individual patients to maximize therapeutic benefits while minimizing adverse reactions.

3.11.3. Nonmaleficence: It is crucial to ensure that pharmacogenomic testing and its application in clinical practice do not result in harm to patients. This includes safeguarding against potential misinterpretation of genetic information, protecting patient privacy and confidentiality, and implementing measures to mitigate the risk of genetic discrimination.

3.11.4. Justice: Equitable access to pharmacogenomic testing and personalized medicine is essential to promote fairness and address disparities in healthcare.

3.12. Pharmacogenomics testing limitation [18]

Diagnostic errors can occur due to rare sequence variations. The risk of therapeutic failure or adverse reactions with gene substrates may be affected by genetic and non-genetic factors that are not detected by pharmacogenomic tests. Pharmacogenomic testing results and recommendations do not replace the need for therapeutic drugs or clinical monitoring. In clinical decision-making, it is imperative to integrate pharmacokinetic and pharmacodynamic studies alongside pharmacogenetics. Understanding how drugs are absorbed, distributed, metabolized, and eliminated, as well as their mechanism of action and effect on the body, is crucial for optimizing therapeutic outcomes. Incorporating pharmacogenetic data, which examines how genetic variations influence drug responses, adds another layer of personalized medicine. However, it is equally important to rely on evidence-based knowledge and guidelines derived from rigorous research and clinical trials. Furthermore, clinicians must pay close attention to whether patients are tolerating the therapy and if the therapy is effective despite the pharmacogenomic testing results. Additionally, considering the duration of time the patient has been on medication before testing is crucial for capturing accurate genetic information that reflects the patient's response to treatment over time and determining if clinicians need to change the therapeutic plan or continue it cautiously while monitoring the response. By considering all these factors systematically, clinicians can make more informed and personalized treatment decisions tailored to individual patient needs. A systematic approach ensures that clinical decisions are grounded in reliable data and best practices, enhancing patient safety and treatment efficacy.

3.13 Pharmacogenomic tools and soft wares:

Pharmacogenomic tools vary in functionality, scope, data sources, user interface, scalability, and validation19. They can be broadly categorized based on their focus, such as variant interpretation, drug-gene interaction prediction, or clinical decision support. Understanding these differences can help researchers, clinicians, and healthcare providers choose the most appropriate tool for their specific needs and applications in pharmacogenomics. To ensure the quality and effectiveness of any new pharmacogenomic software or tool, it’s advisable for developers and stakeholders to undergo evaluation by the Department of Health Abu Dhabi’s Health Technology and Innovation Impact Assessment Sector via: ADHTAC@doh.gov.ae. This evaluation process helps to assess the

tool's safety, accuracy, reliability, and relevance to local healthcare needs, ultimately promoting the adoption of high-quality tools in clinical practice.

3.14 Pharmacogenomic research:

Advancements in genetic technologies and research have expanded the horizons of exploratory PGx and its integration into safety and efficacy studies, influencing various aspects of drug discovery and development endeavors. Recent PGx findings demonstrate the potential of this approach to provide actionable insights applicable to target identification, dosage determination, efficacy assessment, and safety considerations. Consequently, these advancements offer substantial opportunities to shape strategies in drug discovery, clinical development, and increase the likelihood of successful outcomes 20. Conducting research in this field is imperative and obtaining Institutional Review Board (IRB) approval is essential for investigators and researchers to ensure ethical standards and participant safety. To initiate this process, researchers need reach out to the Division of the Medical Research and Development through the following email: medical.research@doh.gov.ae. This division serves as the regulatory body overseeing research activities, providing guidance on protocol submission, ethical considerations, and compliance with local regulations.

5.Relevant References Documents			
No.	**Reference Date**	**Reference Name**	**Relation Explanation / Coding / Publication Links**
1	2015	An introduction to pharmacogenomics	https://www.pacificu.edu/sites/default/files/press/Final%20Pharmacogenomics%20Chapter%20Woo%2006102015.pdf
2	2024	Polymorphism	https://www.genome.gov/genetics-glossary/Polymorphism
3	2021	Phenoconversion	https://www.universiteitleiden.nl/en/research/research-projects/science/phenoconversion
4	2024	Sequance2Script	https://www.sequence2script.com/#/
5	2024	Types of pharmacogenes	https://www.pharmgkb.org/page/typesOfPgx
6	2024	VIPs: Very Important Pharmacogenes	https://www.pharmgkb.org/vips#tier0
7	2020	A model-based cost-effectiveness analysis of pharmacogenomic panel testing in cardiovascular disease management: preemptive, reactive, or none?	https://www.nature.com/articles/s41436-020-00995-w
8	2022	Approaches and hurdles of implementing pharmacogenetic testing in the psychiatric clinic	https://onlinelibrary.wiley.com/doi/full/10.1002/pcn5.26
9	2020	Technologies for Pharmacogenomics: A Review	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7761897/
10	2024	The Clinical Pharmacogenetics	https://cpicpgx.org/
11	2024	PharmGKB	https://www.pharmgkb.org/

12	2024	Dutch Pharmacogenetics Working Group	https://www.pharmgkb.org/page/dpwg
13	2024	The Pharmacogene Variation (PharmVar) Consortium	https://www.pharmvar.org/
14	2024	dbSNP overview	https://www.ncbi.nlm.nih.gov/projects/SNP/get_html.cgi?whichHtml=overview
15	2024	GTR: Genetic Testing Registry	https://www.ncbi.nlm.nih.gov/gtr/
16	2024	Drug Label Annotations	https://www.pharmgkb.org/labelAnnotations
17	2024	Ethical Consideration in	https://www.pharmgkb.org/page/ethics
18	2024	Pharmacogenomic report	Biogenex lab report, G42, 2024.
19	2021	PharmaKU: A Web-Based Tool Aimed at Improving Outreach and Clinical Utility of Pharmacogenomics	https://www.mdpi.com/2075-4426/11/3/210
20	2012	The Impact of Pharmacogenomics Research on Drug Development	https://www.sciencedirect.com/science/article/abs/pii/S1347436715304602