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PRECISION PHARMACOTHERAPY: PHARMACOGENOMICS, BIOMARKERS AND OMICS TECHNOLOGIES: IDENTIFICATION OF DRUGS AND DOSES IN COMPLEX DISEASES IN PATIENTS

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ABSTRACT

The trends of a booming rate of therapeutic failure and drug reactions in the management of complex diseases, are causing the current clinical paradigm of the one-size-fits-all pharmacotherapy quickly going out of business. Precision pharmacotherapy is intended to replace this type of empiricism with a solution that uses medical therapy based on the biological profile of each patient. This literature review involves a thorough critical review of how pharmacogenomics, multi-omics integration, and artificial intelligence came together to redefine the selection of drugs and dose optimization. We review the move to genomic profiling in general rather than single gene testing and ascertain the clinical utility of germline variants in drug metabolizing enzymes and transporters. Besides, the recent contribution of transcriptomics and proteomics to the unravelling of the non-genetic factors of drug resistance are discussed, particularly in the area of oncology and immunology. The use of companion diagnostics is investigated as a critical process of a biomarker-based therapy, which requires that targeted agents will be withheld from a patient with necessary molecular pathology. In addition, we assess the potential of artificial intelligence algorithms to be used for the transformative interpretation of high-dimensional omics data to predict complex pharmacokinetic phenotypes. Lastly, the review discusses the high translational obstacles, in the fields of informatics, economics and ethics, to be overcome in order to allow the smooth assimilation of these technologies into the daily practice of clinical care. We conclude that multimodal precision-dosing framework is one of the essential requirements of the future sustainability of the healthcare system in the world.

Keywords: Precision Medicine; Pharmacogenomics and Multi-omics; Artificial Intelligence; Companion Diagnostics; Clinical Decision Support.

1. INTRODUCTION

1.1 The Therapeutic Imprecision Clinical and Economic Meltdown.

Real-world evidence is slowly undermining the very core of the modern pharmacology, that a drug approved to do a particular thing will work and be safe on the average patient. (1) Response rates to the first line therapies, in important areas of medicine such as oncology, psychiatry and rheumatology, are dismal in the range of 30% to 60% which means that a significant percentage of patients are exposed to useless chemical agents. (2) This inaccuracy comes at an unbelievable human price; currently, Adverse Drug Reactions (ADR) is estimated to be the fourth cause of death in the United States, and this is more than diabetes and pulmonary diseases. (3) The economic aspects are also deep rooted and the cost of dealing with the morbidity that has been brought about by drugs is estimated to cost over 30 billion dollars every year in the US health care system alone. (4) These side effects are not commonly some hi-fi accidents but, often, a predictable result of the incompatibility between patient physiology and drug characteristics. (5) As a result, the old trial and error fashion of prescribing is not only becoming not only efficient but to ethics of the era in which the information of bio-logic data is easily accessible. (6)

1.2 The dawn of History: Pharmacogenetics to Precision Medicine.

The heredity factor in drug response was established first in the 1950s when it was found that the incidence of prolonged apnea to the administration of succinylcholine was correlated with an inherited deficiency in plasma cholinesterase. (7) Nevertheless, pharmacogenetics had a long history as a fringe science that focused on monogenic outliers. (8) The watershed of the field was the completion of the Human Genome Project in 2003, which shifted the direction of the field to be interested in rare phenotypes but to have a systematic mapping of the effects of common genetic variation on drug response. (9) It was the time when such important relationships were confirmed, such as those involving TPMT variants in the prediction of thiopurine toxicity and HLA-B variants in the prediction of hypersensitivity to antiretrovirals. (10) However, the original promise that the practice of genetics was promising an adequate answer to the dosing riddle has been tempered by the fact that biology is complex. (11) Genetic variations usually only explain 20-40 percent of the degree of clearance of drugs, and this lack generates a gap in heritability that needs to be clarified through a larger investigative lens. (12)

1.3 The Paradigm Shift for Multi-Omics.

The solution to this gap is changing the field from DNA-centric (Pharmacogenetics) to a systems biology approach (Precision Pharmacotherapy).(13) This novel paradigm unifies the information

of some of the biological levels: the genome (blueprint), the transcriptome (the message), the proteome (the machinery), and the metabolome (the condition of the functioning). (14) Most recent developments in high-throughput mass spectrometry and next generation sequencing (NGS) can ensure that these layers are now captured simultaneously to make a high definition 'digital twin' of the physiology of the patient. (15) An example is that a patient could have a normal metabolism according to their CYP2D6 genotype, but a metabolomic profile can inform that they have been phenocopied by concomitant inflammation into being a poor metabolizer. (16) By combining these orthogonal data, it is possible to realize real-time and dynamic dose optimization and dynamically change of the health state of the patient. (17)

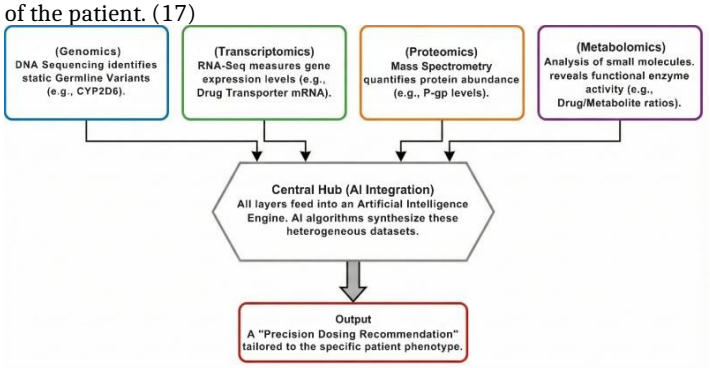


Figure 1: The Workflow of Multi-Omics Integration.
Description: Conceptual flowchart of merging of data layers
Caption: Figure 1. The integrative approach of the multi-omics data towards accuracy pharmacotherapy. Although with genomics there is a point of view picture of the potential drug metabolism process, when using transcriptomics, proteomics, and metabolomics, this information is dynamic and provides us with information about the actual physiological state of the patient. These heterogeneous datasets are synthesized using AI algorithms to predict the best drug choices and dosages.

1.4 Objectives of this Review

The aim of the article is to present a comprehensive synthesis of the state of the art of precision pharmacotherapy. (18) We shall hapless direction on mechanistic producing pharmacogenomics dissimilarities in phase I and II metabolism. (19) We will evaluate the integration of the non-genomic biomarkers, like the circulating tumor DNA (ctDNA) and proteomic signatures, in clinical decision-making. (20) We will also critically think about how artificial intelligence can be utilized to decipher these complex datasets to predict the ideal dosing regimens. (21) Lastly, we shall recommend an implementation plan to break the walls of implementation that are currently holding these innovations in the academic centers so that they do not trickle down to the practice in the community. (22)

2. Pharmacogenomics: Mechanistic Foundation of dosing

Pharmacogenomics (PGx) is the cornerstone of precision medicine, as germline DNA is permanent, easily accessible, and risk forecasts throughout a lifetime. (23) Alterations in genes that code the Drug Metabolizing Enzymes (DMEs) and transporters determine the pharmacokinetic (PK) profile of a drug, which determines the concentration of a drug that reaches the target tissue. (24)

2.1 Phase I Metabolism: The Cytochrome P450 Superfamily

Phase I Metabolism involves alteration of drug molecule by oxidation, reduction or hydrolysis and major process is increase in polarity.(25) Cytochrome P450 (CYP) Superfamily of enzymes are found in the perihepatic location and are mostly found in the hepatic endoplasmic reticulum and play an important role in the coordination of the metabolism of about 80% of all the clinically used drugs.(26) Inter-individual variability in the clearance of drugs is the most common and occurs because of the genetic polymorphisms of CYP genes. (27)

2.1.1 CYP2D6: The Prototype of Genetic Variability

The most important and challenging pharmacogenomics gene is CYP2D6, located on chromosome 22q13.1. (28) It is extremely polymorphic and more than 130 identified "star alleles" (*) are documented by the Pharmacogene Variation Consortium (PharmVar). (29)

Mechanistic Diversity: These variants include those that disrupt splicing by deletion of a single nucleotide (SNP) (e.g., CYP2D64) or deletion of up to the entire gene (CYP2D65) or even gene duplication (CYP2D61xN). (30)

- **Clinical Signs in Psychiatry**: CYP2D6 is a liver metabolism and degradation enzyme that is involved in the metabolism of around 50% of antidepressants and antipsychotics. (31) It has been established in the clinical trials that Poor Metabolizers (PMs) on the standard doses of tricyclic antidepressants have plasma concentrations 5-10 times greater than those of PMs on other metabolic systems, resulting in cardiotoxicity and anticholinergic side effects. (32) On the other hand, the Ultra-Rapid Metabolizers (UMs) do not typically respond to SSRIs due to their fast clearance, and they typically require doses that are above the maximum standard. (33)
- **Tamoxifen Controversy**: Tamoxifen is a metal in the treatment of ER-positive breast cancer, a prodrug that needs to be bioactivated by the CYP2D6 to an active end, resulting in endoxifen. (34) Although the initial retrospective studies indicated that PMs were much more likely to recur, the later large-scale trials, including the BIG 1-98 were conflicting, which indicates the complexity of establishing the utility of the use of PGTs in poly-medicated oncology groups. (35) Notwithstanding this, CPIC guidelines recommend against the use of CYP2D6 inhibitors for patients under tamoxifen treatment because of the risk of iatrogenic recurrence. (36)

2.1.2 CYP2C19: Cardio Neuropharmacological Effects

CYP2C19 polymorphism is one of the important predictors of antiplatelet treatment and proton pump inhibitor (PPI) activity. (37)

Clopidogrel Bioactivation: Clopidogrel is an inactive pro-drug, which is converted by two-step bioactivation and the first step is irreversibly dependent on the CYP2C19 enzyme. (38) The carriers of loss of function alleles (2, 3) produce 30-50 % of active metabolite. (39) The addressing trial, which was the TAILOR-PCI trial, was focused on genotype-directed intensification of antiplatelet treatment.(40) The main endpoint in the intent-to-treat analysis has not reached the statistical significance threshold, but the post hoc analysis found a significant difference in ischemic event among the patients with the loss-of-function genotype following the switch to ticagrelor, which proved the biological validity of this interaction.(41)

Helicobacter pylori Eradication: Use of PPIs like omeprazole is inhibited by CYP2C19. (42) In Rapid Metabolizers (particularly the 17 allele carriers), PPIs are eliminated very rapidly that intragastric pH does not reach the level to achieve antibiotic efficacy against H. pylori. (43) In turn, Japanese and European guidelines recommend that the dose of PPI increased up to 100-200 percent in such phenotypes in the achievement of success for eradication. (44)

Table 1: Notable Biomarkers in Pharmacogenomics and Clinical Recommendation (Standard of Care).

Drug Class	Drug Name	Target Gene	Phenotype Implication	Clinical Recommendation (CPIC/FDA)	References
Antiplatelet	Clopidogrel	*CYP2C19*	PM: Reduced active metabolite	Switch to Ticagrelor or Prasugrel	(32)
Opioid	Codeine	*CYP2D6*	UM: Rapid conversion to morphine	Contraindicated; risk of respiratory depression	(33)
Oncology	5-Fluorouracil	*DPYD*	PM/IM: Decreased clearance	Reduce dose by 50% or avoid use	(34)
Antiretroviral	Abacavir	*HLA-B*57:01*	Carrier: Hypersensitivity risk	Strict Contraindication	(35)
Statin	Simvastatin	*SLCO1B1*	Carrier: Reduced hepatic uptake	Lower dose or switch to Rosuvastatin	(36)

Description: Table of high-evidence gene-drug pairs as identified by CPIC and FDA.

2.1.3 The Narrow Therapeutic Index of Warfarin and Cytochrome P450 2C9

CYP2C9 is involved in the elimination of drugs with a small therapeutic index, which are primarily warfarin and phenytoin. (45) CYP2C92 variant and 3 variants give rise to the enzymes having low catalytic activities (46). In the case of warfarin, a vitamin K antagonist, the presence of such alleles reduces its clearance, requiring a 20-40% dose reduction due to the risk of life-threatening haemorrhage. (47) A combination of CYP2C9 genotyping and VKORC1 (the drug target) status into the dosing algorithm accounts for almost half of the variation in dose, a massive improvement over a clinical algorithm that administers based on age and weight only. (48) The ENGAGE AF-TIMI 48 trial also helped elucidate that edoxaban, a direct oral anticoagulant, is also influenced by CYP2C9, suggesting that the relevance of PGx is also relevant for newer agents. (49)

2.2 Phase II Metabolism: Conjugation, Determinants of Toxicity.

Phase I allows the removal of the drug while Phase II allows the excretion of the metabolite with the endogenous substrates, including glucuronic acid, sulfate, or methyl group. (50) Malfunctions in these pathways due to genetic defects tend to cause the accumulation of toxic intermediates, causing severe and dose-dependent adverse events that can be clinically differentiated from an allergic reaction. (51)

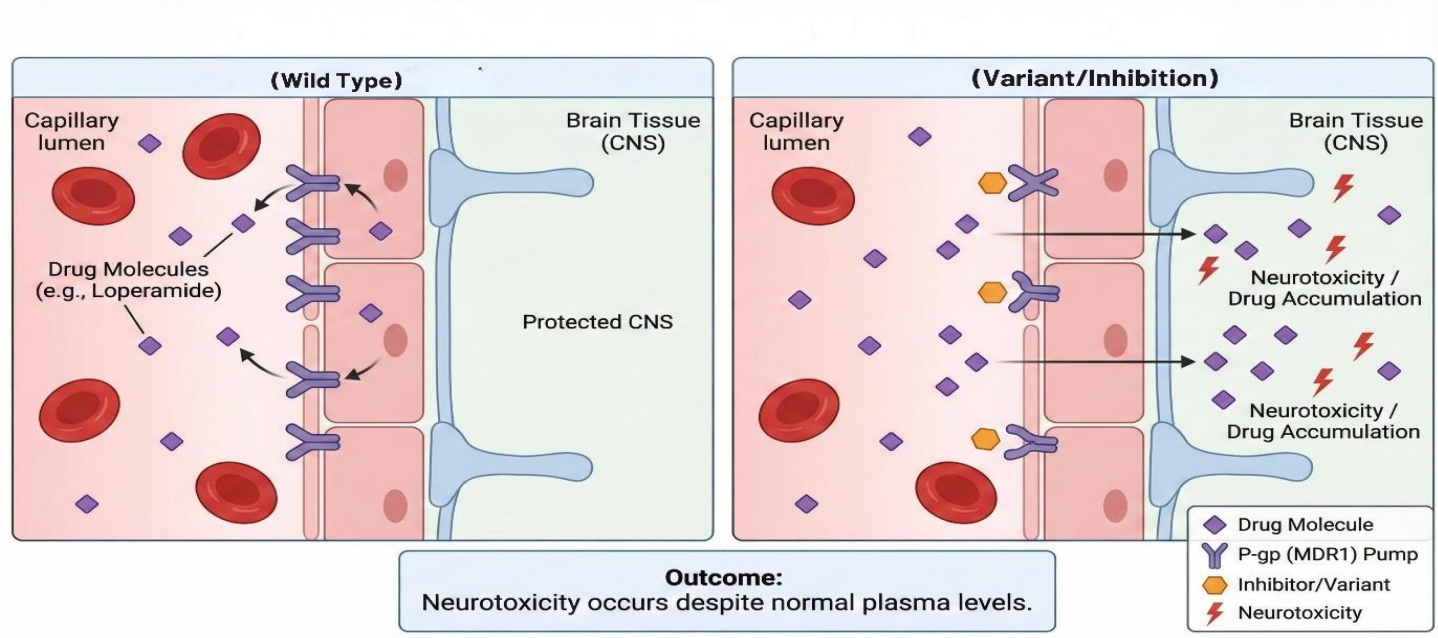
2.2.1 UGT1A1 and Irinotecan-Associated Neutropenia.

The Sn 38 is the active metabolite of the topoisomerase-1 inhibitor irinotecan and is glucuronidated by Uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1).(52) Six repeats lie in the wild-type promoter region and seven repeats lie in the allele UGT1A128 which is a polymorph that downregulates the gene transcription by up to about 70 percent.(53) Homozygous 28 individuals (with SN-38 homozygously related to Gilbert Syndrome) have a far lower rate of clearance of SN-38. (54) In conventional dosages, it has always been clinically proved that such patients are 3-fold to 5-fold more likely to have grade 4 neutropenia and severe diarrhea with irinotecan. (55) As a result, the dose has been recommended to be decreased in the labeling (FDA package insert) in case there is a known patient homozygous to the 28' allele and is one of the first examples of PGx being integrated into labeling for oncology. (56)

2.2.2 The Thiopurine Methyltransferase (TPMT) and NUDT 15 Paradigm

Tiopurines (azathioprine, 6-mercaptopurine) have a backbone drug, prescribed in the treatment of acute lymphoblastic leukemia (ALL), and inflammatory bowel disease, which has a low therapeutic index in the form of hematopoietic toxicity (57). These drugs are made inert (S-methylated) by an enzyme called TPMT. (58) Homozygotes for non-functional TPMT alleles (2, 3A, 3C) are estimated to occur at a frequency of 1 in 300 and lack enzyme activity. (59) These homozygotes, when administered with normal doses, start having colossal levels of cytotoxic thioguanine nucleotide (TGNs), which lead to lethal myelosuppression. (60)

Nevertheless, the concept of TPMT-centricity came under observation when it turned out that TPMT variants could not account for thiopurine toxicity in the Asian and Hispanic population. (61) This was followed by genome-wide association studies (GWAS), which identified variants at NUDT15 (particularly R139C), the determining factor of thiopurine intolerance in these groups. (62) Functional analyses have led to the conclusion that NUDT15 is involved in slicing of active thiopurine metabolites and inhibiting the incorporation of these into DNA; therefore loss-of-function mutations cause uncontrolled damage to DNA. (63) Subsequently, the recommendations of the Clinical Pharmacogenetics Implementation Consortium (CPIC) have been revised recommending the application of preemptive analysis of the TPMT and NUDT15 tests in which multi-ethnic validation of pharmacogenomics is their key. (64)



2.3 Drug Transporters: The Pharmacokinetic Stearers

Drug transporters regulate the movement of therapeutic agents in and out of the cell membrane that affect the absorption, distribution and excretion of drugs known as drug absorption, distribution and excretion. (65) Fluctuations in genes coding for the transporters has the potential to alter concentration of drugs in certain compartments and most cases that are not determined by its systemic clearance. (66)

2.3.1 Myopathy SLCO1B1 and Statin-Induced Myopathy

SCLO1B1 the organic anion-transporting polypeptide 1B1 (OATP1B1) helps with the uptake of statins in the hepatocytes via the portal circulation. (67) c.521T>C (SLCO1B1*5) is a non-synonymous mutation that interferes with the transporter activity, decreasing the uptake in the liver, leading to a compensatory increase in plasma statin levels. (68) A historic SEARCH trial showed that the 5 allele is strongly associated with simvastatin-induced myopathy, where the odds ratio of homozygotes is 16.9 as compared to non-carriers.(69) This is purely dose-dependent, and hence instead of the recommended 20mg of simvastatin, it is recommended that one switches to rosuvastatin/pravastatin, which has a lesser dependence on OATP1B1 to be cleared, as carrier of the risk allele. (70)

Figure 2: Blood Brain Barrier Pharmacokinetics of Drugs

Description: The role of the P-glycoprotein (MDR1) at the Blood - Brain Barrier (BBB) is represented in the following figure.

a) **Panel A (Wild Type):** P-gp pumps are "on" and the endothelium of the brain actively pumps the drug molecules (e.g. Loperamide or Antipsychotics) into the capillary blood to protect the CNS.
b) **Panel B (Variant/Inhibition):** Shows an instance of defective P-gp (due to the variants of the ABCB1 or due to a chemical inhibitor). The drug molecules not go through the efflux pump and it is responsible for the accumulation of the brain's tissue.

Findings: Despite normal levels of plasma, there is neurotoxicity.
Caption: Figure 2. Such is the protective action of efflux transporters. A protein called ABCB1, known as P-gp, is a blood-brain barrier gatekeeper. Polymorphism in genes which encode P-gp may result in central nervous system toxicity with substrates which are otherwise inactive, including the opioid antidiarrheal loperamide.

2.3.2 ABCB1 (MDR1) and Multidrug Resistance

This is a multidrug-resistant gene, which is resistant to amantadine. unfosine (ABCB1 or MDR1). P-glycoprotein (P-gp) is an ATP-dependent efflux pump of ABCB1 gene which is expressed at the blood-brain-barrier, intestinal epithelium and tumor cells. (71) Even though, the ABCB1 overexpression is a famous way of developing chemotherapy resistance in tumors, germline variants of the ABCB1 protein also affects drug kinetics of such substances as 'digoxin' and 'dabigatran'. (72) Even though the clinical usefulness of ABCB1 genotyping is controversial based on the inconsistent reports of the studies, however, it is an important variable in toxicology models, especially to predicting CNS penetration of antiretrovirals and antipsychotics. (73)

2.4 HLA-Mediated Adverse Drug Reaction: The Immunological Frontier

In comparison to the metabolic ADRs, which are dose-dependent, immune-mediated ADRs are idiosyncratic and usually severe and are due to particular interaction between drug antigens and Human Leukocyte Antigen (HLA) molecules. (74) Such reactions include Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) and the reactions have high mortality rates. (75)

2.4.1 Abacavir and HLA-B*57:01

HIV reverse transcriptase inhibitor abacavir-HLA-B57:01 is the best predictive test result of immunopharmacogenomics. (76) It is estimated that about 5-8% of Caucasian groups carry this allele; when treated with abacavir, 100 percent of these people develop a CD8+ T-cell-mediated hypersensitivity reaction. (77) One randomised double masked study, known as the Prospective Evaluation of Drug-Response to Immunotherapy in Cancer Harboring Leukaemia/M Multiple Myeloma Patients -1 (aka the Prospective Evaluation of adenohistiocyte immune cellular Tolerance for immunologic Statement (PREDICT-1) study, showed immunologically confirmed reactions during prospective screening with HLA B*57:01 were removed. (78) Consequently, screening is now a requirement as part of the mainstream guidelines of HIV treatment in the world. (79)

2.4.2 Carbamazepine and HLA-B*15:02 / HLA-A31:01

A common antiepileptic drug is carbamazepine, which is a common cause of SJS/ TEN among Southeast Asians. (80) The allele HLA-B*15:02 tends to occur in up to 15 % of people of Han Chinese and Thai ancestry and is closely related to the SJS, a reaction caused by carbamazepine (Odds Ratio exceeds 1000).(81) Before this allele is initiated, this allele is required to be screened in the at-risk populations by the FDA (82). Interestingly, there is another allele, HLA-A31:01 that contributes to the hypersensitivity in European and Japanese people; this illustrates the ethnic-specific architecture of immune-mediated ADRs.(83)

3. Multi-Omics Integrations: More than just the Genome

Although the genomics provides the fixed blueprint, it does not record the dynamic physiological alterations which is caused by disease situation, environment or epigenetic adjustments. (84) Pharmacotherapy should be combination of the downstream features of omics to become perfectly accurate. (85)

3.1 Transcriptomics: Gene expression as a biomarker

The transcriptomics, which is examination of the RNA transcripts, are indicative of the degree to which the genetic commands are being implemented. (86)

Oncology Signatures: Transcriptomics have found the best clinical use in breast cancer prognostications. (87) Oncotype DX assessment looks at the expression of 21 genes that are obtained on tumor tissue to calculate Recurrence Score (RS). (88) The trial, called the TAILORx, has proved that women intermediate for RS do not require adjuvant chemotherapy, thus sparing thousands of patients who are exposed to unnecessary toxicity. (89) This shifts the decision-making process into an anatomical staging to a molecular staging. (90)

Drug Response Prediction: Apart from prognosis, transcriptomic signatures are to be used in drug sensitivity prediction. As an example, decreased mRNA level of excision repair cross-carbonation 1 (ERCC1) gene is related to increased sensitivity to platinum based chemotherapy in non-small cell lung cancer (NSCLC). (91) On the other hand, elevated ERCC1 would mean that there are effective DNA repair processes that will render cisplatin useless hence alternative therapy is required. (92)

3.2 Proteomics: The Functioning Effectors.

Proteomics provides an estimate of the actual proteins involved in performing the biological processes and the the phenotype of the protein can be detailed to a greater extent than that of mRNA levels because not necessarily proportional to protein levels due to post translational regulation. (93)

Measuring Drug Targets: In breast cancer with HER2, Immunohistochemistry (IHC) used as a standard test, or FISH. (94) Nevertheless, quantitative mass spectrometry (Selected Reaction Monitoring - SRM) has proved that absolute concentration of HER2 protein is significantly different even in patients with the status of being HER2-positive, which is more correlated with the strength of jinhaeng response of HER2 (trastuzumab). (95)

Activation of Signalling Pathways: Utilizing phosphoproteomics the level of the phosphorylated (activated) proteins in signalling cascades can be measured. (96) Kinase inhibitor treatment: The existence of a mutation (e.g. GOV0600E) suggests the existence of a susceptibility but measurement of the phosphorylation state of downstream effectors (MEK/ERK) demonstrates whether the pathway is indeed controlling tumor proliferation and the drug is working or not. (97) This functional proteomics-based approach can be applied to characterise adaptive resistance mechanisms whereby bypass pathways are activated that can be activated in the presence of a successful target inhibitor. (98)

4. Companion Diagnostics: Precision Regulation's Bridge to Regulation

4.1 The Co-Development Paradigm

A Companion Diagnostic (CDx) is defined as an in vitro diagnostic apparatus that provides information to allow for the safe and effective administration of a therapeutic product.(99) In 1998, the regulation model of CDx was crystallized and approved along with trastuzumab (Herceptin) and HercepTest. (100) This theranostics combination created a two-phase clinical reality, which is that the lack of diagnostic confirmation of the overexpression of the HER2 protein or the amplification of the corresponding gene renders the drug medically inappropriate. (101) This step B co-evolution maintains the efficacy signal of the drug in clinical trials by weeding out non-responders, and this is a practice that has been taken over as the method of developing an oncology drug. (102) The FDA has, at present, a list of over 45 approved companion diagnostics and therapeutic targets, including ALK rearrangement in lung cancer to BRCA mutation in ovarian cancer. (103)

4.2 Evolution: The Single-analyte to NGS Panels.

Originally, CDx assays were devised to be drug, one test systems, and are primarily based on immunohistochemistry (IHC) or Polymerase chain reaction (PCR).(104) Nonetheless, a generally accepted method of sub-classification of cancer into the rare and molecular subtypes has made this approach tissue-depleting and logistically inefficient. (105) EGFR, ALK, ROS1, BRAF, MET, RET and KRAS testing may be required in a patient with non-small cell lung cancer (NSCLC), sequential testing may in most cases exhaust the biopsy sample before a complete molecular picture can be obtained. (106)

To be able to deal with this, the field has been shifted to Next-Generation Sequencing (NGS) panels. In 2017, FDA has approved the Foundation One CDx which is the first comprehensive-based genomic profiling (CGP) assay for all solid tumors. (107) This test concurrently finds variations in 324 genes and complicated genomic characteristics including Tumor Mutational Burden (TMB) and Microsatellite Instability (MSI).(108) The clinical utility of CGP was proven by the fact that CGP can detect NTRK fusions, and rare occurrences (less than 1% for common cancers) but occurrences (more than 90% cancers) were found for rare tumors including infantile fibrosarcoma.(109) The larotrectinib NGS tissue-agnostic TRK block has been conditional upon the ability of NGS to look for these rare incidences of fusion in a broad range of histology. (110)

Table 2: Development of Critical Companion Diagnostics in Precision Oncology

Drug (Therapy)	Biomarker Target	Methodology	Clinical Indication	FDA Approval	References
Trastuzumab	HER2 overexpression	IHC / FISH	Breast Cancer	1998	(100)
Vemurafenib	*BRAF* V600E	PCR (Cobas)	Melanoma	2011	(111)
Crizotinib	*ALK* fusions	FISH	NSCLC	2011	(112)
Olaparib	*BRCA1/2* mutations	NGS	Ovarian Cancer	2014	(113)
Pembrolizumab	MSI-High / dMMR	IHC / PCR	Solid Tumors (Tissue Agnostic)	2017	(114)
Alpelisib	*PIK3CA* mutations	PCR (Liquid Biopsy)	Breast Cancer	2019	(115)

Description: Comparison of Timeline of CDx technologies.

4.3 The Agony of Harmonization

The lack of harmonization between CDx assays is regarded as one of the major obstacles in this day of technology. (116) The testing for pd l 1 immune checkpoint inhibitors is the area where the same is manifested more. The proprietary drugs (pembrolizumab, nivolumab, atezolizumab) were developed using different antibody clones (e.g., 22C3, 28-8, SP142) and different scoring algorithms. (117) An industrial-academic project, known as the Blueprint Project showed that while there are instances of analytically concordant assays, there are also instances which are not similar in sensitivity and therefore may misclassify patients. (118) A patient may have a positive result with one test and a negative result with another which leads to confusion about determining if a patient is eligible to receive a certain immunotherapy.(119) It goes to emphasize the truth that there is an urgent need to standardize the science of regulation in an effort to avoid the disintegration of care. (120)

5. Liquid Biopsy: Non-Invasive Pharmacomonitoring

5.1Circulating tumor DNA (ctDNA) dynamics

Circulating tumor DNA (ctDNA) is made of minute fragments of DNA that are circulating throughout the body and are present in normal cells. Although, the gold standard of diagnosis, the traditional tissue biopsy is a one-dimensional picture of a heterogeneous tumor in space and time. (121) It is not so easily repeatable how to see the response of a drug. As an alternative to invasive methods, Liquid biopsy, the analysis of circulating tumor DNA (ctDNA) emitted into the bloodstream, is a minimally invasive procedure, which describes in its entirety, the picture of metastatic disease. (122) Because the half-life of ctDNA is not more than two hours, this makes the biomarker a highly dynamic biomarker, which can be used to monitor the efficacy of treatment in real time. (123)

5.2. Identification of Acquired Resistant.

The identification of mutations of resistance before radiographic progress is one of the best uses of liquid biopsy. (124) There is inevitability of resistance in the form of T790M mutation in the first generation of tyrosine kinase inhibitors (TKIs) when they are used in the form of epidermal growth factor receptor (EGFR) mutated non-small cell carcinoma of lung. (125) The re-biopsy of the lung, however, is invasive and dangerous. The T790M can now be detected directly using liquid biopsy assays in plasma with high specificity to allow rapid switching to third generation inhibitors including Osimertinib. (126) The NCCN guidelines have now formally admitted this to be more of a plasma first approach where tissue biopsy is only undertaken if the plasma test is negative. (127)

5.3 Minimal Residual Disease (MRD) and Dose De-Escalation

Apart from mutations, liquid biopsy is changing the concept of dose optimization by informing the course of adjuvant treatment. (128) The standard of care for colorectal cancer associated with surgical resection is CTDNA as the best predictive factor of recurrence.(129) Traditionally, adjuvant chemotherapy was offered on the basis of the pathological staging and consequently over-treated patients who were cured and under-treated the patients with unknown micro metastases. (130)

The results of a historic trial DYNAMIC showed a huge reduction in adjuvant chemotherapy guided by ctDNA and did not have an adverse impact on the timeline of recurrence-free survival. (131) As we have seen, ctDNA-negative patients after surgery could safely avoid the toxicity of chemotherapy based on oxaliplatin, but patients with ctDNA-positive received higher dosage. (132) This is the ideal of pharmacotherapy: molecular diagnostics in order to de-escalate dosage, for low-risk patients, and escalation of dosage for high-risk patients, to treat bi-workers, thereby increasing the therapeutic index. (133)

6. Artificial Intelligence: The Thinking Machine Behind Precision Dosing

A combination of the genomics molecular legacy, transcriptomics, proteomics and real time sensor measurements form a dataset of this dimensionality and complexity so that it is beyond the ability of the human mind to process it in real time. (134) Machine Learning (ML) and Artificial Intelligence (AI) are the central drivers behind the process of converting such data to a wide-ranging, actionable dosing recommendation. (135)

6.1 Pharmacokinetics Prediction using Deep Learning

Conventional PK modeling are based on linear regression, population means (e.g. the Cockcroft-Gault equation of renal clearance).(136) Nonlinear interaction of genes and drugs with environmental factors are however not considered in these models. (137) These complex dependencies can be modeled by means of Deep Learning (DL), i.e Neural Networks.

Re-examination of Warfarin Dosing: In spite of the fact that warfarin linear pgx algorithms improved the outcomes, these algorithms ceased to improve. (138) Modern research based on Deep Neural Networks (DNN) has also included not only CYP2C9/VKORC1 genotypes, but hundreds of clinical factors stored by Electronic Health Records system (EHR), including the dietary habits and medication interaction. (139) The latter black box models have shown 15-20 % dose predictivity superior to conventional pharmacometric equations especially in populations of outliers. (140)

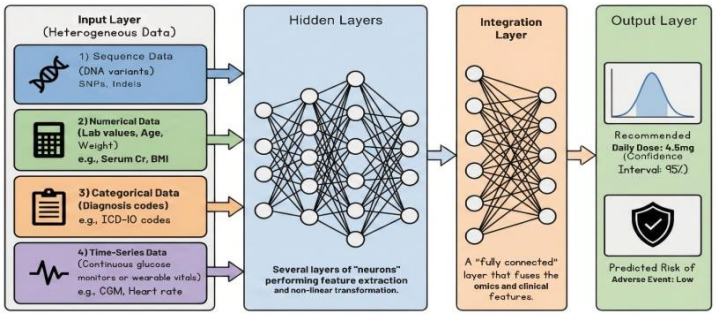


Figure 3: Deep Learning Framework on Precision Dose

Description: the diagram of Multimodal Neural Network

Caption: Figure 3. Dosing architecture based on AI In comparison to linear regression, Deep Learning models can ingest unstructured and multimodal data in order to be able to find non-linear relations between the omics profile of a patient and drug metabolism and predict a Supplementation with increased accuracy.

6.2 AI in Drug Repurposing and Drug Discovery

AI is also enhancing the discover of new signs of already available drugs (repurposing), that is one of the Aspects of precision medicine in rare diseases. (141) The method used in CMap to do pattern matching disease state gene expression with library of drug-induced expression profile using pattern matching algorithms. (142) When a drug induces an expression signature that represents the opposite of the expression signature induced by the disease, then that drug has a good potential to be curative. (143)

This has been known to be used during the Covid-19 crisis where the frequently used AI algorithms were used to filter the FDA-approved compounds based on their interaction with the viral-host interactome, leading to the discovery of the potential therapeutic baricitinib only within weeks of the clinical trials. (144) Precision oncology AI models are based on the analysis of the molecular

structure of tumor proteins based on which the binding affinity with large libraries of small molecules can be predicted, which can be used to find potential off-label targeted therapy in patients who have exhausted standard options. (145)

6.3 Digital Twins: A The Ultimate Simulation

The intersection between multi-omics and AI is also leading to the creation of so-called Digital Twins virtual computational models of the physiology of an individual patient. (146) A digital twin combines the genome of the patient, information on the metabolism of real-time metabolism and parameters of the organ function. (147) A clinician might be able to run the dosing regimen on the digital twin before prescribing a toxic drug with a narrow therapeutic index. (148) The model would give an idea of how the drug would be dispersed, metabolised, and how toxic the drug may be in that particular biological environment. (149) This in silico trial and error has a chance at eradicating the susceptibility of the actual patient which, is a hypothetical aim of precision pharmacotherapy. (150)

7. Clinical Implementation Barriers: The Translational Gap

Although the scientific validity of the process and the increasing accessibility of technologies for precision pharmacotherapy are undeniable, there is a deeper translational gap in translating discoveries into everyday clinical use. (151) Although several major academic medical facilities have been successful in running pilot programs, it yet to be adopted on a wide scale in community-based health settings. (152) This section delays the complicated issues that exist in insurmountable barrier to the easy introduction of these innovations in everyday practice.

7.1 The Issues in Informatics and Interoperability

The problem with the short-term logistical challenge stems from constraints in the current Electronic Health Records (EHR). (153) Throughout most health systems, the result of the pharmacogenomics testing - the test result PDF is scanned and saved to be buried in the Media or lab section of the patient chart. (154) unlinked to the medication ordering system. Such format makes the data not visible to the automated Clinical Decision Support (CDS) algorithms and rely solely on the memory of the prescriber to determine if a result was obtained - a technique that is likely to fail. (155) Scalability of precision dosing requires that genomic data be represented as discrete and structured, which utilizes interoperability standards such as HL7 FHIR, and can be activated by real-time and active alerts during the point of prescribing.(156) Moreover, such alerts should be created with particular attention not lead to the occurrence of the so-called alert fatigue. (157) which is widely reported to occur when Good CDS systems must not create interruption of the workflow when the patient is getting high-evidence and actionable data (ex: "Stop Code Word - Patient is CYP2D6 Ultra-Rapid Metabolizer") but not low-impact informational messages. (158)

7.2 Economic Viability and Reimbursement.

Economic cause of precision medicine is complicated and misconstrued. (159) While the cost of sequencing have dropped recently, the cost of interpretation, storage of the data and genetic counseling are quite expensive. (160) Payers (insurance companies) in the past have never been keen about covering preemptive panel testing and have often referred to them as in investigational or experimental. (161) They usually demand evidence of Randomized Controlled Trials (RCTs) that will prove that the use of PGx testing improves hard outcomes, which may include death or hospitalization rates.(162) Nevertheless, for the practical and economical reasons, large-scale RCTs on all pair of genes-drugs are impossible. (163) As a result, this discipline is leaning towards where Real-World Evidence (RWE) and pragmatic trials are being used to provide proof of value. (164) According to recent cost-effectiveness studies, preemptive panels were economically dominant to reactive testing and their benefits when taken throughout the life of a patient as a result of the fact that a single panel can inform decades of prescribing in many areas of therapy.(165)

7.3 EDUCATION AND WORKFORCE READINESS

There is a huge gap in genomic literacy in between the practicing clinicians. (166)It has been found continuously that although physicians believe that pharmacogenomics is important, less than a fifth of them are confident of ordering or interpreting this kind of test. (167) Discovery is so hot that even medicine school curricula a decade ago are out of date in terms of molecular diagnostics.(168) The efforts to remedy this disparity are through the introduction of specialized clinical team-based subject matter experts, also known as precision pharmacists, through professional societies, such as the American Society of Health System Pharmacists (ASHP). (169) Also, point-of-care tools, such as the CPIC guidelines and PharmGKB database, must be integrated directly into the EHR in order for the clinicians to be educated on the job as they practice medicine. (170)

Table 3: Strategic Clinical Implementation Strategies Obstacles Solutions

Barrier Category	Specific Challenge	Proposed Solution	References
Informatics	Static PDF results; lack of interoperability	Adoption of HL7 FHIR standards; discrete data storage	(153)
Economic	High upfront cost; lack of payer reimbursement	Cost-effectiveness studies of preemptive panels; value-based care models	(165)
Education	Clinician lack of confidence/knowledge	Point-of-care decision support; "Just-in-time" learning modules	(167)
Ethical	Data privacy; fear of genetic discrimination	Blockchain security; dynamic consent models; GINA legislation enforcement	(171)
Evidence	Lack of RCTs for every gene-drug pair	Adoption of Real-World Evidence (RWE) and pragmatic clinical trials	(164)

Description: A table of translational bottlenecks analysis which summarizes the translational bottlenecks

Health equity considers not only the health needs of individuals but also the social context of their lives as a whole and the social and ethical issues that may affect them. Human|>Ethical considerations and health equity 7.4 Ethical considerations and health equity Entails the consideration of both the health needs of individuals and the greater social context of their lives as well as the social and ethical matters which may affect their lives.

The development of precision medicine raises significant ethical concerns that should be addressed equally to ensure its credibility with the public.(171) The incidental findings problem or identification of high-risk variants (e.g., breast cancer 1 and 2 (BRCA1 and 2) or apolipoprotein E 4 (APOE4)), not related to the pharmacologic query of interest in the first place, requires strong methods of consent. (172) Patients should have a choice of being ignorant of these risks of secondary diseases and not lose access to the knowledge of pharmacogenomics. In addition, the risk of worsening the health disparities is high. (173) Genomic analysis has been done on people who are of European origin in the most significant numbers (174). The algorithms that were trained on this biased information could lead to falsification or even harm and can be problematic for the underrepresented minorities. (175) An instance to illustrate this dosing algorithms of warfarin was not specific to Africans, such as CYP2C95, 6, 8, 11, which has demonstrated a consistent overdosing effect on African Americans. (176) An essential ethical need is the recent diversification of biobanks and validation of biomarkers in all ancestries to make precision medicine equitable medicine. (177)

8. Future Directions: The Road Map To 2035

The action of pharmacotherapy progresses from reactive to preemptive to predictive. (178)

8.1 Pre-emptive Pharmacogenomics as Standard of Care

It is believed that by the year 2030, a pharmacogenomic panel will be a routinely performed lab test, just as the Complete Blood Count (CBC) or metabolic panel. (179) Ideally, such data would be generated once (possibly at birth or when a patient first goes to a hospital) and safely kept in the cloud to be accessed whenever a prescription is being written (180). This model has been demonstrated to be viable and

valuable in its operationalization in several health systems, including St. Jude Children's Research Hospital and the Mayo Clinic. (181)

8.2 Risk for Polygenic Risk Scores (PRS)

PGx is currently focused on monogenic high-impact variants. Polygenic Risk Scores (PRS) are the future of medicine because the response to drugs and disease risks are determined by thousands of common variants, each with a minor impact on the individual. (182) PRS has already been demonstrated to help assess response to statins and antidepressants and provides more granular stratification of patients than testing with individual genes. (183)

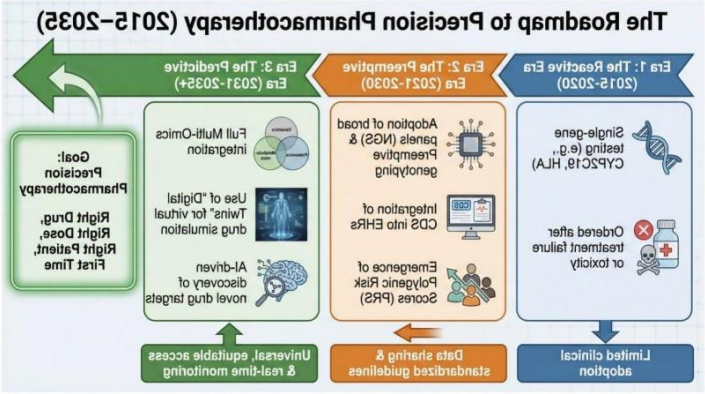


Figure 4: Road map to Precision Pharmacotherapy (2015 - 35)

Description: Timeline visualization with three different eras

- **Era 1 The Reactive Era (2015-2020):** It involves doing single gene testing (CYP2C19, HLA) in the instance of failure to treatment or toxicity to treatment.
- **Era 2 The Pre-emptive Era 2021-2030:** The usage of broad panels (NGS) and pre-emptive genotyping, Integration of CDS into EHRs. Polybrene name->Polygenic Risk Score Emergence.
- **Era 3 The Predictive Era (2031-2035 +):** Comprehensive integration of multi-omics (referring to the combination of Genomics, Proteomics, and Metabolomics). Application of Digital Twins in the Virtual Drug Discovery - AI-based Drug Discovery overcomes the challenge of finding drug targets.

Caption: Figure 4. Strategic plan for precision pharmacotherapy. The sphere is moving from a reactive, single-gene-based assay to a predictive, multi-omics-based ecosystem powered by artificial intelligence.

9. Conclusion

Precision pharmacotherapy is a radical reconceptualization of the medical contract: the replacement of treating the average patient with respect to the patient's biological specialisation. (184) Pharmacogenomics, multi-omics and liquid biopsy are giving important scientific teeth that can be used to unlock the mystery of human physiology. (185) This tsunami of data is being translated into some clinical intelligence that can be translated into clinical action with the integration of artificial intelligence. (186)

However, technology is not enough. (187) Breaking down research-practice silos require a concerted effort to do so successfully. (188) It entails investment in the IT infrastructures, an interest in learning the workforce, and a strict code of ethics that allows these developments to be advantageous to all populations equally. (189) With the elimination of such obstacles, the trial-and-error model of prescribing will be left to the past and a new evidence-based field where the right drug, in the correct dose gets to the right patient the first time around. (190) The future of medicine is not an esoteric series of personalizations, but it is specific. (191)

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