WHITE PAPER

Personalized Medicine: A Primer on the Role of Pharmacogenetics and Pharmacogenomics in Oncology

Advancing drug development safely and effectively with the use of genetic profiles

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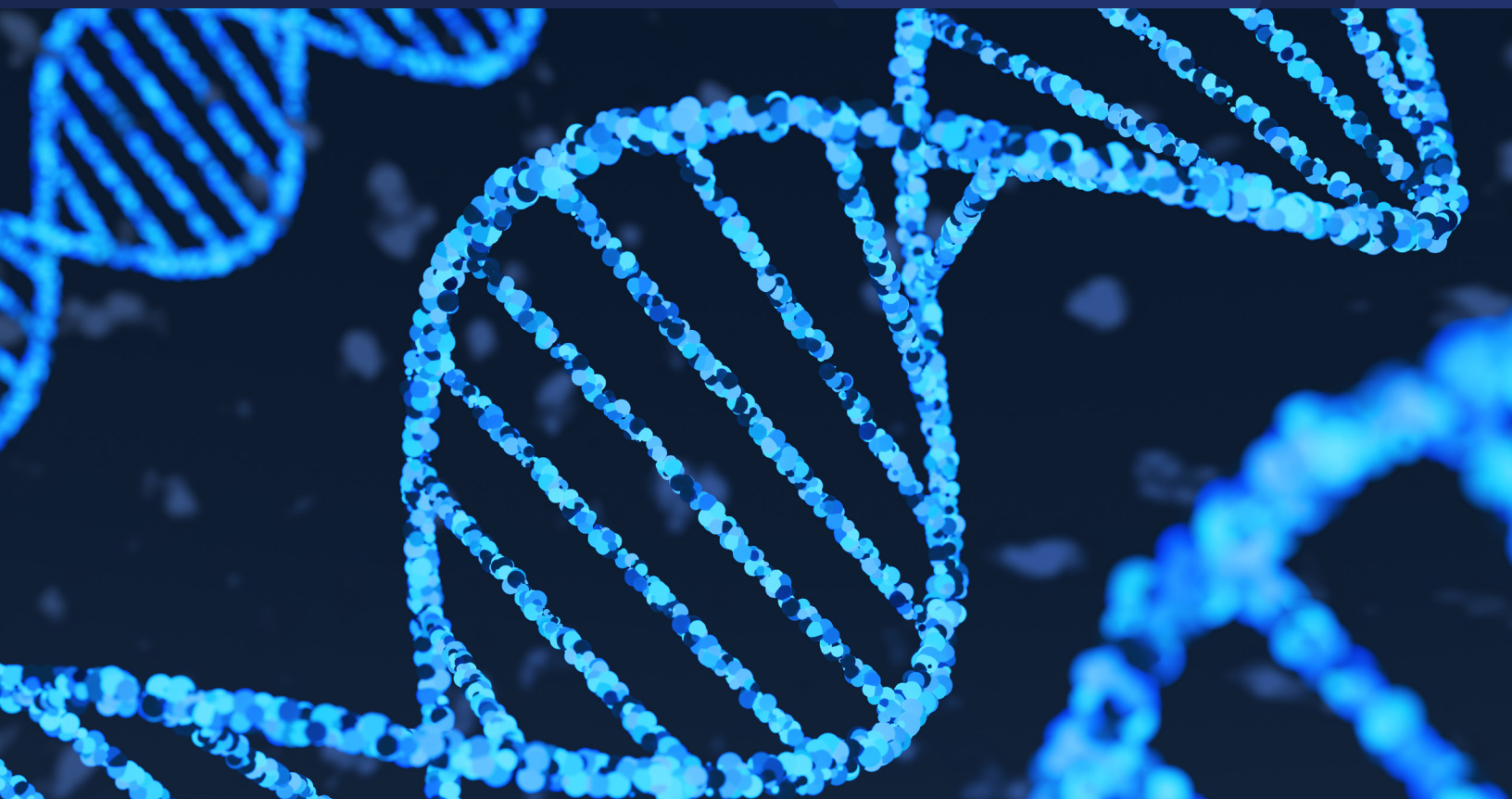

A Personalized Medicine Approach in Oncology

Adverse drug reactions (ADRs) are estimated to be the fourth leading cause of death in the United States[1]. A societal goal in the treatment of disease has always been to develop therapies with positive benefit-risk. With the conclusion of the Human Genome Project and later the International HapMap Project, scientists and physicians are now moving toward an understanding of how variations in human and tumor genetics can guide rational development of specific treatment targets and new drugs directed to these targets. Pharmacogenetics and pharmacogenomics, types of personalized medicine, have evolved from such advances, and have implications in the development of screening tools, diagnostics, and targeted therapies. Some of the more common cancers where personalized medicine is leveraged include colorectal, breast, lung, certain types of leukemia and lymphoma, melanoma, esophageal, stomach, ovarian, and thyroid[2].

Pharmacogenomic testing allows for identification of patients who are more likely to benefit from a therapy, as well as those who are prone to ADRs. There is currently a lot of attention around a recent multi-country European study, the PREPARE study, which demonstrated the utility of a 12-gene pharmacogenetic panel in reducing the incidence of ADRs[3]. The panel included DPYD, a widely recognized genetic marker that is associated with a higher risk of ADRs and death from fluoropyrimidines, common chemotherapy treatments for solid tumors[4].

This report will provide a primer on: 1) recent advances and applications of pharmacogenetics and pharmacogenomics in oncology and 2) the positive impact of pharmacogenetics and pharmacogenomics on drug development.

Definitions

Personalized Medicine is an emerging practice of medicine that uses an individual's genetic profile to guide decisions made regarding the prevention, diagnosis, and treatment of disease[5].

Pharmacogenetics is the study of how genes affect the way medicines work in a person and uses information from a person's genes to see how the body responds to a medicine[6].

Pharmacogenomics is the study of how genes affect a person's response to drugs. This field combines pharmacology (the science of drugs) and genomics (the study of genes and their functions) to develop effective, safe medications that can be prescribed based on a person's genetic makeup[7].

Recent Advances in Pharmacogenetics and Pharmacogenomics

MOLECULAR TARGETING IN DRUG DEVELOPMENT

Pharmacogenetics provides information on gene variations such as point mutations, duplication, and frame shifts. This can inform the development of specific small molecules (to inhibit signal transduction) or biologics that target cell surface receptors. As molecular targeting gains momentum, specific drugs for specific mutations are becoming more common, as seen with HER2/neu expression in breast cancer[8]. As more mutations are identified, it is becoming apparent that older drugs that did not prove effective in a general population may be useful in a subpopulation of patients with a specific genetic mutation[9-10].

DIAGNOSIS AND SCREENING

Some current screening tests lack the accuracy needed for a definitive diagnosis, including pap smears for cervical cancer, BRCA1/BRCA2 for breast cancer, prostate specific antigen (PSA) for prostate cancer, chest X-rays for lung cancer, and other biomarkers. With the advent of high throughput genetic screening (Next Generation Sequencing, NGS) and microarrays, more rapid, accurate, and specific results may be obtained. This may result in earlier and more accurate diagnosis, especially in those at higher risk for certain cancers based on their genetic profile.

TREATMENT AND BENEFIT/RISK ANALYSIS

Targeted drug therapy and immunotherapy are the two most common types of treatments used in precision medicine for oncology. For patients with some types of cancer, changes in certain genes or proteins may inform the use of targeted treatments at different stages of progression. Tests include biomarker testing, tumor subtyping, genomic testing/ profiling, molecular testing/ profiling, somatic testing, and NGS[11].

Mutations in genes that play a role in drug metabolism systems or cellular or nuclear transporter systems impact both pharmacokinetics (what the body does to the drug) and pharmacodynamics (what the drug does to the body) of the drug. Such mutations may result in a lack of efficacy or a serious ADR. The patient's genetics control these processes. Typically, however, drug development addresses potential drug-drug interactions with concomitant medications but not the patient's polymorphisms. Several drug metabolism systems are important, including the cytochrome P450 system (Table 1) where single nucleotide polymorphisms (SNPs) are common, and the glucuronyl system. Mutations in transport systems, such as the P-glycoprotein transport system (PgP), the organic anion transport system (OAT), and the nuclear karyopherin (importins-exportins) system, can lead to lack of efficacy by removal of the drug or severe adverse events by intracellular accumulation of the drug. Each patient has a myriad of polymorphic changes in all of these systems that can (and often do) adversely affect almost any type of therapy, especially oncology and psychiatric drugs.

Table 1. The Role of Cytochrome P450 System

DRUG	MOA	INDICATION	CYP	CONSIDERATIONS
Imatinib[12-13]	Tyrosine kinase inhibitor	Chronic myelogenous leukemia (CML)	CYP3A4	**DDI with 3A4 Inhibitors** (azole antifungals, simvastatin, verapamil, metoprolol, et. Al.) may increase imatinib to toxic levels **DDI with 3A4 Inducers** (rifampin, St. John's Wort, phenytoin, et. Al.) may rapidly metabolize imatinib, reducing effectiveness
Tacrolimus[12,14*]	Immuno-suppression	Prevent rejection of transplanted organs or bone marrow	CYP3A4	**DDI with 3A4 Inhibitors** may increase tacrolimus levels and increase toxicity **DDI with 3A4 Inducers** may decrease plasma levels of tacrolimus and risk organ rejection
TAMOXIFEN[12,15**]	Estrogen receptor inhibitor	Breast Cancer	CYP2D6	**DDI with 2D6 Inhibitors** may lead to sub-therapeutic plasma levels and treatment failure
Clopidogrel[16***]	Platelet inhibitor	Cardiovascular disease, cancers associated with thrombosis risk	CYP2C19	CYP2C19 mutants CYP2C19*2 and Cyp2C19*3, have been associated with failure to activate and lead to the patient's continued risk for coronary artery thrombosis and death.
CODEINE[12****]	Analgesia	Pain control	CYP2D6	Duplication of the gene coding for CYP2D6 results an estimated 50% increase in the plasma level of the active product morphine, resulting in severe adverse events
Metoclopramide[12]	Anti-emetic	Emesis	CYP2D6	At elevated plasma levels can lead to dystonic reactions in patients with homozygous mutations in CYP2D6

MOA = mechanism of action; DDI = drug-drug interaction

*Tacrolimus is also a substrate for the PgP and OAT transport systems and may act synergistically with CYP3A4 inducers to further reduce plasma levels of tacrolimus to subtherapeutic levels.

**Tamoxifen is metabolized by multiple cytochrome pathways, but CYP2D6 seems predominant. It is a prodrug that requires conversion by CYP2D6 to the active metabolite, endoxifen. Selective Serotonin Reuptake Inhibitors (SSRI) are potent CYP2D6 inhibitors that may lead to recurrent disease in breast cancer patients treated with both drugs.

***Clopidogrel is a prodrug activated by CYP2C19. Cyp2C19*17 is a rapid metabolizer of Clopidogrel.

****Codeine is metabolized by CYP2D6 to its active metabolite morphine

There are 18 families of enzymes within the cytochrome P450 system and 58 genes that produce 58 specific enzymes that are involved in the activation of prodrugs, detoxification of drugs as well as the metabolism of other native molecules such as fatty acids, especially polyunsaturated fatty acids, and steroids. Ultimately, six cytochromes metabolize 90% of drugs: CYP4A4/5, CYP2D6, CYP2C9, CYP2C19, CYP1A2, and CYP2E1. Examples are provided below of common oncology drugs metabolized by these six cytochromes, as well as drugs typically used in conjunction. with these oncology drugs to demonstrate the importance of concomitant medications.

Personalized Medicine – Better for the Patient. Better for the Future.

POSITIVE IMPACT ON NEW DRUG DEVELOPMENT

All cancers are caused by gene changes of some kind. Pharmacogenetics and pharmacogenomics are valuable tools in the pursuit of personalized medicine approaches in oncology, providing opportunities for faster diagnosis or targeted treatments. Knowing that a specific mutation occurs in a certain tumor cell surface receptor or in a signal transduction pathway molecule, the development of a safer, more efficacious drug can be pursued.

COMPELLING INFLUENCE ON PROTOCOL DESIGN AND EXECUTION

Genotyping to identify patients with a high potential for drug response may result in a smaller sample size to achieve statistical power. Inclusion of genotyping in protocol development to determine trial eligibility should also reduce time to trial completion and cost. Furthermore, exclusion of patients lacking the identified genotype reduces unnecessary risk to that group. Shorter trials could result in earlier approval by regulatory bodies.

SUBHEAD: PHARMACOGENOMICS AS A STANDARD OF CARE IN ONCOLOGY

Pharmacogenomics is transforming therapeutic practice. As more genetic biomarkers become available, the immense potential of genetic testing for prevention and screening is being recognized. This builds on current practice in treating cancer based genetic analysis of tumor cells. The recent attention given to pre-emptive testing for DPYD gene variants to guide treatment with fluoropyrimidines is a step in the right direction, demonstrating the role that pharmacogenomics can play in ensuring patient safety and optimizing benefit / risk, further supporting pharmacogenomic testing as a standard of care.

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About the Authors

DON A. GABRIEL, MD, PHD

Senior Director
Scientific Strategy and Medical Oncology

Expertise in the development of clinical and scientific strategies, helping to bring therapeutics to patients with high unmet needs.

JUDY LYTLE, PHD, MBEE, PMP

Executive Director
Evidence Development Study Solutions

Evidence generation strategies, powered by rigorous science, designed to demonstrate value

References

1. Siddiqui, MK, Luzum, J., Coenen, M., Mahmoudpour, SH. 2022. Editorial: Pharmacogenomics of Adverse Drug Reactions. Frontiers in Genetics. Vol. 13. https://www.frontiersin.org/articles/10.3389/fgene.2022.859909/full#:~:text=ADRs%20are%20estimated%20to%20be,Evaluation%20and%20Research%2C%202021)

2. American Cancer Society. Precision or Personalized Medicine. https://www.cancer.org/cancer/managing-cancer/treatment-types/precision-medicine.html. Accessed October 20, 2023.

3. Swen, JJ, van der Wouden, CH, Manson, L., Abdulllah-Koolmees, H., Balgec, K., Blagus, T., et al. (2023). A 12-gene pharmacogenetic panel to prevent adverse drug reactions: an open-label, multicentre, controlled, cluster-randomised crossover implementation study. The Lancet, 401(10374):347-356. DOI: https://doi.org/10.1016/S0140-6736(22)01841-4.

4. Miller, J. Association for Diagnostics and Laboratory Medicine (ADLM). 2023. Progress on Pharmacogenomics Becoming the Standard of Care. https://www.aacc.org/cln/articles/2023/june/progress-on-pharmacogenomics-becoming-the-standard-of-cancer-care. Accessed 10/26/2023.

5. National Institutes of Health (NIH) National Human Genome Research Institute (NHGRI). https://www.genome.gov/genetics-glossary/Personalized-Medicine. Accessed October 20, 2023.

6. National Institutes of Health (NIH) National Library of Medicine (NLM), Medline Plus. https://medlineplus.gov/ency/article/007794.htm. Accessed October 20, 2023.

7. National Institutes of Health (NIH) National Library of Medicine (NLM), Medline Plus. https://medlineplus.gov/genetics/understanding/genomicresearch/pharmacogenomics/. Accessed October 20, 2023.

8. Griffin, R, and Ramirez, RA. Molecular targets in Non-Small cell Lung Cancer. Ochner J. 2017. 17:388=392.

9. Buffery D. New Indication Approved by the FDA in 2018 for Oncology Drugs. 2019. Oncology Guide to FDA Approvals. Spring 2019. https://jhoponline.com/2019-fourth-annual-oncology-guide-to-new-fda-approvals/17769-new-indications-approved-by-the-fda-in-2018-for-oncology-drugs#:~:text=On%20December%2019%2C%202018%2C%20the,tube%2C%20or%20primary%20peritoneal%20cancer

10. US FDA. FDA Approves new and updated indications for Temozolomide under Project Renewal. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-new-and-updated-indications-temozolomide-under-project-renewal. Accessed October 26, 2023.

11. American Cancer Society. Precision or Personalized Medicine. https://www.cancer.org/cancer/managing-cancer/treatment-types/precision-medicine.html. Accessed 10/20/23.

12. McDonnell AM and Dang CH. Basic Review of the Cytochrome P450 System. J Adv Pract Oncol. 2013. 4(4):263-268. DOI: 10.6004/jadpro.2013.4.4.7

13. Filppula AM, Laitila J, Neuvonen PJ, and Blackman JT. Potent mechanism-based inhibition of CYP3A4 by Imatinib explains it liability to interact with CYP3A4 Substrates. Br. J Pharmacology. 2012. 165:2787-2798. DOI:10.1111/j.1476-5381.2011.01732.x

14. Xu Q, Yu Z, Hao Z et al. Metabolism and Transporter based drug-drug interaction of Tacrolimus with nine co-medication injections. Med in Drug Discovery 2021. 10:1-7. https://creativecommons.org/licenses/by-nc-nd/4.0

15. Singh M, Francis PA, and Michael M. Tamoxifen, cytochrome P450 genes and Breast Cancer Outcomes. The Breast. 2011. 20:111-118. DOI: 10.1016/j.breast.2010.11.003.

16. Rossi JS, Commarata M, Dharmavaram J, Weck K, Walko C, Gabriel D, Kuritzky J, Muldrew K, and Stouffer GA. Clopidogrel Dose Adjustment After Outpatient Screening for CYP2D19 Variant Alleles: a Pilot Study. Pharmacogenomics. 2014. 15(7):14-17. DOI: 10.2217/pgs.14.17.

contact@ubc.com
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