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# PHARMACOGENOMICS: PAVING THE WAY FOR THE EVOLUTION OF PRECISION MEDICINE

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## ABSTRACT

*In the recent years, there has been a radical shift from a 'one drug fits all' conventional approach to a personalized patient orientated approach. Pharmacogenomics (PGx), an integral part of Personalized Medicine (PM), is the analysis of how genetic factors can influence drug responses.[72] It considers the needs of each patient and provides customized therapeutic approaches.[47] While this scientific area originally focused on the correlation between drugs and single genes (pharmacogenetics), pharmacogenomics at present, subsumes information from the entire genome inclusive of germ line variation (single nucleotide polymorphisms (SNPs), gene copy number alterations) and acquired alterations (tumor mutations) as they associate with drug response or toxicity.[57] The potential of genomic evaluation as a fundamental element of Personalized Medicine is rapidly becoming a reality in many nations across the globe.[60] This article is all about the comprehensive review of the various advances in the field of personalized medicine with Pharmacogenomics at its cornerstone. It includes studies on identification of novel biomarkers, therapies based on the genetic profile of individual patients, better prognosis of chronic diseases like diabetes, TB, cardiovascular disorders, neoplasm's and pulmonary diseases, to detect a genetic predisposition to adverse drug reaction (ADR), to predict the susceptibility to disease onset among populations for attaining maximum efficacy and minimal toxicity, with the goal of improving the overall patient experience and reduction in health-care costs. Accordingly, utilizing large empirical data, bibliography, with authentic unstructured treatment designs, we extensively analyzed review on the Pharmacogenomic evidence, in several randomized, prospective, observational and multicenter studies and its association with Precision Medicine.*

***Key words:*** *Pharmacogenomics, biomarkers, precision medicine, drug response, ADR*

## INTRODUCTION:

Pharmacogenomics is the study of genetic components governing drug response or toxicity. The significance of knowing patients as individuals has been focused all through the history of medicine. **Sir William Osler** conceded that "it is considerably more critical to perceive what type of a patient has a disease than what kind of a disease a patient has".[45] The proclaimed objective of "personalized "or "precision" approaches is to accommodate individual disparity, as determined through genomic and numerous other biomarkers, implementing it to predict risk of disease or

response to treatment, to acquire the best clinical outcome for each human being and to customize interventions and design therapies so as to increase benefit and decrease risk for each patient and improve the effectiveness of the healthcare system.[59]A novel and extremely crucial characteristic of personalized medicine is the development of drugs targeting distinct mutated variants of endogenous proteins. By examining the mutated target with specific low molecular weight compounds, 'hits' can be detected that are able to refold proteins that were initially improperly folded as a consequence of inherited mutations.[62]The present notion of 'Personalized medicine' approach thus encompasses the conventional evaluation techniques, genotyping, and genomic assessment in estimating disease progression and treatment results.[61]The increasing evidence of pharmacogenomic data can now guide health care professionals to decide the safest and most efficacious supportive medications for an individual patient. "What links pharmacogenomics to specified treatment"- is its influence on the evolution of precision medicine as a field and how it confers to patient-specific, in place of symptom-specific patient outcomes.[53] Eventually, having pharmacogenomic data at the place of care has significant suggestions for preventative medication management, all through the treatment course which can be consolidated to personalize therapy.[72]

## DISCUSSION:

Precision medicine depends on how an individual's distinct molecular form effects their susceptibility to disease and reaction to medical treatment. It involves the use of clinical evidences corresponding to the patient along with their multi-omics/genomic data to arrive at an outcome regarding how a medical practitioner should continue with a definitive treatment. In comparison to the symptom-directed avenue in medicine, precision medicine acknowledges the captious fact that all patients do not respond to the same treatment or medication in the same way [54]. Pharmacogenomics (PGx), an integral part of personalized medicine (PM), is the analysis of how genetic factors can influence drug responses,[72]Used in concert, patient and disease-specific biomarkers can lead to a more accurate stratification of patients into distinguishable response/risk groups, allowing more suitable drug prescription and more precise dose selection [66].A pharmacogenetic or pharmacogenomic biomarker is characterized as any "genetic or genomic marker that is linked to drug response. Contrary to disease genetics, pharmacogenomics concentrates particularly on predictive genetic markers of outcome from pharmacologic intercessions.

The conclusive aim of personalized medicine is to authorize physicians to prescribe the right medicine to the right patient at the right time with the highest efficacy and lowest toxicity, [59] or to assume the sensitivity to disease onset between populations in advance. To attain these objectives, substantial attempts have been made to equate drug responses with host genetic polymorphisms, i.e., pharmacogenomics.

Table I and II provides a concise, evidence-based observation on the role of pharmacogenomics in the evolution of precision medicine.

| *Author, Place, Journal, Year,* | **Study design, Sample size** | **Therapeutic Area (Disease, Drug)** | **AIM OF THE STUDY** | **CONCLUSIONS** |
|---|---|---|---|---|
| ***Notarangelo et al, USA, Journal of the American college of cardiology vol. 71, no. 17, (2018)*** | Prospective, Randomized, Multicenter Study, 888 patients. | Acute coronary syndrome, Clopidogrel, prasugrel, ticagrelor | To assess whether selecting antiplatelet therapy (clopidogrel, prasugrel, or ticagrelor) based on a patient's genetic and clinical features leads to superior clinical endpoints in contrast to the standard of care. | An individualized perspective in selecting antiplatelet therapy for patients with ACS may lower ischemic and bleeding episodes. |
| ***Russmann et al, Switzerland, European Journal of Clinical Pharmacology 77:709–716, (2021)*** | Multivariate case-control analysis, 56 patients. | Cardiovascular, Clopidogrel | To analyze the relationship of repeated ischemic episodes under clopidogrel with CYP2C19 loss of function (LoF) variants and other components in patients that underwent PGx testing. | PGx-aimed clopidogrel therapy can recognize patients with an increased risk of ischemic incidences and provide authentic alternative treatments. |
| ***M.C. Etienne Grimaldi et al, England, Br J Clin Pharmacol /73:5 / 776–785, (2011)*** | A Prospective study, 52 patients. | Oncology, Cetuximab, Fluoropyrimidine | To inspect the predictive value of gene polymorphisms likely related to toxicity, clinical response, time to progression and universal survival, following cetuximab–tegafur-uracil (UFT)–irinotecan therapy. | Current data indicate the significance of *FCGR3A* 158Phe>Val and *TYMS* 5′ UTR polymorphisms in receptiveness and survival of patients obtaining cetuximab–fluoropyrimidine-based therapy. |
| ***Wellmann et al, USA, Cancer.124(14): 3052–3065, (2018)*** | Systemic Review, 125 Oncology drugs. | Oncology | To postulate that a critical number of clinically applicable germline pharmacogenomic associations exist, illustrating clinical implementation advancements. | A number of oncology drugs have practicable germline pharmacogenomic data, justifying delivery through conventional pharmacogenomic implementations, to determine clinical usefulness |

| *Author, Place Journal, Year* | **Study design, Sample size** | **Therapeutic Area (Disease, Drug)** | **AIM OF THE STUDY** | **CONCLUSIONS** |
|---|---|---|---|---|
| ***Amber Dahlin, USA, PLOS ONE, (2015)*** | Genome-wide association study (GWAS), Twenty-eight SNP associations. | Asthma, Leukotriene receptor antagonists (LTRA), Montelukast | To recognize novel pharmacogenetic single nucleotide polymorphisms (SNPs) corelated with the response to the Leukotriene receptor antagonists (LTRA), montelukast, in asthma patients. | Via GWAS, a novel pharmacogenomic locus associated with enhanced montelukast effect in asthmatics was recognized. |
| ***Kho AT et al, USA, Thorax; 77:452–460, (2021)*** | Unsupervised (without a prior clinical criteria) principal component analysis, 19 subjects. | Asthma, Corticosteroids | To expand the notion of molecular endotype recognition in asthma in novel directions through RNA-sequencing (RNA-seq) of sputum airway cells. | Transcriptomic PCs from this unsupervised procedure describes molecular pharmacogenomic endotypes that may yield novel biologic underlying distinct subject-specific effects of corticosteroid therapy in asthma, and optimum personalized asthma care. |
| ***Jung et al, Korea, Dove press:9 5433–5438 (2015)*** | A Prospective pilot study, 206 patients. | Tuberculosis (TB), Isoniazid (INH) | To design a personalized Isoniazid (INH) dosing procedure using a pharmacogenetic-guided model and to employ this regimen in a pilot study. | The use of personalized pharmacogenetic-driven INH dosage regimens that include *NAT2* genotype and body weight may assist to guarantee attainment of therapeutic concentrations of INH in the TB patients. |
| ***Habeb et al, Saudi Arabia, Diabetologia 61:1027–1036, (2018)*** | Cohort-Observational study, 32 individuals | Diabetes, Thiamine (vitamin B1) | To inquire the genotype, phenotype and reaction to thiamine (vitamin B1) in a cohort of individuals with thiamine-responsive megaloblastic anemia (TRMA) -related diabetes. | In TRMA syndrome, diabetes can be asymptomatic and occur prior to the emergence of other attributes. Rapid identification is necessary as early treatment with thiamine can lead to enhanced glycemic control, with some individuals becoming insulin-independent. |

## Pharmacogenomics of Blood thinners :

**Nutescu et al**[5] supervised a prospective observational study to find out the systemic practicability of a pharmacist-driven integrative service for furnishing genotype-guided warfarin dosing for hospitalized patients newly initiating warfarin. Eighty patients were started on warfarin and governed by a newly applied pharmacogenetics program in a 483-bed hospital, federated with a large academic institution. They notably found that of 436 genotype orders throughout the initial 6 months of the service, 190 were judged to be appropriate. For 80 patients on the service who agreed to data collection, 77% of genotypes were accessible prior to the second warfarin dose. Seventy-three percent of warfarin doses recommended by the healthcare

staff were within 0.5 mg of the dose proposed by the pharmacogenetics consult program. They concluded that providing a routine genotype-guided warfarin regimen assisted by a pharmacogenetics consult facility is suitable from a methodological viewpoint, with most of the genotypes accessible prior to the second warfarin dose and excellent compliance to genotype-guided dose suggested by the healthcare staff.

**Notarangelo et al** [9] conducted a prospective, randomized, multicenter study to assess whether selecting antiplatelet therapy (clopidogrel, prasugrel, or ticagrelor) based on a patient's genetic and clinical features leads to superior clinical outcomes in contrast to the standard of care, which bases the selection on clinical attributes alone. Patients hospitalized for acute coronary syndrome (ACS) were arbitrarily designated to standard of care or the pharmacogenomic arm, which incorporated the genotyping of ABCB1, CYP2C19*2, and CYP2C19*17 using an ST Q3 structure that yields data within 70 min at each patient's bedside. The patients were investigated for 12 ± 1 month for the chief composite endpoint of cardiovascular death and the primary incident of nonfatal myocardial infarction, nonfatal stroke, and major bleeding. After enrolling 888 patients, the study was untimely ceased. They observed that Clopidogrel was used more routinely in the standard-of-care arm (50.7% vs. 43.3%), ticagrelor in the pharmacogenomic arm (42.6% vs. 32.7%; p ¼ 0.02), and prasugrel was uniformly used in both arms. The primary endpoint appeared in 71 patients (15.9%) in the pharmacogenomic arm and in 114 (25.9%) in the standard-of-care arm (hazard ratio: 0.58; 95% confidence interval: 0.43 to 0.78; $p < 0.001$). They concluded that an individualized perspective in selecting antiplatelet therapy for patients with ACS may decrease ischemic and bleeding episodes.

**Russmann, S et al** [6] carried out a multivariate case-control analysis to evaluate the relationship of repeated ischemic episodes under clopidogrel with CYP2C19 loss of function (LoF) variants and other components in patients that went through PGx testing for clopidogrel therapy at two Swiss hospitals. Amidst 56 patients that underwent PGx testing, 18 (32.1%) were categorized as CYP2C19 intermediate or poor metabolizers. This led to 17 proposals for a change of antiplatelet therapy, which were administered in 12 patients (70.1%). Repeated ischemic episodes under clopidogrel were corelated with LoF variants (OR 2.2, 95% CI 0.3–14.4) and numerous cardiovascular risk factors. They found that the associations were not mathematically notable in their small study, but credible and in line with estimates from large prospective studies and concluded that a PGx-led clopidogrel therapy can recognize patients with an increased risk of ischemic incidences and provide authentic alternative treatments.

## Pharmacogenomics in Oncology

**M.C. Etienne-Grimaldi et al**[11] conducted a prospective study on advanced colorectal cancer patients to inspect the predictive value of gene polymorphisms likely related to toxicity, clinical response, time to progression and universal survival, following cetuximab–tegafur-uracil (UFT)–irinotecan therapy. 52 patients with end stage colorectal cancer were registered in an auxiliary pharmacogenetic study of the phase II CETUFTIRI trial. Treatment comprised of 21-

daycycles of cetuximab (day 1–day 8–day 15, 250 mgm-2 week-1 ensuing a 400 mgm-2 primary dose) in conjunction with irinotecan (day 1, 250 mgm-2) and UFT–folinic acid (days1–14, 250 mgm-2 day-1 UFT, 90mg day-1 folinic acid). Examined gene polymorphisms (blood DNA) were hence observed: *EGFR* (CA repeats in intron 1, –216G>T, -191C>A), *EGF* (61A>G), *FCGR2A* (131Arg>His), *FCGR3A* (158Phe>Val), *UDP-glycosyltransferase1-polypeptide A1* (TA repeats), *TYMS* (28 bp repeats, together with the G>C mutation on the3R allele, 6 bp deletion in 3′ UTR) and *MTHFR* (677C>T, 1298A>C). They notably found that increased toxicity grade was related to *EGFR* -191C>A polymorphism, with 71.1% type 3–4 toxicity in CC patients *vs.* 28.6% in other patients ($P$ = 0.010). A disposition to a superior response was perceived in patients posing the *TYMS* 3RG allele ($P$ = 0.029) and those posing the *FCGR3A* 158Val genotype ($P$ = 0.020). The larger the score of appropriate *TYMS* and *FCGR3A* genotypes, the preferable the response level ($P$ = 0.009) and more prolonged the universal survival ($P$ = 0.007) and in a multivariate analysis, the score of suitable genotypes was a powerful survival estimator than the performance degree. They concluded that the current data indicate the significance of *FCGR3A* 158Phe>Val and *TYMS* 5′ UTR polymorphisms in receptiveness and survival of patients obtaining cetuximab–fluoropyrimidine-based therapy.

**Wellmann et al**[12] analyzed 125 oncology drugs for conclusive germline pharmacogenomic relations in journals with impact factors ≥5 to postulate that a critical number of clinically applicable germline pharmacogenomics associations exist, illustrating clinical implementation advancements. Studies were evaluated for patterns and genotyping standards, clinically-pertinent endpoints, statistical accuracy, and proof of drug-gene outcome. They recognized the germline pharmacogenomic outcomes for 56/125 (45%) oncology drugs across 173 publications. Applicable correlations were identified for 12 drugs, including six with germline pharmacogenomic data within FDA labels or published guidelines (capecitabine/fluorouracil/DPYD, irinotecan/UGT1A1, mercaptopurine/thioguanine/TPMT, tamoxifen/CYP2D6), while six more were novel (asparaginase/NFACT2/HLA-DRB1, cisplatin/ACYP2, doxorubicin/ABCC2/RAC2, lapatinib/HLA-DQA1, sunitinib/CYP3A5, vincristine/CEP72). Using AGREE II, evolved CDS synopsis had elevated scores (mean ± standard deviation [SD]; highest score=100) for Scope and Objective (92.7 ± 5.1) and precision of Advancement (87.6 ± 7.4) and median, still strong scores for Transparency of Demonstration (58.6 ± 25.1) and Relevancy (55.9 ± 24.6). Universal mean guideline standard score was 5.2 ± 1.0 (highest score=7). Germline pharmacogenomic CDS synopsis for these 12 drugs were approved for execution. They concluded that a number of oncology drugs have practicable germline pharmacogenomic data, justifying delivery through conventional pharmacogenomic implementations, to determine clinical usefulness.

## Pharmacogenomics in Asthma

**Amber Dahlin et al**[1] carried out a Genome-wide association study (GWAS) to recognize novel SNPs corelated with the response to the Leukotriene receptor antagonists (LTRA), montelukast, in asthmatics. They utilized genome-wide genotype and phenotypic information

accessible from American Lung Association - Asthma Clinical Research Center (ALA-ACRC) cohorts, and estimated 8-week change in FEV1 associated to montelukast management in a discovery population of 133 asthmatics. The peak 200 SNPs from the discovery GWAS were then examine in 184 ancillary samples from two individualistic cohorts. They notice that Twenty-eight SNP correlations from the discovery GWAS were duplicated. Of these, rs6475448 accomplished genome-wide importance (combined P = 1.97 x 10-09), and patients from all four studies who were homozygous for rs6475448 exhibited elevated ΔFEV1from baseline in response to montelukast. From the given data they notably identified a novel pharmacogenomic locus associated with enhanced montelukast effect in asthmatics.

**Alvin T Kho et al**[2] applied unsupervised (without a priori clinical criteria) principal component analysis on sputum airway cells RNA-sequencing transcriptomic data from 19 asthmatics from the Severe Asthma Research Program, to expand the notion of molecular endotype recognition in asthma in novel directions through RNA-sequencing (RNA-seq) of sputum airway cells at baseline and 6–8 weeks follow-up after a 40mg dose of intramuscular corticosteroids. They explored principal components PC1, PC3 for relationship with 55 clinical determinants. They observed that PC3 was linked with baseline Th2 clinical element's including blood (rank-sum p=0.0082) and airway (rank-sum p=0.0024) eosinophilia, FEV1 change (Kendall tau-b R=−0.333 (−0.592 to −0.012)) and follow-up FEV1 albuterol effect (Kendall tau-b R=0.392 (0.079 to 0.634)). PC1 with blood basophilia (rank-sum p=0.0191). The initial 5% genes supplying to PC1, PC3 were enhanced for definite immune system/inflammation ideologies insinuating marked subject-specific groups of transcriptomic response to corticosteroids. PC3 association with FEV1 change was reproduced in silico in a comparable independent 14-subject (baseline, 8 weeks after routinely inhaled corticosteroids (ICS)) airway epithelial cells microRNAome dataset. They concluded that Transcriptomic PCs from this unsupervised procedure describes molecular pharmacogenomic endotypes that may yield novel biologic underlying distinct subject-specific effects of corticosteroid therapy in asthma, and optimum personalized asthma care.

## Pharmacogenomics in other Diseases (TB, Diabetes)

**Jung et al**[17] performed a prospective study to design a personalized Isoniazid (INH) dosing procedure using a pharmacogenetic-guided model and to employ this regimen in a pilot study. A sum of 206 patients with TB who acquired anti-TB therapy were incorporated in this prospective study. By using polymerase chain reaction and sequencing, the 2-hour post-dose concentrations of INH were attained, and their NAT2 genotype was discovered. A multivariate regression examination that involved the components of age, sex, body weight, and NAT2 genotype was implemented to assess the greatest model for evaluating the INH dose that a concentration of 3.0–6.0 mg/L. This dosing algorithm was then used for newly enlisted 53 patients. They observed that the Serum concentrations of INH were remarkably lower in the fast acting-acetylators than in the slow-acetylators (2.55 mg/L vs 6.78 mg/L, median, P<0.001). A multivariate gradual linear retrogression study disclosed that NAT2 and body weight separately affected INH concentrations: INH concentration (mg/L) =13.821-0.1× (body weight, kg)

−2.273× (number of high activity alleles of NAT2; 0, 1, 2). In 53 newly enlisted patients, the prevalence at which they were within the therapeutic level of 3.0–6.0 mg/L was increased in the model-based treatment batch in contrast to the standard treatment batch (80.8% vs 59.3%). Hence it was concluded that the use of personalized pharmacogenetic-driven INH dosage regimens that include *NAT2* genotype and body weight may assist to guarantee attainment of therapeutic concentrations of INH in the TB patients.

**Abdelhadi M. Habeb et al**[18] conducted an observational study, to inquire the genotype, phenotype and reaction to thiamine (vitamin B1) in a cohort of individuals with thiamine-responsive megaloblastic anemia (TRMA) -related diabetes. They investigated 32 individuals with biallelic SLC19A2 mutations recognized by Sanger or next generation sequencing. Clinical characteristics were gathered by a follow-up questionnaire. They recognize 24 distinct mutations, of which nine were novel. The onset of the initial TRMA symptom ranked from birth to 4 years (average 6 months [interquartile range, IQR 3–24]) and average age at diabetes onset was 10 months (IQR 5–27). At demonstration, three individuals had underling diabetes and 12 had asymptomatic hyperglycemia. Follow-up data was obtainable for 15 individuals treated with thiamine for an average of 4.7 years (IQR 3–10). Four patients were able to ceased insulin and seven attained superior glycemic control on lower insulin doses. These 11 patients were notably younger at diabetes diagnosis ($p = 0.042$), at genetic testing ($p = 0.01$) and when beginning thiamine ($p = 0.007$) contrast with the rest of the cohort. All patients became transfusion-independent when treated with thiamine. They concluded that, In TRMA syndrome, diabetes can be asymptomatic and occur prior to the emergence of other attributes. Rapid identification is necessary as early treatment with thiamine can lead to enhanced glycemic control, with some individuals becoming insulin-independent.

## CONCLUSION:

We have reviewed thoroughly all the above-mentioned articles, and have reached the conclusion of the clear importance of pharmacogenomics in the development of precision medicine. Most of the researches, observational studies, randomized clinical trials proved a distinct enhancement in the patient's therapeutic outcomes with the implementation of pharmacogenomic driven personalized therapy. However, some studies were inconclusive, or did not provide significant improvement in therapeutic regimen and hence should be taken into consideration to develop better medicinal approaches. Ongoing research is essential to continue to advance the field of PGx and to generate the necessary data to allow for its widespread clinical implementation. Pharmacogenetic investigation has shed light on the possibilities and power from the knowledge of just a few genes that influence the metabolism of many drugs. As these data grow, seemingly exponentially, with ever-cheaper analytic technology, it will soon be the standard of care to perform routine pharmacogenomic testing on all patients with disease prior to treatment.

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