



## UNRAVELING PRECISION MEDICINE: A PHARMACOGENOMIC PERSPECTIVE OF ANTI-TUBERCULAR THERAPY - A NARRATIVE REVIEW

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### ABSTRACT

Tuberculosis (TB) treatment has undergone an evolutionary shift with the advent of precision medicine, which provides individualized treatment plans based on patient characteristics, including genetics. Precision medicine's cornerstone, pharmacogenomics, clarifies the impact of genetic variations on anti-TB medication response and informs customized treatment plans. The concepts of precision medicine in anti-TB medication are examined in this review, with particular attention to the contribution of pharmacogenomics to treatment outcome optimization and reduction of side effects. Important genetic variations that impact medication metabolism are covered, along with how they may affect customized tuberculosis therapy. These variations include those in the NAT2, CYP2E1, GSTM1, GSTT1, and ABCB1 genes. This study seeks to demonstrate precision medicine's potential to transform tuberculosis therapy and improve patient outcomes by dissecting its intricacies.

**KEYWORDS:** Tuberculosis, Precision Medicine, Pharmacogenomics, NAT2.

### INTRODUCTION

As a major worldwide health concern, tuberculosis (TB) requires novel strategies to enhance treatment results and counter medication resistance. Precision medicine has become a promising method in tuberculosis treatment because it offers individualized treatment plans that are based on the unique characteristics of each patient. With the goal of optimizing treatment results by taking into account unique patient features like as genetic variables, microbial genomes, and host immunological responses, precision medicine offers a customized approach to tuberculosis therapy. Pharmacogenomics studies the effects of genetic variants on medication responsiveness, allowing for individualized dosage schedules that maximize effectiveness and reduce side effects. Researchers and healthcare professionals will gain insight into the possibility of tailored methods to improve treatment results for tuberculosis and support international efforts to control the disease by learning about the role of precision medicine in tuberculosis.<sup>[1,2,3]</sup>

About 25% of people worldwide are thought to be infected with *Mycobacterium tuberculosis*, the primary cause of tuberculosis (TB) illness. Approximately 10% of this total will progress to active TB, while the remaining 90% will acquire non-communicable tuberculosis. Based on statistics released by the World Health Organization (WHO) in 2022, 10.6 million

persons worldwide are predicted to have contracted TB in 2021, leading to 1.6 million fatalities. These figures demonstrate how common TB is in low- and middle-income nations, where 98% of cases are recorded. Only COVID-19, which will exceed HIV/AIDS in 2020, will cause more fatalities from a single infectious agent than tuberculosis (TB), which is now the 13th most common cause of death worldwide.<sup>[4,5]</sup>

For patients with drug-susceptible strains of tuberculosis, standard short-course chemotherapy regimens containing isoniazid, rifampicin, pyrazinamide, and ethambutol can achieve cure rates >95%; a small percentage of patients, however, do not respond to treatment or experience serious adverse events.

The two main medications used to treat TB are RF and INH. Treatment may need to be halted owing to severe side effects, or it may be extended for a further six to nine months depending on the mycobacteria's resistance to the medications or the unpleasant reaction they induce. Since the dosage or PK of the medications affects their effectiveness and early antibacterial action, differences in the PK of INH and RF have an impact on the clinical outcome of tuberculosis treatment. Along with the positive results, INH therapy can have a number of negative consequences, the most notable of which are peripheral neuropathy and hepatotoxicity.<sup>[6,7]</sup>

### Pharmacogenomics

Over the past 20 years, pharmacogenomics—the study of the genetically determined molecular underpinnings of pharmacological treatment outcomes—has taken shape. At the forefront of the field of precision medicine is pharmacogenomics, which combines genomics and pharmacology to tailor medicinal interventions to each patient's specific genetic profile. Pharmacogenomics holds great potential for improving treatment effectiveness, minimizing adverse medication responses, and optimizing drug therapy. Healthcare professionals can choose drugs and doses that are most appropriate for a patient's genetic profile by knowing the genetic variants that affect drug metabolism, transport, and mechanisms of action.<sup>[8,9]</sup>

Pharmacogenomics is a just beginning difficult science with little present clinical value or applicability, but its influence is expanding quickly thanks to US Food and Drug Administration (FDA) approvals of biomarker-based tailored therapies. Significant obstacles stand in the way of the practical implementation of pharmacogenomics, including real-world validation, underlying bias in healthcare, and unclear validity across ethnic groups. The Pharmacogenomic Clinical Decision Support System (PGx-CDS), a recent advancement in the application of pharmacogenomics in personalized care, has been essential in reducing complexity and empowering physicians to make knowledgeable medication decisions based on patients' genetic profiles. Clinical pharmacogenomics implementation is becoming more and more important, and recommendations for incorporating pharmacogenomic data into clinical decision support (CDS) and electronic health records (EHRs) are being developed.<sup>[10]</sup>

The two main categories of treatment outcomes are toxicity and effectiveness. It is known that different people react differently to the same medications. These variations are greater between members of the same population than between members of the same person at various points in time. The existence of large population variances accompanied by small within-subject variability explains the role of inheritance in determining medication response. Sequence variants in genes coding for drug-metabolizing enzymes, drug transporters, or targets are known to cause interindividual variations in drug response; however, genetic factors account for only about 20% to 95% of variations in drug pharmacokinetics and effects. Medication effects can also be influenced by nongenetic variables, including age, organ function, concurrent therapy, nutritional condition, medication interactions, and illness type. On the other hand, genetic factors don't change during the course of a person's life.<sup>[11,12]</sup>

Numerous predictive sciences have emerged as a result of technological innovation and advances in the biomedical sciences. Among the novel prediction sciences that have resulted from the information gleaned

from biomedical research are pharmacogenetics and pharmacogenomics. These disciplines' study may hold the key to a significant advancement in individualized care. It is essential to comprehend how medications behave and end up in the body, or their PK and pharmacodynamics, which encompass both positive and negative therapeutic effects. Drug transport, metabolism, potency, and detoxification are all governed by intricate mechanisms that include most proteins, which are encoded by a wide range of genes. These processes also impact the PK and pharmacodynamics of medicines.

Enzymes encoded by mutant or polymorphic genes determine metabolic activities, drug affinity for its receptor, and effectiveness. These changes might affect an individual's or some ethnic group's pharmacological response within a community. The most well-known kind of genetic variations are single-nucleotide polymorphisms (SNPs), which are mostly caused by the replacement of a single base pair. Research has shown that differences in PK vulnerability to drugs across individuals might explain certain unfavorable outcomes, even for patients who do not skip doses. This has called into question the widely held belief that inadequate adherence is the main cause of treatment failure, recurrence, and the development of antibiotic resistance.<sup>[13,14]</sup>

### Significance of Pharmacogenomics

Effective treatment tactics are greatly aided by pharmacogenomics analysis, which customises drug regimens for each patient according to their genetic profiles.

**Enhancing medication Selection:** Genetic differences influencing medication metabolism, effectiveness, and toxicity can be found by pharmacogenomics study. Clinicians can select the best treatment from the start by looking at a patient's genetic composition, taking into account variables like expected response and risk of side effects. This individualized strategy reduces the possibility of negative medication responses while optimizing the effectiveness of treatment.

**Personalized Dosage Plans:** Genetic differences can affect how quickly drugs are metabolized, which can change how much of a medicine is in the body. Physicians can tailor dose regimens to the unique genetic profiles of their patients with the use of pharmacogenomics analysis.

**Anticipating Treatment Reaction:** Pharmacogenomics investigation offers information on a patient's propensity to react to particular drugs. Clinicians can anticipate which patients are more likely to benefit from a specific medication and modify their therapeutic strategy appropriately by discovering genetic markers linked to drug response. This predictive capacity enhances the choice of treatments and raises patient outcomes generally.

**Reducing harmful Drug responses:** An individual's sensitivity to harmful drug responses is mostly influenced by hereditary factors. Based on their genetic profiles, pharmacogenomics analysis assists in identifying individuals who are more likely to experience adverse responses. Clinicians can proactively avoid drugs that may cause damage and choose alternative therapies that the patient will tolerate better by screening for genetic variations linked to drug toxicity.

**Directing therapy Modifications:** Based on a patient's changing genetic profile and response to therapy, pharmacogenomics analysis can direct treatment modifications over the duration of the course of treatment. By tracking changes in genetic markers over time, clinicians may make well-informed judgments on the modification of pharmaceutical regimens to maximize efficacy and reduce side effects.

**Improving individualized Treatment:** The foundation of personalized medicine is pharmacogenomics analysis, which enables customized treatment plans based on the distinct genetic composition of each patient. Healthcare professionals may give patients with more targeted and efficient medicines, which will eventually improve patient outcomes and quality of life, by incorporating pharmacogenomics data into clinical decision-making.<sup>[15,16]</sup>

#### Pharmacogenomics and Tuberculosis

Pharmacogenomics clarifies how genetic variants affect medication metabolism and treatment results, which is crucial in determining how the body reacts to anti-TB therapy. Variants in important genes including NAT2, CYP2E1, GSTM1, GSTT1, and ABCB1 affect how anti-TB medications like isoniazid and rifampicin are metabolized.

Comprehending these hereditary variables allows customized dosage schedules, enhancing therapeutic results while reducing unfavorable responses. Healthcare professionals can improve efficacy and lower the risk of drug resistance by customizing TB therapy for each patient by incorporating pharmacogenomic findings into clinical practice.<sup>[17,18]</sup>

#### Gene Variants Impacting Anti-Tubercular Medications

##### 1. NAT2 Gene Polymorphisms

N-acetyltransferase 2, an enzyme essential to the metabolism of isoniazid (INH), a mainstay of conventional tuberculosis treatment, is encoded by the NAT2 gene. Different acetylation phenotypes, such as slow, moderate, and fast acetylators, are caused by genetic variations in NAT2. INH is metabolized more slowly by slow acetylators, which raises plasma concentrations and increases the risk of hepatotoxicity. However, quick acetylators could have inadequate medication levels, which would reduce the effectiveness of therapy. Comprehending a patient's NAT2 acetylator

status can help tailor dosage schedules to strike a balance between safety and effectiveness.<sup>[19]</sup>

##### 2. CYP2E1 Gene Variants

Another enzyme involved in INH metabolism is cytochrome P450 2E1 (CYP2E1), which is especially important in the creation of hazardous intermediates linked to hepatotoxicity. Changes in the CYP2E1 gene can impact the risk of liver damage and INH clearance by changing the activity of the enzyme. A person's susceptibility to INH-induced hepatotoxicity may be determined by certain genetic polymorphisms, which emphasizes the need of genotype-guided treatment in reducing adverse drug effects.<sup>[20]</sup>

##### 3. GSTM1 and GSTT1 Deletion Polymorphisms

Enzymes involved in phase II detoxification, glutathione S-transferases (GSTs) are involved in the metabolism of reactive drug intermediates. The absence of functional enzyme activity caused by null deletion polymorphisms in the GSTM1 and GSTT1 genes may increase vulnerability to the toxicity caused by anti-tubercular drugs. To reduce the likelihood of adverse effects, patients with homozygous deletions of GSTM1 and GSTT1 may need more frequent monitoring and individualized dose regimens.<sup>[21]</sup>

##### 4. ABCB1 Gene Variants

P-glycoprotein, a drug transporter implicated in the efflux of several medications, including rifampicin (RIF), is encoded by the ABCB1 gene. Variations in the ABCB1 gene can affect the pharmacokinetics of RIF, resulting in differences in the drug's clearance and effectiveness. By knowing how RIF metabolism is affected by ABCB1 polymorphisms, treatment plans may be optimized to guarantee appropriate drug exposure and therapeutic response.<sup>[22]</sup>

Genetic variations have a major impact on how each patient responds to anti-tubercular medication therapy. Pharmacogenomic insights provide useful direction for individualized treatment strategies, enabling physicians to customize regimens according to a patient's genetic profile.

Healthcare professionals can increase treatment results and reduce the chance of adverse reactions in tuberculosis patients by taking genetic characteristics that affect medication metabolism and efficacy into account. The use of pharmacogenomics to clinical practice has the potential to transform tuberculosis therapy and enhance individualized patient care.<sup>[23]</sup>

#### Pharmacogenomics' Clinical Implications in Tb Therapy

**Individualized Dosing Techniques:** Patients who are more likely to experience negative medication responses or treatment failure can be identified by pharmacogenomic testing. Treatment results for tuberculosis patients are improved by personalized

dosage regimens that enhance medication efficacy while avoiding toxicity, thanks to specific genetic profiles.

**Risk Assessment and Avoidance:** In the treatment of tuberculosis, genotype-guided therapy makes risk prediction and preventative measures easier. Doctors can limit adverse effects by proactively monitoring patients with genetic variations linked to drug-induced toxicity and taking preventative interventions.

**Therapy Modification in medication-Resistant Tuberculosis:** Given the scarcity of treatment choices and the high risk of medication toxicity associated with this condition, pharmacogenomics is especially important in the management of drug-resistant tuberculosis. therapy results are improved and the likelihood of side effects is decreased in tuberculosis patients using personalized therapy techniques based on genetic characteristics.<sup>[24,25]</sup>

### Challenges and Future Directions

**Standardizing testing for genes:** The broad use of pharmacogenomic-guided medication in tuberculosis treatment requires standardization of genetic testing techniques and result interpretation. To guarantee the accuracy and dependability of test findings, consensus criteria and best practices are required for genetic testing in tuberculosis treatment.

**Accessibility to Genetic Analysis:** Pharmacogenomic-guided therapy implementation may face difficulties due to restricted access to genetic testing in resource-constrained environments. To guarantee that all patients have equal access to individualized TB therapy, strategies to increase access to genetic testing are required, including capacity building and cost-reduction programs.

**Incorporation into Medical Practice:** In order to enhance awareness among healthcare professionals, education and training activities are needed to facilitate the integration of pharmacogenomics guided treatment into ordinary clinical practice. Promoting the implementation of personalized medicine methods in tuberculosis therapy requires multidisciplinary teamwork and stakeholder participation.<sup>[26,27]</sup>

### CONCLUSION

Since pharmacogenomics clarifies how genetic variants affect medication metabolism, effectiveness, and toxicity, it plays a critical role in determining how the body responds to anti-tubercular treatment (ATT). Variants in important genes including NAT2, CYP2E1, GSTM1, GSTT1, and ABCB1 affect how anti-TB medications like isoniazid and rifampicin are metabolized. The relationship between medication response and genetics highlights the significance of precision medicine in tuberculosis treatment. Precision medicine provides a customized approach to tuberculosis care, maximizing treatment results and decreasing

adverse responses by utilizing pharmacogenomics and individualized treatment techniques. Healthcare professionals may customize ATT for each patient by using pharmacogenomic data into clinical practice, opening the door to safer and more successful TB therapy. To overcome implementation obstacles and progress genotypic-guided therapy in tuberculosis management, more research and innovation are needed. This will eventually support international efforts to eradicate tuberculosis.

### REFERENCES

1. Dohál M, Porvazník I, Solovič I, Mokry J. Advancing tuberculosis management: the role of predictive, preventive, and personalized medicine. *Front Microbiol*, 2023 Oct 4; 14: 1225438.
2. Yadav, Jyoti & Verma, Sonali & Choudhary, Darshna & Jaiwal, Pawan & Jaiwal, Ranjana. Tuberculosis: Current Status, Diagnosis, Treatment and Development of Novel Vaccines. *Current Pharmaceutical Biotechnology*, 2019.
3. Velayati AA, Masjedi MR, Farnia P, et al. Emergence of new forms of totally drug-resistant tuberculosis bacilli: super extensively drug-resistant tuberculosis or totally drug-resistant strains in iran. *Chest*, 2009; 136: 420-5.
4. Millet JP, Moreno A, Fina L, del Baño L, Orcau A, de Olalla PG, Caylà JA. Factors that influence current tuberculosis epidemiology. *Eur Spine J*, 2013 Jun; 22(Suppl 4): 539-48.
5. Khan MK, Islam MN, Ferdous J, Alam MM. An Overview on Epidemiology of Tuberculosis. *Mymensingh Med J*, 2019 Jan; 28(1): 259-266.
6. Jang JG, Chung JH. Diagnosis and treatment of multidrug-resistant tuberculosis. *Yeungnam Univ J Med*, 2020 Oct; 37(4): 277-285.
7. Mitnick CD, McGee B, Peloquin CA. Tuberculosis pharmacotherapy: strategies to optimize patient care. *Expert Opin Pharmacother*, 2009 Feb; 10(3): 381-401.
8. Cecchin E, Stocco G. Pharmacogenomics and Personalized Medicine. *Genes (Basel)*, 2020 Jun 22; 11(6): 679.
9. Relling M.V., Klein T.E., Gammal R.S., Whirl-Carrillo M., Hoffman J.M., Caudle K.E. The Clinical Pharmacogenetics Implementation Consortium: 10 Years Later. *Clin. Pharmacol. Ther*, 2019; 107: 171–175.
10. Chenoweth M.J., Giacomini K.M., Pirmohamed M., Hill S.L., Van Schaik R.H.N., Schwab M., Shuldiner A.R., Relling M.V., Tyndale R.F. Global Pharmacogenomics Within Precision Medicine: Challenges and Opportunities. *Clin. Pharmacol. Ther*, 2019; 107: 57–61.
11. Hippman C, Nislow C. Pharmacogenomic Testing: Clinical Evidence and Implementation Challenges. *J Pers Med*, 2019 Aug 7; 9(3): 40.
12. Stanek E.J., Sanders C.L., Taber K.A.J., Khalid M., Patel A., Verbrugge R.R., Agatep B.C., Aubert R.E., Epstein R.S., Frueh F.W., et al. Adoption of



- pharmacogenomic testing by US physicians: Results of a nationwide survey. *Clin. Pharmacol. Ther.*, 2012; 91: 450–458.
13. Swen J.J., Nijenhuis M., De Boer A., Grandia L., Der Zee A.H.M.-V., Mulder H., Rongen G.A.P.J.M., Van Schaik R.H.N., Schalekamp T., Touw D.J., et al. Pharmacogenetics: From Bench to Byte—An Update of Guidelines. *Clin. Pharmacol. Ther.*, 2011; 89: 662–673.
  14. Kalinin AA, Higgins GA, Reamaroon N, Soroushmehr S, Allyn-Feuer A, Dinov ID, Najarian K, Athey BD. Deep learning in pharmacogenomics: from gene regulation to patient stratification. *Pharmacogenomics*, 2018 May; 19(7): 629-650.
  15. T P A, M SS, Jose A, Chandran L, Zachariah SM. Pharmacogenomics: the right drug to the right person. *J Clin Med Res.*, 2009 Oct; 1(4): 191-4.
  16. David V, Fylan B, Bryant E, Smith H, Sagoo GS, Rattray M. An Analysis of Pharmacogenomic-Guided Pathways and Their Effect on Medication Changes and Hospital Admissions: A Systematic Review and Meta-Analysis. *Front Genet*, 2021 Jul 30; 12: 698148.
  17. Ramachandran G, Swaminathan S. Role of pharmacogenomics in the treatment of tuberculosis: a review. *Pharmgenomics Pers Med*, 2012; 5: 89-98.
  18. Weiner M, Peloquin CA, Burman W, et al. Effects of tuberculosis, race, and human gene *SLCO1B1* polymorphisms on rifampin concentrations. *Antimicrob Agents Chemother*, 2010; 54(10): 4192–4200.
  19. Hemanth Kumar AK, Ramesh K, Kannan T, Sudha V, Haribabu H, Lavanya J, Swaminathan S, Ramachandran G. N-acetyltransferase gene polymorphisms & plasma isoniazid concentrations in patients with tuberculosis. *Indian J Med Res.*, 2017 Jan; 145(1): 118-123.
  20. Bao, Yifan & Ma, Xiaochao & Rasmussen, Theodore & Zhong, Xiao-bo. Genetic Variations Associated with Anti-Tuberculosis Drug-Induced Liver Injury. *Current Pharmacology Reports*, 2018; 4: 10.1007/s40495-018-0131-8.
  21. Chanhom N, Wattanapokayakit S, Satproedprai N, Suvichapanich S, Mahasirimongkol S, Chaikledkaew U, Udomsinprasert W, Mushiroda T, Jittikoon J. CYP2E1, GSTM1, and GSTT1 genetic polymorphisms and their associations with susceptibility to antituberculosis drug-induced liver injury in Thai tuberculosis patients. *Heliyon*, 2021 Apr 20; 7(4): e06852.
  22. Pontual, Yasmin & Pacheco, Vanessa & Monteiro, Sergio & Quintana, Marcel & Costa, Marli & Rolla, Valeria & Castro, Liane. ABCB1 gene polymorphism associated with clinical factors can predict drug-resistant tuberculosis. *Clinical Science*, 2017; 131.
  23. Khan A, Abbas M, Verma S, Verma S, Rizvi AA, Haider F, Raza ST, Mahdi F. Genetic Variants and Drug Efficacy in Tuberculosis: A Step toward Personalized Therapy. *Glob Med Genet*, 2022 Feb 25; 9(2): 90-96.
  24. Choi R, Jeong BH, Koh WJ, Lee SY. Recommendations for Optimizing Tuberculosis Treatment: Therapeutic Drug Monitoring, Pharmacogenetics, and Nutritional Status Considerations. *Ann Lab Med*, 2017 Mar; 37(2): 97-107.
  25. Dohál M, Porvazník I, Solovič I, Mokry J. Advancing tuberculosis management: the role of predictive, preventive, and personalized medicine. *Front Microbiol*, 2023 Oct 4; 14: 1225438.
  26. Hippman C, Nislow C. Pharmacogenomic Testing: Clinical Evidence and Implementation Challenges. *J Pers Med*, 2019 Aug 7; 9(3): 40.
  27. Mathias P.C., Hendrix N., Wang W.-J., Keyloun K., Khelifi M., Tarczy-Hornoch P., Devine B. Characterizing Pharmacogenomic-Guided Medication Use with a Clinical Data Repository. *Clin. Pharmacol. Ther.*, 2017; 102: 340–348.