








The Role of Pharmacogenomics Studies for Precision Medicine Among Ethiopian Patients and Their Clinical Implications: A Scoping Review

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Background: Pharmacogenomics research is currently revolutionizing treatment optimization by discovering molecular markers. Medicines are the cornerstone of treatment for both acute and chronic diseases. Pharmacogenomics associated treatment response varies from 20% to 95%, resulting in from lack of efficacy to serious toxicity. Pharmacogenomics has emerged as a useful tool for therapy optimization and plays a bigger role in clinical care going forward. However, in Africa, in particular in Ethiopia, such studies are scanty and not generalizing. Therefore, the objective of this review was to outline such studies, generating comprehensive evidence and identify studied variants' association with treatment responses in Ethiopian patients.

Methods: The Joanna Briggs Institute's updated 2020 methodological guidelines for conducting and guidance for scoping reviews were used. We meticulously adhered to the systemic review reporting items checklist and scoping review meta-analyses extension.

Results: Two hundred twenty-nine possibly relevant studies were searched. These include: 64, 54, 21, 48 and 42 from PubMed, Scopus, Google Scholar, EMBASE, and manual search, respectively. Seventy-seven duplicate studies were removed. Thirty-nine papers were rejected with justification, whereas 58 studies were qualified for full-text screening. Finally 19 studies were examined. The primary pharmacogene that was found to have a significant influence on the pharmacokinetics of efavirenz was CYP2B6. Drug-induced liver injury has frequently identified toxicity among studied medications.

Conclusion and Future Perspectives: Pharmacogenomics studies in Ethiopian populations are less abundant. The studies conducted focused on infectious diseases, specifically on HAART commonly efavirenz and backbone first-line anti-tuberculosis drugs. There is a high need for further pharmacogenomics research to verify the discrepancies among the studies and for guiding precision medicine. Systematic review and meta-analysis are also recommended for pooled effects of different parameters in pharmacogenomics studies.

Keywords: Ethiopian, pharmacogenomics, single nucleotide polymorphisms, treatment outcome, pharmacogenetics, precision medicine

Background

Scientific evidence identified inter-individual variabilities in treatment response due to genetics. Recently, there has been a global upsurge in the application of precision medicine in a variety of medical sectors.^{1–3} Pharmacogenomics research currently holds the promise of revolutionizing in identifying molecular markers

associated with treatment response and optimize therapy.^{4,5} Medicines are the cornerstone of treatment for both acute and chronic diseases. However, patients' response to medication treatment varies because of their genetic make-up greatly ranging from 20% to 95% experiencing from lack of efficacy to adverse drug reactions (ADRs) or serious toxicity.^{4,6,7} Given that genetic variants (polymorphisms) account for this variability. Pharmacogenomics has emerged as a useful tool for therapy optimization and is expected to play a bigger role in clinical care going forward.^{2,6} Precision medicine refers to a therapeutic strategy that considers a patient's genetics, behavior, surroundings, and way of life.² Pharmacogenomics offer opportunities to researchers and physicians from the most molecular to the most clinical. Knowledge in computational biology, physiology, endocrinology, molecular biology, human genetics, bioinformatics, genomics, epidemiology, statistics, pharmacology, toxicology, and internal medicine are all relevant to the study of pharmacogenetics and pharmacogenomics.⁸ Consequently, pharmacogenomics knowledge of a drug's molecular effects is useful for both drug development and customized therapy.⁹ Although pharmacogenetics and pharmacogenomics are different, nowadays, they are used interchangeably for the sake of simplicity.^{2,10}

A Synopsis of Pharmacogenetics and Pharmacogenomics' Distinctions

It was suggested that pharmacogenetics is back about 510 B.C when Pythagoras was in southern Italy, in Croton, the first to identify some of the dangers, but not other. Individuals who eat the fava beans, hemolytic anemia was an adverse effect in individuals with insufficient glucose-6-phosphate dehydrogenase. Some contend that the field of current pharmacogenetics began with Snyder's 1932 study on the "phenylthiourea nontaster" phenotype, which is inherited as an autosomal recessive trait. Others still related to its origin a few decades back because of the human genome project.⁹ Drug response is a trait that can range from potentially fatal ADRs to an equally severe ineffectiveness of treatment. The enquiry of pharmacogenetics and pharmacogenomics delves into the impact of genetics on individual variations in medicine's response. The fast progress in both genomics and molecular pharmacology led to the evolution of this specialty. Pharmacogenetics research was first primarily concerned with monogenic features, which frequently involved genetic variation in metabolic drug states. Additionally, pharmacogenomics is integrated into the drug regulation and drug development process and moves beyond the "translational interface" into health sectors more significantly.¹¹

Although the concept of pharmacogenetics was founded in 1950's by Arno Motulsky and his colleagues,^{12,13} the term was coined for the first time in 1959 by Friedrich Vogel.^{2,14} The study of pharmacogenomics focuses on how a person's genetic makeup influences how their body responds to medications. The phrase refers to the area where genetics and pharmacology converge, and it originated from molecular pharmacology and genomics.^{11,15} Pharmacogenomics offers hope that medications may eventually be customized to each person's unique genetic makeup.¹⁵

Pharmacogenomics is the enquiry of differences in Deoxyribonucleic acid (DNA) and ribonucleic acid properties in relation to medicines' response, whereas the impact of differences in DNA sequence on medication response is known as pharmacogenetics. Within the field of precision medicine, pharmacogenomics examines how genetic differences impact how medicines are processed and respond. More precisely, pharmacogenetics uses genetic, epigenetic, and nutrigenetic methods to examine the effects of changes in one or a few genes on medication responsiveness.^{2,16}

Applying pharmacogenetics to the full genome, pharmacogenomics studies the relationships between individual genes and medications. Pharmacogenetics studies the effects of genetic variations on pharmacological action, dose, and use in individuals. Pharmacogenetics investigation can determine which patient is responsive before medication is administered, which is the foundation of precision medicine. Genetic variations affecting drug transporter proteins and liver enzymes (the cytochrome P450 group) are of particular interest in the field of pharmacogenetics. Similarly, genetic variations affecting drug pharmacodynamic profiles, such as variations in

receptor protein expressions, are of particular interest. Pharmacogenomics, on the other hand, is associated with the entire genome rather than just a single gene's SNP. It is the study of all the genes in an organism, both expressed and non-expressed, in every physiological state.¹⁷

Pharmacogenomics, beyond academic research contexts, is becoming more widely accepted as a tool for being informed by objective evidence medicine management. Pharmacogenomics tests are used to predict the efficacy and possible negative effects of pharmacological prescriptions. However, research in pharmacogenomics in African continent is not keeping up with global norms. Researchers throughout Africa must have access to infrastructural assistance and information sharing in order to integrate pharmacogenomics into clinical practice. The application of pharmacogenomics necessitates digital storage and quick, safe access to information for authorized users. Pharmacogenomics data is frequently integrated with electronic healthcare record systems,² which are very poor in Africa, particularly in Ethiopia. Due to genetic, environmental, and illness heterogeneity, different people respond differently to medicines. Genetic variations can alter a drug's pharmacokinetics and pharmacodynamics, which in turn can alter the drug's response by influencing the drug target's function as well as local and systemic drug exposure. Many pharmacogenomics indicators that have been shown to improve therapeutic outcomes.¹⁸

Many of the inter-individual differences in therapeutic efficacy and adverse effect risk are due to variations in the genes encoding proteins implicated in immunological or pharmacological responses to medications. The number of genetic variants important for medication action is substantially more than previously believed, and given the tremendous advancements in genetic analysis technology, a true personalized drug response prediction necessitates consideration of millions of rare mutations.¹⁹

As more people undertake acute or long-term therapeutic interventions, ADRs are emerging as a significant global health concern. In affluent nations, ADRs rank in the top ten causes of illness and death. Pharmacogenomics is accountable in 20–95% of variability in medication response and plays a major part in the frequency and severity of ADRs.⁷ Pharmacogenomics profiles have been established for around 50% of currently available medications. These profiles can be used for preemptive genotyping and provide clinical benefits for patients, such as increased efficacy and less ADRs.⁶

Research on pharmacogenomics in Africa over the previous 20 years has produced a wealth of information regarding variant alleles that affect plasma exposure variability in patients and the effectiveness of treatment outcomes from drugs used to treat malaria, TB, and HIV.^{1,20} Widespread pharmacogenetics research in several African nations will greatly improve patient care and maximize treatment success of HIV, TB, and malaria on the continent.^{7,20} Similarly in Ethiopia, even though a few research were conducted on TB and HIV in the capital Addis Ababa, Pharmacogenomics data utilization and knowledge are at its infant stage.^{7,21}

To the greatest of reviewers' knowledge, there is no thorough investigation conducted in Ethiopia either by scoping or systematic reviews to investigate the pharmacogenetics and pharmacogenomics associated impacts. Scoping review is a useful method for outlining the body of existing literature and identifying topics that may require more researches.²² Therefore, the objective of this review was to outline main study areas, to generate comprehensive evidence and identify studied variants' association with treatment responses in Ethiopian patients.

Methods

The Joanna Briggs Institute's updated 2020 methodological guidelines for conducting scoping and guidance for scoping reviews were used in this review.^{23–25} The draft protocol was developed by the principal author and reviewed by the second co-author, and as a result, few amendments were made. We meticulously adhered to the systemic review reporting items checklist and scoping review meta-analyses extension.²⁵

The Scoping Review Question

To ascertain whether our main research questions were eligible, we employed the Population, Concept, and Context (PCC) framework created by the Joanna Briggs Institute. The following were the primary research questions addressed: What are the relevant genomic markers from pharmacogenomics and pharmacogenetics studies that can help Ethiopian patients receive precision medicine, and what are the clinical consequences of these findings? Furthermore, what research in the fields of pharmacogenomics and pharmacogenetics is lacking?

Eligibility Criteria

The following criteria were used to determine which studies to be included: research with patients; any type of study, including original, review, and grey literature articles; and only studies published in English. No limitations on publication years or ages. Studies lacking pharmacogenes, medications, and markers were excluded.

Data Sources and Searching Strategies

PubMed, MEDLINE through PubMed, Scopus, EMBASE, and Google Scholar were systematically searched without language, publication status or date restrictions. Manual search, as a supplemental approach, was also employed to identify additional primary studies. Searching medical subject heading terms used were: “Pharmacogenetic”, OR “pharmacogenomics”, OR “human”, OR “humans”, OR “patients”, OR “gene”, OR “-genetics”, “pharmacokinetics”, OR “genomics”, OR “pharmacodynamics”, OR “GWAS”, OR “-kinetics”, OR “-dynamics”, OR “precision medicine”, OR “mutations”, OR “Ethiopia” OR/AND “Ethiopian” and “population”.

Study Selection and Reliability

Two expert reviewers who have conducted systematic reviews carried out our initial searches. These reviewers individually screened the titles, abstracts, and entire texts. A disagreement between the two reviewers about whether or not to include certain articles was settled by consensus. A second reviewer was blinded to the first reviewer’s selections while choosing papers and gathering data.

Data Charting (Extraction)

The lead author extracted the data, and the second reviewer confirmed it. A consensus was achieved regarding the outcomes. After deliberation, the third reviewer decided how to handle disagreements. From every study, we took out the following information: initial author name, year of publication, age in year, study type, patient category, research region, primary genes or chromosomes found, alleles, variants, and single nucleotide polymorphisms (SNPs). The clinical consequences of the key findings and related medications are summarized in table.

Predicated on the scoping review methodology framework,^{24,25} we included a narrative, graphs, and a tabulation of our findings. First, the breadth and distribution of the research included in the review were analyzed numerically in a basic manner. Next, thematic content analysis was used to present the research findings from the literature. The themes that arose from the study’s conclusions or findings then guided the organization of our narrative content.

Result

Two hundred twenty-nine candidate studies were found from the first search, including 64 from PubMed, 54 from Scopus, 21 from Google Scholar (advanced searching), 48 from EMBASE, and 42 articles that were found manually. There were 152 studies after removal of duplicate studies. A total of fifty-eight studies qualified for full-text screening. On further screening 39 studies excluded because of reasons described in PRISMA-ScR study flow chart see [Figure 1](#). No scoping review, meta-analysis and grey literature were found in the area. Although 5 conference reports were identified, there was no single report that fulfils the criteria. Finally, 19 full articles were reviewed.^{26–44}

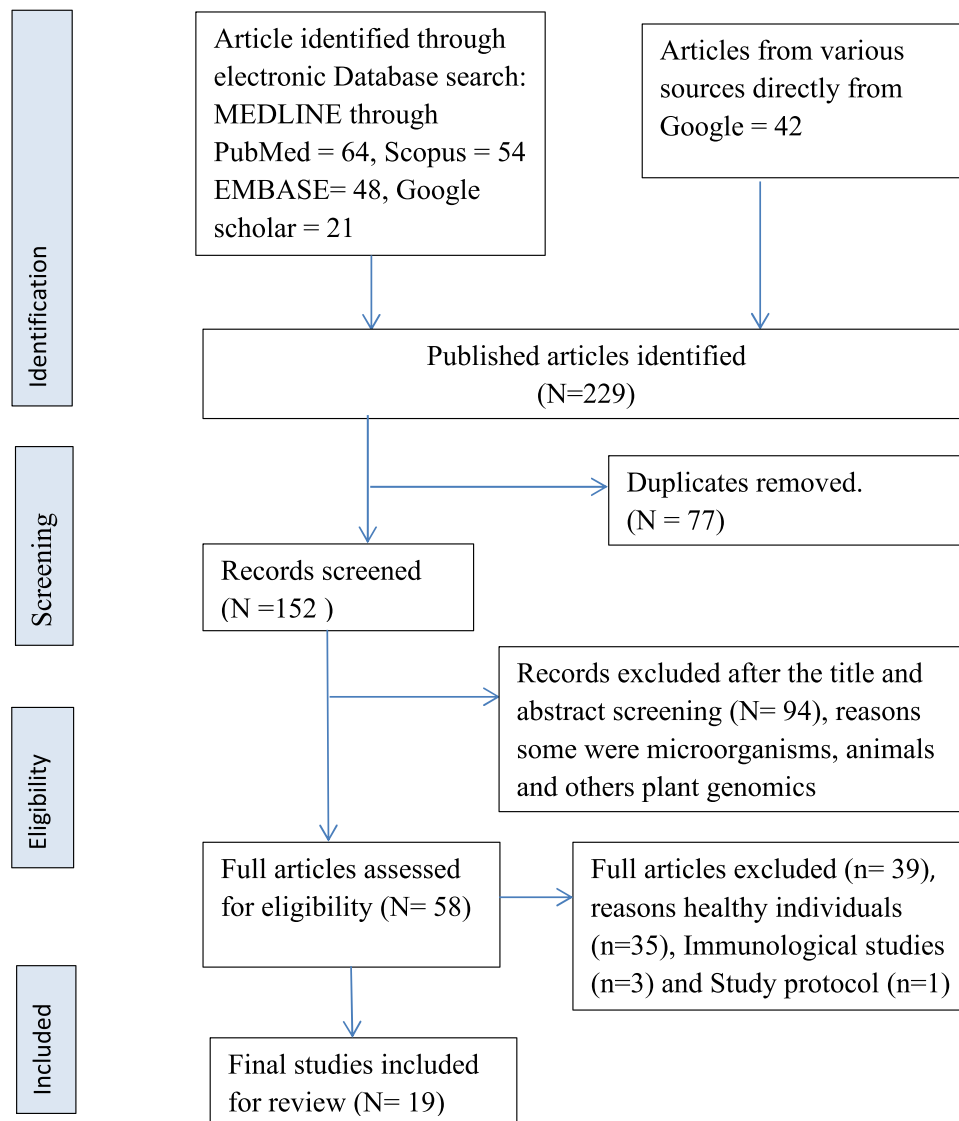


Figure 1 Flow diagram for study selection.

Characteristics of Included Studies

Most studies, 89.47%, were conducted in Addis Ababa, and almost all are prospective cohort studies in their types. The main findings, their clinical implications and pertinent extracted data were tabulated in [Table 1](#).

After filtering, the only research that remained was the pharmacogenetics and pharmacogenomics studies done on Ethiopian inhabitants and diaspora. [Figure 2](#) depicts pharmacogenetics, and pharmacogenomics conducted on Ethiopian patients.

On our systematic research, we found that about 58 studies on human population more than half of them were conducted on healthy individuals. Most of the research is done on infectious disease in particular of tuberculosis co infected with human immune virus. We found two studies on breast cancer and only a single study on malaria as shown in [Figure 3](#).

Table 1 Summary of Extracted Data and the Main Outcomes

First Author & Year	Study area	Study type	Sample size	Age in year	Patient category	Main Identified Genes	Alleles/Variants/SNP	Clinical implications	Associated Drug(s)
A.H/Wold (2011) ²⁶	AA	Prospective	163	28–42	TB-HIV	ABCB1 CYP2B6, CYP3A5 and UGT2B7	CYP2B6*6, CYP3A5*3, CYP3A5*6, ABCB1 3435C>T and UGT2B7*2 (2327G>A, rs7662029) were 29.7%, 66.9%, 10.6%, 20.9% and 48.1%, respectively CYP2B6*1/*1 and UGT2B7*1/*1	Significant variability between patients was found, partially explained by sex as well as the genotypes of CYP2B6 and UGT2B7. Continuous EFV autoinduction may put patients with the CYP2B6*1/*1 and UGT2B7*1/*1 genotypes at risk for subtherapeutic plasma concentrations. Genotyping is advised to identify patients who are extensive metabolizers, who may be at risk of suboptimal concentration on long-term therapy due to pronounced induction, and slow metabolizers, who, because of high efavirenz concentrations, are susceptible to CNS damage.	Efavirenz
Getnet Yimer (2011) ²⁷	AA	Prospective case-control	373	18–72	TB-HIV	NAT2, CYP2B6 and ABCB1	CYP2B6*6, ABCB1 3435TT and UGT2B7*2/*2	Significant association of DILI with CYP2B6*6 and ABCB1 3435TT genotype. It was observed that the UGT2B7*2/*2 genotype had a nearly significant effect on DILI. In Ethiopia dual infected patients, the genotypes of slow NAT2 acetylators, ABCB1 3435TT as well CYP2B6*6/*6 were found to be pharmacogenetic indicators for the development of ARV and anti-TB DILI.	D4T30/3TC/EFV, CBV/EFV and TDF/3TC/EFV, Isoniazid
Yimer Getnet (2012) ²⁸	AA	Prospective cohort study	285	28–40	HIV	CYP2B6, CYP3A5, ABCB1 and UGT2B7	CYP2B6*6, CYP3A5*3, CYP3A5*6, ABCB1 3435C4T and UGT2B7- 372G4A	Following the start of EFV-based HAART, 15.7% of patients experienced DILI. The onset of DILI was well-predicted by elevated levels of CYP2B6*6, plasma EFV, and common liver enzymes.	D4T30/3TC/EFV D4T40/3TC/ EFV/ CBV/EFV TDF/ 3TC/EFV
Abiy Habtewold (2012) ²⁹	AA	Prospective Cohort	77	30–43	HIV	ABCB1, CYP3A5, CYP2B6, and UGT2B7	ABCB1 - 3435C4T, CYP3A5*3, CYP2B6*6, CYP3A5*6, and UGT2B7*2(-327G4A rs7662029) were 21.3, 66.9, 30.6, 10.6, and 46.7%, consecutively.	Up to week 48, CYP3A enzyme induction in HIV patients on long-term EFV-based HAART is sustained. Due to increased plasma efavirenz exposure, patients with the CYP2B6*6/*6 genotype exhibit the most marked CYP3A induction. Variability in plasma EFV exposure among individuals, partially attributed to the CYP2B6 genotype, may impact the degree of variability in CYP3A induction. When CYP3A substrates are used concurrently with EFV, unexpected medication interactions may occur, especially in CYP2B6 slow metabolizers.	Efavirenz

Misgana Ibrahim (2013) ³⁰	AA	Prospective Cohort	29	1 to 15	TB	NAT2 Rapid acetylators	4*/4*, 4*/5*, 4*/6* and 4*/14*. NAT2*5 (341T > C) was the most common SNP, with a frequency of 36.2%; NAT2*6(590G >A) is second, with 27.6%.	Thirteen (45%) of the 29 youngsters were identified as slow acetylators and 16 (55%) as rapid acetylators with a median age of 9 years. This study suggests that among quick acetylators, a 5 mg/kg INH might not be sufficient to produce acceptable plasma levels. Therefore, children should be given a larger dose of INH (mg/kg body weight) based on their acetylator status in order to guarantee that acetylators, especially homozygous ones acquire an appropriate INH plasma concentration as quickly as possible.	Isoniazid
						NAT2 Slow acetylators	5*/5*, 5*/6*, 5*/7* and 6*/7*		Isoniazid
Eliford Ngaimisi (2013) ³¹	AA	Parallel-Group Prospective Cohort Study	285	28–40	HIV	CYP2B6, and ABCB1	CYP2B6*6, ABCB1 c.4036A/G (rs3842)	Pharmacokinetics of efavirenz were notably predicted by ethnicity, CYP2B6*6, and ABCB1 c.4036A.G (rs3842A.G), which collectively accounted for approximately 20% of patient variability in plasma levels. The extent of EFV auto-induction varies depending on pharmacokinetic and pharmacogenetic differences, which highlights the significance of environment and ethnicity factors in addition to ABCB1 and CYP2B6 when considering an efavirenz dosage optimization strategy.	D4T/3TC/EFV or AZT/3TC/EFV or TDF/3TC/EFV
Abiy Habtewold (2015) ³²		Two arm Prospective comparative	493	≥18	TB– HIV	CYP2B6	CYP2B6*6, CYP2B6*1/*1	In weeks 4 and 16, higher EFV plasma concentrations were seen in the RIF-co-treatment group compared to the non-RIF-based anti-TB therapy group, especially in CYP2B6*6 carriers. Nevertheless, there was no difference in the plasma EFV concentration between the two groups at either week in the CYP2B6*1/*1 genotype groups. Patients with TB-HIV coinfection receiving dual therapy for TB and HIV had a significantly greater incidence of DILI/toxicity, mostly because of overlapping toxicity from ARV and anti-TB and disease load (TB and HIV coinfection).	Paradoxically rifampicin increased EFV concentration as a result overlapping hepatotoxicity.
Abiy Habtewold (2016) ³³	AA	Prospective, comparative, two-arm	53	28–40	TB– HIV	CYP2B6	CYP2B6*6 CYP2B6*1/*1	Even after adjusting for the influence of either sex or CYP2B6 genotypes, patients' EFV PK values were unaffected by long-term co-administration of a RIF-based anti-TB treatment. On the other hand, co-administration did considerably raise the PK exposure parameters of the major metabolite, 8-OH-EFV; this impact was more noticeable in females or CYP2B6*6 carriers.	There's no need to change the daily dosage of EFV from 600 to 800 mg when taken with RIF.
Zelalem Petros (2016) ³⁴	AA	Prospective Cohort, GWAS	646	18–72	TB-HIV	6(24,967,240)	A/G (A), rs10946737	ATD-induced liver toxicity, which accounts for 11.6% of ATDILI, may be linked to potential genetic variants.	Rifampicin, Isoniazid, Pyrazinamide

(Continued)

Table I (Continued).

First Author & Year	Study area	Study type	Sample size	Age in year	Patient category	Main Identified Genes	Alleles/Variants/SNP	Clinical implications	Associated Drug(s)
Zelalem Petros (2017) ³⁵	AA	Prospective Cohort, GWAS	719	≥18	TB-HIV, ARV-Group	17(62,121,526) 7(116,857,547), 17 (61,770,954)	T/C (T), rs199650082, A/C (A), rs7804397, T/C (T), rs16947045	Developed DIH by ARV or ARV-ATD drugs are identified.	ARV Drugs
					ARV-ATD Group	12(79,201,073) 10(21,292,923), 5 (115,050,362)	T/C (C), rs4842407 A/G (A), rs11012476 A/C (A), rs251891	Developed DIH by ARV or ARV-ATD drugs are identified.	Both ARV and ATB Drugs
Zelalem Petros (2017) ³⁶	AA	Case-control comparative study	495	≥18	TB-HIV	HLA-B	HLA-B*57, HLA-B*14	Anti-TB and ARV medication-induced liver injury is more likely to occur in patients with HLA-B57:03 and HLA-B57:02 variant alleles, namely in situations of cholestatic liver injury and mild DILI.	Anti-TB and ARV drugs
Abiy Habtewold (2017) ³⁷	AA	Prospective cohort	313	≥18	TB-HIV	CYP2B6	CYP2B6*1/*1, CYP2B6*1/*6, and CYP2B6*6/*6	Three genotypes were found: CYP2B6*1/*1, CYP2B6*1/*6, and CYP2B6*6/*6. This study confirmed that CYP2B6 genotype-derived dose optimization of EFV is necessary.	EFV
Eugenia Lo (2019) ³⁸	Regions	Prospective cohort	344	All	Malaria	G6PD	G267+119C/T (rs782000110, C→T), A376G (rs1050829, A→G) and G1116A (rs2230036, G→A)	Among feverish patients throughout Ethiopia, G6PD deficiency is mildly prevalent. Therefore, before giving patients with Plasmodium vivax an extreme treatment, G6PD deficiency testing is advised.	Primaquine
Jemal Hussien Ahmed (2019) ³⁹	AA	Prospective cohort study	285	≥18	Breast Cancer	CYP2J2, CYP2C9, CYP2B6, ABCB1, CYP2C19, CYP3A5, POR	CYP2B6* 6, CYP2C9* 2, CYP2C9* 3, CYP2C19* 2, CYP2C19* 3, CYP3A5* 3, CYP2J2* 7, POR* 28, and ABCB1 rs3842G variant alleles were identified	In Ethiopian breast cancer patients, CYP2J2*7 was found to be a new pharmacogenetic risk factor for hematopoietic damage caused by chemotherapy. There was an association of hematologic toxicities among breast cancer caring CYP2C9 and CYP2J2 genotype. However, no significant hematologic toxicity risk between CYP2B6, CYP2C19, or POR* 28 and ABCB1 genotype. Neutroponic toxicity (50.2%) was the predominant manifestation of a higher prevalence of either grade 3 or 4 blood toxicities (51%). Conversely, low CYP2C9 enzyme activity and incorrect CYP2C9 variant alleles provide protection against the development of blood toxicity.	CPA
Jemal Hussien Ahmed (2020) ⁴⁰	AA	Prospective cohort study	267	33–48	Breast Cancer	CYP3A5, CYP2C9, POR	CYP3A5*3 or *6, CYP3A5*1/*1, CYP2C9 *2 or *3, CYP2C9 *2 or *3	In Ethiopian breast cancer patients, a single compartment model describes the PK profile of CPA. Wide variations in BSA, BMI, CYP3A5, and CYP2C9 genotypes, as well as CPA dosing regimens, all contribute to the 54.5% patient variability in CPA clearance. CYP3A5 activity was discovered to be altered by POR. Exposure to CPA plasma is predictive of neutropenic damage related to chemotherapy.	CPA

Eleni Aklilu (2020) ⁴¹	AA	Prospective cohort study	102	30–55	TB-HIV	ABCB1, CYP3A5, CYP2B6, SLCO1B1 and UGT2B7	Allele frequencies overall: CYP3A5*1, CYP2B6*6, CYP3A5*3, CYP3A5*6, ABCB1c.4036 A>G, ABCB1c.3435C>T, SLCO1B1c.388A>G (*1B, UGT2B7-327G>A (*2), SLCO1B1 c.521T>C*5)* were documented.	Patients receiving concurrent rifampicin-based anti-TB therapy are more likely than those receiving EFV-based ART alone to experience unexpected medication interactions with CYP3A substrates. This research verified the minimal possibility of CYP3A-mediated medication interaction between EFV and RIF. The risk of death can be decreased by starting ART and TB medications together as soon as a patient is diagnosed with TB and HIV co-infection.	EFV and RIF
Sabina Mugusi (2020) ⁴²	AA	Prospective multicenter Parallel comparative	481	≥18	TB-HIV	CYP2B6	In general, long-term co-treatment with RIF raised the concentration of EFV in plasma in Ethiopians with CYP2B6*6/*6 > *1/*6 > *1/*1.	The effects of efavirenz auto-induction, pharmacokinetics, and immunologic outcomes are all influenced by the CYP2B6 genotype, anti-TB co-medication, and demographic variance. Regardless of demographic variance or co-treatment with anti-tuberculosis medication, the CYP2B6 genotyping is a stronger predictor of EFV plasma concentration. Optimizing the dosage of efavirenz requires considering variations in CYP2B6 genotype, population, and geography.	EFV and RIF
Adugna Chala (2021) ⁴³	Oromia, SNNP	Prospective Cohort	111	3–16	HIV	CYP2B6 and ABCB1	CYP2B6*6, CYP2B6*1/*1 and ABCB1c.3435 C>T	CYP2B6 genotype-based dose adjustments may be more significant in determining the ideal pediatric efavirenz dose.	EFV
Wondmagegn Tamiru (2022) ⁴⁴	AA	Case-control comparative study	240	≥18	HIV & Diabetes	CYP3A4, CYP3A5, CYP2B6, and ABCB1	CYP2B6*6 and CYP3A5*6 (3A4*1B/ 3A5*3/*3A5*6)	The haplotype combination of 3A5*3/3A4*1B/*3A5*6 and the defective functional CYP3A5*6 allele were the predominant independent predictors of the total GMDs, IFG and IR. Captivatingly, the CYP2B6*6 genotype was a strong predictor of DM incidence (higher risk) on long-term EFV-based cART.	EFV

Abbreviations: AA, Addis Ababa; ABCB1, ATP-binding cassette subfamily-B member-1; ADRs, adverse drug reactions; AZT/3TC/EFV, Zidovudine, Lamivudine, Efavirenz; ATDLI, anti-tuberculosis drug-induced liver injury; CYP450, cytochrome P450; DILI, Drug induced liver injury; DNA, Deoxyribonucleic acid; D4T/3TC/EFV, Stavudine/Lamivudine/Efavirenz; G6DP, Glucose 6-phosphate dehydrogenase; GWAS, Genome wide association study; HAART, Highly active antiretroviral therapy HIV, Human Immunodeficiency Virus; HLA, human leukocyte antigen; INH, isoniazid; NAT2, N-acetyl transferase 2; PZA, pyrazinamide; RIF, rifampicin; NA, not available; SNP, single nucleotide Polymorphism; SLCO1B1, solute carrier organic anion transporter family member-1B1; D4T, stavudine; RCT, randomized clinical trial; SNNP, South Nation Nationality People; TDF, Tenofovir; TB, tuberculosis; UGT1A1, Uridine diphosphate glucuronosyltransferase.

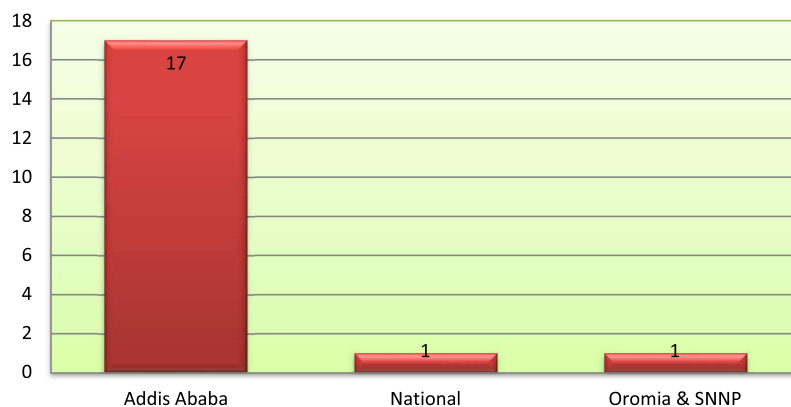


Figure 2 Distributions of research undertaken in Ethiopia on pharmacogenomics by study area.

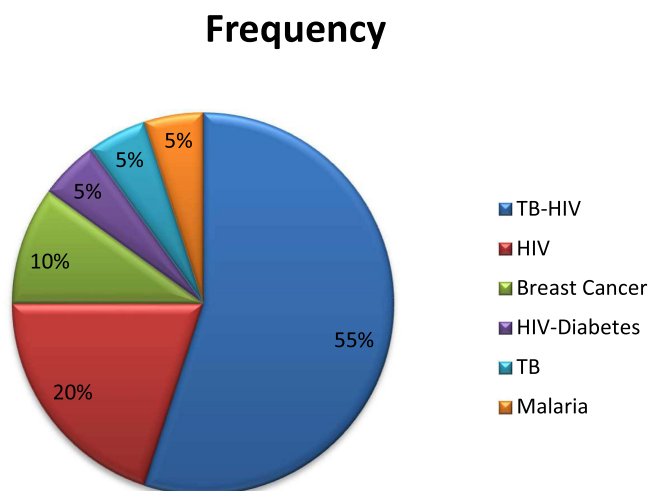


Figure 3 Frequency distribution of diseases category.

Discussion

Currently, pharmacogenomics, the foundation for precision medicine, is the major area of research to manage and treat patients better. In certain industrialized nations, they have become the cornerstones of healthcare. Nonetheless, pharmacogenomics research and clinical application is still in their infancy in Africa, specifically in Ethiopia. Therefore, to provide thorough evidence, we have gathered pertinent Ethiopian pharmacogenetic and pharmacogenomics studies for this review. We found that the largest percentage of cytochrome P450 isozymes, together with three-quarters of all the genes examined, were included in our review. Among which, CYP2B6 is the primary gene responsible for 29% of the metabolism of efavirenz, a popular antiretroviral non-nucleoside transcriptase inhibitor. In [Figure 4](#), the primary pharmacogenes found in the Ethiopian patients under study are displayed. This review also identified many pharmacogenes or drug-metabolizing enzymes, along with their alleles and variants, in accordance with identifications from quality control and global research. These summarized data validate existing markers and augment pharmacogenomics that holds the promise of revolutionizing clinical research and enhancing healthcare in sub-Saharan Africa. In addition, the importance of the variety of the African genome is emphasized, as are the prospects for pharmacogenomics research, which will make it possible to identify new genetic pathways.⁴⁵

The genes found out in Ethiopian patients are in line with 28 genes identified by quality control studies (*CYP3A4*, *CYP2B6*, *CYP2C9*, *CYP2C8*, *CYP3A5*, *CYP2D6*, *CYP2C19*, *CYP2E1*, *CYP4F2*, *GSTM1*, *NAT1*, *SLC22A2*, *NAT2*,

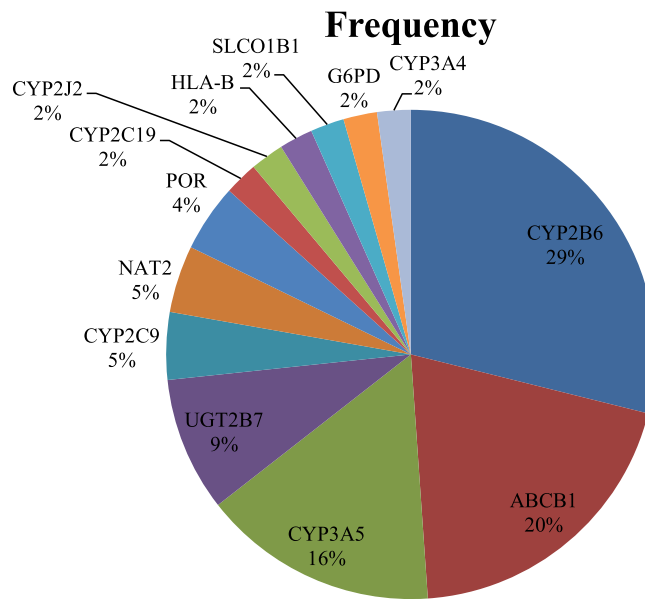


Figure 4 The major genes identified among Ethiopian patients.

SLC15A2, SLCO1B1, SLCO2B1, UGT2B7, UGT1A1, UGT2B15, and UGT2B17) by consensus confirmation, verified the existence of 108 or more variant pharmacogenetic alleles.⁴⁶

The medications that are most frequently studied are isoniazid, efavirenz, rifampicin, and other very effective anti-retroviral medications combined with an anti-tuberculosis regimen. High variability between patients was discovered in terms of pharmacogene expression, pharmacokinetic characteristics, and adverse drug events. Drugs that were used to treat tuberculosis combined with antiretrovirals caused a serious medicine-induced liver injury (DILI). Hematologic toxicity, neurotoxicity, and a little deficit of glucose-6-phosphoglucose dehydrogenase, which may result in hemolytic anemia, were the other toxicities that were reported. [Figure 5](#) presents the medications under investigation that have been linked to the aforementioned toxicities.

Our genetic diversity exceeds that of many larger geographic locations on a worldwide scale, as we Ethiopians continuously demonstrate with our substantial degree of cultural and linguistic diversity.⁴⁷ Therefore, owing to 20–95%

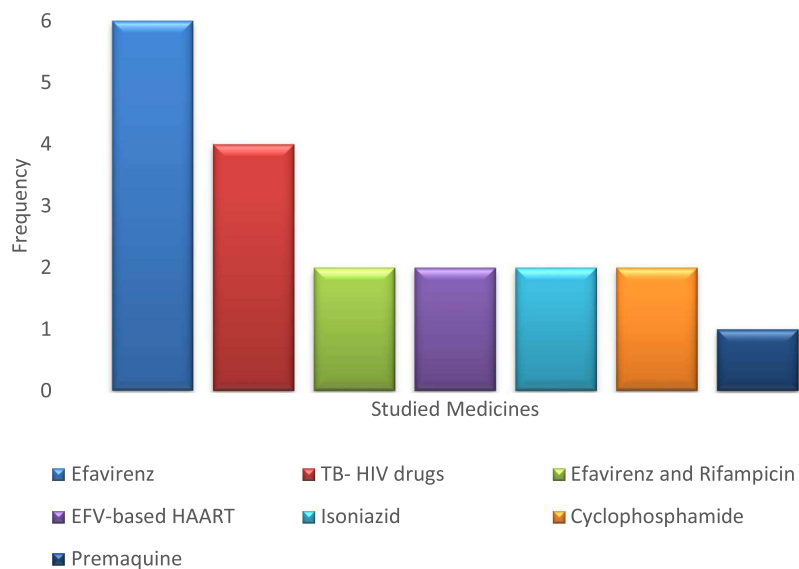


Figure 5 Studied drugs distributions in association with identified genes.

pharmacogenomics variability⁴ in drug response and toxicity especial consideration should be given as far as severity of ADRs and efficacy are concerned. Among Ethiopians, a wide range of DILI which is 11.6%–30% found out similar patients might be associated with this genetic variability.^{27,28,34,47} Higher incidence of cyclophosphamide toxicity hematologic grade 3 or 4 (51%) largely appeared as neurotoxicity (50.2%) also needs due clinicians' attention for breast cancer Ethiopian patients. We discovered that research on pediatric patients from Ethiopia is extremely lacking. In order to prevent ADRs, special consideration should be given to special population like women, elderly patients, and children due to their distinct physiological and pathological conditions complemented with pharmacogenomics features may impacts differently than any other population. Additionally, due to the pharmacogenomics differences among African continent populations, particularly Ethiopians, when extrapolating findings from clinical trials conducted in Caucasians to other populations, caution should be taken.

According to two investigations in Ethiopian health professionals to assess their knowledge and attitude, huge gap was found, although professionals have good attitude toward pharmacogenomics.^{7,21} The current review also come up with very few research that was done in Ethiopia and no practical startup of pharmacogenomics was here in Ethiopia. Ethiopian data/studies on elite athlete genetics, high altitude adaptation, milk consumption, tuberculosis, and drug metabolizing enzymes for the discovery of novel genes and greatest asset for the world have been incorporated. This is because Ethiopians have the highest genetic variability, which makes it easier to identify novel variants.⁴⁸

The main allele that was found in most of Ethiopian study participants was CYP2B6*6 and associated with low EFV concentration,^{26,37} whereas patients who express CYP2B1*1 alleles was found to have insignificant pharmacokinetics impact and inconsistency.³² CYP2D6, CYP2C9, CYP2C19, and CYP3A4/5 are the most significant CYPs involved in the metabolism of common medications. Although, there are variations in age, sex, circadian rhythm, and ethnicity, these four CYP genes encode the enzymes that are in charge of 60–80% of the medications that are currently prescribed.⁴⁹ The current review finding is in line with such scientific known facts except CYP2D6. We also found many discrepancies among the study results in Ethiopia.^{39,40,50} The effect of CYP2B6 on EFV pharmacokinetic parameters, its major metabolites, the effect of CYP2J2 on cyclophosphamide,³⁹ and different percent findings of DILI are among the most common.^{27,28,34}

Patients with HLA-B57:03 and HLA-B57:02 variant alleles are more likely to experience cholestatic liver injury and mild DILI, respectively, as a result of anti-TB and ARV medication-induced liver injury which is similar to a study done by Qihui Shao et al.⁵¹ HLA molecules or HLA antigens are encoded by the human major histocompatibility complex (MHC), commonly referred to as the HLA gene complex. It is separated into three subgroups: Class I, Class II, and Class III, and is found on chromosome 6, which has more than 200 genes. CD8+ T cells are able to identify class I MHC molecules, which are made up of the HLA-A, HLA-B, and HLA-C genes. CD4+ T cells detect class II MHC molecules, which include HLA-DRA, HLA-DRB1, HLA-DPB1, HLA-DQB1, and HLA-DPA1. Complement components, tumor necrosis factor (TNF), heat shock protein 70 (HSP70), and the 21 hydroxylase gene (CYP21A and CYP21B) are mostly encoded by class III MHC.⁵¹

Despite the great genetic diversity of Ethiopian populations, there is currently a dearth of genetic data on them. Pharmacogenomics research has the potential to completely change how diseases are treated, and thus Ethiopian communities stand to gain from its ability to pinpoint prospective responders, minimize medicines' side effects, and optimize medication dosage.⁵² Inadequate training and education of pharmacogenomics for healthcare providers; non-specific biomarkers of medicines efficacy and toxicity; cost-effectiveness; administrative issues in health organizations; and a lack of regulation for the widespread use of pharmacogenomics in clinical settings are the main obstacles that Ethiopians face in attempting to prevent ADRs through the routine use of pharmacogenomics procedures.⁷ Providing individualized therapies is essential in preventing ADRs and optimizing efficacy because of different ethnic communities within the same country.

Conclusion and Future Perspective

There are few investigations on pharmacogenomics in Ethiopian populations. Studies on infectious diseases were conducted commonly on efavirenz and the first-line anti-tuberculosis medications. The primary discovery of pharmacogene that affects the pharmacokinetics of efavirenz is CYP2B6. Drug-induced liver damage was frequently discovered to be harmful in relation to medicines and genes that were studied. Given Ethiopians' considerable genetic variability, careful consideration must be given to assessing the efficacy and potential side effects of medications that dictate the

importance of precision medicine implementation. Additional pharmacogenomics research will be crucial to confirm the differences between the studies. The pooled impacts of several pharmacogenomics study parameters were also suggested by systematic review and meta-analysis.

Ethical Approval

Ethical approval is not needed for this investigation.

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Author Contributions

The corresponding author conceptualized the study and the idea from the inception. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation. Then, all authors critically reviewed the article; gave final approval for the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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