

Pharmacogenomics of Chemotherapies for Childhood Cancers in Africa: A Scoping Review

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Background: Pharmacogenomics holds significant promise in improving the efficacy and safety of chemotherapy for childhood cancers. However, the field remains underexplored in Africa, where high genetic diversity and substantial disease burdens, including cancers, create unique challenges. This review investigates the current state of pharmacogenomics research in childhood cancer chemotherapies across Africa, focusing on genetic variations influencing chemotherapy efficacy and adverse drug reactions. It also highlights critical gaps, such as limited infrastructure and insufficient healthcare worker knowledge, and emphasizes the importance of capacity-building initiatives in the region.

Methods: A scoping review was conducted encompassing studies published up to September 2024 that examined pharmacogenomic variations associated with chemotherapies in childhood cancer patients across Africa. The review included laboratory genetic analyses and surveys assessing healthcare workers' knowledge, attitudes, and perceptions regarding pharmacogenomics, particularly in the context of pediatric oncology.

Results: A total of 12 genes were identified across eight studies, including *TPMT*, *CYP3A5*, *MDR1*, *MAPT*, *NUDT15*, *ITPA*, *IMPDH1*, *SLC29A1*, *SLC28A2*, *SLC28A3*, *ABCC4*, and *MTHFR*. The most studied genes were *TPMT* and *CYP3A5*, which are involved in the metabolism of 6-mercaptopurine (6-MP) and vincristine, respectively. These studies spanned five African countries, including Kenya, Egypt, Zimbabwe, Nigeria, Tunisia, and Libya, and focused primarily on childhood cancers, particularly acute lymphoblastic leukemia. Chemotherapies frequently studied were 6-MP (reported in five studies), vincristine, cyclophosphamide, and methotrexate. Knowledge of pharmacogenomics among healthcare workers in Africa remains low, though a positive attitude towards its clinical applications was observed.

Conclusion: Pharmacogenomic variants, such as *TPMT**3A, 3C, and *CYP3A5**6, significantly impact drug metabolism in African children with cancer. However, research remains regionally limited, and gaps in infrastructure and healthcare worker training persist. Expanding research efforts and improving pharmacogenomics capacity through pharmacist training and capacity-building initiatives are essential to advancing personalized medicine in Africa, ultimately improving treatment outcomes for pediatric cancer patients.

Keywords: pharmacogenomics, genetic variants, childhood cancer, anticancer drugs, children, pediatrics, individualized medicine, cytochrome P450, Africa

Background

Childhood cancer is a serious public health concern globally. World Health Organization (WHO) estimates that there are over 400,000 children who are diagnosed with cancer every year.¹ This number highlights a significant burden, however, it may not be the correct estimate, because over 43% of children with cancer go undiagnosed or untreated.² It is also estimated that approximately 80% of childhood cancer cases occur in low- and middle-income countries, particularly in Africa, where the cure rate remains low.³ This low cure rate can be attributed to various factors, including disparities in

individual responses to treatment due to differences in genetic makeup. This concept, where individuals within a population differ in drug response due to genetic variations, is known as pharmacogenomics.⁴

Although pharmacogenomics has been an established field of research for over five decades, its integration into routine clinical practice has gained significant traction in recent years, particularly in developed countries, where it has demonstrated benefits in treatment outcomes, especially for childhood cancers.⁵ A useful example of pharmacogenetic application is the prescription of 6-mercaptopurine (6-MP) for treating Acute Lymphocytic Leukemia (ALL), guided by genetic testing for the thiopurine S-methyltransferase (*TPMT*) gene.⁶ Individuals with low or absent *TPMT* activity are poor metabolizers and are at a higher risk of accumulating excessive levels of the active metabolite, 6-thioguanine nucleotides (6-TGNs). This can lead to severe bone marrow suppression and life-threatening myelosuppression, resulting in severe infections or even death. Conversely, individuals with high or normal *TPMT* activity metabolize 6-MP more efficiently, producing less of the active metabolite, and are generally less likely to experience toxicity at standard doses.⁷

Despite its promise, the research and application of pharmacogenomics in Africa remain in their infancy, hindered by economic constraints, resource scarcity, and limited training opportunities for healthcare professionals. Ethical issues and policy gaps also present significant barriers to implementation.⁸ Most of the major consortiums, organizations, and associations advocating for pharmacogenomics, such as the Clinical pharmacogenetic Implementation Consortium (CPIC), the pharmacogenomics Knowledge Base (PharmGKB), the Canadian pharmacogenomics Network for Drug Safety (CPNDS), and the Dutch Pharmacogenetic Working Group, are based outside of Africa and are primarily used in non-African regions.⁹ Furthermore, Africa faces unique healthcare challenges, including fragmented health systems, inadequate funding, and insufficient infrastructure to support pharmacogenomics research and clinical applications. Consequently, the extent of publications on pharmacogenomics in childhood cancers from the African continent is scant compared to other regions.¹⁰

It is projected that by the year 2050, the number of children diagnosed with cancer in Africa will constitute 50% of all global childhood cancer cases.¹¹ Implementing pharmacogenomics practices could play a transformative role in optimizing treatments, especially in resource-constrained settings. These interventions must be accompanied by strategic investments in research, healthcare professional training, and policy development. Therefore, it is crucial to take action now by implementing pharmacogenomics practices to improve cure rates for childhood cancer patients, particularly through better use of limited resources such as medications. Our review aimed to assess the extent of research, report existing findings, and identify the factors influencing the applicability of pharmacogenomics in childhood cancer chemotherapy in Africa.

We examined all aspects of pharmacogenomics in childhood cancer chemotherapy in Africa, guided by the research question: “What is the extent, existing findings, and factors influencing the applicability of pharmacogenomics in childhood cancer in Africa?” From this, we developed the following objectives: [1] to map the existing literature on pharmacogenomics in childhood cancer chemotherapy in Africa, [2] to describe the main findings in the available literature on pharmacogenomics of childhood cancer therapy in Africa, and [3] to explore the factors influencing the applicability of pharmacogenomics in childhood cancer therapy in Africa.

Methods

We utilized the scoping review framework proposed by Arksey and O’Malley to define our research approach. By this framework we identified childhood cancer patients as the population of interest, pharmacogenomics as the key concept, and the available literature from Africa as the context.¹² The outcomes of interest included reports on specific genes and variants, chemotherapy-gene association outcomes in children harboring variant genes, and the knowledge and attitudes of healthcare workers (HCWs) regarding pharmacogenomics in pediatric cancer care.

The protocol was prepared and registered on the Open Science Framework (OSF) with the DOI: <https://doi.org/10.17605/OSF.IO/DSBWE>. We identified relevant literature, selected studies, mapped ideas, and synthesized evidence based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for scoping reviews (PRISMA-ScR),¹³ as shown in Figure 1 (Additional file 1, supplementary materials). This guide was reviewed by two independent reviewers (DMK and SM), and a consensus was reached after several discussion meetings.

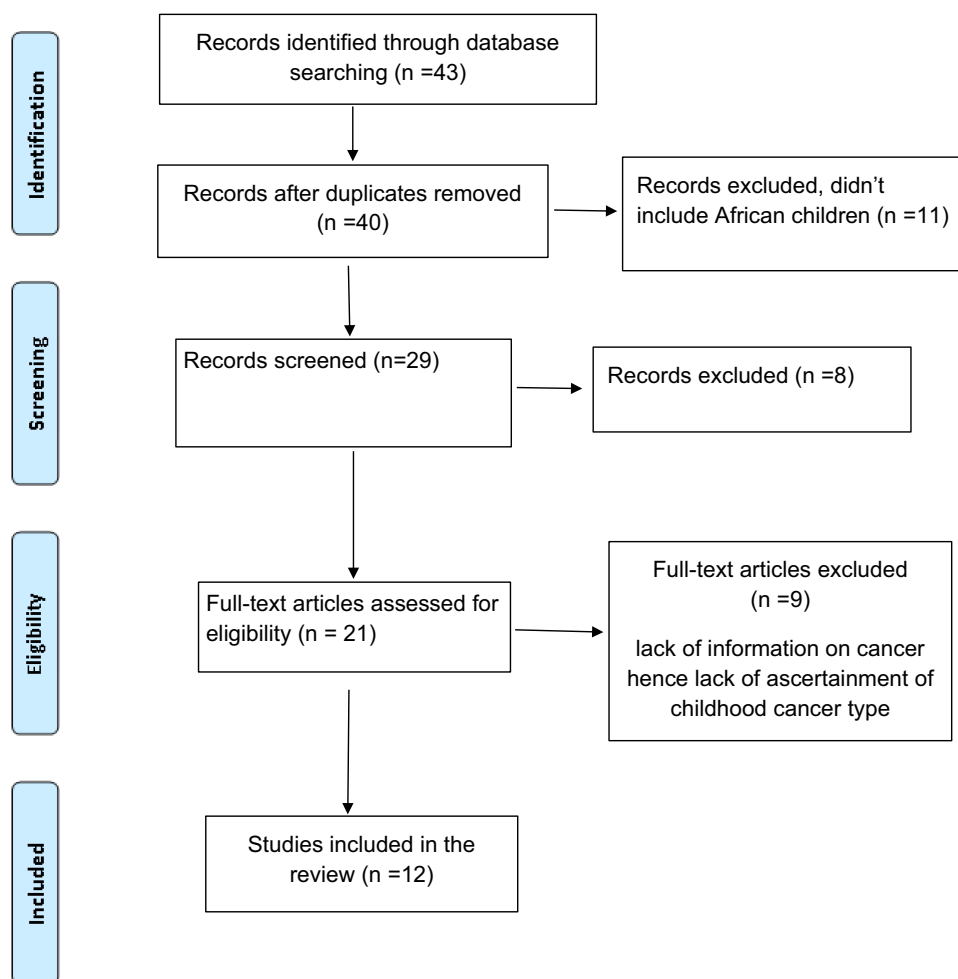


Figure 1 Flow diagram of literature search results and study selection.

Search Strategy

An experienced librarian, Mr. Oliver Bondo, at the Catholic University of Health and Allied Sciences Library, drafted the search strategies, which were shared with all reviewers to ensure a standardized approach for the online searches. A pilot search conducted before the actual search revealed a paucity of literature on the topic, prompting the creation of various search strings, which were incorporated into a checklist for comprehensive literature searches.

The primary search terms included “pharmacogenomics”, “pharmacogenetics”, “genomic medicine”, “childhood cancer”, “children with cancer”, “pediatric oncology”, and regional terms such as “East Africa”, “South Africa”, “Central Africa”, “Northern Africa”, “Western Africa”, and “Africa”, with “Africa” subsequently replaced by individual country names ([Additional File 2, supplementary materials](#)). Additionally, “precision medicine”, ‘personalized medicine’, and “individualized medicine” were included as secondary terms, as they have similar meanings to pharmacogenomics and pharmacogenetics. Using Boolean operators, the search string was set as: (pharmacogenomics OR pharmacogenetics) AND (childhood cancers OR pediatric cancers AND chemotherapies) AND Africa. Truncation (*) was applied to some words to capture variations in English, such as “pediatric” and “paediatric”.

The following biomedical research databases were searched: Google Scholar, African Index Medicus (AIM) via the WHO Global Index Medicus, Medline via PubMed, the Cochrane Library, Embase, and African Journals Online (AJOL). The search was limited to articles published in English from the inception of the databases until September 2024. The final search results were exported to Zotero, a reference management software, where they were organized, and

duplicates were removed. The complete search strategies for all databases can be found in [Additional File 3 \(supplementary materials\)](#).

Study Eligibility Criteria

The eligible studies were review studies, observational studies (both quantitative and qualitative), and laboratory-based studies. The emphasis was on studies involving the principles of pharmacogenomics in childhood cancer. Therefore, any study that included information on genomic medicine and children with cancer was considered. Furthermore, any study that explored genes known to influence the pharmacokinetics and/or pharmacodynamics of chemotherapies used in the treatment of childhood cancer was included. In addition, studies that examined factors influencing the applicability of pharmacogenomics testing or use (ie, knowledge and attitudes of caregivers) were included, as the groups benefiting from such practices involve children. Moreover, only studies published in English and conducted in, or about African populations were eligible for inclusion.

We excluded studies that were published on genomics but focused on cancer disease genetics, as well as those that were unclear regarding the study population or did not include humans. Likewise, we did not include preprint articles, conference abstracts, thesis, commentaries, comment letters, protocols, and grey literature.

Selection of Sources of Evidence

To identify potentially relevant documents, the four bibliographic databases described earlier were chosen based on the predefined criteria of being reputable, reproducible, and accessible sources of biomedical research published in English. The selection criteria and search techniques were established earlier to standardize the process under the guidance of an experienced librarian. A test was conducted to assess the usability of the selection and search checklist to ensure that all potential sources of evidence were fully utilized.

Screening Process

Because the process was standardized, two reviewers, DMK and SM, used the same checklist to review the titles, abstracts, and full texts of publications from the database sources and created their own lists of included literature. The two lists were then compared, and any inconsistencies and disagreements were resolved through discussion among the reviewers. One final list was chosen and shared with other reviewers for confirmation.

Data Items, Extraction, and Analysis

Through an iterative approach, the identification and extraction of variables were continually refined to obtain the final items, which included the study type, authors, country of publication, study design, time of publication, predefined primary terms, main findings (common gene variants, gene-chemotherapy relationship and healthcare workers' knowledge and attitudes regarding pharmacogenomics), and overall recommendations from the study.

Critical Appraisal for Individual Sources of Evidence

A structured checklist, regarded as a critical appraisal tool ([Additional File 4, supplementary materials](#)), for the standard appraisal of evidence, was created and tested before being used by two reviewers, DMK and SM, to systematically evaluate the extracted items against the objectives of the current review. Because we included studies with different methodologies, it was agreed that the included studies must produce items that fulfill at least one objective of the current review. In addition, the appraisal involved assessing the methodological quality of the included sources of evidence and determining whether the results were valid and could be used to inform practice and policy regarding children with cancer.

Results

Search Results

We initially identified 43 publications. During the initial screening, 11 articles were removed because they lacked evidence of including children from Africa. In the next step, we removed 3 duplicate articles, leaving 29 publications for

further review. We then screened the titles and abstracts, excluding 8 publications based on our predefined eligibility criteria. The remaining 21 articles were assessed for eligibility through a full-text review. Of these, 9 papers were found to be ineligible: 6 were descriptive reviews lacking cancer information (thus unable to ascertain childhood cancer types), 1 systematic review included a study that had been previously included, and 1 systematic review and 1 lab-based study addressed pharmacogenomics outside the context of pediatric cancer (details in [Additional File 5, supplementary materials](#)). As a result, 12 studies were included in this review ([Figure 1](#)).

Characteristics of Included Sources of Evidence

The included studies were published between 2010 and 2024. Six out of the 12 studies were authored by researchers from Northern Africa (4 from Egypt, 1 from Tunisia, and 1 from Libya). Additionally, 8 of the 12 studies were laboratory-based, investigating genetic variations in a total of 429 children with cancer (279 with Acute Lymphoblastic Leukemia (ALL) and 150 with Rhabdomyosarcoma (RMS)) and 491 normal adult volunteers. The remaining studies focused on the knowledge and applicability of pharmacogenomics among healthcare workers (HCWs), involving 338 participants ([Table 1](#)).

Summary of the Key Findings

[Table 1](#) summarizes the results from the genetic analysis of samples from children with cancer and adult volunteers, as well as observations on the level of knowledge regarding the concept of pharmacogenomics among relevant healthcare workers and academicians, as reported in the studies included in this scoping review.

Table 1 Key Features and Results of Reviewed Studies

Authors	Year	Country	Study Design	Population	Sample Size	Key Findings
Skiles et al ¹⁴	2017	Kenya	Laboratory-based	Children with cancer	78 patients	The study found no significant differences in the occurrence or severity of neuropathy when comparing individuals with high- and low-expressing <i>CYP3A5</i> genotypes, nor between different <i>MDR1</i> and <i>MAPT</i> haplotypes.
Chikondowa et al ¹⁵	2023	Zimbabwe	Laboratory-based	Children with cancer	41 patients	The study found that 9.8% of participants carried the defective <i>TPMT</i> *3C allele, which was linked to a lower median maintenance dose intensity of 6-MP (47% compared to 77% in those with the wild-type allele). This allele is important because it affects drug metabolism and can increase the risk of toxicity.
Kudzi et al ¹⁶	2015	Ghana	Cross-section	Health care professionals	90 health Care Workers	Healthcare professionals in Ghana rated their Pharmacogenetics knowledge as mostly good (60%), with only 5.6% considering it excellent. Additionally, 37% of faculty members reported that Pharmacogenetics was not included in their curriculum, highlighting a significant gap in educators' understanding of the subject.

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Table 1 (Continued).

Authors	Year	Country	Study Design	Population	Sample Size	Key Findings
Madadi et al ¹⁷	2010	Nigeria	Cross-section	Pharmacist and pharmacologist	9 pharmacists and pharmacologists	Pharmacists and pharmacologists in Nigeria recognize the benefits of pharmacogenomics, including better treatment outcomes and fewer adverse drug reactions. However, challenges like insufficient funding, inadequate infrastructure, a shortage of trained personnel, and ethical issues must be resolved before pharmacogenomic testing can become a regular part of clinical practice
Nagy et al ¹⁸	2020	Egypt	Cross-section	Pharmacist and physicians	184 pharmacists and physicians	Pharmacists and physicians in Cairo, Egypt, have limited knowledge of pharmacogenetics, with an average score of 41.7%. However, they generally have positive attitudes toward pharmacogenetic testing and its clinical use, especially among pharmacists. Major barriers to implementation include insufficient knowledge and skills, lack of testing devices, and limited funding.
Hareedy et al ¹⁹	2015	Egypt	Laboratory-based	Children with Acute Lymphoblastic Leukemia	70 patients	Genetic variants (SNPs) in the <i>ITPA</i> , <i>IMPDH1</i> , <i>SLC29A1</i> , <i>SLC28A2</i> , <i>SLC28A3</i> , and <i>ABCC4</i> genes are significantly associated with hematological toxicities, including neutropenia, agranulocytosis, and leukopenia, in pediatric acute lymphoblastic leukemia (ALL) patients on 6-MP.
ElShereef et al ²⁰	2024	Egypt	Laboratory-based	Children with Rhabdomyosarcoma	150 RMS pediatric patients	Approximately 61.3% of pediatric RMS patients were poor metabolizers of Cyclophosphamide, with a significant link between <i>CYP3A5</i> genotypes and cyclophosphamide (CPA) toxicity, especially hemorrhagic cystitis and pancytopenia. Nephrotoxicity was observed in 87.3% of patients. Importantly, intermediate and poor metabolizers had a higher incidence of hemorrhagic cystitis. The <i>CYP3A5</i> *3 and <i>CYP3A5</i> *6 polymorphisms were strongly associated with both CPA efficacy and toxicity.

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Table 1 (Continued).

Authors	Year	Country	Study Design	Population	Sample Size	Key Findings
Tantawy et al ²¹	2010	Egypt	Laboratory-based	Children with Acute Lymphoblastic Leukemia	40 patients	The <i>MTHFR</i> 677 TT genotype in Egyptian children with acute lymphoblastic leukemia (ALL) is associated with significantly increased methotrexate toxicity, leading to severe diarrhea, mucositis, elevated liver enzymes, and neutropenia. This genotype also correlates with a higher 5-year relapse rate of 56.3% and a lower overall survival rate of 50%. In contrast, the <i>MTHFR</i> A1298C polymorphism does not show a significant association with therapy-induced complications or relapse.
Jongeneel et al ²²	2022	South Africa	Cross-section	Physicians, postgraduate students, laboratory heads, scientists engaged in research activities, and an administrator	55 participants	African scientists and stakeholders possess differing levels of knowledge and awareness regarding genomic medicine, facing significant barriers like inadequate infrastructure, limited translational research, and a shortage of specialized personnel. Recommendations for improvement include prioritizing infrastructure development, enhancing training programs, promoting information dissemination, and engaging political and public stakeholders. Additionally, a checklist is provided to evaluate the readiness for integrating genomic medicine into African health systems.
Salah et al ²³	2011	Tunisia	Laboratory based	Adults of Tunisia	119 participants	Approximately 98.3% of participants were homozygous for the wild-type allele <i>TPMT</i> *1, while 1.68% were heterozygous for <i>TPMT</i> *1/3A. The frequency of the <i>TPMT</i> *3A mutant allele was low at 0.009, highlighting its rarity but also its unique presence in Tunisia. This mutant allele is associated with reduced enzyme activity, which may impact drug metabolism and increase the risk of adverse reactions.

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Table 1 (Continued).

Authors	Year	Country	Study Design	Population	Sample Size	Key Findings
Zeglam et al ²⁴	2015	Libya	Laboratory based	Children with ALL and normal adult volunteers of Libya	246 participants	In a study of 246 adults from the Libyan population, two mutant alleles of the thiopurine S-methyltransferase (<i>TPMT</i>) gene were identified: <i>TPMT</i> *3A at 0.61% and <i>TPMT</i> *3C at 1.02%, resulting in an overall mutant allele frequency of 1.63%. No variants of <i>TPMT</i> *2 or <i>TPMT</i> *3B were detected, and 98.4% of adults carried the normal wild-type allele. Importantly, no mutant alleles were found in 50 children with acute lymphoblastic leukemia. These results highlight the need for testing <i>TPMT</i> variants in patients undergoing treatment with thiopurine drugs to prevent severe myelosuppression.
Adehin et al ²⁵	2017	Nigeria	Laboratory-based	Adult of tribes of Nigeria	180 participants	Approximately 10% of the Nigerian population, have defective thiopurine S-methyltransferase (<i>TPMT</i>) alleles, with <i>TPMT</i> *3C being the most common at 9.4%. Other alleles, such as <i>TPMT</i> *2, <i>TPMT</i> *3B, and <i>TPMT</i> *4, were not found. The prevalence of the <i>TPMT</i> *3C allele aligns with the Hardy-Weinberg equilibrium and could play a significant role in adverse reactions to thiopurine medications in this population.

Genes, Variants, and Chemotherapies

In eight studies,^{14,15,19–21,23–25} 12 genes associated with the pharmacokinetics of chemotherapies used to treat childhood cancers were analyzed. These genes included *CYP3A5*, *MDR1*, *MAPT*, *TPMT*, *NUDT15*, *ITPA*, *IMPDH1*, *SLC29A1*, *SLC28A2*, *SLC28A3*, *ABCC4*, and *MTHFR*, with various genetic variants identified. Among these, the most common were *TPMT* variants (*3A and *3C), which are linked to the metabolism of 6-mercaptopurine (6-MP) and were explored in two and three studies, respectively.^{15,23–25} Additionally, *CYP3A5* variants (*3, *6, *7), which encode enzymes involved in the metabolism of vincristine, were identified in two studies.^{14,20} Variants of the *ITPA*, *IMPDH1*, *SLC28A2*, *SLC29A1*, and *ABCC4* genes, all involved in the transport of 6-MP, were reported in one study.¹⁹ Finally, the *MTHFR* variants *C677>T* and *A1298>C*, associated with methotrexate transport across cells, were identified in one study.²¹

There is considerable variation in the frequencies of these variants across different populations in Africa. One study by Skiles et al reported that 91% of the Kenyan children tested for the *CYP3A5* gene were carriers of high expresser variants (homozygous wild-type and heterozygous) for the enzyme involved in vincristine metabolism. The low expressers had higher dose- and body surface area-normalized areas under the curve compared to high expressers ($0.28 \pm 0.15 \text{ hr} \cdot \text{m}^2/\text{l}$ vs $0.15 \pm 0.011 \text{ hr} \cdot \text{m}^2/\text{l}$, $P = 0.027$). The 9% low expressers were those who carried homozygous *3, *6, or *7 alleles, although individual allele frequencies were not provided.¹⁴ In contrast, ElShereef et al reported that 61.3% of pediatric Egyptian cancer patients were poor metabolizers (homozygous *3/*3 or *3/*6) of *CYP3A5*.²⁰

Regarding *TPMT* gene variants, Chikondowa et al reported a frequency of 9.8% in Zimbabwe, followed by 9.4% in Nigeria as reported by Adehin et al. In both studies, *TPMT**3C was the predominant variant.^{15,25} Salah et al reported a frequency of 1.68% in Tunisia, predominantly *TPMT**3A, while Zeglam et al found a frequency of 1.63% in Libya, largely *TPMT**3A.^{23,24} Despite the varying frequencies, all studies linked *TPMT* variants to the metabolism of 6-MP, used during the maintenance phase of acute lymphoblastic leukemia (ALL) treatment. Hareedy et al in Egypt reported frequencies of 4–14%, 32–38%, 14%, 44%, 9%, and 1–10% for *ITPA*, *IMPDH1*, *SLC29A1*, *SLC28A2*, *SLC28A3*, and *ABCC4*, respectively, all associated with 6-MP transport.¹⁹

For *MTHFR* gene variants, the common variations C677>T had frequencies of 40%, 27.5%, and 32.5% for the TT, CT, and CC genotypes, respectively. The TT homozygous variant was associated with grade 3 and 4 toxicities induced by methotrexate. In contrast, the A1298>C variant had frequencies of 40%, 35%, and 25% for the AA, AC, and CC genotypes, respectively, but was not associated with increased toxicity risk from methotrexate.²¹

The included studies explored the pharmacogenomics of four cancer chemotherapies, with 6-MP being the most studied, reported in five out of eight studies with genetic analysis results. Four studies focused on enzymes involved in the activation of 6-MP, while one examined its transport across cells. Vincristine, cyclophosphamide, and methotrexate were each reported in one study (Table 2).

Table 2 Gene-Drug Combinations, Frequency of Variants, and Associated Outcomes for Chemotherapeutic Agents

Reference	Genes	Frequency of Variants	Chemotherapeutic Agent	Outcome
Skiles et al ¹⁴	Cyp3A5, MDR1, MPT	71 (91%) carried variants for CYP3A5, high expresser	Vincristine	No statistical difference between high-expresser and low-expresser gene carriers
Chikondowa et al ¹⁵	TPMT and NUDT15	9.8 harbored TPMT*3C	6-mercaptopurine	Median dose intensity of 6-MP was lower among carriers of defective variants compared to non-carriers; however, the difference was not statistically significant (p = 0.1779)
Hareedy et al ¹⁹	ITPA, IMPDH1, SLC29A1, SLC28A2, SLC28A3 and ABCC4	ITPA (4–14%), IMPDH1 (32–38%), SLC29A1 (14%), SLC28A2 (44%), SLC28A3 (9%), ABCC4 (1–10%)	6-mercaptopurine	Carrying these variants was significantly associated with developing one or more hematological toxicities including neutropenia, agranulocytosis and leukopenia
ElShereef et al ²⁰	CYP3A5	CYP3A5*1*3 (22%), CYP3A5*1*6 (1.3%), CYP3A5*3*3 (61.3%), CYP3A5*3*6 (10.7%)	Cyclophosphamide	The presence of heterozygous or homozygous variant alleles was significantly associated with increased toxicities (pancytopenia, hemorrhagic cystitis, nephrotoxicity) and higher efficacy, compared to having two wild-type alleles.
Tantawy et al ²¹	MTHFR	MTHFR C677>T (40%, 27.5%, and 32.5% for TT, CT, and CC respectively) MTHFR A1298>C (40%, 35%, and 25% for AA, AC, and CC, respectively)	Methotrexate	Carriers of the TT genotype had a statistically significant higher risk of grade 3 and 4 toxicities, including diarrhea, oral mucositis, elevated liver transaminases, and neutropenia, compared to CC carriers (p<0.0001 for all except p=0.003 for neutropenia). The 677 TT genotype was also significantly associated with relapse within five years and lower survival rates (p=0.001). A1298C was not linked to toxicity or relapse.

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Table 2 (Continued).

Reference	Genes	Frequency of Variants	Chemotherapeutic Agent	Outcome
Salah et al ²³	TPMT	Heterozygous, TPMT*1/*3A (1.68%) at a frequency of 0.009	6-Mercaptopurine	The TPMT*3A variant, unique to the Tunisian population, leads to reduced enzyme activity. Heterozygous individuals showed intermediate enzyme activity and experienced a 35% increase in hematopoietic toxicity compared to 7% in homozygous wild-type carriers.
Zeglam et al ²⁴	TPMT	The total mutant allele was 1.63% with TPMT*3A (0.61%), and TPMT*3C (0.02%)	6-mercaptopurine	The presence of *3A and *3C variants in the Libyan population highlights the need for monitoring patients on thiopurine drugs to prevent severe myelosuppression.
Adehin et al ²⁵	TPMT	TPMT*3C constituted 9.4%	6-mercaptopurine	Around 10% of Nigerians carry the *3C variant as the only defective TPMT allele, indicating the need for monitoring during thiopurine treatment to prevent adverse drug reactions. No other defective alleles were detected.

Knowledge, Attitude, and Perception of Pharmacogenomics Among Health Care Workers in Africa

Four studies examined the knowledge, attitudes, and perceptions of healthcare workers (HCWs) regarding pharmacogenomics across different African countries, using various methodologies.^{16–18,22} In Ghana, Kudzi et al explored these aspects among HCWs, including medical doctors, pharmacists, nurses, and university faculty members. They found that the majority of healthcare professionals (60%) rated their knowledge as “good”, while 21.4% rated it as “poor”. Only a small portion (5.6% and 11.2%) considered their knowledge to be “excellent” or “very good”, respectively. This trend was also observed among university faculty members, even though 40.6% stated that pharmacogenetics was part of their curriculum. However, 37% said it was not included, and 22% were unsure.¹⁶

Similarly, Nagy et al reported low overall pharmacogenetics knowledge (mean score = 41) among physicians and pharmacists in Egypt. Despite this, respondents displayed a positive attitude towards the potential benefits of pharmacogenetics, with pharmacists being more receptive than physicians. The study also identified key challenges to implementing clinical pharmacogenetic testing, such as a lack of knowledge, skills, testing devices, and funding.¹⁸ These barriers were echoed by Madadi et al in a study from Benin City, Nigeria, where all participants (pharmacists and pharmacologists) were familiar with pharmacogenetics and recognized its benefits.¹⁷

In a broader study by Jongeneel et al, involving authors from South Africa, Sudan, Mauritius, Tunisia, Egypt, and Morocco, respondents were from a diverse range of countries, including Morocco, Tunisia, Egypt, Mali, Ghana, Nigeria, Uganda, Rwanda, Malawi, Zimbabwe, Botswana, and South Africa. Nearly all regions of Africa, except Central Africa, were represented. Most respondents, including physicians, postgraduate students, and laboratory heads, were familiar with precision medicine, with over 80% either already using or planning to adopt advanced genomic technologies in their research. However, fewer than half had access to local infrastructure, which led many to rely on external collaborations. About a third of respondents reported that their institutions hosted genomic projects, another third said they did not, and the remaining third were unsure.²² Overall, clinician’s and researcher’s awareness of genomic medicine across these regions was low. Common barriers to implementation included insufficient information on local disease susceptibility, the perception that it was a low-priority investment, and concerns that genomic medicine would primarily benefit wealthier patients. These barriers were consistent with those identified in other studies.

Discussion

The current review presents the extent, existing findings, and factors influencing pharmacogenomics research in childhood cancer therapy in Africa. This concept is still relatively new and rarely applied, as shown by the small number of studies identified in our search. This is despite its foreseeable importance, as reported in other studies examining pharmacogenomics in Africa.²⁶ The African population exhibits the highest level of genetic variation globally, which has significant health implications for many genes relevant to pharmacogenomics. However, it is important to note that this variability is gene-dependent, as some genes, such as *UGT2B17* and *GSTM1*, demonstrate more specific patterns, such as high deletion frequencies in certain populations. These distinctions further shows the importance of region-specific pharmacogenomics research in Africa.^{27,28}

The 12 studies included in this review utilized various study methodologies, with eight reporting on 12 genes related to the pharmacokinetics of four commonly used chemotherapies in 429 children with acute lymphoblastic leukemia (ALL) and rhabdomyosarcoma (RMS). This reflects the low level of laboratory genetic exploration in Africa which may be due to a lack of economic investment in necessary infrastructures.²⁹ The other four studies focused on knowledge, attitudes, perceptions, and challenges related to the clinical application of pharmacogenomics among healthcare workers (HCWs) in Africa. The limited scope of pharmacogenomic studies presented in this review reflects earlier findings by Radouani et al, who reported that only 10% of clinical pharmacogenetic studies in Africa involved cancer.³⁰

In Africa, great emphasis is placed on infectious diseases particularly HIV/AIDS, and Malaria. That is why during our review process we encountered many studies reporting on the *CYP2B6* gene and its influence on the pharmacokinetics of Efavirenz, nevirapine, and artemisinin drugs. The same gene also influences the metabolism of cyclophosphamide, a commonly used chemotherapy in the treatment of childhood cancers. This has been widely documented in reviews on pharmacogenomics in Africa.^{31–33}

Half of the studies included in this review were conducted by researchers from North African countries, highlighting the region's more developed economic and healthcare infrastructure, which supports the funding and execution of clinical pharmacogenomics research. Countries like Egypt, Tunisia, and Libya, which contributed most of the studies, have relatively higher GDPs compared to other African nations, with Egypt's GDP estimated at approximately 476.7 billion USD, while Tunisia and Libya's GDPs are around 46.3 billion and 45.75 billion USD, respectively, these are higher than most sub-Saharan African countries except South Africa and Nigeria.³⁴

In this review, most (279) childhood cancer patients tested were children with ALL in the maintenance phase of treatment with 6-mercaptopurine (6-MP). This is because the *TPMT* gene, which codes for the enzyme involved in the biotransformation of thiopurines, is the most researched globally. Its effects on drug metabolism are well known, and it is incorporated in the clinical guidelines of the Clinical Pharmacogenetics Implementation Consortium (CPIC).³⁵ Additionally, *TPMT* and 6-MP have an established gene-drug relationship in the pharmacogenomics knowledge base (PharmGKB, <https://www.pharmgkb.org/>), a large web-based database. The inclusion of this gene in guidelines and its clinical utility has been shown to optimize ALL treatments in developed countries,³⁶ but this practice is not widely adopted in most African countries.³⁷

Interestingly, studies conducted in Sub-Saharan Africa (SSA) showed that approximately 10% of children carried the *3C variant of *TPMT*, in contrast to children from North Africa, where the majority carried the *3A variant. This can be explained by genetic differences between the two regions, with northern Africans being predominantly Arab and those in SSA being primarily of African descent. Other studies have shown that *3C is more common in African and Asian populations, while 3A is more prevalent in European and Caucasian populations.³⁸ It is also reported that there are notable differences between children with cancer who carry the *TPMT**3C variant and those with the 3A variant. For example, *TPMT**3C causes a moderate reduction in *TPMT* enzyme activity, leading to intermediate metabolism of thiopurines. Patients with this variant may have an increased risk of toxicity but not as severe as those with the *3A variant.^{39,40}

Two studies reported on the association of *CYP3A5* variants and adverse drug reactions (ADRs). In Kenyan children, carrying variants of this gene was not associated with vincristine-induced neuropathy (VINP), but in Egyptian children with RMS, carrying variants was associated with cyclophosphamide-induced toxicities. These two studies had different

objectives but explored the same gene on its influence on two different chemotherapies. However, this observation also explains that carrying a defective variant of a gene will not always translate into phenotypic presentation because there are other explanations that may include different genes, for instance vincristine-induced neuropathy which is also influenced by other genes reported in other studies. The gene, such as *CEP72*, has been shown to influence the occurrence of VINP.^{41,42} Additionally, factors like hydration and the use of supportive drugs to prevent hemorrhagic cystitis in patients on cyclophosphamide play a role.⁴³

Moreover, two studies presented results on genes associated with drug transport across cells, all of which yielded significant findings. Variants in the *MTHFR* gene (related to methotrexate transport) and *ITPA*, *IMPDH1*, *SLC29A1*, *SLC28A2*, *SLC28A3*, and *ABCC4* (related to 6-MP transport) showed that pharmacogenomic testing may need to involve multiple genes for it to be clinically actionable. These findings align with other reviews that did not exclusively focus on African children.^{44,45}

Pharmacogenomics knowledge among HCWs in Africa is generally low, as indicated by the included studies. Only one study reported that all HCWs were familiar with the concept of pharmacogenetics, but it did not specify the level of familiarity or whether “being familiar” equated to having sufficient knowledge. Familiarity with the concept can be influenced by several factors, including the type of personnel surveyed, their economic status, and the level of healthcare advancement in their region.¹⁰ Other included studies categorized HCWs’ knowledge levels, with some self-reporting good knowledge when asked to choose between “excellent”, “very good”, “good”, and “poor”. In general, the level of knowledge on pharmacogenomics is shown to be low among HCWs in Africa.

This lack of knowledge can be attributed to several factors. One is the limited inclusion of pharmacogenomics topics in medical and pharmacy curricula. Traditional pharmacology and clinical training often take precedence, as illustrated by a study from Ghana, where one-third of faculty members at health training institutions reported that pharmacogenomics was not part of their curricula.^{16,46} Additionally, there are few continuous professional development (CPD) opportunities focused on pharmacogenomics, with limited workshops or conferences available to update HCWs on advances in the field.^{47,48} This educational gap is compounded by inadequate infrastructure and resources, as the absence of genetic testing facilities and high costs limit practical exposure to pharmacogenomics tools.⁴⁹

Nevertheless, nearly all of the HCWs included in the studies demonstrated a positive attitude and perception of the application and benefits of clinical pharmacogenomics. This is likely due to their motivation to provide more precise, individualized care, a core principle of pharmacogenomics. By understanding how genetic variations influence drug response, HCWs are increasingly convinced of the clinical value of pharmacogenomics in improving treatment outcomes, especially for chronic diseases like cancer and cardiovascular conditions.⁵⁰

This review is limited to the African healthcare systems and policies related to pharmacogenomics, particularly in countries where English is one of the official languages. Since it includes studies from all African regions except Central Africa, it provides a broad picture of the genetic variants influencing the pharmacokinetics of chemotherapies commonly used to treat childhood cancers and the knowledge, attitudes, and perceptions of HCWs on pharmacogenomics in Africa.

Conclusion

Based on the studies included in this review, twelve genes known to be associated with adverse drug reactions (ADRs) and/or chemotherapy efficacy in childhood cancer have been explored in Africa. *TPMT* is the most studied, followed by *CYP3A5*. The chemotherapies most commonly examined for drug-gene associations include 6-mercaptopurine (6-MP), vincristine, cyclophosphamide, and methotrexate. The pediatric cancers investigated include acute lymphoblastic leukemia (ALL) and rhabdomyosarcoma, highlighting regional disparities in pharmacogenomics studies across Africa. While healthcare workers’ pharmacogenomics knowledge remains low, they show a positive attitude toward its applications. To enhance understanding, targeted educational programs and expanded research on additional genes and cancer types are necessary to improve pharmacogenomics’ application in childhood cancer treatment.

Abbreviations

ADR, Adverse Drug Reactions; ALL, Acute Lymphoblastic Leukemia; CYP, Cytochrome P450; HCWs, Health Care Workers; RMS, Rhabdomyosarcoma; 6-MP, Six-Mercaptopurine.

Data Sharing Statement

All data generated or analyzed during this study are available and included in this published article (and its [supplementary information files](#)).

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Author Contributions

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, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of 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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Disclosure

The authors declare that they have no competing interests.

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