Frontiers in Bioscience Scholar

Front. Biosci. (Schol Ed) **2026**; 18(3): 50635
https://doi.org/10.31083/FBS50635

Original Research

TPMT and *NUDT15* Pharmacogenomic Profiles in Peruvian Patients With Pediatric Hematologic Malignancies

Julio A. Poterico[1,2,*], Francisco Sánchez-Pinto[1], Gerardo Noriega-Manrique[3], Kelly Franco-Bustamante[1], Gioconda Manassero-Morales[1], Julissa Fuentes-Vera[1], Luis Jaramillo-Valverde[4], Alicia Mafaldo-Rengifo[5], Jorge Contreras-Saavedra[6]

[1]Servicio de Genética, Instituto Nacional de Salud del Niño-San Borja, 15037 Lima, Peru
[2]Faculty of Health Sciences, Universidad de Huánuco, 10001 Huánuco, Peru
[3]Facultad de Ciencias Biológicas, Universidad Nacional Mayor de San Marcos, 15081 Lima, Peru
[4]School of Medicine, Universidad Continental, 12000 Huancayo, Peru
[5]Servicio de Hematología Clínica, Instituto Nacional de Salud del Niño-San Borja, 15037 Lima, Peru
[6]Servicio de Transplante de Progenitores Hematopoyéticos, Instituto Nacional de Salud del Niño-San Borja, 15037 Lima, Peru
*Correspondence: jpoterico@insnsb.gob.pe; jpotericor@gmail.com (Julio A. Poterico)
Academic Editor: Gustavo Caetano-Anollés
Submitted: 3 February 2026 Revised: 29 April 2026 Accepted: 7 May 2026 Published: 27 July 2026

Abstract

Background: Thiopurines remain a cornerstone of treatment for pediatric acute lymphoblastic leukemia (ALL); however, interindividual variability in drug metabolism,largely driven by polymorphisms in the thiopurine S-methyltransferase (*TPMT*) and nucleoside diphosphate–linked moiety X–type motif 15 (*NUDT15*) genes, can predispose patients to severe, dose-dependent toxicities. Latin American populations have been underrepresented in several global pharmacogenomic (PGx) datasets, limiting the applicability of current dosing recommendations. **Methods:** Thus, this study aimed to analyze *TPMT* and *NUDT15* variants in 302 pediatric patients diagnosed with hematological malignancies at the Instituto Nacional de Salud del Niño-San Borja (INSN-SB). Targeted sequencing of the coding regions was performed using custom AmpliSeq™ panels and Illumina platforms, followed by variant annotation and star allele classification based on the Clinical Pharmacogenetics Implementation Consortium (CPIC) and PharmGKB guidelines. **Results:** Among the *TPMT* alleles, **3A* (8.97%) was the most prevalent actionable variant, followed by **2* (0.32%) and **3C* (0.32%). For *NUDT15*, the most frequent reduced-function allele was **2* (9.29%), with additional findings of **4* (0.64%), **6* (0.32%), **3* (0.16%), and **15* (0.16%). A substantial proportion of the cohort was classified as intermediate or poor metabolizer categories, indicating an increased risk of thiopurine-related toxicity. The observed allele distribution suggests potential geographic variation, although these patterns should be interpreted as exploratory given the limited regional sample size. **Conclusions:** This study provides one of the first comprehensive characterizations of clinically relevant *TPMT* and *NUDT15* variants in a Peruvian pediatric population. The findings highlight a substantial burden of actionable pharmacogenetic variants and support the implementation of preemptive genotyping to guide thiopurine dosing. These results help addressing the underrepresentation of Latin American populations in PGx research and provide a foundation for advancing precision medicine in the region.

Keywords: thiopurine S-methyltransferase; NUDT15; pharmacogenetics; precursor cell lymphoblastic leukemia-lymphoma; polymorphism; genetic; indigenous peoples

1. Introduction

Thiopurines such as 6-mercaptopurine and azathioprine are foundational components of maintenance chemotherapy protocols in pediatric acute lymphoblastic leukemia (ALL), yet their therapeutic utility could be shadowed by the adverse drug reactions (ADR) such as myelotoxicity or liver damage [1,2,3]. The ADR risk is influenced by germline variations in the genes thiopurine S-methyltransferase (*TPMT*) and nucleoside diphosphate–linked moiety X–type motif 15 (*NUDT15*), which govern key metabolic pathways converting thiopurines into cytotoxic or inactive metabolites [4].

The relevance of *TPMT* polymorphisms in thiopurine therapy was first recognized in the 1980s, when studies demonstrated that patients with reduced enzyme activity experienced severe myelosuppression during 6-mercaptopurine treatment for acute lymphoblastic leukemia (ALL) [5]. In pharmacogenetics, “star alleles” are standardized haplotype designations defined by the Clinical Pharmacogenetics Implementation Consortium (CPIC) and PharmVar; most correspond to a single genetic variant within a gene, but some, such as *TPMT*3A* or *NUDT15*2*, are defined by the presence of multiple variants in cis that together determine enzyme function [6,7]. Thus, *TPMT* clinically relevant star alleles **2* (c.238G>C, rs1800462), **3A* (c.460G>A, rs1800460 and c.719A>G, rs1142345), **3B* (c.460G>A, rs1800460) and **3C* (c.719A>G, rs1142345) are well-characterized and as-

sociated with reduced or absent enzyme function that leads to excessive accumulation of thioguanine nucleotides and increased toxicity risk [8]. Recently, *NUDT15* emerged as a critical determinant of thiopurine intolerance in patients with normal *TPMT* metabolizing genotypes. *NUDT15* was firstly described East Asian cohorts of children with ALL in 2014 [9,10], with subsequent studies confirming the relevance of loss-of-function variants—particularly the alleles **2* (c.415C>T, rs116855232 and c.50_55dup, rs746071566), **3* (c.415C>T, rs116855232), **4* (c.416G>A, rs147390019), **6* (c.50_55dup, rs746071566), and **15* (c.467T>A, rs139551410)—in individuals of Hispanic and Native American ancestry [11].

The CPIC recommends genotype-guided dosing of thiopurines based on combined *TPMT* and *NUDT15* metabolizer status, noting that individuals with intermediate or poor metabolism may require dose reductions of 20–50% (or more) to minimize severe toxicities while maintaining therapeutic efficacy [12,13]. In this framework, metabolizer phenotypes are inferred directly from the combination of alleles carried by a patient: individuals with two wild type alleles are classified as normal metabolizers (NM) and generally tolerate standard doses, whereas those with one clinically relevant polymorphic allele are considered intermediate metabolizers (IM) and face a heightened risk of toxicity at standard dosing. Patients with two clinically relevant polymorphic alleles are categorized as poor metabolizers (PM) and typically require substantial dose reductions or alternative therapies to avoid life-threatening adverse effects. Despite this guidance, most pharmacogenetic evidence originates from cohorts of European or East Asian descents, leaving substantial gaps in knowledge regarding allele frequencies and clinical impacts within Latin American populations [14]. In big reference datasets like gnomAD v4 (2023), Native American and Andean populations are underrepresented, resulting in incomplete allele frequency baselines for thiopurine metabolism genes like *TPMT* and *NUDT15* [15,16,17,18].

Recent studies in Latin America have begun to address these gaps. In Colombian pediatric ALL patients, *NUDT15* variant allele frequencies were estimated at around 3%, with *TPMT*2* and **3A* frequencies of 0.4% and 5%, respectively, values diverging from those observed in European or Asian cohorts and highlighting ancestry-specific variability within the region [8,19]. Similarly, research in Brazil found that *TPMT* and *NUDT15* intermediate metabolizer phenotypes occurred in approximately 10–11% and 2–3% of patients, respectively; poor metabolizer phenotypes for a single gene are rare (<1%). However, individuals carrying one defective allele in *TPMT* and one in *NUDT15*, although uncommon, may present a disproportionately high risk of thiopurine-related toxicity [20].

Peru has one of the largest percentages of Amerindian ancestry globally, often exceeding 60–80% in many regions, making it a unique genetic environment for pharmacogenomic marker evaluation [21]. Given the genetic admixture and ethno-geographic diversity across Latin America, region-specific PGx profiling is vital. In pediatric oncology settings where toxic thresholds are particularly unforgiving, accurate mapping of variant prevalence—especially for actionable alleles—can support safer, more precise thiopurine dosing.

Therefore, we aimed to describe the PGx profile of *TPMT* and *NUDT15* in a cohort of 302 Peruvian pediatric patients with hematological malignancies attended in a nationally specialized institution in Peru.

2. Materials and Methods

2.1 Patients

The National Institute of Child Health San Borja (Instituto Nacional de Salud del Niño San Borja, Lima, Peru) is a national referral center for pediatric hematologic malignancies, receiving patients from across the country. This broad catchment ensures that the population attended represents diverse geographic and sociodemographic backgrounds within Peru. Pediatric participants diagnosed with Acute Lymphoblastic Leukemia were selected from the Genetics Service of the National Institute of Child Health San Borja. In Peru, the incidence of pediatric acute lymphoblastic leukemia is estimated at approximately 3–4 cases per 100,000 children per year, supporting the representativeness of our cohort. The subset of 54 participants corresponded to a research-specific cohort, whereas the remaining samples were derived from a clinical leukemia panel; both datasets were harmonized for analysis. A total of 302 participants were analyzed: 132 girls and 170 boys. Clinical outcome data, including toxicity profiles, were not available and therefore genotype–phenotype correlations could not be assessed, representing a limitation. For both groups, approximately 3 mL of peripheral blood was collected per participant using vacutainers containing EDTA as an anticoagulant. All sample collections were conducted following informed consent and/or assent from patients and their legal guardians, and each sample was anonymized using a unique identification code to ensure confidentiality in compliance with institutional requirements.

2.2 Detailed Panel Design

Custom AmpliSeq™ panels for *TPMT* and *NUDT15* genes were designed for both cohorts using Illumina's web-based platform, selecting coding regions (CDS only) for amplification. The number of amplicons generated for each gene differed between groups, reflecting platform-specific optimization and target coverage requirements. For the research project (Iseq100), the panel comprised 11 amplicons for *TPMT* and 8 amplicons for *NUDT15*, whereas the leukemia panel (MiSeq) comprised 9 amplicons for *TPMT* and 4 amplicons for *NUDT15*. Both AmpliSeq panels were designed to ensure complete coverage of all coding exons (CDS) of *TPMT* and *NUDT15*, including all clinically rele-

vant variants defined by CPIC and PharmGKB, thereby ensuring comparability between cohorts despite differences in amplicon number.

2.3 DNA Extraction, Quantification, and Integrity Assessment

Genomic DNA was extracted from peripheral blood samples using silica column-based purification kits. Research project samples (Iseq100) were processed with the Monarch® Genomic DNA Purification Kit (cat. no. T3010, New England Biolabs, Ipswich, MA, USA), while leukemia panel samples (MiSeq) were processed with the GeneJET Whole Blood Genomic DNA Purification Mini Kit (cat. no. K0781, Thermo Fisher Scientific, Waltham, MA, USA). For both cohorts, DNA concentration was measured using the Qubit dsDNA High Sensitivity Assay Kit (cat. no. Q32851, Thermo Fisher Scientific, Waltham, MA, USA) on a Qubit Fluorometer v2 (cat. no. Q32866, Thermo Fisher Scientific, Waltham, MA, USA), and DNA integrity was assessed by electrophoresis on a 1% agarose gel in 1X TAE buffer.

2.4 Next Generation Sequencing

Library preparation was performed using the AmpliSeq™ for Illumina® kit (Illumina, San Diego, CA, USA) for both sample sets, following the manufacturer's protocol. In both workflows, target regions were amplified using two primer pools corresponding to the customized AmpliSeq panels, followed by partial digestion of amplicons with the FuPa reagent, ligation of i7 and i5 dual-index adapters, and purification using Agencourt AMPure XP beads (Beckman Coulter Life Sciences, Indianapolis, IN, USA). Libraries were amplified to increase DNA yield, subjected to a second bead-based cleanup, and verified for size distribution and concentration. Research project libraries had an average size of ~245 bp (125–275 bp) and were normalized to 2 nM in 20 µL, whereas leukemia panel libraries had an average size of ~353 bp (130–375 bp) and were normalized to 4 nM in 20 µL. Loading concentrations of 50 pM and 12 pM were used for the iSeq 100 and MiSeq samples, respectively.

2.5 Data Analysis

Sequencing data were processed using a shared bioinformatics pipeline for both cohorts. Base calling was performed by the instrument software, followed by alignment to the hg19 reference genome and variant identification and annotation. Quality control metrics were generated using the Sequencing Analysis Viewer (SAV) package. Across both cohorts, the average sequencing depth exceeded 500×, with high coverage uniformity across target regions. Variant calling was restricted to high-confidence variants based on quality metrics implemented in the BaseSpace Variant Interpreter pipeline, ensuring reliable detection of clinically relevant variants. Variant filtering and interpretation were conducted with the BaseSpace Variant Interpreter (version 2.14, Illumina, Inc., San Diego, CA, USA).

While targeted Next Generation Sequencing (NGS) panels enable accurate detection of known clinically relevant variants, they may not capture rare or novel variants and may not represent the most cost-effective strategy for comprehensive variant discovery. Additionally, although two sequencing platforms (iSeq100 and MiSeq) were used, a unified bioinformatics pipeline and consistent filtering criteria were applied to minimize platform-specific bias. However, no formal concordance analysis between platforms was performed; therefore, subtle platform-specific differences in variant detection or allele frequency estimation cannot be fully excluded.

2.6 Pharmacogenetic Variant Calling and Interpretation

Clinically relevant variants in the *TPMT* and *NUDT15* genes were identified from the annotated variant call files (VCFs) by cross-referencing them against a curated reference list of pharmacogenetically relevant positions compiled from CPIC and PharmGKB resources. Variants were matched using genomic coordinates and alternate alleles (CHR:POS:ALT) to ensure accurate identification. Star allele assignment was based on the co-occurrence of defining variants according to CPIC guidelines; however, phasing was not directly assessed, and haplotypes were inferred based on known linkage patterns. For *NUDT15*, the *2 allele was assigned only when both defining variants were detected; however, overlap with variants present in 3 and 6 cannot be fully excluded without phasing. For each participant, diplotypes were derived from the combination of detected star alleles, and phenotype categories (e.g., normal, intermediate, or poor metabolizer) were assigned following CPIC guidelines. Allele, genotype, and phenotype frequencies were computed, and summary tables were generated to report their distributions. All analyses were performed in R version 4.4.1 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1 Allele Frequencies of NUDT15 and TPMT

In the study cohort, the *TPMT* wild-type allele (**1*) was the most frequent at 90.40%, followed by *TPMT*3A* at 8.94%, while **2* and **3C* were both detected at 0.33%. For *NUDT15*, the wild-type allele (**1*) occurred at 89.57%, with *NUDT15 *2* observed at 9.27%; **4* at 0.50%; **6* at 0.33%; **3*, and **15* detected at 0.17% each (Table 1). Variant definitions followed CPIC and PharmVar standardized star allele nomenclature; corresponding rsIDs are provided in Table 1 for reference.

3.2 Diplotype Distribution and Predicted Phenotypes

Diplotype assignment based on CPIC guidelines revealed that for *NUDT15*, the most frequent diplotype was **1/*1* (240 individuals; 79.47%), followed by intermedi-

Table 1. Distribution and 95% confidence intervals of *TPMT* and *NUDT15* star allele frequencies (n = 604).

Allele	Count	Frequency (%) [95% CI]
TPMT		
*1	546	90.4 [87.8–92.6]
*2	2	0.3 [0.0–1.2]
*3A	54	8.9 [6.8–11.5]
*3C	2	0.3 [0.0–1.2]
NUDT15		
*1	541	89.6 [86.9–91.9]
*2	56	9.3 [7.1–11.9]
*3	1	0.2 [0.0–0.9]
*4	3	0.5 [0.1–1.4]
*6	2	0.3 [0.0–1.2]
*15	1	0.2 [0.0–0.9]

CI, Confidence interval; *TPMT*, thiopurine S-methyltransferase; *NUDT15*, nucleoside diphosphate–linked moiety X–type motif 15.

ate metabolizer combinations such as **1/*2*, **1/*3*, **1/*4*, **1/*6*, **1/*15* and **2/*4* (62 individuals; 20.53%) (Table 2). For *TPMT*, **1/*1* was the most common diplotype (244 individuals; 80.79%), with intermediate metabolizer diplotypes (**1/*3A*, **1/*2*, and **1/*3C*) observed in 58 patients (19.20%).

Table 2. Distribution and 95% confidence intervals of *TPMT* and *NUDT15* diplotypes (n = 302).

Diplotype	Count	Frequency (%) [95% CI]
TPMT		
*1/*1	244	80.8 [75.9–85.1]
*1/*2	2	0.7 [0.1–2.4]
*1/*3A	54	17.9 [13.7–22.7]
*1/*3C	2	0.7 [0.1–2.4]
NUDT15		
*1/*1	240	79.5 [74.5–83.9]
*1/*2	55	18.2 [14.0–23.0]
*1/*3	1	0.3 [0.0–1.8]
*1/*4	2	0.7 [0.1–2.4]
*1/*6	2	0.7 [0.1–2.4]
*1/*15	1	0.3 [0.0–1.8]
*2/*4	1	0.3 [0.0–1.8]

CI, Confidence interval.

When translated into predicted metabolizer phenotypes according to CPIC guidelines, 80.8% of patients were classified as normal metabolizers and 19.2% as intermediate metabolizers for *TPMT*, while for *NUDT15*, 79.5% were normal metabolizers and 20.5% were intermediate metabolizers. Diplotypes categorized as "possible intermediate metabolizers" for *NUDT15* (*1/*4, *1/*15, 2/4) were grouped within the intermediate metabolizer category, consistent with CPIC dosing recommendations.

3.3 Geographic Distribution of Variant Alleles in Peru

Mapping of allele frequencies showed regional differences in the distribution of pharmacogenetic variants. For *NUDT15*, the **2* allele exhibited higher frequencies in regions such as Cerro de Pasco, Lambayeque, Puno, and Cajamarca, while the **4* allele was almost exclusively detected in Loreto (Fig. 1A). For *TPMT*, the **3A* allele appeared more frequently in Loreto and Cuzco, whereas the **3C* allele was observed in Cuzco and Ica (Fig. 1B). Although these observations do not confirm population substructure, they reveal potential geographic variation in allele prevalence within Peruvian territory, which may be relevant for understanding regional patterns of thiopurine metabolism. However, given the limited sample size per region, these findings should be considered exploratory and interpreted with caution rather than as definitive evidence of geographic differences. Ancestry composition may contribute to these observations and warrants further investigation.

3.4 Variant-Level Visualization

Lollipop plots summarizing clinically relevant variants for *TPMT* and *NUDT15* highlight the distribution of detected alleles across exonic regions. For *TPMT* variants were distributed across exons 4, 6, and 9 (Fig. 2A), while *NUDT15*, one variant cluster was identified in exon 1 and three in exon 3 (Fig. 2B). The plots provide a visual representation of the positional distribution of the variants identified in the study cohort, visually contextualizing the overlap between global pharmacogenetic data and local variation.

4. Discussion

In this study, we characterized the distribution of *TPMT* and *NUDT15* variants with established clinical relevance to thiopurine metabolism in a Peruvian cohort. Patterns observed in our dataset aligned with previously reported variant profiles across diverse populations, with *TPMT* *3A and *3C emerging as the most relevant non-wild-type alleles, and *NUDT15* *2 and *4 detected at lower frequencies (Table 1). To complement these findings visually, variant-level genomic localization was displayed using lollipop plots for each gene (Fig. 2), and continental ancestry patterns were contextualized through a comparative geogenetic map (Fig. 1) highlights their distribution across different regions of Peru. These findings represent, to our knowledge, the first attempt to visualize regional variation in pharmacogenetic markers within the country, and they provide a foundation for understanding how population structure may influence thiopurine response in Peruvian patients.

The frequencies of *TPMT*3A* and **3C* in our Peruvian cohort align with observations in other Latin American populations. In Ecuadorian Mestizo and Indigenous groups, *TPMT*3A* frequency was approximately 5.5% and **3C* about 1.5%, suggesting similar variant prevalence

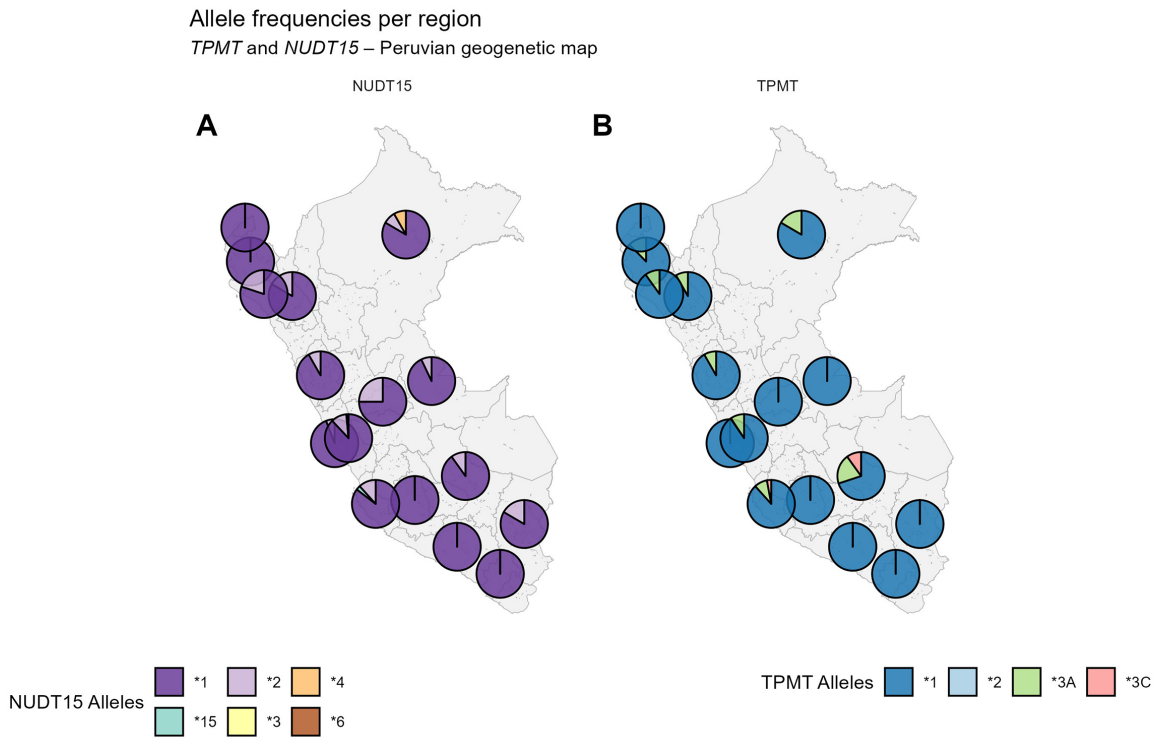

Fig. 1. Geographic distribution of pharmacogenetic variants across Peruvian regions. (A) Regional allele frequency distribution of *NUDT15* variants. (B) Regional allele frequency distribution of *TPMT* variants.

[22]. Comparable patterns have been observed in a cohort of Guatemalan admixed and indigenous individuals, where at least 10% carried one of the common *TPMT* deficiency alleles (**2*, **3A*, or **3C*) [23]. In contrast, a study from a Mexican cohort indicate a slightly lower frequency of **3A* than what we observed in Peru, suggesting possible differences even within Latin America [24]. Populations of European ancestry tend to show lower prevalence of **3A*, whereas **3C* is more characteristic of some Asian and African groups [25,26,27]. Regarding *NUDT15*, our detection of **2* allele frequencies aligns with findings from Amerindian and Latin American cohorts, in which *NUDT15* variants contribute significantly to thiopurine intolerance [11,28]. Although **3* and **6* are individually more frequent in East Asian populations, the composite *2 allele shows comparable frequencies in Peruvians, underscoring its clinical relevance [29]. It is important to note that *NUDT15 *2* represents a composite allele of variants also present in *3 and *6; therefore, without phasing, some individuals classified as 1/2 could correspond to alternative diplotype configurations, potentially influencing the predicted functional impact.

The identification of *TPMT* and *NUDT15* variants in our cohort has direct clinical relevance, as both genes are well-established determinants of thiopurine toxicity [8,13]. The prevalence of *TPMT *3A* (8.94%) and *NUDT15 *2* (9.27%) suggests that a notable proportion of Peruvian patients may be at increased risk for adverse drug reactions if treated with standard thiopurine doses, reinforcing the importance of preemptive genotyping before therapy initiation [8,13,30]. Although mapping of allele frequencies revealed higher *NUDT15 *2* representation in regions such as Cerro de Pasco, Lambayeque, Puno, and Cajamarca, and *TPMT *3A* in Loreto and Cuzco, the low sample size per region precludes robust conclusions about geographic substructure. These findings should therefore be interpreted as exploratory signals rather than definitive population-level trends. Despite these caveat, our results highlight the potential utility of pharmacogenetic screening in Peru and provide a preliminary framework for larger studies aimed at clarifying regional and clinical variability in *TPMT* and *NUDT15* allele distribution [20,28].

Significantly, our findings demonstrate that Peruvians have a significant burden of actionable alleles, especially *NUDT15*2*, at frequencies that are comparable to those found in East Asian groups. This result casts doubt on the notion that PGx profiles in Latin American groups are similar to those in Europe and emphasizes the necessity for clinical guidelines to include risk categories unique to Latin America. It also emphasizes that admixed and Indigenous people may not be adequately protected by the current global PGx frameworks.

To contextualize these findings in a clinically actionable framework, we generated a CPIC-based dosing concept map summarizing how combined *TPMT* and *NUDT15* phenotypes could guide thiopurine dose adjustments (Fig.

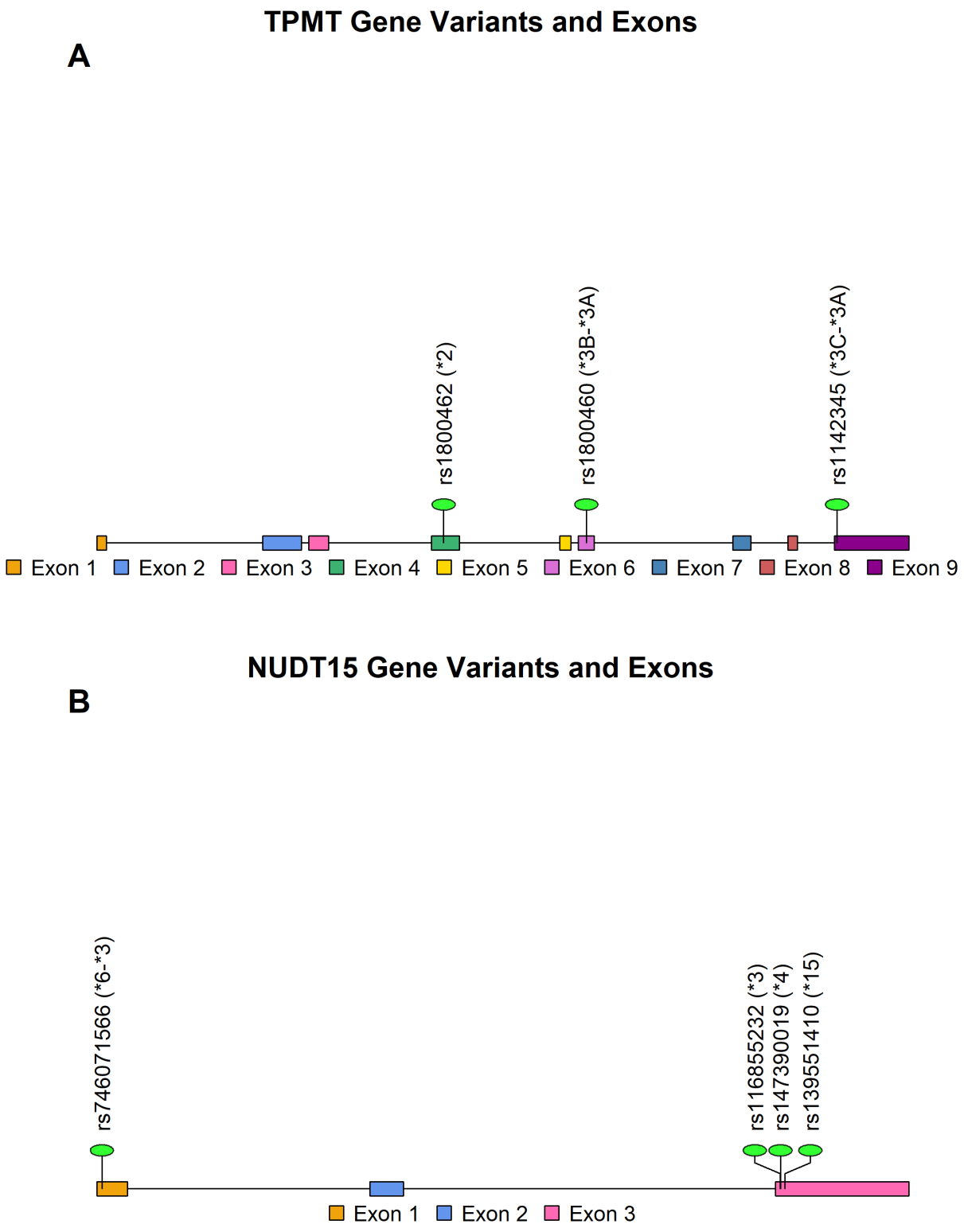

Fig. 2. Genomic distribution of variants identified in the study cohort. (A) *TPMT* Lollipop plot showing the genomic positions of variants detected in the study cohort along the gene structure. Each lollipop represents a variant positioned according to its genomic location. (B) *NUDT15* Lollipop plot showing the genomic positions of variants detected in the study cohort along the gene structure. Each lollipop represents a variant positioned according to its genomic location. All variants are displayed using uniform color and size to emphasize their positional distribution rather than frequency or relative importance.

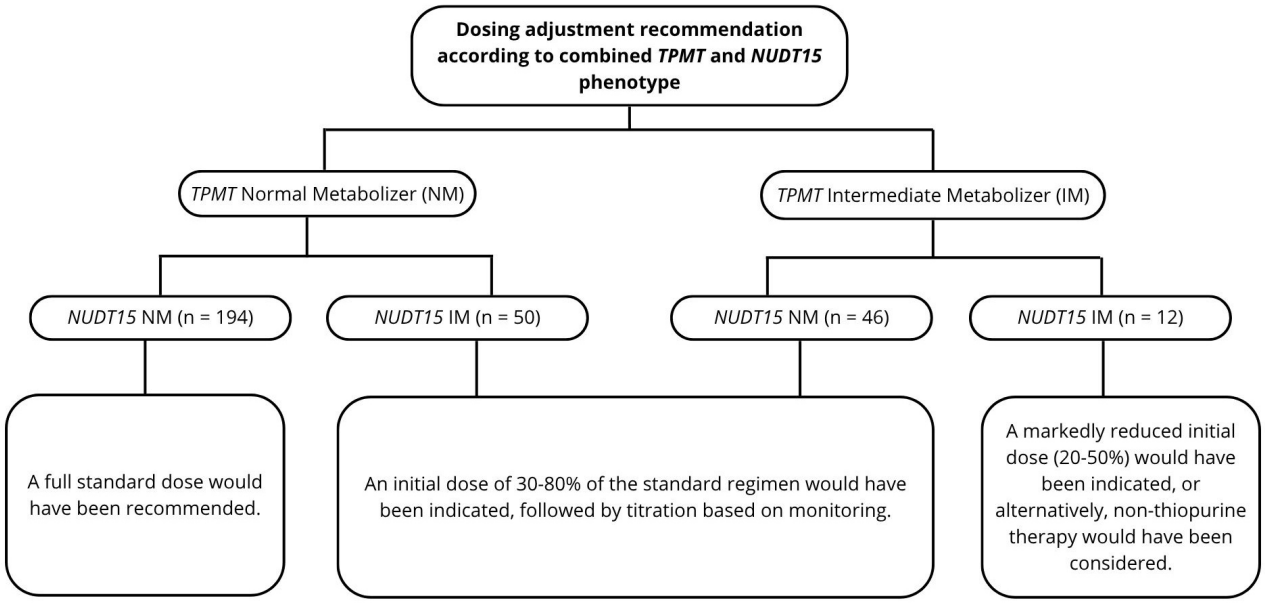

Fig. 3. CPIC-Based Thiopurine Dosing Recommendations According to Combined *TPMT–NUDT15* Phenotypes. This concept map summarizes the recommended relative dose reductions for thiopurines according to CPIC guidelines, based on combined *TPMT* and *NUDT15* metabolizer status. Although exact starting doses can differ across hospitals and treatment protocols, the percentage reductions shown here represent standardized CPIC dose-adjustment guidance applicable regardless of clinical setting or thiopurine agent (azathioprine, mercaptopurine, or thioguanine). At INSN-SB, the standard initial mercaptopurine dose is 50 mg/m^2, providing a local reference point for interpreting these percentage reductions. Because the patients described in this study had already undergone treatment, the diagram reflects what would have been indicated according to current CPIC recommendations for each combined phenotype. CPIC, Clinical Pharmacogenetics Implementation Consortium; INSN-SB, Instituto Nacional de Salud del Niño-San Borja.

3). While our study did not evaluate treatment outcomes, the distribution of diplotypes indicates that a substantial proportion of Peruvian patients may fall into reduced-metabolism categories. Specifically, 31.79% of participants were classified as NM/IM or IM/NM, and an additional 3.97% were classified as IM/IM, phenotype groups known to confer increased myelotoxicity risk under standard thiopurine dosing. According to CPIC recommendations, patients classified as NM/IM or IM/NM should initiate therapy at approximately 30–80% of the full thiopurine dose, whereas those classified as IM/IM may require more substantial reduction (approximately 20–50% of the full dose) alongside intensive clinical monitoring [12]. At INSN-SB, the standard initial dose of mercaptopurine is 50 mg/m² [31], providing a practical reference point for interpreting how these percentage reductions would translate into actual starting doses in local clinical practice. The concept map is therefore presented as a translational reference to illustrate how population-level pharmacogenetic distributions may influence real-world prescribing decisions and to emphasize the importance of implementing genotype-guided dosing protocols in Peru. However, these recommendations are based on established CPIC guidelines and have not been clinically validated in this specific population; therefore, they should be interpreted as a conceptual framework rather than directly applicable dosing guidance. These results demonstrate the critical need for PGx-informed dosage strategies in the Peruvian healthcare system and are directly applicable to national pediatric cancer programs.

Further research should extend to larger, multi-regional and ideally multi-ethnic cohorts across Peru and Latin America, allowing for more robust evaluations of *TPMT* and *NUDT15* allele distribution as well as the discovery of novel pharmacogenetic markers, potentially through genome-wide association strategies [32]. Integrating functional validation studies and longitudinal clinical follow-up would strengthen genotype–phenotype correlations and enhance predictive utility for thiopurine toxicity in clinical settings. Establishing regional allele frequency databases and standardized genotyping platforms will also facilitate the broader implementation of pharmacogenetic screening in Peru. Although challenges remain, such as limited infrastructure and disparities in healthcare access [33], our study offers a foundational step toward precision medicine in underrepresented populations, aiming to improve therapeutic safety and efficacy through locally relevant pharmacogenetic insights.

In general, worldwide disparities are exacerbated by the underrepresentation of Latin Americans in pharmacogenomics, particularly those who are highly Amerindian. Our findings support the inclusion of Latin American PGx pro-

files in international recommendations and aid in closing this disparity. Our results offer crucial evidence that Peru is well-positioned to further this endeavor.

Limitations

The limitations of the study include uneven regional sampling, lack of comprehensive genome-wide ancestry analyses to rule out stratification, and the inability to assess rare or novel alleles beyond the selected set. Additionally, the lack of clinical outcome data, including thiopurine-related toxicity, precluded genotype–phenotype correlation, limiting the direct translational applicability of the findings. Estimates for low-frequency alleles (e.g., *3C, *6, *15) showed wide confidence intervals, reflecting limited precision. Moreover, no formal statistical analyses (e.g., Hardy–Weinberg equilibrium or comparisons with external populations) were performed, as the study was designed to provide a descriptive characterization of allele and diplotype distributions. Furthermore, although data from two sequencing platforms were combined, no direct cross-platform concordance analysis was conducted, and potential platform-specific biases in variant detection or frequency estimation cannot be entirely ruled out. Therefore, the observed allele frequency patterns should be interpreted as descriptive and exploratory, and may not fully capture the underlying population genetic structure.

5. Conclusion

In this study, we characterized the frequency and geographic distribution of clinically relevant *TPMT* and *NUDT15* alleles in a Peruvian cohort, revealing the presence of intermediate-function variants—including the composite star alleles *TPMT *3A* and *NUDT15 *2*—that indicate a substantial subset of Peruvian patients may be genetically predisposed to thiopurine-related toxicity under standard dosing. While regional differences were only suggestive due to limited sample size and uneven geographic representation, the integration of a CPIC-based dosing concept map based on combined *TPMT–NUDT15* phenotypes illustrates the translational potential of our findings and underscores how genotype-guided prescribing could meaningfully improve therapeutic safety. Together, these results show how CPIC-guided frameworks may convert PGx data into safer thiopurine dose and highlight the necessity of pharmacogenetic testing and reliable local reference datasets in Peru's highly admixed population. To promote egalitarian precision medicine in Peru, broader sample, ancestry-informed studies, and clinical outcome integration will be crucial.

Availability of Data and Materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions

.JAP designed the study. JAP, KFB, GMM, AMR and JCS collected the patient samples and data. FSP and JFV conducted the research and laboratory experiments. JAP, GNM and LJV performed the statistical analysis of the data. Project administration, JAP and JCS. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work. All authors contributed to editorial changes in the manuscript. All authors read and approved the final version of the manuscript.

Ethics Approval and Consent to Participate

Our study was approved by the Institutional Research Ethics Committee of the Instituto Nacional de Salud del Niño San Borja (CIEI-INSN-SB; Approval No. 077-2025, Project Code PI 364), in accordance with the Declaration of Helsinki. Written informed consent was obtained from the parents or legal guardians of all pediatric participants prior to inclusion in the study.

Acknowledgment

We acknowledge the support of local health authorities and participants in Cusco, Peru.

Funding

This research was funded by the Instituto Nacional de Salud del Niño San Borja (INSN-SB) through the grant "Fondo Concursable para el Desarrollo de Proyectos de Investigación" (Resolución Directoral No. 199-2019-DG-INSNSB).

Conflicts of Interest

The authors declare no conflicts of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work the authors used ChatGpt-5.2 in order to check spelling and grammar. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/FBS50635.

References

[1] Levinsen M, Rosthøj S, Nygaard U, Heldrup J, Harila-Saari A, Jonsson OG, et al. Myelotoxicity after high-dose methotrexate in childhood acute leukemia is influenced by 6-mercaptopurine dosing but not by intermediate thiopurine methyltransferase activity. Cancer Chemotherapy and Pharmacology. 2015; 75: 59–66. https://doi.org/10.1007/s00280-014-2613-7

[2] Bayoumy AB, Crouwel F, Chanda N, Florin THJ, Buiter HJC, Mulder CJJ, et al. Advances in Thiopurine Drug Delivery: The Current State-of-the-Art. European Journal of Drug Metabolism and Pharmacokinetics. 2021; 46: 743–758. https://doi.org/10.1007/s13318-021-00716-x

[3] Marinaki AM, Arenas-Hernandez M. Reducing risk in thiopurine therapy. Xenobiotica; the Fate of Foreign Compounds in Biological Systems. 2020; 50: 101–109. https://doi.org/10.1080/00498254.2019.1688424

[4] Krynetski EY, Evans WE. Pharmacogenetics as a molecular basis for individualized drug therapy: the thiopurine S-methyltransferase paradigm. Pharmaceutical Research. 1999; 16: 342–349. https://doi.org/10.1023/a:1011909315614

[5] Weinshilboum RM, Sladek SL. Mercaptopurine pharmacogenetics: monogenic inheritance of erythrocyte thiopurine methyltransferase activity. American Journal of Human Genetics. 1980; 32: 651–662.

[6] Gaedigk A, Casey ST, Whirl-Carrillo M, Miller NA, Klein TE. Pharmacogene Variation Consortium: A Global Resource and Repository for Pharmacogene Variation. Clinical Pharmacology and Therapeutics. 2021; 110: 542–545. https://doi.org/10.1002/cpt.2321

[7] Relling MV, Klein TE. CPIC: Clinical Pharmacogenetics Implementation Consortium of the Pharmacogenomics Research Network. Clinical Pharmacology and Therapeutics. 2011; 89: 464–467. https://doi.org/10.1038/clpt.2010.279

[8] Relling MV, Schwab M, Whirl-Carrillo M, Suarez-Kurtz G, Pui CH, Stein CM, et al. Clinical Pharmacogenetics Implementation Consortium Guideline for Thiopurine Dosing Based on TPMT and NUDT15 Genotypes: 2018 Update. Clinical Pharmacology and Therapeutics. 2019; 105: 1095–1105. https://doi.org/10.1002/cpt.1304

[9] Yang SK, Hong M, Baek J, Choi H, Zhao W, Jung Y, et al. A common missense variant in NUDT15 confers susceptibility to thiopurine-induced leukopenia. Nature Genetics. 2014; 46: 1017–1020. https://doi.org/10.1038/ng.3060

[10] Yang JJ, Landier W, Yang W, Liu C, Hageman L, Cheng C, et al. Inherited NUDT15 variant is a genetic determinant of mercaptopurine intolerance in children with acute lymphoblastic leukemia. Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology. 2015; 33: 1235–1242. https://doi.org/10.1200/JCO.2014.59.4671

[11] Ioannou S, Beecham A, Gomez L, Dauer R, Khakoo N, Pascual L, et al. Ancestral Diversity in Pharmacogenomics Affects Treatment for Hispanic/Latine Populations With Inflammatory Bowel Disease. Clinical Gastroenterology and Hepatology : the Official Clinical Practice Journal of the American Gastroenterological Association. 2025; 23: 1008–1018.e7. https://doi.org/10.1016/j.cgh.2024.07.032

[12] CPIC® Guideline for Thiopurines and TPMT and NUDT15 – CPIC. Available at: https://cpicpgx.org/guidelines/guideline-for-thiopurines-and-tpmt/ (Accessed: 15 August 2025).

[13] Maillard M, Nishii R, Yang W, Hoshitsuki K, Chepyala D, Lee SHR, et al. Additive effects of TPMT and NUDT15 on thiopurine toxicity in children with acute lymphoblastic leukemia across multiethnic populations. Journal of the National Cancer Institute. 2024; 116: 702–710. https://doi.org/10.1093/jnci/djae004

[14] Esperón P, Martínez MF, Redal MA, Lazarowski A, López-Cortés A, Varela NM, et al. Editorial: Pharmacogenetics and Pharmacogenomics in Latin America: Ethnic Variability, New Insights in Advances and Perspectives: A RELIVAF-CYTED Initiative. Frontiers in Pharmacology. 2022; 12: 833000. https://doi.org/10.3389/fphar.2021.833000

[15] Bergström A, McCarthy SA, Hui R, Almarri MA, Ayub Q, Danecek P, et al. Insights into human genetic variation and population history from 929 diverse genomes. Science (New York, N.Y.). 2020; 367: eaay5012. https://doi.org/10.1126/science.aay5012

[16] Soler AM, Olano N, Méndez Y, Lopes A, Silveira A, Dabezies A, et al. TPMT and NUDT15 genes are both related to mercaptopurine intolerance in acute lymphoblastic leukaemia patients from Uruguay. British Journal of Haematology. 2018; 181: 252–255. https://doi.org/10.1111/bjh.14532

[17] Farfan MJ, Salas C, Canales C, Silva F, Villarroel M, Kopp K, et al. Prevalence of TPMT and ITPA gene polymorphisms and effect on mercaptopurine dosage in Chilean children with acute lymphoblastic leukemia. BMC Cancer. 2014; 14: 299. https://doi.org/10.1186/1471-2407-14-299

[18] Aráoz HV, D'Aloi K, Foncuberta ME, Sanchez La Rosa CG, Alonso CN, Chertkoff L, et al. Pharmacogenetic studies in children with acute lymphoblastic leukemia in Argentina. Leukemia & Lymphoma. 2015; 56: 1370–1378. https://doi.org/10.3109/10428194.2014.951844

[19] Correa-Jimenez O, Yunis JJ, Linares-Ballesteros A, Sarmiento-Urbina I. Susceptibility to thiopurine toxicity by *TPMT* and *NUDT15* variants in Colombian children with acute lymphoblastic leukemia. Colombia Medica (Cali, Colombia). 2021; 52: e2074569. https://doi.org/10.25100/cm.v52i3.4569

[20] Suarez-Kurtz G, Almeida CW, Chapchap E, Schramm MT, Ikoma-Coltutato MRV, Lins MM, et al. Pharmacogenetic testing for thiopurine drugs in Brazilian acute lymphoblastic leukemia patients. Clinics (Sao Paulo, Brazil). 2023; 78: 100214. https://doi.org/10.1016/j.clinsp.2023.100214

[21] Harris DN, Song W, Shetty AC, Levano KS, Cáceres O, Padilla C, et al. Evolutionary genomic dynamics of Peruvians before, during, and after the Inca Empire. Proceedings of the National Academy of Sciences of the United States of America. 2018; 115: E6526–E6535. https://doi.org/10.1073/pnas.1720798115

[22] Gallardo-Cóndor J, Naranjo P, Atarihuana S, Coello D, Guevara-Ramírez P, Flores-Espinoza R, et al. Population-Specific Distribution of *TPMT* Deficiency Variants and Ancestry Proportions in Ecuadorian Ethnic Groups: Towards Personalized Medicine. Therapeutics and Clinical Risk Management. 2023; 19: 1005–1018. https://doi.org/10.2147/TCRM.S432856

[23] Garrido C, Santizo VG, Müllers P, Soriano DR, Avila GB, Dean M, et al. Frequency of thiopurine S-methyltransferase mutant alleles in indigenous and admixed Guatemalan patients with acute lymphoblastic leukemia. Medical Oncology (Northwood, London, England). 2013; 30: 474. https://doi.org/10.1007/s12032-013-0474-2

[24] Jiménez-Morales S, Ramírez-Florencio M, Mejía-Aranguré JM, Núñez-Enríquez JC, Bekker-Mendez C, Torres-Escalante JL, et al. Analysis of Thiopurine S-Methyltransferase Deficient Alleles in Acute Lymphoblastic Leukemia Patients in Mexican Patients. Archives of Medical Research. 2016; 47: 615–622. https://doi.org/10.1016/j.arcmed.2016.11.018

[25] Pratt VM, Cavallari LH, Fulmer ML, Gaedigk A, Hachad H, Ji Y, et al. TPMT and NUDT15 Genotyping Recommendations: A Joint Consensus Recommendation of the Association for Molecular Pathology, Clinical Pharmacogenetics Implementation Consortium, College of American Pathologists, Dutch Pharmacogenetics Working Group of the Royal Dutch Pharmacists Association, European Society for Pharmacogenomics and Personalized Therapy, and Pharmacogenomics Knowledgebase. The Journal of Molecular Diagnostics : JMD. 2022; 24: 1051–1063. https://doi.org/10.1016/j.jmoldx.2022.06.007

[26] Jantararoungtong T, Wiwattanakul S, Tiyasirichokchai R, Prommas S, Sukprasong R, Koomdee N, et al. *TPMT*3C* as a Predictor of 6-Mercaptopurine-Induced Myelotoxicity in Thai Children with Acute Lymphoblastic Leukemia. Journal of Personalized Medicine. 2021; 11: 783. https://doi.org/10.3390/jp

m11080783
[27] Adehin A, Bolaji OO, Kennedy MA, Adeagbo BA. Allele frequencies of thiopurine S-methyltransferase (TPMT) variants in the Nigerian population. Polish Annals of Medicine. 2017; 24: 144–147. https://doi.org/10.1016/j.poamed.2016.06.007
[28] Owen GI, Cordova-Delgado M, Bustos BI, Cerpa LC, Gonzalez P, Morales-Pison S, et al. Assessing the Occurrence and Influence of Cancer Chemotherapy-Related Pharmacogenetic Alleles in the Chilean Population. Pharmaceutics. 2024; 16: 561. https://doi.org/10.3390/pharmaceutics16040561
[29] Zhang F, Amat G, Tang Y, Chen R, Tian X, Hu W, et al. *NUDT15* Genetic Variants in Chinese Han, Uighur, Kirghiz, and Dai Nationalities. Frontiers in Pediatrics. 2022; 10: 832363. https://doi.org/10.3389/fped.2022.832363
[30] Zimdahl Kahlin A, Helander S, Wennerstrand P, Vikingsson S, Mårtensson LG, Appell ML. Pharmacogenetic studies of thiopurine methyltransferase genotype-phenotype concordance and effect of methotrexate on thiopurine metabolism. Basic & Clinical Pharmacology & Toxicology. 2021; 128: 52–65. https://doi.org/10.1111/bcpt.13483
[31] National Institute of Child Health San Borja (Instituto Nacional de Salud del Niño – San Borja); Subunit of Comprehensive Specialized Care for Hematopoietic Stem Cell Transplant Patients – Clinical Hematology. Guía de Práctica Clínica de Diagnóstico y Tratamiento de Leucemia Linfoblástica Aguda. 2021. Available at: https://cdn.www.gob.pe/uploads/document/file/7682037/6504886-rd-n-000188-2021-dg-insnsb-gpc-leucemia-linfoblastica-aguda.pdf.
[32] Zhou Y, Lauschke VM. Population pharmacogenomics: an update on ethnogeographic differences and opportunities for precision public health. Human Genetics. 2022; 141: 1113–1136. https://doi.org/10.1007/s00439-021-02385-x
[33] Carrillo-Larco RM, Guzman-Vilca WC, Leon-Velarde F, Bernabe-Ortiz A, Jimenez MM, Penny ME, et al. Peru - Progress in health and sciences in 200 years of independence. Lancet Regional Health. Americas. 2021; 7: 100148. https://doi.org/10.1016/j.lana.2021.100148