Available online **www.ijpras.com**

International Journal of Pharmaceutical Research & Allied Sciences, 2026, 15(2):181-191

https://doi.org/10.51847/RHFRWu8p3T



Original Article

ISSN : 2277-3657
CODEN(USA) : IJPRPM

Whose Genome Guides the Prescription After Allogeneic Transplantation? A Tissue-of-Origin Framework for Pharmacogenomic Sampling, Donor–Recipient Chimerism, and Drug-Specific Interpretation

Aisha Rahman[1]*, Johan de Vries[2], Aiko Nakamura[3], Grace Okafor[4]

[1]Department of Pharmacogenomics, Lahore University of Management Sciences, Lahore, Pakistan.
[2]Department of Clinical Pharmacy, Utrecht University, Utrecht, Netherlands.
[3]Department of Clinical Pharmacology, Osaka University, Osaka, Japan.
[4]Department of Pharmaceutical Sciences, University of Ibadan, Ibadan, Nigeria.

***Email:** aisha.rahman@lums.edu.pk*

ABSTRACT

Allogeneic hematopoietic stem cell transplantation creates a persistent interpretive problem for pharmacogenomics: DNA recovered from an accessible post-transplant specimen may belong partly or predominantly to the donor while drug metabolism and response involve distinct recipient and donor-derived tissues. To extend genotype-guided prescribing theory by specifying when a specimen-derived pharmacogene result can be assigned to the biological compartment responsible for a drug-specific effect. This nonempirical analysis integrates verified work on post-transplant sampling, lineage-specific chimerism assays, pharmacogene mechanisms, transplant pharmacokinetics, and genotype-based prescribing. Genotype attribution is treated as a conditional inference linking specimen composition, molecular origin, tissue persistence, the relevant pharmacological process, and time relative to transplantation. The analysis separates evidence that identifies donor or recipient DNA from evidence that establishes enzyme or transporter function and clinical actionability. Recipient-derived nonhematopoietic DNA may be needed to recover inherited metabolic genotypes, whereas donor-derived hematopoietic genotype could matter for selected cellular effects; the latter remains a testable drug-specific proposition, not a general dosing rule. The appropriate genome for prescribing is defined by the drug-relevant functional compartment and a validated sampling-to-phenotype relationship, not by donor chimerism or sampling convenience alone.

Key words: *Allogeneic hematopoietic stem cell transplantation, Pharmacogenomic sampling, Donor–recipient chimerism, Tissue-of-origin attribution, CYP3A5, Therapeutic drug monitoring*

Received: 25 July 2026; **Revised:** 28 August 2026; **Accepted:** 04 September 2026

INTRODUCTION

Pharmacogenomic interpretation commonly assumes that a constitutional genotype measured in accessible tissue represents the inherited genotype relevant to prescribing. That assumption is unstable after allogeneic hematopoietic stem cell transplantation (allo-HSCT). When blood cells are replaced by donor-derived hematopoiesis, a technically accurate genotype from peripheral blood may describe the donor. Buccal material can also contain donor-derived leukocytes. In a published post-transplant sampling investigation, hair-follicle DNA provided a possible recipient-origin alternative, although yield and assay capacity were limiting [1]. Such a result raises a question of biological attribution, not merely laboratory specimen quality.

© 2026 The International Journal of Pharmaceutical Research and Allied Sciences (IJPRAS). **Open Access** - This article is under the **CC BY NC SA** license (https://creativecommons.org/licenses/by-nc-sa/4.0).

The clinical importance of this distinction follows from the structure of pharmacogenomics itself. Variants are interpreted through functions such as metabolism, transport, drug-target interaction, and pathway-specific toxicity, and their implementation depends on treatment context [2]. Thus, recovering an authentic inherited allele and determining whether that allele predicts a drug response are separate achievements. In the PREPARE implementation study, multigene pharmacogenetic decision support reduced clinically relevant adverse drug reactions in a broad healthcare setting [3]. This supports the clinical value of actionable pharmacogenetics, but the trial did not test post-HSCT donor–recipient discordance, organ provenance, or transplantation-specific dosing.

Here, the theoretical problem is the presumed equivalence of four objects: the sampled genome, the genotype of the biological compartment mediating a drug effect, the expressed functional phenotype, and the clinically useful prescribing prediction. After allo-HSCT these objects can diverge. We extend the usual interpretation domain by asking which compartment contributes causally to each drug pathway, which genotype is identifiable in an available specimen, and what comparator would falsify a tissue-specific attribution. The account concerns conditional interpretation rather than an empirically evaluated clinical algorithm.

Pharmacogenomic attribution after allogeneic transplantation

The primary distinction is between whose DNA was measured and whose cells determine pharmacological disposition or effect. Donor hematopoietic engraftment changes the lineage of circulating and marrow-derived cells without replacing the recipient's liver or intestinal epithelium. A useful counterexample arises in liver transplantation, where the donor liver and recipient intestinal tissues can carry different CYP3A genotypes. An early post-transplant analysis found that recipient CYP3A5 status could be particularly informative for tacrolimus dose requirements in that solid-organ setting [4]. Its anatomy and findings cannot be transferred directly to allo-HSCT; its relevance is the demonstration that compartment identity changes the attribution question.

For drugs whose disposition depends substantially on nonhematopoietic tissues, recipient genomic provenance remains a strong initial biological hypothesis. The statin guideline identifies hepatic SLCO1B1 uptake, ABCG2 transport, and CYP2C9 metabolism as distinct pharmacogenetic pathways [5]. In ordinary allo-HSCT anatomy, donor-derived blood cannot be assumed to replace the genotype of hepatocytes mediating hepatic uptake. The genotype from a donor-dominant blood sample may therefore be analytically authentic yet inappropriate for the causal mechanism being inferred.

An analogous distinction appears with clopidogrel: CYP2C19 genotype informs the capacity for metabolic activation, while platelet effects occur downstream of active-metabolite formation [6]. Although platelets originate from donor hematopoiesis after engraftment, that lineage fact alone cannot determine the recipient's hepatic bioactivation genotype or establish a donor-specific clinical dosing adjustment. Pharmacological attribution must specify the molecular reaction, the relevant tissue, and whether the effect is systemic or cell-autonomous. For mixed pathways, more than one compartment may require study. These distinctions give the post-transplant problem an experimentally answerable form rather than a binary choice of donor versus recipient DNA.

Current evidence on donor–recipient chimerism and genotyping practices

Chimerism assays are designed chiefly to characterize hematopoietic engraftment, relapse risk, or immune reconstitution. UK consensus recommendations specify specimen selection, whole-blood or lineage-specific analysis, timing, assay sensitivity, and reporting of subset purity [7]. Those requirements show why a reported donor percentage is meaningful only relative to the cells actually analyzed. It is not an estimate of donor-derived hepatocytes, intestinal enterocytes, or drug-metabolizing enzyme activity.

Highly sensitive molecular approaches can distinguish small donor or recipient contributions in hematopoietic samples; Kanaan and colleagues situated ultrasensitive chimerism alongside measurable residual disease assessment [8]. Comparative testing of next-generation sequencing with short-tandem-repeat and quantitative-PCR strategies illustrates that methods address different analytical operating conditions [9]. Validation work on sequencing-based engraftment monitoring likewise emphasizes assay-specific performance and the clinical identity of the sample [10]. These advances improve the detection and quantification of genomic admixture without directly testing drug exposure or adverse-response prediction.

Biological distribution further complicates the inference. Reports of naturally occurring body-wide chimerism and mosaicism establish that genotype discordance can differ among tissues, although those developmental phenomena are not equivalent to acquired donor hematopoiesis after allo-HSCT [11]. Standardized

pharmacogenetic terminology distinguishes allele status, metabolizer phenotype assignment, and clinical interpretation [12]. The missing field is *genomic provenance*: the result must state whether the tested molecules represent the recipient, donor, or unresolved mixture before translating alleles into an assumed organ phenotype. A specimen-dependent claim can therefore be assessed at several levels: sampling origin, cell lineage composition, assay detection, recipient genotype recovery, and drug-mechanism relevance. The distinctions between these levels are summarized in **Table 1**. In particular, a reliable donor-fraction measurement is evidence about the analyzed material, not a universal correction factor for pharmacogenetic allele calling.

Table 1. Specimen provenance and pharmacogenomic inferential limits after allogeneic hematopoietic transplantation

Material or assay context	Genomic identity directly represented	Principal interpretive vulnerability	Conditional use in pharmacogenomics
Archived pretransplant recipient material	Recipient DNA before donor engraftment	Availability, identity, storage quality	Preferred historical comparator when quality and identity are confirmed
Peripheral blood after engraftment	Mixture determined by sampled hematopoietic lineages	Donor-dominant allele may be mistaken for recipient constitutional genotype	Useful for lineage-aware chimerism; requires provenance qualification for inherited metabolic PGx
Buccal swab after engraftment	Epithelial DNA with potentially substantial donor leukocyte admixture	Variable cell composition across collection methods	Recipient attribution requires independent proof of composition or concordance
Hair-follicle/root material	Potential recipient nonhematopoietic DNA	Low DNA recovery; specimen and assay feasibility	Candidate recipient-genotype source, subject to identity and assay-quality confirmation
Sorted blood-cell subsets	Specified donor/recipient hematopoietic lineage	Purity, assay sensitivity, lineage evolution	Supports lineage-specific biological hypotheses, not automatic systemic clearance predictions
STR, qPCR, or NGS chimerism assay	Proportions or markers within tested material	Platform-dependent detection and target selection	Establishes admixture only within its validated specimen and analytical range

Abbreviations: PGx, pharmacogenomics; STR, short tandem repeat; qPCR, quantitative polymerase chain reaction; NGS, next-generation sequencing. The conditional uses are an evidence-bounded synthesis; they do not constitute validated drug-specific sampling instructions. No cell-mixture threshold is assumed.

Unresolved relationships between sample genotype and drug-relevant tissue

Tacrolimus provides a stringent test because oral exposure depends on metabolic processes in gut and liver, concomitant medication, and changing transplant physiology. In an allo-HSCT cohort selected for a rapid-metabolism phenotype, CYP3A5 expression was associated with tacrolimus concentration-to-dose behavior and acute graft-versus-host disease outcomes [13]. The observed association has pharmacological relevance, yet the study does not show that post-transplant donor-derived blood acquires the recipient's hepatic genotype or that donor hematopoietic CYP3A5 drives systemic clearance.

A separate prospective allo-HSCT investigation associated CYP3A5 expression with oral tacrolimus pharmacokinetics, while effects of investigated ABCB1 variants and some other CYP3A markers were not independently demonstrated [14]. These differences matter: lack of detectable association for a candidate locus need not imply that genotyping generally lacks value, and a CYP3A5 effect cannot identify its tissue of action through blood concentrations alone. Exposure may reflect genotype-dependent intestinal or hepatic processes together with formulation and clinical covariates.

A systematic review of calcineurin-inhibitor pharmacogenetics in hematopoietic transplantation identified heterogeneity across candidate genes, protocols and clinical settings, with stronger coherence for CYP3A5–tacrolimus relationships than for several alternatives [15]. This warrants treating CYP3A5 as a prioritized mechanistic candidate, while resisting any claim of a validated donor-versus-recipient dosing fraction. A recent allo-HCT population pharmacokinetic model incorporated transplant-context characteristics and CYP3A5 phenotype for tacrolimus prediction [16]. Predictive adequacy in a fitted population remains distinct from isolating a causal cell lineage.

Three competing accounts may yield a similar measured tacrolimus concentration: recipient gastrointestinal/hepatic enzyme genotype, drug interactions or transplant-related organ dysfunction, and model

misspecification or sampling time. None can be excluded by a donor fraction measured in peripheral blood. The unresolved problem is consequently an *identification problem*: which genotype–function link survives when origin, treatment route, concomitant inhibition, organ function, and repeated measured exposure are jointly observed?

Scientific foundations for tissue-of-origin pharmacogenomic interpretation

Mechanism determines where a genotype may matter. For voriconazole, CYP2C19 activity is a well-established source of exposure variability and underlies a clinical pharmacogenetic guideline [17]. In an allo-HSCT recipient, a donor-derived hematopoietic genotype is not automatically a surrogate for the hepatic genotype relevant to systemic CYP2C19 metabolism. Whether a recipient-derived specimen produces better drug-exposure prediction than donor-derived blood is an empirical question requiring comparable assay methods and therapeutic drug monitoring.

Thiopurines illustrate a different tissue emphasis. TPMT and NUDT15 variants inform toxicity-related prescribing because their functional consequences intersect intracellular thiopurine metabolism and hematopoietic susceptibility [18]. Following allo-HSCT, donor-derived marrow may plausibly alter lineage-local responses to a post-engraftment exposure. However, donor-cell genotype, recipient systemic handling, indication, and treatment timing would need to be separated before transplant-specific decisions could follow. A donor-marrow hypothesis is therefore plausible but clinically unvalidated here.

Time changes the meaning of lineage attribution. Busulfan conditioning often occurs before donor infusion. In an allo-HCT study, recipient GSTA1 polymorphisms were associated with busulfan exposure during conditioning [19]. Busulfan metabolite measurements immediately before allograft infusion further locate metabolic observations on the pre-engraftment side of the transition [20]. A later donor-dominant blood genotype cannot retroactively determine which inherited liver genotype mediated a previous conditioning dose.

Nor does every conditioning drug admit the same genotype inference. An exposure–outcome investigation of treosulfan in thalassemia transplantation supports a clinically important drug-specific pharmacokinetic relationship without establishing donor–recipient genotype attribution [21]. The relevant units may thus be an enzyme-producing organ for systemic clearance, a donor-derived cell for intracellular injury, or a pretransplant recipient at the time of exposure. The scientific contrasts are assembled in **Table 2.** They are mechanistic interpretations, and none assigns a general post-HSCT dose adjustment.

Table 2. Pharmacological compartment and temporal conditions that determine which genotype could be informative

Drug pathway or process	Functionally implicated tissue or cell process	Provenance-sensitive interpretation	Boundary that prevents automatic clinical transfer
Voriconazole oxidation via CYP2C19	Predominantly recipient hepatic metabolic capacity in ordinary allo-HSCT anatomy	Recover recipient metabolic genotype when post-HSCT blood is donor-derived	Measured exposure also varies with interacting drugs, inflammation, and organ function
Oral tacrolimus handling via CYP3A5	Intestinal and hepatic metabolism; systemic trough monitoring	Recipient nonhematopoietic genotype is a plausible primary baseline for metabolism	Route, azole exposure, physiology, and model context can modify the genotype–exposure relation
Statin hepatic uptake via SLCO1B1	Hepatocyte uptake transporter	Donor blood genotype cannot establish recipient hepatic transporter function	Drug-specific transporter contribution and clinical indication must be confirmed
Clopidogrel bioactivation via CYP2C19	Metabolite formation with downstream platelet inhibition	Enzyme genotype and platelet lineage should be evaluated as separate mechanisms	Donor platelets do not by themselves identify hepatic prodrug activation
Thiopurine metabolism and marrow injury	Intracellular metabolism and susceptible hematopoietic cells	Donor-derived marrow may become mechanistically relevant after engraftment	Post-HSCT genotype-guided clinical benefit is not established by general-population guidance
Busulfan during conditioning	Recipient hepatic metabolism before donor infusion	Pretransplant recipient genotype is temporally relevant	Later engraftment cannot change genotype responsible for earlier exposure
Treosulfan conditioning exposure	Systemic exposure associated with transplant outcomes	Exposure and clinical response require a drug-specific kinetic account	A donor–recipient germline attribution rule has not been demonstrated

Note: "Plausible" denotes a proposed anatomical or mechanistic inference, not proven transplant-specific actionability. Cell and organ assignments assume conventional allo-HSCT without solid-organ replacement.

Development of the proposed precision pharmacotherapy framework

The hidden assumption exposed by allo-HSCT is that the genotype obtained from a clinically convenient specimen is exchangeable with the genotype producing the relevant drug phenotype. The revised interpretation domain requires an explicit chain of attribution. First, the laboratory result has an observed specimen identity: cell mixture, collection time, and assay characteristics. Second, a genome-origin claim specifies whether donor, recipient, or admixture is represented. Third, a pharmacological locus identifies the organ or cell population in which the gene's function changes drug disposition or response. Only then can a clinical prediction be evaluated against measured exposure or outcome.

This chain is conditional, not deterministic. Inhibition of CYP2C19 in genotyped volunteers demonstrates phenoconversion: co-medication can change observed enzyme activity relative to a genetically predicted phenotype [22]. Furthermore, population pharmacokinetic models of tacrolimus differ in the covariates and contexts they use to estimate exposure [23]. Failure of a model developed for kidney recipients to transport without validation to allo-HSCT recipients exemplifies a clinical-context boundary independent of DNA provenance [24]. A correct recipient genotype may accordingly yield a poor dose prediction when enzyme inhibition, absorption, hematocrit, or disease physiology dominate.

Three refutable propositions follow. P1, provenance: if a post-transplant sample is donor-dominant and the drug pathway is predominantly recipient-organ mediated, independently established recipient genotype should better represent the inherited pharmacogene state than the unqualified sample call. P2, lineage relevance: for a drug whose toxicity is predominantly cell-autonomous within donor-derived marrow, donor-lineage genotype may add explanatory value beyond recipient genotype; this requires direct testing. P3, conditional actionability: even with the correct tissue genotype, improved prediction of concentration or clinical response must be shown beyond standard therapeutic monitoring and clinical covariates. P1 follows an anatomical inference, whereas P2 and P3 are hypotheses requiring drug-specific validation.

Figure 1 distinguishes genomic identity measurements, compartment-level mechanisms, and exposure-dependent decisions. It also shows why an accurate chimerism result can coexist with uncertain pharmacogenetic actionability and why phenotype measurement can trigger reassessment of the proposed origin–function link.

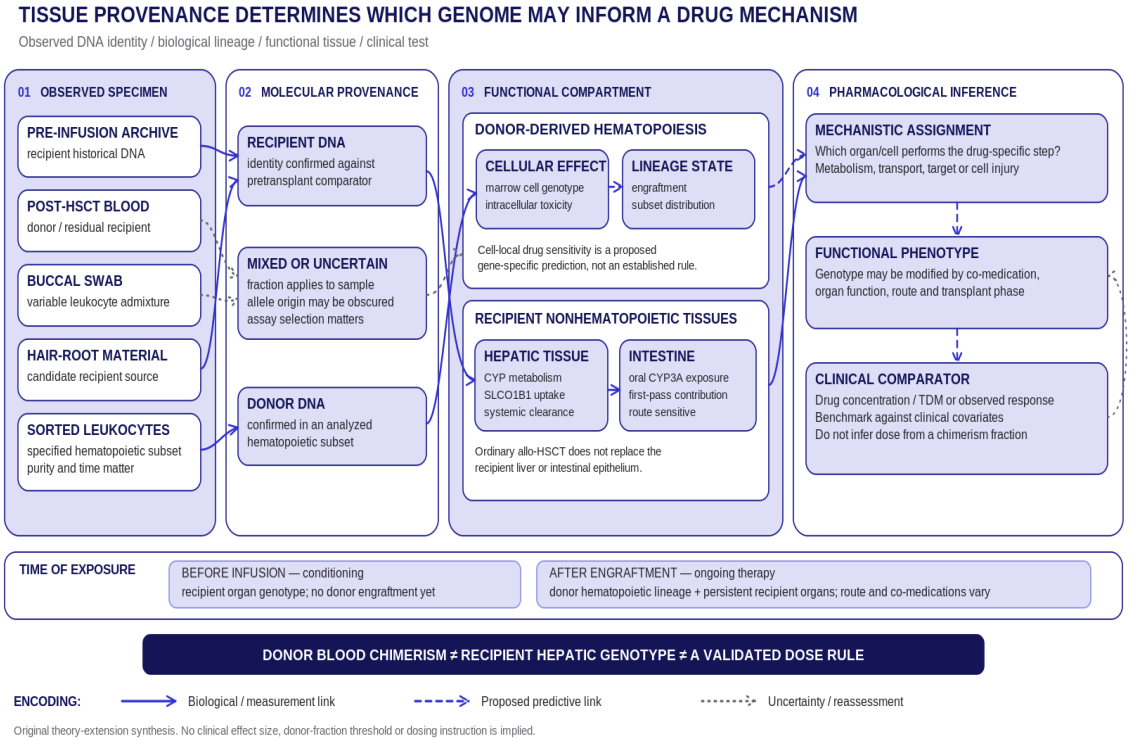


Figure 1. Sampling provenance constrains—but does not determine—drug-specific pharmacogenomic attribution after allogeneic hematopoietic transplantation

Caption and legend. The tissue-provenance decision network reads from specimen identity at left, through donor–recipient attribution and biologically relevant compartments in the center, to drug-specific phenotype and clinical testing at right. Solid connectors mark evidence-grounded biological or measurement relationships; dashed arrows represent proposed, unvalidated predictive links; dotted connectors mark confounding pathways or reassessment. Bounded regions distinguish hematopoietic donor contribution from persistence of recipient nonhematopoietic organs. Preconditioning exposure and post-engraftment treatment occupy different temporal bands. A chimerism fraction characterizes sampled cells only; a genotype-based medication change requires independent exposure or outcome evidence. PGx, pharmacogenomics; TDM, therapeutic drug monitoring; allo-HSCT, allogeneic hematopoietic stem cell transplantation.

Alt text. Wide asymmetric network with specimen sources on the left, a donor–recipient provenance region in the center-left, vertically separated donor-derived hematopoietic cells and recipient hepatic or intestinal organs in the center, and drug-mechanism, phenotype, and actionability nodes on the right. Solid connectors indicate source-supported links; dashed connectors denote proposed genotype–function predictions; dotted paths from medication effects and observed drug concentrations feed back to reassess predictions. Bottom time bands distinguish conditioning before infusion from treatment after engraftment. A boxed warning prevents treating blood chimerism as liver genotype.

Potential drug-specific applications and interpretation scenarios

The proposed attribution rule produces different questions even for drugs administered to the same allo-HSCT recipient. For tacrolimus given with posaconazole, the route of tacrolimus administration is especially informative. In a prospective observational allo-HCT study, posaconazole-associated changes in dose-normalized tacrolimus concentrations differed between oral and intravenous treatment; exposure to the interacting antifungal was also relevant [25]. This contrast could arise through intestinal and systemic inhibition or route-dependent pharmacokinetics. It cannot be assigned to donor-versus-recipient CYP3A genotype from the concentration data alone. An interpretable comparison would pair verified recipient CYP3A5 genotype, drug route, posaconazole concentrations, and repeated tacrolimus measurements, retaining clinical covariates in the analysis.

Voriconazole illustrates a narrower area of existing clinical implementation evidence. An allo-HCT study evaluated CYP2C19-guided prophylactic dosing with subsequent trough measurement and historical comparisons [26]. Its findings support testing genotype-informed starting strategies in this population, while neither identifying a universal post-engraftment sampling source nor isolating donor DNA as a predictor. A specimen collected after substantial donor engraftment would need its recipient-origin status established before its CYP2C19 call was treated as a recipient hepatic genotype. Drug levels provide an independent, actionable check on exposure regardless of the specimen-origin hypothesis.

An antidepressant may present a different combination of longer treatment duration, multiple metabolic routes, and changing concomitant medications. Updated CPIC guidance for serotonin reuptake inhibitors makes gene–drug interpretation dependent on the specific agent and relevant CYP2D6, CYP2C19, or CYP2B6 phenotype [27]. The post-HSCT extrapolation is limited to identifying which inherited metabolic genotype ought to be sampled; it does not establish transplantation-specific efficacy, tolerability, or dosing. Possible donor-derived effects on immune cells would need separate evidence linking the gene and pharmacological endpoint before entering a prescribing decision.

Population and route also matter. A pediatric HSCT tacrolimus model identified body weight, hematocrit, transplant timing, interacting therapies, and CYP3A5 variation as relevant to concentration prediction, but genotype was available in only a subgroup and dosage suggestions were model-based [28]. Neither adult parameter values nor an assumed stable donor fraction should be substituted for pediatric evidence. The scenarios in **Table 3** distinguish what could be tested using measured drug exposure from what would still require a prospective clinical outcome study.

A further attribution problem arises when blood is collected for a pharmacogene test during a period of mixed or changing engraftment. A laboratory may detect a variant correctly but lack evidence to identify its genomic source. Testing an archived specimen, obtaining independently qualified recipient material, or determining donor alleles can clarify that ambiguity, although each strategy introduces its own quality-control requirements. The proposed decision to pursue additional tissue sampling should therefore depend on whether resolving provenance could realistically change drug interpretation after therapeutic monitoring and the patient's current clinical state have been considered.

Table 3. Drug–route–time scenarios for testing which pharmacogene genotype is relevant after allogeneic transplantation

Exposure situation	Genomic provenance to establish	Mechanistic or assay discriminator	Competing explanation to retain	Present interpretation
Oral tacrolimus during posaconazole treatment	Recipient CYP3A5 from independently qualified material; donor/recipient status of tested blood	Serial tacrolimus concentrations paired with antifungal exposure and oral-route history	Gut inhibition, inflammation, hematocrit change	Recipient genotype is mechanistically plausible; interaction-aware TDM remains necessary
Intravenous tacrolimus during antifungal prophylaxis	Same independently established recipient genotype	Intravenous exposure pattern contrasted with oral-route effects	Systemic inhibition and changing clearance	Route contrast can test mechanism; donor chimerism is not a clearance proxy
Voriconazole after hematopoietic engraftment	Recipient CYP2C19 confirmed independently of donor-dominant leukocytes	Drug trough and metabolizer assignment against competing covariates	CYP2C19 phenoconversion and organ dysfunction	Existing genotype-guided evidence informs study design, not a validated sampling rule
Serotonin reuptake inhibitor after transplantation	Recipient metabolizing-enzyme genotype for the actual selected agent	Drug-specific functional genotype, co-medication record, tolerability	Non-genetic interactions and symptom-related confounding	General prescribing guidance may inform interpretation; HSCT benefit is untested
Pediatric tacrolimus during changing transplant phases	Recipient CYP3A5 plus specimen identity across sampling dates	Age/weight, route, hematocrit, interacting drugs and serial troughs	Time-varying clearance and limited model transportability	Population-specific model evaluation precedes any genotype-based change
Conditioning drug given before donor infusion	Pretransplant recipient genotype and exposure-time documentation	Drug AUC or concentration during conditioning	Exposure determinants unrelated to later engraftment	Post-engraftment donor genotype cannot explain earlier host metabolism

Note: TDM, therapeutic drug monitoring; AUC, area under the concentration–time curve; HSCT, hematopoietic stem cell transplantation. All suggested source comparisons are proposed tests. The table contains no validated donor-fraction cutoff or universal drug dose adjustment.

Discussion, clinical evidence requirements, and future research

The strongest challenge to an accessible-specimen assumption is that the required genome depends on the organ and the drug pathway. Longitudinal evidence from a small cohort of Colombian liver recipients associated CYP3A5 expression with tacrolimus dose-adjusted exposure [29]. It is a useful anatomical contrast: liver graft transplantation changes a metabolic organ's genomic provenance, whereas allo-HSCT principally replaces hematopoietic lineages. Consequently, an attribution strategy cannot be transported between these procedures without specifying which tissue was replaced. Population differences and clinical management remain plausible alternative explanations for part of the observed associations.

A decisive clinical study should collect, with consent and appropriate laboratory validation, recipient DNA obtained before transplantation or from a verified nonhematopoietic source, donor DNA, and serial post-HSCT lineage-specific samples. The genotype assay, donor-fraction method, specimen purity, and sampling time must be documented before drug-specific outcomes are assessed. A comparison of donor-derived blood genotype alone, verified recipient genotype alone, and both genotypes alongside measured non-genetic predictors would test whether provenance changes prediction. The independent sampling investigation supplies a starting rationale [1], while existing chimerism practice defines the analytical limits of lineage assignment [7]. Studies should not treat a small measurable donor fraction as a validated threshold for assigning a whole-organ metabolic phenotype.

For tacrolimus, prospective evaluation would prespecify oral and intravenous phases, azole exposure, hematocrit, hepatic function, concomitant medications, and trough-sampling adherence. External validation should compare predictive calibration and clinically relevant endpoints against standard therapeutic drug monitoring, not simply against an unadjusted genotype-only equation. Model transfer from kidney transplantation into allo-HSCT has already been explicitly examined [24], showing why study setting is itself an object of validation. For

voriconazole, the more decisive comparison is whether verified recipient-origin CYP2C19 improves exposure prediction beyond a post-engraftment blood call and measured co-medications [26].

Propositions P1–P3 are not confirmed together by any cited study. P1 would be weakened if donor-dominant blood repeatedly predicts an exposure endpoint as well as verified recipient-organ genotype after covariate adjustment. P2 would require a donor-cell genotype effect on an explicitly hematopoietic endpoint after separating systemic exposure from cell-intrinsic susceptibility. P3 would fail when correct provenance improves molecular classification without improving exposure prediction, treatment choices, or patient-important outcomes. Discordant results should trigger reassessment of assay mixing, functional phenoconversion, or the nominated drug-relevant compartment, rather than automatic revision of medication dose.

For prospective comparisons, an explicitly specified primary endpoint would be essential. Improved agreement between two genotype specimens is an analytical endpoint; reduced tacrolimus concentration prediction error is a pharmacokinetic endpoint; a change in clinically important toxicity is a patient endpoint. Success at the first level does not guarantee success at the second or third. Investigators should assess whether their study is powered and timed for the endpoint it claims, and report missing tissue samples, evolving chimerism, drug discontinuation, and competing causes of treatment change. Such analyses could expose selective availability of high-quality recipient DNA as another source of bias.

Limitations and boundaries of clinical application

This theory assumes conventional allo-HSCT anatomy: donor hematopoietic engraftment with continued recipient ownership of most nonhematopoietic organs. Prior or subsequent solid-organ transplantation, tissue injury, cellular trafficking, unusual mosaicism, and mixed hematopoietic chimerism can alter the relevant attribution. Donor-fraction estimates from blood or a sorted lineage cannot define the genotype of an unsampled organ. Buccal and hair specimens may be variably informative because collection, admixture, DNA yield, and assay validation differ. No single accessible material has been established as adequate for every variant or every patient.

A second limitation is the nonidentity of inherited genotype and expressed phenotype. CYP inhibition, inflammation, organ dysfunction, adherence, route, disease state, and interacting medicines can modify exposure after a genotype has been assigned correctly. Much of the directly relevant evidence concerns tacrolimus, voriconazole, or sampling assays; the donor-marrow hypothesis for intracellular toxicity remains considerably less tested. Historical-control studies, small observational cohorts, and model-derived simulations are useful for hypothesis generation but cannot themselves establish causal benefits of donor–recipient attribution. Applicability to other drugs must be demonstrated at the level of their specific mechanism and outcome.

The framework therefore should not be used as an independent authority to change an immunosuppressant, antifungal, conditioning regimen, antiplatelet drug, or psychiatric medication. Current drug-specific guidelines, transplantation protocols, therapeutic monitoring, and treating-team assessment retain priority. Its immediate practical use is to prevent an unjustified specimen-to-organ inference, document genomic origin explicitly, and identify where prospective validation could change a clinical decision. If adding provenance information fails to improve a predefined endpoint over existing care, the additional testing may have little clinical utility even when scientifically informative.

A final scope restriction concerns clinical governance. Genotype interpretation in transplantation involves molecular laboratories, transplant physicians, pharmacists, and sometimes clinical geneticists, each working with different evidence. The genomic source identified by a laboratory should accompany the result, but an inferred drug-response effect should remain distinguishable from that direct observation in the medical record. Before any practice recommendation is adopted, reporting conventions and independent replication would have to establish that the additional specimen and testing burden produce a clinically meaningful gain. This matters when rapid treatment requires established monitoring-based care.

CONCLUSION

After allogeneic hematopoietic transplantation, a genotype result identifies the DNA present in the tested specimen; it does not necessarily identify the genome governing a drug's metabolism or cellular response. The most defensible attribution follows the drug-specific biological compartment, its donor or recipient lineage, and the treatment time. For systemic hepatic or intestinal mechanisms, verified recipient genotype is generally the anatomically coherent starting hypothesis; donor-derived hematopoietic genotype deserves investigation where a cellular mechanism makes it relevant. Interactions, organ function, pharmacokinetic monitoring, and direct

clinical validation determine whether that molecular distinction improves prescribing. The governing question is therefore not which genome is easiest to sample, but which tissue-specific genotype predicts the relevant outcome under the conditions in which the drug is given.

ACKNOWLEDGMENTS: None

CONFLICT OF INTEREST: None

FINANCIAL SUPPORT: None

ETHICS STATEMENT: None

REFERENCES

1. Bokma A, Matic M, Ralf A, van den Bosch BJC, Kayser M, van Schaik RHN, et al. Recommendations for (pharmaco)genetic sampling in patients following allogeneic hematopoietic stem cell transplantation. Clin Transl Sci. 2025;18(8):e70303. doi:10.1111/cts.70303
2. Pirmohamed M. Pharmacogenomics: Current status and future perspectives. Nat Rev Genet. 2023;24(6):350-62. doi:10.1038/s41576-022-00572-8
3. Swen JJ, van der Wouden CH, Manson LEN, Abdullah-Koolmees H, Blagec K, Blagus T, et al. A 12-gene pharmacogenetic panel to prevent adverse drug reactions: An open-label, multicentre, controlled, cluster-randomised crossover implementation study. Lancet. 2023;401(10374):347-56. doi:10.1016/S0140-6736(22)01841-4
4. Eken E, Duarte S, Angeli-Pahim I, Ladd AD, Warren C, Langaee TY, et al. Recipient versus donor CYP3A4/5 genotypes in adult liver transplant recipients to achieve therapeutic tacrolimus concentrations early post-transplant. Clin Transl Sci. 2025;18(9):e70329. doi:10.1111/cts.70329
5. Cooper-DeHoff RM, Niemi M, Ramsey LB, Luzum JA, Tarkiainen EK, Straka RJ, et al. The Clinical Pharmacogenetics Implementation Consortium guideline for SLCO1B1, ABCG2, and CYP2C9 genotypes and statin-associated musculoskeletal symptoms. Clin Pharmacol Ther. 2022;111(5):1007-21. doi:10.1002/cpt.2557
6. Lee CR, Luzum JA, Sangkuhl K, Gammal RS, Sabatine MS, Stein CM, et al. Clinical Pharmacogenetics Implementation Consortium guideline for CYP2C19 genotype and clopidogrel therapy: 2022 update. Clin Pharmacol Ther. 2022;112(5):959-67. doi:10.1002/cpt.2526
7. Clark A, Clouston H, Rao K, Folarin N, de la Fuente J, Hamblin A, et al. UK recommendations for chimerism testing and monitoring following allogeneic haematopoietic stem cell transplantation (HSCT): Best practice consensus guidelines from the British society for blood and marrow transplant and cellular therapies (BSBMTCT), NHS England genomic laboratory hub (GLH) haematological malignancies working group, UK cancer genetics group (UKCGG) and the UK national external quality assessment service for leucocyte immunophenotyping (UK NEQAS LI). Br J Haematol. 2025;207(5):1802-14. doi:10.1111/bjh.70061
8. Kanaan SB, Urselli F, Radich JP, Nelson JL. Ultrasensitive chimerism enhances measurable residual disease testing after allogeneic hematopoietic cell transplantation. Blood Adv. 2023;7(20):6066-79. doi:10.1182/bloodadvances.2023010332
9. Zhang A, Macecevic S, Thomas D, Allen J, Mandley S, Kawczak P, et al. Engraftment and measurable residual disease monitoring after hematopoietic stem cell transplantation: Comparison of two chimerism test strategies, next-generation sequencing versus a combination of short-tandem repeats and quantitative PCR. J Mol Diagn. 2024;26(4):233-44. doi:10.1016/j.jmoldx.2024.01.007
10. Blouin AG, Nelson W, Geraghty D, Askar M, Ye F. Performance characteristics of next-generation sequencing-based engraftment monitoring and microchimerism detection in allogeneic hematopoietic cell transplantation: A practical approach for clinical assay validation. J Mol Diagn. 2024;26(11):995-1006. doi:10.1016/j.jmoldx.2024.07.003
11. Dauber EM, Haas OA, Nebral K, Gassner C, Haslinger S, Geyeregger R, et al. Body-wide chimerism and mosaicism are predominant causes of naturally occurring ABO discrepancies. Br J Haematol. 2024;205(3):1188-96. doi:10.1111/bjh.19618
12. Caudle KE, Dunnenberger HM, Freimuth RR, Peterson JF, Burlison JD, Whirl-Carrillo M, et al. Standardizing terms for clinical pharmacogenetic test results: Consensus terms from the Clinical

Pharmacogenetics Implementation Consortium (CPIC). Genet Med. 2017;19(2):215-23. doi:10.1038/gim.2016.87

13. Marco DN, Molina M, Guio AM, Julian J, Fortuna V, Fabregat-Zaragoza VL, et al. Effects of CYP3A5 genotype on tacrolimus pharmacokinetics and graft-versus-host disease incidence in allogeneic hematopoietic stem cell transplantation. Pharmaceuticals (Basel). 2024;17(5):553. doi:10.3390/ph17050553
14. Seligson ND, Zhang X, Zemanek MC, Johnson JA, VanGundy Z, Wang D, et al. CYP3A5 influences oral tacrolimus pharmacokinetics and timing of acute kidney injury following allogeneic hematopoietic stem cell transplantation. Front Pharmacol. 2024;14:1334440. doi:10.3389/fphar.2023.1334440
15. da Costa-Junior LC, Freitas-Alves DR, Leão AML, Monteiro HAV, Tavares RCBDS, Moreira MCR, et al. Polymorphisms in CYP3A5, CYP3A4, and ABCB1 genes: Implications for calcineurin inhibitors therapy in hematopoietic cell transplantation recipients—a systematic review. Front Pharmacol. 2025;16:1569353. doi:10.3389/fphar.2025.1569353
16. Dunlap TC, Zhu J, Weiner DL, Kemper RM, DeVane SC, Ma F, et al. A tacrolimus population pharmacokinetic model for adult allogeneic hematopoietic cell transplant recipients provides clinical opportunities for precision dosing. Clin Pharmacokinet. 2025;64(11):1621-37. doi:10.1007/s40262-025-01529-w
17. Moriyama B, Obeng AO, Barbarino J, Penzak SR, Henning SA, Scott SA, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2C19 and voriconazole therapy. Clin Pharmacol Ther. 2017;102(1):45-51. doi:10.1002/cpt.583
18. 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. Clin Pharmacol Ther. 2019;105(5):1095-105. doi:10.1002/cpt.1304
19. Seydoux C, Uppugunduri CRS, Medinger M, Nava T, Halter J, Heim D, et al. Effect of pharmacokinetics and pharmacogenomics in adults with allogeneic hematopoietic cell transplantation conditioned with busulfan. Bone Marrow Transplant. 2023;58(7):811-6. doi:10.1038/s41409-023-01963-z
20. McCune JS, Navarro SL, Risler LJ, Phillips BR, Ren S, Schoch HG, et al. The presence of busulfan metabolites and pharmacometabolomics in plasma drawn immediately before allograft infusion in hematopoietic cell transplant recipients. Clin Transl Sci. 2023;16(12):2577-90. doi:10.1111/cts.13651
21. Pai AA, Mohanan E, Panetta JC, Kulkarni UP, Illangeswaran RSS, Balakrishnan B, et al. Treosulfan exposure predicts thalassemia-free survival in patients with beta thalassemia major undergoing allogeneic hematopoietic cell transplantation. Clin Pharmacol Ther. 2024;115(1):116-25. doi:10.1002/cpt.3078
22. Abouir K, Exquis N, Gloor Y, Daali Y, Samer CF. Phenoconversion due to drug-drug interactions in CYP2C19 genotyped healthy volunteers. Clin Pharmacol Ther. 2024;116(4):1121-9. doi:10.1002/cpt.3378
23. Kirubakaran R, Stocker SL, Hennig S, Day RO, Carland JE. Population pharmacokinetic models of tacrolimus in adult transplant recipients: A systematic review. Clin Pharmacokinet. 2020;59(11):1357-92. doi:10.1007/s40262-020-00922-x
24. Zhu J, Campagne O, Torrice CD, Flynn G, Miller JA, Patel T, et al. Evaluation of the performance of a prior tacrolimus population pharmacokinetic kidney transplant model among adult allogeneic hematopoietic stem cell transplant patients. Clin Transl Sci. 2021;14(3):908-18. doi:10.1111/cts.12956
25. Kuno M, Okayama Y, Yasui Y, Shibata W, Moriguchi M, Nakaya Y, et al. Effects of routes, concentrations and genetic polymorphisms on posaconazole-tacrolimus interactions in allogeneic haematopoietic cell transplantation. Br J Clin Pharmacol. 2025;91(11):3288-96. doi:10.1002/bcp.70264
26. Patel JN, Hamadeh IS, Robinson M, Shahid Z, Symanowski J, Steuerwald N, et al. Evaluation of CYP2C19 genotype-guided voriconazole prophylaxis after allogeneic hematopoietic cell transplant. Clin Pharmacol Ther. 2020;107(3):571-9. doi:10.1002/cpt.1642
27. Bousman CA, Stevenson JM, Ramsey LB, Sangkuhl K, Hicks JK, Strawn JR, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6, CYP2C19, CYP2B6, SLC6A4, and HTR2A genotypes and serotonin reuptake inhibitor antidepressants. Clin Pharmacol Ther. 2023;114(1):51-68. doi:10.1002/cpt.2903
28. Liu XL, Guan YP, Wang Y, Huang K, Jiang FL, Wang J, et al. Population pharmacokinetics and initial dosage optimization of tacrolimus in pediatric hematopoietic stem cell transplant patients. Front Pharmacol. 2022;13:891648. doi:10.3389/fphar.2022.891648

29. Lindarte EF, De Jesus Vasquez G, Toro Rendón LG, Zuluaga Salazar AF, Buendia JA. Effect of CYP3A5 genotypes on pharmacokinetic of tacrolimus in Colombian liver transplant patients. Front Pharmacol. 2025;16:1505490. doi:10.3389/fphar.2025.1505490