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Ancestry Labels Are Poor Substitutes for Functional Pharmacogenomic Evidence

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ABSTRACT

Pharmacogenomics aims to improve drug selection and dosing by identifying biological sources of interindividual variability in pharmacokinetics, pharmacodynamics, toxicity, and treatment response. Population ancestry can contribute useful information because pharmacogene allele frequencies and haplotype structures differ across human populations. Yet ancestry labels operate at a fundamentally different evidentiary level from an individual patient's functional pharmacogenomic state. Broad racial, ethnic, continental, or biogeographic categories compress substantial within-population diversity, perform particularly poorly in admixed individuals, and cannot determine whether a detected variant alters protein function, exposure, or drug response. Their limitations are amplified when genotyping panels incompletely represent population diversity or when environmental and clinical factors modify genotype-predicted phenotypes. This Current Opinion argues that ancestry should be retained as contextual information for discovery, representation assessment, assay design, and population-level uncertainty, but should not be treated as a functional biomarker. The clinically relevant evidentiary progression is instead from accurate variant and haplotype ascertainment, through experimentally or clinically supported functional interpretation, to drug-specific phenotype and actionability assessment. A proposed evidence hierarchy is developed in which ancestry informs where uncertainty should be investigated, whereas direct genomic, functional, pharmacological, and clinical evidence determines what should be acted upon. This distinction can improve both scientific precision and equity by avoiding two opposite errors: ignoring population genetic structure and converting population membership into an assumed individual biological phenotype.

Keywords: Pharmacogenomics, Genetic ancestry, Functional variants, Admixture, Phenoconversion, Precision pharmacotherapy

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INTRODUCTION

Pharmacogenomics has moved beyond the proposition that inherited variation can influence drug response. For selected gene-drug pairs, clinically interpretable genotypes already contribute to treatment selection, dose modification, toxicity avoidance, or monitoring decisions. The more difficult problem is determining which genomic information is sufficiently specific, functionally supported, and contextually relevant to justify an individual clinical inference. Drug response remains a layered phenotype shaped not only by inherited sequence

but also by drug exposure, interacting medications, organ function, disease state, treatment phase, and the pharmacological properties of the drug itself [1].

That evidentiary problem is inseparable from representation. Pharmacogenomic discovery and implementation resources have historically sampled some ancestry groups far more intensively than others, influencing which alleles are recognized, which functional effects have been characterized, and which gene–drug relationships have accumulated sufficient evidence for translation [2]. Underrepresentation therefore creates more than a demographic imbalance. It can alter the completeness of variant catalogues, the sensitivity of assays, and confidence in extrapolating functional interpretation across populations.

Population labels nevertheless contain some information. Analyses of large genomic cohorts show that self-reported race or ethnicity can correlate with pharmacogenomic allele distributions at an aggregate level, while classification becomes substantially less reliable for individuals reporting multiple groups or belonging to admixed populations [3]. This apparent contradiction is central to the argument developed here. A variable can be informative for population description without being sufficiently specific to substitute for the biological state of an individual.

The distinction is reinforced by efforts to standardize population terminology. Biogeographic grouping systems were developed to improve consistency when reporting population frequencies and pharmacogenetic findings, not to establish discrete biological classes or patient-level functional phenotypes [4]. Such categories are useful for organizing evidence, identifying sampling gaps, and comparing allele distributions, but they necessarily simplify continuous and historically complex patterns of human variation.

Greater ancestral diversity in pharmacogenomic research can reveal previously poorly characterized variants, different linkage patterns, and population-dependent allele frequencies that would remain invisible in narrowly sampled cohorts [5]. The appropriate response, however, is not to replace one overly broad population assumption with another. Translation requires movement from population context toward evidence about the patient’s actual genotype, the functional consequence of that genotype, the relevant drug, and the clinical state in which treatment occurs [6].

This Current Opinion therefore treats ancestry as an evidence-context variable rather than a functional endpoint. The central proposed distinction is that ancestry may inform where measurement uncertainty is likely to exist, whereas direct genotype, functional phenotype, and drug-specific evidence should determine the biological and clinical interpretation. The following sections examine where ancestry labels are informative, where they lose resolution, and why substituting them for functional pharmacogenomic evidence can reproduce both scientific imprecision and inequitable care.

What ancestry labels capture and miss

The argument against ancestry substitution should not begin by denying population genetic structure. Pharmacogenomic variants associated with adverse drug reactions and toxicity are distributed nonuniformly across geographic and ancestry-defined populations, and computational analyses can recover population-level differences that vary by drug class [7]. Such information can be valuable for surveillance, discovery prioritization, trial design, assay development, and estimation of where poorly characterized variation may be concentrated.

Genetic ancestry also intersects directly with pharmacogenomic loci. Analyses using whole-genome data and pharmacogenomic annotations have found ancestry-informative structure among drug-response-associated variants [8]. Consequently, ancestry can help describe the probability that particular alleles or haplotypes occur in a population. What it cannot establish is whether a particular patient carries the allele, whether an uncharacterized allele is functional, whether the relevant enzyme activity is modified by the treatment environment, or whether the effect is clinically actionable for the drug being prescribed.

This distinction between frequency information and functional information is essential. A population label may alter the prior probability of encountering a variant but does not reveal the patient’s genotype. Even a genetically inferred ancestry proportion remains an indirect descriptor of genomic background rather than a measurement of the pharmacogene state that is mechanistically relevant to a particular drug. The inferential error occurs when a useful population-level prior is allowed to replace a directly measurable individual variable.

The problem is compounded by unequal knowledge. Human genomic studies have historically captured only a fraction of global diversity, with especially intensive study of populations of European ancestry [9]. A population label may therefore appear predictive partly because known variants, reference sequences, and clinical interpretations were developed unevenly. Conversely, apparent absence of a recognized actionable allele in an understudied population may reflect incomplete discovery rather than true biological absence.

The resulting distinction is asymmetric. Ancestry may legitimately trigger additional scrutiny—such as asking whether a test panel adequately covers alleles common in the relevant population—but it should not normally terminate the reasoning process. Its strongest role is to identify uncertainty in the evidence environment. It is weakest when used to infer the functional state of an individual pharmacogene without direct measurement.

Within-population genetic diversity

Broad ancestry categories lose resolution because clinically relevant pharmacogenomic variation is often heterogeneous within them. CYP2D6 provides a clear example. High-depth sequencing of sub-Saharan African populations identified substantial variation in star-allele composition, structural variation, and predicted metabolizer phenotypes across populations that would often be collapsed into the same continental ancestry category [10]. Novel alleles were also detected, demonstrating that even detailed catalogues remain incomplete. The same problem extends beyond CYP2D6. Whole-genome characterization of CYP2B6 and CYP2A6 showed meaningful differences in allele distributions among sub-Saharan African populations and between those populations and global comparators [11]. These findings undermine the assumption that a single continental label adequately represents pharmacogene architecture. They also show why replacing a broad racial category with a broad genetic-ancestry category does not fully solve the problem.

Variation across absorption, distribution, metabolism, and excretion genes reinforces this point. High-coverage African genomes contain extensive single-nucleotide, copy-number, and predicted high-impact variation distributed nonuniformly across population clusters [12]. Some variants may ultimately prove functionally important; others may not. The scientific lesson is therefore not that every population-specific variant has pharmacological significance, but that broad ancestry labels have insufficient resolution to decide which functional alleles are present in an individual.

Population-scale analyses also reveal limitations in the pharmacogenomic nomenclature itself. In the UK Biobank, potentially deleterious variants outside established pharmacogene allele definitions were disproportionately observed in individuals from less intensively characterized populations [13]. This creates an important distinction between a negative or apparently normal test result and genuine absence of relevant functional variation. A patient can be accurately assigned according to the alleles a system knows how to recognize while still carrying variation that the current interpretive framework does not adequately classify.

Large diverse genomic resources further show that population structure is continuous at finer scales than many routine labels imply. Analysis of more than two hundred thousand unrelated participants in the All of Us Research Program demonstrated substantial continental and subcontinental ancestry gradients within self-identified groups [14]. Such structure can matter analytically, but it does not rescue ancestry as an individual pharmacological phenotype. Increasing ancestry resolution eventually encounters the same conceptual boundary: knowing progressively more about genomic background is still different from identifying and functionally interpreting the pharmacogene variant relevant to the drug under consideration.

A more defensible formulation is therefore that ancestry describes where variation may be distributed, whereas genotyping establishes which variation is present. Neither step alone establishes how that variation changes protein function or clinical response.

Allele frequency versus functional effect

Frequency is especially vulnerable to overinterpretation because it is straightforward to quantify. A variant can be common in one population and rare in another without its biochemical consequence changing between those populations. Conversely, two variants of similar frequency can have markedly different effects on enzyme expression, catalytic activity, transport, or drug disposition. Population frequency and functional magnitude are therefore orthogonal questions.

Even computational tools designed to predict function cannot eliminate this distinction. Benchmarking commonly used in-silico predictors against pharmacogenetic variants with established functional classifications found inconsistent performance, including misclassification of known CYP2C9 alleles [15]. Computational prioritization is useful, particularly for newly discovered variants, but prediction is not equivalent to measured protein function and cannot by itself establish a clinical dose consequence.

Clinical actionability adds another evidentiary layer. The CPIC guideline for serotonin reuptake inhibitor antidepressants demonstrates that recommendations depend on the particular gene, drug, metabolizer phenotype, and quality of the supporting pharmacokinetic, pharmacodynamic, and clinical evidence [16]. The existence of an

allele-frequency difference between populations is therefore not sufficient to justify differential prescribing. A clinically meaningful chain must connect variant detection to function and then to a drug-specific consequence. Before function can even be interpreted, however, the genotype itself must be resolved accurately. Pharmacogenes frequently contain complex haplotypes, copy-number changes, hybrid structures, and combinations of variants that are poorly represented by single-marker testing. WGS-based tools such as Stargazer have demonstrated that star-allele assignment across multiple pharmacogenes can achieve high concordance with reference genotypes while recovering structural complexity that simpler approaches may miss [17]. Analytical validity is thus a prerequisite for functional interpretation, not its substitute.

Direct functional experiments provide a different evidentiary class. Massively parallel characterization of CYP2C9 variants demonstrated that thousands of missense substitutions can be evaluated for effects on enzyme activity and protein abundance [18]. Such assays illustrate why a rare variant cannot simply be dismissed because of frequency and why a common variant cannot be assumed to have a large functional consequence. They also illustrate a second boundary: an experimentally measured cellular or enzymatic effect still requires pharmacological and clinical translation before it can justify patient management.

Population context can additionally modify the apparent transferability of genotype–outcome associations. A genome-wide study of metformin response identified an association in African American patients that replicated in an independent African American cohort but not in a European American comparator population [19]. This does not establish ancestry as the mechanism. Differences in linkage disequilibrium, unmeasured causal variants, environmental factors, treatment context, or other correlated features remain possible. Such results should prompt further mechanistic and functional investigation rather than ancestry-based treatment assumptions.

The proposed evidentiary separation is therefore: allele frequency informs detection strategy; genotype establishes variant state; functional evidence establishes biological consequence; drug-specific clinical evidence establishes actionability. Collapsing these levels is the central inferential error behind ancestry substitution.

Admixed populations

Admixture exposes the limits of categorical ancestry most clearly because the assumption of a single coherent population background becomes visibly untenable. Whole-genome sequencing of an admixed Brazilian cohort demonstrated extensive pharmacogenomic variation across dozens of pharmacogenes, including combinations of alleles arising from a population history that cannot be represented faithfully by assigning each individual to one ancestral category [20]. The clinically relevant unit remains the individual genotype rather than the average frequency expected under any one component ancestry.

For association discovery, local ancestry can provide additional resolution. Tractor and related admixture-aware approaches model ancestry at the locus rather than assigning one genome-wide ancestry value to the individual, improving power and interpretation for genetic associations in admixed cohorts [21]. This is an important methodological advance, but local ancestry still should not be confused with functional evidence. It refines the genomic context surrounding a locus; it does not establish what a specific allele does to protein activity or how the corresponding drug should be prescribed.

The difficult clinical situation therefore arises when a population-based expectation conflicts with direct patient evidence. A broad ancestry label may suggest that an allele is uncommon, yet sequencing may detect it. A local-ancestry segment may increase the plausibility of an association, yet the detected variant may remain functionally unresolved. Conversely, a limited clinical panel may report a conventional genotype even though the patient's admixed genomic background increases concern that relevant alleles were not interrogated. These are not equivalent forms of uncertainty and should not lead to the same response.

The proposed resolution principle is measurement precedence with uncertainty preservation. When reliable direct genotype evidence exists, a population-frequency expectation should not override it. When genotype coverage is incomplete, ancestry or admixture information may justify reassessment of the assay rather than dictate the phenotype. When a variant is detected but function is uncertain, the appropriate next step is functional interpretation or evidence qualification, not substitution of a population average.

The sequence-aware conflicts that follow from this reasoning are difficult to compare in narrative form because the point of uncertainty can occur before genotyping, during variant interpretation, or after a provisional population-based expectation has already been formed. **Table 1** therefore separates these clinically distinct transitions while preserving ancestry as contextual evidence rather than an assumed functional state.

Table 1. Sequence-aware resolution of ancestry–genotype conflicts in admixed pharmacogenomic interpretation

Broad ancestry expectation precedes testing Expected low population frequency conflicts with detected allele Global ancestry is ambiguous but locus ancestry can be estimated			
Admixed-population comparison anchor	Broad ancestry expectation precedes testing	Expected low population frequency conflicts with detected allele	Global ancestry is ambiguous but locus ancestry can be estimated
Population boundary	Patient cannot be represented adequately by one population category	Group-level frequency differs from the individual result	Genome-wide admixture obscures locus-specific association context
Reassessment trigger	Treatment decision would rely on an expected population frequency	Direct genotyping identifies a recognized allele despite the prior expectation	Association interpretation depends on ancestry surrounding the locus
Genomic evidence available	No direct pharmacogene result yet	Patient-specific variant or star allele is resolved	Local-ancestry information plus genotype
Ancestry-label-substitution test	Use ancestry only to identify testing or coverage uncertainty; do not assign a functional phenotype	Direct genotype takes precedence over population expectation	Local ancestry may refine association inference but does not establish variant function
Variant is detected but its functional consequence is uncertain Conventional genotype follows limited-panel testing Functional genotype is established			
Admixed-population comparison anchor	Variant is detected but its functional consequence is uncertain	Conventional genotype follows limited-panel testing	Functional genotype is established
Population boundary	Population enrichment does not determine biochemical magnitude	“Normal” result is conditional on the variants interrogated	Remaining ancestry information concerns background frequency rather than patient state
Reassessment trigger	Allele is absent or weakly represented in established functional classifications	Patient background or updated catalogues indicate plausible untested alleles	No unresolved analytical contradiction remains
Genomic evidence available	Direct sequence evidence without sufficient functional annotation	Negative targeted result with incomplete coverage	Individual haplotype/genotype with supported interpretation
Ancestry-label-substitution test	Preserve uncertainty and seek functional evidence; do not substitute the population-average phenotype	Reassess assay completeness before accepting a functional-normal inference	Do not reintroduce ancestry as an overriding biological classifier

Note: The resolution logic is a proposed synthesis. The table distinguishes population context, direct genomic measurement, and functional interpretation rather than assigning quantitative scores or ancestry-based treatment recommendations.

Reference-panel bias

Ancestry substitution becomes particularly hazardous when the measurement system itself is uneven. A pharmacogenetic panel may appear to provide direct individual evidence while interrogating only a restricted set of alleles selected from historically dominant reference populations. In that situation, the clinically relevant uncertainty is not the patient’s ancestry label but the mismatch between assay content and the patient’s possible variant repertoire.

Empirical evaluation of pharmacogenetic panel coverage illustrates this problem. In a diverse clinical cohort, estimated false-negative results exceeded 1% for several pharmacogenes when broader known-allele catalogues were considered, but the pattern was gene specific and was not confined uniformly to non-European participants [22]. This is important because it prevents a simplistic equity narrative. Undercoverage can disproportionately

affect some populations while also affecting individuals from well-represented groups. The correct target for correction is inadequate variant coverage, not race-based reinterpretation of every normal result.

Large-scale whole-genome sequencing resources can reduce this blind spot by expanding the catalogue of human variation. The All of Us genomic dataset contains hundreds of thousands of clinical-grade genomes and exceptionally large numbers of variants, including variation poorly represented in previous databases [23]. Expanded discovery, however, solves only the first part of the problem. Most newly observed variants do not arrive with experimentally established functional consequences, pharmacokinetic effects, or validated prescribing recommendations.

Assay design can respond directly to known population gaps. GenoPharm, for example, was developed as a multi-gene clinical pharmacogenotyping panel that intentionally incorporated variants relevant to African populations and demonstrated high analytical accuracy and reproducibility in validation work [24]. Its significance is methodological rather than universal: a test becomes more equitable when its content reflects the diversity of the population it is intended to serve. No fixed panel can permanently eliminate the need for updating, particularly for structurally complex pharmacogenes or newly characterized alleles.

Reference-panel bias also begins upstream of clinical testing. Increasing diversity in genomic research requires sustained changes in recruitment, sequencing infrastructure, analytic methods, capacity building, and partnership with populations historically excluded from genomic studies [25]. Otherwise, downstream assay developers and guideline groups inherit the same incomplete catalogue. Equity cannot be engineered solely at the point of prescription if the evidence-generating system has already excluded substantial human variation.

Yet expanding reference diversity should not become another proxy-based endpoint. The purpose of discovering population-enriched or previously missing variants is to permit more accurate individual ascertainment and subsequent functional evaluation. Multi-omics approaches offer one route for connecting genomic variation to transcript, protein, metabolic, and other biological consequences in populations that have historically lacked such characterization [26]. These approaches are especially valuable when sequence data identify variants whose functional meaning is uncertain, although omic association itself still does not prove drug-specific mechanism or clinical utility.

Reference-panel bias therefore reveals why the ancestry-versus-function question cannot be solved by choosing one side of a false dichotomy. Population information is necessary to discover where existing tests and databases are incomplete. It becomes problematic only when that information substitutes for measurement. The more equitable strategy is to use ancestry and population structure to improve discovery, assay coverage, and uncertainty detection, then move the individual patient's interpretation toward directly observed genotype and experimentally or clinically supported function.

Environmental and clinical covariates

A functional pharmacogenomic interpretation can change after genotyping because genotype is fixed while drug exposure and physiological context are not. In human liver samples, CYP2C19 genotype-predicted phenotype showed only partial concordance with measured enzyme activity, with concomitant CYP2C19 inhibitors and clinical factors contributing to discordance [27]. The implication is not that genotype lacks value, but that genotype-derived phenotype is an initial state estimate rather than an immutable description of enzyme activity. Prospective pharmacokinetic evidence strengthens this distinction. In healthy volunteers, exposure to CYP2C19 inhibitors shifted measured metabolic phenotype, producing phenoconversion whose frequency and magnitude depended on inhibitor context and baseline genotype [28]. Thus, an ancestry label cannot rescue an interpretation that already fails to account for treatment-state modification. Functional pharmacogenomic evidence is strongest when it integrates what the patient inherited with what the patient is currently exposed to.

This distinction motivates **Figure 1**, which separates population context, genotype ascertainment, functional interpretation, and clinical-state modification so that ancestry information remains visible without being allowed to cross the clinical-action boundary by itself.

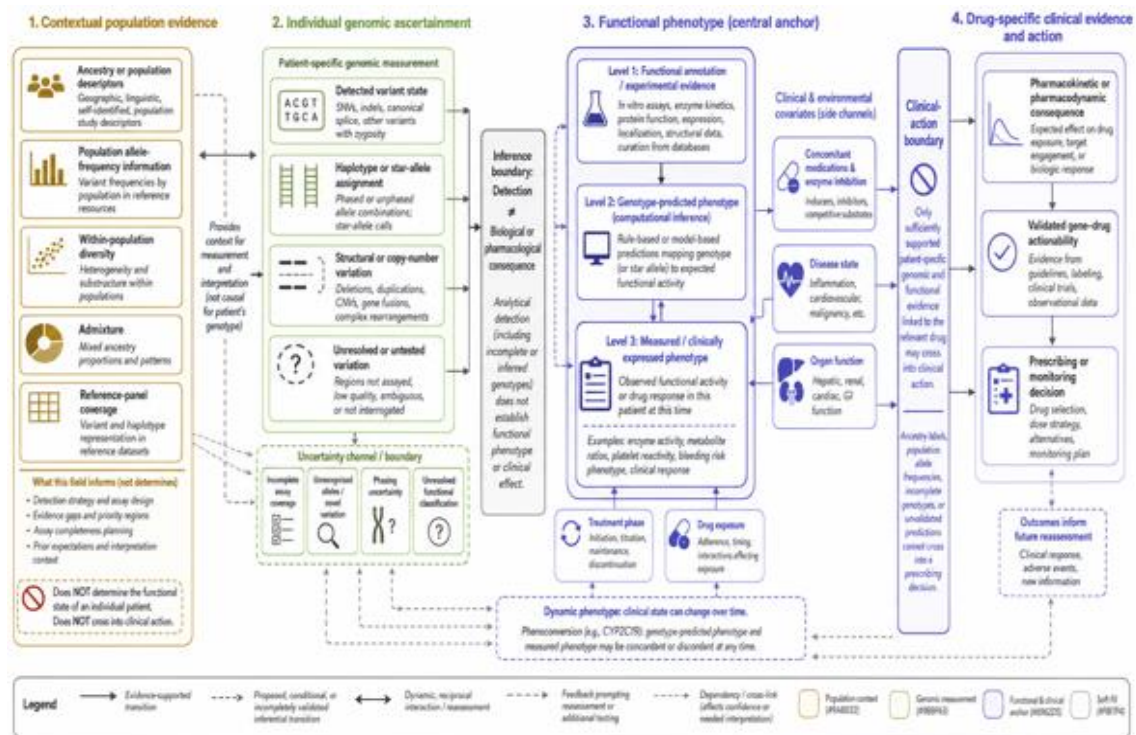


Figure 1. Where population context stops and functional pharmacogenomic evidence begins

Moving from ancestry proxies to functional evidence

Large linked genomic and clinical datasets make it increasingly possible to replace proxy reasoning with direct evidence. Their value lies not simply in scale but in connecting sequence variation with phenotype, medication exposure, outcomes, and repeated clinical observations across the evidence pathway [29]. The proposed replacement for ancestry-based inference is therefore staged rather than binary: establish the genotype accurately, characterize or support its functional effect, determine the drug-specific consequence, and then interpret that consequence in the patient's current clinical state.

Clinical pharmacogenomic guidelines illustrate the final step. CPIC translates sufficiently supported gene–drug evidence into prescribing recommendations while leaving unsupported genes, alleles, and relationships outside the actionable layer [30]. This boundary is important. Functional evidence can supersede ancestry only when it is itself sufficiently validated; an uncertain variant should remain uncertain rather than being converted into a population-average phenotype.

Equitable implementation standards

Equity begins with evidence generation that represents the populations expected to receive precision pharmacotherapy [31]. Representation should extend beyond recruitment totals to adequate variant discovery, reference data, functional characterization, and validation across relevant populations.

Equity also depends on where actionable medications are actually used. National prescribing data indicate that exposure to medications carrying evidence-based pharmacogenomic information varies across patient groups [32]. Implementation planning therefore requires attention to access, indication, prescribing patterns, and clinical opportunity rather than ancestry alone.

Once evidence exists, it must reach the prescribing workflow. Structured genomic results and clinical decision support can convert patient-specific pharmacogenomic information into reusable, point-of-care guidance [33]. Gene-specific implementation remains essential: DPYD testing for systemic fluoropyrimidines, for example, requires dedicated testing, interpretation, workflow, stakeholder, and decision-support arrangements that should not be assumed to transfer unchanged to other pharmacogenes [34].

The final proposed standard is that testing decisions should be driven by actionability, severity of the preventable outcome, availability of alternatives, timing, cost, turnaround, and the clinical decision at hand [35]. Ancestry may identify where evidence gaps or assay limitations deserve attention, but it should not function as a standalone rule for who receives a test or how a detected genotype is interpreted.

CONCLUSION

Ancestry is useful context but an inadequate substitute for functional pharmacogenomic evidence. Population labels can reveal differences in allele distributions, expose gaps in reference resources, and guide more inclusive discovery, yet they cannot establish the genotype, functional phenotype, or drug-specific response of an individual patient. A more defensible hierarchy gives precedence to accurate variant and haplotype ascertainment, experimentally or clinically supported function, treatment-state modifiers, and validated gene–drug actionability. The practical goal is therefore not ancestry-blind pharmacogenomics, but ancestry-aware evidence generation combined with ancestry-independent requirements for individual functional inference. This approach preserves genuine population structure without converting it into biological determinism and provides a clearer route toward both precision and equity.

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