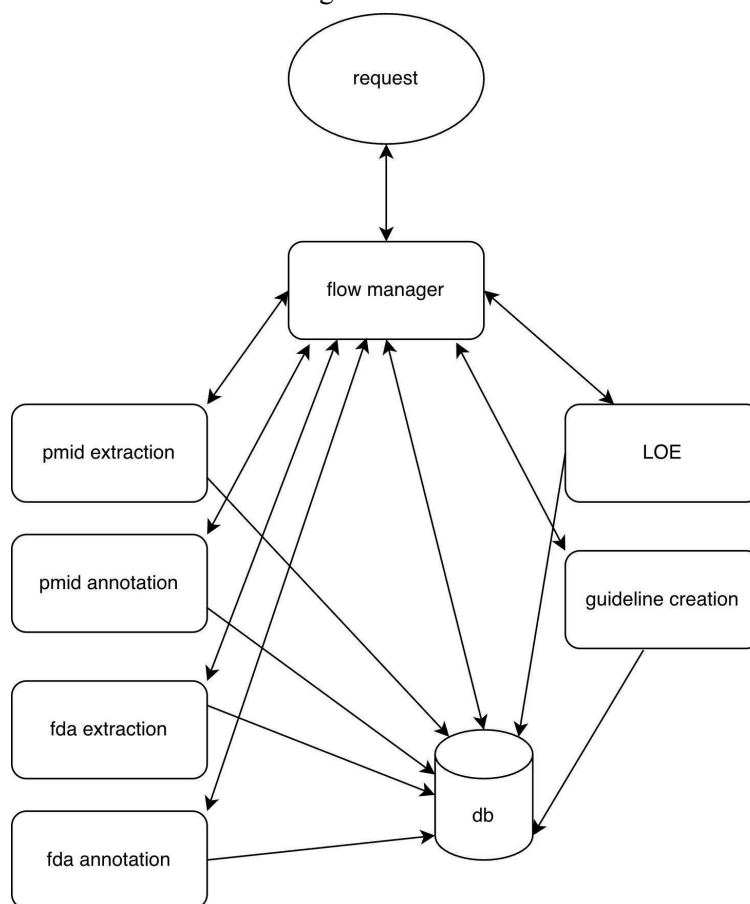
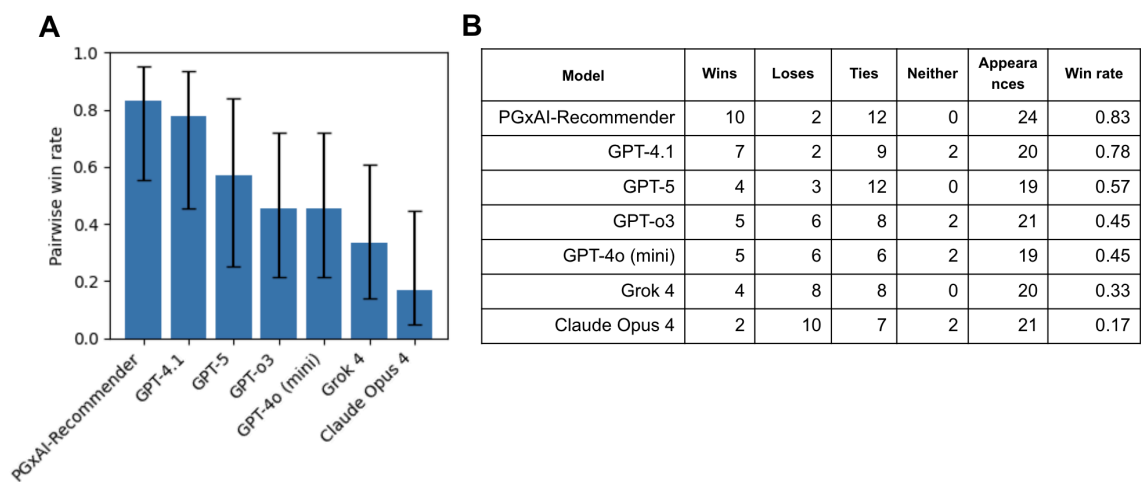


Supplementary Figure 1. Architecture of the agentic orchestration workflow.



A flow manager coordinates PMID extraction, PMID annotation, FDA extraction, and FDA annotation modules, writes intermediate outputs to a central database, and triggers downstream Level-of-Evidence (LOE) aggregation and guideline-generation components.

Supplementary Figure 2. Pairwise CPIC-guideline conformance evaluation of pharmacogenomic recommendation models.



(A) Pairwise win rates for each model, defined as the proportion of pairwise comparisons in which the model was selected as more consistent with the corresponding CPIC reference recommendation. Error bars indicate 95% Wilson confidence intervals. Ties were excluded from the win-rate denominator.

(B) Summary of pairwise comparison outcomes, including the number of wins, losses, ties, and “Neither” selections, as well as total model appearances and corresponding win rates. Pairwise comparisons were conducted in a blinded and randomized manner across 72 evaluations covering 24 clinical cases.

Supplementary Table 1. Example of the Annotated Result (PMID: 18057928)

This table illustrates a structured annotation produced during the evidence extraction stage. Each field corresponds to a standardized metadata element captured by the system for every primary study. It summarizes study design, genotyping details, population context, phenotype definitions, and key outcomes relevant to gene–drug associations. The **Phenotypes reported** section provides harmonized mappings between genotypes, functional activity, pharmacokinetic effects, and suggested clinical implications. This structured format enables consistent comparison and aggregation of findings across multiple studies.

Field	Value
Study design	Retrospective cohort study with population pharmacokinetic modeling
Was the study prospective?	No
Sample size (total)	n = 74
Genotype distribution	GG = 30%, GT = 44%, TT = 27%
Ethnic background	Black African HIV-positive patients from Zimbabwe
Was population stratified by ancestry?	No
Genes and alleles studied	CYP2B6 516G→T (*6)
Genotyping method	PCR-RFLP method
Allelic coverage (completeness)	Only CYP2B6*6 variant tested, no rare alleles or CNVs included
Phenotype classification method	Custom - based on genotype (GG = extensive, GT = intermediate, TT = poor metabolizers)
Outcomes measured	Efavirenz plasma concentrations at steady state (11-16 h post-dose)
Were outcomes associated with genotype?	Yes
Is there a plausible biological mechanism?	Yes - CYP2B6 is the primary enzyme metabolizing efavirenz, and the *6 variant reduces enzyme activity
Were multiple hypotheses tested?	Yes

Statistical significance and strength	Genotype effect: OFV reduction of 13 points ($p < 0.05$); Sex effect: OFV reduction of 7 points ($p < 0.05$)
Were clinical outcomes evaluated (not just PK/PD)?	No
Did genotype influence clinical efficacy or safety?	No - only PK outcomes measured, though 50% of patients exceeded safety threshold of 4 mg/L
Is the result supported by other studies or guidelines?	Yes - multiple references cited supporting CYP2B6*6 effect on efavirenz metabolism
Study limitations or conflicts of interest	Single time point sampling, no clinical outcomes, concomitant medications not recorded, no conflicts of interest reported
Clinical implication summary	Dose reduction to 400 mg daily recommended for TT genotype patients; females may need additional dose adjustments
Strength of evidence (high/medium/low)	Medium - good sample size and modeling but lacks clinical outcomes
Should the gene be considered in prescribing?	Yes
Number of genes tested	1 (CYP2B6)
Number of alleles tested	1 (*6 variant)
Number of phenotypes or outcomes tested	1 (plasma concentration)
Number of drugs tested and what drug(s)?	1 (efavirenz)
Total number of genotype-phenotype associations tested	3 (GG vs GT vs TT)
Was multiple testing correction applied?	No
Were primary hypotheses pre-specified?	Yes

What types of gene–drug relationship were evaluated?	Metabolism/PK
What disease or clinical condition was studied?	HIV/AIDS
What phenotype translation system was used?	Custom - GG/GT/TT to extensive/intermediate/poor metabolizer
What role does the gene play in drug response?	Metabolism - CYP2B6 is the primary enzyme metabolizing efavirenz
Was dose adjustment shown to normalize PK/PD or clinical response?	Yes - simulations showed dose reduction could normalize exposure in poor metabolizers

Phenotypes reported

Name	Genotype definition	Functional activity	Pharmacokinetic effect	Pharmacodynamic effect	Clinical impact	Frequency in study population
Extensive Metabolizer	CYP2B6 GG	Normal function	CL/F = 9.4 L/h in males	37% had concentrations >4 mg/L	Standard dose may be appropriate	30%
Intermediate Metabolizer	CYP2B6 GT	Decreased function	CL/F = 7.2 L/h (77% of extensive metabolizers)	50% had concentrations >4 mg/L	Dose reduction to 500 mg may be appropriate for females	44%
Poor Metabolizer	CYP2B6 TT	Significantly decreased function	CL/F = 4.0 L/h (42% of extensive metabolizers)	77% had concentrations >4 mg/L	Dose reduction to 400 mg recommended	27%

Supplementary Table 2. Example of the Evidence Structure (Efavirenz–CYP2B6).

Each row represents an aggregated evidence record produced at the evidence-synthesis stage (see Methods, Evidence Aggregation). Variant concatenates the allele designation, rsID(s), and nucleotide/protein change; Parameter indicates the endpoint evaluated (e.g., activity, PK/PD, dose, toxicity, efficacy). Major findings gives a standardized CPIC-style summary. References list PMIDs in human-readable groups (Supports / Does not support / Inconclusive). Experiment type reflects the study designs included in the synthesis. Level of Evidence (High/Moderate/Weak) is assigned using the qualitative rules described in Methods. This exemplar illustrates the table structure and formatting used throughout.

Variant (Allele; rsID; Nucleotide / Protein change)	Parameter	Major findings	References	Experiment type	LOE
CYP2B6*6 (c.516G>T, rs3745274), c.983T>C (rs28399499), composite haplotypes; rsID: ["rs3745274", "rs28399499"]; Change: ["c.516G>T (Q172H)", "c.983T>C (I328T)"]	Activity	CYP2B6*6, particularly 516TT or *6/*6 genotype and compound slow metabolizer genotypes with c.983T>C, confer reduced CYP2B6 enzyme activity, lower mRNA expression, and decreased metabolic clearance. Consistent evidence from clinical, ex vivo, and in vitro studies demonstrates that poor and intermediate metabolizers exhibit decreased activity compared to wild-type, with composite genotypes conferring the most pronounced reduction.	Supports: 34474119, 35194103, 29081796, 27709010, 26622191, 24390631, 23837472, 19188761, 17082249, 17054410. Does not support: —. Inconclusive: —.	Clinical, In vitro, Ex vivo, Population genetics, Narrative review	High
CYP2B6*6 (c.516G>T), c.983T>C (rs28399499), composite genotypes; rsID: ["rs3745274", "rs28399499"]; Change: ["c.516G>T (Q172H)", "c.983T>C (I328T)"]	PK/PD (Efavirenz and other CYP2B6 substrates)	Slow metabolizer genotypes (516TT, 983CC/CT, and compound heterozygotes) show 2–4 fold higher efavirenz concentrations, higher AUC, and lower metabolic ratio compared to extensive/rapid metabolizers. Intermediate metabolizers (GT or TC) have moderately increased exposure. This relationship is robust across populations, including children and adults of various ethnicities.	Supports: 35235559, 34415664, 34115651, 34945777, 36840416, 39380207, 37078251, 38934229, 34882770, 32116703, 32451120, 31061724, 32909316, 30397233, 29855606, 29636682, 29629676, 29170492, 28145050, 28886044, 28816644, 26991336, 27299708, 27067333, 26622191, 26779253, 26107645, 25889207, 24497997, 24390631, 24359841, 23861838, 17356468, 18839779, 18503405, 18188549. Does not support: 35115810, 35512066, 30864294, 30003275, 28145050, 28931220, 23970651. Inconclusive: —.	Clinical, PK Modeling, Population PK, Observational, Retrospective/Prospective cohort	High

CYP2B6*6 (c.516G>T), c.983T>C (rs28399499), composite genotypes; rsID: ["rs3745274", "rs28399499"]; Change: ["c.516G>T (Q172H)", "c.983T>C (I328T)"]	PK/PD in Pediatric Populations	In children and adolescents, CYP2B6*6 and/or c.983T>C carriage predicts 2–8 fold higher efavirenz concentrations versus wild-type. Maternal CYP2B6 genotype predicts newborn efavirenz exposure. The composite metabolizer phenotype explains about half the pharmacokinetic variability in African pediatric cohorts; slow and ultrarapid metabolizers experience supratherapeutic and subtherapeutic efavirenz levels, respectively. Several studies recommend genotype-guided dosing or monitoring in children.	Supports: 39380207, 38934229, 37078251, 36840416, 34945777, 32909316, 32451120, 28886044, 28816644, 27211824, 26991336, 27067333, 24390631, 24293076, 22057858, 22481606, 21846671, 20881953, 20860463, 21814190, 18503405, 18839779, 17356468. Does not support: —. Inconclusive: —.	Clinical, PK Modeling, Observational cohort	High
CYP2B6*6 (c.516G>T, rs3745274); rsID: rs3745274; Change: c.516G>T (Q172H)	Dose	CYP2B6 poor metabolizers (516TT/*6/*6 or compound slow metabolizer genotypes) require approximately 2–3-fold lower efavirenz doses to avoid toxicity and maintain therapeutic concentrations. Standard 600 mg doses risk excessive exposure and CNS side effects in slow metabolizers. Pediatric studies recommend 0.33–0.66× the standard dose (weight-adjusted) for slow/intermediate metabolizers, especially in African populations.	Supports: 36840416, 38974617, 34474119, 34882770, 29636682, 28886044, 28816644, 27299708, 29170492, 26622191, 26991336, 27067333, 25889207, 24497997, 24390631, 23861838, 22057858, 22481606, 21846671, 20881953, 20860463, 21814190, 18503405, 18839779, 17356468. Does not support: 35512066, 30003275, 31061724, 30084103, 28145050. Inconclusive: —.	Clinical, PK Modeling, RCT, Observational	Moderate
CYP2B6*6 (c.516G>T), c.983T>C (rs28399499), composite genotypes; rsID: ["rs3745274", "rs28399499"]; Change: ["c.516G>T (Q172H)", "c.983T>C (I328T)"]	Toxicity (CNS, hepatic, metabolic)	Slow metabolizer genotypes (516TT, *6/*6, 983C carriers) are associated with increased risk of efavirenz-related CNS toxicity (insomnia, neuropsychiatric events), and sometimes hepatic/metabolic side effects, especially in populations of African or mixed ancestry. However, not all studies show an association with late/severe neurotoxicity or discontinuation.	Supports: 39604537, 34093191, 35887584, 34882770, 31920362, 29629676, 31628422, 30864294, 28886044, 28816644, 26765416, 26288843, 25831219, 25889207, 24551111, 24316028, 22808112, 22162992, 20723261, 18655316, 16611850. Does not support: 34415664, 35512066, 35115810, 30003275, 28145050, 26715213, 23970651. Inconclusive: —.	Clinical, Meta-analysis, PK analysis, Case series, Review	Moderate
CYP2B6*6 (c.516G>T), c.983T>C (rs28399499), composite with CYP2A6; rsID: ["rs3745274", "rs28399499", "CYP2A6: rs28399433"]; Change: ["c.516G>T (Q172H)", "c.983T>C (I328T)", "CYP2A6 -48T>G"]	Efficacy	Most studies do not observe a statistically significant direct association between CYP2B6 genotype and virologic efficacy. Some report higher virologic failure in rapid/extensive metabolizers (due to subtherapeutic levels) and lower failure in slow metabolizers, who have higher toxicity risk. Routine efficacy prediction based on CYP2B6 genotype alone is not currently justified.	Supports: 39380207, 37004096, 33758532, 28816644, 29170492, 27067333, 20625352, 20338069, 20723261, 20881953. Does not support: 38934229, 39764089, 31061724, 29855606, 26715213, 26044067. Inconclusive: 24390631, 24293076.	Clinical, Observational, Modeling	Moderate
CYP2B66 (c.516G>T), CYP2B64, CYP2B6*5 and population/novel alleles; rsID: ["rs3745274", "rs2279343", "rs3211371"]; Change:	Activity and Population Variation	CYP2B6*6 confers a poor metabolizer phenotype; *4 and *5 generally increase activity, contributing to rapid/ultrarapid metabolism. Interethnic differences in allele and genotype	Supports: 34474119, 35505645, 34386299, 33599403, 36320932, 26681005, 28492729, 27709010, 23837472, 19188761, 17686225, 17054410. Does not support: —. Inconclusive: —.	In vitro, Epidemiologic, Population genetics,	Moderate

["c.516G>T (Q172H)", "c.785A>G (K262R)", "c.1459C>T (R487C)"]		frequencies are pronounced. Novel and rare alleles show diverse activity in vitro; most lack defined clinical consequences.		Clinical sequencing	
CYP2B6 3' UTR variant (rs70950385, CA vs AG); rsID: rs70950385; Change: 3'UTR (miR-1275 site alteration)	Activity, Dose (emerging evidence)	The CA variant, which creates a miR-1275 site, results in decreased gene expression and about 33% lower in vitro activity. It is associated with higher plasma substrate exposure (efavirenz, bupropion) in early studies. Clinical significance is not yet established.	Supports: 33872945. Does not support: —. Inconclusive: —.	In vitro, Functional genomics, Pilot clinical	Weak
NR1I2 (PXR) rs3814057/rs2472677, NR1I3 (CAR) rs3003596; rsID: ["rs3814057", "rs2472677", "rs3003596"]; Change: ["NR1I2 c.1536A>C", "NR1I2 c.1060C>T", "NR1I3 c.540T>C"]	Metabolism modifier (CYP2B6 activity, PK)	NR1I3 rs3003596 T/T is associated with increased efavirenz concentrations; NR1I2 rs2472677 T-carriers and rs3814057 C/C correlate with increased CYP2B6 activity and lower efavirenz levels. These effects are most evident in CYP2B6*6 carriers from African populations. Clinical utility remains investigational.	Supports: 35690682. Does not support: —. Inconclusive: —.	Clinical, PK Genetic Association	Moderate
ABCB1 c.3435C>T (rs1045642); rsID: rs1045642; Change: c.3435C>T (silent)	PK/PD (Efavirenz)	The ABCB1 3435T allele (CT/TT genotypes) is associated with modestly higher efavirenz concentrations, although effects are small and inconsistent across different populations. Current evidence does not support clinical action based on this genotype.	Supports: 35887584, 34945777, 23861838, 25264502. Does not support: 29205871, 26715213. Inconclusive: —.	Clinical, PK analysis	Moderate
SULT1A1 (rs6839, rs1042157, c.638G>A), SULT1A1 copy number; rsID: ["rs6839", "rs1042157", "c.638G>A"]; Change: ["rs6839 GG/GA/AA", "rs1042157 TT/TC/CC", "c.638G>A (Arg213His)"]	Activity, PK/PD (Efavirenz)	SULT1A1 copy number ≥3 is associated with lower efavirenz levels at week 12, suggestive of increased clearance. SULT1A1*2 (c.638G>A) shows a minor, non-significant effect after adjusting for CYP2B6. Clinical relevance is unclear.	Supports: 34335044. Does not support: —. Inconclusive: —.	Clinical	Weak
CYP2B6*6 (c.516G>T), c.983T>C (rs28399499); rsID: ["rs3745274", "rs28399499"]; Change: ["c.516G>T (Q172H)", "c.983T>C (I328T)"]	Toxicity (Population diversity)	Slow metabolizer genotypes (*6/*6, c.983C carriers) are common in African, Asian, and Latin American populations and predict increased risk of CNS toxicity from efavirenz. Population screening may be beneficial in high-risk groups.	Supports: 34093191, 31920362, 30864294, 27940179, 27125860, 26604812, 25831219, 23089673, 23172109, 22354160. Does not support: —. Inconclusive: —.	Clinical (Case–Control, Cohort), Review	Moderate
CYP2B6*6, *2, *3 (population alleles, frequency studies); rsID: ["rs3745274", "rs8192709", "rs45482602"]; Change: ["c.516G>T (Q172H)", "c.64C>T (*2, P22S)", "c.777C>A (*3, S259R)"]	Allele frequency, population metabolism risk	CYP2B6*6, *2, and *3 have high frequencies in South Asian, African, and mixed populations; a substantial fraction of individuals may have poor or intermediate metabolizer status. These are frequency data without direct clinical outcomes.	Supports: 25305768, 24831655, 23640958, 17686225. Does not support: —. Inconclusive: —.	Population genetics, Genotyping	Low

CYP2B6*6 (c.516G>T), c.983T>C (rs28399499), composite with CYP2A6 and additional haplotypes; rsID: ["rs3745274", "rs28399499", "CYP2A6: rs28399433"]; Change: ["c.516G>T (Q172H)", "c.983T>C (I328T)", "CYP2A6 -48T>G"]	Population/ Allele Frequency and Composite Activity	Composite CYP2B6/CYP2A6 genotypes define metabolizer phenotypes (EM, IM, SM, USM) and are strong predictors of efavirenz clearance and exposure, especially in African pediatric cohorts. Dose ratios (EM:IM:SM:USM) are approximately 1:0.66:0.33:0.1.	Supports: 26991336, 27299708, 28816644, 28886044, 27211824, 24390631, 24293076. Does not support: —. Inconclusive: —.	Clinical, PK Modeling, Dosing Simulation	Moderate
CYP2B6 516G>T (rs3745274) (single SNP studies); rsID: rs3745274; Change: c.516G>T (Q172H)	Dose/PK/PD (Efavirenz)	CYP2B6 516TT (poor metabolizer) is associated with markedly higher efavirenz concentrations; GT is intermediate. Dose reduction is advisable for TT genotypes; standard dosing typically adequate for GG/GT, though few studies have prospectively evaluated genotype-based adjustment.	Supports: 29170492, 28145050, 27299708, 24551111, 24521642, 23861838, 20723261, 18188549, 17047492. Does not support: —. Inconclusive: 26715213.	Clinical, PK/PD Modeling, TDM	Moderate
CYP2B6 multiple alleles (including *6, *4, *5, novel alleles in Asian populations); rsID: Multiple; Change: Multiple (Q172H, K262R, R487C, others)	Activity (in vitro – novel alleles)	CYP2B6*6 demonstrates poor metabolizer activity; *4 and *5 indicate rapid/ultrarapid function. Numerous missense variants impact enzymatic function in vitro, with variable effects not yet confirmed clinically.	Supports: 34474119, 26681005, 28492729, 27709010, 23837472, 19188761, 17686225, 17054410. Does not support: —. Inconclusive: —.	In vitro, Population sequencing, Case-control clinical, Narrative review	Moderate
CYP2B66 (c.516G>T), c.983T>C (rs28399499), composite with UGT1A128; rsID: ["rs3745274", "rs28399499", "UGT1A128"]; Change: ["c.516G>T (Q172H)", "c.983T>C (I328T)", "UGT1A128: TA repeat expansion"]	Toxicity/Population diversity (risk)	Composite poor metabolizer genotypes (CYP2B6*6/6 or T/T at 516G>T and UGT1A128/*28) robustly predict CNS toxicity from efavirenz and hyperbilirubinemia, with effects especially pronounced in specific ancestry groups.	Supports: 34093191, 31920362, 27940179. Does not support: —. Inconclusive: —.	Clinical (Case-Control), Narrative Review	Moderate
CYP2B6*6 (c.516G>T), c.983T>C (rs28399499), c.15582C>T; rsID: ["rs3745274", "rs28399499", "rs4803419"]; Change: ["c.516G>T (Q172H)", "c.983T>C (I328T)", "c.15582C>T"]	Metabolic-lipid interaction (toxicity/safety; with isoniazid)	CYP2B6 slow metabolizers, especially those co-treated with isoniazid, demonstrate increased cholesterol, HDL, and efavirenz concentrations. No clear association with neuropsychiatric toxicity within 24 weeks.	Supports: 34882770, 40182085, 29629676, 26765416, 24080498, 23990572, 21862974. Does not support: —. Inconclusive: —.	Clinical, PK Modeling	Moderate
CYP2B6*9 (G516T, rs3745274); rsID: rs3745274; Change: c.516G>T (Q172H)	Efficacy, Toxicity (Cyclophosphamide regimens)	In Egyptian B-CLL patients, *9 carriers are associated with higher disease risk and less hematologic response to cyclophosphamide. Lower toxicity but reduced efficacy observed in one cohort. Replication is needed.	Supports: 28492729, 27709010. Does not support: —. Inconclusive: —.	Clinical (Case-Control), Review	Low-Moderate

CYP2B6 loss-of-function (including c.516G>T, c.983T>C), composite CYP2B6/CYP2A6/CYP3A4; rsID: ["rs3745274", "rs28399499", "rs4646437", "rs35303484", "rs35979566", "rs28399433"]; Change: ["c.516G>T (Q172H)", "c.983T>C (I328T)", "CYP3A4 rs4646437", "CYP2A6 -48T>G", "others"]	Drug discontinuation (Toxicity-driven, Efavirenz)	Presence of decreased-function alleles in CYP2B6, CYP2A6, and CYP3A4 increases risk of CNS adverse events and efavirenz discontinuation, supporting composite genotyping for toxicity risk prediction. Effect on viral efficacy is not significant.	Supports: 26288843, 27709010. Does not support: —. Inconclusive: —.	Clinical (Nested Cohort), Narrative Review	Moderate
CYP2B6, CYP2A6, CYP2D6, CYP3A4, NAT2 (multiple alleles, African cohorts); rsID: ["rs3745274", "rs28399499", "others"]; Change: Various (see primary reports)	Toxicity (Isoniazid hepatotoxicity, Efavirenz toxicity, INH exposure)	NAT26 and other slow acetylator alleles are associated with greater isoniazid-induced hepatotoxicity. CYP2B66 is linked to higher efavirenz levels and risk of drug-induced liver injury/neurotoxicity in Africans, supporting genotype-guided dosing/monitoring.	Supports: 26247717, 27125860, 25831219, 24909419, 23089673, 22162992, 22808112. Does not support: —. Inconclusive: —.	Clinical (Case-Control, Prospective cohort), Review	Moderate
Novel or rare CYP2B6 promoter and 3' UTR variants, including -82T>C and rs70950385; rsID: ["rs70950385"]; Change: Promoter -82T>C, 3'UTR CA/AG	Activity modulation	Rare -82T>C promoter variant alters inducibility of CYP2B6; rs70950385 (3'UTR) reduces expression via miRNA-binding, thereby decreasing activity. These may contribute to outlier PK profiles, but clinical utility is not established.	Supports: 27709010, 33872945. Does not support: —. Inconclusive: —.	In vitro, Functional genomics	Weak
Composite PK/PD modifier (NR1I2, NR1I3, transporter genes, regulatory regions); rsID: ["rs3814057", "rs2472677", "rs3003596", "rs1045642", "others"]; Change: Multiple (PXR/CAR SNPs, ABCB1, SULT1A1)	Metabolism modifier, transporter effects (Efavirenz, other ARVs)	Variants in transporters (ABCC2, ABCG2), nuclear receptors (NR1I2, NR1I3), and SULT1A1 influence antiretroviral drug concentrations in CYP2B6 slow metabolizers. Most findings have emerging research support and lack sufficient evidence for clinical actionability.	Supports: 35790682, 29205871, 26774523, 34335044, 27665700, 23859571. Does not support: —. Inconclusive: —.	Clinical PK, GWAS, Functional	Weak-Moderate
CYP2B6*6 (c.516G>T, rs3745274), c.983T>C (rs28399499); rsID: ["rs3745274", "rs28399499"]; Change: ["c.516G>T (Q172H)", "c.983T>C (I328T)"]	PK/PD & Efficacy in HIV/TB coinfection	CYP2B6 516 TT and c.983C alleles are linked to higher efavirenz concentrations, increased CNS toxicity risk, and, in some studies, higher rates of virologic failure or resistance in extensive metabolizers. Dose reduction is frequently suggested for slow metabolizers.	Supports: 24521642, 24551111, 24390631, 24293076, 25889207, 23861838, 20338069. Does not support: 23970651. Inconclusive: —.	Clinical, TDM, Observational cohort	Moderate
CYP2B6*6 (516G>T, rs3745274); rsID: rs3745274; Change: c.516G>T (Q172H)	Efficacy and Toxicity (Efavirenz and Artemether)	CYP2B6 516TT (poor metabolizer) is associated with elevated efavirenz levels and potential increased CNS toxicity, with no consistent effect on viral suppression in HIV. For artemether-lumefantrine, intermediate metabolizers (GT) show delayed parasite clearance and possibly reduced efficacy; however, antimalarial data are limited.	Supports: 20723261, 20338069, 20952418, 18171905, 18057928, 17638512, 16392090. Does not support: —. Inconclusive: —.	Clinical, PK/PD, Efficacy, Observational	Moderate

CYP2B66 (<i>rs3745274</i>), <i>CYP2B618</i> (<i>rs28399499</i>), CYP3A5, CYP3A4 (selected African alleles); rsID: ["rs3745274", "rs28399499", "rs776746", "others"]; Change: ["c.516G>T", "c.983T>C", "CYP3A5*3, *6, *7"]	Antimalarial PK/PD (artemether /lumefantrine)	CYP2B6*6 and *18 genotypes alter artemether and DHA exposure; CYP3A5 expressors have lower lumefantrine/desbutyl-lumefantrine levels. Genotype effects on PK are consistent but clinical differences in parasite clearance are minimal and infrequently statistically significant.	Supports: 16392090. Does not support: —. Inconclusive: —.	Clinical PK/PD, Observational	Low–Moderate
TPH2 rs7305115, rs4570625, rs1386493; rsID: ["rs7305115", "rs4570625", "rs1386493"]; Change: Various noncoding and missense variants in TPH2	Toxicity (Neuropsychiatric effect: Depression risk under ART)	TPH2 rs1386493 GG homozygosity is associated with an increased risk (~5-fold) of severe depression following initiation of efavirenz- or atazanavir/ritonavir-based ART. rs4570625 TT may have a weaker effect. Evidence is strongest for early (4-week) depressive outcomes and requires replication.	Supports: 19218571, 17968817, 16857630. Does not support: —. Inconclusive: —.	Clinical (Prospective cohort, Case-control)	Low
ABCB1 1236T-2677T-3435T haplotype; rsID: ["rs1128503", "rs2032582", "rs1045642"]; Change: ["1236C>T", "2677G>A/T", "3435C>T"]	PK (Carbamazepine)	Pediatric carriers of the ABCB1 1236T-2677T-3435T haplotype exhibited significantly higher carbamazepine clearance in population PK modeling, suggesting potential need for higher doses or intensified TDM. Effect on serum concentrations showed a non-significant trend; no clinical outcome data were available.	Supports: 16267764. Does not support: —. Inconclusive: —.	Clinical, Population PK Modeling (Pediatric, Cross-sectional)	Low
CYP2B6*6 (c.516G>T), c.983T>C, composite genotype (Bieczak et al. classification), Pediatric population; rsID: ["rs3745274", "rs28399499"]; Change: ["c.516G>T (Q172H)", "c.983T>C (I328T)"]	PK/PD, Efficacy (Efavirenz in pediatric HIV)	CYP2B6 composite genotypes (516/983) classified as EM, IM, SM demonstrated strong stepwise effect on efavirenz exposure: EM (516GG	983TT) had lowest exposure and higher risk for sub-therapeutic levels (median 1,500–2,000 ng/mL, 18% subtherapeutic), IM (516GG	983TC or 516GT	983TT) had moderately increased exposure, SM (516GT
CYP2B6 (simulated poor vs normal metabolizer, e.g., *6), interacting with Efavirenz dosing on Levonorgestrel PK (PBPK simulation); rsID: ["rs3745274"]; Change: c.516G>T (Q172H)	PK/PD (Drug–Drug–Gene interaction: Levonorgestrel–Efavirenz)	Simulation studies predict that CYP2B6 poor metabolizers (higher efavirenz exposure due to reduced clearance) may require both increased levonorgestrel (LNG) implant dose (300 mg) and reduced efavirenz (400 mg) daily for normalization of LNG concentrations due to stronger CYP3A4 induction. In typical metabolizers, LNG 300 mg offsets efavirenz 600 mg induction; in poor metabolizers, further efavirenz dose reduction does not always fully restore LNG levels.	Supports: 12151999, 15194512. Does not support: —. Inconclusive: —.	PBPK simulation modeling (Virtual African female populations)	Low

**CYP2B6 (*6, 2, 4, 5, 7, 9, 11, 18, 26), <i>ABCB1</i> (<i>rs1045642</i>, etc.), <i>CYP2D6</i> (2/3/4/5/10/11), <i>CYP3A4/5</i>, others; rsID: ["<i>CYP2B66</i>: <i>rs3745274</i>", "<i>CYP2B62</i>: <i>rs8192709</i>", "<i>CYP2B64</i>: <i>rs2279343</i>", "<i>CYP2B65</i>: <i>rs3211371</i>", "<i>CYP2B67</i>: <i>rs2279344</i>", "<i>CYP2B69</i>: <i>rs3745274</i>", "<i>CYP2D62</i>", "<i>CYP2D63</i>", "<i>CYP2D64</i>", "<i>CYP2D65</i>", "<i>CYP2D610</i>", "<i>CYP2D611</i>", "<i>rs1045642</i>", "<i>rs9282564</i>", "<i>rs2032582</i>", "<i>rs1128503</i>"]; Change: Multiple (see primary review for details)	PK/PD, Efficacy, Toxicity (Methadone Maintenance Therapy)	CYP2B6*6 poor metabolizers had elevated (S)-methadone plasma levels and increased QTc prolongation risk; CYP2D6 ultrarapid metabolizers had lower (R,S)- and (S)-methadone concentrations with lower treatment satisfaction. Evidence for ABCB1 3435TT genotype and other transporters is inconsistent. Dose adjustment/ECG monitoring may benefit CYP2B6 PMs; evidence for other genes remains exploratory.	Supports: 14628297. Does not support: —. Inconclusive: —.	Systematic Review (Observational studies)	Moderate
Multiple CYPs (CYP1A2, CYP2A6, CYP2B6, CYP2C8/9/19, CYP2D6, CYP3A4/5/7), transporters (OAT1/2/3, OATP1B1/1B3, OCT1/2, MATE1/2-K, P-gp, PEPT1/2), and known variants (e.g., CYP2C19*2, *3, 17; CYP2C92, *3; SLCO1B1 521C); rsID: Various (see narrative review); Change: Multiple functional and loss-of-function SNPs (review article)	Activity (Enzyme and transporter function)	Allelic variation in CYPs and transporters modulates metabolism, PK, and drug response. Functional and loss-of-function alleles affect drug clearance, efficacy, and toxicity risk for a wide range of medications. Specific dosing recommendations rely on existing guidelines, not on this summary.	Supports: 12676886. Does not support: —. Inconclusive: —.	Narrative Review	Low

Supplementary Table 3. Example of Drug Label Annotation (Efavirenz)

This example illustrates the structured pharmacogenomic annotation automatically extracted from the U.S. prescribing information for Efavirenz. The output summarizes key sections of the label relevant for pharmacogenomic reasoning, safety, and dosing personalization.

Each section is represented as a normalized field within the PGxAI-Recommender schema, preserving structure and clinical context.

Section	Annotated Content
Indications and Usage	Efavirenz is a non-nucleoside reverse transcriptase inhibitor (NNRTI) indicated, in combination with other antiretroviral agents, for treatment of HIV-1 infection in adults and pediatric patients ≥ 3 months of age who weigh ≥ 3.5 kg.
Dosage and Administration	Oral, once daily on an empty stomach, preferably at bedtime. Adults: 600 mg daily. Increase to 800 mg daily when co-administered with rifampin (≥ 50 kg). When given with voriconazole, use efavirenz 300 mg once daily and increase voriconazole to 400 mg q12h. Pediatrics: weight-based once-daily dosing (100–400 mg for 3.5–40 kg; 600 mg ≥ 40 kg). Capsules may be opened and sprinkled; tablets must not be crushed. Hepatic impairment: not recommended in Child-Pugh B or C; monitor LFTs. Always use in combination with other active antiretrovirals; bedtime dosing may lessen CNS symptoms.
Contraindications	1) Clinically significant hypersensitivity to efavirenz (e.g., Stevens–Johnson syndrome). 2) Concomitant use with elbasvir/grazoprevir. 3) Not recommended with ATRIPLA coadministration unless required for rifampin dose adjustment.
Warnings and Precautions	• QTc prolongation: avoid in patients at high torsade risk. • Drug interactions: CYP3A/2B6 induction/inhibition. • Psychiatric events: depression, suicidal ideation, aggression, psychosis. • CNS symptoms: dizziness, insomnia, abnormal dreams, impaired concentration; typically resolve in 2–4 weeks. • Embryo-fetal toxicity: avoid in 1st trimester; require contraception. • Severe rash: Stevens–Johnson, more frequent in children. • Hepatotoxicity: monitor LFTs. • Seizures: monitor anticonvulsant levels. • Hyperlipidemia: monitor cholesterol/triglycerides. • Immune reconstitution syndrome and fat redistribution may occur.

Adverse Reactions	Common ($\geq 5\%$): dizziness, impaired concentration, abnormal dreams, insomnia, headache, fatigue, rash, nausea, vomiting. Serious: psychiatric disorders (suicidality), Stevens–Johnson, hepatotoxicity, seizures, lipid elevations. Pediatric: rash in 32% (3% grade 3–4).
Drug Interactions	Potent inducer of CYP3A and CYP2B6, moderate inhibitor of CYP2C9/2C19. Significant interactions: rifampin ($\uparrow$ EFV dose to 800 mg), voriconazole ($\downarrow$ EFV to 300 mg, $\uparrow$ VOR to 400 mg q12h), rifabutin ($\uparrow$ dose), lopinavir/ritonavir ($\uparrow$ dose), oral contraceptives ($\downarrow$ progestin levels), warfarin (monitor INR), methadone (withdrawal), anticonvulsants (monitor levels). Contraindicated: elbasvir/grazoprevir. Avoid QT-prolonging drugs and high-fat meals ($\uparrow$ exposure).
Pharmacokinetics	T _{max} 3–5 h; steady-state t _{1/2} 40–55 h. 99.5% protein bound. Metabolized by CYP2B6 and CYP3A4, auto-induction. Excreted as metabolites: 14–34% urine, 16–61% feces. CSF $\approx 0.7\%$ plasma. High-fat meal $\uparrow$ AUC 28%, $\uparrow$ C _{max} 79%. Avoid with food.
Use in Specific Populations	Pregnancy: avoid 1st trimester (neural tube defect risk); use two effective contraceptive methods. Lactation: not recommended. Pediatrics: approved ≥ 3 mo & ≥ 3.5 kg; higher rash risk. Geriatrics: limited data. Hepatic impairment: not recommended Child-Pugh B/C; caution A. Renal impairment: no adjustment needed.
Pharmacogenetic Information	CYP2B6 polymorphisms markedly affect efavirenz exposure. Homozygous *6/*6 individuals have $\sim 2.3\times$ higher C _{max} after 600 mg, greater QTc prolongation (mean +8.7 ms), and risk of late-onset neurotoxicity. No formal genotype-guided dosing provided; clinical monitoring or alternative therapy advised in poor metabolizers.
Clinical Studies	Study 006 (n=1266): EFV+ZDV+LAM achieved viral load <400 copies/mL in 69% vs 50% with IDV+ZDV+LAM (48 wk). ACTG 364 (n=196): EFV arms 63–71% vs 41% (48 wk). Pediatric trials (n=182, 3 mo–21 y): 57–77% viral suppression at 48 wk; median CD4 ⁺ gain 128–238 cells/mm ³ .

Supplementary Table 4. Example of CPIC-Style Recommendation (Efavirenz–CYP2B6).

This example illustrates the final, guideline-style output generated by the PGxAI-Recommender for the Efavirenz–CYP2B6 pair.

Each record corresponds to a predicted phenotype-based recommendation, including a concise implication statement, actionable guidance, and strength of recommendation.

The structure and tone follow CPIC-style conventions for clinical pharmacogenomic guidelines.

Phenotype	Implication	Recommendation	Strength
Normal Metabolizer	Individuals with CYP2B6 normal metabolizer genotype (e.g., 516GG or *1/*1) have typical efavirenz metabolism and exposure, with no increased risk of toxicity or subtherapeutic levels.	Use efavirenz at the standard adult dose of 600 mg once daily. No dose adjustment is necessary for normal metabolizers.	Strong
Intermediate Metabolizer	Moderately increased efavirenz exposure; higher risk of CNS side effects. Standard dosing often acceptable but requires monitoring.	Efavirenz can be used. Consider a 25–33% dose reduction (e.g., 400–450 mg once daily in adults, or 0.66_ standard pediatric dose) to avoid supratherapeutic concentrations, especially in populations with high risk of CNS toxicity. Standard dosing may suffice if therapeutic drug monitoring is available.	Moderate
Poor Metabolizer	2–4× higher efavirenz concentrations; significantly increased toxicity risk.	Use efavirenz at 1/2 to 1/3 the standard dose (e.g., 200–400 mg once daily in adults, 0.33–0.66_ standard weight-adjusted dose in children); standard dosing (600 mg once daily in adults) is not recommended.	Moderate
Rapid Metabolizer	Increased CYP2B6 activity → lower efavirenz exposure → risk of virologic failure.	Use efavirenz; consider standard dose (600 mg once daily) with awareness of possible lower drug exposure. Genotype-guided dose increase has been	Moderate

		suggested in some studies for rapid/extensive metabolizers, but insufficient evidence for a specific increased dose recommendation.	
Ultrarapid Metabolizer	High clearance → risk of low efavirenz levels and virologic failure. Evidence insufficient for dose changes.	Consider using standard or potentially increased efavirenz dose (e.g., up to 800 mg once daily) in ultrarapid metabolizers, with close therapeutic drug monitoring. Dose adjustment should be guided by efavirenz plasma concentrations and clinical response.	No recommendation
Indeterminate	Evidence insufficient for phenotype-based guidance.	No recommendation	No recommendation

Supplementary Note 1. Example of model-generated JSON output.

```
{'gene': 'CYP2B6',  
  'drug': 'efavirenz',  
  'phenotype': 'poor metabolizer',  
  'implication': 'CYP2B6 poor metabolizers (e.g., *6/*6 or 516TT genotype) have  
2-4-fold higher efavirenz concentrations, increased risk of CNS toxicity  
(including late-onset neurotoxicity and QTc prolongation), and require lower  
doses to avoid adverse effects. Standard 600 mg daily dosing leads to  
excessive exposure and toxicity in this group.',  
  'recommendation': 'Use efavirenz at 1/2 to 1/3 the standard dose (e.g.,  
200-400 mg once daily in adults, 0.33-0.66_ standard weight-adjusted dose in  
children); standard dosing (600 mg once daily in adults) is not recommended.',  
  'strength': 'Moderate'}
```

Supplementary Note 2. Agentic controller prompt.

You are an AI coordinator agent responsible for automating the extraction and synthesis of pharmacogenomic data. Your goal is to produce a clinical recommendation for a specific drug-gene pair using available PMIDs and FDA documents.

Input state:

- "pmids": list of PMIDs with their status (not_downloaded, downloaded, annotated)
- "sources": available sources for each PMID (e.g., Elsevier, PMIC, FDA)
- "annotations": list of already processed document annotations
- "loe_results": Level of Evidence results, if available
- "fda_info": any FDA document information already retrieved

Tools you can use:

1. download_pdf(pmid, source) – download a PDF document for a PMID from a given source
2. annotate_document(doc) – extract alleles, cohorts, assays, results, and other relevant entities
3. aggregate_evidence(annotations_batch) – group annotated documents by evidence level and phenotype
4. generate_recommendation(loe_results, fda_info) – output a clinical recommendation in CPIC guideline format

Your task:

1. Choose the next action to progress towards the goal.
2. Consider the status of each PMID, source availability, number of annotated documents, and priority for LOE aggregation.
3. Actions can be: "download", "annotate", "aggregate", "recommend".

Output format (JSON only, no additional text):

```
{
  "action_type": "<action_type>",    # download, annotate, aggregate, recommend
  "parameters": { ... },            # e.g., PMID, source, document, annotations
  "reasoning": "<short explanation why this action was selected>"
}
```

Repeat recursively until a final recommendation is generated.

Supplementary Note 3. Pseudocode of the perceive–reason–act controller

```
goal = "Complete processing for case_id X"
while True:
    # Perceive: read current state from the database
    state = read_case_state(case_id=X)
    # Example structure:
    # state = {
    #     "extract": "pending" | "done" | "failed",
    #     "annotate": "pending" | "done" | "failed",
    #     "fda": "pending" | "done" | "failed",
    #     "recs": "pending" | "done" | "failed"
    # }

    # Check if all steps have been successfully completed
    if (state.extract == "done" and
        state.annotate == "done" and
        state.fda == "done" and
        state.recs == "done"):
        log("Case X completed")
        break

    # Reason: select the next action based on the current state
    action = LLM_select_action(
        goal=goal,
        state=state,
        available_tools=["run_extract", "run_annotate", "run_fda", "run_recs"]
    )

    if action == "STOP":
        log("Controller stopped early for case X")
        break

    # Act: invoke the chosen tool
    result = call_tool(action, case_id=X)

    # Update: write the output and any errors back to the database
    update_case_state(case_id=X, result=result)

    # Feedback loop: the updated state is used on the next iteration
    continue
```

Supplementary Note 4. Prompt template for recommendation generation (baseline version).
[ROLE]

You are a pharmacogenetics expert generating a clinical recommendation based on the strength of evidence for a gene-drug-phenotype association.

DONT RETURN EMPTY STRING

[TASK]

You must produce a CPIC-style therapeutic recommendation for:

- Drug: '<drug>'
- Gene: '<gene>'
- Phenotype of diplotype: '<phenotype>'

Classify the **Strength of Recommendation** into one of the following categories:

- **Strong**: High-quality evidence and the benefits clearly outweigh the risks.
- **Moderate**: Moderate evidence; benefit likely outweighs risks, but uncertainty remains.
- **No recommendation**: Evidence is insufficient or inconsistent to make a recommendation.
- Explicitly state whether the recommended dose differs from the standard dose.
- If the dose differs, include the percentage change from the standard (e.g., "reduce dose by 50%").
- If you see information in the documents provided, then for a specific drug, gene and phenotype, issue

If you need a standard dose, write it in numbers.

If you need a change in the standard dose, then say what the current doses are in numbers, and also indicate the changes from the standard dose in percent. Do not indicate the values of the standard dose

If there is information about how often to take the medicine, then write this information.

NB: information in the 'implication' and 'recommendation' fields MUST not differ in meaning

NB: Be sure to say. If there is a little information on changing the dose, then use it.

- The answer for the 'recommendation' field MUST contain the following structure

1. determine whether to use this medicine or not.
2. if we use it, what dose: standard, reduced, increased
3. describe the dose in numbers
4. describe how often to take the medicine per day

Your answer MUST be short and precise.

DO NOT RETURN ANY OTHER TEXT.

DONT RETURN EMPTY STRING

[OUTPUT FORMAT]

Return the result strictly in this format (JSON list with a single object):

```
[
  {
    "gene": "<gene>",
    "drug": "<drug>",
    "phenotype": "<phenotype>",
    "implication": "<concise implication>"
    "recommendation": "<concise recommendation or 'No recommendation'>",
    "strength": "<Strong | Moderate | Optional | No recommendation>"
  }
]
```

DO NOT RETURN ANY OTHER TEXT.

DONT RETURN EMPTY STRING

Response:

Supplementary Note 5. Prompt template for recommendation generation using structured evidence and FDA label data.

[ROLE]

You are a pharmacogenetics expert generating a clinical recommendation based on the strength of evidence for a gene-drug-phenotype association.

You are provided with a block of structured evidence from various clinical and preclinical studies:

[EXPERIMENTS AND EVIDENCE]

<evidence>

[FDA]

You also have FDA label data (information about dosage):

FDA LABELS:

<fda>

[TASK]

You must produce a CPIC-style therapeutic recommendation for:

- Drug: '<drug>'
- Gene: '<gene>'
- Phenotype of diplotype: '<phenotype>'

Classify the **Strength of Recommendation** into one of the following categories:

- **Strong**: High-quality evidence and the benefits clearly outweigh the risks.
- **Moderate**: Moderate evidence; benefit likely outweighs risks, but uncertainty remains.
- **No recommendation**: Evidence is insufficient or inconsistent to make a recommendation.
- If you see information in the documents provided, then for a specific drug, gene and phenotype, issue
- The answer for the 'recommendation' field **MUST** contain the following structure

1. determine whether to use this medicine or not if you have this information
2. if we use it, what dose: standard, reduced, increased if you have this information
3. You SHOULD describe the dose in numbers if you have this information
4. describe how often to take the medicine per day if you have this information

DONT USE RANGE IN VALUES

NB: information in the 'implication' and 'recommendation' fields MUST not differ in meaning

NB: Be sure to say. If there is a little information on changing the dose, then use it.

Your answer MUST be short and precise. Dont use a lot of words in your answer

[CONSTRAINTS]

- Only use the information available in the `[EXPERIMENTS AND EVIDENCE]` block above. Do not rely on external sources or assumptions.
- You SHOULD ANALYSE ONLY INFORMATION THAT WAS PROVIDED IN THIS MESSAGE. DONT USE EXTERNAL SOURCES OR YOUR KNOWLEDGE

[OUTPUT FORMAT]

Return the result strictly in this format (JSON list with a single object):

```
[
  {
    "gene": "<gene>",
    "drug": "<drug>",
    "phenotype": "<phenotype>",
    "implication": "<concise implication>"
    "recommendation": "<concise recommendation or 'No recommendation'>",
    "strength": "<Strong | Moderate | Optional | No recommendation>"
  }
]
```

DO NOT RETURN ANY OTHER TEXT.

RETURN ONLY PYTHON DICTIONARY. DONT RETURN EMPTY STRING

[OUTPUT]