

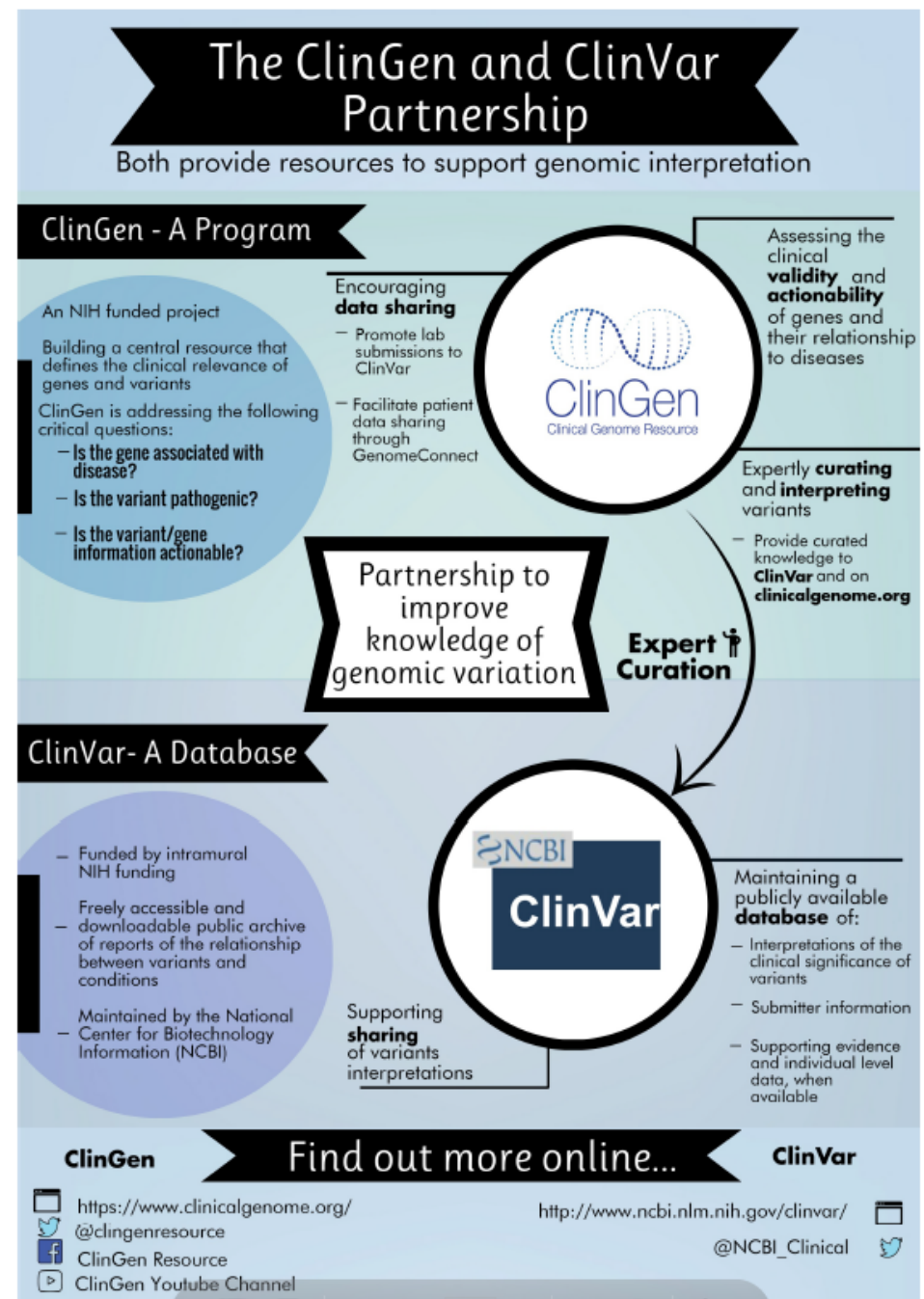
ClinGen PGx WG Acknowledgments

- **Chairs:** Teri Klein (Stanford) and Howard McLeod (Moffitt)
- **Coordinator:** Andy Rivera (UNC)
- **WG Members:**
 - Gillian Bell
 - Jonathan Berg
 - Ulrich Broeckel
 - Kelly Caudle
 - Cyrine Haidar
 - Mary Relling
 - Stuart Scott
 - Michelle Whirl-Carrillo
 - Marc Williams
 - Ken Wiley

ClinGen and ClinVar

<https://www.clinicalgenome.org/>

<http://www.ncbi.nlm.nih.gov/clinvar/>

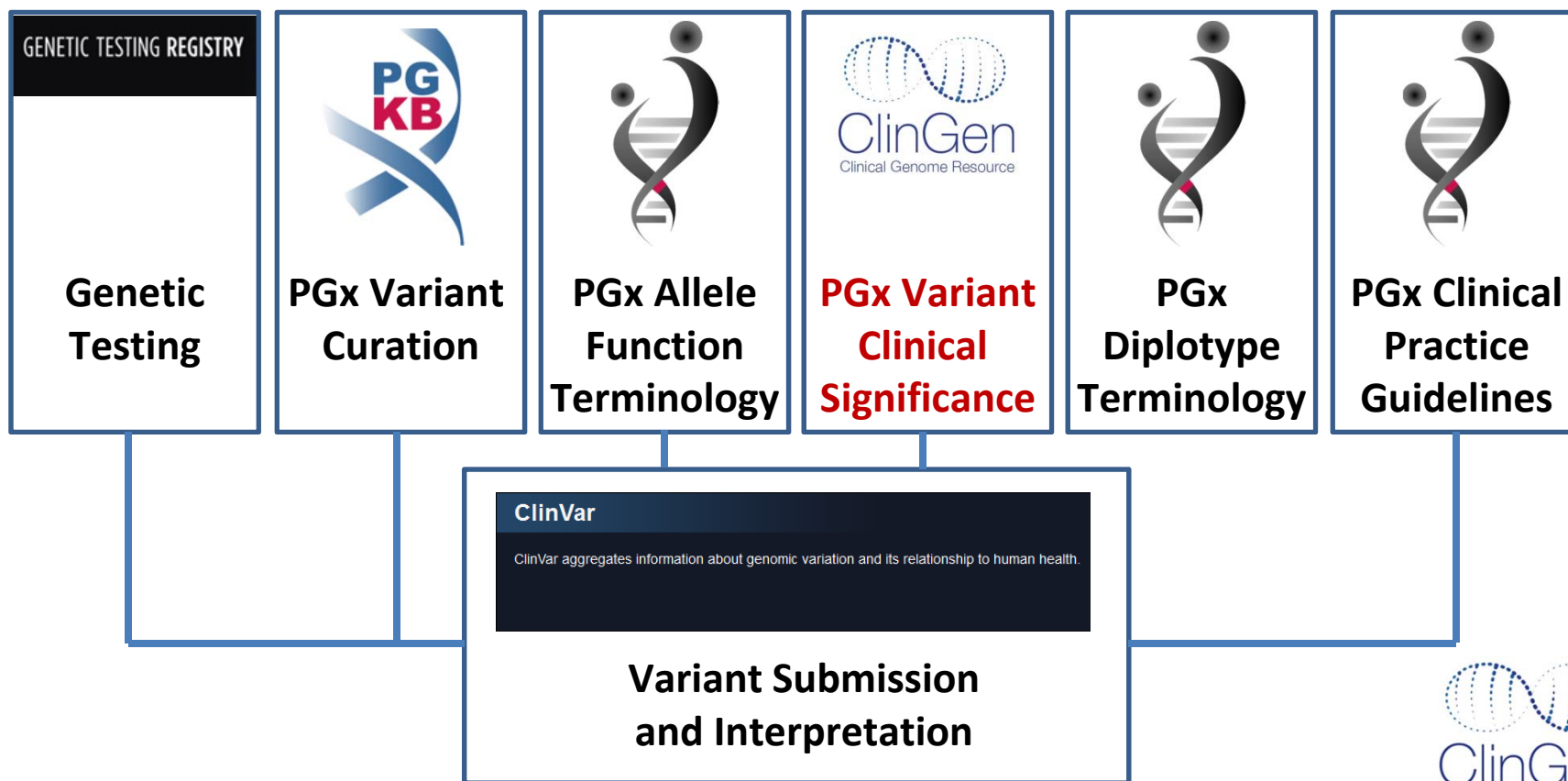


ClinGen PGx WG Goals

- **Purpose:** The PGx Working Group aims to integrate knowledge about human genetic variation to inform drug response.
- **Goals:**
 - Evaluate PGx genes, their impact on drugs, and provide additional annotation that supplements existing pharmacogenetic guidelines.
 - Develop systematic methods for representing and depositing knowledge from the Pharmacogenomics (PGx) Working Group, Clinical Pharmacogenetics Implementation Consortium (CPIC) and PharmGKB into ClinGen and ClinVar.
 - Collaborate with other groups involved in pharmacogenetics such as:
 - a) **CPIC** –Term Standardization Project
 - b) **American College of Medical Genetics and Genomics (ACMG)** – Develop a nomenclature appropriate for PGx variants similar to that of disease variants for pathogenicity.
 - c) **Center for Disease Control (CDC)** Nomenclature group – Ensure transparency for PGx assays such that it is clear what is being tested on a specific gene (e.g., CYP2D6 star system means what actual SNPs were tested).
 - Interact with other ClinGen WGs to harmonize the final contributions to the ClinGen resource.

ClinGen PGx – Relationship to PharmGKB / CPIC

Pharmacogenomic clinical interpretation and implementation



ClinGen PGx – Clinical Significance

- **Objective:**

Propose an evidence-based classification system for the clinical significance of pharmacogenetic variants (haplotypes).

- Leverages the expert curation of PharmGKB and CPIC and is analogous to the ACMG five-tier system for clinical annotation of Mendelian variants.

ClinGen PGx – ACMG

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ACMG STANDARDS

Standards and guidelines for the variants: a joint consensus recommendation from the American College of Medical Genetics and Genomics and the Association for Molecular Diagnostics

Sue Richards, PhD¹, Nazneen Aziz, PhD^{2,16}, Sherri Balasubramanian, PhD³, Julie Gastier-Foster, PhD^{6,7,8}, Wayne W. Grody, MD⁹, Elaine Lyon, PhD¹³, Elaine Spector, PhD¹⁴, Karl Voelker, PhD¹⁵, on behalf of the ACMG Laboratory Quality Assurance Committee

Table 5 Rules for combining criteria to classify sequence variants

Pathogenic	<ul style="list-style-type: none"> (i) 1 Very strong (PVS1) <i>AND</i> <ul style="list-style-type: none"> (a) ≥ 1 Strong (PS1–PS4) <i>OR</i> (b) ≥ 2 Moderate (PM1–PM6) <i>OR</i> (c) 1 Moderate (PM1–PM6) and 1 supporting (PP1–PP5) <i>OR</i> (d) ≥ 2 Supporting (PP1–PP5) (ii) ≥ 2 Strong (PS1–PS4) <i>OR</i> (iii) 1 Strong (PS1–PS4) <i>AND</i> <ul style="list-style-type: none"> (a) ≥ 3 Moderate (PM1–PM6) <i>OR</i> (b) 2 Moderate (PM1–PM6) <i>AND</i> ≥ 2 Supporting (PP1–PP5) <i>OR</i> (c) 1 Moderate (PM1–PM6) <i>AND</i> ≥ 4 supporting (PP1–PP5)
Likely pathogenic	<ul style="list-style-type: none"> (i) 1 Very strong (PVS1) <i>AND</i> 1 moderate (PM1–PM6) <i>OR</i> (ii) 1 Strong (PS1–PS4) <i>AND</i> 1–2 moderate (PM1–PM6) <i>OR</i> (iii) 1 Strong (PS1–PS4) <i>AND</i> ≥ 2 supporting (PP1–PP5) <i>OR</i> (iv) ≥ 3 Moderate (PM1–PM6) <i>OR</i> (v) 2 Moderate (PM1–PM6) <i>AND</i> ≥ 2 supporting (PP1–PP5) <i>OR</i> (vi) 1 Moderate (PM1–PM6) <i>AND</i> ≥ 4 supporting (PP1–PP5)
Benign	<ul style="list-style-type: none"> (i) 1 Stand-alone (BA1) <i>OR</i> (ii) ≥ 2 Strong (BS1–BS4)
Likely benign	<ul style="list-style-type: none"> (i) 1 Strong (BS1–BS4) and 1 supporting (BP1–BP7) <i>OR</i> (ii) ≥ 2 Supporting (BP1–BP7)
Uncertain significance	<ul style="list-style-type: none"> (i) Other criteria shown above are not met <i>OR</i> (ii) the criteria for benign and pathogenic are contradictory

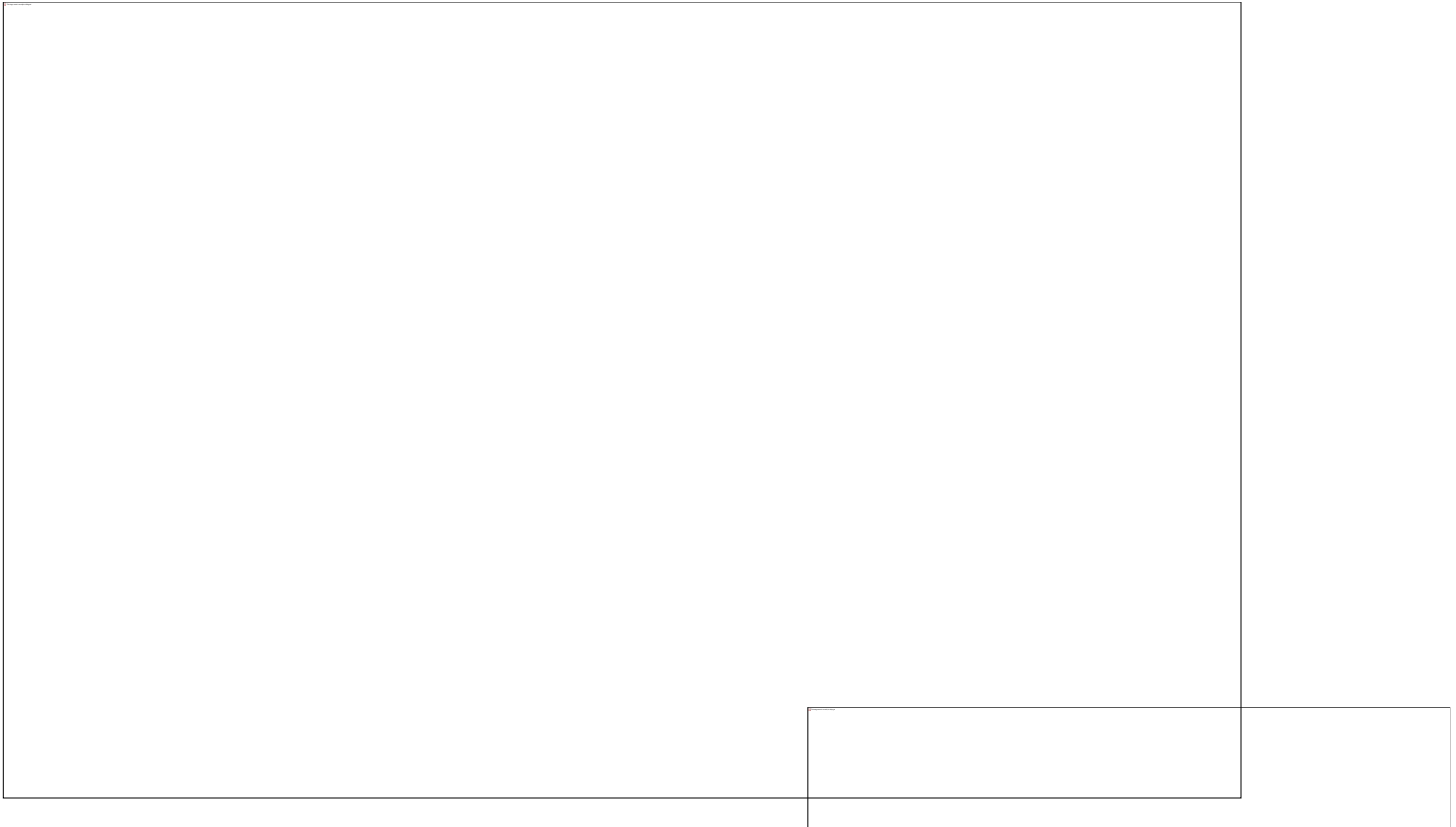
ClinGen PGx – CPIC

CPIC Level Definitions for Genes/Drugs

CPIC Level	Clinical Context	Level of evidence	Strength of Recommendation
A	Genetic information should be used to change prescribing of affected drug	Preponderance of evidence is high or moderate in favor of changing prescribing	At least one moderate or strong action (change in prescribing) recommended.
B	Genetic information could be used to change prescribing of the affected drug because alternative therapies/dosing are extremely likely to be as effective and as safe as non-genetically based dosing	Preponderance of evidence is weak with little conflicting data	At least one optional action (change in prescribing) is recommended.
C	There are published studies at varying levels of evidence, some with mechanistic rationale, but no prescribing actions are recommended because (a) dosing based on genetics convincingly makes no difference or (b) alternatives are unclear, possibly less effective, more toxic, or otherwise impractical. Most important for genes that are subject of other CPIC guidelines or genes that are commonly included in clinical or DTC tests.	Evidence levels can vary	No prescribing actions are recommended.
D	There are few published studies, clinical actions are unclear, little mechanistic basis, mostly weak evidence, or substantial conflicting data. If the genes are not widely tested for clinically, evaluations are not needed.	Evidence levels can vary	No prescribing actions are recommended.

ClinGen PGx – PharmGKB

PharmGKB Clinical Annotation Levels of Evidence for Variants/Drugs





PharmGKB	
Level: 1A, 1B	CLINICALLY ACTIONABLE
Level: 2A, 2B	CLINICALLY INFORMATIVE
Level: 3, 4	UNCERTAIN CLINICAL SIGNIFICANCE

1. Clinically Actionable

Curated variants: All variants with CPIC guidelines and/or PharmGKB Level 1A and 1B variants.

Novel variants:

- A. Variants with the same amino acid change as a Level 1A or 1B variant regardless of nucleotide change.
- B. Truncating variant in a PharmGKB Level 1A or 1B variant gene when loss-of-function is consistent with 1A/1B variant biology.

2. Clinically Informative

Curated variants: All PharmGKB Level 2A and 2B variants.

Novel variants:

- A. Variants with the same amino acid change as a Level 2A variant regardless of nucleotide change.
- B. Truncating variant in a PharmGKB Level 2A or 2B variant gene when loss-of-function is consistent with 2A or 2B variant biology.

3. Uncertain Clinical Significance

Curated variants: All PharmGKB Level 3 and 4 variants.

Novel variants:

- A. Variants in a gene implicated in drug response with computational evidence supporting a deleterious effect.
- B. Variants in a gene implicated in drug response not meeting criteria for other tiers.



PharmGKB	
Level: 1A, 1B	CLINICALLY ACTIONABLE
Level: 2A, 2B	CLINICALLY INFORMATIVE
Level: 3, 4	UNCERTAIN CLINICAL SIGNIFICANCE

- Test cases:**

CYP2C9, CYP2C19, CYP3A5, DPYD, HLA-B, SLCO1B1, TPMT

GENE	ACTIONABLE	INFORMATIVE	UNCERTAIN
<i>TPMT</i>	7	28	7
<i>SLCO1B1</i>	3	9	23
<i>CYP2C19</i>	17	6	10
<i>HLA-B</i>	3	2	19
<i>CYP3A5</i>	4	0	5
<i>CYP2C9</i>	7	7	43
<i>DPYD</i>	8	7	0
TOTAL:	49	59	107

TPMT*3A – Haplotype

Variation ID: [?](#) 12722
 Review status: [?](#) ★ ★ ★ ★ (0/4) no assertion criteria provided

Interpretation [?](#) Go to: [?](#)

Clinical significance: [drug response](#)
 Last evaluated: Jun 28, 2005
 Number of submission(s): 1
 Condition(s): Thiopurine methyltransferase deficiency [[MedGen](#) - [Orphanet](#) - [OMIM](#)]
[See supporting ClinVar records](#) [?](#)

Allele(s) [?](#) Go to: [?](#)

NM_000367.3(TPMT):c.460G>A (p.Ala154Thr)

Allele ID: 27761
 Variant type: single nucleotide variant
 Cytogenetic location: 6p22.3
 Genomic location:

- Chr6: 18138997 (on Assembly GRCh38)
- Chr6: 18139228 (on Assembly GRCh37)

 Other names:

- TPMT*3
- TPMT*3B
- 460G>A

 Protein change: A154T
 HGVS:

- NG_012137.2:g.21147G>A
- NM_000367.3:c.460G>A
- NC_000006.12:g.18138997C>T (GRCh38)

[...more](#)
 Links:

- OMIM: [187680.0002](#)
- OMIM: [187680.0004](#)
- dbSNP: [1800460](#)

 NCBI 1000 Genomes Browser: [rs1800460](#)
 Molecular consequence: NM_000367.3:c.460G>A: missense variant [Sequence Ontology [SO:0001583](#)]
 Allele frequency:

- GO-ESP 0.02822 (T)
- GMAF 0.01280 (T)

Assertions for related alleles [?](#)

NM_000367.3(TPMT):c.719A>G (p.Tyr240Cys) [Help](#)

Clinical significance: drug response
 Review status: ★ ★ ★ ★ (0/4)
 Number of submission(s): 1

Condition(s)

Thiopurine methyltransferase deficiency [[MedGen](#) - [Orphanet](#) - [OMIM](#)]

[See supporting ClinVar records](#)

NM_000367.3(TPMT):c.460G>A (p.Ala154Thr) [Help](#)

Clinical significance: drug response
 Review status: ★ ★ ★ ★ (0/4)
 Number of submission(s): 1

Condition(s)

Thiopurine methyltransferase deficiency [[MedGen](#) - [Orphanet](#) - [OMIM](#)]

[See supporting ClinVar records](#)

1 Affected gene [?](#)

thiopurine S-methyltransferase (TPMT) [[Gene](#) - [OMIM](#) - [Variation Viewer](#)]

- [Search ClinVar for variants within TPMT](#)
- [Search ClinVar for variants including TPMT](#)

Variant frequency in dbGaP [?](#)

NM_000367.3(TPMT):c.460G>A (p.Ala154Thr) GRCh37 Chr6:18139228

	Called variants	Potential variants
Sample count	674 of 9432	2383 of 40995

NM_000367.3(TPMT):c.719A>G (p.Tyr240Cys) GRCh37 Chr6:18130918

	Called variants	Potential variants
Sample count	805 of 9470	3254 of 40803

ClinGen PGx – Clinical Significance

- **Utility:**
 - Will allow for more consistent pharmacogenomic variant interpretation by clinical laboratories.
 - Could facilitate more rapid agreement on the clinical significance of rare or novel pharmacogenomic variants as they are identified by ClinVar submitters.
- **Ongoing discussion:**
 - Reconciling ‘actionable’ with the ClinGen Actionability WG
 - Incorporating levels of evidence.
 - Normal function variants as ‘actionable’
 - Significance centered on haplotypes: many functional haplotypes have ‘benign’ variants among them
 - ClinVar can support HGVS haplotype nomenclature and star (*) alleles.
 - Transparent haplotype definitions will be critical.
- **Questions?**