# ClinGen PGx WG Acknowledgments


- **Chairs:** **Teri Klein** (Stanford) and **Howard McLeod** (Moffitt)

- **Coordinator:** **Andy Rivera** (UNC)

- **WG Members:**
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  - **Jonathan Berg**
  - **Ulrich Broeckel**
  - **Kelly Caudle**
  - **Cyrine Haidar**
  - **Mary Relling**
  - **Stuart Scott**
  - **Michelle Whirl-Carrillo**
  - **Marc Williams**
  - **Ken Wiley**


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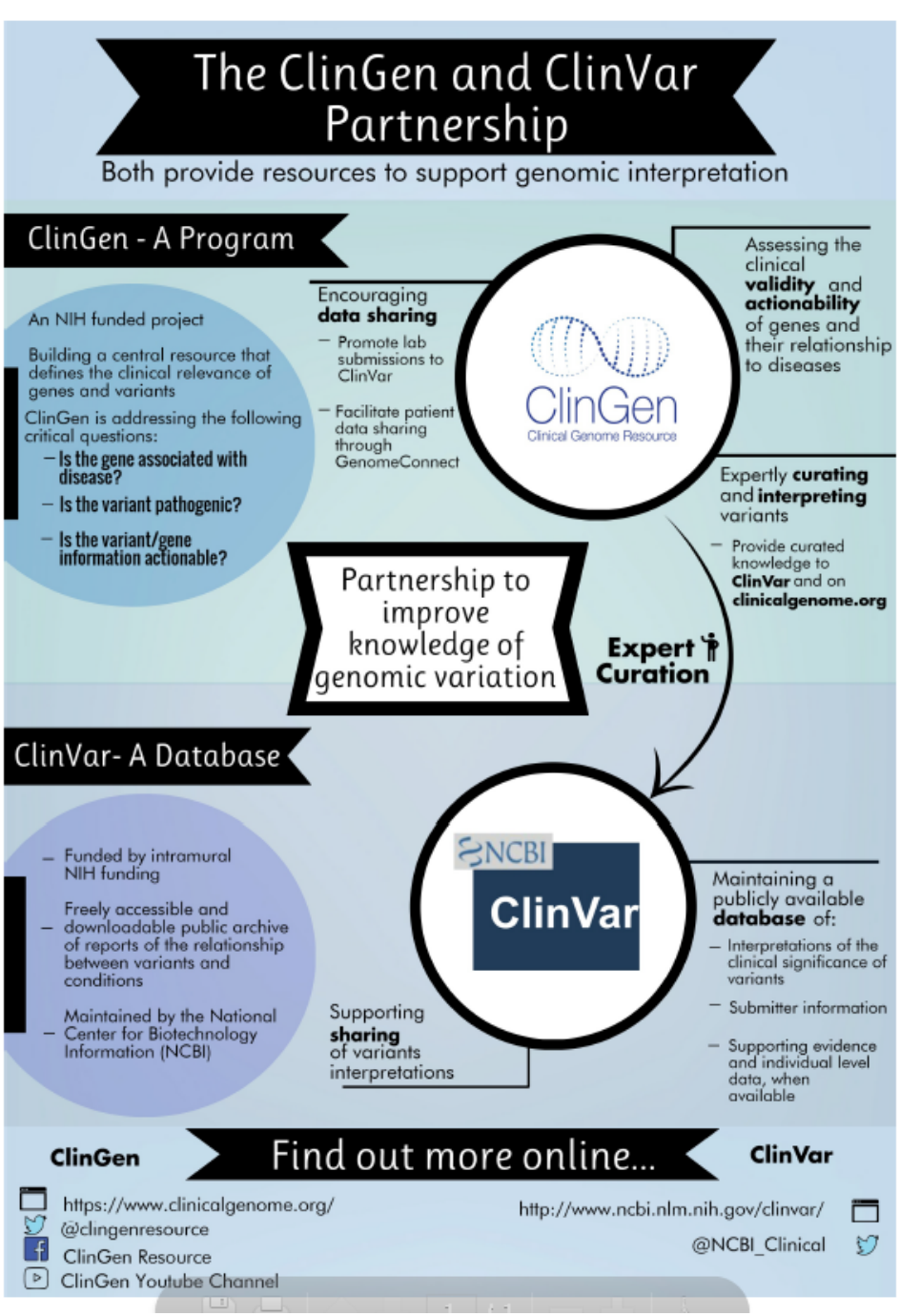
# ClinGen and ClinVar

**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.

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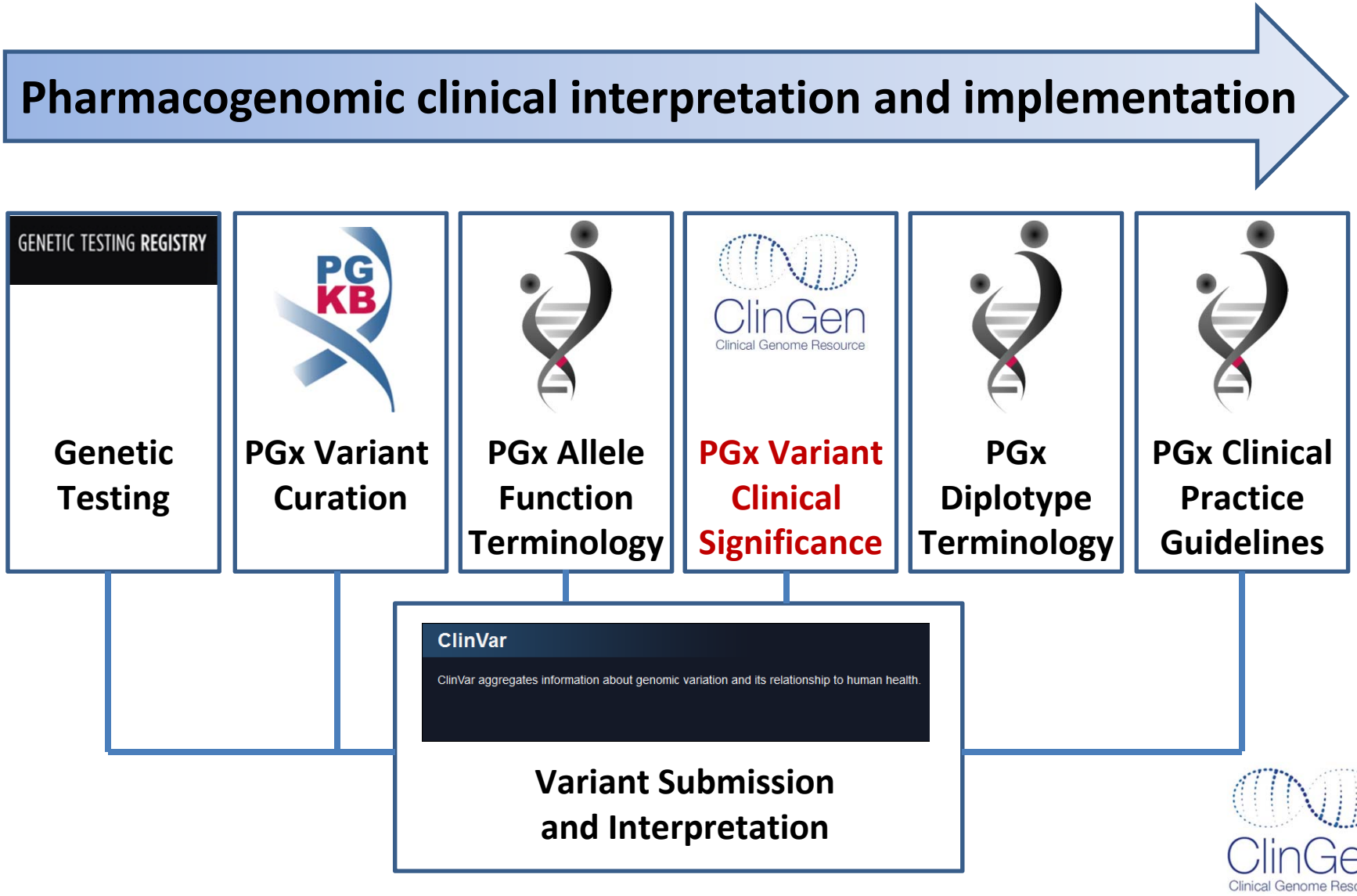
# ClinGen PGx – Relationship to PharmGKB / CPIC



# 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.

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# ClinGen PGx – ACMG



**ACMG STANDARDS**

## Standards and guidelines for the
## variants: a joint consensus recomm
## College of Medical Genetics
## Association for Molec

Sue Richards, PhD[1], Nazneen Aziz, PhD[2,16], Sherri Bal
Julie Gastier-Foster, PhD[6,7,8], Wayne W. Grody, M
Elaine Lyon, PhD[13], Elaine Spector, PhD[14], Karl Voel
on behalf of the ACMG Laboratory Qu

**Table 5** Rules for combining criteria to classify sequence variants

| | |
|---|---|
| Pathogenic | (i) 1 Very strong (PVS1) *AND*<br>(a) ≥1 Strong (PS1–PS4) *OR*<br>(b) ≥2 Moderate (PM1–PM6) *OR*<br>(c) 1 Moderate (PM1–PM6) and 1 supporting (PP1–PP5) *OR*<br>(d) ≥2 Supporting (PP1–PP5)<br>(ii) ≥2 Strong (PS1–PS4) *OR*<br>(iii) 1 Strong (PS1–PS4) *AND*<br>(a)≥3 Moderate (PM1–PM6) *OR*<br>(b)2 Moderate (PM1–PM6) *AND* ≥2 Supporting (PP1–PP5) *OR*<br>(c)1 Moderate (PM1–PM6) *AND* ≥4 supporting (PP1–PP5) |
| Likely pathogenic | (i) 1 Very strong (PVS1) *AND* 1 moderate (PM1–PM6) *OR*<br>(ii) 1 Strong (PS1–PS4) *AND* 1–2 moderate (PM1–PM6) *OR*<br>(iii) 1 Strong (PS1–PS4) *AND* ≥2 supporting (PP1–PP5) *OR*<br>(iv) ≥3 Moderate (PM1–PM6) *OR*<br>(v) 2 Moderate (PM1–PM6) *AND* ≥2 supporting (PP1–PP5) *OR*<br>(vi) 1 Moderate (PM1–PM6) *AND* ≥4 supporting (PP1–PP5) |
| Benign | (i) 1 Stand-alone (BA1) *OR*<br>(ii) ≥2 Strong (BS1–BS4) |
| Likely benign | (i) 1 Strong (BS1–BS4) and 1 supporting (BP1–BP7) *OR*<br>(ii) ≥2 Supporting (BP1–BP7) |
| Uncertain significance | (i) Other criteria shown above are not met OR<br>(ii) the criteria for benign and pathogenic are contradictory |

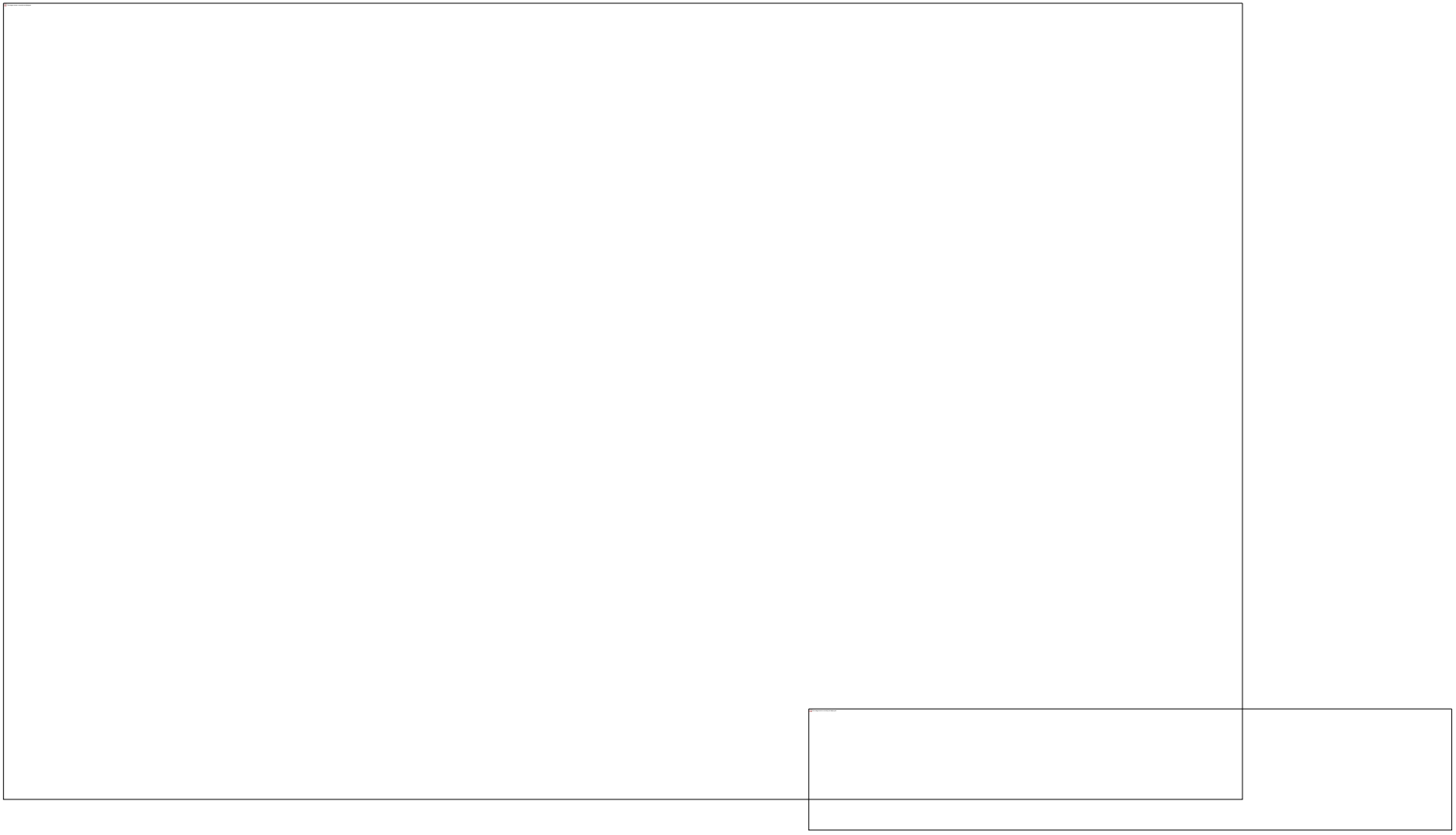
# ClinGen PGx – CPIC

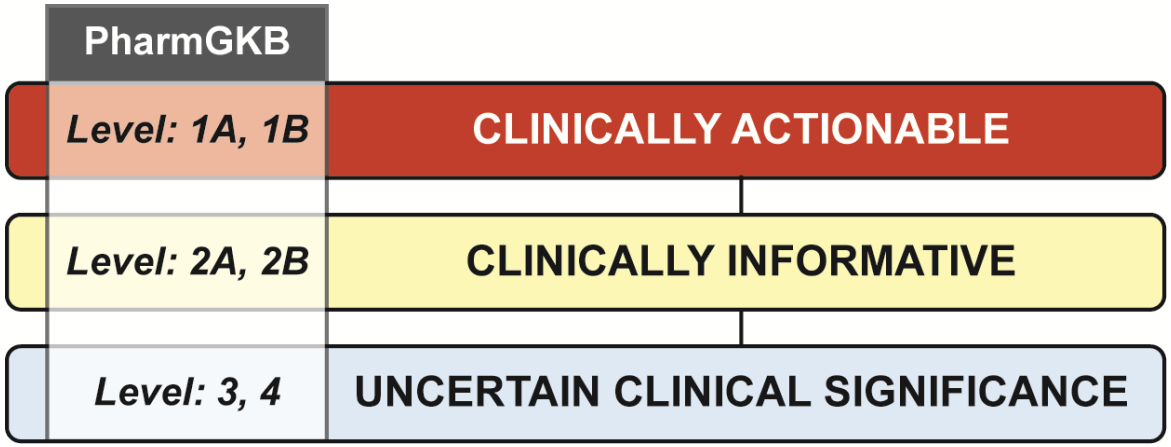
## CPIC Level Definitions for Genes/Drugs

| 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






## 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.**

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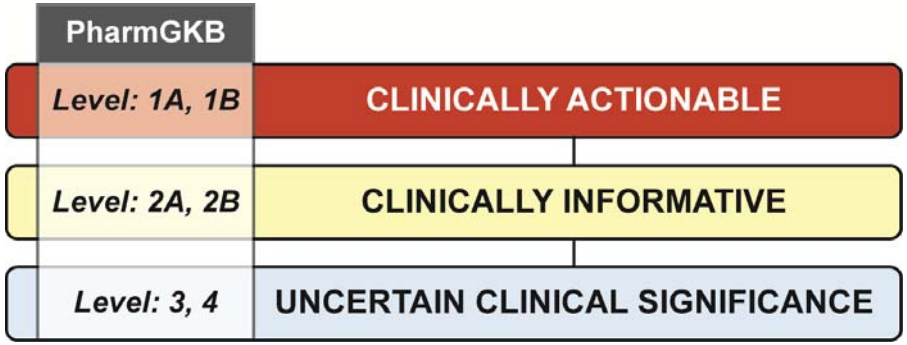
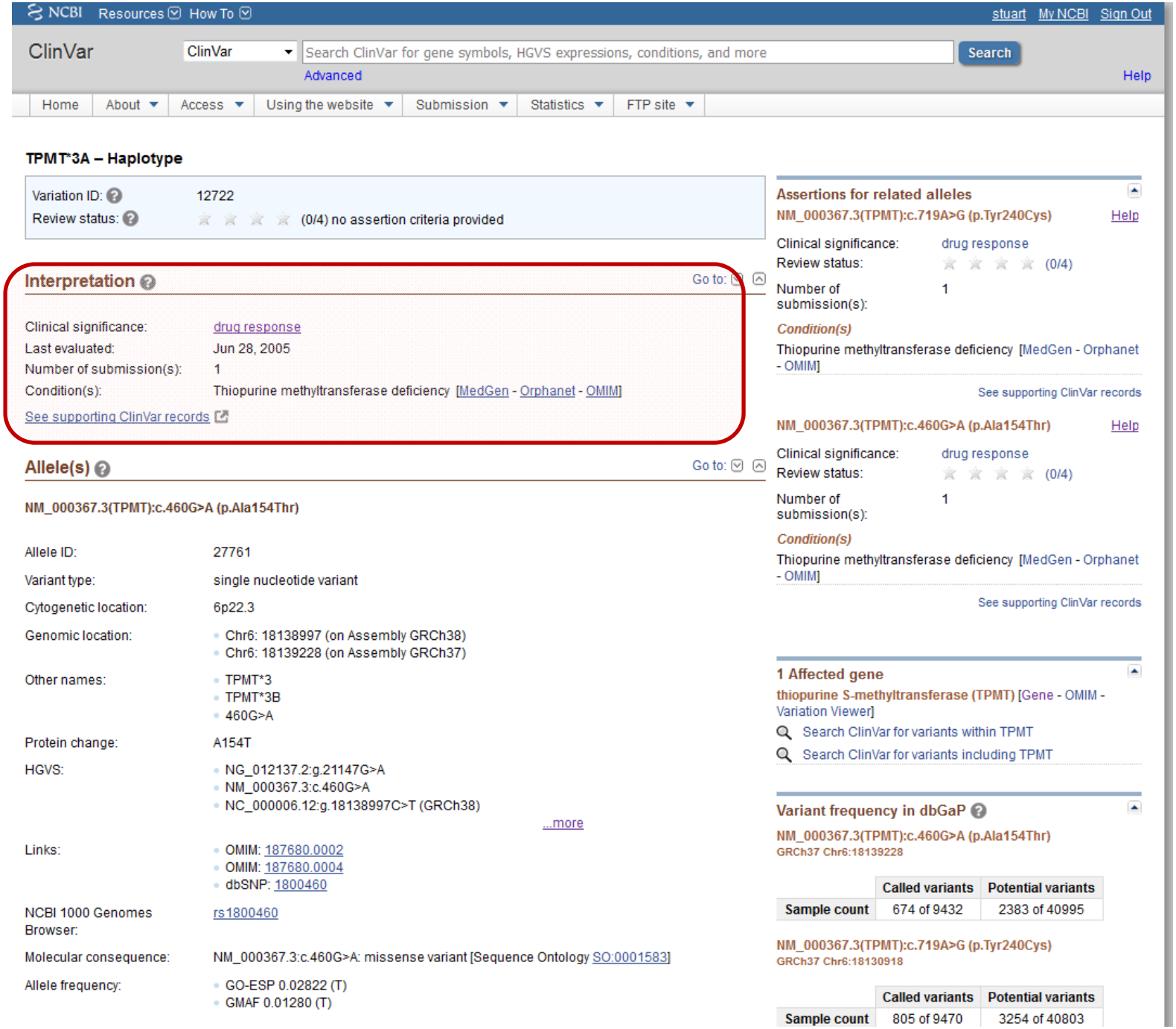



- **Test cases:**
  ***CYP2C9, CYP2C19, CYP3A5, DPYD, HLA-B, SLCO1B1, TPMT***

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

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# 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?**

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