



HHS Public Access

Author manuscript

J Mol Diagn. Author manuscript; available in PMC 2025 June 01.

Published in final edited form as:

J Mol Diagn. 2025 June ; 27(6): 457–464. doi:10.1016/j.jmoldx.2025.02.008.

New Resources to Identify Characterized DNA Reference Materials for PGx and HLA Testing: The Genetic Testing Reference Material (GeT-RM) Program PGx Search Tool and GeT-RM Consolidated PGx and HLA Table

Laura Scheinfeldt, PhD,

Coriell Institute for Medical Research, Camden, NJ

Dara Kusic, PhD,

Coriell Institute for Medical Research, Camden, NJ

Andrea Gaedigk, PhD,

Children's Mercy Research Institute (CMRI), Division of Clinical Pharmacology, Toxicology and Therapeutic Innovation, and University of Missouri-Kansas City School of Medicine, Kansas City, MO

Amy J. Turner, MS,

RPRD Diagnostics and the Medical College of Wisconsin, Department of Pediatrics, Section on Genomic Pediatrics, Milwaukee, WI

Ann M. Moyer, MD, PhD,

Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN

Victoria M. Pratt, PhD,

Indiana University School of Medicine, Department of Medicine, Division of Clinical Pharmacology, Indianapolis, IN, Agena Bioscience, San Diego, CA

Lisa V. Kalman, PhD

Division of Laboratory Systems, Centers for Disease Control and Prevention, Atlanta, GA

Abstract

Regulations, accreditation standards, and professional guidance require laboratories to use reference materials for assay development, validation, quality control, and proficiency testing of clinical genetic tests. There are, however, few publicly available reference materials for most genetic tests. To address this issue, the Centers for Disease Control and Prevention's Genetic Testing Reference Material Program (GeT-RM), the Coriell Institute for Medical Research, and the genetic testing community have conducted 19 studies, including nine for pharmacogenetic (PGx) and Human Leukocyte Antigen (HLA) testing, to create characterized, renewable, and

Corresponding Author: Lisa Kalman, PhD, Quality and Safety Systems Branch, Division of Laboratory Systems, Centers for Disease Control and Prevention, 1600 Clifton Road, Mailstop H24-2, Atlanta, GA 30329, LJK0@cdc.gov.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention/the Agency for Toxic Substances and Disease Registry. Use of trade names and commercial sources is for identification only and does not imply endorsement by the Centers for Disease Control and Prevention, the Public Health Service, or the US Department of Health and Human Services.

publicly available DNA samples for use as reference materials. Because new PGx alleles are frequently identified, and allele designations change over time, many samples were reanalyzed for the same gene(s) in subsequent GeT-RM studies. These studies utilized more comprehensive and sensitive methods and panels that examined additional single nucleotide variants (SNVs) and/or star alleles to expand and update the consensus genotypes. Up to date information is available in two newly established resources: the GeT-RM Consolidated PGx and HLA Table and the GeT-RM PGx Search Tool. These resources contain all available PGx and HLA genotypes for 363 publicly available samples characterized during nine GeT-RM PGx or HLA studies for 34 genes/loci in a consolidated and searchable format.

Introduction

Reference materials are critical for many activities in clinical laboratories, including quality control, development and validation of tests, proficiency testing, validating variant calling algorithms, and inter-laboratory standardization, and are needed to comply with regulations, accreditation standards, and professional guidance^{1–5} (American College of Medical Genetics and Genomics <https://www.acmg.net/PDFLibrary/ACMG%20Technical%20Lab%20Standards%20Section%20G.pdf>, last accessed 7/12/2024, Washington State Legislature, <http://app.leg.wa.gov/WAC/default.aspx?cite=246-338-090>, last accessed 7/12/2024, College of American Pathologists (Northfield, IL) <https://www.cap.org/> last accessed 7/12/2024, New York State Clinical Laboratory Evaluation Program, <https://www.wadsworth.org/regulatory/clip>, last accessed 7/12/2024, MMWR <https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5806a1.htm>, last accessed 7/12/2024).

Clinical laboratories often develop pharmacogenetic and other genetic tests as laboratory developed tests or procedures (LDT or LDP), and use residual patient samples, genomic DNA from cell lines, or synthetic DNA containing variants of interest as reference materials. However, despite the regulatory and professional guidelines requiring their use, there are few, if any, publicly available reference materials for most clinical genetic tests.

To address this issue, the CDC created the Genetic Testing Reference Materials Program (GeT-RM) in 2004 (GeT-RM, <https://www.cdc.gov/lab-quality/php/get-rm/index.html>, last accessed 11/4/2024).⁶ The GeT-RM is a collaborative program whose goal is to improve the availability of genomic DNA reference materials for genetic testing. GeT-RM works with a variety of partners, including clinical and research laboratories, in vitro diagnostics (IVD) manufacturers, professional organizations, patient advocacy groups, and the Coriell Institute for Medical Research to identify reference material needs and create publicly available and renewable genomic DNA reference materials.

GeT-RM has created cell-line based genomic DNA reference materials for a large number of clinically important genes for hereditary genetic disorders, including cystic fibrosis, fragile X, Rett syndrome, and Duchenne muscular dystrophy^{7–10}, 11 Human Leukocyte Antigen (HLA) loci¹¹, and many pharmacogenes and loci.^{12–19} Each sample is experimentally characterized in two or more laboratories using a variety of analytical methods, including targeted genotyping and Sanger sequencing. For some genes, experimental testing also includes copy number variants (CNVs) and structural variation (SVs) analysis or phasing

of variants into star alleles.²⁰ In addition, publicly available high-coverage (30x) whole genome sequencing (WGS) data from the 1000 Genomes Project (1kGP)²¹ or 10x Genomics Linked-Read data (Illumina <https://github.com/Illumina/Polaris/wiki/HiSeqX-PGx-Cohort> last accessed 8/19/2024) was also analyzed. Results were assessed for quality, discordances, and determination of a consensus genotype for each sample. All characterized genomic DNA samples are publicly available from the National Institute of General Medical Sciences (NIGMS) Human Genetic Cell Repository or the National Human Genome Research Institute (NHGRI) Sample Repository for Human Genetic Research, which are both housed at the Coriell Institute for Medical Research.

The GeT-RM has conducted nine studies over the last 14 years to create reference materials for pharmacogenetic and HLA testing.^{11–19} In many cases, samples were reanalyzed for the same gene(s) in subsequent studies using more comprehensive and sensitive methods and panels with additional single nucleotide variants (SNVs) and/or star alleles that were not included in previous characterizations along with other data that became publicly available. This approach allowed updating and expanding consensus genotypes for a considerable number of samples. Often, additional samples were added in later characterization studies to identify SNVs and star alleles that were defined after the original study. In addition, samples characterized during the earliest studies may also have been assigned outdated designations as allele definitions evolve over time and new alleles are identified frequently. These allele designations were updated during subsequent studies.

We created two resources, the GeT-RM Consolidated PGx and HLA Table as well as a searchable database tool, GeT-RM PGx Search, to provide the most up to date pharmacogenetic genotypes for each characterized sample. Both resources provide information about 363 DNA samples that were characterized during nine GeT-RM PGx or HLA studies for 34 genes/loci including *CYP2C9*, *CYP2C19*, *CYP3A4*, *CYP3A5*, *CYP2D6*, *TPMT*, *NUDT15*, *DPYD*, and 11 HLA loci.^{11–19}

Methods

GeT-RM samples

For each GeT-RM study, genomic DNA from cell lines identified by study team members to contain variants of interest were selected from the NIGMS Human Genetic Cell Repository and/or the NHGRI Sample Repository for Human Genetic Research at the Coriell Institute for Medical Research. Each sample was characterized using a variety of methods and test platforms by two or more laboratories.^{11–19} Results were assessed for quality, discordances, and determination of consensus genotype for each sample. These data were subsequently used to create two consolidated information resources.

Creation of the GeT-RM Consolidated PGx and HLA Table

Consensus genotypes for all samples (n= 363) characterized during the nine GeT-RM PGx or HLA reference material studies were consolidated into a single, publicly available spreadsheet (in Excel format), referred to as the “GeT-RM Consolidated PGx and HLA” Table (<https://www.cdc.gov/lab-quality/php/get-rm/reference-materials.html> last accessed

11/4/2024). This consolidated table (Figure 1), includes information regarding the study or studies in which each sample was characterized, the NIGMS or NHGRI Repository sample ID, and each sample's genotype for the interrogated genes and loci (Table 1). The GeT-RM Consolidated PGx and HLA Table also provides information regarding the availability of Binary Alignment Map (BAM) files, FASTQ files, as well as high-quality 30x coverage WGS data from the 1000 Genomes Project.²¹ Each allele annotation is accompanied by the associated reference(s) that include a detailed description of the methodologies employed to characterize the sample and construct the consensus genotype or star allele annotation. In cases where a given annotation was described in more than one corresponding publication, and the consensus annotation was consistent, all references are included. In cases where a given annotation was described in more than one corresponding publication, and the consensus annotations were inconsistent, the most recent publication and annotation are shown. The GeT-RM consolidated PGx and HLA Table also contains tabs with information about the columns and definitions of terms used, as well as GeT-RM references.

Creation of a searchable database: GeT-RM PGx Search Tool

The GeT-RM Consolidated PGx and HLA Table was used to create a searchable, web-based tool, GeT-RM PGx Search. For each DNA sample included in the GeT-RM Consolidated PGx and HLA Table, the annotation for each characterized pharmacogene was formatted into a single genotype, apart from *DPYD* for which all variants identified are listed. Most included pharmacogenes are annotated with star (*) alleles. In these cases, the two star alleles are separated by a slash delimiter ("/"); however, a subset of pharmacogenes and regions (e.g., *CYP2C*Cluster, *DPYD*, *GGCX*, *SLCO2B1*, *VKORC1*) include variant specific annotations. Finally, HLA gene annotations are included as previously described.¹¹ Reference(s) for each allele annotation are provided as described above.

Results

The GeT-RM Consolidated PGx and HLA Table (<https://www.cdc.gov/lab-quality/php/get-rm/reference-materials.html>, last accessed 11/4/2024) shows consensus genotypes determined during the nine GeT-RM PGx studies for all 363 samples in an Excel format. This table was used to develop an interactive, web-based search tool, "GeT-RM PGx Search", which is available on the Coriell Institute for Medical Research website (<https://www.coriell.org/GetRM/PGxSearch>, last accessed 8/13/2024). Each gene is given a unique key in a Structured Query Language (SQL) Server relational database that is linked to sample level data. Users can query GeT-RM PGx Search using a web-based interface and select a gene of interest from the dropdown menu (Figure 2). GeT-RM PGx Search returns the following: links to PharmVar annotations (<https://www.pharmvar.org/>, last accessed 7/22/2024), and the NCBI gene entry (if available) (NCBI <https://www.ncbi.nlm.nih.gov/gene/?term=>, last accessed 8/13/2024), additional documentation regarding allele information and allele definitions, an option to export annotations for the chosen gene to an Excel spreadsheet, and an interactive data display (Figure 3). The number of samples viewable in the interactive table can be adjusted to the user's preference, and the annotated samples can be sorted by sample ID, description, gene, genotype, reference, product, source, or genetic sex. Each sample ID is hyperlinked to a

sample-specific page that includes the detailed overview, characterizations, associated data and publications, and related external links. In addition, the viewable samples can be filtered by star allele, variant(s), or genotype.

Discussion

Reference material organizations including the National Institute of Standards and Technology (NIST, <https://www.nist.gov/>, last accessed 1/3/2025), the National Institute for Biological Standards and Control (NIBSC, Hertfordshire UK) and the Joint Research Centre (Geel, Belgium) as well as commercial vendors produce reference materials and standards for product control and forensic testing. Availability of reference materials encompassing a range of human genetic variation, however, has been an ongoing challenge for clinical laboratorians. This limited availability has negatively impacted the ability to develop and validate new tests and provide quality control and ongoing quality assurance for existing tests. To address this gap, the GeT-RM has characterized hundreds of publicly available and renewable genomic DNA reference materials, many of these for pharmacogenetic testing. Unlike other PGx annotation approaches^{22–24}, the GeT-RM requires that each sample be experimentally characterized in two or more laboratories using a variety of analytical methods. These reference materials can then be used by laboratories as they implement clinical practice guidelines such as those developed by the Association for Molecular Pathology PGx Working Group.^{25–30}

Most pharmacogenes are highly polymorphic^{31, 32} with new alleles and haplotypes still being discovered, especially in non-European populations;^{33, 34} thus the catalog of haplotype-based (i.e., star allele) definitions continues to grow and is anticipated to be updated regularly.^{20, 35, 36} In addition, there has been a rapid evolution of the technologies and methods available to perform pharmacogenetic testing. Over the last 15 years, pharmacogenetic tests, which started as targeted genotyping and Sanger sequencing assays, have come to incorporate more comprehensive analyses³⁷ including testing for copy number variation, as well as short and long-read NGS.^{38, 39} This has enhanced our understanding of many pharmacogenetic loci, such as *CYP2D6*, which often requires extensive analysis to resolve its many structural variants.⁴⁰ Historically, simpler assays were only able to detect full *CYP2D6* gene deletions, duplications and multiplications, while recent more advanced assays can also detect hybrid genes and more comprehensively characterize complex genotypes. These higher resolution analyses have resulted in the identification and naming of many new *CYP2D6* star alleles by PharmVar. While copy number analysis is now commonly performed for *CYP2D6*, testing for copy number variation is not widely used for other loci. For example, the most recent GeT-RM study utilized copy number analysis and identified a relatively common intragenic deletion in *DPYD*.¹⁹ Finally, at present, the phase of most pharmacogene variants is determined empirically. As single molecule long read NGS becomes more widely available, it is anticipated that previously analyzed samples may be re-tested to determine phase, which may require further updates to the “gold standard” genotype data in GeT-RM for some samples. Although the reference material DNA does not change over time, the ability to precisely characterize genotype continues to improve.

Since 2010, GeT-RM has performed eight studies characterizing genomic DNA samples for pharmacogenetic loci^{12–19} and one study for 11 HLA loci.¹¹ Due to the changing nature of PGx testing and the identification of important new alleles, reference materials for many of the commonly tested PGx genes, including *CYP2C9*, *CYP2C19*, *CYP2D6*, and *DPYD*, have been characterized in more than one GeT-RM study.^{12–19} Some samples were characterized for the same gene during multiple studies, and their consensus genotype was revised based on the information gleaned from analyses using more comprehensive assays. This has resulted in some sample genotypes seeming to change between GeT-RM studies, which may have been interpreted as being “discrepant” and caused confusion amongst users of the reference material samples.

Assignment of PGx genotypes during GeT-RM studies is dependent on the assays used for sample characterization as well as the PharmVar star allele definitions existing at the time of the study. Newly available assay technologies can be used to recharacterize samples to overcome limitations of assays used during earlier studies. For example, genotyping assays, Sanger or short read NGS assays employed in previous studies could often not resolve the phase of variants. This limitation may now be overcome by single molecule long read NGS technologies. In addition, PharmVar may have revised allele definitions and added new star alleles since samples were first characterized. GeT-RM aims to not only update reported genotypes of previously characterized samples by testing with new technologies, but also identify samples with newly discovered star alleles. It is important to note that genotypes listed in the GeT-RM Consolidated PGx and HLA Table are based on the nomenclature available at the time of analysis and may not be consistent with current nomenclature. This explains, for example, why some genotypes contain “letter” extensions (e.g., for *CYP1A2*). Furthermore, *NAT2* was only transferred to PharmVar in 2024 and its nomenclature underwent substantial changes. Future recharacterization of sample materials for *NAT2* will not only include testing for many additional star alleles with the latest technologies but will also report genotypes using PharmVar’s current star allele definitions.

There are several bioinformatic tools that can be used to call PGx variants and star alleles for the 1000 Genomes Project samples^{22–24, 41, 42}. These tools can be useful to identify publicly available samples that may contain PGx variants of interest, however the variants in these samples should be confirmed using orthogonal methods prior to use as reference materials.

The GeT-RM Consolidated PGx and HLA Table and the GeT-RM PGx Search tool were created to provide an easily accessible and searchable resource with up-to-date information about publicly available, well-characterized reference DNA samples that can be used to support quality assurance programs of laboratories performing clinical PGx and HLA testing. The GeT-RM Consolidated PGx and HLA Table and GeT-RM PGx Search tool will be updated and synchronized as additional GeT-RM PGx studies are completed. All reference materials characterized by GeT-RM are publicly available from the NIGMS and NHGRI Repositories at the Coriell Institute for Medical Research.

Funding:

This study was supported in part by NHGRI 5U24HG008736 to LS.

Disclosures:

RPRD Diagnostics LLC is a fee-for-service laboratory that offers clinical pharmacogenetic testing. A.J.T.'s efforts were supported in part by RPRD Diagnostics and holds equity. A.G. is the Director of PharmVar. A.J.T., A.M.M., and V.M.P. are members of PharmVar. V.M.P. is an employee of Agena Bioscience. Remaining authors have declared no related conflicts of interest.

References

1. International Organization of Standardization: ISO 15189 Medical Laboratories: Requirements for Quality and Competence. Geneva Switzerland: International Organization for Standardization, 2012.
2. The Clinical Laboratory Improvement Amendments (CLIA): Code of Federal Regulations. Title 42, Chapter IV, Subchapter G, Part 493.
3. Association for Molecular Pathology statement. Recommendations for in-house development and operation of molecular diagnostic tests. *Am J Clin Pathol* 1999, 111:449–463. [PubMed: 10191765]
4. Chen B, OC CD, Boone DJ, Amos JA, Beck JC, Chan MM, Farkas DH, Lebo RV, Richards CS, Roa BB, Silverman LM, Barton DE, Bejjani BA, Belloni DR, Bernacki SH, Caggana M, Charache P, Dequeker E, Ferreira-Gonzalez A, Friedman KJ, Greene CL, Grody WW, Highsmith WE Jr., Hinkel CS, Kalman LV, Lubin IM, Lyon E, Payne DA, Pratt VM, Rohlf s E, Rundell CA, Schneider E, Willey AM, Williams LO, Willey JC, Winn-Deen ES, Wolff DJ: Developing a sustainable process to provide quality control materials for genetic testing. *Genet Med* 2005, 7:534–549. [PubMed: 16247292]
5. Rehder C, Bean LJH, Bick D, Chao E, Chung W, Das S, O'Daniel J, Rehm H, Shashi V, Vincent LM, Committee ALQA: Next-generation sequencing for constitutional variants in the clinical laboratory, 2021 revision: a technical standard of the American College of Medical Genetics and Genomics (ACMG). *Genet Med* 2021, 23:1399–1415. [PubMed: 33927380]
6. Scott SA: The Genetic Testing Reference Materials Coordination Program: Over 10 Years of Support for Pharmacogenomic Testing. *J Mol Diagn* 2023, 25:630–633. [PubMed: 37481236]
7. Kalman L, Leonard J, Gerry N, Tarleton J, Bridges C, Gastier-Foster JM, Pyatt RE, Stonerock E, Johnson MA, Richards CS, Schrijver I, Ma T, Miller VR, Adadevoh Y, Furlong P, Beiswanger C, Toji L: Quality assurance for Duchenne and Becker muscular dystrophy genetic testing: development of a genomic DNA reference material panel. *J Mol Diagn* 2011, 13:167–174. [PubMed: 21354051]
8. Pratt VM, Caggana M, Bridges C, Buller AM, DiAntonio L, Highsmith WE, Holtegaard LM, Muralidharan K, Rohlf s EM, Tarleton J, Toji L, Barker SD, Kalman LV: Development of genomic reference materials for cystic fibrosis genetic testing. *J Mol Diagn* 2009, 11:186–193. [PubMed: 19359498]
9. Amos Wilson J, Pratt VM, Phansalkar A, Muralidharan K, Highsmith WE Jr., Beck JC, Bridgeman S, Courtney EM, Epp L, Ferreira-Gonzalez A, Hjelm NL, Holtegaard LM, Jama MA, Jakupciak JP, Johnson MA, Labrousse P, Lyon E, Prior TW, Richards CS, Richie KL, Roa BB, Rohlf s EM, Sellers T, Sherman SL, Siegrist KA, Silverman LM, Wiszniewska J, Kalman LV, Fragile Xperts Working Group of the Association for Molecular Pathology Clinical Practice C: Consensus characterization of 16 FMR1 reference materials: a consortium study. *J Mol Diagn* 2008, 10:2–12. [PubMed: 18165276]
10. Kalman LV, Tarleton JC, Percy AK, Aradhya S, Bale S, Barker SD, Bayrak-Toydemir P, Bridges C, Buller-Burckle AM, Das S, Iyer RK, Vo TD, Zvereff VV, Toji LH: Development of a genomic DNA reference material panel for Rett syndrome (MECP2-related disorders) genetic testing. *J Mol Diagn* 2014, 16:273–279. [PubMed: 24508304]
11. Bettinotti MP, Ferriola D, Duke JL, Mosbrugger TL, Tairis N, Jennings L, Kalman LV, Monos D: Characterization of 108 Genomic DNA Reference Materials for 11 Human Leukocyte Antigen Loci: A GeT-RM Collaborative Project. *J Mol Diagn* 2018, 20:703–715.
12. Gaedigk A, Boone EC, Turner AJ, van Schaik RHN, Chernova D, Wang WY, Broeckel U, Granfield CA, Hodge JC, Ly RC, Lynnes TC, Mitchell MW, Moyer AM, Oliva J, Kalman LV: Characterization of Reference Materials for CYP3A4 and CYP3A5: A (GeT-RM) Collaborative Project. *J Mol Diagn* 2023, 25:655–664. [PubMed: 37354993]

13. Pratt VM, Wang WY, Boone EC, Broeckel U, Cody N, Edelmann L, Gaedigk A, Lynnes TC, Medeiros EB, Moyer AM, Mitchell MW, Scott SA, Starostik P, Turner A, Kalman LV: Characterization of Reference Materials for TPMT and NUDT15: A GeT-RM Collaborative Project. *J Mol Diagn* 2022, 24:1079–1088. [PubMed: 35931342]
14. Gaedigk A, Boone EC, Scherer SE, Lee SB, Numanagic I, Sahinalp C, Smith JD, McGee S, Radhakrishnan A, Qin X, Wang WY, Farrow EG, Gonzaludo N, Halpern AL, Nickerson DA, Miller NA, Pratt VM, Kalman LV: CYP2C8, CYP2C9, and CYP2C19 Characterization Using Next-Generation Sequencing and Haplotype Analysis: A GeT-RM Collaborative Project. *J Mol Diagn* 2022, 24:337–350. [PubMed: 35134542]
15. Pratt VM, Turner A, Broeckel U, Dawson DB, Gaedigk A, Lynnes TC, Medeiros EB, Moyer AM, Requesens D, Vetrini F, Kalman LV: Characterization of Reference Materials with an Association for Molecular Pathology Pharmacogenetics Working Group Tier 2 Status: CYP2C9, CYP2C19, VKORC1, CYP2C Cluster Variant, and GGCX: A GeT-RM Collaborative Project. *J Mol Diagn* 2021, 23:952–958. [PubMed: 34020041]
16. Gaedigk A, Turner A, Everts RE, Scott SA, Aggarwal P, Broeckel U, McMillin GA, Melis R, Boone EC, Pratt VM, Kalman LV: Characterization of Reference Materials for Genetic Testing of CYP2D6 Alleles: A GeT-RM Collaborative Project. *J Mol Diagn* 2019, 21:1034–1052. [PubMed: 31401124]
17. Pratt VM, Everts RE, Aggarwal P, Beyer BN, Broeckel U, Epstein-Baak R, Hujsak P, Kornreich R, Liao J, Lorier R, Scott SA, Smith CH, Toji LH, Turner A, Kalman LV: Characterization of 137 Genomic DNA Reference Materials for 28 Pharmacogenetic Genes: A GeT-RM Collaborative Project. *J Mol Diagn* 2016, 18:109–123.
18. Pratt VM, Zehnbauser B, Wilson JA, Baak R, Babic N, Bettinotti M, Buller A, Butz K, Campbell M, Civalier C, El-Badry A, Farkas DH, Lyon E, Mandal S, McKinney J, Muralidharan K, Noll L, Sander T, Shabbeer J, Smith C, Telatar M, Toji L, Vairavan A, Vance C, Weck KE, Wu AH, Yeo KT, Zeller M, Kalman L: Characterization of 107 genomic DNA reference materials for CYP2D6, CYP2C19, CYP2C9, VKORC1, and UGT1A1: a GeT-RM and Association for Molecular Pathology collaborative project. *J Mol Diagn* 2010, 12:835–846. [PubMed: 20889555]
19. Gaedigk A, Turner AJ, Moyer AM, Zubiaur P, Boone EC, Wang WY, Broeckel U, Kalman LV: Characterization of Reference Materials for DPYD: A GeT-RM Collaborative Project. *J Mol Diagn* 2024, 26:864–875. [PubMed: 39032822]
20. Gaedigk A, Casey ST, Whirl-Carrillo M, Miller NA, Klein TE: Pharmacogene Variation Consortium: A Global Resource and Repository for Pharmacogene Variation. *Clinical pharmacology and therapeutics* 2021, 110:542–545. [PubMed: 34091888]
21. Byrska-Bishop M, Evani US, Zhao X, Basile AO, Abel HJ, Regier AA, Corvelo A, Clarke WE, Musunuri R, Nagulapalli K, Fairley S, Runnels A, Winterkorn L, Lowy E, Human Genome Structural Variation C, Paul F, Germer S, Brand H, Hall IM, Talkowski ME, Narzisi G, Zody MC: High-coverage whole-genome sequencing of the expanded 1000 Genomes Project cohort including 602 trios. *Cell* 2022, 185:3426–3440 e3419. [PubMed: 36055201]
22. Gharani N, Calendo G, Kusic D, Madzo J, Scheinfeldt L: Star allele search: a pharmacogenetic annotation database and user-friendly search tool of publicly available 1000 Genomes Project biospecimens. *BMC Genomics* 2024, 25:116. [PubMed: 38279110]
23. Sherman CA, Claw KG, Lee SB: Pharmacogenetic analysis of structural variation in the 1000 genomes project using whole genome sequences. *Sci Rep* 2024, 14:22774. [PubMed: 39354004]
24. Scott ER, Bansal V, Meacham C, Scott SA: VarCover: Allele Min-Set Cover Software. *J Mol Diagn* 2020, 22:123–131. [PubMed: 31751680]
25. Pratt VM, Del Tredici AL, Hachad H, Ji Y, Kalman LV, Scott SA, Weck KE: Recommendations for Clinical CYP2C19 Genotyping Allele Selection: A Report of the Association for Molecular Pathology. *J Mol Diagn* 2018, 20:269–276. [PubMed: 29474986]
26. Pratt VM, Cavallari LH, Fulmer ML, Gaedigk A, Hachad H, Ji Y, Kalman LV, Ly RC, Moyer AM, Scott SA, van Schaik RHN, Whirl-Carrillo M, Weck KE: CYP3A4 and CYP3A5 Genotyping Recommendations: A Joint Consensus Recommendation of the Association for Molecular Pathology, Clinical Pharmacogenetics Implementation Consortium, College of American Pathologists, Dutch Pharmacogenetics Working Group of the Royal Dutch

- Pharmacists Association, European Society for Pharmacogenomics and Personalized Therapy, and Pharmacogenomics Knowledgebase. *J Mol Diagn* 2023, 25:619–629. [PubMed: 37419245]
27. Pratt VM, Cavallari LH, Fulmer ML, Gaedigk A, Hachad H, Ji Y, Kalman LV, Ly RC, Moyer AM, Scott SA, van Schaik RHN, Whirl-Carrillo M, Weck KE: TPMT and NUDT15 Genotyping Recommendations: A Joint Consensus Recommendation of the Association for Molecular Pathology, Clinical Pharmacogenetics Implementation Consortium, College of American Pathologists, Dutch Pharmacogenetics Working Group of the Royal Dutch Pharmacists Association, European Society for Pharmacogenomics and Personalized Therapy, and Pharmacogenomics Knowledgebase. *J Mol Diagn* 2022, 24:1051–1063. [PubMed: 35931343]
28. Pratt VM, Cavallari LH, Del Tredici AL, Hachad H, Ji Y, Moyer AM, Scott SA, Whirl-Carrillo M, Weck KE: Recommendations for Clinical CYP2C9 Genotyping Allele Selection: A Joint Recommendation of the Association for Molecular Pathology and College of American Pathologists. *J Mol Diagn* 2019, 21:746–755. [PubMed: 31075510]
29. Pratt VM, Cavallari LH, Del Tredici AL, Hachad H, Ji Y, Kalman LV, Ly RC, Moyer AM, Scott SA, Whirl-Carrillo M, Weck KE: Recommendations for Clinical Warfarin Genotyping Allele Selection: A Report of the Association for Molecular Pathology and the College of American Pathologists. *J Mol Diagn* 2020, 22:847–859. [PubMed: 32380173]
30. Pratt VM, Cavallari LH, Del Tredici AL, Gaedigk A, Hachad H, Ji Y, Kalman LV, Ly RC, Moyer AM, Scott SA, van Schaik RHN, Whirl-Carrillo M, Weck KE: Recommendations for Clinical CYP2D6 Genotyping Allele Selection: A Joint Consensus Recommendation of the Association for Molecular Pathology, College of American Pathologists, Dutch Pharmacogenetics Working Group of the Royal Dutch Pharmacists Association, and the European Society for Pharmacogenomics and Personalized Therapy. *J Mol Diagn* 2021, 23:1047–1064. [PubMed: 34118403]
31. Li J, Zhang L, Zhou H, Stoneking M, Tang K: Global patterns of genetic diversity and signals of natural selection for human ADME genes. *Human molecular genetics* 2011, 20:528–540. [PubMed: 21081654]
32. Scheinfeldt LB, Brangan A, Kusic DM, Kumar S, Gharani N: Common Treatment, Common Variant: Evolutionary Prediction of Functional Pharmacogenomic Variants. *J Pers Med* 2021, 11. [PubMed: 35055326]
33. Caspar SM, Schneider T, Meienberg J, Matyas G: Added Value of Clinical Sequencing: WGS-Based Profiling of Pharmacogenes. *Int J Mol Sci* 2020, 21.
34. Li B, Sangkuhl K, Whaley R, Woon M, Keat K, Whirl-Carrillo M, Ritchie MD, Klein TE: Frequencies of pharmacogenomic alleles across biogeographic groups in a large-scale biobank. *Am J Hum Genet* 2023, 110:1628–1647. [PubMed: 37757824]
35. Nofziger C, Turner AJ, Sangkuhl K, Whirl-Carrillo M, Agundez JAG, Black JL, Dunnenberger HM, Ruano G, Kennedy MA, Phillips MS, Hachad H, Klein TE, Gaedigk A: PharmVar GeneFocus: CYP2D6. *Clinical pharmacology and therapeutics* 2020, 107:154–170. [PubMed: 31544239]
36. Gaedigk A, Sangkuhl K, Whirl-Carrillo M, Twist GP, Klein TE, Miller NA, PharmVar Steering C: The Evolution of PharmVar. *Clinical pharmacology and therapeutics* 2019, 105:29–32. [PubMed: 30536702]
37. van der Lee M, Kriek M, Guchelaar HJ, Swen JJ: Technologies for Pharmacogenomics: A Review. *Genes (Basel)* 2020, 11.
38. Barthelemy D, Belmonte E, Pilla LD, Bardel C, Dupont E, Gautier V, Payen L: Direct Comparative Analysis of a Pharmacogenomics Panel with PacBio HiFi((R)) Long-Read and Illumina Short-Read Sequencing. *J Pers Med* 2023, 13.
39. van der Lee M, Rowell WJ, Menafra R, Guchelaar HJ, Swen JJ, Anvar SY: Application of long-read sequencing to elucidate complex pharmacogenomic regions: a proof of principle. *The pharmacogenomics journal* 2022, 22:75–81. [PubMed: 34741133]
40. Turner AJ, Dereziński AD, Gaedigk A, Berres ME, Gregornik DB, Brown K, Broeckel U, Scharer G: Characterization of complex structural variation in the CYP2D6-CYP2D7-CYP2D8 gene loci using single-molecule long-read sequencing. *Front Pharmacol* 2023, 14:1195778. [PubMed: 37426826]

41. Hari A, Zhou Q, Gonzaludo N, Harting J, Scott SA, Qin X, Scherer S, Sahinalp SC, Numanagic I: An efficient genotyper and star-allele caller for pharmacogenomics. *Genome Res* 2023, 33:61–70. [PubMed: 36657977]
42. Twesigomwe D, Drogemoller BI, Wright GEB, Siddiqui A, da Rocha J, Lombard Z, Hazelhurst S: StellarPGx: A Nextflow Pipeline for Calling Star Alleles in Cytochrome P450 Genes. *Clinical pharmacology and therapeutics* 2021, 110:741–749. [PubMed: 33492672]

- Updated PGx and HLA genotypes for 137 samples characterized by GeT-RM during 2016 study (reference 2, PMID 26621101)
- All DNA samples listed in these tables have been characterized by the CDC Genetic Testing Reference Material program (GeT-RM <https://www.cdc.gov/lab-quality/php/get-rm/index.html>) and are publicly available from the Coriell Institutes for Medical Research (<https://www.coriell.org/>).
- Publications describing each study are shown in the "Study Refs" tab.
- Relevant publications for each sample and genotype are indicated in Column A and the column adjacent to each genotype (e.g., Column I), respectively.

GeT-RM Characterization Study References (see "Study refs" tab)	Coriell ID # https://www.coriell.org/	URL to access BAM and FASTQ files from the European Nucleotide Archive (ENA) (unhide columns D-G for more info)	CYP1A1	CYP1A1 References	CYP1A2	CYP1A2 References	CYP2A6	CYP2A6 References	CYP2B6	CYP2E
2,3,4,6,7	HG00276	http://www.ebi.ac.uk/ena/dataset/*1/*1	2		*1A/*1F	2	*1/*1	2	*2/(#4)	2
2,3,4,7	HG00436	http://www.ebi.ac.uk/ena/dataset/*1/*1	2		*1A/*1F	2	*9/*9	2	*1/*6	2
2,3,4,6	HG00589	http://www.ebi.ac.uk/ena/dataset/*2/*2	2		*1A/*1L or *1C/*1F	2	*1/*1	2	*1/*1	2
2,3,4	HG01190	http://www.ebi.ac.uk/ena/dataset/*1/*1	2		*1A/*1A	2	*1/*1	2	*1(*5)/#1(*27)	2
2,3,4,9	NA06991	http://www.ebi.ac.uk/ena/dataset/*1/*1	2		*1F/*1F	2	*1/*1	2	*1/*6	2
2,4,7	NA06993								*1/*1	2
2,3,4,6	NA07000	http://www.ebi.ac.uk/ena/dataset/*1/*1							*1/*1	2
2,3,4	NA07019	http://www.ebi.ac.uk/ena/dataset/*1/*4	2		*1A/*1F	2	*1/*1	2	*1(*5) or *1(*22)	2
2,3,4	NA07029	http://www.ebi.ac.uk/ena/dataset/*1/*1	2		*1A/*1F	2	*1/*1	2	*6/(#27)	2
2,3,4	NA07048								*1/*1	2

Figure 1. Screenshot of GeT-RM Consolidated PGx and HLA Table. Consensus genotypes for 34 gene/loci determined during nine GeT-RM studies are available. References for each genotype are provided in the adjacent column. BAM and FASTQ files are available for some samples, and many have sequence data from the 1000 Genomes Project. The Excel file contains several tabs, shown at the bottom of the figure. The references in the above image do not reflect the citations in this manuscript.

Search GeT-RM Data by Gene (HUGO symbol):

Gene: ✓ --

- CYP1A1
- CYP1A2
- CYP2A6
- CYP2B6
- CYP2C Cluster NC_000010.10: g.96405502G>A, rs12777823
- CYP2C19
- CYP2C8
- CYP2C9
- CYP2D6
- CYP2E1
- CYP3A4
- CYP3A5
- CYP4F2
- DPYD
- DPYD (* alleles)
- GGCX NM_000821.6:c.2084+45G>C, rs11676382
- GGCX NM_000821.6:c.214+597G>A, rs12714145

Figure 2. Screenshot of user dropdown menu of genes and loci with available GeT-RM PGx and HLA characterizations.

GeT-RM Search Results

Gene:

[Click here to PharmVar annotated pharmacogenes](#)
[Click here to view NCBI entry](#)
[Click here to return to the Genomic Data Search page](#)

Allele information:

- Allele nomenclature or genotypes are listed as published in each corresponding GeT-RM study
- Alleles not included in the test panels used for each study may not be reflected in the data

Definitions:

- Alleles not confirmed by 2 or more assays are shown in parenthesis "()" or "(SNV not confirmed)"
- *1 allele (wild type) designation indicates that no variants were identified. There may be variants present in the sample that were not tested using the study assays.
- rsID=RefSNP accession ID number

ID	Description	Gene	Genotype	Reference	Product	Source
NA02016	HURLER-SCHEIE SYNDROME	CYP2D6	*2XN/*17	1	DNA	Fibroblast
NA10005	TRANSLOCATED CHROMOSOME	CYP2D6	*17/*29	1	DNA	LCL
NA17039	HUMAN VARIATION PANEL - AFRICAN AMERICAN PANEL OF 10	CYP2D6	*2/*17	1	DNA	LCL
NA17073	HUMAN VARIATION PANEL - PUERTO RICAN	CYP2D6	*1/*17	1	DNA	LCL
NA17169	HUMAN VARIATION PANEL - AFRICAN AMERICAN PANEL OF 100 (VE...	CYP2D6	*17/*56	3	DNA	Fibroblast
NA18484	INTERNATIONAL HAPMAP PROJECT - YORUBA IN IBADAN, NIGERIA	CYP2D6	*1/*17	2,3	DNA	LCL
NA18509	INTERNATIONAL HAPMAP PROJECT - YORUBA IN IBADAN, NIGERIA	CYP2D6	*2/*17	2,3	DNA	LCL
NA18518	INTERNATIONAL HAPMAP PROJECT - YORUBA IN IBADAN, NIGERIA	CYP2D6	*17/*29	2,3	DNA	LCL
NA18873	INTERNATIONAL HAPMAP PROJECT - YORUBA IN IBADAN, NIGERIA	CYP2D6	*5/*17	2,3	DNA	LCL
NA19122	INTERNATIONAL HAPMAP PROJECT - YORUBA IN IBADAN, NIGERIA	CYP2D6	*2/*17	2,3	DNA	LCL

Figure 3.

Screenshot of example interactive GeT-RM PGx search data display: search for the *CYP2D6**17 allele.

The display includes annotation definition information and external links to PharmVar and NCBI. The user can choose the number of viewable samples, sort samples by sample ID, description, gene, genotype, reference, product, source, or genetic sex, export the information to an Excel spreadsheet, and click on any sample hyperlink to access a sample-specific page that includes the detailed overview, characterizations, associated data and publications, and related external links.

Table 1.

Genes and loci in the GeT-RM Consolidated PGx and HLA Table and GeT-RM PGx Search tools

Gene or Loci	GeT-RM Study(s) PMID
<i>CYP1A1</i>	26621101 ¹⁷
<i>CYP1A2</i>	26621101 ¹⁷
<i>CYP2A6</i>	26621101 ¹⁷
<i>CYP2B6</i>	26621101 ¹⁷
<i>CYP2C8</i>	26621101 ¹⁷ , 35134542 ¹⁴
<i>CYP2C9</i>	20889555 ¹⁸ , 26621101 ¹⁷ , 35134542 ¹⁴ , 34020041 ¹⁵
<i>CYP2C19</i>	20889555 ¹⁸ , 26621101 ¹⁷ , 35134542 ¹⁴ , 34020041 ¹⁵
<i>CYP2D6</i>	20889555 ¹⁸ , 26621101 ¹⁷ , 31401124 ¹⁶
<i>CYP2E1</i>	26621101 ¹⁷
<i>CYP3A4</i>	26621101 ¹⁷ , 37354993 ¹²
<i>CYP3A5</i>	26621101 ¹⁷ , 37354993 ¹²
<i>CYP4F2</i>	26621101 ¹⁷
<i>DPYD</i>	26621101 ¹⁷ , 39032822 ¹⁹
<i>GSTM1</i>	26621101 ¹⁷
<i>GSTP1</i>	26621101 ¹⁷
<i>GSTT1</i>	26621101 ¹⁷
<i>NAT1</i>	26621101 ¹⁷
<i>NAT2</i>	26621101 ¹⁷
<i>NUDT15</i>	35931342 ¹³
<i>SLC15A2</i>	26621101 ¹⁷
<i>SLCO2B1</i>	26621101 ¹⁷
<i>TPMT</i>	26621101 ¹⁷ , 35931342 ¹³
<i>UGT1A1</i>	20889555 ¹⁸ , 26621101 ¹⁷
<i>UGT2B7</i>	26621101 ¹⁷
<i>UGT2B15</i>	26621101 ¹⁷
<i>UGT2B17</i>	26621101 ¹⁷
<i>HLA-A</i>	29959025 ¹¹
<i>HLA-B</i>	29959025 ¹¹
<i>HLA-C</i>	29959025 ¹¹
<i>HLA-DRB1</i>	29959025 ¹¹
<i>HLA-DRB3</i>	29959025 ¹¹
<i>HLA-DRB4</i>	29959025 ¹¹
<i>HLA-DRB5</i>	29959025 ¹¹
<i>HLA-DQA1</i>	29959025 ¹¹
<i>HLA-DQB1</i>	29959025 ¹¹

Gene or Loci	GeT-RM Study(s) PMID
<i>HLA-DPA1</i>	29959025 ¹¹
<i>HLA-DPB1</i>	29959025 ¹¹
<i>CYP2C</i> Cluster NC_000010.10 [^] : g.96405502G>A, rs12777823 [#]	34020041 ¹⁵
<i>GGCX</i> NM_000821.6:c.214+597G>A, rs12714145	34020041 ¹⁵
<i>GGCX</i> NM_000821.6:c.2084+45G>C rs11676382	34020041 ¹⁵
<i>VKORC1</i> NM_024006.5:c.-1639G>A, rs9923231	20889555 ¹⁸ , 26621101 ¹⁷
<i>VKORC1</i> NM_024006.6:c.106G>A, rs61742245	34020041 ¹⁵
<i>VKORC1</i> NM_024006.6:c.196G>A, rs72547529	34020041 ¹⁵

[^] RefSeq <https://www.ncbi.nlm.nih.gov/refseq/>, last accessed 5/17/2024

[#] dbSNP (<https://www.ncbi.nlm.nih.gov/snp>, last accessed 2/2/2024)