Using NCBI Resources for pharmacogenetics-based medication optimization

For Follow-up:

Search dbGaP (https://www.ncbi.nlm.nih.gov/gap/) to find Clinical Studies examining the impact of genetics on clopidogrel response.

dbGaP houses studies that provide access to demographic, clinical and molecular data. While this data is provided at no cost, due to the nature of the patient-level data full access requires an application to an NIH Data Access Committee.

For more information see the dbGaP website.

eMERGE Network's Multi-Center Pilot of Pharmacogenetic Sequencing in Clinical Practice

dbGaP Study Accession: phs000906.v1.p1

Request Access

Study version history

Study | Phenotype Datasets | Variables | Molecular Datasets | Analyses | Documents

Jump to: Authorized Access | Attribution | Authorized Requests

Study Description

eMERGE-PGx is a multi-site test of the concept that sequence information can be coupled to electronic medical records (EMRs) for use in healthcare. The promise of personalized medicine - health care guided by each individual's biological characteristics - is being fostered by increasingly powerful and economical methods to acquire clinically relevant biomarkers from large numbers of people. One therapeutic area that seems especially ripe for an early test of the personalized medicine concept is pharmacogenomics (PGx) - the idea that individual variation in drug response includes a genomic component. Drug response variation is an accepted feature of virtually all drug treatments, and contemporary molecular biologic tools continue to identify key genes mediating drug metabolism, transport, and targets. Importantly, common variation in these genes is an increasingly well-recognized contributor, sometimes with large effects, to variation in drug responses. As a result, recommendations for genotype-guided therapy are increasing. These evidence-based recommendations, if implemented in health care practice, could reduce adverse drug events and improve time to therapeutic response. Through eMERGE-PGx, we are developing strategies for the optimal implementation of genetic sequence data into the clinical environment with the ultimate goal of improving patient care.

Important Links and Information

- Request access via Authorized Access
  - Instructions for requestors
  - Data Use Certification (DUC) Agreement
- Talking Glossary of Genetic Terms

Site and participants include:

Children's Hospital of Pennsylvania (CHOP): The Center for Applied Genomics (CAG) at the Children's Hospital of Philadelphia (CHOP) is a high-throughput, highly automated genotyping and sequencing facility equipped with state-of-the-art genotyping and sequencing platforms. Children who are treated at the Children's Hospital Healthcare Network and their parents may be eligible to take part in a major initiative to collect more than 100,000 blood samples, covering a wide range of pediatric diseases. The PGx population selected for sequencing with the PGRNseq panel at CHOP is 1,650 children from CAG's biorepository with well-documented drug-related severe adverse events (SAEs) or EHR-based drug response profiles. SAEs were extracted from EPIC records and from CHOP's Adverse Event (AE) database, which documents every AE at CHOP. These AEs are classified by a medical review panel according to the causal relationship with the suspected drug into [illegible] and 'probable'. Individuals with events classified as probable, severe and objective, were selected for sequencing. The drugs more frequently [illegible]se events are antibiotics, antineoplastics, immunosuppressants and psychotropic drugs. This cohort constitutes 50% of the target population. [illegible]s were selected using EHR-based algorithms that we have developed and validated at CAG for identifying patients not responding to ADHD [illegible]atomoxetine) and patients refractory to antiepileptic treatment from responders.

[illegible]s Hospital Medical Center/Boston's Children's Hospital (CCHMC/BCH): 811 CCHMC samples were obtained from children, adolescents [illegible]ed to medication or at risk for needing medication of study interest. 55% of participants were exposed to one or more opioids and their DNA [illegible]study-specific biobank; while 27% of participants were at risk for needing an opioid for surgical pain management and were newly recruited. [illegible]cohort was exposed to methylphenidate and their DNA samples were obtained from a CCHMC study-specific biobank.

[illegible]ildren's Hospital eMERGE PGx project is on individuals with epilepsy. Samples were taken from a current pharmacogenomics study already in [illegible]MET analysis was run and used as confirmation for PGRN-Seq results. A total of 109 samples were sent for PGRN-Seq analysis at University of [illegible]ining 141 epilepsy samples were from Children's Hospital of Philadelphia and underwent testing with PGRN-Seq at CHOP.

View video on Clopidogrel Response

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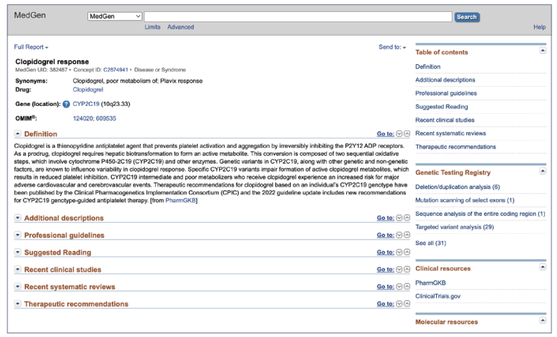
Case Study

Your patient is a 58-year-old woman who has been diagnosed with Acute Coronary Syndrome, scheduled for an angioplasty, and informed that she would need to take clopidogrel for at least three months. She mentions that her father died of a stroke while taking the drug, and is concerned. You look into pharmacogenetic influences on clopidogrel response and use the results of your patient's genetic test to determine if and what change in the prescription is indicated.

Use NCBI resources to gather information useful for optimizing your patient's medication.

Step 1:

Look up Clopidogrel Response in MedGen (https://www.ncbi.nlm.nih.gov/medgen/) to learn more about the phenotype.

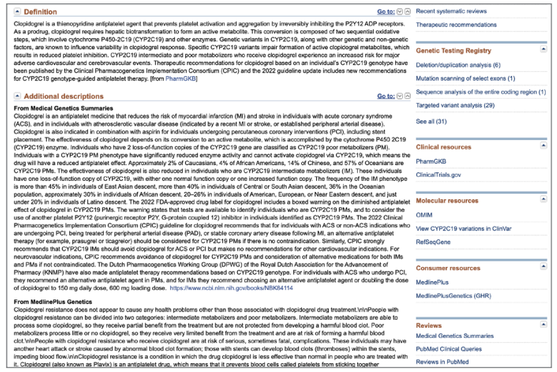


MedGen displays clinical genetics information from authoritative sources. You can find disease descriptions from OMIM® and GeneReviews®, 'Clinical features' from Human Phenotype Ontology (HPO), 'Professional Guidelines' from medical societies and Recent clinical studies and 'Recent systematic reviews' in PubMed.

The database also includes phenotypes such as drug response to assist researchers who want to learn about the impact of genetics on efficacy of medications (pharmacogenetics).

Step 2:

Read more about this phenotypic trait in excerpts from reputable pharmacogenetics sources.



In the sections - 'Definition' and 'Additional Descriptions' you can learn more about genetic variants and clopidogrel drug response.

Medical Genetics Summaries is a growing collection of summaries which describe the impact that specific sequence variations have on human health including how an individual may respond to a specific drug.

MedlinePlus Genetics is a consumer-friendly resource to learn about the effects of genetic variation on human health

PharmGKB is a comprehensive resource that curates knowledge about the impact of genetic variation

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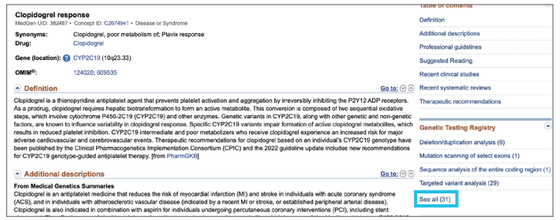
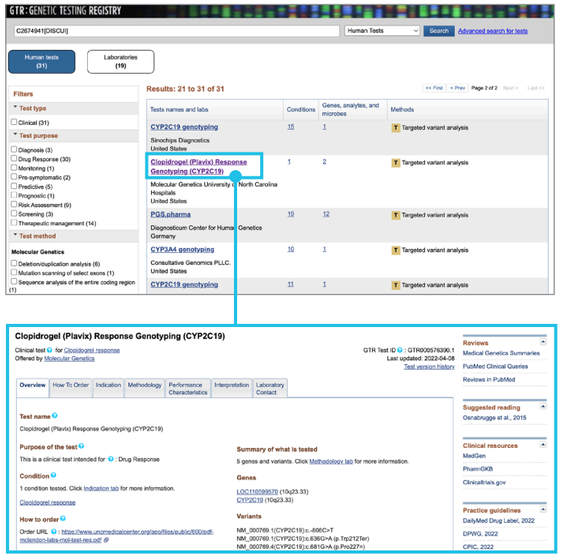
Step 3:

Click a link to find a genetic test in the NIH Genetic Testing Registry (https://www.ncbi.nlm.nih.gov/gtr/).

In MedGen's 'Genetic Testing Registry (GTR)' section, click on the 'See all' link to retrieve a list of genetic tests that are available to test for genetic variants and clopidogrel responsiveness. You can see single gene tests and panels.



GTR includes clinical and research tests for Mendelian disorders, somatic phenotypes, complex diseases and infectious diseases and drug responses. In the list of tests, click on the title of an interesting test from the list to learn about the test's purpose, methodology, clinical and analytic validity, clinical utility, and how to order it.



Step 4:

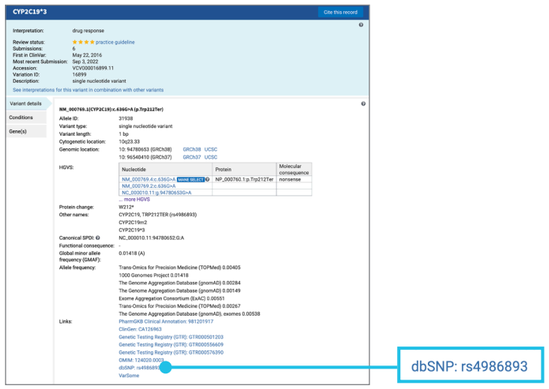
Search ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/) with information from test results to learn about the patient's variant.

In this case study, the patient's genetic test results indicates the existence of two CYP2C19 p.Trp212Ter variants (also known as the CYP2C19*3 allelic variant).

Cyp2C19 p.Trp212Ter

Searching with the patient's variation in ClinVar can retrieve a record with information about the variant and submitted assertions for how it may impact human health and phenotypes such as drug responsiveness.

The record includes variant details such as location, variant descriptions, submission data with descriptive comments, and citations, as well as a link to dbSNP: rs4986893 to learn more.



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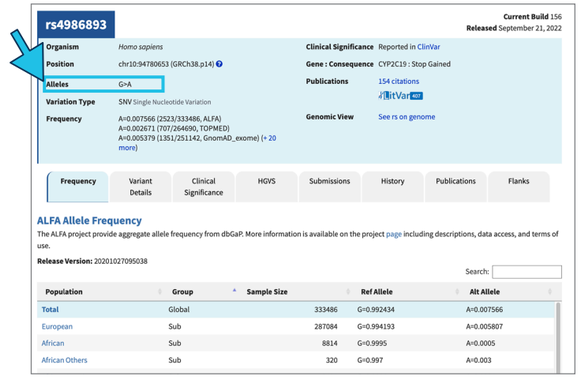
Step 5:

Go to the dbSNP record (https://www.ncbi.nlm.nih.gov/snp/) to find relevant population frequency data for the variant.

The dbSNP report provides allele frequencies from several sources, including our ALFA project, the Allele Frequency Aggregator, which provides population frequencies for millions of variants in dbGaP, the NCBI database of Genotypes and Phenotypes.

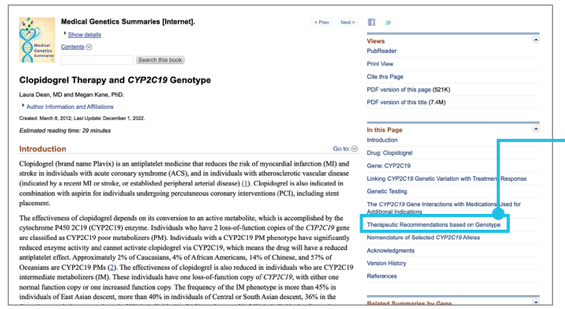


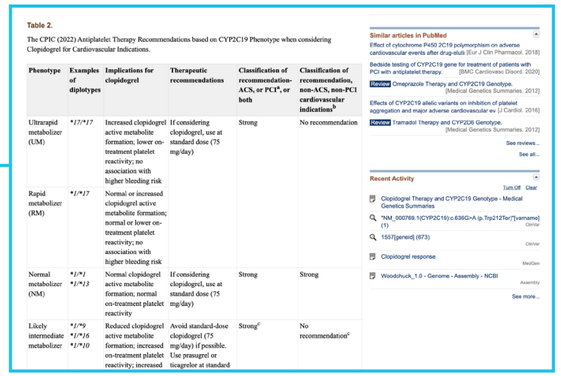
Step 6:

Learn more about the variant and its impact on drug response in the NCBI Bookshelf's Medical Genetics Summaries.

To get a better understanding of the impact of this variant on clopidogrel response and to find Therapeutic Recommendations based on Genotype, access the ***Medical Genetics Summaries*** chapter on "Clopidogrel Therapy and CYP2C19 Genotype".

Note that a homozygous carrier of the CYP2C19 p.Trp212Ter (or CYP2C19*3) allelic variant is classified as a poor metabolizer and is suggested to "Avoid clopidogrel if possible. Use prasugrel or ticagrelor at standard dose if no contraindication."





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