

Saturday, October 13, 2018

EFFECTIVE AND EFFICIENT USE OF NCBI/PUBMED

- TOOLS TO HELP YOU DO WHAT YOU NEED TO DO -



With over 176,000 published peer-reviewed articles related to anesthesia of the 27 million in total, the U.S. National Library of Medicine's PubMed Database is one of the most heavily used resources in clinical settings. The NCBI Account system was designed with various tools to work with PubMed and other NCBI Databases to support each user's specific needs. This presentation will provide specific tips and tricks for use of tools designed to help you use this resource at the point-of-care to enhance your clinical practice and in education/training of future healthcare practitioners.

At the completion of this activity, you should be able to:

- Quickly and efficiently access relevant published information to support optimal anesthesia care and aid in education/training of future healthcare practitioners.
- Create search strategies and set up automated Emails to learn of the availability of new PubMed records, set custom filter and display settings, and create folders for quick and easy access to collected information.

Sunday, October 14, 2018

WHAT DOES GENETICS/GENOMICS HAVE TO DO WITH THE PRACTICE OF ANESTHESIA?

Using information gleaned from a person's genome can assist clinicians in customizing their patient's case management which may increase the likelihood of a positive outcome. This talk will provide background and examples of how genomic medicine is being implemented in the clinic and will demonstrate how you can use free, online resources to assist your own clinical practice.

At the completion of this activity, you should be able to:

- Discuss the utilization of genomic medicine in clinical practice;
- Utilize genomic information in anesthetic management with the goal of improved patient outcome.

MATERIALS FOR YOU!

http://bit.ly/NCBI_VANA2018

<https://ftp.ncbi.nlm.nih.gov/pub/morris/VANA2018/>

PubMed Tools presentation (.pdf) | NCBI Account Guidebook (.pdf)

Genetics & Anesthesia Practice presentation (.pdf)

Presenter: Rana Morris, PhD - an NCBI Customer Experience team member and Team Lead for Educational Programs (Courses/Workshops, Webinars, Educational Materials). Since 2002, she has provided user support and training, as well as working with supervisors and development teams to improve NCBI resources based on user-centered design principles. Her doctoral, post-doctoral and research fellowship work integrated disciplines of computational and experimental biochemistry, molecular and cellular biology and genetics, and has included diagnostic development, drug design and coordination of genetics/genomics components of clinical trials.



What does Genetics/Genomics have to do with the Practice of Anesthesia?

Rana C. Morris, Ph.D.

http://bit.ly/NCBI_VANA2018



ABSTRACT AND GOALS

Using information gleaned from a person's genome can assist clinicians in customizing their patient's case management which may increase the likelihood of a positive outcome. This talk will provide background and examples of how genomic medicine is and may soon be implemented in the clinic and will demonstrate how you can use free, online resources to assist your own clinical practice.

At the completion of this activity, the participant will be able to:

- Discuss the utilization of genomic medicine in clinical practice
- Understand the relevance of genomic information for anesthetic management with the goal of improved patient outcomes



Wait! What?

Personal Genetics/Genomics fever has taken over....

Wide-spread application of genetic/genomic information started out with human migration & ancestry,

The screenshot shows the National Geographic Genographic Project website. The main heading is "Buy the Kit". The product is the "Geno 2.0 Next Generation Genographic Helix DNA Ancestry Kit, U.S. Delivery". The price is listed as \$149.95. There are navigation links for "Home / Buy the Kit", "About", "News", "Buy The Kit", and "Research". A "BUY NOW" button is visible, along with a "PayPal" logo. The page also includes a "Read 19 Reviews" link and a "Check our Terms & Conditions" link.

The screenshot shows the AncestryDNA website. The main heading is "Discover the family story your DNA can tell." Below this is the text "Uncover your ethnic mix, discover distant relatives, and find new details about your unique family history with a simple DNA test." The price is prominently displayed as "ONLY \$99" with an "ORDER NOW" button. A man's face is shown next to a pie chart representing ethnic mix: 52% Ireland, Scotland and 28% Scandinavia. The website navigation includes "ancestry", "FAMILY TREES", "SEARCH", "DNA", "HELP", "EXTRAS", "SUBSCRIBE", and "SIGN IN". There are also "ACTIVATE A KIT" and "FAQS" buttons.

and from there, family history & phenotypes,

what type of diet you should eat,

what sport/position you should play,

DNAFit
 Register Kit Sign In My Cart

Let's talk about you.

Our groundbreaking DNA test will change the way you think about fitness and nutrition forever.

For Fitness & Diet

Whether you're looking to shape up, build muscle or just want to eat a little healthier, your genetics hold valuable information about the best way to do this, just for you.

[FIND OUT MORE](#) [Support](#)

SOCCER GENOMICS

DNA extraction
 Our home-based buccal swab kit is the right way for you to send your DNA to our lab.

Sequencing
 Our labs are CLIA-certified and CAP-accredited in order to process all buccal samples.

Soccer Genes - SNP
 The analyzed genes are those that have direct relation with the skills required of a soccer player needs.

DISCOVER YOUR SOCCER GENETIC BLUEPRINT

Welcome to your specific player DNA

Unique Genetic Soccer Report.

Based on age and gender our multidisciplinary team employs a rigorous process in generating the soccer report, which provides insight into the development of a personalized training program designed to maximize overall performance.

- SPEED
- ENDURANCE
- STRENGTH
- FLEXIBILITY
- RISK OF INJURY
- NUTRITION
- TRAINING GUIDE

No payments • no interest if paid in full in 6 months on purchases of \$99+
 Read our terms and privacy page here.

[PayPal CREDIT](#)

what wine you should buy....

HOME STORE GIFT BLOG CONTACT US LOGIN SIGN UP

VINOME

Your DNA Guide to Wines You'll Love

Take the guesswork out of buying wine. We analyze your DNA and taste preferences, then match you with hard-to-find wines selected for your unique palate. Shop for your bottles in our online store, or join our wine club. Either way, we deliver to your doorstep.

Vino + Genome = Vinome

[SIGN UP](#)

But seriously, folks....

Using Genetic/Genomics to assist in
High-Definition Diagnosis &
Precision Treatment Selection

The NIH Genetic Testing Registry (GTR)

www.ncbi.nlm.nih.gov/gtr

Clinician-orderable
genetic tests....

Disease/condition-related &
some pharmacogenomic tests

- single-gene tests
- multi-gene panels

Methods:

- Targeted variants
- Exome sequencing
- Gene sequencing

*does not include
direct-to-consumer products.*

The screenshot shows the NIH Genetic Testing Registry (GTR) website. At the top, there is a navigation bar with 'NCBI Resources' and 'How to'. Below this is the 'GTR: GENETIC TESTING REGISTRY' header. A search bar is present with a 'Search All GTR' button. Below the search bar, it states 'Search all 55281 tests, 11259 conditions, 16448 genes, and 506 labs'. There is a 'YouTube GTR Tutorials' link. An 'IMPORTANT NOTE' is displayed, stating that NIH does not independently verify information submitted to the GTR and that it is not a substitute for medical advice. Below the note, there are several sections: 'Medical Genetics Summaries' with a DNA helix icon, 'Find GTR Content' with a pie chart showing categories like BRCA1/BRCA2 panels, Mitochondrial genome tests, Human genome and Whole exome tests, Pharmacogenetics, Genomic testing labs, Cancer/somatic tests, CGH tests, and Single gene tests; 'About GTR' with a brief description of the registry's purpose and a list of links; and 'GTR Data' with two bar charts showing the number of tested conditions, genes, labs, and tests from 2012 to 2018. A 'Worldwide Lab Participation in GTR' section is partially visible at the bottom.

NCBI Workshops

THE EVOLUTION OF CLINICAL PRACTICE

The Art of Medicine

The Science of Medicine

Evidence-based Clinical Practice

“Evidence-based medicine is the integration of best research evidence with clinical expertise and patient values.”

“Personalized” Medicine

[AMA – all patient-care should be “personalized”]

Precision (including Genomic) Medicine

“An emerging approach for disease diagnosis treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person.”

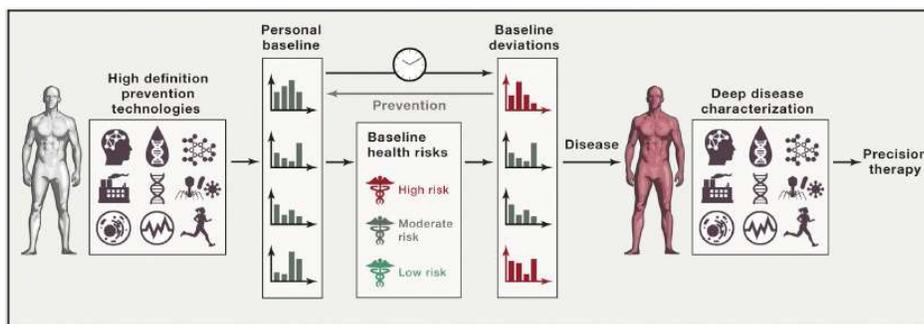


AND NOW....HIGH-DEFINITION MEDICINE?

Establish an Individual’s **Baseline** of Health

Create a Personalized “**Prevention**” Strategy

Perform **High-Definition Diagnosis** & Select **High-Precision Treatment**



“High-Definition Medicine.” Torkamani A, Andersen KG, Steinhubl SR, and EJ Topol. *Cell*. 24 August 2017 170(5), 828–843.

ADDING GENETICS/GENOMICS TO THE CLINICAL TOOL KIT Clinical Research & Case Management Protocols

Undiagnosed Diseases Network
Solving medical mysteries through team science

- Taylor College of Medicine
- Stanford Medicine
- Taylor College of Medicine and University of Oregon
- UCLA
- Brigham and Women's Hospital, Boston Children's Hospital, Massachusetts General Hospital
- University of Miami School of Medicine
- Children's Hospital of Philadelphia and University of Pennsylvania
- University of Utah
- Duke University and Columbia University
- University of Washington School of Medicine and Seattle Children's Hospital
- Harvard Medical School and University of Alabama at Birmingham
- Vanderbilt University Medical Center
- Mayo Clinic
- Washington University in St. Louis
- National Institutes of Health

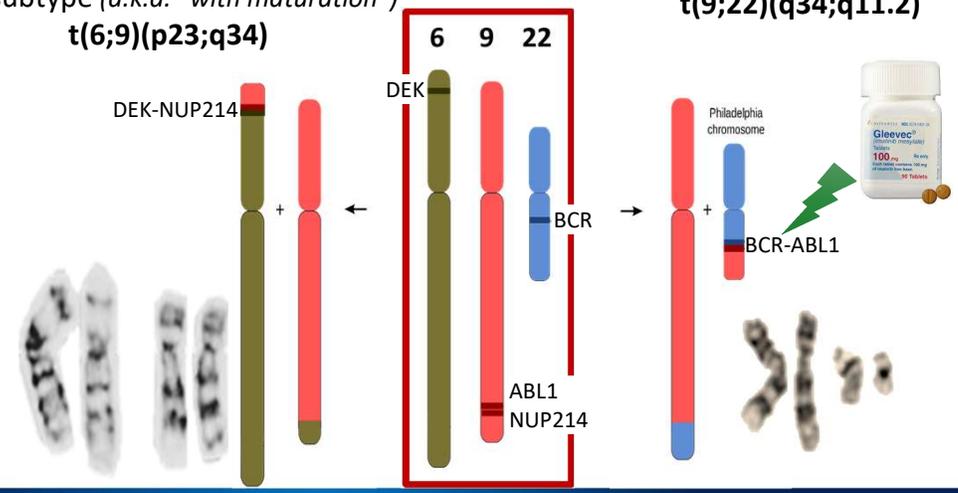
Twelve clinical sites, a coordinating center, a sequencing core, a metabolomics core, two model organisms screening centers, and a central biorepository



GENETIC TESTING FOR DIAGNOSIS & TARGETED THERAPY

Acute Myeloid Leukemia (AML)
M2 subtype (*a.k.a.* "with maturation")
t(6;9)(p23;q34)

Chronic Myelogenous Leukemia (CML)
t(9;22)(q34;q11.2)



PHARMACOGENETICS TESTING - DOSAGE PREDICTION: MAXIMIZING EFFECTIVENESS & MINIMIZING ADVERSE EVENTS

Dosing for warfarin/Coumadin can be complicated....

Inclusion of Pharmacogenomics in a *Dosing Algorithm*

Example:

Young, african american, thin, smoking male

➤ high dose....120 mg

Older, caucasian, slightly heavy female

➤ low dose....2 mg



WARFARINDOSING www.WarfarinDosing.org

Required Patient Information

Age: Sex: Ethnicity:

Race:

Weight: lbs or kgs

Height: feet and inches or cms

Smokes: Liver Disease:

Indication:

Baseline INR: Target INR: Randomize & Blind

Amiodarone/Cordarone® Dose: mg/day

Statin/HMG CoA Reductase Inhibitor:

Any azole (eg. Fluconazole):

Sulfamethoxazole/Septtra/Bactrim/Cotrim/Sulfatrim:

Genetic Information

VKORC1-1639/3673: Not available/pending

CYP4F2-V433M: Not available/pending

GGCX-rs11676382: Not available/pending

CYP2C9*2: Not available/pending

CYP2C9*3: Not available/pending

CYP2C9*5: Not available/pending

CYP2C9*6: Not available/pending

Accept Terms of Use

ESTIMATE WARFARIN DOSE

HOT TOPICS FOR ANESTHESIA PROVIDERS ANESTHESIA CASE MANAGEMENT

Knowing about potential drug sensitivities and the potential for adverse events - *ahead of time* - can prompt the use of alternate protocols ...

-> enabling better patient experience & outcomes!

For example:

- Now: Malignant Hyperthermia Susceptibility (MHS) – “disorder”/”trait”
various blood clotting disorders (ex: Hemophilia, F5 Leiden) – “disorders”
and impact of therapies (ex: warfarin/Coumadin & clopidogrel/Plavix) – “PGx”
- Now-ish & Upcoming: Post-Operative Nausea & Vomiting (PONV/CINV)
– “trait” & drug impact “PGx” (ex: ondansetron/Zofran)
- Soon: Congenital pain sensitivity – “disorder”
Effectiveness of Pain medication – “PGx”
Propofol dose-response variability/Propofol Infusion Syndrome (PRIS) – “trait” & “PGx”
- *Not really* soon: Addiction – “trait”



RECOMMENDATIONS FOR DISORDER GENETIC TESTING GENETIC VARIANT ASSERTION, EVIDENCE & ACTIONABILITY



ClinGen Clinical Genome Resource

Search our knowledge base for genes and diseases...

How to share your data | Learn about ClinGen curation activities

Clinical Actionability

Disorder curated	HGNC Gene Symbol	Outcome/Intervention Pair	Severity	Likelihood	Effectiveness	Nature of the Intervention	Total	Total
Malignant Hyperthermia, Susceptibility To, 1 (OMIM 145600)	RYR1	Morbidity from MH event/Avoidance of triggering anesthetics	2	2D	3B	3	100B	00B
Malignant Hyperthermia, Susceptibility To, 5 (OMIM 601187)	CACNA1S	Morbidity from MH event/Avoidance of triggering anesthetics	2	2D	3B	3	100B	00B

Genetics in Medicine Official Journal of the American College of Medical Genetics and Genomics

Table 1: ACMG SF v2.0 genes and associated phenotypes recommended for return of secondary findings in clinical sequencing

Table 1: ACMG SF v2.0 genes and associated phenotypes recommended for return of secondary findings in clinical sequencing

Phenotype	MIM disorder	PMID Gene Reviews entry	Typical age of onset	Gene	MIM gene	Inheritance*	Variants to report*
Malignant hyperthermia susceptibility	145600	20301325	Child/adult	RYR1 CACNA1S	180901 114208	AD	KP

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

<http://www.acmg.net>

ACMG RECOMMENDATIONS

Disease name and MIM number	Gene via GTR
Adenomatous polyposis coli (MIM 175100)	APC (MIM 611731)
Aortic aneurysm, familial thoracic 4 (MIM 132900)	MYH11 (MIM 160745)
Aortic aneurysm, familial thoracic 6 (MIM 611788)	ACTA2 (MIM 102620)
Arrhythmogenic right ventricular cardiomyopathy, type 5 (MIM 604450)	TMEM63 (MIM 612048)
Arrhythmogenic right ventricular cardiomyopathy, type 6 (MIM 607450)	DSE (MIM 125647)
Arrhythmogenic right ventricular cardiomyopathy, type 9 (MIM 605040)	PKP2 (MIM 602861)
Arrhythmogenic right ventricular cardiomyopathy, type 10 (MIM 610193)	DSG2 (MIM 125671)
Arrhythmogenic right ventricular cardiomyopathy, type 11 (MIM 610476)	DSG2 (MIM 125645)
Breast-ovarian cancer, familial 1 (MIM 604370)	BRCA1 (MIM 113705)
Breast-ovarian cancer, familial 2 (MIM 612555)	BRCA2 (MIM 600185)
Brugada syndrome 1 (MIM 601144)	SCN5A (MIM 600163)
Catecholaminergic polymorphic ventricular tachycardia (MIM 604772)	RYR2 (MIM 190902)
Dilated cardiomyopathy 1A (MIM 115200)	LMNA (MIM 150330)
Dilated cardiomyopathy 1A (MIM 115200)	MYBPC3 (MIM 600958)
Ehlers-Danlos syndrome, type 4 (MIM 130050)	COL3A1 (MIM 120180)
Fabry disease (MIM 301500)	GLA (MIM 300644)
Familial hypercholesterolemia (MIM 143890)	LDLR (MIM 606945)
Familial hypertrophic cardiomyopathy 1 (MIM 192600)	MYH7 (MIM 160760)
Familial hypertrophic cardiomyopathy 3 (MIM 115196)	TPM1 (MIM 191010)
Familial hypertrophic cardiomyopathy 4 (MIM 115197)	MYBPC3 (MIM 600958)
Familial hypertrophic cardiomyopathy 6 (MIM 600858)	PRKAG2 (MIM 602743)
Familial hypertrophic cardiomyopathy 7 (MIM 613690)	TNN3 (MIM 191044)
Familial hypertrophic cardiomyopathy 8 (MIM 608751)	MYL3 (MIM 160790)
Familial hypertrophic cardiomyopathy 10 (MIM 608758)	MYL2 (MIM 160781)
Familial hypertrophic cardiomyopathy 11 (MIM 612098)	ACTC1 (MIM 102540)
Familial medullary thyroid carcinoma (MIM 155240)	RET (MIM 164761)
Hypercholesterolemia, autosomal dominant 3 (MIM 603776)	PCSK9 (MIM 607786)
Juvenile polyposis syndrome (MIM 174900)	BMPR1A (MIM 601299)
Juvenile polyposis syndrome (MIM 174900)	SMAD4 (MIM 600993)
Left ventricular noncompaction 6 (MIM 601494)	TNNT2 (MIM 191045)
Li-Fraumeni syndrome 1 (MIM 151623)	TP53 (MIM 191170)

Disease name and MIM number	Gene via GTR
Loeys-Dietz syndrome type 1A (MIM 609192)	TGFBR1 (MIM 190181)
Loeys-Dietz syndrome type 1B (MIM 610168)	TGFBR2 (MIM 190182)
Loeys-Dietz syndrome type 2A (MIM 608967)	TGFBR1 (MIM 190181)
Loeys-Dietz syndrome type 2B (MIM 610380)	TGFBR2 (MIM 190182)
Loeys-Dietz syndrome type 3 (MIM 613795)	SMAD3 (MIM 603109)
Long QT syndrome 1 (MIM 192500)	KCNQ1 (MIM 607542)
Long QT syndrome 2 (MIM 613688)	KCNH2 (MIM 152427)
Long QT syndrome 3 (MIM 603830)	SCN5A (MIM 600163)
	MLH1 (MIM 120436)
	USH2 (MIM 609309)
	USH2B (MIM 600678)
	PMS2 (MIM 600259)
Lynch syndrome (MIM 120435)	RYR1 (MIM 180901)
	CACNA1S (MIM 114208)
Malignant hyperthermia (MIM 145600)	
Martian's syndrome (MIM 154700)	FBN1 (MIM 134797)
Martian's syndrome (MIM 154700)	TGFBR1 (MIM 190181)
Multiple endocrine neoplasia, type 1 (MIM 131100)	MEN1 (MIM 613733)
Multiple endocrine neoplasia, type 2a (MIM 171600)	RET (MIM 164761)
Multiple endocrine neoplasia, type 2b (MIM 162300)	
MYH-associated polyposis (MIM 608456)	MUTYH (MIM 604933)
Neurofibromatosis, type 2 (MIM 101000)	NF2 (MIM 607379)
Ornithine carbamoyltransferase deficiency (MIM 311250)	OTC (MIM 300461)
Paragangliomas 1 (MIM 168000)	SDHD (MIM 602690)
Paragangliomas 2 (MIM 601650)	SDHAF2 (MIM 613019)
Paragangliomas 3 (MIM 605373)	SDHC (MIM 602413)
Paragangliomas 4 (MIM 115310)	SDHB (MIM 185470)
Peutz-Jeghers syndrome (MIM 175200)	STK11 (MIM 602216)
Piliomatricoma (MIM 132600)	MUTYH (MIM 604933)
PTEN hamartoma tumor syndrome (MIM 153480)	PTEN (MIM 601728)
Retinoblastoma (MIM 180200)	RB1 (MIM 614041)
Tuberous sclerosis 1 (MIM 191100)	TSC1 (MIM 605284)
Tuberous sclerosis 2 (MIM 613254)	TSC2 (MIM 191092)
Von Hippel-Lindau syndrome (MIM 193300)	VHL (MIM 608537)
Wilms' tumor (MIM 194070)	WT1 (MIM 607102)
Wilson disease (MIM 277900)	ATP7B (MIM 606882)

WHAT TO TAKE INTO CONSIDERATION FOR ALL GENETIC TESTS...

Pros

- Genetic tests are decreasing in cost & not particularly invasive.
- A well-known genetic lesion can sometimes help in diagnosis and/or drug/therapy selection

PERHAPS MOST IMPORTANTLY FOR YOU....

- What is the standard-of-care in your Hospital or Healthcare system?
- Is there a Clinical Geneticist or Genetic Counselor available to assist?

- *We are early in our understanding of genes, gene variants and disease.*
- Failure to detect a pathogenic variant *does not rule out* the diagnosis.
- Prediction isn't guaranteed just yet - not all pathogenic variants cause the same symptoms in every patient (*penetrance, severity, multi-genic & environmental influences*).
- Lack of coverage by *some* insurance companies...

EXAMPLE OF A "RELATIVELY SIMPLE" SYSTEM: MALIGNANT HYPERTHERMIA SUSCEPTIBILITY

"LARGELY MONOGENIC"
but exhibits **"INCOMPLETE PENETRANCE"**

RYR1 - Ryanodine Receptor type 1 gene
(green blobs)

CACNA1S - Dihydropyridine Receptor gene *a.k.a.*
L-type Calcium voltage-gated channel subunit alpha1S
(blue blobs)

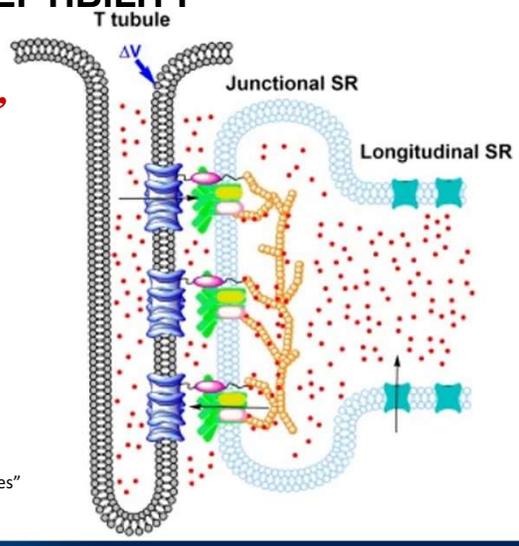


Figure 2A. Membrane contact sites within the ER/SR.
"Calcium Dynamics Mediated by the Endoplasmic/Sarcoplasmic Reticulum and Related Diseases"
Reddish FN, Miller CL, Gorkhali R, Yang JJ. Int J Mol Sci. 2017 May; 18(5): 1024.
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5454937/>

MALIGNANT HYPERTHERMIA SUSCEPTIBILITY VARIATIONS KNOWN & UNKNOWN

NCBI Resources How To

ClinVar ClinVar ("malignant hyperthermia"[Disease/Phenotype]) AND ryr1[gene name]

Create alert Advanced

Home About Access Help Submit Statistics FTP

Repository of
Clinical Assertions for
Human Genetic Variants:
ClinVar

- Gene
Customize this list...
- Clinical significance
Conflicting interpretations (59)
Benign (108)
Likely benign (163)
Uncertain significance (243)
Likely pathogenic (13)
Pathogenic (25)
Risk factor (17)
- Review status
Practice guideline (0)
Expert panel (0)
Multiple submitters (131)
Single submitter (221)
At least one star (411)
Conflicting interpretations (59)

Assertions in ClinVar	All MHS	RYR1 (type 1)	CACNA1S (type 5)
Pathogenic/Risk Factor	49	46	3
Likely Pathogenic	20	20	0
Benign/Likely Benign	530	314	216
Uncertain Significance	377	256	121

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

WHEN TO CONSIDER & WHAT TYPE OF GENETIC TESTING FOR MHS?

- **Symptomatic Patients – Diagnostic validation**
Patient has a confirmed/highly suspicious MH event/positive CHCT (ACMG: OR exercise-related rhabdomyolysis without a known myopathy)
➤ **MHAUS & ACMG:** Full gene sequencing to identify any (esp. pathogenic) variant(s)
- **Asymptomatic patients with a family history of a genetic disorder/trait – Risk prediction**
Family member with a confirmed/highly suspicious MH event/positive CHCT (MHAUS)
➤ **MHAUS:** Full gene sequencing to identify variant(s) (esp. pathogenic ones)
or Partial gene sequencing to detect a *known* pathogenic variant
Family member with a known familial pathogenic variant (ACMG)
➤ **ACMG:** Partial gene sequencing only for a known familial pathogenic variant
- **Asymptomatic Patients with no family history – Risk prediction**
➤ **MHAUS & ACMG** – genetic testing *not recommended yet*
➤ **EMHG** says if there is *any* suspicion, consider genetic testing before muscle biopsy & IVCT

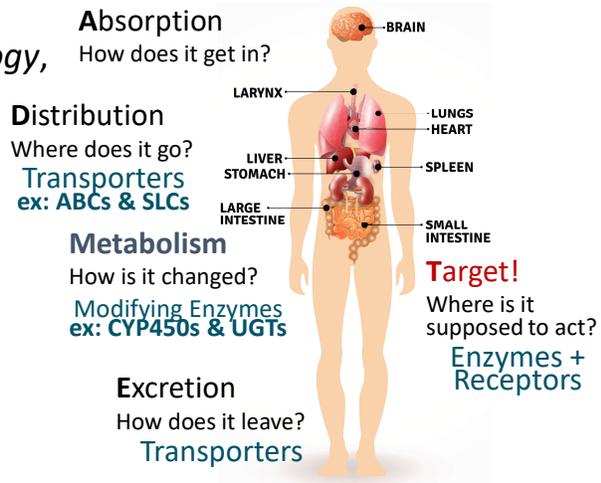
NOW THAT YOU'RE A-GROUND...ONCE YOU KNOW....

- Clinically, what do you *do* with this information?
(*you hopefully knew before the test was ordered*)
- A patient may ask: “*What is wrong with me and how can we fix it?*”
 - Understanding the potential impact of a genetic variant on the patient’s physiology and phenotype and how this relates to your choice of case management.
- Outside of the planned clinical impact: “*What do I do now?*”
 - **A great reason to consult with a Genetic Counselor!**
 - Implications for the patient *beyond* this surgery:
Consider discussing this with their primary care physician, dentist, other clinical professionals who may need to know for their care.
 - Implications for family members: *Should they tell others?*



PHARMACOGENETICS: A PATIENT’S MAKEUP IMPACTS THE EFFECTIVENESS OF YOUR CASE MANAGEMENT.

- Anesthesia is *applied pharmacology*, but at a heightened level.
- It is critical to deliver:
 - the right drug
 - at the right concentration
 - at the right place
 - at the right time!



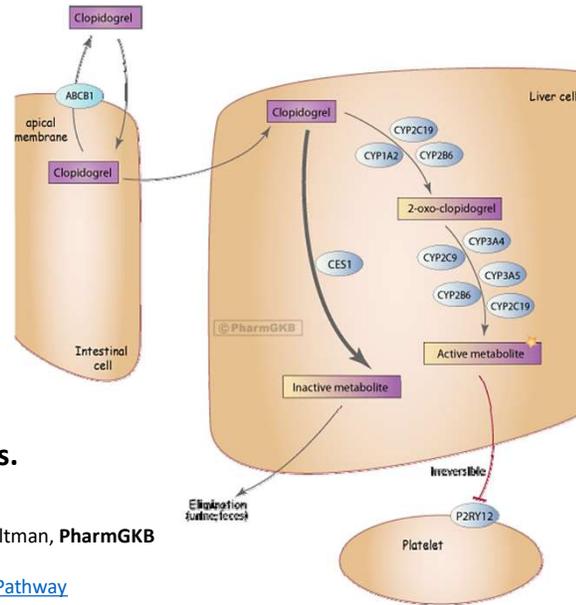
AN EXAMPLE OF PHARMACOGENOMIC COMPLEXITY

“A ‘SIMPLE’ POLYGENIC PROCESS”

A-D-M-E-T

Activation of Clopidogrel is 2-stage largely done by CYP2C19, but also others.

Inactivation and elimination are also factors.



“Clopidogrel pathway.” Katrin Sangkuhl, Teri E. Klein, and Russ B. Altman, *PharmGKB Pharmacogenetics and Genomics*. 2010 Jul; 20(7): 463–465.

<http://www.pharmgkb.org/do/serve?objId=PA154424674&objCls=Pathway>

Pharmacogenomics (2018) 19(3), 285–298

The pharmacogenetics of medications used in general anesthesia

Shangchen Xie^{1,2}, Wenjuan Ma^{1,2}, Qulian Guo², Jie Liu¹, Wei Li¹, Howard L McLeod^{1,2,3} & Yijing He^{1,2,3}
General anesthesia is a state of unconsciousness, amnesia, analgesia and akinesia induced by drugs including opioids, hypnotic-sedative agents, muscle relaxants and antiemetics. Clinical and genetic factors are reported to influence the efficacy and side effects of these agents. Based on the evidence, clinical action is needed to improve clinical outcomes. This review summarizes the latest knowledge with regards to the pharmacogenetics of anesthetics and general anesthesia related complications.

Substrate	Gene	Important allelic variants	Clinical annotations	Ref.
Sevoflurane	GSTP1	rs1695 and rs1138272	Higher serum μ -GST concentration with variant allele	PK [78]
Isoflurane	MCT1R		Increased desflurane requirements with variant allele	PK [6]
Succinylcholine	BCHE	*F5126, *I326414C, *I2380, I3731, G4675, W5188, L1896, V421A, M462I and R577H		[83,84]
Rocuronium	SLCO1B2	-189...188insA	Reduced rocuronium clearance with variant allele	PK [85]
Propofol	CYP2B6	*4 and *6		[70,71]
	UGT1A9			[6]
	HTR2A	rs6819		[72]
	GABRA1	rs3778020		[73]
	SCN9A	rs6746930		[73]
Desmedetomidine	ADRA2A	rs1800544	Higher sedation scores with G allele	PD [77]
Midazolam	CYP3A4	*22	Reduced midazolam oral clearance with T allele	PK [65]
	CYP3A5	*2	Lower midazolam clearance with *2 allele	PK [64]
	PDR	*28	Lower metabolic ratios of midazolam with *28 allele	PK [66]
	GABRA1	rs4263535		[67]
Diazepam	CYP2C19			[6,68]
Ondansetron	CYP2D6		CPC guidelines	CA [31]
	ABCB1	rs1045642 and rs2032582	Higher incidence of nausea and vomiting with C allele	PD [88]
	HTR2A and HTR2B		CPC guidelines	[91,92]
Tropisetron	CYP2D6		CPC guidelines	CA [3]
	OCT1		Higher plasma concentration with loss-of-function alleles	PK [93]

Anesthetics

Anti-emetics

Substrate	Gene	Important allelic variants	Clinical annotations	Ref.
Morphine	UGT2B7	rs7429366	Decreased morphine requirement with C allele	PK [8]
	ABCB1	rs1128503 and rs1045642		[8]
	COMT	rs4680	Predictor for the risk of requiring rescue morphine	PD [9]
OPRM1		rs1799971	Increased dose requirement with G allele	PK PD [11,12]
	OCT1	*2 and *5	Lower morphine clearance with OCT1*2/*5	PK [15]
Codaine	CYP2D6		CPC guidelines	CA [3]
Fentanyl	CYP3A5	*2	Lower plasma concentrations with *2 allele	PK [22,24]
	LAMB2	rs2076222	Lower sensitivity to opioids with C allele	PK [25]
Remifentanyl	OPRM1	rs1799971	Increased remifentanyl requirement with G allele	PK [13]
	ABCB1	rs1045642	Increased incidence of opioid side effects with minor allele	PD [27]
	CACNA2D2	rs3588911	Higher opioid sensitivity with minor allele	PK [27]
Tramadol	CYP2D6		FDA-approved KMP therapeutic recommendations	CA [29]
	OCT1		Higher plasma concentration with active OCT1 allele	PK [30]
Oxycodone	CYP2D6		KMP guidelines	CA [34]
	FAAH	rs1571138, rs324420, rs3760246 and rs4141964		[38]
Methadone	CYP2B6	*4 and *6	Higher oral clearance and metabolism with *4 while lower oral clearance and metabolism with *6	PK [41]
	SPOW1			[43]
	GGT1L			[43]
		rs17180299		[43]
	OPRM1	rs75568641	Higher opioid requirement with C allele	PK [44]
Acetylsalicylic acid	UGT1A6			[48]
	CYP2C9			[48]
	COX-1	rs10306114	Decreased response to acetylsalicylic acid with G allele	PD [45]
Ibuprofen	CYP2C8	*3	Increased R-ibuprofen clearance with *3 allele	PK PD [52]
			Fewer adverse events with *3 allele	
	CYP2C9	*2 and *3	Decreased ibuprofen clearance with *2 and *3	PK [52,53]
Celecoxib	CYP2C9	*2 and *3	FDA-approved drug label annotations	CA [55-57]

Analgesics - opioids

Analgesics - NSAIDs

FDA DRUGS WITH PHARMACOGENOMIC INFORMATION - SOME RELATED TO ANESTHESIA PRACTICE

Drug	Therapeutic Area	Biomarkers	Labeling Section
Codeine	Anesthesiology	CYP2D6	Boxed warning, Warnings and Precautions, Use in Specific Populations, Patient Counseling Information
Clopidogrel	Cardiology	CYP2C19	Boxed warning, Warnings and Precautions
Desflurane	Anesthesiology	Non-specific (genetic susceptibility to Malignant Hyperthermia)	Contraindications
Diazepam		CYP2C19	Clinical Pharmacology
Enflurane	Anesthesiology	Non-specific (genetic susceptibility to Malignant Hyperthermia)	Contraindications
Isoflurane	Anesthesiology	Non-specific (genetic susceptibility to Malignant Hyperthermia)	Contraindications
Lidocaine & Prilocaine	Anesthesiology	Nonspecific (Congenital Methemoglobinemia)	Warnings and Precautions
Lidocaine & Prilocaine	Anesthesiology	G6PD	Warnings and Precautions, Clinical Pharmacology
Lofexidine	Anesthesiology	CYP2D6	Use in Specific Populations
Sevoflurane	Anesthesiology	Nonspecific	Warnings
Succinylcholine	Anesthesiology	BCHE	Warning, Precautions
Tramadol	Anesthesiology	CYP2D6	Boxed warning, Warnings and Precautions, Use in Specific Populations, Clinical Pharmacology
Warfarin	Hematology	VKORC1, CYP2C9, CYP4F2	Boxed warning, Warnings and Precautions, Clinical Pharmacology, Patient Counseling Information

HOT TOPICS FOR ANESTHESIA PROVIDERS

(well...really everyone now-a-days)

PAIN MANAGEMENT

Understanding ***differences in pain perception*** and ***effectiveness of and sensitivity to medications*** can aid in drug selection, dosage and treatment course management -> ***enabling better short-term outcomes!***

Knowing about a physiological ***predisposition to addiction*** for opioids may factor in decision-making for treatment course design -> ***enabling better long-term outcomes!***

CURRENTLY a focus of current national & federal attention!

BUT they are complicated....

**PAIN PERCEPTION & MANAGEMENT
BOTH INVOLVE COMPLEX “POLYGENIC” PROCESSES**

EXAMPLE OF A COMPLEX SYSTEM WITH MANY GENES INVOLVED IN THE PROCESSING OF PAIN SIGNALS.

PAIN MECHANISMS ARE "POLYGENIC PROCESSES"

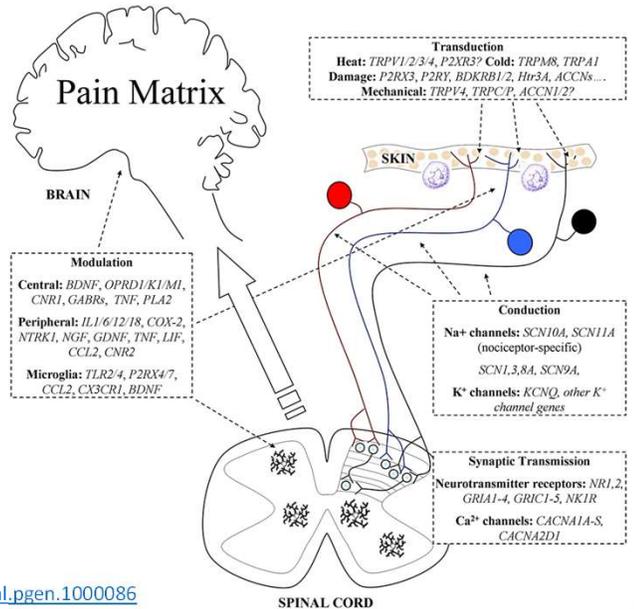


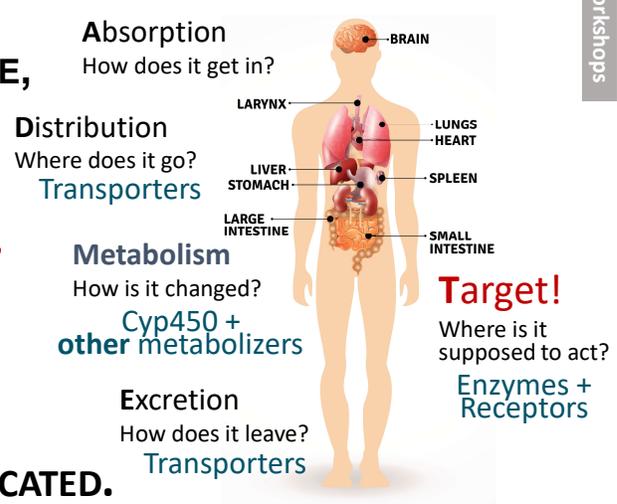
Figure 1. Genes Involved in Pain Perception and Modulation.
 Foulkes T, Wood JN (2008)
 "Pain Genes." PLOS Genetics 4(7): e1000086.
<http://journals.plos.org/plosgenetics/article?id=10.1371/journal.pgen.1000086>

NOW...TO THE PROCESSING OF PAIN SIGNALS, ADD THE BIOPROCESSING OF PAIN MEDICATIONS.

AND LONG-TERM POTENTIAL CONSEQUENCES OF DRUG EXPOSURE, INCLUDING & ESPECIALLY ADDICTION....

PAIN MANAGEMENT MECHANISMS INVOLVE "POLYGENIC PROCESSES"

TREATING PAIN IS EXTREMELY COMPLICATED.



CARDIOLOGY “PGX” CASE STUDY EXAMPLE, BUT ALSO.....

Q: What if my patient is on Plavix?



NCBI Pharmacogenetics Resources for Clinical Care

Current not-uncommon practice in Cardiology:

A patient is diagnosed with Acute Coronary Syndrome, scheduled for an angioplasty, and informed that she will need to take clopidogrel (a.k.a. Plavix) for at least 3-6 months to prevent a heart attack. She mentions that her father died of a stroke while taking the drug. Consider pharmacogenetic influences on clopidogrel response *in this patient* to see if a change in the prescription is indicated.

- **Anesthesia-related implications:** Can you assume the patient’s response is “typical”? (i.e what is her platelet function while “on” clopidogrel and/or what is her clotting like after she stops taking the medication)

LEARNING ABOUT DRUG SENSITIVITY IN MEDGEN

The screenshot shows the MedGen interface with the search term 'clopidogrel response'. The main content area displays the following information:

- Full Report +**
- Clopidogrel response**
- MedGen UID: 382487 • Concept ID: C2674941 • Disease or Syndrome
- Synonyms:** Clopidogrel, poor metabolism of; Plavix response
- Drug:** Clopidogrel
- Gene (location):** CYP2C19 (10q23.33)
- OMIM:** 124020; 609535

Below this information, there are sections for 'Professional guidelines' and 'Genetic Testing Registry'. The 'Professional guidelines' section includes links to clinical pharmacogenetics implementation consortium guidelines. The 'Genetic Testing Registry' section lists various tests such as 'Analyte (1)', 'Sequence analysis of select exons (1)', and 'Targeted variant analysis (17)'. Red arrows in the original image point to the 'Professional guidelines' and 'Targeted variant analysis (17)' entries.

IDENTIFYING A GENETIC TEST TO ORDER IN THE NIH GENETIC TESTING REGISTRY

The screenshot displays the NIH Genetic Testing Registry interface. On the left, a search filter panel shows 'Tests (13)', 'Conditions (1)', 'Genes (1)', and 'Laboratories (14)'. The main results table lists various tests, with 'CYP2C19 genotyping' highlighted. The right side shows the detailed view for 'CYP2C19 genotyping', including its clinical purpose, condition, and a list of associated drug responses.

WHAT DO TEST RESULTS FOR DISORDERS LOOK LIKE? (a sample genetic test result report for a disorder/trait)

ClinGenLab Clinical Testing Lab of California
55472 Spring Street, Suite 201
Vienna, CA 94078-9932 Phone: 510-555-1212

01-12358-1321-34	01-12358-1321-34	01-12358-1321-34	01-12358-1321-34
Tracy	Tracy	Tracy	Tracy
42 y.o.	Female	2 cc	Peripheral Blood
Malignant Hyperthermia Susceptibility Sequencing Panel		Spectrum Type: Peripheral Blood Ethnicity: Northern European Caucasian Indication: Possible Family History	

Clinical test results for Malignant Hyperthermia Susceptibility

GENE	TEST RESULTS	EXPLANATION
CACNA1S	Negative	No known pathogenic variant detected
RYR1	L4824P L4824P	<p>This result confirms the susceptibility for Malignant Hyperthermia type 1. This result should be interpreted in the context of clinical presentation and results of other laboratory tests.</p> <p>A PCR/sequencing study has detected two copies of the NM_000540.2(RYR1):c.14471T>C (p.Leu4824Pro) variation. The L4824P mutation is encoded by a T to C change at nucleotide position 14471 in the RYR1 mRNA and results in a change from leucine to proline at amino acid position 4824 in the protein.</p> <p>In addition, this individual's result has important implications for other family members. Clinical evaluations should be considered and genetic counseling is recommended for at-risk individuals.</p>

DISCLAIMER:
Test results should be interpreted in context of clinical findings, family history, and other laboratory data. Misinterpretation of results may occur if the information provided is inaccurate or incomplete. Rare polymorphisms exist that could lead to false negative or positive results. If results obtained do not match the clinical findings, additional testing

WHAT DO PGX TEST RESULTS LOOK LIKE?

Drug Clonidine **Gene** CYP2C19

Interpretation of Clonidine Ultra-Rapid Metabolism

Ultra-Rapid metabolizers have increased benefit of the drug. Other individuals may increase the risk of bleeding.

Share this information with your healthcare providers. Do not make any changes to any medication without talking to your healthcare provider.

Genetic laboratories may report alleles or genetic variations in:

- “partial HGVS format, ex: **CYP2C12 p.Trp212Ter | p.Trp212Ter**”
- or in “star allele” format, ex: **CYP2C12*3/*3**”
- or use a “SNP ID” format, ex: **rs4986893**”

Major gene-drug interaction

Genotype suggests a possible decrease increase in exposure to clonidinel. Professional guidelines exist for the use of clonidine in patients with this genotype and/or phenotype.

LEARN MORE ABOUT THE VARIATION IN CLINVAR

Allele(s) NM_000769.1(CYP2C19):c.636G>A (p.Trp212Ter)

Interpretation Pathogenic

PGx Clonidine: Drug reported used for: Acute coronary syndrome. Drug reported used for: Acute coronary syndrome/Coronary Artery Disease.

LEARNING MORE ABOUT ACTIONABLE PGX INFORMATION

Professional guidelines

PubMed
Clinical Pharmacogenetics Implementation Consortium guidelines for CYP2C19 genotype and clopidogrel therapy: 2013 update.
 Scott SA, Sangkuh K, Stein CM, Hulot JS, Mega JL, Roden DM, Klein TE, Sabatine MS, Johnson JA, Shuldiner AR, Clinical Pharmacogenetics Implementation Consortium.
Clin Pharmacol Ther 2013 Sep;94(3):317-23. Epub 2013 May 22 doi: 10.1038/clpt.2013.105. PMID: 23686643 Free PMC Article

Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450-2C19 (CYP2C19) genotype and clopidogrel therapy.
 Scott SA, Sangkuh K, Gardner EE, Stein CM, Hulot JS, Johnson JA, Roden DM, Klein TE, Shuldiner AR, Clinical Pharmacogenetics Implementation Consortium.
Clin Pharmacol Ther 2011 Aug;90(2):328-32. Epub 2011 Jun 29 doi: 10.1038/clpt.2011.132. PMID: 21716271 Free PMC Article

ACC/AHA clopidogrel clinical alert: approaches to the FDA "boxed warning": a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the American Heart Association.
 Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons.
 Holmes DR Jr, Dehmer GJ, Kaul S, Lefler D, O'Gara PT, Stein CM
J Am Coll Cardiol 2010 Jul 20;56(4):321-41. doi: 10.1016/j.jacc.2010.05.013. PMID: 20633831

ACC/AHA Clopidogrel clinical alert: approaches to the FDA "boxed warning": a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the American Heart Association.
 Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, Writing Committee Members, Holmes DR Jr, Dehmer GJ, Kaul S, Lefler D, O'Gara PT, Stein CM
Circulation 2010 Aug 3;122(5):537-57. Epub 2010 Jun 28 doi: 10.1161/CIRC.0b013e3181ec06ed. PMID: 20585015

External
 DailyMed Drug Label, Pлавix, 2009

diminished antiplatelet effect of clopidogrel in CYP2C19 poor metabolizers. The warning states that tests are available to identify patients who are CYP2C19 poor metabolizers, and to consider the use of another platelet P2Y12 inhibitor in patients identified as CYP2C19 poor metabolizers. The effectiveness of clopidogrel is also reduced in individuals who are CYP2C19 intermediate metabolizers. These individuals carry one non-functional copy of CYP2C19, with either one normal function copy or one increased function copy. For patients with ACS who are undergoing PCI, the 2013 Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for clopidogrel recommends an alternative antiplatelet therapy (e.g., prasugrel, ticagrelor) for CYP2C19 poor or intermediate metabolizers, if there is no contraindication. The Dutch Pharmacogenetics Working Group (DPWG) of the Royal Dutch Association for the Advancement of Pharmacy (KNMP) have also made antiplatelet therapy recommendations based on CYP2C19 genotype. For patients with ACS who receive PCI, they recommend an alternative drug to clopidogrel in poor metabolizers, and for intermediate metabolizers, they recommend choosing an alternative drug, or doubling the dose of clopidogrel to 150 mg daily dose, 600 mg loading dose. <https://www.ncbi.nlm.nih.gov/books/NBK64114>

Table of contents

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 - RefSeqGene

LEARNING MORE IN THE MEDICAL GENETICS SUMMARIES

Medical Genetics Summaries [Internet].

Clopidoqrel Therapy and CYP2C19 Genotype

Laura Dean, MD.

NCBI
 dean@ncbi.nlm.nih.gov

Created: March 8, 2012; Last Update: April 18, 2018

Introduction

Clopidogrel (brand name Plavix) is an antiplatelet agent. Clopidogrel reduces the risk of myocardial infarction (MI) and stroke in patients with acute coronary syndrome (ACS), and in patients with atherosclerotic vascular disease (indicated by a recent MI or stroke, or established peripheral arterial disease) (1). Clopidogrel is also indicated in combination with aspirin in patients undergoing percutaneous coronary interventions (PCI), e.g., the placement of a stent.

The effectiveness of clopidogrel depends on its conversion to an active metabolite by CYP2C19. Individuals who carry 2 non-functional copies of the CYP2C19 gene are classified as CYP2C19 poor metabolizers. They have no enzyme activity and cannot

In this Page

- Introduction
- Drug: Clopidogrel
- Gene: CYP2C19
- Genetic Testing
- Therapeutic Recommendation
- Nomenclature of Selected CYP
- Acknowledgments
- Version History
- References

Common allele name	Alternative names	HGVS reference sequence	Protein	dbSNP reference identifier for allele location
CYP2C19*2	681G>A Pro227Pro	NM_000769.1:c.681G>A	NP_000760.1:p.Pro227=	rs4244285
CYP2C19*3	Table 2.			
CYP2C19*17	80			

Note: the normal "wild type" is CYP2C19*1.

2017 Statement from the US Food and Drug Administration

WARNING: DIMINISHED ANTIPLATELET EFFECT IN PATIENTS WITH LOSS-OF-FUNCTION ALLELES OF THE CYP2C19 GENE

The effectiveness of clopidogrel tablets results from its antiplatelet activity to an active metabolite by the cytochrome P450 (CYP) system. The effectiveness of clopidogrel is reduced in individuals who are CYP2C19 poor or intermediate metabolizers. Tests are available to identify patients who are CYP2C19 poor or intermediate metabolizers. For patients with ACS who receive PCI, they recommend an alternative drug to clopidogrel in poor metabolizers, and for intermediate metabolizers, they recommend choosing an alternative drug, or doubling the dose of clopidogrel to 150 mg daily dose, 600 mg loading dose.

Please review the complete therapeutic recommendations

DAILYMED

WARNING: DIMINISHED ANTIPLATELET EFFECT IN PATIENTS WITH TWO LOSS-OF-FUNCTION ALLELES OF THE CYP2C19 GENE

The effectiveness of clopidogrel tablets results from its antiplatelet activity, which is dependent on its conversion to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. Tests are available to identify patients who are CYP2C19 poor or intermediate metabolizers. For patients with ACS who receive PCI, they recommend an alternative drug to clopidogrel in poor metabolizers, and for intermediate metabolizers, they recommend choosing an alternative drug, or doubling the dose of clopidogrel to 150 mg daily dose, 600 mg loading dose.

CARDIOLOGY “PGX” CASE STUDY EXAMPLE, BUT ALSO....

Q: What if my patient is on Plavix?



NCBI Pharmacogenetics Resources for Clinical Care

Current not-uncommon practice in Cardiology:

After genetic testing, the patient’s genotype (CYP2C19*3/*3) indicates that she is a poor metabolizer for clopidogrel. Based on the available evidence and therapeutic recommendations, an alternative antiplatelet drug, prasugrel which is not metabolized by CYP2C19, is prescribed.

- **Anesthesia-related implications:** What if the genetic test wasn’t done? If it has, you may not need to worry about clopidogrel for this patient, but what about pharmacogenomics impact on prasugrel?

THERE’S MORE YOU CAN DO THAN JUST CLOPIDOGREL!



Medical Genetics Summaries
Bethesda, Virginia: Pharm. Research Biotech. Unit, University Publications, Laura Kallman, Associate Editor, and Adrienne Matthews, Editor-in-Chief & Editor Administration
Bethesda (MD): National Center for Biotechnology Information, NIH
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 - Introduction
 - Introduction
 - Created: September 15, 2016.
 - Genetic variants and drug responses
 - Abacavir Therapy and *HLA-B*57:01* Genotype
 - Laura Dean
 - Created: September 1, 2015; Last Update: April 18, 2016.
 - Adalimumab Therapy and *HLA-B*39:01* Genotype
 - Laura Dean
 - Created: March 26, 2018; Last Update: March 16, 2018.
 - Amiloride Therapy and *CYP2D6* and *CYP2C19* Genotypes
 - Laura Dean
 - Created: March 23, 2017.



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- Created: September 20, 2012; Last Update
- [Warfarin Therapy and *VKORC1* and *CYP* Genotype](#)
- Laura Dean
- Created: March 8, 2012; Last Update: June 11, 2018.

Wow.....THAT WAS FAST....HOW DO I?

Q: What if my patient is on Plavix?



NCBI Pharmacogenetics Resources for Clinical Care
Step-by-step tutorial

Case Study
You diagnose a patient with Acute Coronary Syndrome and schedule an angioplasty. You realize that the patient's genetic profile will need to take equipment, who knows as you will need to know equipment to prevent a heart attack. This patient tells you that he's been taking Plavix for a while taking clopidogrel. Do you decide to look into the pharmacogenetics of clopidogrel response to see if a change in the prescription is indicated.

Learn about optimizing an initial dose, avoiding side effects and the drug therapy recommendations based on genotype in **MedCen**.

Look up CYP2C19 phenotype information in **MedCen**. The use of CYP2C19 phenotype information is highlighted here. You receive professional recommendations by the FDA and professional societies based on a patient's CYP2C19 genotype.

Go to the **NIH Genetic Testing Registry (GTR)**. Click on the **Site #1** link to get a list of available genetic tests for clopidogrel response registered in GTR.

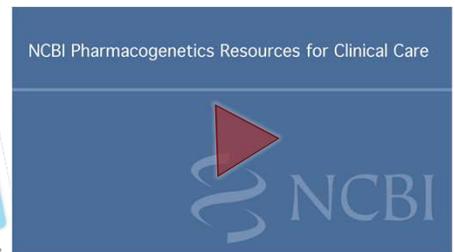
Select an appropriate genetic test to order for your patient in the **NIH GTR**.

Narrow your search
Click on **Site #1** on the left to filter the list of tests based on your desired parameters. For example, you want the specimen type to be a buccal swab from the head in USA, certified in the United States.

Learn about a specific test
Click on the test name to see details about the test. You can also click on the **NIH GTR** to see details about the test.

NIH U.S. National Library of Medicine
National Center for Biotechnology Information

http://bit.ly/NCBI_VANA2018



WHAT IS THE FUTURE OF GENETIC TESTING & WHEN?

NOW: Direct-to-Consumer Tests (Ancestry, Physical Traits & Some Health-related Indicators)

NOW: Baby's First Test

NOW: Clinical Genetic Testing – cancer grading & therapy selection, well-known mendelian metabolic disorders, cardiovascular disorders, infectious agent identification & antibiotic sensitivity assessment, *some* pharmacogenetics for therapeutic selection

NEW: Clinical Genetic Testing – lots of clinical genetic testing in primary care!

NOW-ish: Malignant Hyperthermia Susceptibility

R&D In Progress: Pharmacogenomics also

Prediction of sensitivity & susceptibility for

Predisposition to addiction

Wouldn't it be cool if....
(HBSOTM)

- Pre-operative genetic screen for anesthetic & analgesic drug sensitivity
- Predisposition to bleeding issues,
- Predisposition to PONV & anti-emetic drug sensitivity
- others?

In 5-10 years? Your full genome will be sequenced at birth (or soon) and stored in your EHR.

WHAT TO KEEP AN EYE ON....

Practice Guidelines: AANA & ASA and other clinical professional organizations

Genetic Testing Recommendations:

- ACMG, ClinGen & CDC/NIH/FDA's EGAPP – *Genetic disorders & traits*
- MHAUS & EMHG – *Malignant hyperthermia*
- CPIC & PharmGKB – *Pharmacogenomics*
- FDA & CMS – *Genetic tests approvals & Insurance coverage*

Upcoming Developments:

- Clinical Studies including Genetics/Genomics & Clinical Trials – **dbGaP, ClinicalTrials.gov**
- Collection of Variant Assertions & Identification of Pathogenic Variants – **ClinVar**

How to keep up with what's going on? → NCBI Account: PubMed, MedGed/ClinVar & GTR
(previous talk!)

DOWNLOAD THIS PRESENTATION WITH REFERENCES

http://bit.ly/NCBI_VANA2018

<https://ftp.ncbi.nlm.nih.gov/pub/morris/VANA2018/>

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info@ncbi.nlm.nih.gov

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WE ARE ONLY AT THE BEGINNING!



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NCBI Handbook Chapter: <https://www.ncbi.nlm.nih.gov/books/NBK148949/>

List of many of NCBI’s Databases: <https://www.ncbi.nlm.nih.gov/gquery/>

“NCBI Resources” Factsheet: ftp://ftp.ncbi.nih.gov/pub/factsheets/Factsheet_NCBI_Overview.pdf

NCBI’s Outreach & Education Site: <https://www.ncbi.nlm.nih.gov/home/learn/>

NCBI NEWS & SOCIAL MEDIA:

NCBI Insights Blog: <https://ncbiinsights.ncbi.nlm.nih.gov>

Facebook: <https://www.facebook.com/ncbi.nlm>

Twitter: [@NCBI](https://twitter.com/NCBI)

YouTube Channel: <https://www.youtube.com/user/NCBINLM>

LinkedIn: <https://www.linkedin.com/company/3595640>

HELP EMail Address: info@ncbi.nlm.nih.gov

GLOBAL QUERY (“ALL DATABASES” PAGE)

Gquery – *Listing of most of the databases at NCBI*

Homepage: <https://www.ncbi.nlm.nih.gov/gquery>

LITERATURE RESOURCES

PubMed – *Catalog of research projects with links to publications and datasets*

Homepage: <https://www.ncbi.nlm.nih.gov/pubmed>

PubMed Central (PMC) – *Research studies with high-throughput sequence data*

Homepage: <https://www.ncbi.nlm.nih.gov/pmc>

Bookshelf/Books – *Research studies with functional genomics data*

Homepage: <https://www.ncbi.nlm.nih.gov/books>

Other featured NCBI & NLM Resources: GeneReviews (authored by U.Washington), Genetics Home Reference, Medline Plus

CLINICAL RESOURCES

MedGen – *Aggregated information about medical genetic conditions and phenotypes*

Homepage: <https://www.ncbi.nlm.nih.gov/medgen>

Genetic Testing Registry (GTR) – *NIH’s registry of genetic tests and laboratories*

Homepage: <https://www.ncbi.nlm.nih.gov/gtr>

ClinVar – *Assertions about the relationships of genomic variations with human health*

Homepage: <https://www.ncbi.nlm.nih.gov/clinvar>

MOLECULAR ETIOLOGY RESEARCH

Gene – *Aggregated information with links to genomic, expression, homolog, structure and function data*

Homepage: <https://www.ncbi.nlm.nih.gov/gene>

Conserved Domains Database (CDD) – *A database of protein domains with sequence fingerprints*

Homepage: <https://www.ncbi.nlm.nih.gov/cdd>

Structure – *A database of 3D macromolecular structures and complexes from the protein database*

Homepage: <https://www.ncbi.nlm.nih.gov/structure>