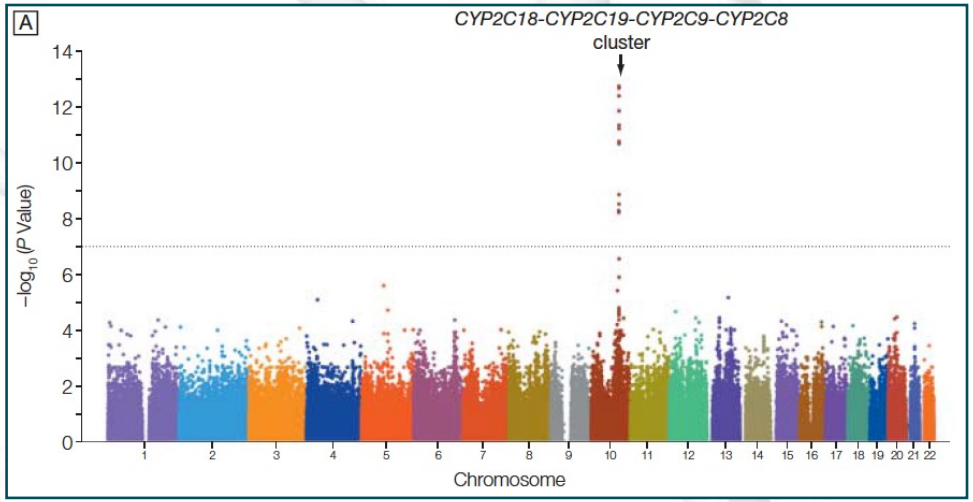
Stanford HEALTH CARE

Stanford Children's Health

Rapid Clinical *CYP2C19* Genotyping for Precision Antiplatelet Prescribing



Stuart A. Scott, PhD, FACMG
Professor,
Department of Pathology
Director,
Clinical Genomics Laboratory

AMP 2023 Annual Meeting
Corporate Workshop – Genomadix
11/15/2023

Stanford MEDICINE

Outline

1. Stanford Medicine Clinical Genomics Laboratory
2. Pharmacogenomics and testing resources
3. CYP2C19 and antiplatelet therapy
4. Rapid *CYP2C19* genotyping for minor stroke/TIA

Stanford Medicine Clinical Genomics Laboratory

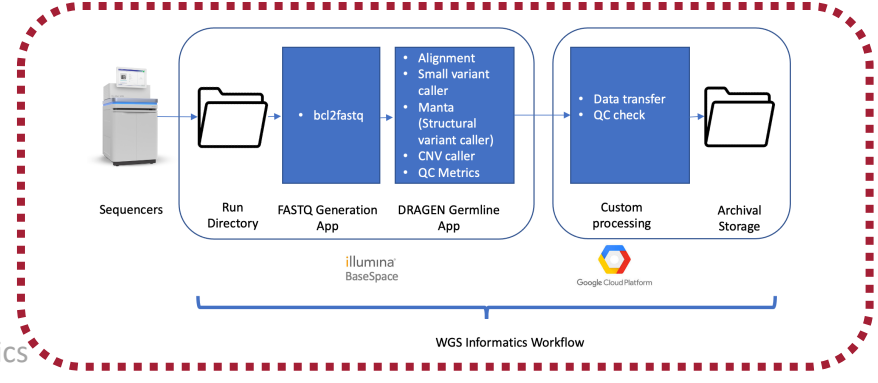
Clinical Genomics Laboratory: Infrastructure

Clinical Genotyping

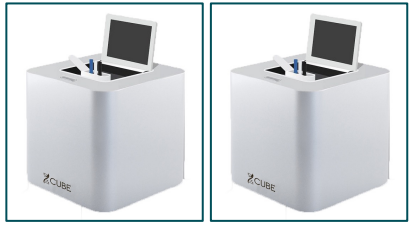
Clinical Short-Read Sequencing

Clinical Long-Read Sequencing

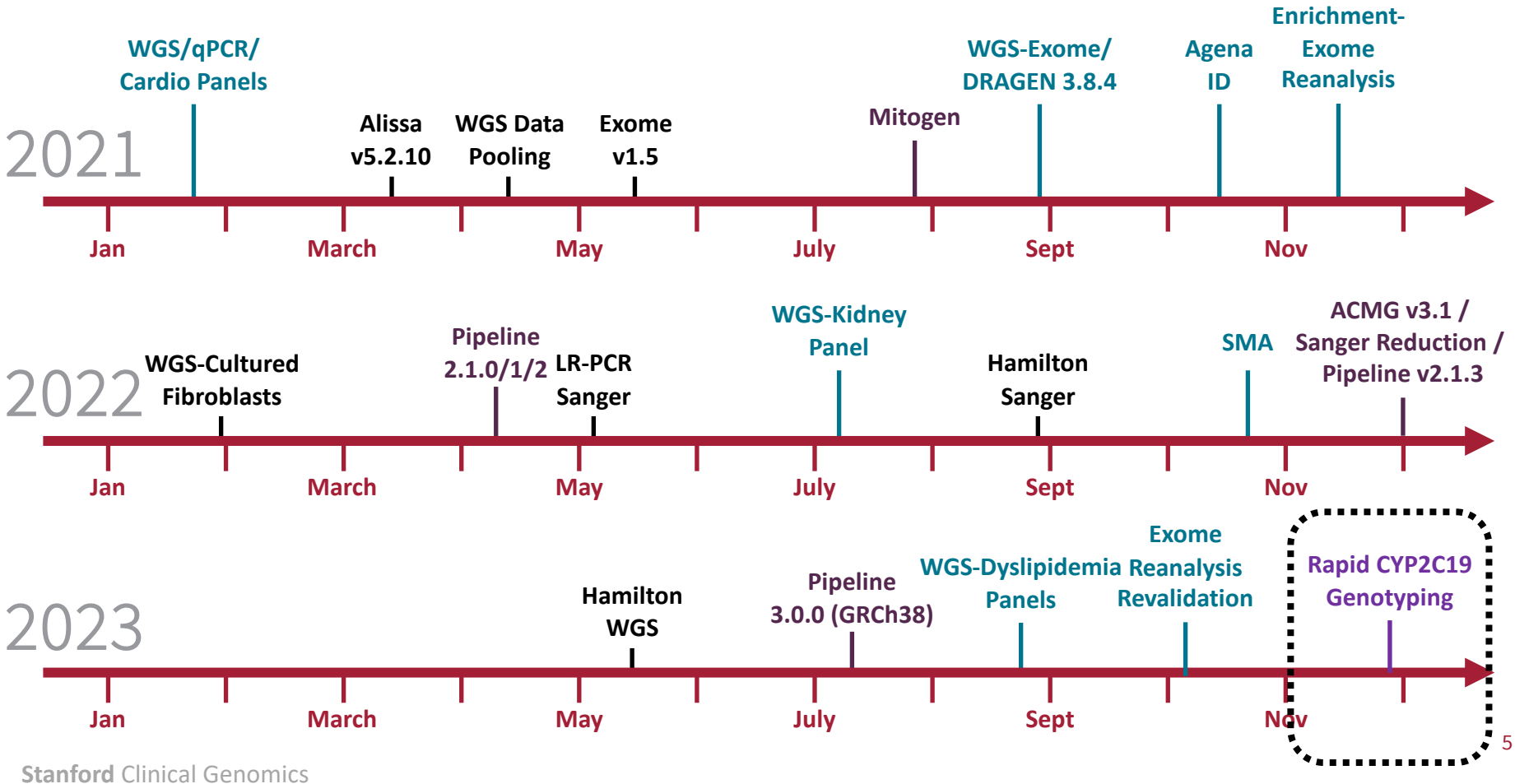
Computation



Clinical Genotyping

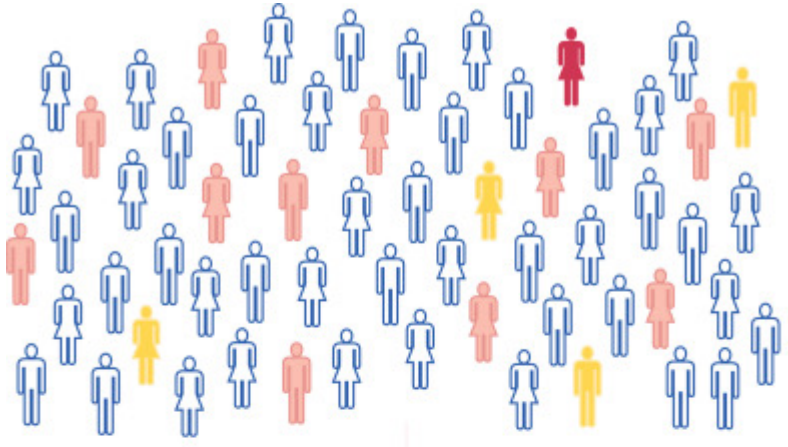


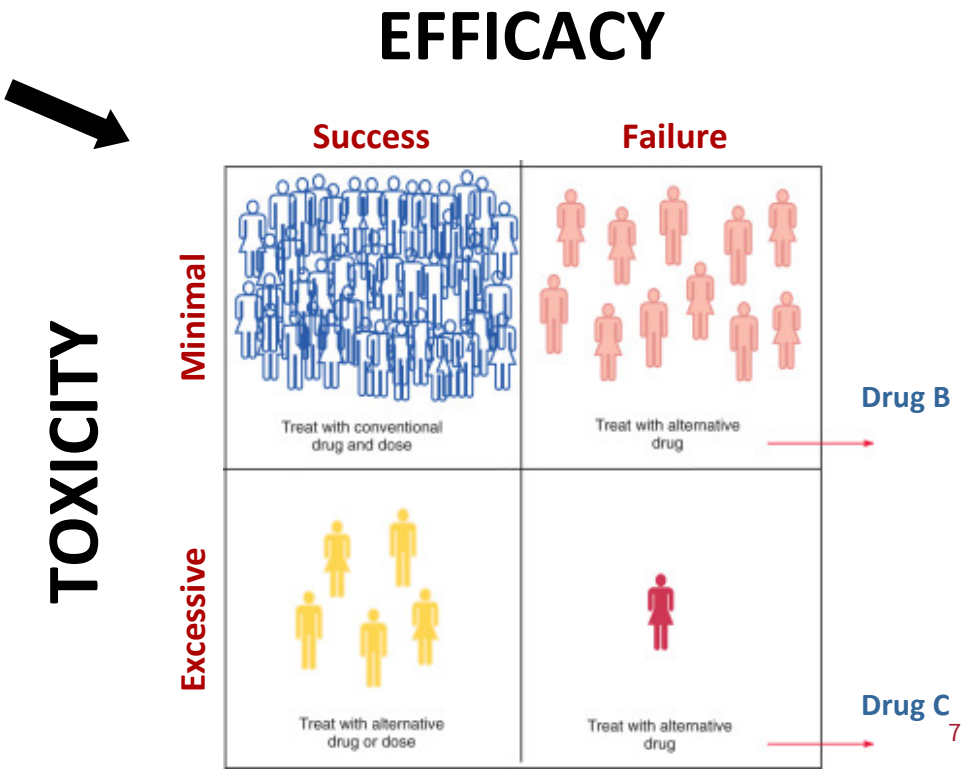
Clinical Genomics Laboratory: 2021-present



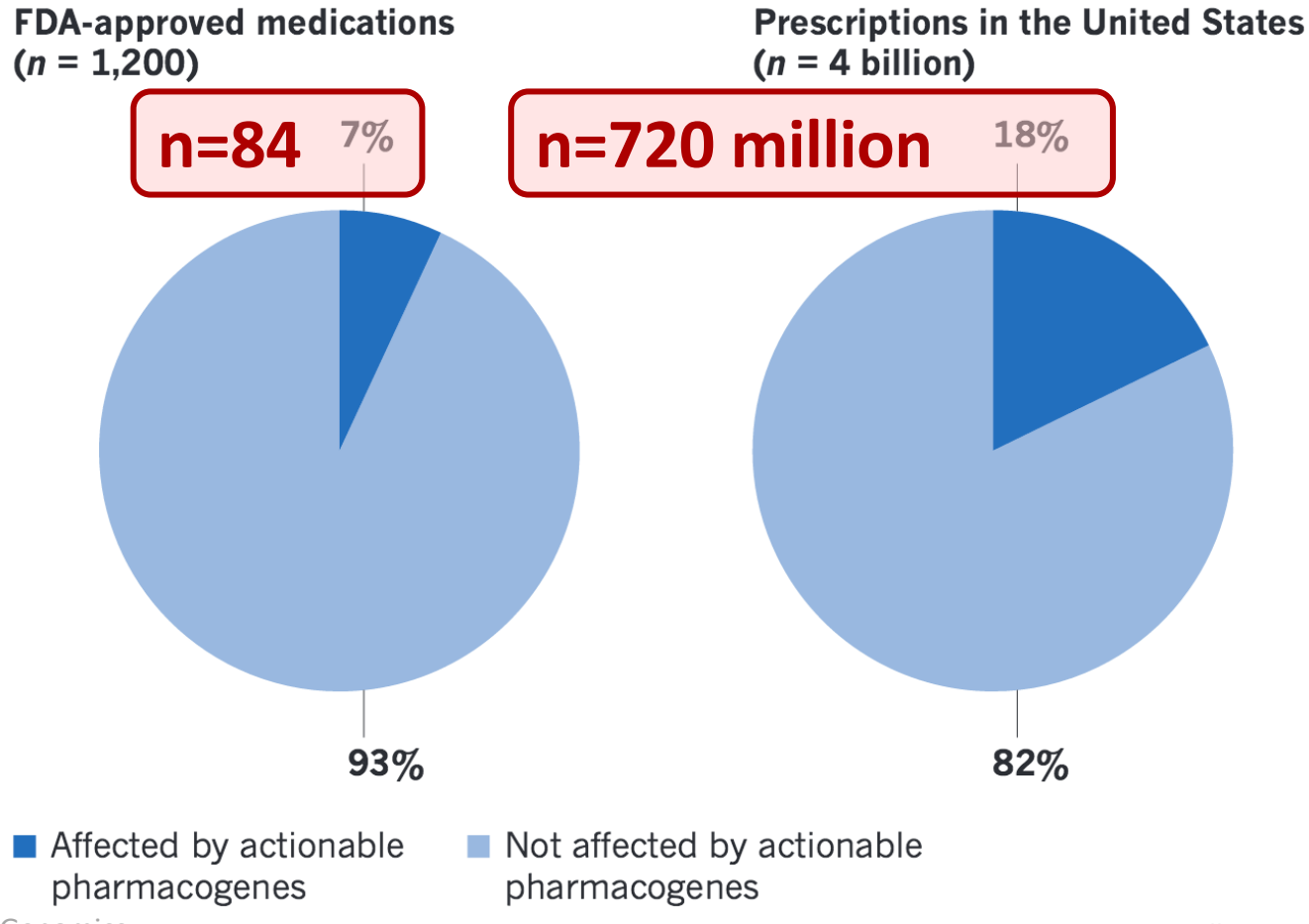
Introduction to Pharmacogenomics

Pharmacogenomics: Stratifying Patients





Pharmacogenomics: Actionable Drugs



Relling MV, Evans WE. Nature, 2015.

Cytochrome P450 Enzymes

- CYP450s: a large diverse superfamily of hemoproteins that catalyze hydroxylation and other metabolic reactions.
  - Exogenous and endogenous compounds
  - MAJOR enzymes involved in drug metabolism and bioactivation
  - HIGHLY polymorphic: *pharmvar.org*

- >60 different CYP450 genes and pseudogenes.

- ~40% of drug metabolism is carried out primarily by CYP2C9, CYP2C19, and CYP2D6.

Cytochrome P450 Enzymes: Nomenclature

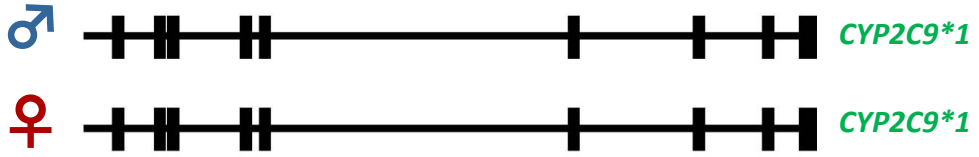
- Many pharmacogenomic genes, including the *CYP450s*, use the star (*) allele nomenclature system: *pharmvar.org*

- Important to note that although initial definitions were often based on single variants (coding), pharmacogenomic star (*) alleles are actually intended to define FULL-GENE HAPLOTYPES.

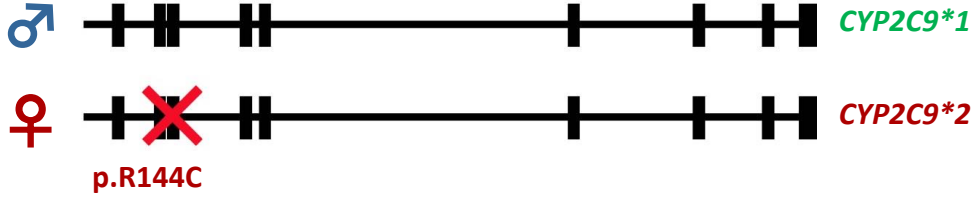
Star (*) allele example: *CYP2C19*2*

CYP450 Nomenclature: Phenotypes

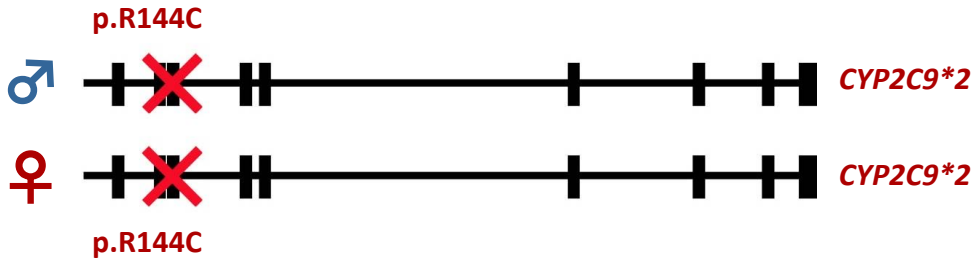
Normal Metabolizer (NM):



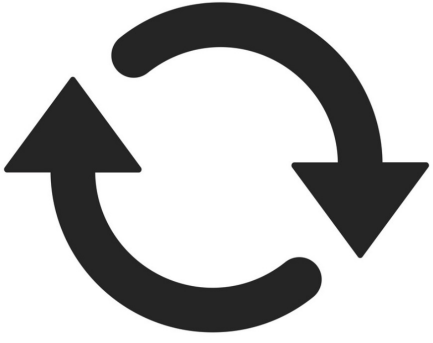
Intermediate Metabolizer (IM):



Poor Metabolizer (PM):



Pharmacogenomic Testing Resources



Pharmacogenomic Resources

- Significant increases in the availability of clinical pharmacogenomic testing RESOURCES have emerged over the past 10 years.

PharmGKB

PGRN Hub

FDA U.S. FOOD & DRUG ADMINISTRATION

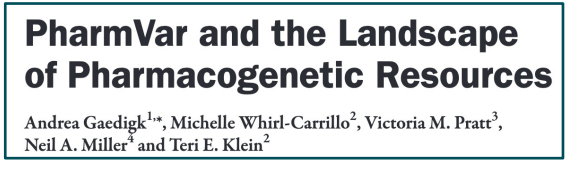
CPIC™ Clinical Pharmacogenetics Implementation Consortium

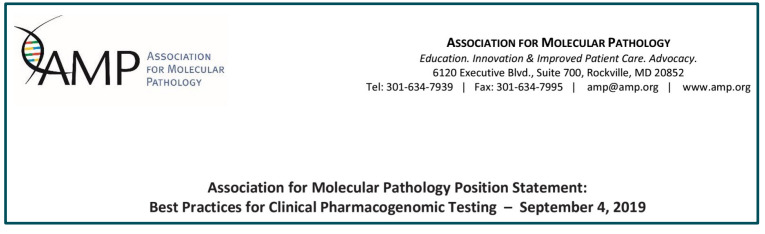
Pharmcat

AMP Association for Molecular Pathology

PharmVar Pharmacogene Variation Consortium

GeT-RM Genetic Testing Reference Materials PROGRAM



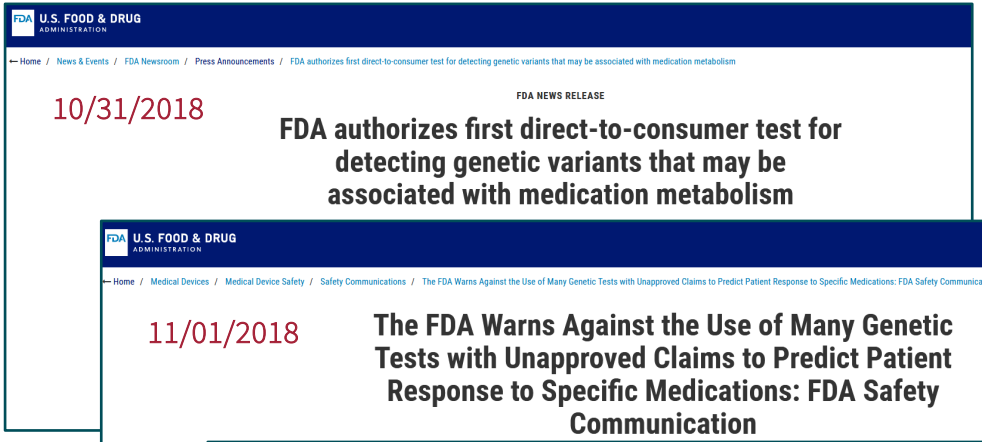


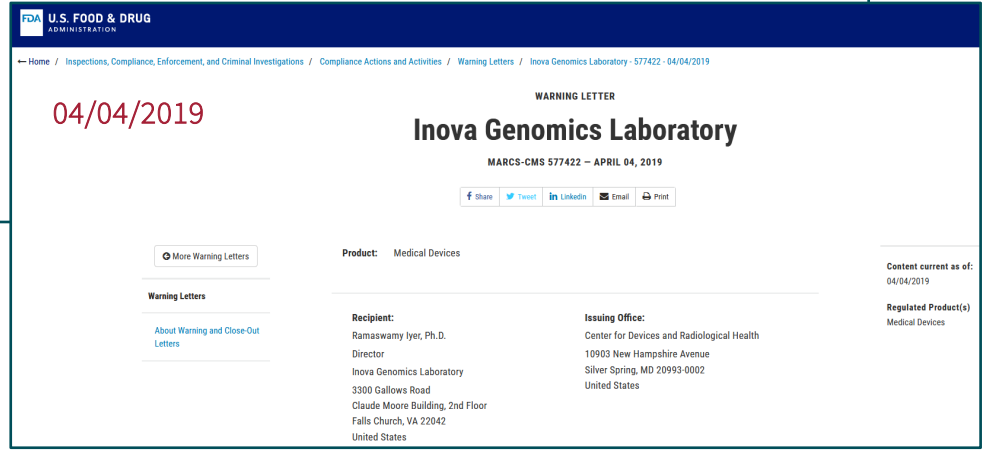
COLLEGE of AMERICAN PATHOLOGISTS

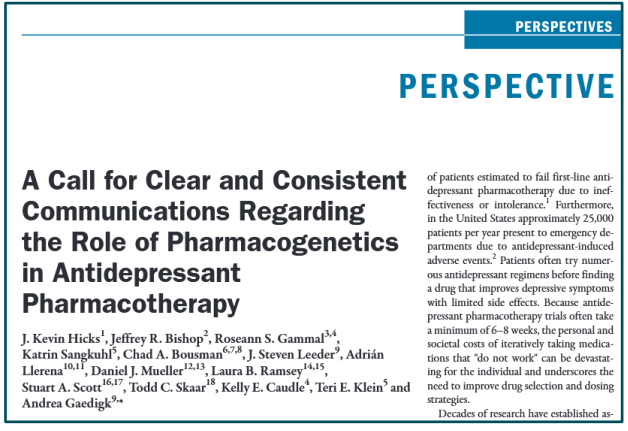
ACMG American College of Medical Genetics and Genomics

Gaedigk A, et al. Clin Pharmacol Ther, 2020.

Pharmacogenomic Resources: FDA 2018-2020







Hicks JK, et al. Clin Pharmacol Ther, 2020.

Pharmacogenomic Resources: FDA 2020-2023

U.S. FOOD & DRUG ADMINISTRATION

Home / Medical Devices / Products and Medical Procedures / In Vitro Diagnostics / Precision Medicine / Table of Pharmacogenetic Associations

Table of Pharmacogenetic Associations

Precision Medicine

Table of Pharmacogenetic Associations

Section 1: Pharmacogenetic Associations for which the Data Support Therapeutic Management Recommendations

Drug	Gene	Affected Subgroups+	Description of Gene-Drug Interaction
Abacavir	HLA-B	*57: posi	
Amifampridine	NAT2	poor meta	
Amifampridine Phosphate	NAT2	poor meta	
Amphetamine	CYP2D6	poor meta	

Section 2: Pharmacogenetic Associations for which the Data Indicate a Potential Impact on Safety or Response

Drug	Gene	Affected Subgroups+	Description of Gene-Drug Interaction
Allopurinol			
Carbamazepine			
Carvedilol			
Cevimeline			

Section 3: Pharmacogenetic Associations for which the Data Demonstrate a Potential Impact on Pharmacokinetic Properties Only

The impact of these genetic variants or genetic variant inferred phenotypes on the safety or response of the corresponding drug has not been established.

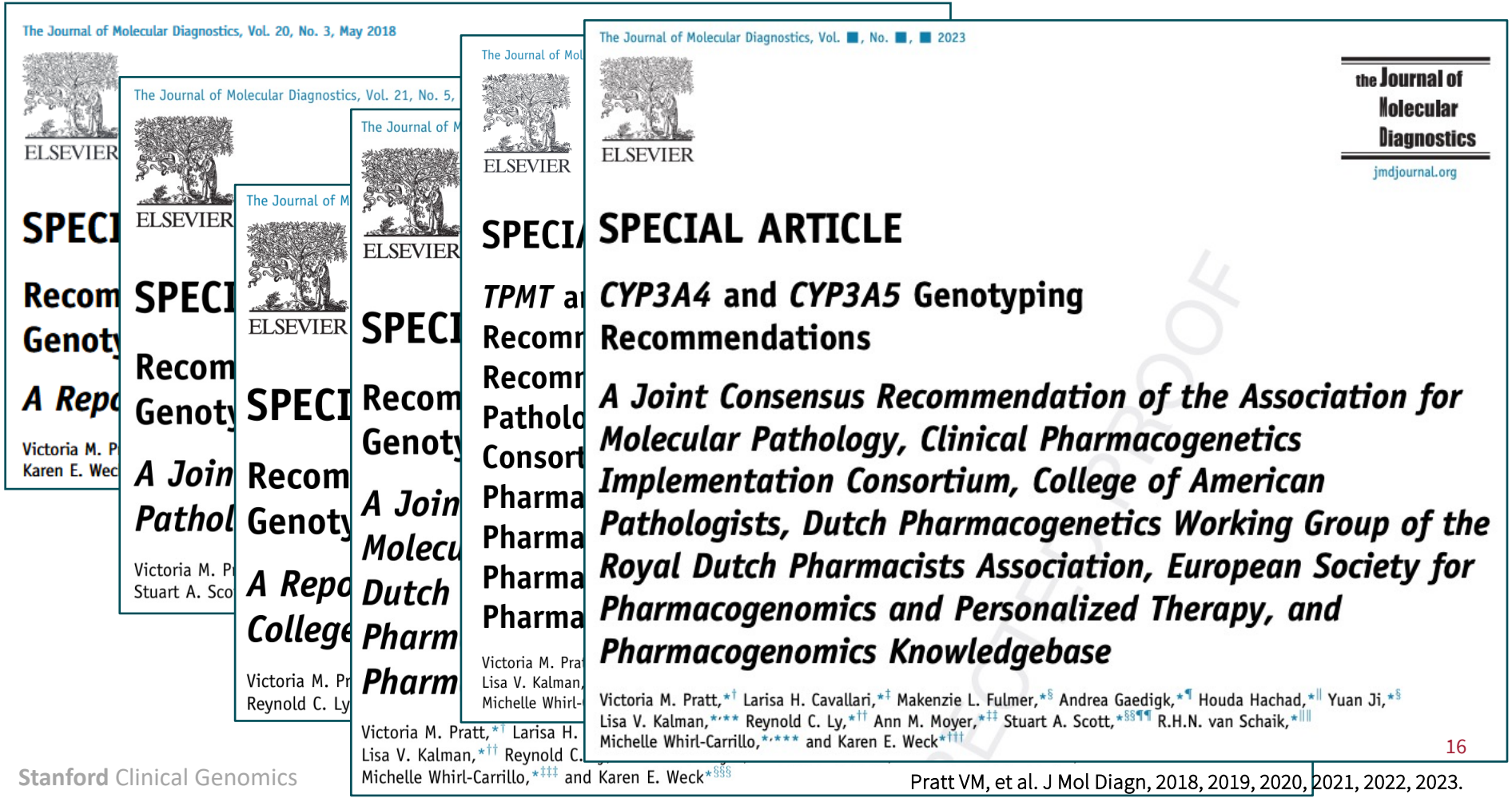
Drug	Gene	Affected Subgroups+	Description of Gene-Drug Interaction
Amitriptyline	CYP2D6	ultrarapid, intermediate, or poor metabolizers	May alter systemic concentrations.
Amoxapine	CYP2D6	ultrarapid, intermediate, or poor metabolizers	May alter systemic concentrations.

Pharmacogenetic Gene-Drug Associations: FDA Perspective on What Physicians Need to Know

Wendy S. Rubinstein, MD, PhD, and Michael Pacanowski, PharmD, MPH, U.S. Food and Drug Administration, Silver Spring, Maryland

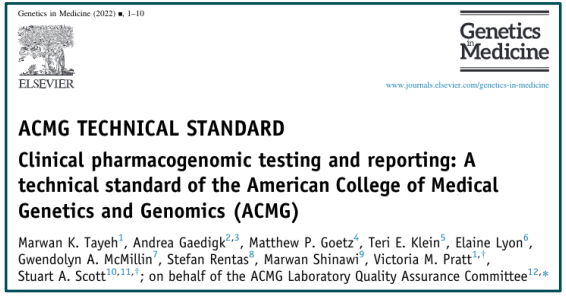
Rubinstein WS, Pacanowski M. Am Fam Physician, 2021.

Pharmacogenomic Resources:



Pratt VM, et al. J Mol Diagn, 2018, 2019, 2020, 2021, 2022, 2023.

Pharmacogenomic Resources:



Genetics in Medicine (2022) ■, 1–10

ELSEVIER

Genetics in Medicine

www.journals.elsevier.com/genetics-in-medicine

ACMG TECHNICAL STANDARD

Clinical pharmacogenomic testing and reporting: A technical standard of the American College of Medical Genetics and Genomics (ACMG)

Marwan K. Tayeh[1], Andrea Gaedigk[2,3], Matthew P. Goetz[4], Teri E. Klein[5], Elaine Lyon[6], Gwendolyn A. McMillin[7], Stefan Rentas[8], Marwan Shinawi[9], Victoria M. Pratt[1,†], Stuart A. Scott[10,11,†]; on behalf of the ACMG Laboratory Quality Assurance Committee[12,*]

1. **Nomenclature**
2. **Methodologies**
    1. Genotyping
    2. Exome/Genome
    3. CNV Interrogation
3. **Validation**
    1. Performance
    2. Specimens
    3. Reference Materials
4. **Reporting/Interpretation**
    1. Reporting
    2. Phenotype Prediction
    3. Clinical Interpretation

ACMG recommendations for pharmacogenomic result interpretation and reporting include the following:

- Provide a list of medications that may be affected by the identified genotype.
- Provide a list of resources that could inform actionable decisions (e.g., FDA tables, CPIC guidelines).
- Include FDA therapeutic management recommendations in the clinical pharmacogenomic test report that currently have supportive evidence.
- Others...

Tayeh MK, et al. Genet Med, 2022.

Pharmacogenomic Resources:

CPIC™ Clinical Pharmacogenetics Implementation Consortium

- Aim to facilitate PGx clinical implementation through clinician education and other initiatives.
- Publish practice guidelines without any recommendation FOR or AGAINST testing.

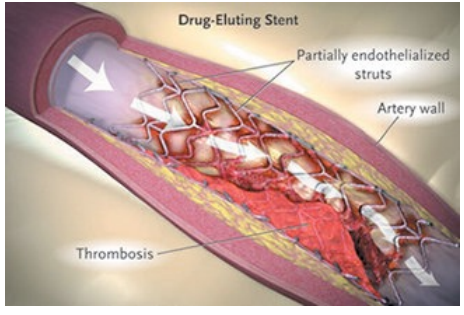
- TPMT / NUDT15 and thiopurines: Relling MV, et al., Clin Pharmacol Ther, 2011, 2013, 2019.
- CYP2C19 and clopidogrel: Scott SA, et al., Clin Pharmacol Ther, 2011, 2013, 2022.
- CYP2C9 / VKORC1 and warfarin: Johnson JA, et al., Clin Pharmacol Ther, 2011, 2017.
- CYP2D6 and opioids: Krews K, et al., Clin Pharmacol Ther, 2012, 2014, 2020.
- HLA-B and abacavir: Martin MA, et al., Clin Pharmacol Ther, 2012, 2014.
- SLCO1B1, ABCG2, CYP2C9 and statins: Wilke RA, et al., Clin Pharmacol Ther, 2012, 2014, 2022.
- HLA-B and allopurinol: Hershfield MS, et al., Clin Pharmacol Ther, 2012, 2015.
- CYP2D6 / CYP2C19 and TCAs: Hicks JK, et al., Clin Pharmacol Ther, 2013, 2016.
- HLA-B and carbamazepine: Leckband SG, et al., Clin Pharmacol Ther, 2013, 2018.
- DPYD and fluoropyrimidines: Caudle KE, et al., Clin Pharmacol Ther, 2013, 2017.
- IFNL3 (IL28B) and interferon-α: Muir AJ, et al., Clin Pharmacol Ther, 2014.
- CFTR and ivacaftor: Clancy JP, et al., Clin Pharmacol Ther, 2014.
- G6PD and rasburicase: Relling MV, et al., Clin Pharmacol Ther, 2014, 2023.
- CYP2C9 / HLA-B and phenytoin: Caudle KE, et al., Clin Pharmacol Ther, 2014, 2020.
- CYP3A5 and tacrolimus: Birdwell KA, et al., Clin Pharmacol Ther, 2015.
- CYP2D6 / CYP2C19 and SSRIs: Hicks JK, et al., Clin Pharmacol Ther, 2015, 2023.
- UGT1A1 and atazanavir: Gammal RS, et al., Clin Pharmacol Ther, 2016.
- CYP2C19 and voriconazole: Moriyama B, et al., Clin Pharmacol Ther, 2016.
- CYP2D6 and ondansetron / tropisetron: Bell GC, et al., Clin Pharmacol Ther, 2017.
- CYP2D6 and tamoxifen: Goetz MP, et al., Clin Pharmacol Ther, 2018.
- RYR1 / CACNA1S and succinylcholine: Gonsalves SG, et al., Clin Pharmacol Ther, 2019.
- CYP2D6 and atomoxetine: Brown JT, et al., Clin Pharmacol Ther, 2019.
- CYP2B6 and efavirenz: Desta Z, et al., Clin Pharmacol Ther, 2019.
- CYP2C9 and NSAIDs: Theken KN, et al., Clin Pharmacol Ther, 2020.
- CYP2C19 and PPIs: Lima JJ, et al., Clin Pharmacol Ther, 2020.
- MT-RNR1 and aminoglycosides: McDermott JH, et al., Clin Pharmacol Ther, 2021.

Relling MV, Klein TE. Clin Pharmacol Ther, 2011, 2020.

CYP2C19 and Antiplatelet Therapy

Clopidogrel: Dual Antiplatelet Therapy

- Antiplatelet therapy (clopidogrel + aspirin) is a common treatment for patients with acute coronary syndromes (ACS) and/or undergoing percutaneous coronary interventions (PCI).
  - Inhibits blood clots for prevention of stent thrombosis

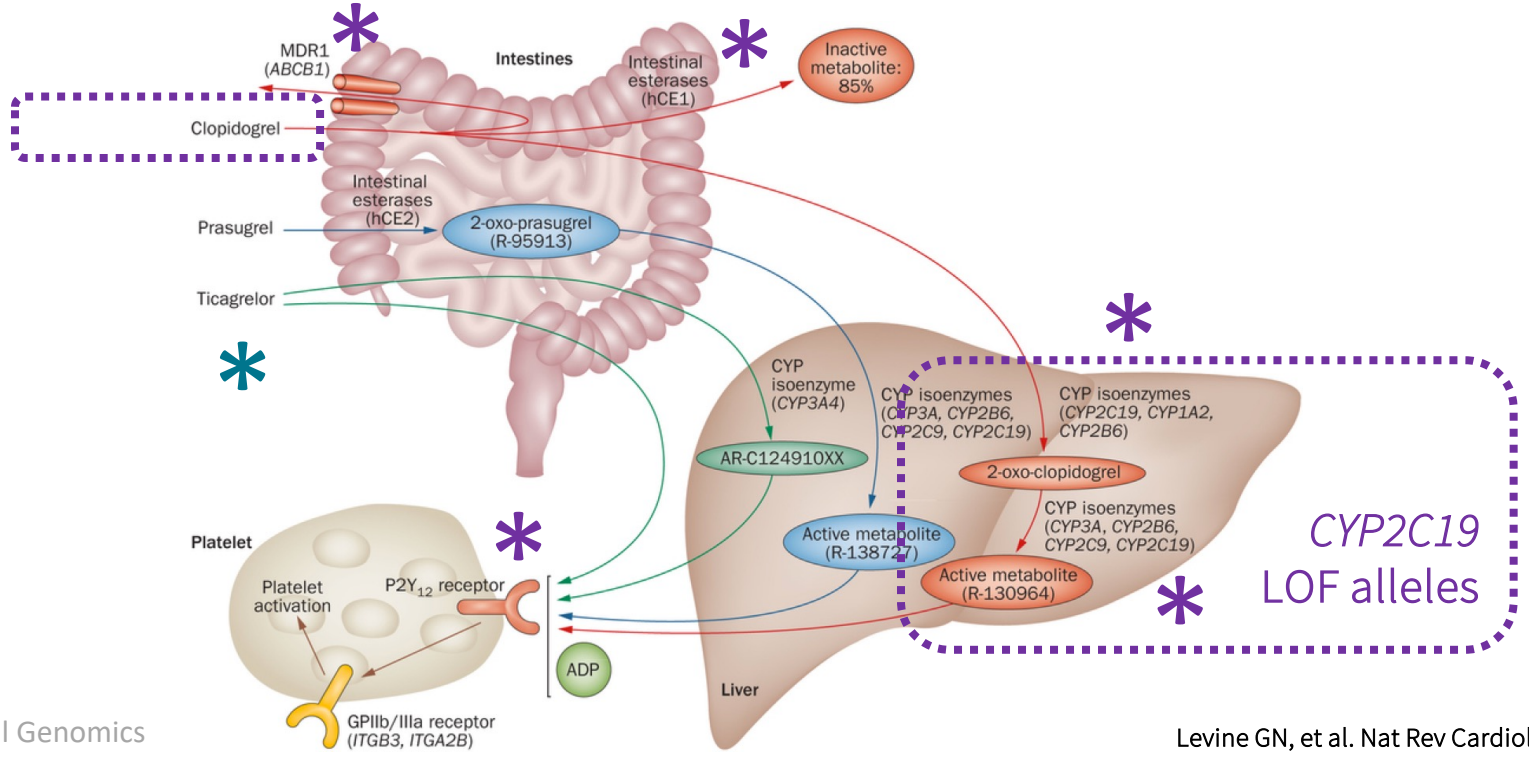


- Variable response is observed among patients.
  - Pharmacokinetics: metabolites
  - Pharmacodynamics: *ex vivo* platelet aggregation

- A considerable fraction of ACS/PCI patients continue to have serious cardiovascular events during treatment.
  - MACE
  - Stent thrombosis

Clopidogrel Metabolism: Bioactivation

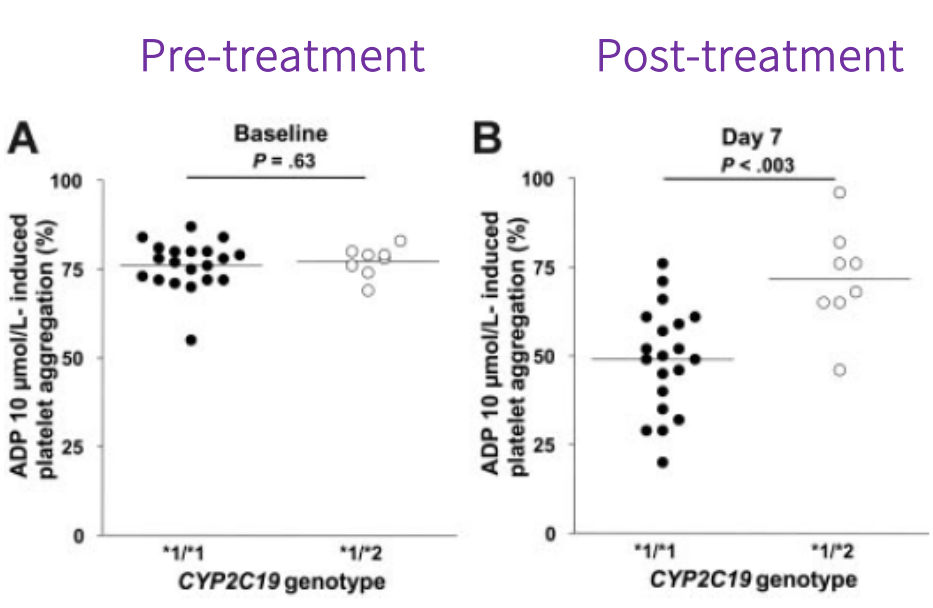
- Antiplatelets: aspirin, clopidogrel, prasugrel, ticagrelor.
  - Indications: ACS, PCI, symptomatic PAD, ischemic stroke
  - Variable response: PK, PD, clinical outcomes



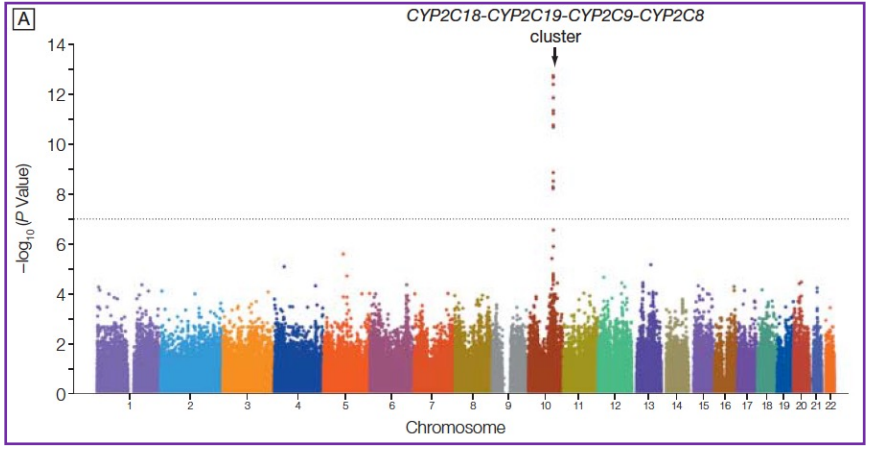
Levine GN, et al. Nat Rev Cardiol, 2014.

Clopidogrel Pharmacogenomics: ACS/PCI

Candidate gene studies:



GWAS:



Hulot JS, et al. Blood, 2006; Shuldiner AR, et al. JAMA, 2009.

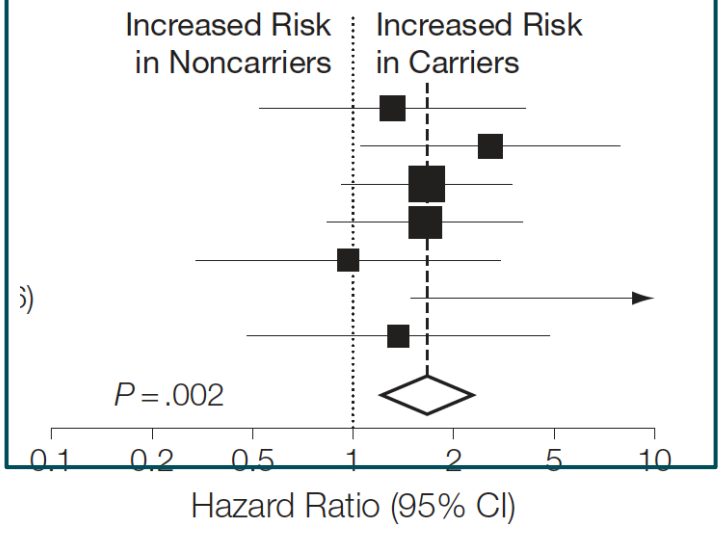
Clopidogrel Pharmacogenomics: ACS/PCI

- Meta analyses on patient cohorts with high frequencies of PCI:

CV death, MI, or stroke:

***1/*2: HR, 1.55; P = .01**

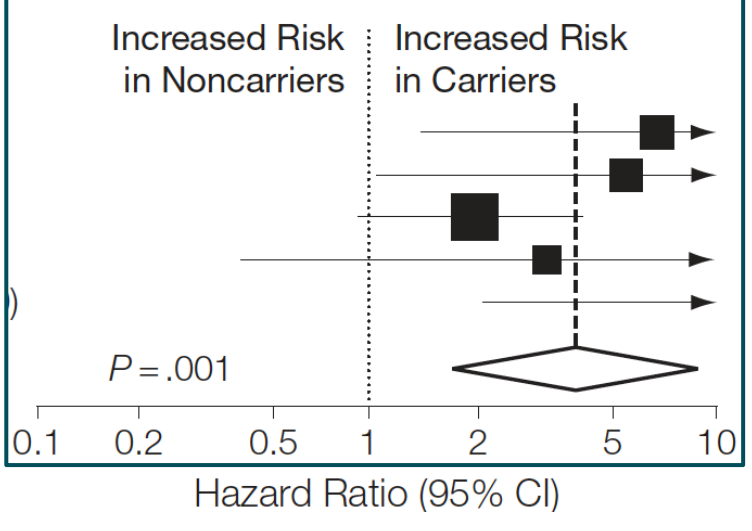
***2/*2: HR, 1.76; P = .002**



Stent thrombosis:

***1/*2: HR, 2.67; P < .0001**

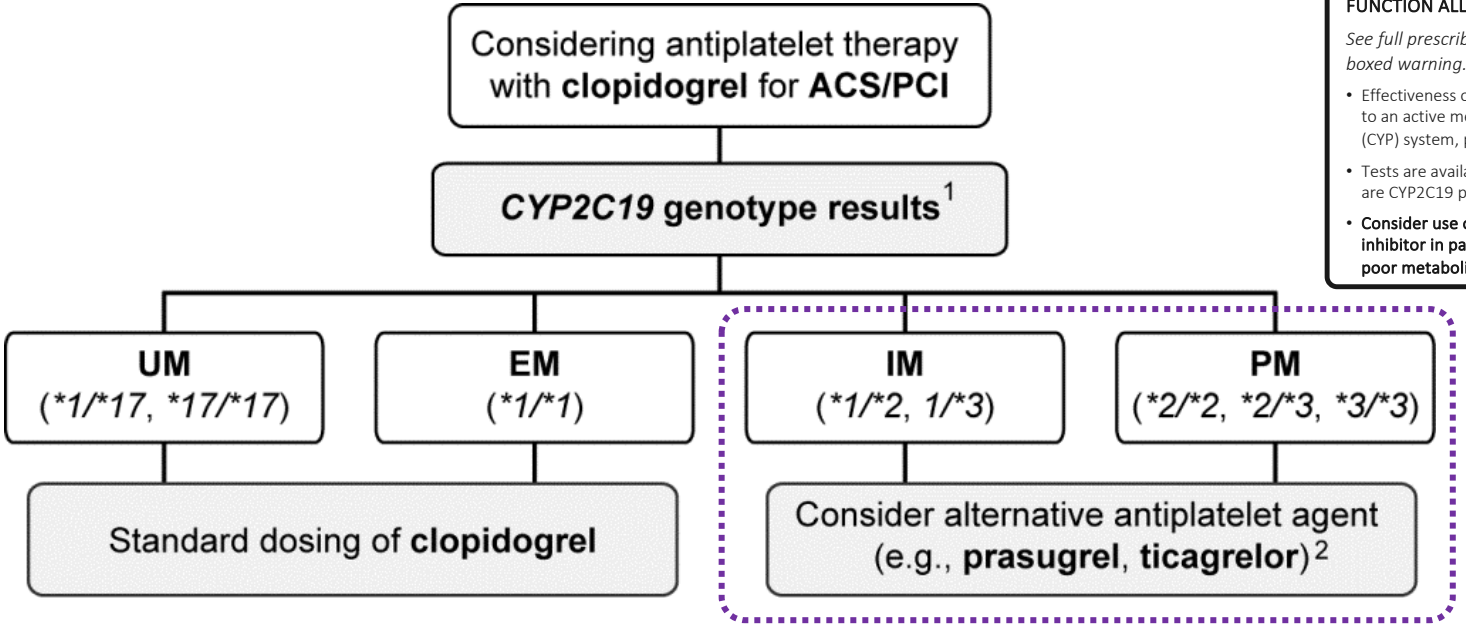
***2/*2: HR, 3.97; P = .001**



Mega JL, et al. JAMA, 2010.

Clopidogrel Pharmacogenomics: CPIC

- CPIC 2011, 2013:



FDA Black Box Warning

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

See full prescribing information for complete boxed warning.

- Effectiveness of Plavix depends on conversion to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19.
- Tests are available to identify patients who are CYP2C19 poor metabolizers.
- **Consider use of another platelet P2Y12 inhibitor in patients identified as CYP2C19 poor metabolizers.**

- Recommend an alternative antiplatelet agent for ACS/PCI patients who are *CYP2C19* loss-of-function allele (e.g., *2, *3) carriers.

Scott SA, et al. Clin Pharmacol Ther, 2011, 2013.

CYP2C19 and Antiplatelet Therapy

Neurovascular Indications

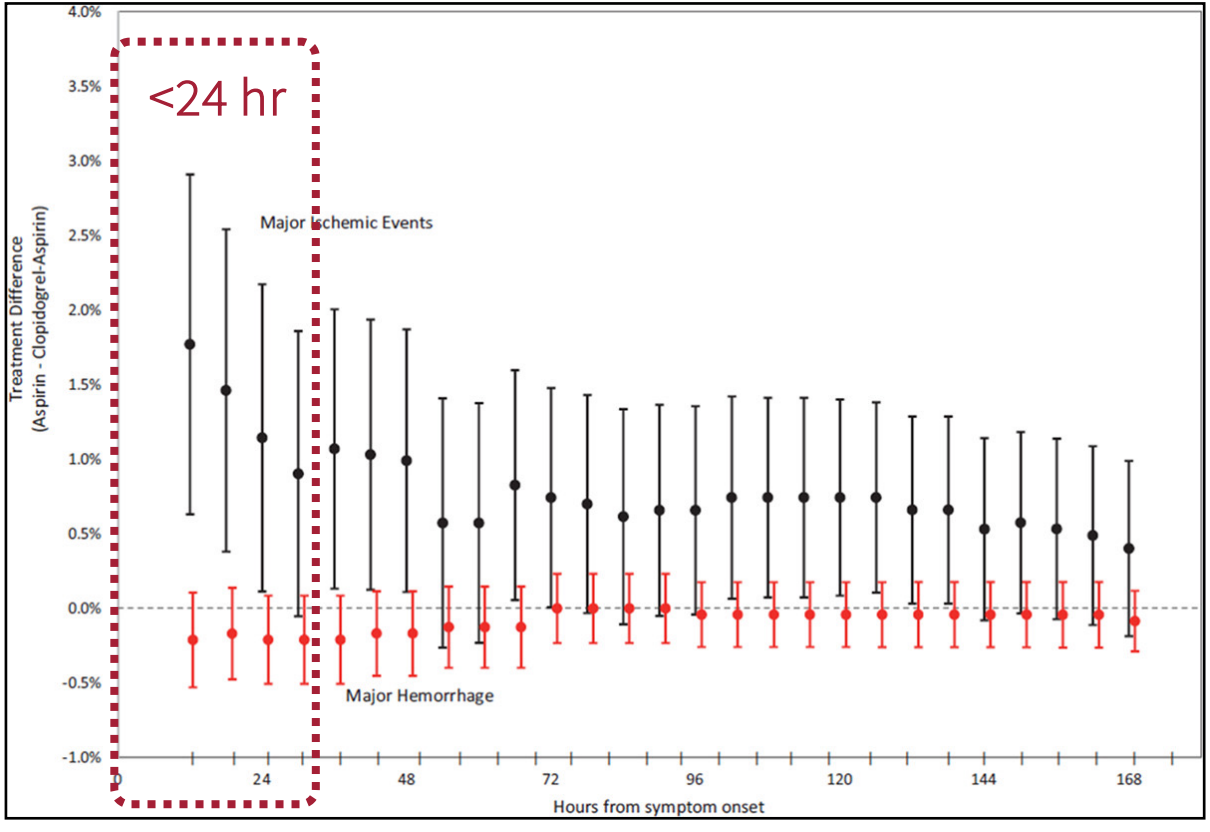
Clopidogrel: Stroke / TIA

- When patients arrive at the ER with a major stroke, they are put on aspirin immediately and clopidogrel within the first two weeks.
- When patients arrive at the ER with a minor stroke or transient ischemic attack (TIA), they are put on aspirin and clopidogrel within the first 12-24 hours to prevent a secondary stroke.
- Dual anti-platelet therapy (DAPT) is now standard of care in minor stroke/TIA.
- Ticagrelor is an alternative to clopidogrel, but it is more potent and has a higher bleeding risk, preventing it from becoming first line.

Kleindorfer DO, et al. Stroke, 2021.

Clopidogrel: Stroke / TIA

- First 24 hours are critical with highest rate of major ischemic events.



- Stroke Risk
- Bleeding Risk

Johnston SC, et al. Circulation, 2019.

Clopidogrel: Stroke / TIA

- Are *CYP2C19* LoF alleles enriched among recurrent stroke patients?
  - Yes.
- In a clopidogrel-treated population with recurrent cerebral ischemia, the frequency of *CYP2C19* LoF alleles was significantly higher than in ancestrally matched healthy controls, especially among patients with early recurrent events.
  - Recurrent Ischemia: 43.9% with 1 or 2 LOF alleles
  - Control Population: 24.7% with 1 or 2 LOF alleles

Minderhoud C, et al. Br J Clin Pharmacol, 2022.

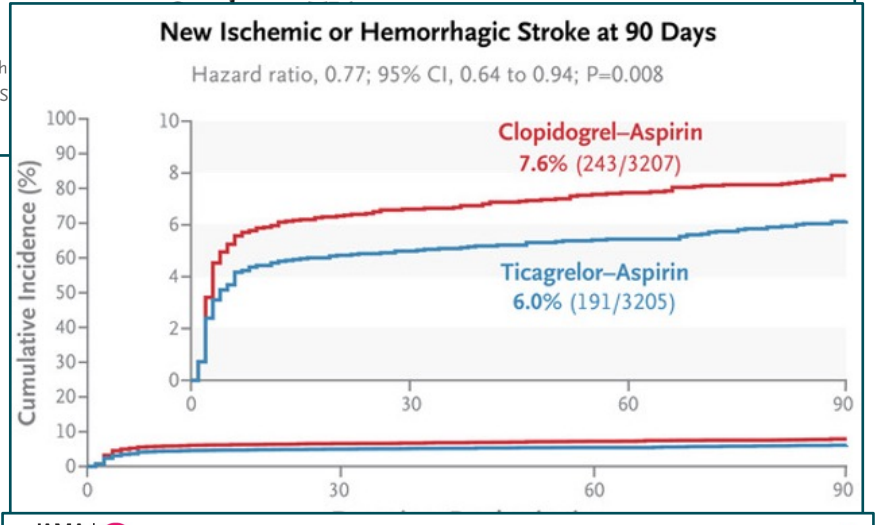
Clopidogrel: Stroke / TIA

- CHANCE-2 Trial:

ORIGINAL ARTICLE

Ticagrelor versus Clopidogrel in *CYP2C19* Loss-of-Function Carriers with

Yongjun Wang, M.D., Xia Meng, M.D., Ph
Li, Ph.D., Philip M. Bath, D.Sc., F.Med.S



- *CYP2C19* LoF patients treated with ticagrelor had a 21% REDUCTION in secondary strokes compared to clopidogrel.
- The reduction of secondary strokes predominantly occurred IN THE FIRST WEEK.
- Ticagrelor may be more effective in BOTH CYP2C19 PMs AND IMs.

JAMA Network | Open

Original Investigation | Neurology

Association of *CYP2C19* Loss-of-Function Metabolizer Status With Stroke Risk Among Chinese Patients Treated With Ticagrelor-Aspirin vs Clopidogrel-Aspirin
A Prespecified Secondary Analysis of a Randomized Clinical Trial

Xuewei Xie, MD, PhD; S. Claiborne Johnston, MD, PhD; Anxin Wang, PhD; Qin Xu, PhD; Philip M. Bath, DSc; Yuesong Pan, PhD; Hao Li, MD, PhD; Jinxi Lin, MD, PhD; Yilong Wang, MD, PhD; Xingquan Zhao, MD, PhD; Zixiao Li, MD, PhD; Yong Jiang, MD, PhD; Liping Liu, MD, PhD; Anding Xu, MD, PhD; Jing Jing, MD, PhD; Xia Meng, MD; Yongjun Wang, MD

Wang Y, et al. NEJM, 2021; Pan Y, et al. JAMA Neurol. 2022; Xie X, et al. JAMA New Open, 2023.

Clopidogrel Pharmacogenomics: CPIC

- CPIC 2022:

The available evidence expanded the previous recommendations to INCLUDE neurovascular indications.

CPIC UPDATE

Clinical Pharmacogenetics Implementation Consortium Guideline for *CYP2C19* Genotype and Clopidogrel Therapy: 2022 Update

Craig R. Lee[1], Jasmine A. Luzum[2], Katrin Sangkuhl[3], Roseann S. Gammal[4,5], Marc S. Sabatine[6], Charles Michael Stein[7], David F. Kisor[8], Nita A. Limdi[9], Yee Ming Lee[10], Stuart A. Scott[11,12], Jean-Sébastien Hulot[13], Dan M. Roden[14], Andrea Gaedigk[15], Kelly E. Caudle[5], Teri E. Klein[3], Julie A. Johnson[16] and Alan R. Shuldiner[17,*]

Predicted phenotype	Genotype	Examples of *CYP2C19* diplotypes[a]
CYP2C19 ultrarapid metabolizer	An individual carrying two increased function alleles	**17/*17*
CYP2C19 rapid metabolizer	An individual carrying one normal function allele and one increased function allele	**1/*17*
CYP2C19 normal metabolizer	An individual carrying two normal function alleles	**1/*1*
CYP2C19 intermediate metabolizer	An individual carrying one normal function allele and one no function allele or one increased function allele and one no function allele	**1/*2, *1/*3, *2/*17, *3/*17*
CYP2C19 poor metabolizer	An individual carrying two no function alleles	**2/*2, *3/*3, *2/*3*

Lee CR, et al. Clin Pharmacol Ther, 2022.

Rapid *CYP2C19* Genotyping

Rapid CYP2C19 testing: Genomadix

- *2023: SHC Clinical Genomics collaboration with SHC Neurology for rapid* CYP2C19 *genotyping to guide antiplatelet management among patients with minor stroke/TIA.*

Fast

- ~1 hour turnaround time
- Direct PCR results
- Alleles *2, *3, and *17

Accurate

- 99.1% accuracy vs. bidirectional sequencing
- Irreversible tube sealing prevents contamination

Easy

- Buccal swab
- No DNA extraction
- No end user calibration
- No end user maintenance

FDA Cleared

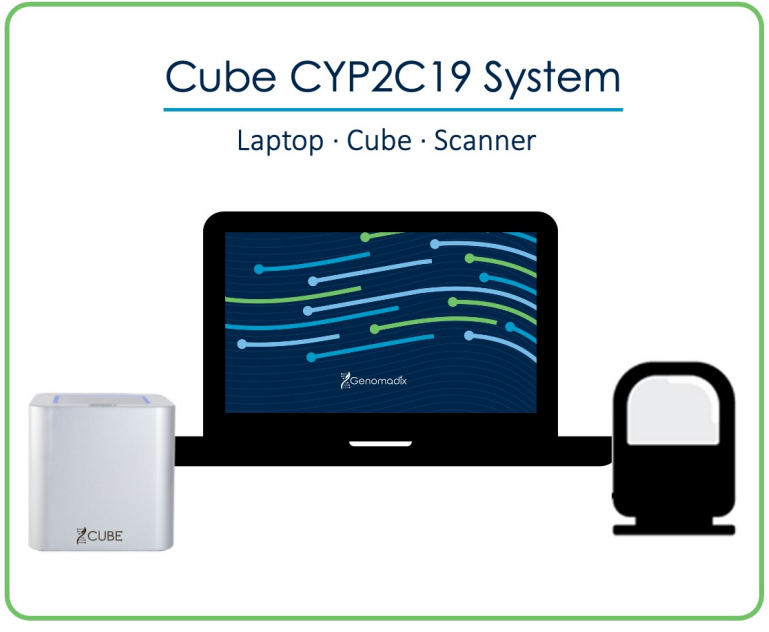
- 510k cleared
- Moderate complexity

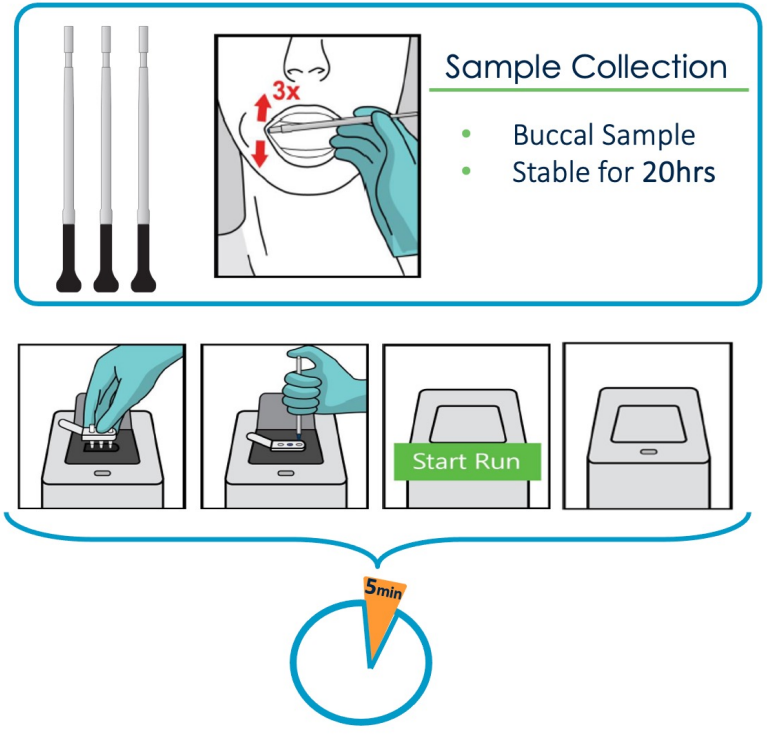
Portable

- Genomadix Cube™
- 4” x 4”

Rapid CYP2C19 testing: Genomadix

- *2023: SHC Clinical Genomics collaboration with SHC Neurology for rapid* CYP2C19 *genotyping to guide antiplatelet management among patients with minor stroke/TIA.*





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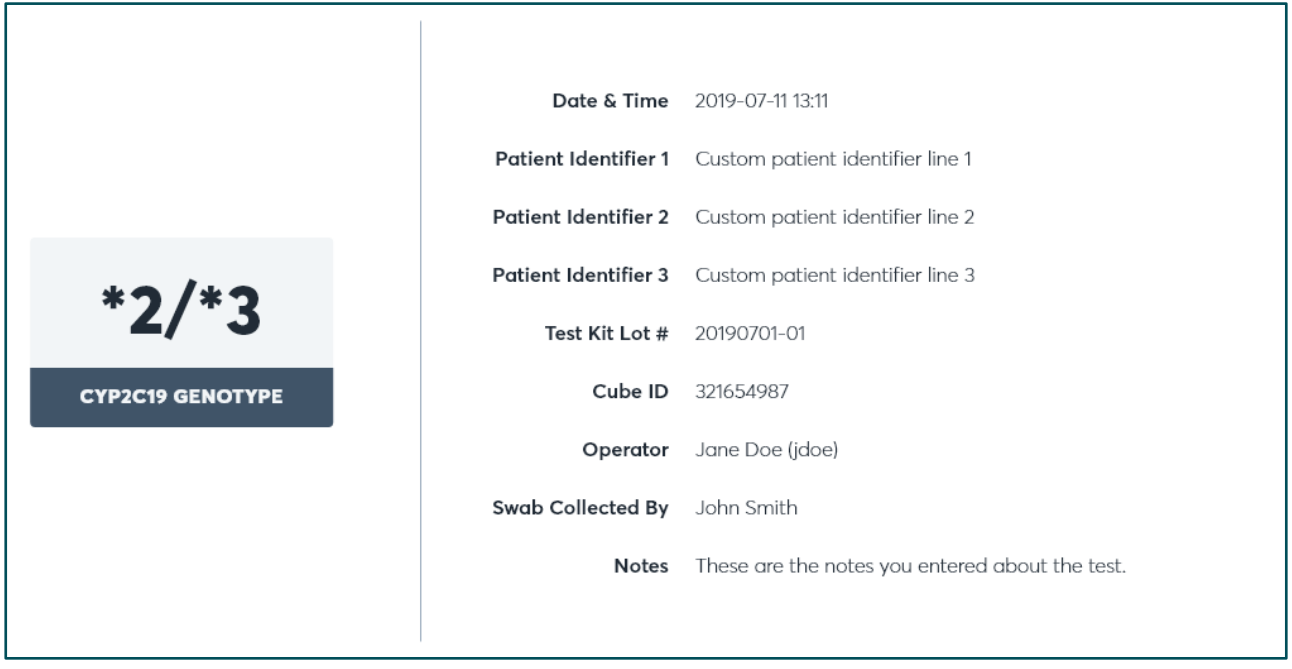
- Assay output:



Rapid CYP2C19 testing: Genomadix

- Assay Performance (FDA submission):

Method Comparison (Genotype accuracy compared to Sanger sequencing)

End User Study	Samples Tested	# INC/PSC	Incorrect Calls	Correct Call	% Agreement	95% Two-sided Confidence Lower Limit	95% One-sided Confidence Lower Limit
Method Comparison First Pass	433	17	2	414	95.6%	93.2%	93.7%
Method Comparison Final	433	2	2	429	**99.1%**	**97.6%**	98.0%

Site to Site Reproducibility

End User Study	Samples Tested	# INC/PSC	Incorrect Calls	Correct Call	% Agreement	95% Two-sided Confidence Lower Limit	95% One-sided Confidence Lower Limit
Reproducibility First Pass	960	9	0	951	99.1%	98.2%	98.4%
Reproducibility Final	960	3	0	957	**99.7%**	**99.1%**	99.2%

Rapid CYP2C19 testing: Genomadix

- Reportable Range:
  - CYP2C19*2: GRCh38.p14 chr 10; rs4244285.
    NC_000010.11:g.94781859G>A; NM_000769.4:c.681G>A; NP_000760.1:p.Pro227=
  - CYP2C19*3: GRCh38.p14 chr 10; rs4986893.
    NC_000010.11:g.94780653G>A; NM_000769.4:c.636G>A; NP_000760.1:p.Trp212Ter
  - CYP2C19*17: GRCh38.p14 chr 10; rs12248560.
    NC_000010.11:g.94761900C>T; NM_000769.4: c.-806C>T

- Reference Range (Reference Interval):

CYP2C19 Diplotype	CYP2C19 Metabolizer Phenotype
*17/*17	Ultrarapid Metabolizer
*1/*17	Rapid Metabolizer
*1/*1	Normal Metabolizer
*1/*2	Intermediate Metabolizer
*1/*3	Intermediate Metabolizer
*2/*17	Intermediate Metabolizer
*3/*17	Intermediate Metabolizer
*2/*2	Poor Metabolizer
*2/*3	Poor Metabolizer
*3/*3	Poor Metabolizer

Rapid CYP2C19 testing: Genomadix

- Analytical Accuracy (Cubes A and B):

Table 2: Summary of CYP2C19 Genotyping Accuracy Results (B20280231, Cube A)

Sample ID	Reference	Genomadix Result
HG00118_A	*1/*1	*1/*1
HG00130_A	*2/*17	*2/*17
HG00332_A	*1/*17	*1/*17
HG00437_A	*2/*2	*2/*2
HG01083_A	*1/*2	*1/*2
HG03225_A	*1/*17	*1/*17
HG03589_A	*2/*17	*2/*17
NA19315_A	*1/*2	*1/*2
NA19395_A	*1/*3	*1/*3
NA20819_A	*1/*2	*1/*2

Patient ID	Genomadix Result
CYP2C19_2	*1/*1
CYP2C19_4	*1/*2
CYP2C19_6	*1/*1
CYP2C19_8	*2/*2
CYP2C19_10	*1/*17
CYP2C19_11	*1/*2
CYP2C19_14	*17/*17
CYP	
CYP	
CYP	

Table 3: Summary of CYP2C19 Genotyping Accuracy Results (B20280483, Cube B)

Sample ID	Reference	Genomadix Result
HG00118_B	*1/*1	*1/*1
HG00130_B	*2/*17	*2/*17
HG00332_B	*1/*17	*1/*17
HG00437_B	*2/*2	*2/*2
HG01083_B	*1/*2	*1/*2
HG03225_B	*1/*17	*1/*17
HG03589_B	*2/*17	*2/*17
NA19315_B	*1/*2	*1/*2
NA19395_B	*1/*3	*1/*3
NA20819_B	*1/*2	*1/*2

Patient ID	Genomadix Result
CYP2C19_1	*2/*2
CYP2C19_3	*1/*1
CYP2C19_5	*1/*1
CYP2C19_7	*1/*1
CYP2C19_9	*2/*2
CYP2C19_12	*1/*2
CYP2C19_13	*1/*2
CYP2C19_15	*1/*1
CYP2C19_17	*1/*1
CYP2C19_19	*17/*17

Rapid CYP2C19 testing: Genomadix

- Analytical Precision (Cubes A and B):

Table 4: Summary of CYP2C19 Genotyping Reproducibility Results (B20280231, Cube A)

Date	Patient ID	Genomadix Result
9/11/23	JL_091123	*1/*2
9/12/23	JL_091223	*1/*2
9/13/23	JL_091323	*1/*2

Table 5: Summary of CYP2C19 Genotyping Reproducibility Results (B20280483, Cube B)

Date	Patient ID	Genomadix Result
9/11/23	JL_091123	*1/*2
9/12/23	JL_091223	*1/*2
9/13/23	JL_091323	*1/*2

Rapid CYP2C19 testing: Genomadix

- Stanford implementation next steps:

1. Finalize *CYP2C19* reporting language.

2. Finalize Epic order for rapid *CYP2C19* genotyping.

3. Align with SHC neurology on clinical workflows.

4. Estimated go-live in December 2023.

Rapid CYP2C19 testing: Regulatory

- Regulatory landscape for clinical *CYP2C19* genotyping:
- CPIC: Peer-reviewed guidelines in 2011, 2013 and 2022, which now include minor stroke/TIA in addition to ACS/PCI.
- FDA: Clopidogrel label has a black box warning on CYP2C19 PMs, and this gene/drug pair is listed as an FDA Table 1 association.
- CPT Code: CYP2C19 single gene testing – 81225
- CMS (Palmetto GBA): Coverage policy: CYP2C19 / 81225 / clopidogrel (Plavix) / platelet aggregation inhibitor / CPIC-FDA (source)

Summary

1. Pharmacogenomics can pre-emptively STRATIFY patients for more PRECISE medication management, including *CYP2C19* testing for antiplatelet therapy.

2. Loss-of-function *CYP2C19* alleles are associate with DECREASED EFFICACY among patients treated with clopidogrel, including both CARDIOVASCULAR and NEUROVASCULAR indications.

3. The Genomadix Cube CYP2C19 System is an FDA-cleared device that enables very rapid (<1hr) *CYP2C19* genotyping, which is highly ACCURATE and ROBUST, and can inform more PRECISE antiplatelet prescribing.

Acknowledgements

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Clinical Operations
- Allison Kerr / Rishi Seth
- Jennifer Fralick
- April Young, MHSA
- Dominique Burns, MS, HTL(ASCP)
- Annette Chen, MS

Laboratory Co-Directors
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- Jennifer Liu, MB(ASCP)
- Tina Tan, MLS(ASCP)

Bioinformatics
- Zena Ng, MS
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- Huanzhi (Steve) Shi, MS
- Pun Wai (AJ) Tong, PhD

Interpretation/GC
- Jessie Chonis, MS, CGC
- Kevin Dumas, PhD
- Dianna Fisk, PhD
- Caitlin Hale, MS, CGC
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- Caitlin Reavey, PhD
- Emma Smith, MS, CGC
- Allyson Thylin, BS (GCA)
- Katelyn Weymouth, PhD

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- Jon Bernstein, MD
- Others!

Neurology
- Neil Schwartz, MD, PhD
- Gregory J. Wong, MD
- Allan Q. Phan, MD
- Prateek B. Thatikunta, MD

PharmGKB / ClinGen
- Teri E. Klein, PhD
- Michelle Whirl-Carrillo, PhD
- Others!

Genomadix
- Jeremy Bridge-Cook, PhD
- Tara Linseman
- Gillian Parker

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