Clinical Care Implementation of Guidelines for Genomic Testing

Naveen Pereira MD, FACC, FAHA, FRCPE
Professor of Medicine, Mayo Clinic

Disclosures

- Funding
  - NHLBI
  - Mayo Clinic

Clinicians follow professional society guidelines

ACC/ AHA Guidelines – Class of Recommendation

- Benefits versus Risk
- Recommendations
  - Class 1 – Is recommended
  - Class 2a – Is reasonable
  - Class 2b – May/might be reasonable
  - Class 3a – Is not recommended
  - Class 3b – Potentially harmful or causes harm

ACC/ AHA Guidelines – Level of Evidence

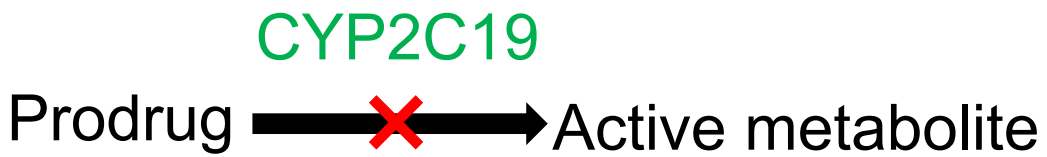
- RCTs
- Meta-analyses of high quality RCTs
- Well-designed, well-executed nonrandomized studies, observational, or registry studies
- Meta-analyses of such studies

Clinicians follow professional society guidelines

Pharmacogenomics as an example

Background

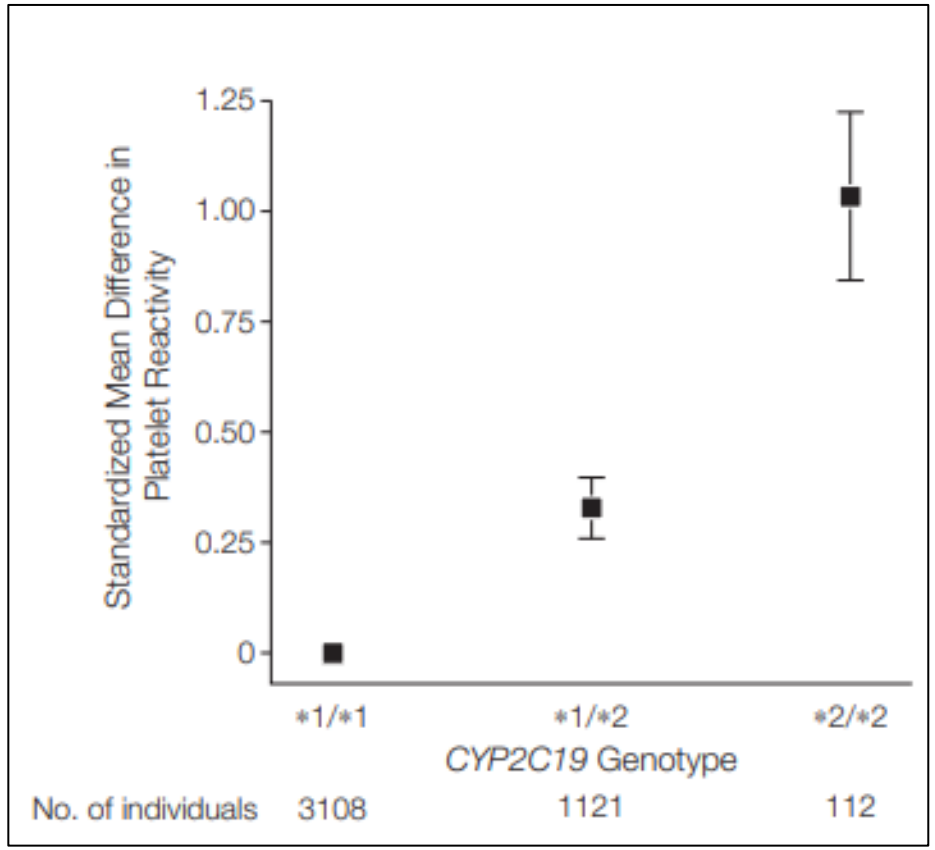
CLOPIDOGREL



Nature Reviews Cardiology 2009

CYP2C19 LOF carriers

- 1 in 3 individuals may be LOF carriers
- AUC_{0-24} is up to 46% and C_{max} up to 40% lower that of non-carriers for the active metabolite

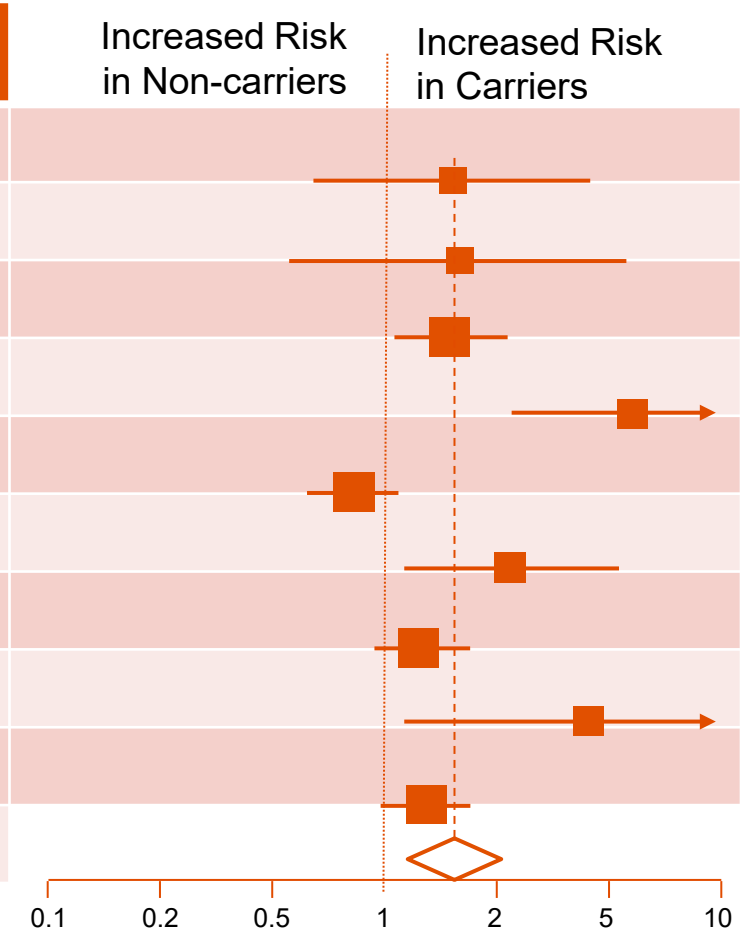


J Thrombosis and Haemostasis 2008; JAMA 2011

CYP2C19 LOF carriers vs Non-carriers

Risk of CV death, MI, or stroke

	No. of Events/ No. individuals at Risk		
	1 or 2	None	Hazard ratio (95% CI)
Clarity-TIMI 28	8/77	10/150	1.56 (0.61-3.94)
EXCELSIOR	5/243	7/554	1.63 (0.52-5.14)
TRITON-TIMI 38	46/395	83/1064	1.53 (1.07-2.19)
AFIJI	15/73	11/186	5.38 (2.32-12.47)
FAST-MI	63/635	193/1573	0.79 (0.59-1.06)
RECLOSE	15/247	14/525	2.32 (1.12-4.81)
ISAR	55/680	119/1805	1.23 (0.89-1.70)
CLEAR-PLATELETS	6/68	4/160	3.95 (1.11-14.02)
Intermountain	68/344	141/906	1.29 (0.97-1.72)
Totals	**281/2762**	**582/6923**	**1.57 (1.13-2.16)**



JAMA 2010

Clopidogrel: Black-box warning

PLAVIX® (clopidogrel bisulfate) tablets
Initial U.S. Approval: 1997

WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

See full prescribing information for complete boxed warning.

- Effectiveness of Plavix depends on activation to an active
- Tests are available to identify a patient's CYP2C19 genotype and can be used as an aid in determining therapeutic strategy. (12.5)
- Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers. (2.3, 5.1)

BLACK BOX WARNING:

- *IDENTIFY*
- *ALTERNATIVE THERAPY*

March 12, 2010

In addition, there are other genetic polymorphisms such as ABCB1 that may also contribute to variation in the response of individual patients to clopidogrel.

Information about the predictive value of pharmacogenomic testing is very limited, but is the focus of multiple ongoing studies. The design of such studies in terms of specific tests and patient populations (eg, acute care versus chronic care settings) will have major implications for the role of testing. A related issue is whether the risk from a given individual's genomic profile changes over time, depending on the specific clinical scenario (eg, ACS versus stable angina pectoris, PCI versus medical therapy, small vessel versus large artery, atherosclerotic ischemic stroke, or carotid stenting versus medical therapy), is relevant. This question has yet to be resolved.

4. The answer to the specific question of the role of genotyping in everyday practice remains unknown at the present time. Although the boxed warning does not mandate testing, proponents would argue that there are common genetic

wide variety of situations. New agents such as prasugrel and ticagrelor, which are not affected by CYP2C19 genetic variants, have been found to be more effective than standard-dose clopidogrel. This relates to the PK characteristics of these newer agents. In very high-risk clinical circumstances (eg, prior stent thrombosis) such agents may be considered alternatives to standard ACCF/AHA and AHA Stroke Council Guideline therapy. This is particularly important in any patient suspected of treatment failure to standard-dose clopidogrel. Other treatment strategies are also being tested, including increased clopidogrel dosing or the addition of a third drug such as cilostazol to aspirin and clopidogrel. In the setting of stroke or transient ischemic neurologic symptoms, the combination of aspirin and extended release dipyridamole and aspirin monotherapy are alternatives recommended by the AHA Stroke Council guidelines for secondary prevention of stroke.[66]

6.2. Recommendations for Practice

The evidence base is insufficient to recommend either routine genetic or platelet function testing at the present time. There is no information that routine testing improves outcome in large subgroups of patients.

Circulation 2010

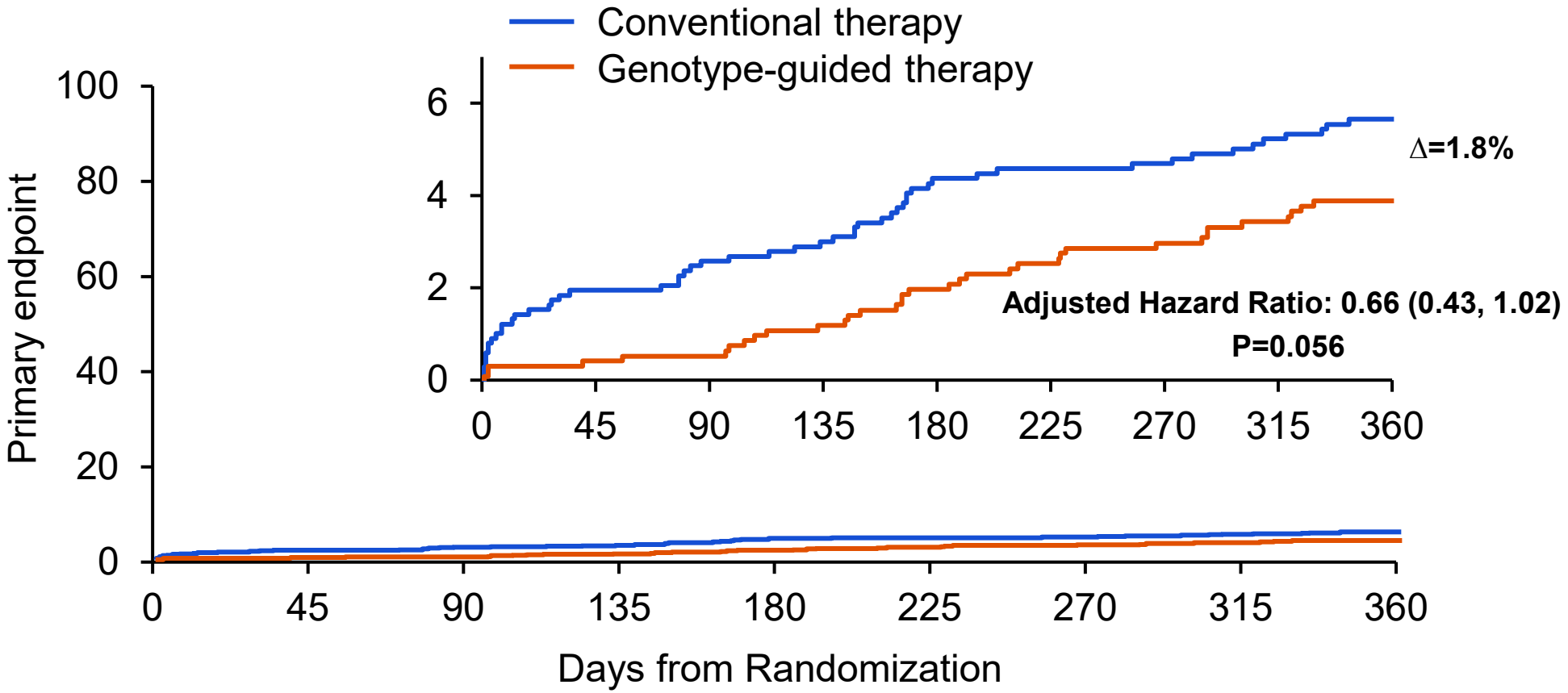
Genotype-based Clinical Trials

- Allele frequency
- Number of homozygotes
- Effect size
- Trial design complexity and sample size
- Ethics
- Regulations and FDA

Circ Cardiovas Interv 2019

Primary Endpoint

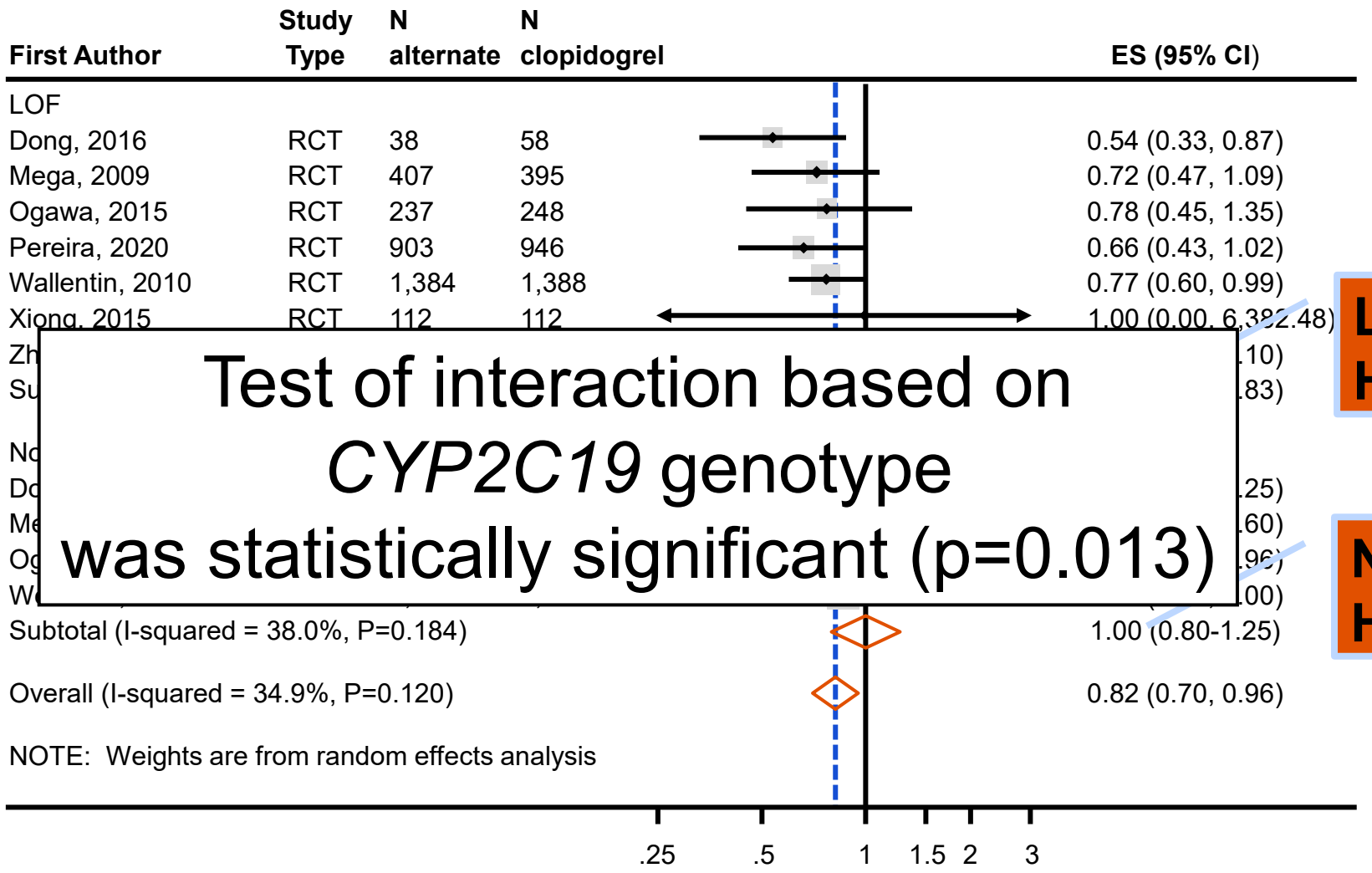
Composite of CV death, MI, stroke, stent thrombosis, severe recurrent ischemia



Conventional therapy	946	906	898	894	876	867	864	859	604
Genotype-guided therapy	903	875	870	863	854	838	833	824	556

JAMA 2020

CYP2C19 Genetic Testing – Meta-Analysis



Test of interaction based on *CYP2C19* genotype was statistically significant (p=0.013)

LOF carriers HR 0.70

Non-carriers HR1.0

JACC Intv. 2021

Guided versus standard antiplatelet therapy in patients undergoing percutaneous coronary intervention: a systematic review and meta-analysis

Mattia Galli, Stefano Benenati, Davide Capodanno, Francesco Franchi, Fabiana Rollini, Domenico D'Amario, Italo Porto, Dominick J Angiolillo

- ↓ Major Cardiovascular Events (RR 0.78, 95% CI 0.63-0.95, p=0.015)
- ↓ Cardiovascular Death (RR 0.77, 95% CI 0.50-1.00, p=0.049)
- ↓ MI (RR 0.76, 95% CI 0.60-0.96, p=0.021)
- ↓ Stent Thrombosis (RR 0.64, 95% CI 0.46-0.89, p=0.011)
- ↓ Stroke (RR 0.66, 95% CI 0.48-0.91, p=0.010)
- ↓ Minor Bleeding (RR 0.78, 95% CI 0.67-0.92, p=0.0030)

Funding None.

Lancet 2021

Circulation

AHA SCIENTIFIC STATEMENT

CYP2C19 Genetic Testing for Oral P2Y12 Inhibitor Therapy: A Scientific Statement From the American Heart Association

Naveen L. Pereira, MD, FAHA, Chair; Sharon Cresci, MD, FAHA, Vice Chair; Dominick J. Angiolillo, MD, PhD; Wayne Batchelor, MD, MHS; Quinn Capers IV, MD; Larisa H. Cavallari, PharmD; Dana Leifer, MD, FAHA; Jasmine A. Luzum, PharmD, PhD, FAHA; Dan M. Roden, MD, FAHA; Konstantinos Stellos, MD, FAHA; Stephanie L. Turrise, PhD, RN, FAHA; Sony Tuteja, PharmD, MS, FAHA; on behalf of the American Heart Association Professional/Public Education and Publications Committee of the Council on Genomic and Precision Medicine; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Peripheral Vascular Disease; and Stroke Council

Circulation 2024

Clinicians follow professional society guidelines

Clopidogrel - *CYP2C19* yet to be addressed

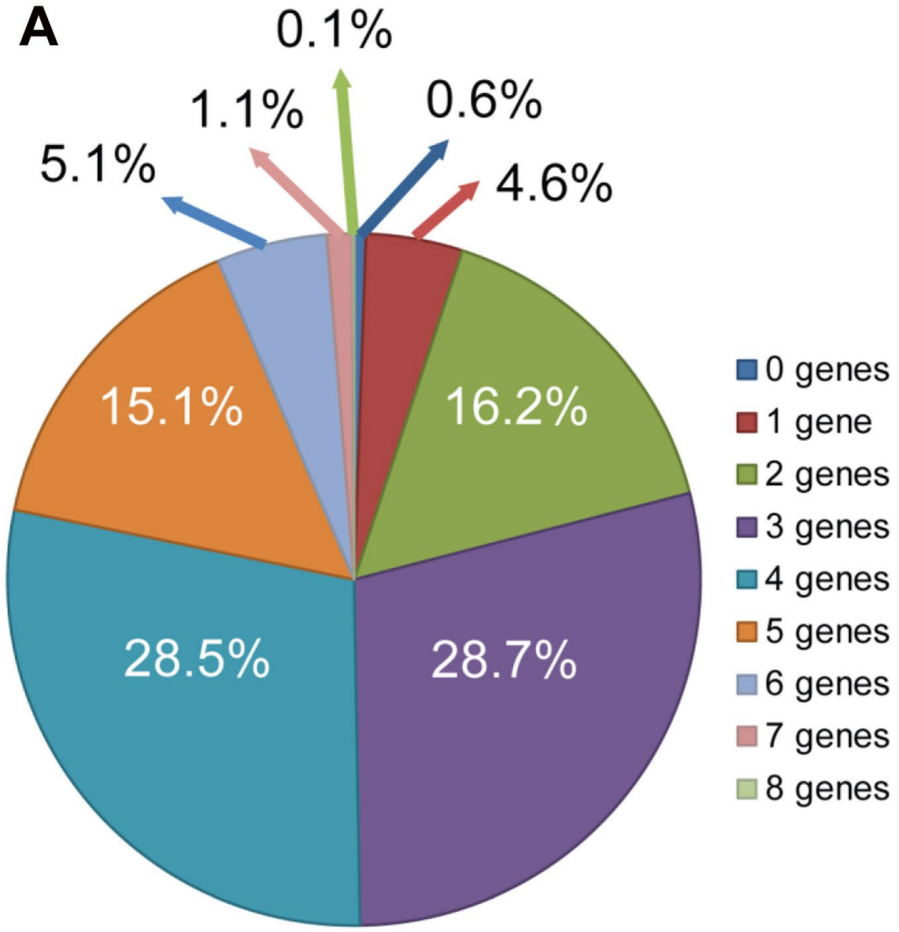
Challenges to Clinical Implementation

- Evidence of clinical utility
- Objective practice guidelines
- Availability of rapid turn-around genotyping performed in a CLIA-approved environment
- Incorporation of genotype data in an electronic medical record
- EHR “alerts” at the point of care
- Education of clinicians – patients
- User friendly decision support software/tools
- Insurance coverage and cost
- Clinician and patient perceptions

Pereira et al, Clin Pharm Therapeutics 2011

Preemptive genetic testing Mayo-Baylor RIGHT 10K Study

A

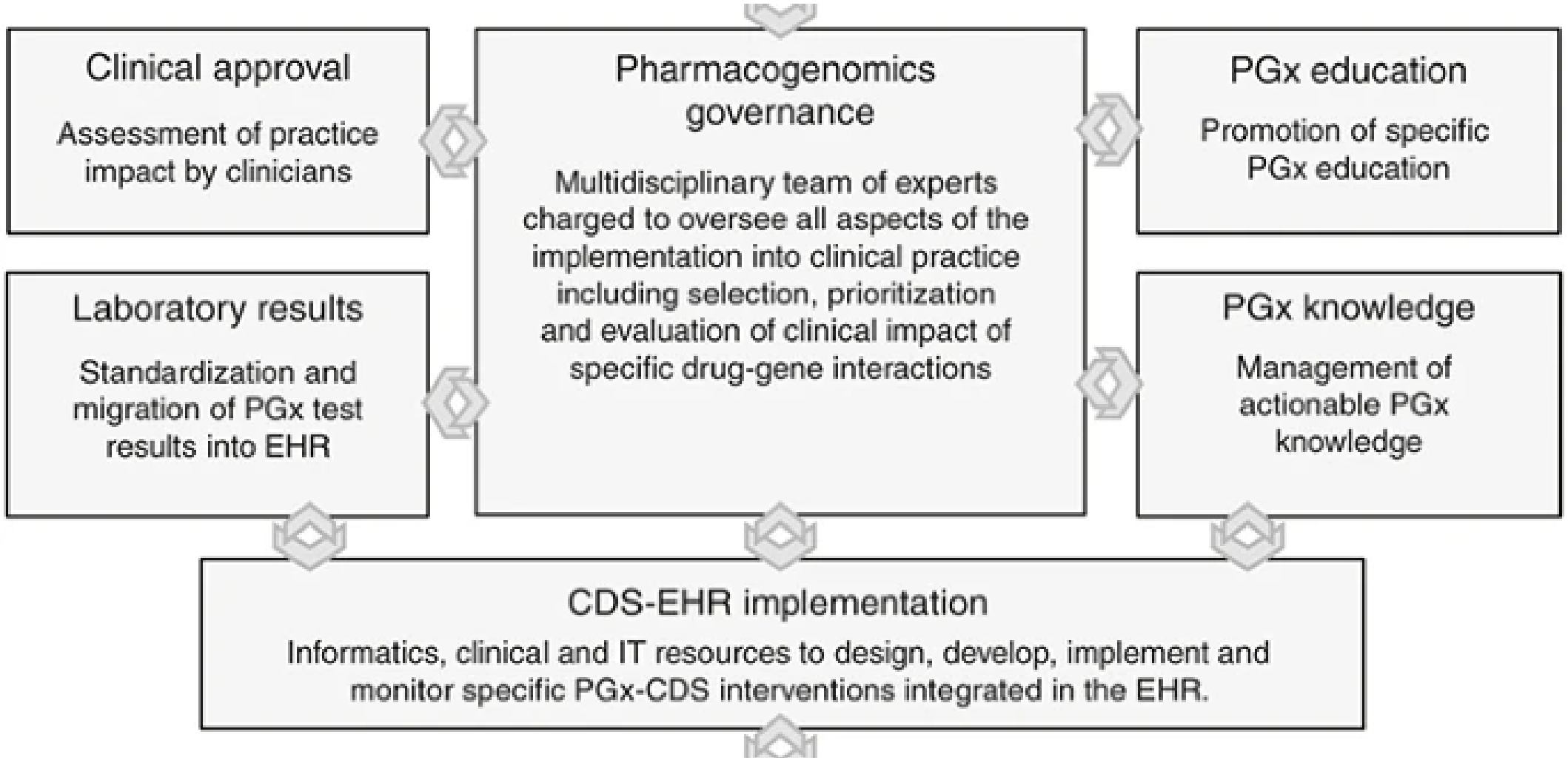


B

Number of Genes	Number of Subjects	% of Subjects
0	59	0.6%
1	465	4.6%
2	1636	16.2%
3	2893	28.7%
4	2869	28.5%
5	1521	15.1%
6	514	5.1%
7	111	1.1%
8	9	0.1%

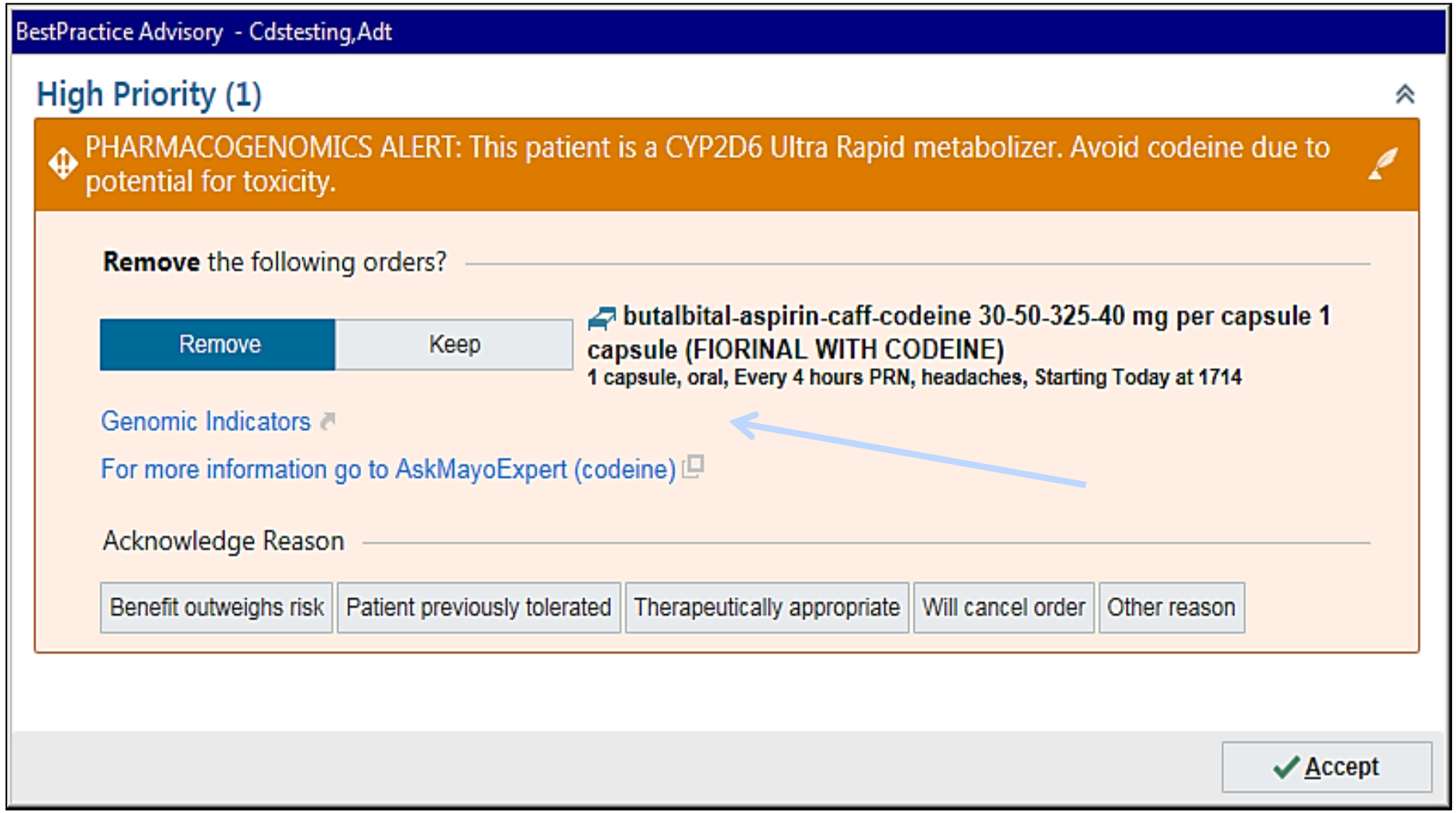
Genetics in Medicine 2022

Operational Model to Implement Genetic Testing *at Point of Care*



Genetics in Medicine 2017

Genetic Test Reporting – Decreasing Complexity



MAYO CLINIC

MAYO CLINIC

Department of Cardiovascular Medicine

Dilated Cardiomyopathy (DCM) Genetic Testing

Only 13% of eligible patients undergo genetic testing

DCM Genetic Testing Process

Genetic testing and clinical workflows

- @ point of clinical care
- Pre-emptive identification of eligible patients and opt-out option
- Use existing clinical resources
- Automate genetic counseling
- Transparency regarding cost
- Virtual engagement to provide results

DCM Genetic Testing: Mayo Clinic Experience

- Genetic counseling pre-INT vs post-INT (14.8% vs 33.5%, OR 2.9, P<.0001)
- Genetic testing pre-INT vs post-INT (13% vs 27.3%, OR 2.5, P=.001)
- Likely pathogenic or pathogenic DCM related genetic variants detection increased from 2 pre to 6 post-intervention

Take home points

- Clinicians follow professional society guidelines
- Guidelines are primarily driven by results of clinical trials but maybe biased when totality of data should be assessed
- Developing and conducting genotype-based clinical trials is complex
- Availability of genetic testing and results at the point of care is essential
- Institutional support and multidisciplinary teams involving clinicians, the laboratory, informatics, and IT resources are required
- Incorporating genetic testing within existing workflows including engaging clinicians, patients with insurance approvals/payments increases its adoption

MAYO CLINIC

Questions?
pereira.naveen@mayo.edu
@nl_pereira