UAB MEDICINE

Precision Medicine in Neuroscience: From Knowledge to Action

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Precision Medicine in Neuroscience: Tools, Translation, and Implementation
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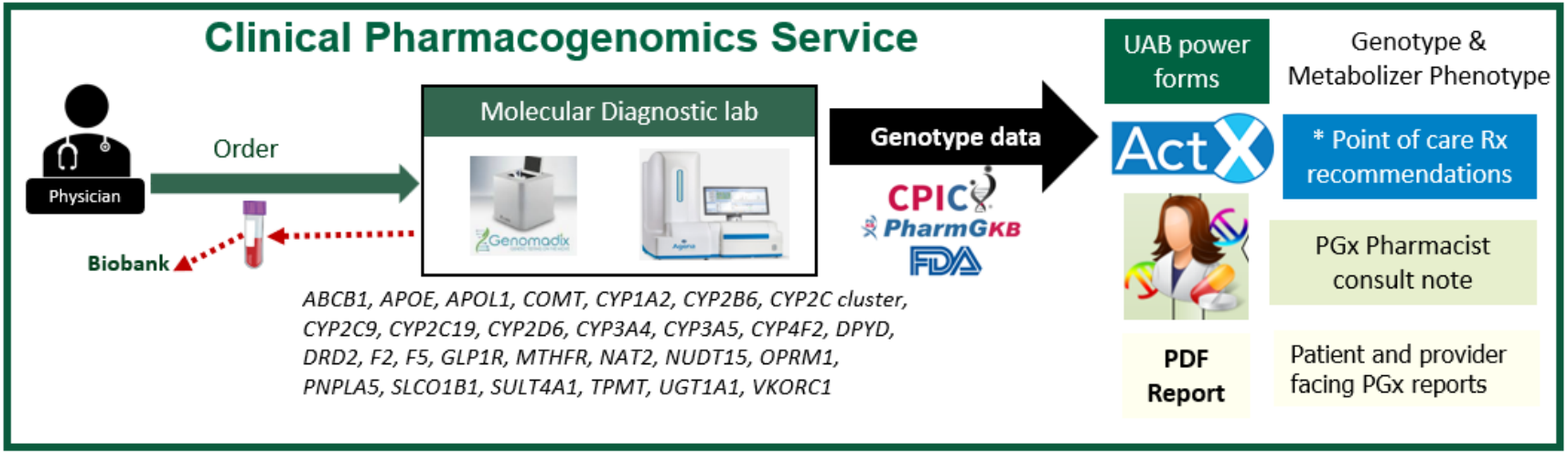
What is Precision Medicine?

Precision medicine is a tailored healthcare approach to disease prevention, diagnosis, and treatment based on an individual's unique genetic makeup, environment, and lifestyle.

How do we translate to inform care?

Clinical Pharmacogenomics Service



Safety stratification

Anti-amyloid therapies - APOE

APOE Testing for Anti-Amyloid Infusions in Alzheimer's Disease

Context: APOE genotyping has moved from research and risk prediction to informing treatment decision
Clinical Impact: APOE ε4 carriers (esp. ε4/ε4), have higher risk of amyloid-related imaging abnormalities

Before Starting Infusion

- Confirm amyloid pathology (PET or CSF/plasma biomarkers).
- Perform baseline MRI.
- Offer APOE genotyping and incorporate genotype into shared decision-making

UAB MDL offers
APOE genotyping
TAT: 5-7 days

*Access and telemedicine

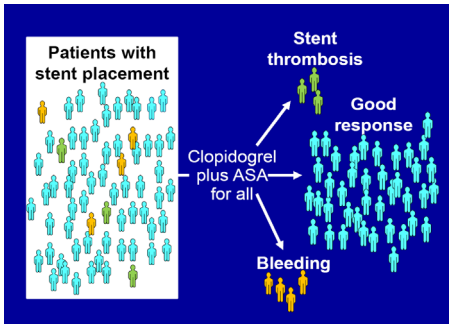
Implementation considerations:

1. Intensity of MRI surveillance: ε4 carriers require more intensive ARIA monitoring. MRI capacity / infrastructure vital to scaling treatment
2. Genetic Counseling: APOE was historically a risk gene. Now it is a clinical decision gene. Requires pre-test education and post-test interpretation.
3. Ethical Complexity: APOE status conveys lifetime dementia risk information, implications for family
4. Insurance and Documentation**:** Concerns about long-term insurability (life/disability insurance), variability in payer expectations.

Efficacy Optimization

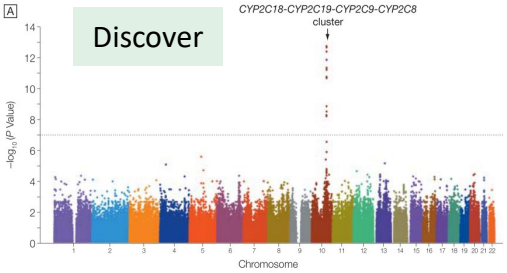
CYP2C19 – Antiplatelet therapy

Coronary stents can be lifesaving in patients with acute myocardial infarction (>1million / year US)



Current approach – Unmet need

Discover



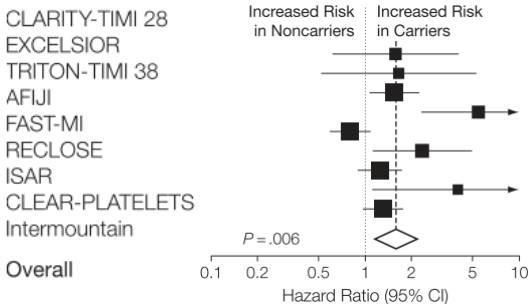
JAMA®

CYP2C19 (12%); Age BMI, Lipids (22%); Overall (73%)

30% Loss-of-Function CYP2C19

Validate

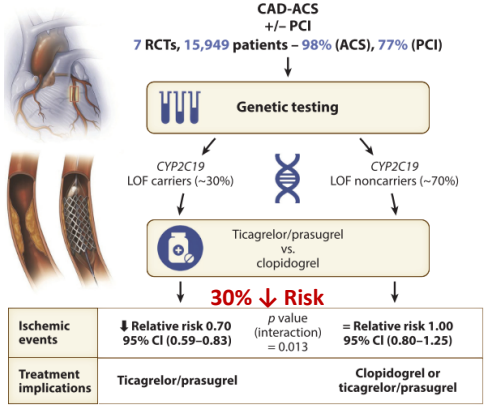
JAMA®

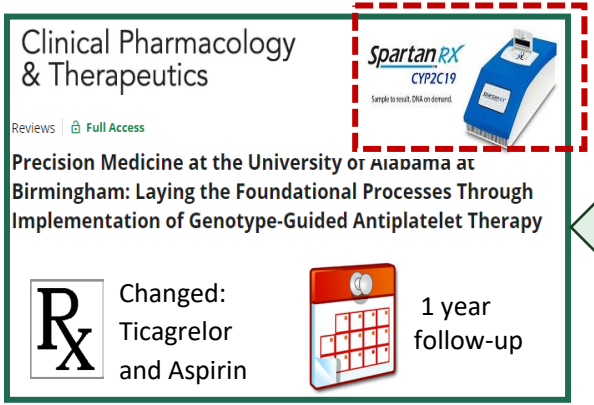


Candidate for testing
ACS +/- stable CAD?

Test Efficacy (RCT)

ANNUAL REVIEWS





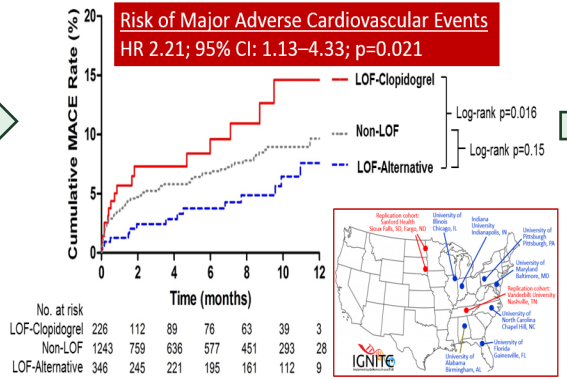
(HSF-GEF grant)

Integrating evidence, assessing effectiveness, informing policy and generating new research

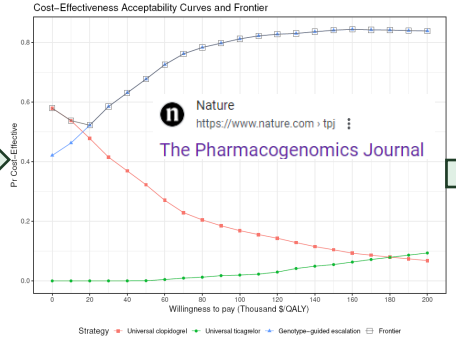
JACC Cardiovascular Interventions

Establish Effectiveness (clinical utility)

Risk of Major Adverse Cardiovascular Events
HR 2.21; 95% CI: 1.13–4.33; p=0.021



Determine Cost- Effectiveness



New Evidence based guideline

CPIC UPDATE

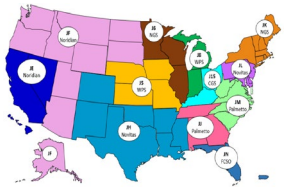
Clinical Pharmacogenetics Implementation Consortium Guideline for *CYP2C19* Genotype and Clopidogrel Therapy: 2022 Update

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,*]

FDA Black Box Warning
Acute coronary Syndrome (2024)
Ischemic Stroke (2021)

Inform Policy

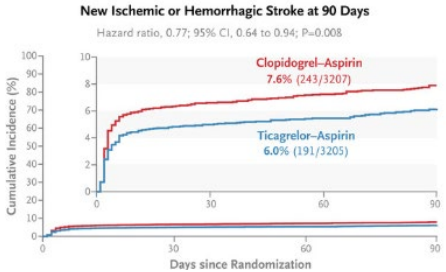
CMS.gov MCD Medicare Coverage Database



CPT code: 81225; $291/test

New Research

The NEW ENGLAND JOURNAL of MEDICINE



UAB MDL offers CYP2C19 testing: TAT 4 hours

CYP-FAST
CYP2C19 **F**easibility **A**ssessment in **S**troke and **T**IA **Trial**

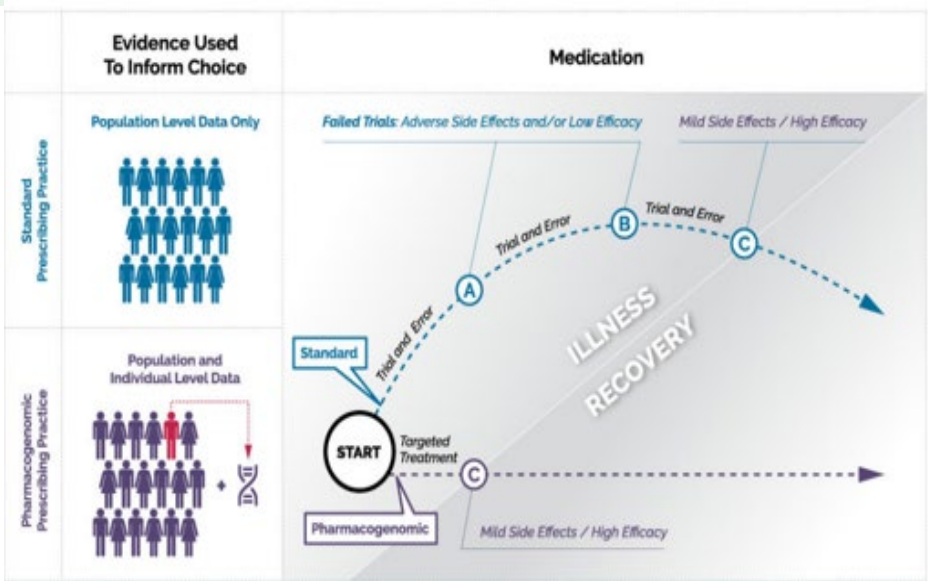
https://www.cms.gov/medicare-coverage-database/view/article.aspx?articleId=58318&ver=51

Multigene Prediction

Pharmacogenetic Panels for Antidepressants

The Burden of Psychiatric Disorders

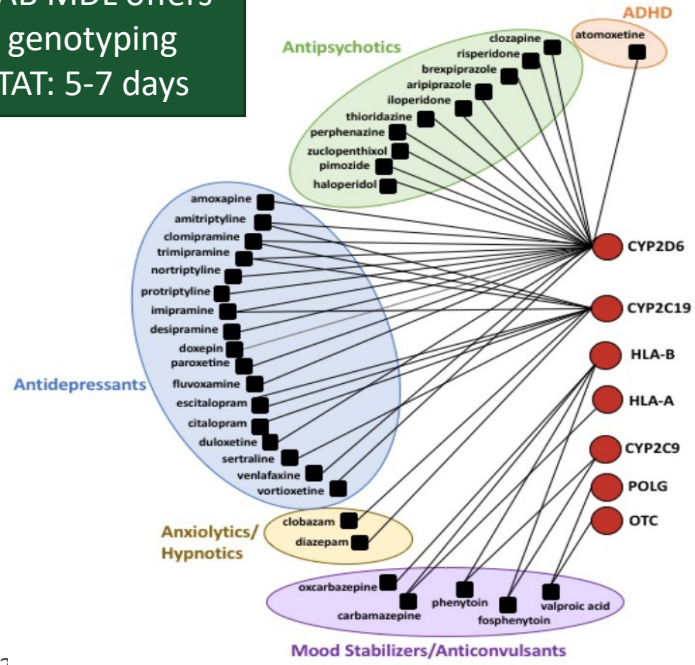
- ~26% of Americans age 18 and older suffer from a mental disorder
- ~9.5% of Americans age 18 and older suffer from a depressive illness
- ~ 18% of people ages 18-54 have an anxiety disorder



44 gene-drug pairs with actionable PGx-based guidelines

CPIC Clinical Pharmacogenetics Implementation Consortium · KNMP · FDA · Pmda 独立行政法人 医薬品医療機器総合機構 Pharmaceuticals and Medical Devices Agency · Health Canada

UAB MDL offers genotyping
TAT: 5-7 days



IGNITE Implementing GeNomics In practicE — A Depression and Opioid Pragmatic Trial in Pharmacogenomics — ADOPT PGx — Coming soon

From National Institute of Mental Health Disorders, Biological Psychiatry. 2016 Oct;80(8):e63-5. PMID: 27663007

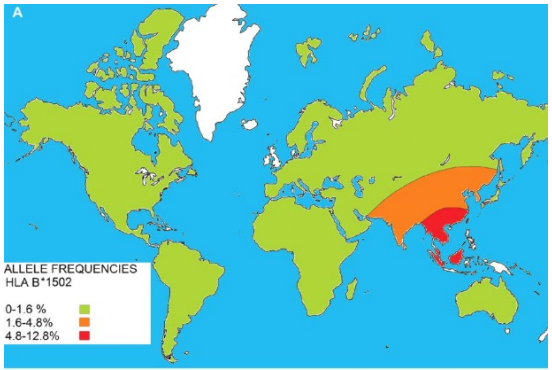
Toxicity Prevention

Carbamazepine - HLA-B*15:02

A marker for SJS

Nature 2004; 428(6982):486

HLA-B*1502 Screening



HLA	CBZ-SJS	CBZ-tolerant	Normal
B*1502	44 (100%)	3 (3%)	8 (8.6%)
Total	44	103	93

*CBZ–SJS/CBZ-tolerant: **OR 2,504** (95% CI, 126–49,522); $P = 10^{-27}$

†CBZ–SJS/normal: **OR 895** (95% CI, 50–15,869); $P = 10^{-21}$

Table 3. Historical Incidence of Carbamazepine-Induced SJS–TEN in 2002, 2003, and 2004, as Compared with the Incidence among Study Subjects.*

Variable	2002	2003	2004
New recipients of carbamazepine (no.)	50,917	48,522	49,670
Subjects with ICD-9-CM diagnostic code 695.1 (no.)	1441	1261	1354
Carbamazepine-induced SJS–TEN (no.)	123	108	116
Incidence of carbamazepine-induced SJS–TEN (%)	0.24	0.22	0.23
P value for comparison between historical incidence and incidence among study subjects†	<0.001	<0.001	<0.001

https://www.cmaj.ca/content/182/5/476

N Engl J Med 2011;364:1126-1133

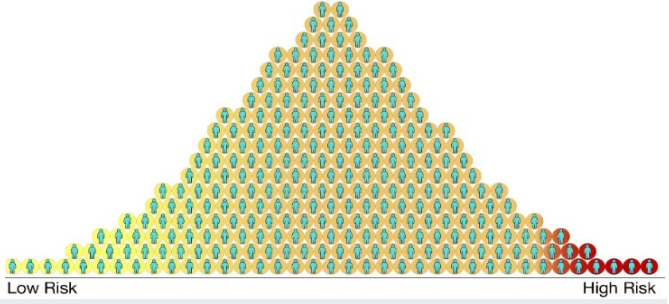
Predict / Prevent

Polygenic Risk Scores

Polygenic Risk Scores

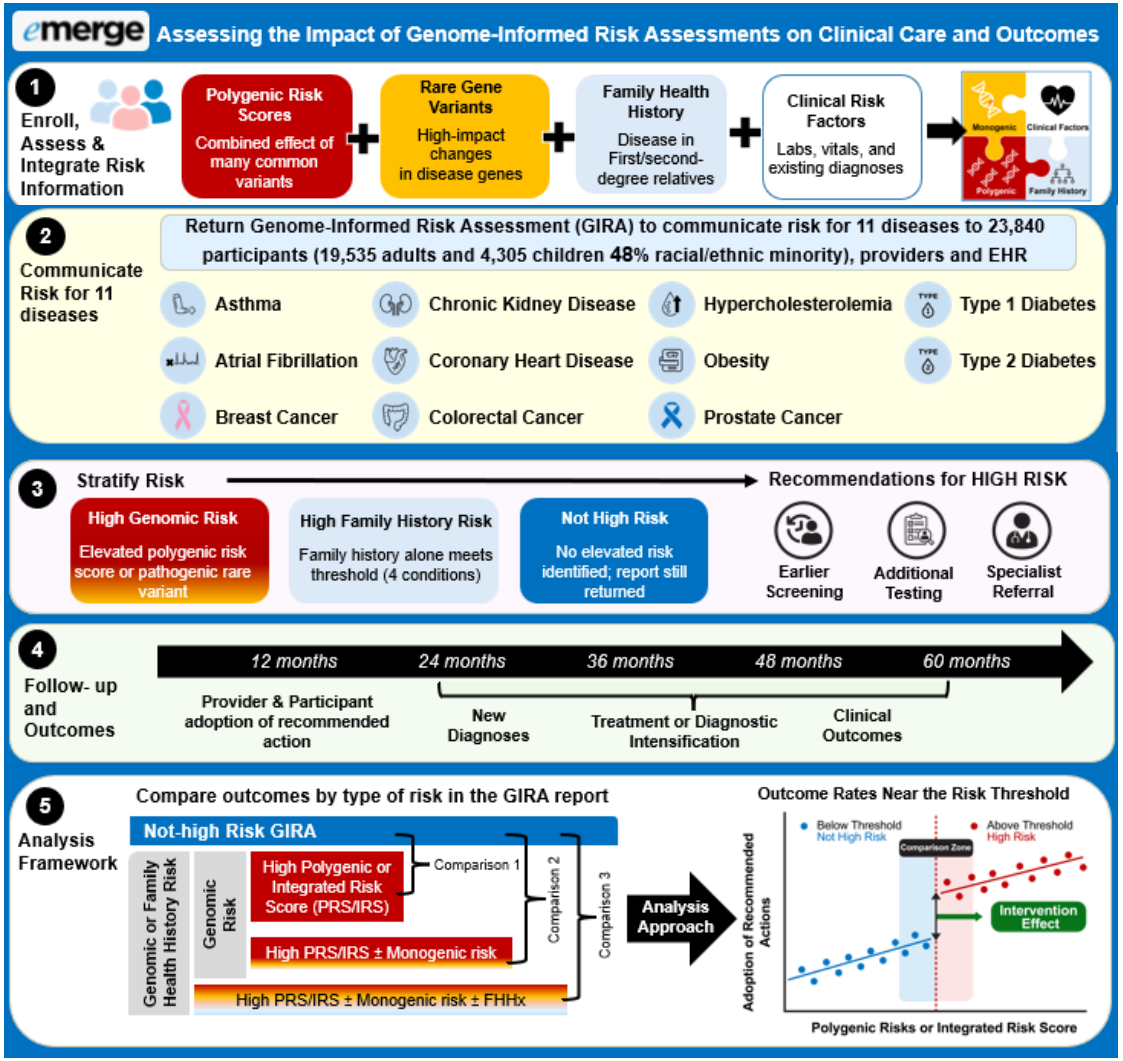
Polygenic risk scores are numerical estimates of an individual's genetic predisposition to developing a complex disease, such as heart disease or diabetes

- GWAS identifies SNPs associated with a trait
- Effect size is estimated for each SNP to assign a weight
- PRS sums up the weighted SNP effect sizes



- A higher PRS indicates a greater predisposition to the disease
- PRSs are not absolute predictions of risk
- PRS provides a relative risk compared to the population

Khan, A. *Nat Rev Nephrol* **21**, 24–38 (2025)
Limdi et al AJHG (2026) in press



From trials and centers of excellence into routine clinical care

What breaks when precision medicine moves into real-world practice?	• Workflow friction and time sensitivity • Workflow constraints • Diagnostic uncertainty
How can implementation barriers be overcome?	• Embed delivery in existing care pathways • Tasks and workforce realignment • Infrastructure investment and value framing
How do health systems decide what is worth adopting and sustaining?	• Does it change outcomes, can we deliver it reliably • Does reimbursement cover costs • Does it benefit all (i.e., not exacerbate disparities)
Where do ethical, economic, and clinical considerations collide?	• Advanced dementia therapies (APOE testing) • Stroke treatment algorithms (CYP2C19 and Antiplatelet) • Polygenic risk scores (uncertain decision thresholds)
Why do some precision approaches stall despite strong biology?	• Small effect size in heterogenous disorders • Operational complexity, Misalignment of incentives • Health-System Readiness

Featured use	Binary Toxicity Prevention	Probabilistic Safety Stratification	Modest Efficacy Optimization	Multigene Predictive Panels	Polygenic Risk Scores (PRS)
Rep. drug	Carbamazepine	Lecanemab	Clopidogrel	SSRIs/SNRIs	-
Gene	Single variant HLA-B*15:02	Single gene APOE	Single gene CYP2C19	Few genes (CYP2D6,2C19 ..)	Thousands of variants
Primary goal	Preventing serious toxicity	Modify safety monitoring	Improve drug efficacy	Improve prescribing efficiency	Predict future disease risk
Effect	large effect	modest effect	modest effect	small effects	tiny effects
Decision type	Binary (avoid)	Monitor/intensify counseling	Consider alternative	Algorithm-informed preference	Risk stratification, surveillance
Clinical actionability	Immediate Cross reactivity	Immediate but nuanced	Conditional	Variable	Often indirect
Infrastructure burden	Point of care CDS, Test TAT	High MRI, Infusion center, Counselor	Moderate, CDS Test TAT	Moderate, CDS Test TAT	Moderate
Ethical load	Low Self-report ancestry consideration	High lifetime, family implication, access	Low, Continuity in care across systems	Moderate genes with limited evidence	Moderate Uncertain decision thresholds
Reimbursement, cost	Reimbursed	Not reimbursed	Hosp pt/ DRG	Hosp vs. ambulatory, variable coverage, preapproval	DTC labs, not reimbursed

Thank you!

It Takes an Average of 17 Years for Evidence to Change Practice

(Rubin et al. JAMA 2023.329,1333-36; J R Soc Med 2011.104, 510-520)