

The need for genetics/genomics literacy in cardiovascular/stroke care



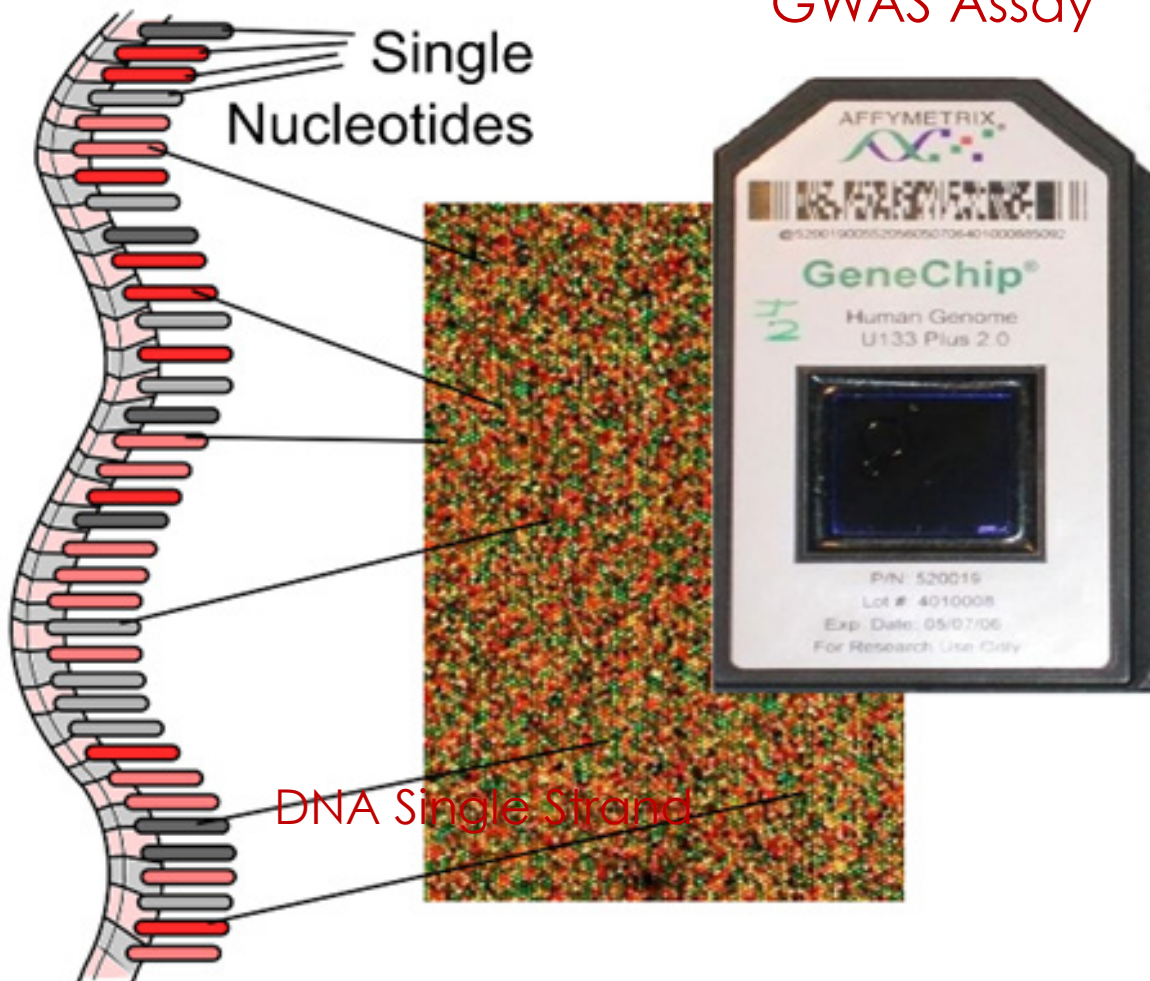
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Tremendous progress in understanding of the genetic basis of cardiovascular and stroke disorders via GWAS studies

GWAS Assay



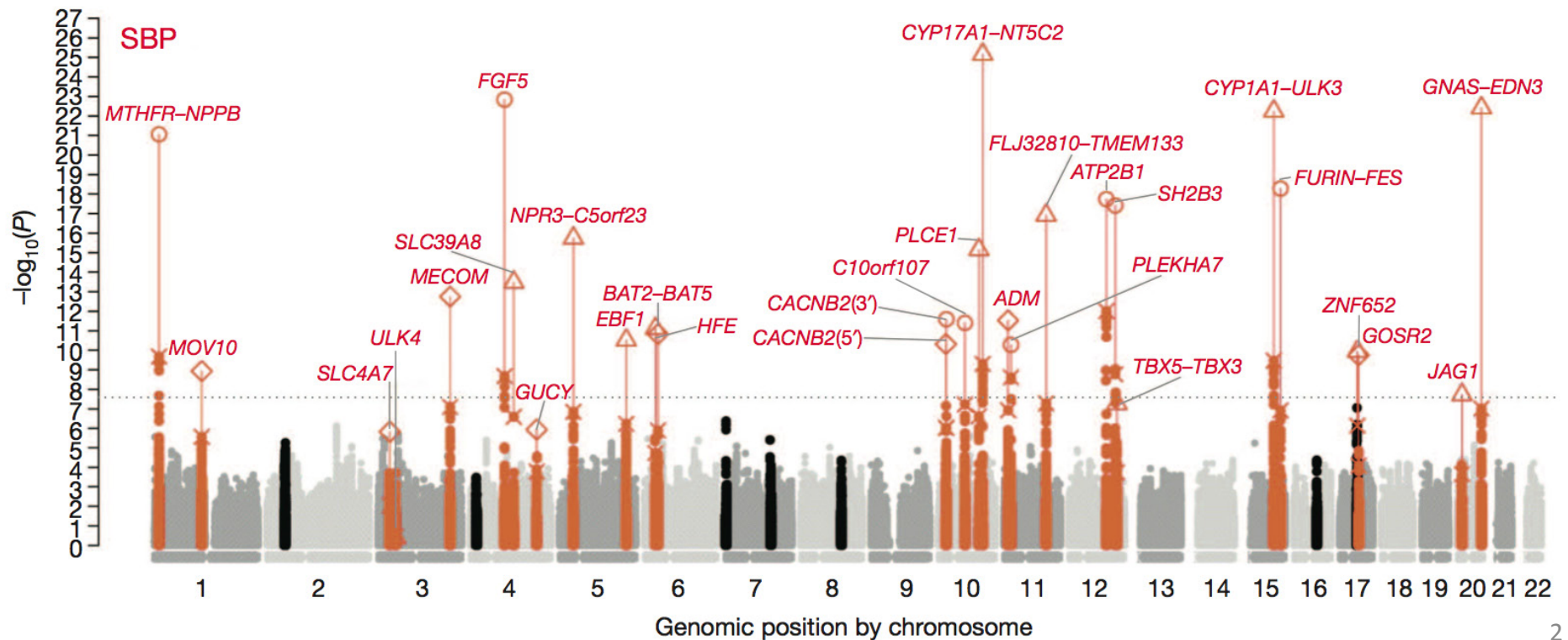
GWAS studies

selectively assay a subset of nucleotides ("single-nucleotide polymorphisms," SNPs) on all chromosomes in the genome. These polymorphisms are relatively common in populations.

GWAS of 200,000 Individuals of European Descent

Genetic Variants Associated with SBP

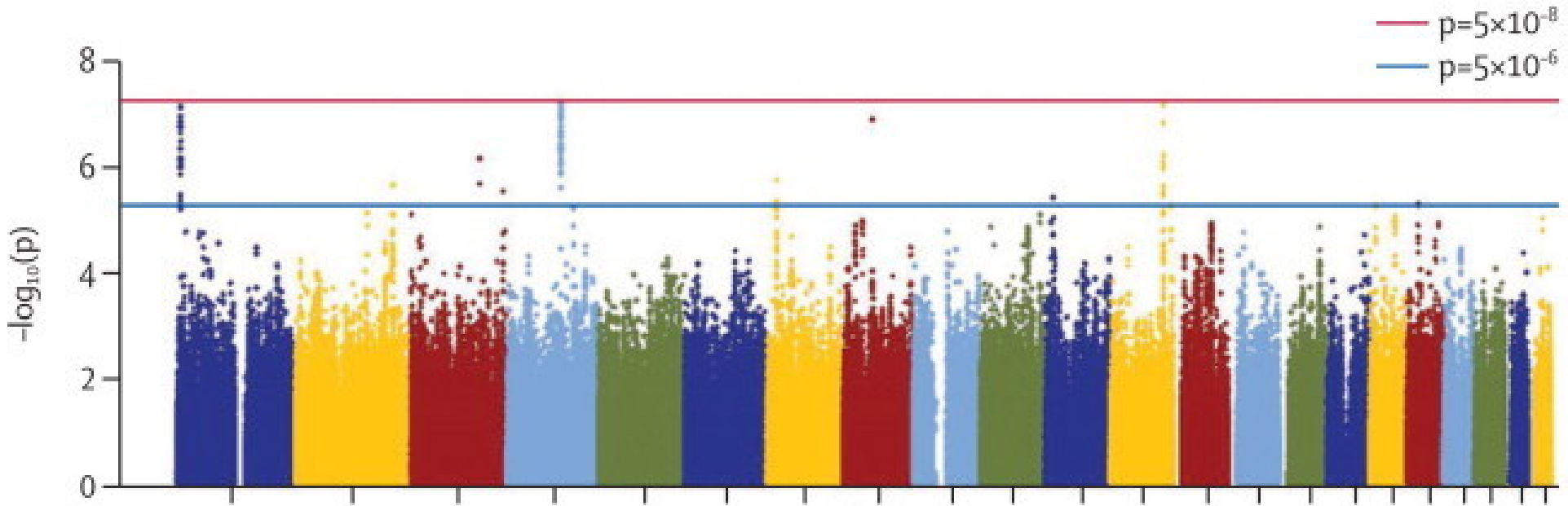
Loci reaching genome-wide significance are labeled in red

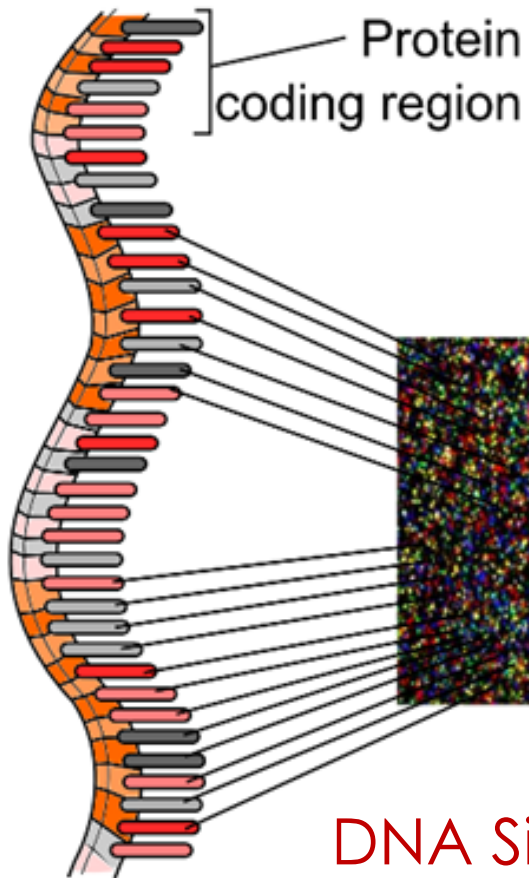


Manhattan plots for All Ischemic Stroke

$-\log_{10}(p)$ by genomic position

A All ischaemic stroke





Exome and Whole Genome Sequencing

Whole **exome/ genome sequencing** studies selectively assay the protein coding regions (“exons”) on all chromosomes in the genome.

Sequence data finds polymorphisms that are common and rare in populations.

State-of-the-science

- Exome sequencing has discovered new genes involved in cholesterol metabolism and blood pressure control
- Functional characterization of novel cardiovascular/stroke loci and genes is underway – among the most advanced of any discipline

From genotype to phenotype

ARTICLES

Biological, clinical and population relevance of 95 loci for blood lipids

A list of authors and their affiliations appears at the end of the paper.

Plasma concentrations of total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglycerides are among the most important risk factors for coronary artery disease (CAD) and are targets for therapeutic

ARTICLES

From noncoding variant to phenotype via *SORT1* at the 1p13 cholesterol locus

Kiran Musunuru^{1,2,3*}, Alanna Strong^{4*}, Maria Frank-Kamenetsky⁵, Noemi E. Lee¹, Tim Ahfeldt^{1,6}, Katherine V. Sachs⁴, Xiaoyu Li⁴, Hui Li⁴, Nicolas Kuperwasser¹, Vera M. Ruda¹, James P. Pirruccello^{1,2}, Brian Muchmore⁷, Ludmila Prokunina-Olsson⁷, Jennifer L. Hall^{2,8}, Eric E. Schadt⁹, Carlos R. Morales¹⁰,

Clinical applications

- Despite the wealth of new knowledge...
- ...cardiovascular and stroke clinical care has not yet been significantly impacted
- Translation into the clinic will ensue and accelerate over the next 5-10 years

Cardiovascular risk prediction

- Common DNA variants
- Rare DNA variants

Common DNA variants

- In most cases, have been discovered by GWAS
- Typically have small effects – no one variant will singlehandedly determine if a patient will develop disease
- Can aggregate the effects of many variants by combining them into genetic risk scores

Genetic risk scores

- Genetic risk scores have been tested for predictive power for several cardiovascular/stroke disorders
- Modest predictive power for incident coronary heart disease – high genetic risk score confers only a ~70% increase in risk
- Limited clinical usefulness (except perhaps for intermediate-risk, “on the fence” patients)

Rare DNA variants

- Rare DNA variants have potential to have large effects, may increase (or decrease) risk several-fold
- However, each variant only found in one or a few people
- Genetic risk scores with common DNA variants do not capture – and may be trumped by – rare variants

Needle in a haystack

- Whole-genome sequencing will identify hundreds of rare variants in each person – most of which are irrelevant to disease
- How to know which rare variants are clinically important? Huge challenge for the field
- May fall in genes already implicated in disease, e.g., hypertrophic cardiomyopathy (HCM)

What does it mean to have a mutation?

- Even if in known gene, two problems
- First: the particular mutation may or may not affect gene function – difficult to predict *a priori*
- Second: even if the mutation changes gene function, penetrance may be affected by genetic background
- Even within a family, some members with HCM mutation will develop disease, some will not

Dangers of genetic information

- DTC testing (e.g., 23andMe) informs patients of genetic risk scores but (for now) not rare variants – possibility of false reassurance (or false worry)
- Problem will get worse with DTC genome sequencing
- Providers need to be aware of the limitations of this information to appropriately counsel patients
- Providers' lack of knowledge about genetics will serve patients poorly – education is critical

Pharmacogenomics

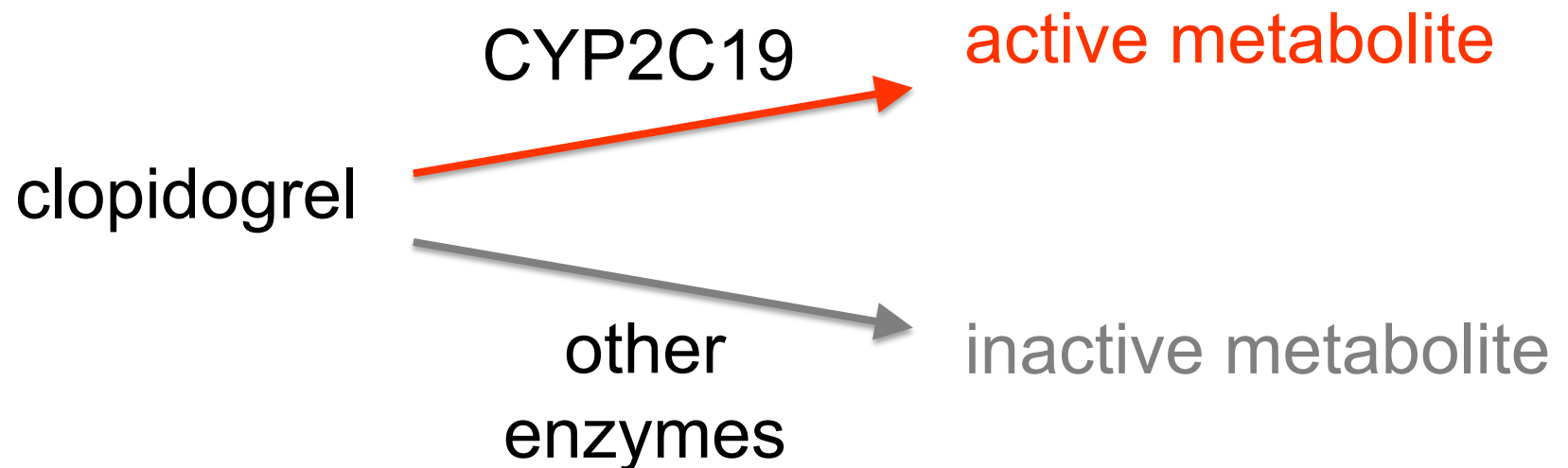
- Getting the right dose of the right medication to the right patient
- Though integrated into clinical practice in some disciplines (e.g., oncology), not yet adopted in cardiovascular/stroke care
- Several emerging applications: warfarin, clopidogrel, beta-blockers, lipid-modifying medications

Clopidogrel and *CYP2C19*

- Patients presenting with myocardial infarction
- Routine practice is to give anti-platelet agent clopidogrel (Plavix), a type of thienopyridine
- Clopidogrel reduces risk of future cardiovascular event as well as the risk of in-stent thrombosis

Clopidogrel and *CYP2C19*

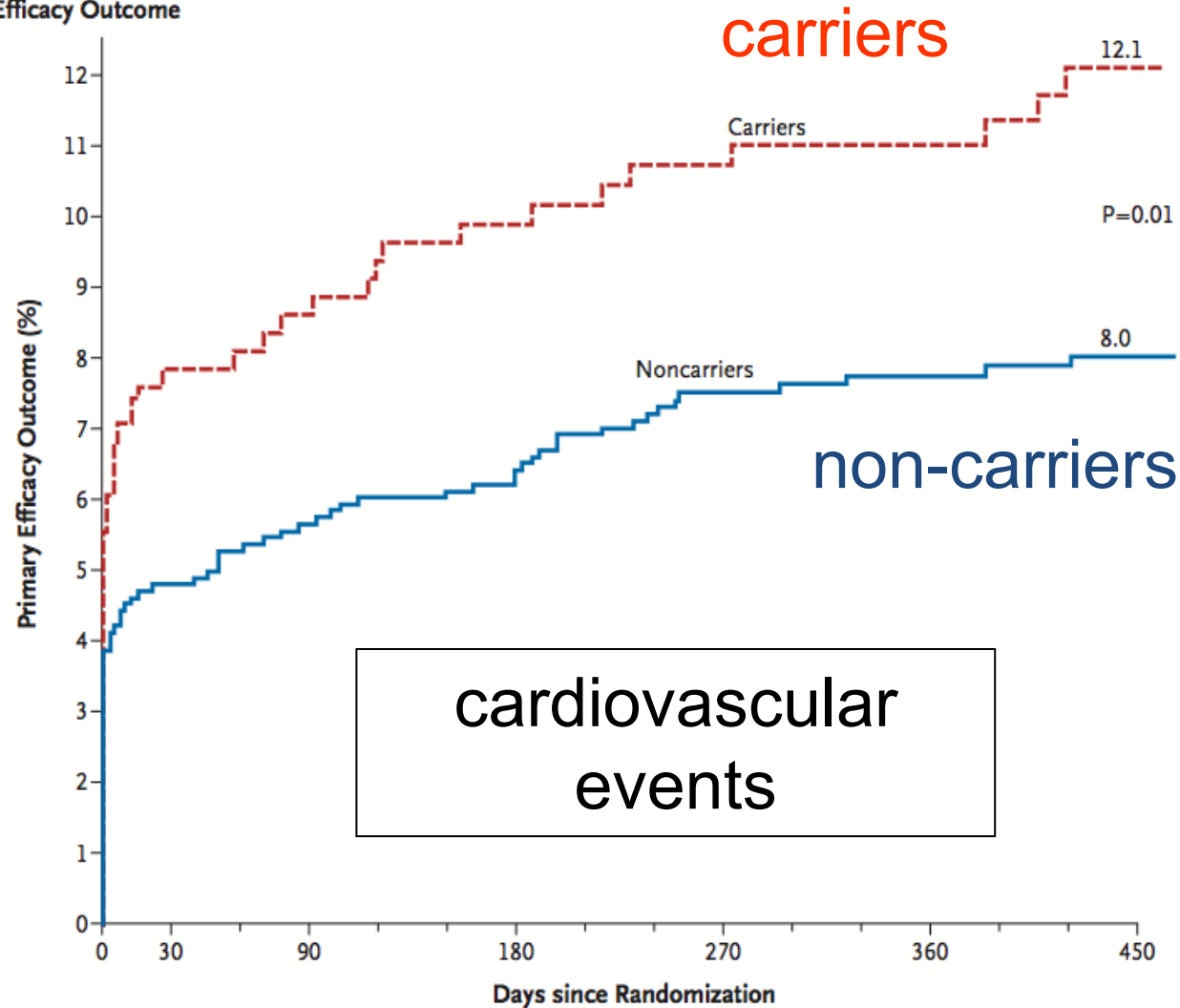
- *CYP2C19* encodes a key enzyme in making active metabolite of clopidogrel



- Reduced-function *CYP2C19* alleles result in decreased clopidogrel efficacy (but not other thienopyridines) – has lead to FDA black box warning

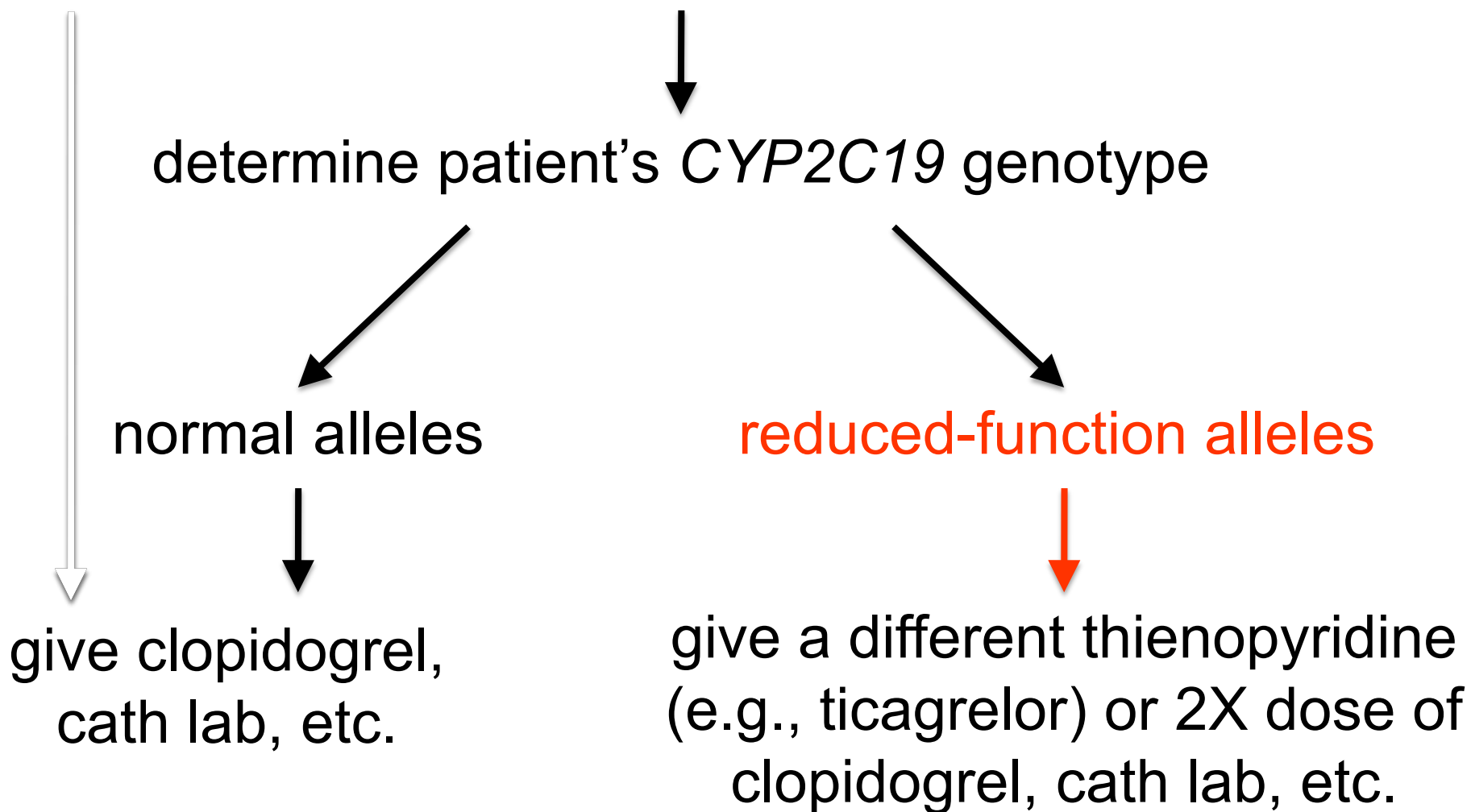
Effect of *CYP2C19* reduced-function alleles

A Primary Efficacy Outcome



Pharmacogenomic strategy using *CYP2C19*

patient presents to hospital with myocardial infarction



Clopidogrel and *CYP2C19*

- Point-of-care *CYP2C19* genotyping presently being piloted by a number of hospitals
- Remains to be validated by clinical studies – unclear which patients, if any, would benefit
- Must be validated before can be recommended for routine clinical use

Adoption of pharmacogenomics

- With several cardiovascular pharmacogenomic applications under evaluation, likely that at least one will be validated within 5 years
- Expect rapid adoption by academic centers and large healthcare networks
- Expect slower adoption by individual practitioners, small group practices due to “knowledge gap” – education is critical

Provider education

- Although lack of provider education on genetics/genomics issues not currently jeopardizing clinical care – anticipate that negative effects of a “knowledge gap” will emerge in 5-10 years
- AHA/ASA is moving to address the anticipated need for provider genetics/genomics literacy in two ways

Scientific Statements

- To date, AHA/ASA has published several scientific statements related to genetics – e.g., “Genetics and Genomics for the Prevention and Treatment of Cardiovascular Disease” – but these are oriented to state-of-the-science and policy, not provider education
- Currently has a working group formulating a statement on “Use of Genetics and Genomics in Cardiovascular and Stroke Patient Care” – exclusively focused on provider education

Outline of Statement

- Primer on genetics and genomics
- Monogenic cardiovascular and stroke disorders
- Polygenic cardiovascular and stroke disorders
- Cardiovascular and stroke risk prediction
- Pharmacogenomics
- Cardiovascular and stroke risk prediction
- Social and ethical implications
- Educational resources

Massively open online course (MOOC)

- AHA/ASA monitoring latest trends in education
- Formulating an online course in Genetics/Genomics that will cover all of the topics outlined in the “Use of Genetics and Genomics in Cardiovascular and Stroke Patient Care” statement
- Plan to make course freely available to the biomedical community – pitched at an undergraduate level, with target audience of physicians, RNs, pharmacists, etc.

Massively open online course (MOOC)

- Will eventually be supplemented with modules on specific cardiovascular genetic disorders – e.g., hypertrophic cardiomyopathy, arrhythmogenic right ventricular dysplasia, long QT syndrome, Brugada syndrome
- Initial versions in English, to potentially be followed by translations into other languages

Special Thanks To:

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