

Genetic testing has changed dramatically...

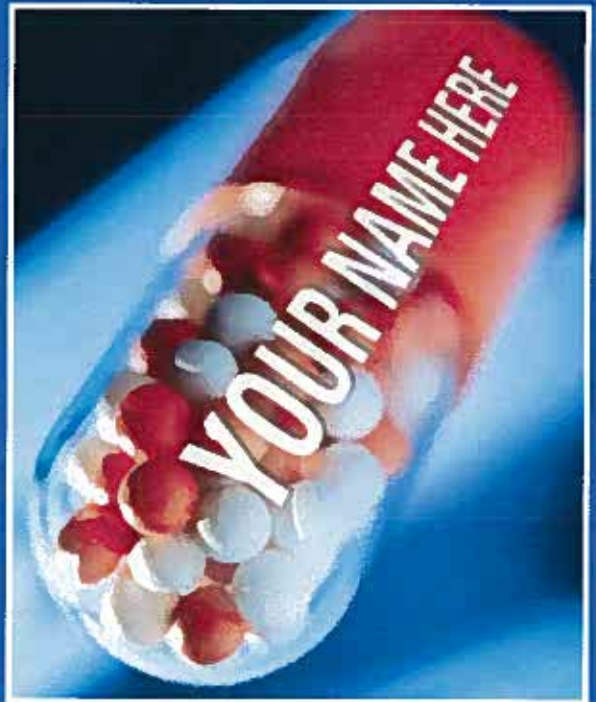
- Increase in number
- Increase in complexity
- Increase in availability

The collage features several advertisements and logos related to genetic testing:

- Order Now!** (Large green text)
- Discover How Your Genes can hold the Secret to your Well-Being** (Text with a DNA helix graphic)
- GeneIwist** (Logo with a DNA helix and pills)
- GENOVATIONS™** (Logo with the tagline "Predictive Genomics for Personalized Medicine" and "Custom Fit for Life!")
- GeneLink** (Logo with the tagline "THE BIOSCIENCES FOR IMPROVING THE QUALITY OF LIFE")
- NUGENIX™** (Logo)
- Breakthrough Genetic Profiling** (Text)
- Gene - Testing Now Available** (Text with a DNA helix graphic)
- NAVIGENICS** (Logo)
- GENETICS IS ABOUT TO GET PERSONAL** (Text with the tagline "don't panic, we're here to help")
- An Amazing Opportunity** (Text with a large 'X' symbol)
- Your skin is as unique as your DNA.** (Text with a DNA helix graphic)
- Purchase Online** (Text with a "CLICK HERE" button)
- Learn about genetic testing for hereditary breast and ovarian cancer.** (Text)

Genetic testing has changed dramatically...

- Increase in number
- Increase in complexity
- Increase in availability
- Increase in clinical relevance



Clopidogrel (Plavix)

- Drug Functions:
 - Works by preventing platelets from forming clots
 - Must be activated by specific enzymes (P450)
- Clinical Observations:
 - Commonly used in patients at risk for heart attacks and strokes
 - *However*, it does **not** work for about **30%** of the U.S. population
- Research Question: *why is this drug ineffective in nearly 1/3 of the population?*

Image: T. Simon, C. Verstuyt, et. al, NEJM

Clopidogrel (Plavix): The Evidence

JAMA[®]

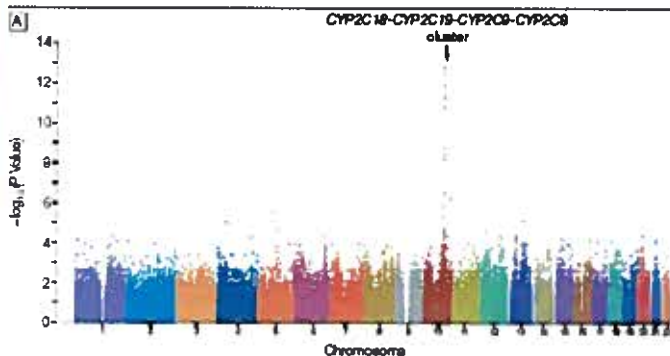
ORIGINAL CONTRIBUTION

Association of Cytochrome P450 2C19 Genotype With the Antiplatelet Effect and Clinical Efficacy of Clopidogrel Therapy

From Shuldiner et al.,
JAMA, 8/26/09, vol 302

CYTOCHROME P450 2C19 GENOTYPE AND CLOPIDOGREL THERAPY

Figure 2. Genome-Wide Association Study of Adenosine Diphosphate–Stimulated Platelet Aggregation in Response to Clopidogrel



Drug Relabeling: Clopidogrel

- November 1997: FDA approved clopidogrel for the reduction of atherosclerotic events
- May 2009: FDA added first pharmacogenomic information to label:

Based on literature data, patients with genetically reduced CYP2C19 function have lower systemic exposure to the active metabolite of clopidogrel and diminished antiplatelet responses, and generally exhibit higher cardiovascular event rates following myocardial infarction than do patients with normal CYP2C19 function

- November 2009: Precaution upgraded to a warning
- March 2010: Warning upgraded to a “Boxed Warning”

WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

See full prescribing information for complete boxed warning.

- Effectiveness of Plavix depends on activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19.
- Poor metabolizers treated with Plavix at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function.
- Tests are available to identify a patient's CYP2C19 genotype and can be used as an aid in determining therapeutic strategy.
- Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers.

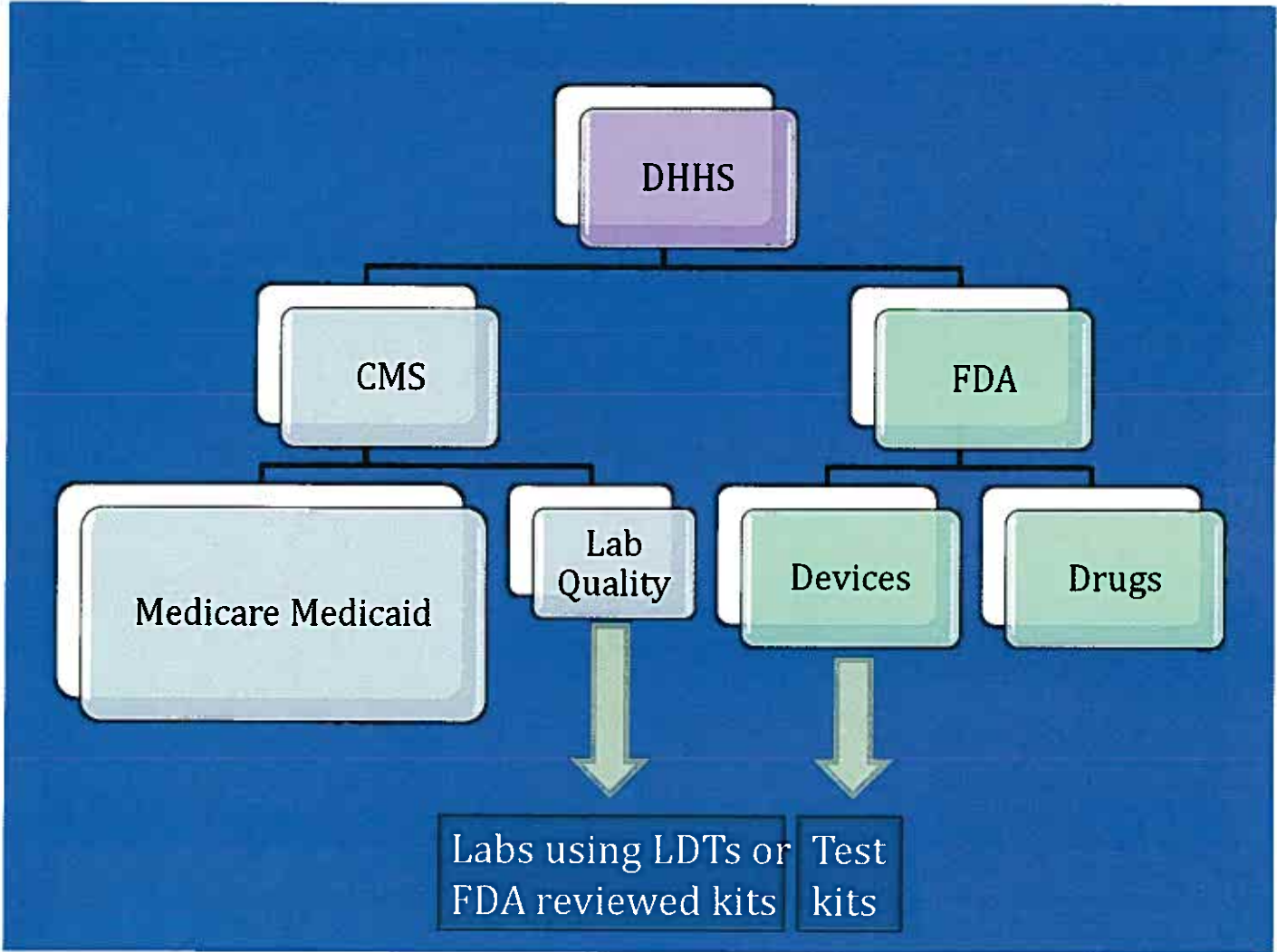
Genetic Tests must provide...

- Analytic Validity
- Clinical Validity
- Clinical Utility



Two types of Genetic Tests

- Level of regulatory oversight oddly disparate
- Difference not apparent to patients and health care providers.



Longstanding and Long recognized Problems

- 1997 NIH/DOE Genetic Testing Task Force Recommendations
- 2000 SACGT Recommendations
- 2008 SACGHS Recommendations

NIH is Building a Genetic Testing Registry

To improve research and public health through:

- Increasing transparency
- Increasing consumer, physician, and researcher access to information
- Increasing marketplace competition

Seeking broad public input on
the design of the registry

