

# **GENETICS**

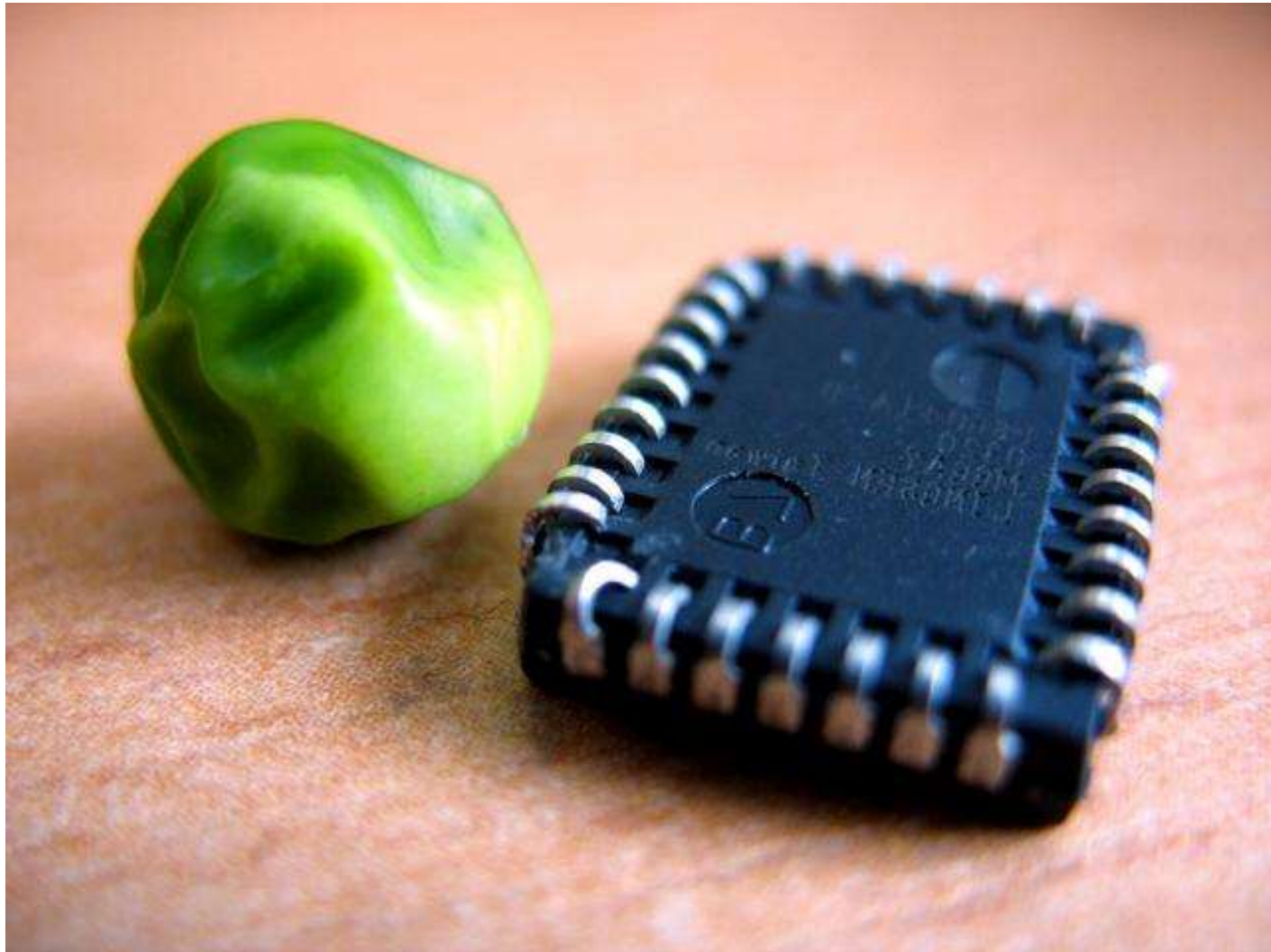
## **Actualities in intensive therapy 2014**

Krisztina Madách

Semmelweis University  
Dept. of Anaesthesiology and Intensive Therapy

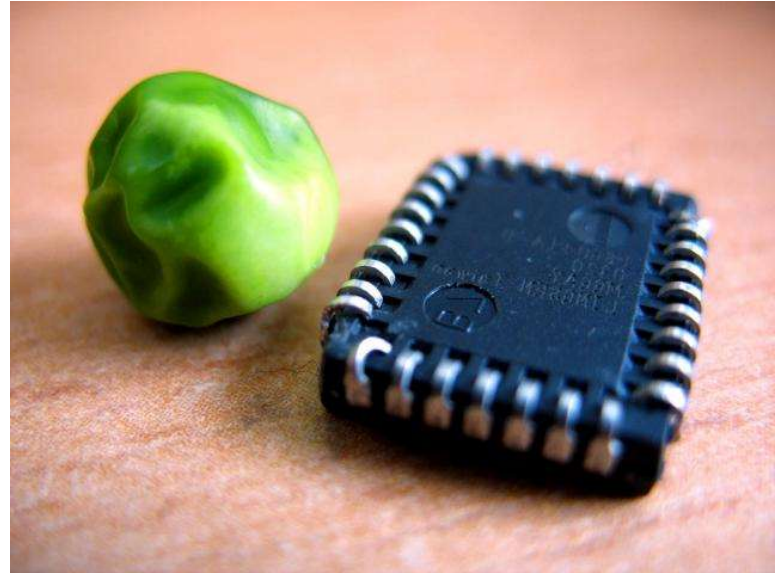


# Genetics 1865-2014: science or everyday practice?

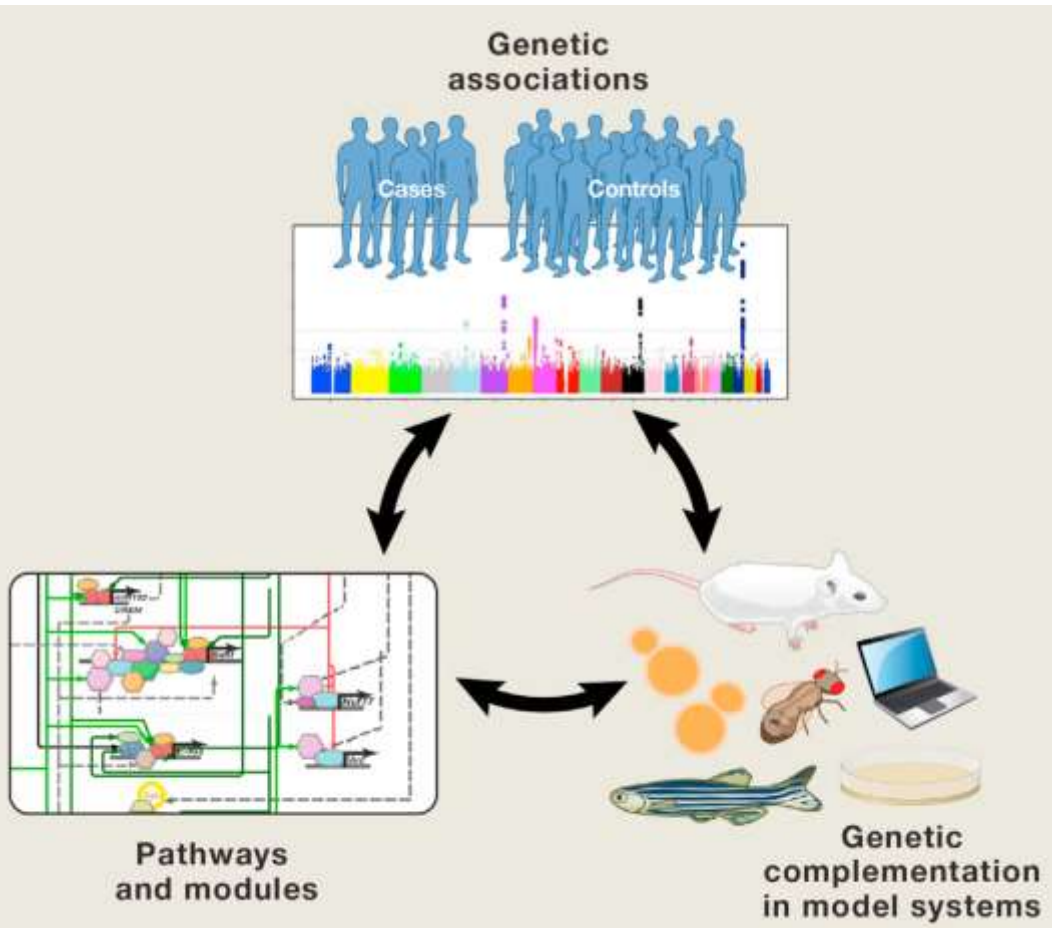


# Genetics 2010-2014: science or everyday practice?

- **Pathophysiology**
- Pharmacogenomics
- Diagnostics
- Reducing risk
- Therapy
- Screening-counseling



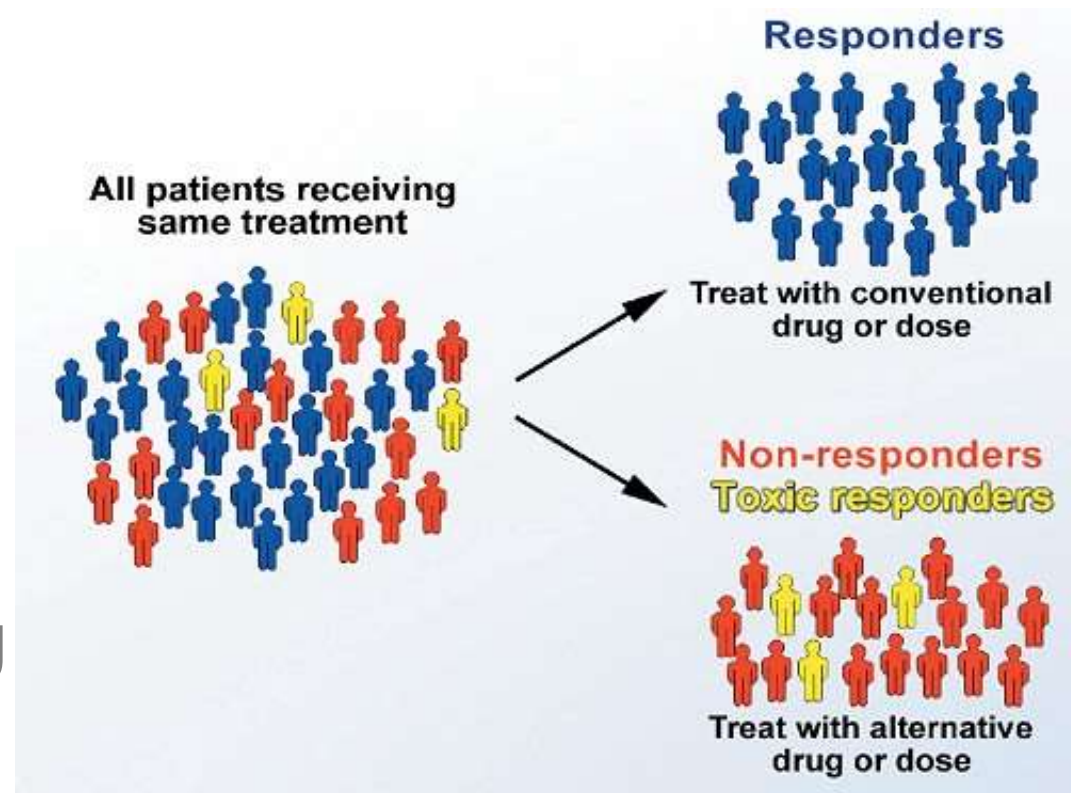
# Genetics ease understanding pathophysiology



- Candidate gene variants are enriched in patients
- Disruption of the gene in a model gives rise to a phenotype that is relevant and “equivalent” to the human phenotype
- The model phenotype
  - can be rescued with the wild-type human alleles
  - cannot be rescued with the mutant human alleles.

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# Genetic predisposition to adverse drug reactions in the intensive care unit

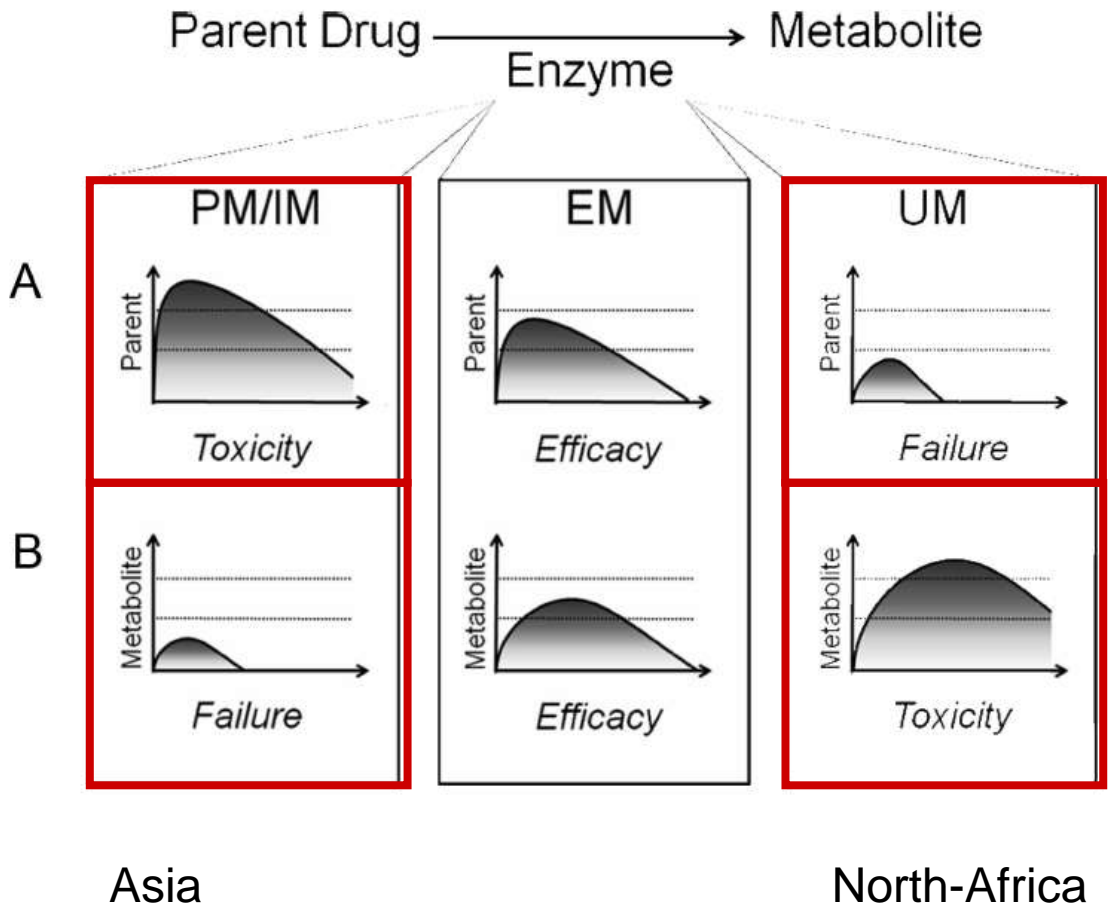
Philip E. Empey, PharmD, PhD, BCPS

Crit Care Med 2010 Vol. 38, No. 6 (Suppl.)


- ADR: 6,7% in hospitalized patients
- 6th cause of death
- Drugs:
  - Succinylcholin-prolonged apnoe (pseudocholinesterase)
  - Primaquine-haemolysis in african (G-6-P dehydrogenase)
  - Analgetics, sedatives, cardiovasc., anticoagulant, antimicrobial agents

# Pharmacokinetics

- A
  - Haloperidol
  - B-blockers
  - **Warfarin**
  - Phenytoin intox.
  - Statin myopathy
  - **PPI** ineffectivity
- B
  - **Clopidogrel**
  - **Codein-morphin**



# Test of Warfarin sensitivity (<21, >49 mg/week) *CYP2C9 and VKORC1*

**FDA** U.S. Food and Drug Administration  U.S. Department of Health and Human Services

[FDA Home Page](#) | [Search FDA Site](#) | [FDA A-Z Index](#) | [Contact FDA](#)


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## FDA News

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*The NEW ENGLAND JOURNAL of MEDICINE*

**CORRESPONDENCE**

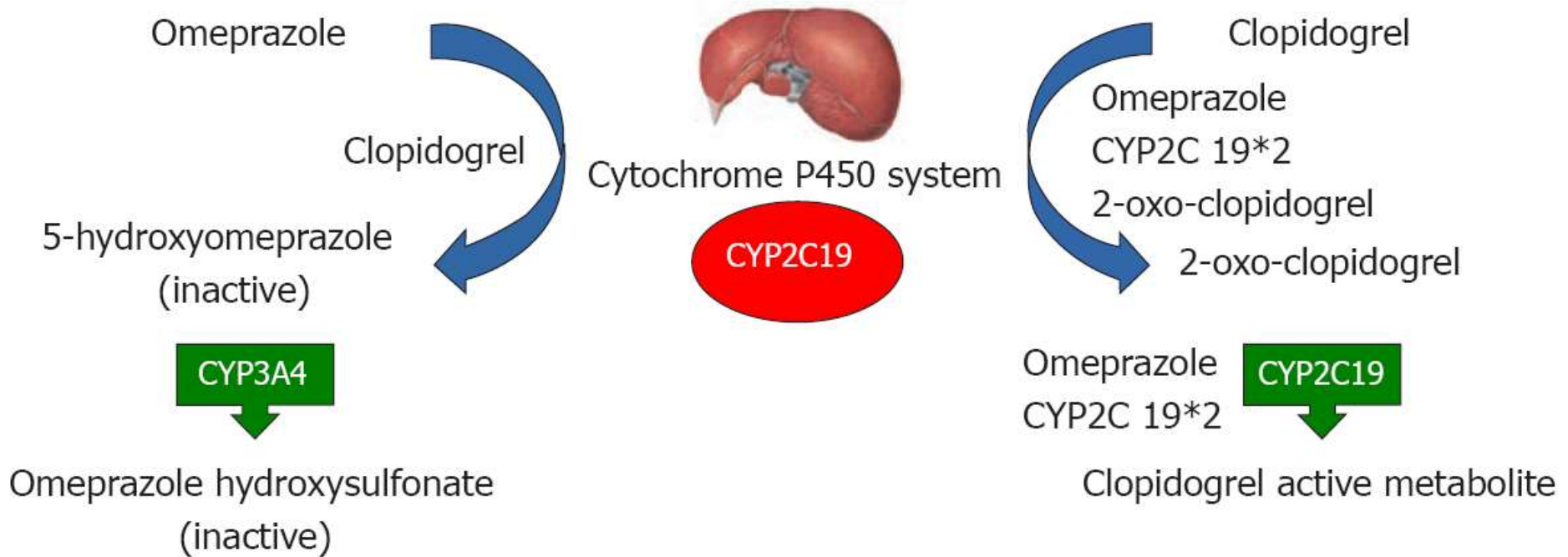


**Genotype-Guided Dosing of Vitamin K Antagonists**

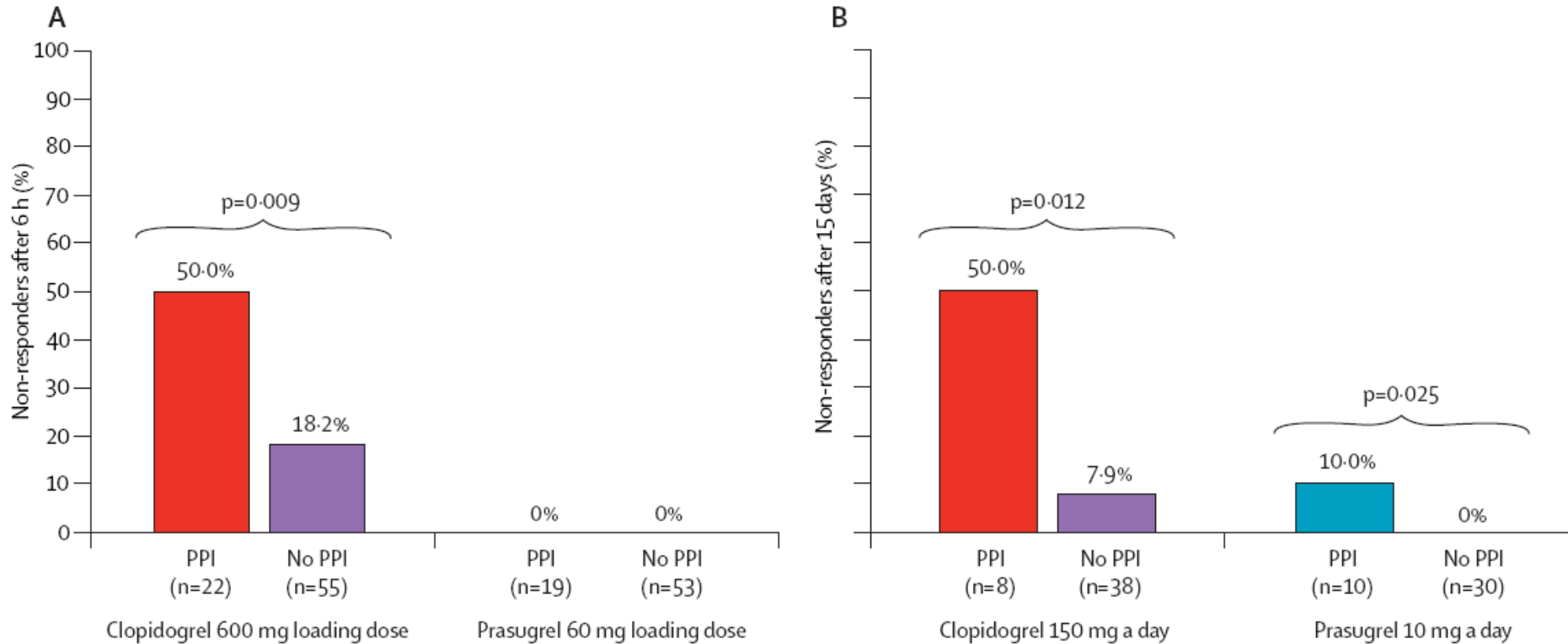
N ENGL J MED 370;18 NEJM.ORG MAY 1, 2014



# PPI-clopidogrel interaction?



# Thienopyridin/PPI interaction in vitro





*World Journal of  
Gastroenterology*

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wjg@wjgnet.com  
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*TOPIC HIGHLIGHT*

**Andrzej S Tarnawski, MD, PhD, DSc (Med), Professor, Series Editor**

## **Clopidogrel and proton pump inhibitors - where do we stand in 2012?**

Michael D Drepper, Laurent Spahr, Jean Louis Frossard

- In high AUGIB risk patients PPI is recommended when clopidogrel is administered.
- If possible choose a drug with lesser inhibitory effect on CYP2C19 (pantoprazole instead of omeprazole)

# Safety of codeine during breastfeeding

*Fatal morphine poisoning in the breastfed neonate of a mother prescribed codeine*

Parvaz Madadi Gideon Koren, MD, FRCPC James Cairns, MD David Chitayat, MD Andrea Gaedigk, PHD  
J. Steven Leeder, PHARM.D, PHD Ronni Teitelbaum, MSC Tatyana Karaskov, MD Katarina Aleksa, PHD

## ABSTRACT

**QUESTION** Recently a newborn died from morphine poisoning when his mother used codeine while breastfeeding. Many patients receive codeine for postlabour pain. Is it safe to prescribe codeine for nursing mothers?

**ANSWER** When a mother is an ultrarapid metabolizer of cytochrome P450 2D6, she produces much more morphine when taking codeine than most people do. In this situation, newborns might be exposed to toxic levels of morphine when breastfeeding. Options to reduce this risk include discontinuing codeine after 2 to 3 days of use and being aware of symptoms of potential opioid toxicity in both mothers and newborns.

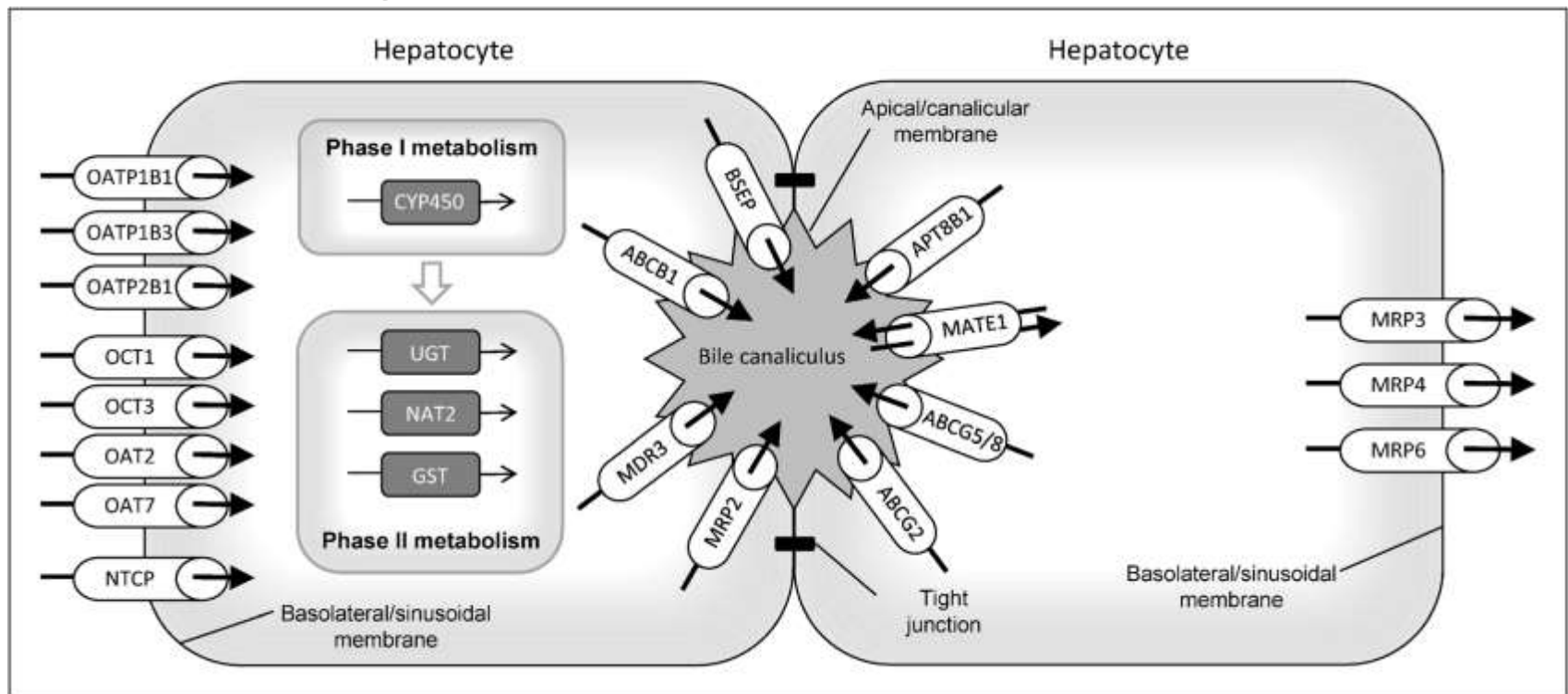
# Pharmacodynamics

- Stevens-Johnson sy., toxic epidermal necrolysis
- FDA: In case of carbamazepine treatment screening for HLA-B\*1502 is recommended in Asian population



# Genetic background of DILI

- SNP tests (key proteins involved in metabolism and transport)
- Genome wide association studies: closely related to HLA II region





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# Polymerase chain reaction-based pathogen detection



# What do we know about human genetic testing?

- 7% knowledgeable, 75% somewhat knowledgeable, 18% little (United Healthcare, 2012)
- Genetics/genomics has been included in baccalaureate degree of nurses since 2008 (American Association of Colleges of Nursing)
- Actually 2300 from 2500 tests are available for daily practice
- „Code of practice”
- Education/training/SPECIALIST
- „GeneTests” : National Center for Biotechnology Information (NCBI)





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Welcome to **GeneTests**, a medical genetics information resource. [NEW TESTS](#)

## Welcome

### The GeneTests website

Welcome to the updated and newly envisioned GeneTests! From its start in 1992, GeneTests has grown and changed to reflect the advances in clinical genetic test capabilities and to address the needs of our ever widening user community. The current changes derive from our efforts to continue this website's history of excellence and growth. Our Goal is to

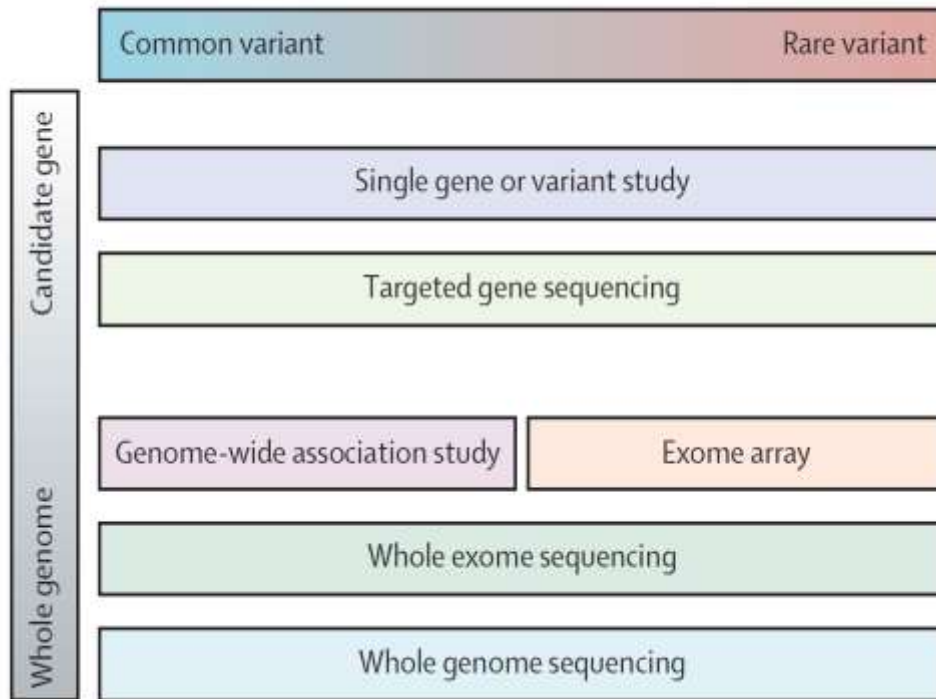
## What's New

### We are back from the ACMG meeting and ready to go

We enjoyed meeting and talking with many of you at the American College of Medical Genetics meeting last week. Hearing your comments about how important GeneTests is to your daily practice has reinforced our enthusiasm for making GeneTests even better. Now that we are back at our desks, our focus is to

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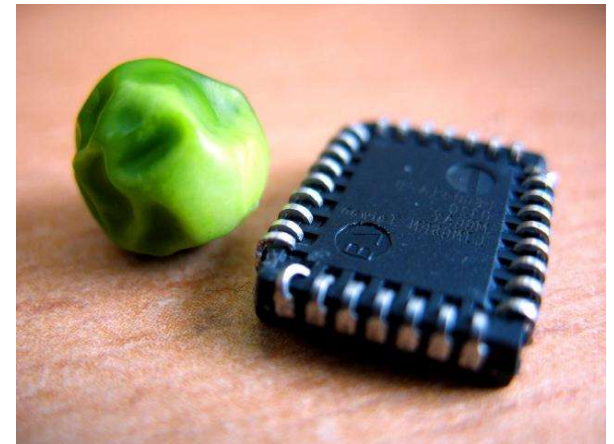
# Depth and accuracy of genetic testing



- Index test
  - 4-8 weeks
  - 2.100 – 4.000 Euro
- Mutation specific confirmatory test
  - 2-4 weeks
  - 70 - 630 Euro

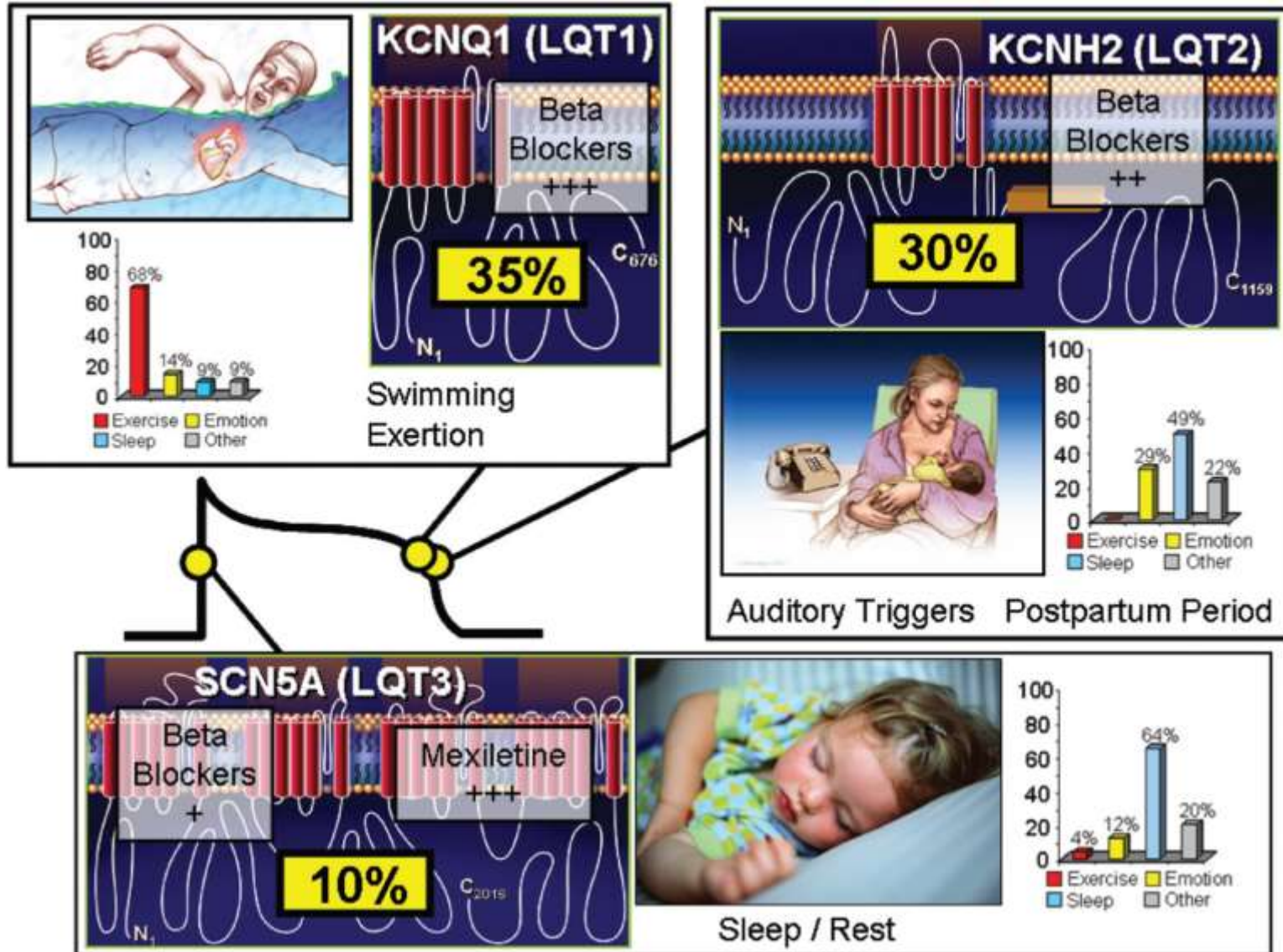
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# Potentially lethal, treatable, hereditary channelopathies



# Genetics *2010-2014*: science or everyday practice?

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# Genetic screening-counseling

*„Knowledge can be dangerous, but  
indifference is far more harmful.“*



*Ede Teller (1908-2003)*

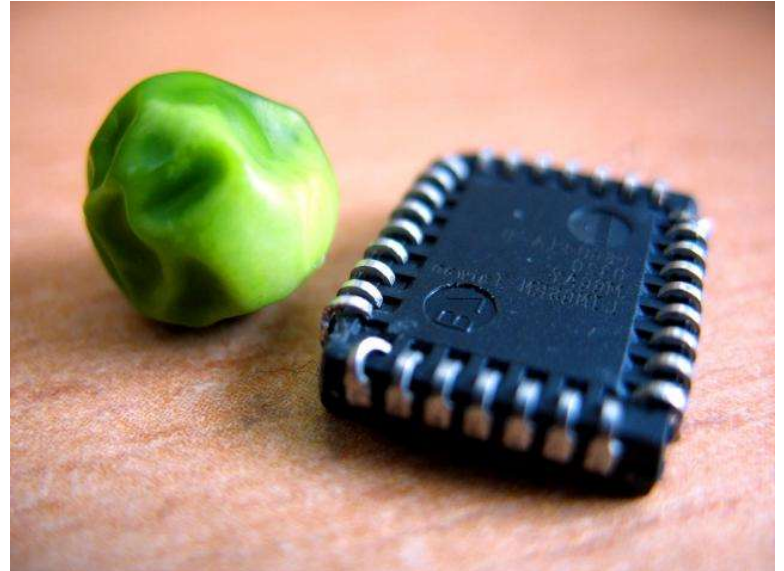
# Genetic screening-counseling



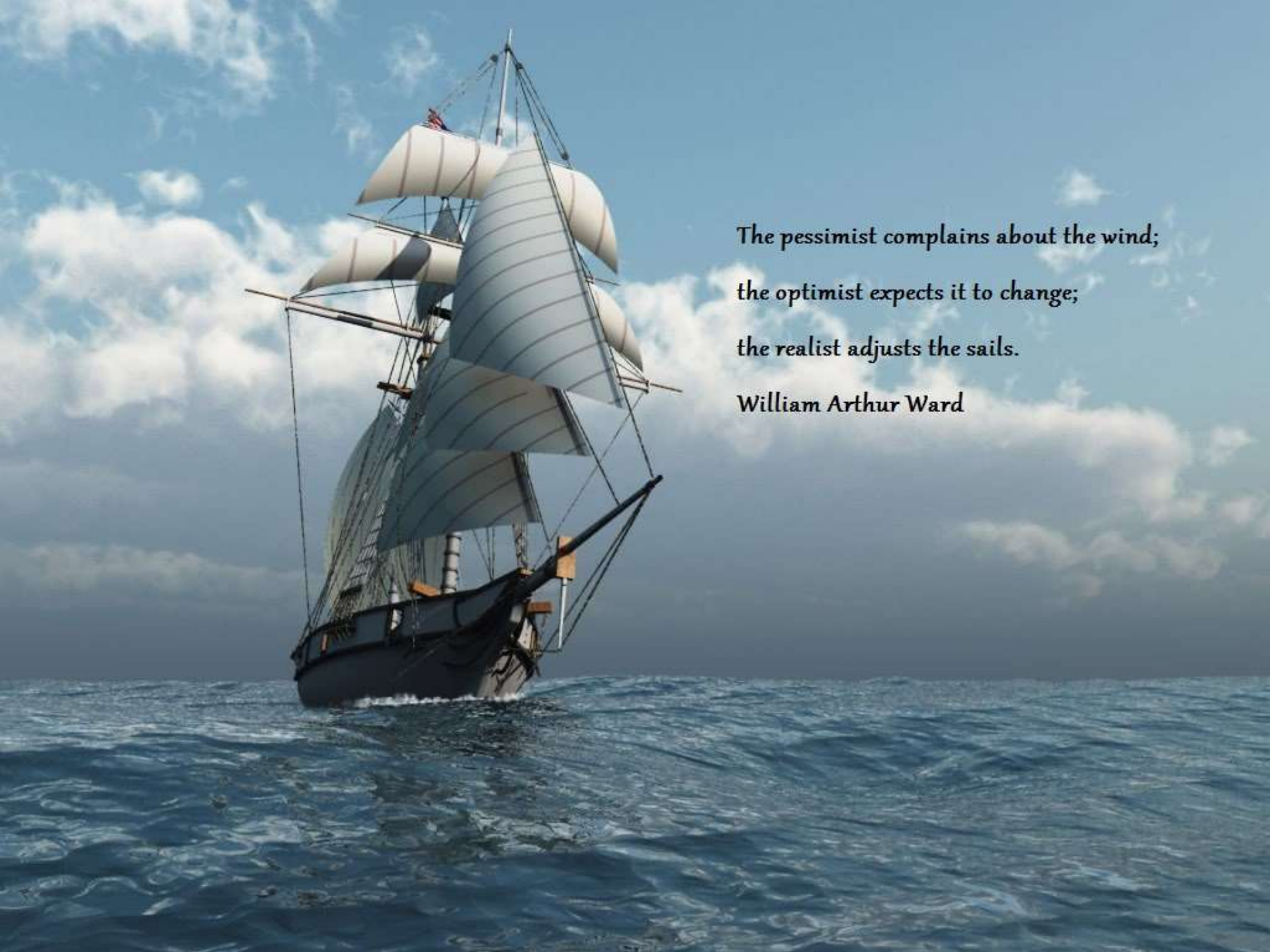
- ~ 2300 available tests, but exact signal to noise ratio is known by only a few of them
- Qualified specialist's opinion is required
  - Detailed family history record
  - Evaluation of type of heredity
  - In case of test **WRITTEN INFORMED CONSENT!**
    - Risk/benefit/limits/cost/availability/consequences
  - Psychosocial/ legal aspects
    - GINA 2008 (Genetic Information Nondiscrimination Act)

# Slowly but surely genetics infiltrates all parts of medicine

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*The pessimist complains about the wind;  
the optimist expects it to change;  
the realist adjusts the sails.*

*William Arthur Ward*