open.michigan

Author(s): David Ginsburg, M.D., 2012

Attribution Key

for more information see: http://open.umich.edu/wiki/AttributionPolicy

Use + Share + Adapt

{ Content the copyright holder, author, or law permits you to use, share and adapt. }

PD-GOV **Public Domain – Government**: Works that are produced by the U.S. Government. (17 USC § 105)

PD-EXP **Public Domain – Expired**: Works that are no longer protected due to an expired copyright term.

PD-SELF **Public Domain – Self Dedicated**: Works that a copyright holder has dedicated to the public domain.

ZERO **Creative Commons – Zero Waiver**

BY **Creative Commons – Attribution License**

BY-SA **Creative Commons – Attribution Share Alike License**

BY-NC **Creative Commons – Attribution Noncommercial License**

BY-NC-SA **Creative Commons – Attribution Noncommercial Share Alike License**

GNU-FDL **GNU – Free Documentation License**

Make Your Own Assessment

{ Content Open.Michigan believes can be used, shared, and adapted because it is ineligible for copyright. }

PD-INEL **Public Domain – Ineligible**: Works that are ineligible for copyright protection in the U.S. (17 USC § 102(b)) *laws in your jurisdiction may differ

{ Content Open.Michigan has used under a Fair Use determination. }

FAIR USE **Fair Use**: Use of works that is determined to be Fair consistent with the U.S. Copyright Act. (17 USC § 107) *laws in your jurisdiction may differ

Our determination **DOES NOT** mean that all uses of this 3rd-party content are Fair Uses and we **DO NOT** guarantee that your use of the content is Fair.

To use this content you should **do your own independent analysis** to determine whether or not your use will be Fair.

The Human Genome II

M1 Patients and Populations

David Ginsburg, MD

Fall 2012

University of Michigan
Medical School

Relationships with Industry

UMMS faculty often interact with pharmaceutical, device, and biotechnology companies to improve patient care, and develop new therapies. UMMS faculty disclose these relationships in order to promote an ethical & transparent culture in research, clinical care, and teaching.

- I am a member of the Board of Directors for Shire plc.
- I am a member of the Scientific Advisory Boards for Portola Pharmaceuticals and Catalyst Biosciences.
- I benefit from license/patent royalty payments to Boston Children's Hospital (VWF) and the University of Michigan (ADAMTS13).

Disclosure required by the UMMS Policy on Faculty Disclosure of Industry Relationships to Students and Trainees.

Learning Objectives

UNDERSTAND:

- The basic anatomy of the human genome [eg. 3 X10^9 bp (haploid genome); 1-2% coding sequence (~20,000 genes); types and extent of DNA sequence variation].
- Recombination and how it allows genes to be mapped
- Genetic data for a pedigree, assigning phase, defining haplotypes
- Linkage: Distinction between a linked marker and the disease causing mutation itself
- Linkage disequilibrium and haplotype blocks
- Genome wide association studies (GWAS) to identify gene variants contributing to complex diseases/traits
- The implications of GWAS findings for clinical care and "Personalized Medicine"
- The implications of "Next-Gen" sequencing for future clinical medicine

genetics/genomics in the clinic

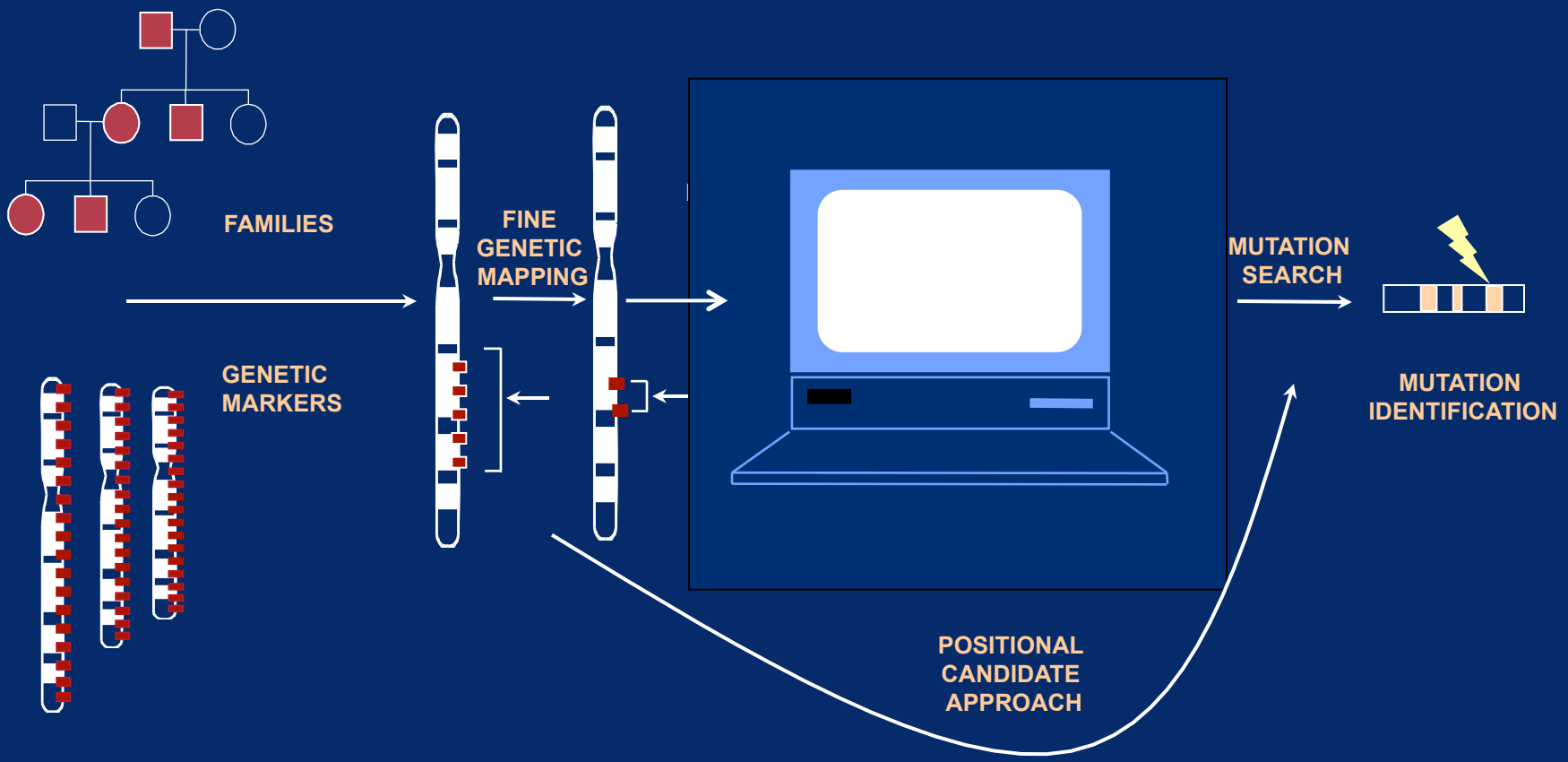
- Better/earlier diagnosis:
  - Mendellian disorders

Exceeding expectations

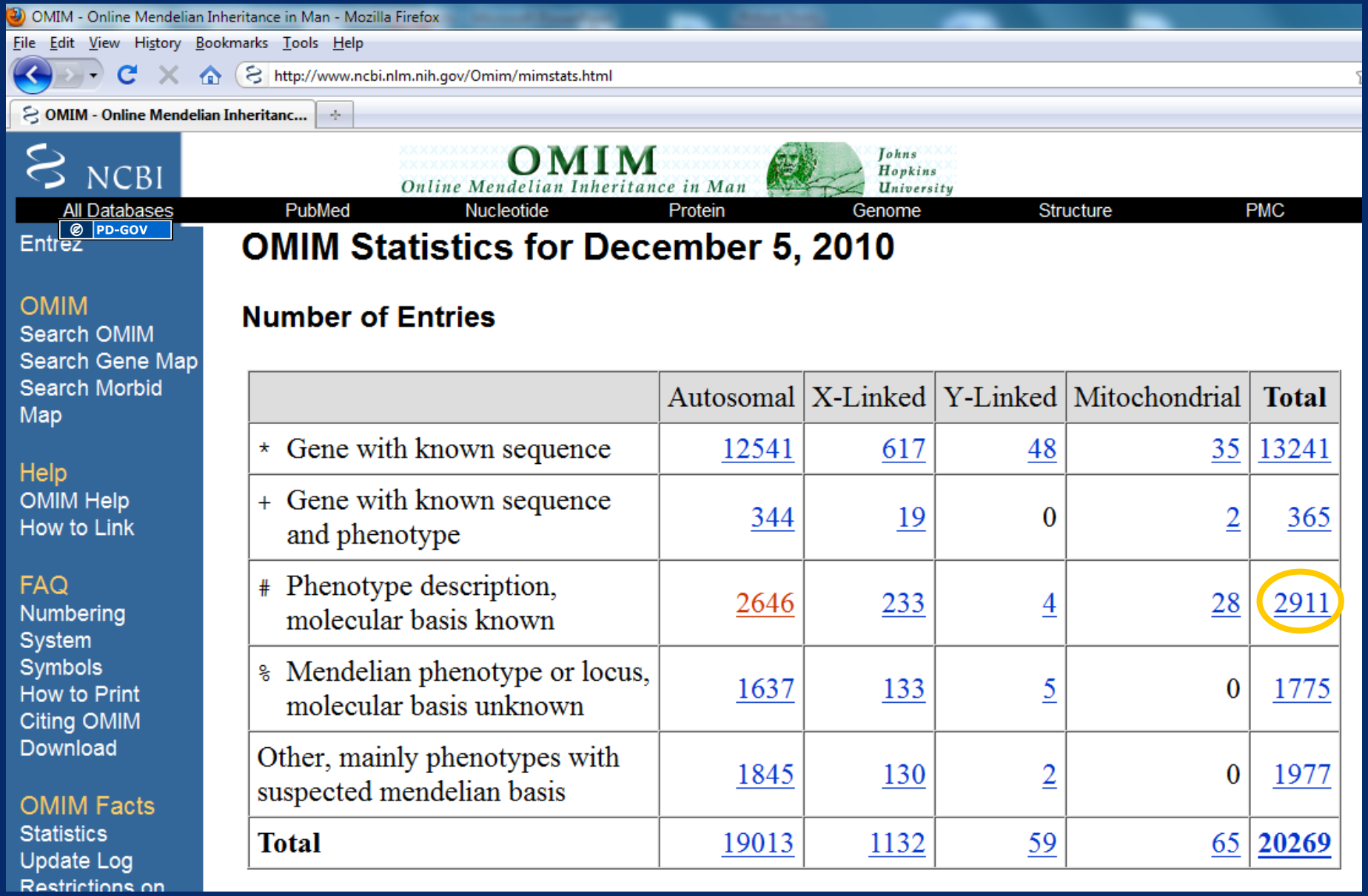
  - Complex disorders
- Guiding/selecting treatment:
  - Subclassifying cancers
    - Somatic mutations
    - Expression profiles
  - Customized/designer treatment
  - Pharmacogenomics

FAR below expectations /promises

Positional Cloning



 Gelehrter, Collins and Ginsburg: *Principles of Medical Genetics 2E;* Figure 9.15



 http://www.ncbi.nlm.nih.gov/Omim/mimstats.html

Complex Diseases

- Hypertension
- Coronary artery disease
- Diabetes
- Obesity
- Cancer
- …

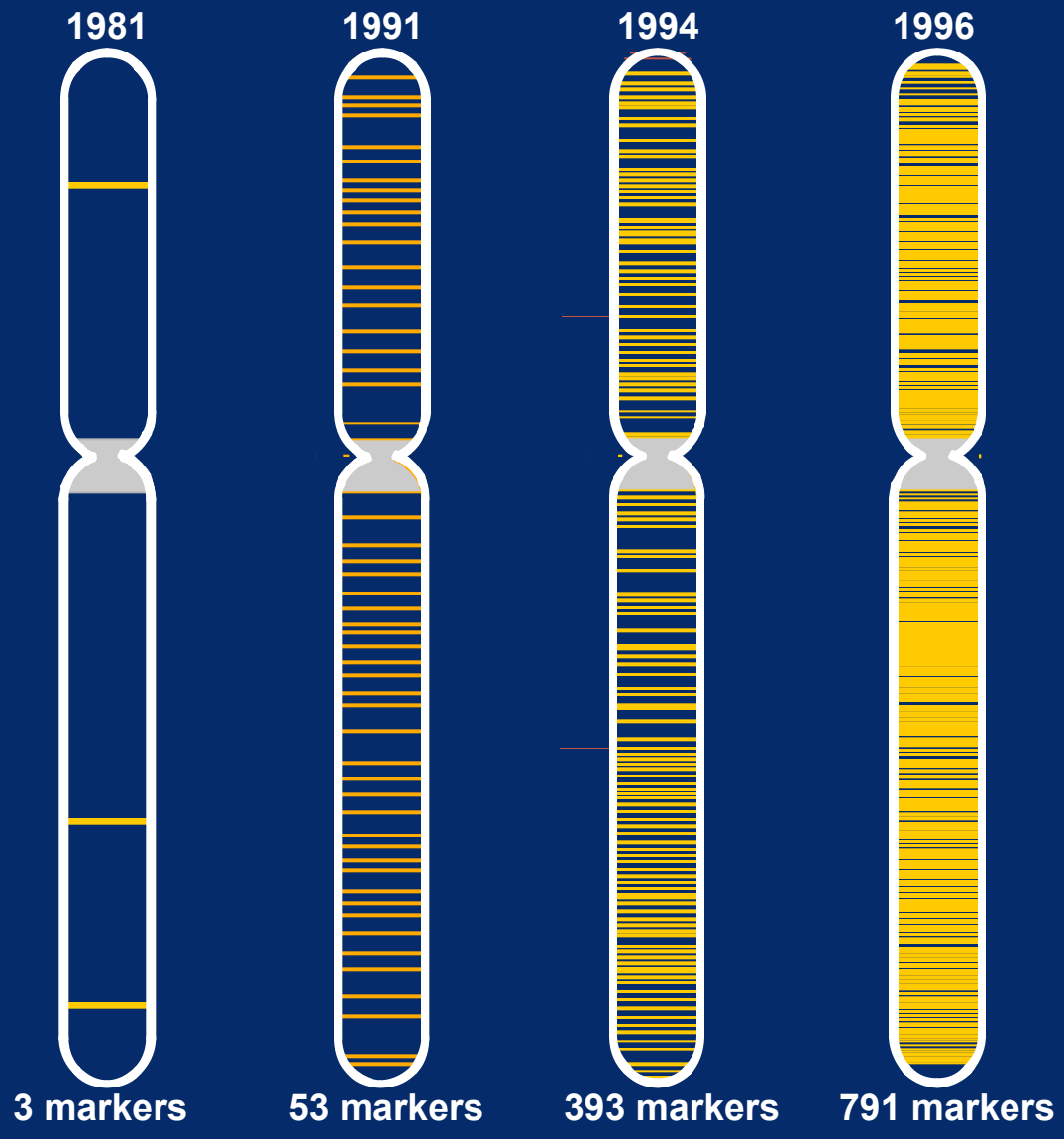
Difficult to map in large pedigrees by conventional linkage (multiple genes, variable effects)

- Candidate gene association study
  - Test a SNP (or SNPs) surrounding your favorite gene for association with disease (more common in patients than controls)
    - Publication bias
    - Multiple observations
    - Population substructure
    - “looking under the streetlamp”

vs.

- Genome-wide association study (GWAS)
  - Unbiased
  - No prior assumptions

Human Chromosome 4



2010

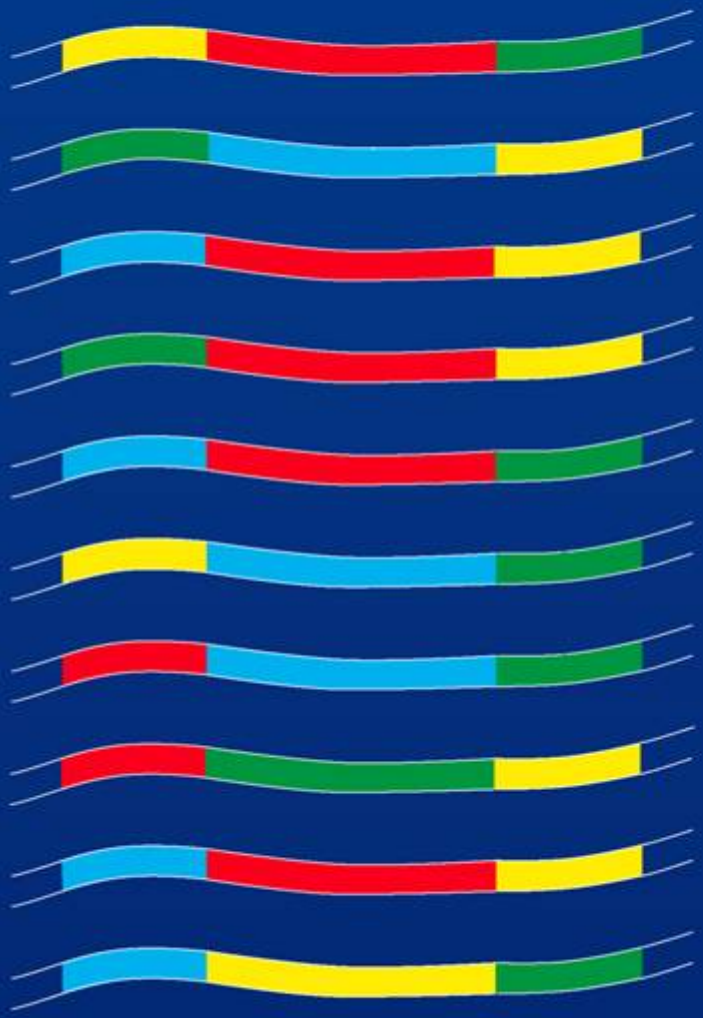
- 23,653,737 total human entries in dbSNP

http://www.ncbi.nlm.nih.gov/projects/SNP/

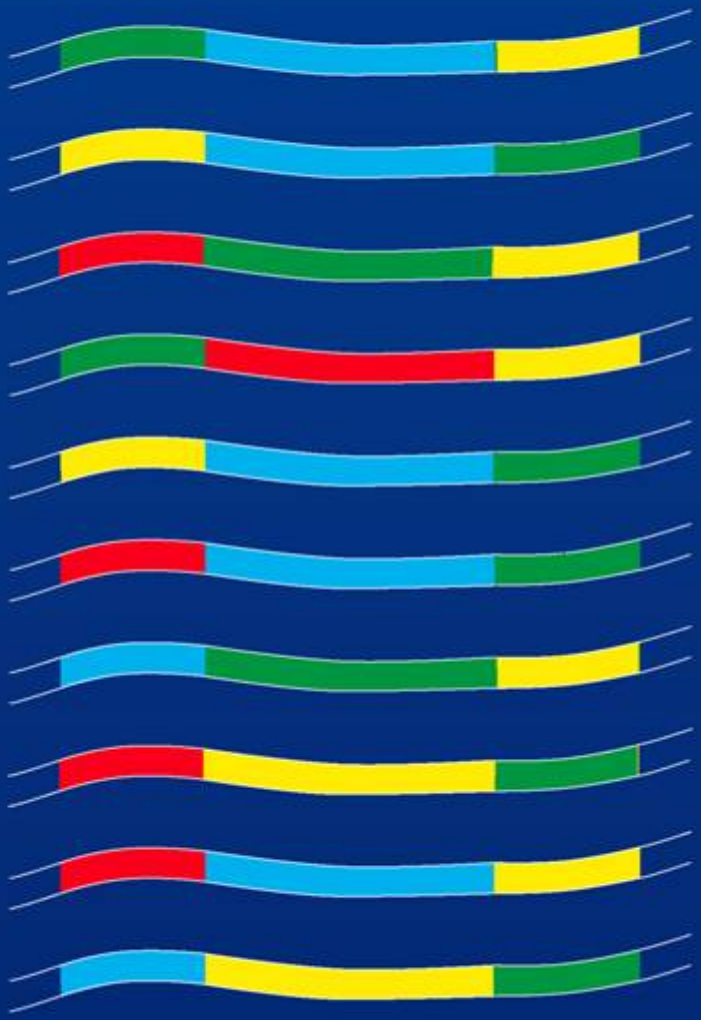
- Chromosome 4
  - 4,311,728 SNPs
- ~1M SNP chip commercially available

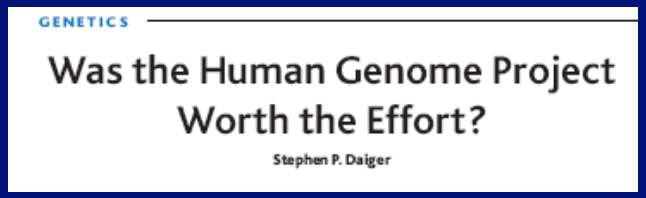
 Gelehrter, Collins and Ginsburg: *Principles of Medical Genetics 2E;* Figure 10.3

Affected



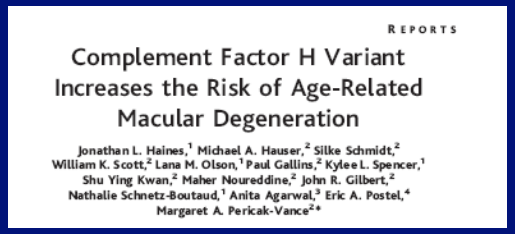
Unaffected




GENETICS

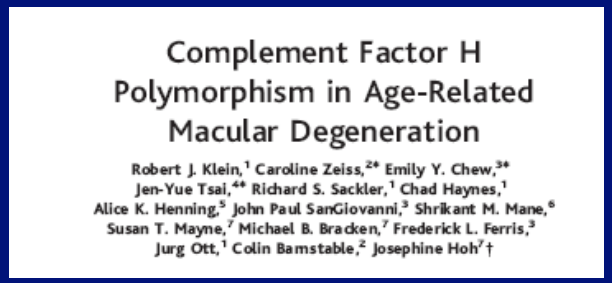
Was the Human Genome Project Worth the Effort?

Stephen P. Daiger

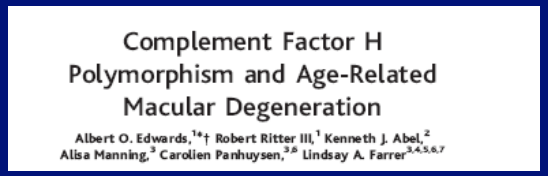

REPORTS

Complement Factor H Variant Increases the Risk of Age-Related Macular Degeneration

Jonathan L. Haines,[1] Michael A. Hauser,[2] Silke Schmidt,[2] William K. Scott,[2] Lana M. Olson,[1] Paul Gallins,[2] Kylee L. Spencer,[1] Shu Ying Kwan,[2] Maher Noureddine,[2] John R. Gilbert,[2] Nathalie Schnetz-Boutaud,[1] Anita Agarwal,[3] Eric A. Postel,[4] Margaret A. Pericak-Vance[2]*


Complement Factor H Polymorphism in Age-Related Macular Degeneration

Robert J. Klein,[1] Caroline Zeiss,[2]* Emily Y. Chew,[3]* Jen-Yue Tsai,[4]* Richard S. Sackler,[1] Chad Haynes,[1] Alice K. Henning,[5] John Paul SanGiovanni,[3] Shrikant M. Mane,[6] Susan T. Mayne,[7] Michael B. Bracken,[7] Frederick L. Ferris,[3] Jurg Ott,[1] Colin Barnstable,[2] Josephine Hoh[7]†


Complement Factor H Polymorphism and Age-Related Macular Degeneration

Albert O. Edwards,[1]*† Robert Ritter III,[1] Kenneth J. Abel,[2] Alisa Manning,[2] Carolien Panhuysen,[3,8] Lindsay A. Farrer[3,4,5,6,7]

Science, April 15, 2005

- Age-related macular degeneration (AMD)
  - > 10 million cases in the US
  - Leading cause of blindness among the elderly
- Common variant in complement factor H (CFH) gene
  - Tyr402His
  - His allele = 2-4 X increase risk of AMD
  - Accounts for 20-50% of AMD risk

Vol 445 | 22 February 2007 | doi:10.1038/nature05616 nature

ARTICLES

A genome-wide association study identifies novel risk loci for type 2 diabetes

Robert Sladek[1,2,4], Ghislain Rocheleau[1]*, Johan Rung[4]*, Christian Dina[5]*, Lishuang Shen[1], David Serre[1], Philippe Boutin[5], Daniel Vincent[4], Alexandre Belisle[4], Samy Hadjadj[6], Beverley Balkau[7], Barbara Heude[7], Guillaume Charpentier[8], Thomas J. Hudson[4,9], Alexandre Montpetit[4], Alexey V. Pshezhetsky[10], Marc Prentki[10,11], Barry I. Posner[2,12], David J. Balding[13], David Meyre[5], Constantin Polychronakos[1,3] & Philippe Froguel[5,14]

Sciencexpress / www.sciencexpress.org / 26 April 2007 / Page 1/ 10.1126/science.1142358

Sciencexpress Report

Replication of Genome-Wide Association Signals in U.K. Samples Reveal for Type 2 Diabetes

Eleftheria Zeggini,[1,2*] Michael N. Weedon,[3,4*] Cecilia M. Lindgren,[1,2*] Timothy M. Frayling, Katherine S. Elliott,[2] Hana Lango,[3,4] Nicholas J. Timpson,[2,5] John R. B. Perry,[3,4] Nigel W. R Rachel M. Freathy,[3,4] Jeffrey C. Barrett,[2] Beverley Shields,[4] Andrew P. Morris,[2] Sian Ellard, Christopher J. Groves,[1] Lorna W. Harries,[4] Jonathan L. Marchini,[7] Katharine R. Owen,[1] Bea Lon R. Cardon,[2] Mark Walker,[8] Graham A. Hitman,[9] Andrew D. Morris,[10] Alex S. F. Doney, The Wellcome Trust Case Control Consortium,[11] Mark I. McCarthy,[1,2†‡] Andrew T. Hatters

Sciencexpress Report

A Genome-Wide Association Study of Type 2 Diabetes in Finns Detects Multiple Susceptibility Variants

Laura J. Scott,[1] Karen L. Mohlke,[2] Lori L. Bonnycastle,[3] Cristen J. Willer,[1] Yun Li,[1] William L. Duren,[1] Michael R. Erdos,[3] Heather M. Stringham,[1] Peter S. Chines,[3] Anne U. Jackson,[1] Ludmila Prokunina-Olsson,[3] Chia-Jen Ding,[1] Amy J. Swift,[3] Narisu Narisu,[3] Tianle Hu,[1] Randall Pruim,[4] Rui Xiao,[1] Xiao-Yi Li,[1] Karen N. Conneely,[1] Nancy L. Riebow,[3] Andrew G. Sprau,[3] Maurine Tong,[3] Peggy P. White,[1] Kurt N. Hetrick,[3] Michael W. Barnhart,[3] Craig W. Bark,[3] Janet L. Goldstein,[3] Lee Watkins,[3] Fang Xiang,[1] Jouko Saramies,[4] Thomas A. Buchanan,[7] Richard M. Watanabe,[8,9] Timo T. Valle,[10] Leena Kinnunen,[10,11] Gonçalo R. Abecasis,[1] Elizabeth W. Pugh,[3] Kimberly F. Doheny,[3] Richard N. Bergman,[9] Jaakko Tuomilehto,[10,11,12] Francis S. Collins,[3]* Michael Boehnke[1]*

Sciencexpress R

Genome-Wide Association Analysis Identifies Loci for Type 2 Diabetes and Triglyceride Levels

Diabetes Genetics Initiative of Broad Institute of Harvard and MIT, Lund University, and Novartis Institutes for BioMedical Research*†

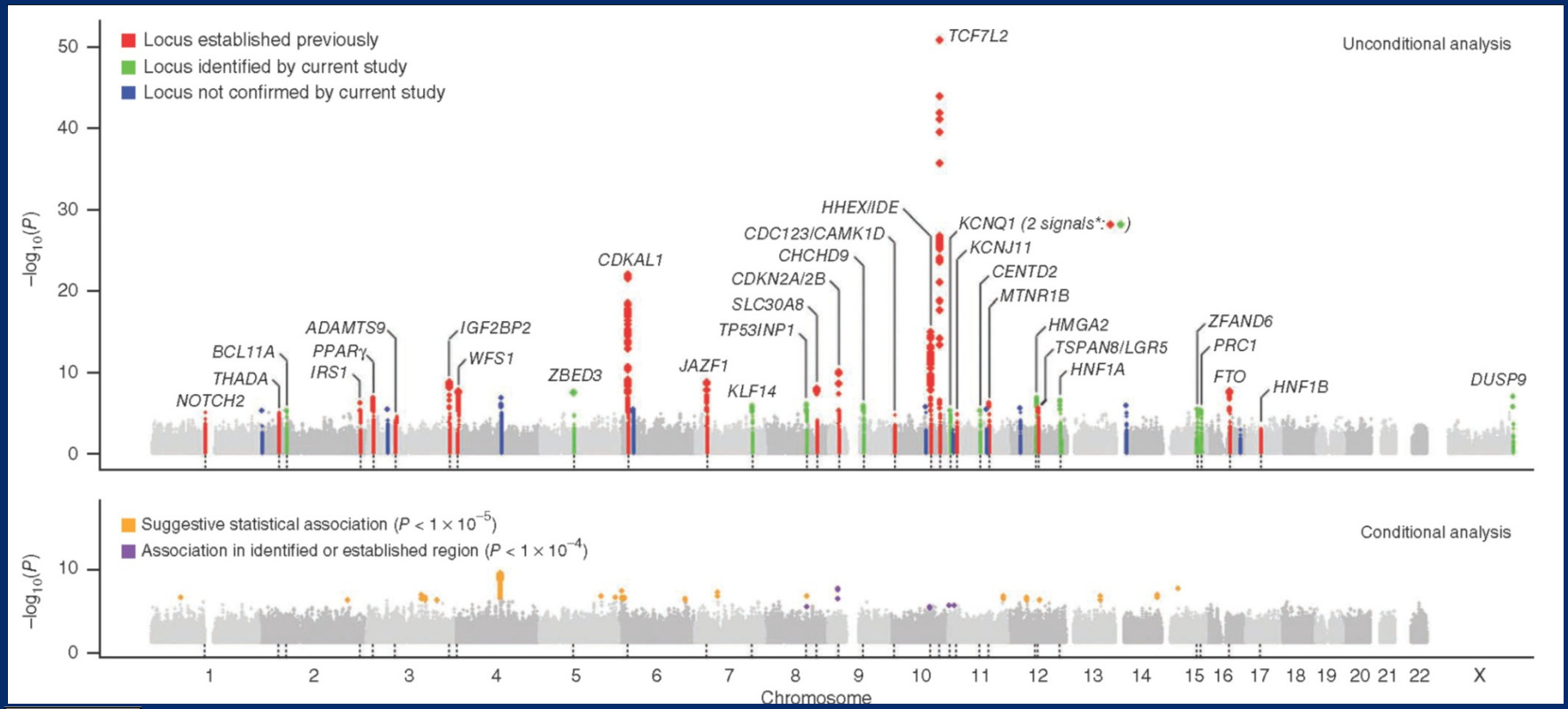
*To whom correspondence should be addressed: David Altshuler, Leif Groop, Thomas E. Hughes. E-mail: altshuler@molbio.mgh.harvard.edu (D.A.), leif.groop@med.lu.se (L.G.), thomase.hughes@novartis.com (T.E.H.)
†All authors with their contributions and affiliations appear at the end of this paper.

The Multiple observations problem

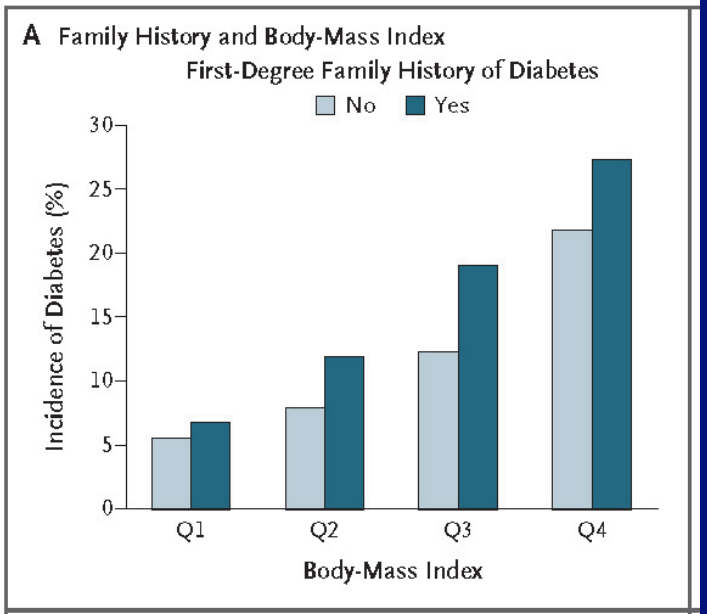
- Roll the dice once
  - Probability of rolling two 6's = 2.8% (1:36=1/6 X 1/6)
- Roll the dice twice
  - Probability of rolling two 6's at least once = 5.5%
- Roll the dice 100 times
  - Probability of rolling two 6's at least once = ***94%***

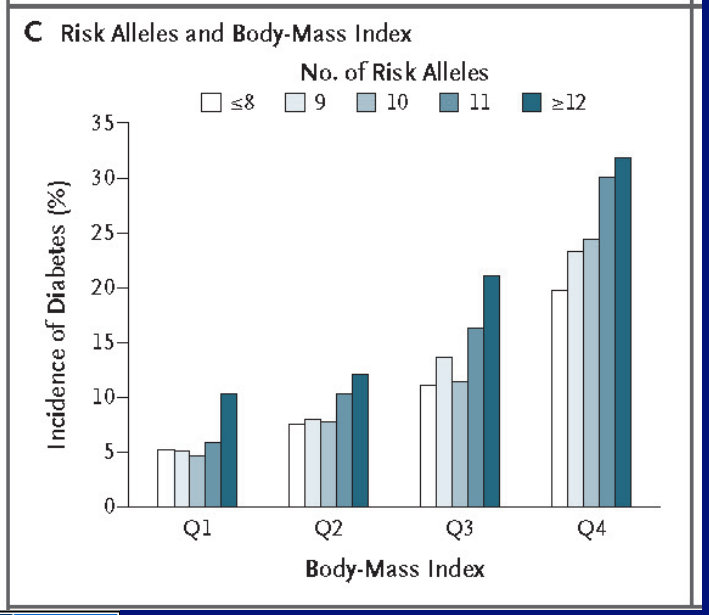
Test 1 million SNPs, 100 phenotypes . . .

Type 2 Diabetes GWAS: Manhattan Plot



PD-INEL Voight et al., *Nature Genetics*, **42**:579, 2010.





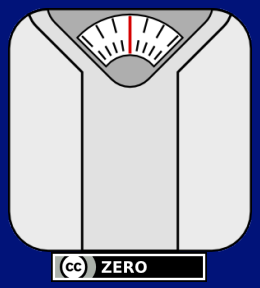
Lyssenko et al. *Clinical risk factors, DNA variants, and the development of type 2 diabetes*. **N Engl J Med**. 359:2220, 2008.

Conclusions:

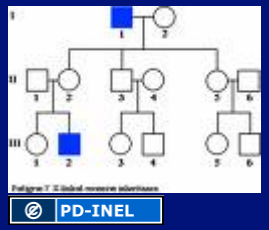
"*As compared with clinical risk factors alone, common genetic variants associated with the risk of diabetes had a small effect on the ability to predict the future development of type 2 diabetes.*"

Diabetes Risk

- Obesity OR=>3
- Family history OR=>3
- GWAS SNPs OR=<<1.4



+



>>

BY-SA Ricardipus (wikipedia)

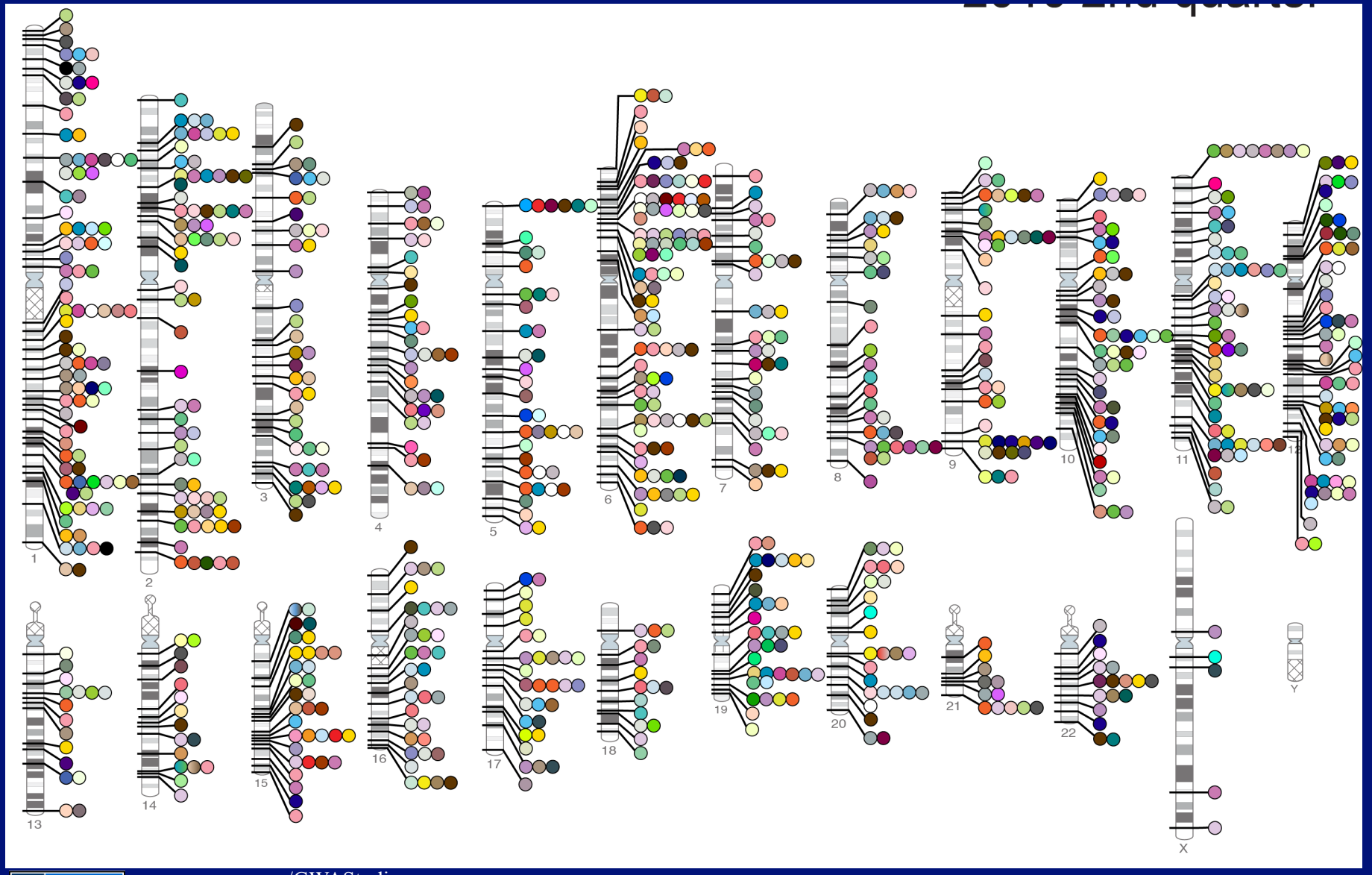
Other Genome Wide Association Studies (GWAS)

- Heart disease
  - MI, AF, QT prolongation, CAD, lipids
- Inflammatory bowel disease
- Asthma
- Neuropsychiatric disorders
  - ALS, MS, Alzheimer, schizophrenia, bipolar disorder
- Rheumatologic disorders
  - RA, SLE
- Cancer risk
  - breast, prostate, colon
- Common traits
  - BMA, height, hair/eye/skin color


Acute lymphoblastic leukemia
Adhesion molecules
Adiponectin levels
Age-related macular degeneration
AIDS progression
Alcohol dependence
Alzheimer disease
Amyotrophic lateral sclerosis
Angiotensin-converting enzyme activity
Ankylosing spondylitis
Arterial stiffness
Asthma
Atherosclerosis in HIV
Atrial fibrillation
Attention deficit hyperactivity disorder
Autism
Basal cell cancer
Bipolar disorder
Biliary atresia
Bilirubin
Birth weight
Bladder cancer
Blond or brown hair
Blood pressure
Blue or green eyes
BMI, waist circumference
Bone density
Breast cancer
C-reactive protein
Cardiac structure/function
Carnitine levels
Carotenoid/tocopherol levels
Celiac disease
Chronic lymphocytic leukemia
Cleft lip/palate
Cognitive function
Conduct disorder
Colorectal cancer
Corneal thickness
Coronary disease
Creutzfeldt-Jakob disease
Crohn's disease
Cutaneous nevi
Dermatitis
Drug-induced liver injury
Eosinophil count
Eosinophilic esophagitis
Erythrocyte parameters
Esophageal cancer
Essential tremor
Exfoliation glaucoma
Eye color traits
F cell distribution
Fibrinogen levels
Folate pathway vitamins
Freckles and burning
Gallstones
Glioma
Glycemic traits
Hair color
Hair morphology
HDL cholesterol
Heart failure
Heart rate
Height
Hemostasis parameters
Hepatitis
Hirschsprung's disease
HIV-1 control
Homocysteine levels
Idiopathic pulmonary fibrosis
IgE levels
Inflammatory bowel disease
Intracranial aneurysm
Iris color
Iron status markers
Ischemic stroke
Juvenile idiopathic arthritis
Kidney stones
LDL cholesterol
Leprosy
Leptin receptor levels
Liver enzymes
LP (a) levels
LpPLA(2) activity and mass
Lung cancer
Major mood disorders
Malaria
Male pattern baldness
Matrix metalloproteinase levels
MCP-1
Melanoma
Menarche & menopause
Multiple sclerosis
Myeloproliferative neoplasms
Narcolepsy
Nasopharyngeal cancer
Neuroblastoma
Nicotine dependence
Obesity
Open angle glaucoma
Open personality
Optic disc parameters
Osteoarthritis
Osteoporosis
Otosclerosis
Other metabolic traits
Ovarian cancer
Pancreatic cancer
Pain
Paget's disease
Panic disorder
Parkinson's disease
Periodontitis
Peripheral arterial disease
Phosphatidylcholine levels
Phytosterol levels
Platelet count
Primary biliary cirrhosis
PR interval
Prostate cancer
Protein levels
Psoriasis
Pulmonary funct. COPD
QRS interval
QT interval
Quantitative traits
Recombination rate
Red vs.non-red hair
Renal function
Response to antidepressants
Response to antipsychotic therapy
Response to hepatitis C treat
Response to statin therapy
Restless legs syndrome
Rheumatoid arthritis
Schizophrenia
Serum metabolites
Skin pigmentation
Smoking behavior
Speech perception
Sphingolipid levels
Statin-induced myopathy
Stroke
Systemic lupus erythematosus
Systemic sclerosis
Telomere length
Testicular germ cell tumor
Thyroid cancer
Tooth development
Total cholesterol
Triglycerides
Type 1 diabetes
Type 2 diabetes
Ulcerative colitis
Urate
Venous thromboembolism
Vertical cup-disc ratio
Vitamin B12 levels
Vitamin D insuffiency
Vitiligo
Warfarin dose
Weight
White cell count
YKL-40 levels
PD-GOV
www.genome.gov/GWAStudies

Published Genome-Wide Associations through 6/2010

904 published GWA at $p \leq 5 \times 10^{-8}$ for 165 traits



 www.genome.gov/GWAStudies

Lessons from GWAS

- Most (nearly all) previous “candidate” gene association studies are wrong
- Most common variants have only modest effects on risk (<< 2 fold OR)
- For most common diseases/traits: identified SNPs only account for <5-10% of overall risk– NOT USEFUL clinically
- But useful new biology (maybe) ??
  - New biologic pathways
  - New drug targets
- Other diseases may be different
  - AMD
  - Thrombosis
  - ***BCL11A and fetal hemoglobin***

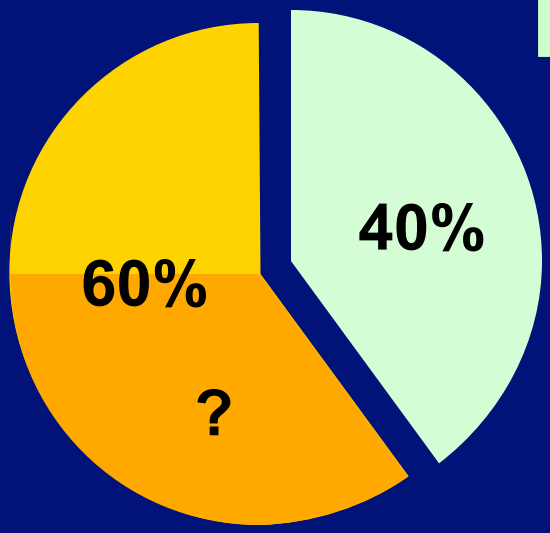
Lots of tests: when should we use them?

- Class I: test result will significantly alter medical management
  - Newborn screening (eg. sickle cell, PKU)
  - Some cancer predisposition syndromes (eg. VHL, MEN2, FAP, ?BRCA)
- Class III: test result will have no impact on medical management
  - Huntington Disease, Alzheimer predisposition
- Class II: the grey zone

Venous Thrombosis

GENES

- **Factor V Leiden**
- Elevated FVIII
- Prothrombin 20210
- Protein C/S deficiency
- AT III deficiency



ENVIRONMENT

- Smoking
- Flying
- Pregnancy

? Others

stochastic/chance

Genetic testing for thrombophilia

- Established risk factors for thrombosis
  - Factor V Leiden– 5% population frequency (European)
  - Prothrombin 20210 mutation– 1%
  - Protein C, Protein S deficiency– each ~1:500
  - Antithrombin III deficiency– ~1:2500
  - ? Elevated plasma FVIII (or ?FIX, FXI)– 5-10%
  - Dysfibrinogenemia, others– rare

- *Commonly tested factors that DO NOT increase thrombosis risk*
  - "Thermolabile" MTHFR (C677T, Ala222Val)– 40% het, 10% homoz
  - PAI-1 4G-5G polymorphism– 25% 4G/4G, 50% 4G/5G

Treatment of Venous Thrombosis

Indication	*Rx with FVL*	*Rx without FVL*

Testing for Factor V Leiden
(and other thrombophilia mutations)

- Current Indications for testing
  - ?????
- Potential future indications:
  - Choice and duration of primary therapy for thrombosis
  - Choice and duration of thrombosis prophylaxis:
    - During pregnancy
    - Postoperatively
    - following 1st or subsequent thrombotic event
  - Screening before OCP prescription

Lots of tests: when should we use them?

- Class I: test result will significantly alter medical management
  - Newborn screening (eg. sickle cell, PKU)
  - Some cancer predisposition syndromes (eg. VHL, MEN2, FAP, ?BRCA)
- Class III: test result will have no impact on medical management
  - Huntington Disease, Alzheimer predisposition
- Class II: the grey zone

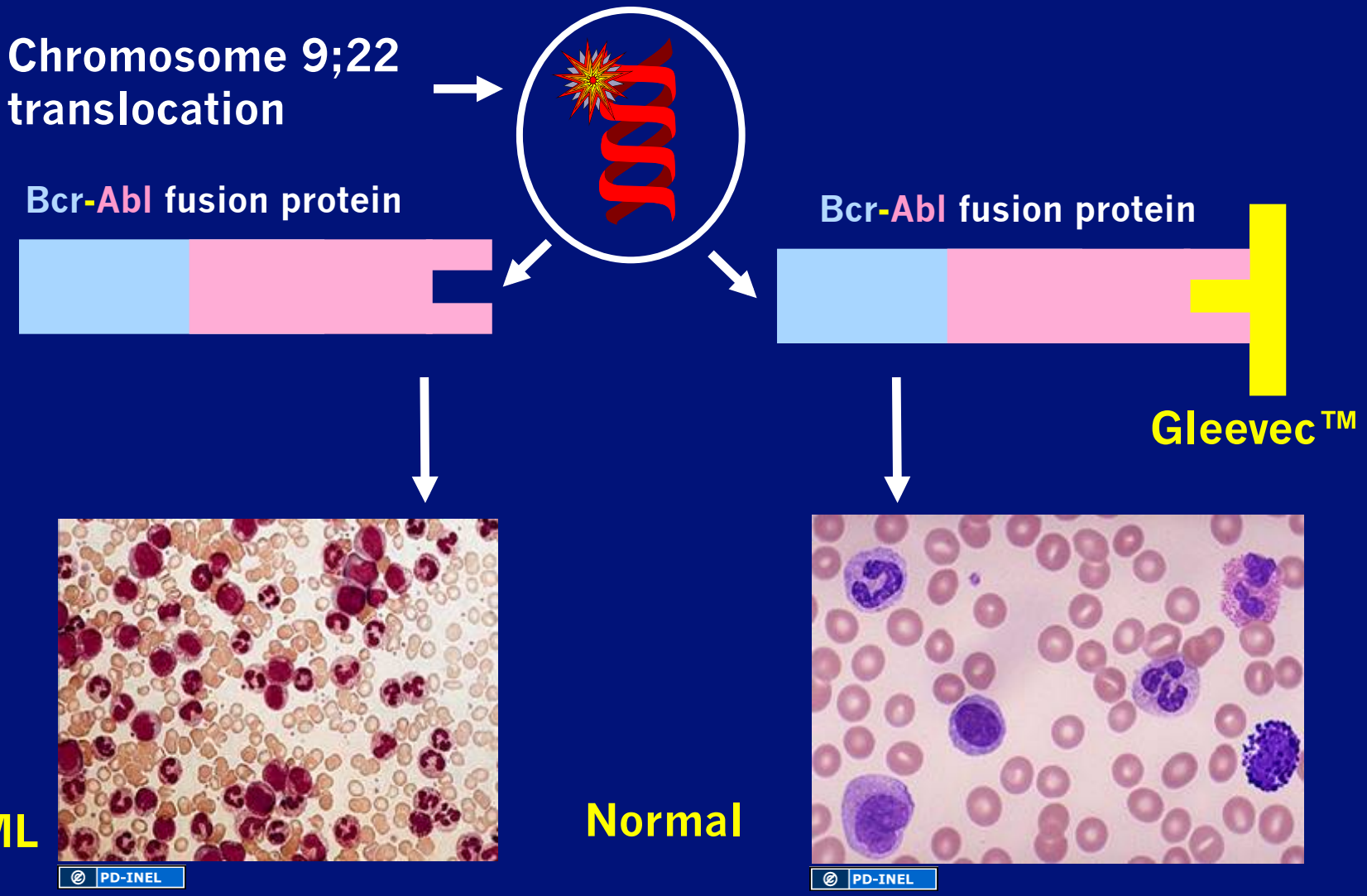
What do we mean by "personalized medicine"?

- Personalized= tailored, individualized, customized
- *Medicine has always been personalized:*
  - The physician's charge– the individual patient
    - Personalized history, physical exam, laboratory tests
    - Personalized diagnosis
    - Personalized treatment
  - Non "personalized" medicine for the whole community = public health
    - Vaccination
    - Safe water and food supply
    - Waste management
    - Much larger global impact than "personalized" medicine

*What **DO** we mean by "personalized medicine"?*

- *Harness the power of genetic information to:*
  - Improve diagnosis
  - Tailor treatment to diagnosis
  - Identify disease susceptibility before illness
  - Facilitate preventive treatment
  - Facilitate treatment prescription with minimum toxicity and maximum efficacy (parmacogenomics)

Gleevec™ – Specifically Targets An Abnormal Protein, Blocking Its Ability To Cause Chronic Myeloid Leukemia



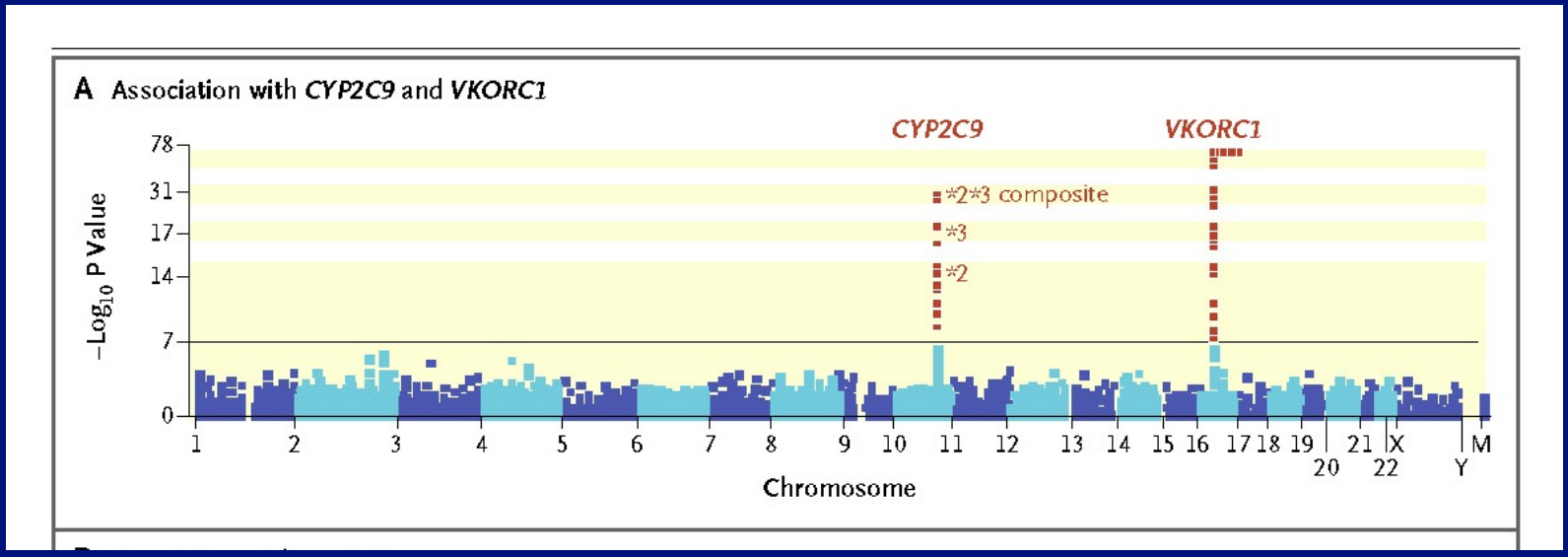
Pharmacogenomics today

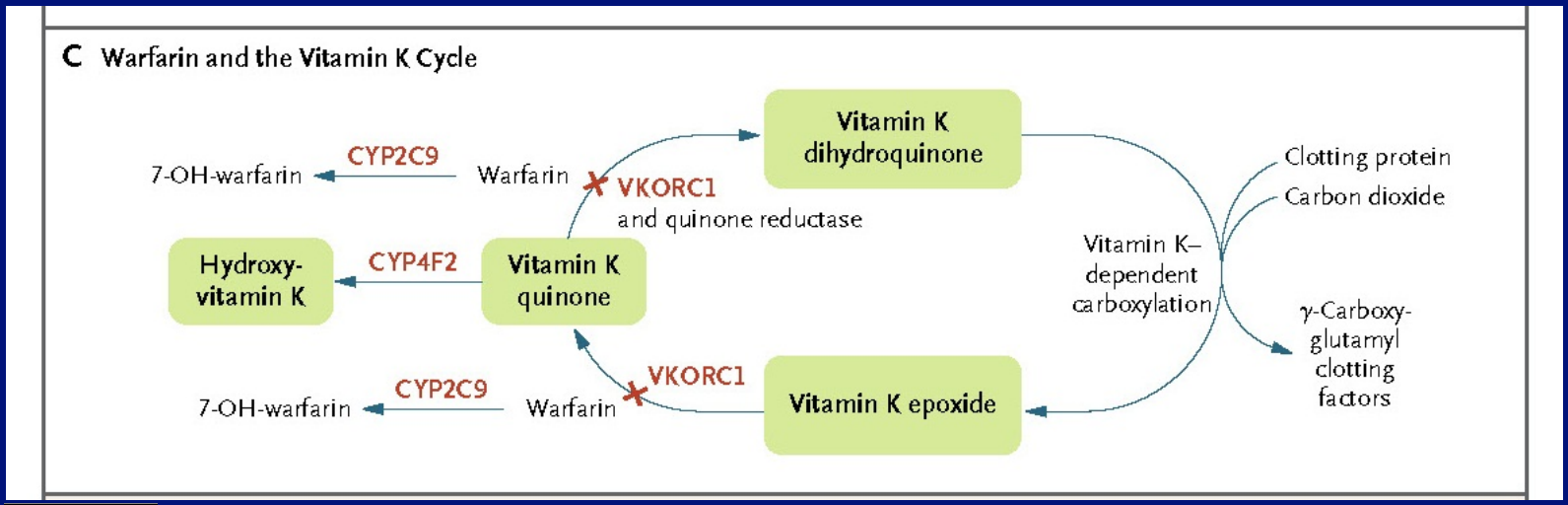
- Pharmacogenomic Biomarkers for 71 drugs (FDA)

http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm

- Oncology applications
  - Her2/Neu, EGFR, BCR/ABL (efficacy)
  - Thiopurine methyltransferase (TPMT)
    - 6-MP, azathioprine
  - UGT1A1 (irinotecan)
  - Dihydropyrimidine dehydrogenase (5-FU)
- Cytochrome P450
  - warfarin
  - Multiple other drugs:
    - antidepressants, tamoxifen, PPIs
- VKORC1
  - warfarin

Genetic determinants of Warfarin dose





 N Engl J Med 2011;364:1144-53.

Coumadin® Prescribing Information

The patient's CYP2C9 and VKORC1 genotype information, when available, can assist in selection of the starting dose. Table 5 describes the range of stable maintenance doses observed in multiple patients having different combinations of CYP2C9 and VKORC1 gene variants. Consider these ranges in choosing the initial dose.

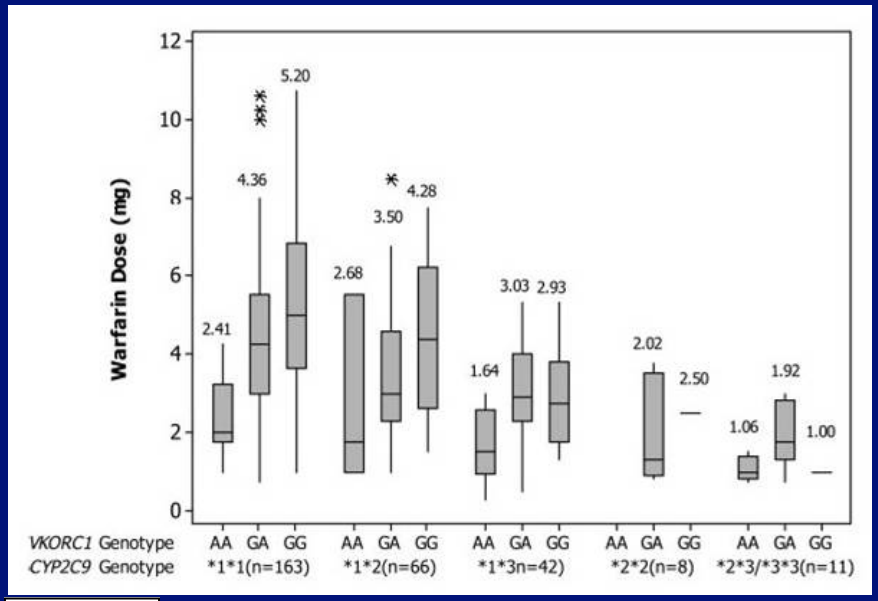
In all patients, subsequent dosage adjustments must be made based on the results of PT/INR determinations.[17,18]

Table 5: Range of Expected Therapeutic Warfarin Doses Based on CYP2C9 and VKORC1 Genotypes†

VKORC1	CYP2C9					
	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3
GG	5-7 mg	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg
AG	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg
AA	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg

†Ranges are derived from multiple published clinical studies. Other clinical factors (eg, age, race, body weight, sex, concomitant medications, and comorbidities) are generally accounted for along with genotype in the ranges expressed in the table. VKORC1 –1639G>A (rs9923231) variant is used in this table. Other co-inherited VKORC1 variants may also be important determinants of warfarin dose. Patients with CYP2C9 *1/*3, *2/*2, *2/*3, and *3/*3 may require more prolonged time (>2 to 4 weeks) to achieve maximum INR effect for a given dosage regimen.

Pharmacogenomics for warfarin dosing



PD-INEL

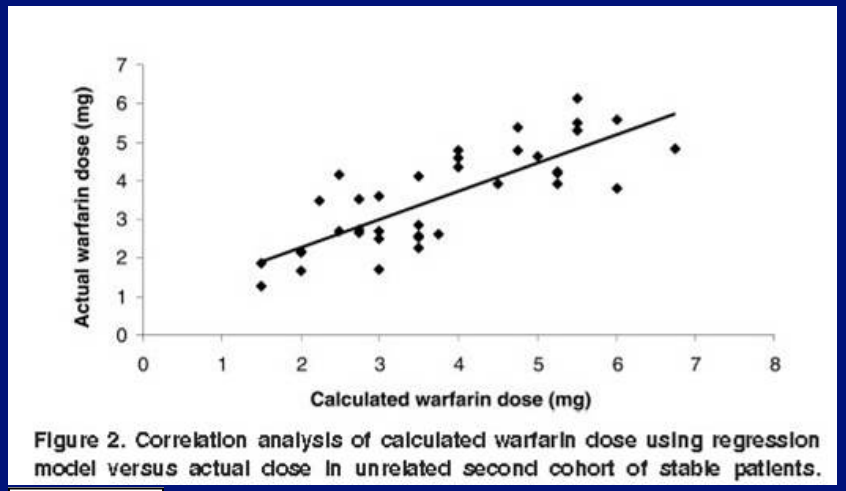


Figure 2. Correlation analysis of calculated warfarin dose using regression model versus actual dose in unrelated second cohort of stable patients.

PD-INEL

Sconce et al., *Blood* **106**:2329, 2005
Rieder et al., *NEJM* **352**:2285, 2005

- Clinical value unproven
- Practical limitations:
  - VKORC1/CYP2C9 genotype only accounts for ~30% of variance in warfarin requirement
  - Turnaround time
  - pill size

Pharmacogenomics today

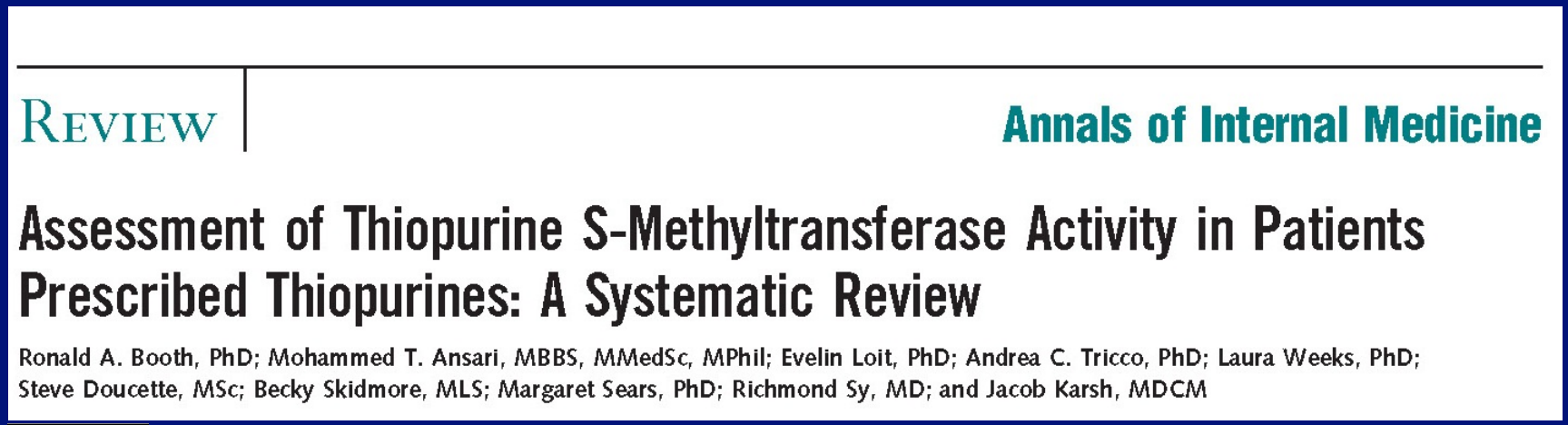
- Pharmacogenomic Biomarkers for 71 drugs (FDA)

http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm

- Oncology applications
  - Her2/Neu, EGFR, BCR/ABL (efficacy)
  - Thiopurine methyltransferase (TPMT)
    - 6-MP, azathioprine
  - UGT1A1 (irinotecan)
  - Dihydropyrimidine dehydrogenase (5-FU)
- Cytochrome P450
  - warfarin
  - Multiple other drugs:
    - antidepressants, tamoxifen, PPIs
- VKORC1
  - warfarin

TMPT variant and chemotherapy toxicity

- TMPT variant alleles (decreased activity)
  - 11% heterozygotes
  - 0.3% homozygotes



REVIEW | Annals of Internal Medicine

Assessment of Thiopurine S-Methyltransferase Activity in Patients Prescribed Thiopurines: A Systematic Review

Ronald A. Booth, PhD; Mohammed T. Ansari, MBBS, MMedSc, MPhil; Evelin Loit, PhD; Andrea C. Tricco, PhD; Laura Weeks, PhD; Steve Doucette, MSc; Becky Skidmore, MLS; Margaret Sears, PhD; Richmond Sy, MD; and Jacob Karsh, MDCM

 Ann Int Med 2011;154:814.

Conclusion: Insufficient evidence addresses the effectiveness of TMPT pretesting in patients with chronic inflammatory diseases.

DTC Genetic Testing

- Mendellian Genetic disorders
- pharmacogenomics
- Complex (multigenic) disorders
- Ancestry

TABLE 1: PREDICTIONS FOR DISEASE RELATIVE RISKS FOR FIVE INDIVIDUALS

Disease	Female A	Female B	Female C	Male D	Male E
Breast cancer	↑↑	↑↑	↓↓		
Coeliac disease	↓↓	↓↓	↓↓	↓↓	↓↓
Colon cancer	==	==	=↓	↑↑	=↓
Crohn's disease	↓↑	↓↑	↓↓	↓↓	↓=
Heart attack	↓↓	=↓	=↓	=↓	↑↑
Lupus	↑↓	↓↓	↓↓	↑=	↑=
Macular degeneration	↓↓	↓↓	↑=	↓↓	↓↓
Multiple sclerosis	↑↑		↓↓	↓↓	↓↓
Prostate cancer				↑↑	↓↑
Psoriasis	↓↑		↑↓	↑↑	↓↓
Restless legs syndrome	=↓	↑↑	↓=	↓↑	↑↑
Rheumatoid arthritis	↑↑	↑↑	↓↓	↓↓	↑↑
Type 2 diabetes	↓↓	=↓	↓↓	↑↓	=↓

↑ increased risk (RR > 1.05), ↓ decreased risk (relative risk (RR) < 0.95), = average risk (0.95 ≤ RR ≤ 1.05). First prediction is from 23andMe; second prediction is from Navigenics. Different predictions are highlighted in beige.

Ng et al., *Nature* 461:724, 2009.

GAO
Accountability • Integrity • Reliability

Highlights

Highlights of GAO-10-847T, a testimony before the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, House of Representatives

July 22, 2010

DIRECT-TO-CONSUMER GENETIC TESTS

Misleading Test Results Are Further Complicated by Deceptive Marketing and Other Questionable Practices

Why GAO Did This Study

In 2006, GAO investigated companies selling direct-to-consumer (DTC) genetic tests and testified that these companies made medically unproven disease predictions. Although new companies have since been touted as being more reputable—*Time* named one company's test 2008's "invention of the year"—experts remain concerned that the test results mislead consumers. GAO was asked to investigate DTC genetic tests currently on the market and the advertising methods used to sell these tests.

What GAO Found

GAO's fictitious consumers received test results that are misleading and of little or no practical use. For example, GAO's donors often received disease risk predictions that varied across the four companies, indicating that identical DNA samples yield contradictory results. As shown below, one donor was told that he was at below-average, average, and above-average risk for prostate cancer and hypertension.

Contradictory Risk Predictions for Prostate Cancer and Hypertension

Gender	Age	Condition	Company 1	Company 2	Company 3	Company 4
Male	48	Prostate cancer	Average	Average	Below average	Above average
		Hypertension	Average	Below average	Above average	Not tested

Source: GAO.

GAO's donors also received DNA-based disease predictions that conflicted with their actual medical conditions—one donor who had a pacemaker implanted 13

 http://www.gao.gov/new.items/d10847t.pdf

Is there any evidence that DTC Genetic Testing will improve your health?

Testimonials:

- *"It convinced me to go to my doctor who found my prostate cancer. ____'s DTC genetic testing saved my life!!"*
- *"When I found out about my increased risk of diabetes, I went out and lost 30 pounds!!"*
- *"When I found out about my increased risk of lung cancer, I stopped smoking!!"*
- *…*
- *…*

Is there any evidence that DTC Genetic Testing will improve your health?

Actual scientific evidence :

- *"It convinced me to go to my doctor who found my prostate cancer. ____'s DTC genetic testing saved my life!!"*
- *"When I found out about my increased risk of diabetes, I went out and lost 30 pounds!!"*
- *"When I found out about my increased risk of lung cancer, I stopped smoking!!"*
- *…*
- *…*

NONE

Minimally regulated tools available to the public for predicting/modifying health

- Traditional:
  - Astrology
  - Tarot cards
  - Palm reading
- Modern "scientific"
  - "Alternative" medicine ($38 billion/yr)
    - Nutraceuticals, homeopathic remedies ($22 billion)
  - SNP genotyping

Recreational Genetics

- Ancestry
- Paternity, long lost relatives

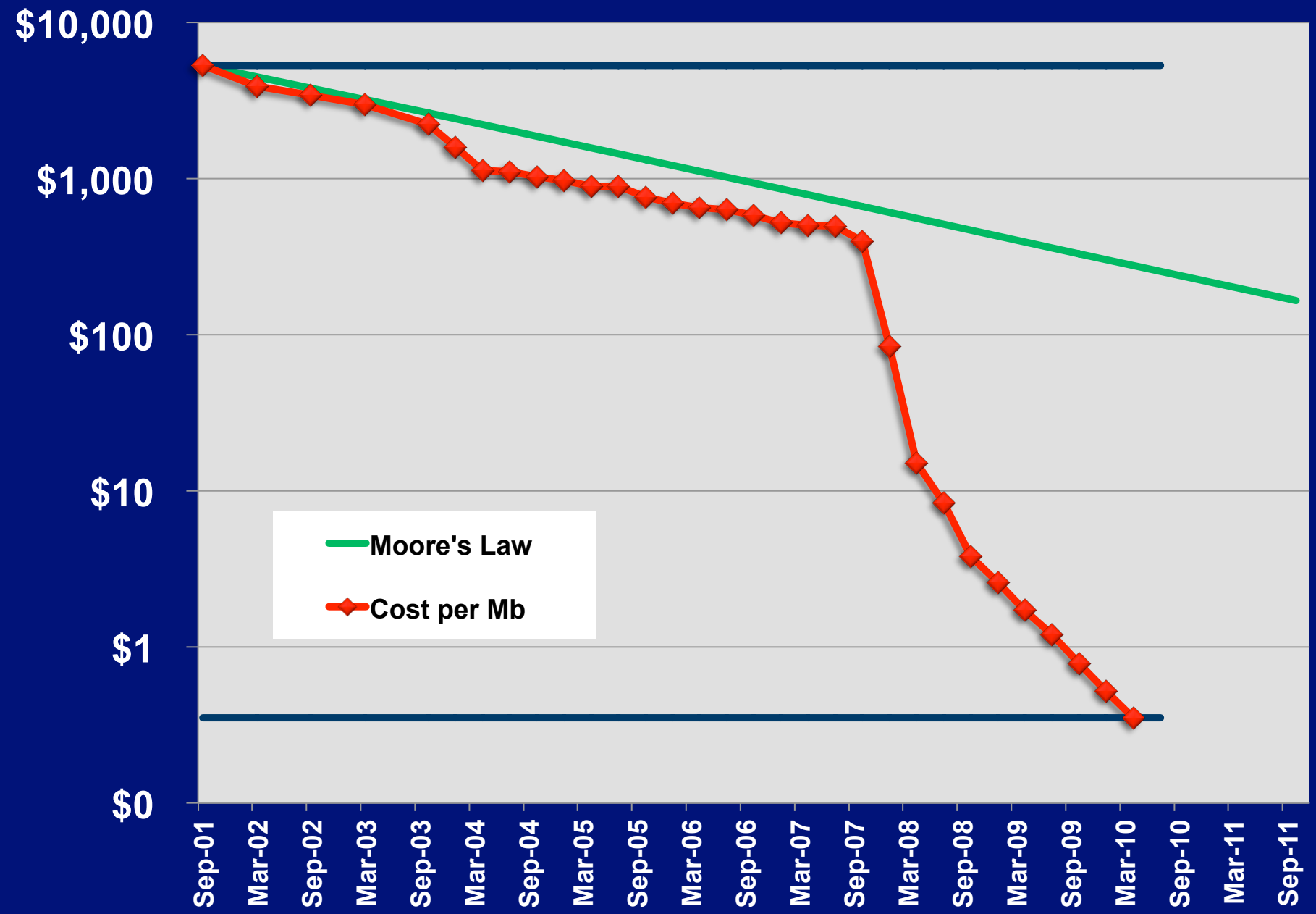
New Sequencing Technologies

Searching for Cheaper Genome Sequencers

Company	Format	Read Length (bases)	Expected Throughput MB (million bases)/day
454 Life Sciences	Parallel bead array	100	96
Agencourt Bioscience	Sequencing by ligation	50	200
Applied Biosystems	Capillary electrophoresis	1000	3–4
Microchip Biotechnologies	Parallel bead array	850-1000	7
NimbleGen Systems	Map and survey microarray	30	100
Solexa	Parallel microchip	35	500
LI-COR	Electronic microchip	20,000	14,000
Network Biosystems	Biochip	800+	5
VisiGen Biotechnologies	Single molecule array	NA	1000

Generation next. Companies racing for the $1000 genome sequence strive simultaneously for low cost, high accuracy, the ability to read long stretches of DNA, and high throughput.

Cost per Megabase of Raw DNA Sequence



How many human genomes can you sequence for $10M?

2000

<1 Human Genome

2010

250-500 Human Genomes

The Future…

- Will be different
  - Newborn screening by full genome sequencing
  - New/improved therapies
  - Complex computational analysis- combinatorial risk factors
  - Much larger data sets– health system wide
  - Data to support genotype-specific therapy/ prophylaxis

Additional Source Information

for more information see: http://open.umich.edu/wiki/AttributionPolicy

Slide 18: Ricardipus, flickr, http://creativecommons.org/licenses/by-sa/2.0/deed.en