What Should Physician Assistants Know about Genetics & Genomics?

Bruce R. Korf, M.D., Ph.D.

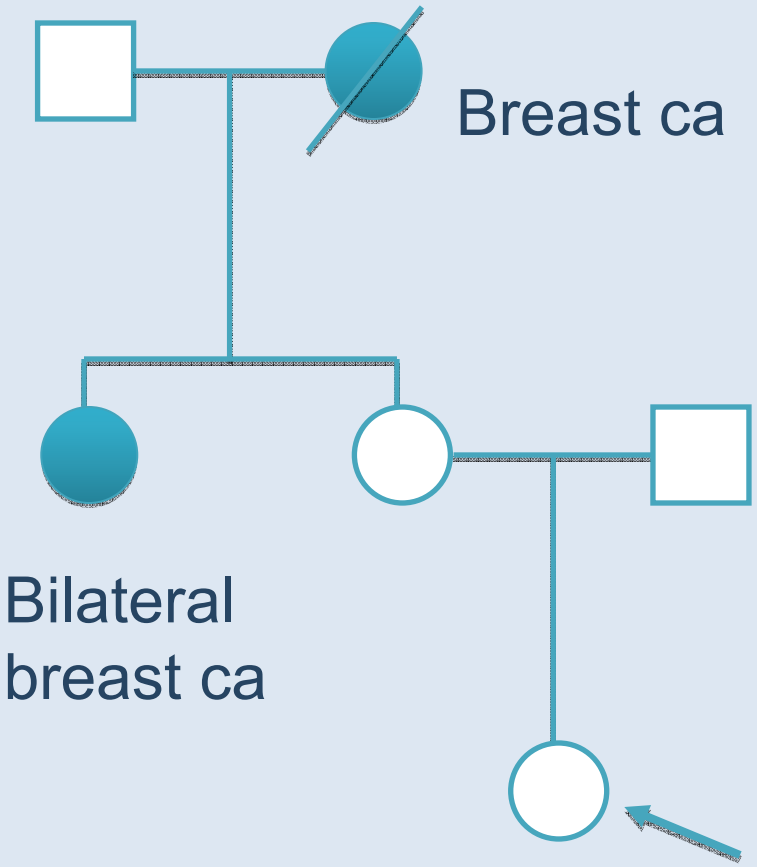
Department of Genetics

Universit of Alabama at Birmingham

"Genetics can truly claim to be the central basic science of medicine at the beginning of the 21st century."

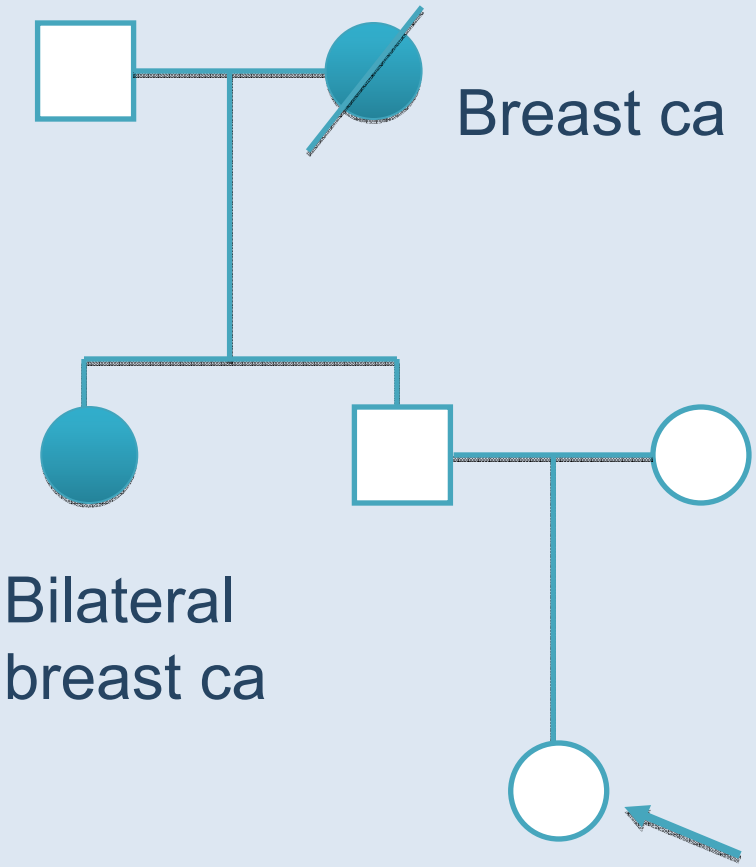
- Francis S. Collins, M.D., Ph.D.
  Director, National Human Genome Research Institute

editorial *Genetics in Medicine* 1:3, 1998.



- 14% internists and ob/gyn did not know that risk is increased
- 75% would provide counseling
- 9% refer to geneticist, 15% to oncologist or surgeon, 22% call colleague

Hayflick, S.J., et al. Genetics in Medicine 1: 13-21, 1998



- 57% internists and ob/gyn did not know that risk is increased
- 55% would provide counseling
- 9% refer to geneticist, 15% to oncologist or surgeon, 22% call colleague

Hayflick, S.J., et al. Genetics in Medicine 1: 13-21, 1998

Psychiatric Genetics: A Survey of Psychiatrists' Knowledge, Opinions, and Practice Patterns

Christine T. Finn, M.D.; Marsha A. Wilcox, Sc.D., Ed.D.; Bruce R. Korf, M.D., Ph.D.; Deborah Blacker, M.D., Sc.D.; Stephanie R. Racette, M.A.; Pamela Sklar, M.D., Ph.D.; and Jordan W. Smoller, M.D., Sc.D.

J. Clin. Psychiatry 2005;66:821-830.

Statement	Agree, %
I feel competent to discuss genetic information regarding psychiatric illness with patients and their families	23
I feel it is my role to discuss genetic information regarding psychiatric illness with patients and their families	83
My medical training has prepared me to discuss genetic information regarding psychiatric illness with patients and their families	15

DNA sequence → RNA → protein → metabolites

Genome → Transcriptome → Proteome → Metabolome

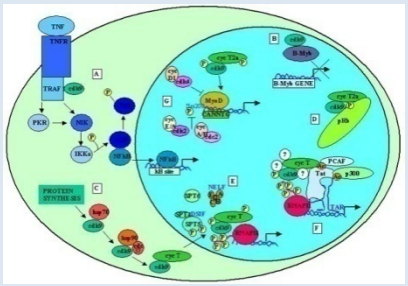
$ = Econome

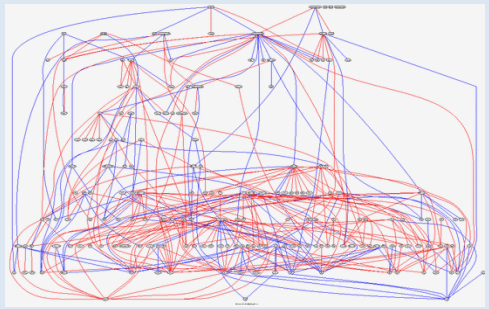
Human Genome

Classical Perspective

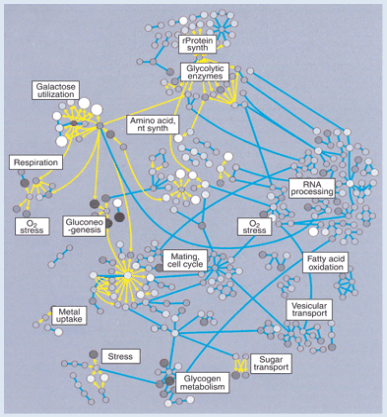
Genome Organization

Biological Pathways



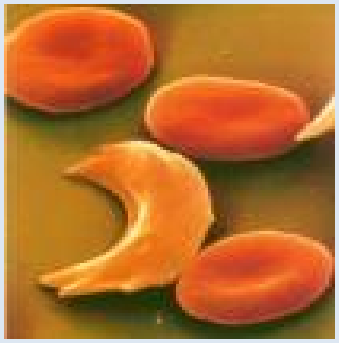


Transcriptional Regulation



Metabolic Networks

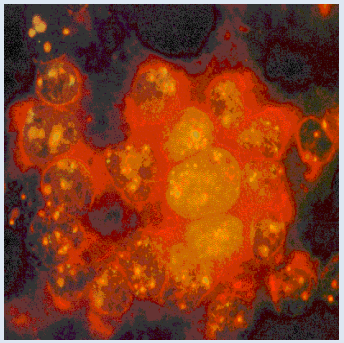
Human Genome
Modern Perspective



Monogenic
- sickle cell
- cystic fibrosis
- Huntington

Multifactorial
- asthma
- hypertension
- diabetes

Pharmacogenomics
- drug metabolism
- new drug targets



Cancer
- familial
- sporadic

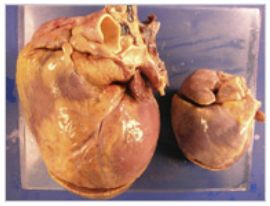
Human “Phenome”

PROSPECTS

A Tale of Two Drugs Hints at Promise for Genetic Testing

By GINA KOLATA
Published: July 11, 2006

A decade or so ago, when the revolution in genetics was getting under way, the air was heady with promises.



Bob Kutys/International Registry of Pathology

IN CONTRAST A failed heart, left, and a normal one. Genetic tests might be used to identify patients who can be helped by certain drugs.

Gene tests, scientists predicted, would become an integral part of drug prescribing. No longer would patients find out too late that a drug did not work for them. No longer would they have to wait to see if they had side effects to one drug before switching to another.

Tests of their genes would make all of this clear. B
the exception of a few tests for genes on certain ca
cells, the genetics revolution has not yet happened

The New York Times

Saved by a drop of blood

Posted 7/10/2006 10:57 PM ET

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SCREENING TESTS BY STATE

Screening for 29 medical conditions

Iowa
Maryland
Mississippi
New Jersey
Virginia
Washington, D.C.

More than 20 conditions

Alaska
Arkansas
California [1]
Connecticut
Florida [1]
Idaho
Illinois
Indiana
Kentucky
Maine

By Rita Rubin, USA TODAY

Thanks to a persistent nurse, Giana Swift's parents only have to worry about whether she should go to public or private kindergarten — not whether she'll be healthy enough to even go to school.

Analysis of a drop of blood taken from her heel revealed that Giana — which means "God is gracious" — has a rare metabolic disorder called 3MCC for short. She can't metabolize leucine, an amino acid found in protein foods.

When Giana was born in Los Angeles in October 2002, dad David Swift says, California routinely screened newborns for only four disorders, none of them 3MCC. But, he says, a nurse persuaded him and his wife to take part in a pilot project of expanded newborn screening.

California now routinely screens for more than 20 of the 29 disorders recommended by the American College of Medical Genetics, says the March of Dimes' latest newborn-screening

USA TODAY

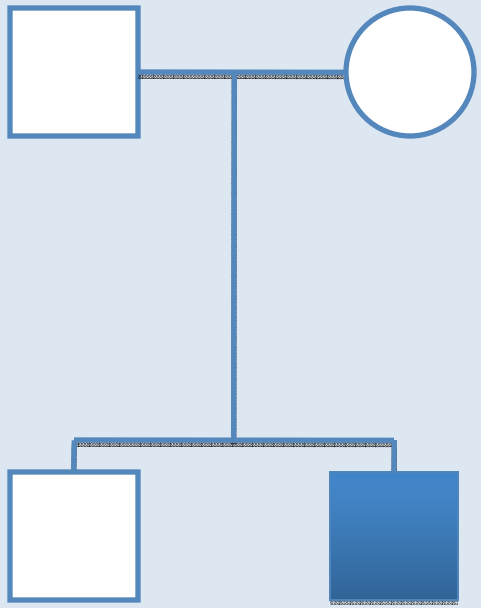
Genetics in the News

Direct to Consumer Genetic Testing


Quality
Professionalism
Evidence-Based Medicine
Genomics
Personalized Medicine

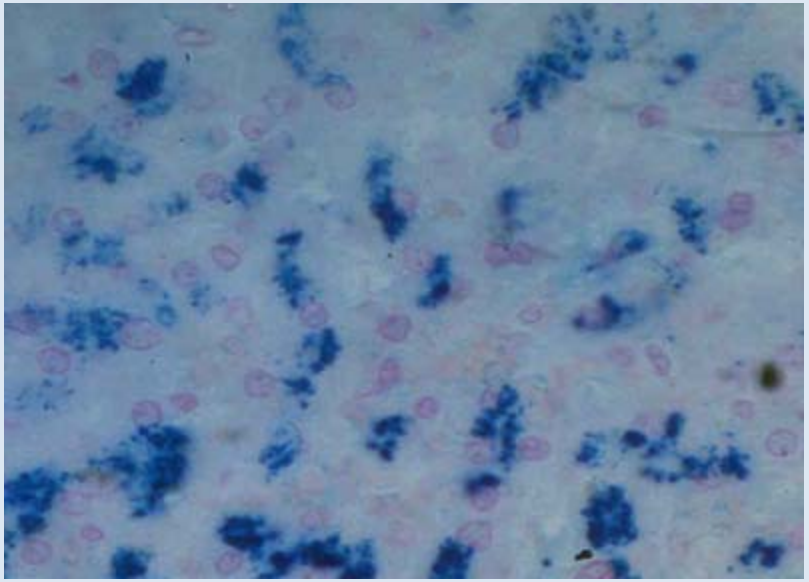
What Should Physician Assistants Know About Genetics?

1.
2.
3. Family history can be a clue to risk.



Hemochromatosis

- Excessive Fe absorption
- Fe overload in tissues
  - cirrhosis
  - diabetes mellitus
  - heart failure
  - bronzing of skin
  - hypogonadotrophic hypogonadism
  - more severe manifestations in males
- Treat with phlebotomy
  - 1 pt = 250 mg Fe



ZAN
LYNN

Variable	Clinically Unselected Homozygous Relatives of Probands (N=214)	
	Men	Women
No. of subjects	113	101
Liver biopsies — no. of subjects	78	40
Disease-related conditions — no. of subjects*		
Cirrhosis	14	2
Fibrosis	13	4
Aminotransferase elevation	11	2
Arthropathy	5	2
Subjects with at least 1 disease-related condition — no. (%)	43 (38)	10 (10)
Other clinical findings — no. of subjects		
Diabetes	3	5
Hypogonadotrophic hypogonadism	4	0
Cardiac arrhythmia†	10	3
Portal hypertension with splenomegaly	9	2
Hepatocellular carcinoma	2	0
Porphyria cutanea tarda	1	1

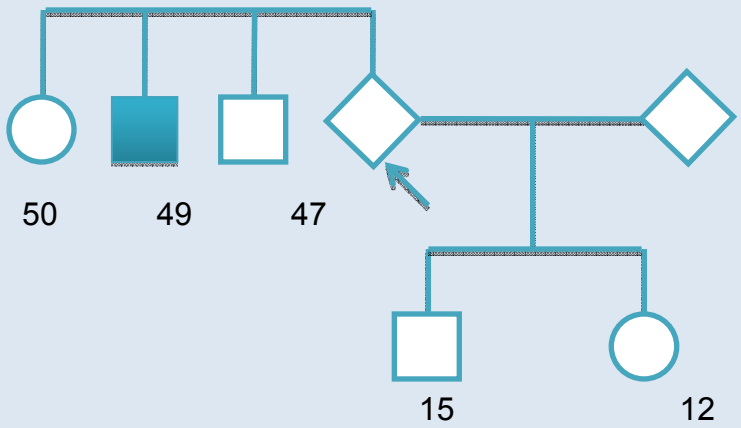
*If a subject had more than one of the fving only the condition listed first.

†Arrhythmia was documented by electroc

Legal Precedents

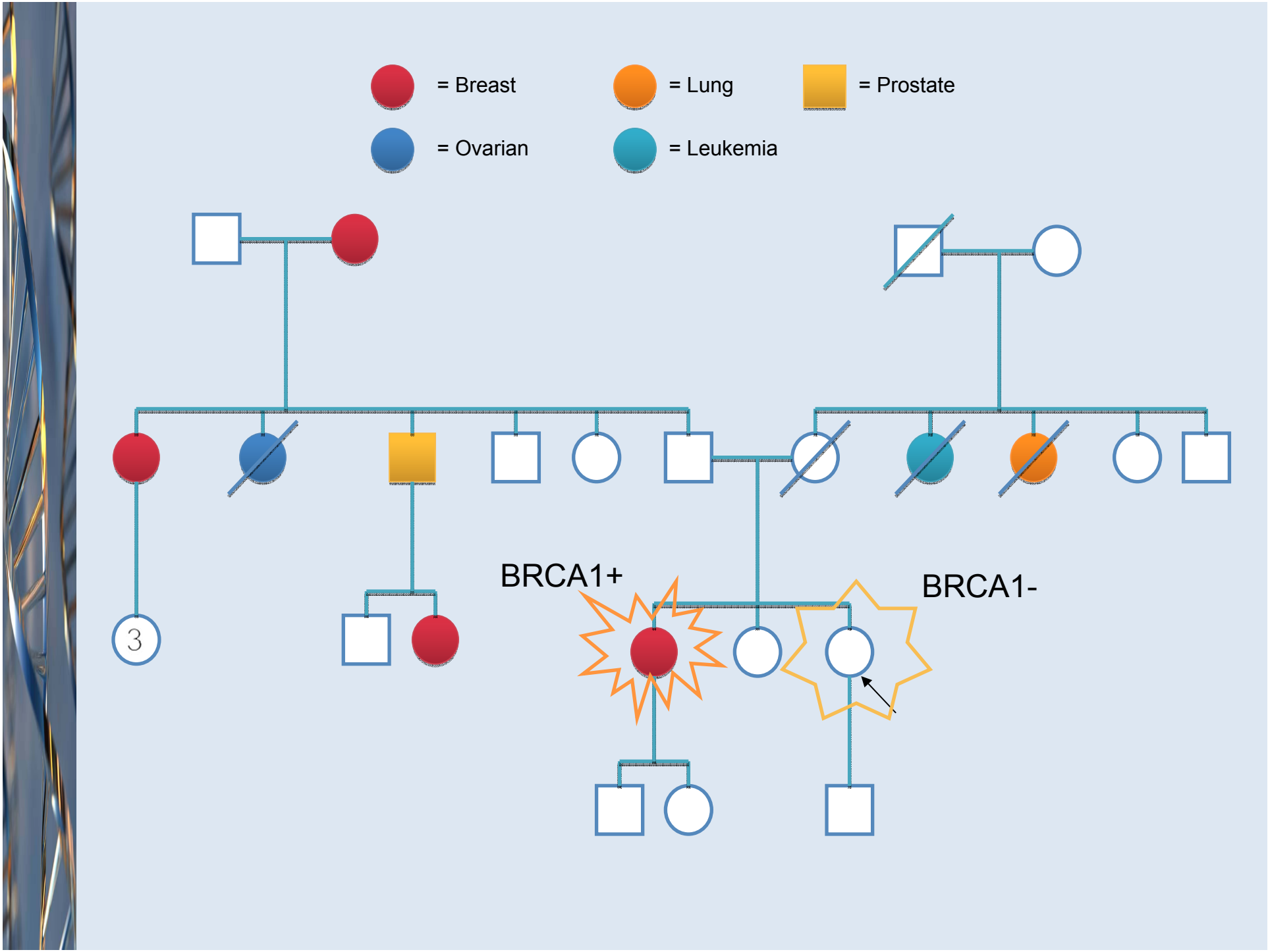
- Pate v. Threkel, 1995
  - Pate discovered she had medullary thryoid carcinoma 3 years after her mother was treated for disease. She sued physician arguing he had a duty to warn her mother of genetic transmission and recommend testing children.
  - Court found no duty to warn children directly, but did find duty to warn the patient about familial implications
- Safer v. Estate of Pack, 1996
  - Safer's father tx for colon cancer associated with adenomatous polyposis coli. Two decades later, once she was diagnosed with colon cancer, she sued her father's physician's estate for a failure to warn.
  - Court upheld a duty to warn those at-risk of avoidable harm from genetic disease


EXPERIENCE THE FUTURE
Genentech
MILLENNIUM
EXPERIENCE THE FUTURE
DISCOVER THE POWER
OF GENETICS
ENDO2002
COMPUTER KIOSK

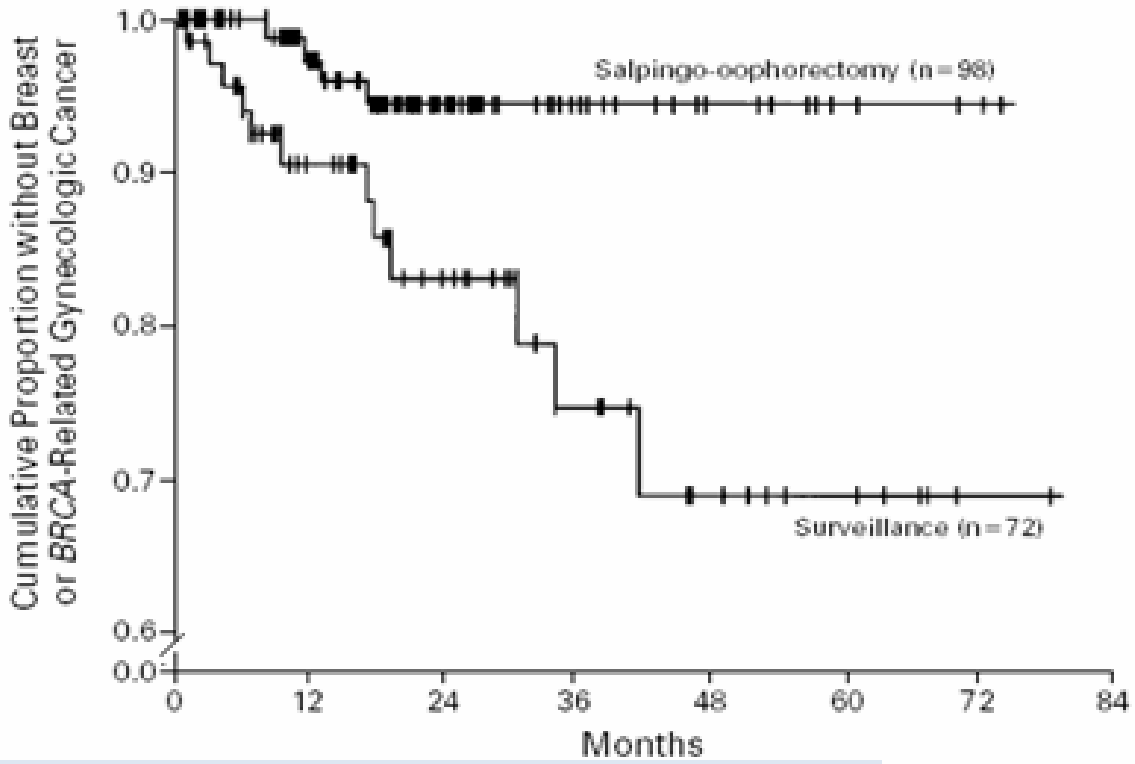

50
49
47
15
12

What Should Physician Assistants Know About Genetics?

1.
2. Clinical decisions will increasingly rely on the results of genetic tests.
3. Family history can be a clue to risk.


= Breast
= Lung
= Prostate
= Ovarian
= Leukemia
BRCA1+
BRCA1-
3

Breast Cancer Prevention



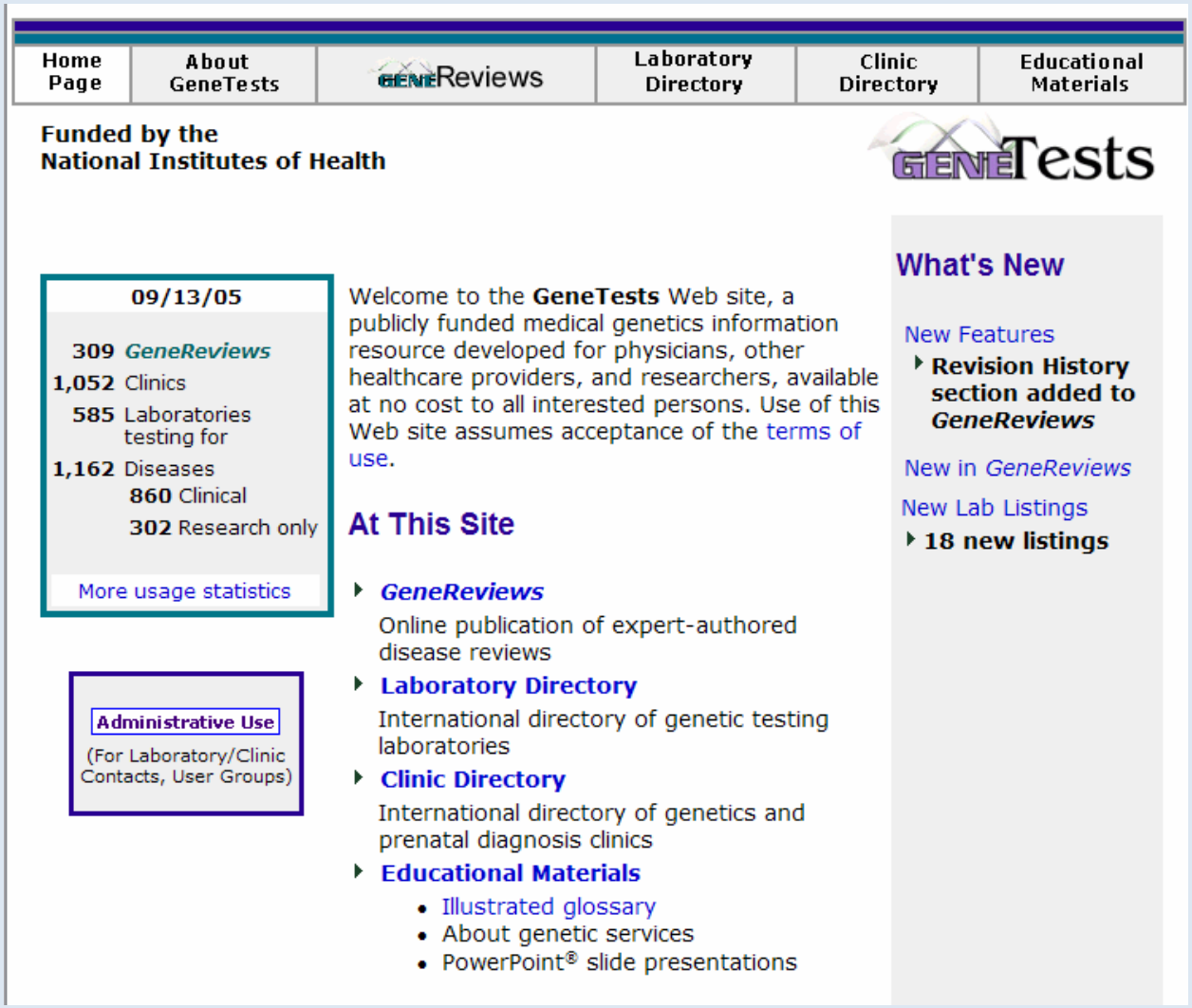
The New England Journal of Medicine

VOLUME 346 MAY 23, 2002 NUMBER 21

RISK-REDUCING SALPINGO-OOPHORECTOMY IN WOMEN WITH A *BRCA1* OR *BRCA2* MUTATION

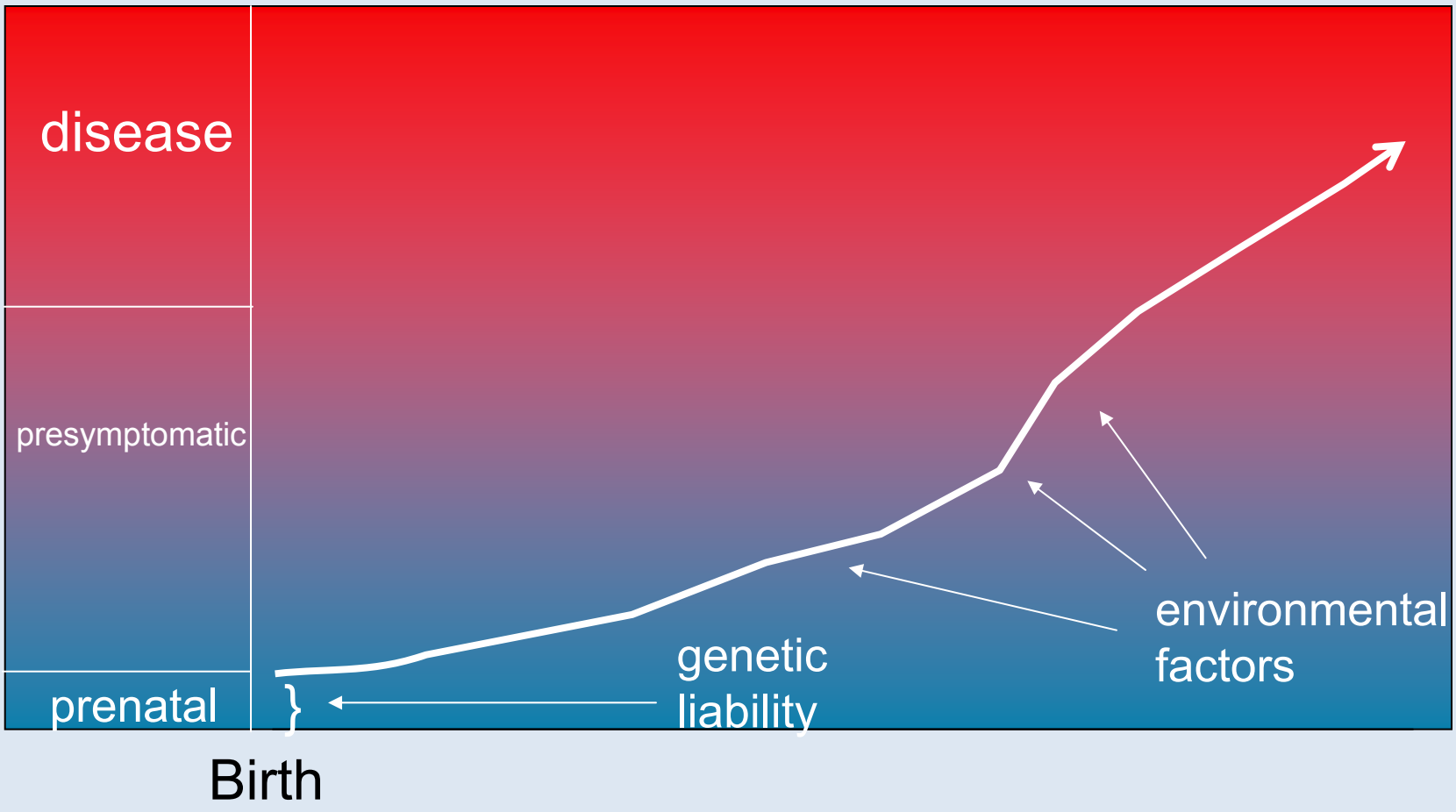
NOAH D. KAUFF, M.D., JAYA M. SATAGOPAN, PH.D., MARK E. ROBSON, M.D., LAUREN SCHNUR, M.S., MARTEE HENSLEY, M.D., CLIFFORD A. HUDIS, M.D., NATHAN A. ELLIS, PH.D., JEFF BOYD, PH.D., PATRICK I. BORGEN, M.D., RICHARD R. BARAKAT, M.D., LARRY NORTON, M.D., AND KENNETH OFFIT, M.D., M.P.H.

GeneTests.org

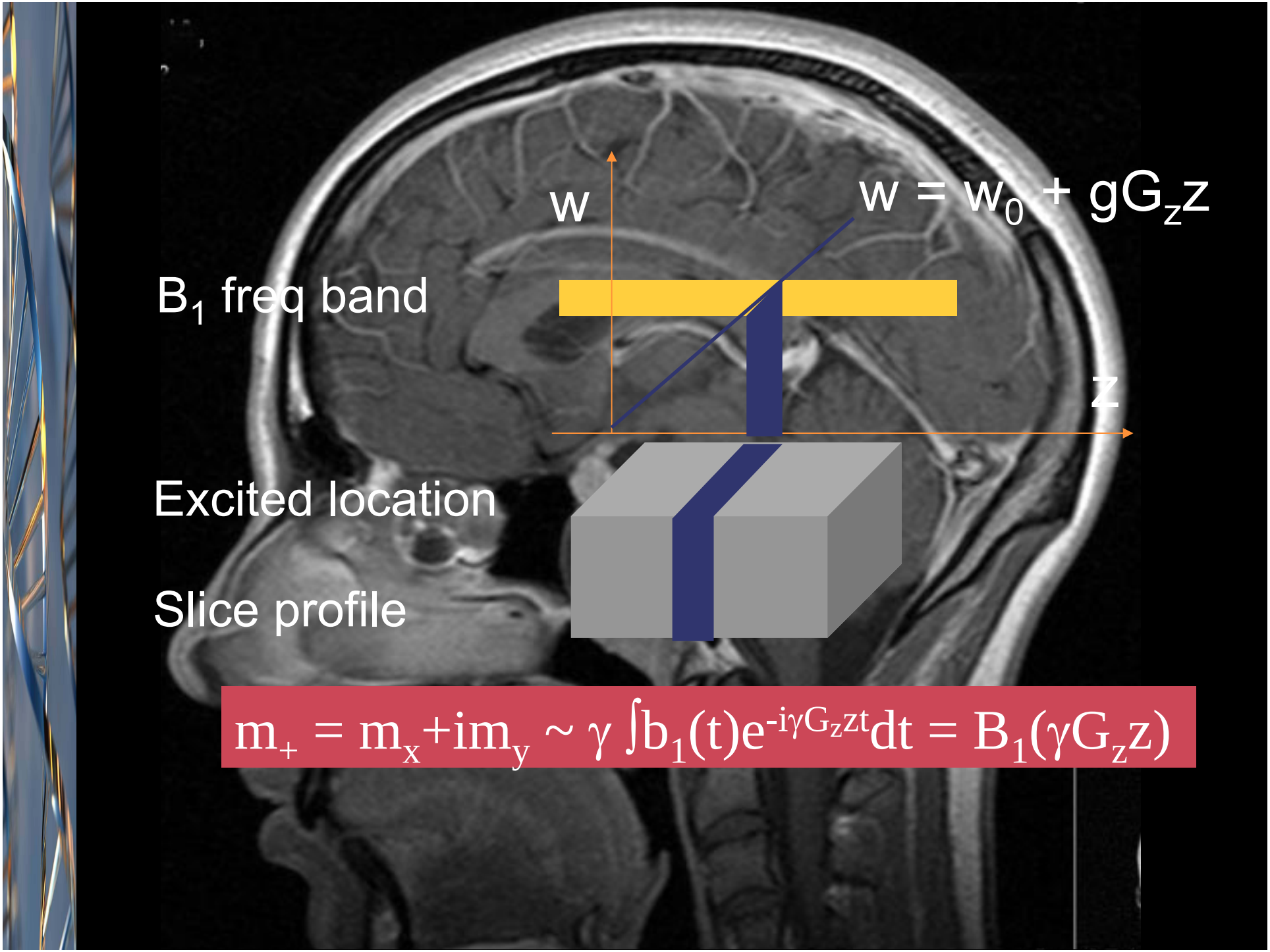


Genetic Variation

Genetics in Medicine



Genetics Dashboard


w
$w = w_0 + gG_z z$
B_1 freq band
z
Excited location
Slice profile
$m_+ = m_x + im_y \sim \gamma \int b_1(t) e^{-i\gamma G_z z t} dt = B_1(\gamma G_z z)$

What Should Physician Assistants Know About Genetics?

1. A new medical paradigm will emerge.
2. Clinical decisions will increasingly rely on the results of genetic tests.
3. Family history can be a clue to risk.

Medicine in Transformation
Two Convergent Forces

Information Technology

Genetics

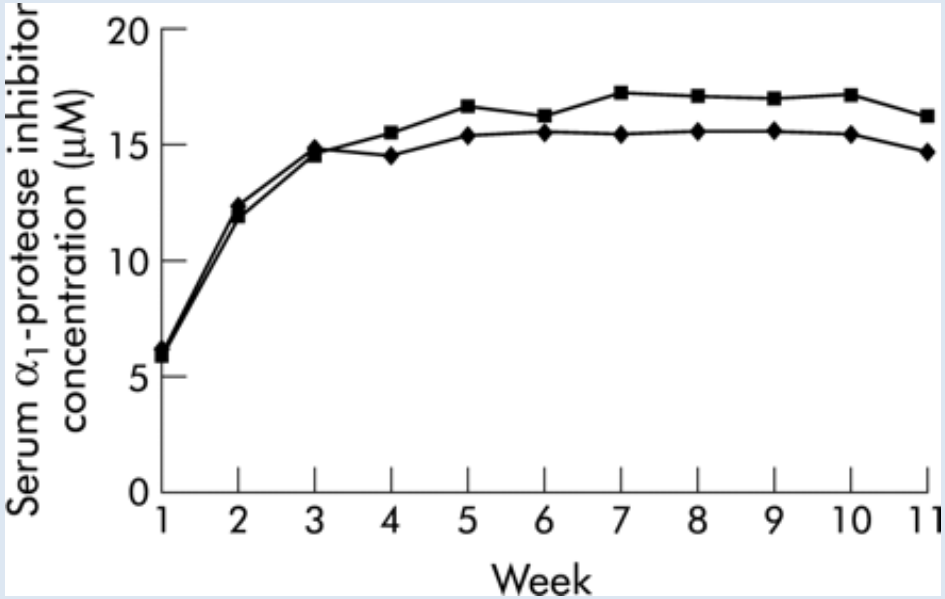
Administer the right dose of the right treatment to the right person at the right time.

"Personalized Medicine"

- Predictive testing and prevention
- Stratification of disease and targeted treatments
- Pharmacogenetics & Pharmacogenomics

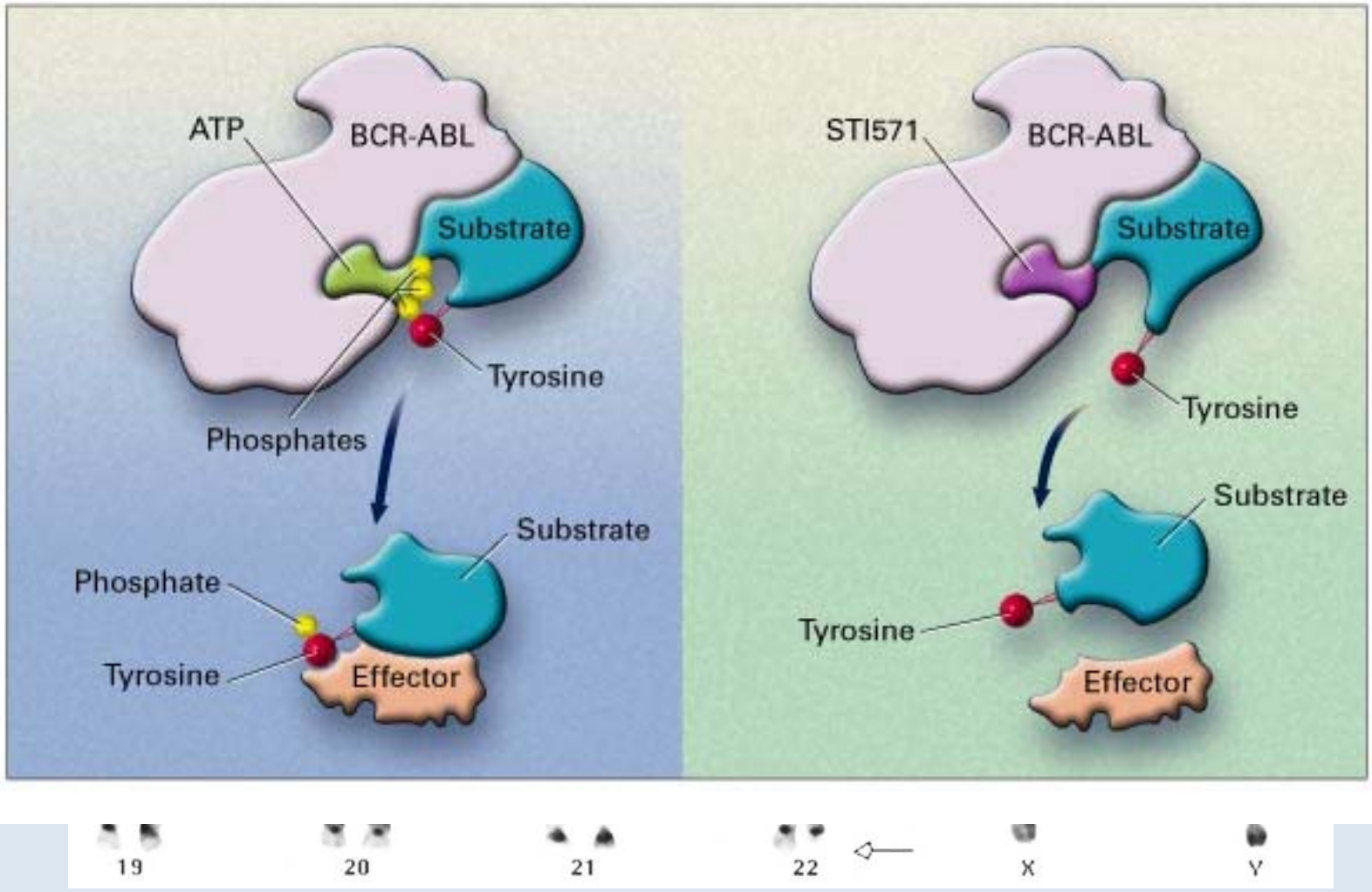
α_1-Antitrypsin Deficiency

- Inhibitor of neutrophil elastase
- Pulmonary emphysem
- Hepatic cirrhosis
- 1:2,500 Caucasians
- Carrier frequency 0.03

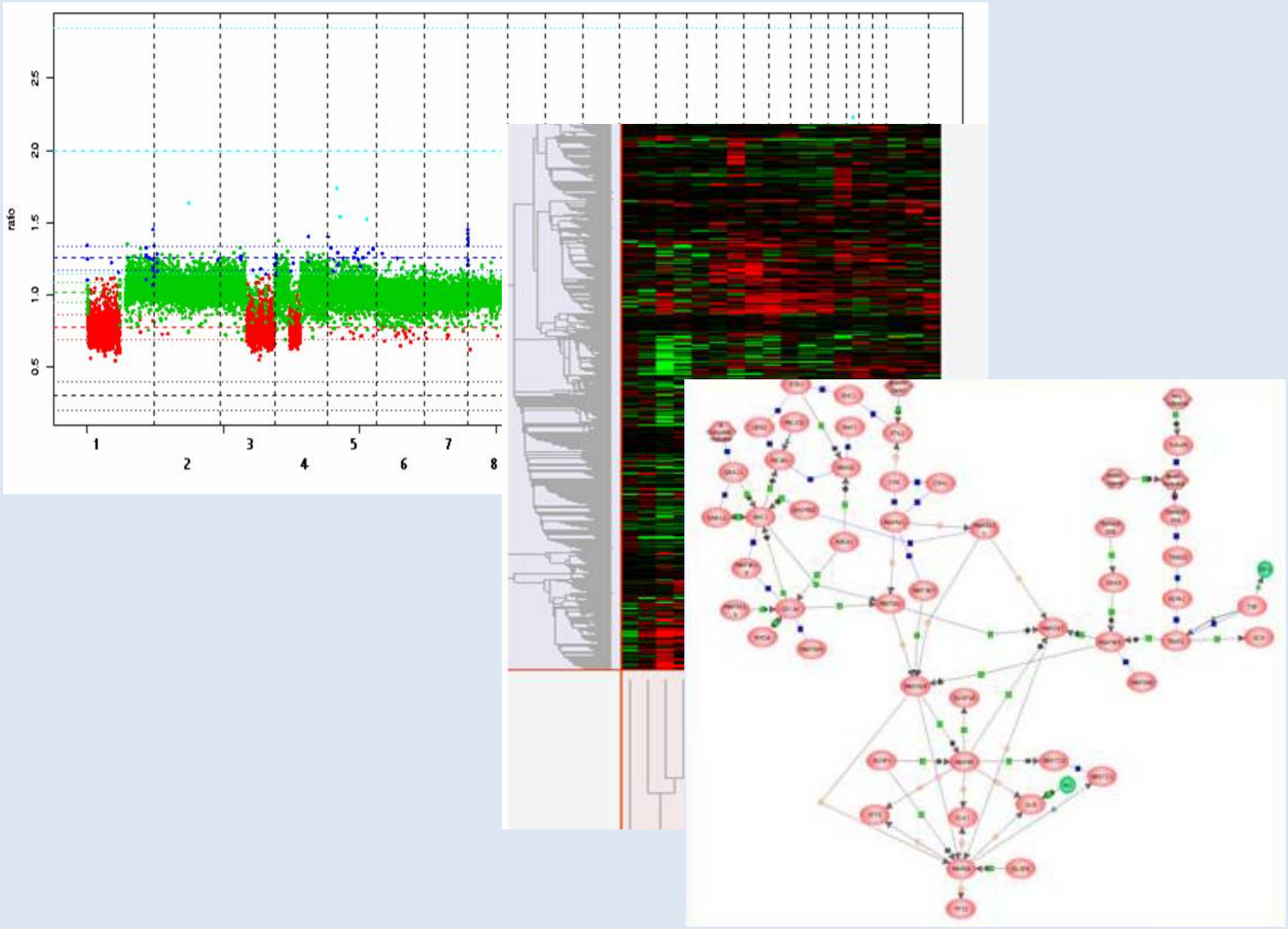


J K Stoller and L S Aboussouan, *Thorax* 2004;**59**:708-712

Targeted Therapy

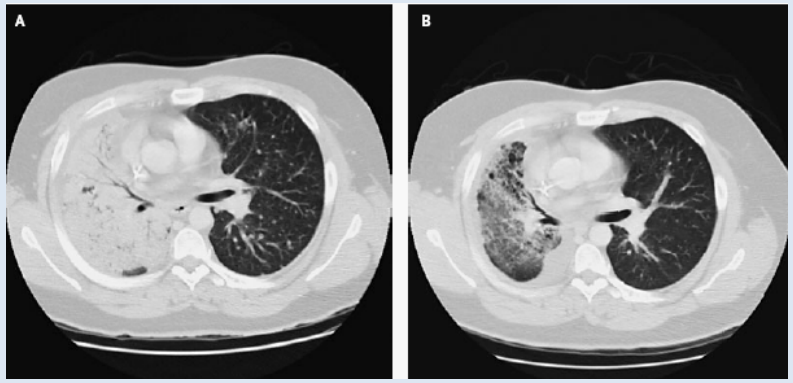


N Engl J Med 2001; 344:1084-1086, Apr 5, 2001.

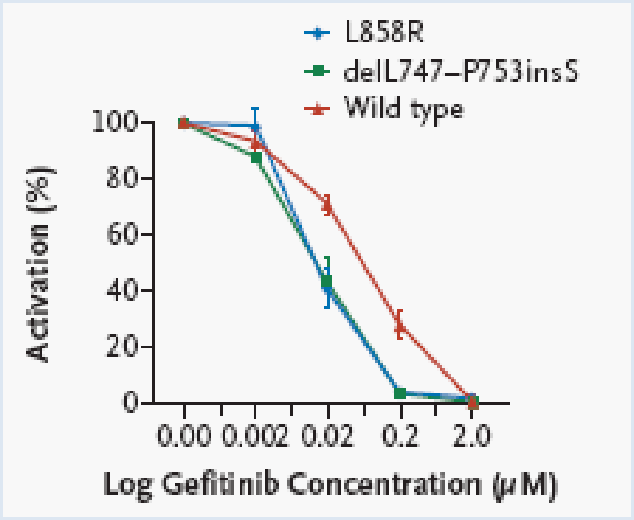


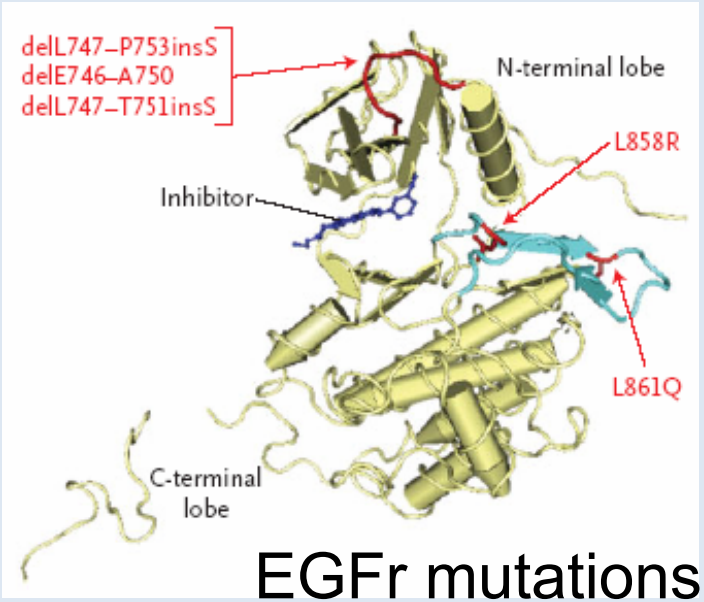
Genomic Analysis

EGFr Mutation and Gefitinib Sensitivity in NSC Lung Cancer



NSCLC response to gefitinib

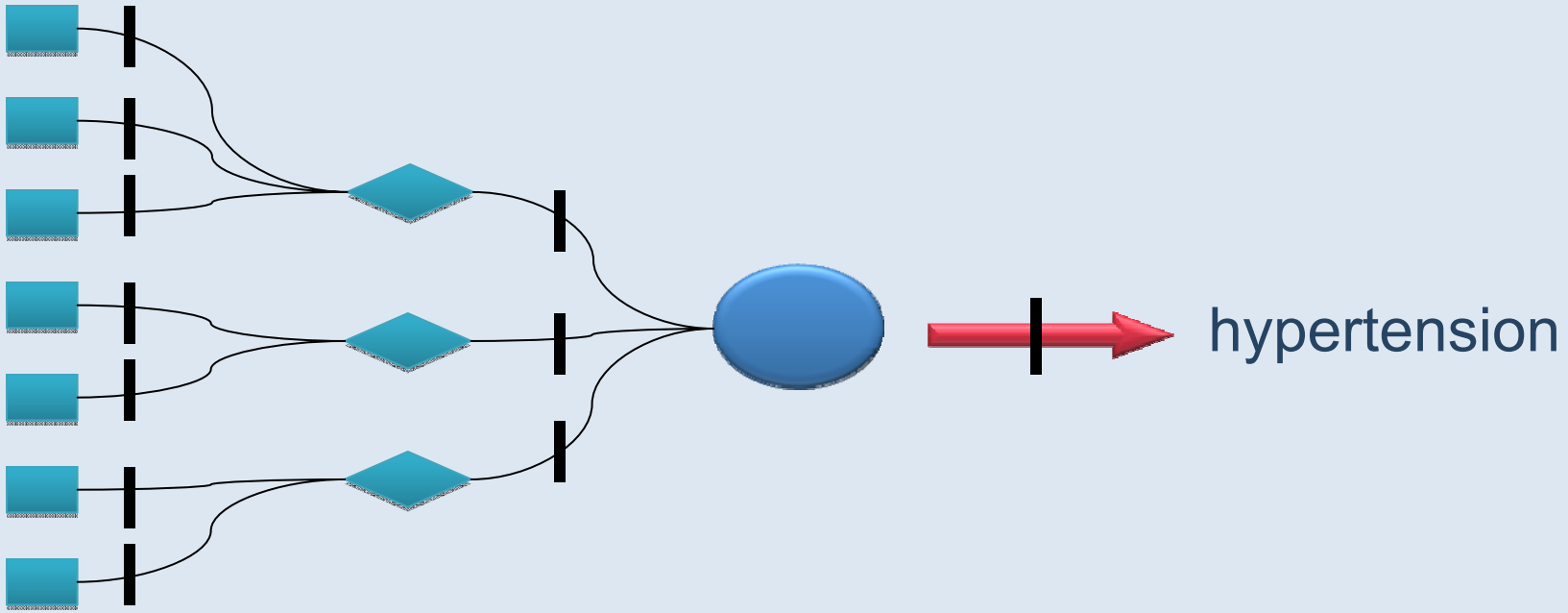




EGFr mutations

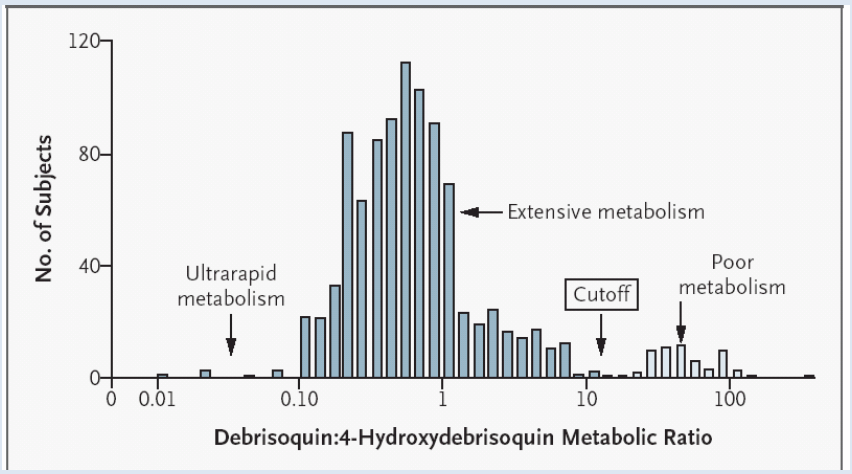
N Engl J Med 2004;350:2130.

Disease Stratification
Targeted Therapy



Pharmacogenetics

- CYP2D6 (debrisoquine hydroxylase)
  - Poor metabolizer (PM)
    - Mutations that decrease expression
      - 5-10% N.A. whites; 1-2% African Americans
  - Ultrarapid metabolizer (UM)
    - Duplications
      - 5-10% whites, 29% Ethiopians

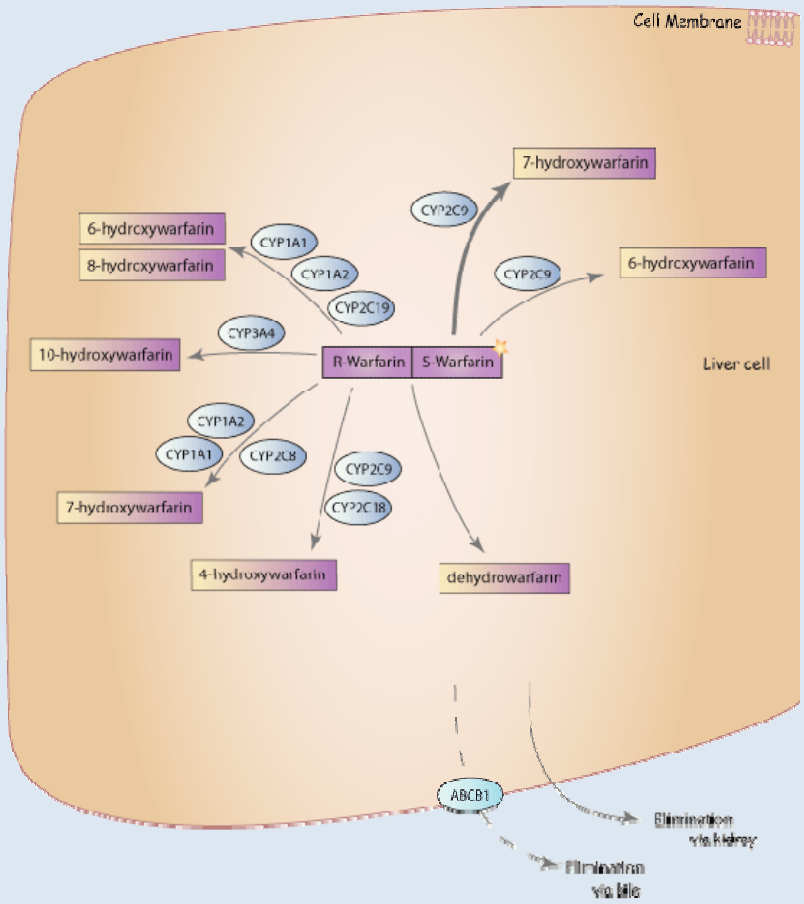


Weinshilbaum,R., NEJM 2003;348:529

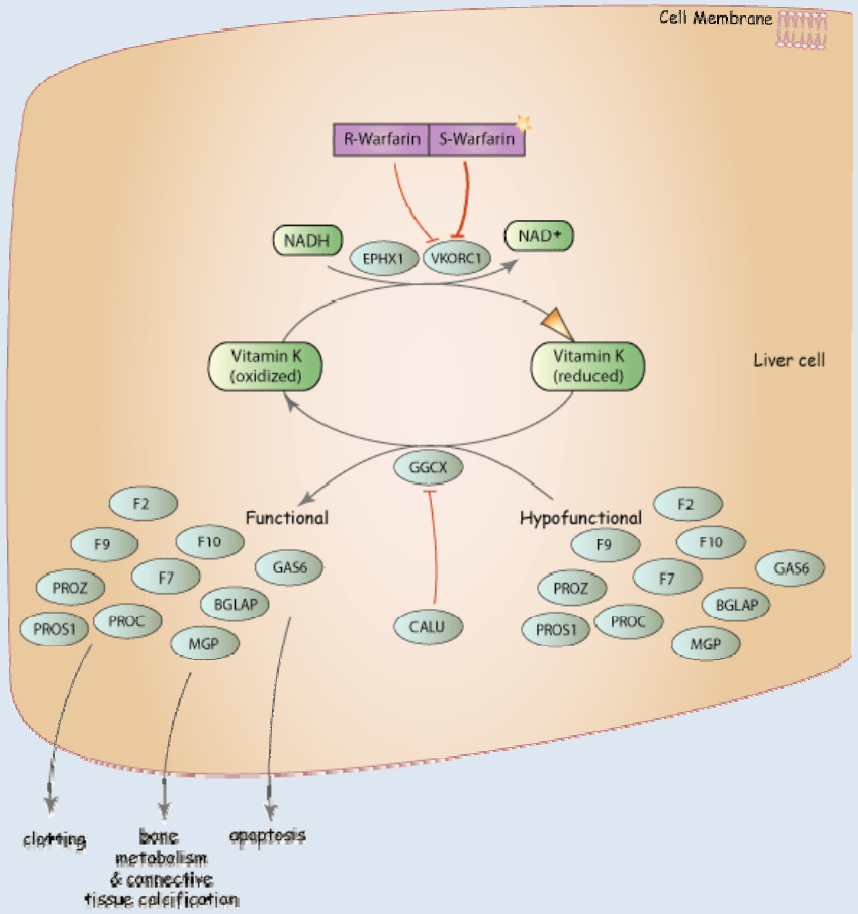
Drugs Metabolized by CYP2D6

Class	Examples
Analgesics	Codeine, hydrocodone, tramadol
Antiarrhythmics	Encainide, flecainide, mexiletene, propafenone
Antidepressants	Amitriptyline, desipramine, fluoxetine, fluvaxamine, imipramine, nortriptyline, paroxetine
Antihistamines	Chlorpheniramine, diphenhydramine, promethazine
Antipsychotics	Haloperidol, perphenazine, thiridazine
Beta Blockers	Carvedilol, metoprolol, propranolol, timolol
Cough suppressants	Codeine, dextromethorphan

Warfarin Pharmacogenetics



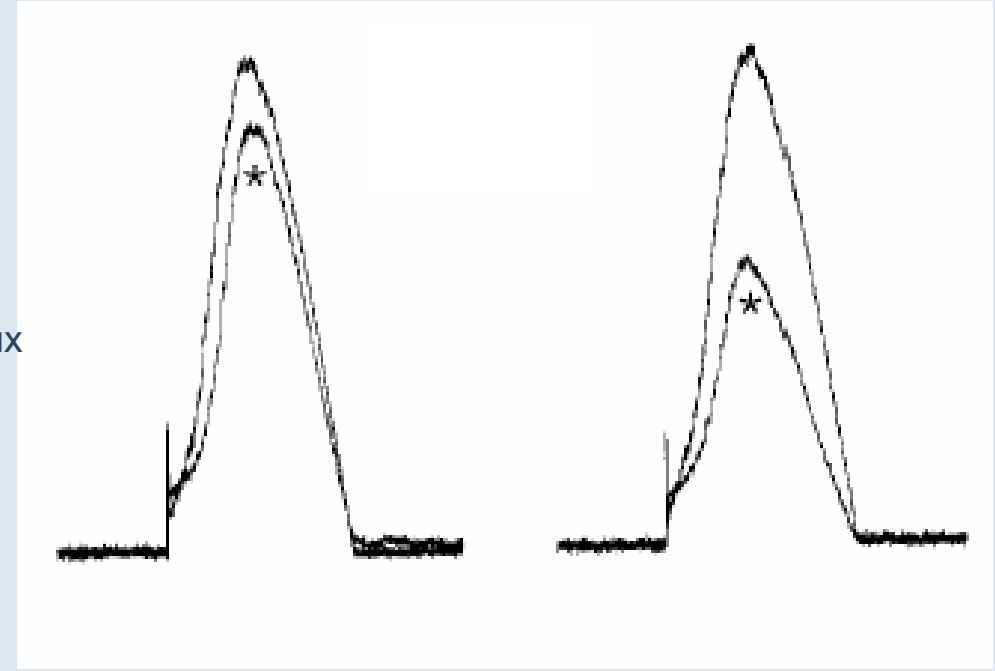
pharmacokinetics



pharmacodynamics

www.pharmgkb.org

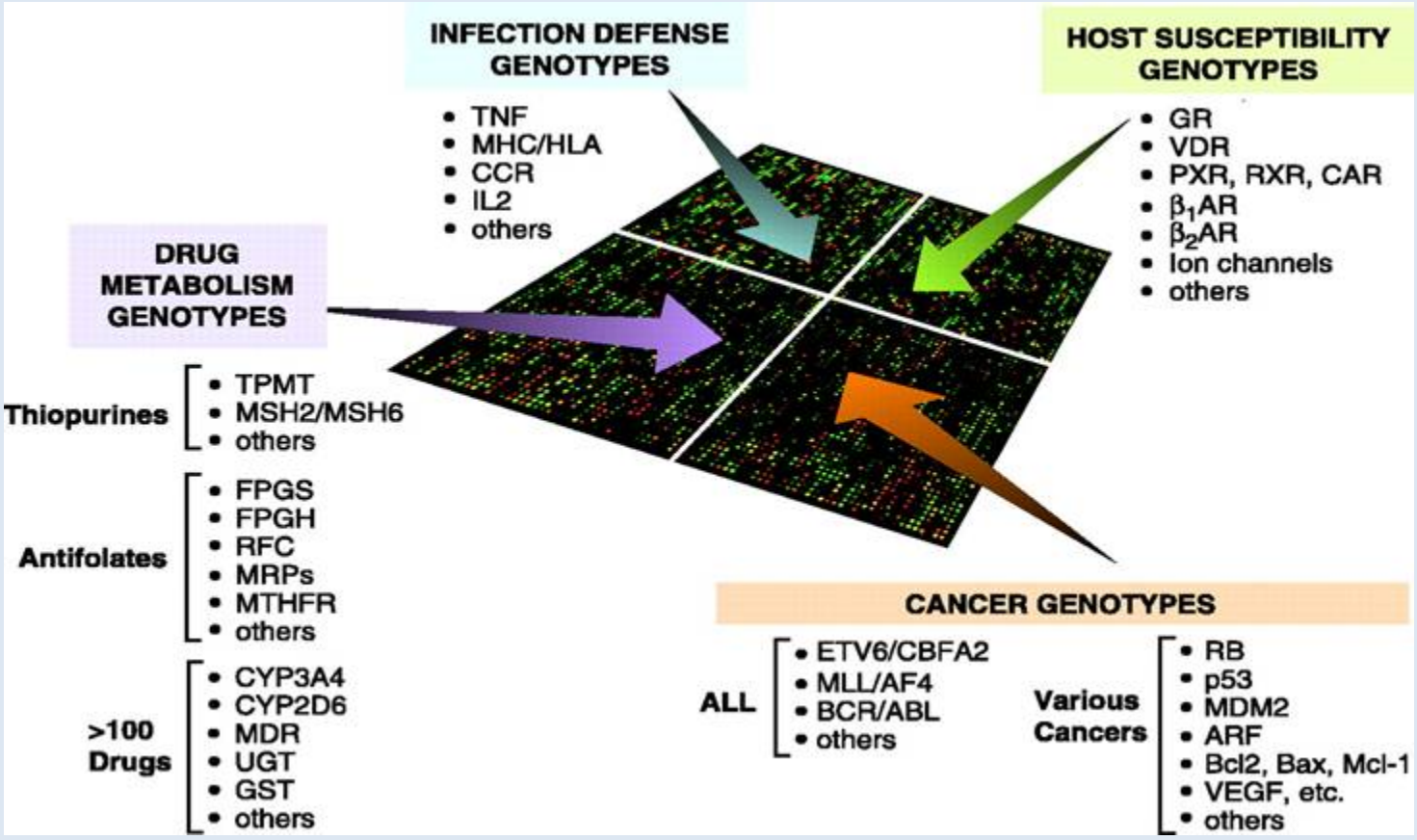
Drug Toxicity



Polymorphism in KCNE2 potassium channel (1.6%) found in patient who developed prolonged QT while treated with Bactrim

Sesti F, et al. Proc. Natl. Acad. Sci. (USA) 2000;97:106133-10618.

Pharmacogenetic Testing



Evans WE, Relling MV. Science 1999;286:487-491.

Revolution Through Competition.

JOIN THE REVOLUTION
X PRIZE Membership

X PRIZEs

- What is an X PRIZE?
- Why X PRIZEs Work
- Ansari X PRIZE
- Archon X PRIZE for Genomics
- Automotive X PRIZE
- Future X PRIZEs

ARCHON GENOMICS X PRIZE

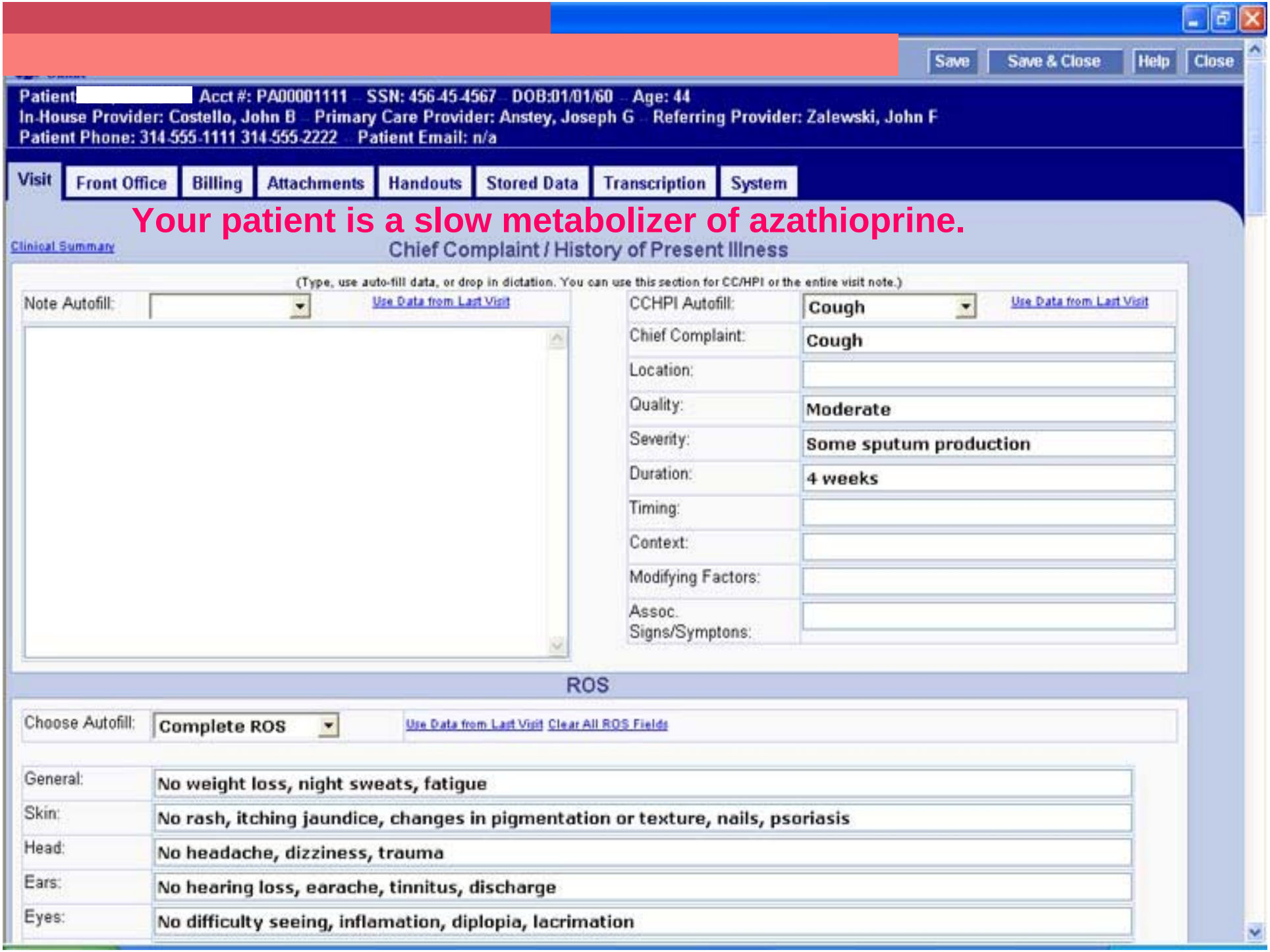
The era of personalized medicine is dawning

As scientists gain knowledge from mapping the Human Genome, they will also find new ways to treat and even prevent disease. To build the library of information necessary to advance the field of genomic medicine, it is imperative that we develop DNA sequencing technology that is faster and affordable.

To stimulate breakthrough innovation in the field of genomic sequencing, the X PRIZE Foundation has launched a global competition with a $10 million prize for the winner of the Archon X PRIZE for Genomics.

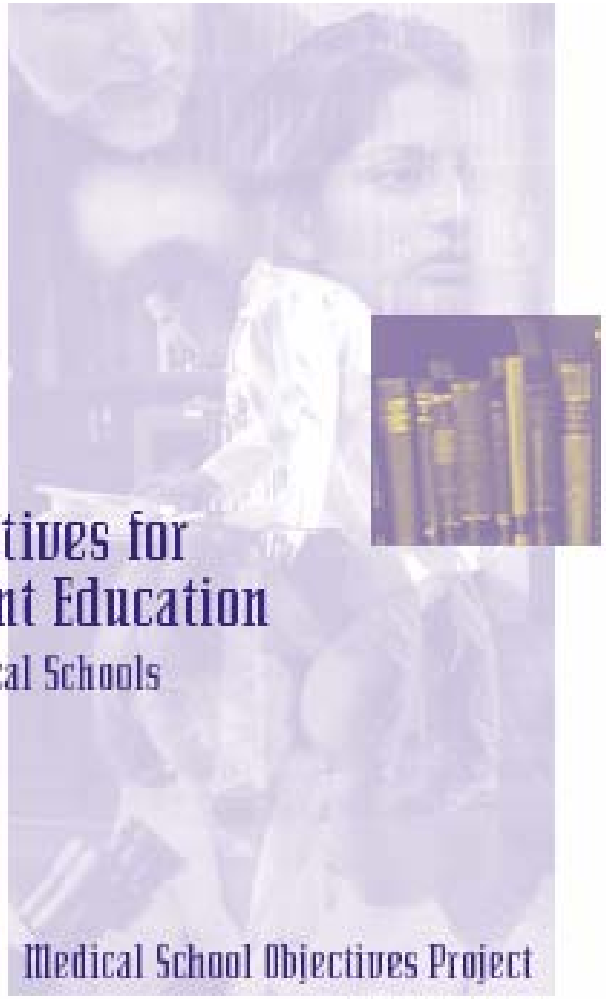
Learn more about the Archon X PRIZE for Genomics.

The $1,000 Genome Sequence


Save
Save & Close
Help
Close
Patient [redacted] Acct #: PA00001111 SSN: 456-45-4567 DOB:01/01/60 Age: 44
In-House Provider: Costello, John B Primary Care Provider: Anstey, Joseph G Referring Provider: Zalewski, John F
Patient Phone: 314-555-1111 314-555-2222 Patient Email: n/a
Visit
Front Office
Billing
Attachments
Handouts
Stored Data
Transcription
System
Your patient is a slow metabolizer of azathioprine.
Clinical Summary
Chief Complaint / History of Present Illness
(Type, use auto-fill data, or drop in dictation. You can use this section for CC/HPI or the entire visit note.)
Note Autofill:
Use Data from Last Visit
CCHPI Autofill: Cough
Use Data from Last Visit
Chief Complaint: Cough
Location:
Quality: Moderate
Severity: Some sputum production
Duration: 4 weeks
Timing:
Context:
Modifying Factors:
Assoc. Signs/Symptons:
ROS
Choose Autofill: Complete ROS
Use Data from Last Visit
Clear All ROS Fields
General: No weight loss, night sweats, fatigue
Skin: No rash, itching jaundice, changes in pigmentation or texture, nails, psoriasis
Head: No headache, dizziness, trauma
Ears: No hearing loss, earache, tinnitus, discharge
Eyes: No difficulty seeing, inflamation, diplopia, lacrimation

The future of healthcare?

ASSOCIATION OF AMERICAN MEDICAL COLLEGES



Report I

Learning Objectives for Medical Student Education

Guidelines for Medical Schools

Medical School Objectives Project

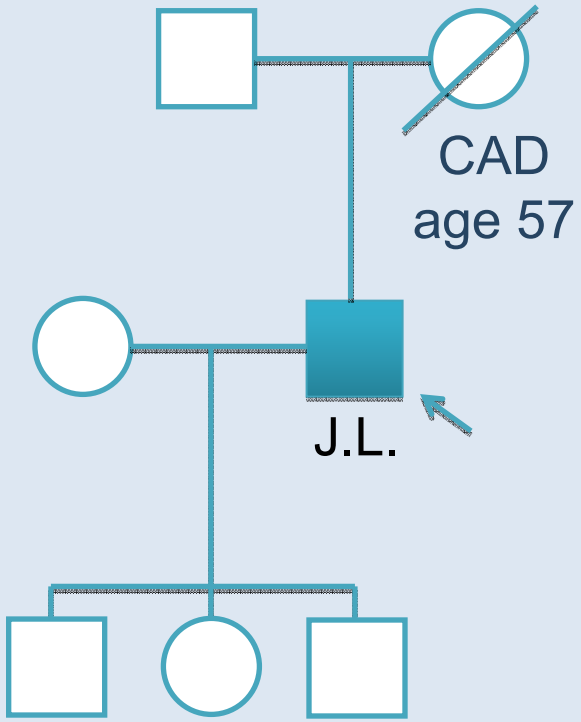
January 1998

	Clinical Years Now	Residency 5 years +	Practice 10 years +
Prevention	• Newborn screening for inborn errors of metabolism and other disorders • Carrier screening for hemoglobinopathies, lysosomal storage disorders, cystic fibrosis • Presymptomatic testing for breast, ovarian, colon cancer • Limited proteomic screening for cancer	• Expanded newborn screening with tandem mass spectrometry • Increased number of prenatal carrier screens • Expanded scope of cancer screening and presymptomatic testing • Limited use of screening panels for common disorders, such as cardiovascular disease or dementia	• Wide array of disorders subject to newborn screening • Routine use of proteomic screens for very early detection of common cancers • Increasing use of screening for risk for common disorders to achieve risk stratification and implement prevention strategies
Diagnosis	• High resolution cytogenetic analysis for constitutional changes and cancer • Molecular diagnostic tests for limited number of monogenic disorders • Prenatal diagnosis by amniocentesis and CVS	• Use of microarrays to diagnose subtle chromosomal abnormalities • Increasingly routine use of molecular testing for wide range of monogenic disorders • Increasing use of expression microarrays in histopathological diagnosis • Use of new modes of prenatal testing, such as preimplantation testing	• Use of panels of molecular tests to stratify common disorders such as asthma or hypertension • Routine molecular characterization of tissues in pathology • Use of panels of tests to achieve precise diagnosis of monogenic and chromosomal disorders
Treatment	• Limited pharmacological treatment of monogenic disorders (e.g., lysosomal disorders) • Limited use of pharmaco genetic testing (e.g., TPMT) • New forms of chemotherapy based on knowledge of cancer biology • Experimental gene therapy protocols	• Increasing array of monogenic disorders amenable to treatment • Expanded panel of pharmacogenetic tests (e.g., CYP2D6) • Increasing number of new cancer-specific therapies • Continued experimentation with gene therapy • Use of expression arrays to determine treatment strategies for certain diseases	• Routine use of pharmaco genetic profiling • Stratification of common disease and selection of specifically targeted therapies • Limited routine use of gene therapy • Use of expression arrays to determine treatment strategies widespread

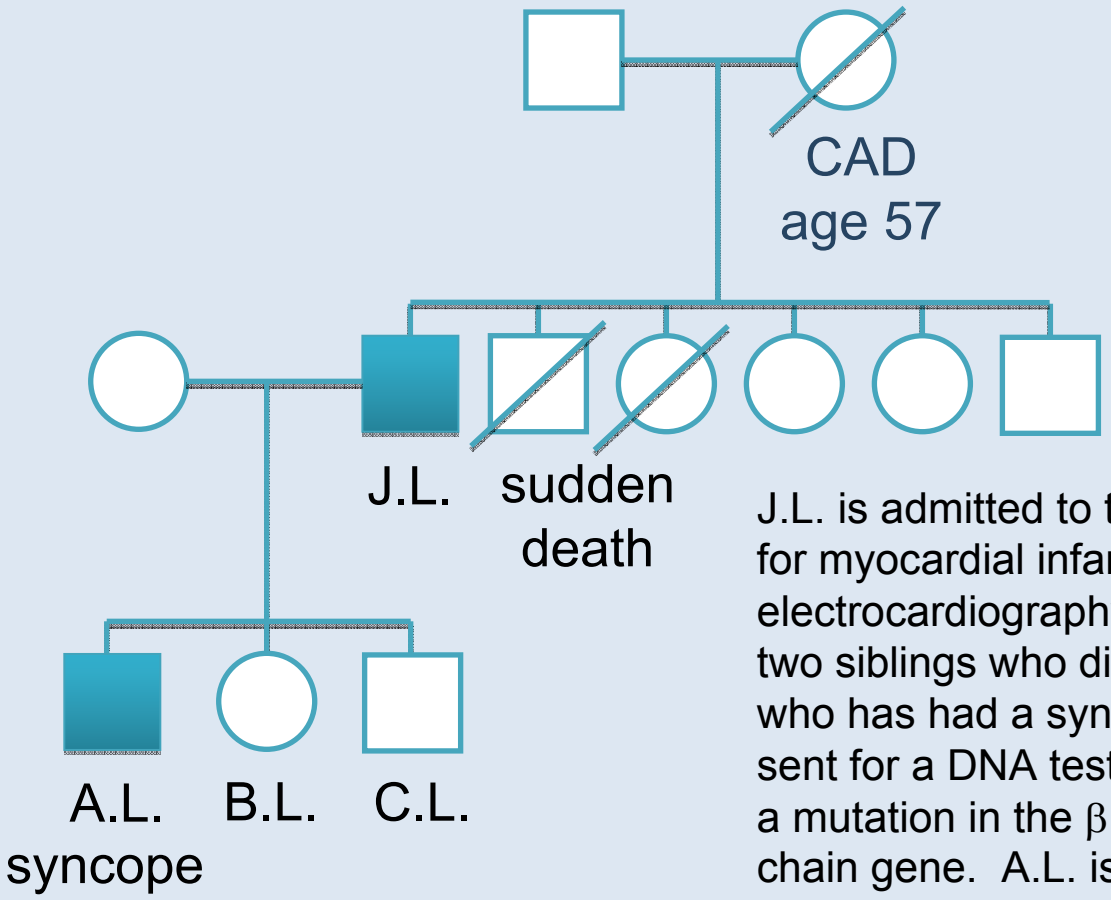
Pedagogy

- Genetics is a natural integrator
- Teach things that matter
- Recognize the importance of roll models

2002

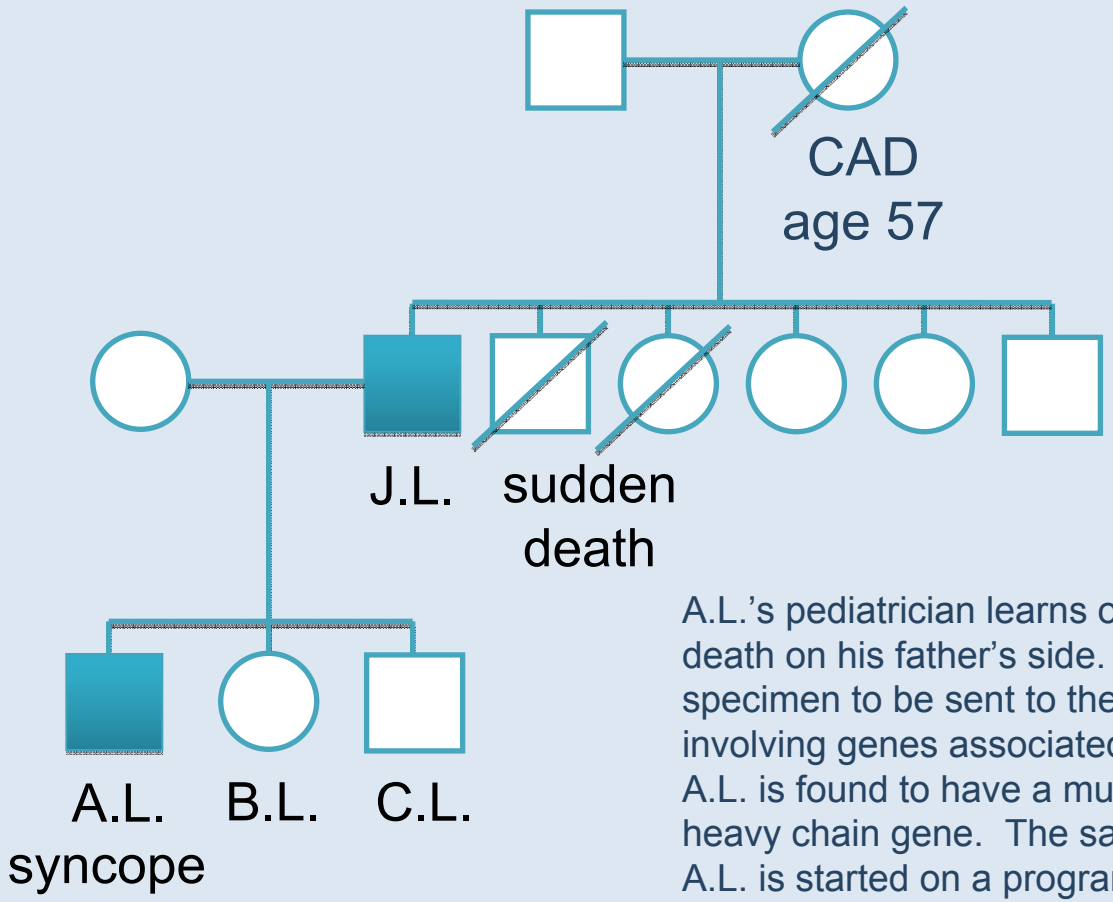


2007



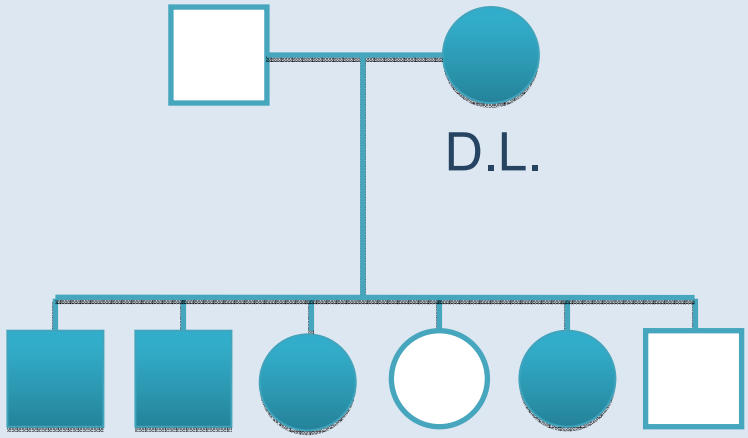
J.L. is admitted to the hospital. He rules out for myocardial infarction by enzymes and electrocardiography. Family history reveals two siblings who died suddenly and a child who has had a syncopal episode. Blood is sent for a DNA test and J.L. is found to have a mutation in the β cardiac myosin heavy chain gene. A.L. is found to have the same mutation, but it is not present in B.L. or C.L. A.L. is started on a program of regular monitoring by echocardiography.

2010



A.L.'s pediatrician learns of a family history of sudden death on his father's side. He arranges for a blood specimen to be sent to the laboratory for a panel of tests involving genes associated with cardiac dysfunction. A.L. is found to have a mutation in the β cardiac myosin heavy chain gene. The same mutation is found in J.L. A.L. is started on a program of monitoring by echocardiography. An echocardiogram done in J.L. reveals signs of advanced hypertrophic cardiomyopathy. He is started on a new β blocker medication, and is advised to consider implantation of a defibrillator.

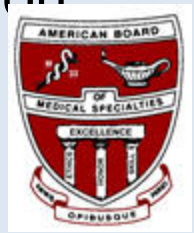
2015



In the course of a routine primary care visit, D.L. is noted to have a family history of early unexplained death (her mother and maternal aunt). She is tested for a set of risk factors known to predispose to early death and is found to have a mutation in the β cardiac myosin heavy chain gene. She is started on a new class of medication known to prevent the occurrence of hypertrophic cardiomyopathy. Four of her children are also found to carry the mutation. They, too, are started on medication and a program of regular monitoring.

Medical Genetics Training

- Medical Genetics
  - 2 year genetics residency
    - 2 prior years of ACGME-accredited residency
  - 5 year combined internal medicine-genetics or pediatrics-genetics program
  - ACGME-accredited, ABMG certification
- Genetic Counseling
  - 2 years masters program
  - ABGC Certification

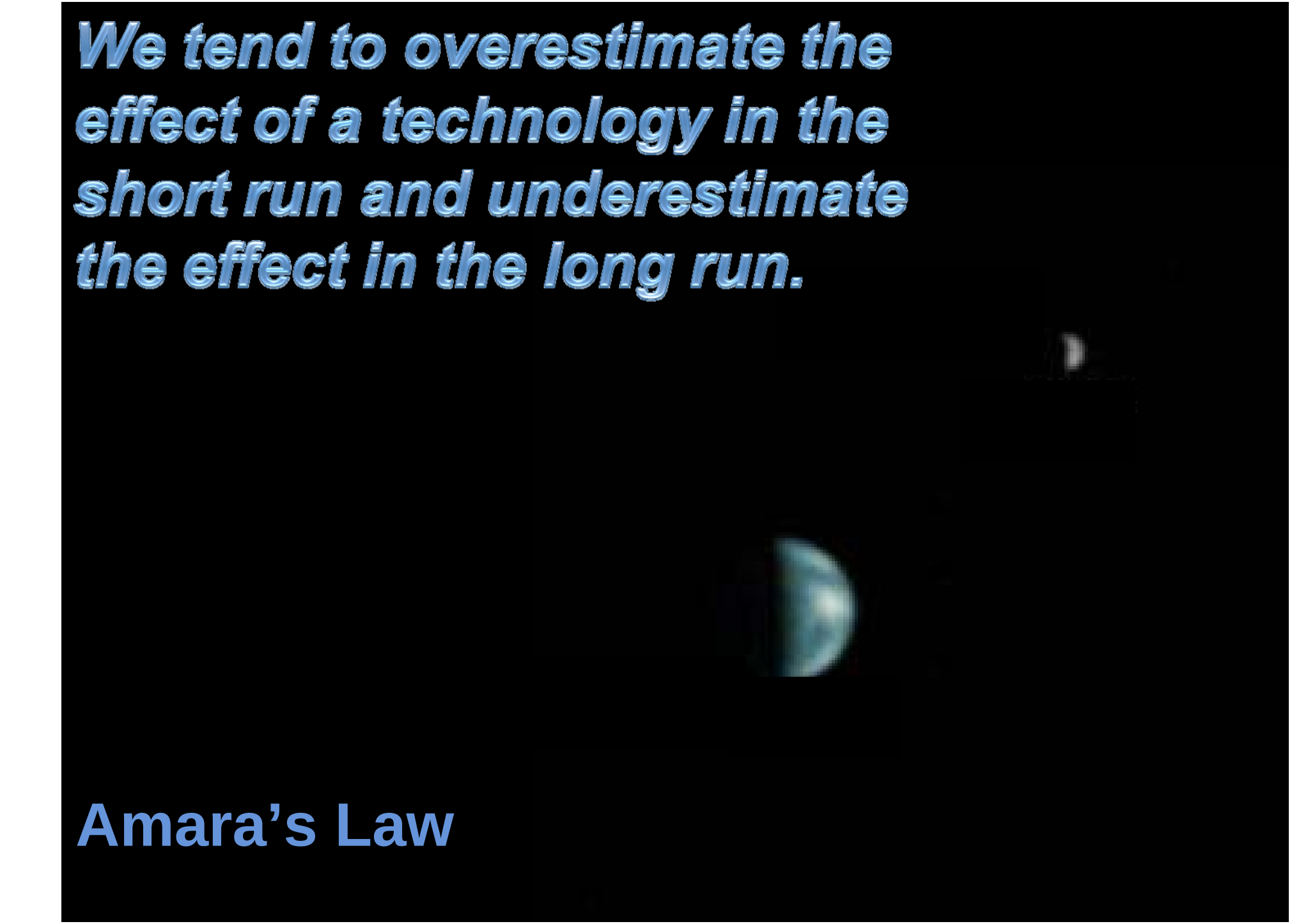


Genetics in Medicine

	Primary Care	Specialist	Medical Geneticist
Single Gene or Chromosomal	recognize signs and symptoms; make referral; support family; longitudinal care	manage specific problems	diagnosis; counseling; longitudinal care
Major Gene Multifactorial	Appreciate role of family history; arrange testing and referral to specialist as needed; provide longitudinal care	Diagnosis and management of system-specific problems	Advise on interpretation of test results; genetic counseling; evaluation of complex cases
Complex Multifactorial	Use of genetic tests to guide treatment	Use of genetic tests to guide treatment	Reservoir of knowledge and handling of complex cases


• Education of health professionals and the general public
• Access to information
• Tools for screening, education
• Protection of individual rights and privacy
• Knowledge of outcomes
• Development of new prevention strategies and treatments

We tend to overestimate the effect of a technology in the short run and underestimate the effect in the long run.



Amara's Law