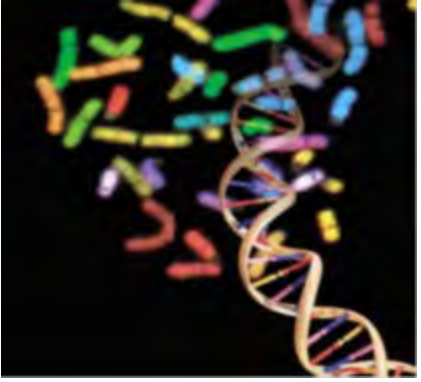


Genomic Medicine

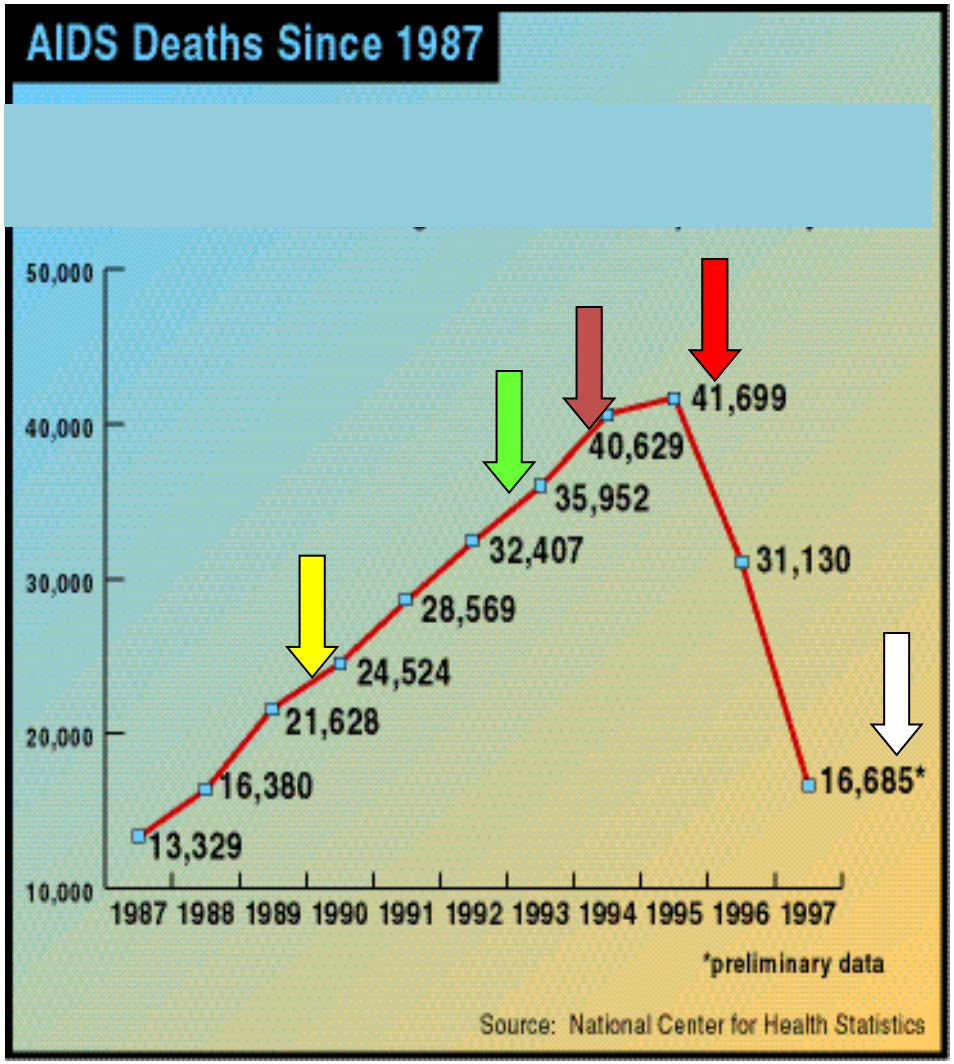
The Development, Economic and Ethical Challenges of Translating Basic Research into Clinical Practice

Thomas J. White, Ph.D.

Regents' Lecture 2012-2013

University of California, Berkeley

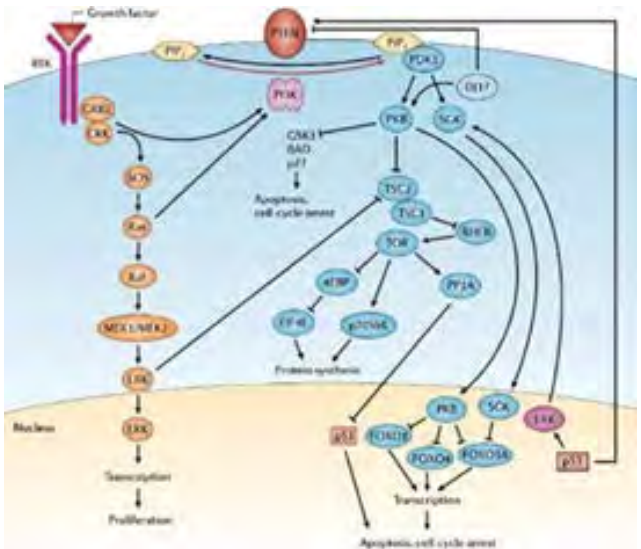
A Diagnostic Test that Changed AIDS Treatment



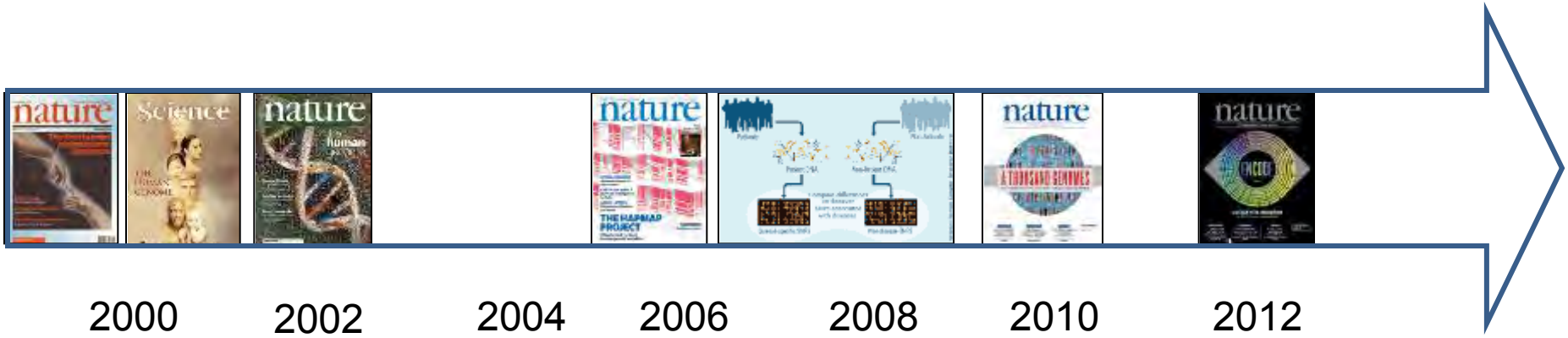
- Monotherapy (AZT)
- Combination therapy
- Reference Lab HIV viral load assay
- FDA approval of HIV viral load kit (prognosis) and protease inhibitors
- FDA approval of HIV viral load kit (monitoring)

Impact of Genomics on Medicine

- Identify the underlying causes of disease and reasons for progression
  - Sub-classify complex diseases
- Design therapies to intervene in disease development
  - Treat cause, not symptoms
- Define patient populations most likely to respond
  - Increase efficacy of therapies
  - Minimize adverse reactions
  - Reduce risk in clinical trials



Genetic and Genomic Projects



Human Genome

HapMap

Genome Wide Association Studies

1000 Genomes

Encyclopedia of DNA Elements (ENCODE)

Overview

- Human genetic variation
- Current genetic tests
- Test availability and reliability
- Evidence for clinical utility
- Medical benefit and cost effectiveness
- Reimbursement
- Privacy and ethical issues

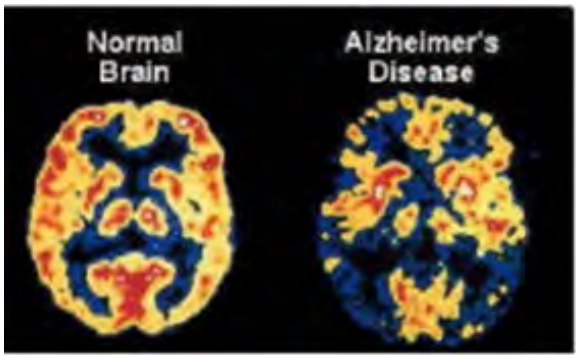
Recent Discoveries in the News

- A report is published on a rare genetic mutation that protects people against late-onset Alzheimer's Disease
- FDA approves a drug that gives a 57% response rate in the 4% of non-small cell lung cancer patients who have a particular gene rearrangement (EML4-ALK)
- Variants accounting for 20% of Autism Spectrum Disorder have been identified; most are "*de novo*" variants. Another report concludes that older men are more likely to father children with autism

"We think it has something to do with your genome."

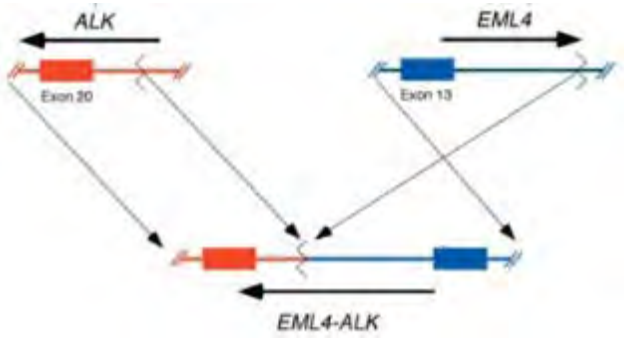
Questions About the Alzheimer's Discovery

- The mother of a 50 year old man had late-onset Alzheimer's at age 85; should he be tested for the specific protective (and risk) mutations?
- Where is testing available, what will it cost, and will his health insurance cover it?
- Although the Genetic Information Non-Discrimination Act prohibits his test results from being used to deny employment and health insurance, what about disability, life and long-term care insurance?



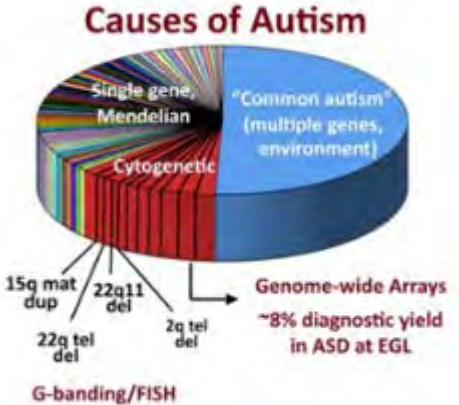
Questions About the Lung Cancer Discovery

- Since 96% of NSCLC patients' tumors do not carry the EML4-ALK variant, is it worthwhile to be tested for it?
- Must a patient's tumor have the variant in order to receive the drug?
- Are there other genetic variants in the tumor that could be used to select other targeted therapies?
- Is there intra-tumor genetic heterogeneity?
- Should the tumor be studied by Whole Exome Sequencing (WES)?



Questions About the Autism Discoveries

- What are "*de novo*" variants?
- Can they be detected by Non-Invasive Prenatal Testing?
- If most of the known autism variants are not inherited, why are the children of older fathers at greater risk?
- Is it worth having a Whole Genome Sequence (WGS) done on an autistic child to identify variants if there is no targeted therapy?
- How will Variants of Unknown Significance be reported?
- Will the discovery of these variants potentially lead to new drugs for autism?

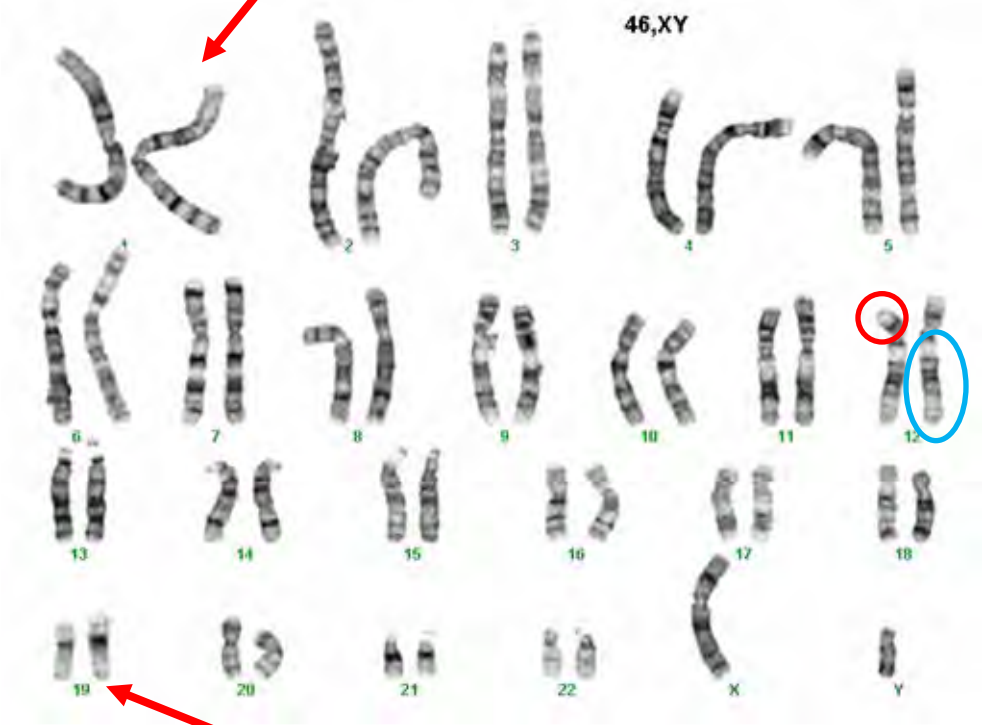


Some Commonly Used Terms

- Gene
- SNP (Single Nucleotide Polymorphism)
- Phenotype
- “Junk DNA”
- Gene Regulation
- “de novo” Variants
- Genetic Test
- Whole Genome Sequencing
- Whole Exome Sequencing

Human Chromosomes

Gene for Factor V Leiden (chromosome 1)

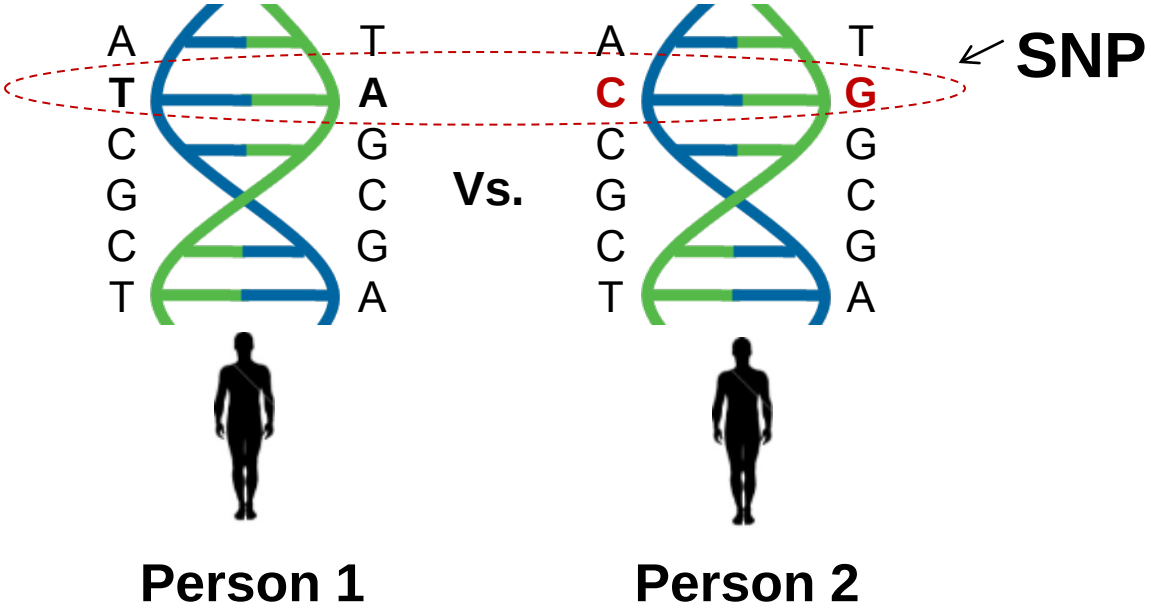


Gene for ApoE (chromosome 19)

- Human cells contain 46 chromosomes in 23 pairs – one of each pair is inherited from each parent
- Chromosome pairs 1 – 22 are called autosomes
- The 23rd pair is called sex chromosomes: XX is female, XY is male

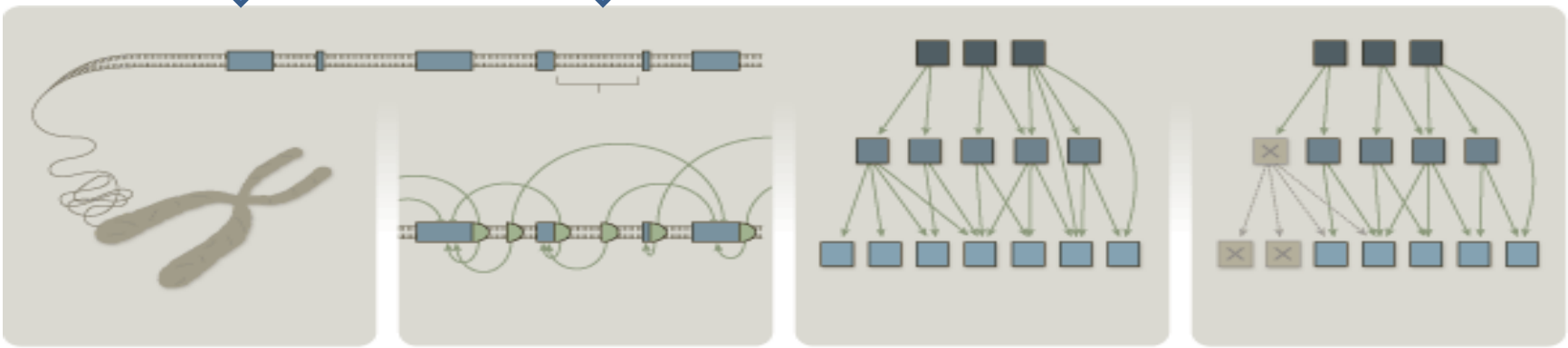
SNPs

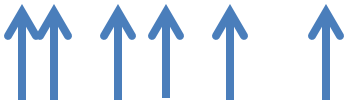
- In humans, there are millions of **single-nucleotide polymorphisms (SNPs)** or genetic variations between two unrelated individuals
- Because of the double-stranded nature of DNA, variants cause base pairs of the DNA helix to change



“Junk DNA” has a Key Role in Gene Regulation

Gene | Junk DNA | Regulation | Disease





>470,000 Genetic Switches

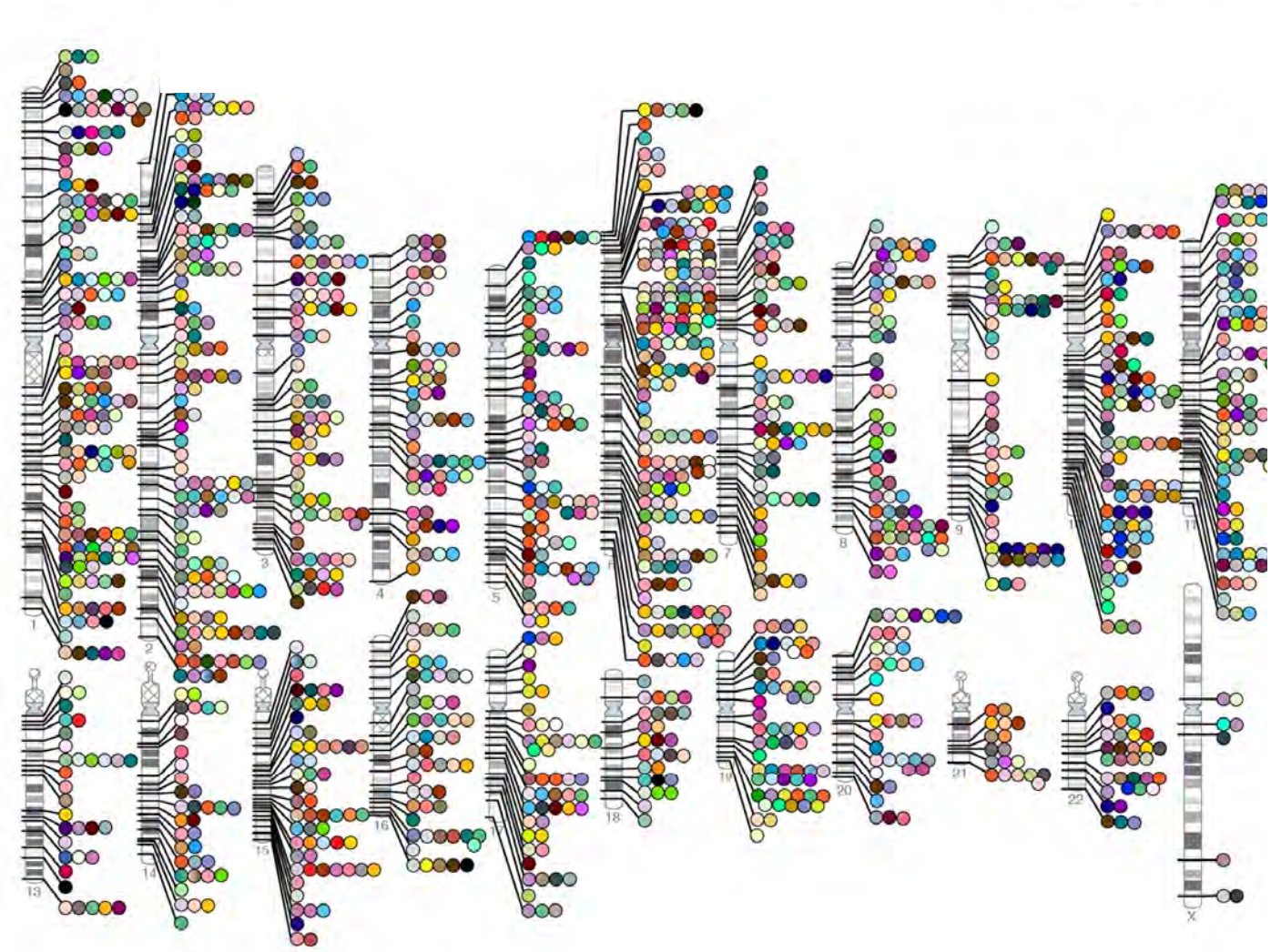
Hierarchy of Genetic Regulators

Malfunctioning Hierarchy

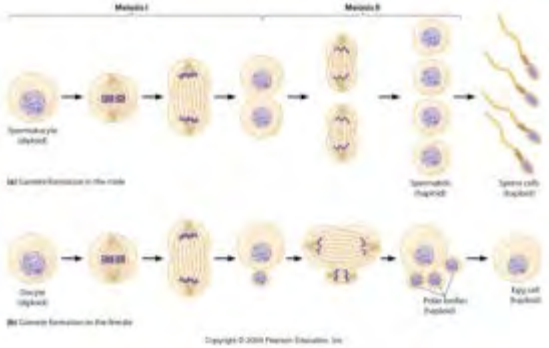
Human Genetic Variation

- The human genome has ~3 billion base pairs
- Humans and chimpanzees are ~98.5% identical
  - 35 million SNPs
  - 5 million insertion/deletions
- Any two people, on average, are ~99.8% identical
  - 3.6 million SNPs
  - 344,000 insertions/deletions
  - 717 large deletions
- Each person has
  - 100 loss-of-function mutations
  - 20 are double mutations that would inactivate the genes

Genome Wide Association Studies

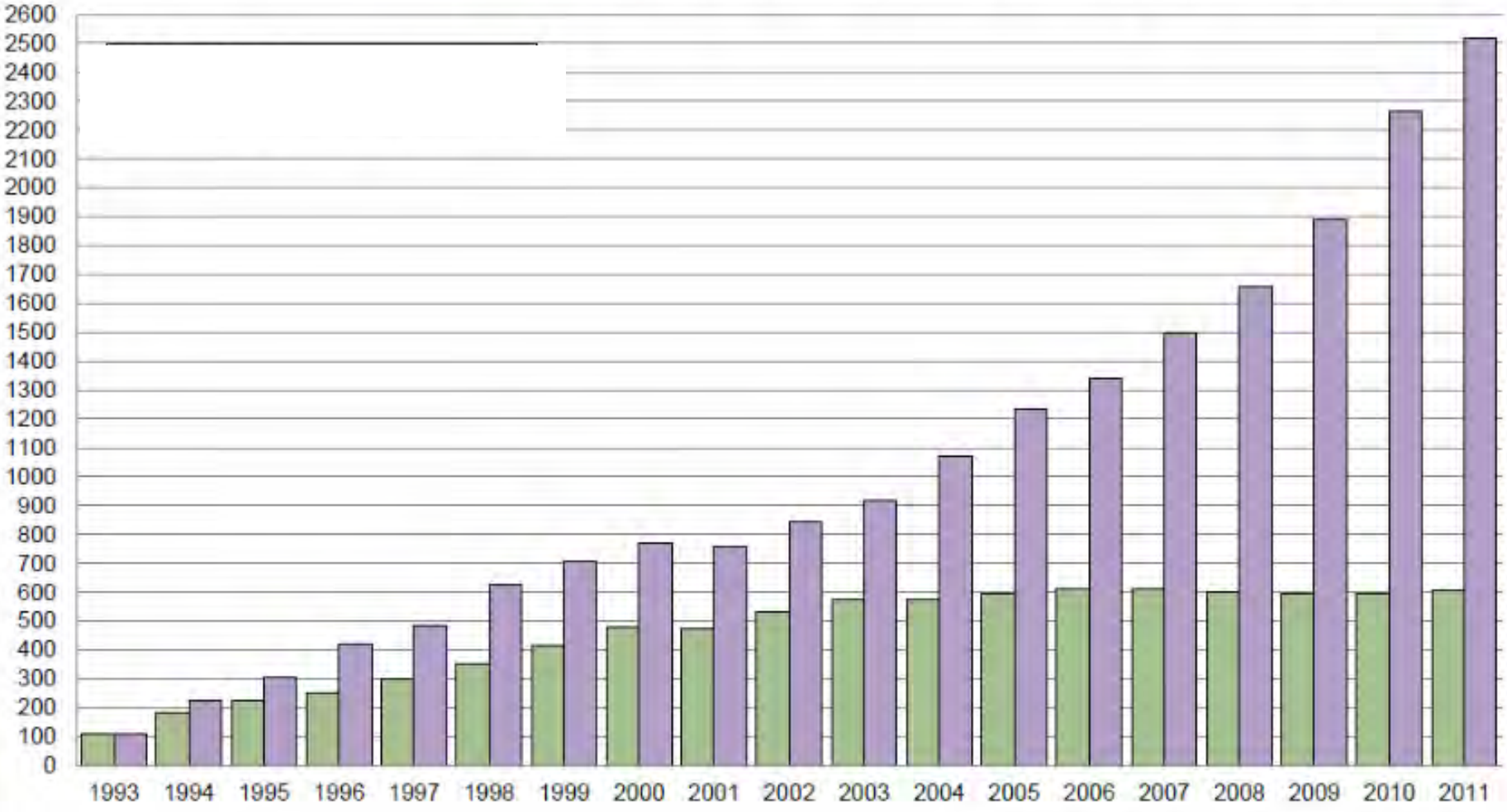


de novo Mutations



- The variant is found in a newborn, but not in either parent's genome
- Result of spontaneous mutations during spermatogenesis and oogenesis
- ~ 60 new variants per generation, depending on age of father at conception (+ 2 per year of paternal age)
  - 25 mutations from a 20 year old father
  - 65 mutations from a 40 year old father
  - 15 mutations from a mother regardless of her age
- ~10 % of the mutations will be deleterious
  - A newborn will have ~ 6 new deleterious mutations

GeneTests: Growth of Laboratory Directory



Data source: GeneTests database (2011)/ www.genetests.org

Genetic Tests for Inherited Diseases

- 12 tests approved by US Food & Drug Agency (FDA)
- 2,667 tests offered by clinical laboratories (CLIA)
- 254 tests available from research labs (not for Dx or Rx)
- Association for Molecular Pathology
  - www.amptestdirectory.org
  - FDA-approved/cleared molecular diagnostic tests (pdf)
- National Center for Biotechnology Information
  - www.ncbi.nlm.nih.gov/sites/GeneTests/?db=GeneTests
  - www.ncbi.nlm.nih.gov/gtr
- Lab Tests Online
  - labtestsonline.org

FDA-Approved/Cleared Diagnostic Tests

- Cystic Fibrosis
- HLA Typing for Transplantation
- Factor V Leiden and Prothrombin
- Four Drug Metabolizing Enzymes
- Prenatal (chromosome 13, 18, 21, X and Y)
- Chromosome 8 (AML, CML, MPD, MDS)
- MTHFR
- Heart Transplant Rejection

Laboratory Developed Tests (LDTs)

Clinical Laboratory Improvement Amendments (CLIA)

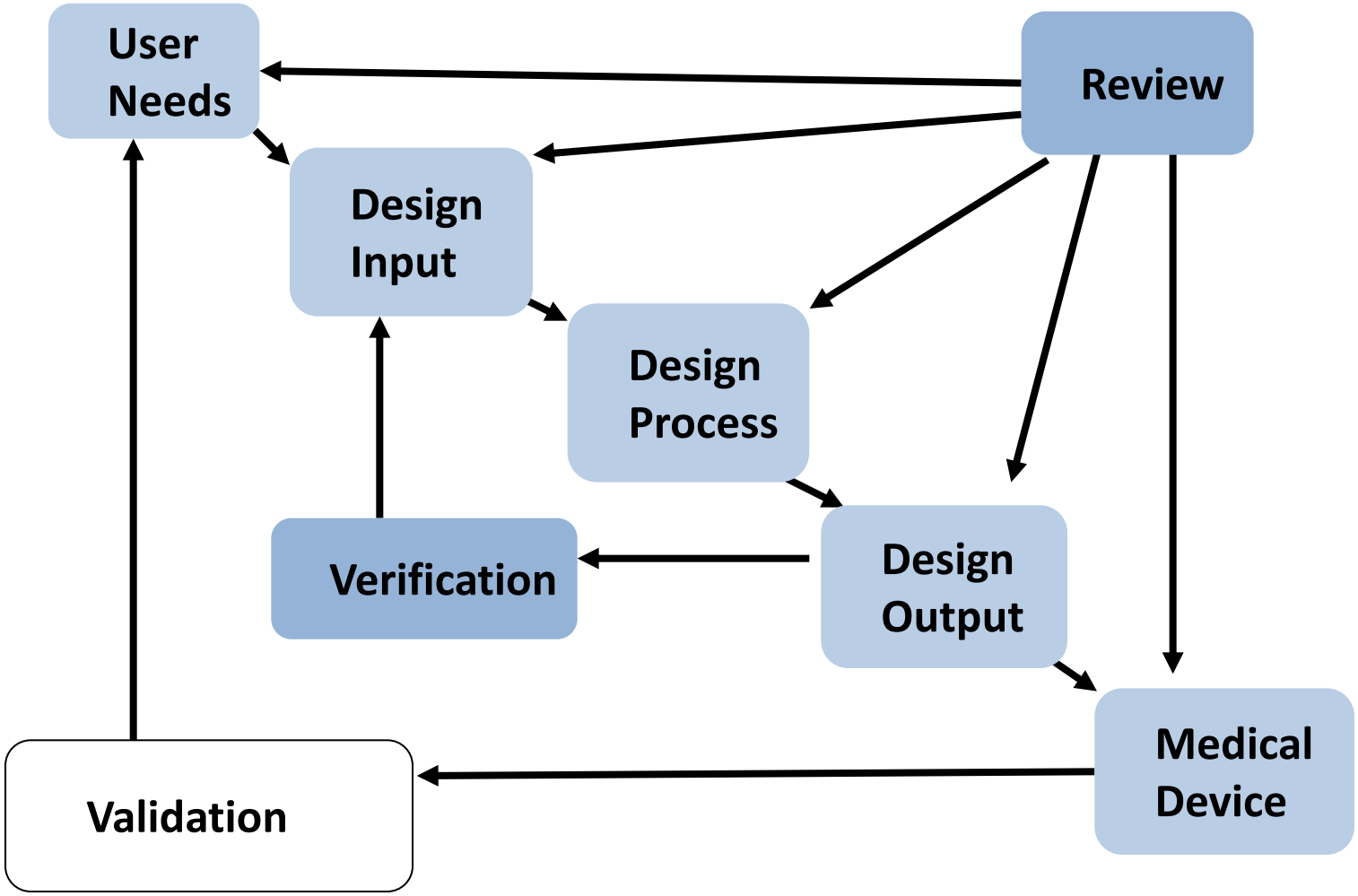
- 2,667 tests for rare inherited diseases & cancer
- LDTs are called “home-brew” tests
- Overseen by Center for Medicare and Medicaid Services
- Requires analytical validation (internal)
- Does not require or establish clinical utility
- Lab can offer test as a service; cannot sell reagents

Genetic Tests Offered by Research Laboratories

- 254 tests
- For basic research
- For identifying potential clinical utility
- Reagents must be labeled: “For Research Use Only (RUO). Not for use in diagnostic procedures”
- May not be represented as an effective diagnostic product

FDA QSR

Quality System Regulations



Quality System Components

Personnel skills and training

Audit preparedness

Document controls

Record keeping

Design controls

Purchasing controls

Component and test acceptance criteria

Component and test ID and traceability

Production and process controls

Non-conforming test criteria

Corrective and preventative actions

Complaint file procedures

Device labeling procedures

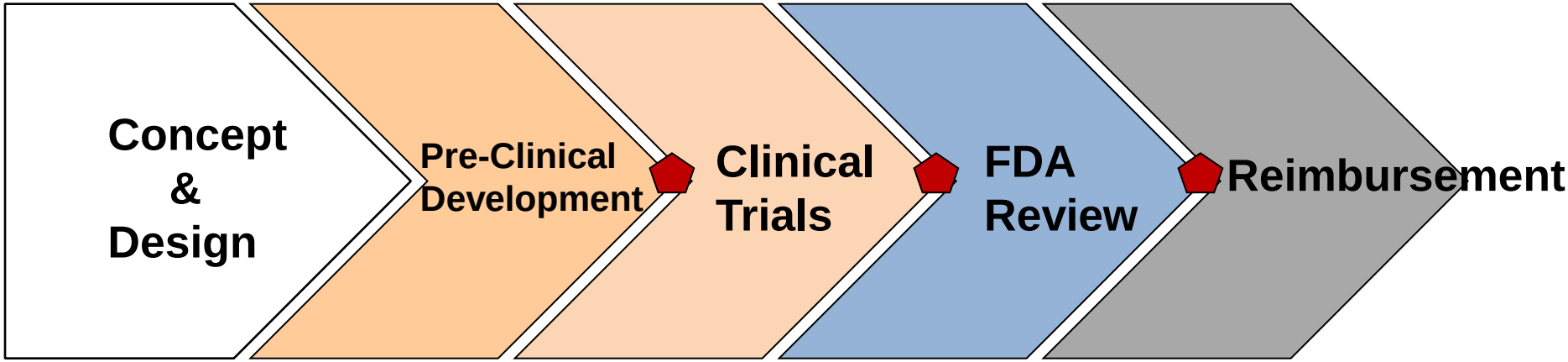
Device packaging criteria

Handling & storage methods

Distribution control

Installation and servicing

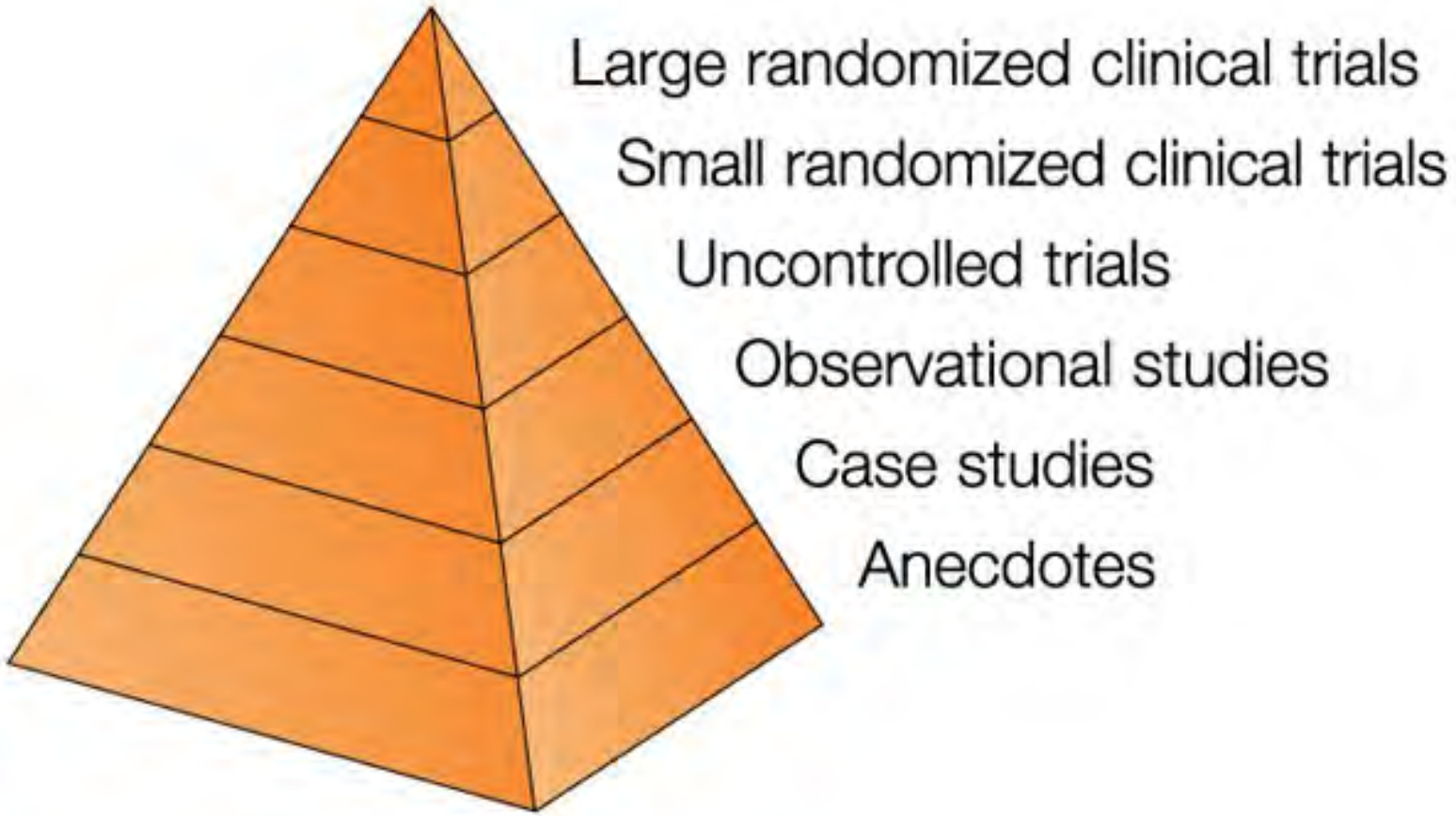
FDA Medical Device Process



2-3 years 1-3 years 1-2 years

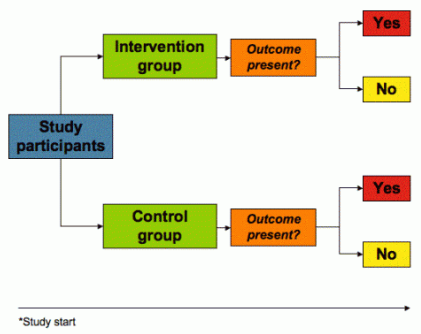
Hierarchy of Evidence

Meta-analysis of large randomized trials



Evidence for Clinical Utility

- Gold standard: a prospective, randomized clinical trial to prove that a test improves clinical outcomes
  - Impractical, lengthy, too costly, or even impossible to enroll patients in a treatment-by-genotype trial, when giving a placebo would now be unethical
- *Post hoc* analysis of previously conducted randomized clinical trials - if informed consent was given for genetic studies and samples are available
- Professional organization's recommendation
  - American College of Obstetrics and Gynecology
  - American Society of Clinical Oncology
- Multiple peer-reviewed publications



Evidence for Clinical Utility

- Need for a national, dynamically updated, interpretative database of evidence for clinical utility of genetic variants
- A means to convey updates to patient and/or physicians
- Government, academic and commercial databases
  - Clin Var www.ncbi.nlm.nih.gov/clinvar
  - EuroGentest Clinical Utility Gene Cards www.eurogentest.org
  - GET-Evidence evidence.personalgenomes.org
  - 23andMe www.23andme.com

Personal Genome Project

Home | Project Overview | Participation Overview | PGP Community | Blog | DONATE

Volunteers from the general public working together with researchers to advance personal genomics.

We believe individuals from the general public have a vital role to play in making personal genomes useful. We are recruiting volunteers who are willing to share their genome sequence and many types of personal information with the research community and the general public, so that together we will be better able to advance our understanding of genetic and environmental contributions to human traits. Learn more about how to participate in the Personal Genome Project.

Project Overview. The PGP hopes to make personal genome sequencing more affordable, accessible, and useful for humankind. Learn more about our mission.

Want to participate? We aim to enroll 100,000 informed participants from the general public. Learn more about participation in the PGP and how you can get involved.

Meet our volunteers. Participants may volunteer to publicly share their DNA sequence and other personal information for research and education. Meet the "PGP-1K".

Participant Login

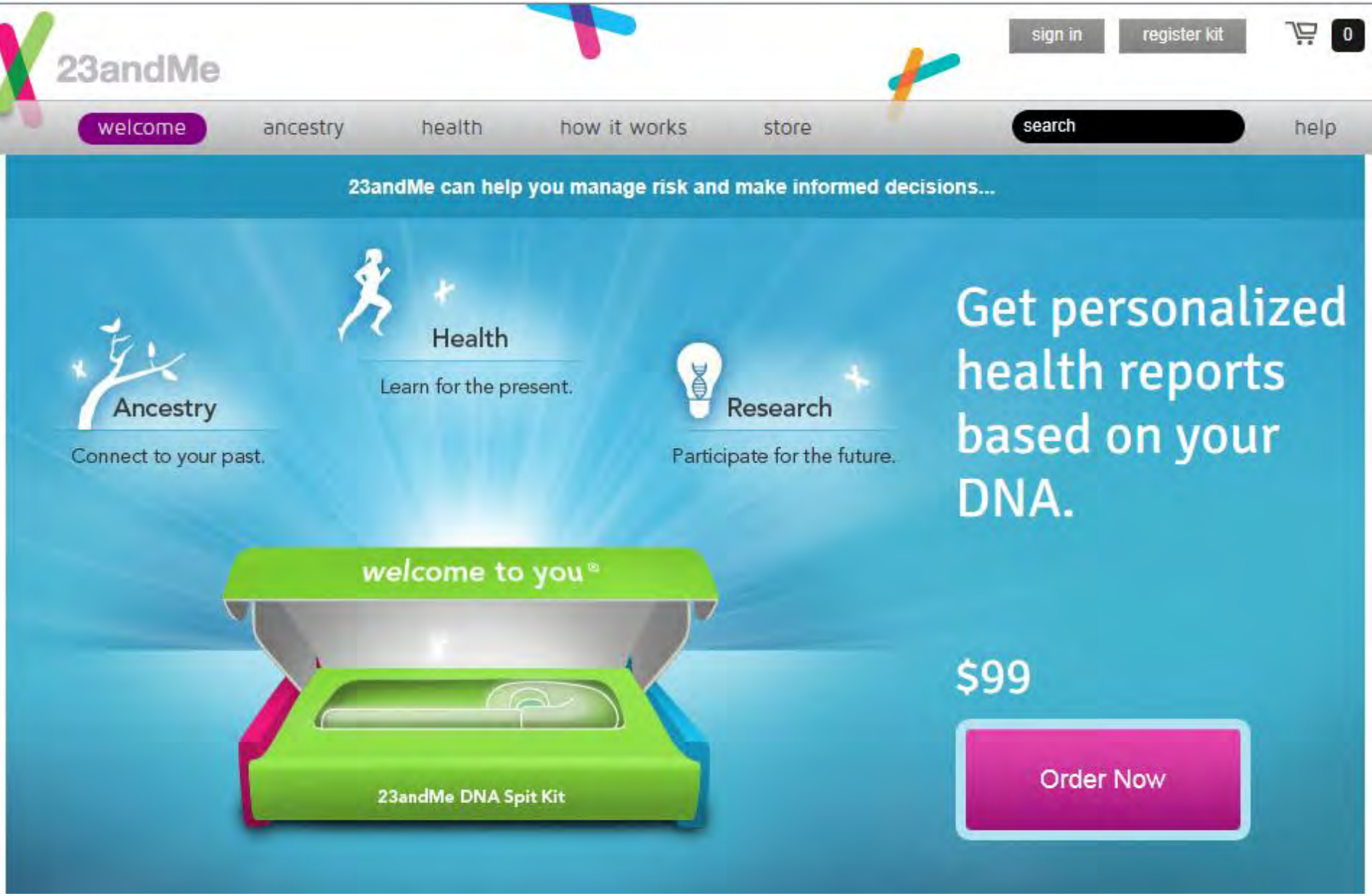
Login Now

Project News

Subscribe to our newsletter

Visit our blog

April 25, 2012: The 2012 GET Conference was held at Harvard Medical School. Learn more.


23andMe
sign in
register kit
0
welcome
ancestry
health
how it works
store
search
help
23andMe can help you manage risk and make informed decisions...
Health
Learn for the present.
Ancestry
Connect to your past.
Research
Participate for the future.
Get personalized health reports based on your DNA.
welcome to you®
23andMe DNA Spit Kit
$99
Order Now

Locked Reports

Name	Confidence	Your Risk	Avg. Risk	Compared to Ave
Alzheimer's Disease	★★★★	🔒	🔒	🔒

Elevated Risk

Name	Confidence	Your Risk	Avg. Risk	Compared to Ave
Psoriasis	★★★★	16.8%	11.4%	1.48x
Esophageal Squamous Cell Carcinoma (ESCC)	★★★★	0.43%	0.36%	1.21x
Stomach Cancer (Gastric Cardia Adenocarcinoma)	★★★★	0.28%	0.23%	1.22x
Alcohol Dependence	★★★			
Alopecia Areata	★★★			
Ankylosing Spondylitis	★★★			
Gout	★★★			
Hay Fever (Allergic Rhinitis)	★★★			
Hodgkin Lymphoma	★★★			
High Blood Pressure (Hypertension)	★★★			

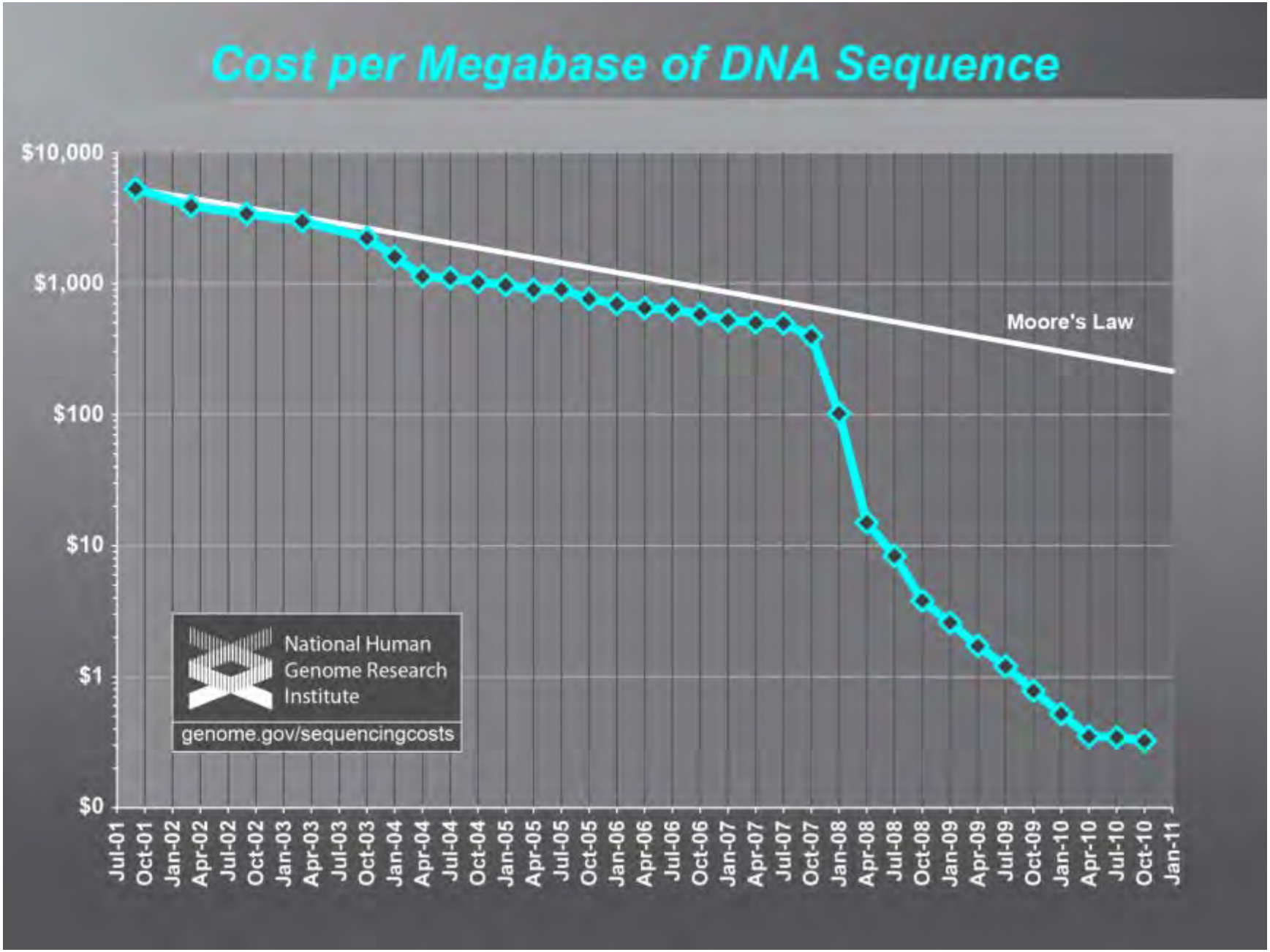
Contradictory Risk Predictions

A 48 year old man has a 1 million SNP test yielding the following results

Lab	Prostate Cancer	Hypertension
1	Average	Average
2	Average	Below Average
3	Below Average	Above Average
4	Above Average	Not Tested

Test Report Issues for WGS Results

- Interpretation
  - Need protocols for censoring results that are meaningless, misleading, or harmful
  - Need a process for updating the patient/physician when new clinically meaningful information becomes available
  - Duty to report (ethical issues)
  - Patent infringement
- Sample/results storage
  - Is it more cost effective to store the data securely or to store the DNA and run the sample again when needed?
- Informed consent
  - What does it mean to the patient, physician and researcher?
  - How will it apply to updated genetic and clinical information on previously unknown disease risks and new therapies?
  - Is the lab responsible for informing the patient or physician?


Cost per Megabase of DNA Sequence
$10,000
$1,000
$100
$10
$1
$0
Moore's Law
National Human Genome Research Institute
genome.gov/sequencingcosts
Jul-01
Oct-01
Jan-02
Apr-02
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Jan-11

Is Whole Genome Sequencing Cost-Effective?

- It's not about the costs of the sequencing reagents and data interpretation, as much as …

  what is the outcome being measured?

  - number of true variants identified
  - multiple diagnoses and relevance to current condition
  - clinical actions over a lifetime
  - patient outcomes – morbidity and mortality

- … and what is the comparator?
- The answers may be different for the patient, healthcare provider, insurer(s) and public health

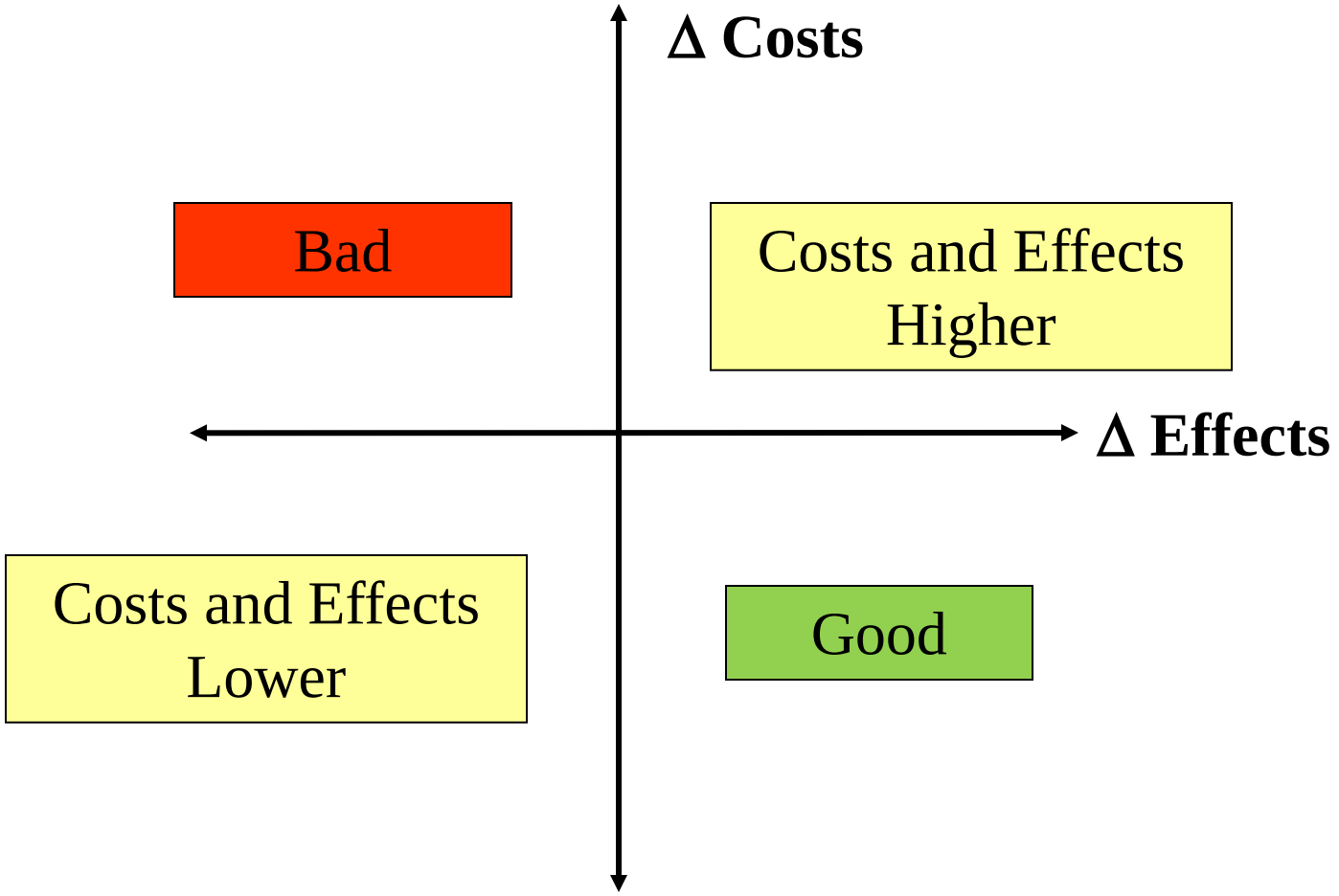
Cost Effectiveness Analysis

- Evaluation of costs and benefits of a healthcare intervention to assist in decision making
- Does an intervention, when used to prevent, diagnose or treat an illness:
  - improve clinical outcomes…enough to
  - justify the additional dollars spent compared with alternative uses of the same money?

Incremental Cost Effectiveness of B vs A

$$\frac{\text{Cost (B) - Cost (A)}}{\text{Effectiveness (B) - Effectiveness (A)}}$$

Interpretation of CEA Results



Cost-Effectiveness of Common Interventions (per life-year gained)

Bone marrow transplant for relapsed Hodgkins	$421,000
Liver transplantation	$237,000
Mammography (<50 years)	$232,000
2-vessel coronary artery bypass graft	$106,000
ACE inhibitor for moderate hypertension	$82,600
Mammography (>50 years)	$20-50,000
Diuretic for moderate hypertension	$23,500
Left main coronary artery bypass graft	$17,400
Genome Test	**$10,000-100,000?**
Smoking cessation (men)	$1,300