Personalized Medicine Technology Trends: Impact on Anesthesiology

Society for Technology in Anesthesia
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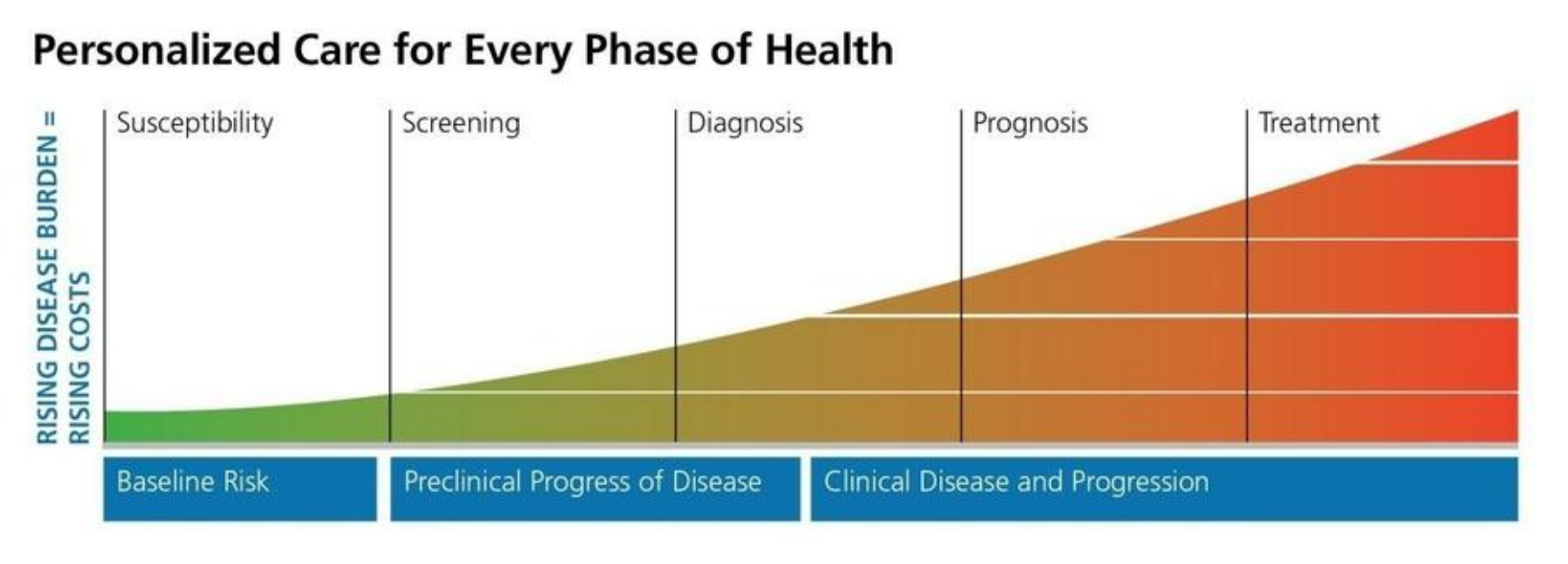
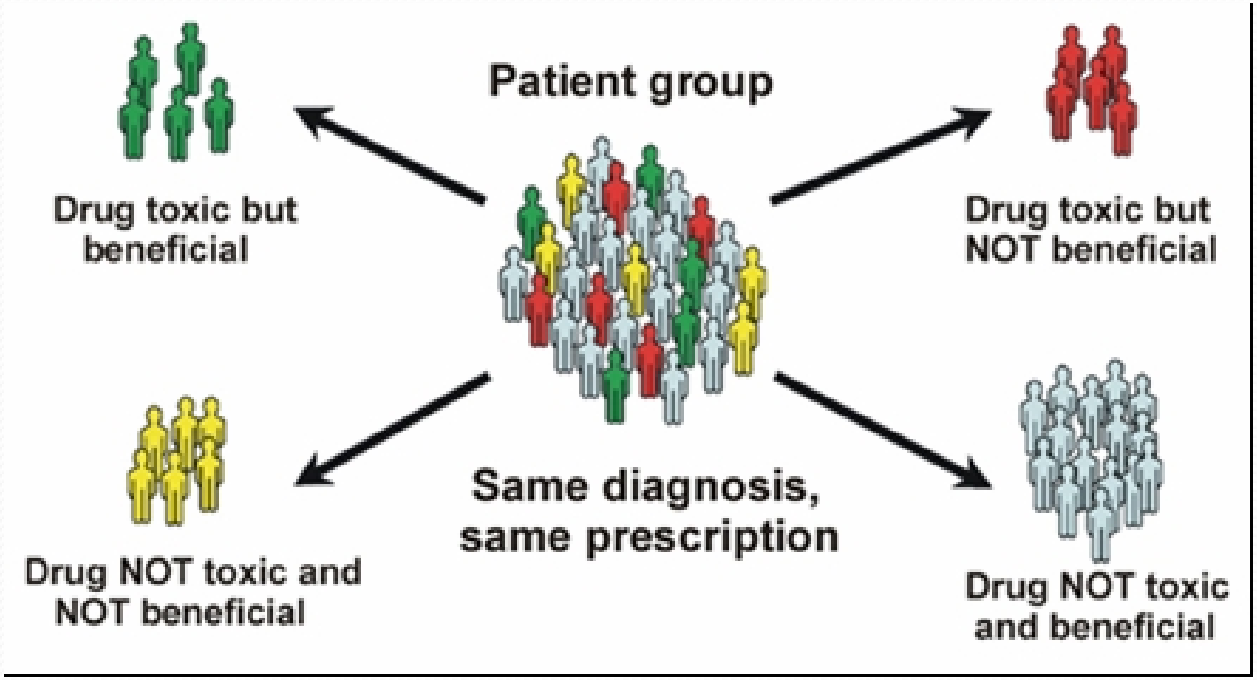
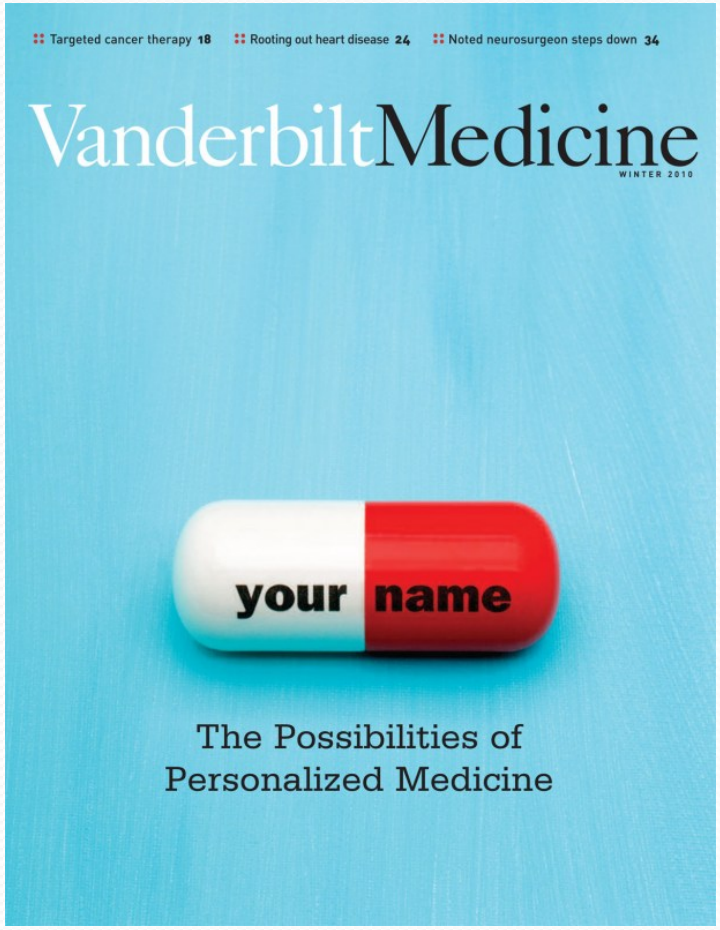
Ken Holroyd, MD, MBA
Associate Professor of Anesthesiology and Medicine
Medical Director, Center for Technology Transfer and Commercialization
Assistant Vice Chancellor for Research

Personalized Healthcare



Personalized Medicine:
Right Drug, Right Dose, The First Time



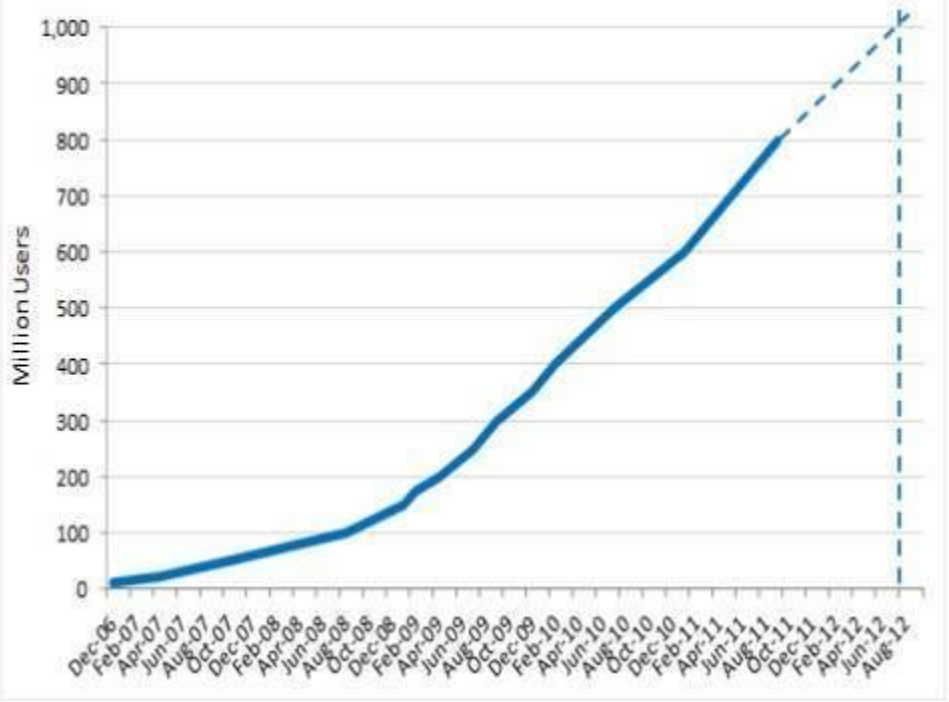

Targeted cancer therapy 18
Rooting out heart disease 24
Noted neurosurgeon steps down 34
VanderbiltMedicine
WINTER 2010
your name
The Possibilities of
Personalized Medicine

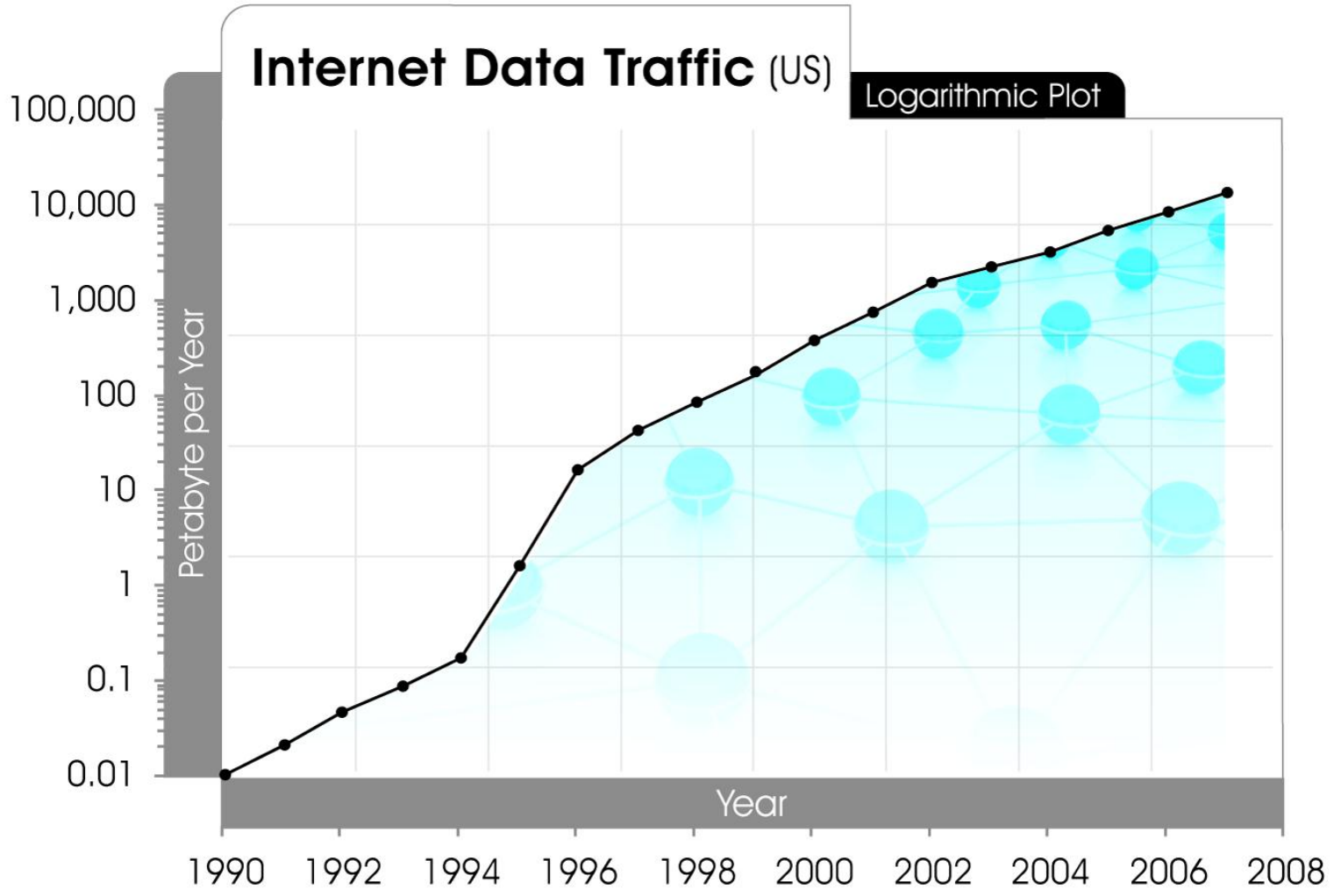
“Any sufficiently advanced technology is indistinguishable from magic”

Arthur C. Clarke

"Hazards of Prophecy: The Failure of Imagination",
in *Profiles of the Future* (1962)

Facebook Millions of Users

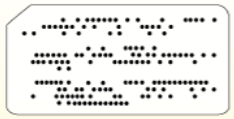
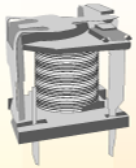


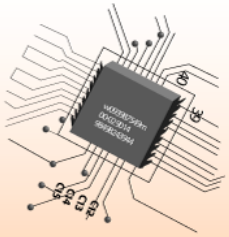

Internet Data Traffic (US)
Logarithmic Plot
100,000
10,000
1,000
100
10
1
0.1
0.01
Petabyte per Year
Year
1990
1992
1994
1996
1998
2000
2002
2004
2006
2008

Exponential Growth of Computing for 110 Years

Moore's Law was the Fifth, not the First, Paradigm to Bring Exponential Growth in Computing

Logarithmic Plot

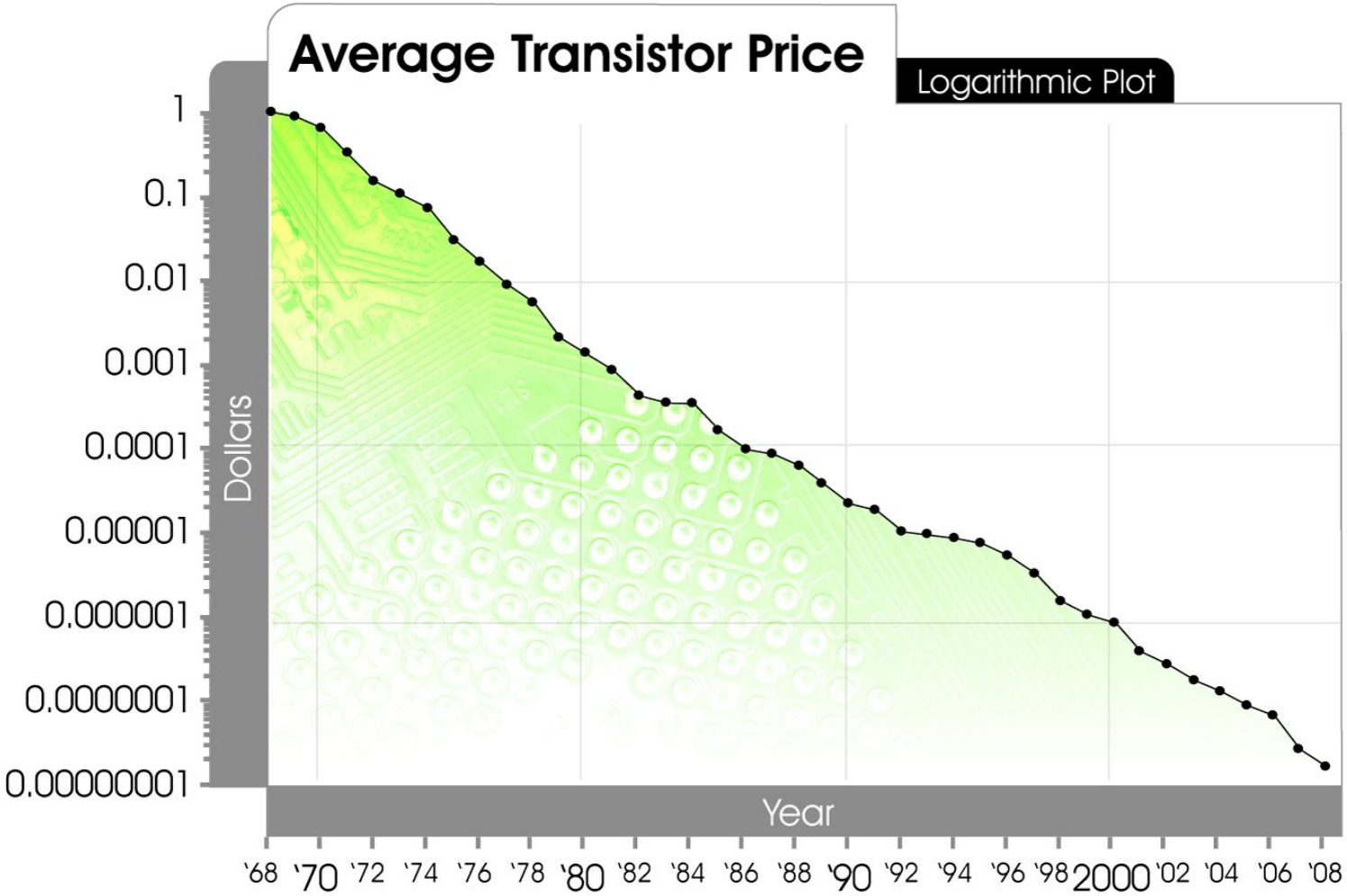
Calculations per Second per $1000

10^{15}
10^{10}
10^{5}
10^{0}
10^{-5}
10^{-10}

Electromechanical | *Relay* | *Vacuum Tube* | *Transistor* | *Integrated Circuit*

Year

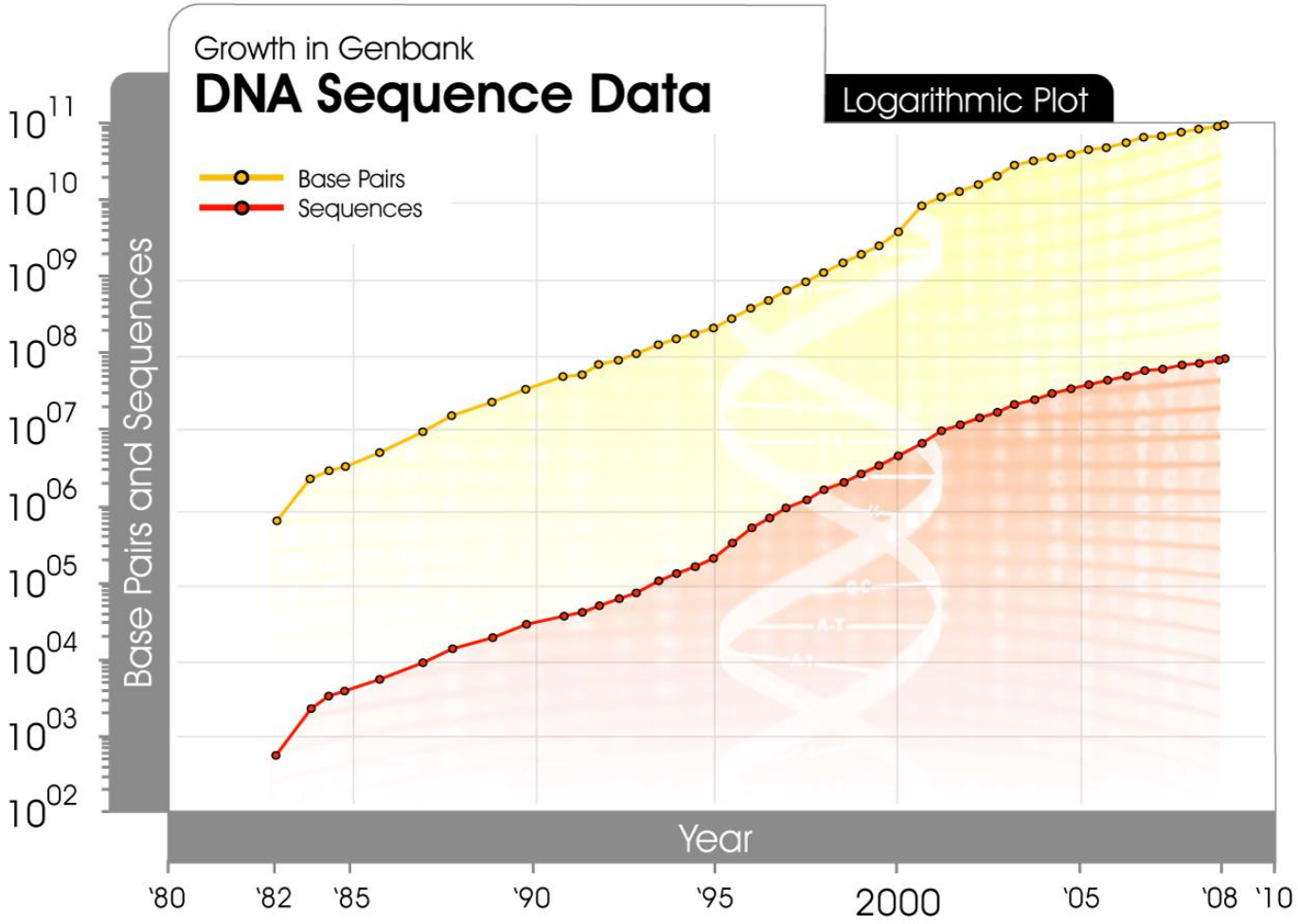
1900 '10 '20 '30 '40 '50 '60 '70 '80 '90 2000 '08 '10


Average Transistor Price
Logarithmic Plot
Dollars
1
0.1
0.01
0.001
0.0001
0.00001
0.000001
0.0000001
0.00000001
Year
'68 '70 '72 '74 '76 '78 '80 '82 '84 '86 '88 '90 '92 '94 '96 '98 2000 '02 '04 '06 '08

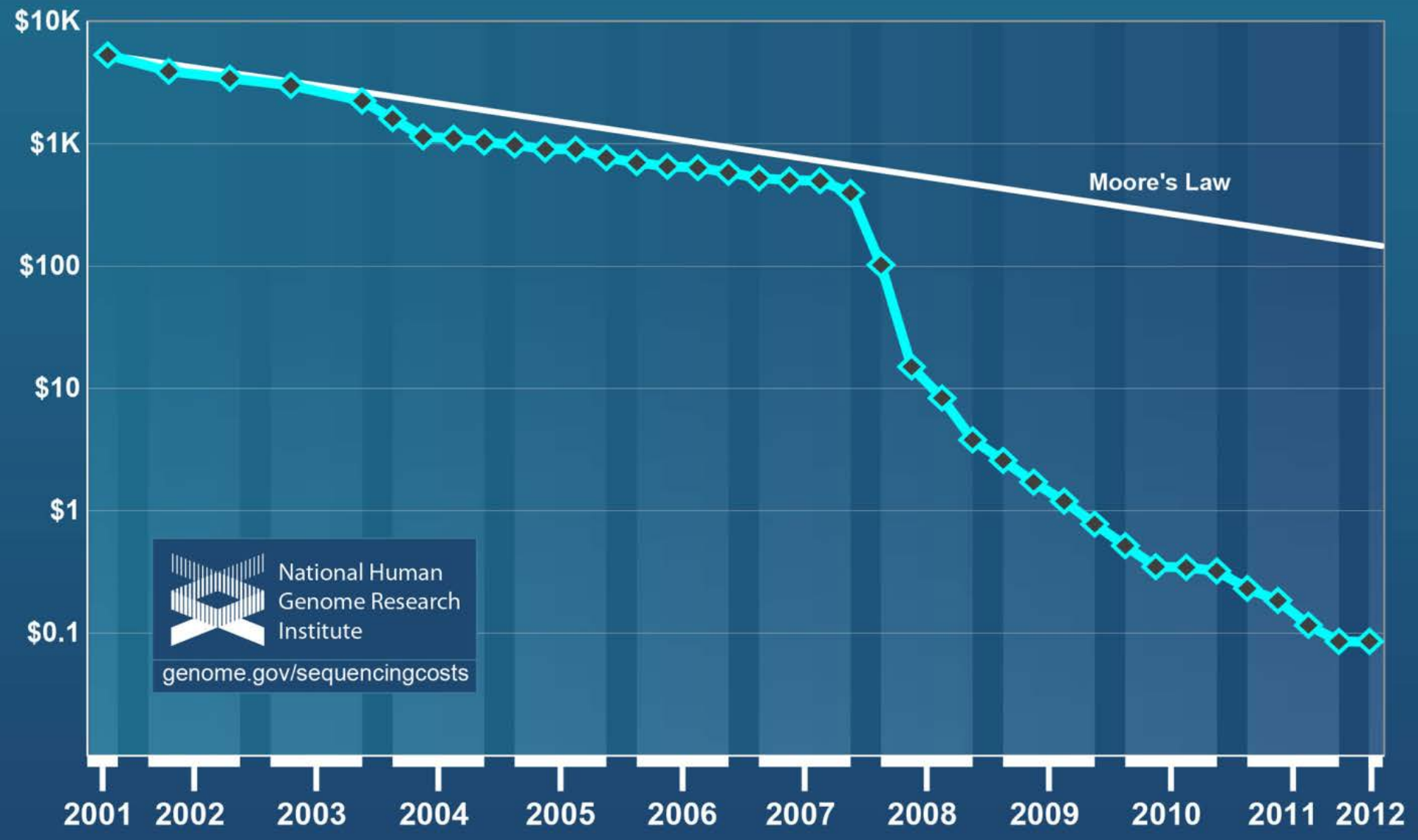
"We tend to overestimate what can be achieved in the short term (because we tend to leave out necessary details)

We underestimate what can be achieved in the long term (because the exponential growth is ignored)"

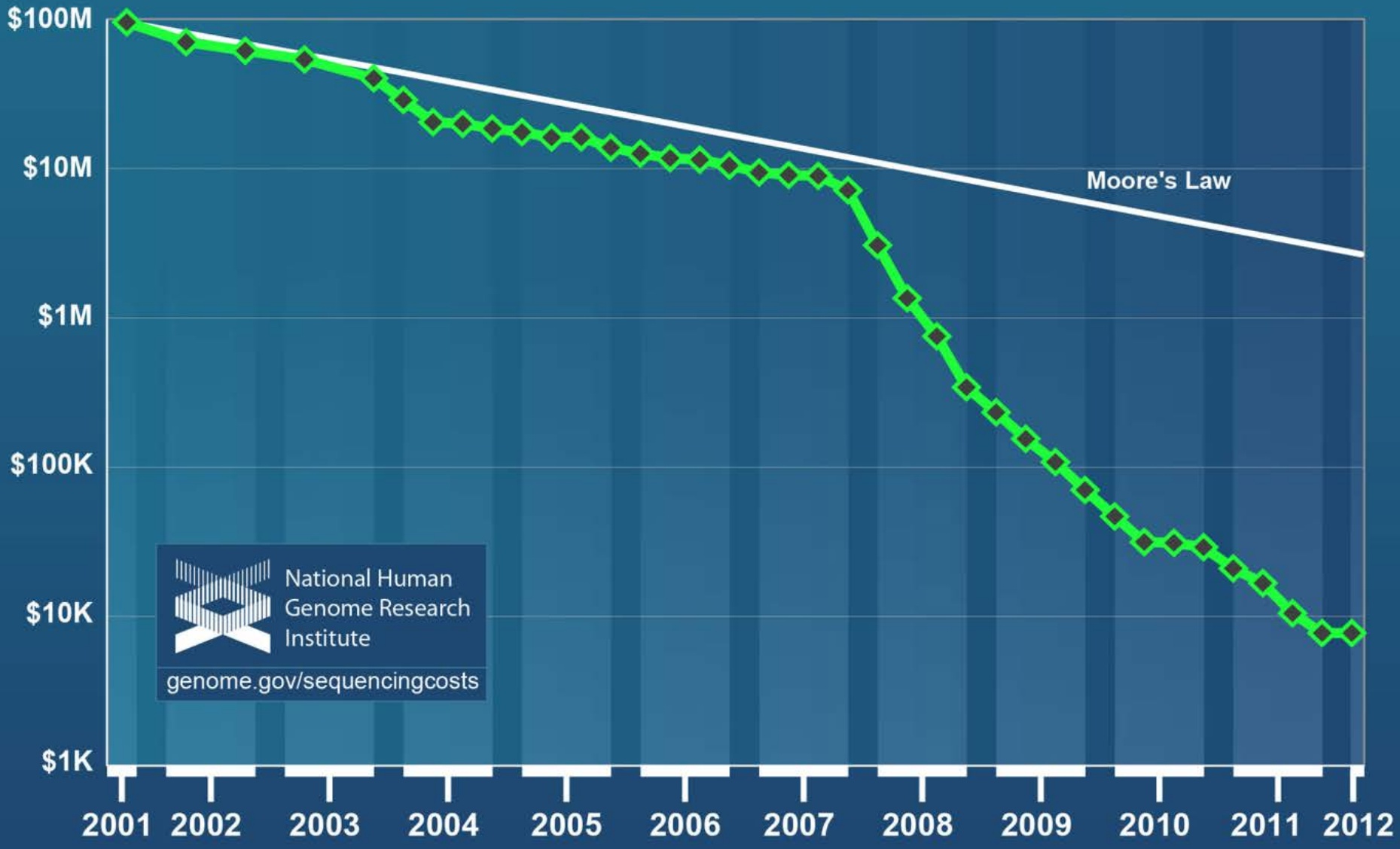
Ray Kurzweil—modified from Roy Amara


Growth in Genbank
DNA Sequence Data
Logarithmic Plot
Base Pairs
Sequences
Base Pairs and Sequences
10^{11}
10^{10}
10^{09}
10^{08}
10^{07}
10^{06}
10^{05}
10^{04}
10^{03}
10^{02}
Year
'80
'82
'85
'90
'95
2000
'05
'08
'10

Cost per Raw Megabase of DNA Sequence



Cost per Genome



Whole Genome Sequence Data

Cost of whole genome sequencing to 0.1% accuracy projected continuing to decline

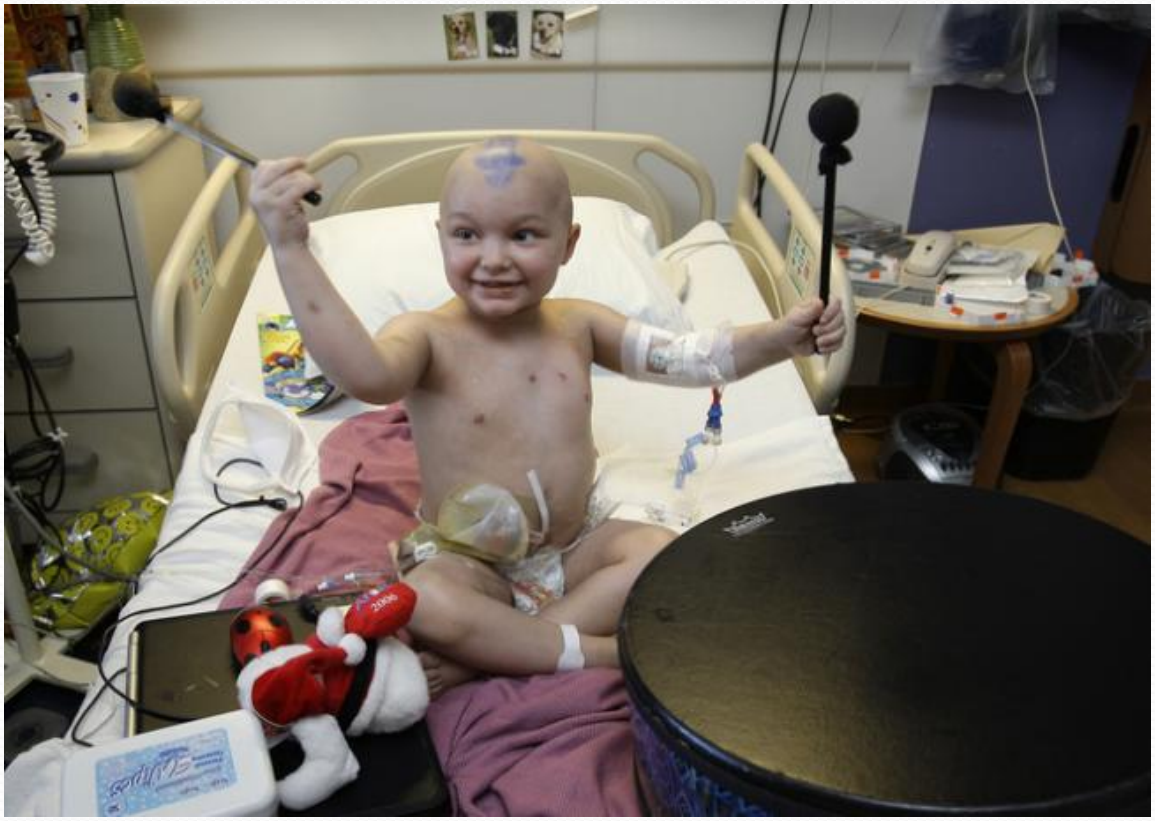
Whole exome sequencing now $999

Still greater accuracy of sequence needed for clinical care

Managing and annotating the data, delivering to point of patient care a challenge

Understanding the meaning will require a lot of additional research and significant costs as it develops

First Life Saved by Genome Sequencing?




Vivitar
HIGH

Other New Applications

- Diagnosing other rare conditions thought clinically likely to be genetic in origin—has guided therapy—including "compound heterozygote" disorders
- The first "sequencing autopsy"
- Genetic characterization of cancer guiding targeted cancer therapy
- "Consumer" genomics including pharmacogenomics—some controversies—about 100,000 consumer have bought the tests over four years

Human Complexity—DNA Level Information

DNA sequence 3 billion base pairs

Genes 20,000

Genes are about 1.5% of the genome (make proteins)

Another 3.5% of the genome makes regulatory and other RNA

Single Nucleotide Polymorphisms (SNPs) 3 million
(0.1% of genome—used in genome wide association studies)

Duplicated “Copies” Gene Sequences (12% of genome)

Copy Number Variation (0.4% of genome)

DNA Sequence and Common Diseases

Identical and fraternal twins used to estimate heritability of common diseases such as diabetes, asthma, schizophrenia, coronary artery disease

Hope was that genome wide association studies (GWAS) with one million SNPs would explain a lot of the heritability

However, only 10% of heritability explained thus far for most common diseases (macular degeneration risk best explained)

Thus far about as good as taking a good family history

Human Complexity—DNA Sequence Information What Might Explain the "Heritability Gap"

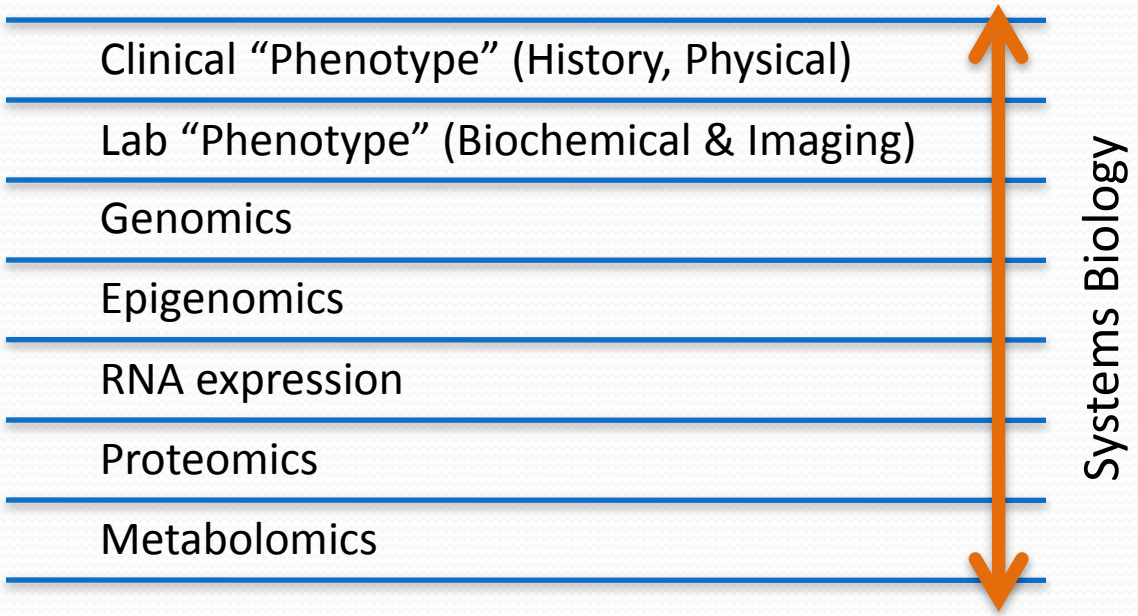
Copy number variation

Maternal or fraternal inheritance effects

DNA modifications that inactive or activate genes

Somatic cell mutation processes

Contribution of Different Categories of "Omics" Information to Clinical Decisions: Undergoing Intense Investigation and Logarithmic Data Growth



All Lab Tests for Normal and Diseased Tissues

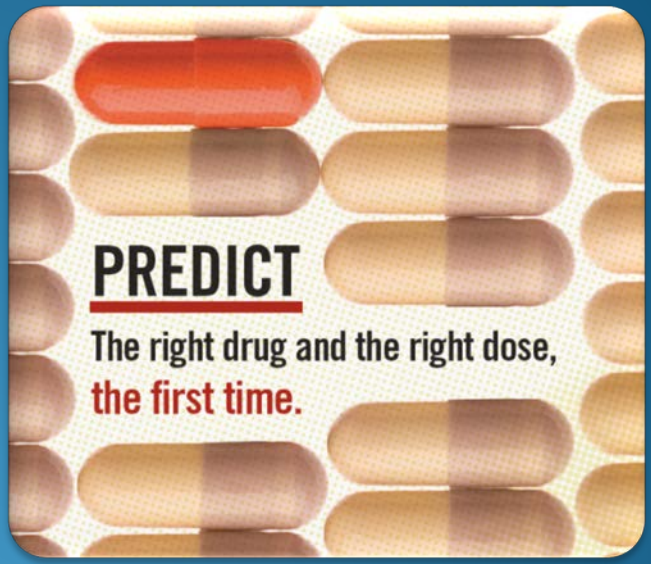
DNA Sequence: Predictive Pharmacogenomics

- Succinylcholine
- Inhalational agents
- Clopidogrel activity and dosing—ongoing in Vanderbilt Cardiac Catheterization for clinical care, for last year and a half
- Warfarin dosing
- Statins induced myopathy
- Tamoxifen activity
- Hepatitis C drug activity
- Azathioprine toxicity
- Beta adrenergic receptor agonist and antagonists?

DNA sequence level information dose predict some of the variable metabolism and resultant efficacy or safety of a number of drugs investigated thus far—a relative success story thus far

PREDICT

Pharmacogenomic Resource
For Enhanced Decisions
In Care & Treatment



Prospective Genetic Testing

Using the **Prognostic Model**

Prognostic Model identifies patients who are highest risk for starting warfarin, clopidogrel, or statin therapy within the next three years as candidates for preemptive genotyping

Factors include:

- Age, gender, race, and BMI when height is available (or weight when BMI is not available)
- History of…Type II Diabetes, coronary disease, atrial fibrillation, hypertension, atherosclerosis, congestive heart failure, previous clot, and dialysis

What is Tested?

- DNA extracted from the patient's blood

- Specimen genotyped for 184 common polymorphisms within 34 genes associated with drug absorption, distribution, metabolism, and excretion

Illumina Vera Code ADME Core Panel Assay

FDA Labels with Pharmacogenomic Biomarkers

CytochromeP450

- Quinidine
- Carvedilol
- **Clopidogrel***
- Metoprolol
- Prasugrel
- Propafenone
- Propranolol
- Ticagrelor
- **Warfarin***
- Atomoxetine
- Fluoxetine
- Fluvoxamine
- Risperidone
- Tiotropium
- **Tamoxifen***
- **Tacrolimus***

Other

Simvastatin*
Azathioprine*
Warfarin*

Estimated Adverse Events Prevented Over 5 years

Abacavir	3
Azathioprine	17
Clopidogrel	79
Simvastatin	19
Tamoxifen	15
Warfarin	265
Total	**398**

Preemptive Genetic Testing Launched

Prognostic Model testing began early 2012 in several outpatient clinics

- Internal Medicine—Medical Center East (MCE) Adult Primary Care Ste I-IV & Hillsboro Medical Group, One Hundred Oaks (OHO), Green Hills Clinic, Edward Curd Lane in Franklin
- VHVI & Cardiology—cardiac catheterization lab, MCE, OHO, Franklin-TN, Murfreesboro
- Eskind Adult Diabetes
- MyHealthTeam at Vanderbilt (MHTAV)

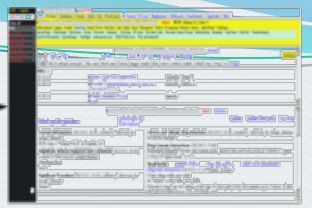
Represent over 300 providers

PREDICT information flow

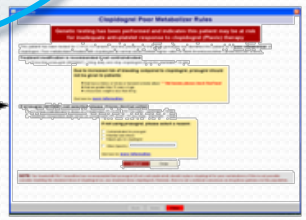
Illumina BeadXpress

Molecular diagnostics

Patient Summary Service (PSS)



StarPanel



Horizon Expert Orders (HEO)

RxStar

Plavix Dashboard

MyHealth at Vanderbilt

PREDICT Program Evolution

Project Planning

Project Team:

Marc Beller
Jill Pulley
Josh Denny
Jim Jirjis
John McPherson

Pilot Launch

Project Team:

Marc Beller
Jill Pulley
Josh Denny
Jim Jirjis
Josh Peterson
Bill Gregg
Jennifer Mitchell
Erica Bowton
Jonathan Schildcrout
Wendy Kiepek
John McPherson
Cindy Vnencak-Jones
Kyle Brothers
Holli Dilks
Leslie Mackowiak
P&T committee
Karla Davis
Collin Mothupi

Program Expansion:

Project Team:

Jim Jirjis
Jill Pulley
Josh Denny
Josh Peterson
Bill Gregg
David Gregory
Marc Beller
Jennifer Mitchell
Azim Munivar
Marla Carter
Wendy Kiepek
Azim Munivar
Neal Patel
Leslie Mackowiak
Jack Starmer
Frank Harrell
Cindy Vnencak-Jones
Mike Laposata
Jonathan Schildcrout
Ellen Clayton
Tracy McGregor
Ann Neff
Holli Dilks
Kyle Brothers
Matt Weinger
Anne Miller
Nate Gilmer
Candis Kinkus

Emily Kurtz
John Howser

P&T committee
Kelly Birdwell
Doug Selph
Mike Stein
Trent Rosenbloom
Sergio Fazio
Sara van Driest
Betsy Brandes
Ed Shultz
Ken Holroyd
Kevin Johnson
Mary Beth Bauer
Russ Wilke
Dana Crawford
Beverly Coccia
Adeola Davis
Karla Davis
Jay Cowan
Melissa Basford
Yaping Shi
Lijun Wang
Dario Giuse
Ioana Danicu
Jana Shirey-Rice
Gladys Garrison
Alan Bentley
Hassan Naqvi
Jeannine Courtney

Medical tech staff
Collin Mothupi

Full Scale:

Integration into operations

BioVU

- De-identified ongoing medical record
- Matched DNA sample
  (gradually being partially sequenced)
- Research tool including for genetic associations
  (with IRB controls)
- Unique resource for research
- Match a well defined clinical condition (“phenotype”) to DNA sequence information (“PheWAS”)

MyCancerGenome.Org

- Informatics approach matching genetic tests on cancer tissue to specific genetically targeted therapies
- Includes matching to clinical trials, for genetically targeted drugs in development
- Implemented at Vanderbilt -Ingram Cancer Center with results incorporated into StarPanel / StarChart

Impact of Whole Genome Sequencing for Anesthesiology

We will know our patients' genetic risk factors including

- Pseudocholinesterase deficiency—implications for succinylcholine and cocaine use in the operating room
- Malignant hyperthermia
- Codeine metabolism—genetics clinically most important now for maternal use passing on to newborns
- Oxycodone metabolism
- Morphine metabolism
- Risk factors for common diseases with anesthetic and perioperative implications

Impact of Whole Genome Sequencing for Anesthesiology Translational Research

- Ask association of a heritable clinical condition or perioperative outcomes with gene sequence, with large numbers of individuals de-identified medical records

- Examples:
  - beta-blocker perioperative use?
  - post-operative cognitive dysfunction?
  - predicting the difficult airway based on the medical record before the patient is seen?

Further in the Future

Real time diagnosis and monitoring of the following rapidly developing information sources in fluids and tissues:

- epigenome
- RNA (transcriptome)
- protein (proteome)
- metabolome
- microbiome

This complex information will power better clinical and healthcare decisions

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We underestimate what can be achieved in the long term (because the exponential growth is ignored)"

Ray Kurzweil—modified from Roy Amara

Interested in Learning More About New Digital Technologies in Medicine?

View Online Eric Topol's Fall 2011 Vanderbilt Discovery Lecture

Thank you for your time and attention!

Your questions and discussion?