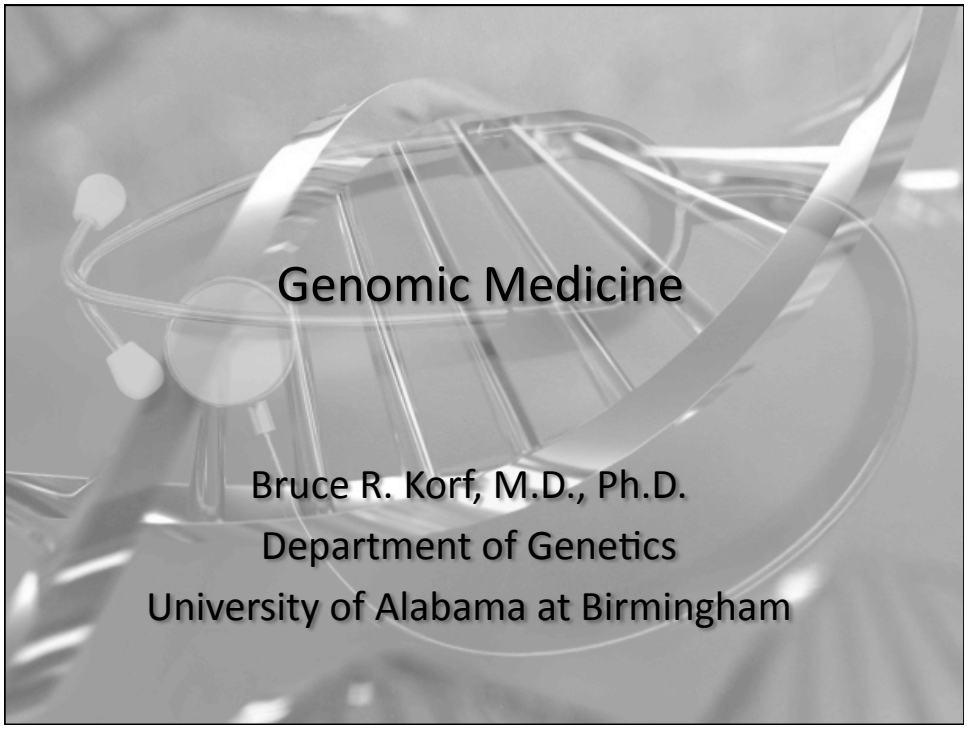
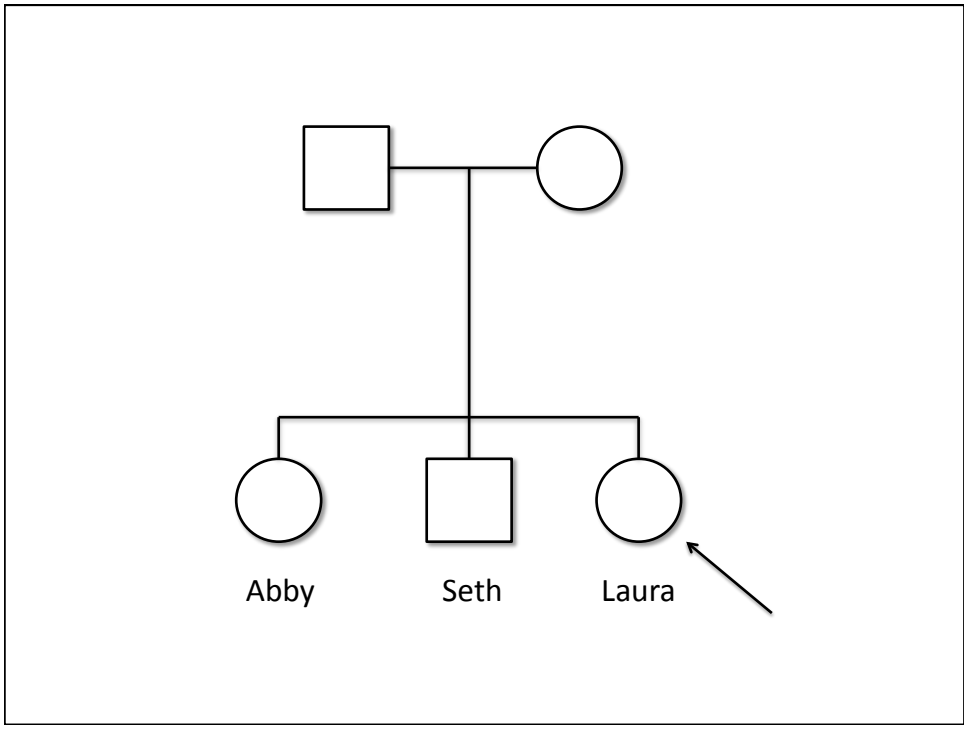
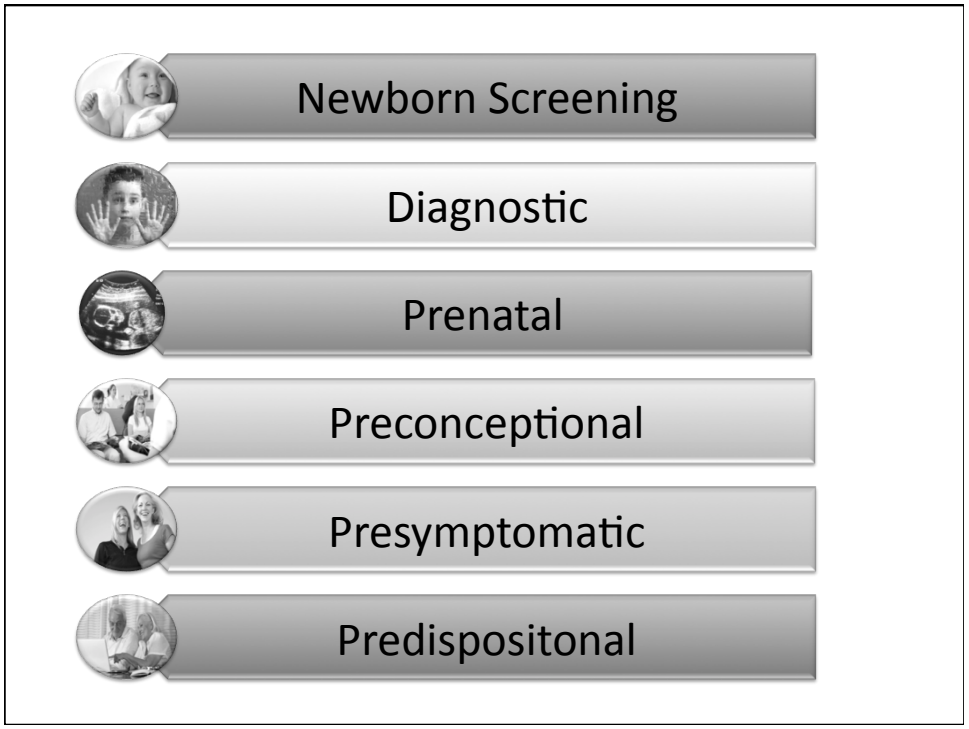



## Disclosures

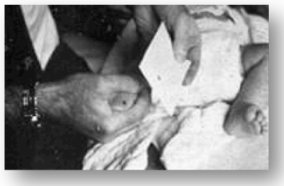
- Medical Director, UAB Medical Genomics Laboratory
- Chair, Medical Affairs Committee, Children's Tumor Foundation
- Grant Funding: NIH, Department of Defense, Novartis
- Advisory Boards: Novartis NF Advisory Board, March of Dimes

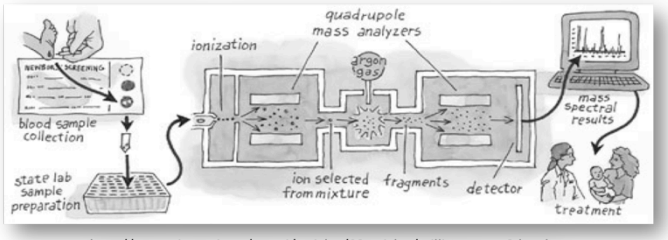

Abby
Seth
Laura


Newborn Screening
Diagnostic
Prenatal
Preconceptional
Presymptomatic
Predispositonal

# Newborn Screening

Shortly after birth, blood is taken from Laura's heel and sent to the State Newborn Screening Laboratory. Her parents are told that this is a routine test. No problems are found, and no follow-up is needed.






http://www.sigmaxi.org/amsci/articles/02articles/millingtoncap3.html

# Newborn Screening by DNA Sequencing?

RESEARCH ARTICLE

HUMAN GENOMICS www.ScienceTranslationalMedicine.org 12 January 2011 Vol 3 Issue 65 65ra4

**Carrier Testing for Severe Childhood Recessive Diseases by Next-Generation Sequencing**

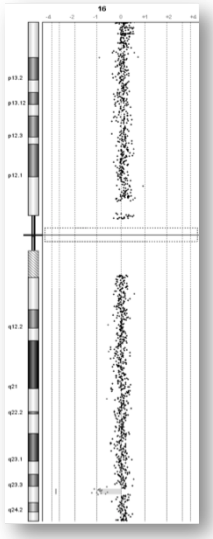
Callum J. Bell,[1]* Darrell L. Dinw
Elena E. Ganusova,[1] Joann Mud
Faye D. Schilkey,[1] Vrunda Shetl
Gary P. Schroth,[3] Ryan W. Kim,

"We found an unexpectedly high proportion of literature-annotated disease mutations that were incorrect, incomplete, or common polymorphisms."

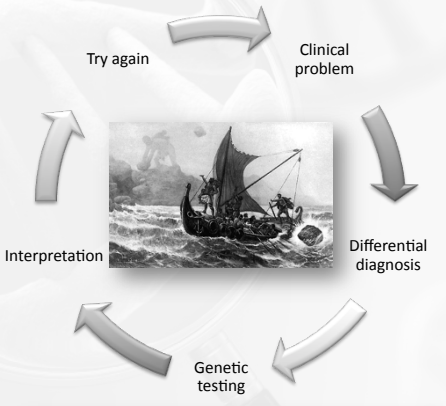
# Diagnostic Testing

Laura is now 3 and her brother Seth is 5. Seth has been experiencing developmental problems, and is diagnosed as having autism

# Genetic Evaluation in Autism



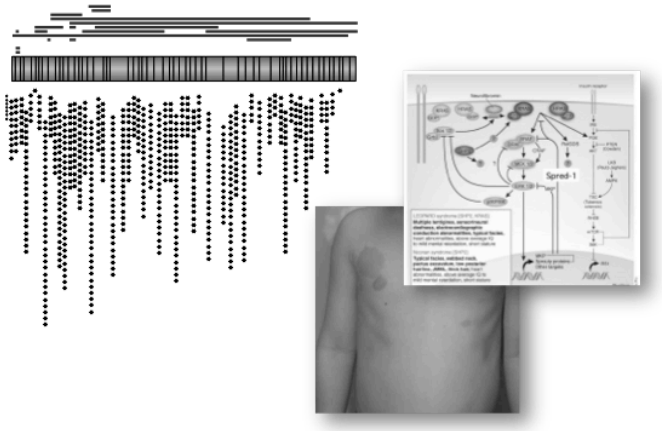
# The Diagnostic Odyssey



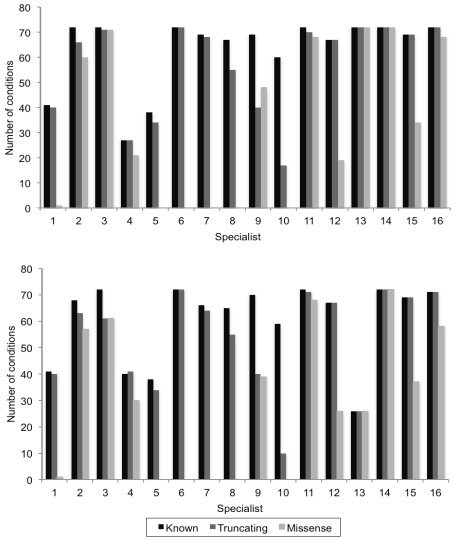

**Making a definitive diagnosis: Successful clinical application of whole exome sequencing in a child with intractable inflammatory bowel disease**

*Elizabeth A. Worthey, PhD[1,2], Alan N. Mayer, MD, PhD[2,3], Grant D. Syverson, MD[2], Daniel Helbling, BSc[2], Benedetta B. Bonacci, MSc[2], Brennan Decker, BSc[2], Jaime M. Serpe, BSc[2], Trivikram Dasu, PhD[2], Michael R. Tschannen, BSc[1], Regan L. Veith, MSc[2], Monica J. Basehore, PhD[4], Ulrich Broeckel, MD, PhD[1,2,3], Aoy Tomita-Mitchell, PhD[1,2,3], Marjorie J. Arca, MD[3,5], James T. Casper, MD[3,5], David A. Margolis, MD[3,5], David P. Bick, MD[1,2,3], Martin J. Hessner, PhD[1,2], John M. Routes, MD[1,3], James W. Verbsky, MD, PhD[1,3], Howard J. Jacob, PhD[1,2,6], and David P. Dimmock, MD[1,2,3]*

# Genome Annotation




# Secondary Findings

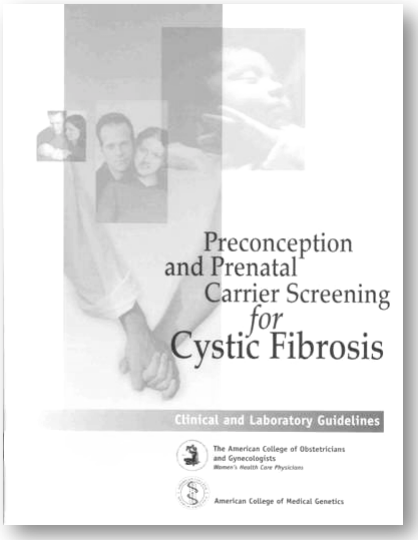


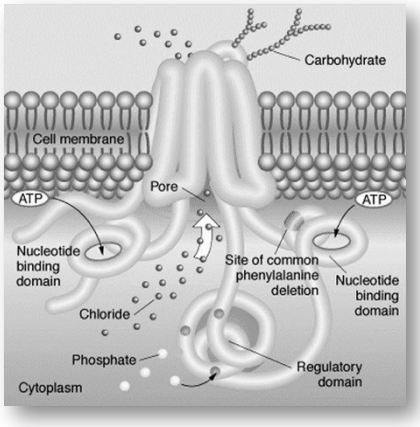

Green R, et al. *Genetics in Medicine* (2012) **14**, 405–410

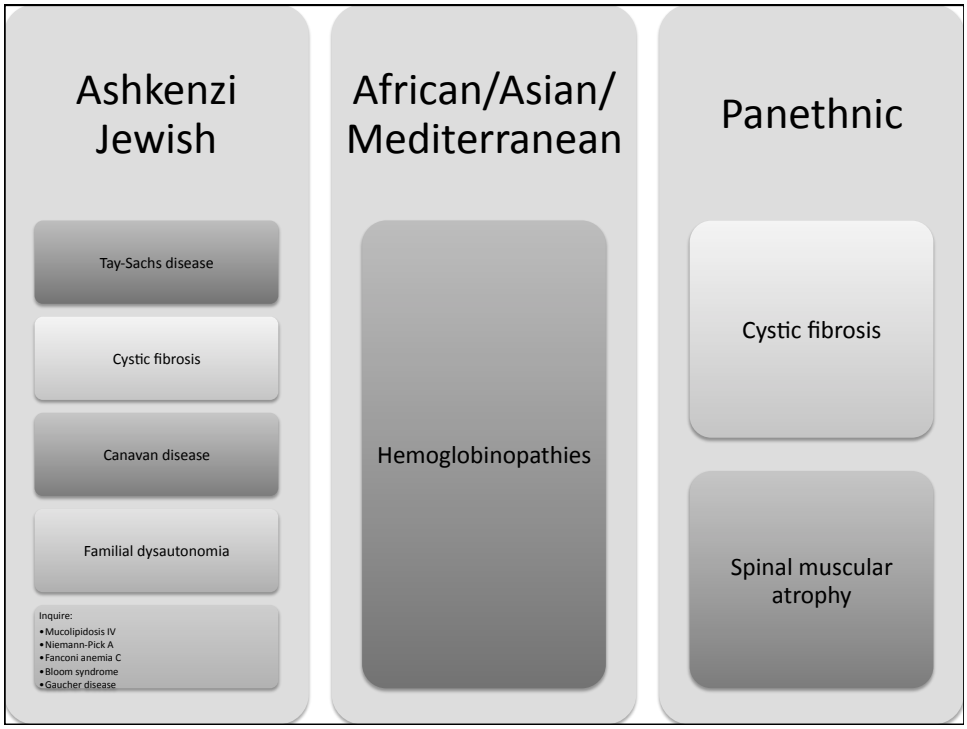
# Preconceptional Testing

Laura is now married. She and her husband are considering starting a family and meet with her obstetrician-gynecologist. They are both of Northern European ancestry and are offered carrier testing for cystic fibrosis.

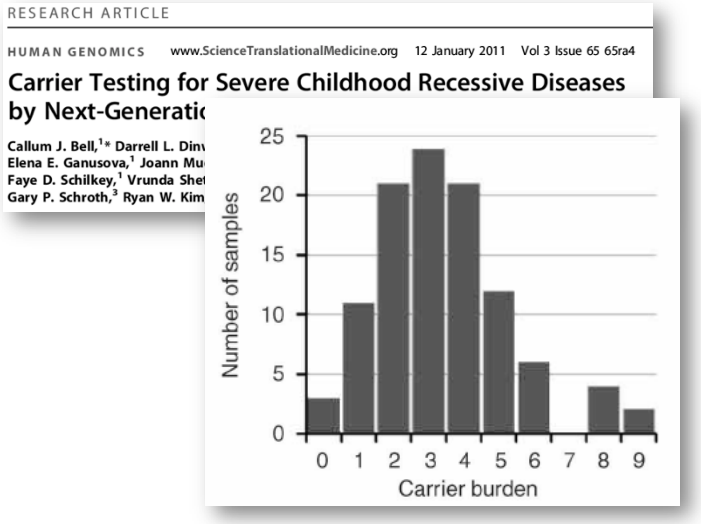
# CF Carrier Screening



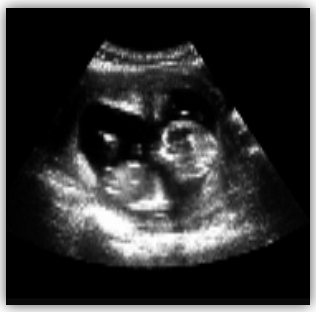






# Genomic Carrier Testing

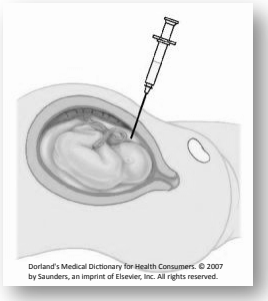


# Prenatal Testing



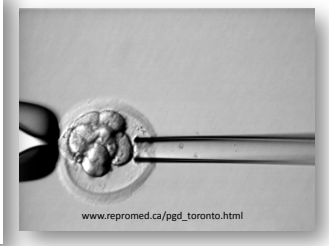
Laura and her Tom are indeed found to both be cystic fibrosis carriers. They elect to have prenatal diagnosis by amniocentesis at 16 weeks of pregnancy. The fetus is found to be a CF carrier.

# Prenatal Diagnosis




amniocentesis


chorionic villus biopsy



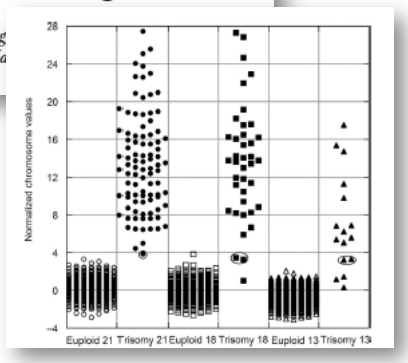

preimplantation diagnosis

# Next Generation Prenatal Screening

## Genome-Wide Fetal Aneuploidy Detection by Maternal Plasma DNA Sequencing

*Diana W. Bianchi, MD, Lawrence D. Platt, MD, James D. Goldberg*
*Amy J. Sehnert, MD, and Richard P. Rava, PhD, on behalf of the Ma*
*Accurately diagnose fetal aneuploidy (MELISSA) Study Group**

*(Obstet Gynecol 2012;119:00–00)*
*DOI: 10.1097/AOG.0b013e31824fb482*

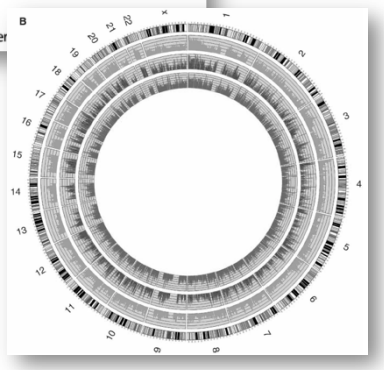



# Genomic Prenatal Diagnosis

## Maternal Plasma DNA Sequencing Reveals the Genome-Wide Genetic and Mutational Profile of the Fetus

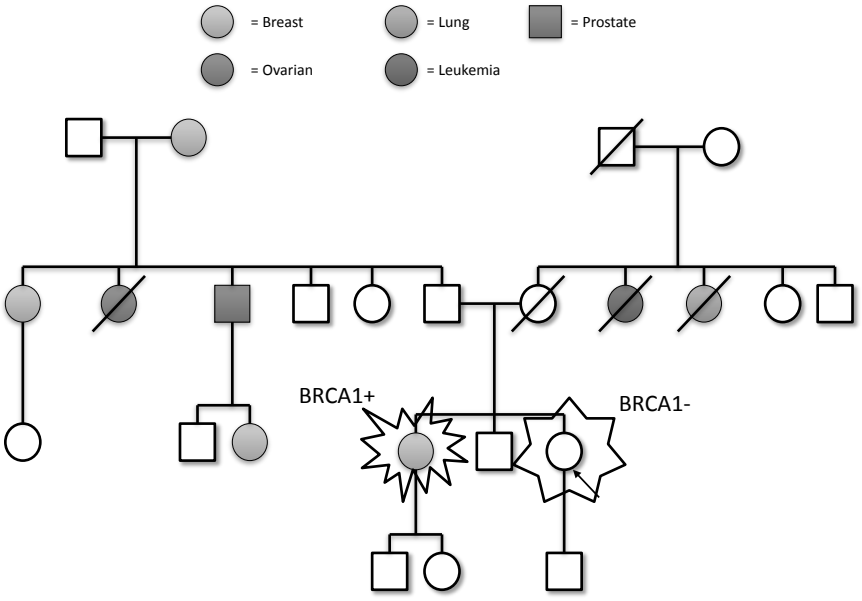
Y. M. Dennis Lo,[1,2]* K. C. Allen Chan,[1,2] Hao Sun,[1,2] Eric Z. Chen,[1,2] Peiyong Jiang,[1,2] Fiona M. F. Lun,[1,2] Yama W. Zheng,[1,2] Tak Y. Leung,[3] Tze K. Lau,[3] Charles R. Cantor,[4] Rossa W. K. Chiu[1,2]

(Published 8 December 2010; Volume 2 Issue 61 61ra91)
www.ScienceTranslationalMedicine.org 8 December

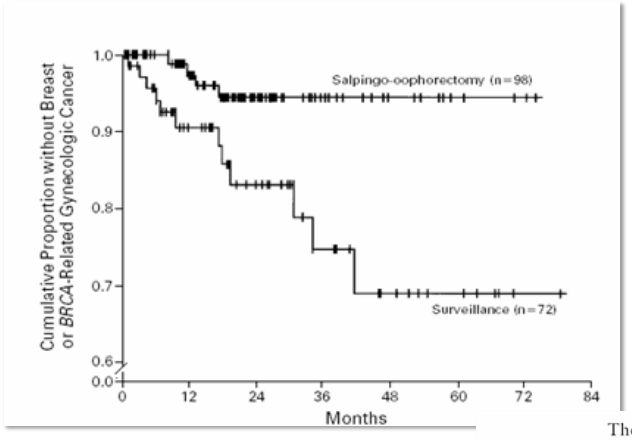


# Presymptomatic Testing

Laura is now 45. She has just learned that her older sister Abby, age 49, has been diagnosed as having breast cancer. She is concerned about her own risks, given that there is a family history of others with breast cancer.



# Breast Cancer Prevention





The New England Journal of Medicine

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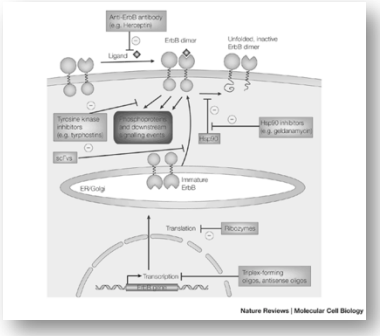
VOLUME 346 MAY 23, 2002 NUMBER 21

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

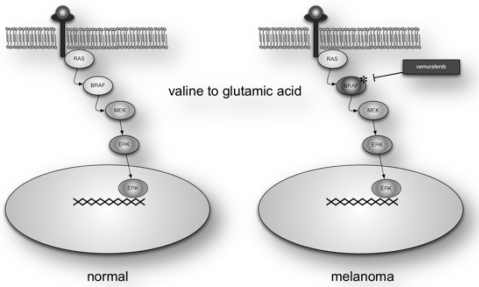
# Therapeutics

Herceptin




*Nature Reviews Molecular Cell Biology* **2**, 127-137 (2001)

BRAF V600E in Melanoma



# The Redactome

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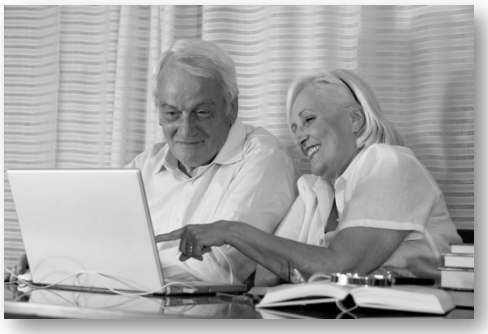
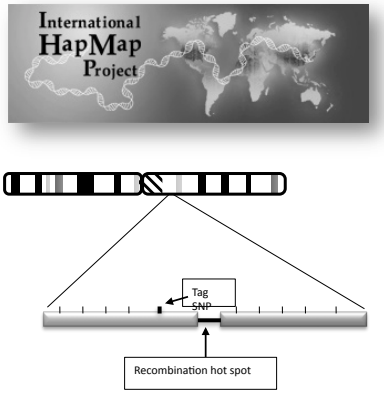
# Predispositional Testing



Laura is now 60 years old. She has been in good health. She and her husband have heard about the possibility of having genomic testing, and explore the possibilities on the internet.

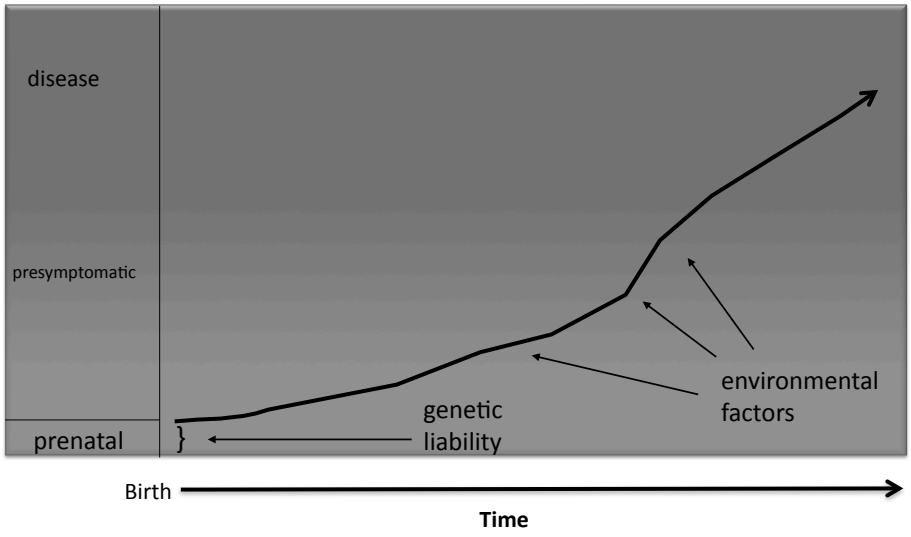
# Genome-Wide Association Studies



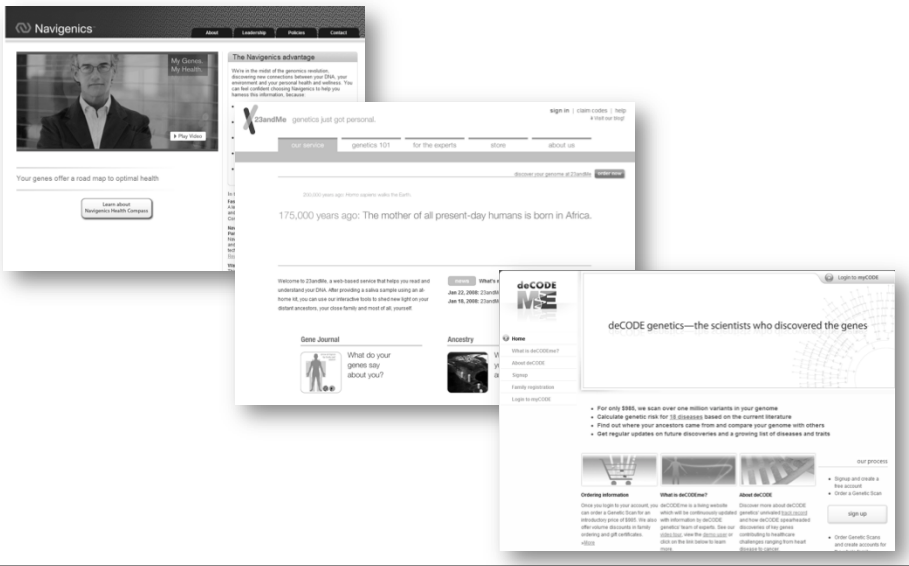

| Gene | Symbol |
|---|---|
| Interleukin | *IL-4, IL-13* |
| Cluster of differentiation | *CD14* |
| $\beta_2$-Adrenergic receptor | *B2AR* |
| Human leukocyte antigen DRB1, DQB1 | *HLA-DRB1, HLA-DQB1* |
| Tumor necrosis factor | *TNF* |
| High-affinity IgE receptor β | *FCER1B* |
| Interleukin-4 receptor | *IL4RA* |
| Disintegrin and metalloproteinase domain 33 | *ADAM33* |

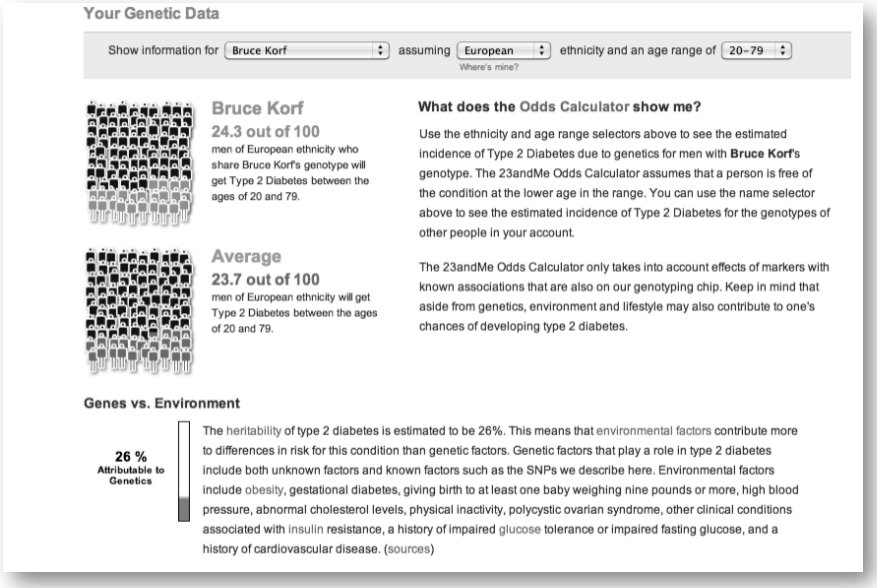
Bierbaum, S., Heinzmann, A. Resp Med
doi:10.1016/j.rmed.2007.01.018

# Paradigm of Genetic Prevention



# Direct to Consumer Genomic Testing

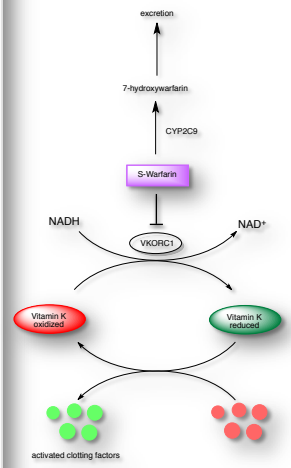


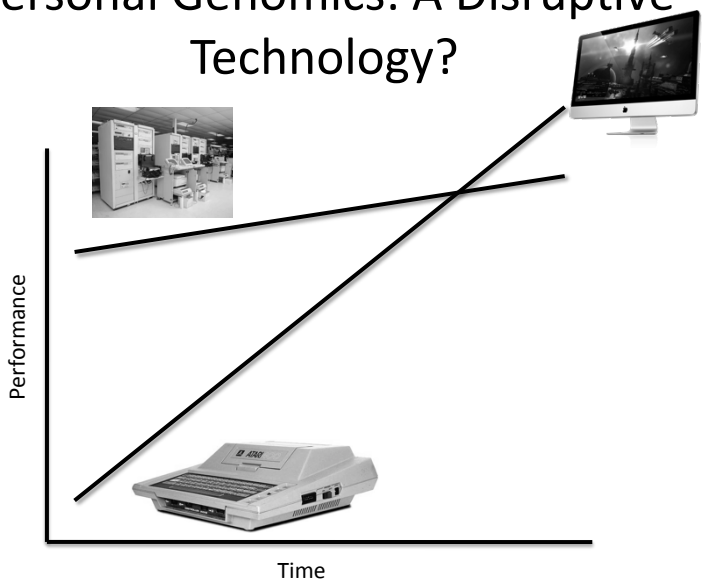
# Pharmacogenetics

| Name | Confidence | Status |
|---|---|---|
| Warfarin (Coumadin®) Sensitivity | ☆☆☆☆ | Increased |
| Abacavir Hypersensitivity | ☆☆☆☆ | Typical |
| Alcohol Consumption, Smoking and Risk of Esophageal Cancer | ☆☆☆☆ | Typical |
| Clopidogrel (Plavix®) Efficacy | ☆☆☆☆ | Typical |
| Fluorouracil Toxicity | ☆☆☆☆ | Typical |
| Response to Hepatitis C Treatment | ☆☆☆☆ | Typical |
| Pseudocholinesterase Deficiency | ☆☆☆☆ | Typical |
| Oral Contraceptives, Hormone Replacement Therapy and Risk of Venous Thromboembolism ♀ | ☆☆☆☆ | Not Applicable |
| Caffeine Metabolism | ★★★ | Slow Metabolizer |
| Hepatitis C Treatment Side Effects | ★★★ | See Report |
| Metformin Response | ★★★ | Higher Odds of Positive Response |
| Antidepressant Response | ★★ | See Report |
| Beta-Blocker Response | ★★ | See Report |
| Floxacillin Toxicity | ★★ | Typical Odds |
| Heroin Addiction | ★★ | Typical Odds |
| Lumiracoxib (Prexige®) Side Effects | ★★ | Typical Odds |
| Naltrexone Treatment Response | ★★ | See Report |
| Postoperative Nausea and Vomiting (PONV) | ★★ | Higher Odds |
| Response to Interferon Beta Therapy | ★★ | Increased Odds of Responding |
| Statin Response | ★★ | See Report |

The genotyping services of 23andMe are performed in LabCorp's CLIA-certified laboratory. The tests have not been cleared or approved by the FDA but

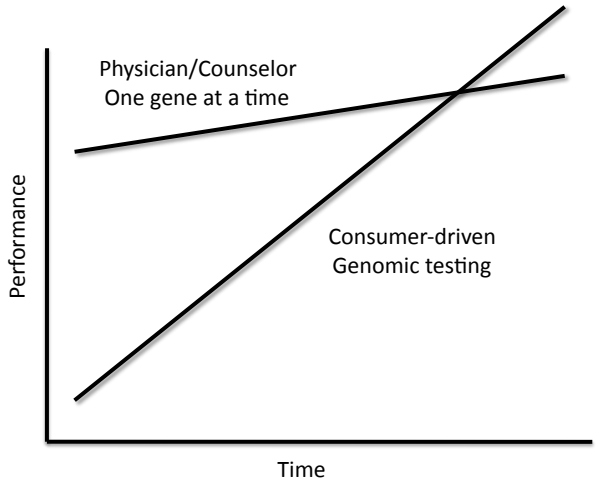



# Personal Genomics: A Disruptive Technology?



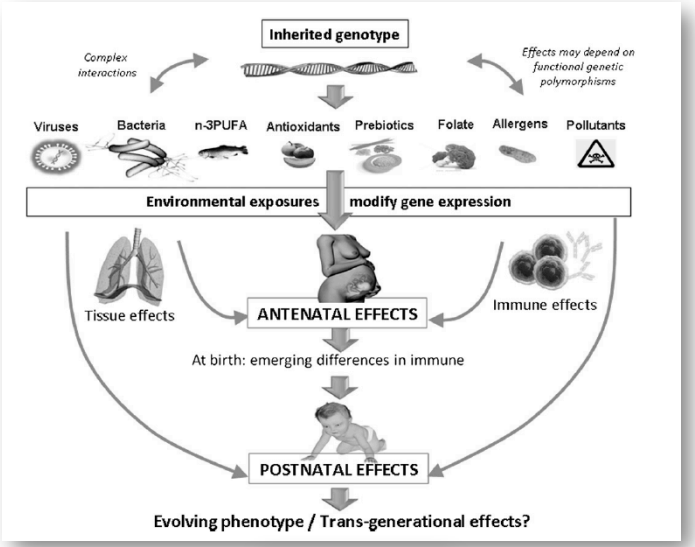

Modified from Christensen et. al. The Innovator's Prescription

# Personal Genomics: A Disruptive Technology?



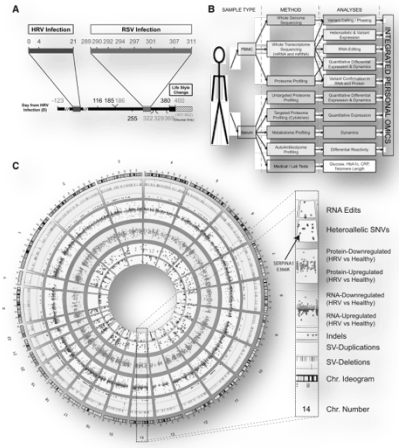

Modified from Christensen et. al. The Innovator's Prescription

# Genomics and Epigenomics

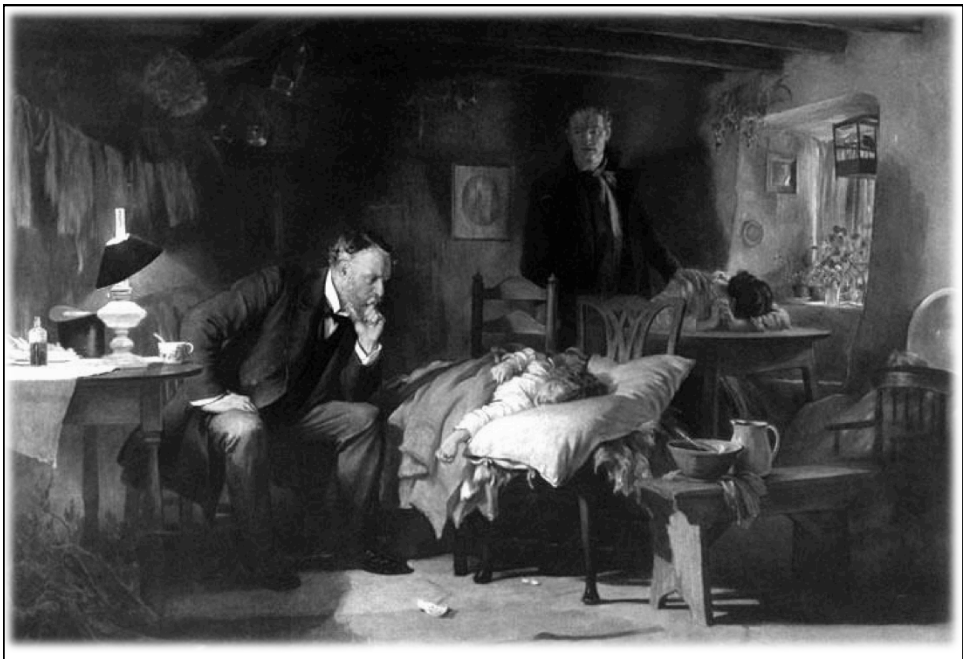



David Martino and Susan Prescott
*Chest* 2011;139;640-647
DOI 10.1378/chest.10-1800

# Personalized Genomics




Chen R et al. Cell 2012;148:1293-1307.

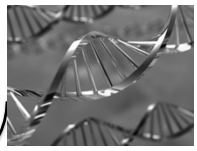


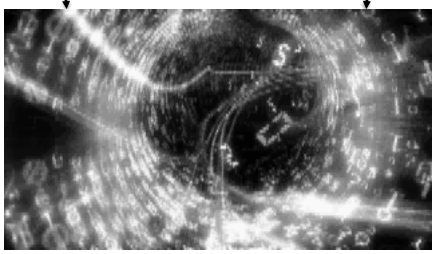
Sir Luke Fildes – The Doctor (1887)

# Medicine in Transformation
## *Two Convergent Forces*

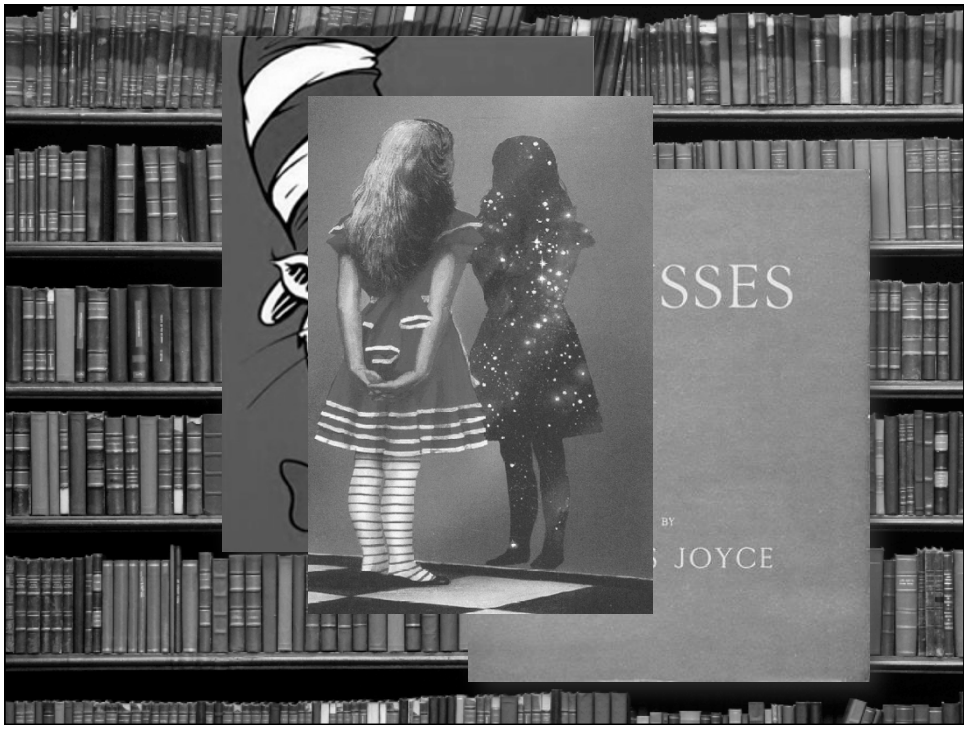
Information Technology

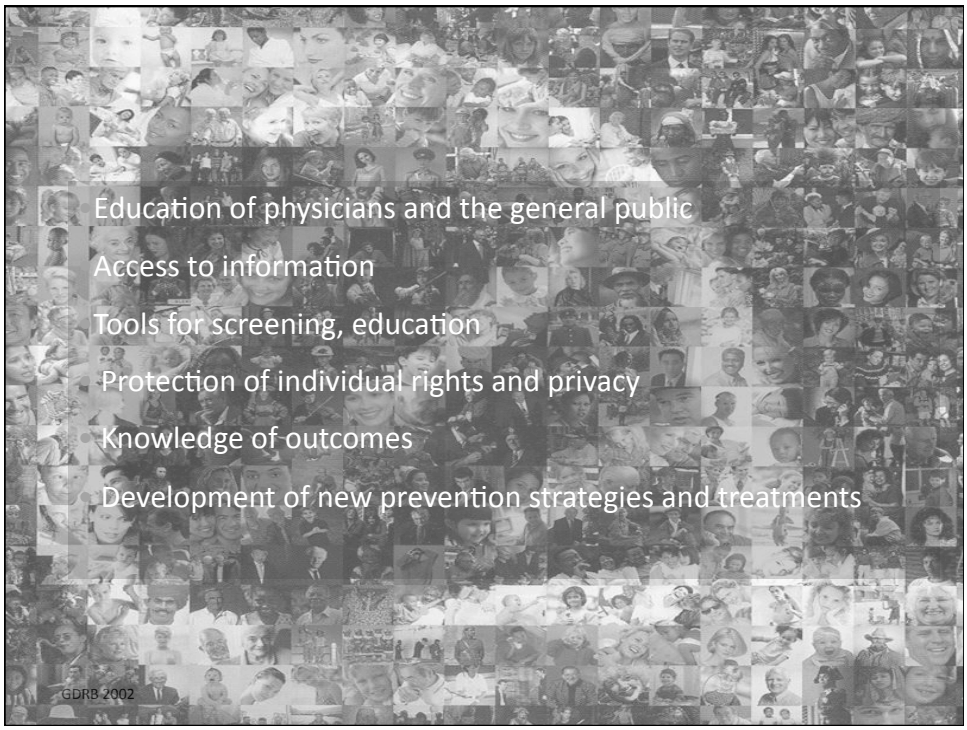
Genetics & Genomics

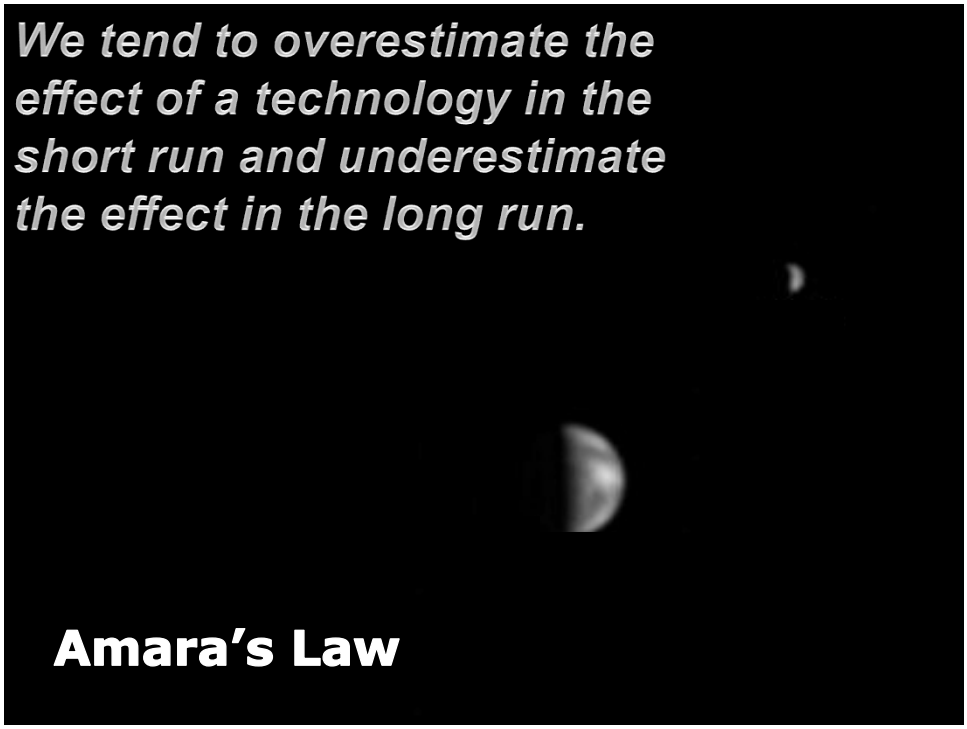


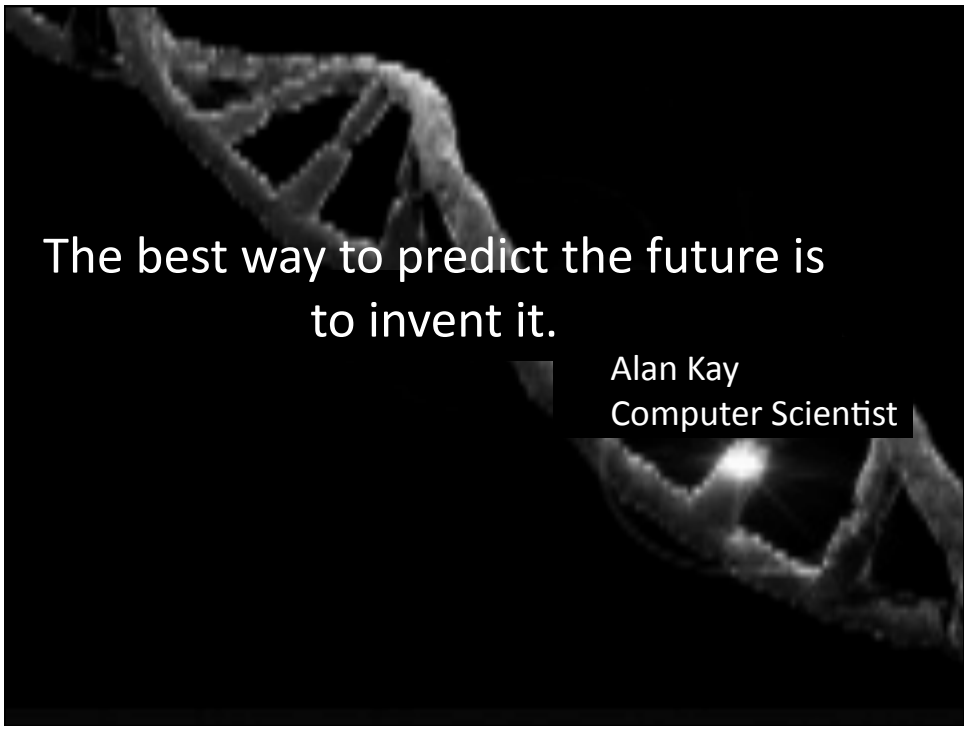


# Where Will Personal Genomes Live?


SSES
BY
JOYCE


Education of physicians 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
GDRB 2002


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


The best way to predict the future is to invent it.
Alan Kay
Computer Scientist