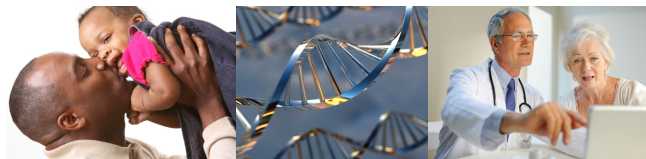


# Integration of Genomics into Medical Practice

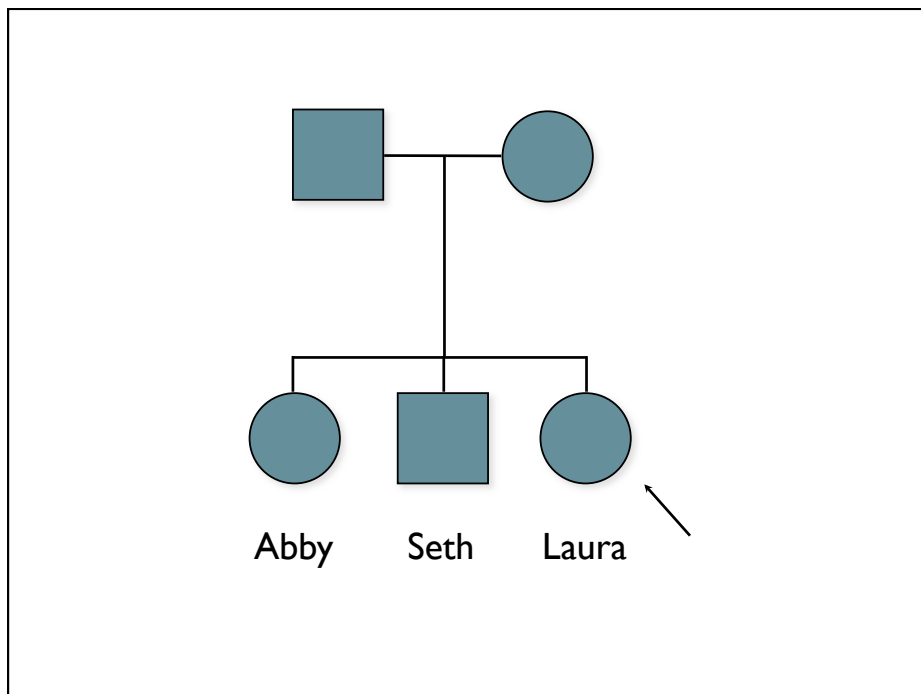
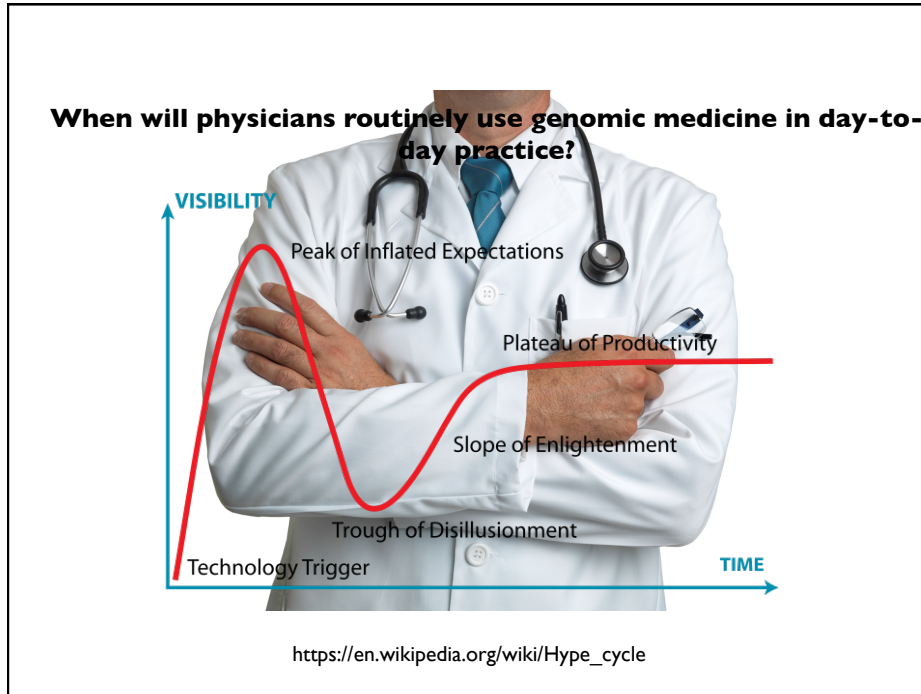
Bruce R. Korf, MD, PhD  
Department of Genetics  
University of Alabama at Birmingham









## Disclosures


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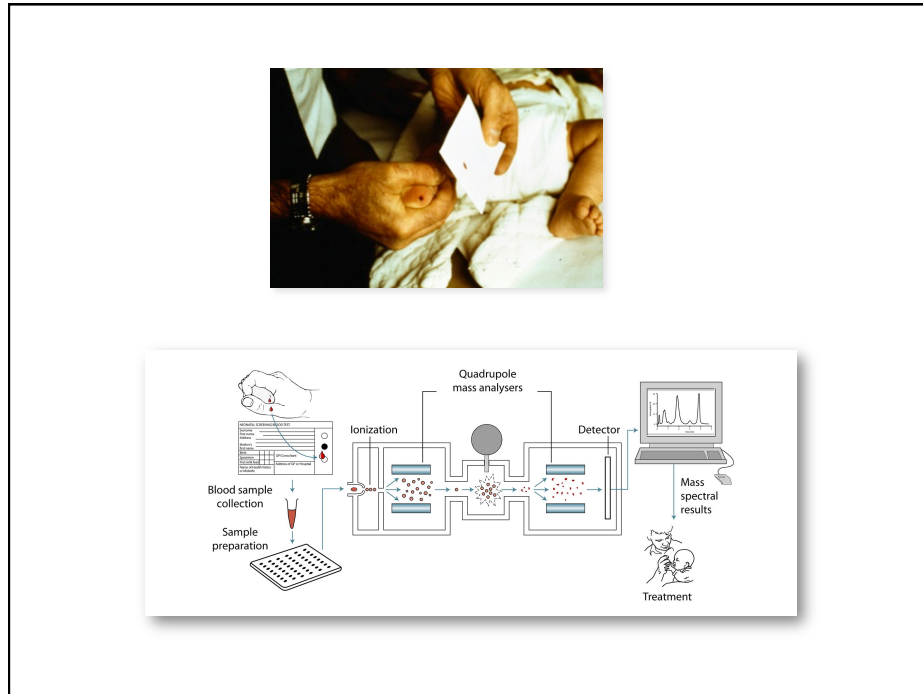
Relationship	Entity
Consultant	Novartis Alexion AstraZeneca
Educational Program	Axis
Advisory Board	Accolde
Board of Directors	American College of Medical Genetics and Genomics Children's Tumor Foundation
Advisor	Neurofibromatosis Therapeutic Acceleration Project
Founding Member	Envision Genomics
Salary	University of Alabama at Birmingham



	Newborn Screening
	Diagnosis
	Preconceptional Screening
	Prenatal Diagnosis
	Presymptomatic Testing
	Predispositional Testing







## Newborn Screening

	<p>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.</p>
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## Genomic Newborn Screening



	Newborn Screening
	Diagnosis
	Preconceptional Screening
	Prenatal Diagnosis
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	Predispositional Testing

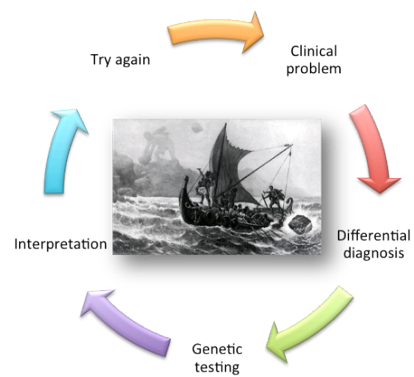
## Diagnostic Testing

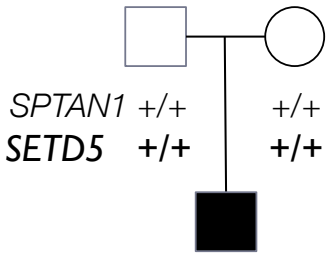


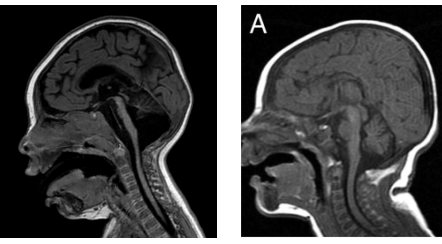
Laura is now 3 and her brother Seth is 5. Seth has been experiencing developmental problems, and is diagnosed as having autism.



## The Diagnostic Odyssey



  
*SPTAN1* +/+      +/+  
*SETD5* +/+      +/+



*SPTAN1* +/-c.[6908\_6916dup]    UDP13-001  
*SETD5* +/-c.[2346+1G>A]

*SPTAN1*: nonerythrocytic alpha-spectrin-I cytoskeletal protein –  
Infantile epileptic encephalopathy-5

*SETD5*: SET domain containing protein 5 (methyltransferase) –  
autosomal dominant intellectual disability

Progressive diffuse brain atrophy in West syndrome with marked hypomethylation due to *SPTAN1* gene mutation  
Takeshi Hoshino, M.D., Hiroaki Saito, M.D., Shigehiko Inagaki, M.D., Masayuki Saito, M.D., Toshiyuki Inoue, M.D., Hiroyuki Yamashita, M.D., Masahito Saito, M.D., Hiroaki Saito, M.D.  
© 2013 The Author(s)  
doi:10.1002/ajmg.b.32400

## Incidental Findings

American College of Medical Genetics and Genomics

### ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing

Robert C. Green, MD, MPH<sup>1,2</sup>, Jonathan S. Berg, MD, PhD<sup>3</sup>, Wayne W. Grody, MD, PhD<sup>4-6</sup>, Sarah S. Kalia, ScM, CGC<sup>1</sup>, Bruce R. Korf, MD, PhD<sup>7</sup>, Christa L. Martin, PhD, FACMG<sup>8</sup>, Amy McGuire, JD, PhD<sup>9</sup>, Robert L. Nussbaum, MD<sup>10</sup>, Julianne M. O'Daniel, MS, CGC<sup>11</sup>, Kelly E. Ormond, MS, CGC<sup>12</sup>, Heidi L. Rehm, PhD, FACMG<sup>2,13</sup>, Michael S. Watson, MS, PhD, FACMG<sup>14</sup>, Marc S. Williams, MD, FACMG<sup>15</sup>, Leslie G. Biesecker, MD<sup>16</sup>

Genet Med. 2013 Jul;15(7):565-74. doi:  
10.1038/gim.2013.73. Epub 2013 Jun 20.

## ACMG Incidental Findings Recommendations

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- Constitutional mutations on minimal list should be reported regardless of age of patient
- Laboratories should seek and report specific types of mutations on list
- Ordering clinician responsible for pre- and post-test counseling
- Patients may opt out of learning about incidental findings

## Gene List

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Type	Genes
Tumor Predisposition (Breast/ovarian, Li-Fraumeni, Peutz-Jeghers, Lynch, FAP, Polyposis, Von Hippel-Lindau, MEN1/2, Medullary thyroid ca, PTEN hamartoma, retinoblastoma, Paraganglioma/Pheo, TSC, WT1-related Wilms', NF2)	<i>BRCA1, BRCA2, TP53, STK11, MLH1, MSH2, MSH6, PMS2, APC, MUTYH, VHL, MEN1, RET, NTRK1, PTEN, RB1, SDHD, SDHAF2, SDHC, SDHB, TSC1, TSC2, WT1, NF2</i>
Connective Tissue Dysplasia (EDS vascular type, Marfan, Loeys-Dietz, Familial thoracic and aortic aneurysms/dissections)	<i>COL3A1, FBN1, TGFB1, TGFB2, SMAD3, ACTA2, MYLK, MYH11</i>
Cardiomyopathy (Hypertropic, dilated)	<i>MYBPC3, MYH7, TNNT2, TNNI3, TPMN1, MYL3, ACTC1, PRKAG2, GLA, MYL2, LMNA</i>
Arrhythmia (Arrhythmogenic RVCN, Romano-Ward, Brugada)	<i>RYR2, PKP2, DSP, DSC2, TMEM43, DSG2, KCNQ1, DCNH2, SCN5A</i>
Hypercholesterolemia	<i>LDLR, APOB, PCSK9</i>
Malignant hyperthermia	<i>RYR1, CACNA1S</i>



	Newborn Screening
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## Preconceptional Testing

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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.

**Ashkenzi Jewish**

- Tay-Sachs disease
- Cystic fibrosis
- Canavan disease
- Familial dysautonomia
- Inquire:
  - Microdeletion IV
  - Niemann-Pick A
  - Niemann-Pick C
  - Gaucher disease
  - Gaucher disease

**African/Asian/Mediterranean**

- Hemoglobinopathies

**Panethnic**

- Cystic fibrosis
- Spinal muscular atrophy

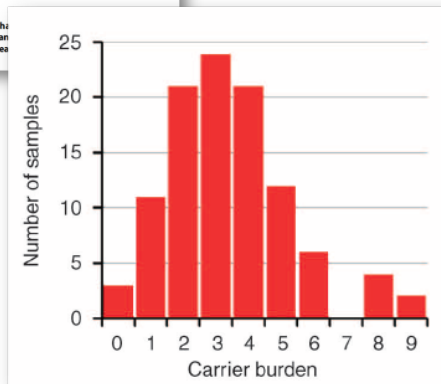
**Disease List**







Panel	Disease	Gene
Ashkenazi Jewish	Tay-Sachs disease	HexA
	Canavan disease	ASPM
	Familial dysautonomia	IKBAP5
	Spina-1	SPIN1
	Spina-2	SPIN2
	Spina-3	SPIN3
	Spina-4	SPIN4
	Spina-5	SPIN5
	Spina-6	SPIN6
	Spina-7	SPIN7
African/Asian/Mediterranean	Hemoglobinopathies	HBB
	Hemoglobinopathies	HBD
	Hemoglobinopathies	HBE
	Hemoglobinopathies	HBF
	Hemoglobinopathies	HBG
	Hemoglobinopathies	HBI
	Hemoglobinopathies	HBJ
	Hemoglobinopathies	HBK
	Hemoglobinopathies	HBL
	Hemoglobinopathies	HBM
Panethnic	Cystic fibrosis	CFTR
	Spinal muscular atrophy	SMN2
	Spinal muscular atrophy	SMN1
	Spinal muscular atrophy	SMN3
	Spinal muscular atrophy	SMN4
	Spinal muscular atrophy	SMN5
	Spinal muscular atrophy	SMN6
	Spinal muscular atrophy	SMN7
	Spinal muscular atrophy	SMN8
	Spinal muscular atrophy	SMN9

www.counsyl.com


## Genomic Carrier Screening

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,<sup>1\*</sup> Darrell L. Dinwiddie,<sup>1,2\*</sup> Neil A. Miller,<sup>1,2</sup> Shi Elena E. Ganusova,<sup>3</sup> Joann Mudge,<sup>3</sup> Ray J. Langley,<sup>3</sup> Lu Zhan,<sup>3</sup> Faye D. Schilkey,<sup>3</sup> Vrunda Sheth,<sup>3</sup> Jimmy E. Woodward,<sup>3</sup> Hea Gary P. Schroth,<sup>3</sup> Ryan W. Kim,<sup>3</sup> Stephen F. Kingsmore<sup>1,2,3</sup>

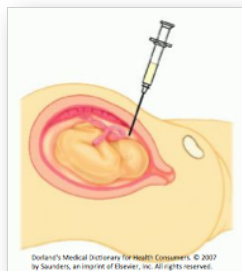


	Newborn Screening
	Diagnosis
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	Prenatal Diagnosis
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	Predispositional Testing

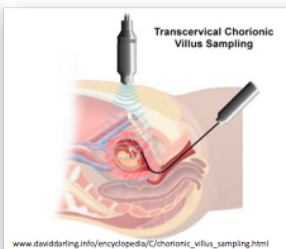
## Prenatal Testing

	<p>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.</p>
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## Prenatal Diagnosis



amniocentesis



chorionic villus biopsy



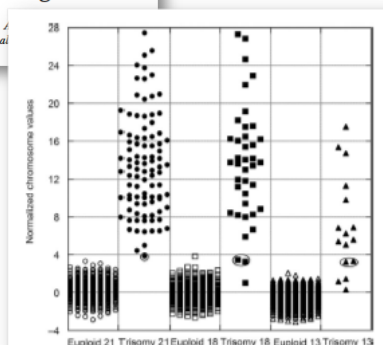
preimplantation diagnosis

## 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, MD, /  
Amy J. Sehner, MD, and Richard P. Rava, PhD, on behalf of the Maternal  
Accurately diagnose fetal aneuploidy (MELISSA) Study Group\*

(Obstet Gynecol 2012;119:00-00)  
DOI: 10.1097/AOG.0b013e318240b482

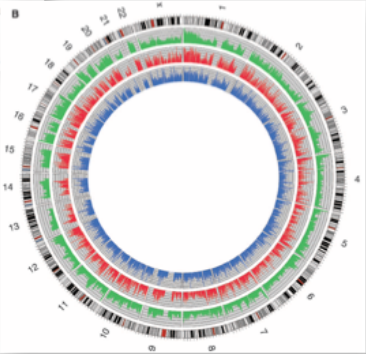








# Genomic Prenatal Diagnosis

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

Y. M. Dennis Lo,<sup>1,2\*</sup> K. C. Allen Chan,<sup>1,2</sup> Hao Sun,<sup>1,2</sup> Eric Z. Chen,<sup>1,2</sup> Peiyong Fiona M. F. Luo,<sup>1,2</sup> Yama W. Zheng,<sup>1,2</sup> Tak Y. Leung,<sup>2</sup> Tze K. Lau,<sup>3</sup> Charles R. Cantor,<sup>4</sup> Rossa W. K. Chiu<sup>1,2</sup>

(Published 8 December 2010; Volume 2 Issue 61161091)  
www.ScienceTranslationalMedicine.org 8 December 2010 Vol 2 Issue 61161091

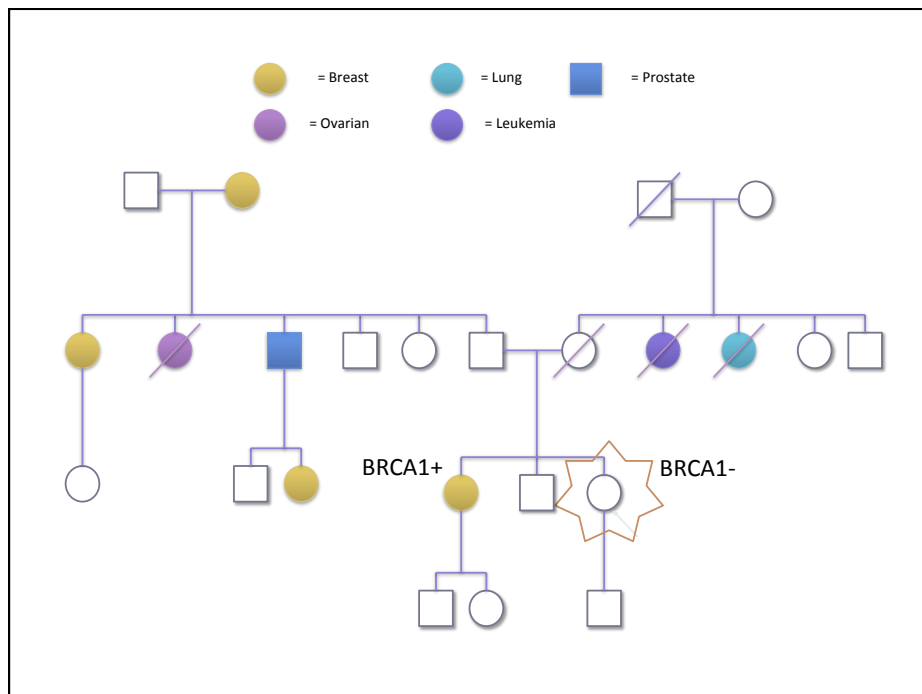


	Newborn Screening
	Diagnosis
	Preconceptional Screening
	Prenatal Diagnosis
	Presymptomatic Testing
	Predispositional Testing

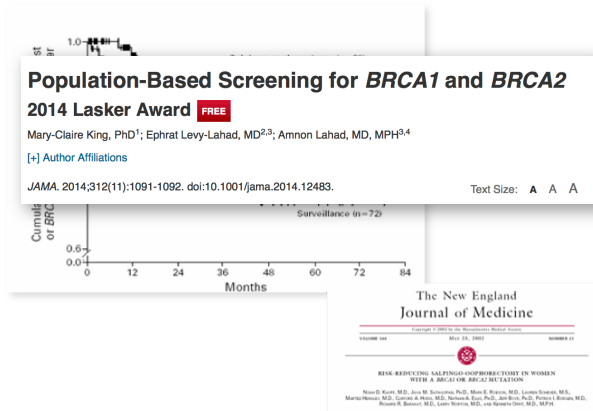
## Presymptomatic Testing



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.

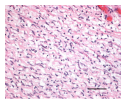


## Breast Cancer Prevention

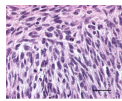


## Cancer Genomes

Normal

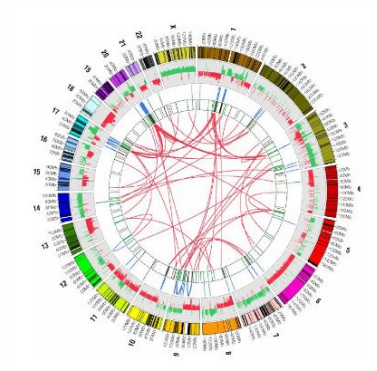


Tumor

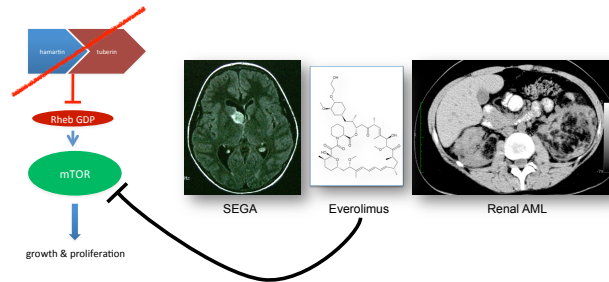


Sequence

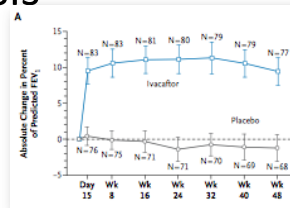
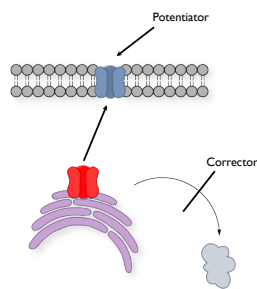
Difference =  
cancer-specific genetic  
changes



## Everolimus Treatment of Tuberous Sclerosis









## Mutation-Guided Treatment of Cystic Fibrosis



**The NEW ENGLAND JOURNAL of MEDICINE**

**A CFTR Potentiator in Patients with Cystic Fibrosis and the G551D Mutation**  
 Barnes W, Barmatz M, D. Jane Davies, M.D., M.B., Ch.B., N. Gerald McEvoy, M.D., Elizabeth Tuller, M.D., Scott E. Bell, M.B., B.S., M.D., Peter D. Brannan, M.D., Matthew Greene, M.D., Edward F. Michelson, M.D., Claire E. Wainwright, M.D., M.B., B.S., Michael W. Roemer, M.D., Richard Moss, M.D., Fara Hagen, M.D., Ph.D., Fabrice Sermet-Caudron, M.D., Ph.D., Stephen M. Rowe, M.D., MS PhD, Quynh Dang, Ph.D., Sally Rodriguez, M.S., Karl Froese, M.D., Christian Oroszko, M.D., and Paul H. Brown, M.D., for the CFTR Potentiator Study Group



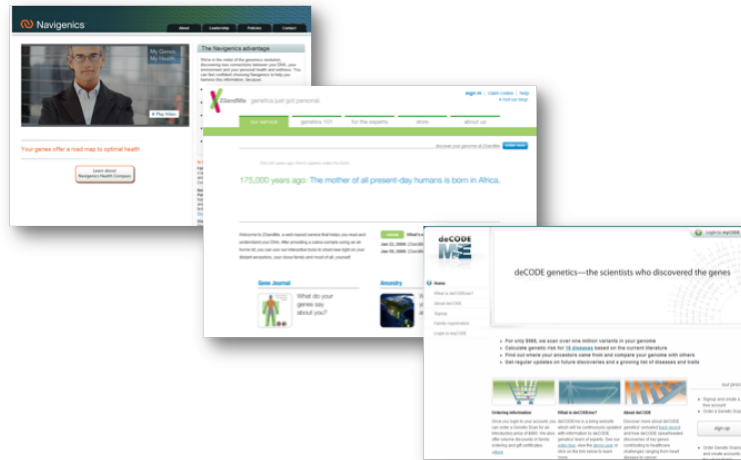
	Newborn Screening
	Diagnosis
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	Predispositional Testing

## 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.

# Direct-to-Consumer Testing



## Your Genetic Data

Show information for **Bruce Korf** assuming **European** ethnicity and an age range of **20-79**

**Bruce Korf**  
**24.3 out of 100**  
 men of European ethnicity who share Bruce Korf's genotype will get Type 2 Diabetes between the ages of 20 and 79.

**Average**  
**23.7 out of 100**  
 men of European ethnicity will get Type 2 Diabetes between the ages of 20 and 79.

**Genes vs. Environment**

**26 %** Attributable to Genetics

The **heritability** of type 2 diabetes is estimated to be 26%. This means that **environmental factors** contribute more to differences in risk for this condition than genetic factors. Genetic factors that play a role in type 2 diabetes include both unknown factors and known factors such as the SNPs we describe here. Environmental factors include **obesity**, gestational diabetes, giving birth to at least one baby weighing nine pounds or more, high blood pressure, abnormal cholesterol levels, physical inactivity, polycystic ovarian syndrome, other clinical conditions associated with **insulin** resistance, a history of impaired **glucose** tolerance or impaired fasting glucose, and a history of cardiovascular disease. ([sources](#))

**What does the Odds Calculator show me?**

Use the ethnicity and age range selectors above to see the estimated incidence of Type 2 Diabetes due to genetics for men with **Bruce Korf's** genotype. The 23andMe Odds Calculator assumes that a person is free of the condition at the lower age in the range. You can use the name selector above to see the estimated incidence of Type 2 Diabetes for the genotypes of other people in your account.

The 23andMe Odds Calculator only takes into account effects of markers with known associations that are also on our genotyping chip. Keep in mind that aside from genetics, environment and lifestyle may also contribute to one's chances of developing type 2 diabetes.

# Pharmacogenetics

Show results for **Bruce Korf** Print summary of elevated risks

[Return to Overview](#) | [Disease Risks](#) | [Carrier Status](#) | [Traits](#) | [Drug Response](#) | [Recently Updated](#)

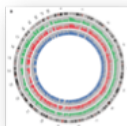
Name	Status	Last Updated
Warfarin (Coumadin®) Sensitivity	Increased	Mar 19, 2009
Abacavir Hypersensitivity	Typical	Oct 8, 2009
Clopidogrel (Plavix®) Efficacy	Typical	May 7, 2009
Drinking, Smoking, and Risk of Esophageal Cancer <b>new</b>	Typical	Jan 14, 2010
Fluorouracil Toxicity	Typical	Oct 1, 2009
Pseudochoolinesterase Deficiency	Typical	Nov 19, 2009
Response to Hepatitis C Treatment <b>new</b>	Typical	Jan 14, 2010
Oral Contraceptives, Hormone Replacement Therapy and Risk of Venous Thromboembolism <b>new</b>	n/a	Feb 11, 2010

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 have been analytically validated according to CLIA standards.

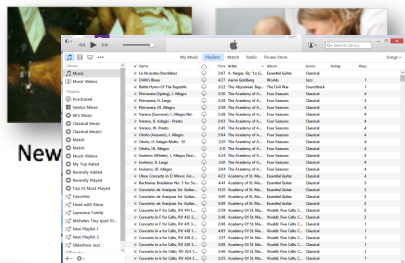
23andMe Name	Genotype	Combination
rs1799853	CC	
rs1057910	AA	CYP2C9 *1/*1, VKORC1 -1639/3673 AG
rs9923231	CT	

# WGS Workflow

When?



Prenatal



New



Adulthood

Where?



EHR



Cloud



Personal Device



Cell Nucleus

