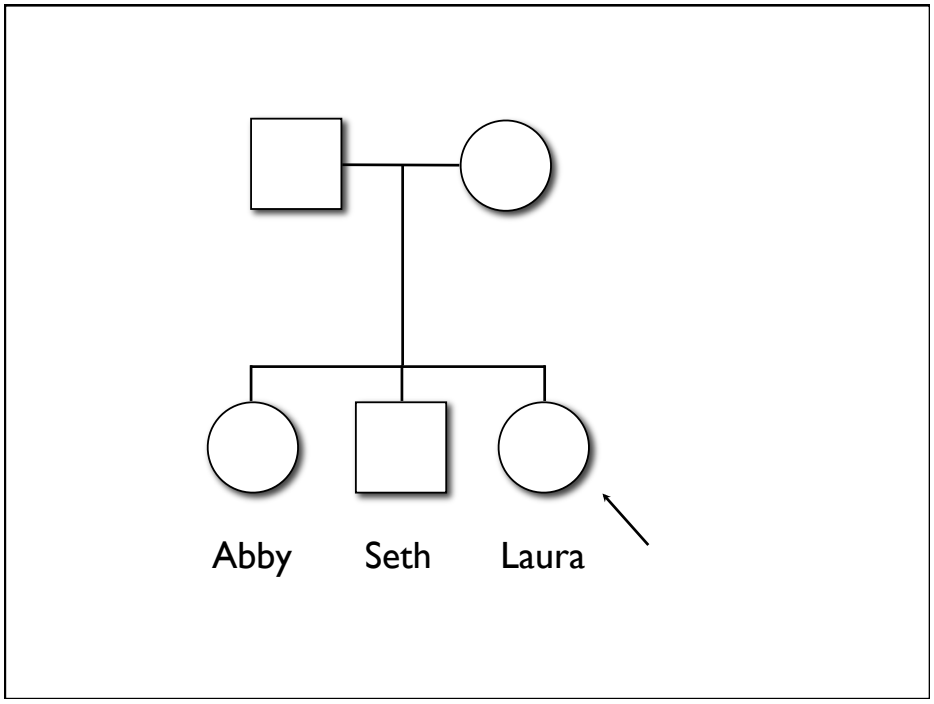
Genomic Medicine

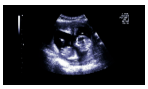
Bruce R. Korf, MD, PhD
Department of Genetics
University of Alabama at Birmingham




Newborn Screening


Diagnosis


Preconceptional Screening

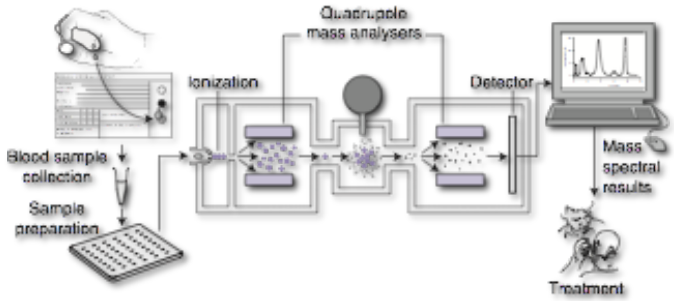

Prenatal Diagnosis


Presymptomatic Testing


Predispositional Testing

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.



Newborn Screening by Genome Sequencing?


RESEARCH ARTICLE

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

Carrier Testing for Severe Childhood Re... by Next-Generation Sequencing

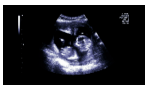
Callum J. Bell,[1]* Darrell L. Dinwiddie,[1,2]* Neil A. Miller,[1,2] Shannon ... Elena E. Ganusova,[1] Joann Mudge,[1] Ray J. Langley,[1] Lu Zhang,[3] Cl... Faye D. Schilkey,[1] Vrunda Sheth,[4] Jimmy E. Woodward,[1] Heather E... Gary P. Schroth,[5] Ryan W. Kim,[1] Stephen F. Kingsmore[1,2†]

"We found an unex... portion of literature-annotate... ...ns that were incorrect, incomplet... ...olymorphisms."

Newborn Screening

Diagnosis

Preconceptional Screening



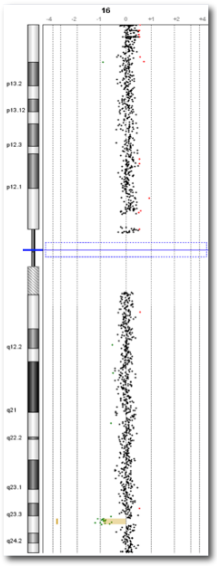
Prenatal Diagnosis

Presymptomatic Testing

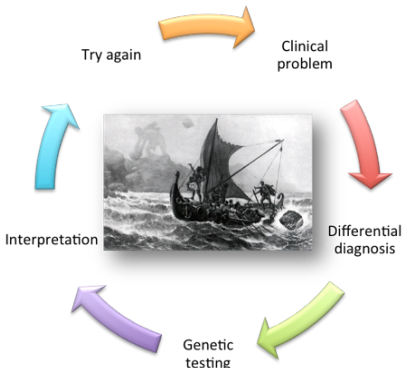
Predispositional Testing

Diagnostic Testing

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



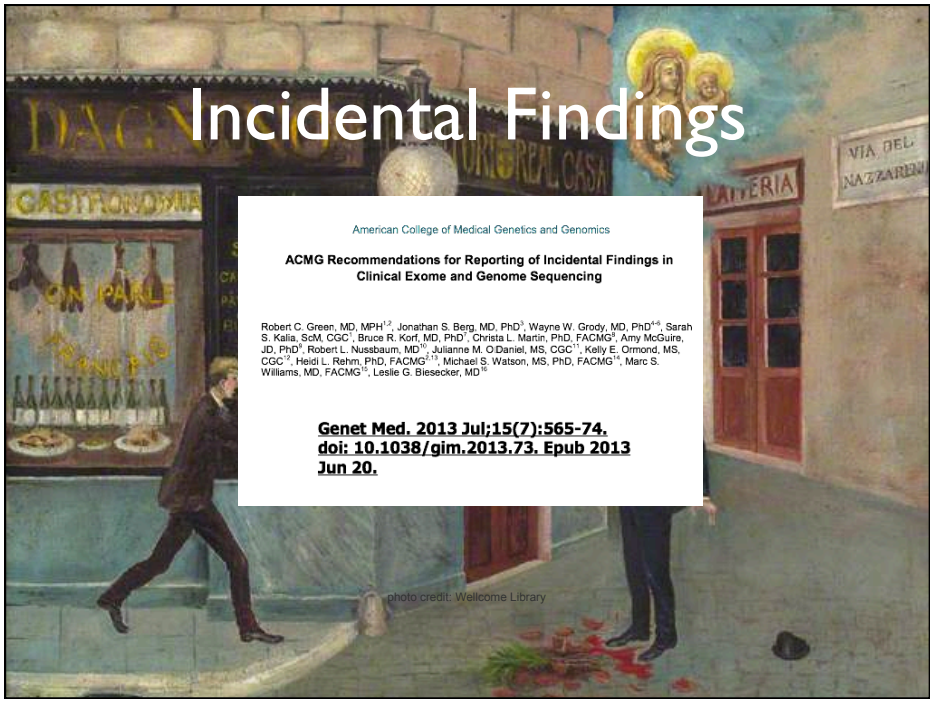
The Diagnostic Odyssey



Clinical Whole-Exome Sequencing for the Diagnosis of Mendelian Disorders

Yaping Yang, Ph.D., Donna M. Muzny, M.Sc., Jeffrey G. Reid, Ph.D., Matthew N. Bainbridge, Ph.D., Alecia Willis, Ph.D., Patricia A. Ward, M.S., Alicia Braxton, M.S., Joke Beuten, Ph.D., Fan Xia, Ph.D., Zhiyv Niu, Ph.D., Matthew Hardison, Ph.D., Richard Person, Ph.D., Mir Reza Bekheirnia, M.D., Magalie S. Leduc, Ph.D., Amelia Kirby, M.D., Peter Pham, M.Sc., Jennifer Scull, Ph.D., Min Wang, Ph.D., Yan Ding, M.D., Sharon E. Plon, M.D., Ph.D., James R. Lupski, M.D., Ph.D., Arthur L. Beaudet, M.D., Richard A. Gibbs, Ph.D., and Christine M. Eng, M.D.
N Engl J Med 2013; 369:1502-1511 | October 17, 2013 | DOI: 10.1056/NEJMoa1306555

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

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

photo credit: Wellcome Library

Recommendations

- Constitutional mutations on minimum list should be reported by laboratory regardless of patient age
- Laboratories should seek and report specific types of variants in genes on list
- Ordering clinician responsible for pre- and post-test counseling
- Patients may opt out of having analysis of incidental findings

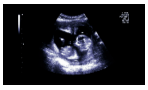
List of Genes

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)	BRCA1, BRCA2, TP53, STK11, MLH1, MSH2, MSH6, PMS2, APC, MUTYH, VHL, MEN1, RET, NTRK1, PTEN, RB1, SDHD, SDHAF2, SDHC, SDHB, TSC1, TSC2, WT1, NF2
Connective Tissue Dysplasia (EDS vascular type, Marfan, Loeys-Dietz, Familial thoracic and aortic aneurysms/dissections	COL3A1, FBN1, TGFBR1, TGFBR2, SMAD3, ACTA2, MYLK, MYH11
Cardiomyopathy (Hypertropic, dilated)	MYBPC3, MYH7, TNNT2, TNNI3, TPMN1, MYL3, ACTC1, PRKAG2, GLA, MYL2, LMNA
Arrhythmia (Arrhythmogenic RVCM, Romano-Ward, Brugada)	RYR2, PKP2, DSP, DSC2, TMEM43, DSG2, KCNQ1, DCNH2, SCN5A
Hypercholesterolemia	LDLR, APOB, PCSK9
Malignant hyperthermia	RYR1, CACNA1S


Newborn Screening


Diagnosis


Preconceptional Screening


Prenatal Diagnosis

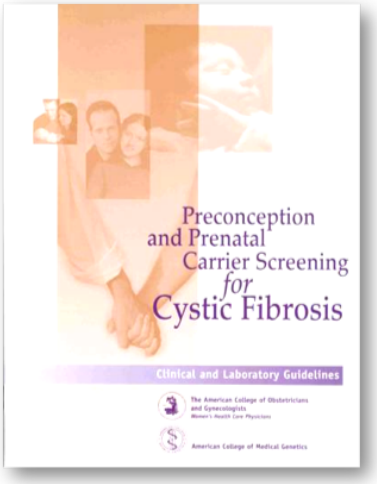

Presymptomatic Testing

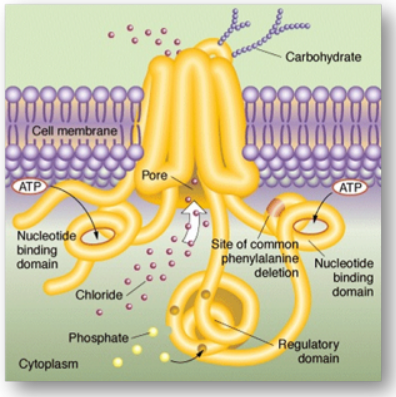

Predispositional Testing

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.

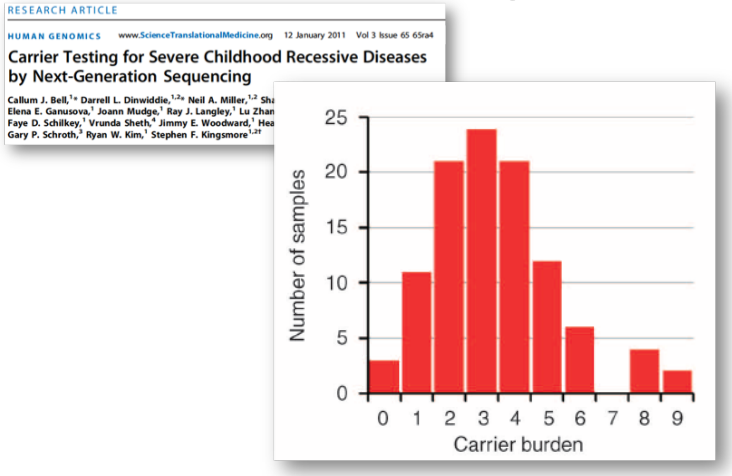
CF Carrier Screening





Ashkenzi Jewish	African/Asian/ Mediterranean	Panethnic
Tay-Sachs disease	Hemoglobinopathies	Cystic fibrosis
Cystic fibrosis		Spinal muscular atrophy
Canavan disease		
Familial dysautonomia		
Inquire: •Mucolipidosis IV •Niemann-Pick A •Fanconi anemia C •Bloom syndrome •Gaucher disease		

Genomic Carrier Screening


RESEARCH ARTICLE

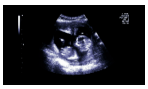
HUMAN GENOMICS www.ScienceTranslationalMedicine.org 12 January 2011 Vol 3 Issue 65 65ra4

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


Newborn Screening


Diagnosis

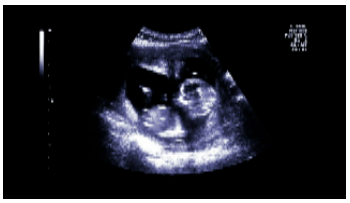

Preconceptional Screening


Prenatal Diagnosis


Presymptomatic Testing

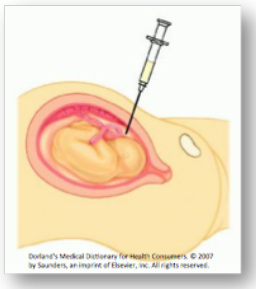

Predispositional Testing

Prenatal Testing

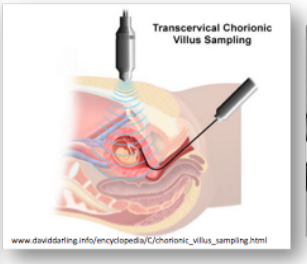


Laura and her Tom are indeed found to both be cystic fibrosis carriers. They elect to have prenatal diagnosis by amniocentesis at 16 weeks of pregnancy. The fetus is found to be a CF carrier.

Prenatal Diagnosis



amniocentesis



chorionic villus biopsy

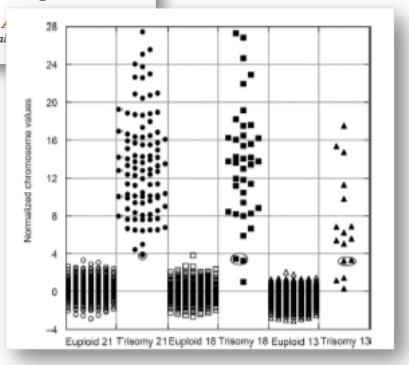
preimplantation diagnosis

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, MD, A
Amy J. Sehnert, 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.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
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 2010 Vol 2 Issue 6

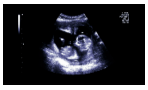
Prenatal Whole-Genome Sequencing — Is the Quest to Know a Fetus's Future Ethical?

Ilana R. Yurkiewicz, B.S., Bruce R. Korf, M.D., Ph.D., and Lisa Soleymani Lehmann, M.D., Ph.D.

Newborn Screening

Diagnosis

Preconceptional Screening



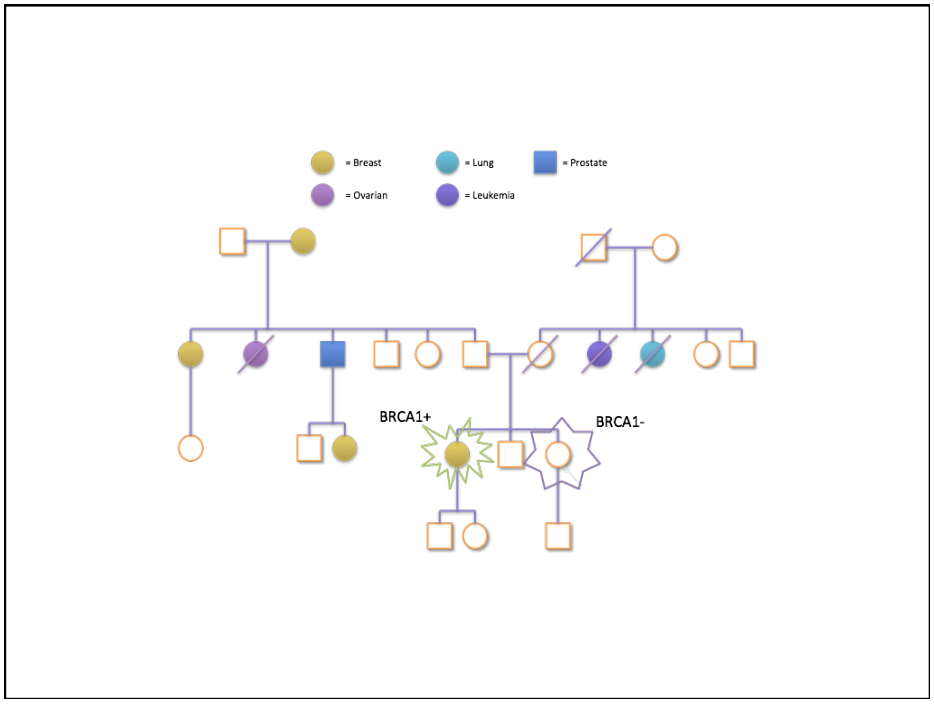
Prenatal Diagnosis

Presymptomatic Testing

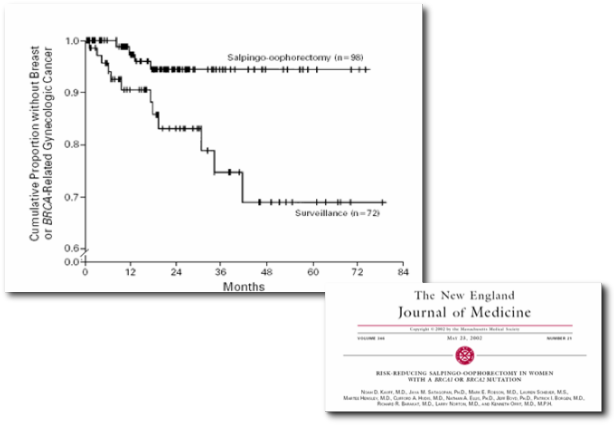
Predispositional Testing

Presymptomatic Testing

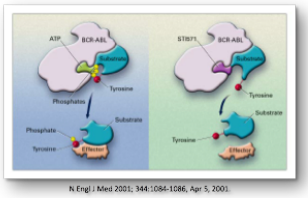
Laura is now 45. She has just learned that her older sister Abby, age 49, has been diagnosed as having breast cancer. She is concerned about her own risks, given that there is a family history of others with breast cancer.



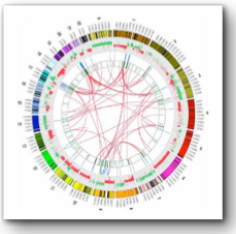
Breast Cancer Prevention

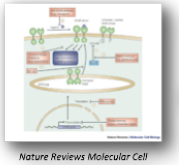


Therapeutics: Common Disease

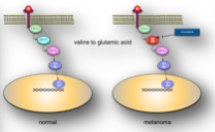


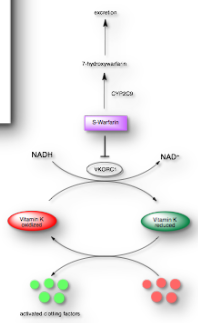
N Engl J Med 2001; 344:1084-1086, Apr 5, 2001





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



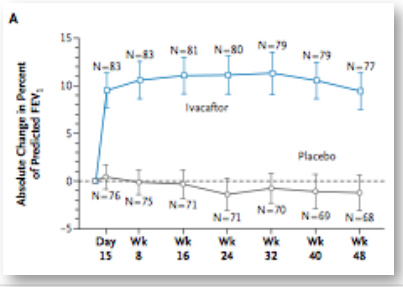


Therapeutics: Rare Disease

ivacaftor

Potentiator

Corrector



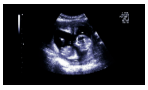
A CFTR Potentiator in Patients with Cystic Fibrosis and the *G551D* Mutation

Bonnie W. Ramsey, M.D., Jane Davies, M.D., M.B., Ch.B., N. Gerard McElvaney, M.D., Elizabeth Tullis, M.D., Scott C. Bell, M.B., B.S., M.D., Pavel Dřevínek, M.D., Matthias Griese, M.D., Edward F. McKone, M.D., Claire E. Wainwright, M.D., M.B., B.S., Michael W. Konstan, M.D., Richard Moss, M.D., Felix Ratjen, M.D., Ph.D., Isabelle Sermet-Gaudelus, M.D., Ph.D., Steven M. Rowe, M.D., M.S.P.H., Quanmei Dong, Ph.D., Sally Rodriguez, M.S., Karl Yen, M.D., Claudia Ordoñez, M.D., and J. Stuart Elborn, M.D., for the VX08-770-102 Study Group*

Newborn Screening

Diagnosis

Preconceptional Screening



Prenatal Diagnosis

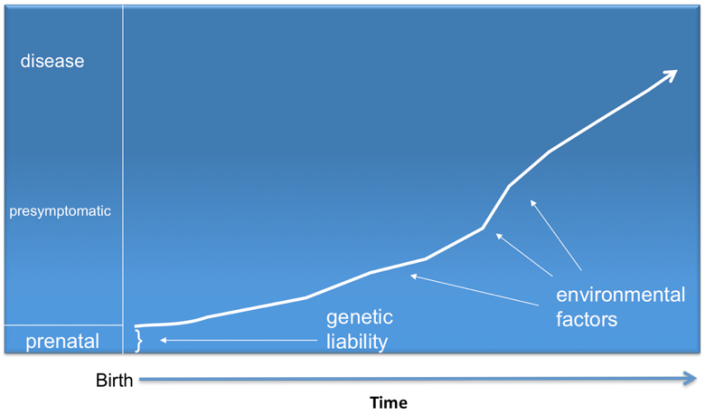
Presymptomatic Testing

Predispositional Testing

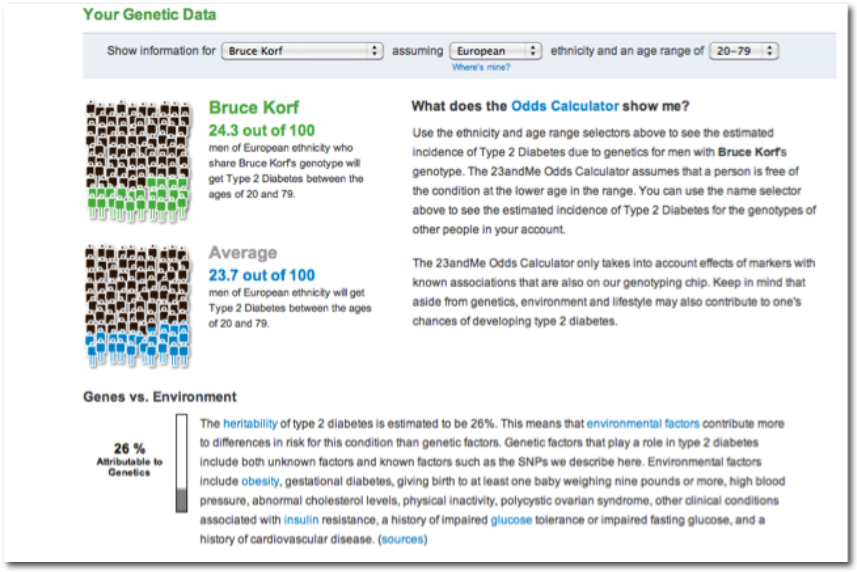
Predispositional Testing

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.

Genetic Prevention



Direct-to-Consumer Testing



Your Genetic Data

Show information for Bruce Korf assuming European ethnicity and an age range of 20–79
Where's mine?

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.

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.

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)

Consistency of Results

TABLE 1: PREDICTIONS FOR DISEASE RELATIVE RISKS FOR FIVE INDIVIDUALS

Disease	Female A	Female B	Female C	Male D	Male E
Breast cancer	↑↑	↑↑	↓↓		
Coeliac disease	↓↓	↓↓	↓↓	↓↓	↓↓
Colon cancer	==	==	=↓	↑↑	=↓
Crohn's disease	↓↑	↓↑	↓↓	↓↓	↓=
Heart attack	↓↓	=↓	=↓	=↓	↑↑
Lupus	↑↓	↓↓	↓↓	↑=	↑=
Macular degeneration	↓↓	↓↓	↑=	↓↓	↓↓
Multiple sclerosis	↑↑		↓↓	↓↓	↓↓
Prostate cancer				↑↑	↓↑
Psoriasis	↓↑		↑↓	↑↑	↓↓
Restless legs syndrome	=↓	↑↑	↓=	↓↑	↑↑
Rheumatoid arthritis	↑↑	↑↑	↓↓	↓↓	↑↑
Type 2 diabetes	↓↓	=↓	↓↓	↑↓	=↓

↑ increased risk (RR > 1.05), ↓ decreased risk (relative risk (RR) < 0.95), = average risk (0.95 ≤ RR ≤ 1.05). First prediction is from 23andMe; second prediction is from Navigenics. Different predictions are highlighted in beige.

Ng PC et al. Nature 2009; 461:724

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 new	Typical	Jan 14, 2010
Fluorouracil Toxicity	Typical	Oct 1, 2009
Pseudocholinesterase Deficiency	Typical	Nov 19, 2009
Response to Hepatitis C Treatment new	Typical	Jan 14, 2010
Oral Contraceptives, Hormone Replacement Therapy and Risk of Venous Thromboembolism new	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	

Multiple Endocrine Neoplasia

Parathyroid tumors

Framework for development of physician competencies in genomic medicine: report of the Competencies Working Group of the Inter-Society Coordinating Committee for Physician Education in Genomics

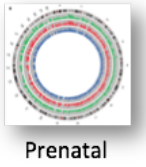
Bruce R. Korf MD, PhD, Anna B. Berry MD, Melvin Limson PhD, Ali J. Marian MD, Michael F. Murray MD, P. Pearl O'Rourke MD, Eugene R. Passamani MD, Mary V. Relling PharmD, John Tooker MD, MBA, Gregory J. Tsongalis PhD & Laura L. Rodriguez PhD

Affiliations | **Corresponding author**

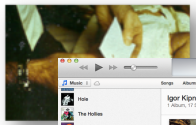
Genetics in Medicine (2014) | doi:10.1038/gim.2014.35
Received 20 February 2014 | Accepted 12 March 2014 | Published online 24 April 2014

WGS Workflow

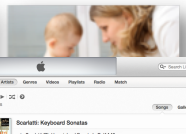
When?



Prenatal



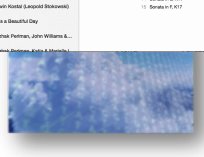
New



Adulthood

Where?

EHR



Cloud

Personal Device

Cell Nucleus


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