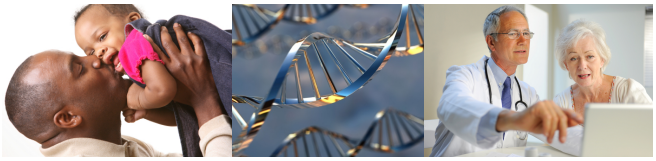
Integration of Genomics into Medical Practice

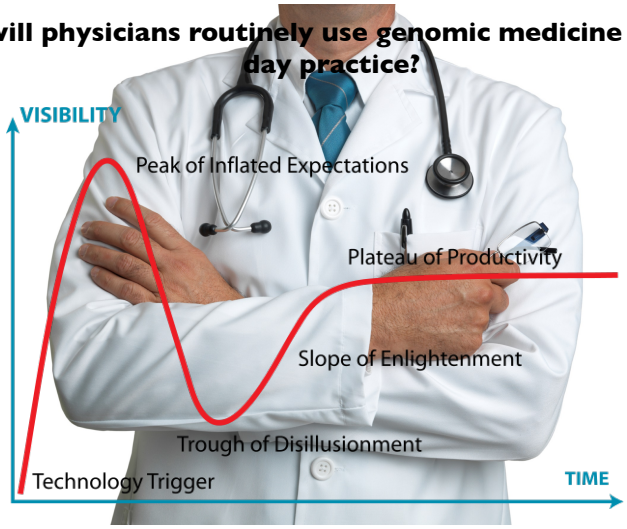
Bruce R. Korf, MD, PhD
Department of Genetics
University of Alabama at Birmingham



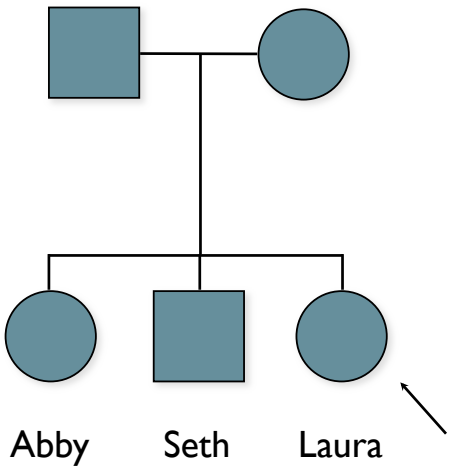
Disclosures

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

When will physicians routinely use genomic medicine in day-to-day practice?



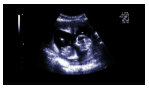
https://en.wikipedia.org/wiki/Hype_cycle



Newborn Screening

Diagnosis

Preconceptional Screening



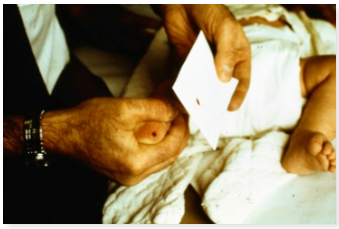
Prenatal Diagnosis

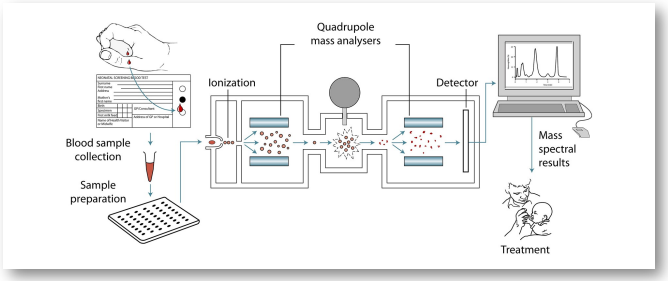
Presymptomatic Testing

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.



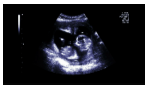


Genomic Newborn Screening

Newborn Screening

Diagnosis

Preconceptional Screening



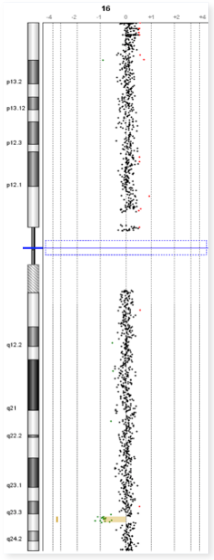
Prenatal Diagnosis

Presymptomatic Testing

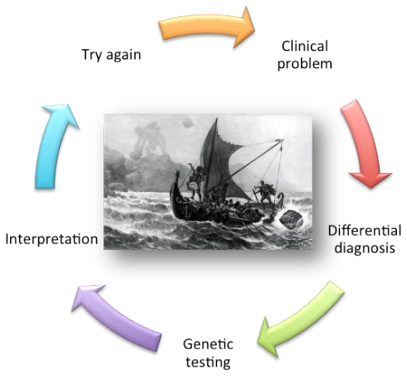
Predispositional Testing

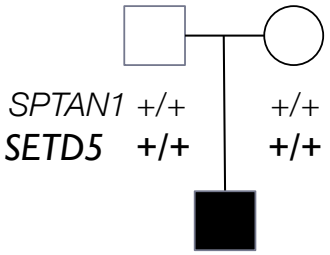
Diagnostic Testing

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

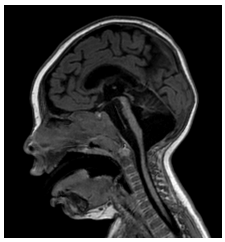


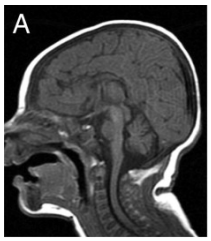
The Diagnostic Odyssey





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





Case report
Progressive diffuse brain atrophy in West syndrome with marked hypomyelination due to *SPTAN1* gene mutation
Yutaka Nozaki[a], Yoshiaki Saito[a], Shigehiro Nagai[a], Masayuki Sasaki[a], Toshiyuki Iwasaki[a], Naomichi Matsumoto[b], Masahiro Ishii[a], Hirotomo Saitsu[b]
Show more
doi:10.1016/j.braindev.2012.05.002 Get rights and content

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

SPTAN1: nonerythrocytic alpha-spectrin-1 cytoskeletal protein – Infantile epileptic encephalopathy-5

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

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[1], 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.

ACMG Incidental Findings Recommendations

- 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

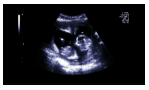
Gene List

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



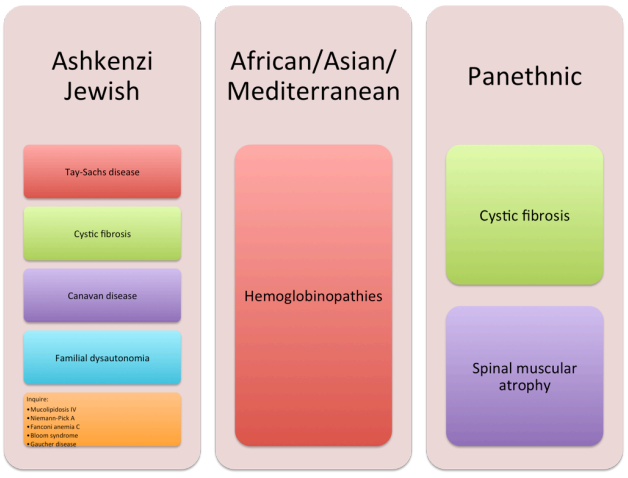
Prenatal Diagnosis

Presymptomatic Testing

Predispositional Testing

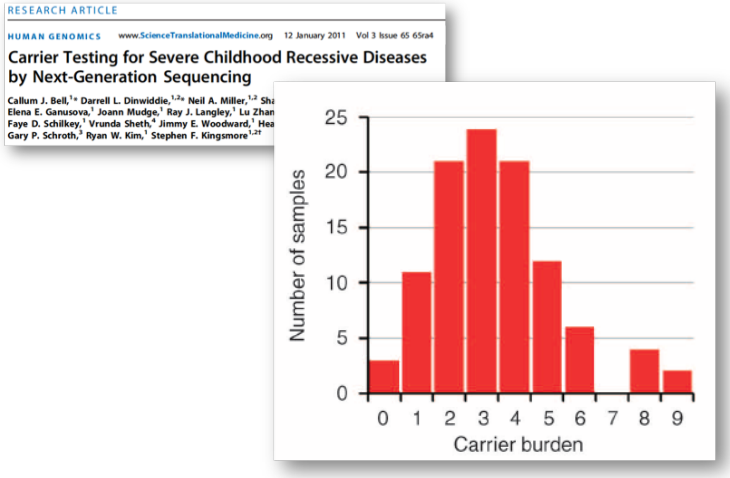
Preconceptional Testing

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.



www.counsyl.com

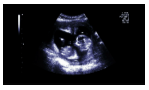
Genomic Carrier Screening



Newborn Screening

Diagnosis

Preconceptional Screening

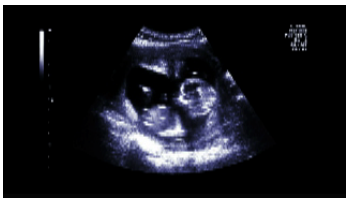


Prenatal Diagnosis

Presymptomatic Testing

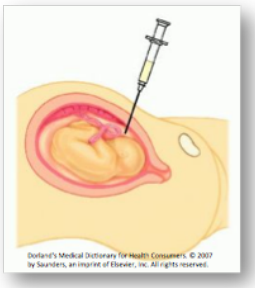
Predispositional Testing

Prenatal Testing

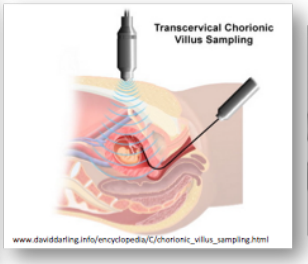


Laura and her Tom are indeed found to both be cystic fibrosis carriers. They elect to have prenatal diagnosis by amniocentesis at 16 weeks of pregnancy. The fetus is found to be a CF carrier.

Prenatal Diagnosis



amniocentesis



chorionic villus biopsy

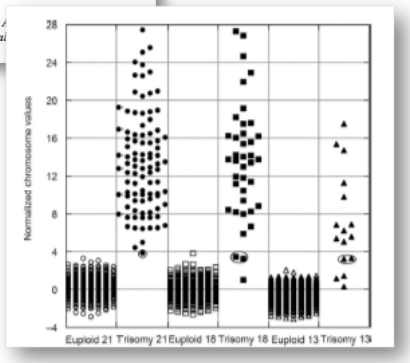
preimplantation diagnosis

Next Generation Prenatal Screening

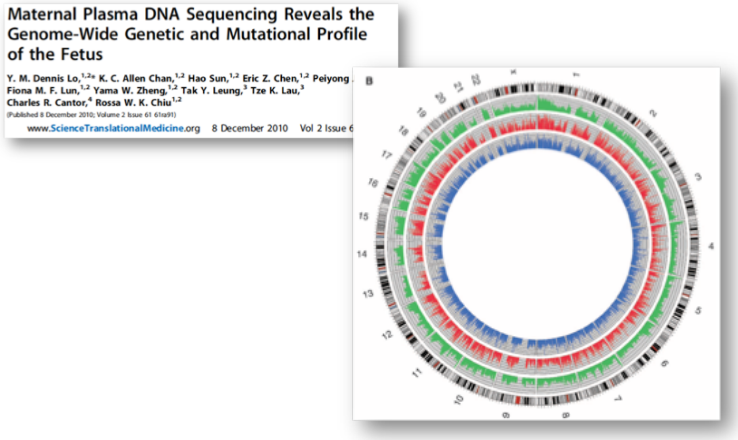
Genome-Wide Fetal Aneuploidy Detection by Maternal Plasma DNA Sequencing

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



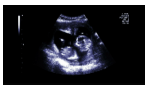
Genomic Prenatal Diagnosis




Newborn Screening


Diagnosis


Preconceptional Screening

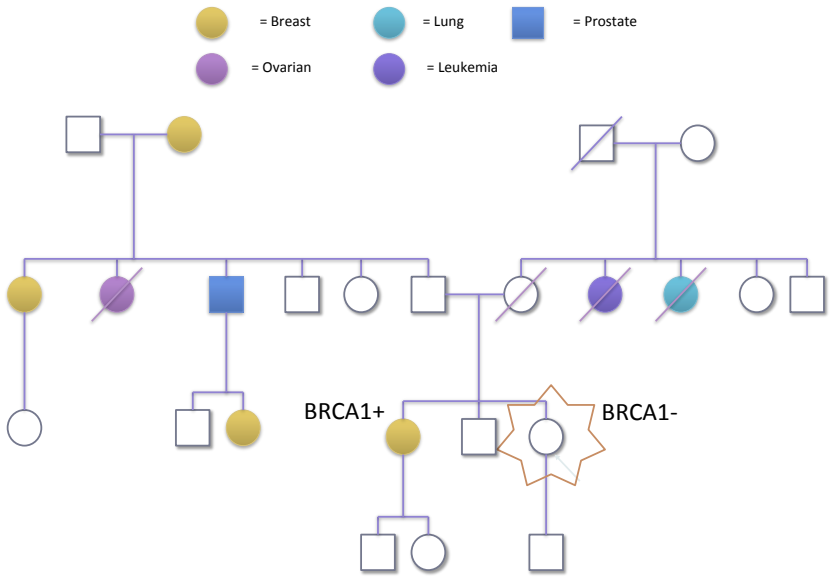

Prenatal Diagnosis


Presymptomatic Testing

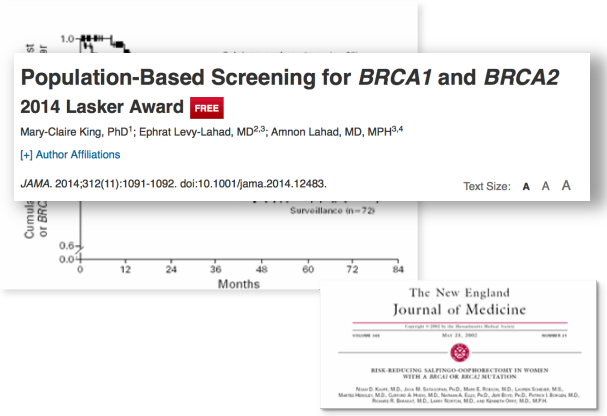

Predispositional Testing

Presymptomatic Testing

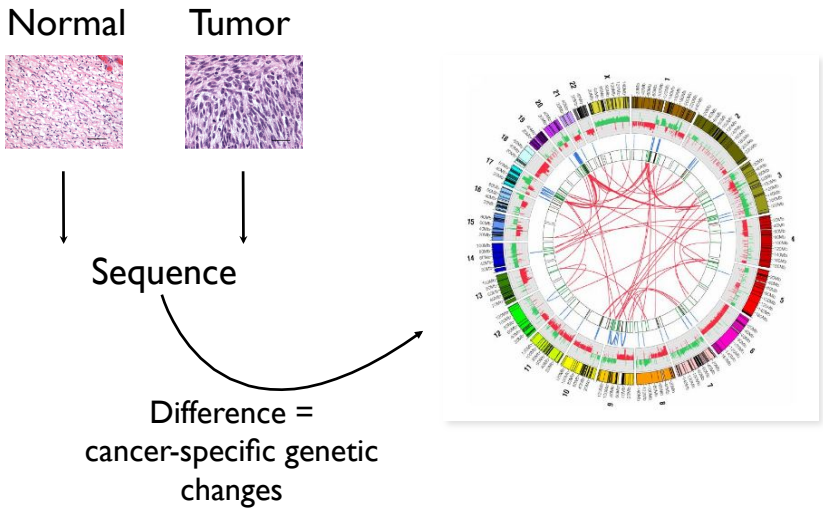
Laura is now 45. She has just learned that her older sister Abby, age 49, has been diagnosed as having breast cancer. She is concerned about her own risks, given that there is a family history of others with breast cancer.



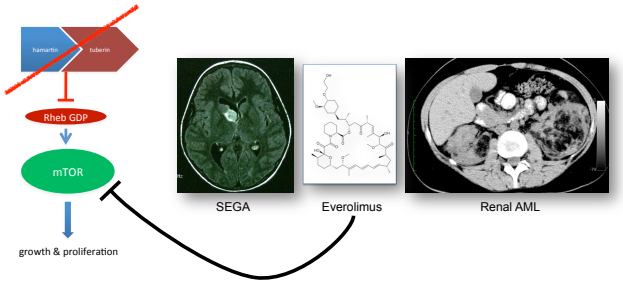
Breast Cancer Prevention



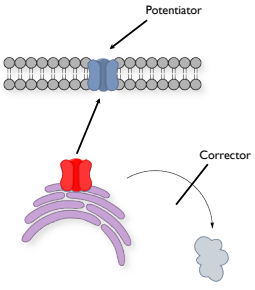
Cancer Genomes

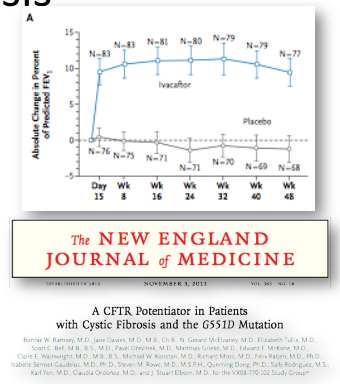


Everolimus Treatment of Tuberous Sclerosis



Mutation-Guided Treatment of Cystic Fibrosis





Newborn Screening

Diagnosis

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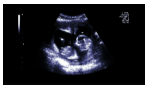


Prenatal Diagnosis

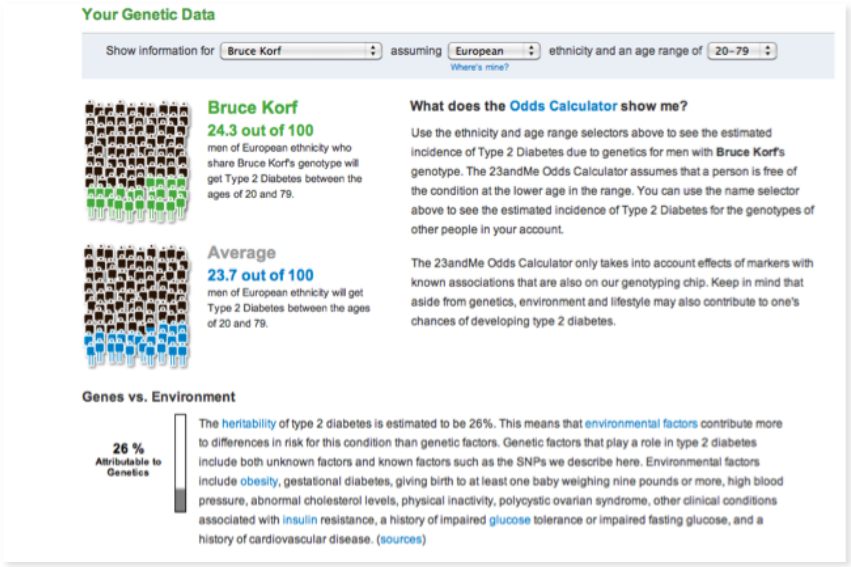
Presymptomatic Testing

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.

Direct-to-Consumer Testing



Pharmacogenetics

Show results for Bruce Korf

Print summary of elevated risks

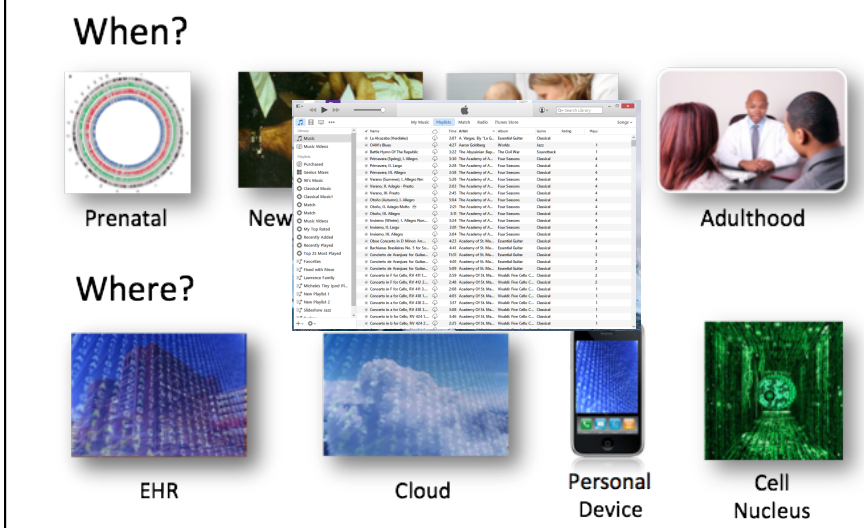
« Return to Overview | Disease Risks | Carrier Status | Traits | Drug Response | Recently Updated

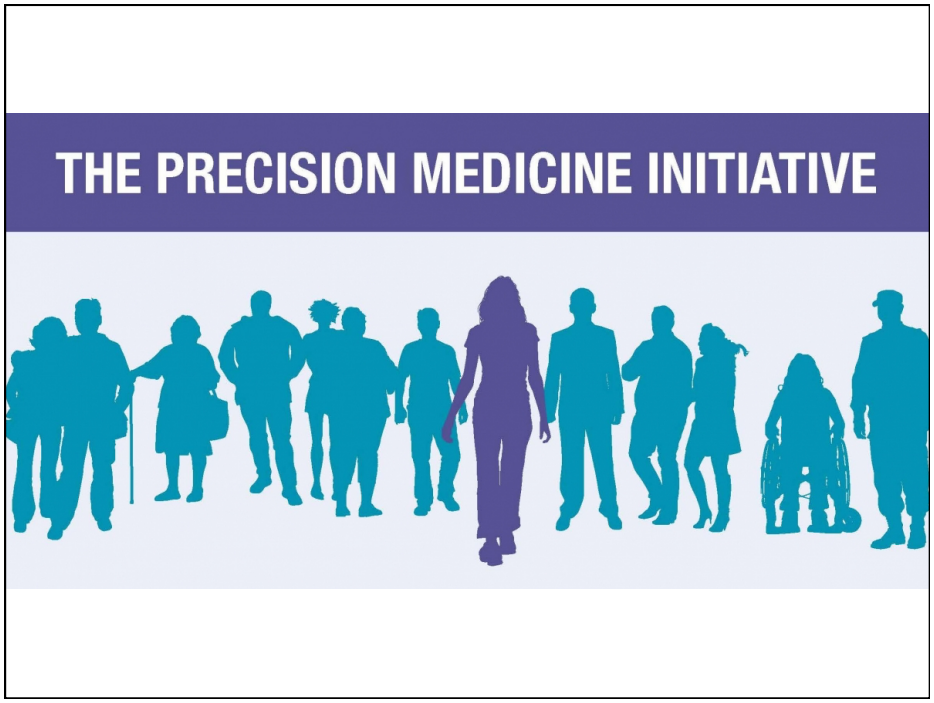
Name	Status	Last Updated
Warfarin (Coumadin®) Sensitivity	Increased	Mar 19, 2009
Abacavir Hypersensitivity	Typical	Oct 8, 2009
Clopidogrel (Plavix®) Efficacy	Typical	May 7, 2009
Drinking, Smoking, and Risk of Esophageal Cancer new	Typical	Jan 14, 2010
Fluorouracil Toxicity	Typical	Oct 1, 2009
Pseudocholinesterase 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	

WGS Workflow




THE PRECISION MEDICINE INITIATIVE


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