

Genomic Medicine

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



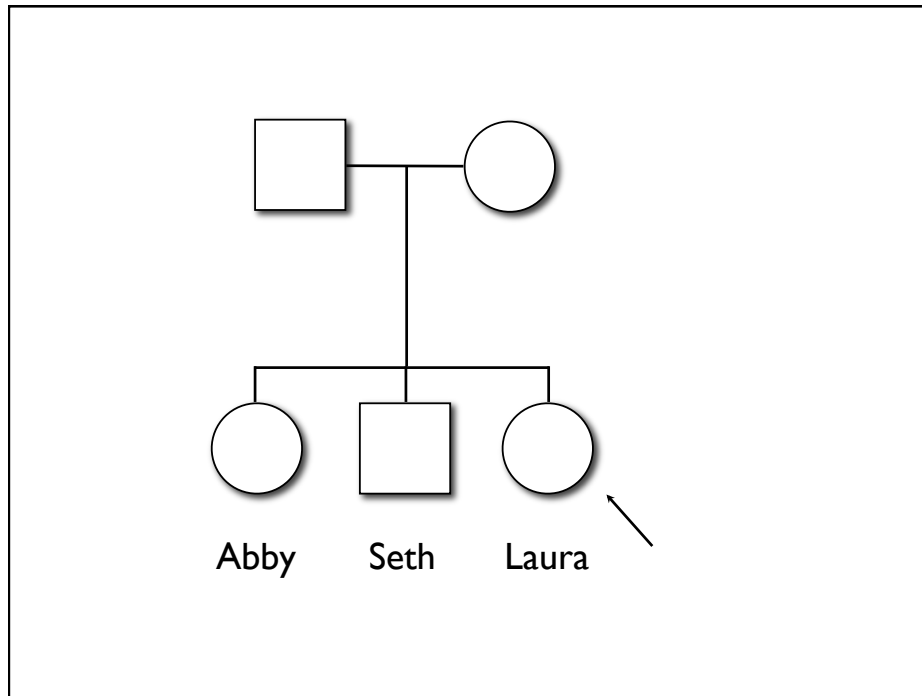
Current Topics in Genome Analysis 2014







Bruce R. Korf, MD, PhD

Financial Relationships

Illumina - consultant

Accolade - Medical Advisory Board member

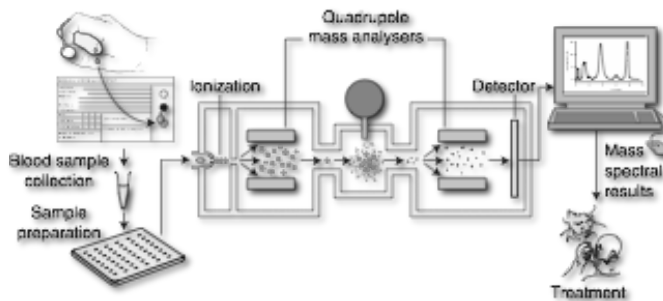
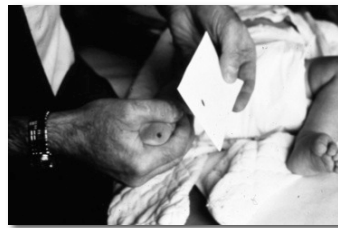


	Newborn Screening
	Diagnosis
	Preconceptional Screening
	Prenatal Diagnosis
	Presymptomatic Testing
	Predispositional Testing

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?



"We found an unex... portion of
literature-annotate... ions that were
incorrect, incomplete, or common polymorphisms."
NHGRI Newborn Screening Grants



Newborn Screening



Diagnosis



Preconceptional Screening



Prenatal Diagnosis



Presymptomatic Testing

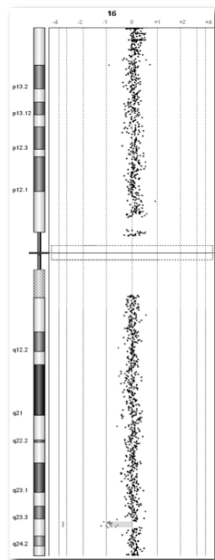


Predispositional Testing

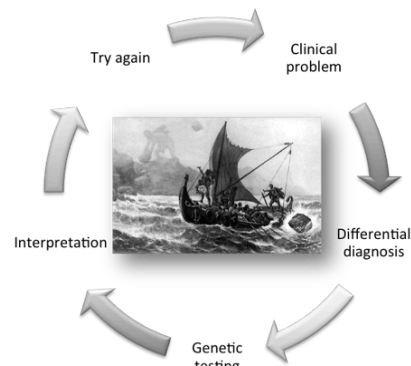
Diagnostic Testing



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. Murray, M.Sc., Jeffrey G. Reid, Ph.D., Matthew N. Bainbridge, Ph.D., Alicia Willis, Ph.D., Patricia A. Ward, M.S., Alicia Braston, M.S., Jake Beulien, Ph.D., Fan Xia, Ph.D., Zhiyi Niu, Ph.D., Matthew Harrison, 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 Soule, Ph.D., Ben Wang, Ph.D., Yan Ding, M.D., Sharon E. Flinn, 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/NEJMa1306555

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, PhD³, Wayne W. Grody, MD, PhD^{4,5}, Sarah S. Kalia, ScM, CGC⁶, Bruce R. Korf, MD, PhD⁷, Christi L. Martin, PhD, FACMG⁸, Amy McGuire, JD, PhD⁹, Robert L. Nussbaum, MD¹⁰, Julianne M. O'Daniel, MS, CGC¹¹, Kelly E. Ormond, MS, CGC⁷, Heidi L. Rehm, PhD, FACMG^{12,13}, Michael S. Watson, MS, PhD, FACMG¹⁴, Marc S. Williams, MD, FACMG¹⁵, Leslie G. Biesecker, MD¹⁶

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, TGFB2, SMAD3, ACTA2, MYLK, MYH11
Cardiomyopathy (Hypertrophic, 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

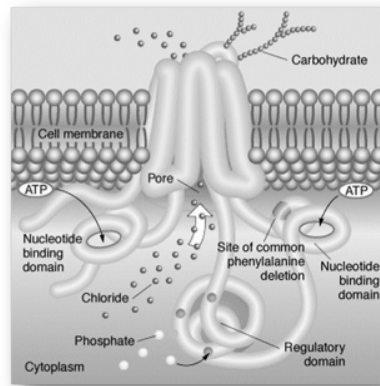
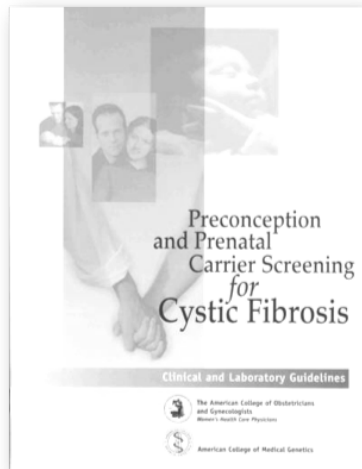
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Preconceptional Testing



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		
Cystic fibrosis		Cystic fibrosis
Canavan disease		
Familial dysautonomia		
Inquire: • Mucopolidosis IV • Niemann-Pick A • Fanconi anemia C • Bloom syndrome • Gaucher disease	Hemoglobinopathies	Spinal muscular atrophy

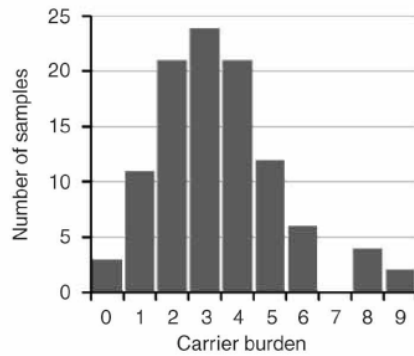
Genomic Carrier Screening

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,^{1*} Darrell L. Dinwiddie,^{1,2*} Neil A. Miller,^{1,2} Shi Elena E. Gerasova,¹ Joann Hudge,¹ Roy J. Langley,¹ Lu Zhan Faye D. Schilkey,¹ Vrunda Sheh,¹ Jimmy E. Woodward,¹ Hea Gary P. Schroth,¹ Ryan W. Kim,¹ Stephen F. Kingsmore^{1,2†}



Newborn Screening



Diagnosis



Preconceptional Screening



Prenatal Diagnosis



Presymptomatic Testing



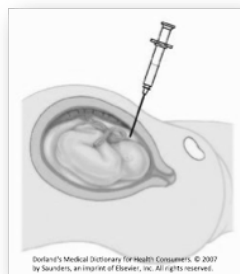
Predispositional Testing

Prenatal Testing

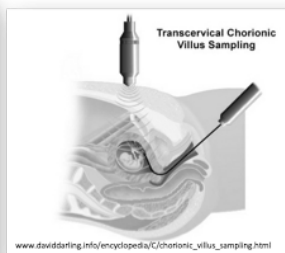


Laura and her Tom are indeed found to both be cystic fibrosis carriers. They elect to have prenatal diagnosis by amniocentesis at 16 weeks of pregnancy. The fetus is found to be a CF carrier.

Prenatal Diagnosis



amniocentesis



chorionic villus biopsy



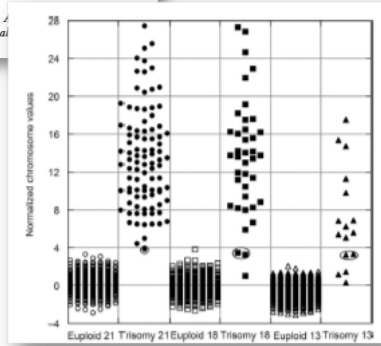
preimplantation diagnosis

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

Obstet Gynecol 2012;119:98-100
DOI: 10.1097/AOG.0b013e31824b402



Genomic Prenatal Diagnosis

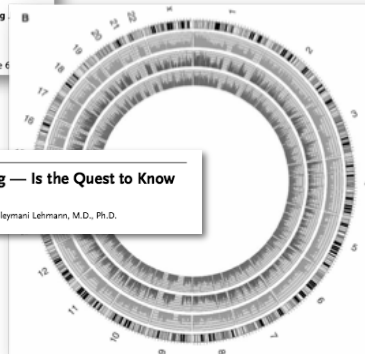
Maternal Plasma DNA Sequencing Reveals the Genome-Wide Genetic and Mutational Profile of the Fetus







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,¹ Tze K. Lau,³ Charles R. Cantor,⁴ Rossa W. K. Chiu^{1,2}

Published 8 December 2010; Volume 2 Issue 41 41a911
www.ScienceTranslationalMedicine.org 8 December 2010 Vol 2 Issue 41

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.

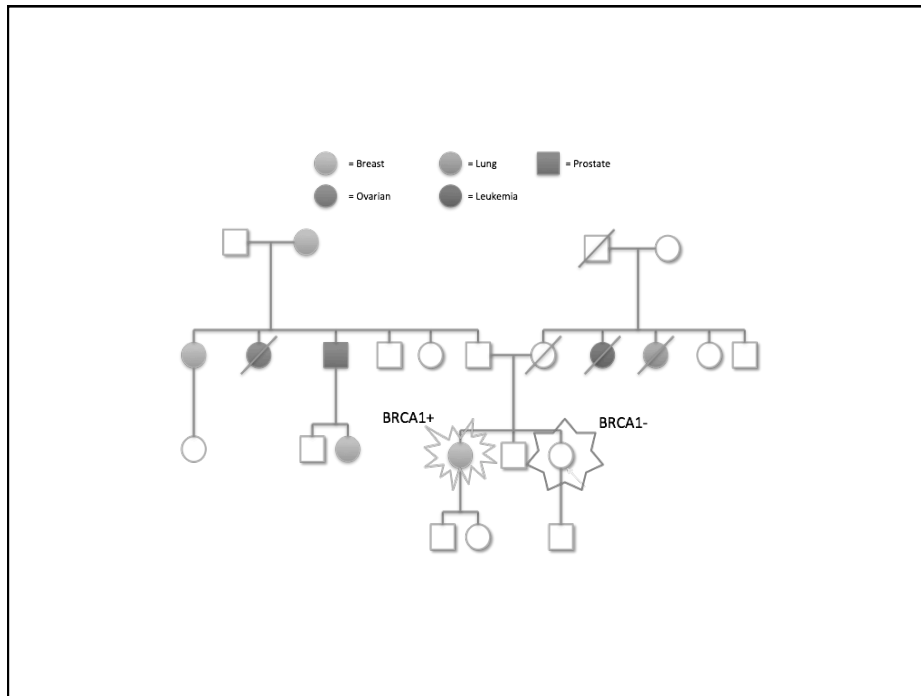


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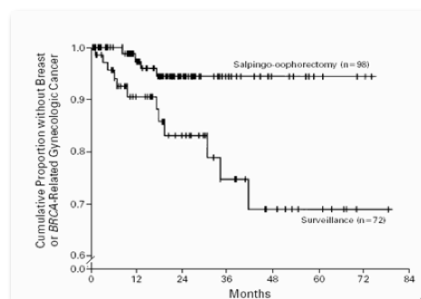
Presymptomatic Testing



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; 344:1064-1066, Apr 5, 2001.

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

Therapeutics: Rare Disease

ivacaftor

Potentiator

Corrector

A







Time Point	ivacaftor (N)	ivacaftor (Mean % Change)	Placebo (N)	Placebo (Mean % Change)
Day 15	83	~10	76	~0
Wk 8	83	~10	75	~0
Wk 16	81	~10	71	~0
Wk 24	80	~10	71	~0
Wk 32	79	~10	70	~0
Wk 40	79	~10	69	~0
Wk 48	77	~10	68	~0

The NEW ENGLAND JOURNAL of MEDICINE


ESTABLISHED IN 1812 NOVEMBER 3, 2011 VOL 363 NO 18

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

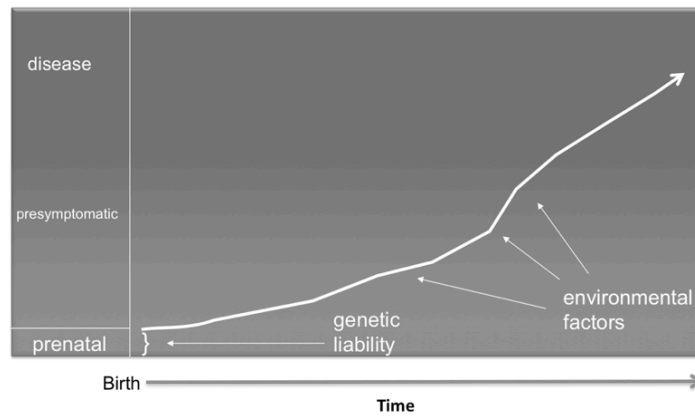
Borrie W. Ramsey, M.D., Jane Davies, M.D., M.B., Ch.B., N. Gerard McElvaney, M.D., Elizabeth Tullis, M.D., Scott C. Bell, M.B., B.S., M.D., Pavel Ojovinski, M.D., Matthias Griese, M.D., Edward F. McKone, M.D., Claire E. Wainwright, M.D., M.B., B.S., Michael W. Konstan, M.D., Richard Moss, M.D., Felix Ratjen, M.D., Ph.D., Isabelle Serrat-Casademunt, M.D., Ph.D., Steven M. Rowe, M.D., M.S.P.H., Quanning Dong, Ph.D., Sally Rodriguez, M.S., Kaili Yen, M.D., Claudia Ordóñez, M.D., and Stuart Elborn, M.D., for the V0808-770-102 Study Group

	Newborn Screening
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Predispositional Testing

	<p>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.</p>
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Genetic Prevention



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.

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 Navigerics. 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 tumours



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

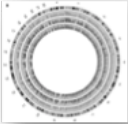
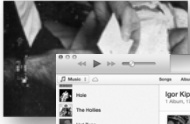

Bruce R. Korf MD, PhD, Anna B. Berry MD, Melvin Limson PhD, Ali J. Marian MD, Michael F. Murray MD, P. Pearl O'Rourke MD, Eugene R. Passamani MD, Mary V. Relling PharmD, John Tooker MD, MBA, Gregory J. Tsongalis PhD & Laura L. Rodriguez PhD

Affiliations | Corresponding author

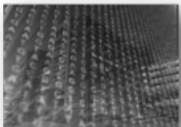


Genetics in Medicine (2014) | doi:10.1038/gim.2014.35
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WGS Workflow

When?

Prenatal  Newborn  Adulthood 

Where?

EHR  Cloud  Personal Device  Cell Nucleus 