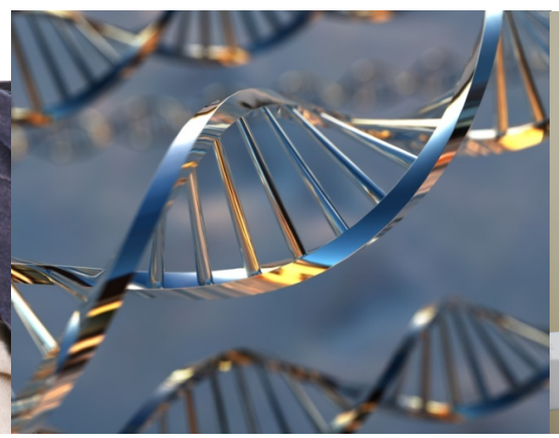
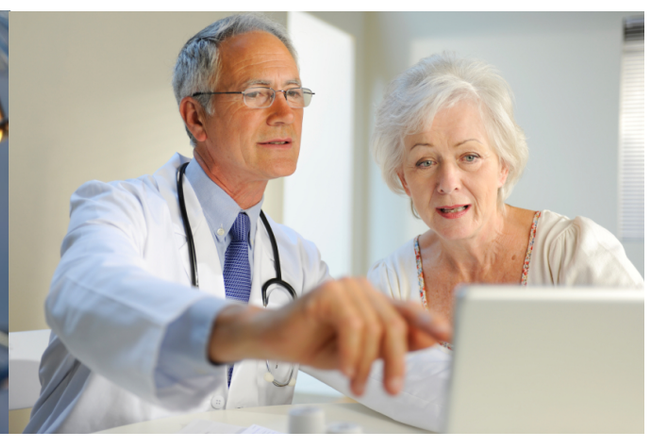
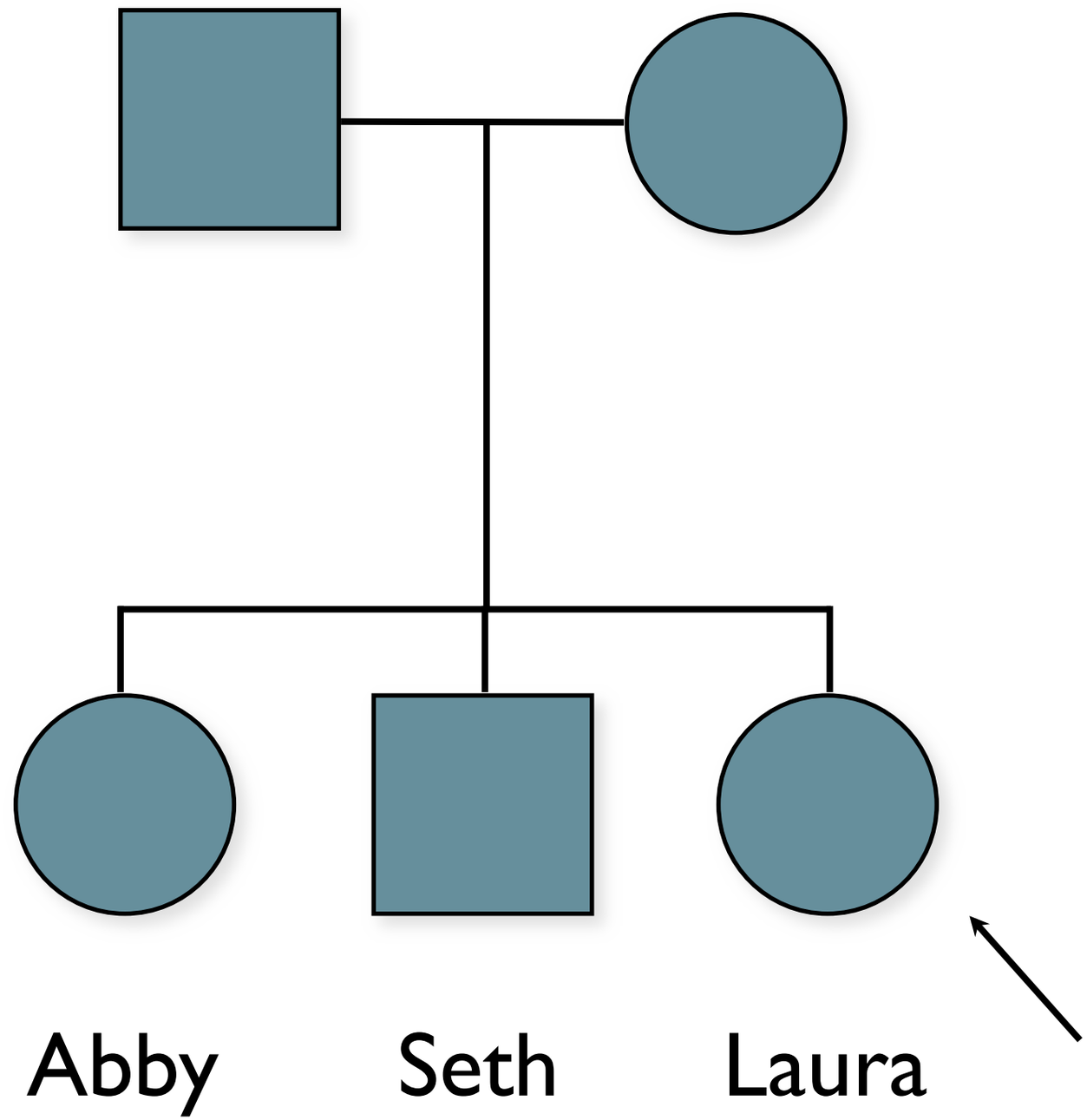
Genomic Medicine

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


Abby
Seth
Laura

Newborn Screening

Diagnosis

Preconceptional Screening

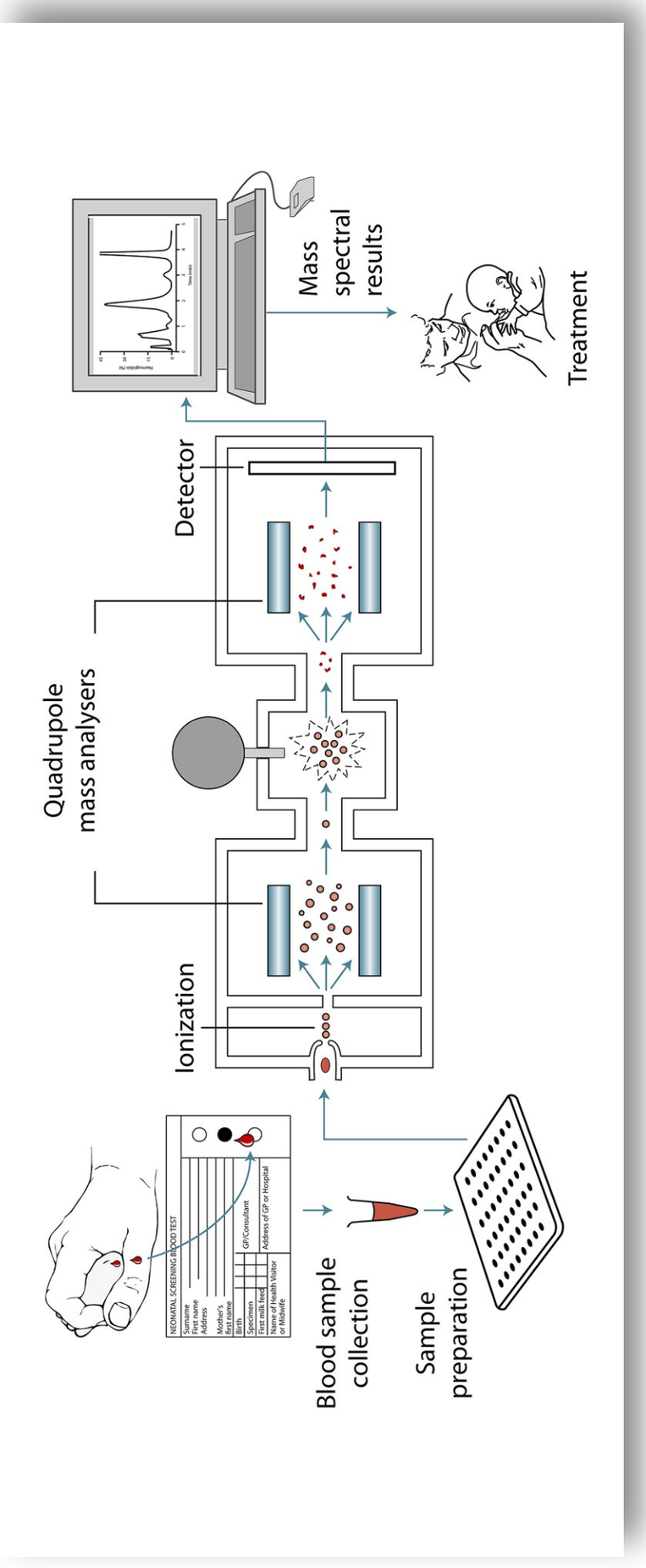
Prenatal Diagnosis

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.


Quadrupole mass analysers
Detector
Mass spectral results
Treatment
Ionization
NEONATAL SCREENING BLOOD TEST
Surname
First name
Address
Mother's first name
Birth
Specimen
First milk feed
Name of Health Visitor or Midwife
GP/Consultant
Address of GP or Hospital
Blood sample collection
Sample preparation

Genomic Newborn Screening

Newborn Screening

Diagnosis

Preconceptional Screening

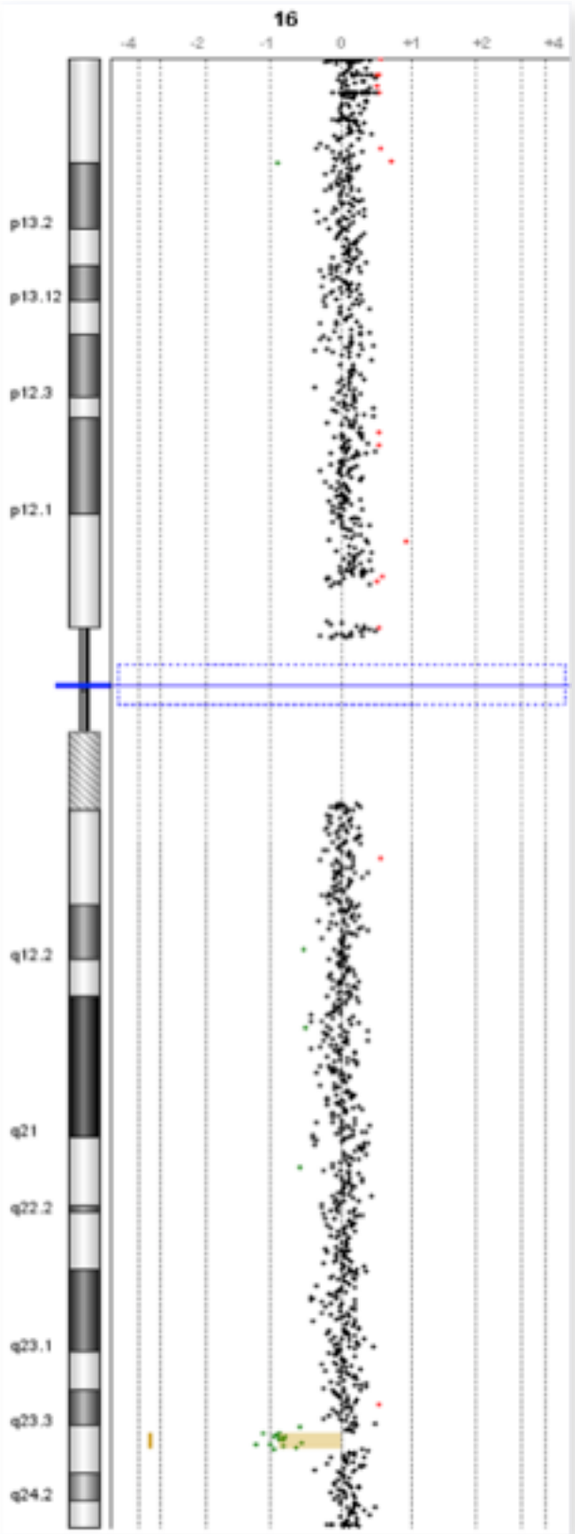
Prenatal Diagnosis

Presymptomatic Testing

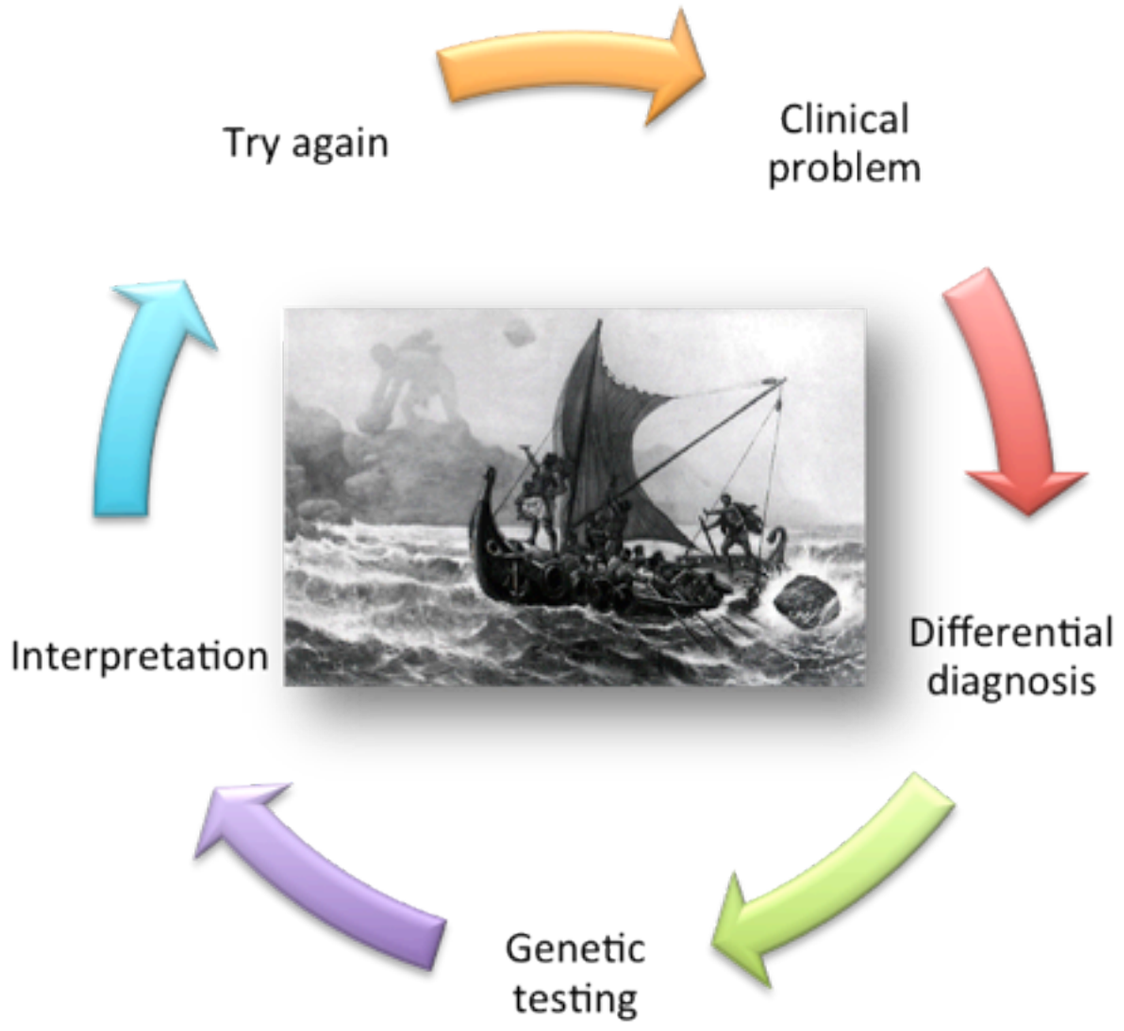
Predispositional Testing

Diagnostic Testing

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


16
-4
-2
-1
0
+1
+2
+4
p13.2
p13.12
p12.3
p12.1
q12.2
q21
q22.2
q23.1
q23.3
q24.2

The Diagnostic Odyssey



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.

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

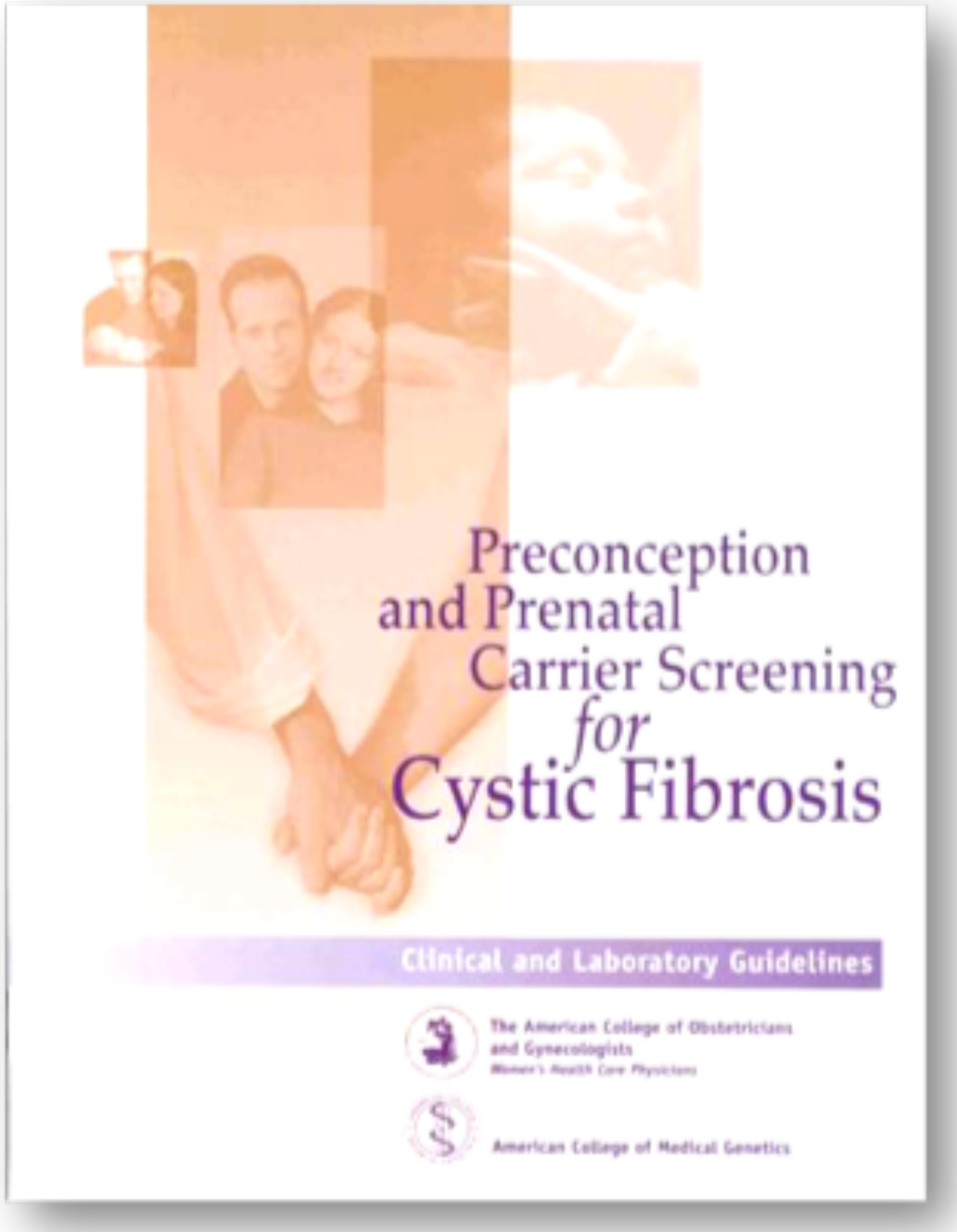
Presymptomatic Testing

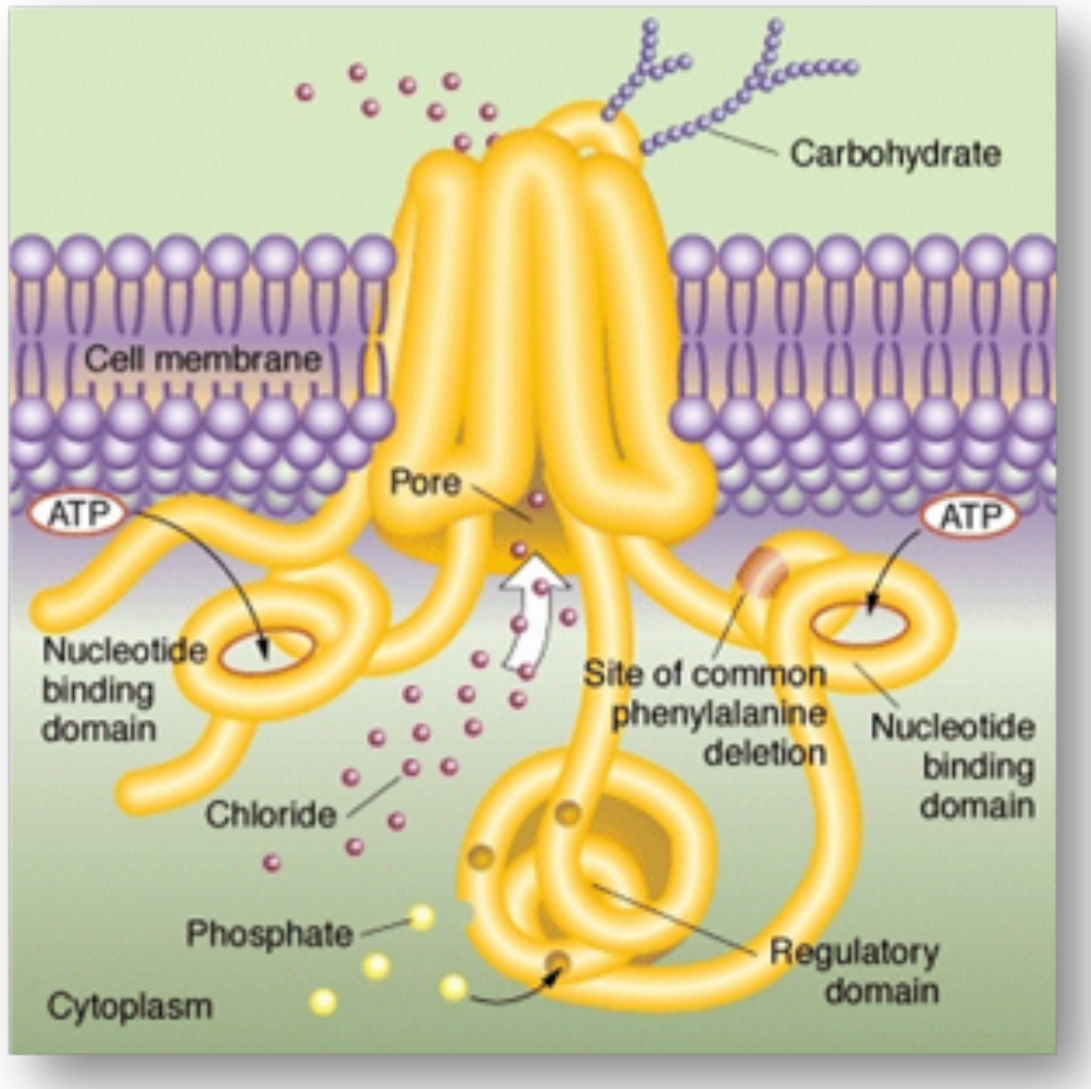
Predispositional Testing

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.

CF Carrier Screening





Ashkenzi Jewish

- Tay-Sachs disease
- Cystic fibrosis
- Canavan disease
- Familial dysautonomia
- Inquire:
  - Mucolipidosis IV
  - Niemann-Pick A
  - Fanconi anemia C
  - Bloom syndrome
  - Gaucher disease

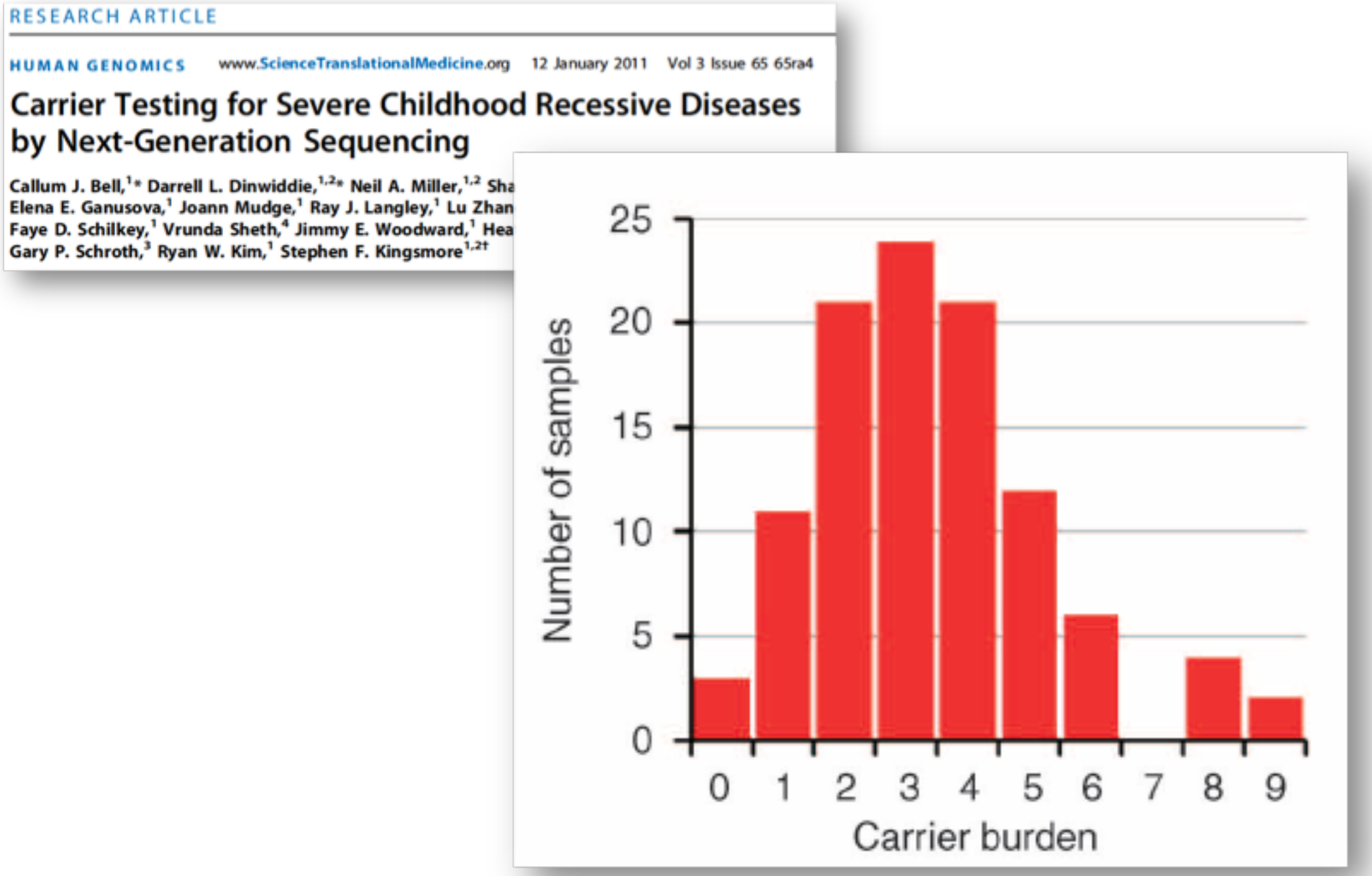
African/Asian/ Mediterranean

- Hemoglobinopathies

Panethnic

- Cystic fibrosis
- 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] Sha
Elena E. Ganusova,[1] Joann Mudge,[1] Ray J. Langley,[1] Lu Zhan
Faye D. Schilkey,[1] Vrunda Sheth,[4] Jimmy E. Woodward,[1] Hea
Gary P. Schroth,[3] Ryan W. Kim,[1] Stephen F. Kingsmore[1,2†]

Newborn Screening

Diagnosis

Preconceptional Screening

Prenatal Diagnosis

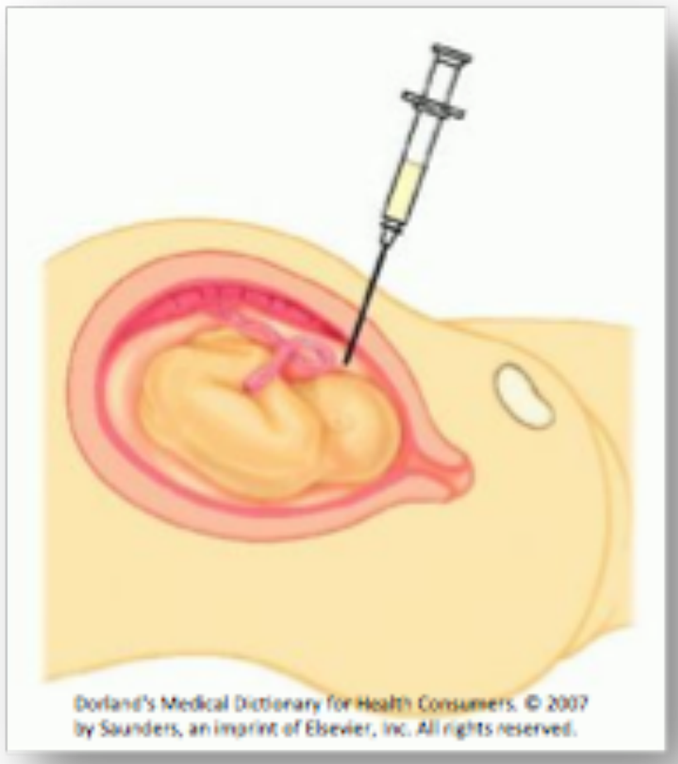
Presymptomatic Testing

Predispositional Testing

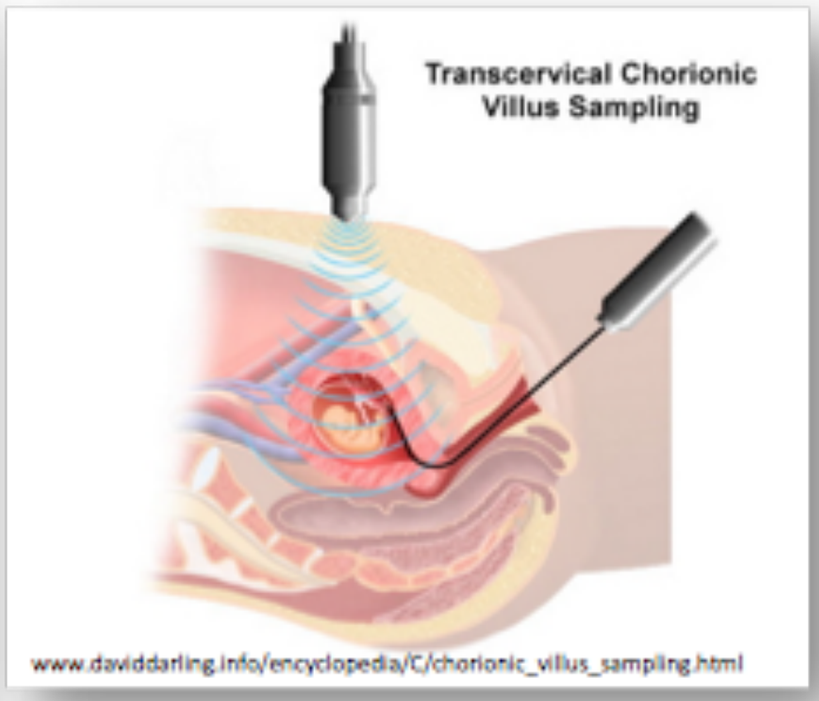
Prenatal Testing

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

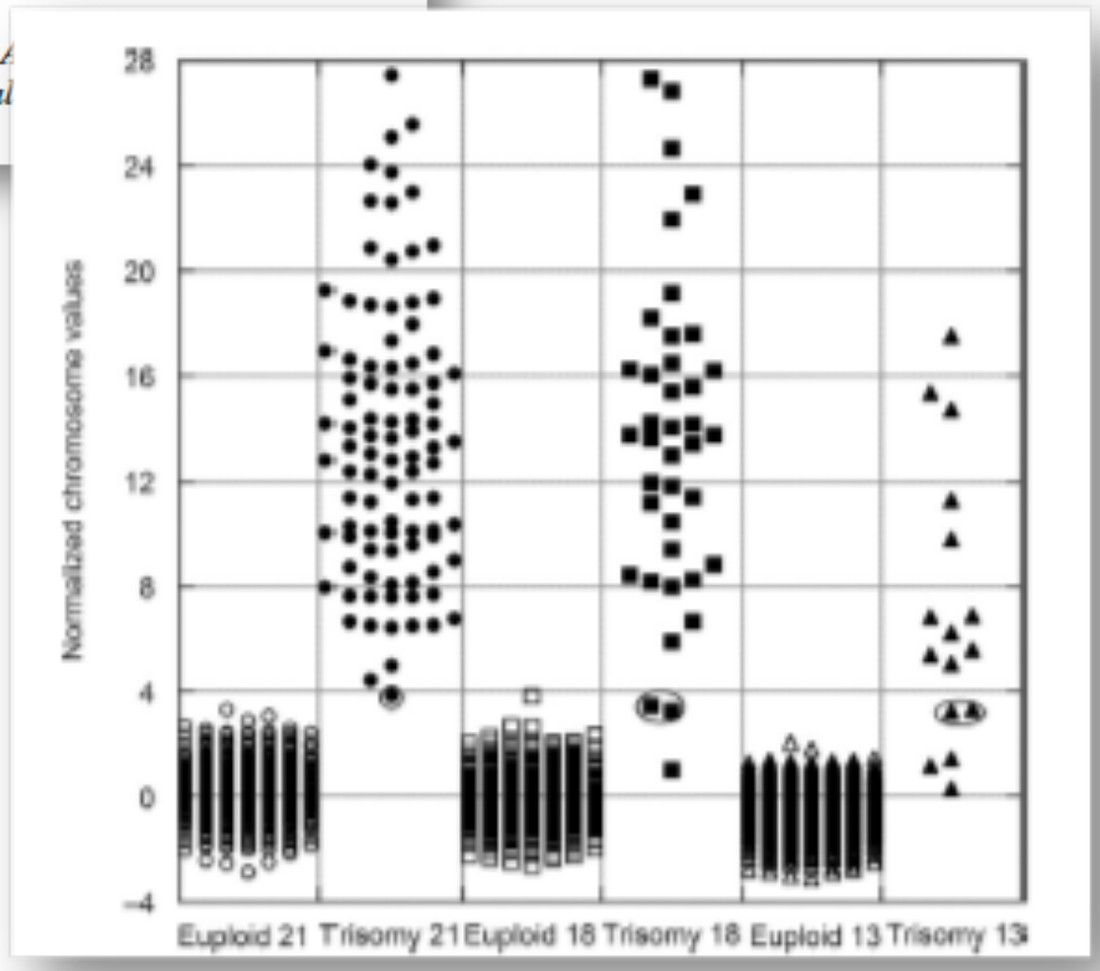
preimplantation diagnosis

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, 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



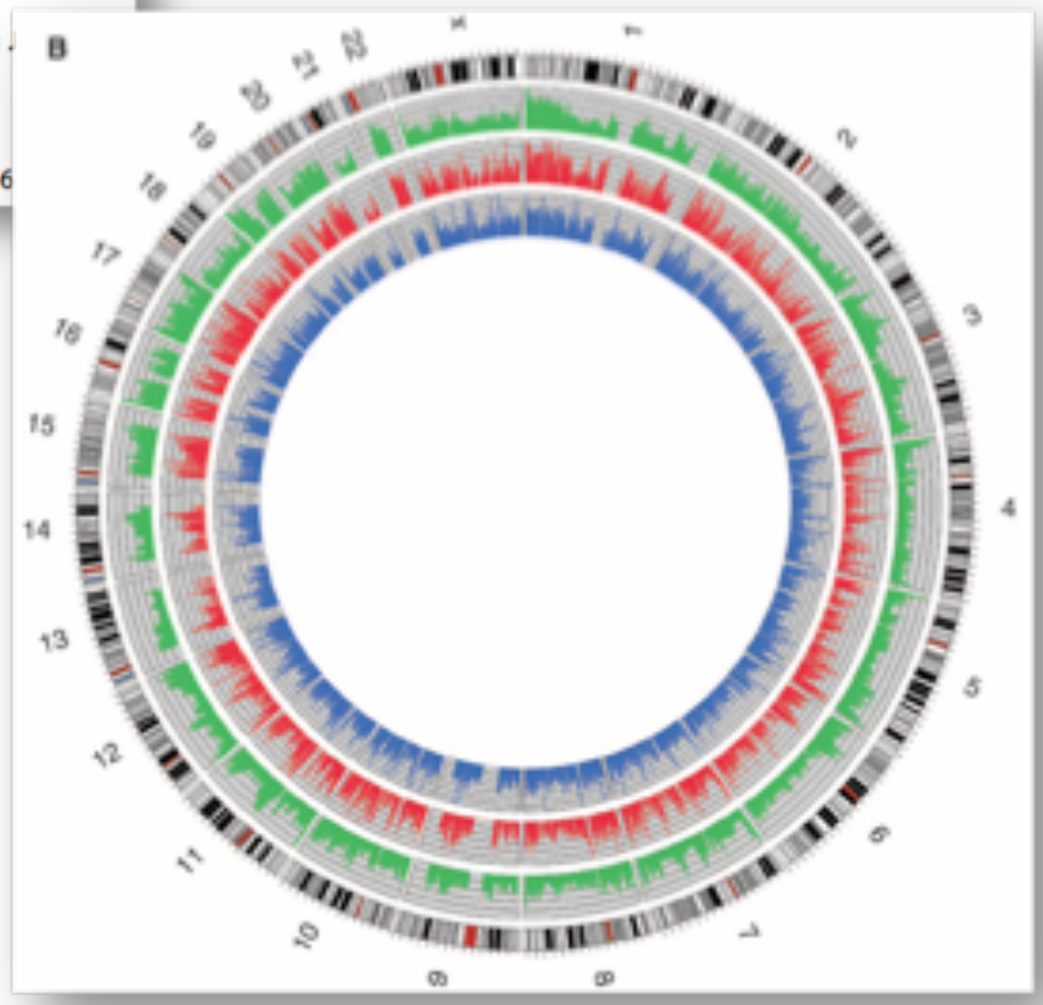
Genomic Prenatal Diagnosis

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



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.

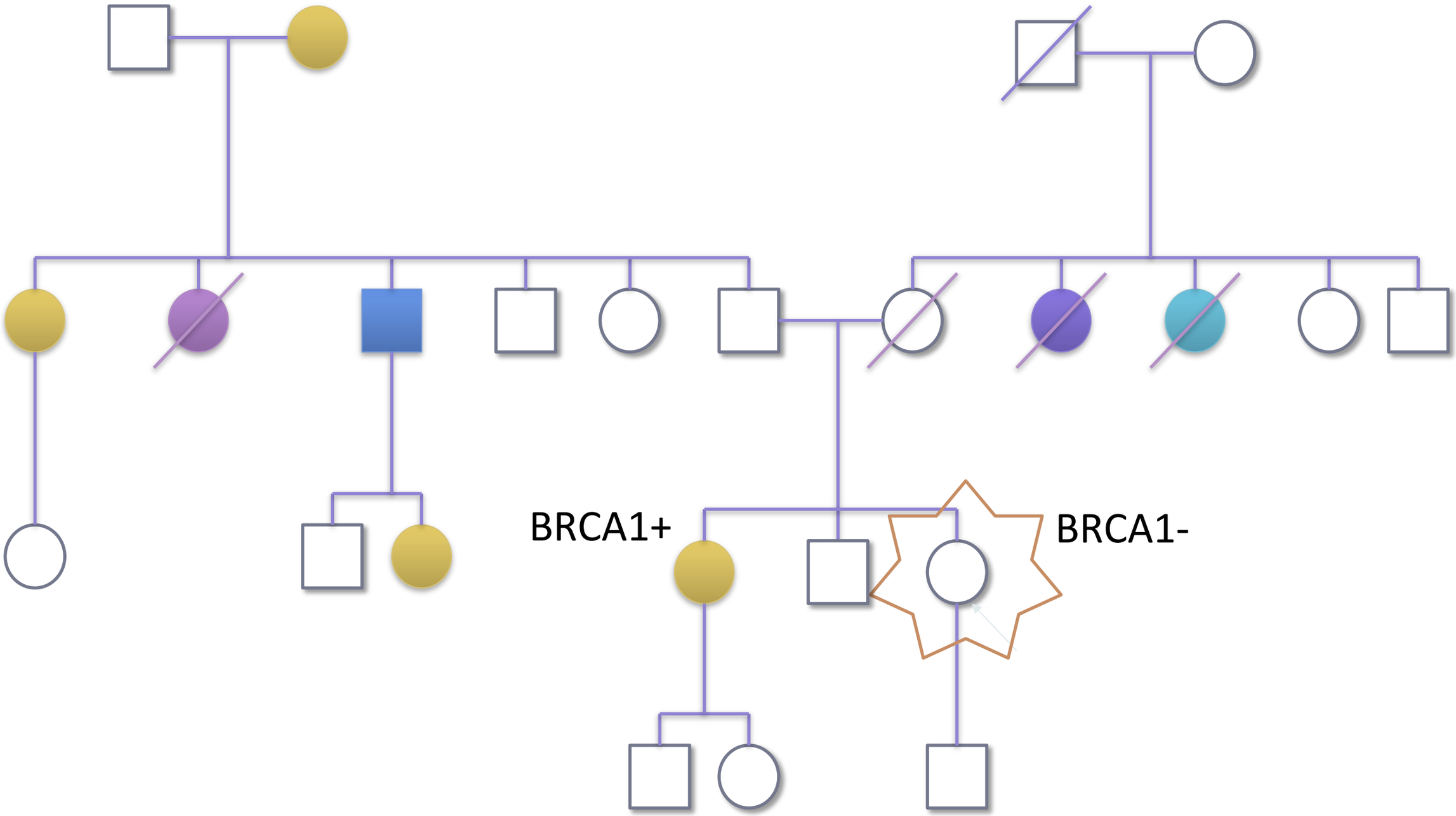
= Breast

= Lung

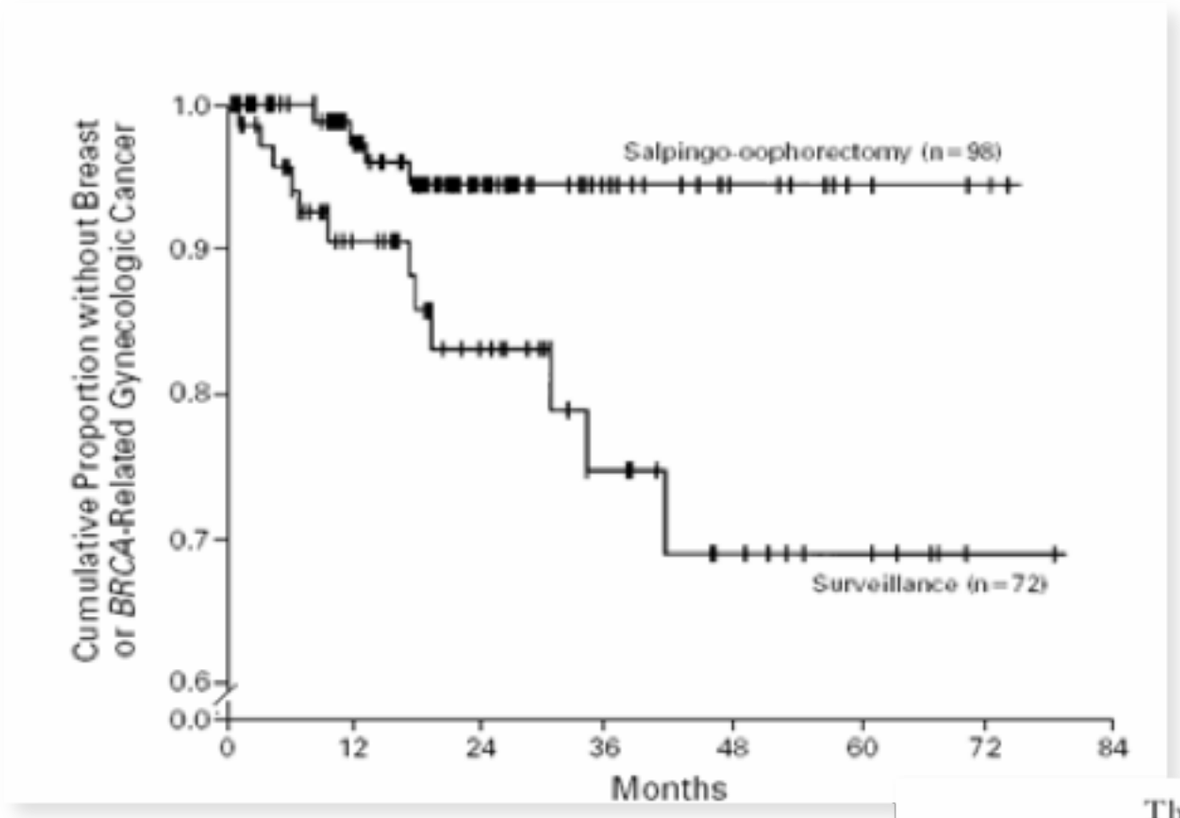
= Prostate

= Ovarian

= Leukemia



Breast Cancer Prevention




The New England
Journal of Medicine

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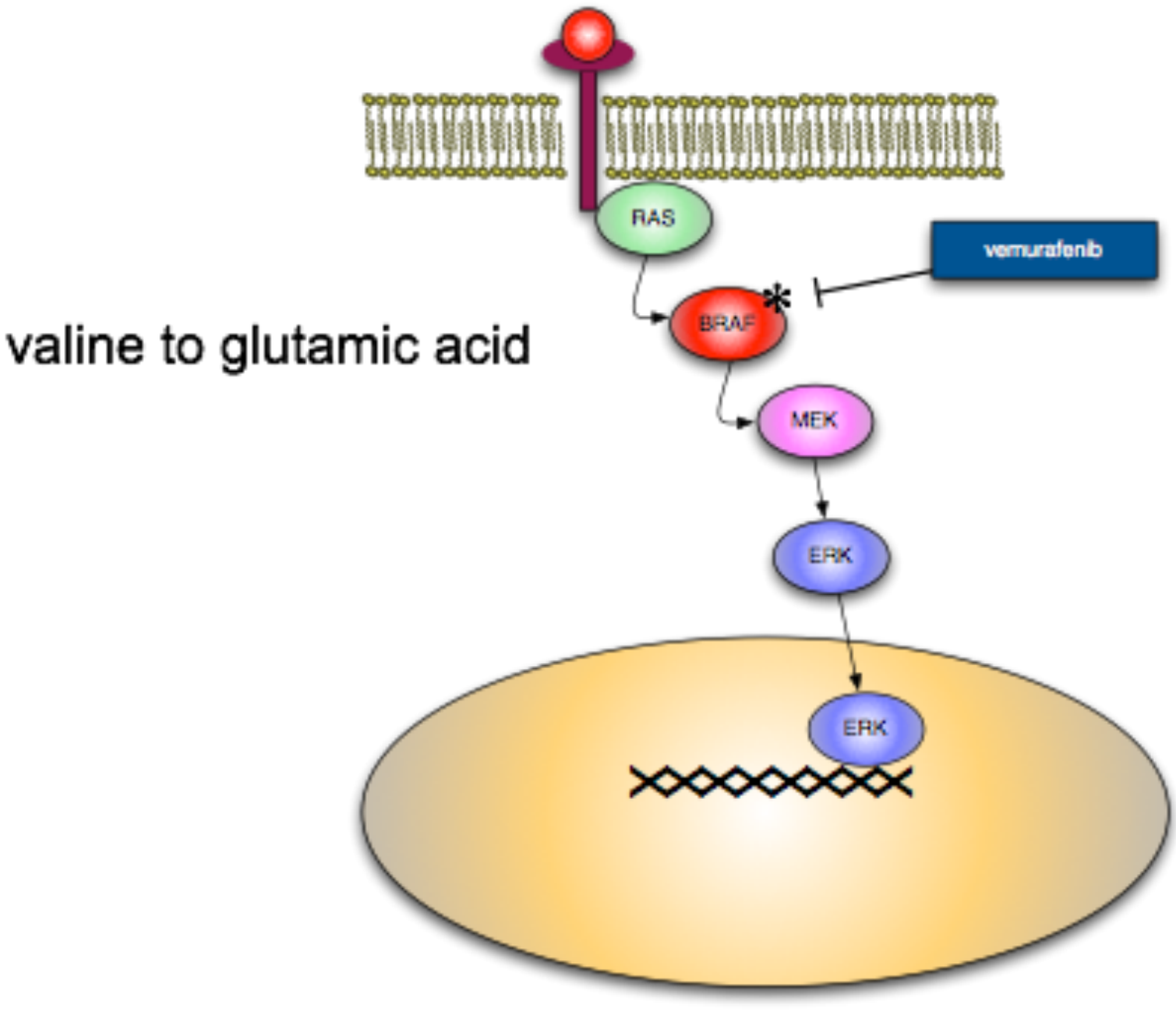
VOLUME 346 MAY 23, 2002 NUMBER 21

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

Noah D. Kauff, M.D., Jada M. Satagopan, Ph.D., Mark E. Robson, M.D., Lauren Scheuer, M.S., Martee Hensley, M.D., Clifford A. Hudis, M.D., Nathan A. Ellis, Ph.D., Jeff Boyd, Ph.D., Patrick I. Borgen, M.D., Richard R. Barakat, M.D., Larry Norton, M.D., and Kenneth Offit, M.D., M.P.H.

Therapeutics

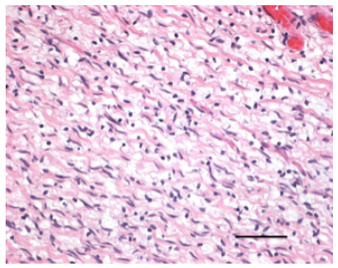


valine to glutamic acid

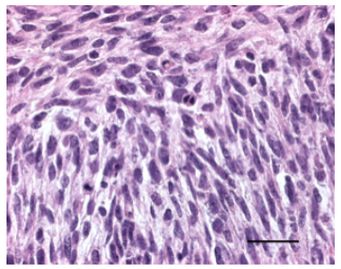
melanoma

Cancer Genomes

Normal

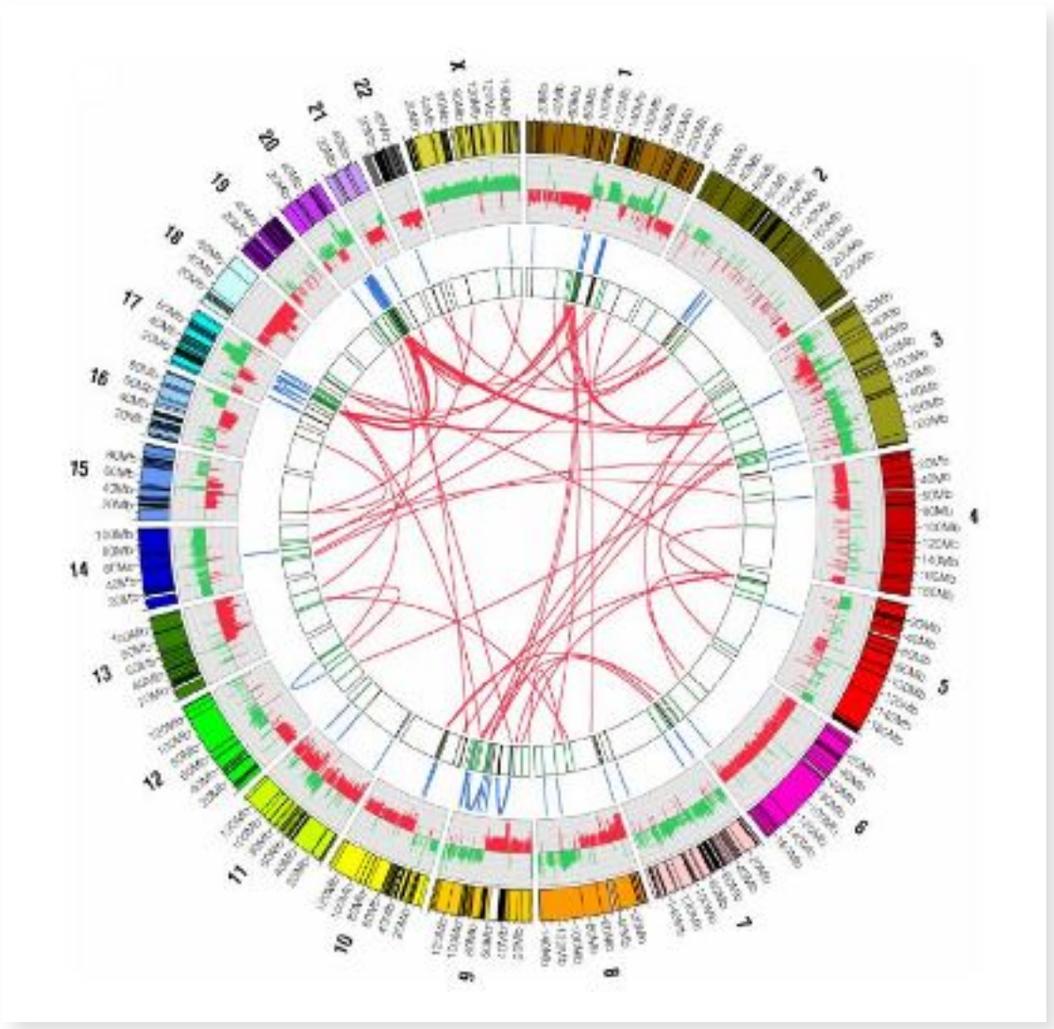


Tumor



Sequence

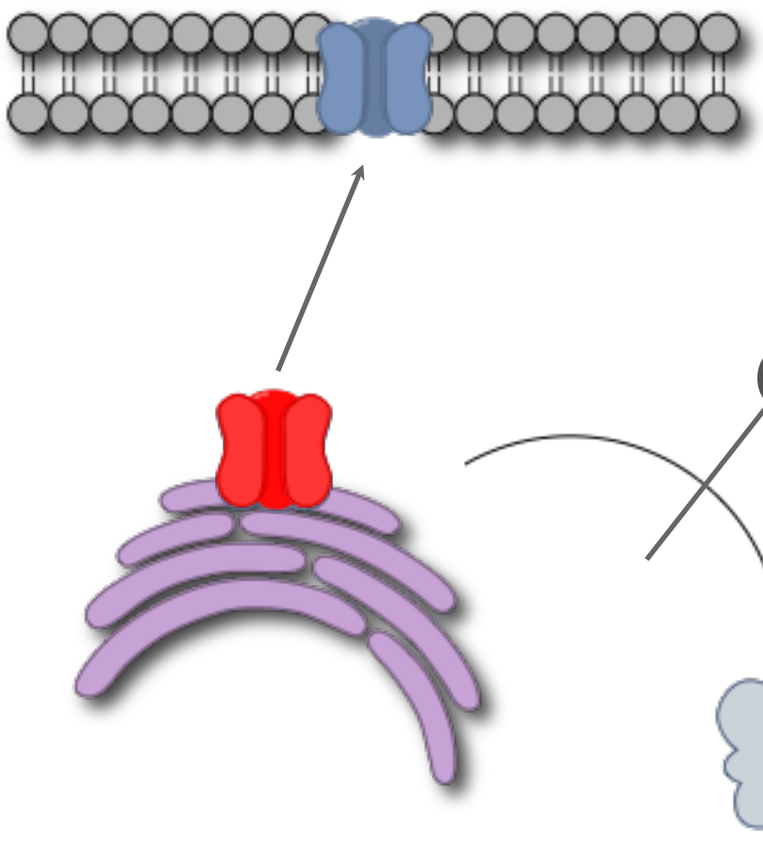
Difference =
cancer-specific genetic
changes



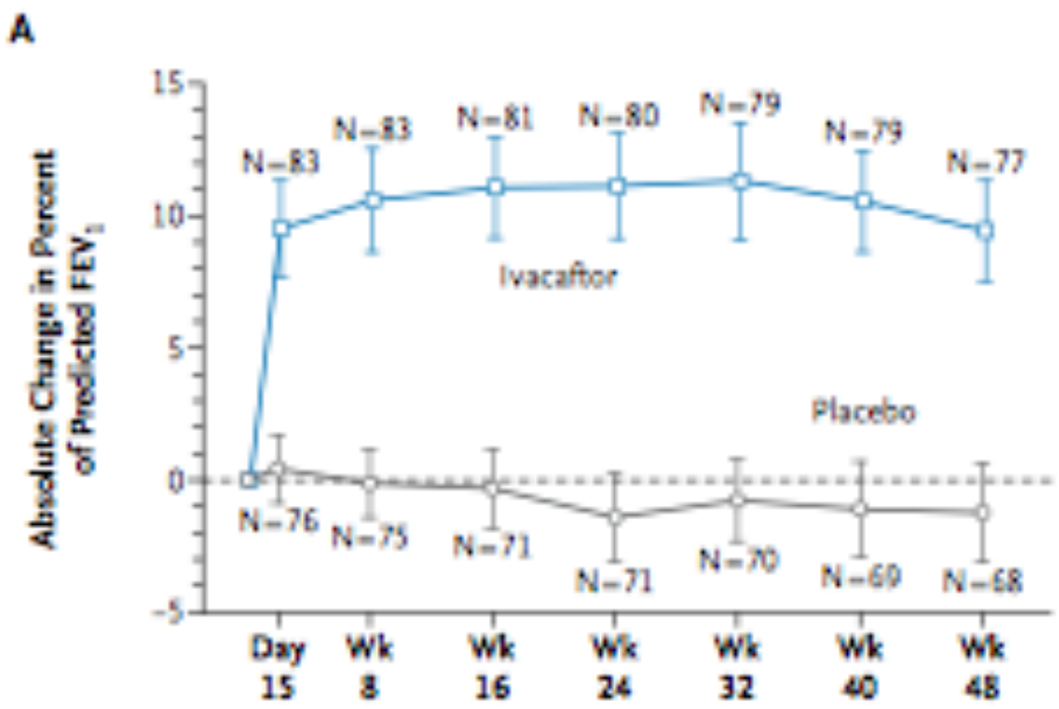
Treatment of Genetic Disease

ivacaftor

Potentiator



Corrector



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 3, 2011 VOL. 365 NO. 18

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., Qunming 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

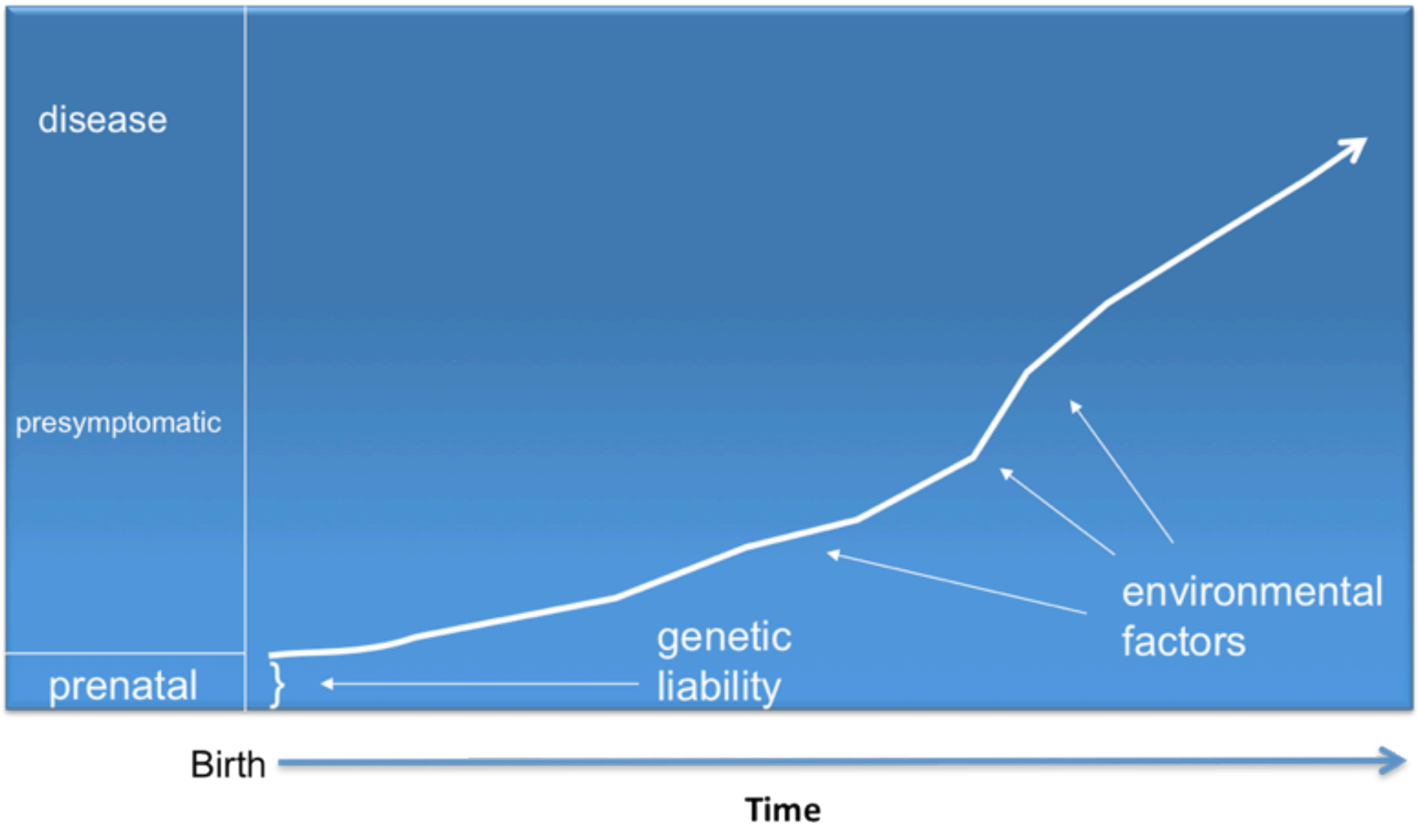
Presymptomatic Testing

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

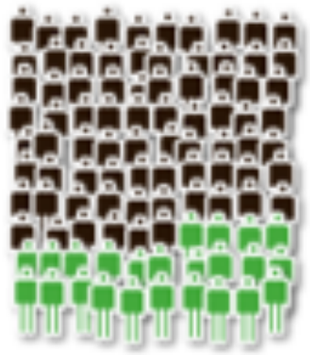


Direct-to-Consumer Testing

Your Genetic Data

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

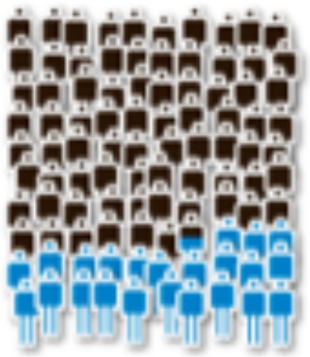
Where's mine?



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

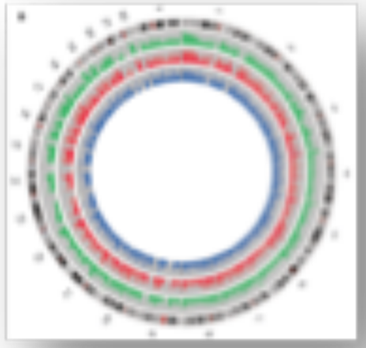
Name	Status	Last Updated
Warfarin (Coumadin®) Sensitivity	Increased	Mar 19, 2009
Abacavir Hypersensitivity	Typical	Oct 8, 2009
Clopidogrel (Plavix®) Efficacy	Typical	May 7, 2009
Drinking, Smoking, and Risk of Esophageal Cancer new	Typical	Jan 14, 2010
Fluorouracil Toxicity	Typical	Oct 1, 2009
Pseudocholinesterase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

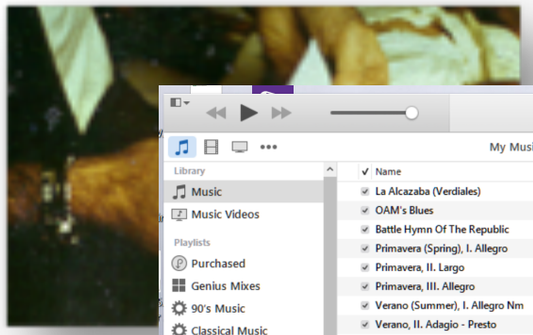
23andMe Name	Genotype	Combination
rs1799853	CC	
rs1057910	AA	CYP2C9 *1/*1, VKORC1 -1639/3673 AG
rs9923231	CT	

WGS Workflow

When?



Prenatal



New

Adulthood

Where?

EHR

Cloud

Personal Device

Cell Nucleus

- … point-of-care decision support tools may guide clinical use …

- … but a health provider should be able to explain why, not only what and how

SPECIAL ARTICLE | Genetics inMedicine

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[1], Anna B. Berry, MD[2,3], Melvin Limson, PhD[4], Ali J. Marian, MD[5], Michael F. Murray, MD[6], P. Pearl O'Rourke, MD[7], Eugene R. Passamani, MD[8], Mary V. Relling, PharmD[9], John Tooker, MD, MBA[10], Gregory J. Tsongalis, PhD[11,12] and Laura L. Rodriguez, PhD[8]

Completion of the Human Genome Project, in conjunction with dramatic reductions in the cost of DNA sequencing and advances in translational research, is gradually ushering genomic discoveries and technologies into the practice of medicine. The rapid pace of these advances is opening up a gap between the knowledge available about the clinical relevance of genomic information and the ability of clinicians to include such information in their medical practices. This educational gap threatens to be rate limiting to the clinical adoption of genomics in medicine. Solutions will require not only a better understanding of the clinical implications of genetic discoveries but also training in genomics at all levels of professional development, including for individuals in formal training and others who long ago completed such training. The National Human Genome Research Institute has convened the Inter-Society Coordinating Committee for Physician Education in Genomics (ISCC) to develop and share best practices in the use of genomics in medicine. The ISCC has developed a framework for development of genomics practice competencies that may serve as a starting point for formulation of competencies for physicians in various medical disciplines.

Genet Med advance online publication 24 April 2014

Key Words: competencies; education; genomic medicine; genomics

The promise of genomics to maintain health, facilitate diagnosis, and cure or mitigate disease is dependent on the skillful translation of genomic science into meaningful action at the bedside and in the clinic.[1,2] Surveys of both primary-care and specialist physicians, often by their professional societies, reveal unease, and even unwillingness, to use genomic data.[3,4] The use of genomics in caring for patients with certain cancers and for some pediatric patients is increasing in routine diagnosis and treatment, and this trend is likely to expand to other areas of medical practice in the coming years.[5,6]

Nearly half of practicing clinicians in the United States are more than 50 years of age; medical school and residency training for these physicians occurred before the completion of the Human Genome Project and the breakthrough advances in genomic medicine.[7] Current trainees are faced with a rate of progress in genomics that renders much of what they have learned out of date by the time they enter practice. Considering this rapid rate of change, substantial reductions in the cost of genome sequencing, and the increasing relevance of genomic information to the practice of medicine, the barriers to implementing genomic discoveries within medical practice have to be overcome. Moreover, misuse of genomics by untrained health-care providers may incur cost without advantage and may result in harm to patients based on inaccurate diagnosis or use of unnecessary or incorrect tests.

The National Human Genome Research Institute, together with 23 professional societies, 15 other institutes at the National Institutes of Health, and other organizations interested in physician education, developed the Inter-Society Coordinating Committee for Physician Education in Genomics (ISCC) in the spring of 2013 (see **Supplementary Data S1** online). ISCC member organizations focus on physician training, starting with medical school matriculation and continuing through residency and fellowship, for active clinicians.[8] The ISCC seeks to "improve genomic literacy of physicians and other practitioners and to enhance the practice of genomic medicine through sharing of educational approaches and joint identification of educational needs." The ISCC developed four working groups: Genomic Medicine Competencies, Educational Products, Use Cases, and Specialty Boards (see **Supplementary Data S1** online).

The Genomic Medicine Competencies Working Group was charged with the development of a framework whereby

[1]Department of Genetics, University of Alabama at Birmingham, Birmingham, Alabama, USA; [2]CellNetix Pathology & Laboratories, Swedish Cancer Institute, Seattle, Washington, USA; [3]Department of Pathology, University of California, San Francisco, San Francisco, California, USA; [4]Association for Molecular Pathology, Bethesda, Maryland, USA; [5]Center for Cardiovascular Genetics, University of Texas Health Sciences Center, Houston, Texas, USA; [6]Genomic Medicine Institute, Geisinger Health System, Danville, Pennsylvania, USA; [7]Partners HealthCare System, Boston, Massachusetts, USA; [8]National Human Genome Research Institute, Bethesda, Maryland, USA; [9]Department of Pharmaceutical Sciences, St Jude Children's Research Hospital, Memphis, Tennessee, USA; [10]American College of Physicians, Philadelphia, Pennsylvania, USA; [11]American Association for Clinical Chemistry, Washington, DC, USA; [12]Department of Pathology, Geisel School of Medicine at Dartmouth, Dartmouth Hitchcock Medical Center and Norris Cotton Cancer Center, Lebanon, New Hampshire, USA. Correspondence: Bruce R. Korf (bkorf@uabmc.edu)

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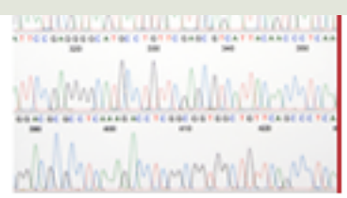

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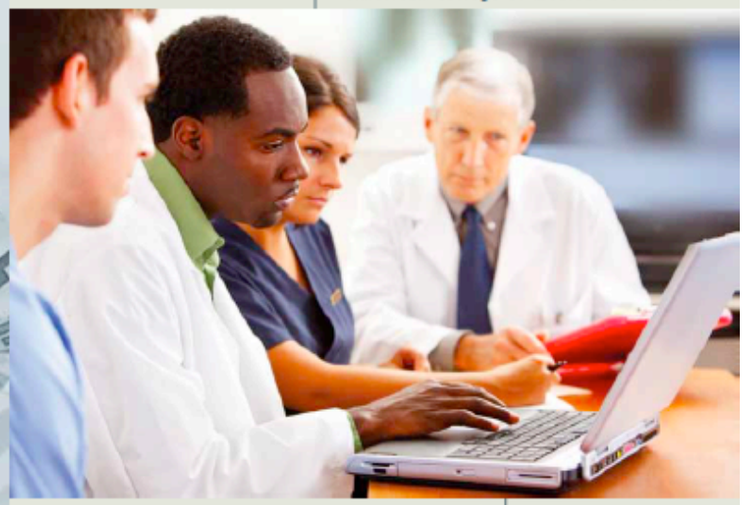

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