Requisite Knowledge and Skill Sets for Large-Scale Genomic Data Utilization

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Background

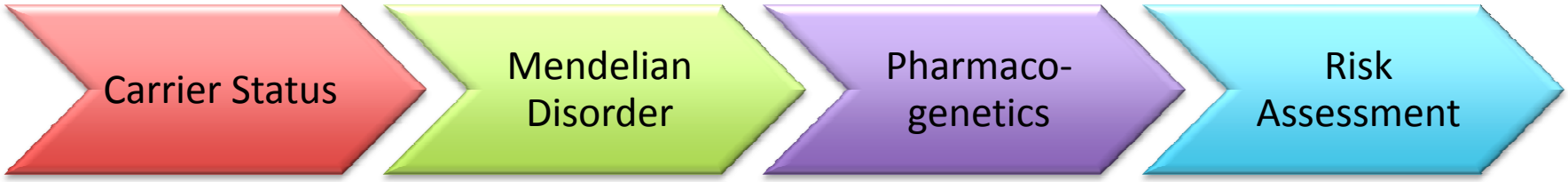
- Premises
  - Sequencing technology will advance enough to produce clinically meaningful results
  - Whole genome sequencing will be cost-effective and comparable to other diagnostic tests
- Questions
  - What are the necessary knowledge and skill sets required for analyzing, interpreting, and utilizing genomic information? From a laboratory perspective? From a clinical perspective?
  - Given the range of skills needed to turn genomic information into clinically actionable medical practice, what are the training needs for an individual and what is not being addressed?
  - What is needed to translate genomic information from the lab to the provider? Will collaborative medicine be needed to interpret genomic information?

But first…

- What can be learned from WGS that will contribute to medical care?
- How will WGS be incorporated into the clinical workflow?

Whole Genome Sequencing

Germline Sequencing



Tissue Sequencing

Carrier Testing

Table 3 | SNPs matching HGMD mutations causing disease or other phenotypes

HGMD accession	Chromosome	Coordinate	HUGO symbol	Gene name	Cytogenetic	Phenotype	Zygosity
CM003589	1	97937679	DPYD	Dihydropyrimidine dehydrogenase	1q22	Dihydropyrimidine dehydrogenase deficiency	Heterozygous
CM950484	1	157441978	FY	Duffy blood-group antigen	1q	Duffy blood group antigen, absence	Homozygous*
CM942034	4	619702	PDE6B	Phosphodiesterase 6B, cGMP-specific, rod, beta	4p16.3	Retinitis pigmentosa 40	Heterozygous
CM021718	9	36208221	GNE	UDP-N-acetylglucosamine 2-epimerase	9p	Myopathy, distal, with rimmed vacuoles	Heterozygous
CM980633	10	50348375	ERCC6	Excision repair cross-complementing rodent repair deficiency, complementation group 6 protein (CSB)	10q	Cockayne syndrome	Homozygous†
CM050716	11	76531431	MYO7A	Myosin VIIA	11q13.5	Usher syndrome 1b	Homozygous†
CM950928	12	46812979	PFKM	Phosphofructokinase, muscle	12q13.3	Glycogen storage disease 7	Homozygous*
CM032029	14	20859880	RPGRIP1	Retinitis pigmentosa GTPase regulator interacting protein 1	14q11	Cone–rod dystrophy	Heterozygous
CM984025	19	18047618	IL12RB1	Interleukin-12 receptor, beta 1	19p13.1	Mycobacterial infection	Heterozygous
CM024138	19	41014441	NPHS1	Nephrosis-1, congenital, Finnish type	19q	Congenital nephrotic syndrome, Finnish type	Heterozygous
CM910052	22	49410905	ARSA	Arylsulphatase A	22q	Metachromatic leukodystrophy	Heterozygous

nature Vol 452|17 April 2008|doi:10.1038/nature06884

LETTERS

The complete genome of an individual by massively parallel DNA sequencing

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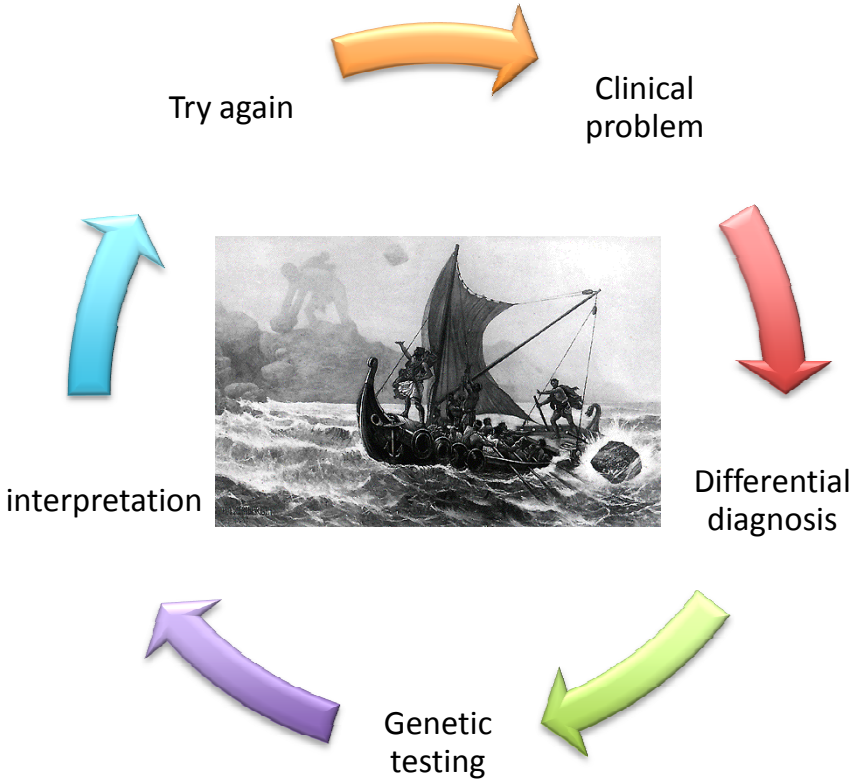
Mendelian Disorders



Making a definitive diagnosis: Successful clinical application of whole exome sequencing in a child with intractable inflammatory bowel disease

Elizabeth A. Worthey, PhD[1,2], Alan N. Mayer, MD, PhD[2,3], Grant D. Syverson, MD[2], Daniel Helbling, BSc[1], Benedetta B. Bonacci, MSc[2], Brennan Decker, BSc[1], Jaime M. Serpe, BSc[2], Trivikram Dasu, PhD[2], Michael R. Tschannen, BSc[1], Regan L. Veith, MSc[2], Monica J. Basehore, PhD[4], Ulrich Broeckel, MD, PhD[1,2,3], Aoy Tomita-Mitchell, PhD[1,2,3], Marjorie J. Arca, MD[3,5], James T. Casper, MD[2,3], David A. Margolis, MD[2,3], David P. Bick, MD[1,2,3], Martin J. Hessner, PhD[1,2], John M. Routes, MD[2,3], James W. Verbsky, MD, PhD[2,3], Howard J. Jacob, PhD[1,2,3,6], and David P. Dimmock, MD[1,2,3]

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

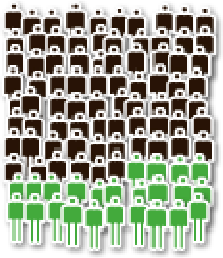
The genotyping services of 23andMe are performed in LabCorp's CLIA-certified laboratory. The tests have not been cleared or approved by the FDA but have been analytically validated according to CLIA standards.

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

Your Genetic Data

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

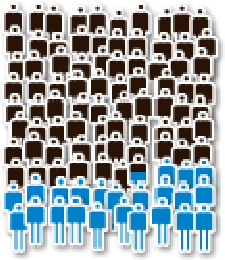
Where's mine?



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.

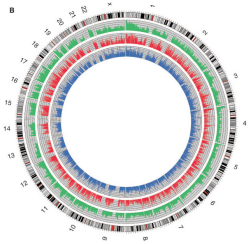
Genes vs. Environment

26 %
Attributable to Genetics

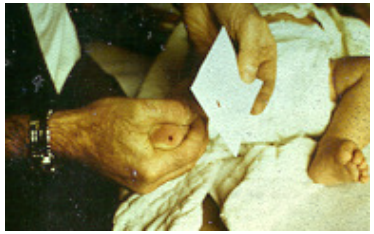
The heritability of type 2 diabetes is estimated to be 26%. This means that environmental factors contribute more to differences in risk for this condition than genetic factors. Genetic factors that play a role in type 2 diabetes include both unknown factors and known factors such as the SNPs we describe 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)

WGS Workflow

When?



Prenatal



Newborn screen

Childhood

Adulthood

Where?

EHR

Cloud

Personal Device

Cell Nucleus

What are the necessary knowledge and skill sets required for analyzing, interpreting, and utilizing genomic information?

- Focus on competencies, not knowledge …
  - … 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

Non-Specialist Health Provider Competencies for WGS

- Explain the concept of carrier status and provide referral to a genetic counselor.
- Recognize indications for cytogenomic testing and WGS in diagnostic evaluation and order tests as appropriate.
- Use pharmacogenetic data to guide choice of medication and dosage.
- Formulate an individualized management plan to mitigate risks of chronic disease.
- Refine differential diagnosis based on genomic tests for disease susceptibility.

Laboratory Geneticist Competencies for WGS

- Use bioinformatic tools and databases to interpret results of WGS.
- Annotate genomic data in light of phenotypic information.
- Provide point-of-care tools and information to guide clinical decision-making.
- Interpret genomic data for use by clinicians.

What are the training needs for an individual and what is not being addressed?

- Need to establish a vector of competency
  - Attract students to careers
  - Health professional students should enter better prepared
  - Integrate genetics into health professional education and residency
  - MOC may present an opportunity

Medical Education

HHMI

AAMC

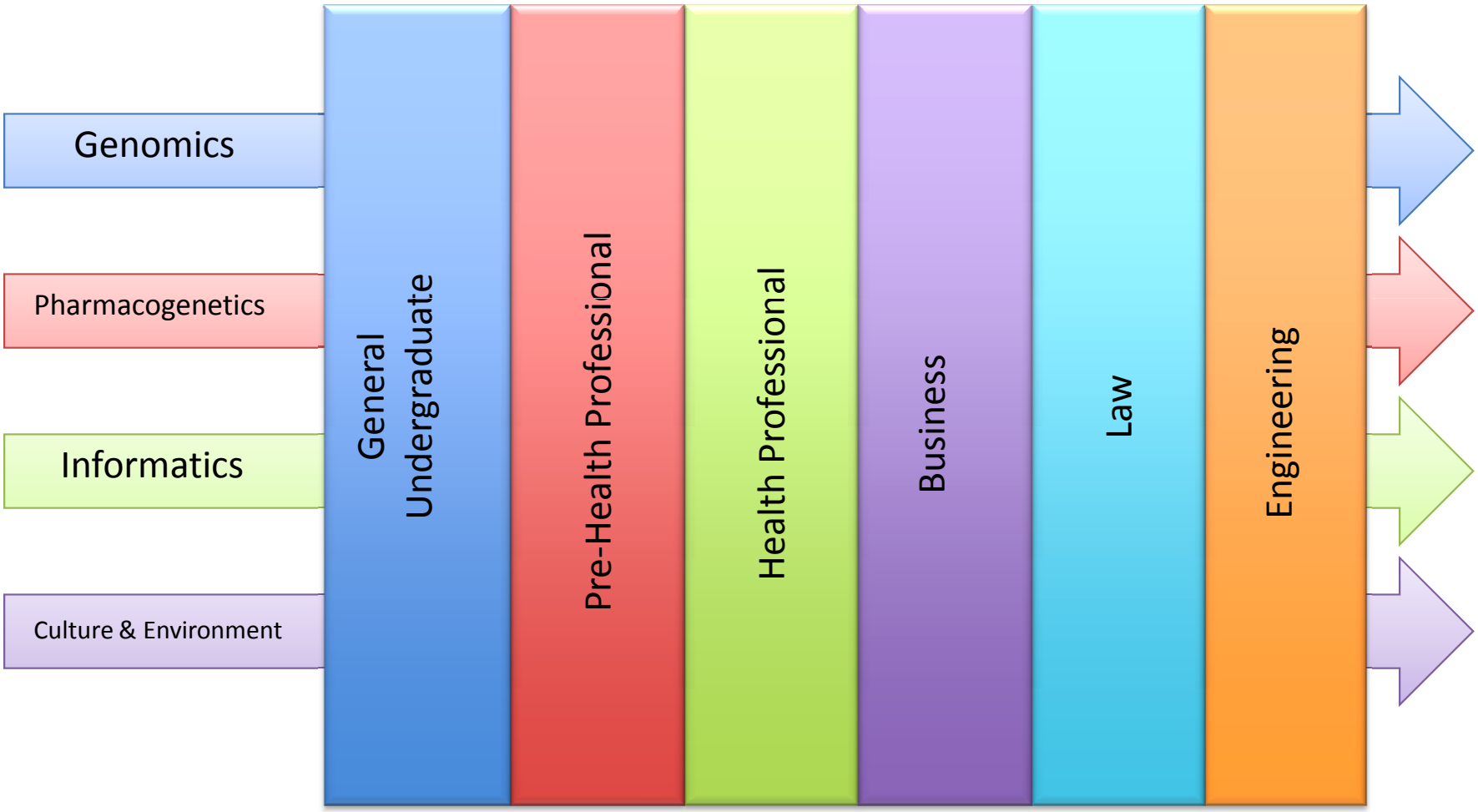
Competency M3

Use the principles of genetic transmission, molecular biology of the human genome, and population genetics to infer and calculate risk of disease, to institute an action plan to mitigate this risk, to obtain and interpret family history and ancestry data, to order genetic tests, to guide therapeutic decision making, and to assess patient risk.

Report of the AAMC-HHMI Committee

ACMGF Summer Scholars Program

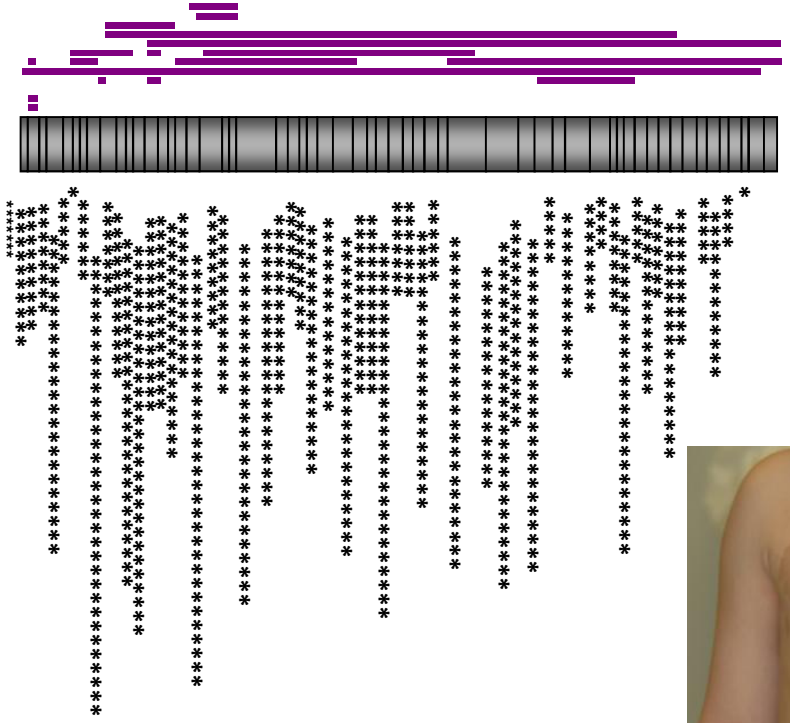
Personalized Healthcare Competencies Project

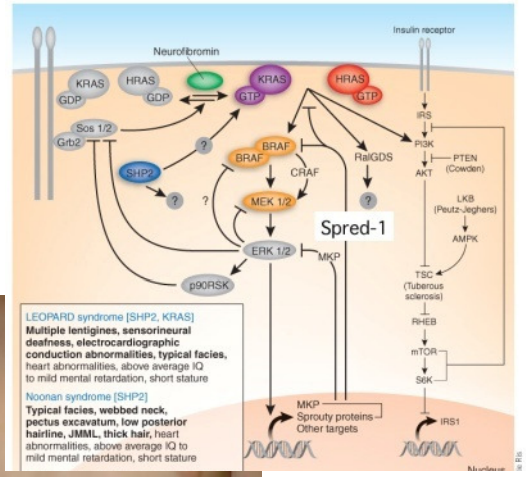


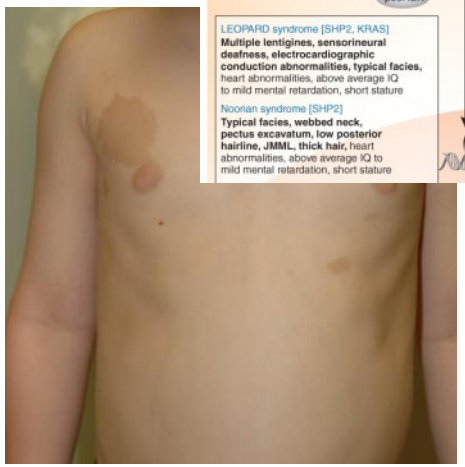
What is needed to translate genomic information from the lab to the provider? Will collaborative medicine be needed to interpret genomic information?

- We are a long way from having fully annotated the genome
- Point-of-care decision support tools need to be deployed
- Collaborative partnerships will be key
- New counseling paradigms will be needed

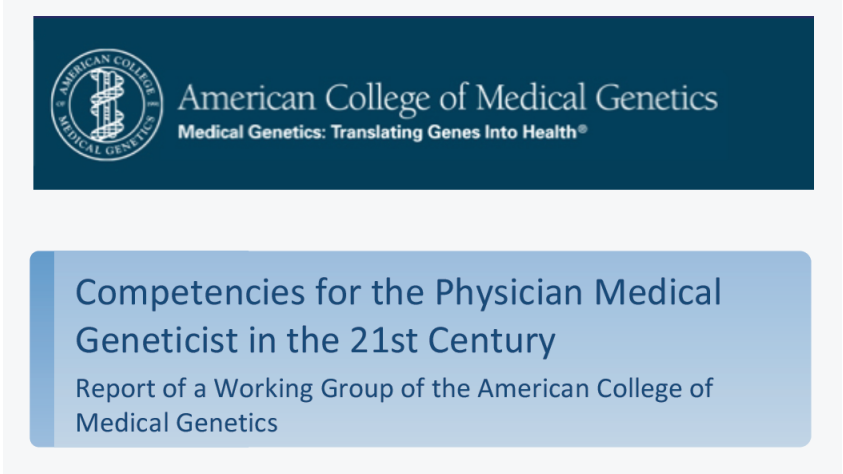
Genome Annotation








THE CAT IN THE HAT
By Dr. Seuss
ULYSSES
by
JAMES JOYCE



Competency 9: Provide counseling to individuals regarding the application of whole genome or whole exome sequencing.

Learning Objectives:

1. Explain to an individual contemplating whole exome or genome analysis the potential risks, benefits and limitations of the information that will be obtained and facilitate informed decision-making.
2. Prioritize the information obtained from whole exome or genome analysis, including carrier status for recessive disorders, single gene disorders, pharmacogenetic traits, and alleles that confer risk of common disease, in providing feedback and counseling.
3. Describe potential risks and benefits that may be associated with disclosing risks of adult-onset disorders in children.
4. Utilize genomic databases and bioinformatics tools to filter results on genetic variants and assess their clinical significance.
5. Explain the difference between variants of known clinical significance and variants of unknown clinical significance in providing counseling on whole exome or genome analysis.
6. Explain the concepts of odds ratio and relative and absolute risk, and the limitations in interpretation of genotypic data regarding risk of common disease.

Newborn Screening ACT Sheet
[Elevated C14:1 +/- other long-chain acylcarnitines]
Very Long-Chain Acyl-CoA Dehydrogenase (VLCAD) Deficiency

Differential Diagnosis: Very long-chain acyl-CoA dehydrogenase (VLCAD) def.

Condition Description- VLCAD deficiency is a fatty acid oxidation (FAO) disorders. Fatty acid oxidation occurs during prolonged fasting and/or periods of increased energy demands (fever, stress) when energy production relies increasingly on fat metabolism. In a FAO disorder, fatty acids and potentially toxic derivatives accumulate because of a deficiency in one of the mitochondrial FAO enzymes.

MEDICAL EMERGENCY - TAKE THE FOLLOWING IMMEDIATE ACTIONS:

- Contact family to inform them of the newborn screening result and ascertain clinical status (poor feeding, vomiting, lethargy).
- Consult with pediatric metabolic specialist.
- Evaluate the newborn (poor feeding, lethargy, hypotonia, hepatomegaly, arrhythmia, evidence of cardiac decompensation). If signs are present or infant is ill, initiate emergency treatment with IV glucose and oxygen. Transport to hospital for further treatment in consultation with metabolic specialist. If infant is normal initiate timely confirmatory/diagnostic testing, as recommended by specialist.
- Educate family about need for infant to avoid fasting. Even if mildly ill, immediate treatment with IV glucose is needed.
- Report findings to newborn screening program.

Diagnostic Evaluation: Plasma acylcarnitine profile may show increased **C14:1 acylcarnitine** (and lesser elevations of other long chain acylcarnitines). Diagnosis is confirmed in consultation with the metabolic specialist by mutation analysis of the **VLCAD gene** and additional biochemical genetic tests.

Clinical Expectations: VLCAD deficiency may present acutely in the neonate and is associated with high mortality unless treated promptly; milder variants exist. Features of severe VLCAD deficiency in infancy include hepatomegaly, cardiomyopathy and arrhythmias, lethargy, hypoketotic hypoglycemia, and failure to thrive. Treatment is available.

Additional Information:

(Click on the name to take you to the website. Complete URLs are listed in the Appendix)

New England Consortium of Metabolic Programs

VLCAD Emergency Protocol

Genetics Home Reference

***Referral** (local, state, regional and national):*

Testing

Gene Tests

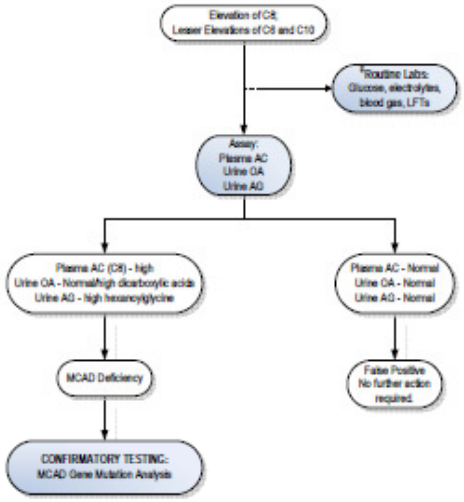
Clinical

(Funded in part through MCHB/HRSA/HHS grant #U22MC03957)

ELEVATED C14:1 +/- OTHER LONG-CHAIN ACYLCARNITINES

Very Long-Chain Acyl-CoA Dehydrogenase (VLCAD) Deficiency

C8 Elevated + Lesser Elevations of C6 and C10



Abbreviations/Key
LFTs = liver function tests
MCAD = Medium-chain acyl-CoA dehydrogenase
AC = acylcarnitine
OA = organic acid
AG = acylglycine

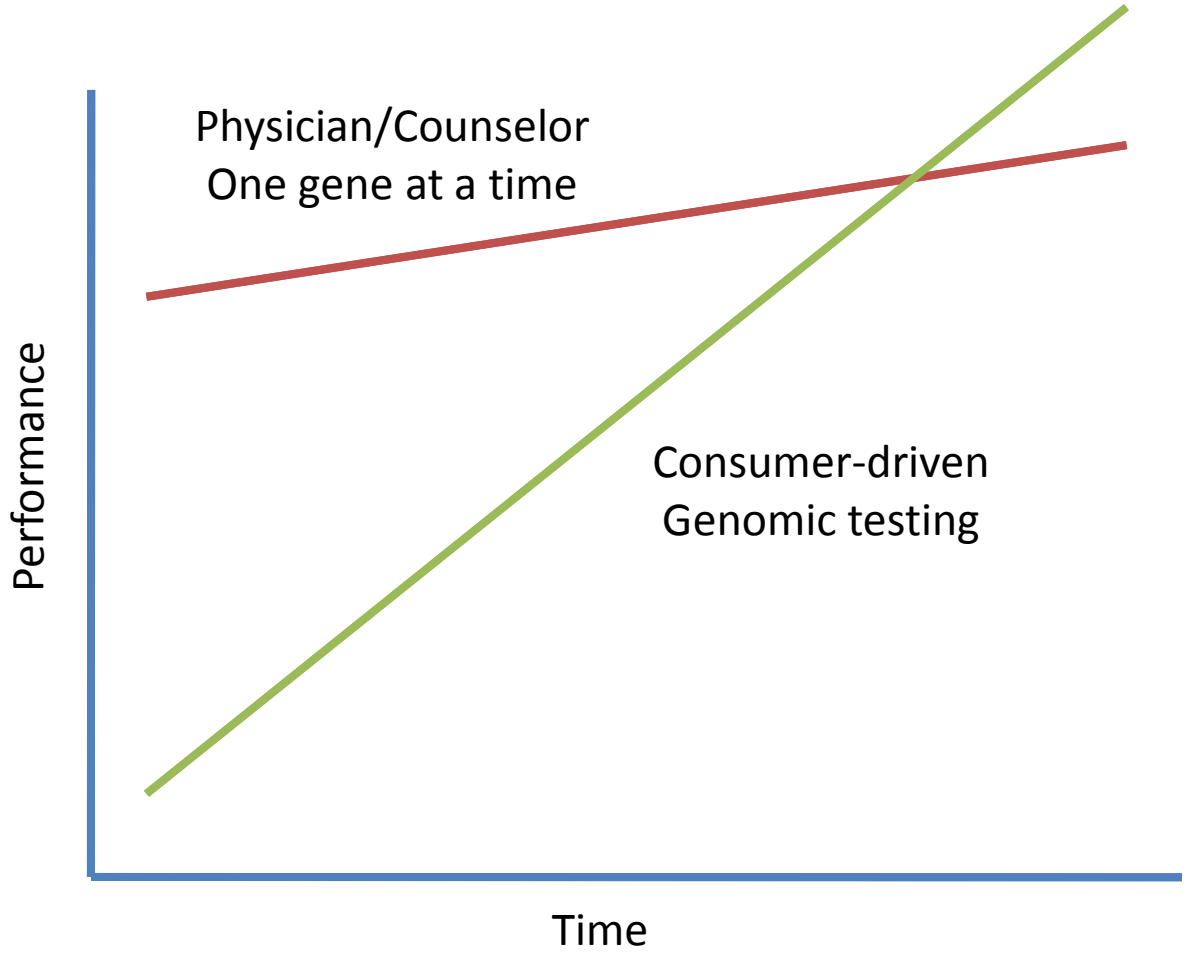
‡ = When the positive predictive value of screening is sufficiently high and the risk to the newborn is high, some initiate diagnostic studies that are locally available at the same time as confirmation of the screening result is done.

Actions are shown in shaded boxes; results are in the unshaded boxes.

Disclaimer: These standards and guidelines are designed primarily as an educational resource for physicians to help them provide quality clinical services. Adherence to these standards and guidelines does not necessarily ensure a successful medical outcome. These standards and guidelines should not be considered inclusive of all proper procedures and tests or exclusive of other procedures and tests that are reasonably directed to obtaining the same results. In determining the propriety of any specific procedure or test, the healthcare provider should apply his or her own professional judgment to the specific clinical circumstances presented by the individual patient or specimen. It may be prudent, however, to document in the patient's record the rationale for any significant deviation from these standards and guidelines.

(Funded in part through MCHB/HRSA/HHS grant #U22MC03957)

Personal Genomics: A Disruptive Technology?



Modified from Christensen et. al. The Innovator's Prescription

Disruptive Technology Examples

Sustaining Technology

Disruptive Technology

Consumer Education

about this site | site map
enhanced glossary

In Their Own Words

Megan | Andres | Syrel | Miguel

understanding NF1 A medical resource about Neurofibromatosis 1 for parents, patients, and providers

Identifying	Explaining	Managing	Supporting	Consultation Video
•What is NF1? •How do I know if I have it? •How is it diagnosed?	•What causes NF1? •What can I expect? •What are we learning about it?	•What are my medical options? •Are other resources and tools available?	•How do I care for and support my child? •How do I talk about NF1?	Parents Abby and Paul speak with an expert about their daughter Hannah's NF1. You will need QuickTime 5 to view the video resources in this site.

A resource from the Harvard Medical School Center for Neurofibromatosis and Allied Disorders. Development of this Web site was made possible by funds from the Massachusetts Department of Public Health.

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