Clinical Medicine and Genomics

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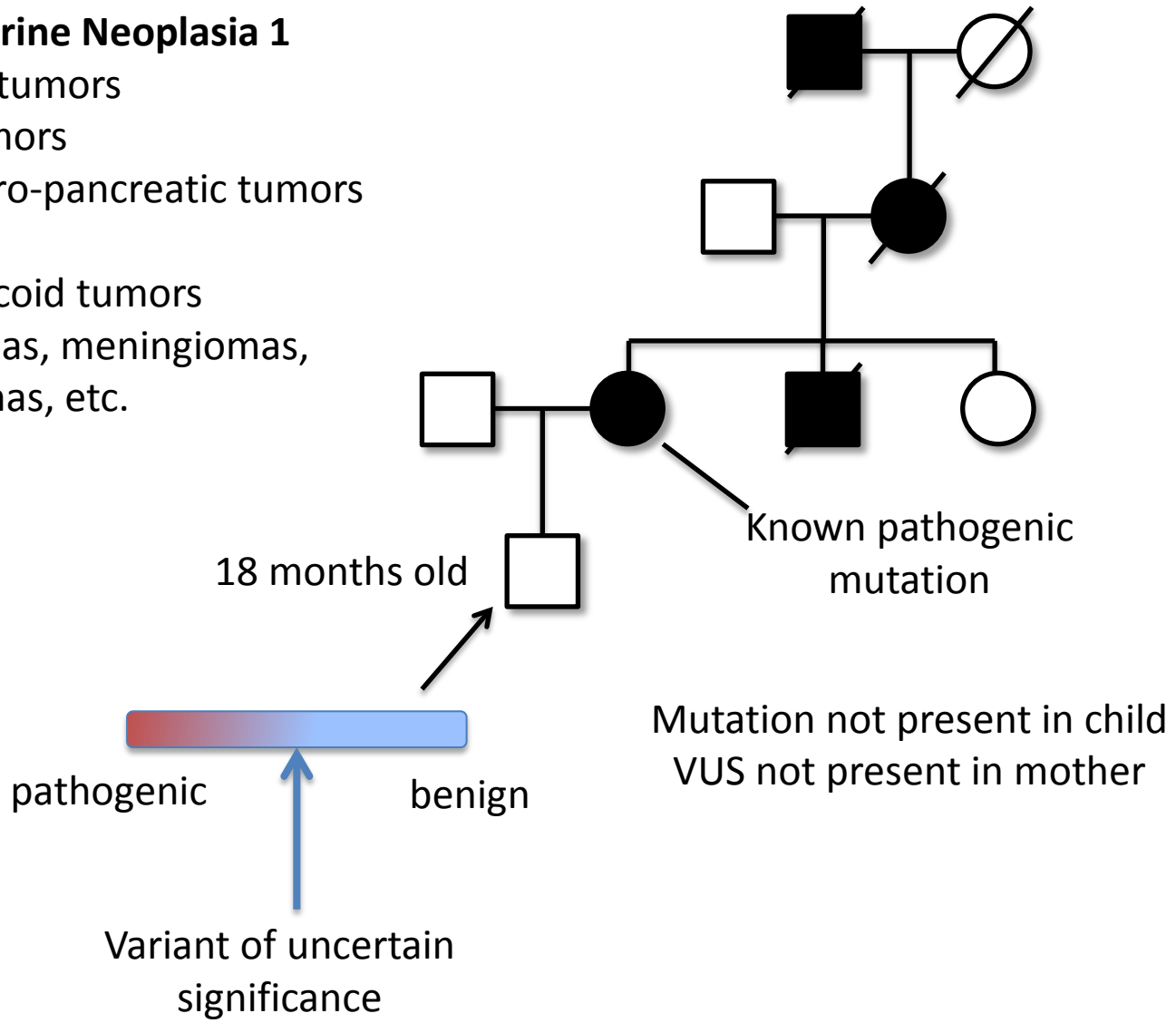
Evidence from the United States and abroad suggests inadequate genetics education of health care professionals as a significant factor limiting the integration of genetics into clinical care. Specific inadequacies include the amount and type of genetics content included in undergraduate professional school curricula and the small amount of genetics-related knowledge and skills of physicians, nurses, and other health professionals once they enter clinical practice. Modifications in medical, dental, nursing, public health, and pharmacy school curricula and in medical residency training programs are needed to ensure that health care professionals entering the workforce are well-trained in genetics.

Multiple Endocrine Neoplasia 1

- Parathyroid tumors
- Pituitary tumors
- Gastro-entero-pancreatic tumors
- Carcinoid
- Adrenocorticoid tumors
- Angiofibromas, meningiomas, ependymomas, etc.



Competencies

- ☑ Determine risk to child based on dominant inheritance of MEN1
- ☑ Recognize that child will benefit from diagnosis (? at 18 months)
- ☑ Order MEN1 genetic testing
- ☒ Appreciate significance of VUS
- ☒ Test affected relative first
- ☑☒ Formulate appropriate care plan

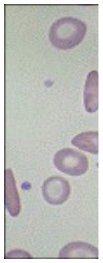
What are the necessary knowledge and skill sets required for analyzing, interpreting, and utilizing genomic information?

- 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

Diagnostic Testing

RESEARCH ARTICLE



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

Carrier Testing for Severe Childhood Recessive Diseases by Next-Generatic

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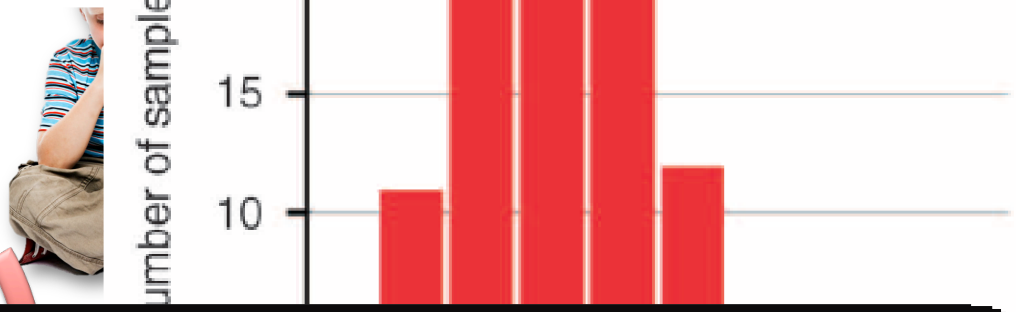
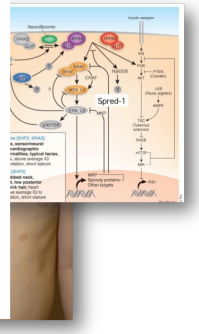
Elena E. Ganusova,[1] Joann Mu
Faye D. Schilkey,[1] Vrunda She
Gary P. Schroth,[3] Ryan W. Kim



Try again

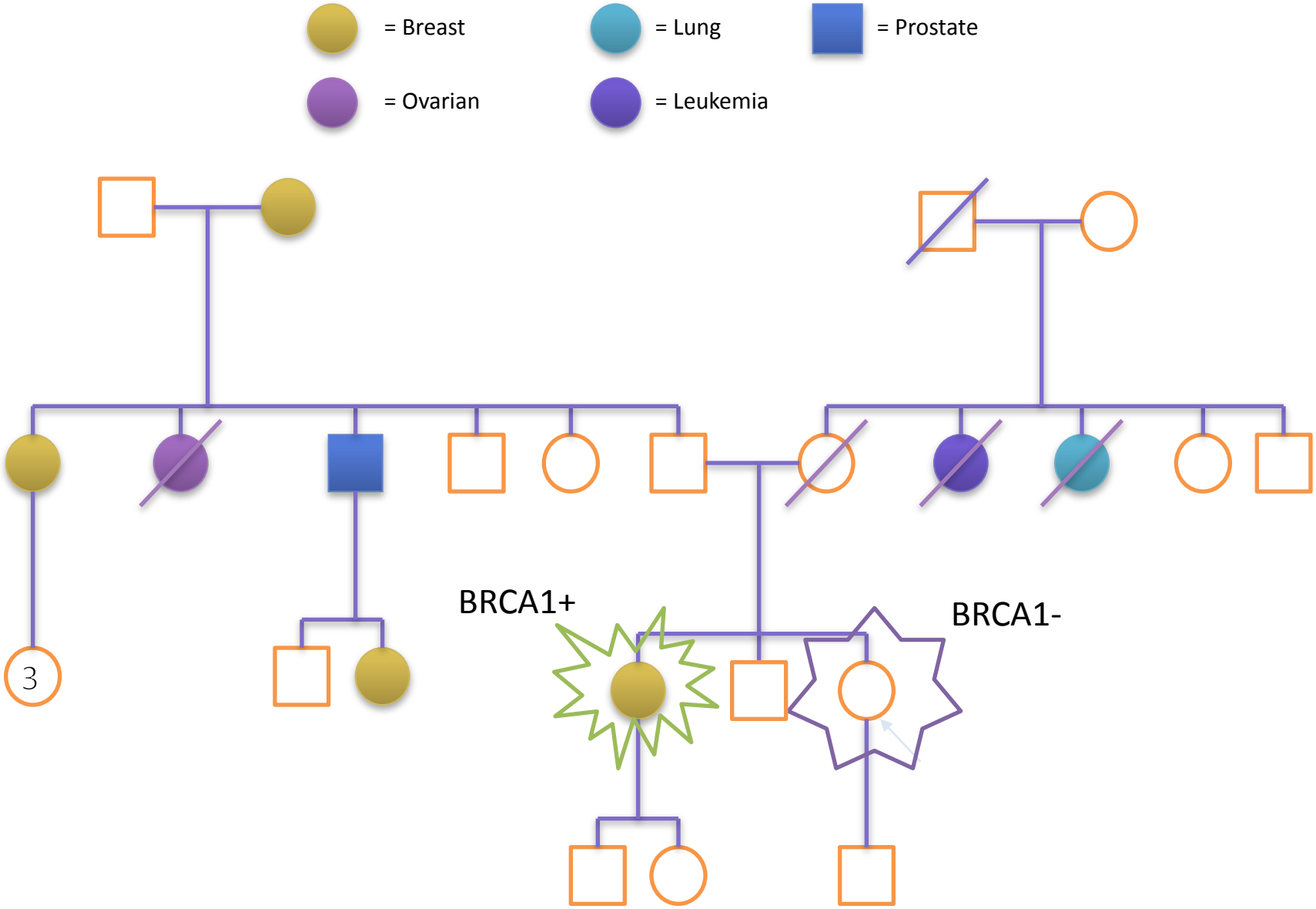
Clinical problem

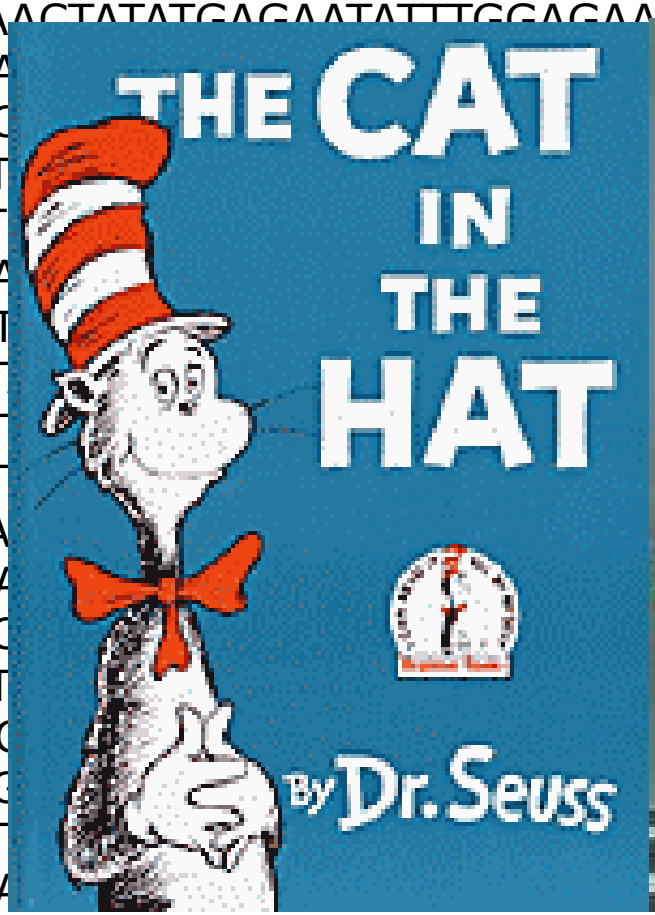


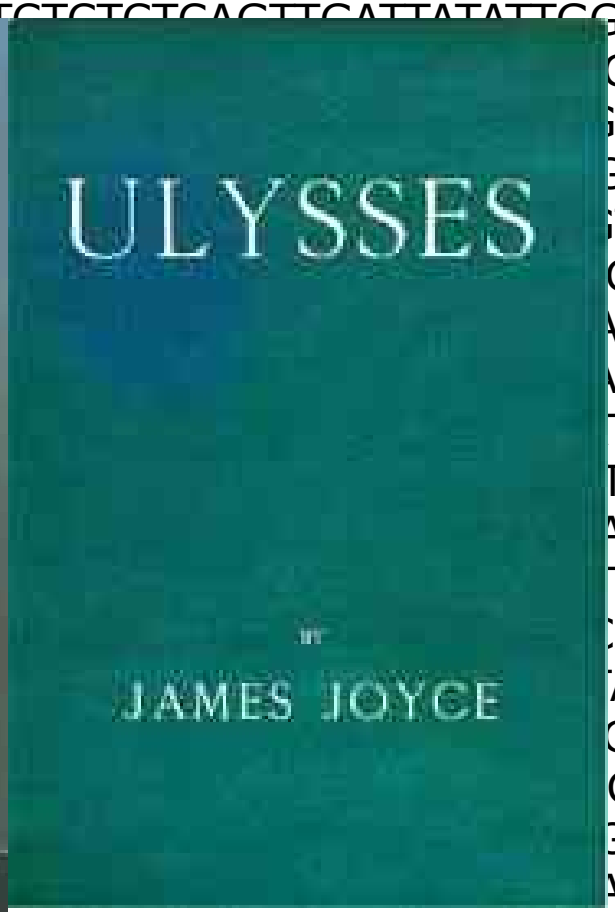
"We found an unexpectedly high proportion of literature-annotated disease mutations that were incorrect, incomplete, or common polymorphisms."

inter

testing


= Breast
= Lung
= Prostate
= Ovarian
= Leukemia
BRCA1+
BRCA1-
3

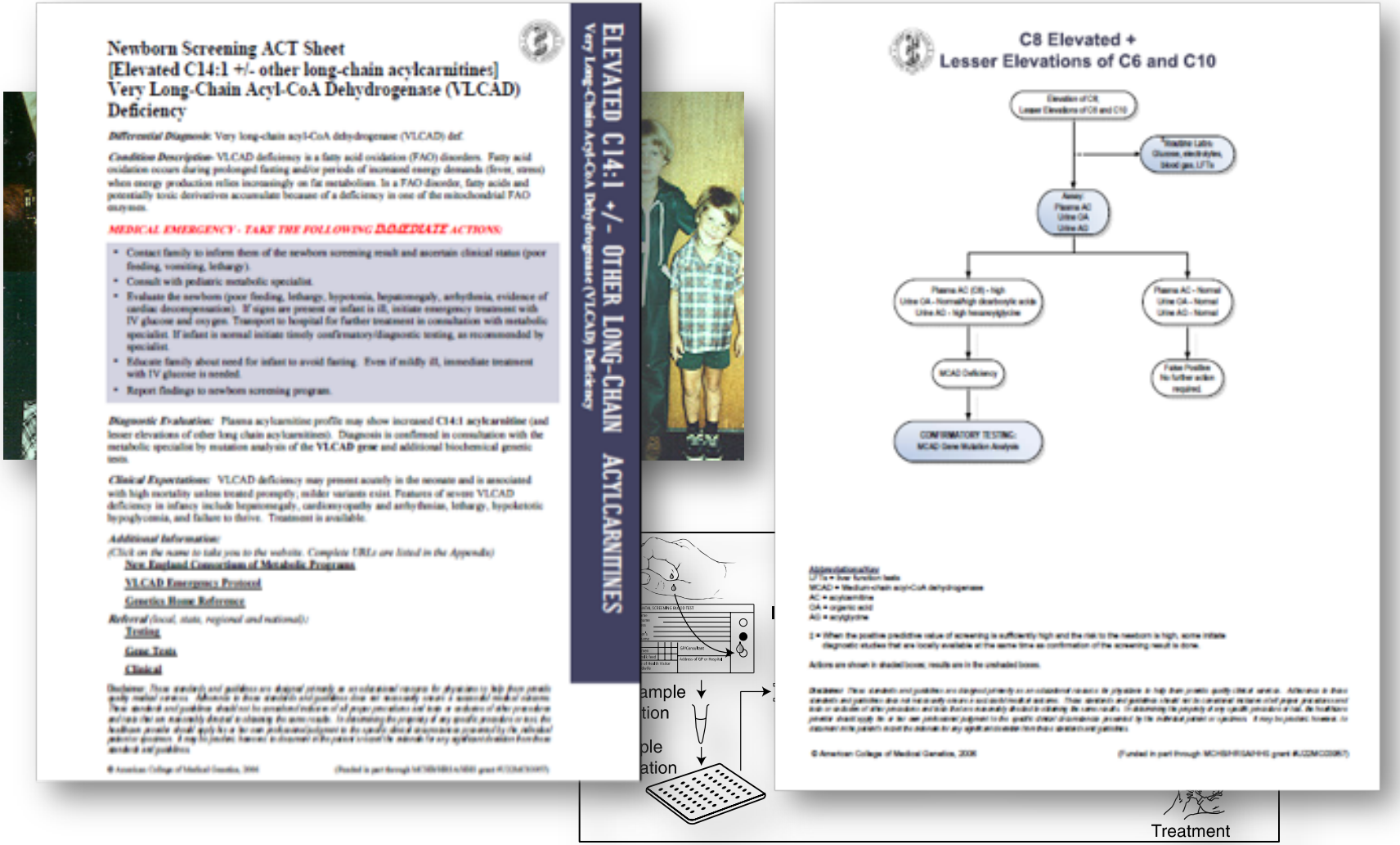

THE CAT IN THE HAT
By Dr. Seuss


ULYSSES
by
JAMES JOYCE

Competencies

- Recognize indications for testing
- Select appropriate family member to test first
- Discuss issues of payment/risks/benefits
- Select a laboratory
- Interpret report – recognize limitations
- Genomic sequencing – recognize potential for secondary findings
- Refer to specialist as needed
- Discuss results with family

Newborn Screening



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

ELEVATED C14:1 +/- OTHER LONG-CHAIN ACYLCARNITINES
Very Long-Chain Acyl-CoA Dehydrogenase (VLCAD) Deficiency

C8 Elevated +
Lesser Elevations of C6 and C10

Elevation of C8
Lesser Elevations of C6 and C10

Baseline Labs:
Glucose, electrolytes,
blood gas, LFTs

Assay:
Plasma AC
Urine OA
Urine AC

Plasma AC (C8) - high
Urine OA - Normal/high dicarboxylic acids
Urine AC - high hexanoylglycine

Plasma AC - Normal
Urine OA - Normal
Urine AC - Normal

MCAD Deficiency

False Positive
No further action
required.

CONFIRMATORY TESTING:
MCAD Gene Mutation Analysis

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

1 = 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.

ample
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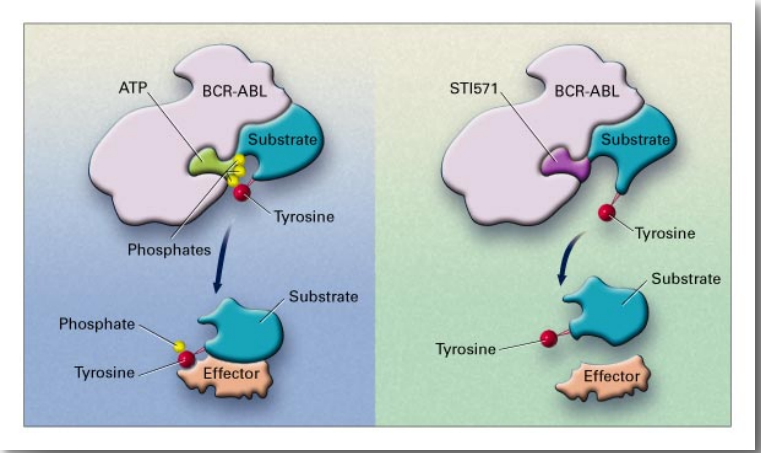
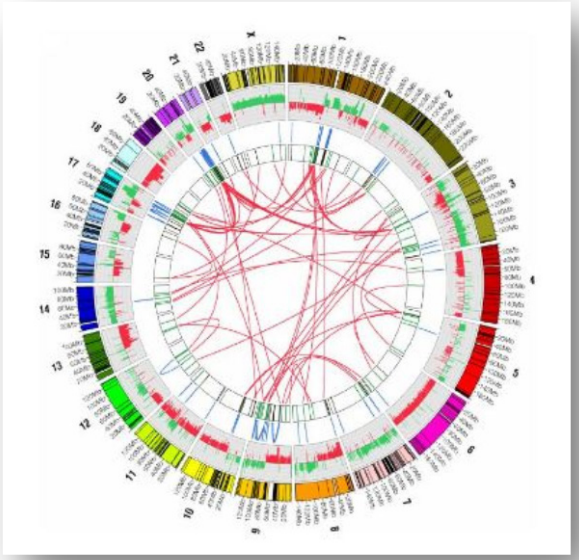
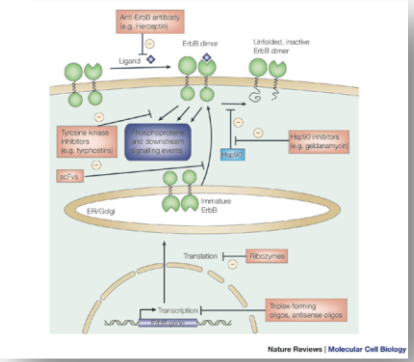
Treatment

Therapeutics



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





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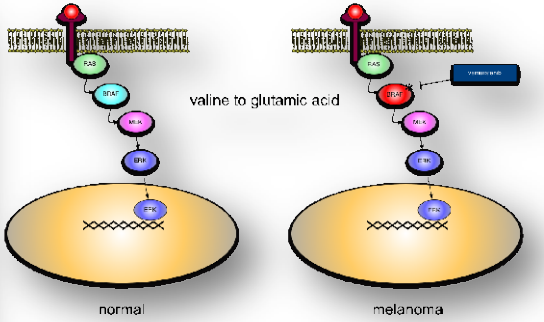
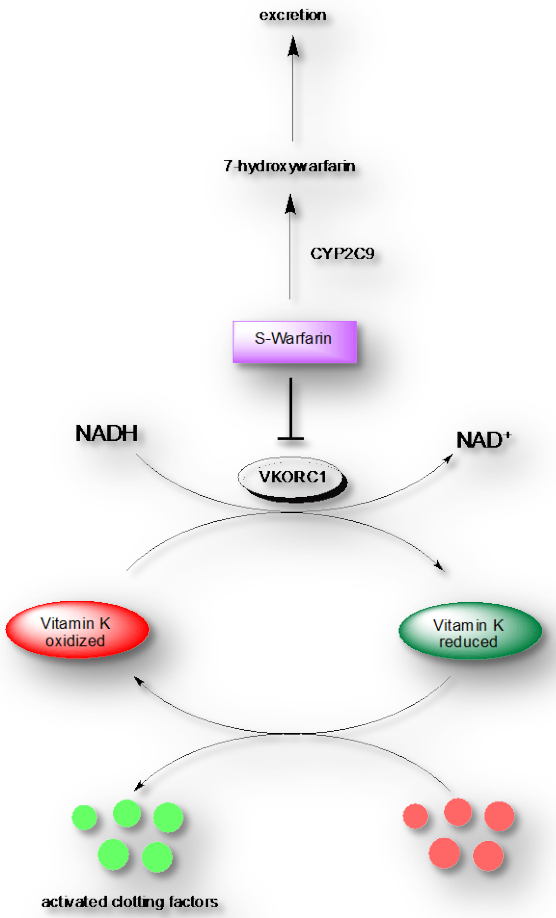
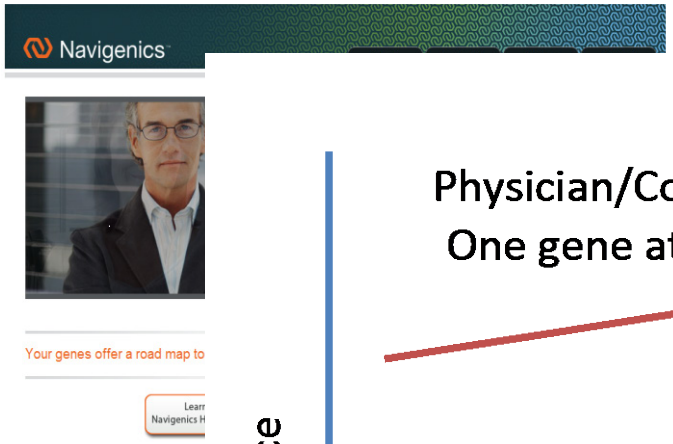
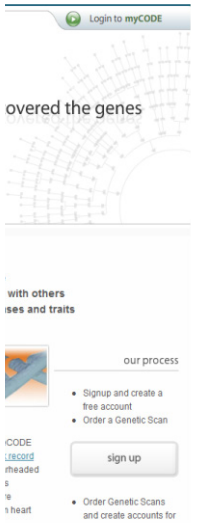


Pharmacogenetics



Risk Assessment

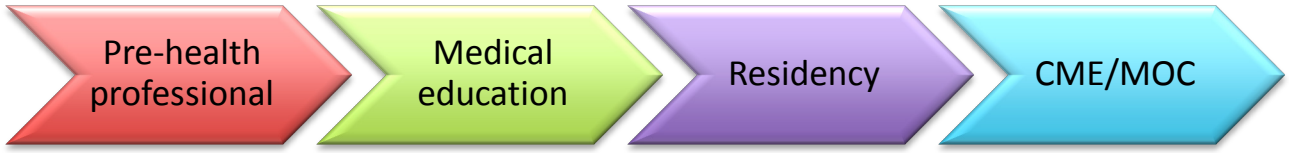




Modified from Christensen et. al. The Innovator's Prescription

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

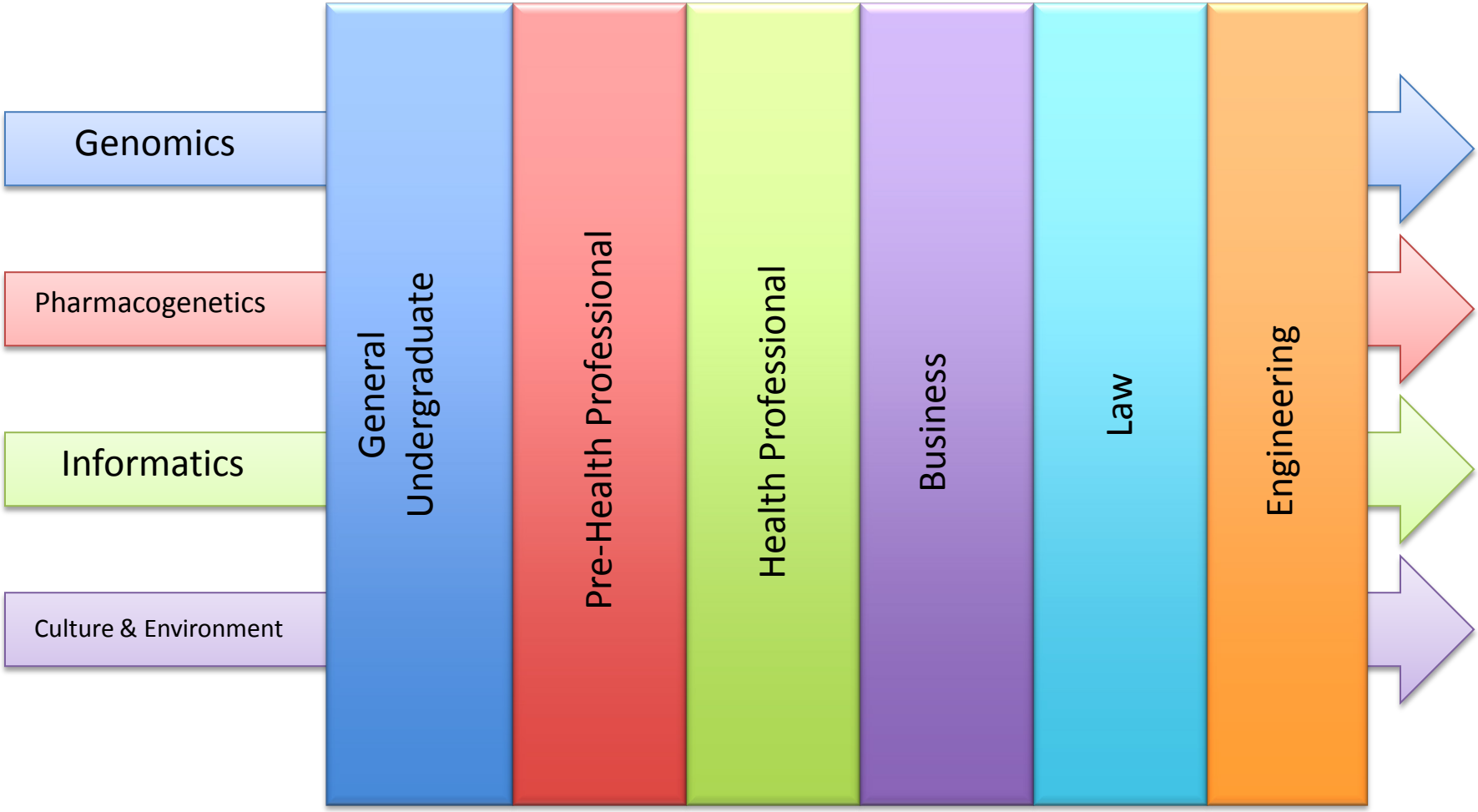


Medical Education

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.

Personalized Healthcare Competencies Project



ACMGF Summer Scholars Program

Banbury Summit I & II (2004, 2006)

- Increase numbers of trainees
- What is a medical geneticist?

ACMG Competencies

Competency 6: Assess and participate in a clinical or translational research study or clinical trial involving patients with or at-risk for a genetic disorder.

Learning Objectives:

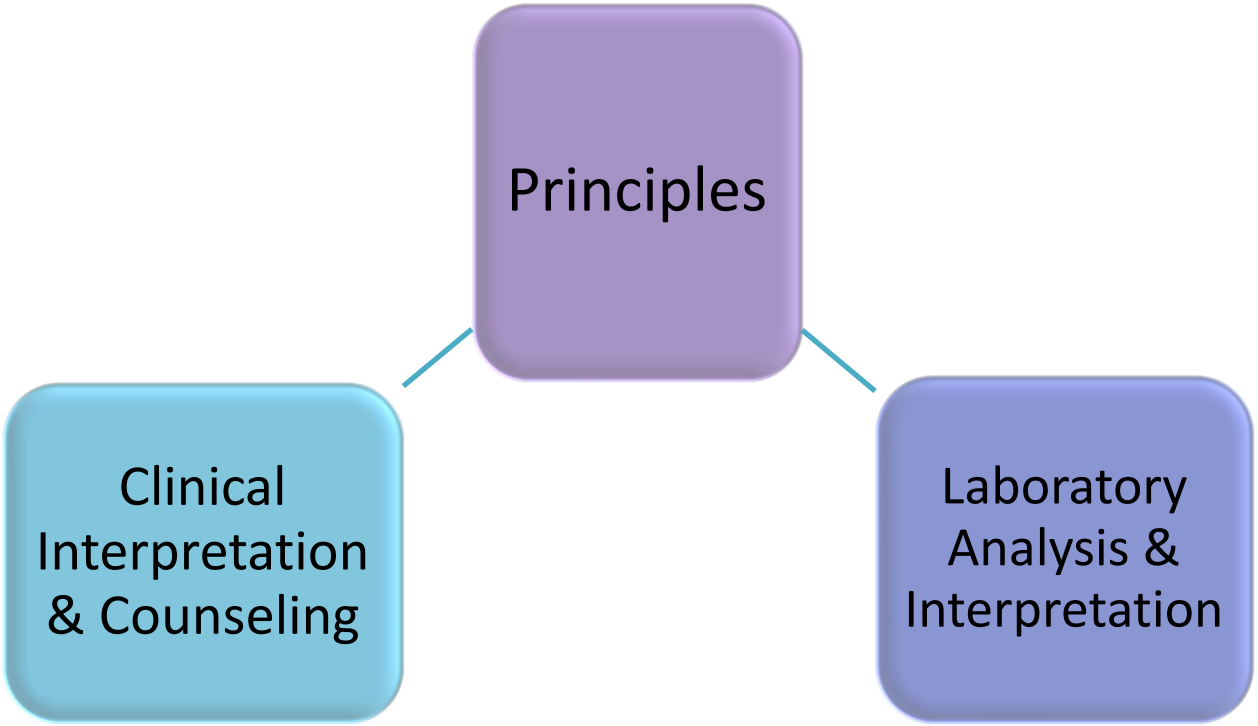
1. Critically evaluate protocols and/or publications reporting results of clinical research studies and clinical trials relevant to genetic disorders.
2. Achieve IRB certification to participat
3. Appreciate the ethical issues that are such as return of research results, ide data, revelation of unexpected family findings that may be clinically significa
4. Educate participants regarding risks a obtain informed consent and/or asse

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

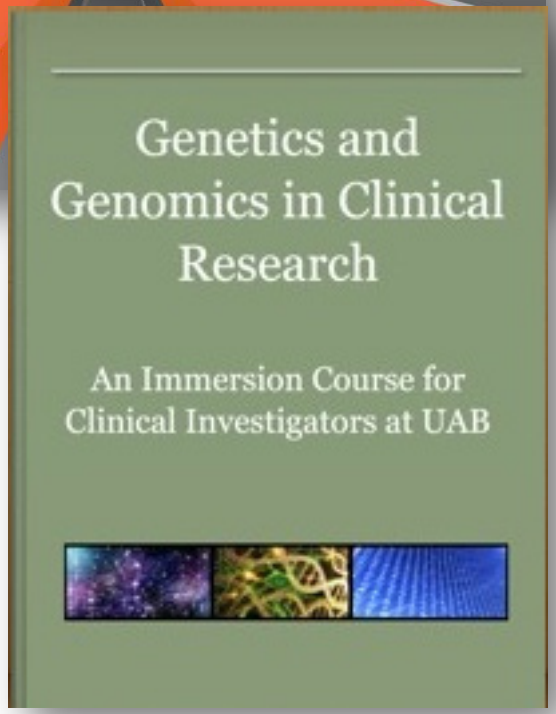
Learning Objectives:

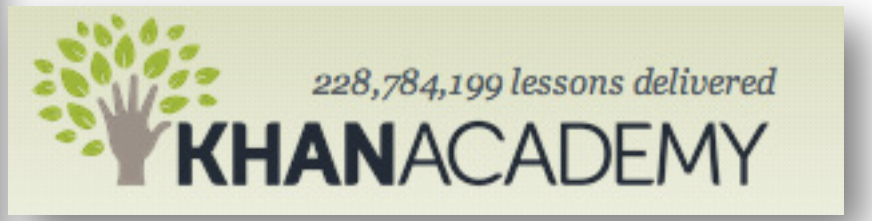
1. Explain to an individual contemplating whole exome or genome analysis the potential risks, benefits and limitations of the information that will be obtained and facilitate informed decision-making.
2. Prioritize the information obtained from whole exome or genome analysis, including carrier status 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.

ACMG Genomics Academy



New Educational Paradigms





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