Genetics and Primary Care: Preparing Primary Care Physicians for the Future of Genomic Medicine

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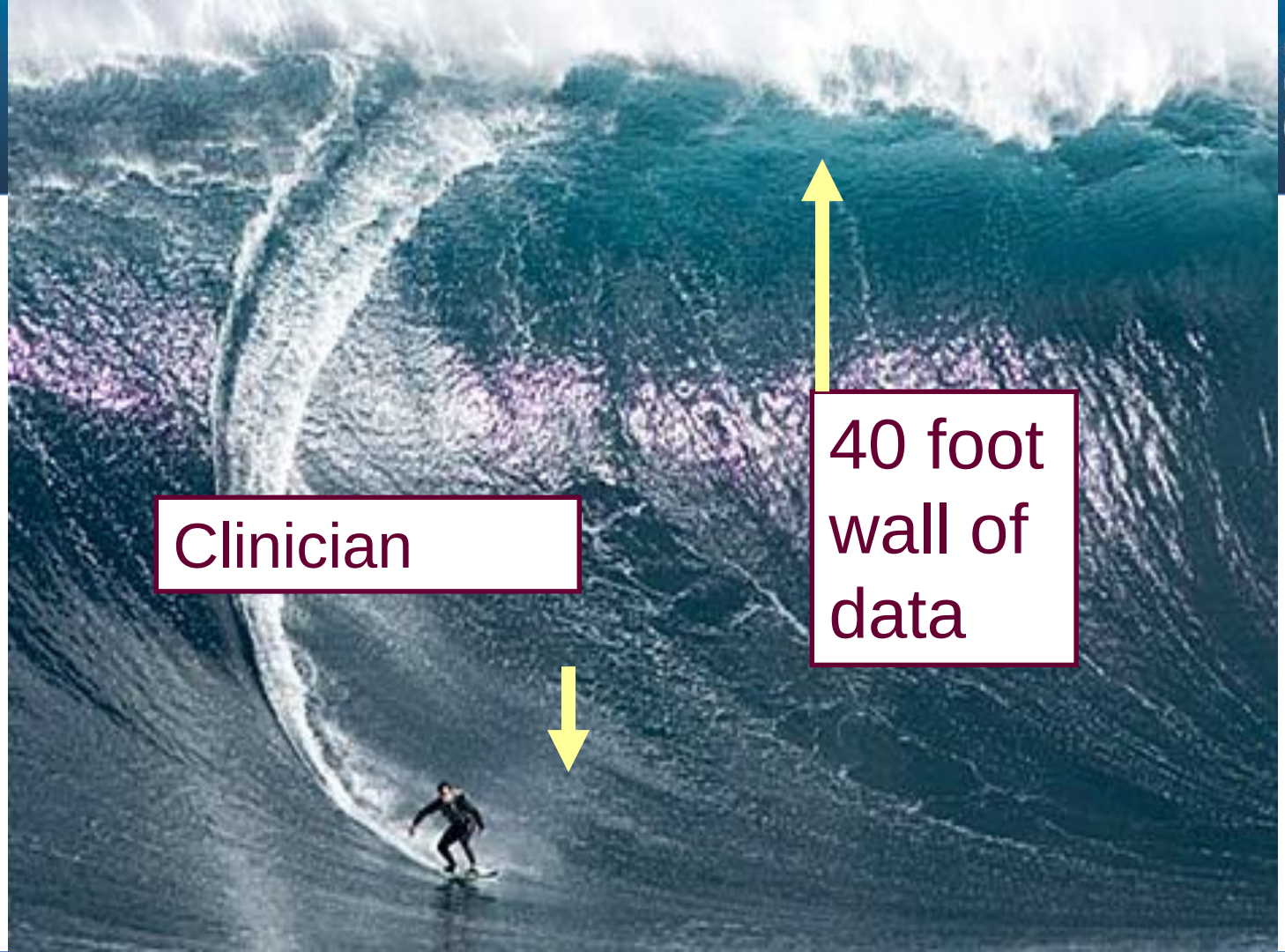
THE RESULTS ARE IN! FINDINGS FROM THE MEDSEQ PROJECT



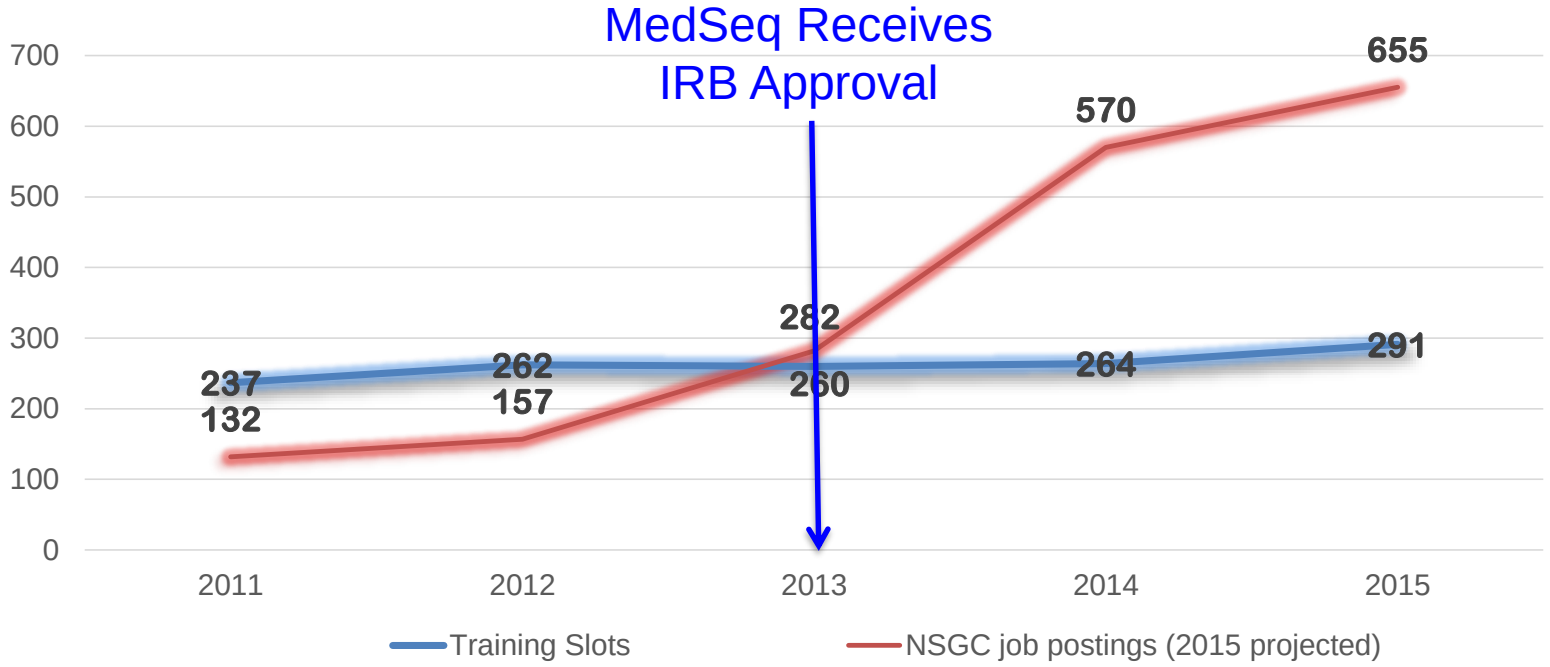
National Society of Genetic Counselors

MedSeq

Not Enough Genetic Counselors and Geneticists

National Society of Genetic Counselors

GC Student Training Slots vs. Job Postings



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The MedSeq Project

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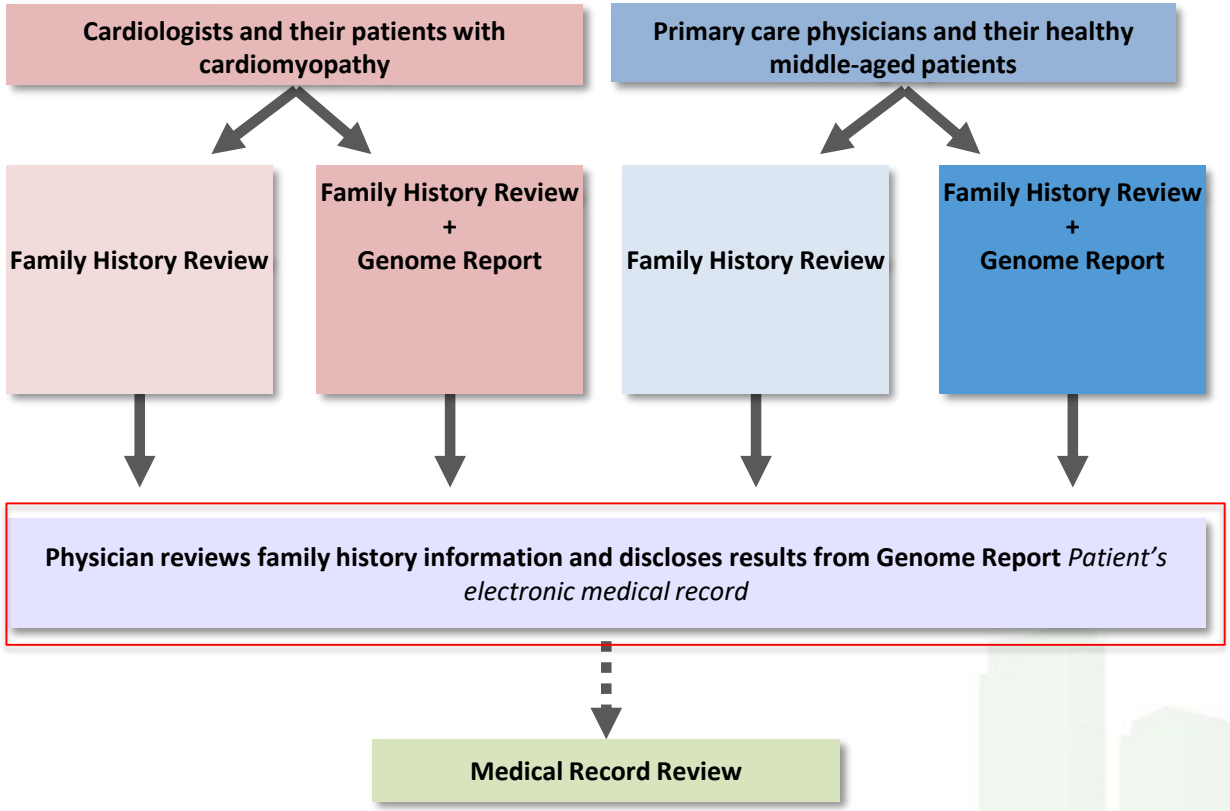

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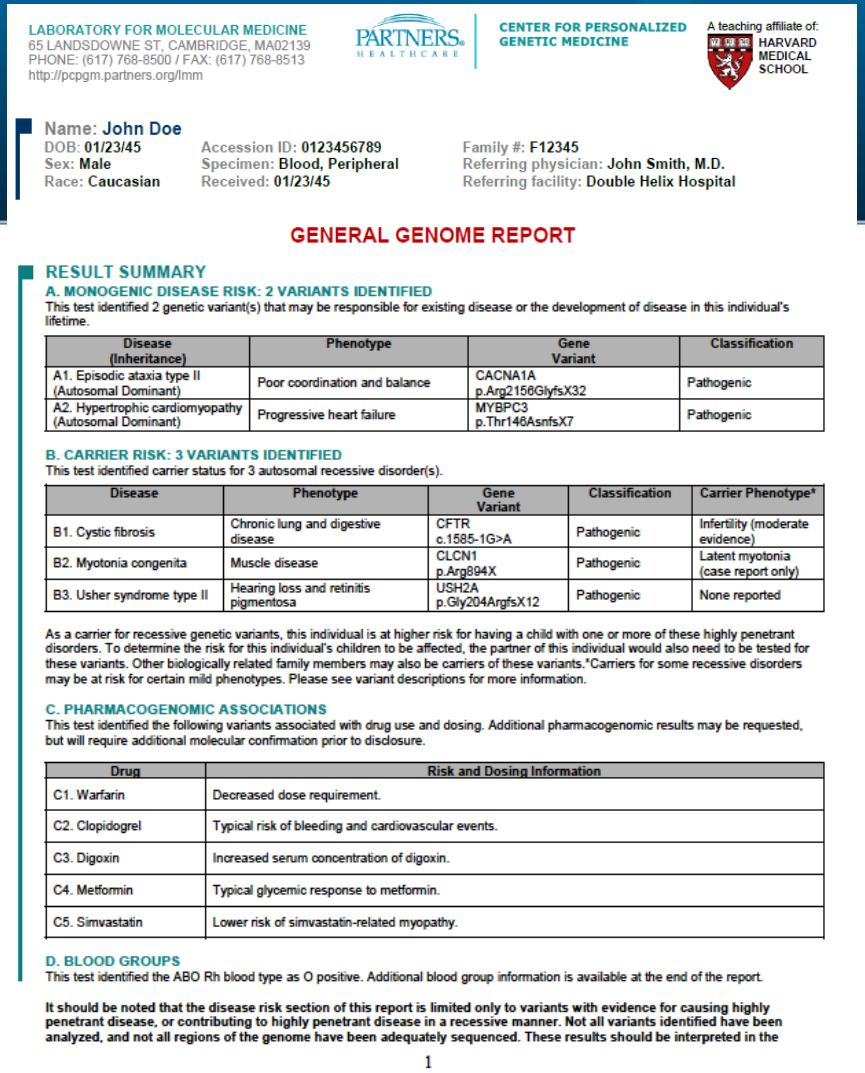
MedSeq Project Genome Reports

General Genome Report

- Disease causing variants
- Carrier variants
- Pharmacogenomic variants
- Blood groups



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PARTNERS HEALTHCARE | CENTER FOR PERSONALIZED GENETIC MEDICINE | A teaching affiliate of: HARVARD MEDICAL SCHOOL

Name: John Doe
DOB: 01/23/45
Sex: Male
Race: Caucasian
Accession ID: 0123456789
Specimen: Blood, Peripheral
Received: 01/23/45
Family #: F12345
Referring physician: John Smith, M.D.
Referring facility: Double Helix Hospital

GENERAL GENOME REPORT

RESULT SUMMARY

A. MONOGENIC DISEASE RISK: 2 VARIANTS IDENTIFIED

This test identified 2 genetic variant(s) that may be responsible for existing disease or the development of disease in this individual's lifetime.

Disease (Inheritance)	Phenotype	Gene Variant	Classification
A1. Episodic ataxia type II (Autosomal Dominant)	Poor coordination and balance	CACNA1A p.Arg2156GlyfsX32	Pathogenic
A2. Hypertrophic cardiomyopathy (Autosomal Dominant)	Progressive heart failure	MYBPC3 p.Thr146AsnfsX7	Pathogenic

B. CARRIER RISK: 3 VARIANTS IDENTIFIED

This test identified carrier status for 3 autosomal recessive disorder(s).

Disease	Phenotype	Gene Variant	Classification	Carrier Phenotype*
B1. Cystic fibrosis	Chronic lung and digestive disease	CFTR c.1585-1G>A	Pathogenic	Infertility (moderate evidence)
B2. Myotonia congenita	Muscle disease	CLCN1 p.Arg894X	Pathogenic	Latent myotonia (case report only)
B3. Usher syndrome type II	Hearing loss and retinitis pigmentosa	USH2A p.Gly204ArgfsX12	Pathogenic	None reported

As a carrier for recessive genetic variants, this individual is at higher risk for having a child with one or more of these highly penetrant disorders. To determine the risk for this individual's children to be affected, the partner of this individual would also need to be tested for these variants. Other biologically related family members may also be carriers of these variants.*Carriers for some recessive disorders may be at risk for certain mild phenotypes. Please see variant descriptions for more information.

C. PHARMACOGENOMIC ASSOCIATIONS

This test identified the following variants associated with drug use and dosing. Additional pharmacogenomic results may be requested, but will require additional molecular confirmation prior to disclosure.

Drug	Risk and Dosing Information
C1. Warfarin	Decreased dose requirement.
C2. Clopidogrel	Typical risk of bleeding and cardiovascular events.
C3. Digoxin	Increased serum concentration of digoxin.
C4. Metformin	Typical glycemic response to metformin.
C5. Simvastatin	Lower risk of simvastatin-related myopathy.

D. BLOOD GROUPS

This test identified the ABO Rh blood type as O positive. Additional blood group information is available at the end of the report.

It should be noted that the disease risk section of this report is limited only to variants with evidence for causing highly penetrant disease, or contributing to highly penetrant disease in a recessive manner. Not all variants identified have been analyzed, and not all regions of the genome have been adequately sequenced. These results should be interpreted in the

1

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Vassy et al. Public Health Genomics 2014

MedSeq Project
Cardiac Supplement

Cardiac Risk Supplement

- Prediction of lipid levels based on genetic variants
- Risk prediction from disease-associated common genetic variants

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*****EXAMPLE REPORT*****

Name: DOE, JOHN
DOB: 01/23/1900 MRN: 0123456789
Sex: Female Specimen: Blood, Peripheral
Race: Caucasian Received: 05/03/2013
Indication for testing: MedSeq, Primary Care

Accession ID: PMXX-12345
Family #: F1234657
Referring physician: Dr. Med Seq
Referring facility: Brigham and Women's
Test: WGS-pnlA, SeqConV2, WGS-GGR

CARDIAC RISK SUPPLEMENT

RESULTS

A. POLYGENIC PREDICTED FASTING LIPID PROFILE

The following lipid profile is predicted by known genetic factors, age, and gender and is not reflective of environmental, medication or other factors. These values are based on large epidemiologic studies and are not intended to substitute for measured values.

- LDL 116 mg/dL
- HDL 47 mg/dL
- Triglycerides 140 mg/dL

B. ALLELES CONFERRING SMALL-MODERATE RISK MODIFICATION FOR 8 CARDIOVASCULAR PHENOTYPES

	Contextual Data		Patient Results			
Phenotype	Population Prevalence of Phenotype for Age 54	Proportion of Variation in Phenotype Liability Explained by Common Genetic Variants	Number of Risk Loci Evaluated	Number of Total Risk Alleles Identified*	Polygenic Relative Risk**	Percentile Rank of Relative Risk**
Abdominal aortic aneurysm	1%	Unknown	3	2/6	0.9	20-30th %ile
Atrial fibrillation	<1%	10%	11	6/22	0.6	10-20th %ile
Coronary heart disease	6% (Age 40-59)	<10%	60	57/120	1.4	60-70th %ile
Type 2 Diabetes	13% (Age 45-64)	5-10%	70	69/140	1.4	60-70th %ile
Hypertension	38%	<10%	3	1/6	1.3	70-80th %ile
Obesity	37% (Age 40-59)	1-2%	7	6/14	1.0	50-60th %ile
Platelet aggregation	Unknown	5-10%	4	0/8	≤0.6	0-10th %ile
QT prolongation	Unknown	7%	3	5/6	1.0	40-50th %ile

*# of total possible risk alleles = # risk loci x 2 alleles per loci.
** As data utilized in this analysis were derived from non-longitudinal association studies, "Relative Risk from Common Genetic Variation" pertains to near-term risk of developing a phenotype (e.g. approximately 5 year risk), not lifetime risk. "Relative Risk from Common Genetic Variation" and "Percentile Rank of Relative Risk from Common Genetic Variation" values have been estimated using the 1000 Genomes European cohort.

METHODOLOGY

Genomic sequencing is performed using next generation sequencing on the Illumina HiSeq platform. Genomes are sequenced to at least 30X mean coverage and a minimum of 95% of bases are sequenced to at least 8X coverage. Paired-end 100bp reads are aligned to the NCBI reference sequence (GRCh37) using the Burrows-Wheeler Aligner (BWA), and variant calls are made using the Genomic Analysis Tool Kit. Risk alleles identified at 161 loci involved in cardiac disease are determined and odds ratios are combined to provide overall assessment of risk for broad phenotypes. The technical component of this test as developed and its performance characteristics determined by the Illumina CLIA Lab (San Diego, CA CLIA# 05D1092911) and the interpretive algorithms and clinical reports were generated by the Laboratory for Molecular Medicine at the Partners Healthcare Center for Personalized Genetic Medicine (LMM, 65 Landsdowne St, Cambridge, MA 02139; 617-768-8500; CLIA#22D1005307). This test has not been cleared or approved by the U.S Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary.

LIMITATIONS

It should be noted that the polygenic predicted values for lipid levels are based on large epidemiologic studies and may not apply to each individual patient (model from N. Stitziel and S. Sunyaev, personal communication). The summary risk assessments above, for small-moderate effect alleles, are based on combining individual risk allele data in ways that may not always apply to each individual patient.

Research Questions

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- Can non-geneticist physicians safely and disclose genomic sequencing results to their patients?

- What education and support are needed, and how heavily will such resources be utilized by non-geneticist physicians?

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Stated Education Objectives

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1. Discuss Mendelian risks, including carrier status
2. Analyze a pedigree to provide accurate risk assessment
3. Convey complex genomic risk information
4. Discuss genomic results of uncertain clinical significance
5. Communicate the current limitations of whole genome sequencing
6. Navigate results found in any given MedSeq Project Genome Report

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Educational Topics

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- Inheritance
- Penetrance, Expressivity
- Anticipation
- Syndromic vs. Non-syndromic disease
- Common disease
- GWAS
- ELSI
- GINA
- Pedigree analysis

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Physician Education

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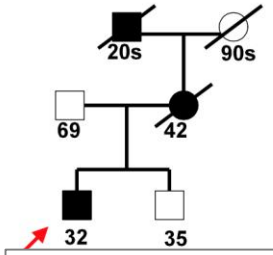
32 year old man presents to ER with chest pain and diaphoresis

Family Health History:

- The patients mother died of MI at 42yo; she was an only child.
- Maternal grandmother died at 92yo of pneumonia.
- He never knew his maternal grandfather who had a heart attack in his 20s.
- His father is "healthy as a horse."



CASE 1 QUESTIONS

1. **This family history pattern of early coronary artery disease suggests.**
   a. Autosomal dominant (**AD**) inheritance
   b. Autosomal recessive (**AR**) inheritance
   c. X-linked recessive (**XLR**) inheritance
   d. Mitochondrial (**MT**) Inheritance

2. **Which of the following is true regarding this skin change.**
   a. It's a sign of **psoriasis**
   b. It's **unrelated** to his present illness
   c. It represents a new **thromboembolic** event
   d. It is secondary to **cholesterol deposition**

3. **Which of the following is <u>false</u> regarding the expected genetic mutation in this case.**
   a. It's likely caused by a single mutated allele (i.e. heterozygous) at one loci.
   b. A mutation in either LDLR or APOB is possible.
   c. Homozygous mutations in LDLRAP1 are ruled out by the pedigree analysis.
   d. Examining DNA from a liver biopsy would be more sensitive than a peripheral blood sample DNA.
   e. The patient his mother and his grandfather are expected to have shared the same exact mutation.

- 12 case-based modules (4 hours)
- 2 one-hour didactic sessions

Credit: Mike Murray, MD and Monica Giovanni, CGC

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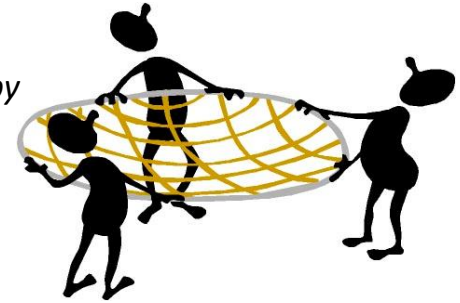
MedSeq Genome Resource Center and Safety Monitoring

National Society of Genetic Counselors

On-demand clinical genomics support

Transcript review by genetic counselors and clinical geneticists



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Genome Resource Center (GRC): Experience To Date

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- **13/18** MDs planned to use the GRC
- **8** study physicians utilized GRC
- **15** total consultations

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What Questions Are Physicians Asking?

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Testing Coverage and Limitations (n=5)
There is a question of Ehlers-Danlos syndrome in my patient's family… Would that have come up in the [genome] screen?

GR Review (n=2)
Can I go over the full WGS Report to make sure I am understanding it correctly?

Common Complex/ Pharmocogenomics
(n=3) How should I manage my patient based on this result?

Carrier Status (n=4)
Are there standard recommendations for counseling patients concerning the significance of [the patient's] carrier status for their [adult] children?

Family History (n=1)
My Patient has a strong family history of Breast Cancer- should I refer them?

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Types of Physician Errors/ Miscommunications

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- High-risk
  - Invasive testing based on misinterpreted genetic results

→ **Urgent feedback, notify safety board**

- Low/medium-risk
  - Over-reassurance about reproductive risks for carriers of common AR diseases

→ **Real-time feedback**

- Very low-risk
  - Miscommunication not impacting management decisions
  - Includes family history omissions

→ **End-of-study feedback**

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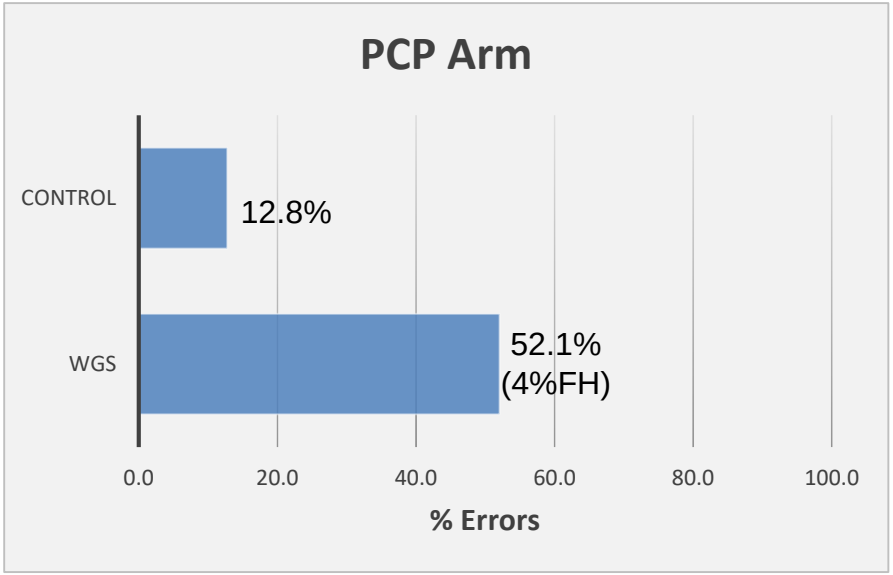
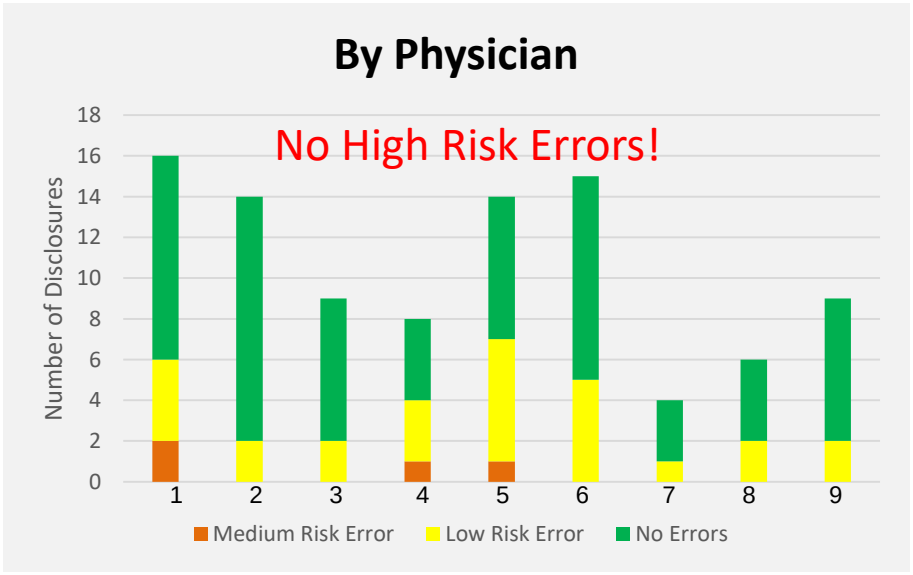
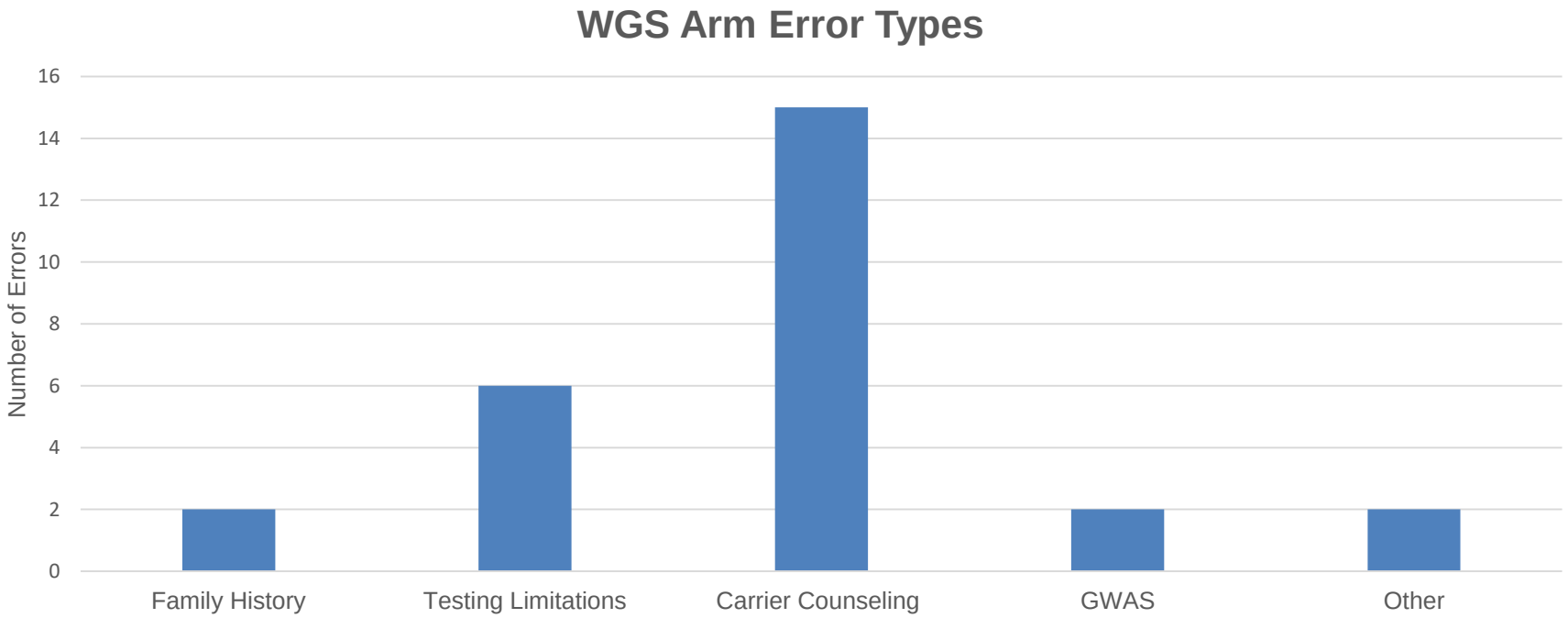
PCP Errors/Miscommunications





PCP Errors/Miscommunications



Monogenic Disease Variants Found in 11 of 50 Healthy Patients

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Gene	Disease	Classification
RDH5	Fundus albipunctatus (homozygous)	Pathogenic
PPOX	Variegate porphyria	Pathogenic
HFE	Hereditary hemochromatosis (homozygous)	Pathogenic
LHX4	Combined pituitary hormone deficiency	Pathogenic
KCNQ1	Romano-Ward syndrome	Likely pathogenic
COL2A1	Spondyloepiphyseal dysplasia congenita	Likely pathogenic
ANK2	Ankyrin-B related cardiac arrhythmia	Likely pathogenic
TNNT2	Hypertrophic cardiomyopathy	VUS: Favor pathogenic
PDE11A	Primary pigmented micronodular adrenocortical disease	VUS: Favor pathogenic
ARSE	Chondrodysplasia punctata	VUS: Favor pathogenic
F5	Factor V Leiden thrombophilia	Risk allele

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RAND/UCLA Appropriateness Scale

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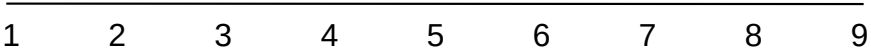
"Management is considered to be appropriate if the expected health benefit (e.g., increased life expectancy, relief of pain, reduction in anxiety, improved functional capacity) exceeds the expected negative consequences (e.g., mortality, morbidity, anxiety, pain, time lost from work) by a sufficiently wide margin that the procedure is worth doing, exclusive of cost."



1 = Extremely inappropriate
5 = Equivocal (neither clearly appropriate nor clearly inappropriate)
9 = Extremely appropriate

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Appropriateness of Clinical Management

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Gene	Disease	Classification	Median Appropriateness Score (Range 1-9)
RDH5	Fundus albipunctatus	P	9
PPOX	Variegate porphyria	P	8
KCNQ1	Romano-Ward syndrome	LP	7
TNNT2	Hypertrophic cardiomyopathy	VUS: FP	7
PDE11A	Primary pigmented micronodular adrenocortical disease	VUS: FP	7
COL2A1	Spondyloepiphyseal dysplasia congenita		7
ANK2	Ankyrin-B related arrhythmia		7
HFE	Hereditary hemochr		7
ARSE	Chondrodysplasi		4
F5	Factor V Leiden th		3
LHX4	Combined pituitary hormone deficiency	P	3

Miscommunicated inheritance pattern and risk to children

Under-evaluated a pathogenic variant

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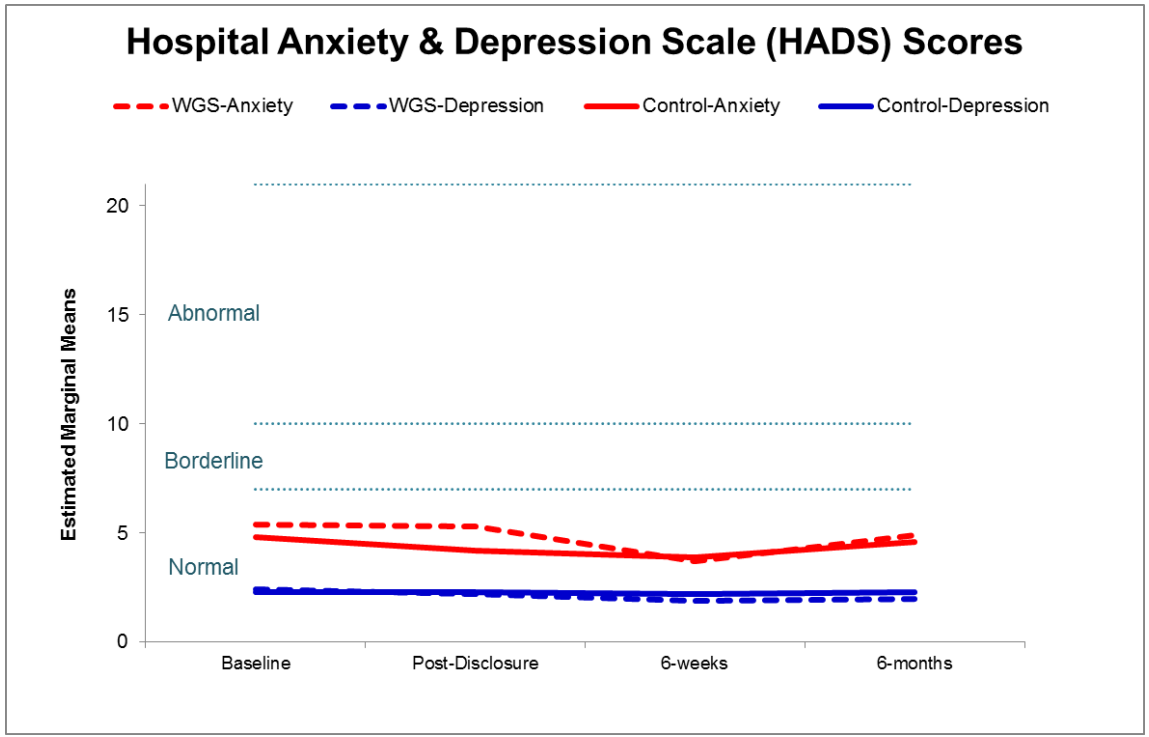
Impact on Psychological Distress



No significant differences by Randomization arm

Physician Perspectives

- **Education Quality- "**I thought it was very helpful. I don't know how to grade it, but I think it was definitely instrumental in taking me from maybe a C+ to a B+."
- **Carrier Status- "**I really hadn't been thinking about the difference between when I need to worry about somebody having an autosomal recessive trait. What about the rest of their family? I mean, I just wasn't – it wasn't even on my radar."
- **Common Complex- "**I had no trouble explaining monogenic (OR), the carrier results, (OR) the pharmacogenomic, but I sort of struggled a little bit in terms of being able to explain the polygenic risk."
- **Family History-** "Even when we had the disclosure, the genome sequence, there are many very important things that came from the family history. That was learning to pay more attention to that and learning to see how much that piece can help you advise the patient was a good experience."

Physician Perspectives

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- **Time-** “The other group (WGS) was much more time-consuming, so I would get the report and then I would have to go look up and see what in heaven’s name this something or other is that they’re telling me the patient has, dominant, recessive…and try to figure out”

- **Improvements-** “ Well, the first patient who had his genome sequenced, I thought I did a horrible job because it’s stressful— because it was the first time I ever did….I went home and I was worried, concerned…Then I think I got better as I did a second one and a third one, and then and so on, I'm more familiar… I think you get a little better idea of what is important to the patient, so you can, in a way, emphasize that.”

- **Increased Comfort- “**I really didn't know what to expect …. I think what it did do is it made me feel more comfortable when patients come and are talking about doing genomic sequencing on themselves, it's a little bit more familiar.”

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End of Study- Physician Feedback

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- Importance of family history- need better tools
- Disappointment that WGS results did not reveal more to guide healthcare
- Used GWAS to motivate positive health behavior
- Importance of family communication (letters)
- Would you offer this to your patients for $1000 vs $100

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Take Home Messages

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- There were no high risk safety errors
- Target education efforts to address:
  - Carrier Status
  - Family History
  - Testing Limitations
  - GWAS Implications
- Need for better family history tools
- Increased comfort with increased exposure

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The MedSeq Project Collaborators

cser Clinical Sequencing Exploratory Research

National Society of Genetic Counselors

BWH

Baylor College of Medicine

G2P GENOMES to People

DukeMedicine

Geisinger

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