Translation of Genomics for Patient Care and Research: **The Clinical End-User**

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Institute of Medicine Roundtable on Translating Genomic-Based Research for Health: Genomics-Enabled Learning Health Care Systems

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Question

What information do clinical end-users need to successfully make decisions about health?

Physicians report unpreparedness for genomic medicine

Barriers to using genomic medicine in clinical practice:

- Lack of genomics knowledge and low self-efficacy
- Electronic health records not equipped to incorporate genomic information
- Lack of evidence for clinical utility

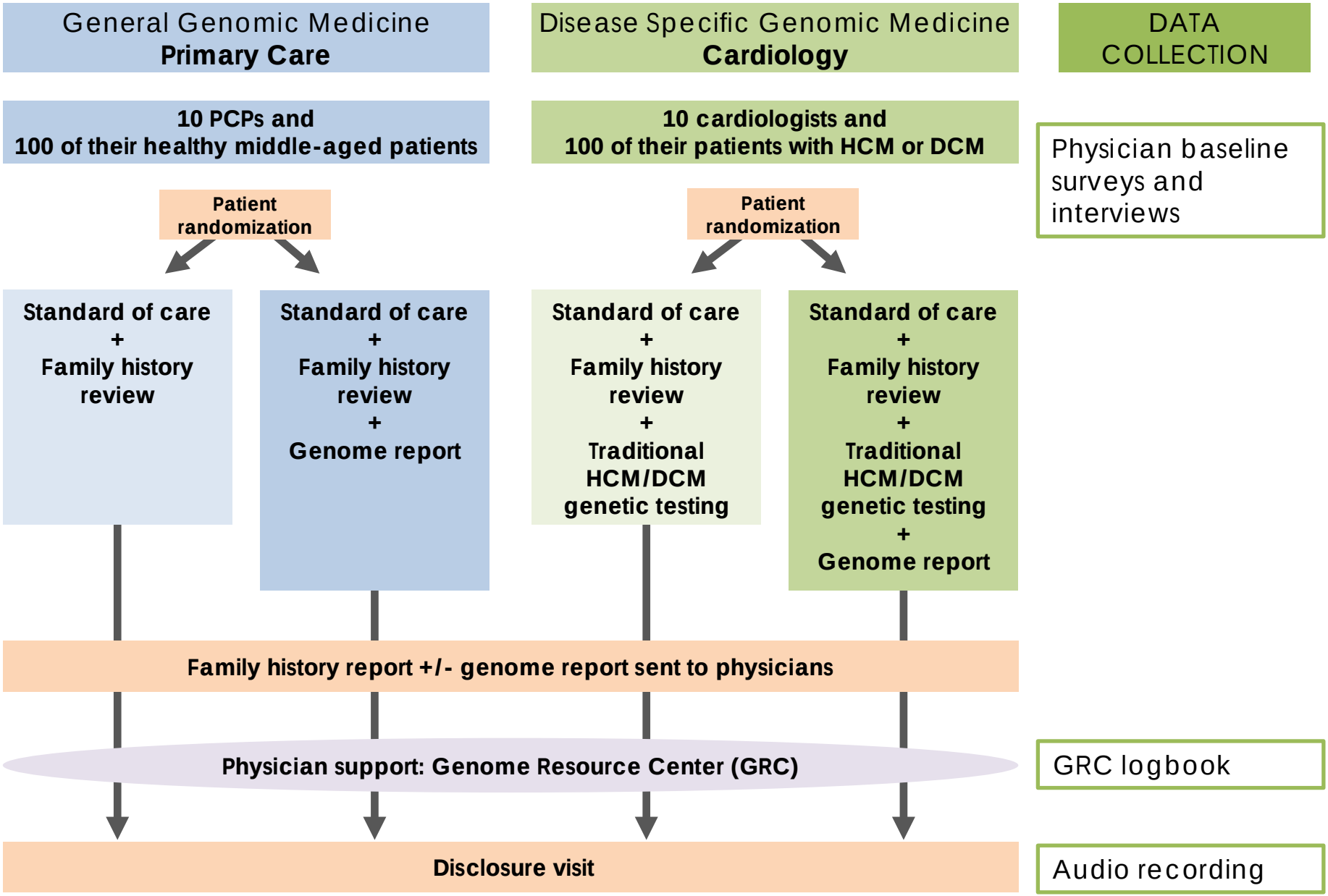
Scheuner, *et al. JAMA* 2008 2012
Klitzman, *et al. J Genet Couns* 2013 Selkirk, *et al. Genet Test Mol*
Najafzadeh, *et al. Genet Med Bio* 2013

The MedSeq Project (U01 HG006500)

- Integrating whole-genome sequencing into the clinical care of:
  - Generally healthy adult primary care patients
  - Patients with cardiomyopathy
- Physicians and patients are all study participants

MEDSEQ™

Principal investigators Robert Green, Heidi Rehm, and Amy McGuire


General Genomic Medicine
Primary Care
Disease Specific Genomic Medicine
Cardiology
DATA COLLECTION
10 PCPs and
100 of their healthy middle-aged patients
10 cardiologists and
100 of their patients with HCM or DCM
Physician baseline surveys and interviews
Patient randomization
Patient randomization
Standard of care + Family history review
Standard of care + Family history review + Genome report
Standard of care + Family history review + Traditional HCM/DCM genetic testing
Standard of care + Family history review + Traditional HCM/DCM genetic testing + Genome report
Family history report +/- genome report sent to physicians
Physician support: Genome Resource Center (GRC)
GRC logbook
Disclosure visit
Audio recording

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PARTNERS HEALTHCARE

CENTER FOR PERSONALIZED GENETIC MEDICINE

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MEDSEQ

Name: DOE, JONATHAN
DOB: 12/34/5678 **MRN:** 123456780
Sex: Male **Specimen:** Blood, Peripheral
Race: Caucasian **Received:** 05/03/2013
Indication for testing: MedSeq, Primary Care

Accession ID: PMXX-12345
Family #: F12345
Referring physician: MedSeq
Referring facility: MedSeq
Test: WGS-pnlA, SeqConV2, WGS-GGR

GENOME REPORT

RESULT SUMMARY

Sequencing of this individual's genome was performed and covered 95.7% of all positions at 8X coverage or higher, resulting in over 5.2 million variants compared to a reference genome. These data were analyzed to identify previously reported variants of potential clinical relevance as well as novel variants that could reasonably be assumed to cause disease (see methodology below). All results are summarized on page 1 with further details on subsequent pages.

Monogenic disease risk

MONOGENIC DISEASE RISK: 1 VARIANT IDENTIFIED

This test identified 1 genetic variant that may be responsible for existing disease or the development of disease in this individual's lifetime.

Disease Inheritance	Gene Transcript	Zygosity Variant	Classification
Chondrodysplasia punctata X-linked	ARSE NM_000047.2	Hemizygous c.410G>C p.Gly137Ala	Uncertain Significance: Favor Pathogenic

CARRIER STATUS: 2 VARIANTS IDENTIFIED

This test identified carrier status for 2 autosomal recessive disorders.

Carrier status

Disease Inheritance	Gene Transcript	Zygosity Variant	Classification	Carrier Phenotype*
Cystic Fibrosis Autosomal Recessive	CFTR NM_000492.3	Heterozygous c.3846G>A p.Trp1282X	Pathogenic	None reported
Glycogen storage disease 7 Autosomal recessive	PFKM NM_000289.5	Heterozygous c.237+1G>A	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 future children to be affected, the partner of this individual would also need to be tested for variants in these genes. Other biologically related family members may also be carriers of these variants. *Carriers for some recessive disorders may be at risk for certain phenotypes. Please see variant descriptions for more information.

Pharmaco-genomics

PHARMACOGENOMIC ASSOCIATIONS

This test identified the following pharmacogenomic associations. Additional pharmacogenomic results may be requested, but will require additional molecular confirmation prior to disclosure.

Drug	Risk and Dosing Information
Warfarin	Increased dose requirement
Clopidogrel	Typical response to clopidogrel
Digoxin	Intermediate metabolism and serum concentration of digoxin
Metformin	Decreased glycemic response to metformin
Simvastatin	Typical risk of simvastatin-related myopathy

RED BLOOD CELL AND PLATELET ANTIGENS

This test identified the ABO Rh blood type as AB Negative. Based on their results, this person is a very desirable universally compatible platelet donor. Additional RBC and platelet antigen information is available at the end of the report.

Blood groups

It should be noted that the disease risk section of this report is limited only to variants with strong 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 context of the patient's medical evaluation, family history, and racial/ethnic background. Please note that variant classification and/or interpretation may change over time if more information becomes available. For questions about this report, please contact the Genome Resource Center at GRC@partners.org.

Vassy, *et al. In press*

Genomics Education for Physicians

Case #	Clinical Content Area	Genomic Concepts
1	Familial Hypercholesterolemia	▪ Autosomal dominant and recessive ▪ Modifying genes and penetrance
2	MODY (Maturity Onset Diabetes of the Young)	▪ Family history and pedigree analysis ▪ Monogenic forms of common disease
3	Myotonic Dystrophy	▪ Expansion repeat disease and anticipation ▪ Variable expressivity
4	*BRCA*-related Disease	▪ Monogenic forms of common disease ▪ Deletion as a mutation mechanism
5	Alzheimer's Disease	▪ Monogenic forms of common disease ▪ Non-Mendalian genetic risk for common disease
6	Cystic Fibrosis	▪ Autosomal recessive carrier state ▪ Incidental diagnosis of mild disease
7	Hypertrophic Cardiomyopathy	▪ Variants of Unknown significance ▪ Database variability
8	Clopidogrel Pharmacogenomics	▪ Cytochrome p450 genetics ▪ Splice inducing mutations
9	Vascular Ehlers-Danlos Syndrome	▪ Ethical, legal and social implications of genomic information ▪ GINA and MA genetic privacy law
10	Age-related Macular Degeneration	▪ Genome Wide Association Studies (GWAS) and risk
11	Atrial Fibrillation	▪ Management advice in the setting of pre-symptomatic risk
12	Thoracic Aortic Aneurysm	▪ Syndromic vs. non-syndromic disease

Courtesy
Michael Murray

First 10 “healthy” genomes

- Monogenic disease risk in 3 patients:

Gene	Condition	Variant classification
LHX4	Combined pituitary hormone deficiency	Pathogenic
KCNQ1	Romano-Ward syndrome (long QT)	Likely pathogenic
ARSE	Chondrodysplasia punctata	VUS: Favor pathogenic

- Carrier variants in all 10 patients (mean 2.2 variants/patient)

Vassy, *et al. In press*

What questions are physicians asking?

Are there standard recommendations for counseling patients concerning the significance of their carrier status for their children?

Would Ehlers-Danlos syndrome have come up on the WGS screen? There is a question of this in my patient's family.

Given that my patient's directed screening for HCM genes was negative, are there standard recommendations on the frequency and means for subsequent genetic reassessments?

What are physicians doing with the results?

PATIENT'S RESULT	TEST ORDERED
MONOGENIC RESULT *KCNQ1* c.826delT: Likely Pathogenic Romano-Ward syndrome	EKG Referral to Cardiovascular Geneticist
CARRIER STATUS *HFE* c.845G>A: Pathogenic Hereditary hemochromatosis	Iron/ferritin studies

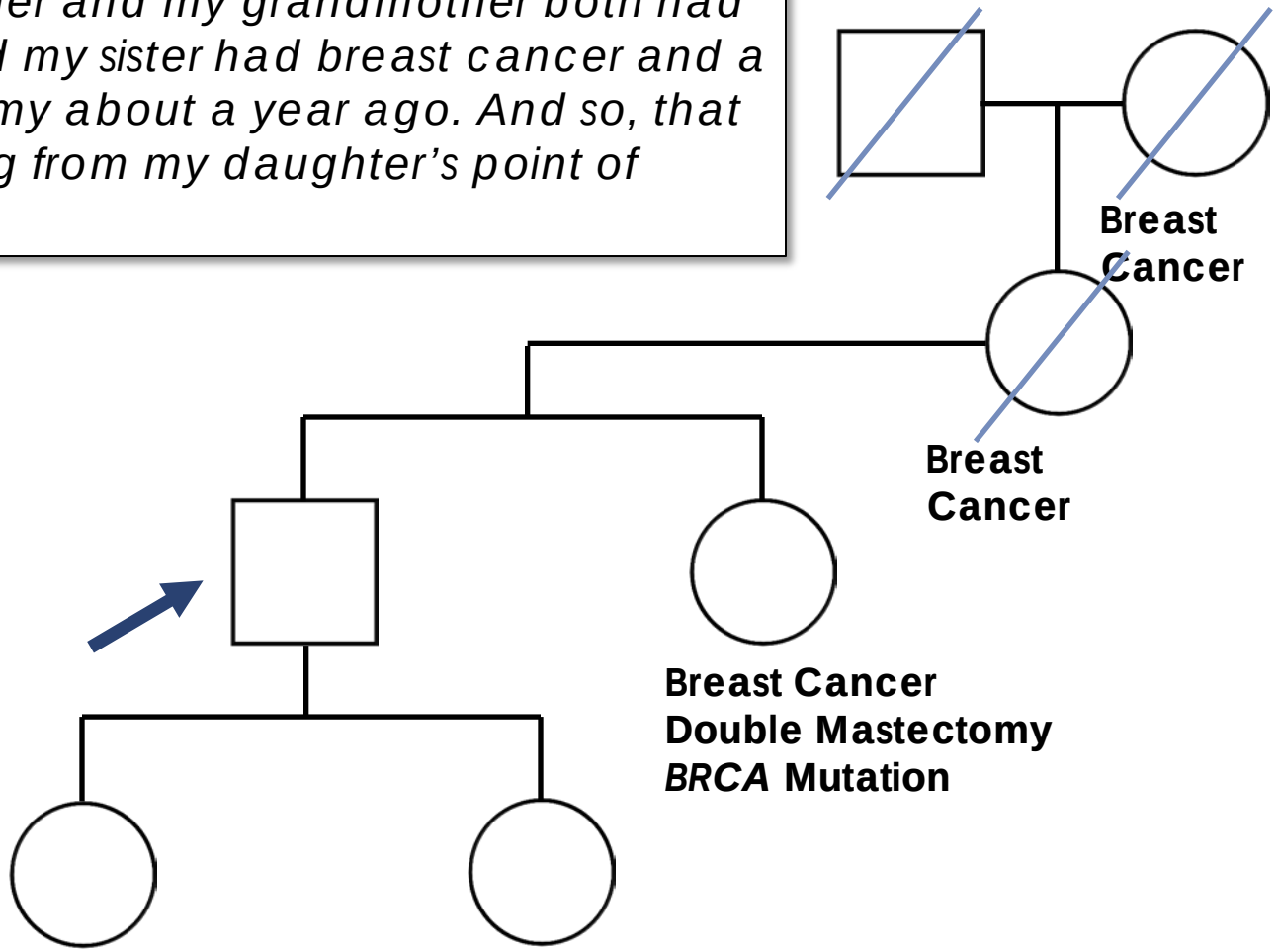
MedSeq™

How are physicians talking about the results with their patients?

“Negative” Finding

PCP asked what type of information the patient thought he might learn through sequencing:

“Actually, my mother and my grandmother both had breast cancer, and my sister had breast cancer and a bilateral mastectomy about a year ago. And so, that might be interesting from my daughter’s point of view.”



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Name: [redacted]
DOB [redacted]
Sex: Male
Race: Caucasian

Accession ID: PM13-00410
Specimen: P
Received: 02

MRN: [redacted]
Family #: F013375 [redacted]

Patient: "I didn't have anything monogenic, which I thought was the main thing I would look for."

RESULT SUMMARY

Sequencing of this individual's genome was performed and covered 95.8% of all positions at 8X coverage or higher, resulting in over 5.1 million variants compared to a reference genome. These data were analyzed to identify previously reported variants of potential clinical relevance as well as novel variants that could reasonably be assumed to cause disease (see methodology below). All results are summarized on page 1 with further details provided on subsequent pages.

A. MONOGENIC DISEASE RISK: 0 VARIANTS IDENTIFIED

This test did NOT identify genetic variants that may be responsible for existing disease or the development of disease in this individual's lifetime.

B. CARRIER RISK: 1 VARIANT IDENTIFIED

This test identified carrier status for 1 autosomal recessive disorder.

Disease (Inheritanc	Phenotype	Gene	Classification	Carrier
B1. Hypothyro (Autosomal rec				

As a carrier for a r
determine the risk
these genes. Othe
may be at risk for

PCP: "Don't assume that *BRCA 1* and *2* were checked here … Don't assume it … I would not make any assumptions whatsoever that this covered that."

C. PHARMACO

This test identified
but will require adc

Drug	Risk and Dosing Information
C1. Warfarin	Increased dose requirement

Themes from Physician-Patient Disclosure Discussions

Theme	Description
Contextualization	Physicians use additional patient information to interp… significance of a WGS result (e.g. age, family hi… …amination) Additional information may be concor… …r uninformative with a WGS result
Limitations of WGS and WGS results	Interpretation … …may be limited by technical deficiencies of sequenci… …cientific understanding …GS result may have no impact on clinical decision-making
Empha… d… …g …esult	The physician indicates whether a WGS result is important or not important for the patient
Recommendation	The physician recommends a clinical action to the patient

Just like other tests in clinical medicine

What information do clinical end-users need to successfully make decisions about health?

- Genetic non-exceptionalism
- Just-in-time information:
  - Test characteristics: limitations, the "denominator"
  - Guidelines or expert recommendations for decision-making
  - Time limits on the validity of the information
- Demonstration of clinical utility

The MedSeq Project Collaborators

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