Challenges to Guideline Development in the Era of NGS

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Disclosures

Research Grants:	NIH
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R01 HG005092 (Green)

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U19 HD077671 (Green/Beggs)

R21 HG00603 (Wang)

R01 HG06379 (Kullo)

U01 AG024904 (Weiner)

R01 HG006615 (Holm)

P60 AR047782 (Kats/Karlson)

P50 HG003170 (Church)

R01 HG007063 (Phillips)

R01 CA154517 (Petersen/Koenig/Wolf)

T32 GM007748 (Morton)

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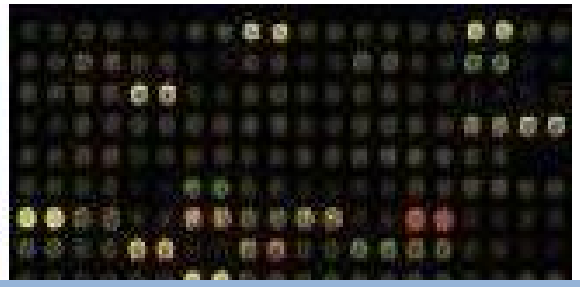
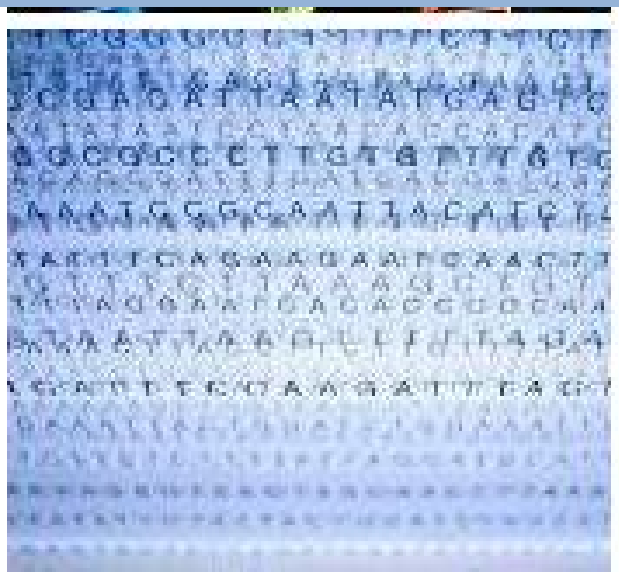
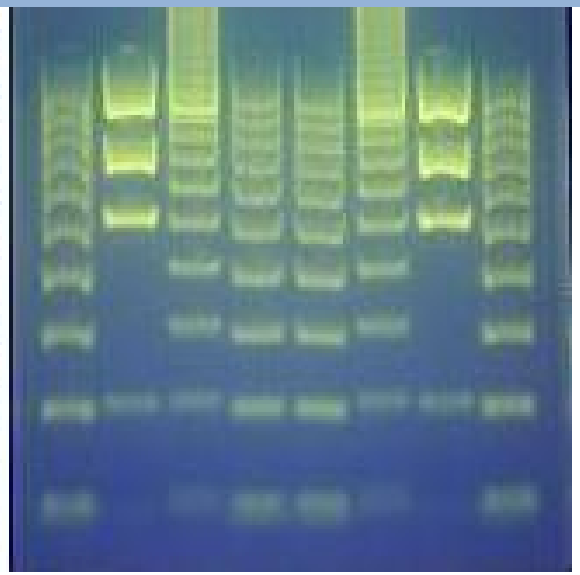


Top 3 Challenges to Guideline Development in the Era of NGS



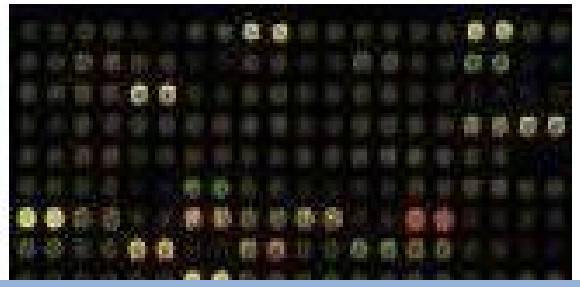


3 Ghosts of Clinical Genomics

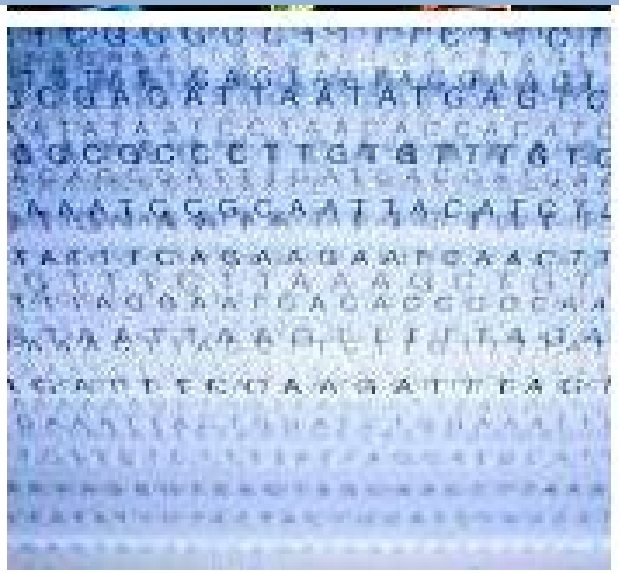
Ghost of Genetic Exceptionalism and False Determinism

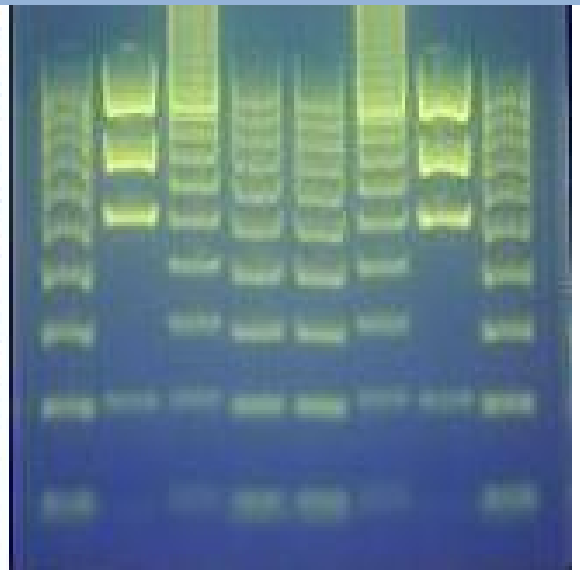
Ghost of Evidentiary Flux

Ghost of Uneven Disintermediation



Gathering Evidence: Observational Studies





Observational Interventions

Personal Genome Project

About ▾ Participate ▾ Researc

Impact of Personal Genomics (PGen) Study

HG005092 (2010-2014)

PATHWAY GENOMICS

23andMe

Share Print

e Also:

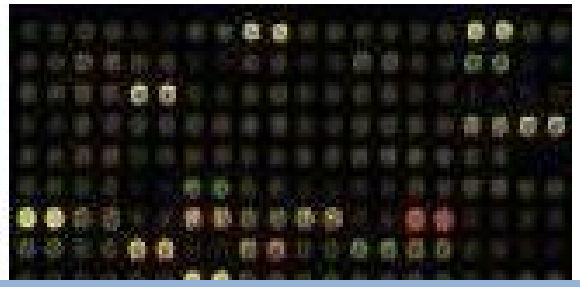
ns-NIH Study Explores
dical Role for Genome
quencing
rn more about ClinSeq

bout the role that your
sample from you,
ing that to what we
Ve are able to look at
nclude things like heart

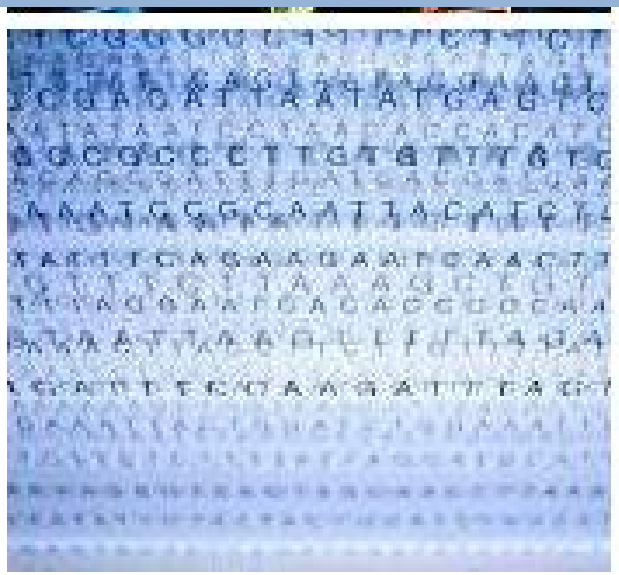
far, we have over 900
study. Each member of
ealth. Study members

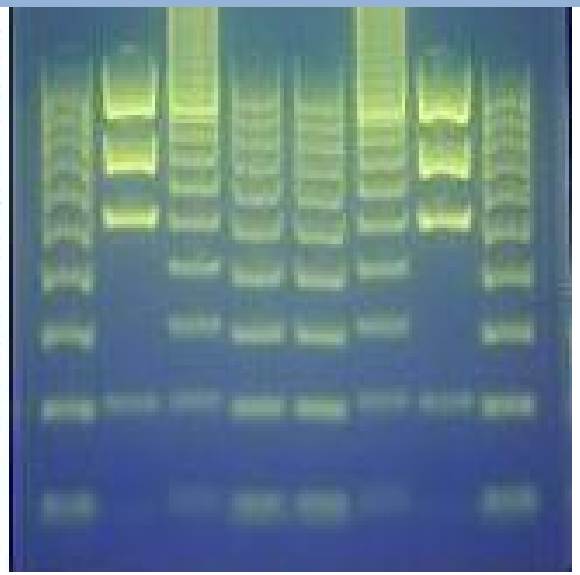
Welcome to the Cori

also give us information on their family and medical histories. Finally, blood samples are taken for routine tests that look for health problems such as diabetes and high cholesterol, as well as for genetic testing. Participants get the results of all their testing (except the genetic tests) about one month after their visit. Study members receive the results of their genetic testing when they are available.



Gathering Evidence: Randomized Trials





The REVEAL Study

HG002213 (2000-2014)

The MedSeq Project

HG006500 (2013-2017)

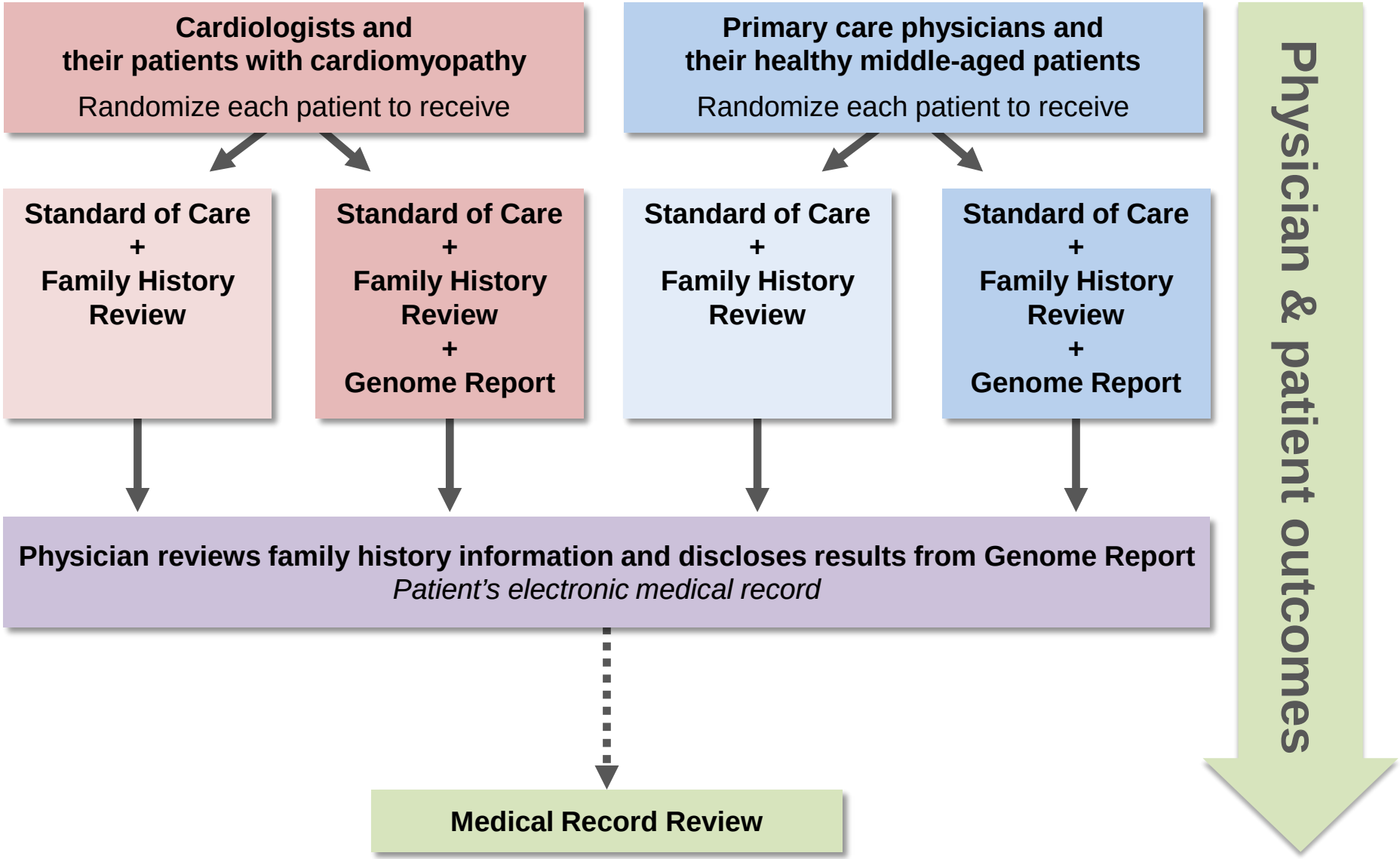
BWH

Baylor College of Medicine

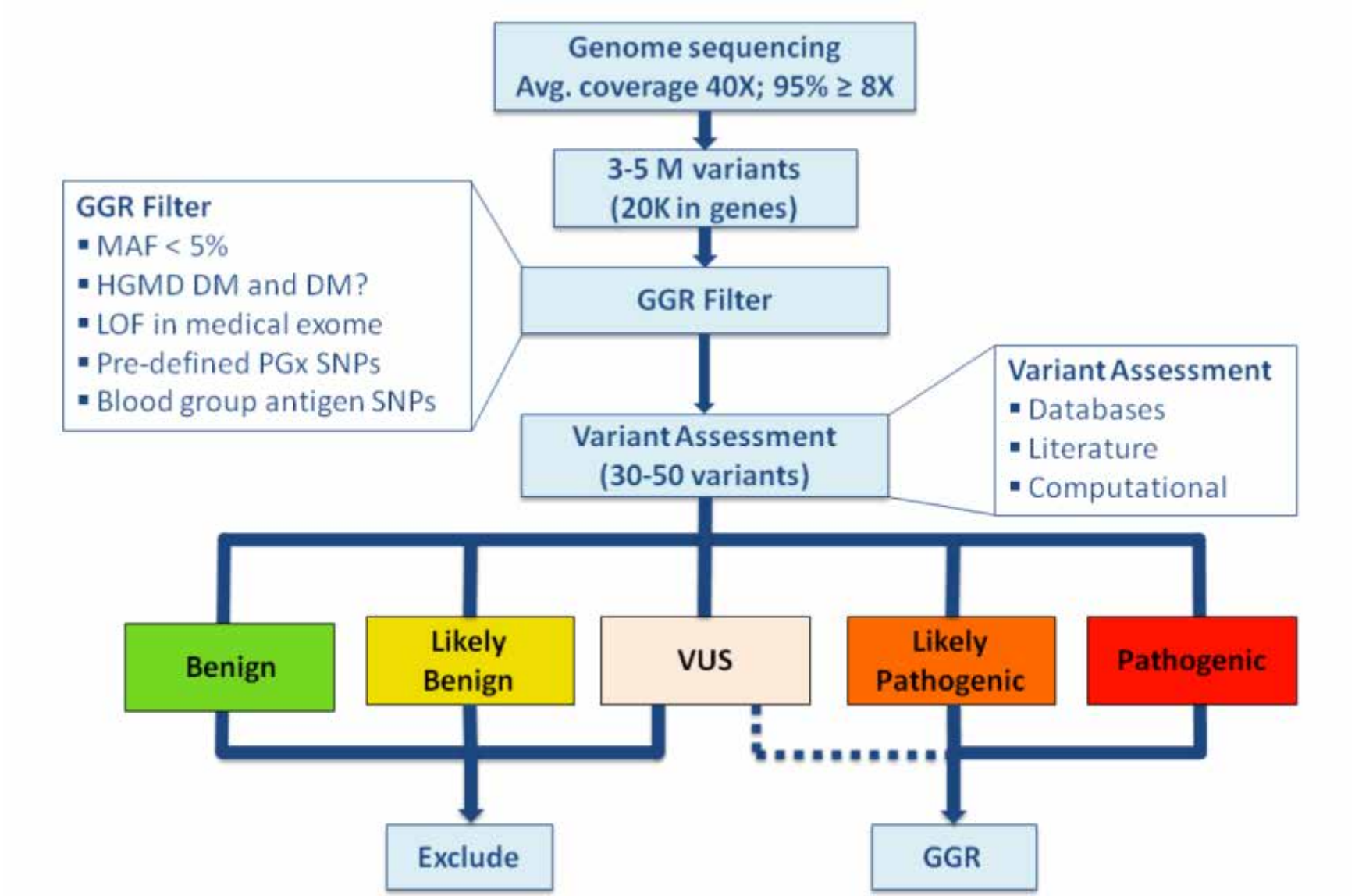
GEISINGER

The MedSeq Project

U01 HG006500 (2012-2016)



Variant Filtering and Interpretation



Slide courtesy of Heidi Rehm

MedSeq Project
"General Genome Report"

1 Page Summary…

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

- Additional Pages…
  - Structured variant data
  - Variant evidence
  - Disease/inheritance
  - Supporting references

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http://pcpgm.partners.org/lmm

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

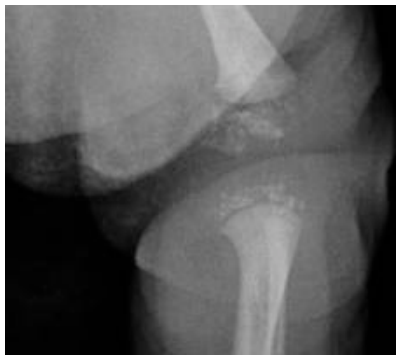
This test identified the ABO Rh blood type as O positive. Additional blood group information is available at the end of the report.

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

Incidental Positive Finding

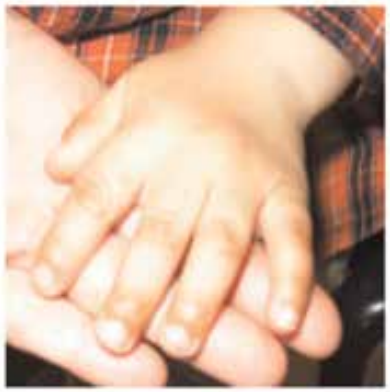
ARSE c.410G>C (p.Gly137Ala) Hemizygous
Pathogenic ARSE variants à XLR chrondodysplasia punctata 1 (CDPX1)

- Most males have mild disease that improves by adulthood
- Variable intrafamilial disease expression



Epiphyseal stippling (100%)
Brachytelephalangy (68%)
Nasomaxillary hypoplasia (58%)

Minimal morbidity



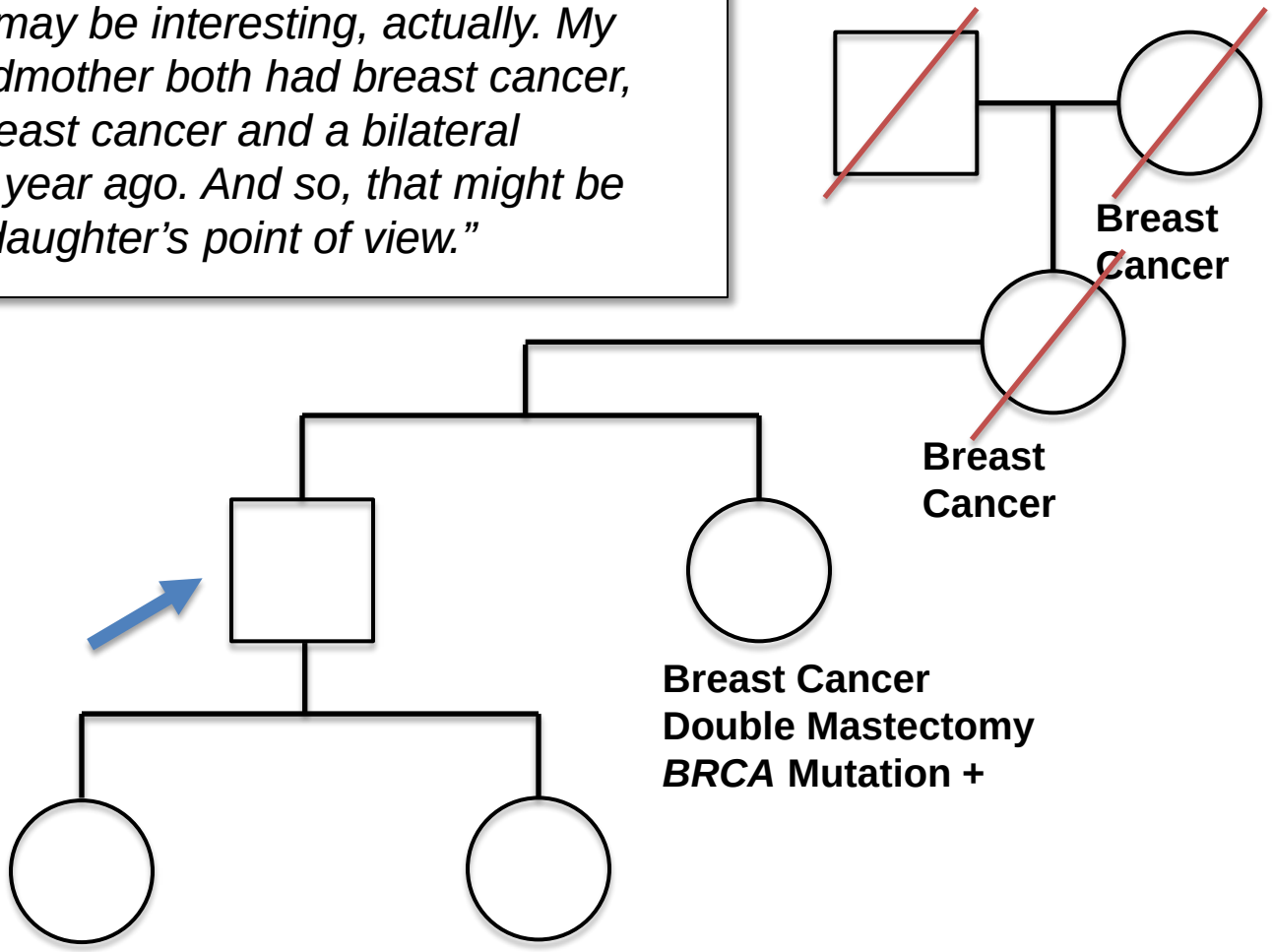
Severe morbidity
Respiratory disease (32%)
Cervical spine stenosis (19%)
Hearing loss (26%)
Cognitive delay (16%)
Eye abnls (16%)
Cardiac abnls (13%)
Infant demise (13%)

Slide courtesy of Heidi Rehm

Incidental “Negative” Finding

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

“Only one thing that may be interesting, 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.”



Recent Disclosure via Primary Care MD

GENERAL GENOME REPORT

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.

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

"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."

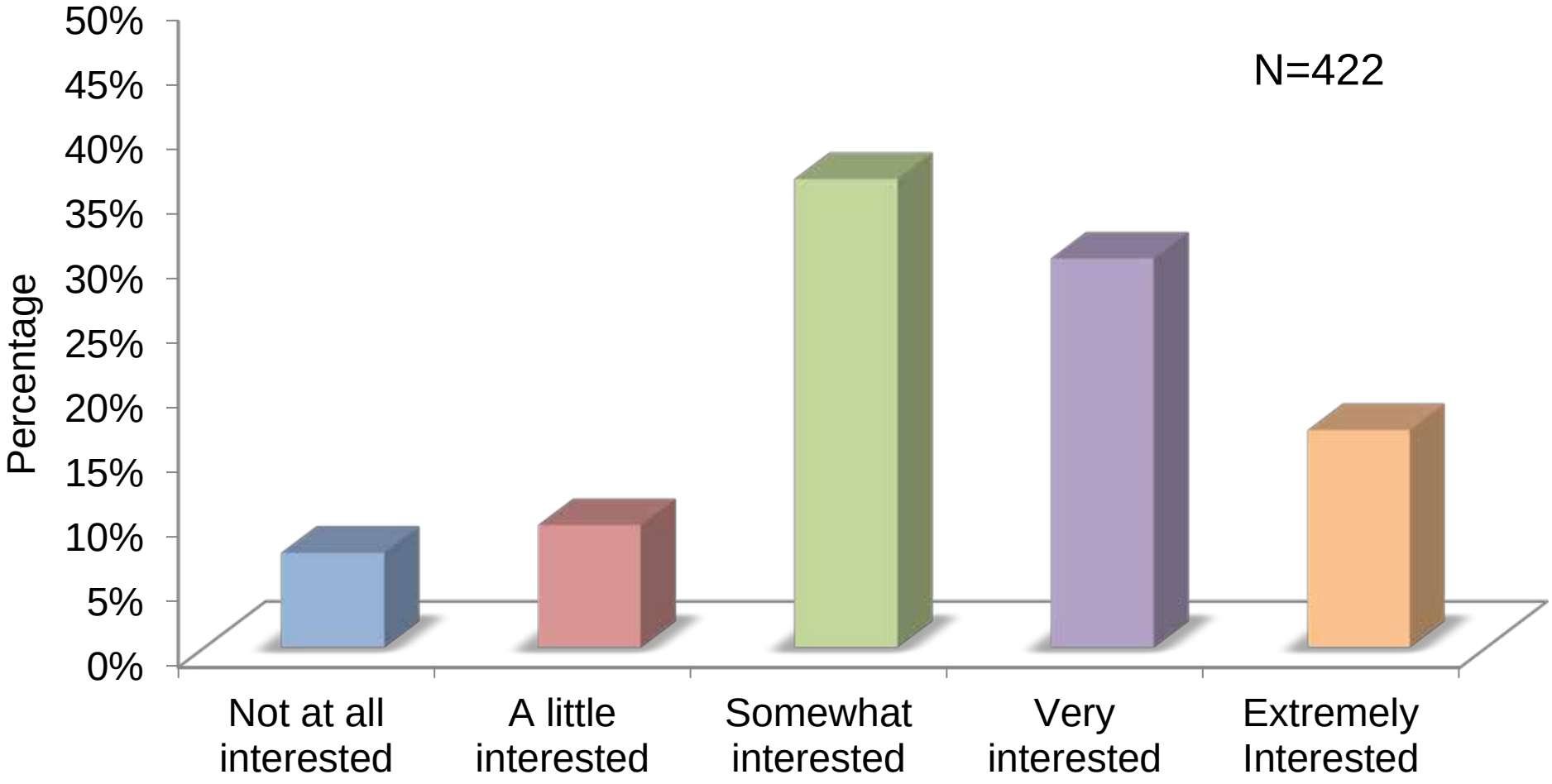
The BabySeq Project

HD077671 (2013-2018)

Alan Beggs/Robert Green (PIs)

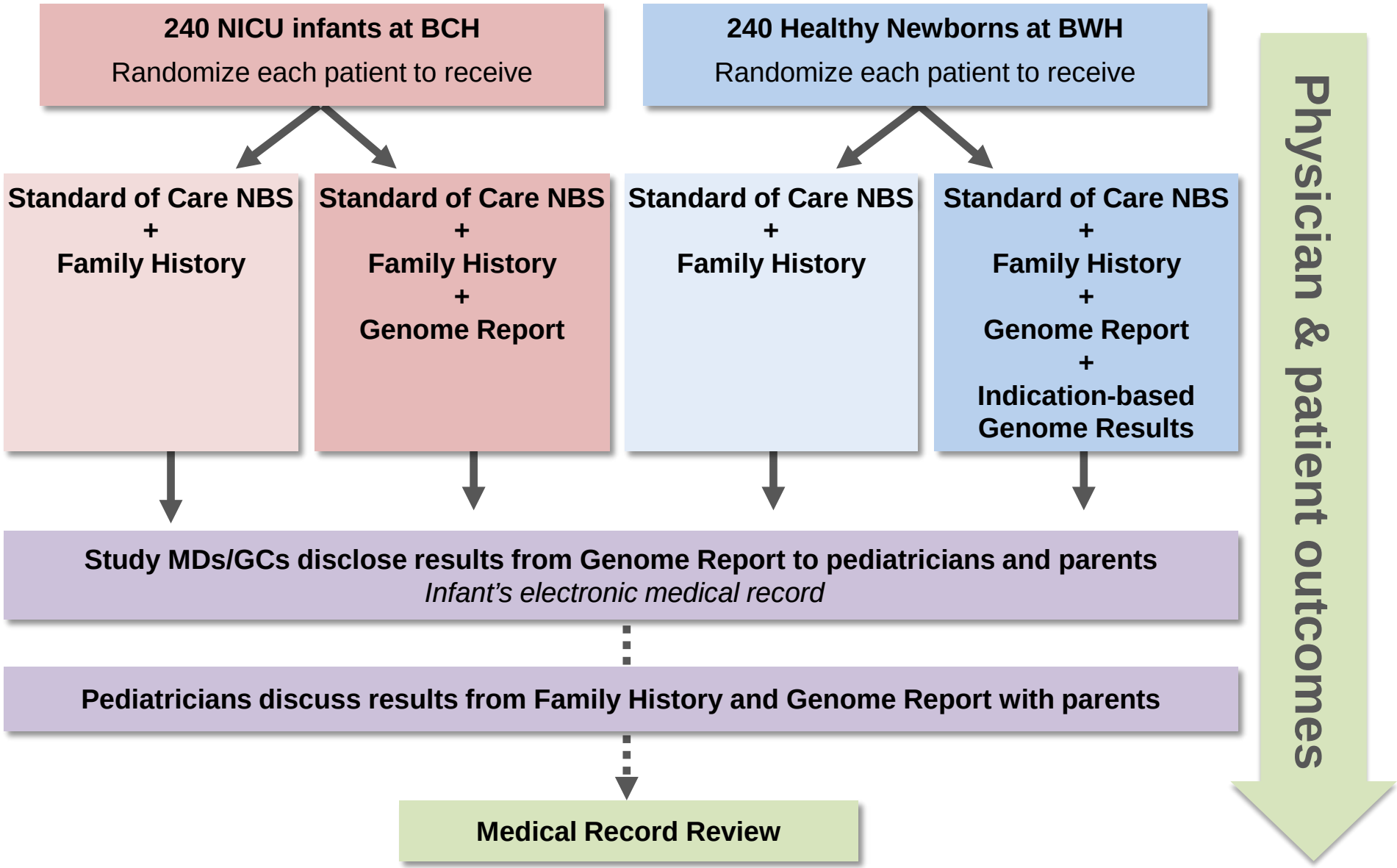
Peter Park, Heidi Rehm, Pankaj Agrawal, Richard Parad, Ingrid Holm, Amy McGuire (co-PIs)

How interested would you be in genome screening for your baby?



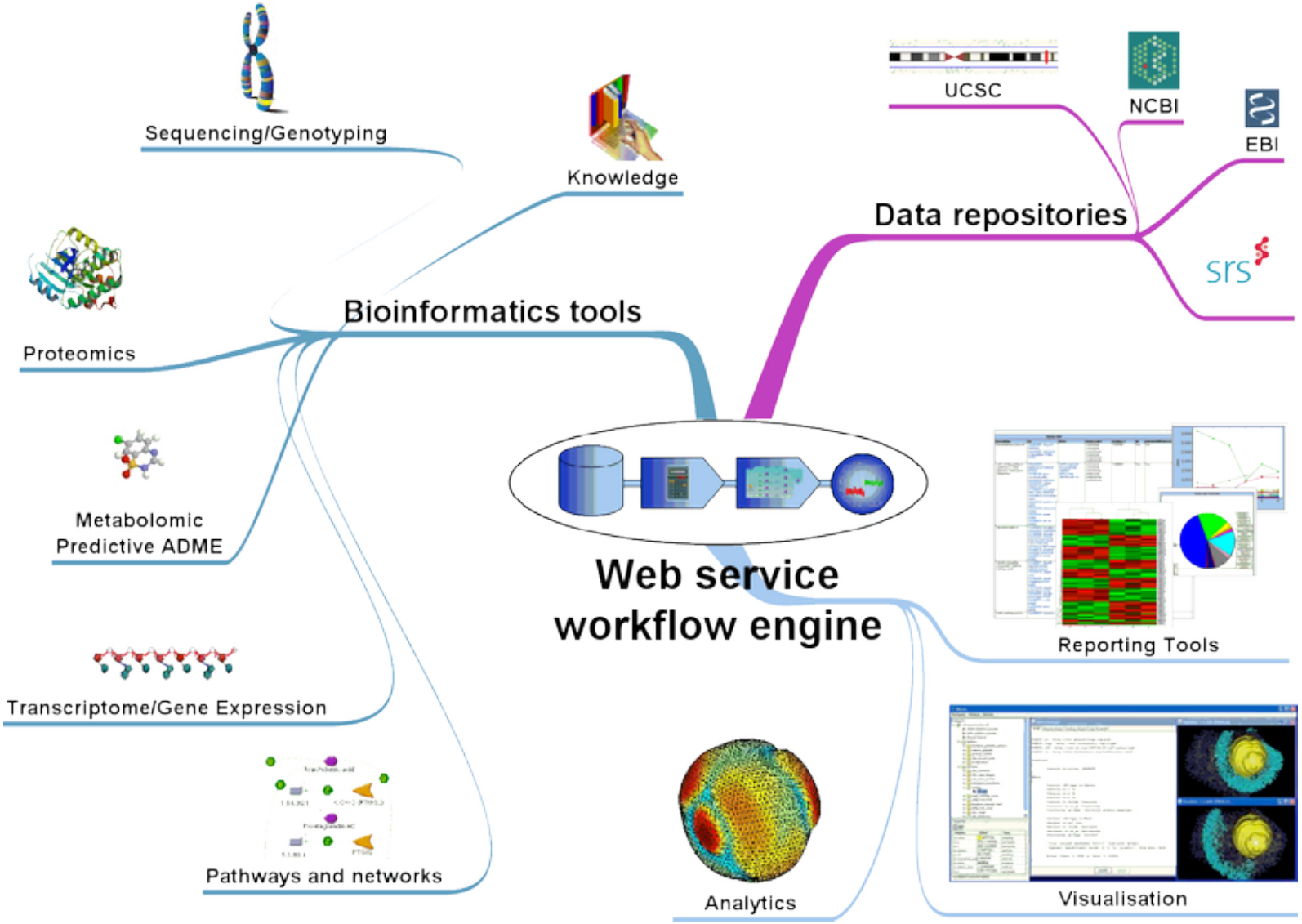
The BabySeq Project

U19 HD077671 (2013-2018)

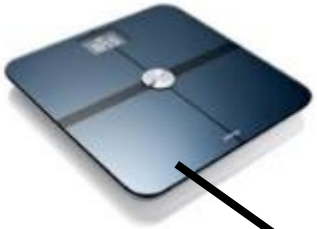


DNA Guide's Personal Genome Browser: Mobile Application for iPhone, Droid, or Blackberry

Analytic Integration in Genomics

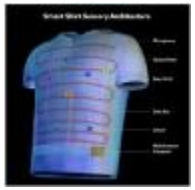


The Quantified Self
self knowledge through numbers



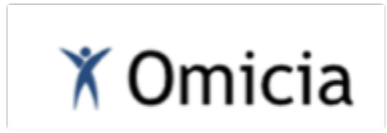
Intelligent
Integration

Making it
ACTIONABLE



Slide courtesy of Daniel Kraft

Commercial Genomics Solutions



Regulation of Consumer Genomics

COMMENT

A lab technician scans a consumer gene-testing kit.

The FDA is overcautious on consumer genomics

The US drug agency's clampdown is unwarranted without evidence of harm, say **Robert Green** and **Nita Farahany**.

consumer genomic testing u
empirical evidence of harm.

Certainly, there are legit
about 23andMe's approach
accuracy of the technology
ered to be high, there are n
ards to which the company
validating hundreds of simu
calls. There is also controver
evaluate the accuracy of risks
multiple variants or across e
consumers might not read
stand the company's clear st
tests identify only the most
variants and cannot substitut
ing ordered by physicians t
indications, such as a family

Nonetheless, as scholars
individuals respond to the
information, we contend
precautionary approach ma
threat to consumer health
that it seeks to prevent. Data
5,000 participants suggest
genomics does not provoke
propriate treatment.

EMERGING EVIDENCE

Over the past five years, we
surveyed people receiving co
ics results, asking whether t
them and whether the fin
distress, prompted a visit
change in medication or life

In 2009, the Scripps G

Ghosts of Clinical Genomics

Genetic Exeptionalism & False Determination

Evidentiary Flux

Uneven Disintermediation


The Problem of
Incidental Findings

ACMG POLICY STATEMENT | Genetics inMedicine

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 L. McGuire, JD, PhD[9], Robert L. Nussbaum, MD[10], Julianne M. O'Daniel, MS, CGC[3], Kelly E. Ormond, MS, CGC[11], Heidi L. Rehm, PhD, FACMG[2,12], Michael S. Watson, PhD, FACMG[13], Marc S. Williams, MD, FACMG[14] and Leslie G. Biesecker, MD[15]

"minimum list"

standardized search and reporting

consistent with practice of medicine and patient expectation

expert consensus and regular revision

ACMG Recommendations
Divergence from Current Genetics Practice

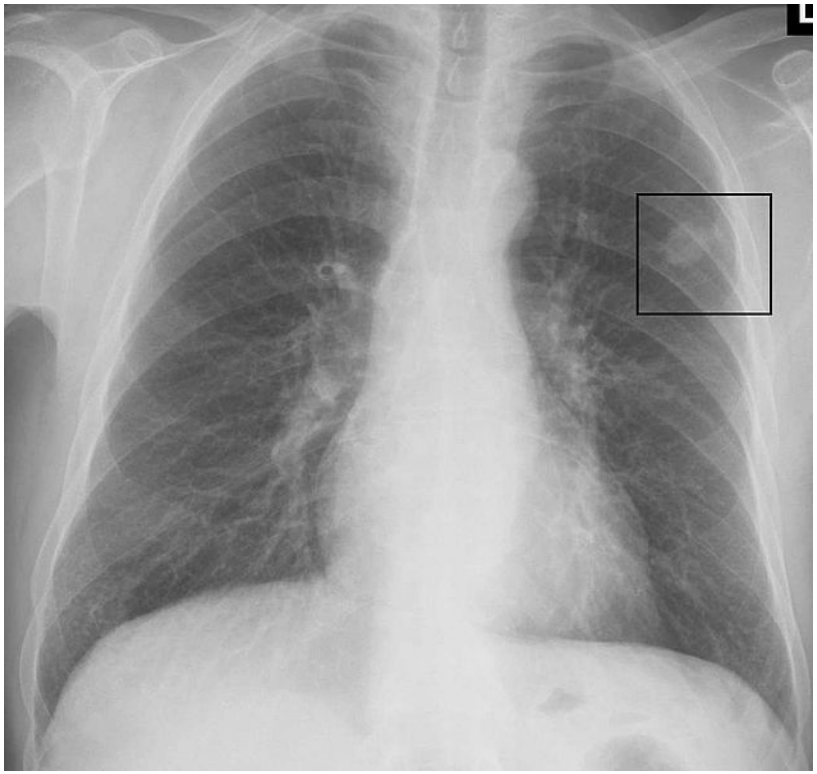
- Systematically include positive findings in the report returned to clinicians for exome and genome sequencing.

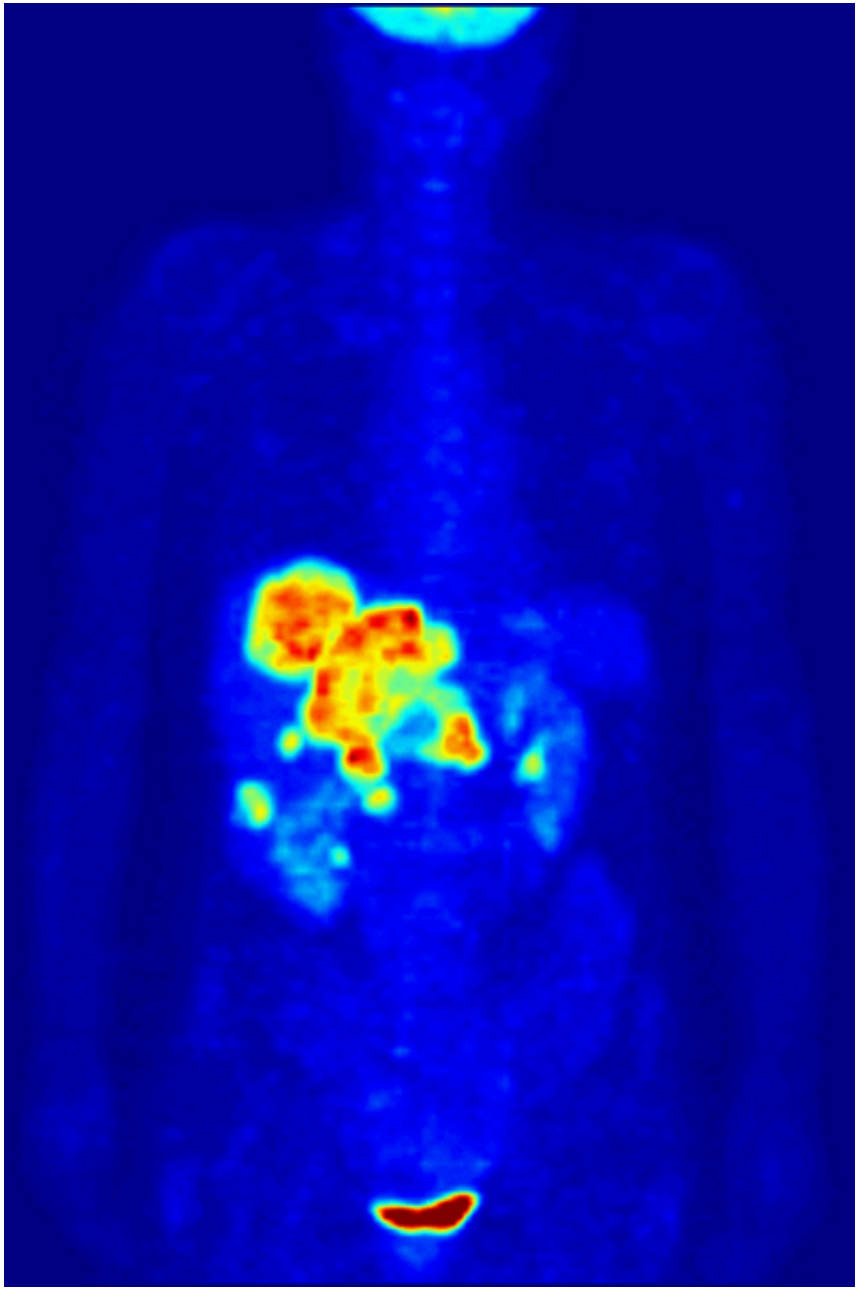
- Return same findings regardless of the age of the patient.

Convergence with Current Medical Practice!

Incidental Findings:

What is the right analogy?





SPECIAL ARTICLE | Genetics inMedicine

Recommendations for returning genomic incidental findings? We need to talk!

Wylie Burke, MD, PhD[1], Armand H. Matheny Antommaria, MD, PhD[2], Robin Bennett, MS, CGC[3], Jeffrey Botkin, MD, MPH[4], Ellen Wright Clayton, MD, JD[5], Gail E. Henderson, PhD[6], Ingrid A. Holm, MD, MPH[7-9], Gail P. Jarvik, MD, PhD[3], Muin J. Khoury, MD, PhD[10], Bartha Maria Knoppers, JD, PhD[11], Nancy A. Press, PhD[12], Lainie Friedman Ross, MD, PhD[13], Mark A. Rothstein, JD[14], Howard Saal, MD[15], Wendy R. Uhlmann, MS, CGC[16], Benjamin Wilfond, MD[17], Susan M. Wolf, JD[18] and Ron Zimmern, FRCP, FFPHM[19]

Sciencexpress

Patient Autonomy and Incidental Findings in Clinical Genomics

Susan M. Wolf,[1*] George J. Annas,[2] Sherman Elias[3]

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*Corresponding author. E-mail: swolf@umn.edu

Returning genetic incidental findings without patient consent is misguided.

VIEWPOINT

Mandatory Extended Searches in All Genome Sequencing

"Incidental Findings," Patient Autonomy, and Shared Decision Making

Lainie Friedman Ross, MD, PhD
Department of Pediatrics, University of Chicago, Chicago, Illinois.

Mark A. Rothstein, JD
Institute for Bioethics, Health Policy and Law, University of Louisville School of Medicine, Louisville, Kentucky.

Ellen Wright Clayton,

Should incidental findings discovered with whole-genome sequencing or testing be sought and reported to ordering clinicians and to patients (or their surrogates)? —**No.**

An incidental finding occurs when a medical test or procedure directed at one condition unexpectedly reveals a separate finding. An example would be when a radiologist notices a chest mass on abdominal computed tomography. By contrast, the American College of Medical Genetics and Genomics (ACMG) statement proposes that whenever genome sequencing is ordered in the clinical setting, laboratories have a mandatory duty to analyze 57 genes (revised to 56 genes) and

chemotherapy (eg, tamoxifen) or surgery to reduce their risk of developing cancer. All of these recommendations have health risks of their own: radiation exposure from mammograms, increased risk of thrombophlebitis from the medication, and operative and postoperative complications from surgery as well as the psychosocial costs of perceiving oneself as high risk. As the US Preventive Services Task Force reaffirmed in its 2013 draft update on "Risk Assessment, Genetic Counseling, and Genetic Testing for *BRCA*-Related Cancer," these interventions may cause more harm than good when offered and used by women who are less likely to develop disease.[5]

Sciencexpress

Ethics and Genomic Incidental Findings

Amy L. McGuire,[1*] Steven Joffe,[2*] Barbara A. Koenig,[3] Barbara B. Biesecker,[4] Laurence B. McCullough,[1] Jennifer S. Blumenthal-Barby,[1] Timothy Caulfield,[5] Sharon F. Terry,[6] Robert C. Green[7†]

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Children's Hospital, Harvard Medical Sch
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*Corresponding authors. E-mail: amcgui

†Although some of us (A.L.M., R.C.G.) v
recommendations, this paper does not re

Laboratories have an obligation

COMMENTARY | Genetics inMedicine

When is a medical finding "incidental"?

James P. Evans, MD, PhD[1]

VIEWPOINT

Reporting Genomic Sequencing Results to Ordering Clinicians

Incidental, but Not Exceptional

Robert C. Green, MD, MPH
Division of Genetics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts.

James R. Lupski, MD, PhD, DSc
Departments of Molecular and Human

Should incidental findings discovered with whole-genome sequencing or testing be sought and reported to ordering clinicians and to patients (or their surrogates)?—**Yes.**

The use of genomic sequencing in medicine is increasing substantially as this technology becomes less expensive and of demonstrated diagnostic utility.[1,2] Potentially clinically relevant incidental findings from clinical exome or genome sequencing (hereafter referred to as genomic sequencing) will arise whenever an individual undergoes genomic sequencing. There is a great deal of controversy regarding how such findings should be addressed by clini-

chest x-ray for the evaluation of a possible rib fract
he or she has been trained to perform a systematic
view of the film, reporting any abnormalities that ris
an established professional standard, regardless of
indication for the study.[7] Importantly, radiologists
specifically trained neither to report every conceiva
finding, nor to stop after "satisfaction of search"[8]
veals an indicated finding. Rather radiologists use
fessional standards to assess and report a subse
unexpected findings that are likely to be medically
portant. Even though such findings are not always c
cally useful, depriving clinicians and patients of these

The MedSeq Project Collaborators

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MEDSEQ

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