Changes in Evidence and Thus Updating Recommendations, Treatment/Care

Genomic Medicine VIII

Panel 3: Katrina Goddard, Robert Green, Howard Jacob, Sharon Plon

Challenges: Dynamic Nature of Genomic Medicine Data

- NextGen data continues to evolve with major changes expected in the near term:
  - Increased read-length
  - Decrease cost
  - Increasing use of whole genomes for clinical purposes.
- Genome analytics and laboratory reporting is nascent and will also change rapidly as the knowledgebase increase.
  - Correction of errors in the literature and early reports
  - Conversion of VUS and GUS to knowledge
- Genomic data's impact on treatment will remain dynamic as knowledgebase increases in all aspects of reporting.
  - Primary results
  - Secondary results
  - Incidental results

Sources of Errors in Clinical Reporting

- **Limited genotype/phenotype correlations.**
  - Both correct and incorrect correlations exist in the literature.
  - Range of phenotypic expression is uncertain/unknown.
- **Over/under reporting of results based on varying clinical platforms and guidelines**
- **Errors in sequence data**
  - Including incomplete sequence information
  - Error rates vary depending on the type of variant
- **Errors in sequence analysis pipelines**
- **Errors in sample tracking and other standard clinical laboratory errors.**
- **Errors in combining sequence data with other clinical data at the level of treating physician.**

Changes in Treatment/Care

- **Clinical implementation will change dramatically with emerging definitions of what is Actionable and Clinical Utility.**
  - Different medical specialties could have different definitions of what is actionable.
  - Clinical utility has a different meaning to the patient, physician and payer.
  - How will these different definitions be managed in the context of the dynamic nature of the genomic medicine data?
- **Increasing number of drugs with companion molecular diagnostics (theranostics) are tested and approved.**
  - Indications for existing drugs may also be paired with molecular tests as knowledge is gained, e.g. Erlotinib

Companion Diagnostics

- **Companion Diagnostics are the test(s) that are submitted along with new drug applications to the FDA for targeted/precision medicines:**
  - Relies on a specific method to detect mutations
  - Generally focus on a limited number of mutations with strongest indication for efficacy
  - Alternatively analysis of a specific gene may be approved, e.g. *BRCA* testing by Myriad Genetics
  - Once a clinical genome exists—the data can be used for companion diagnostics. If there is the means to link the data with drug in a physicians office

Changes to Treatment

- **Pharmacogenomics is likely to become more common across the clinical continuum.**
  - Current NextGen tests often have minimal pharmacogenomic reporting.
  - Will this data be regulated differently (e.g. be FDA specific)?
- **How will data related to a patient's genome be stored in EMR for future use when new medications are prescribed?**

Re-analysis of Genomic Data

- **Where will the variant data be stored long term?**
- **Who will do the re-analysis?**
- **How will the rate of re-analysis be set?**
- **How will the re-analysis be paid for?**
- **Will variants be re-analyzed in the context of primary, secondary or incidental?**
- **What category will a variant be for pharmacogenomics**
  - Primary for a new drugs in the future?
  - Secondary for a drug the patient is taking when sequenced for a diagnosis?
- **Need to be prepared for the re-analysis to not only uncover new, actionable findings, but to also result in some prior findings becoming irrelevant**

Duty to Inform

- **Are changes needed to the laws and regulations required around what constitutes duty to inform?**
- **What changes to the dynamic knowledge of a patient's genome data mandates re-contact or re-reporting?**
  - If there were patient portals (e.g. MyChart for genomic medical data). Could/Should all new data simply be put in this patient's portal?
  - Should there be a separate clinical visit?
  - How will it be paid for?
  - Should all data types be updated or only the primary?
- **How can physicians/patients be updated without alert fatigue?**
- **Will there be different rules applied to different specialties?**
- **Are there different rules for the type of variant (primary, secondary, incidental)?**

Guidelines for Reporting Results from Different Types of Testing are still evolving

- **ACMG has recently announced new recommendations for germline testing focused on Mendelian disorders:**
  - Does not include pharmacogenomics or common alleles
- **Efforts underway (AMP/ClinGen/CSER) to define somatic mutations.**
  - Will methylation status be encompassed by these guidelines?
- **No agreed upon guidelines for:**
  - RNA expression (e.g. OncotypeDX, Mammoprint vs. NextGen RNAseq).
  - Circulating DNA
  - Single cell analysis
- **How/who should these guidelines be defined and evolved?**
- **How will the changes in these data types be updated?**
- **It is likely that these different tests will be performed by different laboratories. How will these data be integrated, interpreted and conveyed to the patient and physician?**

Solutions for these Challenges

- **Bring Genetics, Pathology and Specialty Groups (with CMS/Payers?) together to set guidelines.**
  - Include patient advocates when possible
- **Fund and Develop "clinical trial" type studies to study data return, duty to inform, within the three areas: Rare disease, cancer, healthy patients.**
- **What should be done to define clinical utility and what is actionable?**
  - Double blind clinical trials—are not the correct study design.
  - How should/could this be done?

Main Points for Panel 3

- **The dynamic nature of genomic medicine data creates a series of problems in returning of results and to patients and physicians.**
  - Physicians outside genetics have little understanding of this dynamic nature and limitations of different genomic methods
  - Returning genomic data to different ethnic groups, age groups, and levels of education and wealth makes it more complicated.
  - Tests can be rapidly integrated (NIPT) and disrupt current practice
  - Can FDA companion diagnostic process keep up with rapidly evolving genomic data?
- **Genomic data re-analysis/retesting will increase as utility increases.**
- **Genomic sequence is only the first of the 'omic types of dynamic data that will be incorporated into healthcare.**
- **The challenges cross multiple disciplines, governance and legal requirements, making finding solutions problematic.**

Examples of Developing Evidence for the Clinical Practice of Genomic Medicine

- Diagnostic exome and genome sequencing

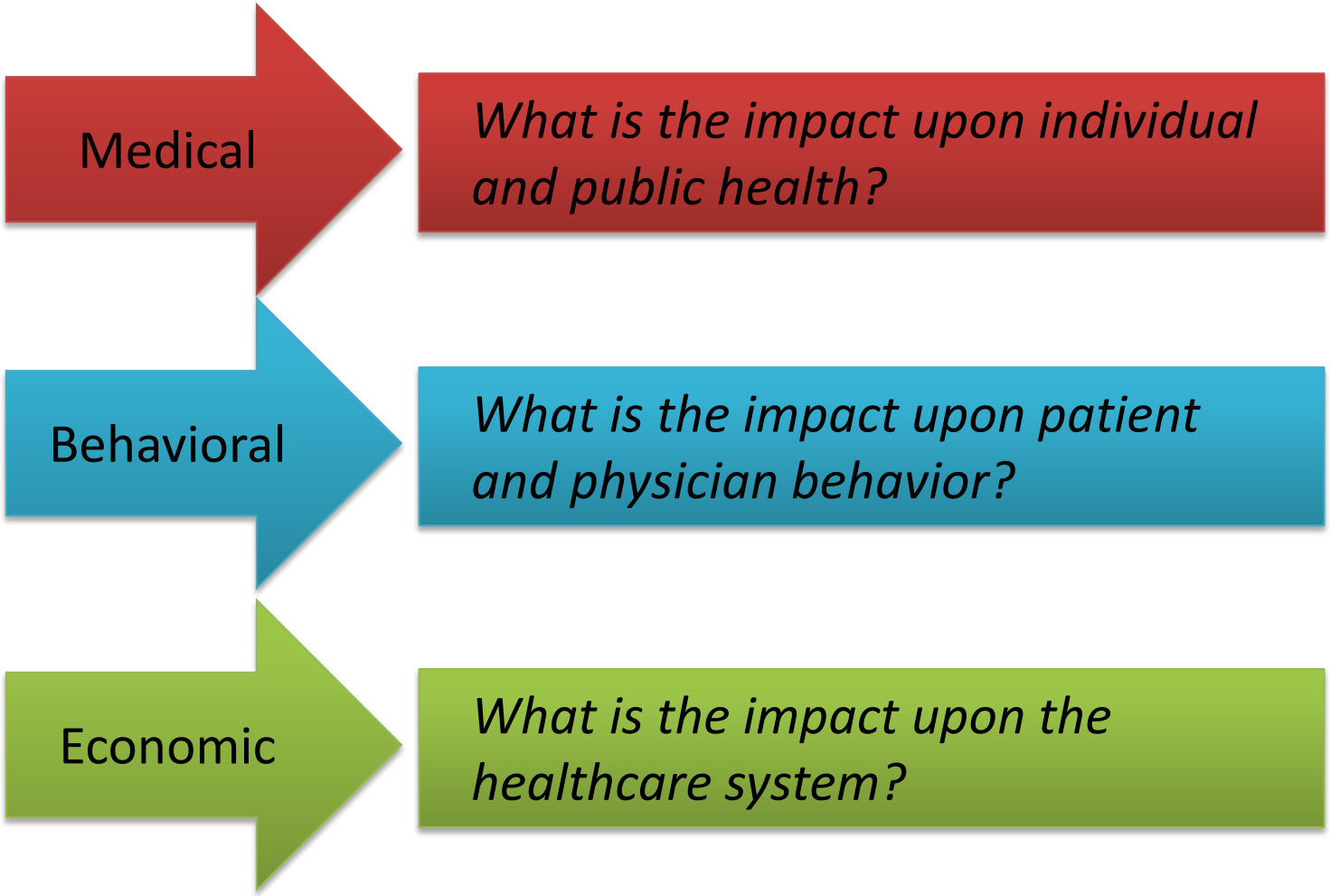
- Incidental or secondary findings
- Medical actionability and other forms of utility
- Penetrance of variants
- Intermediate and scalable phenotyping
- Population screening

CSER sites projected sample sizes

Projected Number of Sequenced Subjects			
Site	Project	Pediatric Sample Size (2017)	Adult Sample Size (2017)
BCM	BASIC3	250	-
NHGRI	ClinSeq	-	1500
DFCI	DFCI	-	250
HudsonAlpha	HudsonAlpha	393	886
BWH/Harvard	MedSeq	-	103
U. Michigan	MI-Oncoseq	247	751
UNC	NCGENES	196	475
Kaiser	NextGen	-	180
U. Washington	NextMed	-	150
CHOP	PediSeq	250	450
Total		**1336**	**4745**

Slide courtesy of Katrina Goddard

Examining Outcomes in Genomic Medicine



Beyond the ACMG-56: Secondary Findings in CSER

Category	Sample Size	Number (%) of subjects with ≥1 Finding	Range (sites)
ACMG Incidental Findings: Pathogenic	2429	41 (1.7%)	0%-8% (10)
ACMG Incidental Findings: Likely Pathogenic	2372	15 (0.6%)	0%-8% (8)
Non-ACMG: Pathogenic	2429	39 (1.6%)	0%-8% (10)
Non-ACMG: Likely Pathogenic	2372	15 (0.6%)	0%-5% (8)
PGx Genes: FDA Indication	1820	28 (1.5%)	0.16%-88% (3)
PGx Genes: Other	206	4 (1.9%)	1.9% (1)
Carrier Genes: Pathogenic	1976	324 (16%)	0%-79% (9)
Carrier Genes: Likely Pathogenic	1968	138 (7%)	0%-40% (8)
Tumor: Potentially Clinically Relevant	120	106 (88%)	28%-100% (3)

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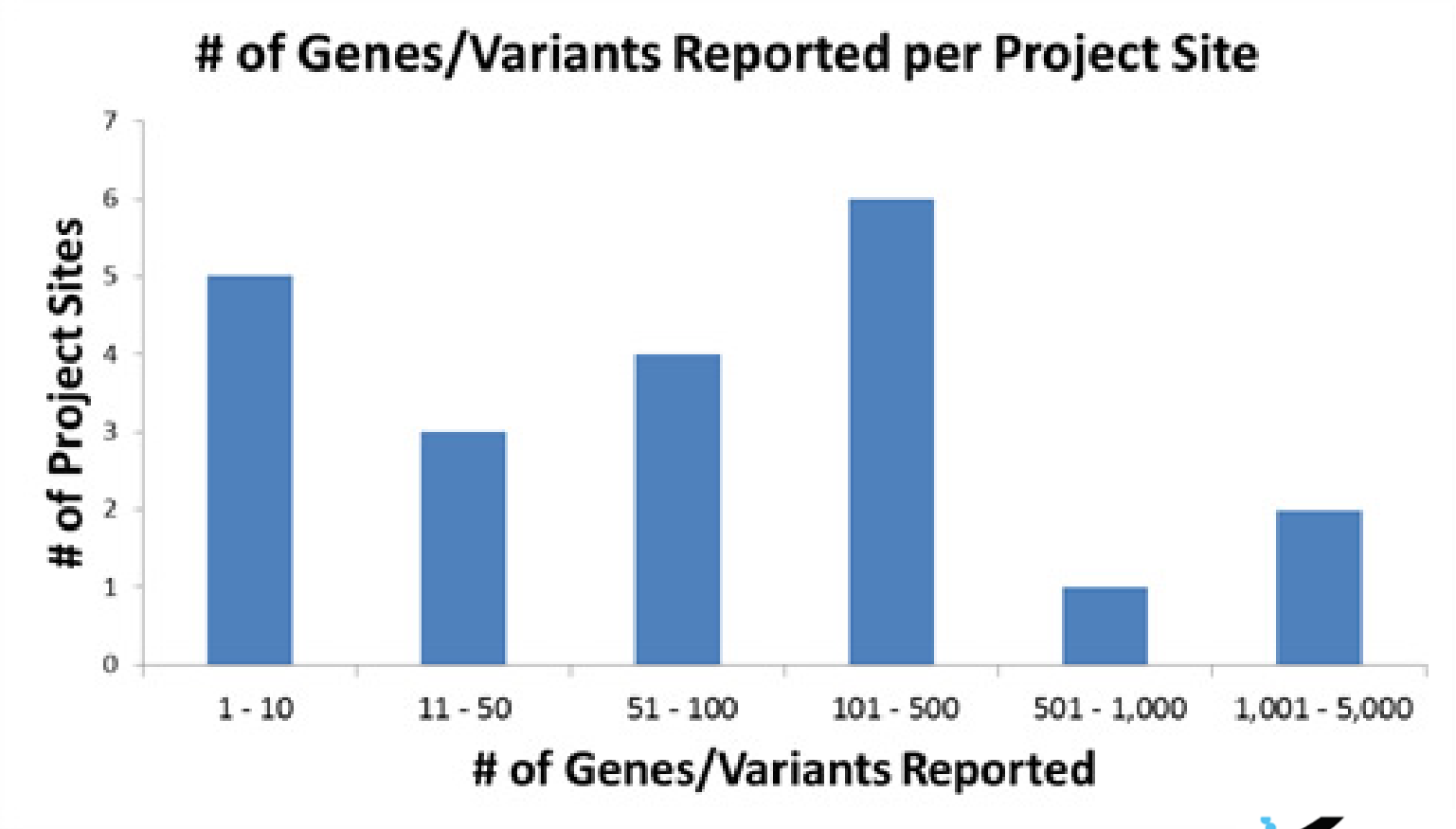
Secondary Findings Reportable by NHGRI Genomic Medicine Research Programs



www.genome.gov/27560596

cser
Clinical Sequencing Exploratory Research

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Modeling Cost-Effectiveness Ratios of Secondary Findings

Compared to Standard of Care or Next Best Strategy	5 Lynch genes	10 genes =5+AD ↑ Penet	11 genes= 10+AR ↑ Penet	19 genes 11+AD ↓ Penet
Δ Costs	$2,800	$4,500	$4,700	$670
Δ Quality Adjusted Life Years (QALY)	0.019	0.121	0.128	0.009
Cost per QALY gained	$144,200	$37,500	$36,500	$77,300

Gallego et al, *J Clin Oncol* 2015

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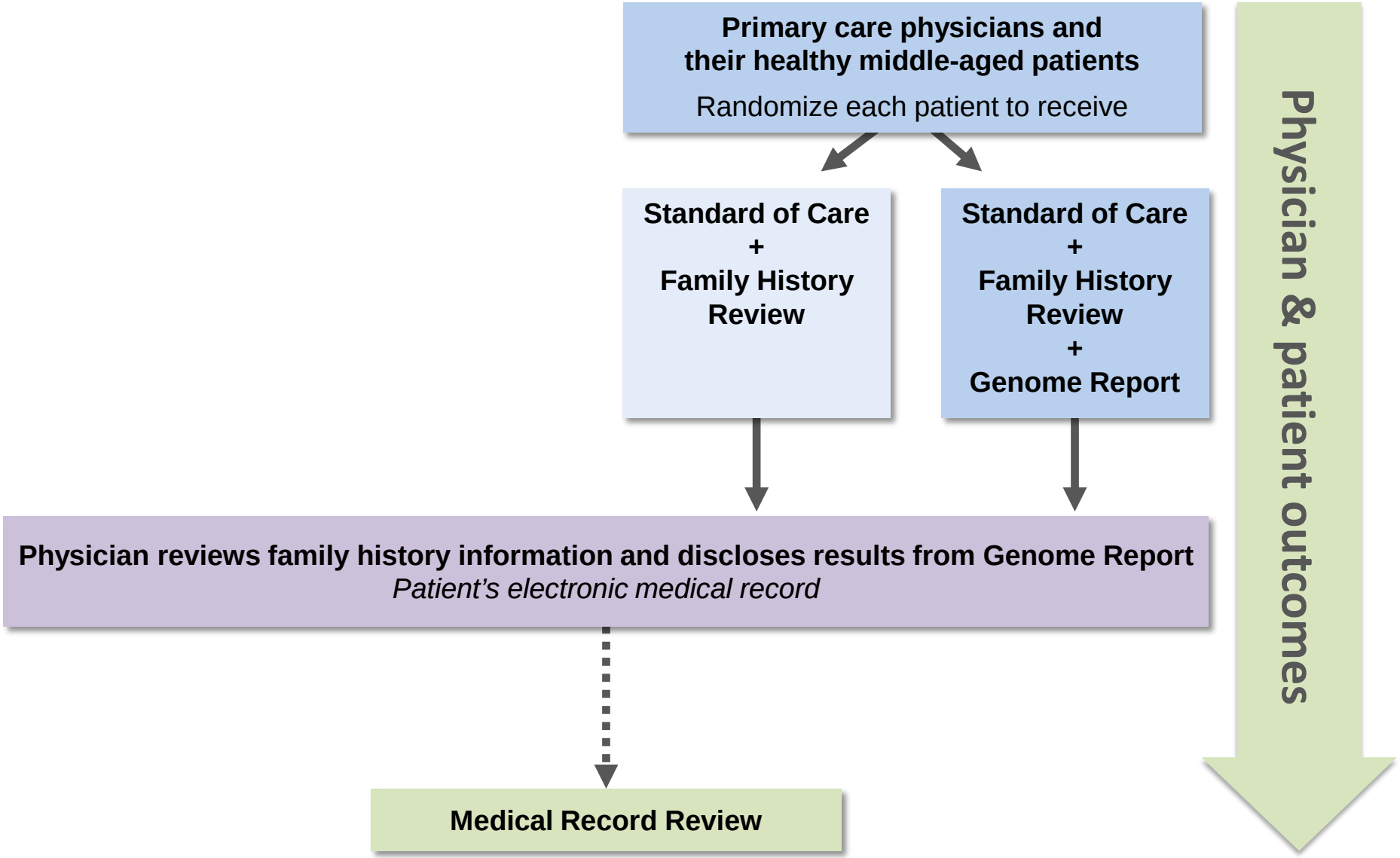
Opportunistic Screening vs Population Screening

Opportunistic		Population
Infrastructure in place		Infrastructure not in
Relatively cost neutral		place
Recommendations exist		Adds cost
Medical model		No recommendations
	yet	
		Public health model

The MedSeq Project



MedSeq reported findings from analysis of variants in ~4600 genes

	Mendelian Disease Risk SFs	Carrier Status SFs
Number of patients	21/100 (21%)*	92/100 (92%)
Mean reported variants per patient	0.21	2.3
Range of reported variants per patient	0-1	0-7

*1/90 (1%) by ACMG list

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MEDSEQ™

Examples of physician decision-making with secondary findings in MedSeq

ARM	PATIENT'S RESULT	TEST ORDERED
Primary Care (023-P05)	**MONOGENIC RESULT** *KCNQ1* c.826delT Likely Pathogenic Romano-Ward syndrome	EKG (And, referral to Cardiovascular Geneticist)
Primary Care (030-P05)	**CARRIER STATUS** *HFE* c.845G>A Pathogenic Hereditary Hemochromatosis	Iron/ferritin studies
Primary Care (030-P05)	**MONOGENIC RESULT** *PPOX* c.199delC Pathogenic Variegate porphyria	Repeat genetic testing for variegate porphyria at Mt. Sinai to confirm findings
Primary Care (038-P11)	**CARDIOVASCULAR RISK ALLELES** - Coronary heart disease - Abdominal aortic aneurysm	- Exercise stress tests - Abdominal ultrasound

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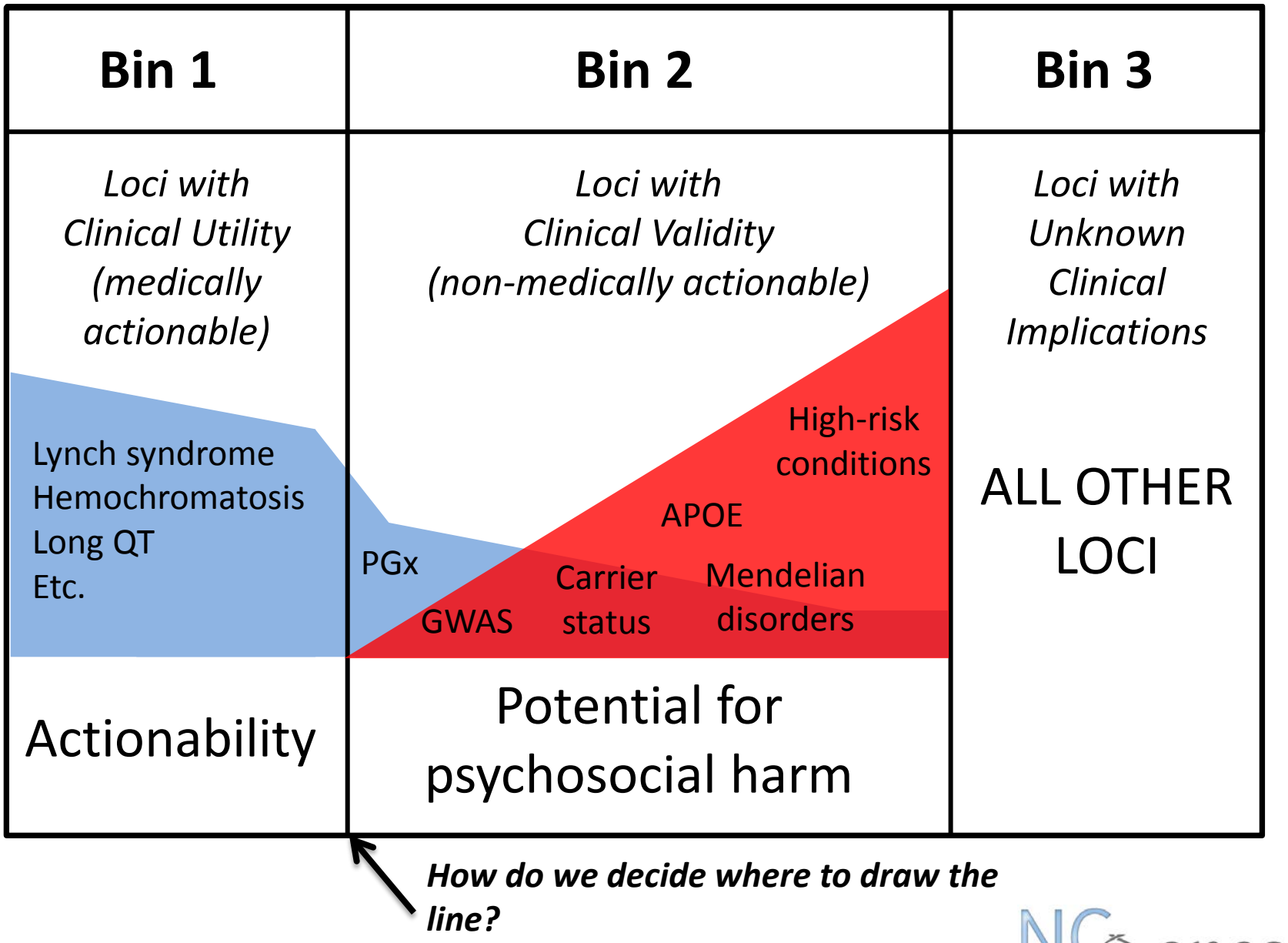
MEDSEQ™



Slide courtesy of Jonathan Berg

A semi-quantitative metric to define actionability

– Severity of disease	(0-3)
– Likelihood of a severe outcome	(0-3)
– Effectiveness of interventions	(0-3)
– Acceptability of interventions	(0-3)
– Knowledge base	(0-3)
	0-15

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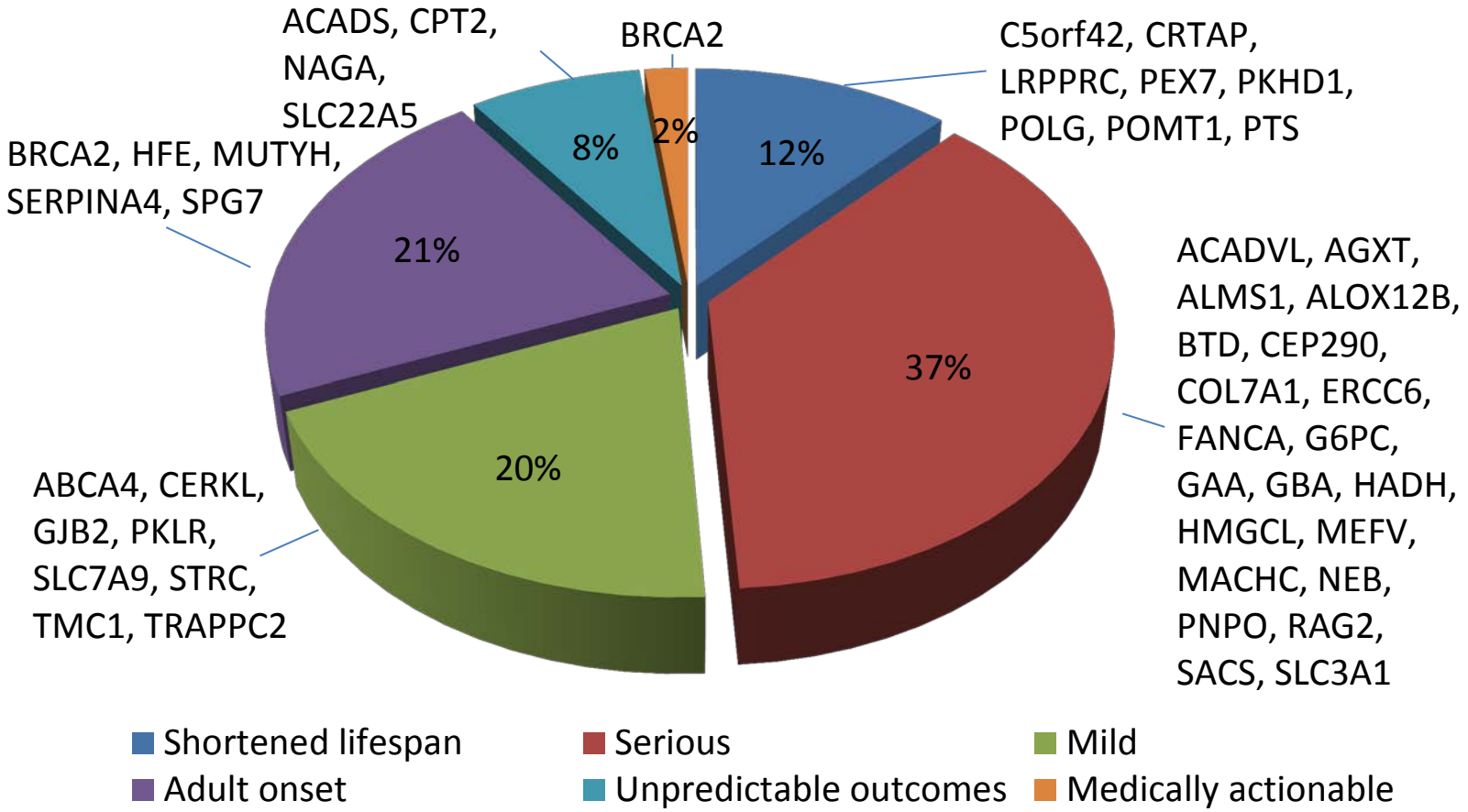
NCGenes

Assessing Actionability of Genetic Conditions



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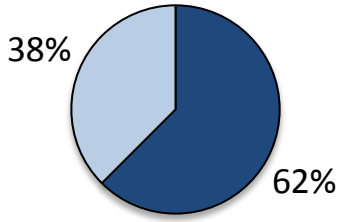
NextGen
Understanding the impact of genome sequencing for reproductive decisions

Penetrance of Actionable Variants in FHS

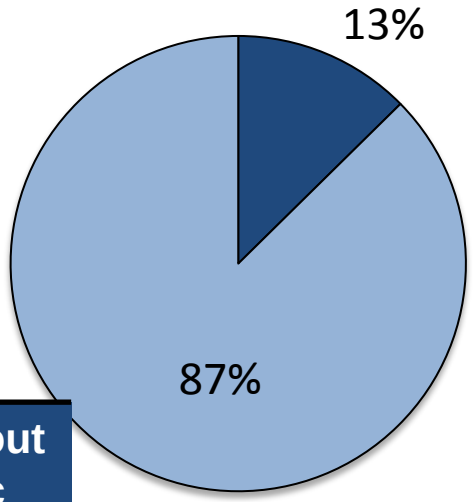
8 subjects with pathogenic variants in an…



With a suggestive clinical feature (SCF)

Without a suggestive clinical feature

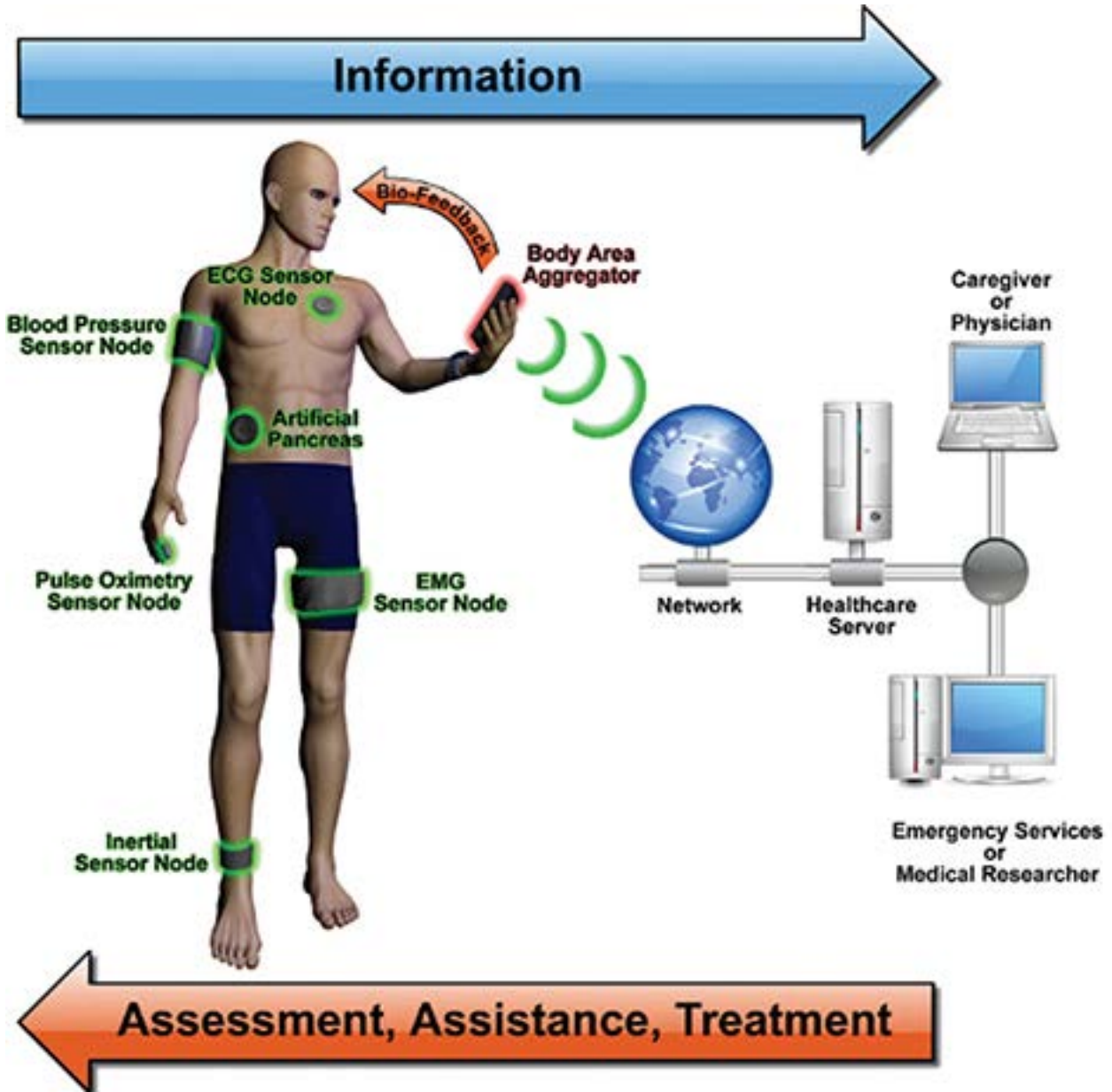
454 subjects without a pathogenic variant in an ACMG gene



Classification of ACMG genes	Subjects with pathogenic variant, + SCF	Subjects without a pathogenic variant, + SCF
Cancer	66.7% (2/3)	5.3% (0.16/3)
Cardiovascular	60.0% (3/5)	16.8% (0.84/5)

Gold et al., *ASHG Annual Meeting*, 2014

Scalable and Intermediate Phenotyping



Research Article

For reprint orders, please contact: reprints@futuremedicine.com

Personalized Medicine

'Someday it will be the norm': physician perspectives on the utility of genome sequencing for patient care in the MedSeq Project

Aim: To describe practicing physician sequencing. **Materials & methods:** We co from 18 primary care physicians and cardi of whole-genome sequencing. Physicia medical education before completing **Results:** Physicians described sequencing a its uncertain interpretation and limited i expressed the idea that its clinical integr for sequencing included complementing motivating patient behavior change and given genomics continuing medical educ based and personalized medicine in desc patient care.

FOCUS

Science Translational Medicine AAAS

EDUCATION

How to know when physicians are ready for genomic medicine

Jason L. Vassy,[1,2,3*] Bruce R. Korf,[4] Robert C. Green[3,5]

Despite perceptions to the contrary, physicians are as prepared for genomic medicine as they are for other medical innovations; educational initiatives and support from genetics specialists can enhance clinical practice.

With the tremendous investment in the genomic sciences over the last two decades, the biomedical community is eager to apply new genomic knowledge to patient care. Genomic testing, including whole-genome and exome sequencing, has demonstrated clinical utility in certain contexts (*1*). However, the workforce of fewer than 2000 remains a challenge for the clinical laboratory. For example, if genomic sequencing for a 60-year-old patient with no signs, symptoms, or family history of heart disease uncovers a rare genetic variant in a known cardiomyopathy gene, the treating clinician has no data to guide her in interpreting the significance of that finding for her

For Some Questions – Precision Precedes Scalability