Assessing Clinical Utility

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for the CSER Consortium

cser
Clinical Sequencing Exploratory Research

Reaction:
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G2P GENOMES *to People*

PARTNERS HEALTHCARE | PERSONALIZED MEDICINE

VE RI TAS

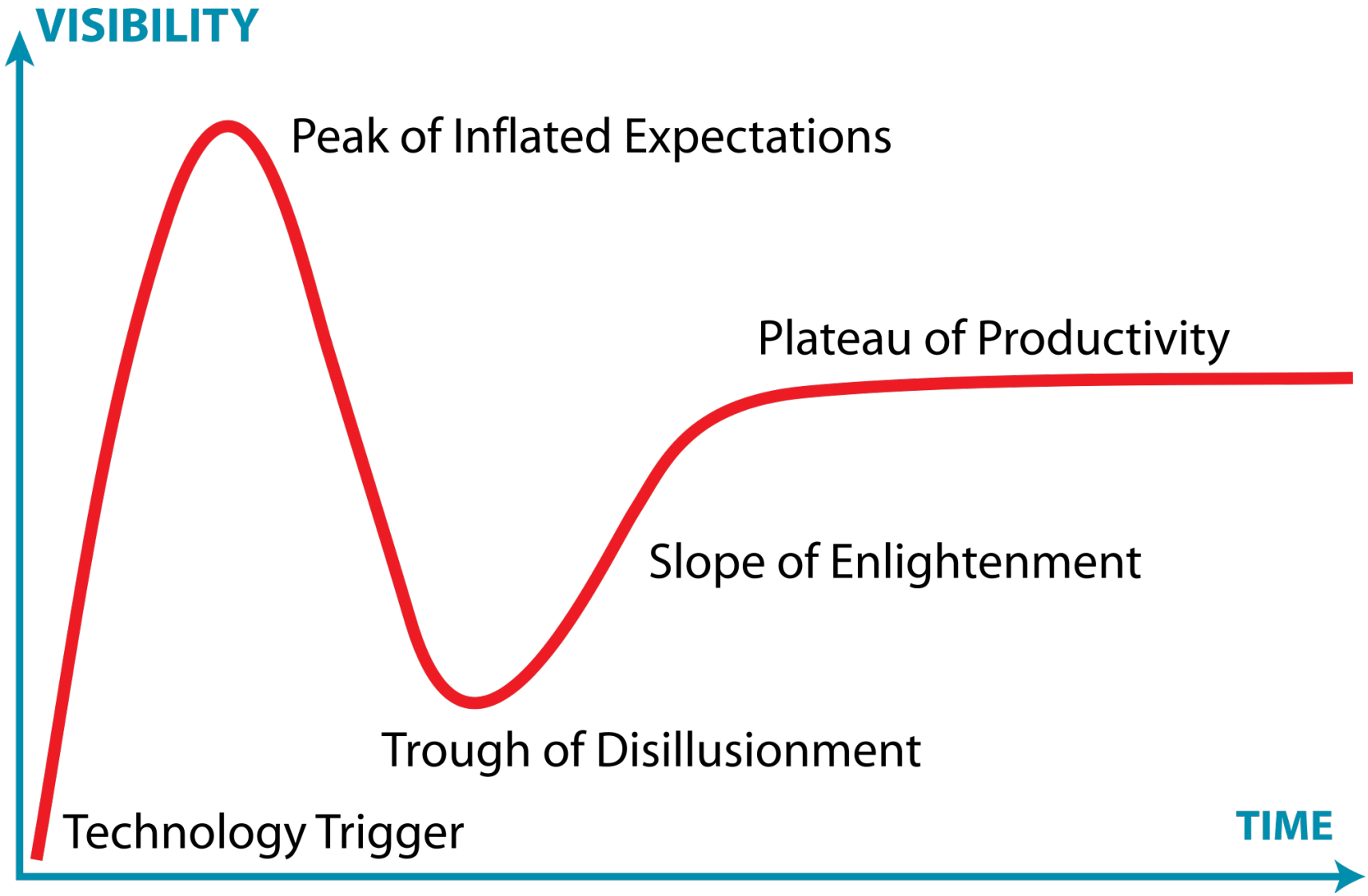
BWH

Not utility… utilities…

- **Personalized Cancer Treatment**
- Non-Invasive Prenatal Testing
- **Diagnosis of Undiagnosed Conditions**
- **Preconception Testing for Carrier Traits**
- **Pharmacogenomics**
- **Predispositional Testing**
  - **Mendelian diseases**
  - **Common complex diseases**

  - **With prior probabilities**
  - **Outright population screening**

Gartner Hype Cycle



A Scientific Framework for Clinical Utility

- "Before a genetic test can be generally accepted in clinical practice, data must be collected to demonstrate the benefits and risks that accrue from both positive and negative results"

- "Clinical utility takes into account the impact and usefulness of the test results to the individual, the family, and society. The benefits and risks to be considered include the psychological, social, and economic consequences of testing as well as the implications for health outcomes"

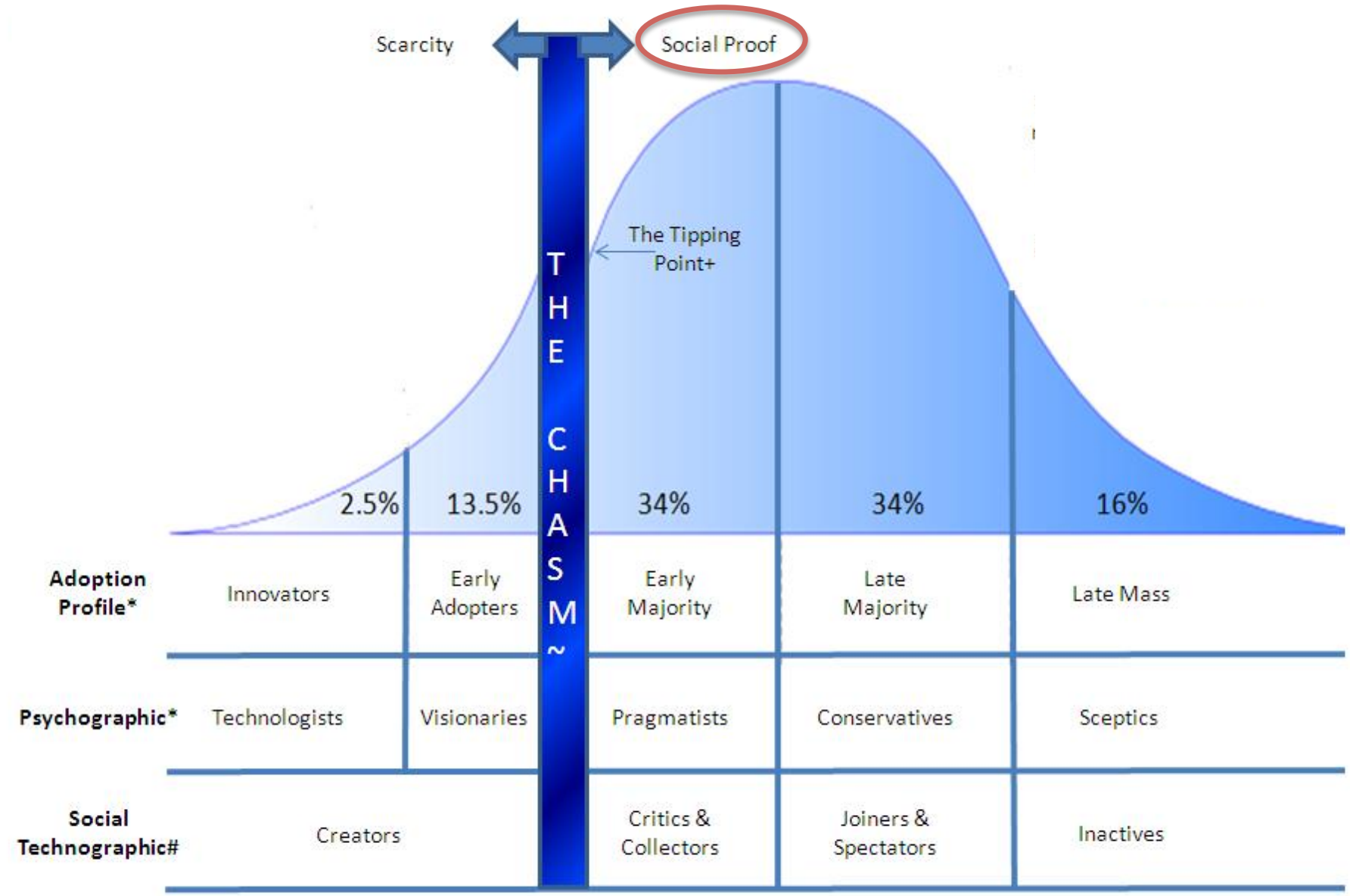
- Narrow sense definition:
  - Ability of a test to prevent or ameliorate adverse health outcomes through adoption of treatments conditioned on test results

- Broader sense definition:
  - Any use of test results to inform clinical decision making

- Broadest sense definition:
  - Any outcomes considered important to individuals, families and society

Holtzman and Watson (eds): NIH-DOE Task Force, 1997
Secretary's Advisory Committee on Genetic Testing, 2000
Grosse and Khoury: *Genetics in Medicine*, 2006

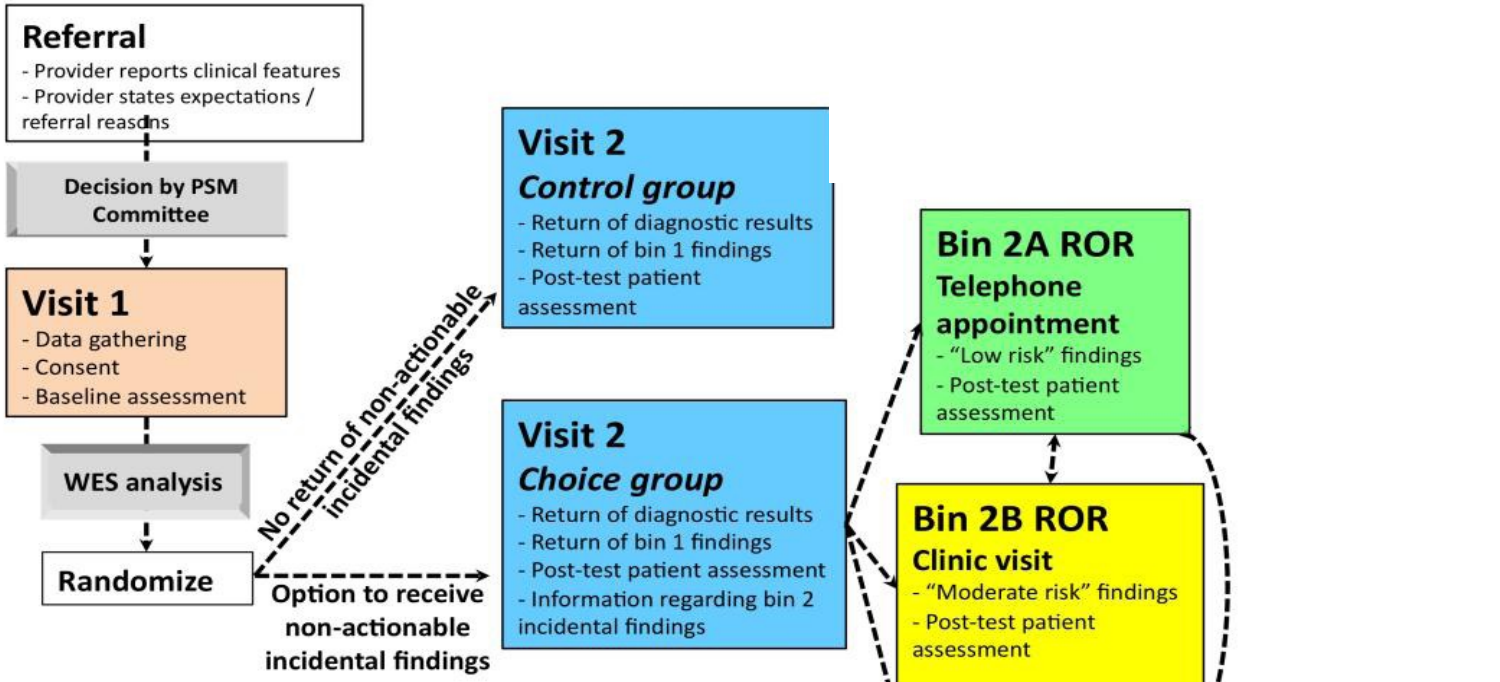
Accelerating Diffusion of Innovation: Maloney's 16% Rule©



^ Robert Cialdini *Everett Rogers #Forresters ~Geoffrey Moore + Malcolm Gladwell

CSER outcomes are rigorous
("exemplar studies" to build the evidence base)

NCGENES RCT Design

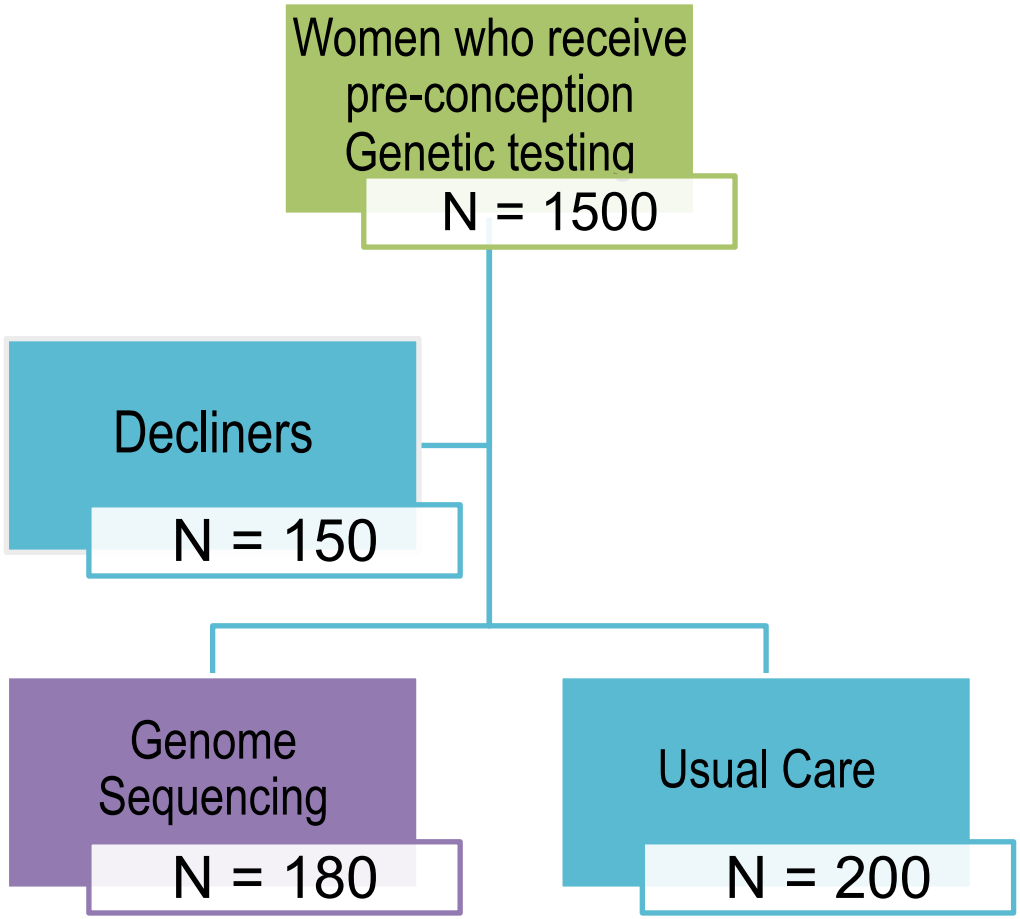


Patient-initiated return of bin 2 results:

- A patient may decline any bin 2 incidental results
- At any time after visit 2, a participant may opt to receive bin 2 results in the order of their choosing, by contacting the study coordinator for a follow-up appointment
- CLIA confirmation of bin 2A and bin 2B variants will be triggered by the scheduling of an appointment
- CLIA confirmation of bin 2C variants will be triggered by completion of the pre-test counseling session

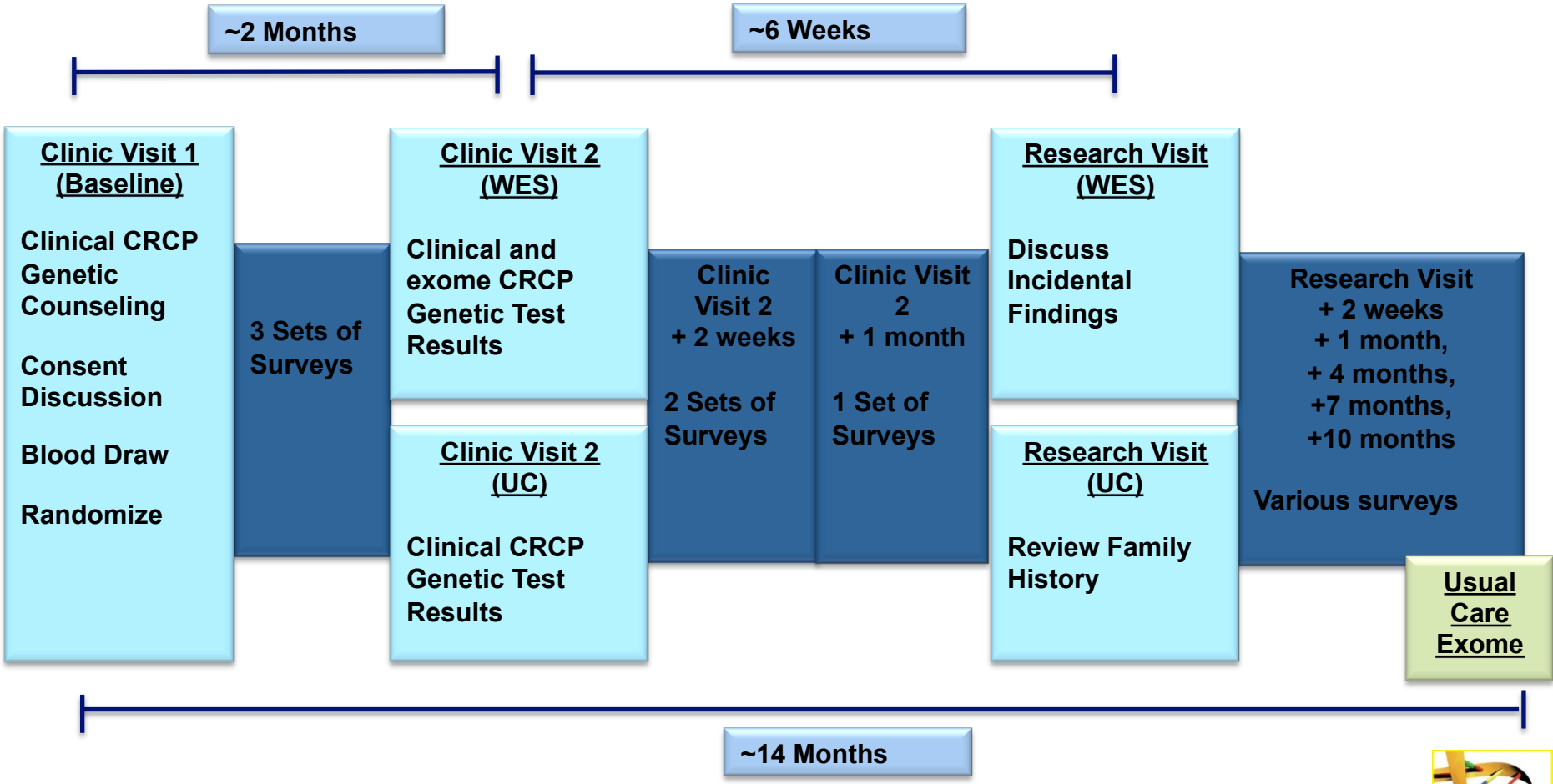
ROR = return of results

NEXTGENE RCT Design



NEXT Med RCT Design

- Enrolling adult patients having clinical genetic testing for hereditary colorectal cancer/polyps; usual care vs. whole exome sequencing



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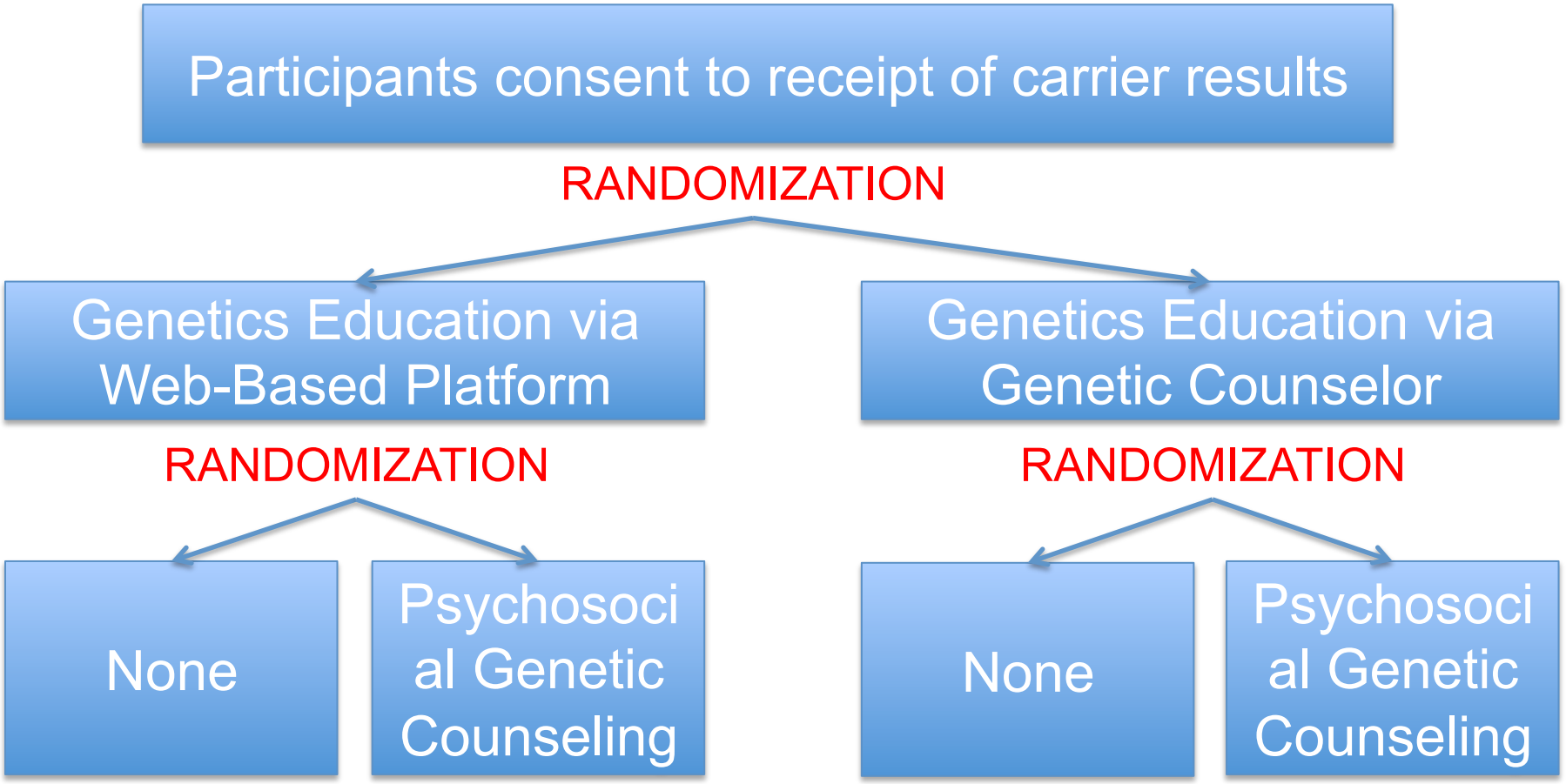
NEXT

ClinSeq RCT Design



Clinical Utility Outcomes:

- Range of findings
- New diagnoses
- Health care utilization

Almost all are broader or broadest sense clinical utility…can we now explore narrow sense utility?

Opportunities around clinical utility for CSER in the next 5-10 years

- Measure actual morbidity and mortality (along with cost) of genomic interventions (will require creative design, larger numbers and longer follow-up)

Examples of Reported MedSeq Findings

Gene	Variant	Disease	Classification	Inheritance	Notes
ELN	c.1150+1G>A	Supravalvular aortic stenosis	Pathogenic	AD	
LHX4	c.452-2A>C	Combined pituitary hormone deficiency	Pathogenic	AD	
PPOX	p.Leu67X	Variegate porphyria	Pathogenic	AD	
RDH5	p.Trp95X	Fundus albipunctatus	Pathogenic	AR	Homozygous
HFE	p.Cys282Tyr	Hereditary hemochromatosis	Pathogenic	AR	3 biallelic cases
CHEK2	c.1100del	CHEK2-related cancer risk	Pathogenic	AD	
F5	p.Arg534Gln	Factor V Leiden thrombophilia	Risk allele	Multi-factorial	3 cases
ANK2	p.Glu1458Gly	Ankyrin-B related cardiac arrhythmia	Likely pathogenic	AD	
COL2A1	p.Thr1439Met	Spondyloepiphyseal dysplasia congenita	Likely Pathogenic	AD	
EYA4	c.1739-1G>A	Postlingual hearing loss	Likely Pathogenic	AD	
KCNQ1*	p.Ser276ProfsX13	Romano-Ward syndrome	Likely Pathogenic	AD	
SQSTM1	p.Pro392Leu	Paget disease of the bone	Likely Pathogenic	AD	2 cases
APP	p.Ala713Thr	Alzheimer's disease, late onset	VUS - Favor Pathogenic	AD	
ARSE	p.Gly137Ala	Chondrodysplasia punctata	VUS – Favor Pathogenic	XL	
PDE11A	p.Thr58ProfsX41	Primary pigmented micronodular adrenocortical disease	VUS – Favor Pathogenic	AD	
TNNT2*	p.Arg278Cys	Hypertrophic cardiomyopathy	VUS – Favor Pathogenic	AD	

Opportunities around clinical utility for CSER in the next 5-10 years

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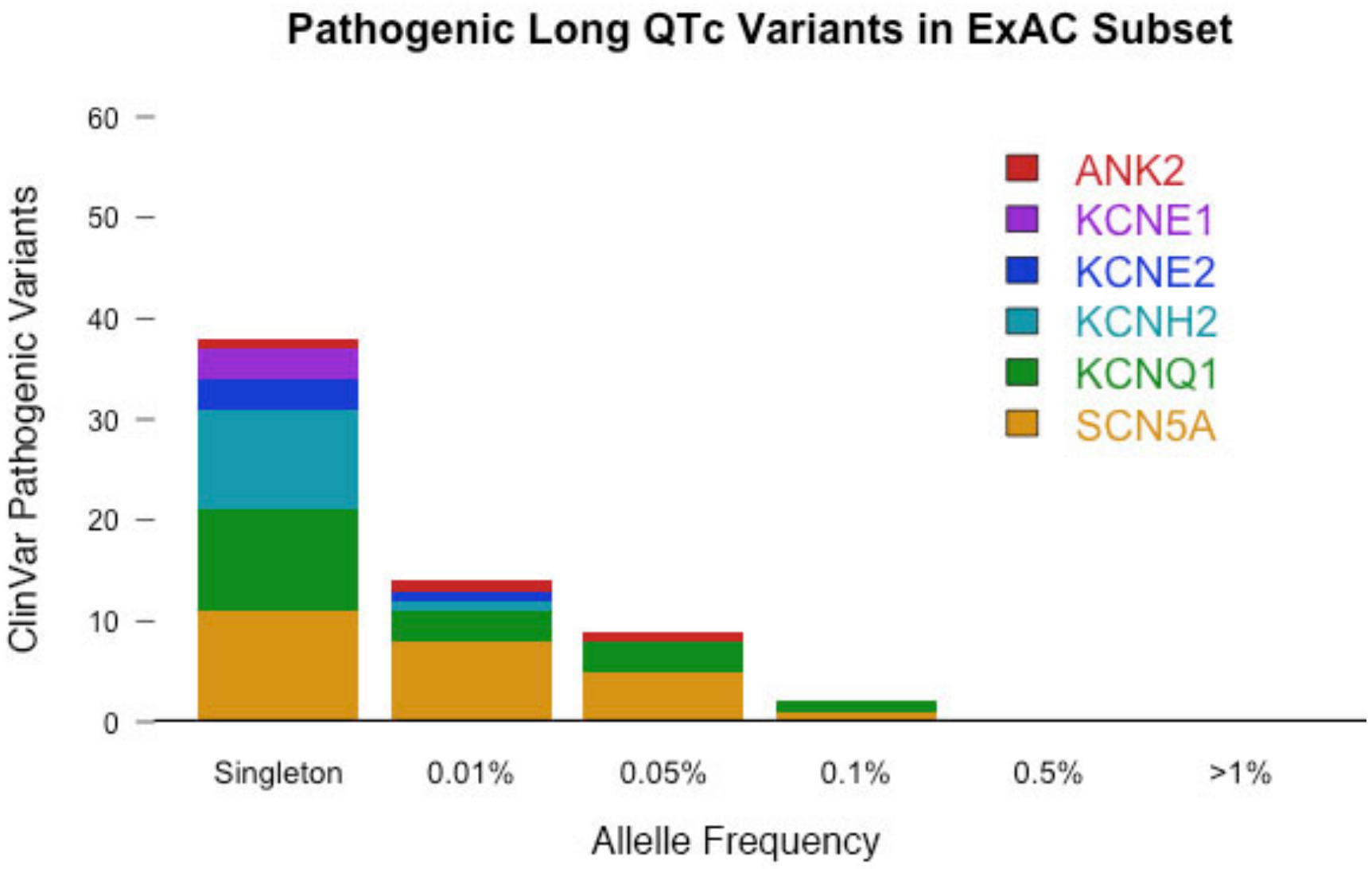
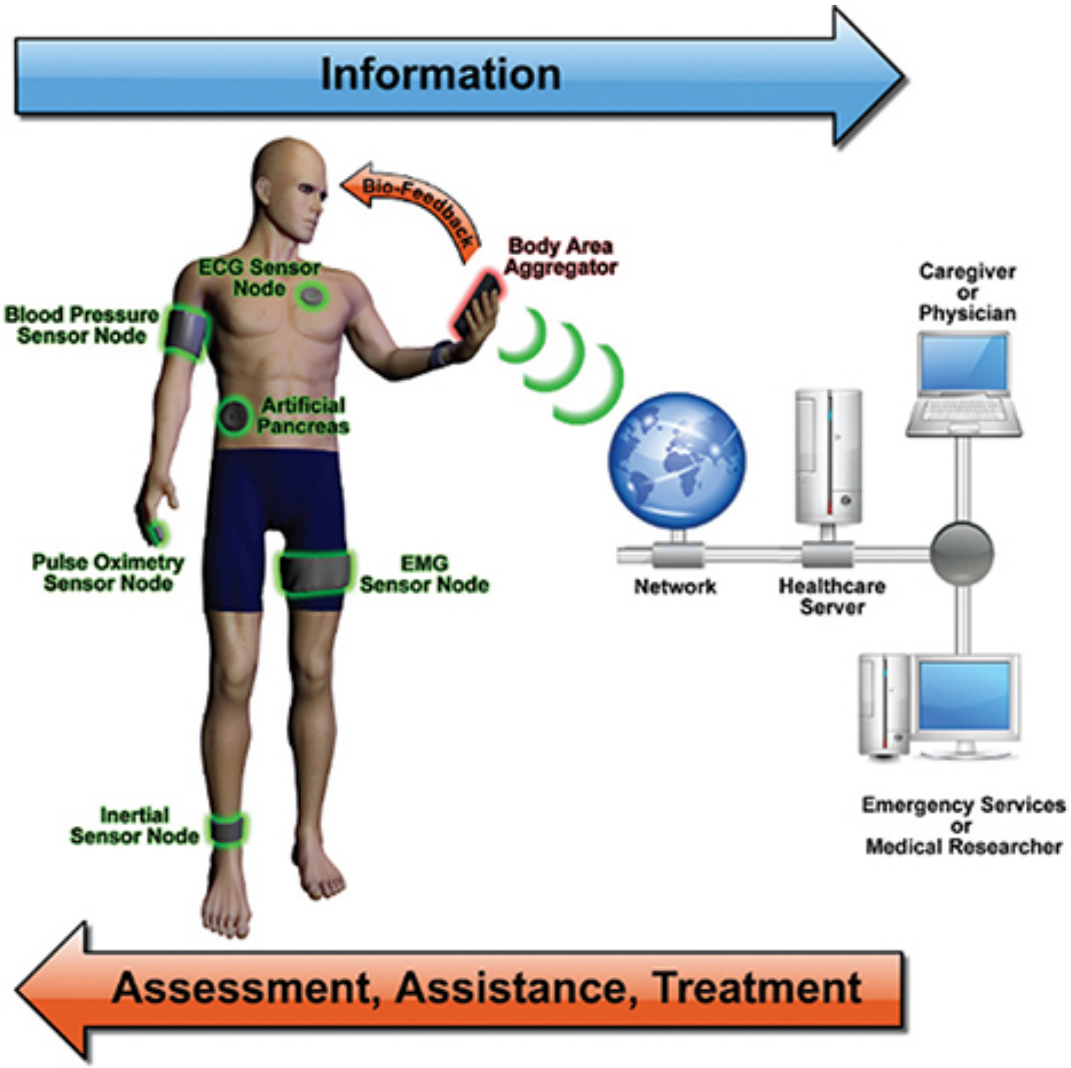
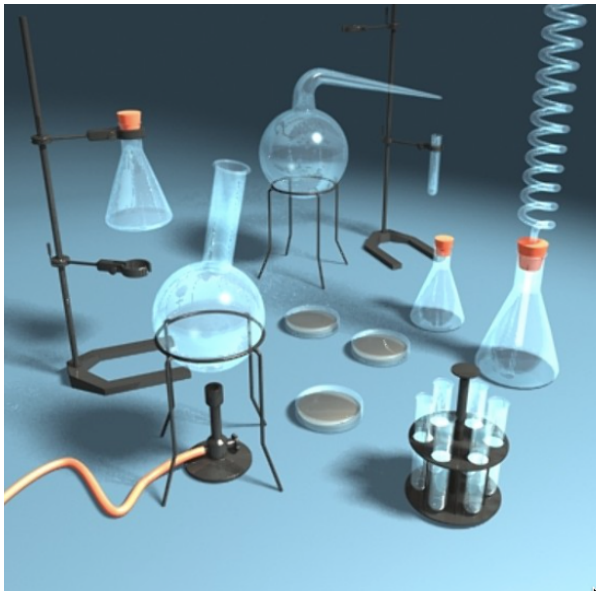
- Elucidate penetrance to better stratify genomic information (will require broad and deep phenotyping to accompany large-scale genome sequencing)



Slide courtesy of Anne O'Donnell, Eric Minikel and Daniel MacArthur

Scalable and Intermediate Phenotyping





Opportunities around clinical utility for CSER in the next 5-10 years

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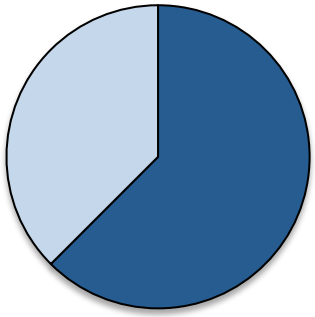
- Using sentinel projects and sound epidemiological principles to explore utility in a discipline where benefits may accrue to a small subset of patients

Aggregate Penetrance of Actionable Variants in Framingham Heart Study and Jackson Heart Study

(3,685 individuals / 5,071 unique variants in 56 genes)

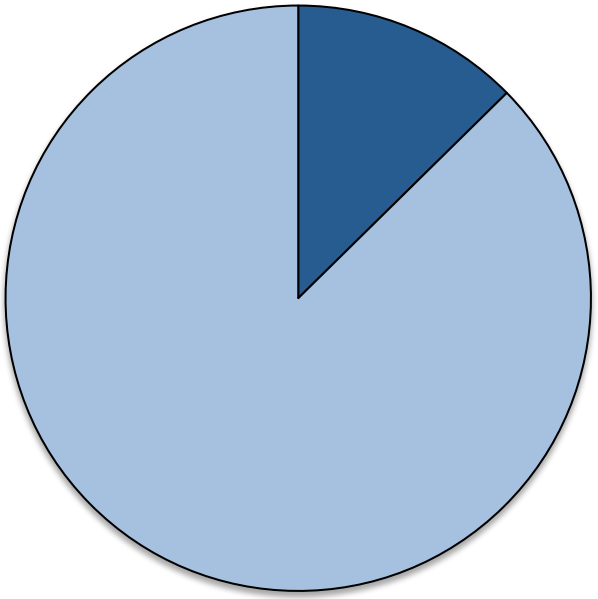
Carry PVs in ACMG56



With a suggestive clinical feature (SCF)

Without a suggestive clinical feature

Do not carry PVs in ACMG56



	SCFs in PVs vs non-PVs	SIR	P value
FHS	80% vs 12.4%	6.4	7×10^{-4}
JHS	26.9% vs 5.4%	4.7	3×10^{-4}

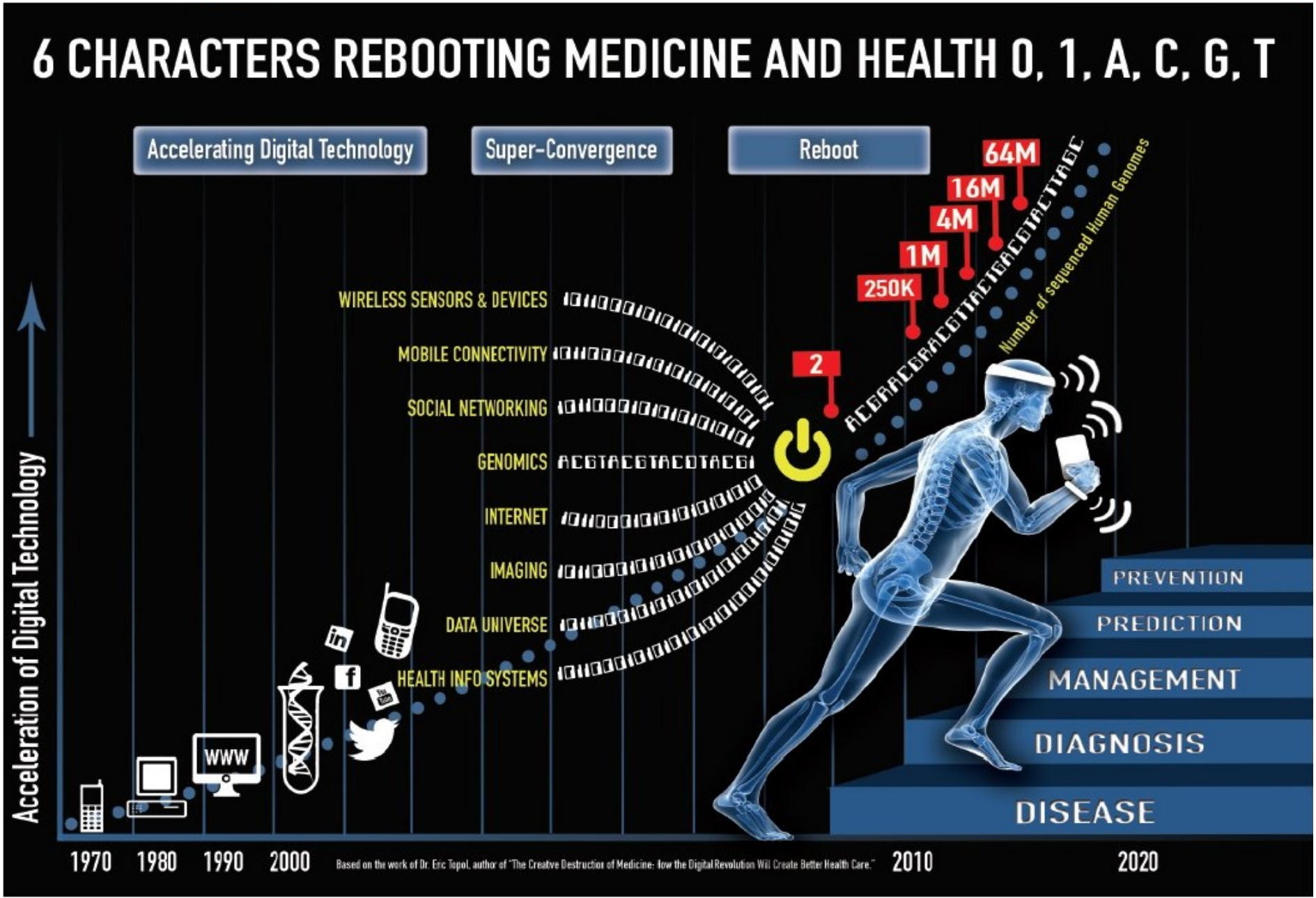
Green et al., *ASHG Annual Meeting*, 2015

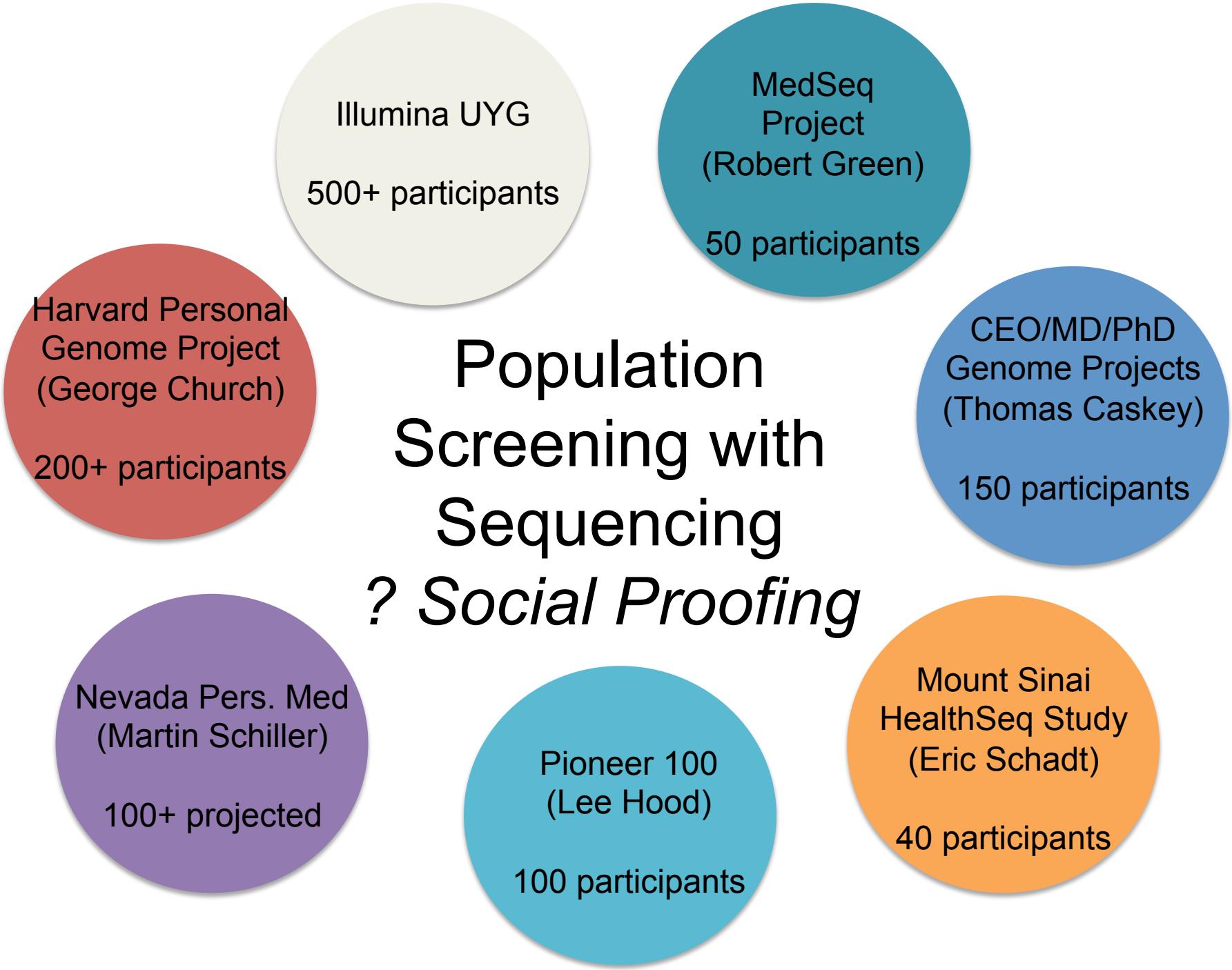
STORY OF DIGITAL HEALTH By Paul Sonnier

DIGITAL HEALTH

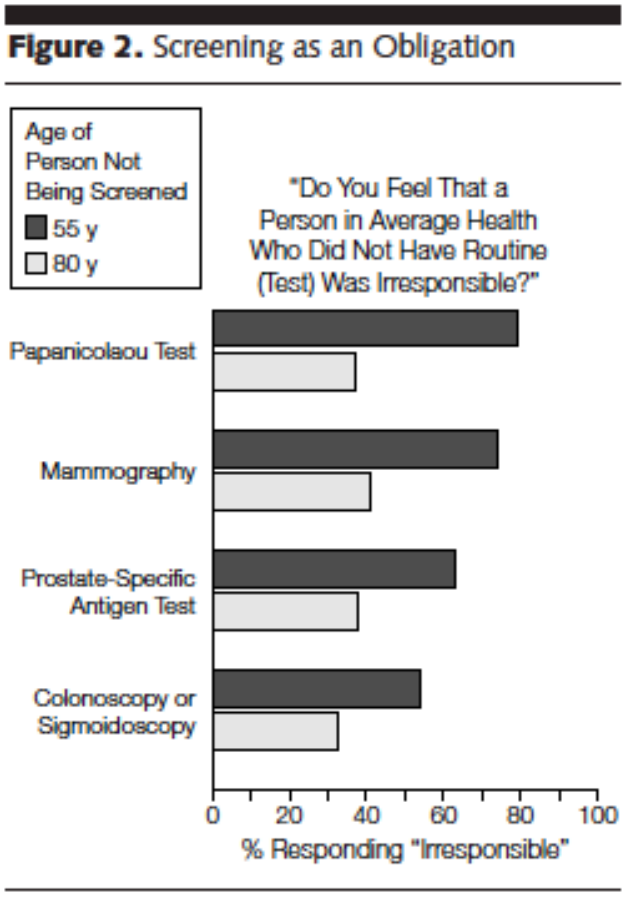
DIGITAL HEALTH Group on LinkedIn

6 CHARACTERS REBOOTING MEDICINE AND HEALTH 0, 1, A, C, G, T




Illumina UYG
500+ participants
MedSeq Project (Robert Green)
50 participants
Harvard Personal Genome Project (George Church)
200+ participants
Population Screening with Sequencing
? Social Proofing
CEO/MD/PhD Genome Projects (Thomas Caskey)
150 participants
Nevada Pers. Med (Martin Schiller)
100+ projected
Pioneer 100 (Lee Hood)
100 participants
Mount Sinai HealthSeq Study (Eric Schadt)
40 participants

Genomics in Population Screening



From public health emergency …

…to public health service

…to public health obligation

Grosse et al: *Pediatrics*, 2006
Schwartz et al: *JAMA*, 2004
Waller et al, *Brit Journal Cancer*, 2015

"…what looms largest is the lack of evidence to demonstrate improved clinical or economic outcomes.."

Manolio et al: *Sci Trans Med*, 2015