Returning Research Results in Oncology: Emerging Challenges and Opportunities

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NIH Department of Bioethics


CHALLENGE
OPPORTUNITY

Three challenges/opportunities

1. Re-classification of research variants that have already been returned

2. Potential germline genetic findings from tumor sequencing results
    1. A “special” case of incidental/secondary findings

3. Returning results to relatives of critically ill or deceased patients

#1: Recontacting research participants when returned results are reclassified – what are researchers' responsibilities?

ASHG POSITION STATEMENT

The Responsibility to Recontact Research Participants after Reinterpretation of Genetic and Genomic Research Results

Yvonne Bombard,[1,2,3,*] Kyle B. Brothers,[1,4] Sara Fitzgerald-Butt,[5,6] Nanibaa' A. Garrison,[1,7,8] Leila Jamal,[1,5,9] Cynthia A. James,[5,10] Gail P. Jarvik,[11,12] Jennifer B. McCormick,[1,13] Tanya N. Nelson,[14,15,16,17,18] Kelly E. Ormond,[1,19] Heidi L. Rehm,[20,21,22] Julie Richer,[14,23,24] Emmanuelle Souzeau,[25,26] Jason L. Vassy,[20,27,28] Jennifer K. Wagner,[1,29] and Howard P. Levy[1,30,31]

ACMG PRACTICE GUIDELINES | Genetics inMedicine

2013

ACMG clinical laboratory standards for next-generation sequencing

Heidi L. Rehm, PhD[1,2], Sherri J. Bale, PhD[3], Pinar Bayrak-Toydemir, MD, PhD[4], Jonathan S. Berg, MD[5], Kerry K. Brown, PhD[6], Joshua L. Deignan, PhD[7], Michael J. Friez, PhD[8], Birgit H. Funke, PhD[1,2], Madhuri R. Hegde, PhD[9] and Elaine Lyon, PhD[4]; for the Working Group of the American College of Medical Genetics and Genomics Laboratory Quality Assurance Committee

"…because the depth of coverage for an exome is not uniform, the **analytical sensitivity for exome sequencing may be lower than the sensitivity for most targeted gene panels**, given that a substantial number of exons in known disease-associated genes may lack sufficient coverage…"

ACMG STANDARDS AND GUIDELINES | Genetics inMedicine

2015

Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology

Sue Richards, PhD[1], Nazneen Aziz, PhD[2,16], Sherri Bale, PhD[3], David Bick, MD[4], Soma Das, PhD[5], Julie Gastier-Foster, PhD[6,7,8], Wayne W. Grody, MD, PhD[9,10,11], Madhuri Hegde, PhD[12], Elaine Lyon, PhD[13], Elaine Spector, PhD[14], Karl Voelkerding, MD[13] and Heidi L. Rehm, PhD[15]; on behalf of the ACMG Laboratory Quality Assurance Committee

"...the ACMG strongly recommends that clinical molecular genetic testing should be performed in a Clinical Laboratory Improvement Amendments–approved laboratory, with results interpreted by a board-certified clinical molecular geneticist or molecular genetic pathologist or the equivalent"

ACMG/AMP/CAP variant interpretation guidelines (2015)

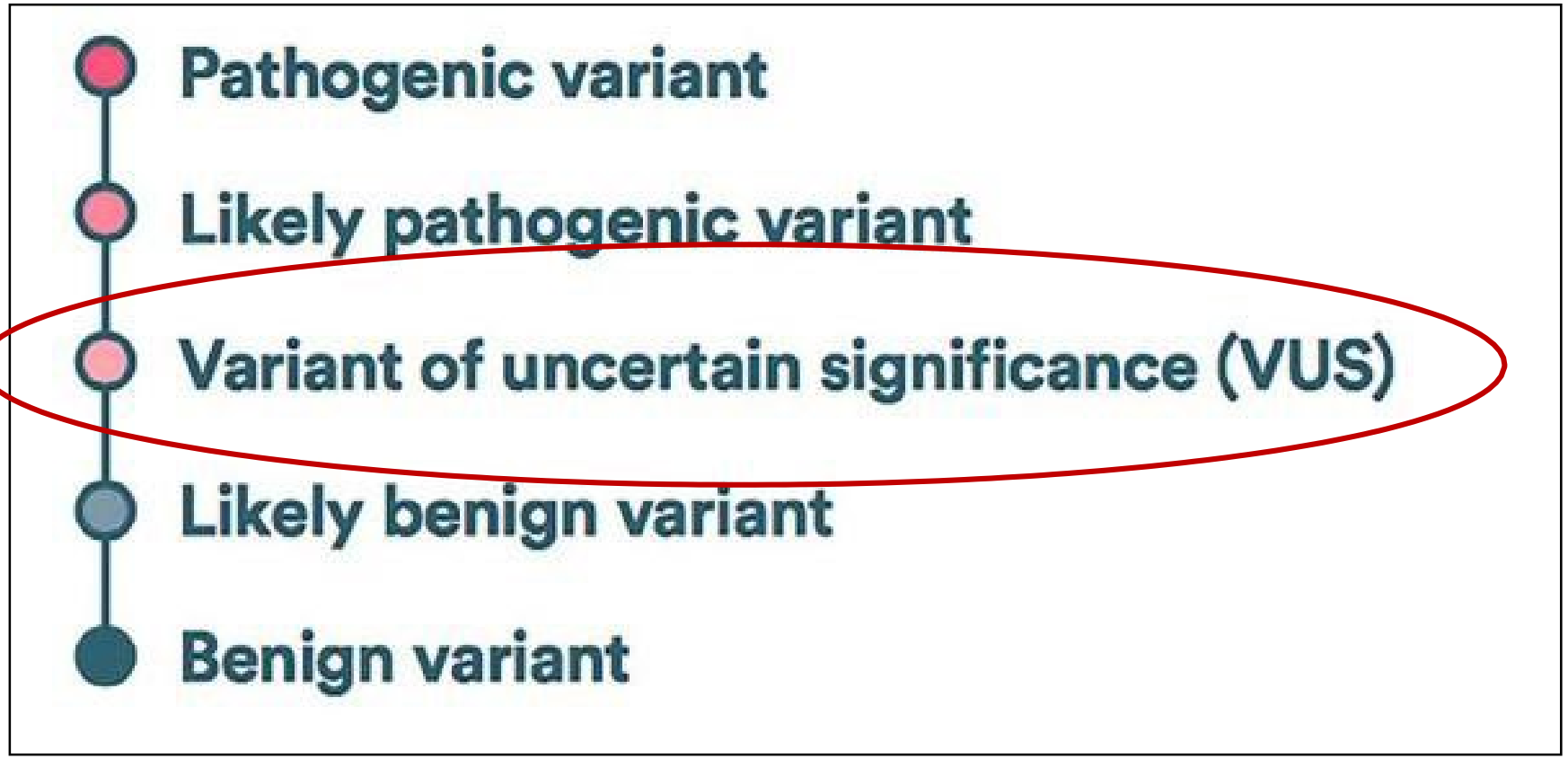
99% certain association with disease

90% certain association with disease

Everything else!

90% certain benign

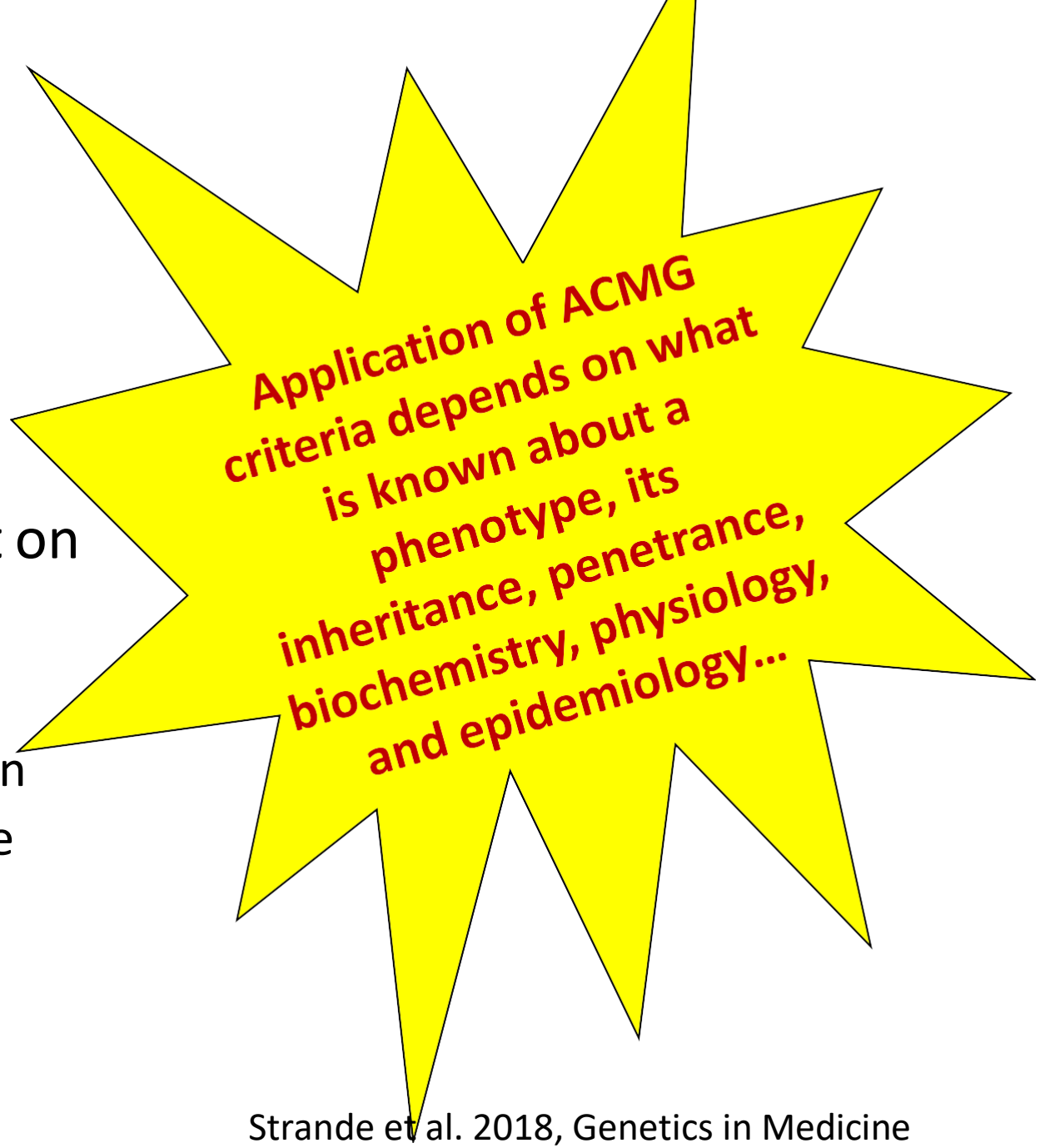
99% certain benign



Richards et al. 2015, Genetics in Medicine

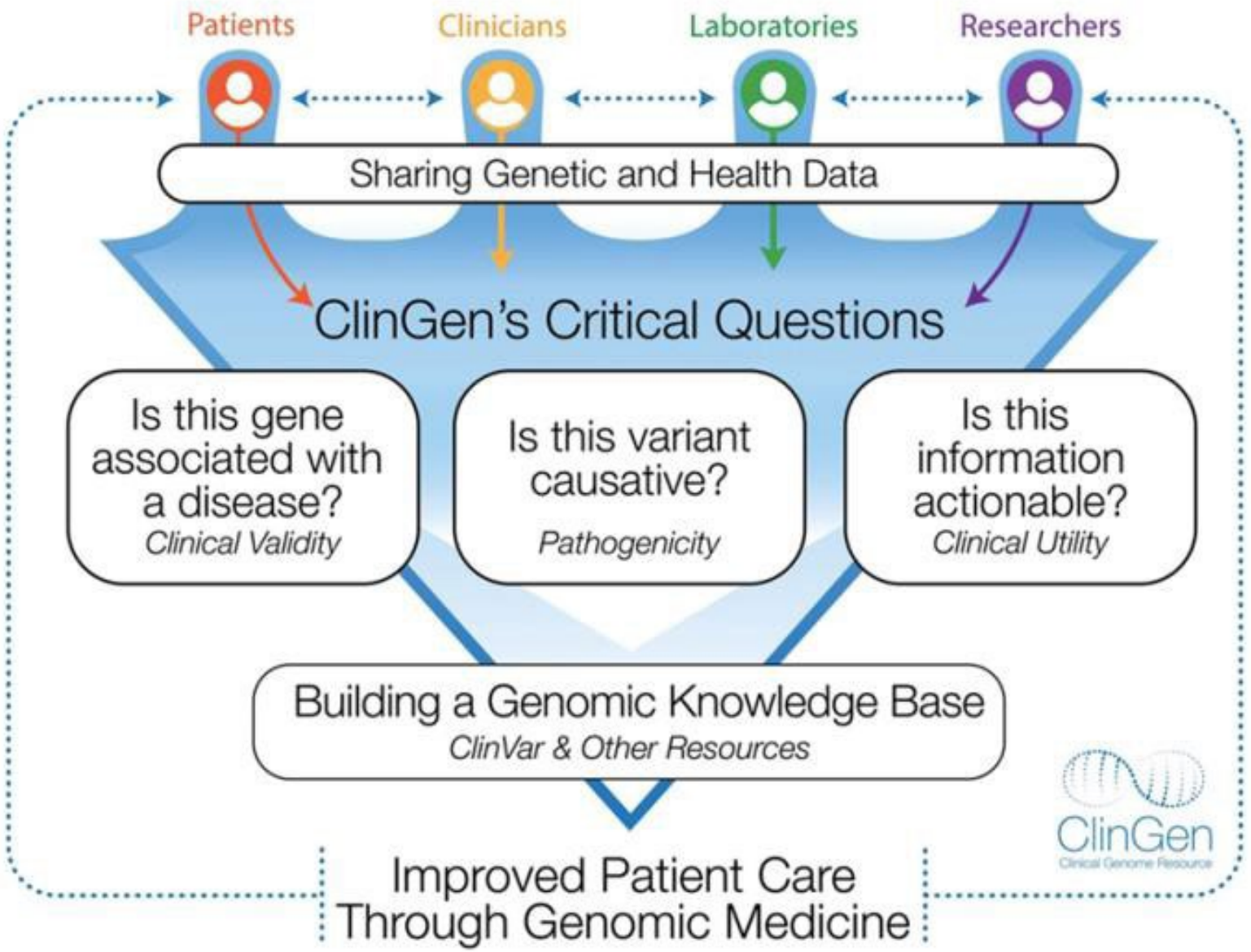
Types of data used

- Population data
- Segregation data
- Allelic data (phase)
- Computational data/predicted impact on protein
- ”Other”
  - Specificity of gene-phenotype association
  - Extent of known benign variation in gene
  - Etc…



Strande et al. 2018, Genetics in Medicine

Since 2015


Patients
Clinicians
Laboratories
Researchers
Sharing Genetic and Health Data
ClinGen's Critical Questions
Is this gene associated with a disease?
Clinical Validity
Is this variant causative?
Pathogenicity
Is this information actionable?
Clinical Utility
Building a Genomic Knowledge Base
ClinVar & Other Resources
ClinGen
Clinical Genome Resource
Improved Patient Care Through Genomic Medicine

Since 2015

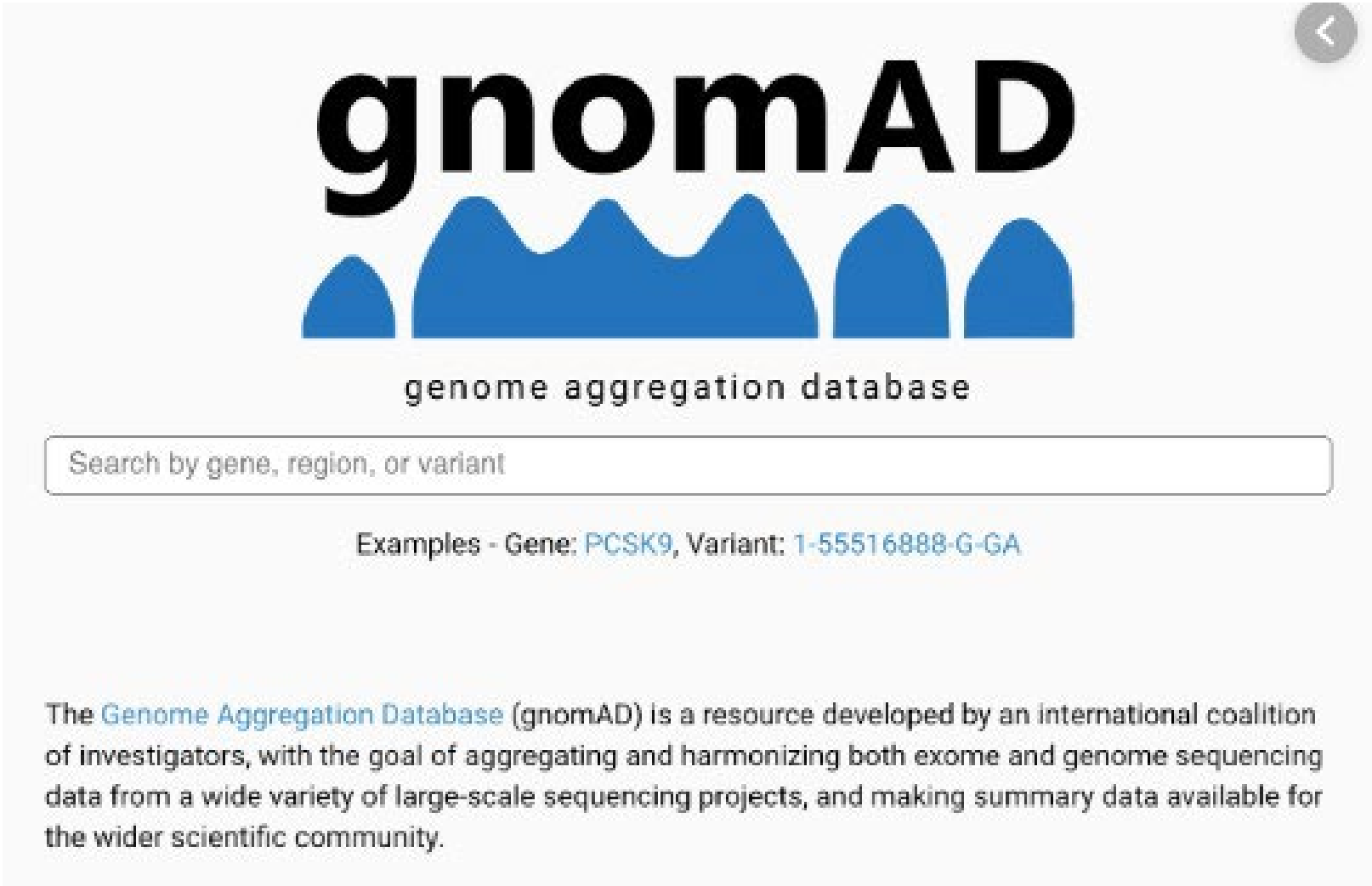
Gene
Browse Classifications by Gene

Expert Panel
Browse Classifications by Expert Panel

Condition
Browse Classifications by Condition

	Benign 238	Likely Benign 110	Uncertain Significance 194	Likely Pathogenic 197	Pathogenic 293
PAH VCEP 275	8	3	64	80	120
PTEN VCEP 111	7	15	31	30	28
CDH1 VCEP 121	20	16	24	26	35
RASopathy VCEP 265	127	51	18	16	53
Hearing Loss VCEP 107	20	19	26	19	23
Myeloid Maligna... 52	10	5	15	8	14
Cardiovascular ... 101	46	1	16	18	20

Since 2016



Credit: Daniel MacArthur and lab@Broad Institute

What does all this mean?

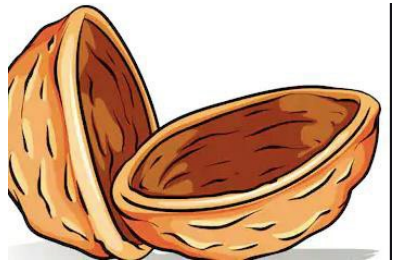
- Reanalysis of exome data after short intervals significantly increases diagnostic yield
- Estimates range from ~11% to ~200% increased diagnostic yield at reanalysis intervals as short as 12 months to six years
- Diagnostic gains vary by phenotype and our knowledge of phenotypes

Liu et al. NEJM 2019; Machini et al. AJHG 2019; Baker et al. J Mol Diag 2019; Ewans et al. GIM 2018; Wright et al. 2018….etc.

What does this have to do with ethics?

- It took a lot of work to convince research institutions that return of *(high-impact, health-related)* results is the ethical thing to do *(and good for science)*
- But what if we are returning incorrect information without realizing it?
- *(Most)* researchers are not clinicians
- Researchers *(still)* have duties to minimize harms and maximize the production of knowledge

ASHG recontact guideline in a nutshell



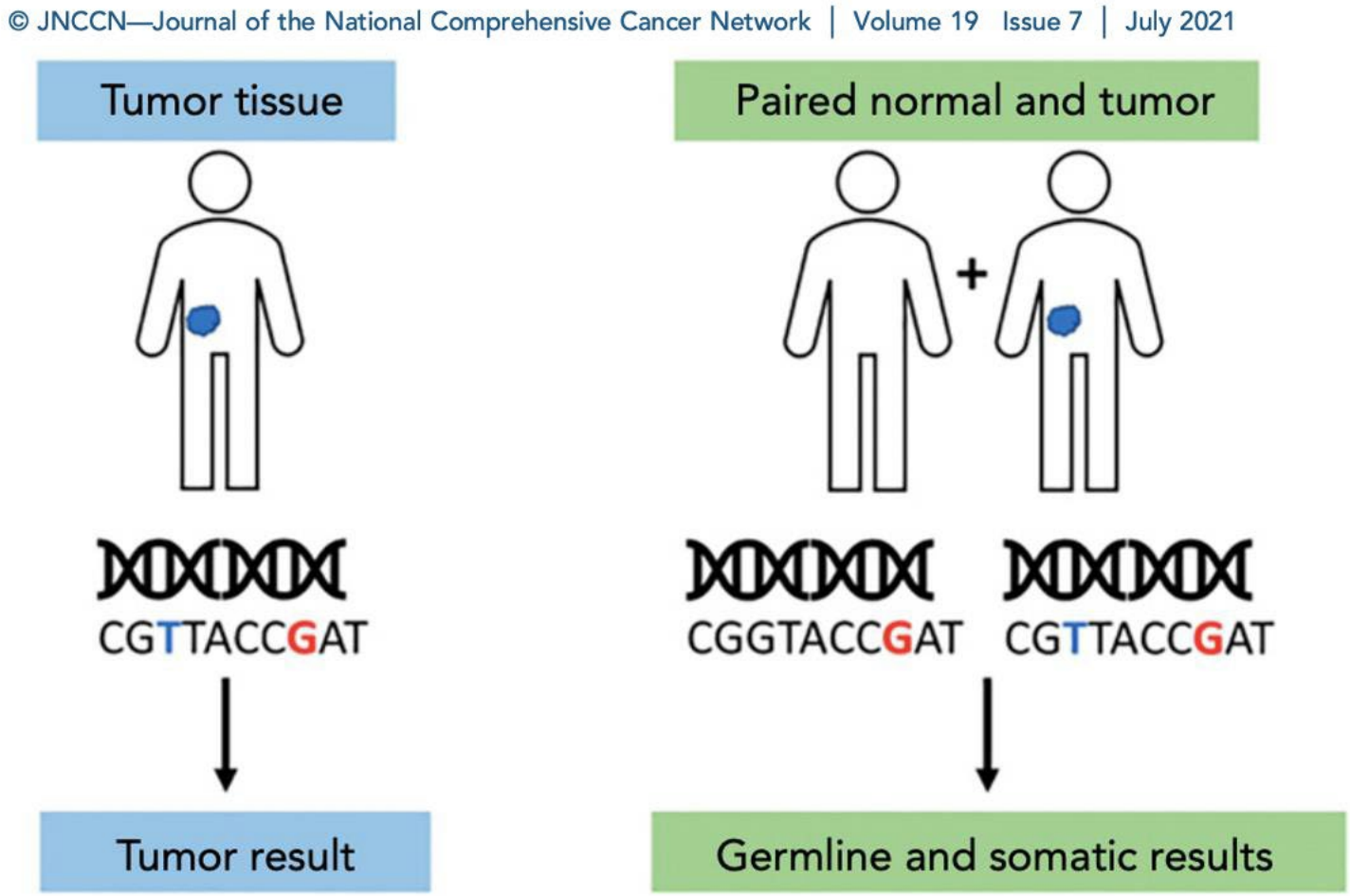
- Recontact is difficult and resource-intensive. It is a responsibility, not a duty.
- No responsibility exists after project funding has ended.
- The responsibility to recontact is stronger if there is compelling evidence for medical benefit (or harm) of NOT re-contacting.
- The degree of relationship with a study participant is key to determining the strength of a responsibility.
- Whatever you do, leave a paper trail. Documentation/communication about the limitations of research results is key.

Bombard et al. AJHG, 2019

#2: Tumor sequencing is an increasingly common method in cancer research and differs from germline sequencing in fundamental ways

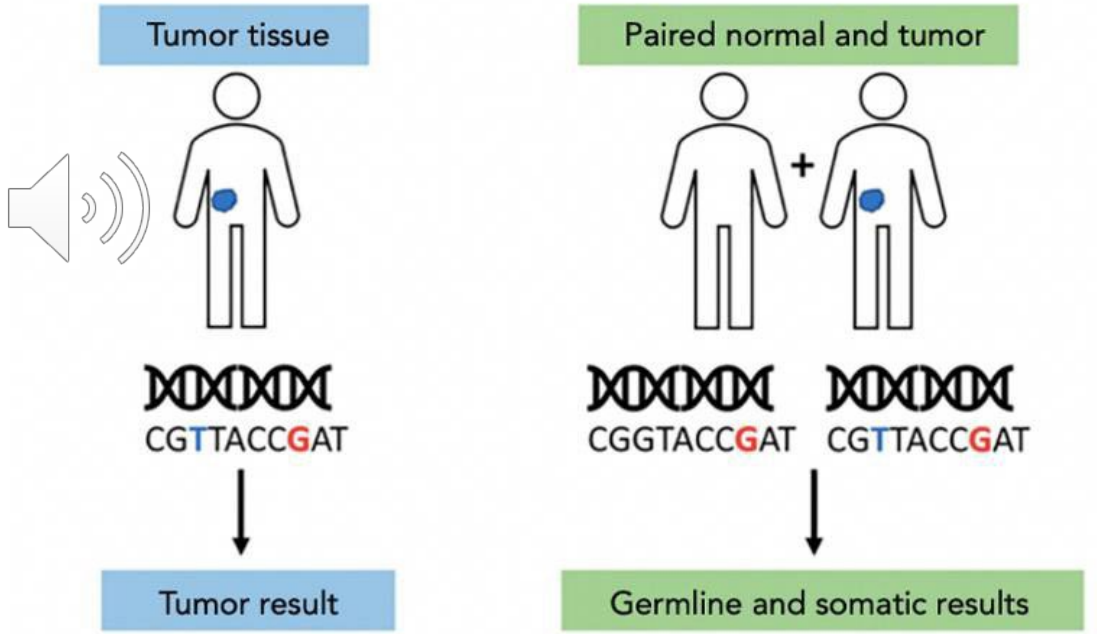
Tumor Testing strategies

- Tumor-only
- Paired normal and tumor



Liu YL, Stadler ZK: The Future of Parallel Tumor and Germline Genetic Testing: Is There a Role for All Patients With Cancer? J Natl Compr Canc Netw 19:871-878, 2021

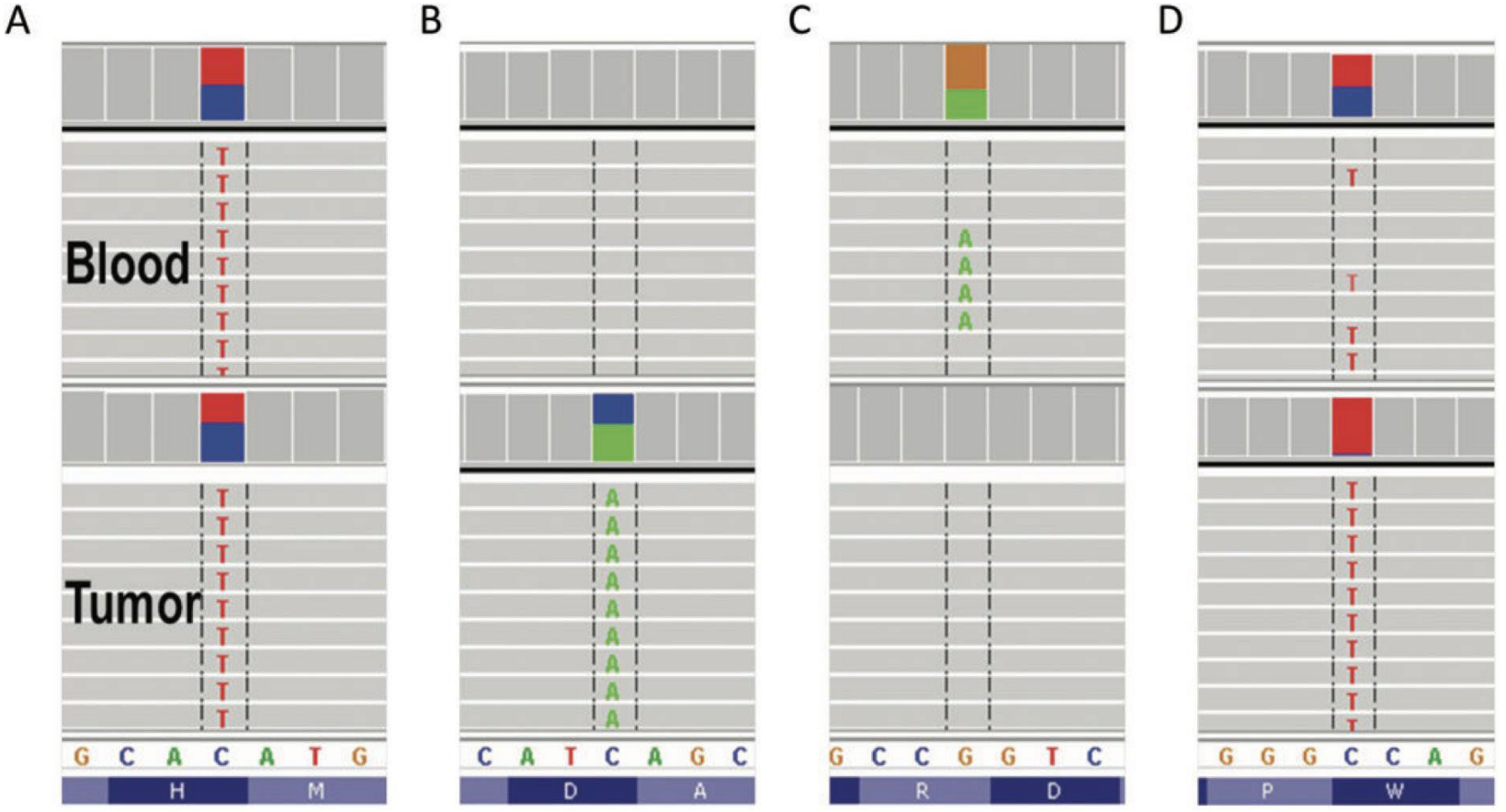
Pros and Cons of tumor-only vs paired tumor/normal genetic testing



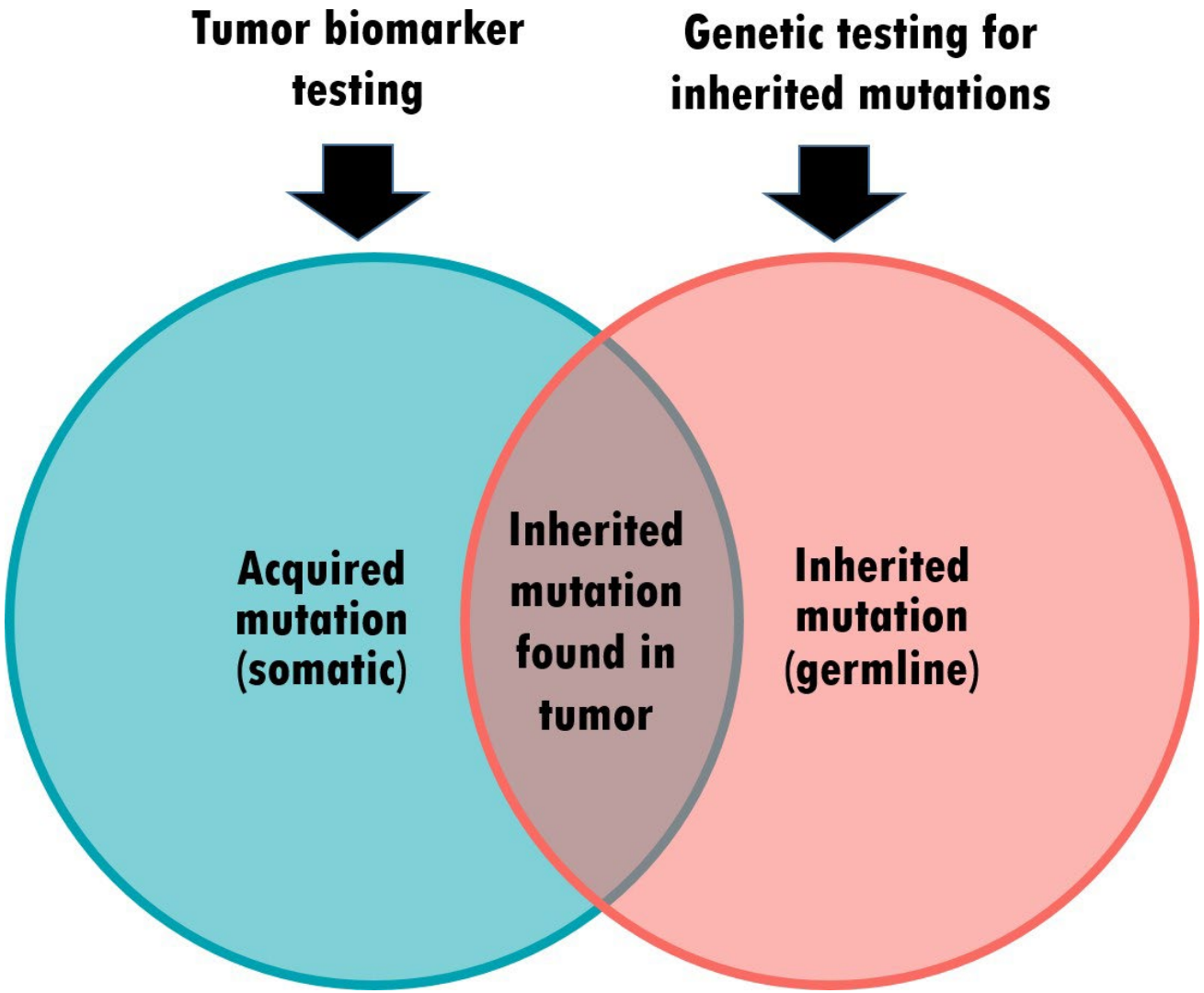
Pros	• Inform diagnosis and prognosis • Guide therapeutic decisions for targeted therapies • Assess MSI for immunotherapies	• Differentiation and integration of germline vs somatic variants • Guides therapy • Allows genetic counseling, screening, and reproductive planning
Cons	• Inability to distinguish somatic vs germline variants. • Inadequate surrogate for direct germline testing • Need for further genetic testing and potential delays in care	• Increased costs and resources, particularly related to genetic consents and counseling • Specialized curation and interpretation by molecular pathologist

Liu YL, Stadler ZK: The Future of Parallel Tumor and Germline Genetic Testing: Is There a Role for All Patients With Cancer? J Natl Compr Canc Netw 19:871-878, 2021

Tumor-normal paired testing and possible outcomes



Mandelker D, Zhang L: The emerging significance of secondary germline testing in cancer genomics. J Pathol 244:610-615, 2018



Picture credit: FORCE, https://www.facingourrisk.org/

In tumor testing, when might we suspect a germline result?

- Well-characterized genes associated with hereditary syndromes
- If tumor is highly specific to a syndrome, it is more likely that the patient carries a germline variant in the associated gene.
  - Eg. Adrenocortical carcinoma/*TP53*; uveal melanoma/*BAP1*
- Founder mutations
  - Eg. *BRCA* c.68_69delAG
  - *MSH2* inversion
- Variant allele frequency (VAF) of germline variants (presumed to be heterozygous) is roughly 40%-60% but can fall outside this range.
  - NO HARD AND FAST CUTOFFS

Li et al. Genetics in Medicine, 2020

Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology

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	Benign		Pathogenic			
	Strong	**Supporting**	**Supporting**	**Moderate**	**Strong**	**Very Strong**
Population Data	MAF is too high for disorder *BA1/BS1* **OR** observation in controls inconsistent with disease penetrance *BS2*			Absent in population databases *PM2*	Prevalence in affecteds statistically increased over controls *PS4*	
Computational And Predictive Data		Multiple lines of computational evidence suggest no impact on gene /gene product *BP4* Missense in gene where only truncating cause disease *BP1* Silent variant with non predicted splice impact *BP7*	Multiple lines of computational evidence support a deleterious effect on the gene /gene product *PP3*	Novel missense change at an amino acid residue where a different pathogenic missense change has been seen before *PM5* Protein length changing variant *PM4*	Same amino acid change as an established pathogenic variant *PS1*	Predicted null variant in a gene where LOF is a known mechanism of disease *PVS1*
Functional Data	Well-established functional studies show no deleterious effect *BS3*		Missense in gene with low rate of benign missense variants and path. missenses common *PP2*	Mutational hot spot or well-studied functional domain without benign variation *PM1*	Well-established functional studies show a deleterious effect *PS3*	
Segregation Data	Non-segregation with disease *BS4*		Co-segregation with disease in multiple affected family members *PP1*	Increased segregation data →		
De novo Data				*De novo* (without paternity & maternity confirmed) *PM6*	*De novo* (paternity & maternity confirmed) *PS2*	
Allelic Data		Observed in *trans* with a dominant variant *BP2* Observed in *cis* with a pathogenic variant *BP2*		For recessive disorders, detected in *trans* with a pathogenic variant *PM3*		
Other Database		Reputable source w/out shared data = benign *BP6*	Reputable source = pathogenic *PP5*			
Other Data		Found in case with an alternate cause *BP5*	Patient's phenotype or FH highly specific for gene *PP4*			

SPECIAL ARTICLE

Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer

A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists

Marilyn M. Li,[*†] Michael Datto,[*‡] Eric J. Duncavage,[*§] Shashikant Kulkarni,[*¶] Neal I. Lindeman,[*‖] Somak Roy,[*,**] Apostolia M. Tsimberidou,[*††] Cindy L. Vnencak-Jones,[*‡‡] Daynna J. Wolff,[*§§] Anas Younes,[*¶¶] and Marina N. Nikiforova[*,**]

Tier I: Variants of Strong Clinical Significance

Therapeutic, prognostic & diagnostic

Level A Evidence
FDA-approved therapy
Included in professional guidelines

Level B Evidence
Well-powered studies with consensus from experts in the field

Tier II: Variants of Potential Clinical Significance

Therapeutic, prognostic & diagnostic

Level C Evidence
FDA-approved therapies for different tumor types or investigational therapies
Multiple small published studies with some consensus

Level D Evidence
Preclinical trials or a few case reports without consensus

Tier III: Variants of Unknown Clinical Significance

Not observed at a significant allele frequency in the general or specific subpopulation databases, or pan-cancer or tumor-specific variant databases
No convincing published evidence of cancer association

Tier IV: Benign or Likely Benign Variants

Observed at significant allele frequency in the general or specific subpopulation databases
No existing published evidence of cancer association

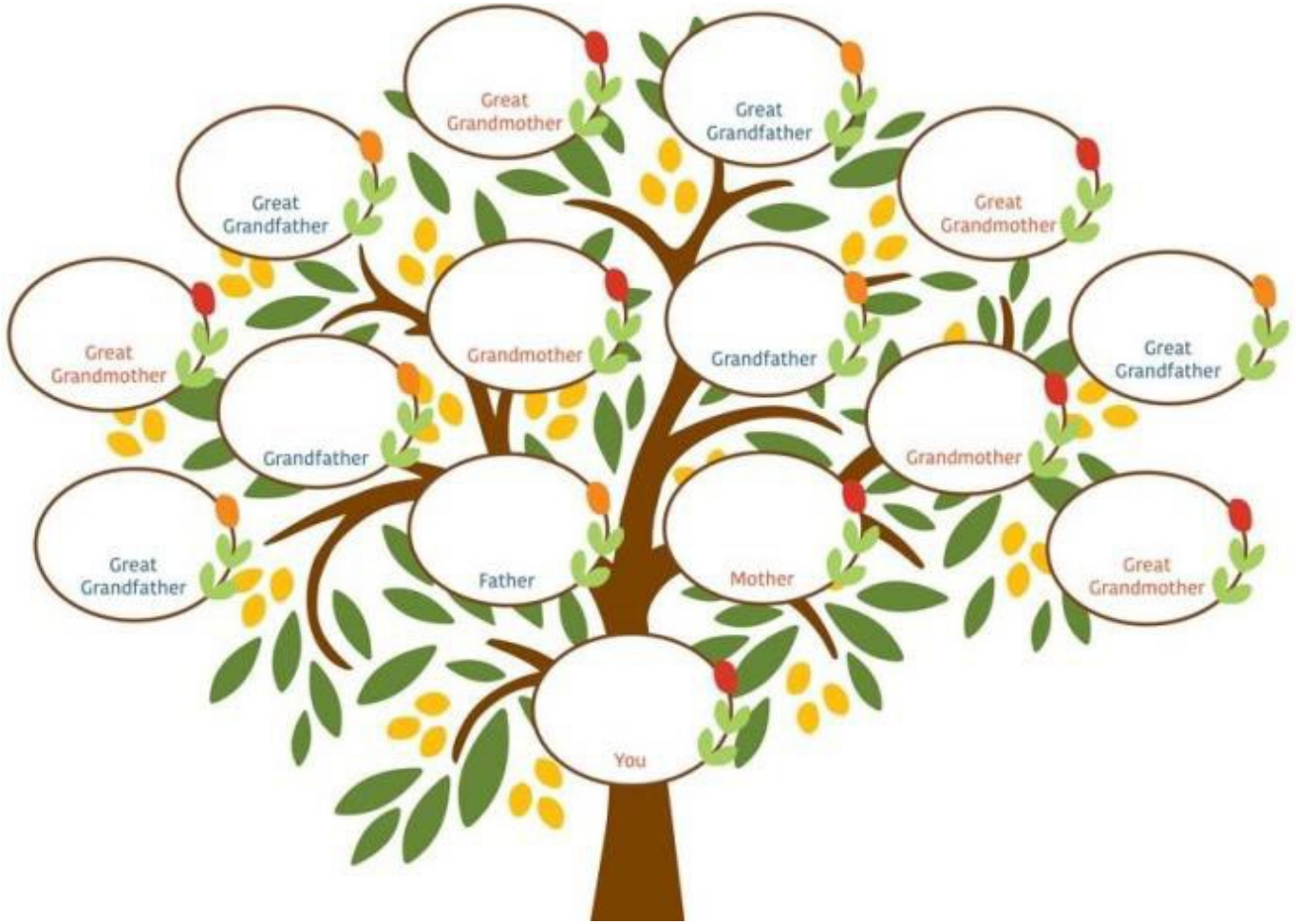
Why do we care about germline variants that crop up in tumor testing?

- Your patient's treatment + management could change
  - Eg. parp inhibitors for people with *BRCA1*-related ovarian cancer
- Risk of additional cancers, cancer recurrence might be much higher than previously appreciated
- Benefits to relatives – prevention and screening!
- Expand our clinical knowledge of cancer syndromes in patients who don't meet current criteria for germline testing

Implications for Informed Consent

- Patients should be informed that tumor testing could detect germline (heritable) genetic changes
- Germline results should be disclosed because they could influence treatment decisions in patient and risk management in relatives
- Current guidelines suggest that patients should be allowed to opt-out of learning germline results

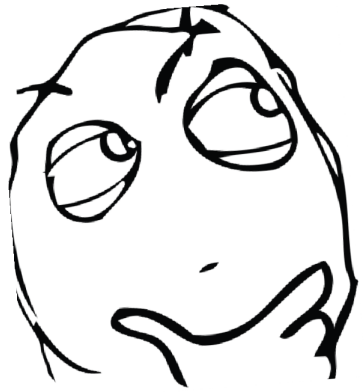
#3: Returning research results to relatives – when and how?



Questions

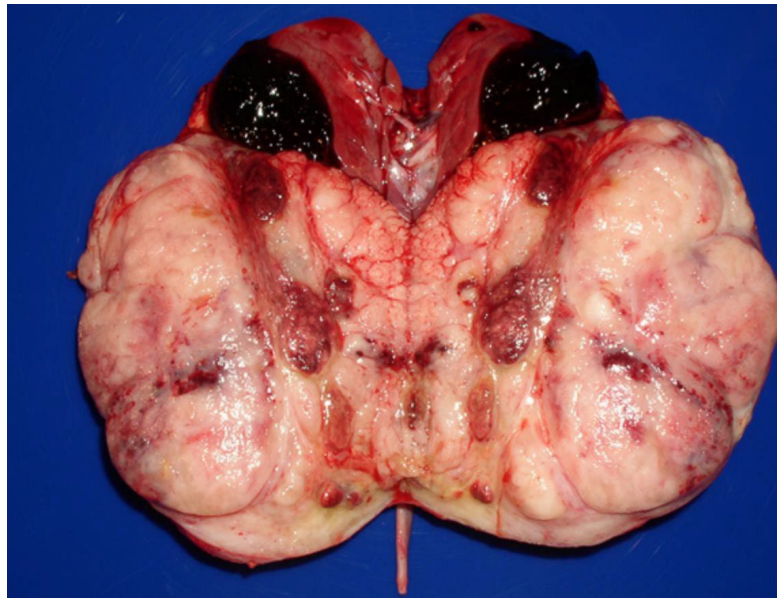
- To what extent do researchers have responsibilities to notify at-risk relatives of critically ill or deceased cancer patients?

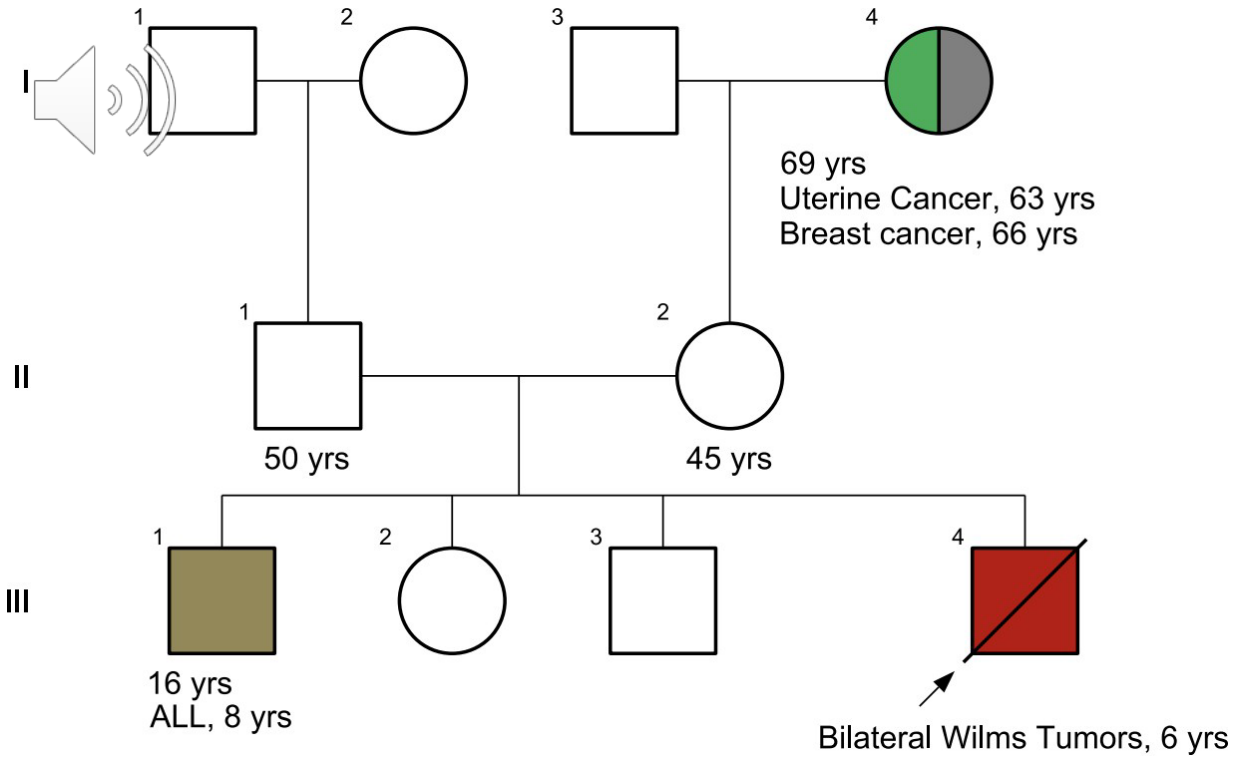
- What is the most efficient way of doing this in a research setting?



Case

- 6 yo w/bilateral Wilms Tumor
  - Histology: Epithelial highly anaplastic

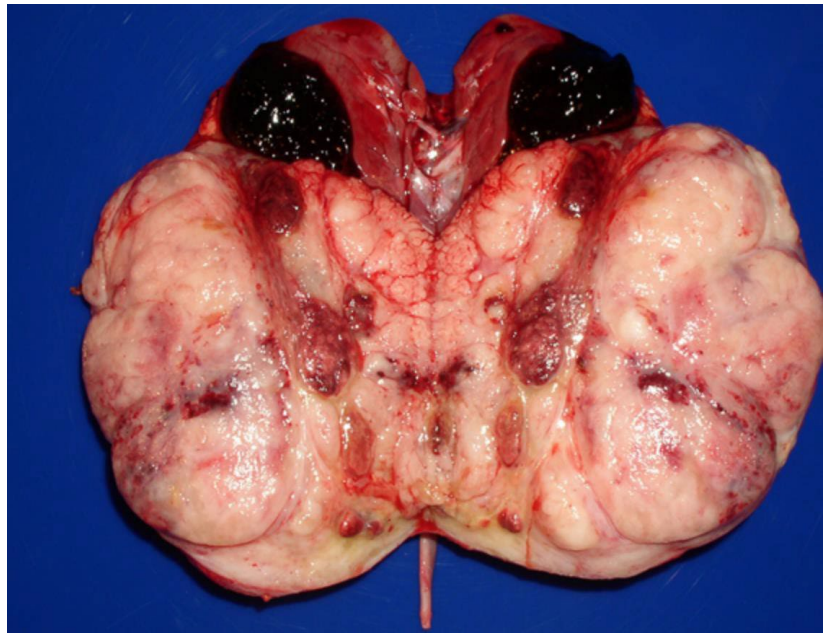




Tumor results

SINGLE NUCLEOTIDE VARIANTS AND INDELS		
Alteration	**HGVS Nomenclature**	**Allele Frequency**
MSH6 R1176*	NM_000179: c.3526A>T; p.Arg1176Ter	45% WGS, 52% WES, 0% RNA
TP53 R158G	NM_000546: c.472C>G; p.Arg158Gly	76% WGS, 70% WES, 62% RNA
TP53 C141F	NM_000546: c.422G>T; p.Cys141Phe	3% WGS, 6% WES, 5% RNA
TP53 R273S	NM_000546: c.817C>A; p.Arg273Ser	10% WGS, 11% WES, 24% RNA
TP53 R342P	NM_000546: c.1025G>C; p.Arg342Pro	7% WGS, 9% WES, 13% RNA
SIX1 Q177R	NM_005982: c.530A>G; p.Gln177Arg	81% WGS, 87% WES, 100% RNA

NOTE: The *TP53* alterations occur in a region of copy neutral LOH, see tumor ploidy



Germline results

- **NGS Germline**
  - MSH6 R1176*➔ Lynch Syndrome

SINGLE NUCLEOTIDE VARIANTS AND INDELS		
Alteration	**HGVS Nomenclature**	**Allele Frequency**
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SIX1 Q177R	NM_005982: c.530A>G; p.Gln177Arg	81% WGS, 87% WES, 100% RNA

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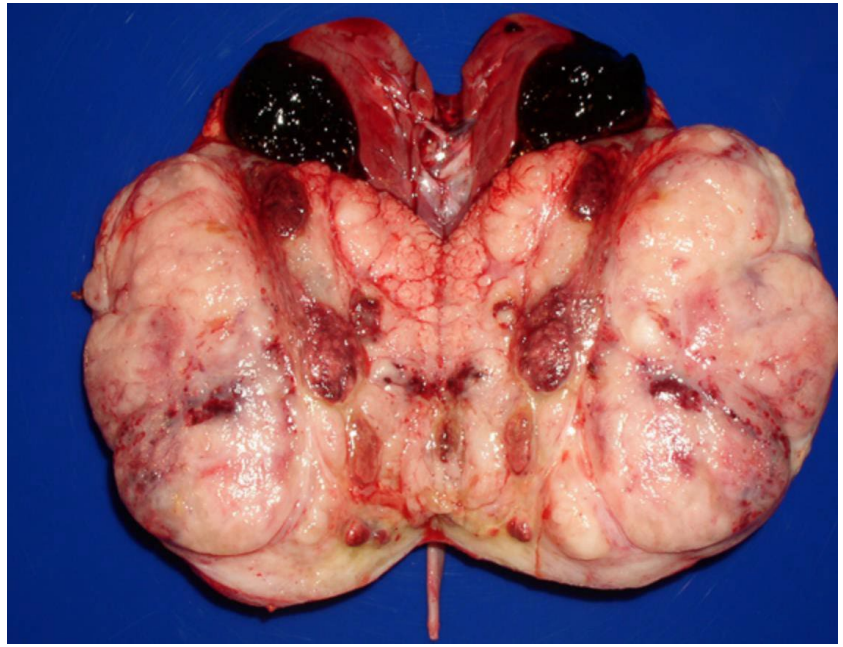


Dominant model: Proband-directed disclosure

- Risk to relatives is disclosed to the proband; who is responsible for informing at-risk relatives
- Relatives must *voluntarily* seek follow-up risk assessment
- Numerous studies show that this is not very effective (Sermijn et al. 2004; Marks et al. 2006; Montgomery et al. 2013; Hampel 2016)
- Family letters do not increase uptake of cascade risk assessment (Dheensa et al. 2017)

Barriers to communication about disease risk

Alternative model: Direct contact w/proband opt-in or out

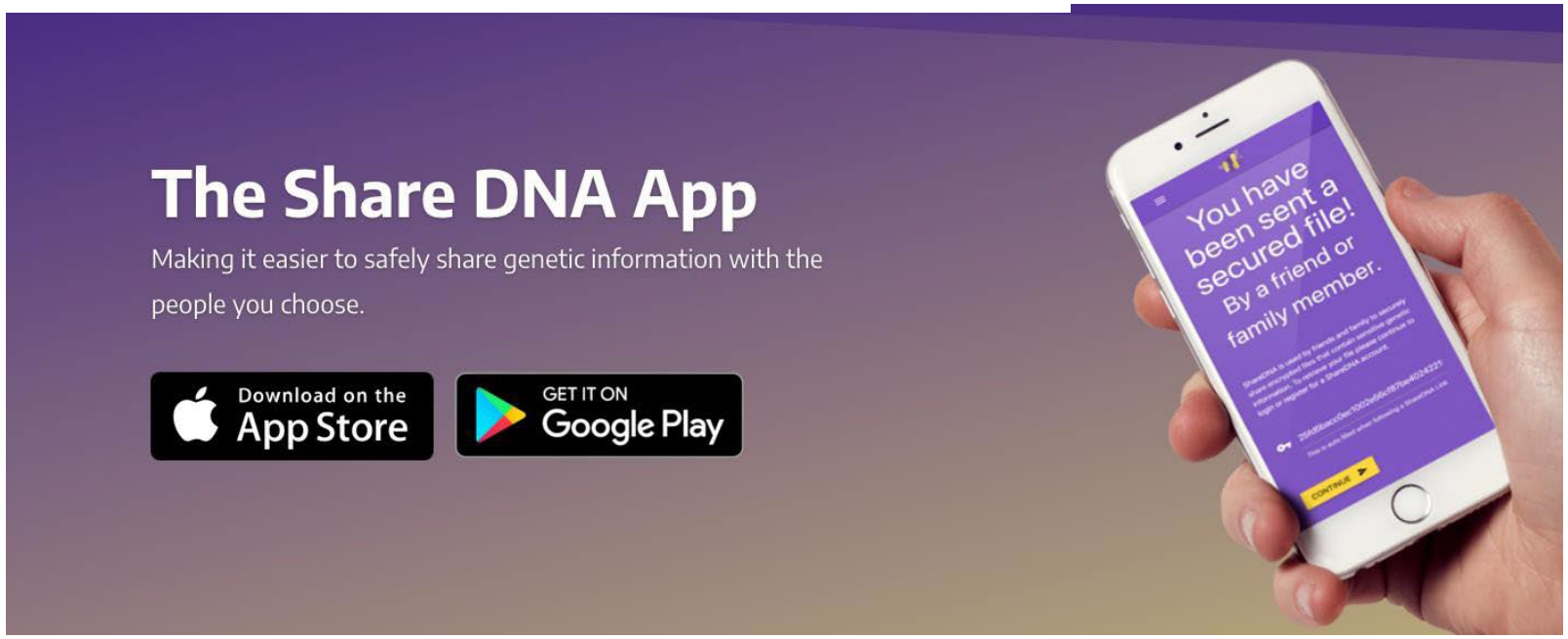
- Research programs contact relatives directly to notify them about their increased risk and test options
  - Via letters, phone, or an invitation to join a research registry
- Probands usually opt in or out of allowing relatives to be contacted
- Cost-effective; identifies more patients at-risk; access to treatment, and helps avoid unnecessary testing

Nordestegaard et al. 2013; Kerr et al. 2017; Costland et al. 2018

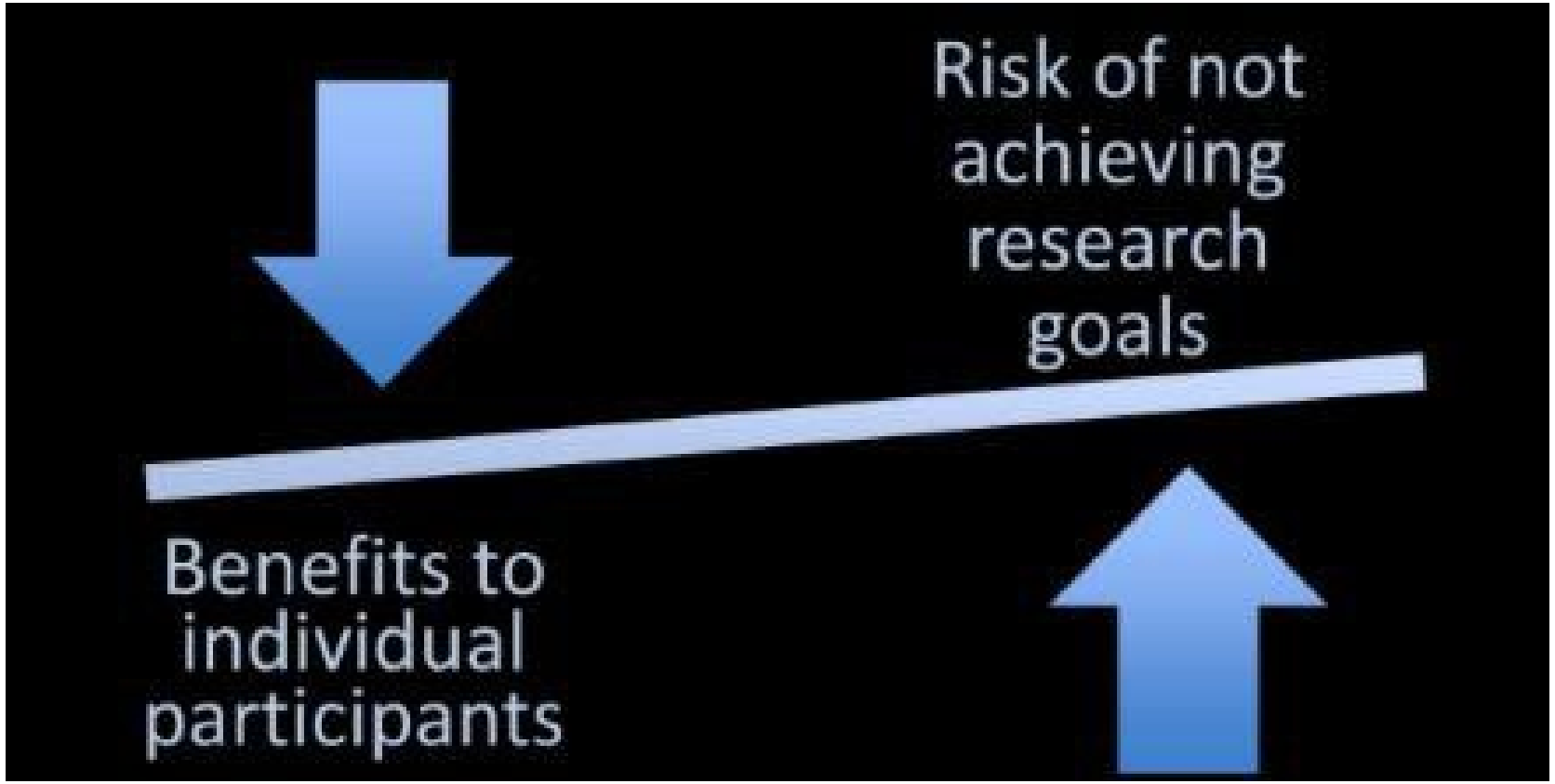
SOFTWARE Open Access

ShareDNA: a smartphone app to facilitate family communication of genetic results

Chethan Jujjavarapu[1], Jeevan Anandasakaran[2], Laura M. Amendola[3], Cameron Haas[4], Elizabeth Zampino[2], Nora B. Henrikson[4], Gail P. Jarvik[3,5] and Sean D. Mooney[1*]



In summary, a new riff on a familiar theme…



Courtesy Howard Levy + Yvonne Bombard

Thank you

leila.jamal@nih.gov