*Genomics: A land where clinical and research ethics must overlap

Leila Jamal ScM, PhD, CGC

Associate Director for Cancer Genomics, Johns Hopkins/NIH Genetic Counseling Training Program

Genomics Education Specialist, National Cancer Institute

SPECIAL REPORT

OPEN ACCESS Check for updates

Genomic testing in healthcare: a hybrid space where clinical practice and research need to co-exist

Rachel Horton and Anneke Lucassen

Clinical Ethics and Law at Southampton (CELS), Faculty of Medicine, University of Southampton, UK; Wessex Clinical Genetics Service, Princess Anne Hospital, Southampton, UK

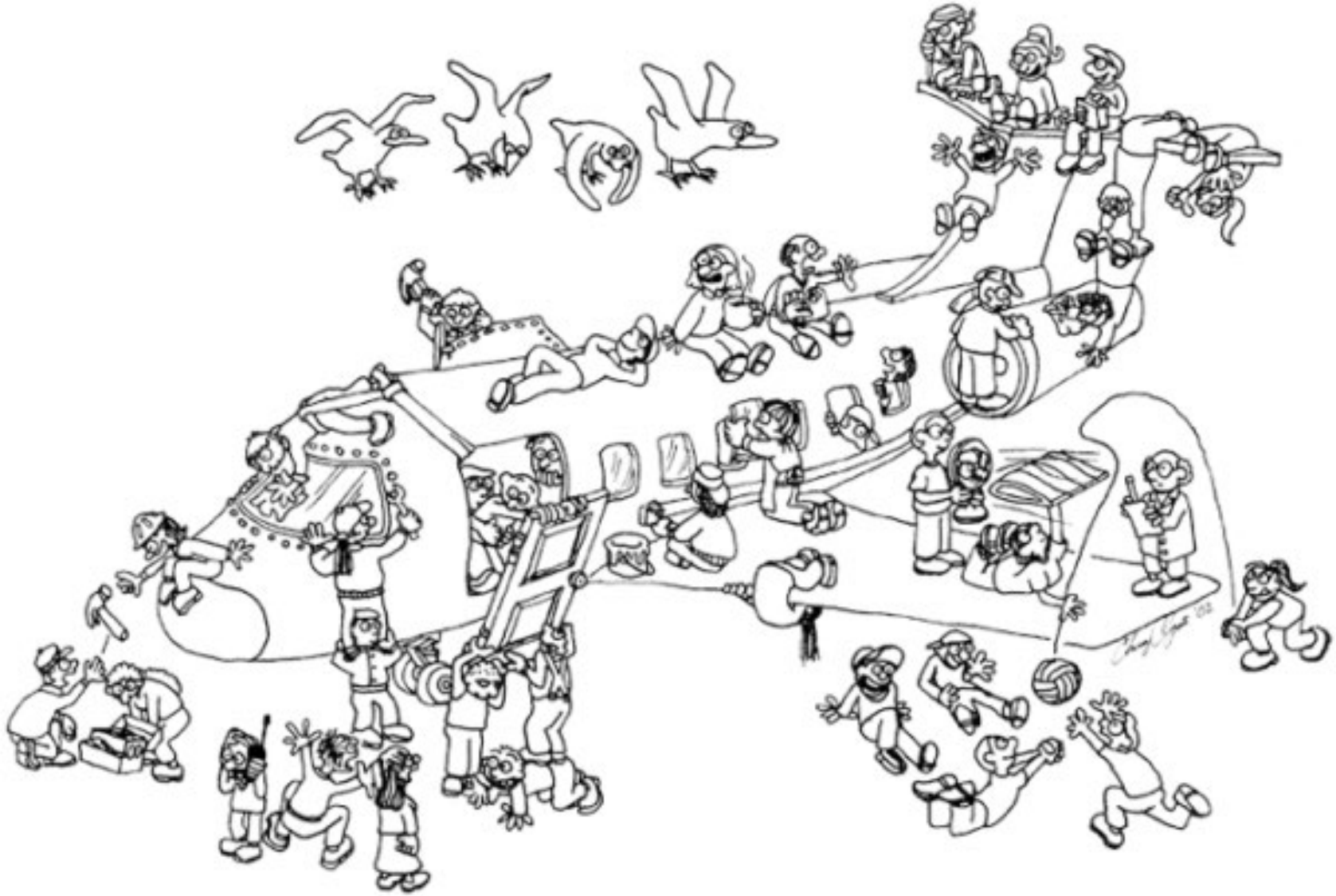
A tale of two innovations

- #1: Advances in genetic variant interpretation – a primer
  - Ethical issues + relevant guidelines
  - Reinterpretation and variant reclassification

- #2: Paired tumor-germline sequencing in cancer
  - A new case of secondary findings

Moral of the story: Unbiased sequencing is our future – and it has consequences for how we think about ethics

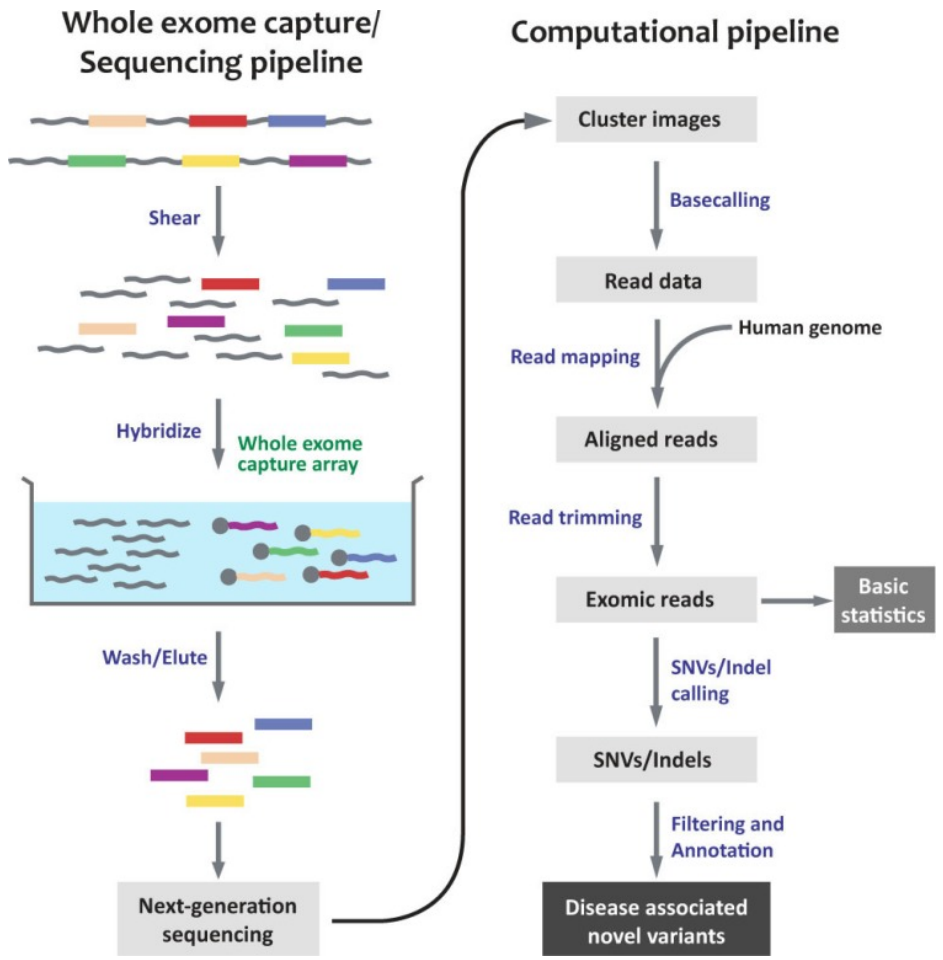
Genomic sequencing 2010-present



*1 – Standards for variant quality control and interpretation

Next Gen Sequencing =

- Base calling
- Read alignment
- Variant calling
- Variant annotation
- **Variant interpretation**



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)

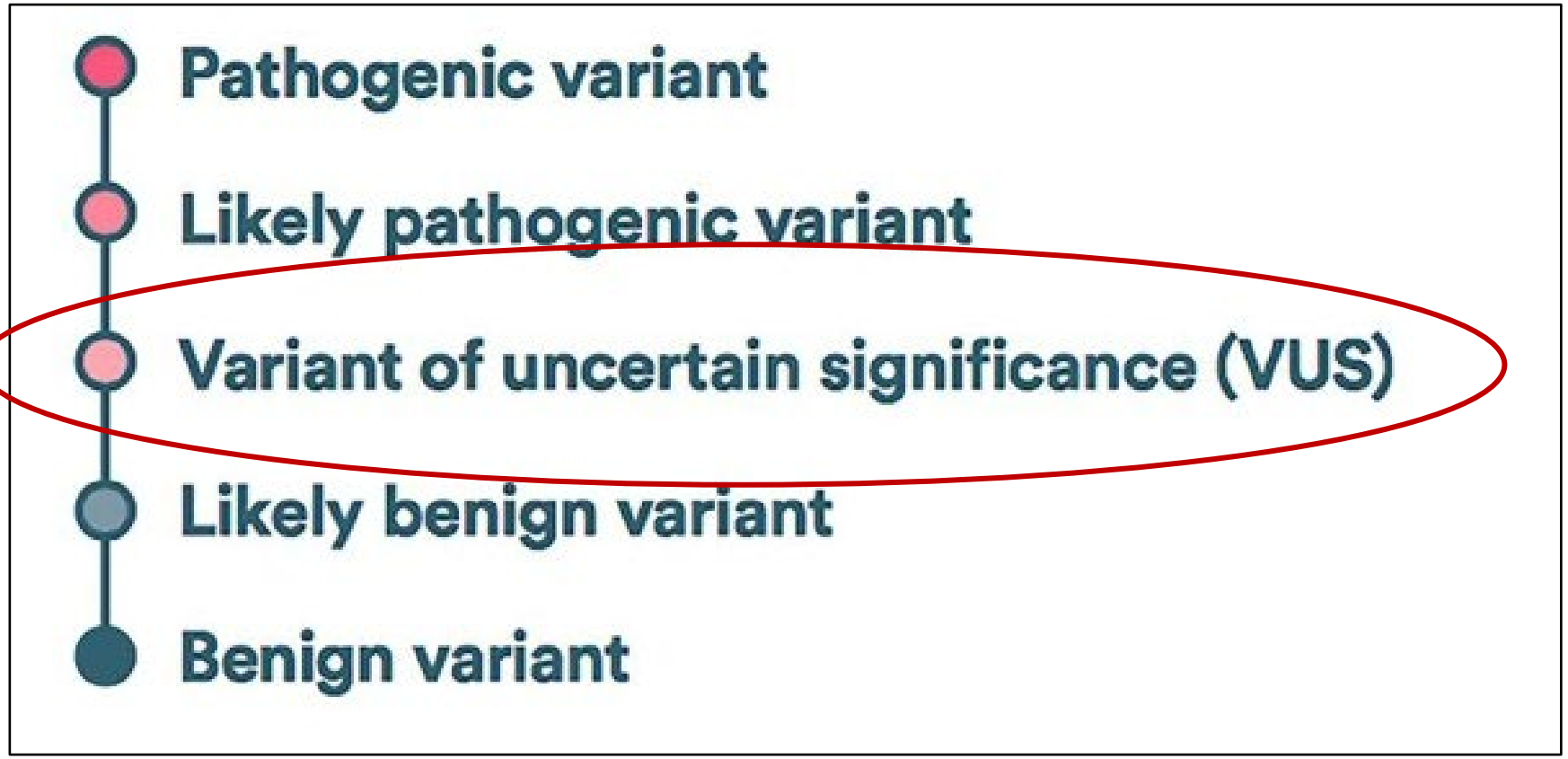
99% certain association with disease

90% certain association with disease

Everything else!

90% certain benign

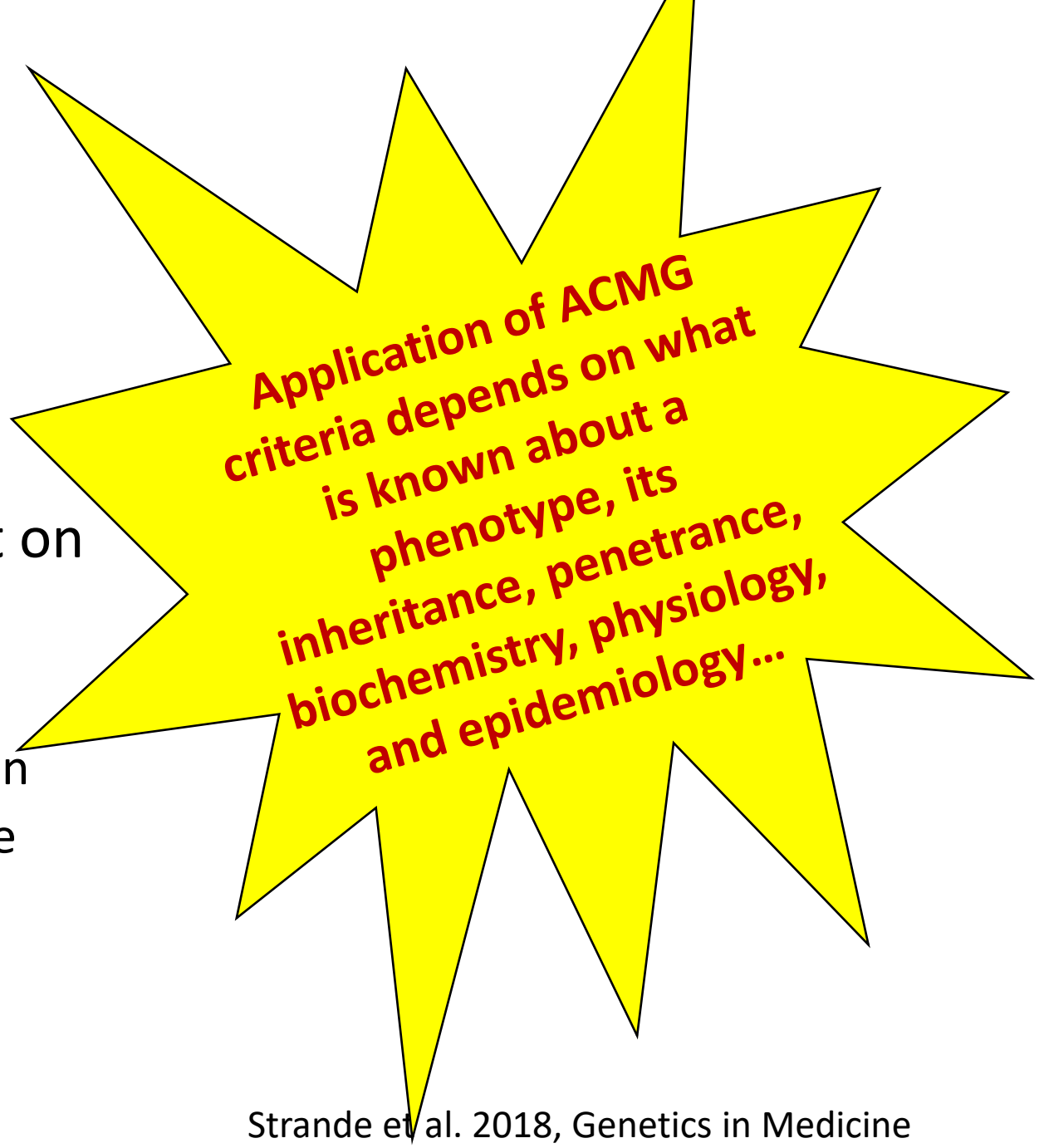
99% certain benign



Richards et al. 2015, Genetics in Medicine

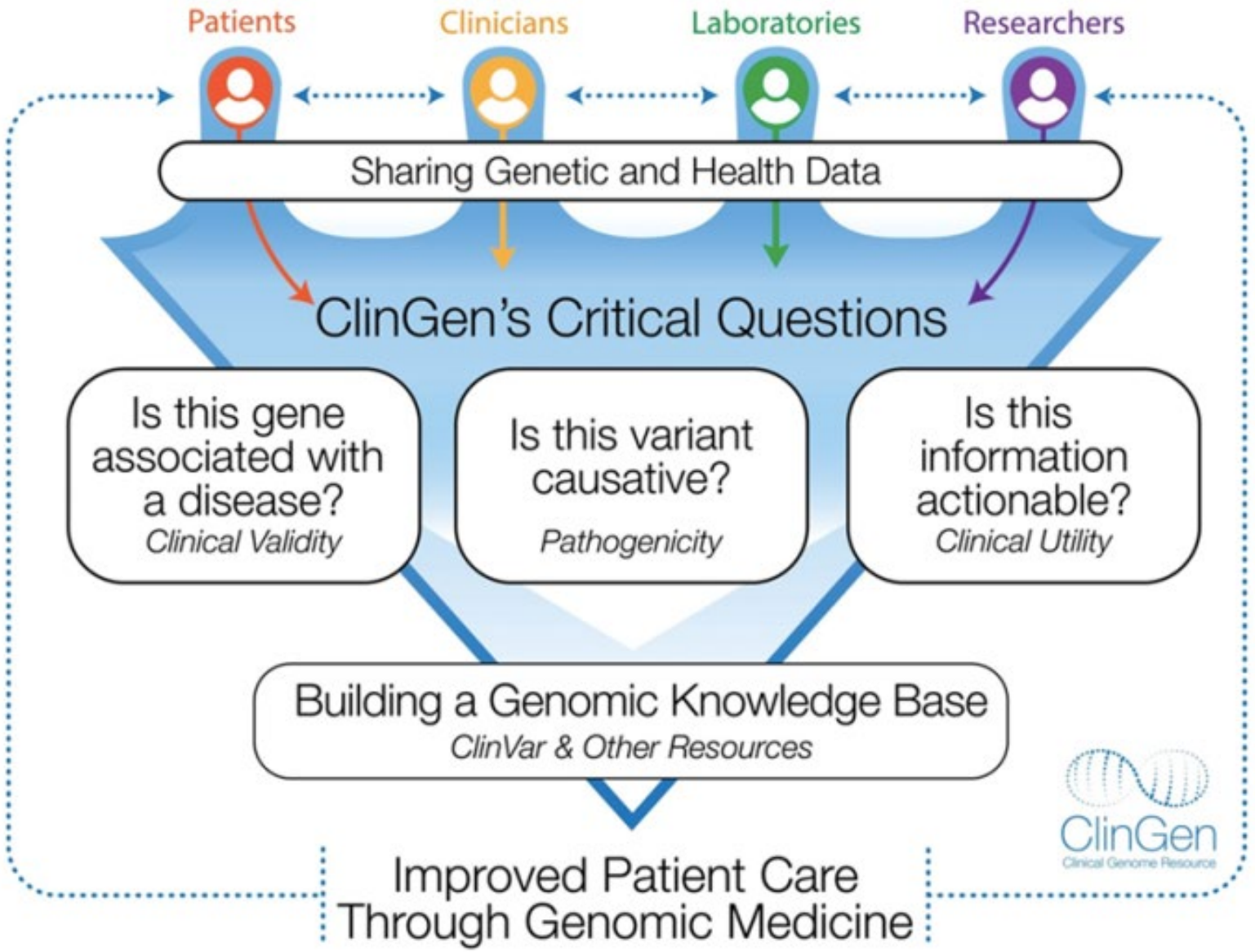
Types of data used

- 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

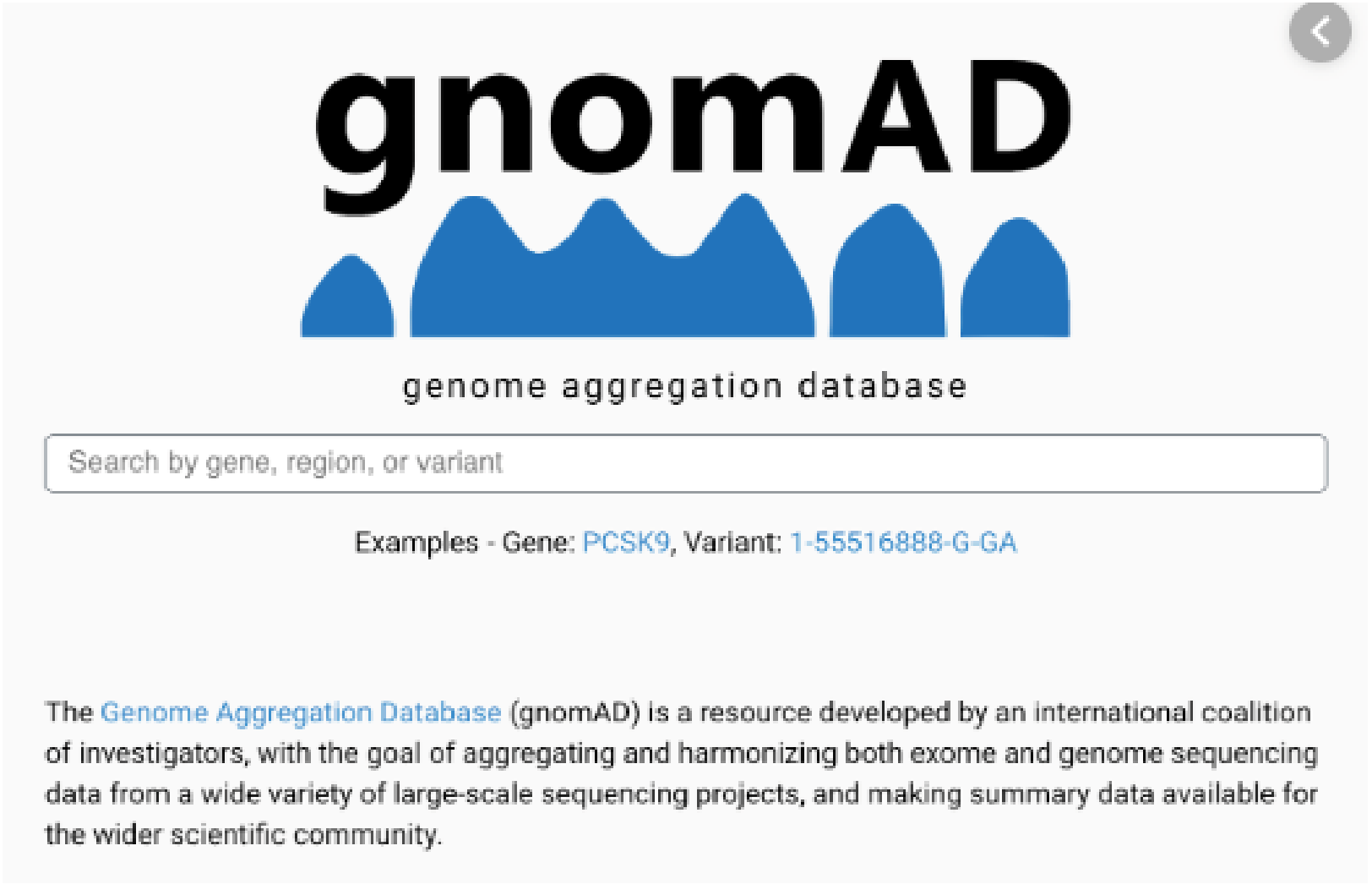
Gene
Browse Classifications by Gene

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

Present day challenge

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]

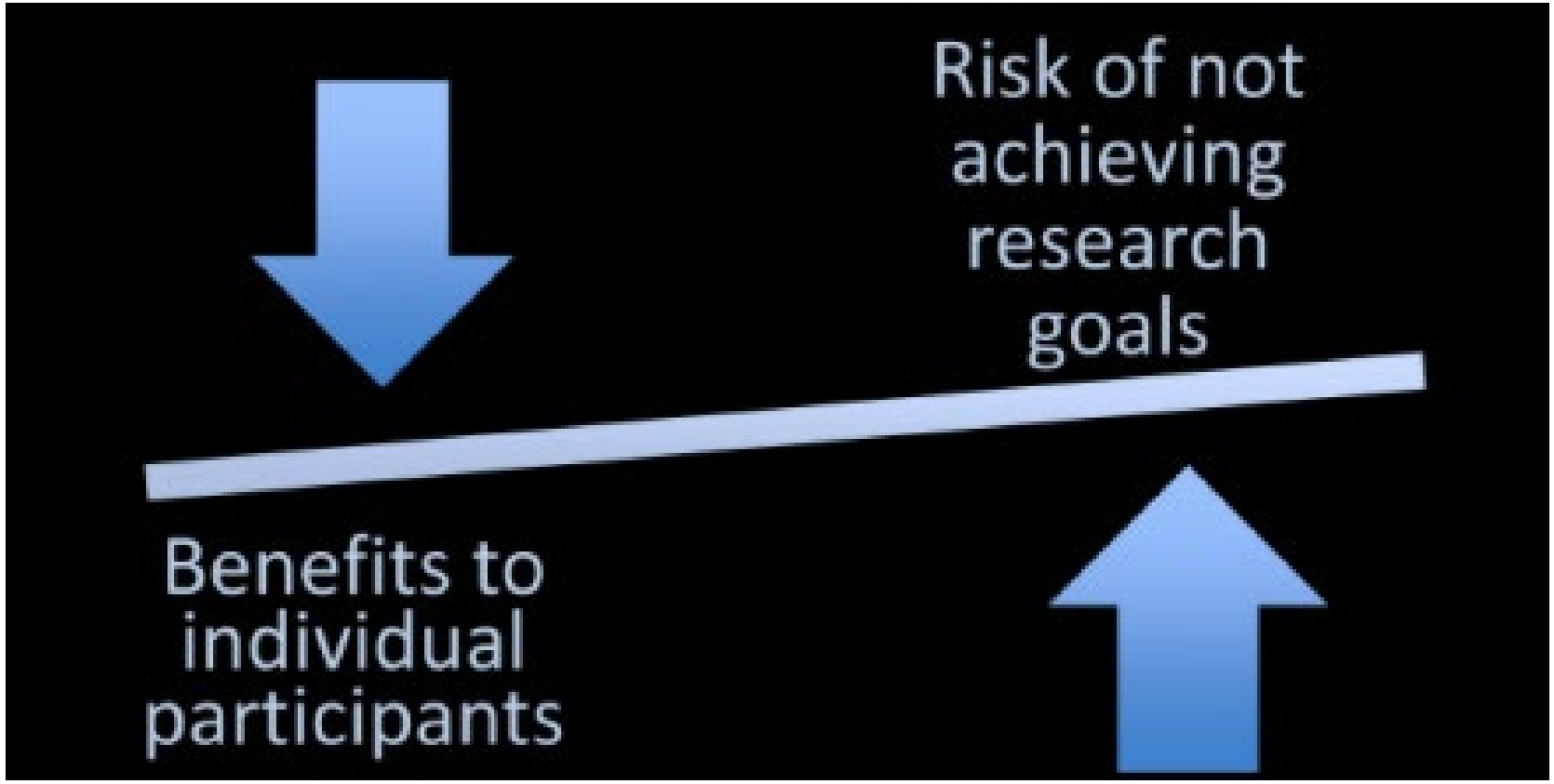
Bombard et al., AJHG, 2019

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.

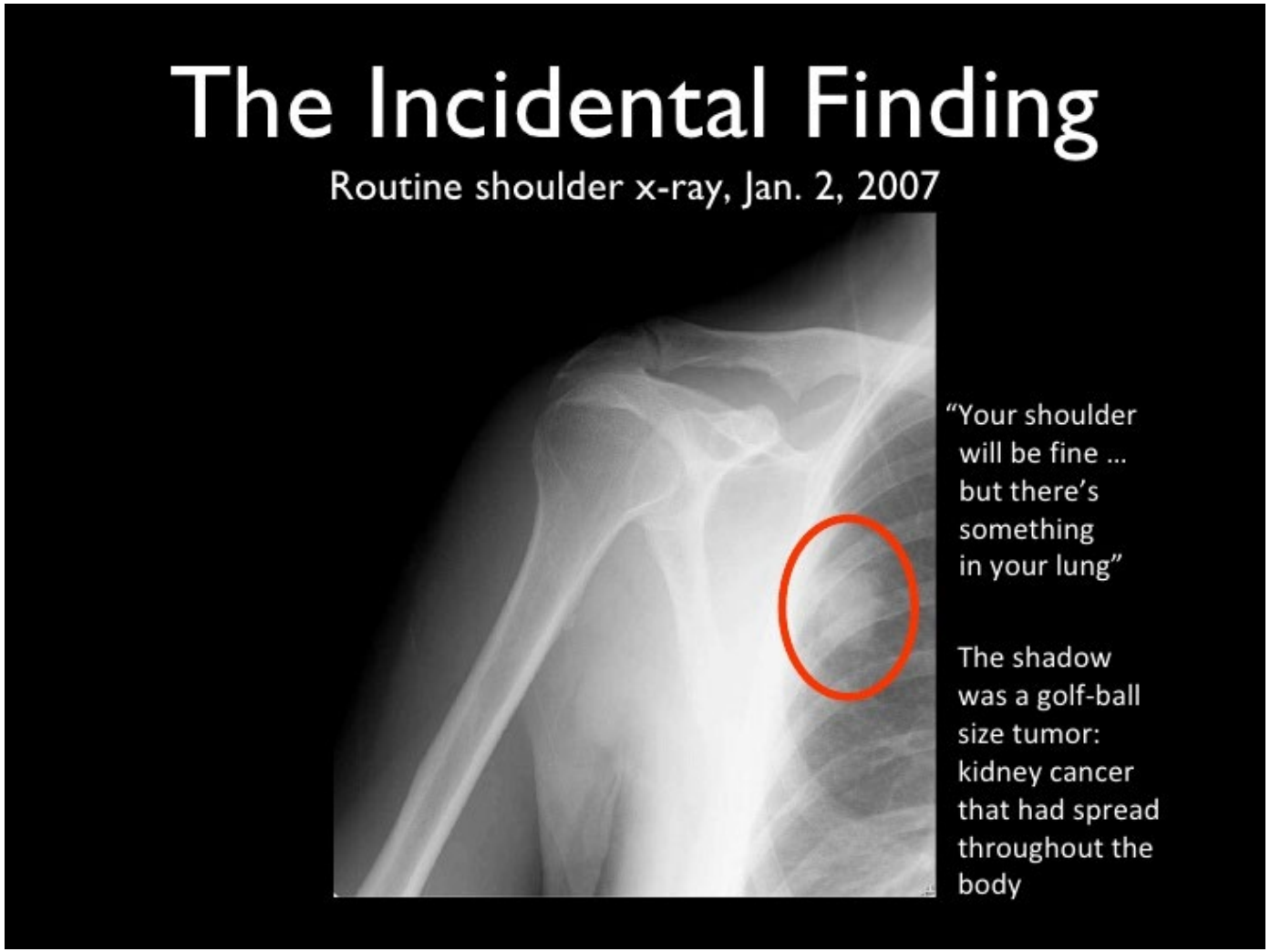
Bombard et al. AJHG, 2019

A new riff on a familiar theme…



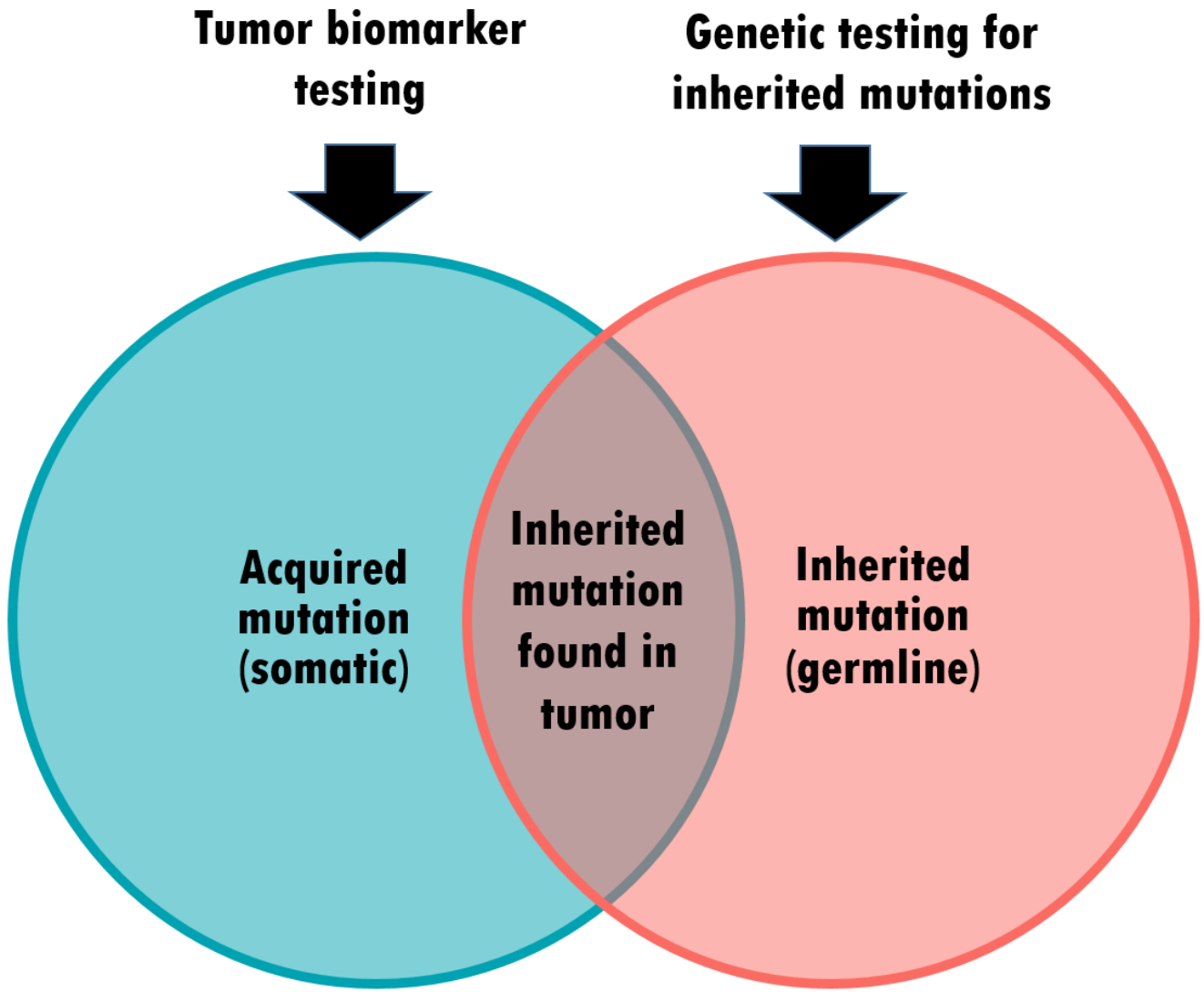
Courtesy Howard Levy + Yvonne Bombard

*2 - Detecting germline genetic variants from somatic tumor sequence information



Somatic (tumor) testing

Test Method	Sample Required	Can Germline Variants be Detected?	Confirmatory Testing Needed?
Somatic (tumor) only	Tumor specimen	Can be inferred	Yes
Somatic (tumor)-normal paired	Tumor and non-tumor specimens	Usually “masked”	Seldom
Somatic (tumor)-normal paired with cancer predisposition genes DELIBERATELY analyzed	Tumor and non-tumor specimens	Detected based on test design	No, as long as germline results are validated as a clinical test



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

”Incidental” germline findings in somatic sequencing

- When testing a tumor…

- Any identified variant could be
  - A somatic change
  - A germline change that has been retained in the tumor

- Germline variants may be
  - Phenotype-concordant (BRCA1 in a breast cancer)
  - Phenotype-discordant (BRCA1 in a lung cancer)

In somatic 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

Pay attention to clinical features

- Family history
- Age of onset
- Rare cancers
- Multiple primary cancers
- Unusual findings or comorbidities
  - Eg. dysmorphic features, congenital heart disease, skin findings

Li et al. Genetics in Medicine, 2020

Clinical implications

- Know the test you are ordering
  - What genes are (or are not) included?
  - What are the technical limitations?
  - Does the test evaluate copy-number variation?
  - Does the lab mask germline findings?

- Informed Consent
  - Patients should be informed that tumor testing could detect germline (heritable) genetic changes
  - Germline results could influence treatment decisions and risk management in relatives
  - Guidelines suggest that patients should be allowed to opt-out of learning germline results

“Tumor testing may uncover DNA changes that increase your risk of cancer. Sometimes, these DNA changes are inherited in families. They could have health implications for you and your relatives. If found, we might refer you for some additional testing and genetic counseling. You can choose to opt-out and not learn about DNA changes that might have been inherited. However, that might mean that we can’t manage your (or your relatives’) cancer risk to the very best of our abilities"

Why do we care about germline variants?

- Your patient's treatment + management could change
- Risk of additional cancers, cancer recurrence might higher than otherwise appreciated
- Benefits to relatives – prevention and screening
- Research: Expand our clinical knowledge of cancer syndromes in patients who don't meet current criteria for germline testing

Unbiased genomic sequencing is our (present?) future

Flipping the script on incidental findings

2013

COMMENTARY

Incidental Variants Are Critical for Genomics

Leslie G. Biesecker[1,*]

The topic of incidental variants detected through exome and genome sequencing is controversial, both in clinical practice and in research. The arguments for and against the deliberate analysis and return of incidental variants focus on issues of clinical validity, clinical utility, autonomy, clinical and research infrastructure and costs, and, in the research arena, therapeutic misconception. These topics are briefly reviewed and an argument is made that these variants are the future of genomic medicine. As a field, we should take full advantage of all opportunities to study these variants by searching them out, returning them to patients and research participants, and studying their utility for predictive medicine.

"In the research arena, we should study incidental variants **to learn what they can tell us about the full spectrum of genotypes and phenotypes. Because this research improves our knowledge of incidental variants, they can be moved onto, or perhaps in some cases off of, the lists of genes and variants known to be medically useful"**

"In the clinical arena, we should return those variants to patients when they meet reasonable standards for proof of causality and can significantly improve the medical care of our patients."

Reduced penetrance and variable expressivity

- Reduced penetrance
  - % of pathogenic variant carriers who develop a condition (penetrance is rarely 100%)
- Variable expressivity
  - Variable features identified in people who carry the same pathogenic variant(s) (most disorders have variable expressivity)
- Both are evidence that we don't understand genetics as well as we would like to

Clin Genet 2015: 87: 311–318
Printed in Singapore. All rights reserved

CLINICAL GENETICS
doi: 10.1111/cge.12461

Review

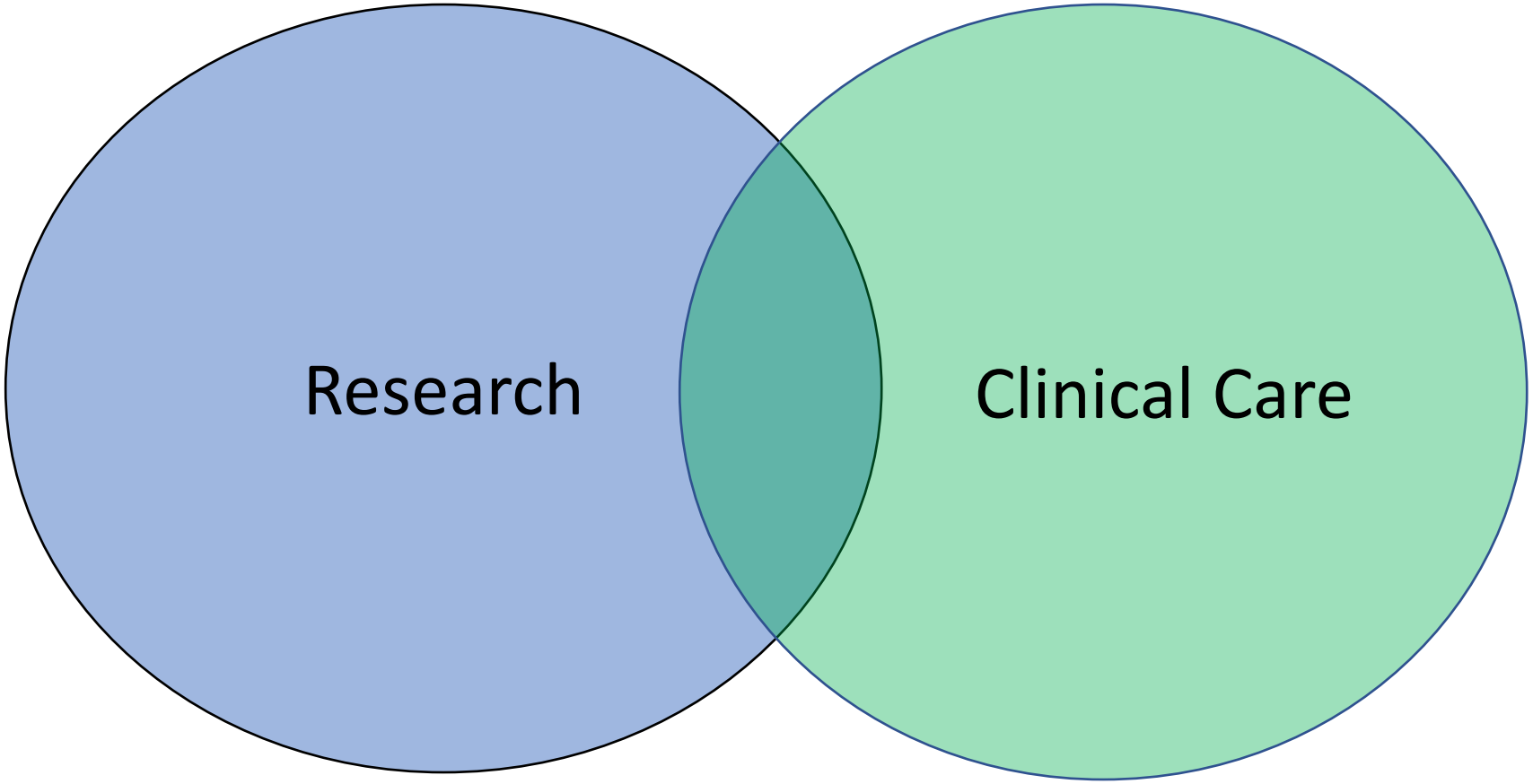
Living laboratory: whole-genome sequencing as a learning healthcare enterprise

Angrist M, Jamal L. Living laboratory: whole-genome sequencing as a learning healthcare enterprise.
Clin Genet 2015: 87: 311–318. © John Wiley & Sons A/S. Published by John Wiley & Sons Ltd, 2014

M. Angrist[a] and L. Jamal[b]

[a]Science and Society, Social Science Research Institute and Sanford School of Public Policy, Duke University, Durham

NIH Clinical Center - Overlapping Worlds



Bottom line

- Research findings can have impactful clinical implications; clinical tests can produce results with little or no associated evidence
- Responsible return of results requires interdisciplinary collaboration and institutional investment
- Policy development is crucial
- Scientific, medical, ethical and legal experts must learn to work together in order to get the difficult cases right

Thank you!