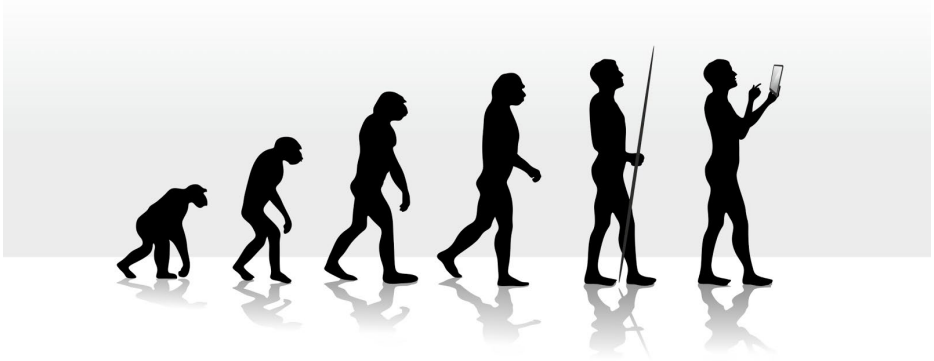


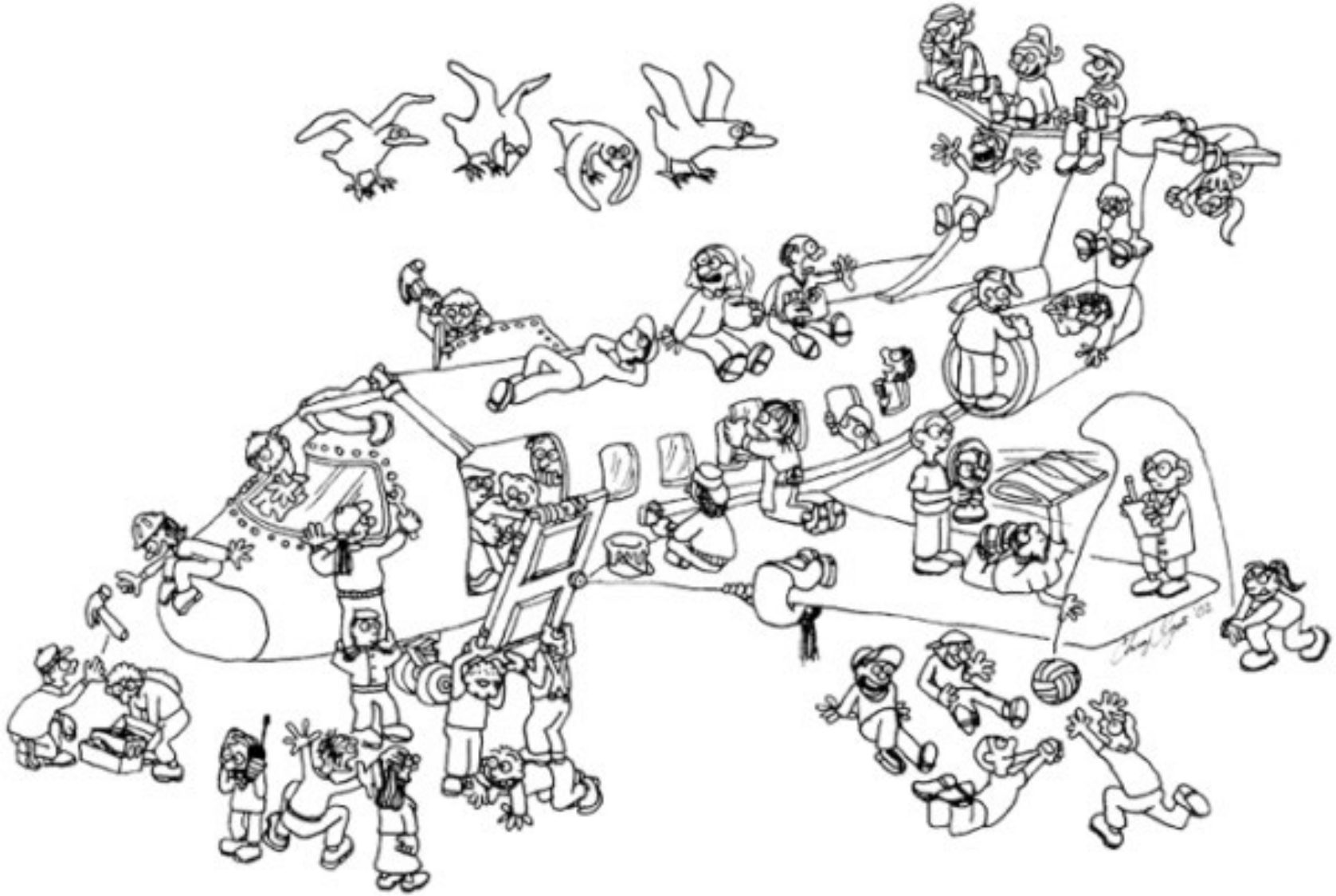
*Returning research results in the context of evolving science

Leila Jamal ScM, PhD, CGC

Certified Genetic Counselor, National Cancer Institute

Affiliated Scholar, NIH Department of Bioethics

Genomic sequencing 2010-present



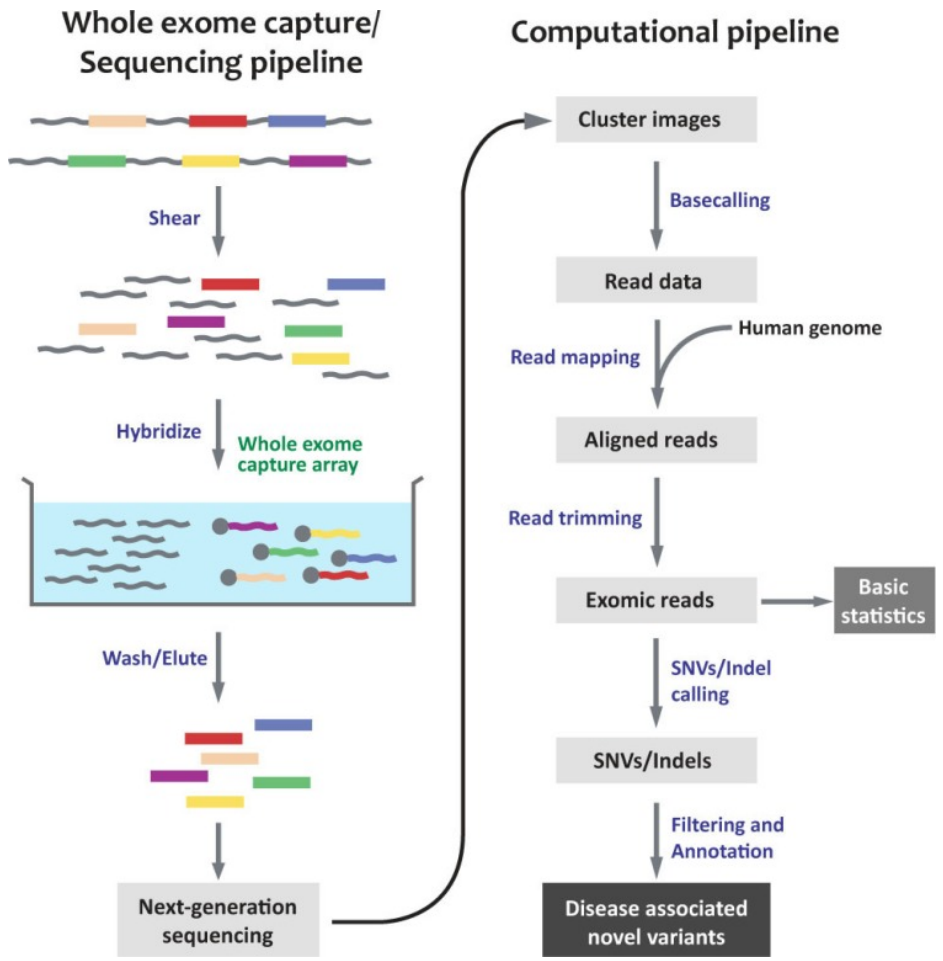
A tale of two innovations

- #1: Advances in genetic variant interpretation – a primer
  - Ethical issues + relevant guidelines
- #2: Discoveries from “unbiased” genomic sequencing research – early findings
  - Ethical issues
  - An illustrative case
- Implications for policy and oversight of the return of research results

*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)

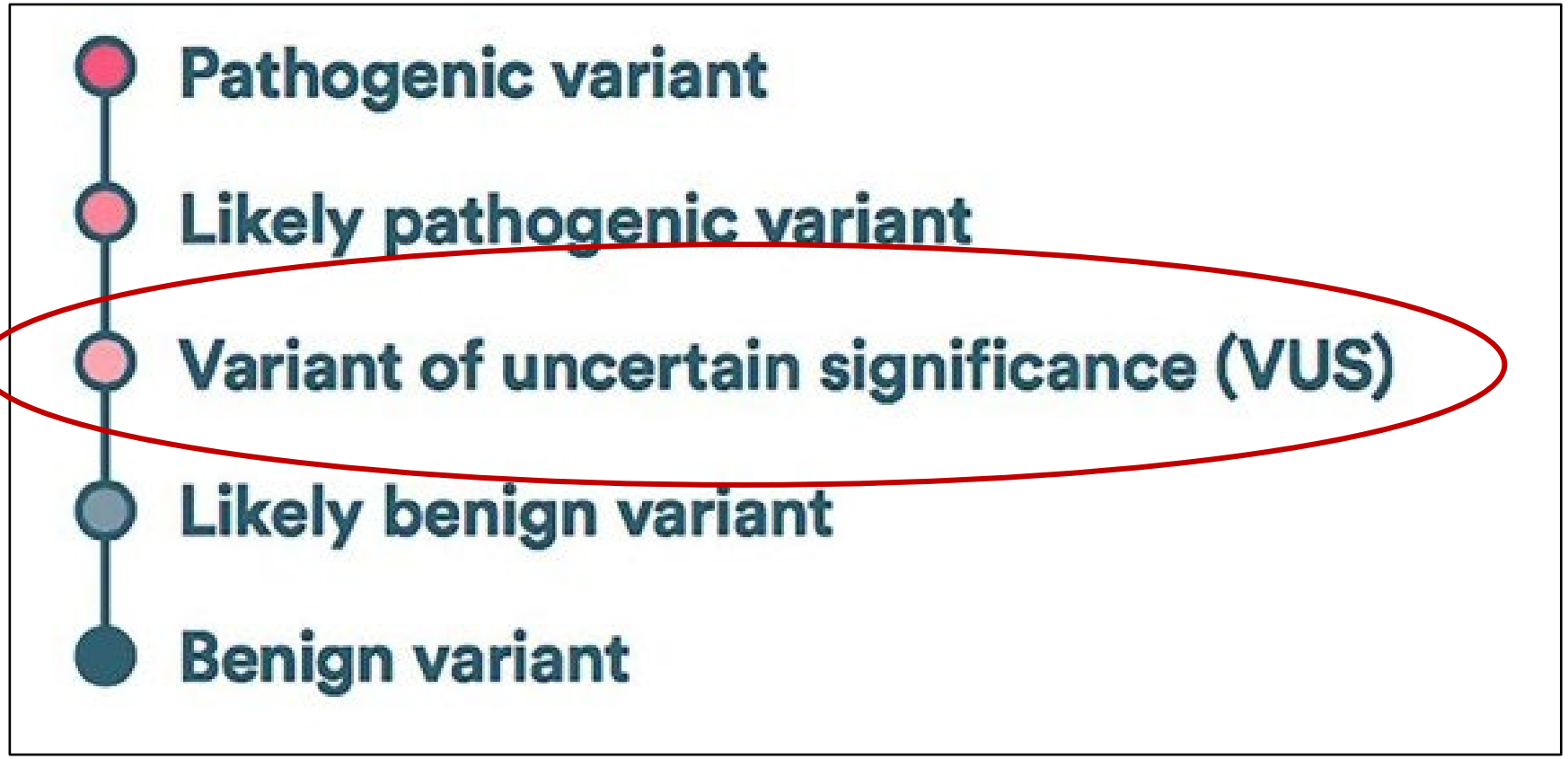
99% certain association with disease

90% certain association with disease

Everything else!

90% certain benign

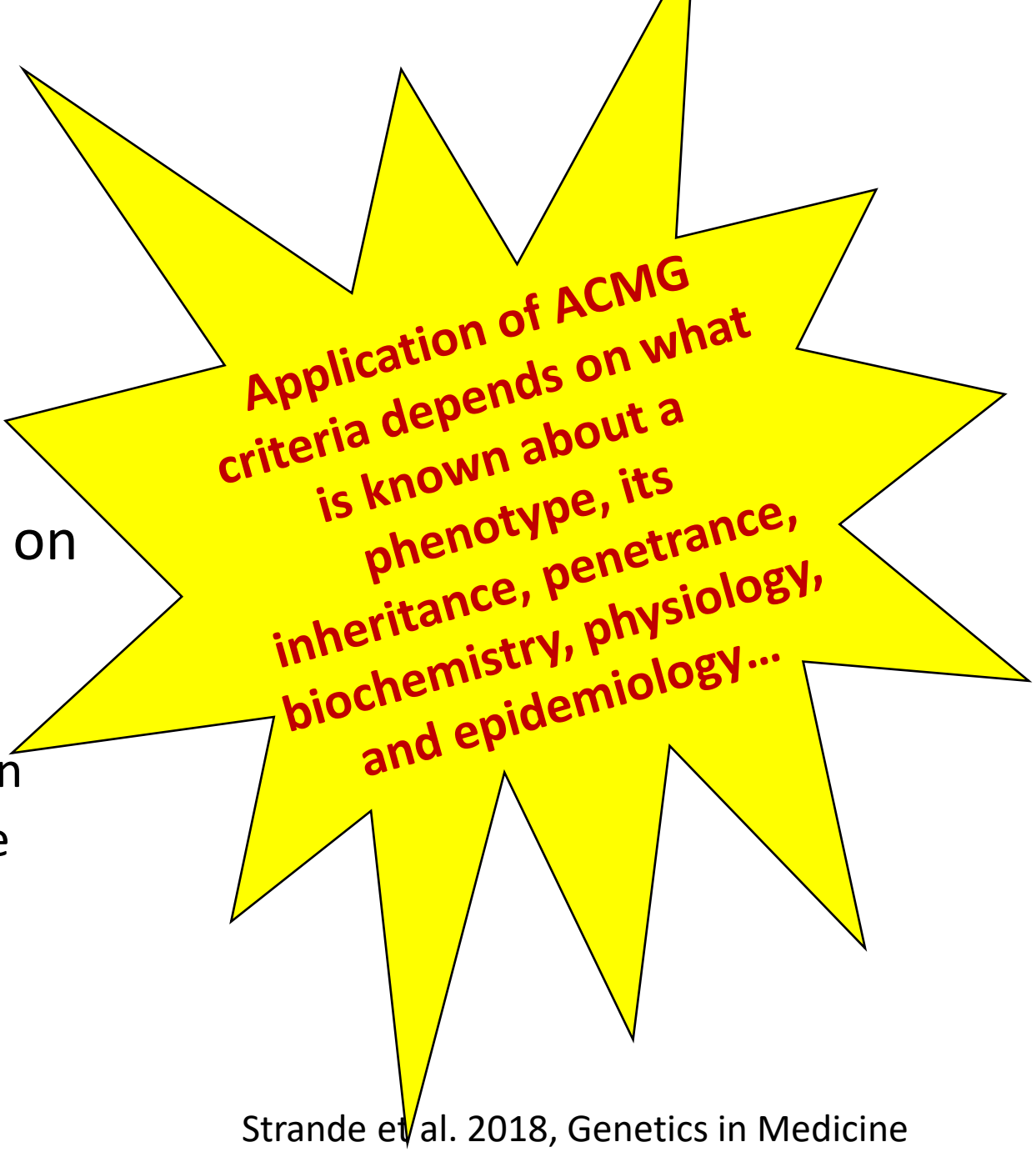
99% certain benign



Richards et al. 2015, Genetics in Medicine

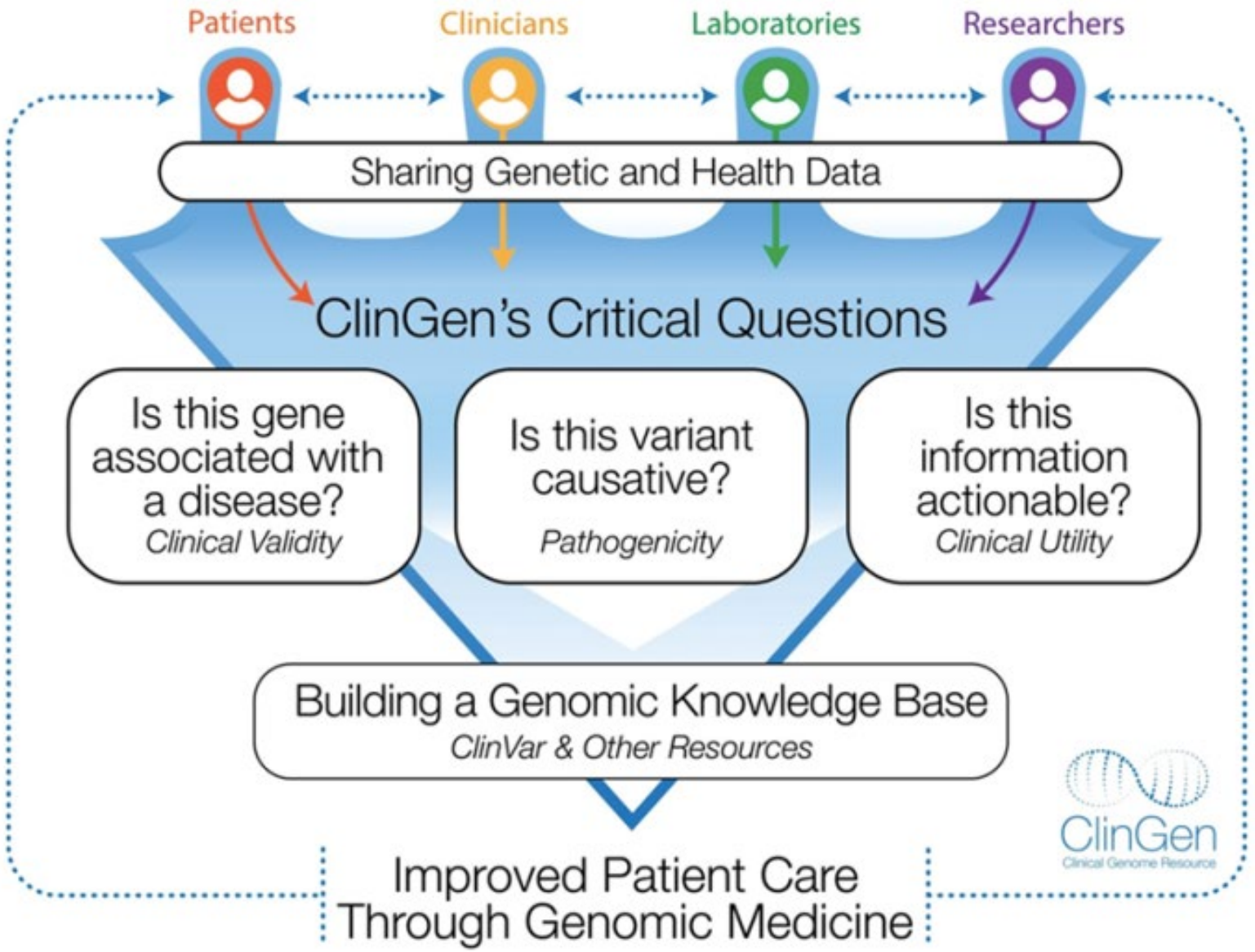
Types of data used

- 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

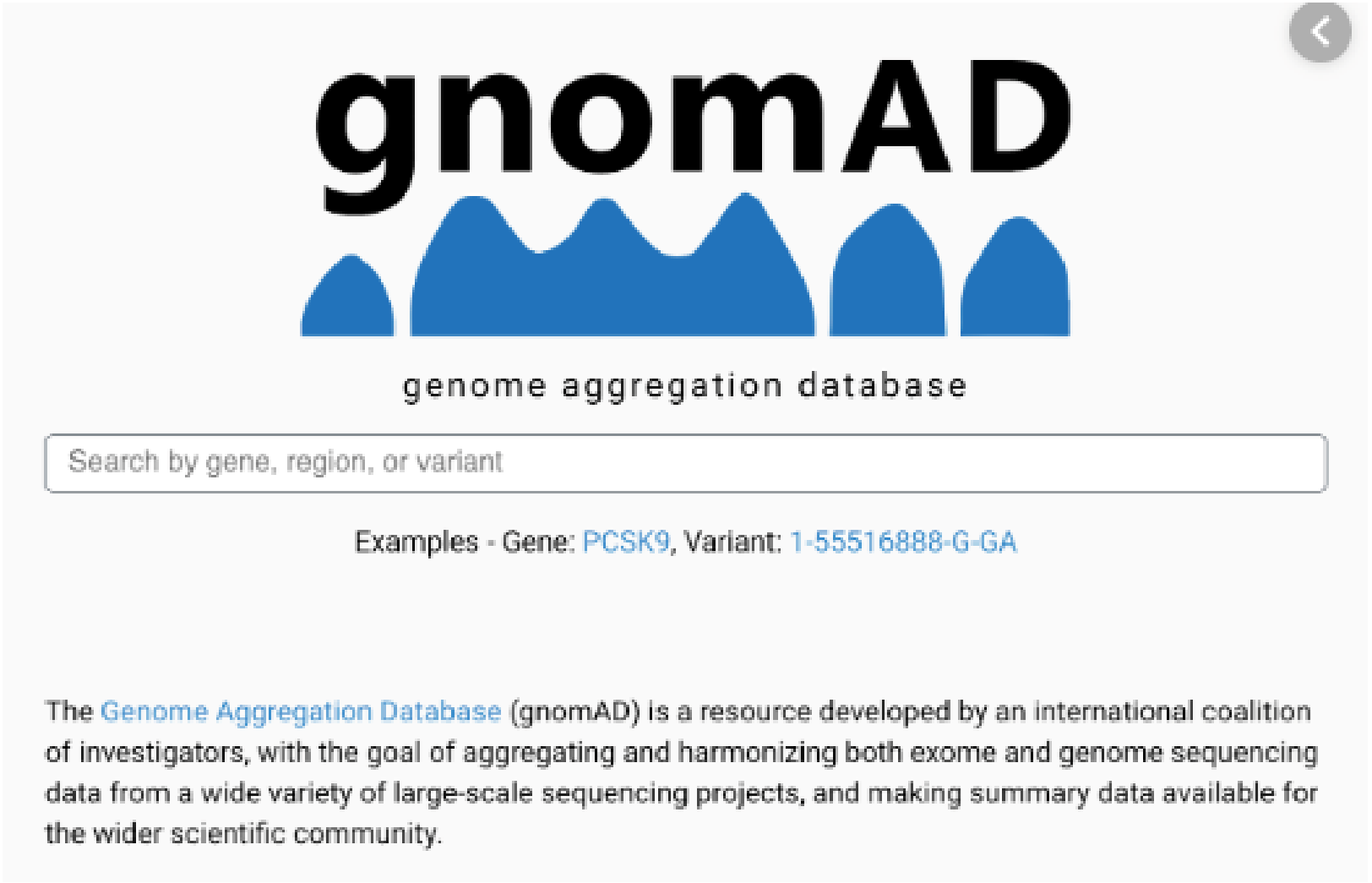
Gene
Browse Classifications by Gene

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]

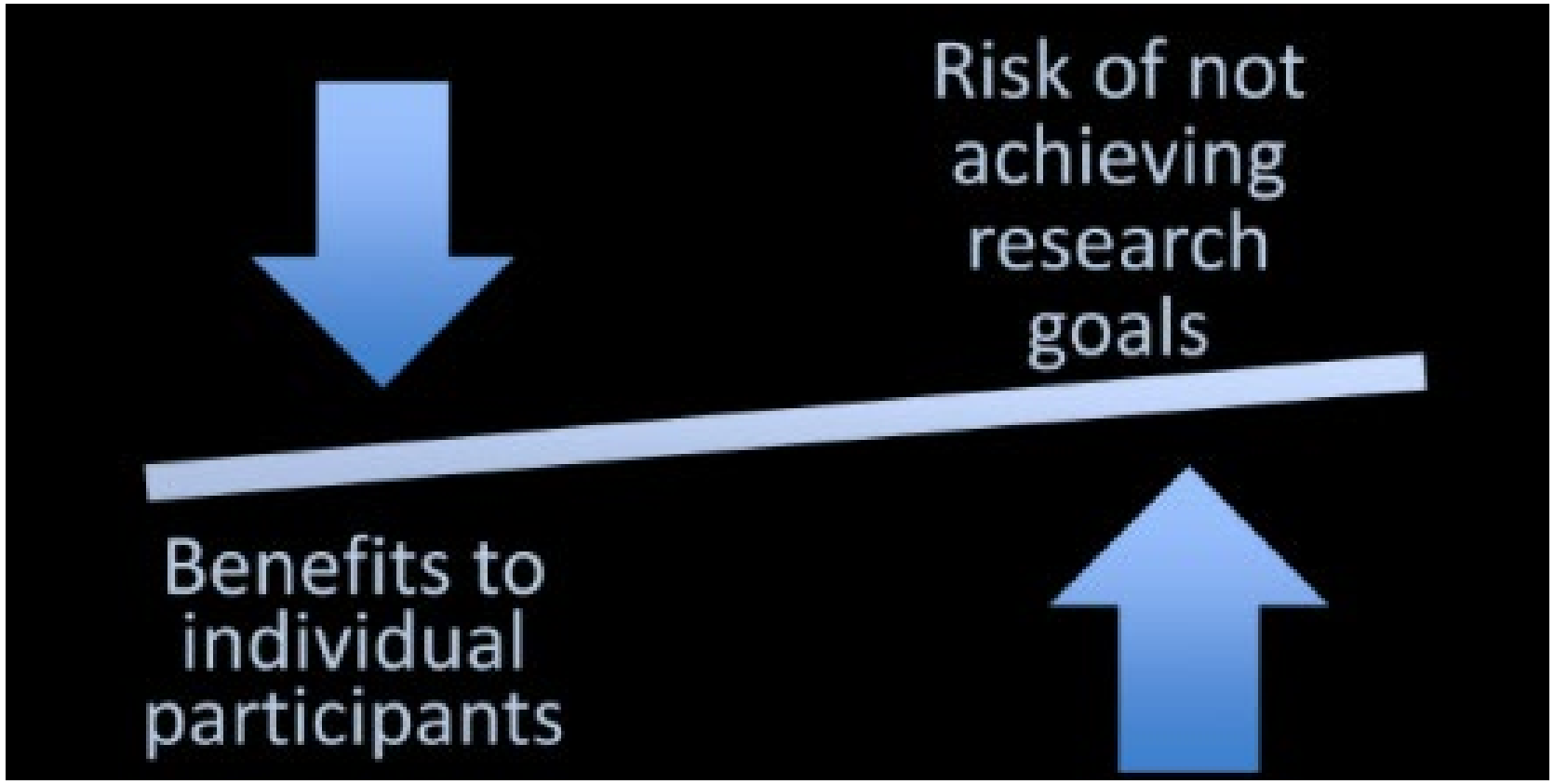
Bombard et al., AJHG, 2019

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

Learning as we go

FORUM

Optimal Integration of Behavioral Medicine into Clinical Genetics and Genomics

William M.P. Klein,[1,*] Colleen M. McBride,[2,*] Caitlin G. Allen,[2] Elva M. Arredondo,[3] Cinnamon S. Bloss,[4] Kimberly A. Kaphingst,[5] Amy C. Sturm,[6] and Catharine Wang[7]

Clinical genetics and genomics will exert their greatest population impact by leveraging the rich knowledge of human behavior that is central to the discipline of behavioral medicine. We contend that more concerted efforts are needed to integrate these fields synergistically, and accordingly, we consider barriers and potential actions to hasten such integration.

Klein et al. AJHG, 2019

*2 – Unbiased genomic ascertainment

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."

The NEW ENGLAND JOURNAL of MEDICINE

2017

ORIGINAL ARTICLE

Resolution of Disease Phenotypes Resulting from Multilocus Genomic Variation

Jennifer E. Posey, M.D., Ph.D., Tamar Harel, M.D., Ph.D., Pengfei Liu, Ph.D., Jill A. Rosenfeld, M.S., Regis A. James, Ph.D., Zeynep H. Coban Akdemir, Ph.D., Magdalena Walkiewicz, Ph.D., Weimin Bi, Ph.D., Rui Xiao, Ph.D., Yan Ding, M.D., Fan Xia, Ph.D., Arthur L. Beaudet, M.D., Donna M. Muzny, M.S., Richard A. Gibbs, Ph.D., Eric Boerwinkle, Ph.D., Christine M. Eng, M.D., V. Reid Sutton, M.D., Chad A. Shaw, Ph.D., Sharon E. Plon, M.D., Ph.D., Yaping Yang, Ph.D., and James R. Lupski, M.D., Ph.D., D.Sc.

"Our results show that structured clinical ontologies can be used to determine the **degree of overlap between two Mendelian diseases in the same patient. Distinct disease phenotypes affect different organ systems, whereas overlapping disease phenotypes are more likely to be caused by two genes encoding proteins that interact within the same pathway.**"

Biased ascertainment is the rule, not the exception in genomics…

ACMG PRACTICE RESOURCE | Genetics inMedicine

Corrected: Correction

2019

Genetic evaluation of cardiomyopathy: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG)

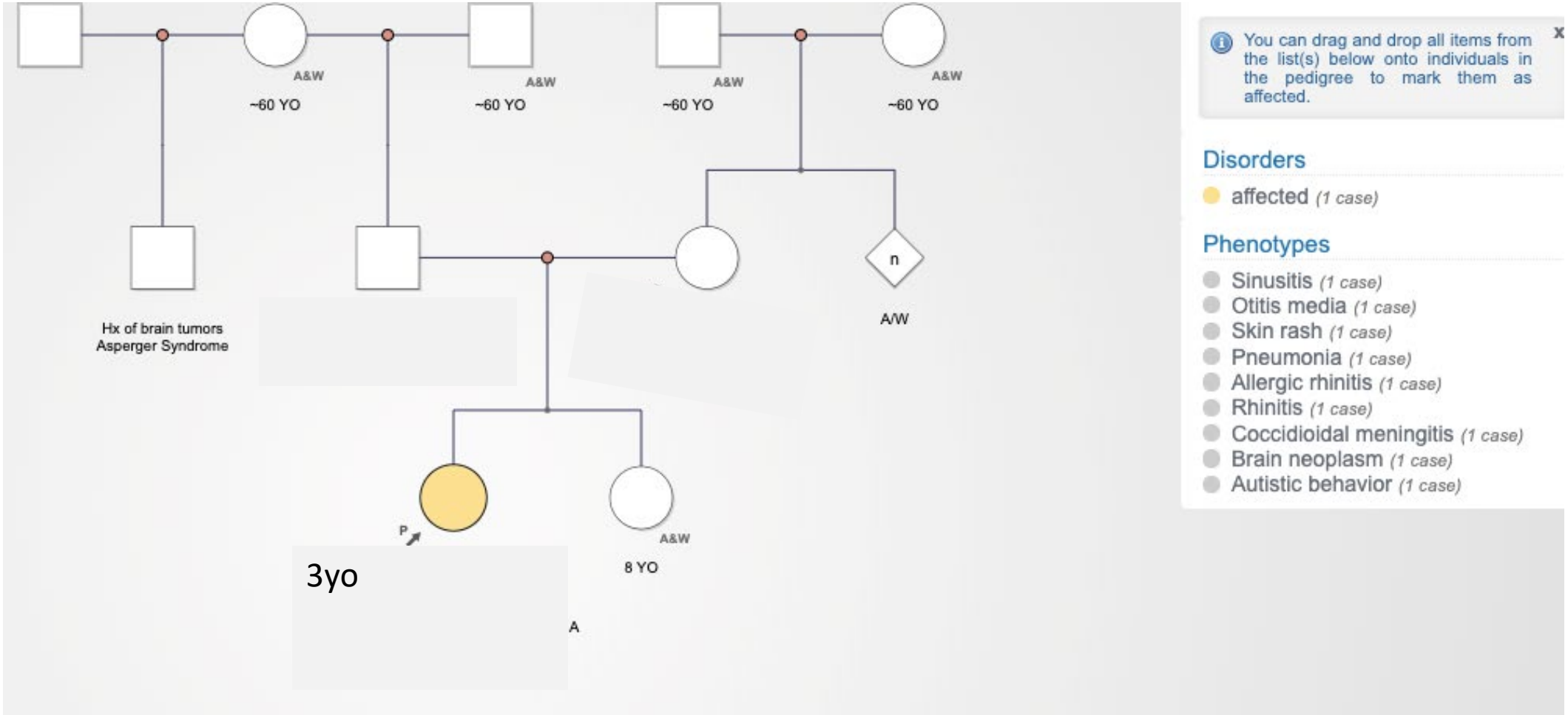
Ray E. Hershberger, MD[1], Michael M. Givertz, MD[2], Carolyn Y Ho, MD[3], Daniel P. Judge, MD[4], Paul F. Kantor, MD[5], Kim L. McBride, MD[6], Ana Morales, MS, LGC[1], Matthew R. G. Taylor, MD[7], Matteo Vatta, PhD[8,9,10] and Stephanie M. Ware, MD, PhD[9,11] on behalf of the ACMG Professional Practice and Guidelines Committee

"…cautiously implemented, cascade clinical (phenotype) screening of putatively at-risk family members may be considered even if the clinical phenotype screening was negative in the individual (in whom a secondary finding was identified)….this statement recognizes the possibility that the proband may be **younger than the usual age of onset of the cardiovascular phenotype"**

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

Case #1– 3yo w/fungal meningitis w/hx of TB + atypical infections



An unexpected result

Indication: Dysregulation of the immune system

Chromosomal Microarray Analysis – NIAID Custom 180K

Method: NIAID Array Slide 258503810033-2

275718-2920009

Result: **ABNORMAL - GAIN**

Change	Chromosome	Min Interval*	Min Size (Mb)	# Probes	Max Interval*	Max Siz
GAIN	**17p12**	**14111772 - 15442069**	**1.330**	**25**	**14063620 - 15490108**	**1.4**

RefSeq Genes: *COX10, CDRT15, HS3ST3B1, MGC12916, CDRT7, PMP22, MIR4731, reg_PMP22_5, TEKT3, CDRT FAM18B2-CDRT4, FAM18B2*

* Nucleotide positions based on hg19

arr 17p12(14111772-15442069)x3

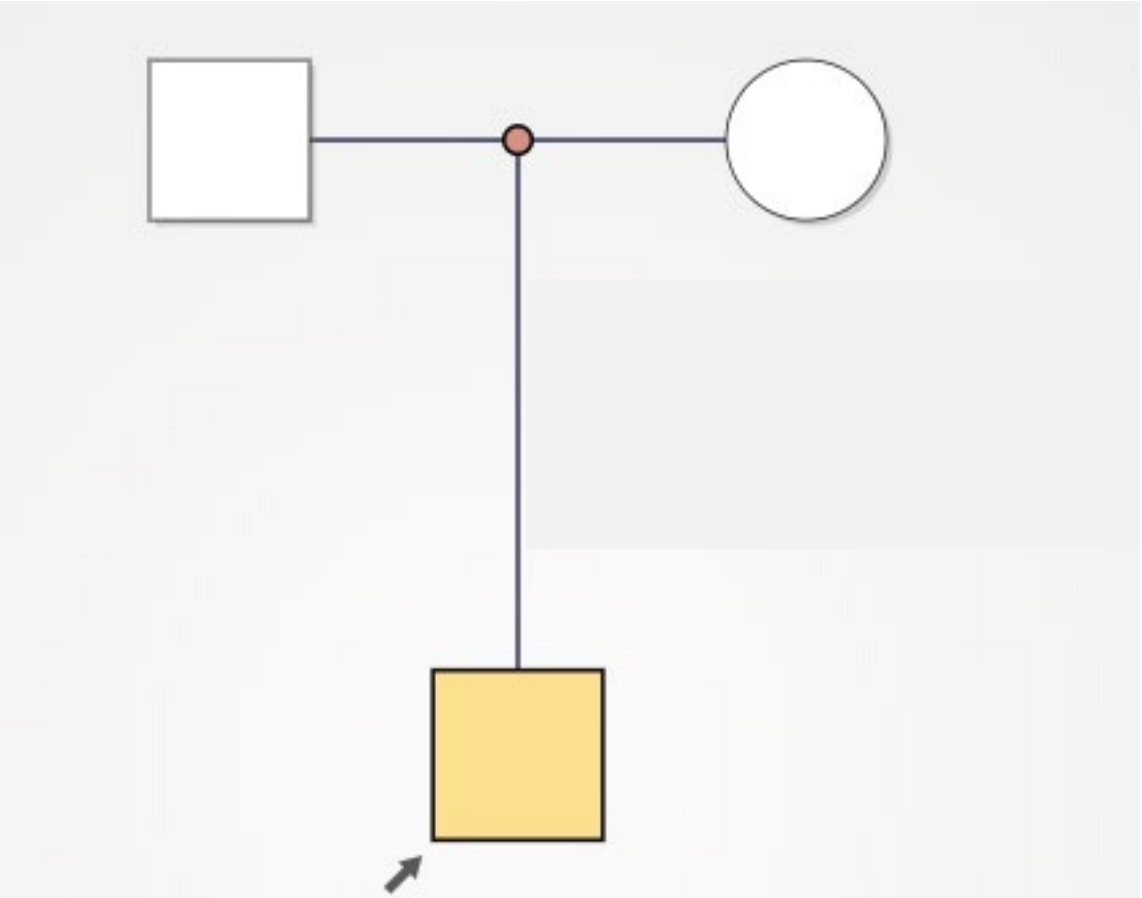
Interpretation:

Chromosomal Microarray Analysis revealed a copy number GAIN of chromosome band 17p12 of approxim in size, encompassing the critical region of Charcot-Marie-Tooth disease type 1A (CMT1A) [MIM:118220], a peripheral neuropathy. Parental FISH studies and FISH studies for relatives at risk are recommended (test a fee-for-service basis). Clinical correlation is recommended and genetic counseling is warranted

Upon re-examination

- Nerve conduction studies showed velocities < 30 m/s, consistent with an early diagnosis of CMT1A
- Referrals were made to physiatry, physical therapy and occupational therapists
- Neurotoxic antibacterial medications (eg. isoniazid, nitrofurantoin, metroidnazole) are contraindicated

Case #2 – 8 yo boy w/APECED (APS1)



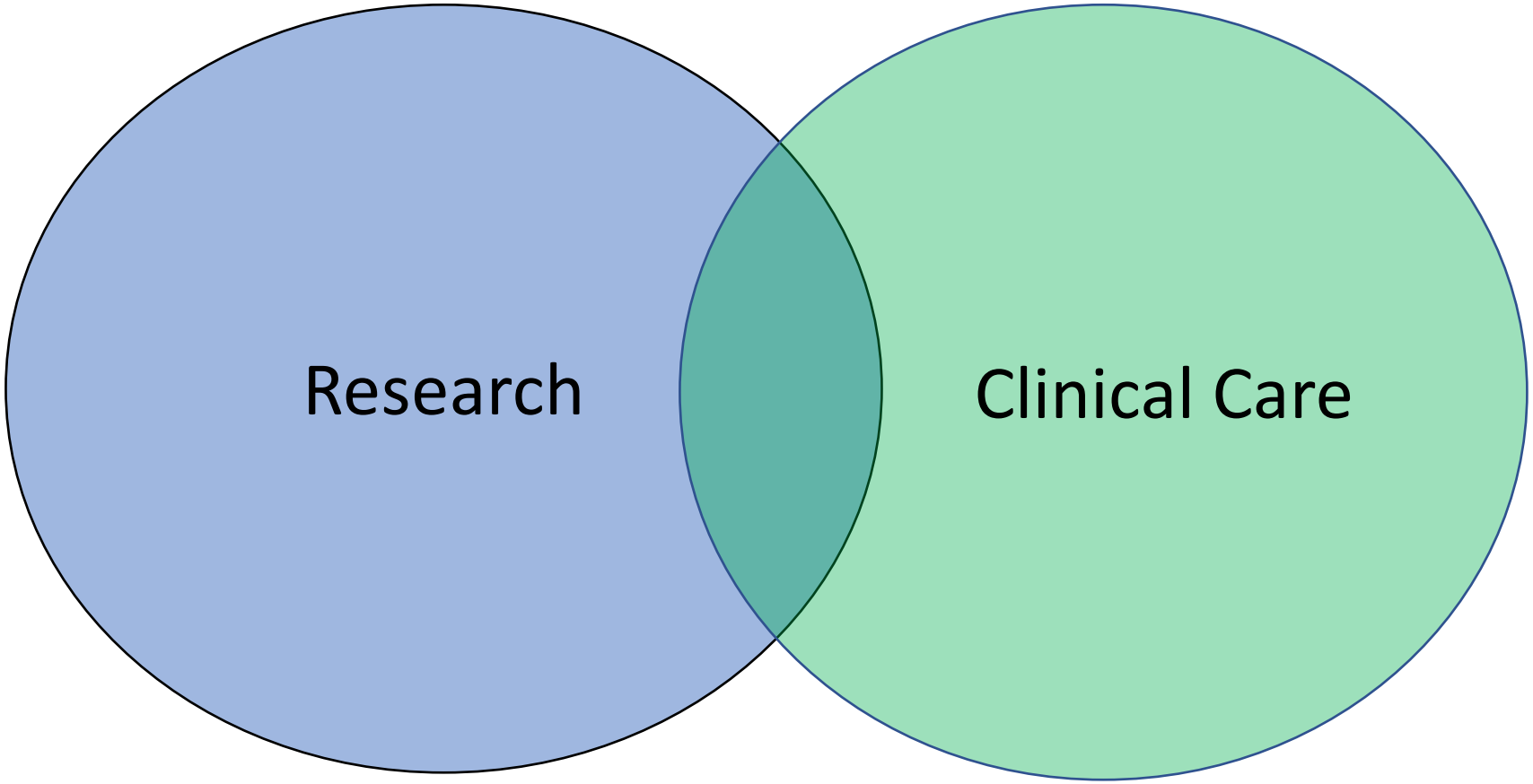
Secondary Findings:
Secondary findings are pathogenic or likely pathogenic variants in genes that cause serious, rare disorders. These disorders can be screened for or treated and are typically unrelated to a patient's NIAID evaluation. We examined the 59 secondary findings genes per the American College of Medical Genetics and Genomics recommendations (PMID: 27854360).

SECONDARY FINDING VARIANT DETECTED

Gene	DNA Change	Protein Change	Zygosity	Classification	Associated disease	OMIM	Disease Inheritance
DSP	c.2437 -1G>C	N/A	Heterozygous	Likely Pathogenic	Arrhythmogenic right ventricular dysplasia 8	607450	Autosomal dominant

- Novel variant, not reported before.
- Mother also carries it; family history not informative
- Family lives in rural, low income area far from nearest medical center

NIH Clinical Center - Overlapping Worlds



Bottom line

- 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!