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Training PAs in Genomics: A Case-Study Approach

Rich Haspel, M.D., Ph.D.

Co-Chair, Inter-Society Coordinating Committee for Practitioner Education in Genomics (ISCC-PEG)
Associate Professor, Beth Israel Deaconess Medical Center and Harvard Medical School

May 23, 2023

The **Forefront** of **Genomics**®

Today's Workshop

MODULE 1:

Test Selection:
Review of Testing Platforms and ELSI Considerations

MODULE 2:

Result Review:
Evaluating and Investigating Genetic Test Reports

MODULE 3:

Result Discussion:
Explaining Results To Patients and Families

- Three modules consisting of 10 minute lectures followed by 15-20 minute small group breakout room sessions
  - There will be a set of questions to work through with your group during each breakout room.
  - A moderator will be available in each breakout room to answer any questions that come up.
- Debriefs of 5-10 minutes with larger group will follow Module 1 and Module 3
- A link to post-workshop survey will be provided. We appreciate your feedback!

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Interested in genomics education? Join ISCC-PEG!

- Inter-Society Coordinating Committee for Practitioner Education in Genomics (ISCC-PEG)
  - Over 200 Members
  - Supported by NHGRI
  - Free to join
  - Collaborate to:
    - Identify educational needs and potential solutions
    - Share best practices in educational approaches
    - Develop educational resources
  - Scholars program:
    - Open to students/trainees
    - Mentored by an ISCC-PEG member
    - Two-year appointment with travel funded for the annual ISCC-PEG in-person meeting
    - Applications due ~October 1, 2023

Please visit:
genome.gov/iscc

ISCC-PEG Rare Diseases Collaboration

AAPA Workshop Speakers

Rich Haspel, MD, PhD
Sabrina Malone Jenkins, MD
Rachel Palmquist, MS,CGC
Wesley G. Patterson, PhD, PA-C

AAPA Workshop Moderators

ISCC-PEG Rare Diseases Group

Ackerman, Kate
Brophy, Patrick
Brunelli, Luca
Burke, Leah
Clements, Eriko
Collins, Heather
Cowan, Brenda
Ellis, Kelsey
Fishler, Kristen
Garman, Karen
Hanson, Karen
Haspel, Richard
Ho, Linda
Hurley, Karen
Iwuchukwu, Otito Frances
Kim, Soohyun
Klein, Sue
Kronk, Rebecca
Kurzlecner, Leonie
Landstrom, Andrew
Lewis, Janine
Malone-Jenkins, Sabrina
Mikail, Claudia
Mills, Rachel
Nurnberger, John I., Jr.
Palmquist, Rachel
Patterson, Wesley
Parisi, Melissa
Sid, Eric
Snyder, Michelle
Steiner, Laurie
Tom-Orme, Lillian

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Part 1: Test Selection: *Review of Testing Platforms and ELSI Considerations*

Sabrina Malone Jenkins, MD

Assistant Professor, Department of Pediatrics, University of Utah

National Human Genome Research Institute

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Approaches to testing

Based on the patient's phenotype and known disease associations

Based on phenotype complexity – not specific for any one disease

Targeted testing – based on known variants in a family

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Types of Genetic Disorders

- **Chromosomal Disorders**
  - Aneuploidies *(e.g. Trisomy 21,18, 13)*
  - Deletion/duplication syndromes *(e.g. 22q11.2 deletion syndrome, Williams syndrome)*
  - Chromosomal Rearrangements *(balanced and unbalanced)*
  - Imprinting Disorders *(e.g. Prader-Willi syndrome)*

- **Gene-specific disorders**
  - Disorders with hotspot variants *(e.g. sickle cell anemia, achondroplasia)*
  - Disorders with single gene *(e.g. cystic fibrosis, PKU)*
  - Disorders with multiple genes *(e.g. Tuberous sclerosis; 2 gene panel, Cornelia de Lange; 8 gene panel)*
  - Disorders with many genes *(e.g. ID/DD, seizures, hearing loss, cardiomyopathy, breast cancer)*

- **Multifactorial disorders**
  - Disorders that result from combination of lower penetrance risk alleles and environmental factors *(e.g., most cancers, heart disease, Alzheimer's disease)*

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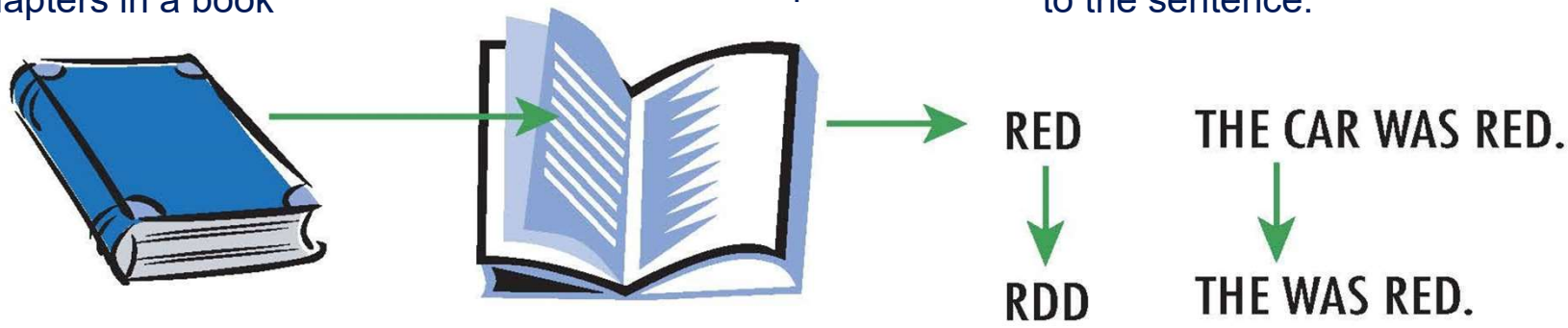
Gene Variants

Chromosomes are like chapters in a book

Genes are like sentences in a chapter

Variants are like changes to the sentence.

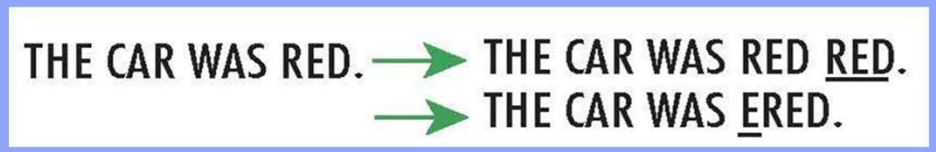


The term ‘Variant’ is now preferred to ‘Mutation’

Common Types of Variants

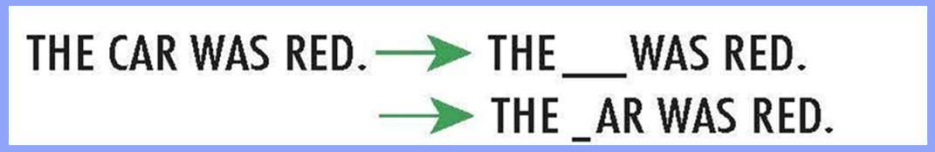
Missense Variants
Change one letter or word

Insertion Variants
Add one letter or word



Nonsense Variants
End the sentence too soon

Deletion Variants
Remove letters or words

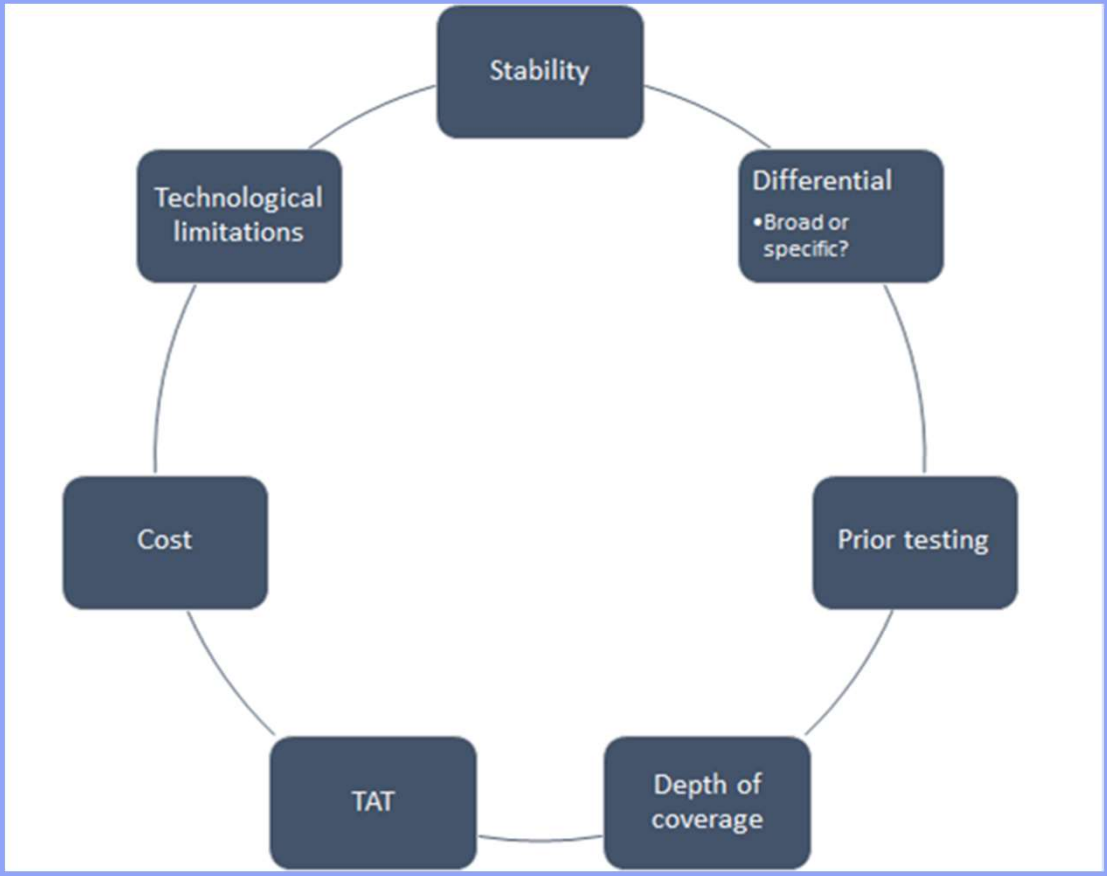


Ethical/Legal Implications

Ethical/Legal Issue	Implications
Region of Homozygosity (ROH) can be identified on microarray and whole genome sequencing	• Suggests that parents are related
Non-paternity can be detected with exome/genome/gene panels	• Suggests lack of biological relationships of parents/siblings
Disease-causing alleles for non-Europeans are underrepresented	• Diminished ability to make a diagnosis in marginalized/underrepresented groups compared to White/European populations
Limited financial resources/billing	• Institutional/other billing • Role of insurance? • What is equitable?
GINA (Genetic Information Non-Discrimination Act)	• Protects patients from discrimination in seeking employment/health insurance • Does NOT protect from access to long-term disability, life insurance, and health insurance/employment for companies <15 people

Types of Genetic Tests

Factors to consider



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FISH

Suggested for: aneuploidy, specific deletion/duplication syndromes (22q11.2, Williams, etc.)

Pro: Fast turnaround to detect aneuploidy/specific deletions

Con: YOU have to say what you want to FISH for; misses translocations

Karyotype

Suggested for: aneuploidy, differences of sexual development

Pro: Best test for aneuploidy detection and recurrence risk

Con: Not as quick as FISH; misses small CNVs

Microarray

Suggested for: multiple congenital anomalies (even VACTERL), isolated anomalies

Pro: Can detect CNVs missed by karyotype and aneuploidy across genome

Con: Many limitations for complex patients

Limitations of Microarray

Does NOT detect single gene conditions	• Panel/exome/genome is best
Does NOT determine whether the change was inherited or not	• Parental testing needed
Does NOT identify translocations	• Karyotype is best for aneuploidy recurrence risk calculation and translocations
Less sensitive in detection of mosaicism	• Karyotype and/or FISH is best

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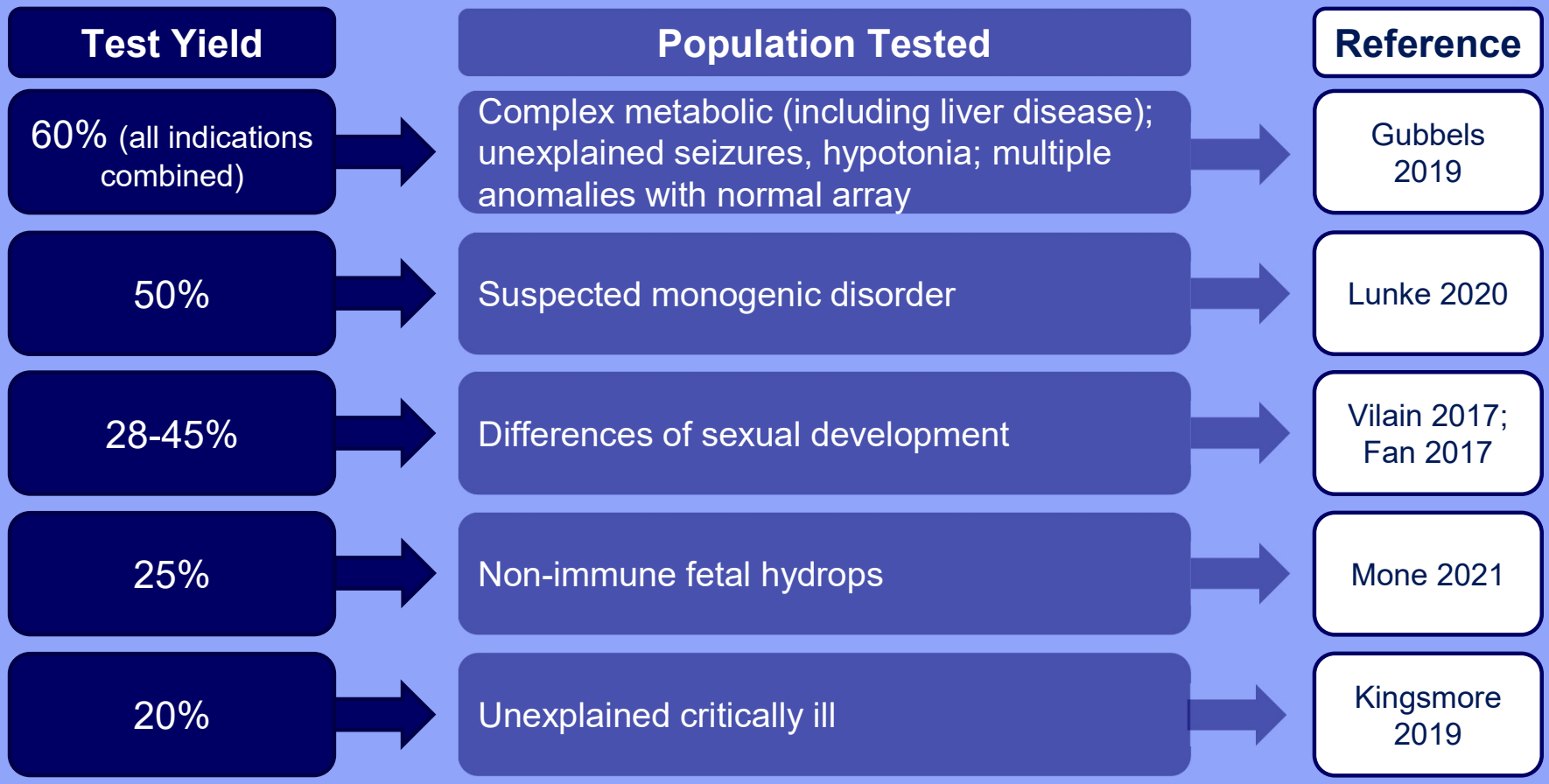
Next-Generation Sequencing (NGS)

Gene Panel	Exome	Genome
Suggested for: specific diagnoses is suspected; single body system	**Suggested for:** wide differential; multiple body systems included	**Suggested for:** wide differential, need multiple tests
Pro: Sequencing of entire gene on list, low VUS risk compared to exome/genome	**Pro:** comprehensive gene list based on the phenotype	**Pro:** Can detect CNVs and sequence changes in introns and exons
Con: may be costly if you ultimately need exome/genome; may miss genes even within the same phenotype	**Con:** misses intronic variants; may miss hard to sequence variants	**Con**: Costly, increase risk of VUS, may not be approved at institutional/insurance level

Exome/Genome Yield



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Inter-Society Coordinating Committee for Practitioner Education in Genomics (ISCC-PEG)

Breakout Room Instructions

- Open the Google Form @ ***
- Work as a team to answer the questions.
- One person should read aloud the questions and submit the group's answers.
- When you are accessing different websites, your group should have one person share their screen.
- Keep an eye on the time! Don't worry if you don't get to every question, as we will go over the answers at the end.

Breakout Room 1

A two-year-old male presents to your clinic to establish care. Reviewing the medical records, he has a history of development delay and multiple congenital anomalies. You think he may have a genetic condition and want to do testing.

What social and ethical factors should be weighed when deciding what genetic test to order?

LOGISTICS/FINANCIAL

LEGAL/ETHICAL

PSYCHOSOCIAL

Breakout 1 Summary

- Social/ethical factors
  - Financial coverage
  - Impact to family, e.g., non-paternity
  - Turnaround time, family anxiety
- Karyotype is best for Turner's and Klinefelter
- When would you order exome/genome?

Part 2: Result Review: *Evaluating and Investigating Genetic Test Reports*

Rachel Palmquist, MS, CGC
Certified Genetic Counselor, Department of Pediatrics, University of Utah School of Medicine

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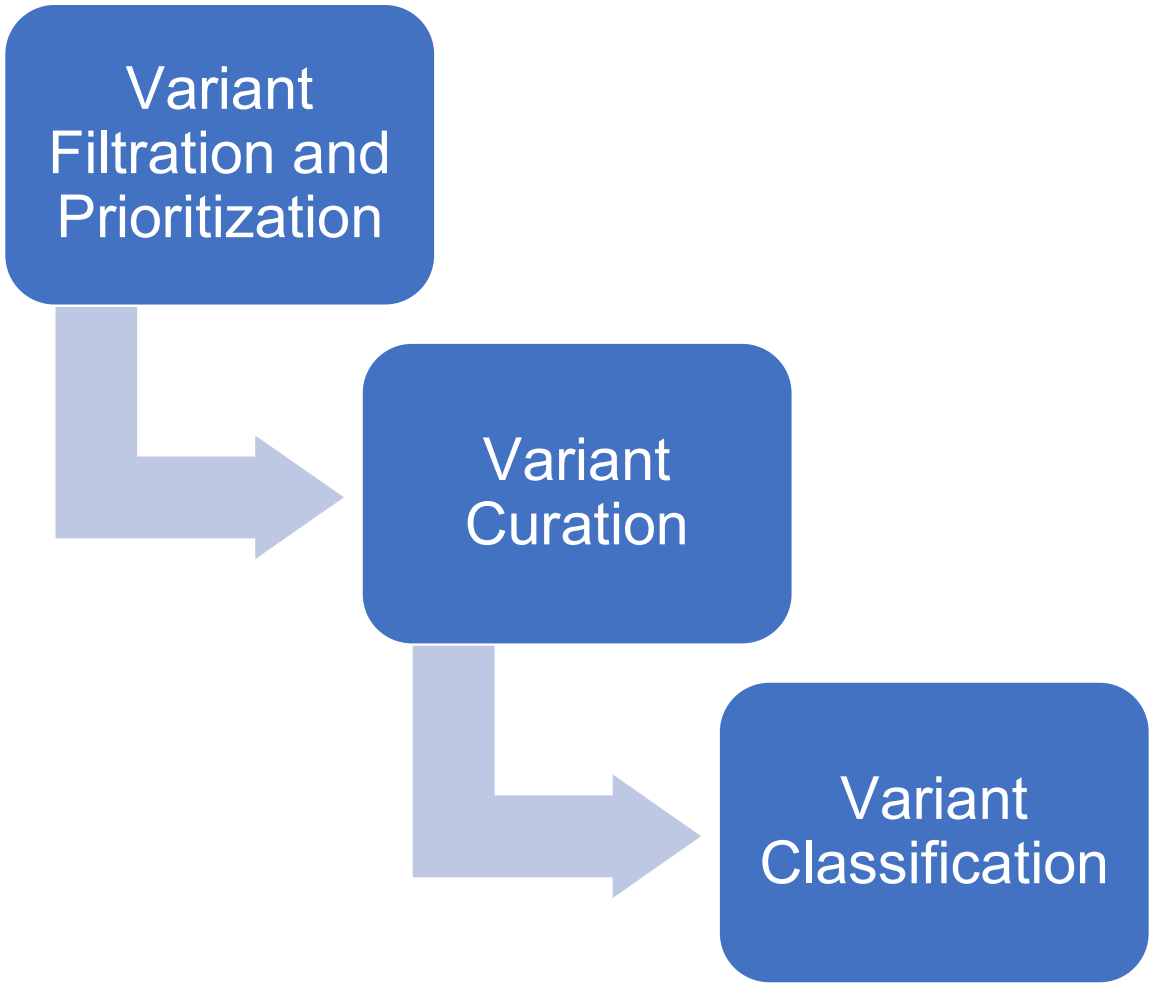
The Variant Interpretation Process



Variant Filtration and Prioritization:
The process of filtering out variants and ranking candidate variants for further evaluation

- Millions of variants within any genome
- Number of variants detected increases with number of genes sequenced

Variant Curation:
The process of researching a variant to collect evidence for or against pathogenicity

- Review of previous reports of the variant in cases and controls (e.g. in literature, variant databases, internal lab cases)
- Review of functional data (predictive algorithms and experimental studies)

Variant Classification:

The process of weighing evidence for or against pathogenicity to assign a variant interpretation

© American College of Medical Genetics and Genomics ACMG STANDARDS AND GUIDELINES | Genetics inMedicine

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

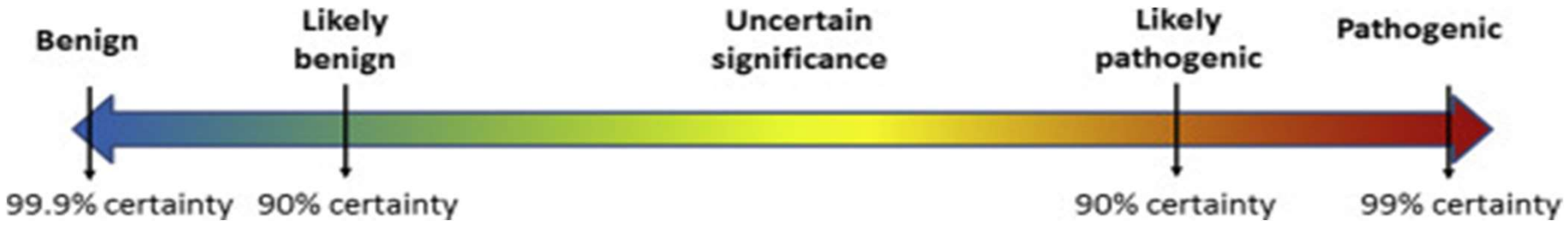
Richards et al., 2015

Each piece of evidence is assigned an evidence type (pathogenic or benign) and a strength level

- Pathogenic: Very Strong, Strong, Moderate, Supporting
- Benign: Strong, supporting

Evidence is added up and must meet minimum requirements for classifying as LP/P or LB/B

If there is not enough evidence to meet minimum requirements OR if there is conflicting evidence supporting both pathogenic and benign, the variant is considered of uncertain significance



Weighing Criteria

1. 1 Very Strong (PVS1) *AND*

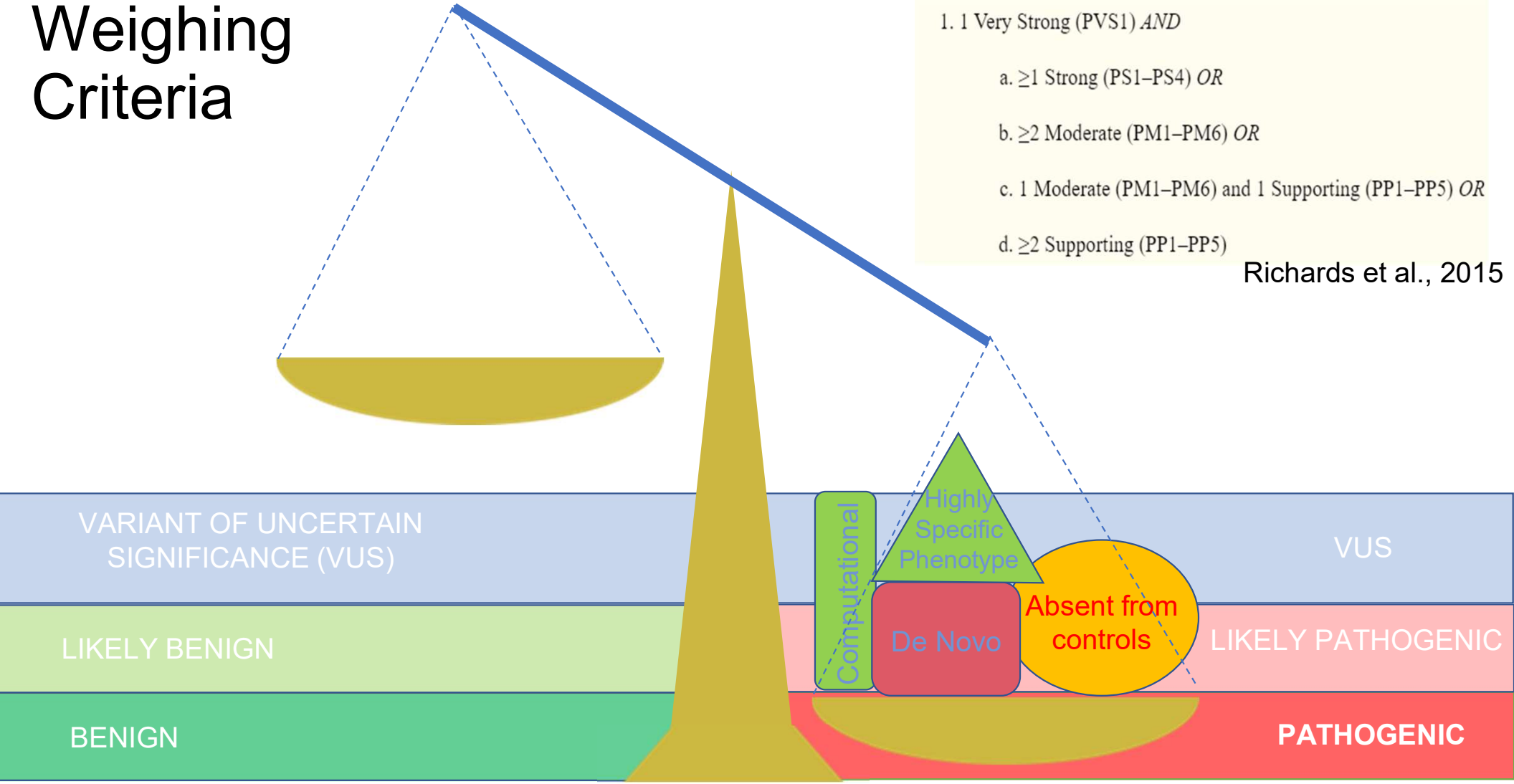
   a. ≥1 Strong (PS1–PS4) *OR*

   b. ≥2 Moderate (PM1–PM6) *OR*

   c. 1 Moderate (PM1–PM6) and 1 Supporting (PP1–PP5) *OR*

   d. ≥2 Supporting (PP1–PP5)

Richards et al., 2015

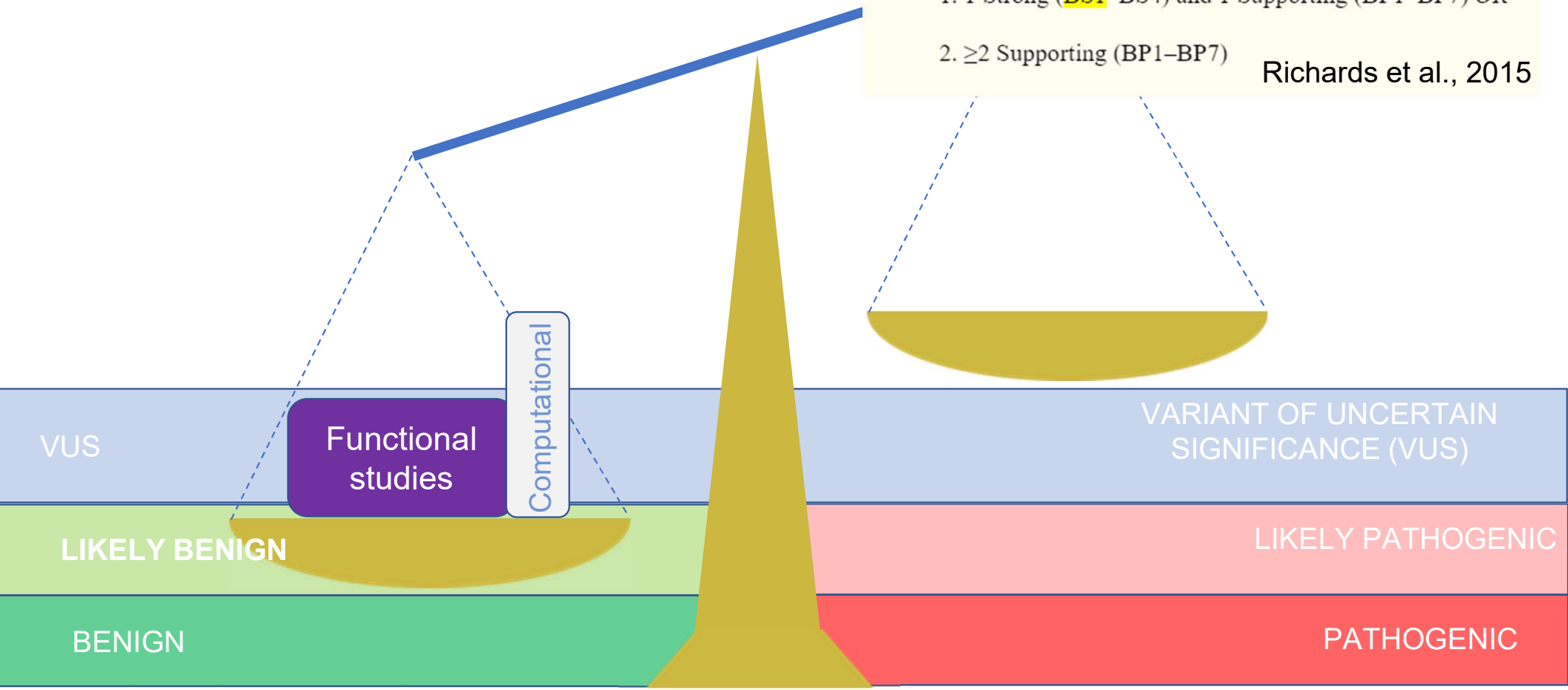


Weighing Criteria

Likely Benign

1. 1 Strong (BS1–BS4) and 1 Supporting (BP1–BP7) *OR*
2. ≥2 Supporting (BP1–BP7)

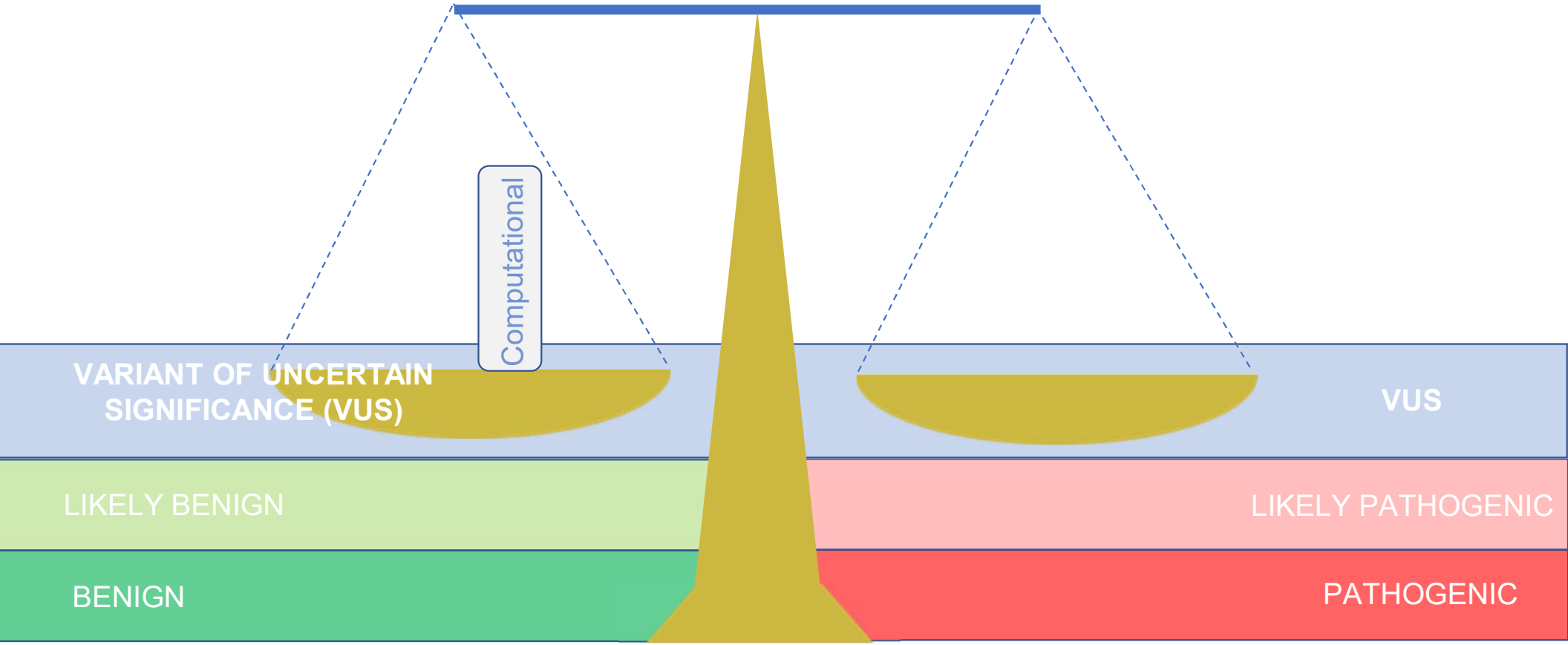
Richards et al., 2015



Inter-Society Coordinating Committee for Practitioner Education in Genomics (ISCC-PEG)

Weighing Criteria

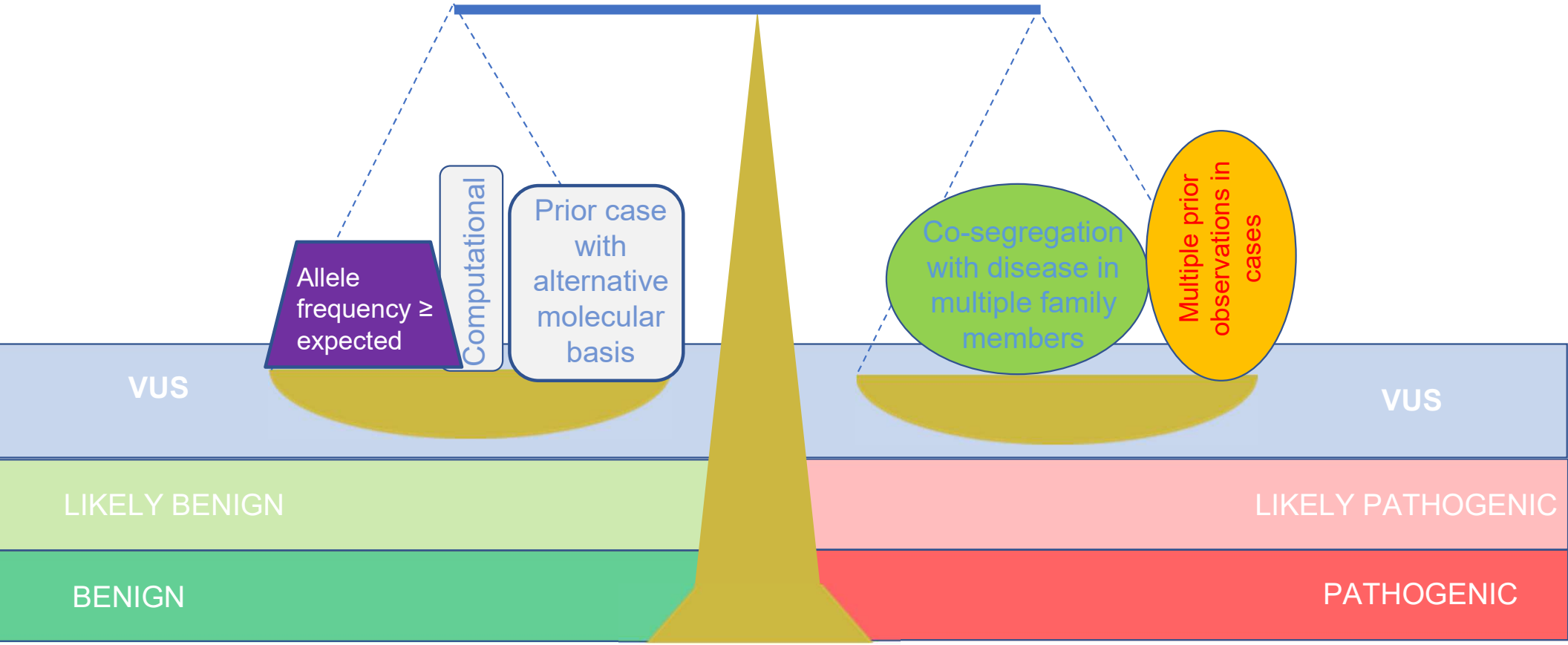
Variants are classified as uncertain if:
-criteria are unmet



Inter-Society Coordinating Committee for Practitioner Education in Genomics (ISCC-PEG)

Weighing Criteria

Variants are classified as uncertain if:
-criteria are unmet OR
-the criteria for benign and pathogenicity are contradictory



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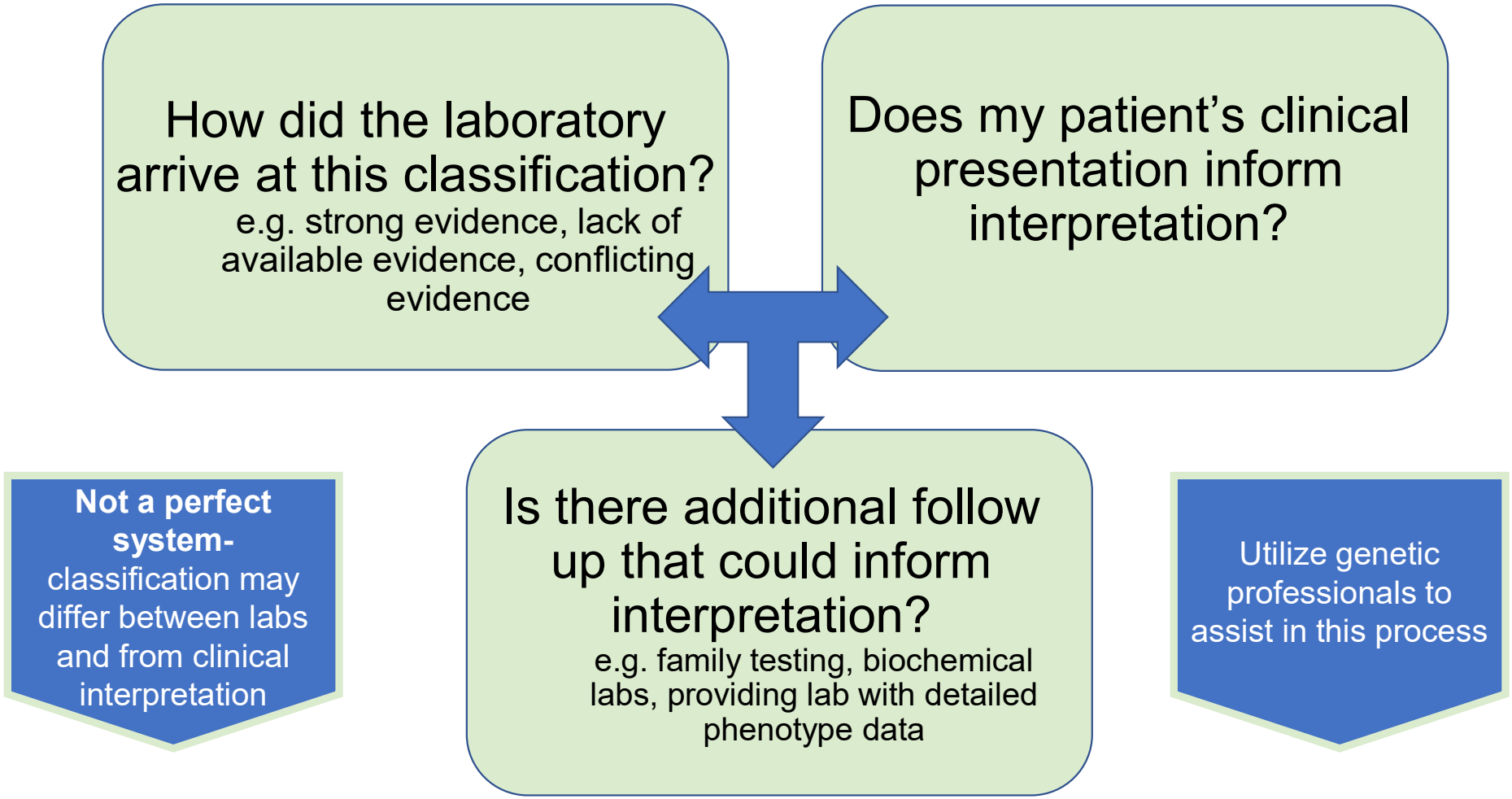
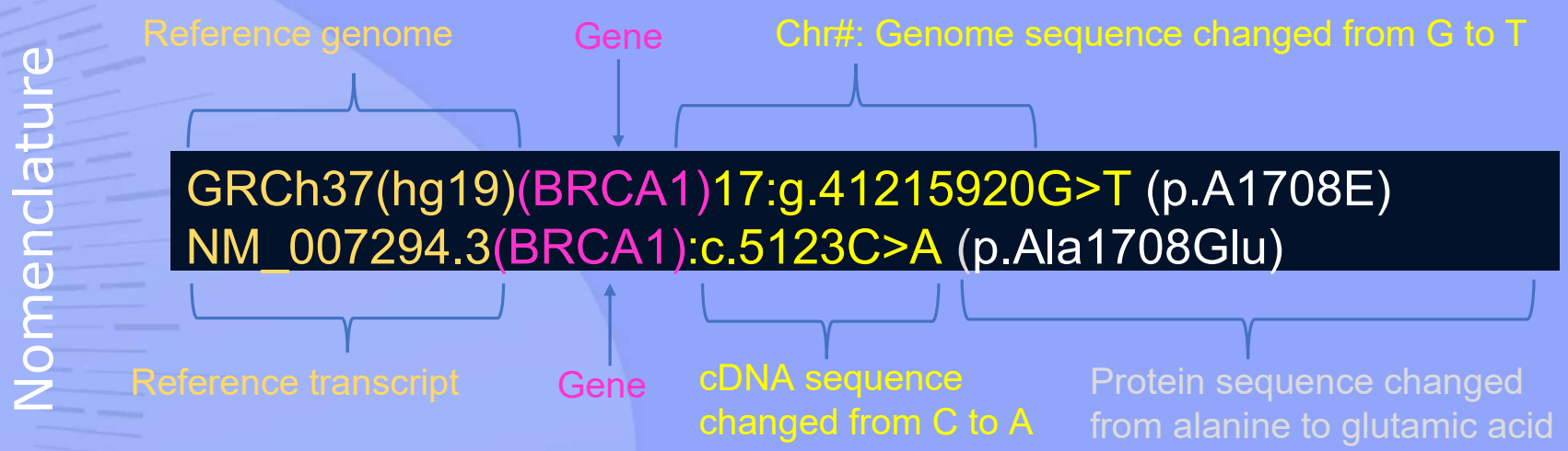
Clinical Interpretation of Variants



Reviewing Genetic Test Reports



- *The Written Test Report Will Describe*
  - If there is predictive or functional evidence that the variant impacts the gene
  - If the change has been seen before in individuals with the associated health condition
  - If the variant is in the “healthy” population
  - If the variant segregates with family history in your case or past cases

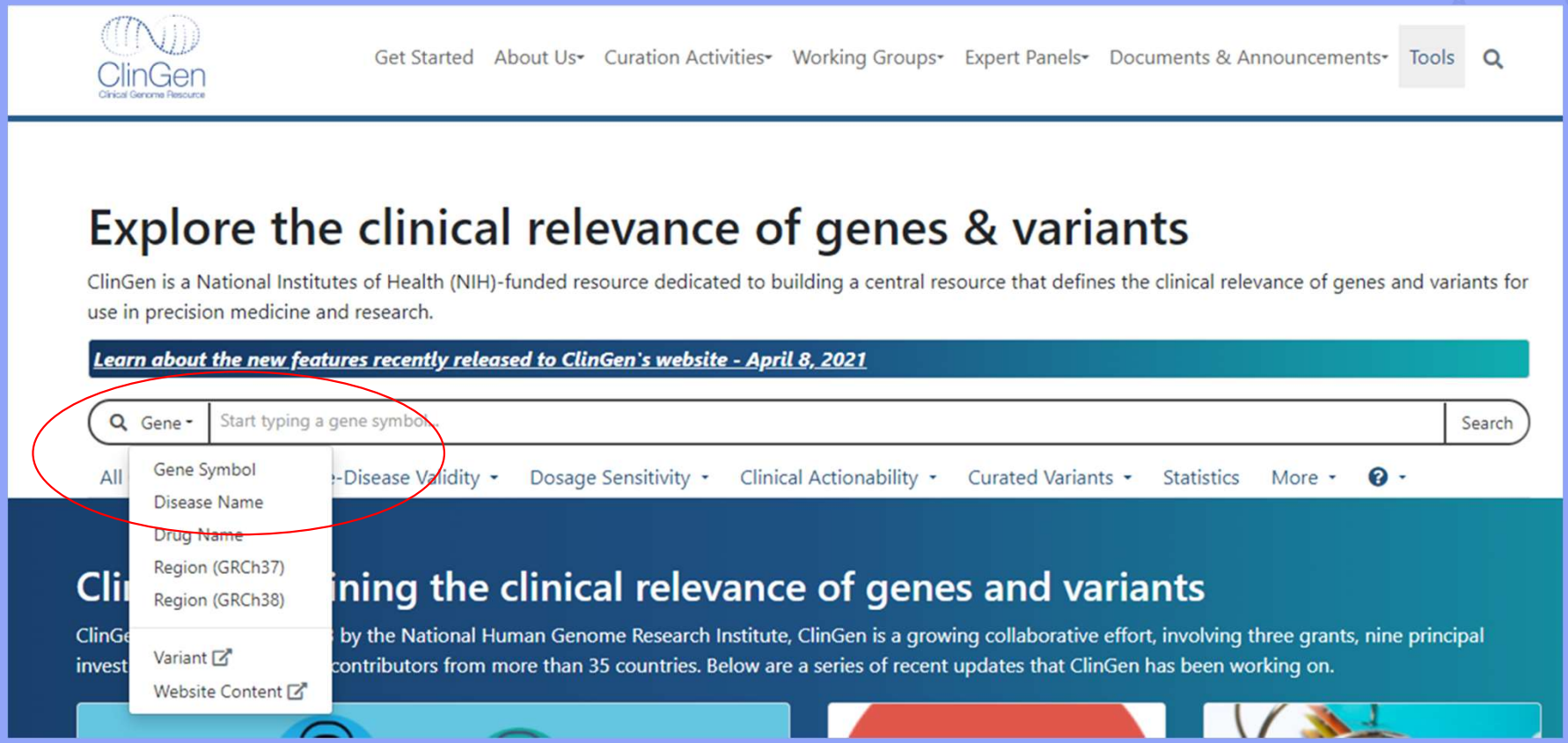
Exploring the Clinical Relevance of Variants

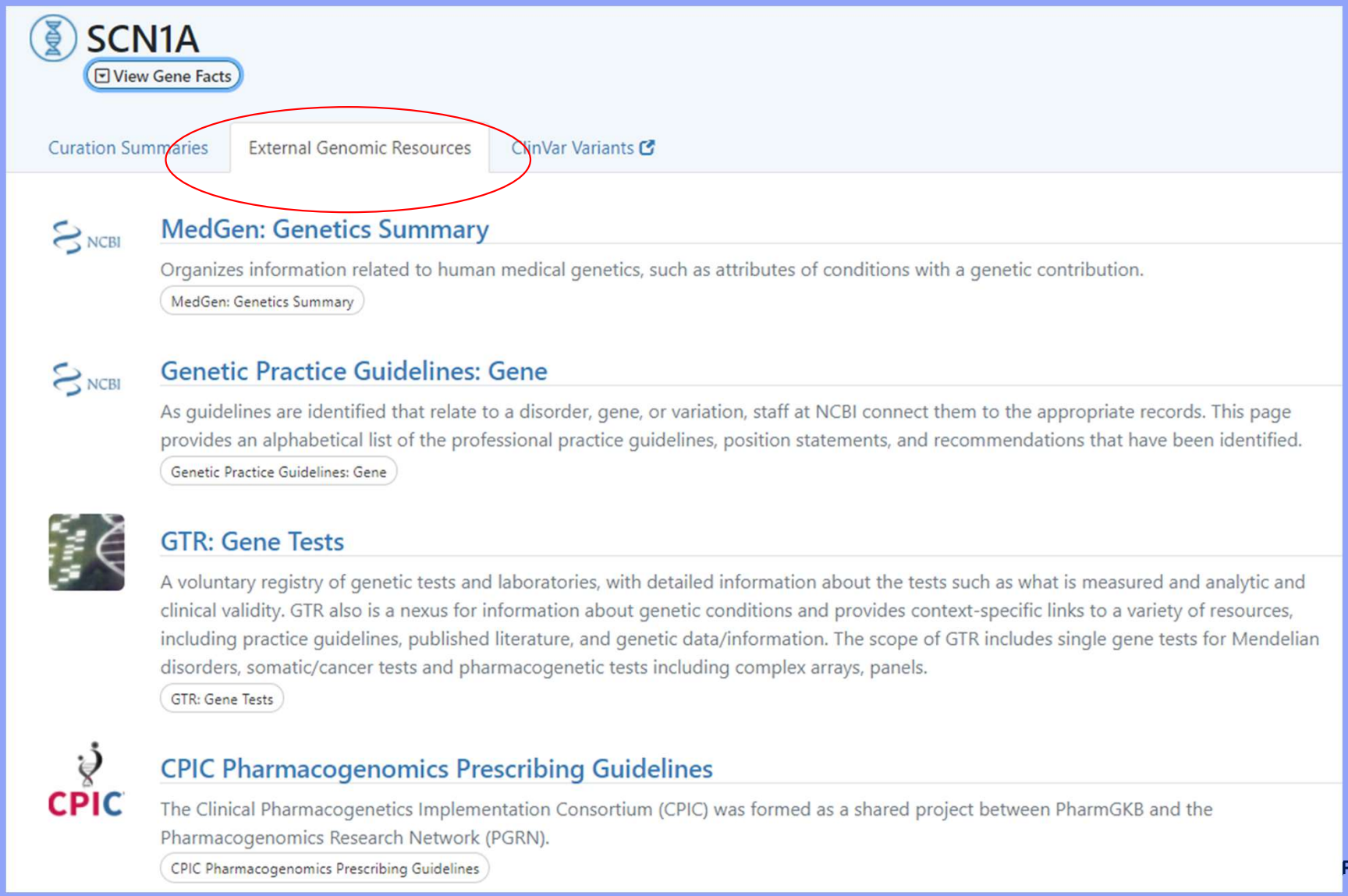
ClinGen
Clinical Genome Resource

GENE Reviews®

OMIM®
Online Mendelian Inheritance in Man®
An Online Catalog of Human Genes and Genetic Disorders

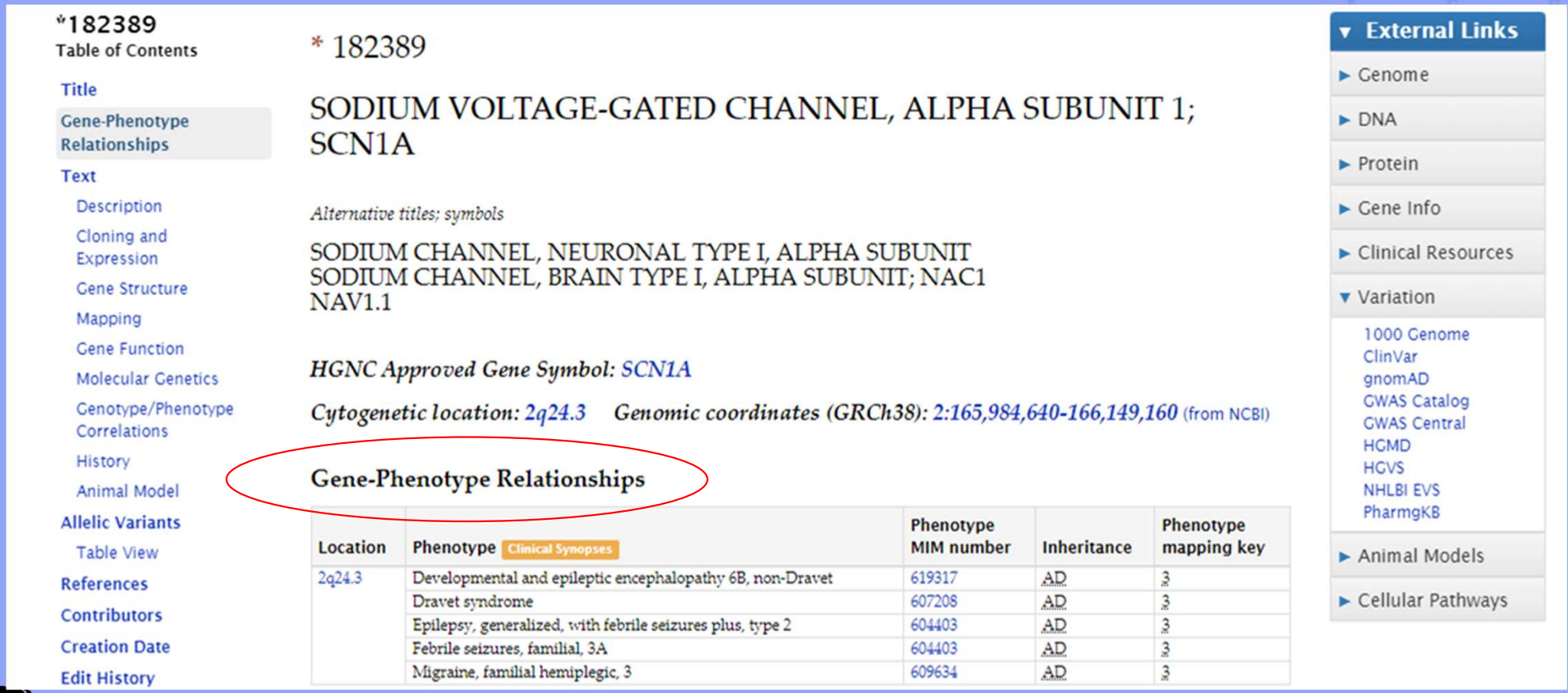
ClinGen - https://clinicalgenome.org/




SCN1A
View Gene Facts
Curation Summaries
External Genomic Resources
ClinVar Variants
NCBI
MedGen: Genetics Summary
Organizes information related to human medical genetics, such as attributes of conditions with a genetic contribution.
MedGen: Genetics Summary
NCBI
Genetic Practice Guidelines: Gene
As guidelines are identified that relate to a disorder, gene, or variation, staff at NCBI connect them to the appropriate records. This page provides an alphabetical list of the professional practice guidelines, position statements, and recommendations that have been identified.
Genetic Practice Guidelines: Gene
GTR: Gene Tests
A voluntary registry of genetic tests and laboratories, with detailed information about the tests such as what is measured and analytic and clinical validity. GTR also is a nexus for information about genetic conditions and provides context-specific links to a variety of resources, including practice guidelines, published literature, and genetic data/information. The scope of GTR includes single gene tests for Mendelian disorders, somatic/cancer tests and pharmacogenetic tests including complex arrays, panels.
GTR: Gene Tests
CPIC
CPIC Pharmacogenomics Prescribing Guidelines
The Clinical Pharmacogenetics Implementation Consortium (CPIC) was formed as a shared project between PharmGKB and the Pharmacogenomics Research Network (PGRN).
CPIC Pharmacogenomics Prescribing Guidelines

PEG)

OMIM - https://omim.org/



*182389
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  - Molecular Genetics
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  - History
  - Animal Model
- Allelic Variants
  - Table View
- References
- Contributors
- Creation Date
- Edit History

* 182389

SODIUM VOLTAGE-GATED CHANNEL, ALPHA SUBUNIT 1; SCN1A

Alternative titles; symbols

SODIUM CHANNEL, NEURONAL TYPE I, ALPHA SUBUNIT
SODIUM CHANNEL, BRAIN TYPE I, ALPHA SUBUNIT; NAC1
NAV1.1

HGNC Approved Gene Symbol: SCN1A

Cytogenetic location: 2q24.3 Genomic coordinates (GRCh38): 2:165,984,640-166,149,160 (from NCBI)

Gene-Phenotype Relationships

Location	Phenotype Clinical Synopses	Phenotype MIM number	Inheritance	Phenotype mapping key
2q24.3	Developmental and epileptic encephalopathy 6B, non-Dravet	619317	AD	3
	Dravet syndrome	607208	AD	3
	Epilepsy, generalized, with febrile seizures plus, type 2	604403	AD	3
	Febrile seizures, familial, 3A	604403	AD	3
	Migraine, familial hemiplegic, 3	609634	AD	3

External Links

- Genome
- DNA
- Protein
- Gene Info
- Clinical Resources
- Variation
  - 1000 Genome
  - ClinVar
  - gnomAD
  - GWAS Catalog
  - GWAS Central
  - HGMD
  - HGVS
  - NHLBI EVS
  - PharmgKB
- Animal Models
- Cellular Pathways

GeneReviews https://www.ncbi.nlm.nih.gov/books/NBK1116/

GeneReviews® [Internet].

< Prev Next >

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GeneReviews Advanced Search Help

SCN1A Seizure Disorders

Ian O Miller, MD and Marcio A Sotero de Menezes, MD.

Author Information

Initial Posting: November 29, 2007; Last Update: April 18, 2019.

Estimated reading time: 36 minutes

Summary

Go to:

Clinical characteristics. ***SCN1A*** seizure disorders encompass a spectrum that ranges from simple febrile seizures and generalized epilepsy with febrile seizures plus (GEFS+) at the mild end to Dravet syndrome and intractable childhood epilepsy with generalized tonic-clonic seizures (ICE-GTC) at the severe end. Phenotypes with intractable seizures including Dravet syndrome are often associated with cognitive decline. Less commonly observed phenotypes include myoclonic astatic epilepsy (MAE), Lennox-Gastaut syndrome, infantile spasms, epilepsy with focal seizures, and vaccine-related encephalopathy and seizures. The phenotype of ***SCN1A*** seizure disorders can vary even within the same family.

Diagnosis/testing. The diagnosis of an ***SCN1A*** seizure disorder is established in a proband by identification of a heterozygous pathogenic variant in ***SCN1A*** by molecular genetic testing.

Management. *Treatment of manifestations*: Care is best provided by a physician (e.g., pediatric epileptologist) familiar with the pharmacotherapy for this disorder. Seizure control is critical to prevent permanent injury and death.

Views

- PubReader
- Print View
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- Disable Glossary Links

In this GeneReview

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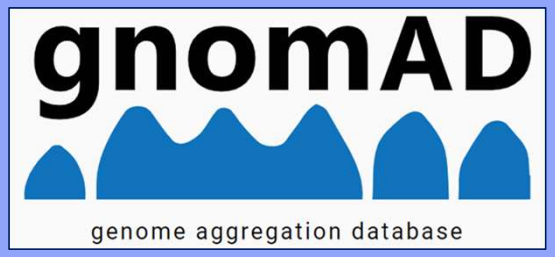
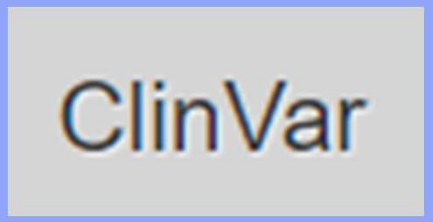
Other Resources



- Determine variant frequency



- Determine if variants previously reported by other labs

- Assess impact of variant on drug response

Breakout Room 2

Your patient's genetic test results have come back.

Review the report as a group and explore genetic databases to investigate clinical relevance of the result.

AVAILABLE EVIDENCE

VARIANT DATA

CLINICAL FEATURES

Breakout 2 Summary

- This patient has a nonsense variant in the *ARID1A* gene that causes Coffin-Siris syndrome (CSS)

- Classified as pathogenic because it:
  - Is predicted to cause loss of function
  - Not previously reported as a common variant
  - Not inherited from a parent

- Hallmarks of CSS include:
  - Developmental disability
  - Characteristic facial features
  - Abnormalities of the fifth fingers or toes

Remember!

- Variant - ClinVar
- Gene - OMIM
- Disease - GeneReviews

Part 3: Result Discussion: *Explaining Results to Patients and Families*

Wesley G. Patterson, PhD, MSPA, PA-C, CAQ-Peds

Genetics PA, Greenwood Genetic Center

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Results are not always "positive" or "negative"

Benign
or
Likely Benign

Variant of Uncertain Significance

Pathogenic
Or
Likely Pathogenic

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Possible genetic results that could show up on a report

Primary findings	Incidental	Secondary

• Aligned with your patients' symptoms
• Can be listed as pathogenic, likely pathogenic, or VUS
• You determine whether this is their diagnosis or not based on the classifications
	• Variant was identified that has medical benefit OR region of homozygosity on microarray
	• May be associated with some of the findings, but not usually all of the findings
		• A list of genes that patients can opt-in/opt-out based on guidance from ACMG (specific to exome/genome)
		  • Cancer susceptibility
		  • Metabolic conditions with early- or late-onset
		  • Cardiac conditions with early or late onset

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Genetic Test Results are Different

- Common misconceptions
  - Genetics test are certain > Need to review the test's limitations
  - Genetic tests are final > Need for reinterpretation!

- Many psychosocial concerns
  - Results impact the patient and family members
  - Identifying adult-onset conditions in a child
  - Families may not be prepared for incidental findings
  - Sense of parental guilt/shame
  - Rare disease patients experience the "diagnostic odyssey"

- Communication of results
  - Setting, time, body language, addressing concerns, active listening

Genetic Counseling

…is the process of helping people understand and adapt to the medical, psychological, and familial implications of genetic contributions to disease. This process integrates

- Interpretation of family and medical histories to assess the chance of disease occurrence or recurrence;
- Education about inheritance, testing, management, prevention, resources, and research;
- Counseling to promote informed choices and adaptation to the risk or condition.

NSGC: *J Genet Counseling* 2006

Integration in Clinical Care

- Medical evaluations after diagnosis
- Treatment of manifestations
- Prevention of secondary complications
- Surveillance
- Agents/circumstances to avoid
- Evaluation of relatives at risk
- Reproductive risks and prenatal testing
- Therapies under investigation

Check if GeneReview article is available for the condition

GENEReviews®

Results Session Format

- Contracting
  - What are your questions today?
  - What do you understand about the genetic test?
  - Describe plan for visit
- Disclosing results
- Communicating screening, management plans, genetic risks, and reproductive options
- Summarizing and planning for follow up

Resources to Share with Families

Information Resources

MedlinePlus® Trusted Health Information for You

- Information pages about genetic conditions and genes
- Handbook that describes basic genetic concepts
- Printable PDFs for all content

GARD Genetic and Rare Diseases Information Center

- Contact an information specialist
- Services in English and Spanish
- Website provides rare disease information and patient resources

NORD® National Organization for Rare Disorders

- Reports and videos about rare diseases
- Patient and caregiver resources
- Connect with rare disease community

Genetic Alliance

- Disease InfoSearch provides curated and crowd-sourced disease information
- *Trust It or Trash It?* tool for reviewing online health information
- WikiAdvocacy has tips for starting or growing a patient organization

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Support Resources

FAMILY VOICES®

- Find your state's parent support centers
- Helpful for finding local resources and disability programs
- Connect families with shared experiences

PARENT TO PARENT USA

- Contact your local Parent to Parent organization
- Parents are matched with an experienced Support Parent

- Disease- or gene-based Facebook groups are growing trend
- Often started by parents and provide a place to create a community
- Encourage families to start their own group if one isn't available

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Research Resources

NIH U.S. National Library of Medicine
ClinicalTrials.gov

- Search for clinical studies by disease name
- Filter results for location
- Useful for finding clinical researchers for a rare disease
- Includes natural history studies and interventional studies

UDN Undiagnosed Diseases Network

- Research study backed by the National Institutes of Health Common Fund
- Aims to solve the most challenging medical mysteries using advanced technologies
- A recommendation letter from a licensed health care provider is necessary

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Breakout Room 3

You are preparing to meet with the patient's family to discuss the results.

Identify patient resources and prepare to answer the parent's questions.

RECURRENCE RISK

CLINICAL MANAGEMENT

PSYCHOSOCIAL ISSUES

FAMILY RESOURCES

Breakout 3 Summary

- Psychosocial issues
  - Results impact the whole family
  - Identify adult-onset conditions in child
  - Family not prepared for incidental findings
  - Parental guilt/shame
- Risk to siblings is 1%
- CSS Foundation and GARD are good referrals for patients

Refer To Your Toolkit!

Initial Clinical Evaluation
- Identify “red flags” for a rare genetic condition
- As appropriate, refer patient to a genetics professional or proceed with genetic testing

Part 1: Test Selection
- Determine appropriate genetic test(s)
- Select genetic testing laboratory
- Consider potential follow-up studies

Part 1: Pre-test Counseling
- Explain genetic testing options
- Facilitate patient decision-making
- Obtain informed consent for testing

Part 2: Diagnostic Result
- Interpret genetic test results (particularly VUS results)
- Using resources such as ClinVar and Franklin to assess variant pathogenicity
- Investigate using resources such as ClinGen, GeneReviews, and OMIM
- Consider whether follow-up genetic testing may be helpful

Part 3: Explaining Results to Patients
- Contract with family about current understanding and purpose of visit
- Disclose results
- Address psychosocial concerns
- Integrate into clinical care

Part 3: Next Steps
- Connect families with rare disease resources and/or condition-specific support groups
- Check for clinical trials/research studies

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How you can get involved

- Join the network of experts: https://www.genome.gov/iscc
- Explore available resources: https://www.genome.gov/health/For-Health-Professionals
- For more information about ISCC-PEG contact Donna Messersmith: Donna.Messersmith@nih.gov
- For more information about the Rare Diseases Project Group contact Sabrina Malone-Jenkins: Sabrina.MaloneJenkins@hsc.utah.edu

Disclaimer: The Inter-Society Coordinating Committee for Practitioner Education in Genomics (ISCC-PEG) provides a venue for individuals to collaborate and develop educational resources. The opinions expressed in this session do not reflect the view of all ISCC-PEG members, the National Institutes of Health, the Department of Health and Human Services, or the United States government.

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