Session III:
Guidelines for Genomic Testing Today

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Disclosures

- I receive research funding from:
  - Microsoft
  - Chan-Zuckerberg Initiative
  - NIH

- I am a clinical lab director for a non-profit laboratory (Broad Clinical Labs)

ACMG Document Types (>200 to date)

ACMG Statements

- Represents the professional judgments of ACMG
- May discuss where ACMG stands on a topic or a debatable issue.
- Three types: Points to Consider, Position Statement or Policy Statement

ACMG Practice Resource (laboratory or clinical)

- Informed by evidence and expert opinion, but lacks the rigor of a systematic evidence review

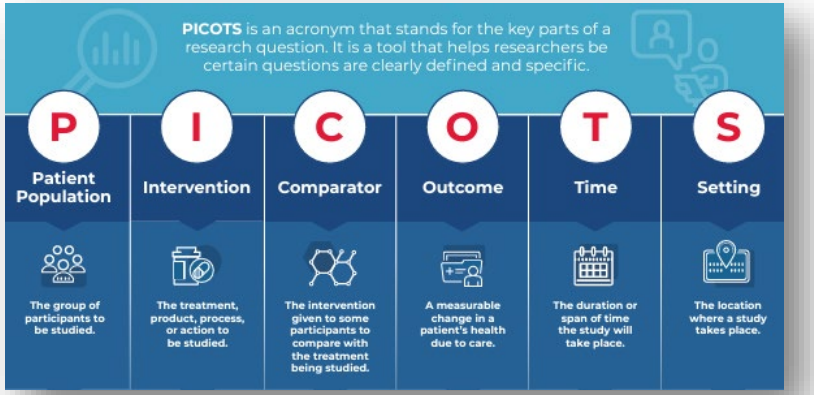
ACMG Technical Standards

- Establishes criteria for clinical genetics laboratory testing
- Written through a consensus development process, by experts in the field
- Increasingly joint with AMP, CAP and ClinGen

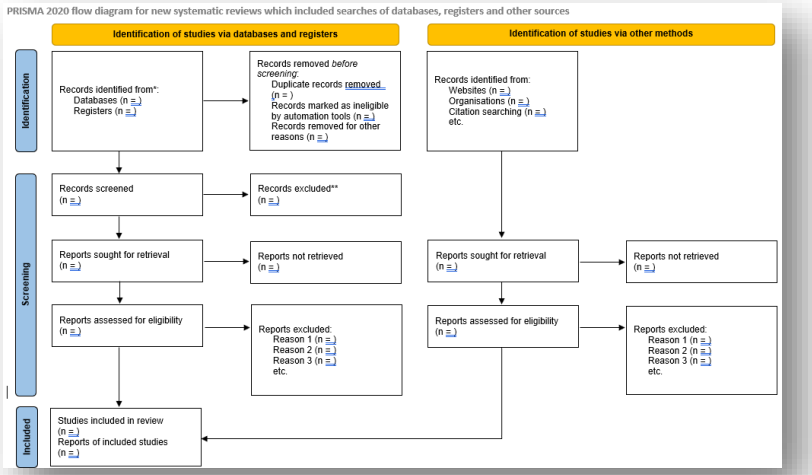
ACMG Systematic Evidence Review and ACMG Practice Guideline

ACMG Systematic Evidence Reviews and Evidence Based Guidelines

- Rigorous COI (conflict of interest) management of WGs
- Requires experienced methodologists and staff
- Follows 100-page ACMG Protocol for Evidence-Based Guideline Development
- Develop key questions using the PICOTS format and report according to PRISMA checklist
- Funding to date from ACMG Foundation fund-raising
- Solicitation of topic proposals from the community
- Topics undergo prioritization process
  - Extent of **practice variation or uncertainty**
  - Impact on **patient outcomes**
  - Is **ACMG the most suitable entity** to lead



https://nationalhealthcouncil.org/wp-content/uploads/2021/04/NHC-PICOTS-Infographic-v10.pdf



https://www.prisma-statement.org/

https://www.acmgfoundation.org/ebg

Nominated SER/EBG Topics Undergoing Prioritization

Topic	Other potential society partners
Exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability	Published
Noninvasive prenatal screening for fetal chromosome abnormalities in a general-risk population	Published
Phenylalanine Hydroxylase (PAH) Deficiency Diagnosis and Management	Published
Rapid exome and genome sequencing in the NICU	AAP to endorse
Genetic testing of autism spectrum disorder	AAP to endorse or collaborate
Genetic testing in monogenic chronic kidney disease	Strategy led by ACMG; kidney society collaboration or endorsement
Diagnosis and management of fatty acid oxidation disorders	SIMD could lead
Utility of multigene diagnostic testing for patients with epilepsy	AAN or AAP to collaborate
Reflexive germline genetic testing following breast cancer diagnosis	ASCO or NCCN to lead
Gonadal germ cell tumor risk in individuals with differences of sex development	Collaborate with endocrine and/or pediatric oncology
Diagnosis and management of urea cycle disorders	SIMD could lead
Genetic evaluation of living kidney donors	Nephrology or transplant society to lead; or ACMG to collaborate
Genetic diagnosis and clinical management of cardiomyopathy	ACC with ACMG input, or narrow scope to genetic testing only
Transfer of mosaic embryos during in-vitro fertilization	Societies focused on OB/IVF; ACOG, ASRM, with NSGC
Referral to Genetics	AAP /child neurology/ACP should lead
Diagnosis and perinatal management of fetal skeletal dysplasia	ACOG or SMFM could lead
Genetic diagnosis and clinical management of inherited retinal diseases	ACMG if limited to genetic testing only; AAO if wider scope
Genetic diagnosis and clinician management of Marfan syndrome	ACA could lead
Diagnosis and management of osteogenesis imperfecta	AAP, Endocrine, Orthopedic societies could lead
Genetic diagnosis and management of Pompe disease	SIMD could lead
Genetic implications of advanced paternal age	NSGC with ACOG or Society for Maternal-Fetal Medicine with ACMG

Related Factors in Clinical Genetic Testing Guidelines

- Primary focus of guidelines: clinical utility for offering a genetic test
- Related Factors:
  - Diagnostic yield and rate of uncertain results (i.e. benefit/risk)
  - Accuracy of results
  - Availability of implementation support for physicians

ClinGen's semi-quantitative framework to classify the strength of evidence for the role of genes in disease

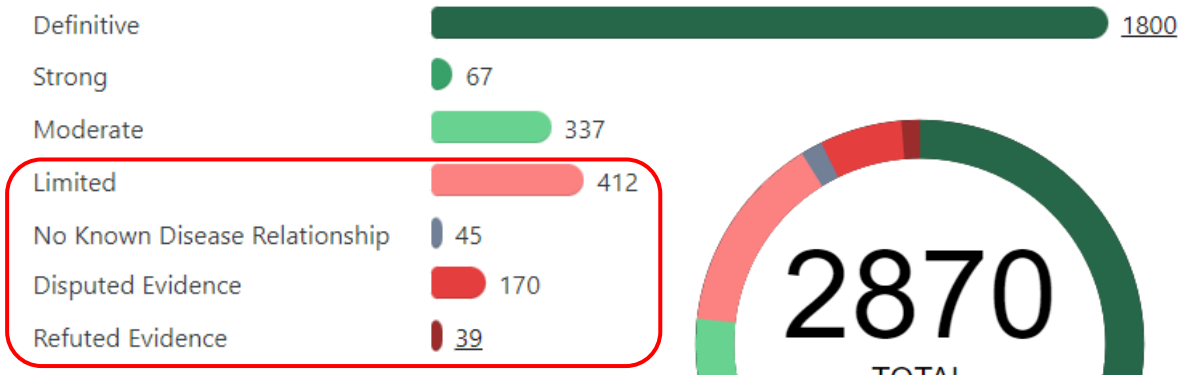
ARTICLE

Evaluating the Clinical Validity of Gene-Disease Associations: An Evidence-Based Framework Developed by the Clinical Genome Resource

Natasha T. Strande,[1,14] Erin Rooney Riggs,[2,14] Adam H. Buchanan,[3] Ozge Ceyhan-Birsoy,[4,5,6,7] Marina DiStefano,[4] Selina S. Dwight,[8] Jenny Goldstein,[1] Rajarshi Ghosh,[9] Bryce A. Seifert,[1] Tam P. Sneddon,[8] Matt W. Wright,[8] Laura V. Milko,[1] J. Michael Cherry,[8] Monica A. Giovanni,[3] Michael F. Murray,[3] Julianne M. O'Daniel,[1] Erin M. Ramos,[10] Avni B. Santani,[11,12] Alan F. Scott,[13] Sharon E. Plon,[9] Heidi L. Rehm,[4,5,6,7] Christa L. Martin,[2,3,*] and Jonathan S. Berg[1,*]

Classification Statistics

Gene-Disease Clinical Validity has **2870 curations** encompassing **2361 genes**.



23% insufficient evidence

ACMG TECHNICAL STANDARDS | Genetics inMedicine

Diagnostic gene sequencing panels: from design to report—a technical standard of the American College of Medical Genetics and Genomics (ACMG)

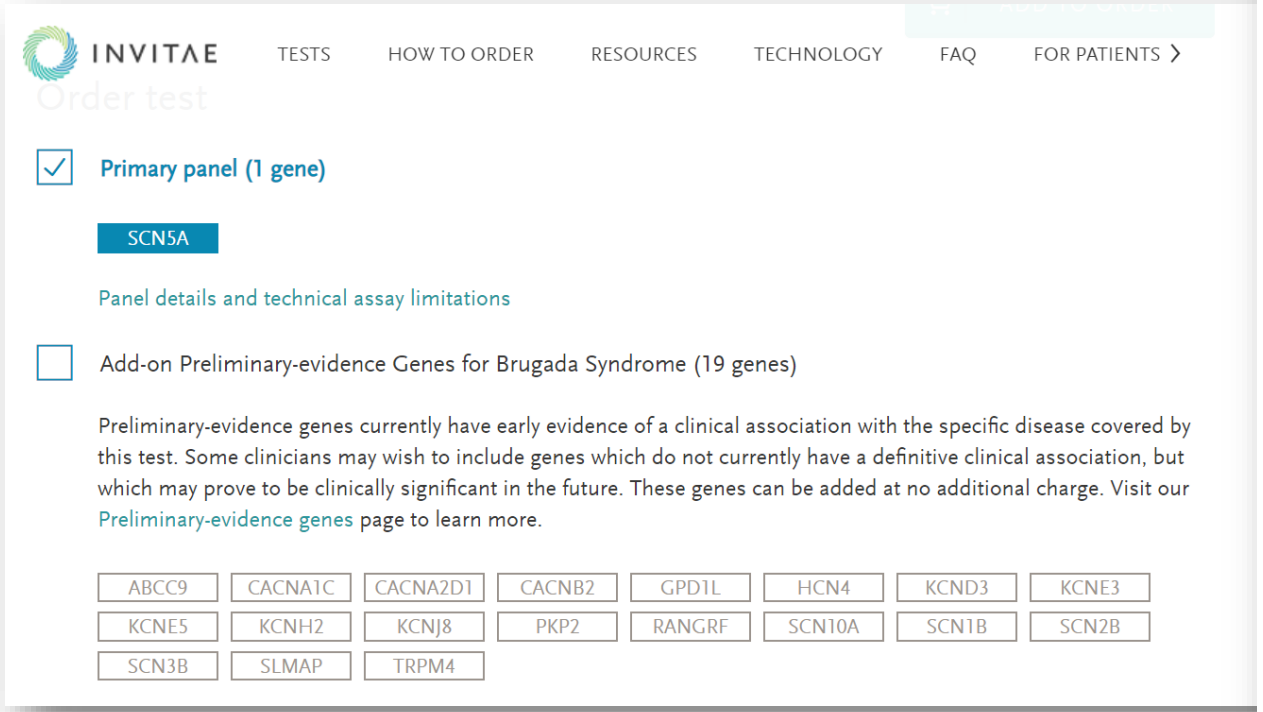
Lora J. H. Bean, PhD[1,2], Birgit Funke, PhD[3,4], Colleen M. Carlston, PhD[5], Jennifer L. Gannon, MD[6,7], Sibel Kantarci, PhD[8], Bryan L. Krock, PhD[9], Shulin Zhang, MD, PhD[10] and Pinar Bayrak-Toydemir, MD, PhD[11,12]; on behalf of the ACMG Laboratory Quality Assurance Committee

Table 3 Inclusion criteria for genes with various gene–disease evidence levels comparing diagnostic gene panels with exome/genome testing

ClinGen framework[3,a]		Definitive	Strong	Moderate	Limited		No evidence
Gene category		**Genes associated with disease**			**Genes of uncertain significance**		
Test purpose	**Predominant diagnostic approach**				**Genes with emerging evidence**	**Genes with no emerging evidence**	**Genes with no evidence**
Confirmation of clinical Dx	Disease-focused multigene panel; other non–sequencing-based ancillary assays	Include	Include	Include[b]	Typically exclude[c,d]	Exclude	Exclude
Establish genetic diagnosis for clinically complex cases	Exome/genome[e]	Include	Include	Include[b]	Additional requirements[d]		

[a]Genes with conflicting evidence reported (disputed, refuted) are not appropriate for diagnostic gene panels.
[b]Indicate in the report that evidence for the disease association is still building. Variants are unlikely to be classified above likely pathogenic.
[c]Although broad inclusion of genes of uncertain significance (GUSs) in diagnostic panels is discouraged, there are scenarios where inclusion may be meaningful (see discussion in "Clinical sensitivity").
[d]Report with specific statement that disease association and inheritance has not been established. Results from these genes should be separated from the clinical result to the extent possible within the reporting system.
[e]Consent process specific to exome/genome testing required.

Implementation of ClinGen's gene curation results



ASCO Guideline: *"The evidence assessment of the ClinGen expert panels informed the final selection of genes and the strength of the recommendation for each."*

Selection of Germline Genetic Testing Panels in Patients With Cancer: ASCO Guideline

Nadine Tung, MD[1]; Charité Ricker, MS, CGC[2]; Hans Messersmith, MPH[3]; Judith Balmaña, MD, PhD[4]; Susan Domchek, MD, FASCO[5]; Elena Martinez Stoffel, MD, MPH[6]; Khaldoun Almhanna, MD, MPH[7]; Banu Arun, MD, FASCO[8]; Yanin Chavarri-Guerra, MD, MSc[9]; Stephanie A. Cohen, MS, LCGC[10]; Deborah Cragun, PhD, CGC[11]; Katherine D. Crew, MD, MS[12]; Michael J. Hall, MD, MS[13]; Gregory Idos, MD, MS[14]; Ghecemy Lopez, DSW(C), MAED[15]; Tuya Pal, MD[16]; Sara Pirzadeh-Miller, MS, CGC[17]; Colin Pritchard, MD, PhD[18]; Huma Q. Rana, MD, MPH[19]; Umang Swami, MD[20]; and Gregory A. Vidal, MD, PhD[21]

DOI https://doi.org/10.1200/JCO.24.00662

ABSTRACT

ASCO Guidelines provide recommendations with comprehensive review and analyses of the relevant literature for each recommendation, following the guideline development process as outlined in the ASCO Guidelines Methodology Manual. ASCO Guidelines follow the ASCO Conflict of Interest Policy for Clinical Practice Guidelines.

Clinical Practice Guidelines and other guidance ("Guidance") provided by ASCO is not a comprehensive or definitive guide to treatment options. It is intended for voluntary use by providers and should be used in conjunction with independent professional judgment. Guidance may not be applicable to all patients, interventions, diseases, or stages of diseases. Guidance is based on review and analysis of relevant literature and is not intended as a statement of the standard of care. ASCO does not endorse third-party drugs, devices, services, or therapies and assumes no responsibility for any harm arising from or related to the use of this information. See complete disclaimer in Appendix 1 and Appendix 2 (online only) for more.

PURPOSE To guide use of multigene panels for germline genetic testing for patients with cancer.

METHODS An ASCO Expert Panel convened to develop recommendations on the basis of a systematic review of guidelines, consensus statements, and studies of germline and somatic genetic testing.

RESULTS Fifty-two guidelines and consensus statements met eligibility criteria for the primary search; 14 studies were identified for Clinical Question 4.

RECOMMENDATIONS Patients should have a family history taken and recorded that includes details of cancers in first- and second-degree relatives and the patient's ethnicity. When more than one gene is relevant based on personal and/or family history, multigene panel testing should be offered. When considering what genes to include in the panel, the minimal panel should include the more strongly recommended genes from Table 1 and may include those less strongly recommended. A broader panel may be ordered when the potential benefits are clearly identified, and the potential harms from uncertain results should be mitigated. Patients who meet criteria for germline genetic testing should be offered germline testing regardless of results from tumor testing. Patients who would not normally be offered germline genetic testing based on personal and/or family history criteria but who have a pathogenic or likely pathogenic variant identified by tumor testing in a gene listed in Table 2 under the outlined circumstances should be offered germline testing.

Additional information is available at www.asco.org/molecular-testing-and-biomarkers-guidelines.

ACCOMPANYING CONTENT

Appendix

Data Supplement

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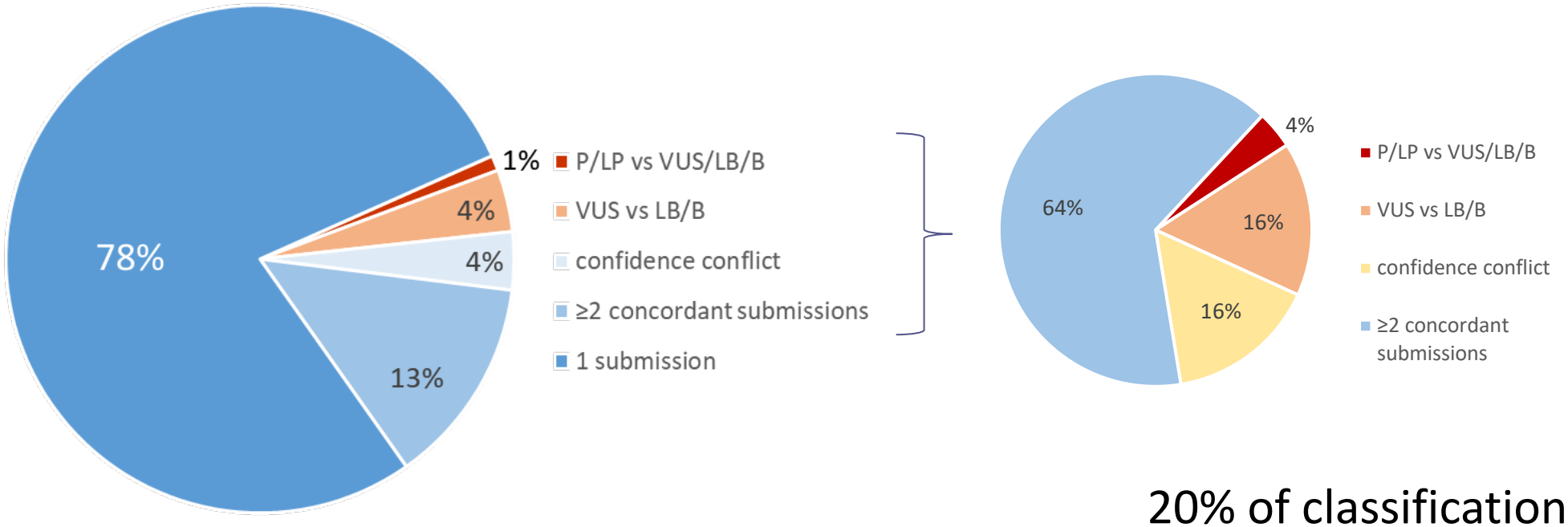
Published May 17, 2024

Evidence-Based Medicine Committee approval: February 7, 2024

J Clin Oncol 00:1-17

View Online Article

Critical role of data sharing and expert consensus in genetic testing



Source of data:
ClinVar Database
10/17/24

78% of variants are only seen by one laboratory

20% of classifications performed by more than one lab are conflicting

ClinGen Expert Panels resolve discrepancies in ClinVar and move VUS to LP/P/LB/B through data sharing, application of professional standards and expert consensus

33% of all diagnostic testing results are inconclusive due to VUS

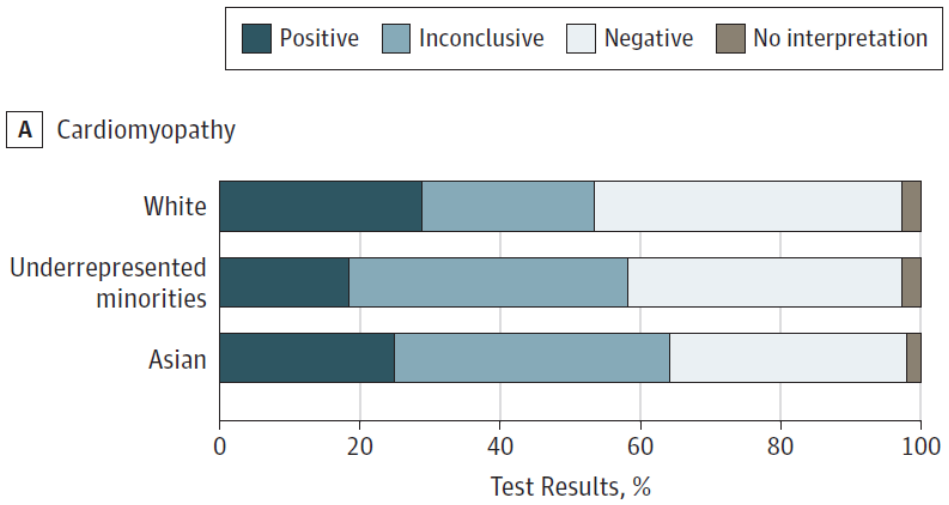
Rehm et al. Genet Med. 2023, PMID: 37534744

JAMA Cardiology | Brief Report

Association of Racial/Ethnic Categories With the Ability of Genetic Tests to Detect a Cause of Cardiomyopathy

Latrice G. Landry, PhD; Heidi L. Rehm, PhD

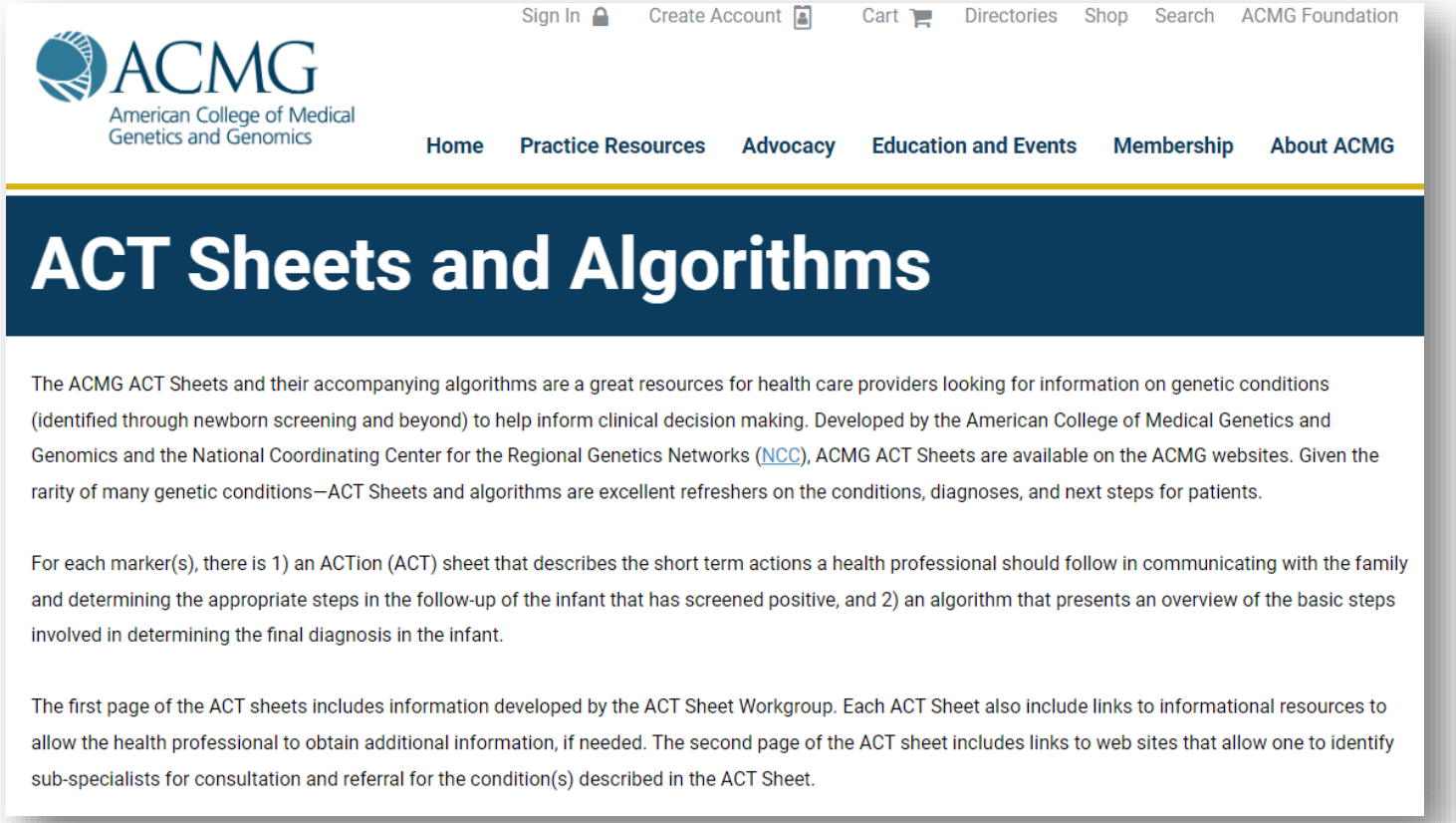
Figure. Genetic Testing Results by Racial/Ethnic Group



- Genetic test detection rates were reduced in underrepresented minorities compared to whites and Asians ($p<0.001$).
- Inconclusive rates were increased in URMs and Asians compared to whites ($p<0.001$).

Landry and Rehm. JAMA Cardiol. 2018. PMID: 29490334

Critical companions to guidelines are implementation resources



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ACT Sheets and Algorithms

The ACMG ACT Sheets and their accompanying algorithms are a great resources for health care providers looking for information on genetic conditions (identified through newborn screening and beyond) to help inform clinical decision making. Developed by the American College of Medical Genetics and Genomics and the National Coordinating Center for the Regional Genetics Networks (NCC), ACMG ACT Sheets are available on the ACMG websites. Given the rarity of many genetic conditions—ACT Sheets and algorithms are excellent refreshers on the conditions, diagnoses, and next steps for patients.

For each marker(s), there is 1) an ACTion (ACT) sheet that describes the short term actions a health professional should follow in communicating with the family and determining the appropriate steps in the follow-up of the infant that has screened positive, and 2) an algorithm that presents an overview of the basic steps involved in determining the final diagnosis in the infant.

The first page of the ACT sheets includes information developed by the ACT Sheet Workgroup. Each ACT Sheet also include links to informational resources to allow the health professional to obtain additional information, if needed. The second page of the ACT sheet includes links to web sites that allow one to identify sub-specialists for consultation and referral for the condition(s) described in the ACT Sheet.

92 ACT Sheets

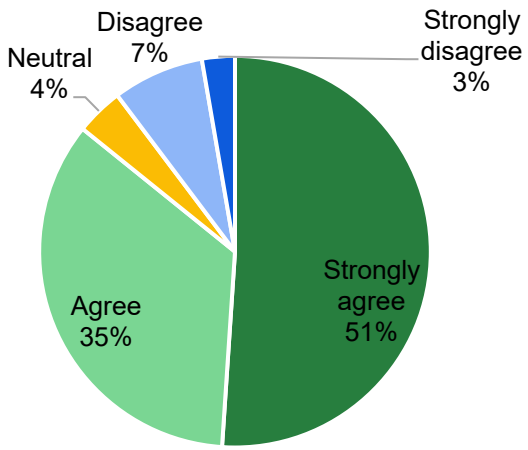
- Newborn Screening ACT Sheets and Algorithms
- Carrier ACT Sheets and Algorithms
- Diagnostic Test ACT Sheets
- Family History ACT Sheets
- Prenatal Cell-Free DNA Screening ACT Sheets
- Secondary Findings ACT Sheets
- Transition ACT Sheets

Patient Perspectives

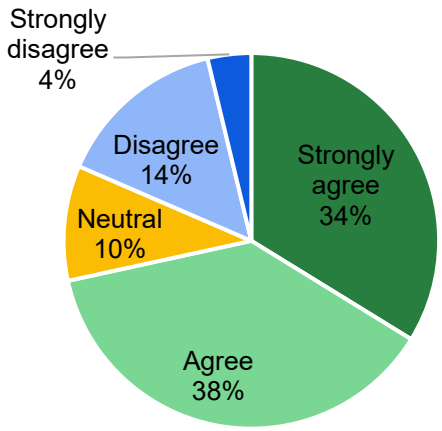
- **ACMG SER/EBG Policy:** Patients, carers of patients, or advocates for patients are required for nearly all SER/EBG projects
- Patients often have distinct perspectives from laboratories and clinicians

Survey question for VUS reporting guidance:
Laboratories should NOT return VUS in genes related to secondary findings

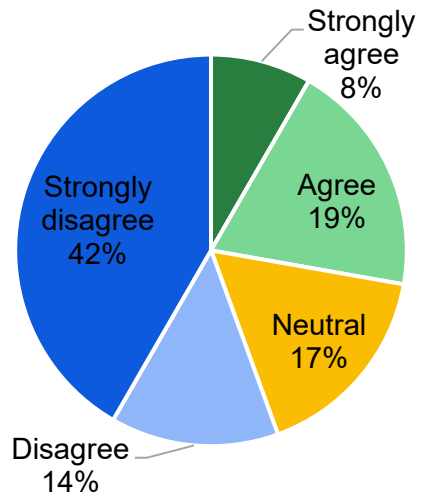
Laboratory (n=331)



Clinician (n=373)



Patient (n=36)



Key Takeaways

- Evidence-based practice guidelines are critical to our field but are labor intensive and require resources and expertise to support, as well as inclusion of patient perspectives
- It is important for clinical genetics and genomic guidelines to address test content, methods, and reporting guidance to ensure tests optimize for highest benefit and lowest risk
- Consideration for implementation is important to ensure that clinical utility is effectively achieved once put into practice
  - Examples: ACMG ACT sheets, data sharing, expert panels, inclusion of data from underrepresented populations