Clinical Sequencing Evidence-generating Research (CSER) Progress Update

Gail Jarvik, MD, PhD and Kyle Brothers, MD, PhD

National Advisory Council for Human Genome Research

September 18, 2023

National Human Genome Research Institute

cser
Clinical Sequencing Evidence-Generating Research

Clinical Sequencing Exploratory Research (CSER) Phase 1 (2011-2016): Motivation

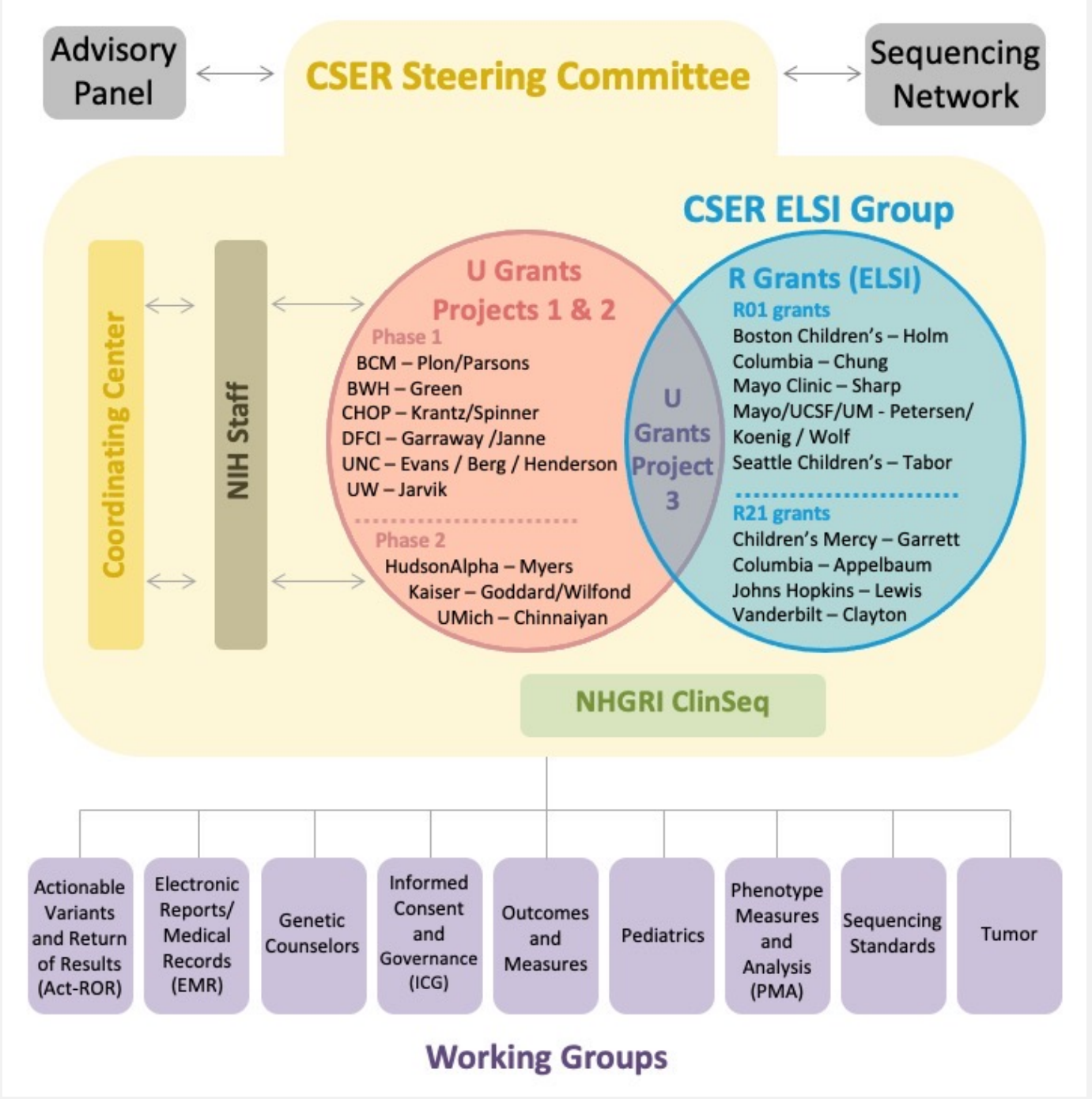
- Explore, within an active clinical setting, the application of genomic sequence data to the care of patients
  - Generation of genomic sequence data
  - Interpretation and translation of data for the physician
  - Communication to the patient

CSER Phase 1: Programmatic and Scientific Goals

- Best practices in moving genome sequencing from medical science to the clinical practice
- Patient characteristics that signal potential utility (or lack thereof) for applying genome-scale sequencing
- Best approaches to analyzing data
- Guide to which results should be returned (and how) to the patient and physician
- Plethora of highly heterogeneous “non-target” data generated when performing sequencing

NIH NHGRI

CSER Phase 1: structure and sites awarded



Clinical Sequencing Evidence-generating Research (CSER) Phase 2 (2017-2023): motivation

- Aim: generate evidence to determine clinical utility of genome sequencing
- Moving from “Exploratory” to “Evidence-generating”
- Focus on clinical utility: likelihood that genomic intervention leads to improved health outcomes
- Expand to diverse populations and care settings

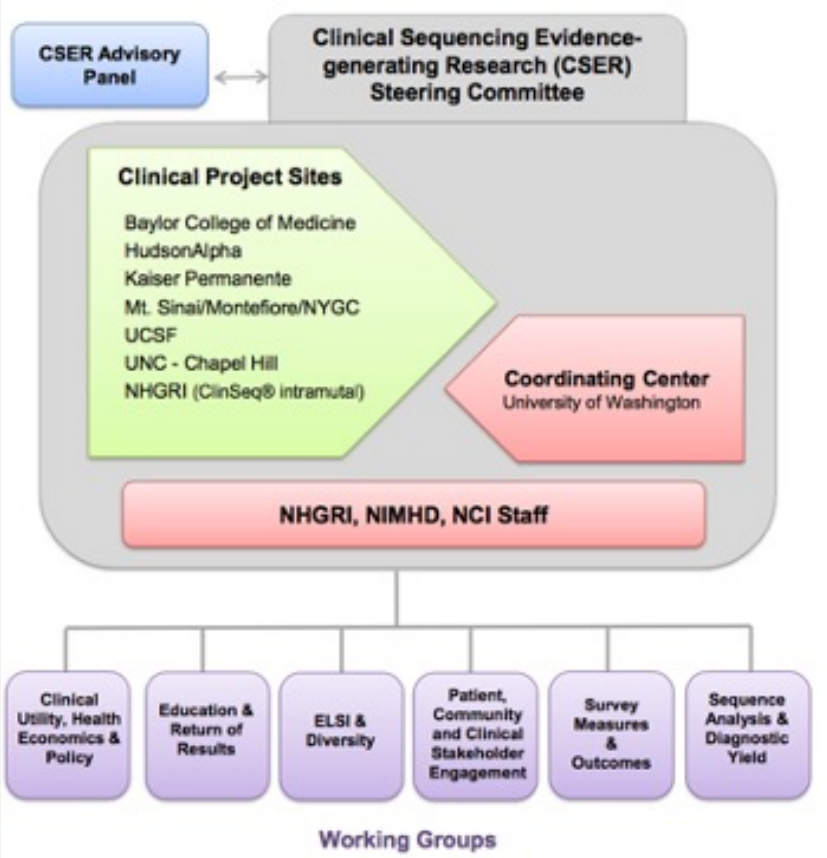
NIH
NHGRI

CSER Phase 2: Programmatic and Scientific goals

- Clinical Genomics
  - Systems to integrate genomics into everyday clinical and public health practice
  - Knowledge bases for genomic medicine in diverse populations
  - Evaluation and assessment of strategies for returning results and capturing recommended medical actions
  - Ensuring genomic health information has utility for all
  - Training of providers to adopt clinical genomics
- Embedded ELSI, diversity and engagement
  - Informed, empowered decision-making about genomics
  - Broadening of clinical utility to include perceived utility
  - Equity in genomic research, medicine, and training
  - Appropriate engagement to include underserved and vulnerable communities

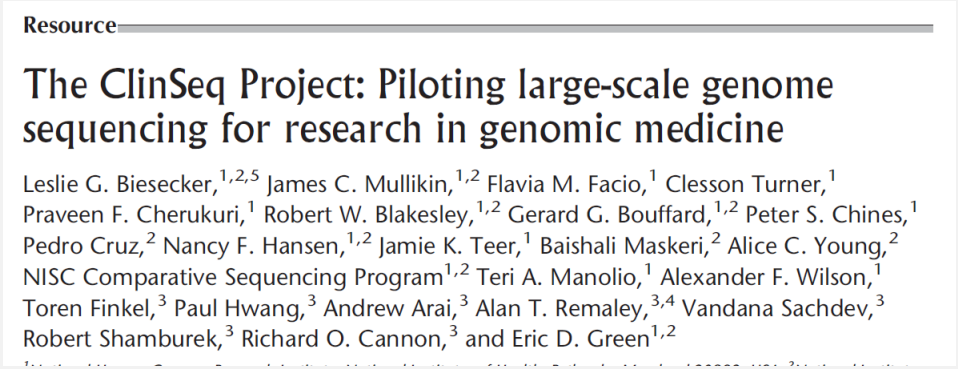
NIH NHGRI

CSER Phase 2: Structure and Sites awarded



NHGRI Intramural ClinSeq® Study

- Phenotype-agnostic study
- Began in 2006
  - Demonstrated feasibility and potential value of CSER
- Sequencing and phenotype data on 1,500 participants, including 500 African ancestry participants
- Contributions to key consortium papers

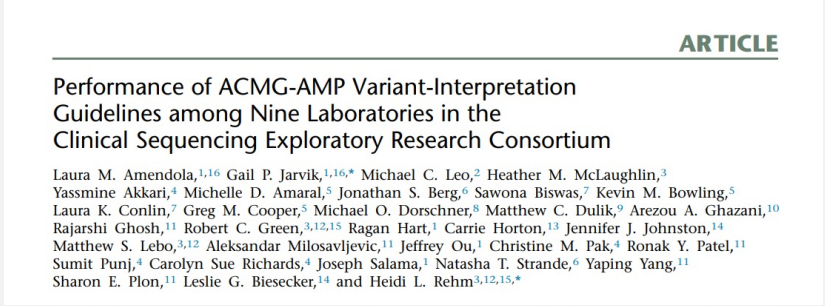


Resource

The ClinSeq Project: Piloting large-scale genome sequencing for research in genomic medicine

Leslie G. Biesecker,[1,2,5] James C. Mullikin,[1,2] Flavia M. Facio,[1] Clesson Turner,[1] Praveen F. Cherukuri,[1] Robert W. Blakesley,[1,2] Gerard G. Bouffard,[1,2] Peter S. Chines,[1] Pedro Cruz,[2] Nancy F. Hansen,[1,2] Jamie K. Teer,[1] Baishali Maskeri,[2] Alice C. Young,[2] NISC Comparative Sequencing Program[1,2] Teri A. Manolio,[1] Alexander F. Wilson,[1] Toren Finkel,[3] Paul Hwang,[3] Andrew Arai,[3] Alan T. Remaley,[3,4] Vandana Sachdev,[3] Robert Shamburek,[3] Richard O. Cannon,[3] and Eric D. Green[1,2]

Biesecker, et al. 2009 PMID 19602640



ARTICLE

Performance of ACMG-AMP Variant-Interpretation Guidelines among Nine Laboratories in the Clinical Sequencing Exploratory Research Consortium

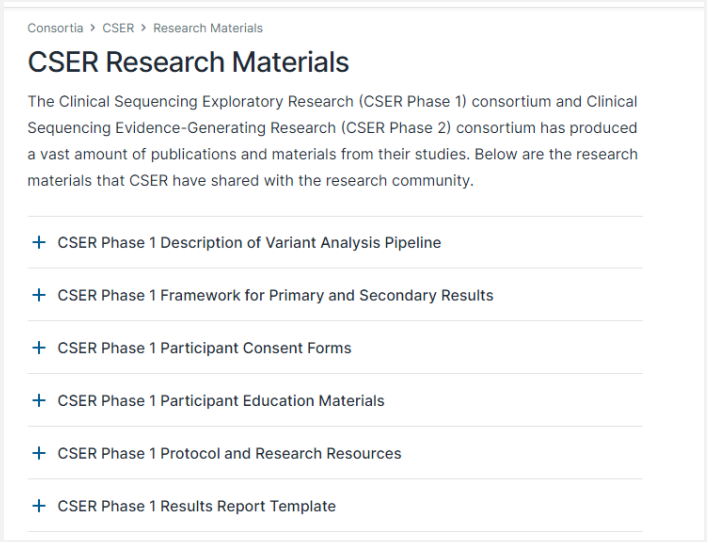
Laura M. Amendola,[1,16] Gail P. Jarvik,[1,16,*] Michael C. Leo,[2] Heather M. McLaughlin,[3] Yassmine Akkari,[4] Michelle D. Amaral,[5] Jonathan S. Berg,[6] Sawona Biswas,[7] Kevin M. Bowling,[5] Laura K. Conlin,[7] Greg M. Cooper,[5] Michael O. Dorschner,[8] Matthew C. Dulik,[9] Arezou A. Ghazani,[10] Rajarshi Ghosh,[11] Robert C. Green,[3,12,15] Ragan Hart,[1] Carrie Horton,[13] Jennifer J. Johnston,[14] Matthew S. Lebo,[3,12] Aleksandar Milosavljevic,[11] Jeffrey Ou,[1] Christine M. Pak,[4] Ronak Y. Patel,[11] Sumit Punj,[4] Carolyn Sue Richards,[4] Joseph Salama,[1] Natasha T. Strande,[6] Yaping Yang,[11] Sharon E. Plon,[11] Leslie G. Biesecker,[14] and Heidi L. Rehm[3,12,15,*]

Amendola, et al. 2016. PMID 27181684

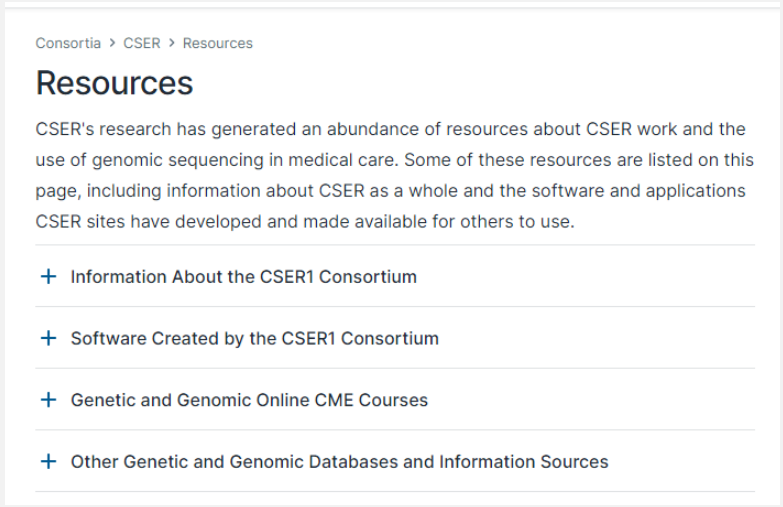
NIH NHGRI

First phase of CSER: *E* is for *Exploratory* 2011-2016

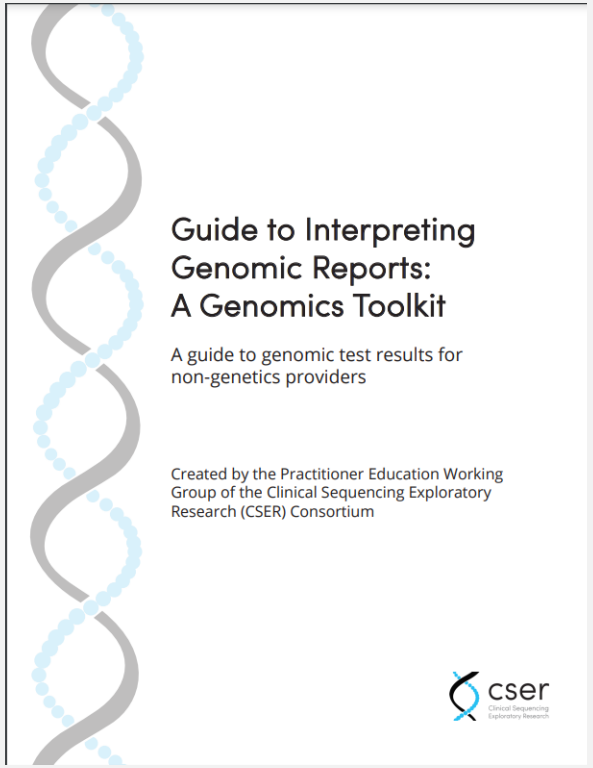
Tools and resources

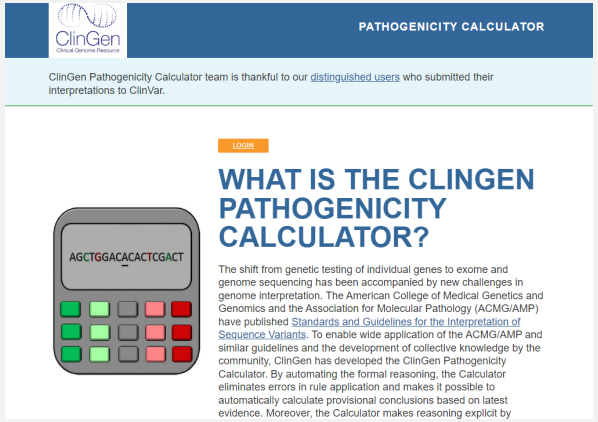


https://anvilproject.org/consortia/cser/research-materials



https://anvilproject.org/consortia/cser/resources





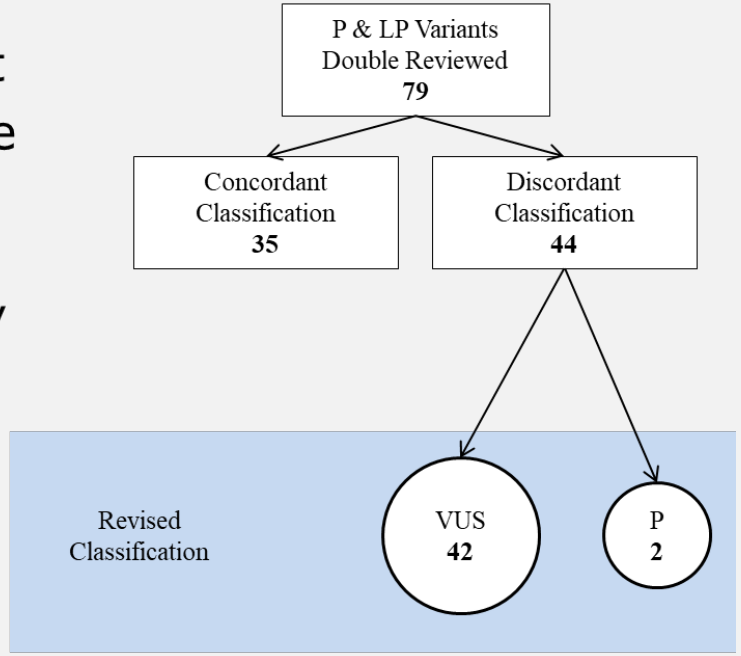
https://calculator.clinicalgenome.org/site/cg-calculator

https://www.genome.gov/sites/default/files/media/files/2020-04/Guide_to_Interpreting_Genomic_Reports_Toolkit.pdf

NIH NHGRI

Investigating additional (secondary) findings

- Recall random 25% of 615 SNVs:
  - 83/156 (53%) discrepant
  - 52 reviewers, a few made systematic errors: all recalled
- Recall all pathogenic & likely pathogenic variants:
  - 44/79 (56%) discordant;
  - 42/44 (95%) overcalled (final call VUS)
- Conclusion: Overcalling is a clinical problem



Prevalence of SFs: 1.7%

Family history

- Pre-disclosure of SFs: 32% had positive family history
- Post-disclosure: 48% had positive family history

Modest near-term induced costs

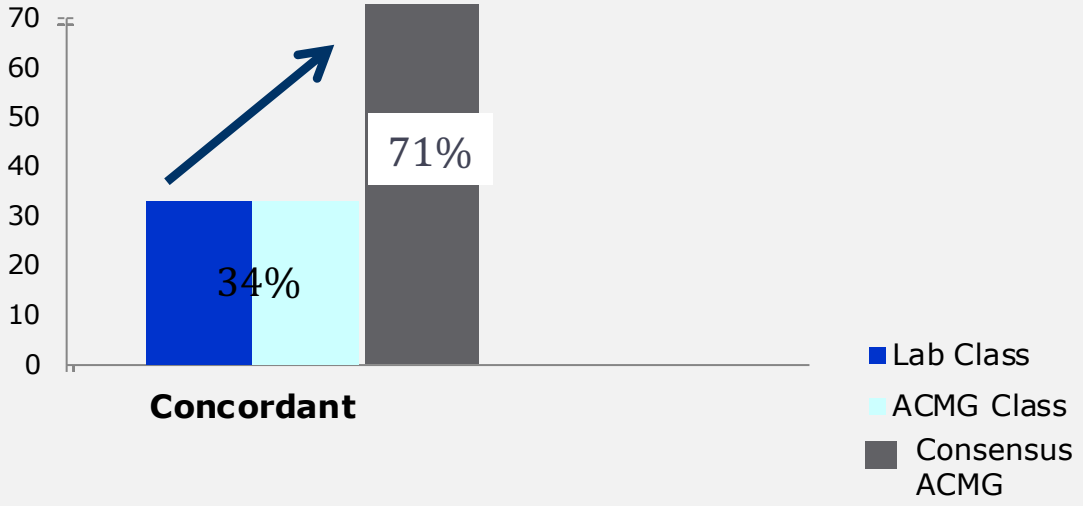
- Average recommended: $421 (range $141-$1114)
- Average observed: $128 (range $0-$678)

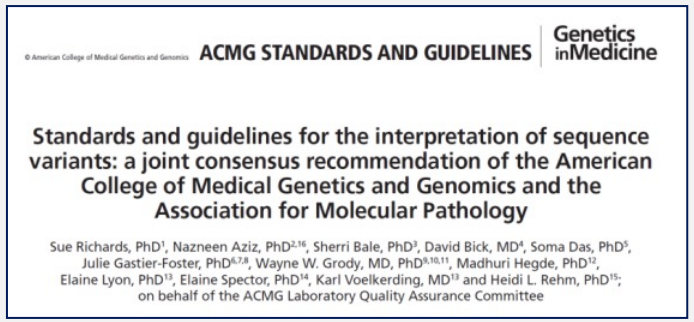
Dorschner, et al. 2013. PMID 24055113., n=1000; 3.4% EU, 1.2% AF
Amendola, et al. 2015. PMID 25637381. n=6503, 2.0% EU, 1.2% AF

Hart, et al. 2019. PMID 30287922

NIH NHGRI

Testing and clarifying new ACMG/AMP guidelines for variant pathogenicity classification (*2015 CSER "bake-off")*





Amendola, et al. 2016. PMID 27181684

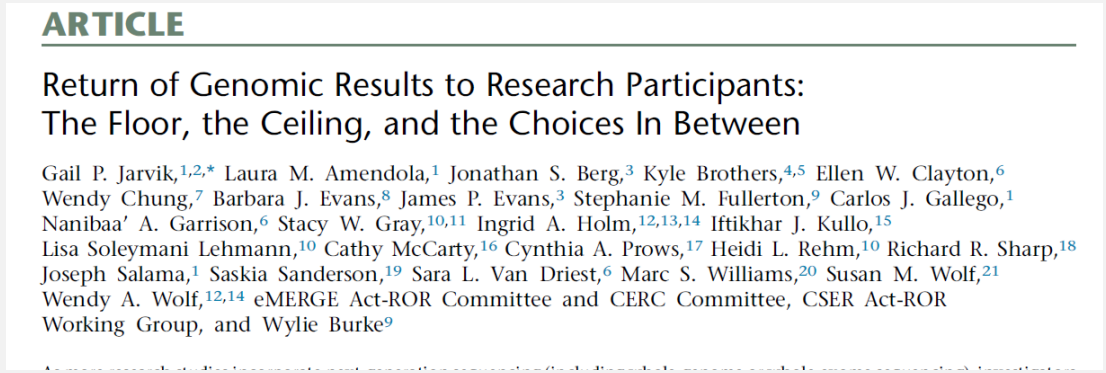
Before consensus work the ACMG/AMP guidelines did not increase concordance across 9 CSER labs (34%)

Discussion and clarification of ACMG/AMP rules increased concordance from 34% to 71%.

Paper describes rule refinement and clarification, and highlights need for training on new guideline

NIH NHGRI

Building policy consensus, including ROR to reach participants



ARTICLE

Return of Genomic Results to Research Participants:
The Floor, the Ceiling, and the Choices In Between

Gail P. Jarvik,[1,2,*] Laura M. Amendola,[1] Jonathan S. Berg,[3] Kyle Brothers,[4,5] Ellen W. Clayton,[6] Wendy Chung,[7] Barbara J. Evans,[8] James P. Evans,[3] Stephanie M. Fullerton,[9] Carlos J. Gallego,[1] Nanibaa' A. Garrison,[6] Stacy W. Gray,[10,11] Ingrid A. Holm,[12,13,14] Iftikhar J. Kullo,[15] Lisa Soleymani Lehmann,[10] Cathy McCarty,[16] Cynthia A. Prows,[17] Heidi L. Rehm,[10] Richard R. Sharp,[18] Joseph Salama,[1] Saskia Sanderson,[19] Sara L. Van Driest,[6] Marc S. Williams,[20] Susan M. Wolf,[21] Wendy A. Wolf,[12,14] eMERGE Act-ROR Committee and CERC Committee, CSER Act-ROR Working Group, and Wylie Burke[9]

Jarvik, et al. 2014. PMID 24814192

"Floor" – individual genomic research results that are valid, medically important, and actionable. No "duty to hunt"

Participants should have the option to refuse research genomic test results

Ethical and scientific justification in returning all genomic information in some format; any level of information between "floor" and "ceiling"

Additional research required that examine benefits and harms of receiving results and evaluate practices for return

NIH NHGRI

emerge network
ELECTRONIC MEDICAL RECORDS AND GENOMICS

cser
Clinical Sequencing Evidence-Generating Research

Guidance on informed consent documents

RESEARCH ARTICLE

AMERICAN JOURNAL OF medical genetics PART A

Experiences with Obtaining Informed Consent for Genomic Sequencing

Barbara A. Bernhardt,[1]* Myra I. Roche,[2,3] Denise L. Perry,[4] Sarah R. Scollon,[5] Ashley N. Tomlinson,[1] and Debra Skinner[6]

Informed consent element	# Interviewees mentioning
Results	
Limitation of testing/meaning of negative result	13
Implications of results for individual tested	10
Which results are non-optional	5
Research-related items	
"Everything" included on consent form	5
What participation involves (surveys, interviews, etc.)	5
Study/testing risks	
Privacy	6
Genetic discrimination	6

Bernhardt, et al. 2015. PMID 26198374

Perspective

For reprint orders, please contact: reprints@futuremedicine.com

Personalized Medicine

Consent for clinical genome sequencing: considerations from the Clinical Sequencing Exploratory Research Consortium

Joon-Ho Yu*,[1,2], Paul S Appelbaum[3], Kyle B Brothers[4], Steven Joffe[5], Tia L Kauffman[6], Barbara A Koenig[7], Anya ER Prince[8], Sarah Scollon[9], Susan M Wolf[10], Barbara A Bernhardt[11] & Benjamin S Wilfond[1,2]
[1]Department of Pediatrics, University of Washington, Seattle, WA 98195, USA

Yu, et al. 2019. PMID 31313633

COMMENTARY www.jpeds.com • THE JOURNAL OF PEDIATRICS

When Participants in Genomic Research Grow Up: Contact and Consent at the Age of Majority

Kyle B. Brothers, MD, PhD[1], Ingrid A. Holm, MD, MPH[2,3,4], Janet E. Childerhose, PhD[5], Armand H. M. Antommaria, MD, PhD[6], Barbara A. Bernhardt, MS, CGC[7], Ellen Wright Clayton, MD, JD[8], Bruce D. Gelb, MD[9], Steven Joffe, MD, MPH[10], John A. Lynch, PhD[11], Jennifer B. McCormick, PhD[12], Laurence B. McCullough, PhD[13], D. Williams Parsons, MD, PhD[14], Agnes S. Sundaresan, MD[15], Wendy A. Wolf, PhD[2], Joon-Ho Yu, MPH, PhD[16], and Benjamin S. Wilfond, MD[17], on behalf of the Pediatrics Workgroup of the Clinical Sequencing Exploratory Research (CSER) Consortium and the Consent, Education, Regulation, and Consultation Workgroup of the Electronic Medical Records and Genomics (eMERGE) Network*

emerge network ELECTRONIC MEDICAL RECORDS AND GENOMICS

cser Clinical Sequencing Evidence-Generating Research

Brothers, et al. 2016. PMID 2647786

The Challenge of Informed Consent and Return of Results in Translational Genomics: Empirical Analysis and Recommendations

Gail E. Henderson, Susan M. Wolf, Kristine J. Kuczynski, Steven Joffe, Richard R. Sharp, D. Williams Parsons, Bartha M. Knoppers, Joon-Ho Yu, and Paul S. Appelbaum

Henderson, et al. 2014. PMID 25264092

NIH NHGRI

Developing best practices for responsible results return

Figure 2C: Negative emotions/distress meta-analysis

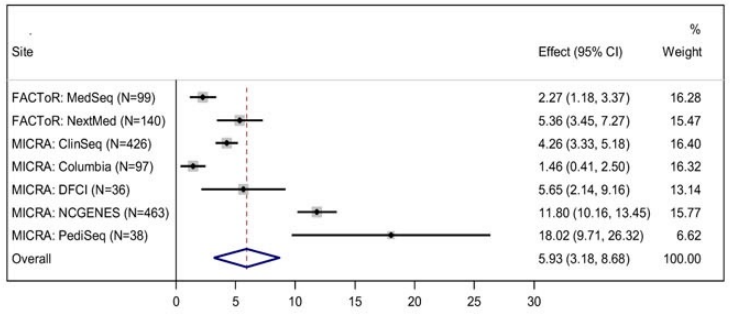


Figure 2F: Uncertainty random effects meta-analysis

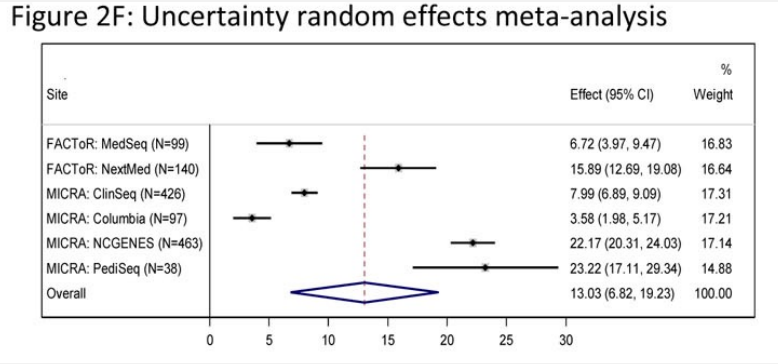
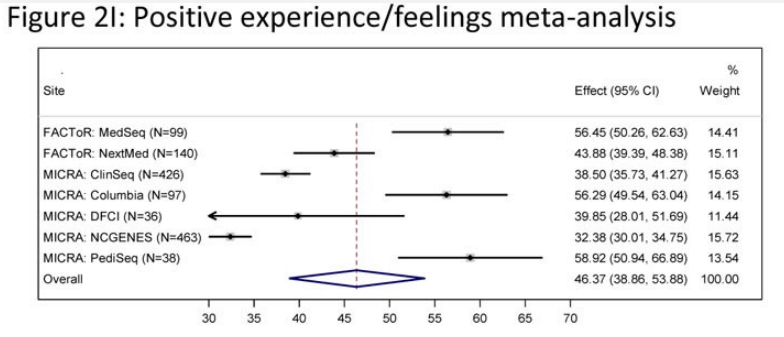
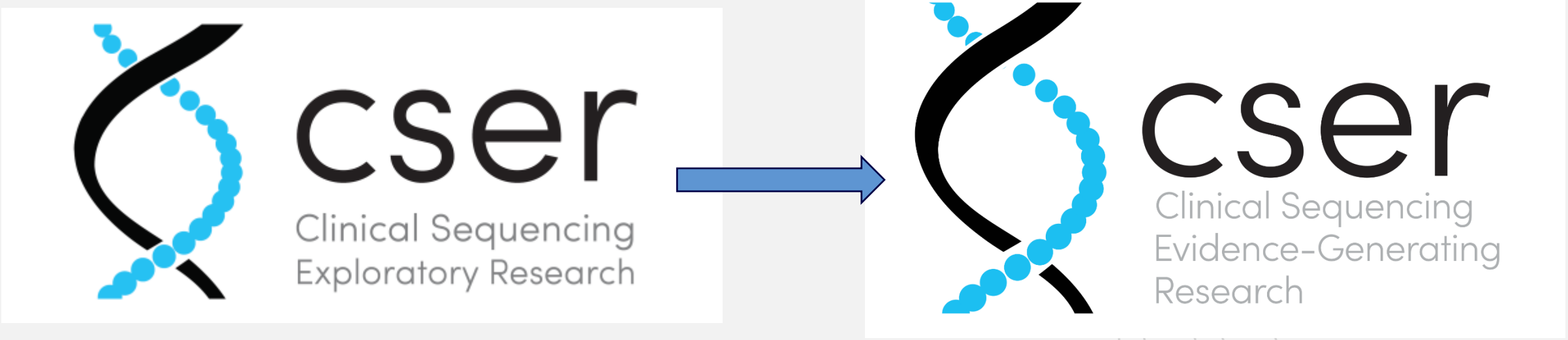


Figure 2I: Positive experience/feelings meta-analysis



Robinson, et al. 2019. PMID 31189963

Second phase of CSER: *E* is for *Evidence-generating* 2017-2023



2011 2017

NIH NHGRI

Harmonized measures for clinical utility

Clinical Sequence Evidence-Generating Research Consortium

CSER Parental Patient Measures – post-ROR Follow-up #1 (0 - 4 weeks post-RoR)
Proposed by: multiple CSER Working Groups
Version 1.4, Dated 7/16/2018

Feelings about Genomic Testing Results (FACToR) – Parent

Citation:

The following questions ask about how you, as a parent, felt after receiving your child's genetic test results. Please indicate how much you had each specific feeling in the past week by circling the one answer for each question: *not at all, a little, somewhat, a good deal*, or *a great deal*.

1. How **upset** did you feel about your child's genetic test result?
2. How **happy** did you feel about your child's genetic test result?
3. How **anxious or nervous** did you feel about your child's genetic test result?
4. How **relieved** did you feel about your child's genetic test result?
5. How **sad** did you feel about your child's genetic test result?
6. How **frustrated** did you feel about recommendations for your child's care based on the genetic test?
7. How **uncertain** did you feel about what your child's genetic test result means for your child?
8. How **uncertain** did you feel about what your child's genetic test result means for other family members' risk of disease?
9. How much did you feel that **you understood clearly your child's choices** for care based on the genetic test

https://anvilproject.org/consortia/cser/resources

Journal of Clinical and Translational Science

www.cambridge.org/cts

Translational Research, Design and Analysis Research Article

Cite this article: Goddard KAB, Angelo FAN, Ackerman SL, Berg JS, Biesecker BB, Danila MI, East KM, Hindorff LA, Horowitz CR, Hunter JE, Joseph G, Knight SJ, McGuire A, Muessig KR, Ou J, Outram S, Rahn EJ, Ramos MA, Rini C, Robinson JO, Smith HS, Waltz M, and Lee SS-J. (2020) Lessons learned about harmonizing survey measures for the CSER consortium. *Journal of Clinical and Translational Science* **4**: 537–546. doi: 10.1017/cts.2020.41

Received: 23 January 2020
Accepted: 5 March 2020
First published online: 24 April 2020

Keywords:
Team science; exome; genome; multidisciplinary; collaboration

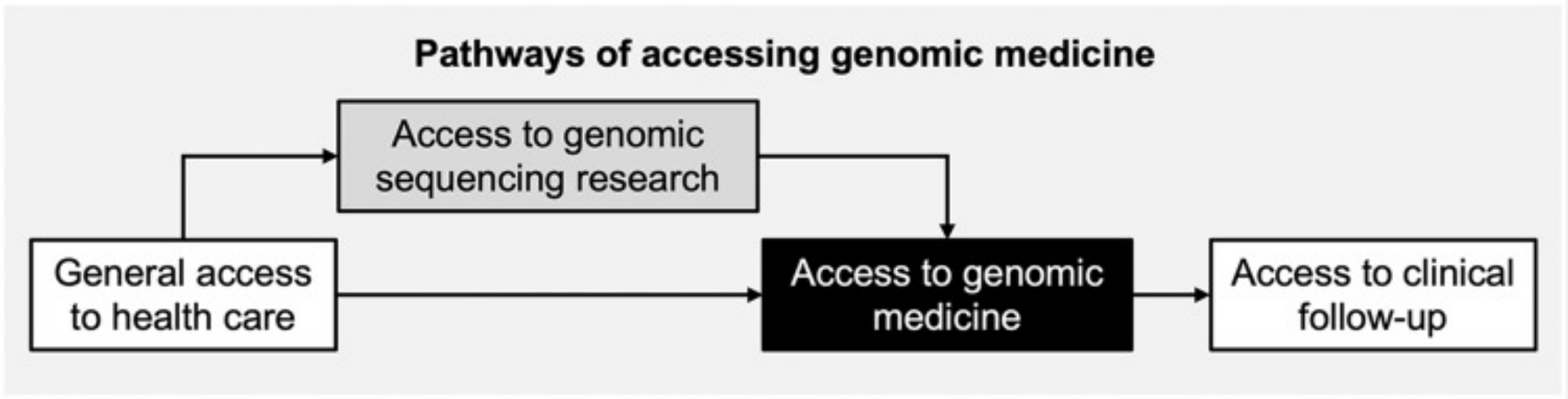
Lessons learned about harmonizing survey measures for the CSER consortium

Katrina A.B. Goddard[1], Frank A.N. Angelo[2], Sara L. Ackerman[3], Jonathan S. Berg[4], Barbara B. Biesecker[5], Maria I. Danila[6], Kelly M. East[7], Lucia A. Hindorff[8], Carol R. Horowitz[9,13], Jessica Ezzell Hunter[1], Galen Joseph[10], Sara J. Knight[11], Amy McGuire[12], Kristin R. Muessig[1], Jeffrey Ou[2], Simon Outram[14], Elizabeth J. Rahn[6], Michelle A. Ramos[13], Christine Rini[15,16], Jill O. Robinson[12], Hadley Stevens Smith[12], Margaret Waltz[17] and Sandra Soo-Jin Lee[18]

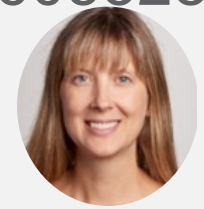
[1]Center for Health Research, Kaiser Permanente Northwest, Portland, OR, USA; [2]Department of Medicine, Division of Medical Genetics, University of Washington, Seattle, WA, USA; [3]Department of Social and Behavioral Sciences, University of California, San Francisco, USA; [4]Department of Genetics, University of North Carolina, Chapel Hill, USA; [5]RTI International, Washington, DC, USA; [6]Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, USA; [7]HudsonAlpha Institute for Biotechnology, Huntsville, AL, USA; [8]Division of Genomic Medicine, NHGRI, NIH, Bethesda, MD, USA; [9]Department of Medicine, General Internal Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [10]Department of Anthropology, History, and Social Medicine, University of California, San Francisco, USA; [11]Division of Epidemiology, Department of Internal Medicine, University of Utah, Salt Lake City, UT, USA; [12]Center for Medical Ethics and Health Policy at Baylor College of Medicine, Houston, TX, USA; [13]Department of Population Health Science and Policy, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [14]Program in Bioethics, University of California, San Francisco, USA; [15]Department of Medical Social Sciences, Northwestern University Feinberg School of Medicine, Chicago, IL, USA; [16]Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL, USA; [17]Department of Social Medicine, University of North Carolina, Chapel Hill, USA and [18]Division of Ethics, Department of Medical Humanities and Ethics, Columbia University, New York, NY, USA

Goddard, et al. 2020 PMID: 33948230

Participant inclusion and diversity



- Access to care (Gutierrez, et al. 2021. PMID: 34888063)
- Accessible Spanish language materials (Lindberg, et al. 2021. PMID: 34448595)
- Models of inclusive genetic counseling (Joseph G, et al. 2022. PMID: 36053287)
- Strategies for results disclosure (Suckiel, et al. 2021. PMID 33805616)



NIH NHGRI

Participant inclusion and diversity

Factors Influencing Participant Understanding	Participant Emotional Response	Disease Burden	Logistical Challenges
• Low health literacy • Language discordance between participant and provider • High-level genetics concepts • Complex results • Ambiguous results • Distrust in the medical system	• Anxiety related to uncertain results • Parental distress • Disappointment due to unmet expectations • Overwhelmed by unexpected results	• Overwhelmed by health issues • Competing medical priorities • Parental condition	• Using a medical interpreter • Mode of delivery • Distance to the academic medical center • Lack of personal transportation • Long work hours • Coordinating family testing

- Strategies for results disclosure (Suckiel, et al. 2021. PMID 33805616)

NIH NHGRI

Stakeholder engagement

Stakeholder pre-meeting, 2018

Genetics in Medicine (2022) 24, 1108–1119

ELSEVIER

Genetics in Medicine

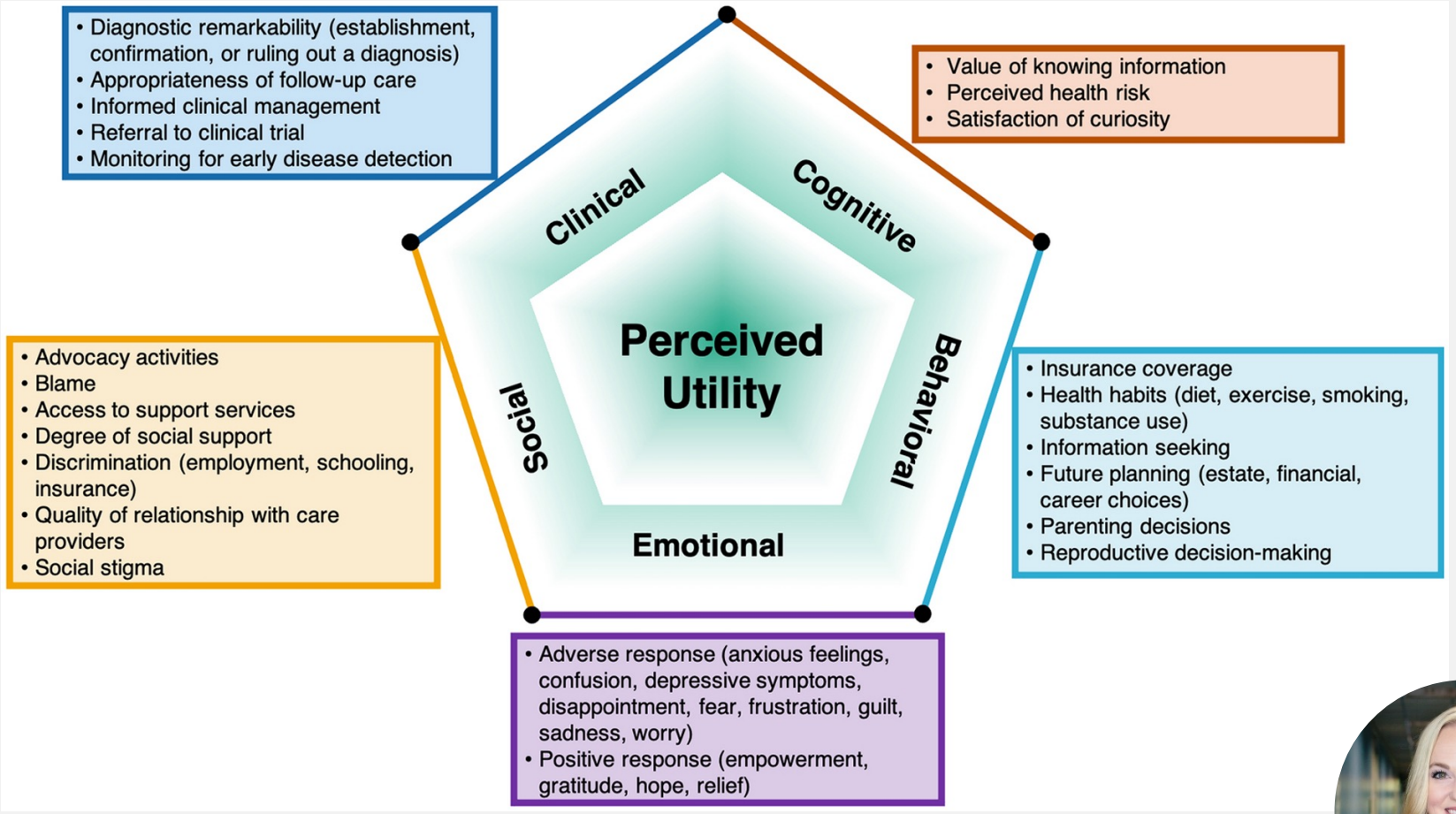
www.journals.elsevier.com/genetics-in-medicine

ARTICLE

Integration of stakeholder engagement from development to dissemination in genomic medicine research: Approaches and outcomes from the CSER Consortium

O'Daniel, et al. 2022. PMID 35227608

Perceived utility



NIH NHGRI

Stevens Smith, et al. 2022. PMID: 34658003

Parent-reported clinical utility

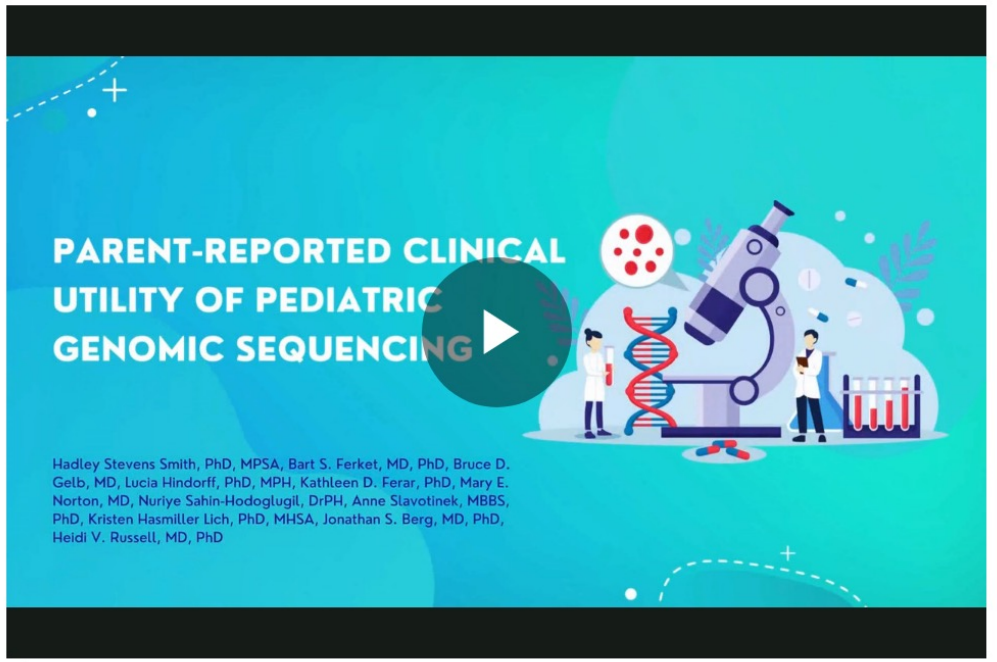
Up to 1187 responses from 5 sites

Clinicians made recommendations to care

- Positive result: 39%
- Inconclusive result: 12%
- Negative result: 12%

Parents initiating health or lifestyle changes

- Change in diet (74%)
- Change in exercise (3.8%)
- Starting vitamins or supplements (3.1%)

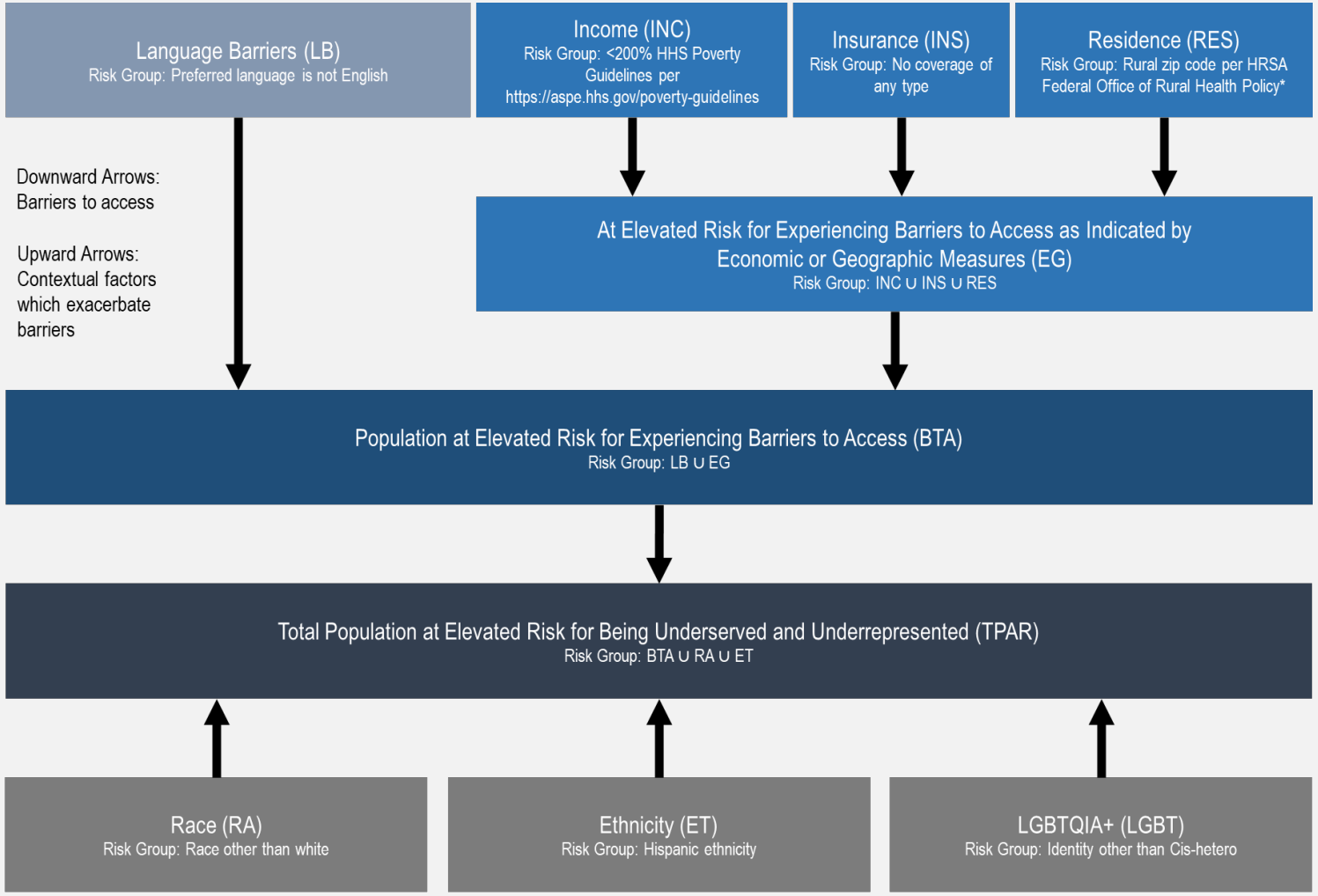


Video Abstract

Stevens Smith, et al. 2023. PMID 37470118. *Video abstract available*

NIH NHGRI

Underserved framework

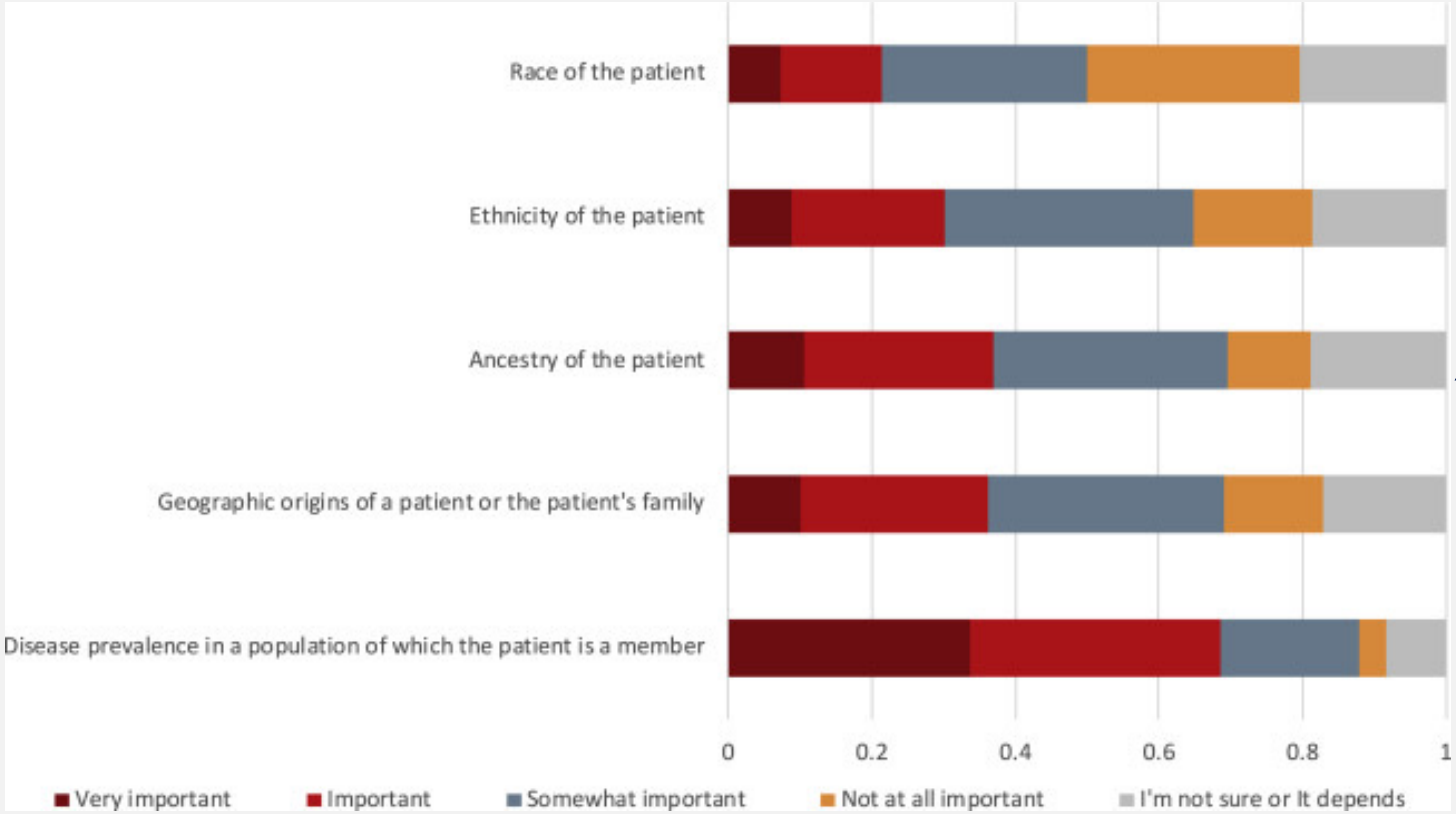


Brothers, et al.
Under review.

∪ denotes the union of two or more sets. A ∪ B = The set of elements which are in *A*, in *B*, or in both *A* and *B*.

Use of diversity measures – genetics survey

Of 217 participants who order clinical genetic tests, % indicating important or very important:



Race of the patient, 21%

Ethnicity of the patient, 30%

Ancestry of the patient, 37%

Geographic origin of patient/family, 36%

Disease prevalence in population, 69%

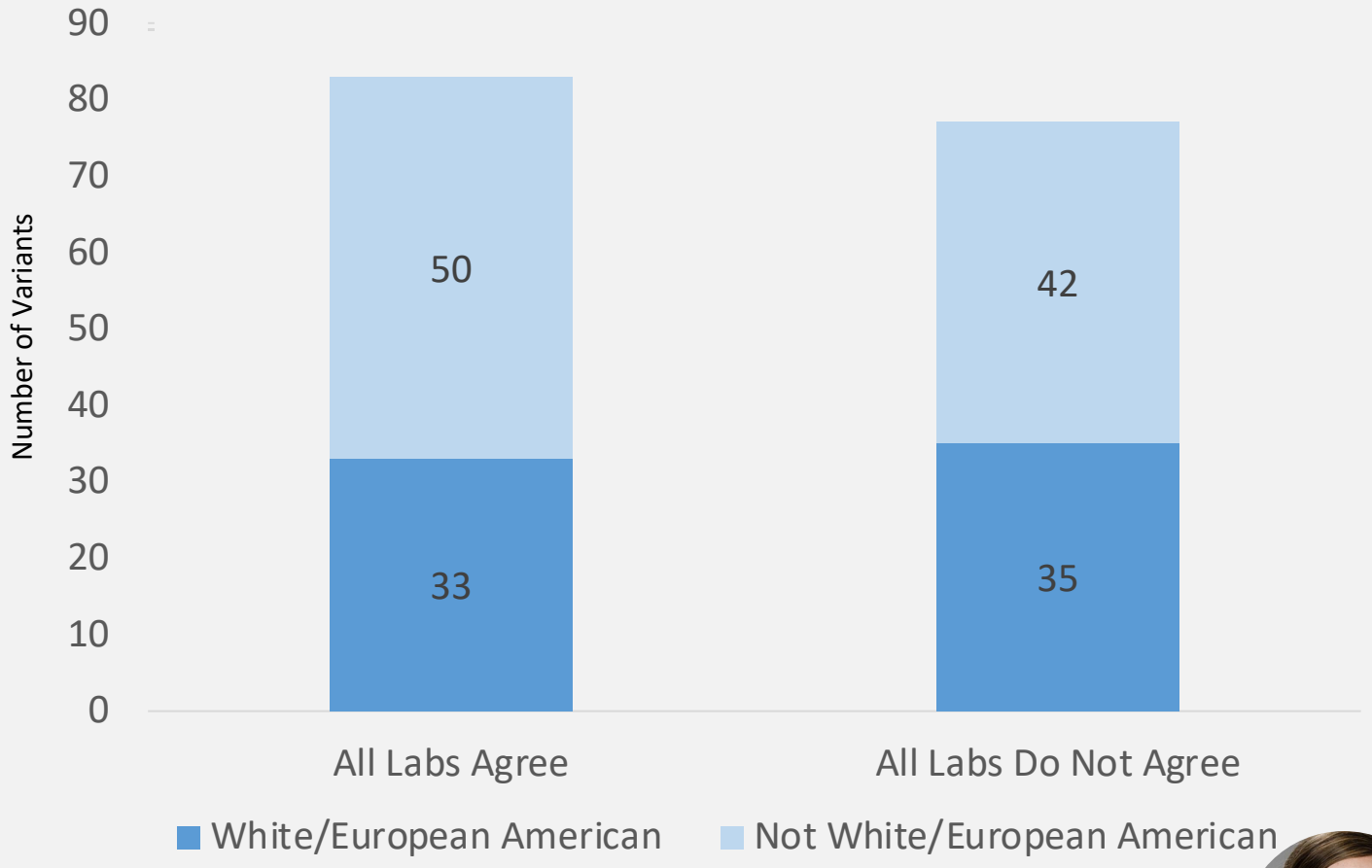
Popejoy A, et al. 2020. PMID: 32504544

NIH NHGRI

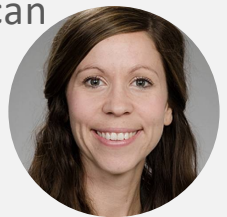
ClinGen Clinical Genome Resource

cser Clinical Sequencing Evidence-Generating Research

Continuing to improve consistency in variant classification across labs (*2019 "bake-off"*)



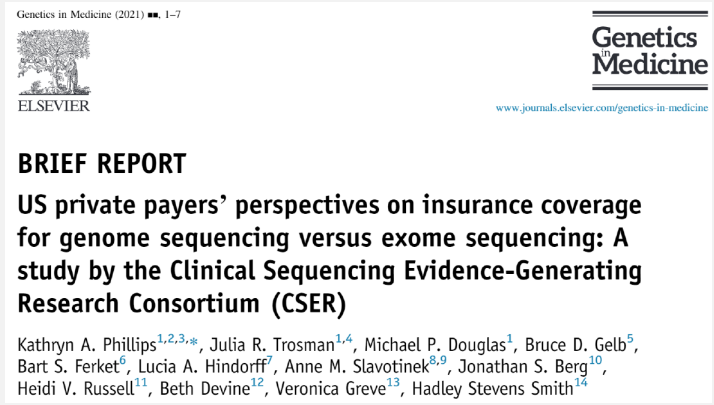
- "Agree" = all P, all LP, all VUS etc. = **52%**
- Agreement does not vary by ancestry (p=0.5)
- 48.5% (33/88) White/EA
  54.3% (50/92) non-EA
- **21%**, 33, of all variants have a discordance that impacts patient recommendations
  - 24/33 are LP vs VUS
  - 9/33 are P vs VUS
- Highlights sources of discordance and considerations for LP



NIH NHGRI

Amendola, et al. 2020. PMID 33108757

Frameworks and data for payers



Genetics in Medicine (2021) ■■, 1–7

ELSEVIER

Genetics in Medicine

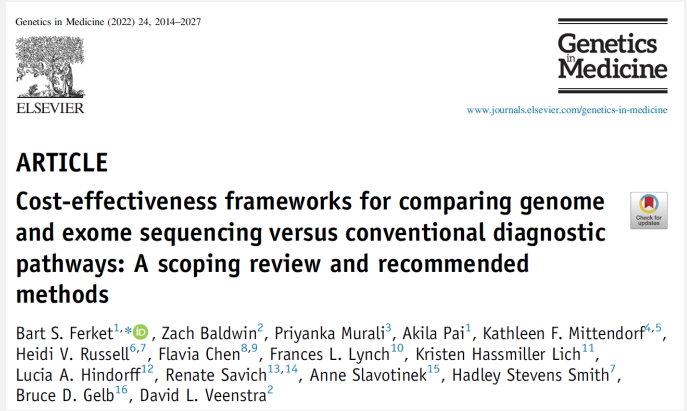
www.journals.elsevier.com/genetics-in-medicine

BRIEF REPORT

US private payers' perspectives on insurance coverage for genome sequencing versus exome sequencing: A study by the Clinical Sequencing Evidence-Generating Research Consortium (CSER)

Kathryn A. Phillips[1,2,3,*], Julia R. Trosman[1,4], Michael P. Douglas[1], Bruce D. Gelb[5], Bart S. Ferket[6], Lucia A. Hindorff[7], Anne M. Slavotinek[8,9], Jonathan S. Berg[10], Heidi V. Russell[11], Beth Devine[12], Veronica Greve[13], Hadley Stevens Smith[14]

Phillips, et al. 2022. PMID 34906461



Genetics in Medicine (2022) 24, 2014–2027

ELSEVIER

Genetics in Medicine

www.journals.elsevier.com/genetics-in-medicine

ARTICLE

Cost-effectiveness frameworks for comparing genome and exome sequencing versus conventional diagnostic pathways: A scoping review and recommended methods

Bart S. Ferket[1,*], Zach Baldwin[2], Priyanka Murali[3], Akila Pai[1], Kathleen F. Mittendorf[4,5], Heidi V. Russell[6,7], Flavia Chen[8,9], Frances L. Lynch[10], Kristen Hassmiller Lich[11], Lucia A. Hindorff[12], Renate Savich[13,14], Anne Slavotinek[15], Hadley Stevens Smith[7], Bruce D. Gelb[16], David L. Veenstra[2]

Ferket, et al. 2022. PMID 35833928

Phillips, et al.

- Group interview of 12 payers
- Opportunities to advance coverage
  - Genome vs. exome sequencing
  - Methods for evidence generation
  - Consistency among labs
  - Implementation and care delivery

NIH NHGRI

Site-specific papers

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Exome Sequencing for Prenatal Diagnosis in Nonimmune Hydrops Fetalis

T.N. Sparks, B.R. Lianoglou, R.R. Adami, I.D. Pluym, K. Holliman, J. Duffy, S.L. Downum, S. Patel, A. Faubel, N.M. Boe, N.T. Field, A. Murphy, L.C. Laurent, J. Jolley, C. Uy, A.M. Slavotinek, P. Devine, U. Hodoglugil, J. Van Ziffle, S.J. Sanders, T.C. MacKenzie, and M.E. Norton, for the University of California Fetal–Maternal Consortium and the University of California, San Francisco Center for Maternal–Fetal Precision Medicine*

Sparks, et al. 2020. PMID 33027564

327 site-specific papers (84% of all "U" grant papers)

DOI: 10.1002/pbc.29859

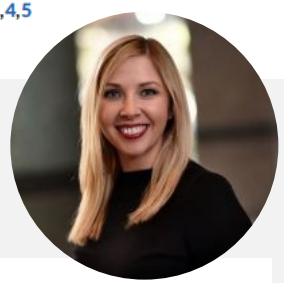
Pediatric Blood & Cancer

ONCOLOGY: RESEARCH ARTICLE

Clinical and molecular features of pediatric cancer patients with Lynch syndrome

Sarah Scollon[1] | Mohammad K. Eldomery[2,3] | Jacquelyn Reuther[2,3] | Frank Y. Lin[1] | Samara L. Potter[1] | Lauren Desrosiers[1] | Kenneth L. McClain[1] | Valeria Smith[1] | Jack Meng-Fen Su[1] | Rajkumar Venkatramani[1] | Jianhong Hu[4] | Viktoriya Korchina[4] | Neda Zarrin-Khameh[3] | Richard A. Gibbs[4,5] | Donna M. Muzny[4,5] | Christine Eng[5] | Angshumoy Roy[1,2,3] | D. Williams Parsons[1,2,4,5] | Sharon E. Plon[1,4,5]

Scollon, et al. 2022. PMID 35713195



HGG Advances

ARTICLE

Long-read genome sequencing for the molecular diagnosis of neurodevelopmental disorders

Susan M. Hiatt,[1] James M.J. Lawlor,[1] Lori H. Handley,[1] Ryne C. Ramaker,[1] Brianne B. Rogers,[1,2] E. Christopher Partridge,[1] Lori Beth Boston,[1] Melissa Williams,[1] Christopher B. Plott,[1] Jerry Jenkins,[1] David E. Gray,[1] James M. Holt,[1] Kevin M. Bowling,[1] E. Martina Bebin,[3] Jane Grimwood,[1] Jeremy Schmutz,[1] and Gregory M. Cooper[1,*]

Hiatt, et al. 2021. PMID 33937879

NIH NHGRI

Influential work and lasting legacy

CSER contributions to ACMG guidelines

ARTICLE

Actionable, Pathogenic Incidental Findings in 1,000 Participants' Exomes

Michael O. Dorschner,[1,4,5] Laura M. Amendola,[2] Emily H. Turner,[1,5] Peggy D. Robertson,[1] Brian H. Shirts,[5] Carlos J. Gallego,[2] Robin L. Bennett,[2] Kelly L. Jones,[2] Mari J. Tokita,[2] James T. Bennett,[2,3] Jerry H. Kim,[8] Elisabeth A. Rosenthal,[2] Daniel S. Kim,[1] National Heart, Lung, and Blood Institute Grand Opportunity Exome Sequencing Project, Holly K. Tabor,[3,6] Michael J. Bamshad,[1,3] Arno G. Motulsky,[1,2] C. Ronald Scott,[2,3] Colin C. Pritchard,[5] Tom Walsh,[2] Wylie Burke,[2,6] Wendy H. Raskind,[2,4] Peter Byers,[2,7] Fuki M. Hisama,[2] Deborah A. Nickerson,[1] and Gail P. Jarvik[1,2,*]

Dorschner, et al. 2013. PMID 24055113

ACMG POLICY STATEMENT | Genetics inMedicine

ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing

Robert C. Green, MD, MPH[1,2], Jonathan S. Berg, MD, PhD[3], Wayne W. Grody, MD, PhD[4-6], Sarah S. Kalia, ScM, CGC[1], Bruce R. Korf, MD, PhD[7], Christa L. Martin, PhD, FACMG[8], Amy L. McGuire, JD, PhD[9], Robert L. Nussbaum, MD[10], Julianne M. O'Daniel, MS, CGC[3], Kelly E. Ormond, MS, CGC[11], Heidi L. Rehm, PhD, FACMG[2,12], Michael S. Watson, PhD, FACMG[13], Marc S. Williams, MD, FACMG[14] and Leslie G. Biesecker, MD[15]

Green, et al. 2013. PMID 23788249

ARTICLE

Performance of ACMG-AMP Variant-Interpretation Guidelines among Nine Laboratories in the Clinical Sequencing Exploratory Research Consortium

Laura M. Amendola,[1,16] Gail P. Jarvik,[1,16,*] Michael C. Leo,[2] Heather M. McLaughlin,[3] Yassmine Akkari,[4] Michelle D. Amaral,[5] Jonathan S. Berg,[6] Sawona Biswas,[7] Kevin M. Bowling,[5] Laura K. Conlin,[7] Greg M. Cooper,[5] Michael O. Dorschner,[8] Matthew C. Dulik,[9] Arezou A. Ghazani,[10] Rajarshi Ghosh,[11] Robert C. Green,[3,12,15] Ragan Hart,[1] Carrie Horton,[13] Jennifer J. Johnston,[14] Matthew S. Lebo,[3,12] Aleksandar Milosavljevic,[11] Jeffrey Ou,[1] Christine M. Pak,[4] Ronak Y. Patel,[11] Sumit Punj,[4] Carolyn Sue Richards,[4] Joseph Salama,[1] Natasha T. Strande,[6] Yaping Yang,[11] Sharon E. Plon,[11] Leslie G. Biesecker,[14] and Heidi L. Rehm[3,12,15,*]

Amendola, et al. 2016. PMID 27392081

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

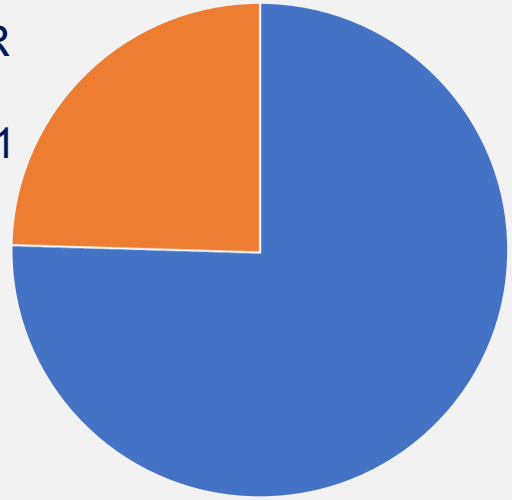
Sue Richards, PhD[1], Nazneen Aziz, PhD[2,16], Sherri Bale, PhD[3], David Bick, MD[4], Soma Das, PhD[5], Julie Gastier-Foster, PhD[6,7,8], Wayne W. Grody, MD, PhD[9,10,11], Madhuri Hegde, PhD[12], Elaine Lyon, PhD[13], Elaine Spector, PhD[14], Karl Voelkerding, MD[13] and Heidi L. Rehm, PhD[15]; on behalf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

Richards, et al. 2015. PMID 25741868

NIH NHGRI

Participant and institutional level diversity

Participants/probands recruited in CSER Phase 2



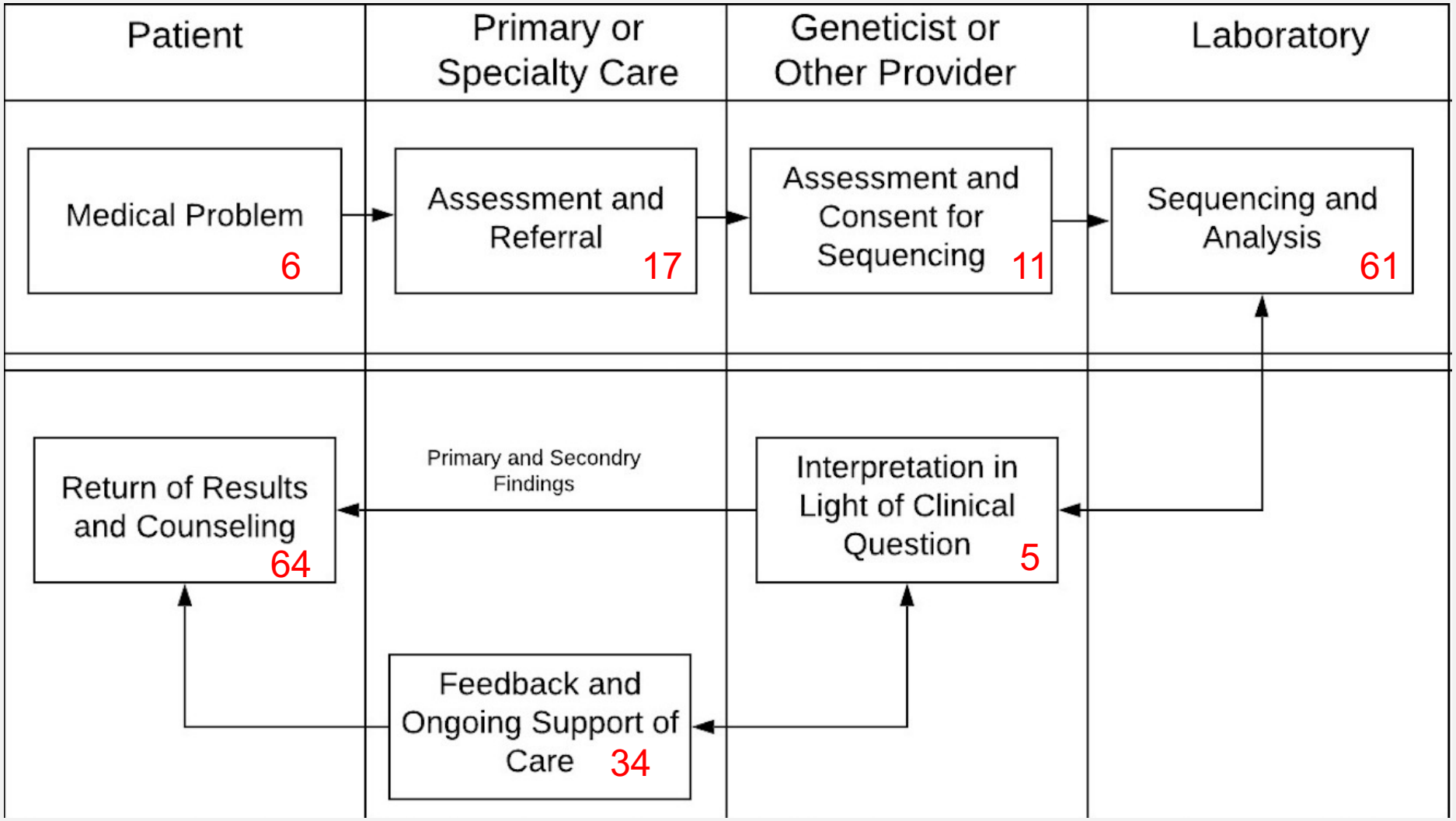
Diversity defined according to race/ethnicity, medically underserved, or at risk for poorer health outcomes

Institutions represented

- Academic medical centers
- Clinical genome centers
- Community hospitals
- Federally qualified health center
- Managed care organizations / healthcare systems

NIH NHGRI

Focus of CSER Phase 2 papers



Bly, Korf, Hindorff, et al. *In progress*

Number of papers for each box shown in red

Consortium best practices

- Resilience during COVID: Kraft SA, et al. - https://pubmed.ncbi.nlm.nih.gov/36341765/

ORIGINAL ARTICLE

American Journal of medical genetics Part A WILEY

Conducting clinical genomics research during the COVID-19 pandemic: Lessons learned from the CSER consortium experience

Stephanie A. Kraft[1,2] | Heidi Russell[3] | Jeannette T. Bensen[4] | Katherine E. Bonini[5] | Jill O. Robinson[6] | Nuriye Sahin-Hodoglugil[7] | Kathleen Renna[8,9] | Lucia A. Hindorff[8] | Dave Kaufman[9] | Carol R. Horowitz[10] | Margaret Waltz[11] | Jamilyn M. Zepp[12] | Sara J. Knight[13]

- Starting multi-institutional genetics research in diverse populations: Russell HV, et al. https://pubmed.ncbi.nlm.nih.gov/36567057

Contemporary Clinical Trials 125 (2023) 107063

Contents lists available at ScienceDirect

Contemporary Clinical Trials

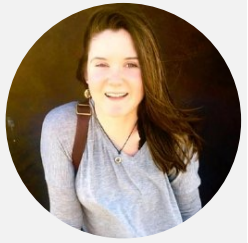
journal homepage: www.elsevier.com/locate/conclintrial

ELSEVIER

Lessons learned while starting multi-institutional genetics research in diverse populations: A report from the Clinical Sequencing Evidence-Generating Research (CSER) consortium

Heidi Russell[a,*], Hadley Stevens Smith[b], Jeannette T. Bensen[c], Priyanka Murali[d], Bart S. Ferket[e], Candice Finnila[f], Lucia A. Hindorff[g], Nuriye Sahin-Hodoglugil[h]

- Data coordination in collaborative research: Muenzen, et al. https://pubmed.ncbi.nlm.nih.gov/35707062/



HGG Advances

ARTICLE

Lessons learned and recommendations for data coordination in collaborative research: The CSER consortium experience

Kathleen D. Muenzen,[1,*] Laura M. Amendola,[2] Tia L. Kauffman,[3] Kathleen F. Mittendorf,[3] Jeannette T. Bensen,[4] Flavia Chen,[5] Richard Green,[1] Bradford C. Powell,[6] Mark Kvale,[5] Frank Angelo,[2] Laura Farnan,[7] Stephanie M. Fullerton,[8] Jill O. Robinson,[9] Tianran Li,[1] Priyanka Murali,[2] James M.J. Lawlor,[10] Jeffrey Ou,[2] Lucia A. Hindorff,[11] Gail P. Jarvik,[2] and David R. Crosslin[12,*]

NIH NHGRI

Expanded Role of Genetic Counselors in Consortia

- CSER Working Group Chairs: Laura Amendola, Carrie Blout, Kate Bonini, Lauren Desrosiers, Kelly East, Denise Lautenbach, Billie Lianglou, Julianne O'Daniel, Sarah Scollon, Sabrina Suckiel, Julia Wynn
- 49 publications with genetic counselors as first or last authors (13% of all "U" grant papers)

Design of CSER policies and practices to promote junior trainees/investigators

- WG Chairs: Sarah Ackerman, Laura Amendola, Kevin Bowling, Laura Conlin, Kurt Christensen, Matt Deardorff, Lauren Desrosiers, Kelly East, Bart Ferket, Stacy Gray, Amanda Gutierrez, Julie Harris-Wai, Ragan Hart, Adam Hott, Sarah Kalla, Stephanie Kraft, Denise Lautenbach, Billie Lianglou, Kathleen Muenzen, Julianne O'Daniel, Simon Outram, Bradford Powell, Christine Rini, Dan Robinson, Jill Robinson, Sarah Scollon, Brian Shirts, Hadley Stevens Smith, Sabrina Suckiel, Eli Van Allen, Jessica Van Ziffle, Jason Vassy, Nic Wagle, Joon-Ho Yu
- Leadership of key consortium papers (shown throughout)
- 149 publications with junior investigators as first or last authors (38% of "U" grant papers)
- Designated presentations at CSER consortium and national meetings

Most highly cited papers – Phase 1

- Amendola, et al. 2016. Performance of ACMG-AMP Variant-Interpretation Guidelines among Nine Laboratories in the Clinical Sequencing Exploratory Research Consortium. PMID 27181684.
- Dorschner, et al. 2013. Actionable, pathogenic incidental findings in 1,000 participants' exomes. PMID 24055113.
- Jarvik, et al. 2014. Return of genomic results to research participants: the floor, the ceiling, and the choices in between. PMID 24814192.
- Amendola, et al. 2015. Actionable exomic incidental findings in 6503 participants: challenges of variant classification. PMID 25637381.
- Mody, et al. 2015. Integrative clinical sequencing in the management of refractory or relapsed cancer in youth. PMID 26325560.

Most highly cited papers – Phase 2

- Popejoy, et al. 2020. Clinical Genetics Lacks Standard Definitions and Protocols for the Collection and Use of Diversity Measures. PMID 32504544
- Trosman, et al. 2020. Perspectives of US private payers on insurance coverage for pediatric and prenatal exome sequencing: Results of a study from the Program in Prenatal and Pediatric Genomic Sequencing (P3EGS). PMID 31501586
- Amendola, et al. 2020. Variant classification concordance using the ACMG-AMP variant interpretation guidelines across nine genomic implementation research studies. PMID 33108757
- Horowitz, et al. 2019. The genomic medicine integrative research framework: a conceptual framework for conducting genomic medicine research. PMID 31104772.
- Kraft, et al. 2018. Engaging populations underrepresented in research through novel approaches to consent. PMID 29512940.

Conclusion/summary

In moving from "exploratory" to "evidence-generating," CSER has improved the practice of genomic medicine

- In a highly interdisciplinary way, embedding multiple disciplines including ELSI
- With attention to the clinical workflow and the need for thoughtful study design
- By engaging diverse populations and clinical care settings
- In support of team science and junior investigators

Key evidence generated by CSER

- Rates of concordance/discordance in variant interpretation
- Frequency of changes to clinical management after receiving genomic results
- Readiness of patients/parents to follow up on genomic results with little evidence of harm
- Need to adapt genomic medicine research to integrate diverse populations and diverse care settings

Acknowledgments

CSER Phase 1 PIs and Project Teams

CSER Phase 2 PIs and Project Teams

- CSER Advisory Panel
  - Phase 1 Chair: Katrina Armstrong
  - Phase 2 Chair: Jeff Botkin
  - CAP members
- CSER CC Program Managers
  - Sara Carlson
  - Lesli Kiedrowski
  - Joseph Salama
  - Jeffrey Ou
- NIH Program Staff
  - Zo Bly
  - Charlisse Caga-Anan
  - Lucia Hindorff
  - Carolyn Hutter
  - Regina James
  - Dave Kaufman
  - Ebony Madden
  - Jean McEwen
  - Brad Ozenberger
  - Sheri Schully
  - NHGRI Program Analysts


The Forefront
of Genomics®