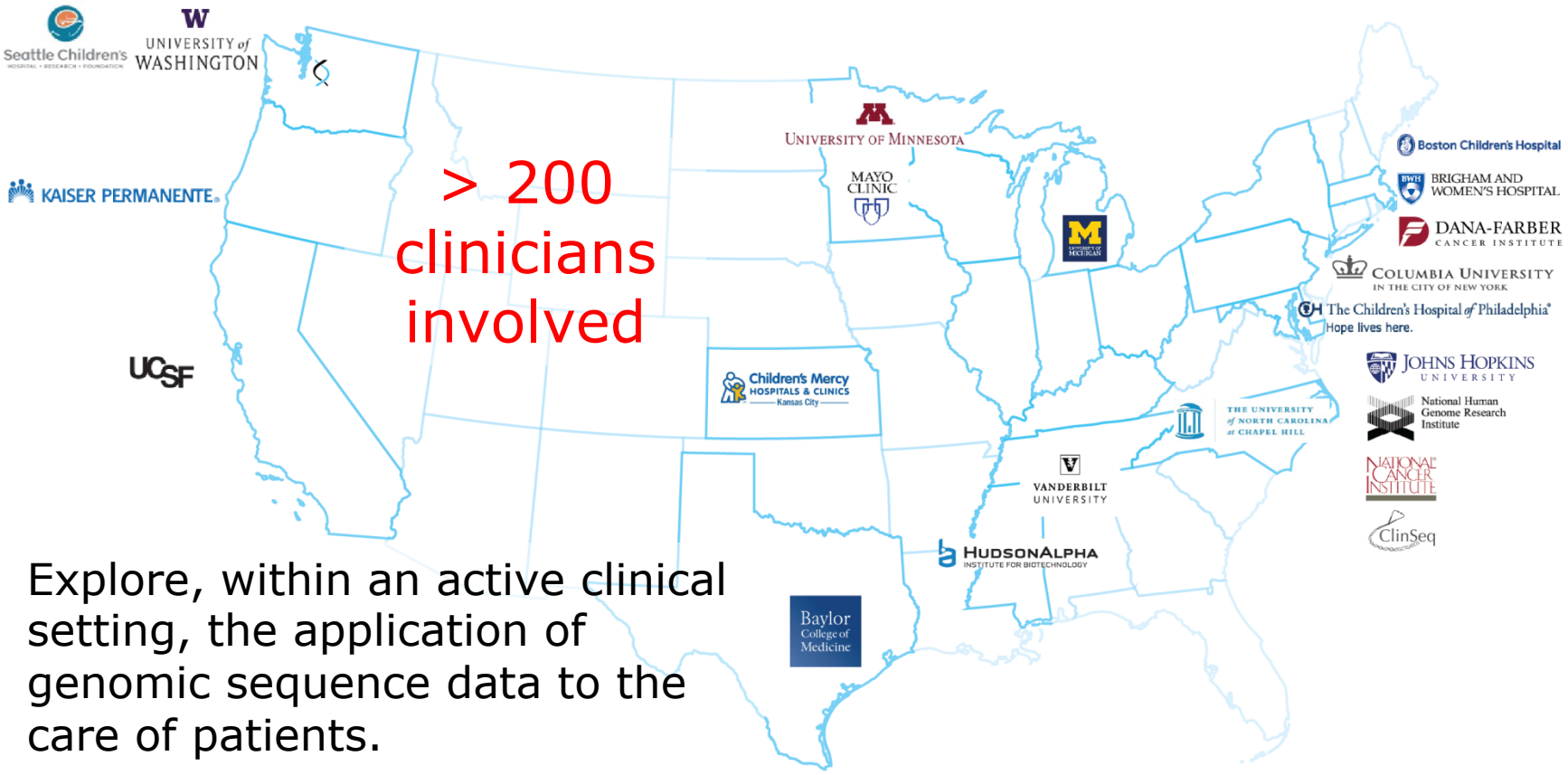
CSER Consortium
Top 5 Consortium-wide Projects

377 Researchers
21 Institutions
1 Consortium



Explore, within an active clinical setting, the application of genomic sequence data to the care of patients.

Manuscripts published: >288

Coordinating Center

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Twitter *@hail_CSER* **Website**: *https://cser-consortium.org/*

LinkedIn via *www.tiny.cc/CSER_on_LinkedIn*

Joint CSER-eMERGE2 papers

CSER and eMERGE: current and potential state of the display of genetic information in the electronic health record

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ABSTRACT

Objective Clinicians' ability to use and interpret
(EHRs). There is a critical need to develop systems
Materials and Methods The National Institutes
Records & Genomics EHR Working Groups condu
to determine how genetic and genomic informatio
information, and prioritize areas for EHR improvem
Results There is substantial heterogeneity in how
genetic information was displayed in multiple loc
multiple laboratory sources and through clinician r
of genetic information in the EHR. The highest pri
decision support for medically actionable genetic i
Conclusion Heterogeneity of genetic information f
mation representation are major barriers to using
receive and consistently display genetic and/or g
recommended.

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]

As more research studies incorporate next-generation sequencing (including whole-genome or whole-exome sequencing), investigators and institutional review boards face difficult questions regarding which genomic results to return to research participants and how. An American College of Medical Genetics and Genomics 2013 policy paper suggesting that pathogenic mutations in 56 specified genes should be returned in the clinical setting has raised the question of whether comparable recommendations should be considered in research settings. The Clinical Sequencing Exploratory Research (CSER) Consortium and the Electronic Medical Records and Genomics (eMERGE) Network are multisite research programs that aim to develop practical strategies for addressing questions concerning the return of results in genomic research. CSER and eMERGE committees have identified areas of consensus regarding the return of genomic results to research participants. In most circumstances, if results meet an actionability threshold for return and the research participant has consented to return, genomic results, along with referral for appropriate clinical follow-up, should be offered to participants. However, participants have a right to decline the receipt of genomic results, even when doing so might be viewed as a threat to the participants' health. Research investigators should be prepared to return research results and incidental findings discovered in the course of their research and meeting an actionability threshold, but they have no ethical obligation to actively search for such results. These positions are consistent with the recognition that clinical research is distinct from medical care in both its aims and its guiding moral principles.

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Exploratory Research

1. Expected Rate of Actionable Exomic Additional Findings

Act-ROR WG

Participants with classification	European ancestry* N=4300	African ancestry N=2203
Pathogenic variants (known)	30 (0.7%)	6 (0.3%)
Likely pathogenic variants (known)	52 (1.2%)	13 (0.6%)
Novel expected disruptive	6 (0.1%)	6 (0.3%)
Total pts with IFs	36 (2.0%)	12 (1.2%)

626 variant classifications deposited to ClinVar

**Caveats:* *No CNV included, HIGHER in Ashkenazi*

Dorschner et al, *AJHG*, 2013 PMID: 25637381
Amendola et al., *Genome Res, 2015. PMID: 25637381*

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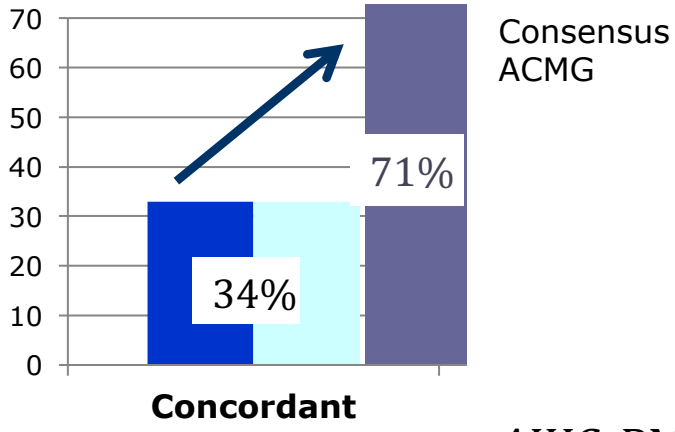
2. CSER tests and clarifies ACMG/AMP guidelines for variant pathogenicity classification: Act-ROR WG "Variant bake-off"



AJHG, PMID: 27181684

Before consensus work the ACMG/AMP guidelines did not increase concordance

Discussion and rule clarification increased concordance from 34% to 71%.

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,*]

Evaluating the pathogenicity of a variant is challenging given the plethora of types of genetic evidence that laboratories consider. Deciding how to weigh each type of evidence is difficult, and standards have been needed. In 2015, the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) published guidelines for the assessment of variants in genes associated with Mendelian diseases. Nine molecular diagnostic laboratories involved in the Clinical Sequencing Exploratory Research (CSER) consortium piloted these guidelines on 99 variants spanning all categories (pathogenic, likely pathogenic, uncertain significance, likely benign, and benign). Nine variants were distributed to all laboratories, and the remaining 90 were evaluated by three laboratories. The laboratories classified each variant by using both the laboratory's own method and the ACMG-AMP criteria. The agreement between the two methods used within laboratories was high (K-alpha = 0.91) with 79% concordance. However, there was only 34% concordance for either classification system across laboratories. After consensus discussions and detailed review of the ACMG-

Related publications:
-Pathogenicity calculator, Patel R et al, *Genome Med* 2017; PMID: 28081714
-Quantitative cosegregation criteria, Jarvik/Browning *AJHG* 2016; PMID: 27236918
-Processes in 21 labs looking for best practices, O'Daniel et al, *GIM 2016;* PMID: 27811861

A survey of current practices for genomic sequencing test interpretation and reporting processes in US labs.

Act-ROR WG O'Daniel et al, *GIM 2016,* PMID: 27811861

Processes in 21 labs looking for best practices.

Recommendations:

1. **Transparency and clarity regarding test methods and limitations**.
   - List of genes targeted for analysis and the phenotype elements used to select them;
   - Stated threshold for minimum coverage and notation when coverage of a targeted gene falls below that threshold; and/or
   - Known pathogenic variation relevant to the indication but not detectable by the test.
2. **Utilization of clinical domain expertise in case review**. …consider implementing group case review with inclusion of varied expertise including clinical domain expertise.
3. **Confirmation of reported variants**.
4. **Data access guidelines**. (patient's right of access)
5. **Data reanalysis**.

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3. Experiences with Obtaining Informed Consent for Genomic Sequencing

Berhardt et al, *Am J Med Genet A 2015,* PMID: 26198374

- Evaluation of all 9 CSER site consent forms
- Interviews of 29 genetic counselors and research coordinators who obtaining informed consent
- Participant questions and misperceptions
- Most important content to cover

Common questions and concerns

Practical details of study
Probability of finding an answer
Possible results
Privacy/ confidentiality
Effect on other family members

Anticipated response to results
Insurance discrimination
Impact of results on management

Common misperceptions

Negative results mean a "clean bill of health"
Negative result means not genetic
Report will contain many incidental findings
Sequencing will identify the cause of a condition
Expect incidental results to explain diagnosis in absence of diagnostic findings
Results will be certain
Genome will change over time
Results will be predictive of future health

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4. Professionally Responsible Disclosure of Genomic Sequencing Results in Pediatric Practice

Pediatrics WG; McCullough *Pediatrics* 2015 PMID: 26371191

3 core concepts of pediatric ethics:

- the **best interests** of the child standard,
- **parental surrogate** decision-making,
- and **pediatric assent**.

Explain the nature of the proposed test, its scope and complexity, the categories of results, and the concept of an incidental finding.

Pediatricians should obtain the informed permission of parents and the assent of mature adolescents.

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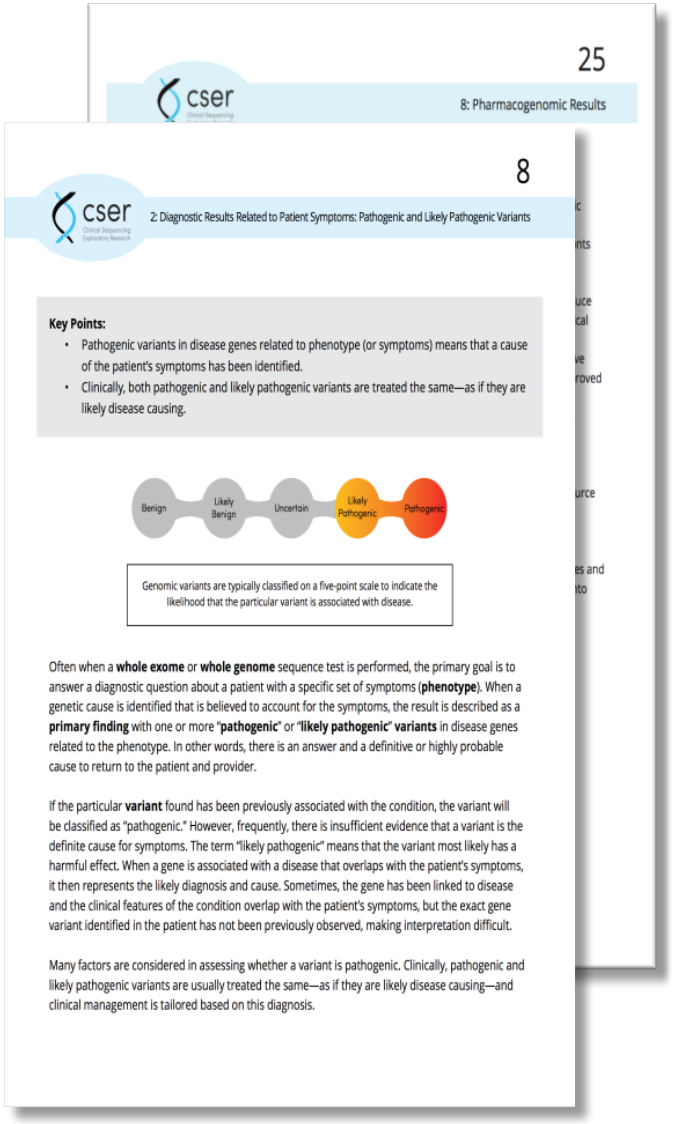
5. Genome Report Toolkit
From Practitioner Education WG



Goal: to develop a just-in-time resource for **healthcare providers** about genomic testing reports that supports understanding of how results may impact medical care and how to discuss results with patients

Key Elements:

- Short, jargon-free written sections supported by visuals
- Platform/laboratory agnostic
- Links to relevant outside resources

Implementation: Toolkit is in pilot testing with target audience. Partnering with ASHG to host resource as a navigable webpage and downloadable document on their provider education website.

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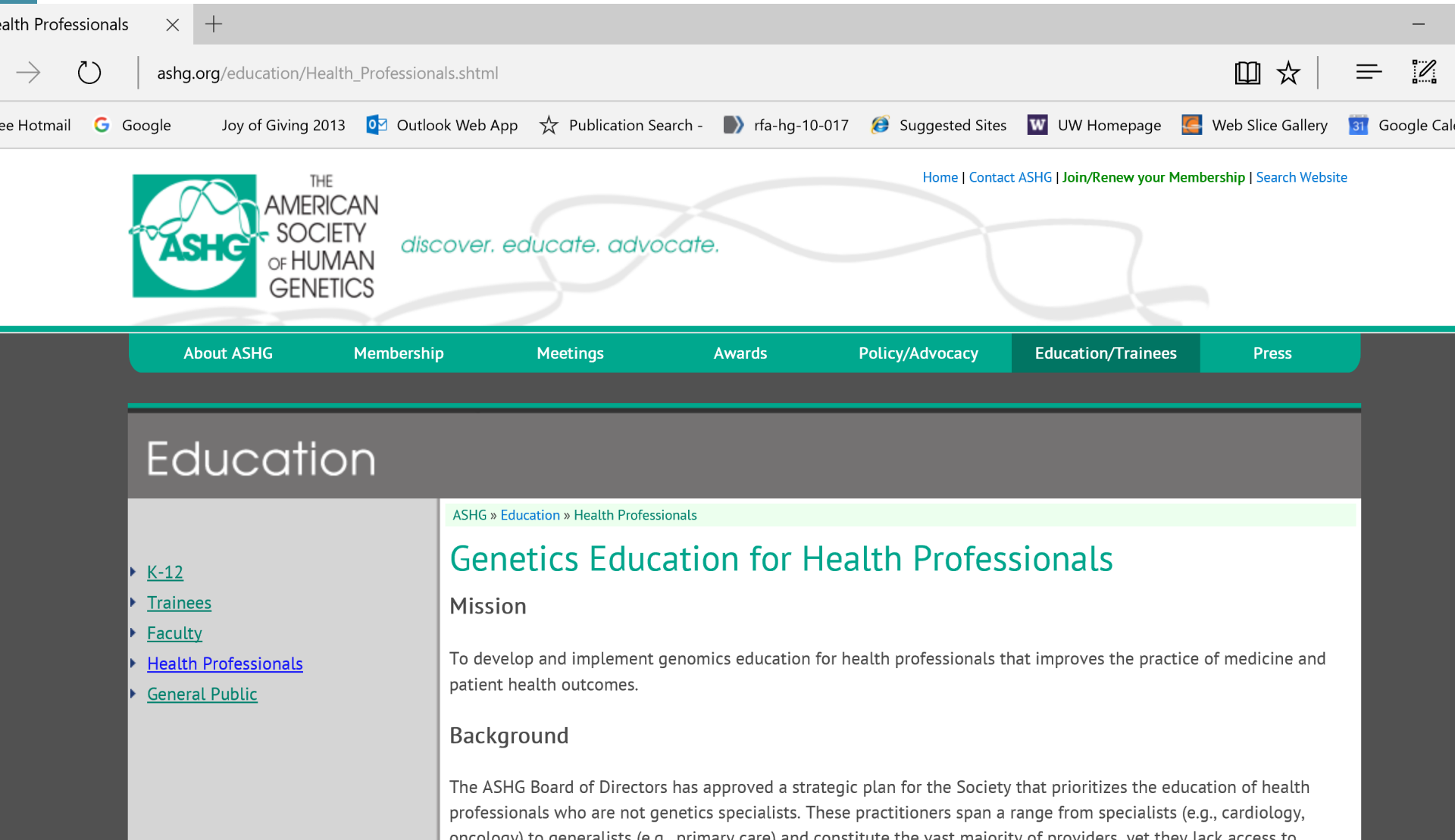
Practitioner Education Tool ASHG Screenshot

http://www.ashg.org/education/Health_Professionals.shtml



For a detailed review of CSER progress, please see the "Marker Paper"

ARTICLE

Clinical Sequencing Exploratory Research Consortium: Accelerating Evidence-Based Practice of Genomic Medicine

Robert C. Green,[1,2,3,4,*] Katrina A.B. Goddard,[5] Gail P. Jarvik,[6,7,8] Laura M. Amendola,[7,8] Paul S. Appelbaum,[9] Jonathan S. Berg,[10] Barbara A. Bernhardt,[11] Leslie G. Biesecker,[12] Sawona Biswas,[11,13] Carrie L. Blout,[1] Kevin M. Bowling,[14] Kyle B. Brothers,[15] Wylie Burke,[7,8,16] Charlisse F. Caga-anan,[17] Arul M. Chinnaiyan,[18,19,20,21] Wendy K. Chung,[22,23] Ellen W. Clayton,[24] Gregory M. Cooper,[14] Kelly East,[14] James P. Evans,[10] Stephanie M. Fullerton,[16] Levi A. Garraway,[2,25,26] Jeremy R. Garrett,[27,28] Stacy W. Gray,[3,29] Gail E. Henderson,[30] Lucia A. Hindorff,[31] Ingrid A. Holm,[3,32] Michelle Huckaby Lewis,[33] Carolyn M. Hutter,[31] Pasi A. Janne,[3,29] Steven Joffe,[34] David Kaufman,[35]

PMID: 27392080

Despite rapid technical progress and demonstra
about clinical genome and exome sequencing (
Research (CSER) consortium includes 18 extram
mural project, and a coordinating center funde
clinical validity and utility, as well as the eth
has thus far recruited 5,577 participants acr
germline and cancer sequencing. The CSER con
to participant preferences and consent, variant
outcomes, and integration with electronic heal
both germline and somatic testing, evaluate the
variants through extensive phenotyping, reduc
parities in the provision of genomics services, ex
CSER consortium has established a shared comm
opment of best practices in genomic medicine.