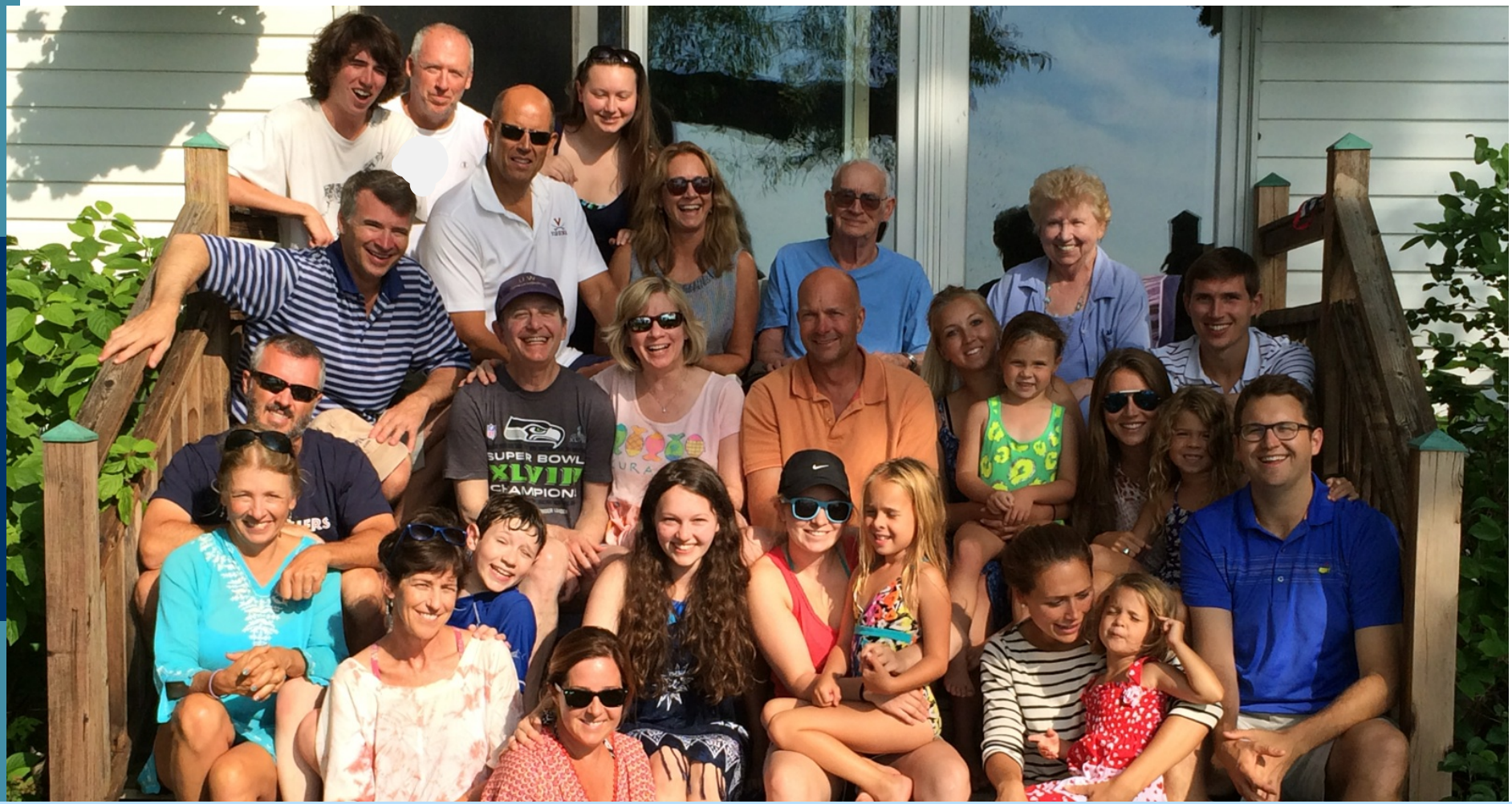
Gail P. Jarvik, M.D., Ph.D.
Arno G. Motulsky Endowed Chair
Medicine and Genome Sciences
Professor and Head, Medical Genetics
University of Washington, Seattle

Genomic Information: Advancing Patient Care

Genomic Medicine Obstacles

- Patient/consent issues
- Need for evidence base
  - When it helps
  - How best to do it
  - What do all those variants mean?
- Lack of practice guidelines / Lack of insurance coverage
- Regulatory climate
- Lack of non-geneticist provider training
- Poor reimbursement for genetic services
- Fewer academic physicians?

Patient/Consent issues



- Explain test / Incidental findings
- EHR communication
- Family communication

Expected rate of actionable variants:

6503 Exome Variant Server (EVS) Results by Ancestry Group

Participants with classification	European ancestry* N=4300	African ancestry N=2203
Disease causing variants (known)	27 (0.6%)	5 (0.2%)
Likely disease causing variants (known)	43 (1.0%)	12 (0.5%)
Disease causing variants (novel disruptive)	6 (0.1%)	8 (0.4%)
Total pts with IFs	**33 (0.7%)**	**13 (0.6%)**

**Caveats: No CNV included, HIGHER in Ashkenazi*
These data in Amendola et al, Genome Research, in press?
Also see (in packet) Dorschner et al. Actionable, Pathogenic Incidental Findings in 1,000 Participants' Exomes, AJHG 93, 631–640,2013.

cser Clinical Sequencing Exploratory Research

Cross-CSER Classification of 6 Variants

Site	MSH6 c.2731C>T; p.Arg911*	RYR1 c.1840C>T; p.Arg614Cys	FBN1 c.4270C>G; p.Pro1424Ala	TSC2 c.736A>G; p.Thr246Ala	TNNT2 c.732G>T; p.Glu244Asp	LDLR c.967G>A; p.Gly323Ser
1	Pathogenic	Likely pathogenic	VUS	VUS	VUS	VUS
2	Pathogenic	Pathogenic	Likely pathogenic/ VUS	VUS	VUS	VUS
3	Pathogenic	Pathogenic	VUS	VUS	VUS	VUS
4	Pathogenic	Pathogenic	VUS	VUS	Likely pathogenic	VUS
5	Pathogenic	Likely pathogenic	Likely pathogenic/ VUS	Likely pathogenic	VUS	VUS
6	Pathogenic	Likely pathogenic	Pathogenic/ Likely pathogenic/	Likely pathogenic	VUS	Likely pathogenic/ VUS

Amendola et al, *Genome Research, in press?*

Infrastructure Needs: Get annotations to ClinGen

- UW has multiple molecular labs
  - UW Exome Lab pipelines to ClinGen
  - UW Lab Med molecular tests: 1000's of cancer variants not submitted
  - UW Collage Diagnostic Lab: 1000 of variants not submitted
- Outside lab reports to Clinical Service
  - Completed submitting BRCA1/2
  - Hundreds more not submitted
- Insufficient resources

What if the EHR pushed annotated variants to ClinGen?

Learning Health Care System, e.g.

- UW Return of Results Committee
  - How to classify challenging variants
  - What IFs are returned (Gene-dz pairs)
  - EHR report formatting
  - EHR clinical decision support
    - Content
    - Usage
  - All variant classifications pushed to ClinVar

e.g. (in packet) Dorschner MO, Amendola LM, Shirts BH, Kiedrowski L, Salama J, Gordon AS, Fullerton SM, Tarczy-Hornoch P, Byers PH, Jarvik GP. 2014. Refining the structure and content of clinical genomic reports. Am J Med Genet Part C Semin Med Genet 166C:85–92.

cser
Clinical Sequencing Exploratory Research

Regence Insurance Policy 64
effective (7/1/14)

- "The following genetic panels are considered **investigational** because the current scientific evidence is not yet sufficient to establish how test results from panels which include a broad number of genes may be used to direct treatment decisions and improve health outcomes associated with all components of the panels."
- List of ALL panels, including cystic fibrosis 32 mutation panel

Steps to access to genomic medicine

Research → Evidence base → Practice Guidelines → Insurance Coverage

Comparative effectiveness of next generation genomic sequencing for disease diagnosis: Design of a randomized controlled trial in patients with colorectal cancer/polyposis syndromes ☆

Carlos J. Gallego [a,b], Caroline S. Bennette [b], Patrick Heagerty [c], Bryan Comstock [c], Martha Horike-Pyne [a], Fuki Hisama [a], Laura M. Amendola [a], Robin L. Bennett [a], Michael O. Dorschner [d], Peter Tarczy-Hornoch [e], William M. Grady [f], S. Malia Fullerton [g], Susan B. Trinidad [g], Dean A. Regier [h], Deborah A. Nickerson [i], Wylie Burke [g], Donald L. Patrick [j], Gail P. Jarvik [a], David L. Veenstra [b,*]

[a] *Division of Medical Genetics, University of Washington, 1705 NE Pacific Street, K253, Box 357720, Seattle, WA 98195-7720, United States*
[b] *Pharmaceutical Outcomes Research and Policy Program, University of Washington, 1959 NE Pacific Street, Health Sciences Building, Room H-375, Box 357630, Seattle, WA 98195-7630, United States*
[c] *Department of Biostatistics, University of Washington, F-600, Health Sciences Building, Box 357232, Seattle, WA 98195-7232, United States*
[d] *Department of Psychiatry and Behavioral Sciences, University of Washington, VAPSHCS GRECC S-182, 1660 S. Columbian Way, Seattle, WA 98108, United States*
[e] *Department of Biomedical Informatics and Medical Education, University of Washington, Box 358047, United States*
[f] *Clinical Research Division, Fred Hutchinson Cancer Research Center, Division of Gastroenterology, University of Washington, 1100 Fairview Ave. N., Box 19024, Mailstop D4-100, Seattle, WA 98109, United States*
[g] *Department of Bioethics and Humanities, University of Washington, 1959 NE Pacific Street, A204 Health Sciences Center, Box 357120, Seattle, WA 98195, United States*
[h] *Canadian Centre for Applied Research in Cancer Control, BC Cancer Agency, 2nd Floor, BC Cancer Research Centre, 675 West 10th Avenue, Vancouver, BC V5Z 1L3, Canada*
[i] *Department of Genome Sciences, University of Washington, 3720 15th Avenue NE, Foege Building S-250, Box 355065, Seattle, WA 98195, United States*
[j] *Department of Health Services, University of Washington, Seattle, 4333 Brooklyn Ave NE, Rm 14-101, Box 359455, Seattle, WA 98195-9455, United States*

ARTICLE INFO

Article history:
Received 26 March 2014
Received in revised form 24 June 2014

ABSTRACT

Whole exome and whole genome sequencing are applications of next generation sequencing transforming clinical care, but there is little evidence whether these tests improve patient outcomes or if they are cost effective compared to current standard of care. These gaps in

cser Clinical Sequencing Exploratory Research

Regulatory Changes: Data Sharing, FDA

SPECIAL ARTICLE | Genetics inMedicine

Regulatory changes raise troubling questions for genomic testing

Barbara J. Evans, PhD, JD[1], Michael O. Dorschner, PhD[2,3], Wylie Burke, MD, PhD[4] and Gail P. Jarvik, MD, PhD[5,6]

By 6 October 2014, many laboratories in the United States must begin honoring new individual data access rights created by recent changes to federal privacy and laboratory regulations. These access rights are more expansive than has been widely understood and pose complex challenges for genomic testing laboratories. This article analyzes regulatory texts and guidances to explore which laboratories are affected. It offers the first published analysis of which parts of the vast trove of data generated during next-generation sequencing will be accessible to patients and research subjects. Persons tested at affected laboratories seemingly will have access, upon request, to uninterpreted gene variant information contained in their stored variant call format, binary alignment/map, and FASTQ files. A defect in the regulations will subject some non-CLIA-regulated research laboratories to these new access requirements unless the Department of Health and Human Services takes swift action to avert this apparently unintended consequence. More broadly, all affected laboratories face a long list of daunting operational, business, compliance, and bioethical issues as they adapt to this change and to the Food and Drug Administration's recently announced plan to publish draft guidance outlining a new oversight framework for lab-developed tests.

Genet Med advance online publication 25 September 2014

Key Words: access rights; CLIA; FDA; HIPAA; return of results

cser Clinical Sequencing Exploratory Research

Regulatory Changes: FDA Oversight of Lab developed tests

- FDA approval of tests
  - Includes
    - Analysis pipeline
    - Which variants have clinical utility
    - Applies to research
- Response to non-genetic test failures
- Amer Asscoc for Cancer Research: "must be FDA-approved"
- Assoc for Molec Path: "Stiffle innovation and freeze tests in time"
- Gail: For genomics where is the public health cost-benefit?

Physician Education Vignette

- *CYP2C9* c.430C>T warfarin sensitivity result returned to a research participant (affects starting dose)

- Email ~1 month after return

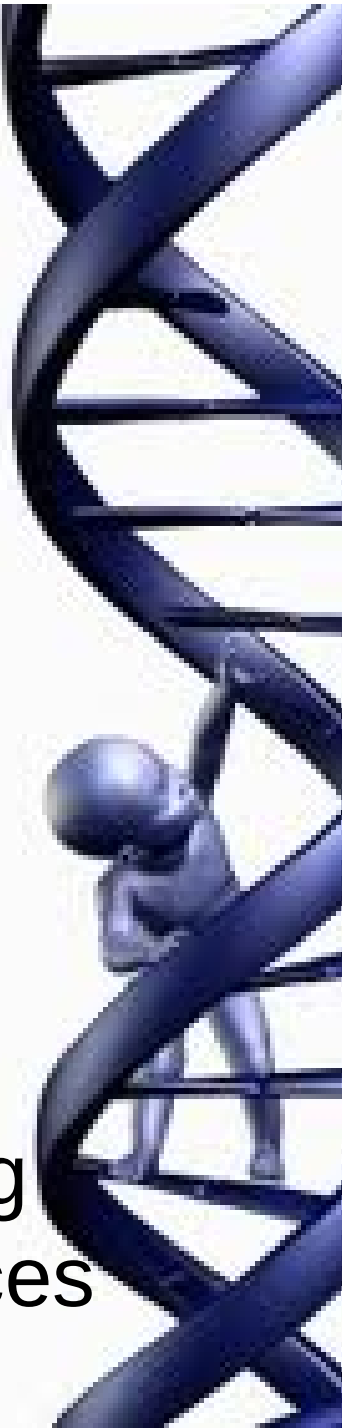
  "The NEXT study indicated I have a moderate sensitivity to Warfarin, the generic Coumadin. With that information, I switched to Rivaroxaban (Xarelto), one of the new blood thinner drugs, to mitigate that sensitivity. The NEXT study provided this useful information that I acted on…

  I feel very fortunate to have been able to have been able to be a part of the NEXT study and benefit from its results"

- Plan: interview primary care physician re experience

Genomic Medicine Obstacles

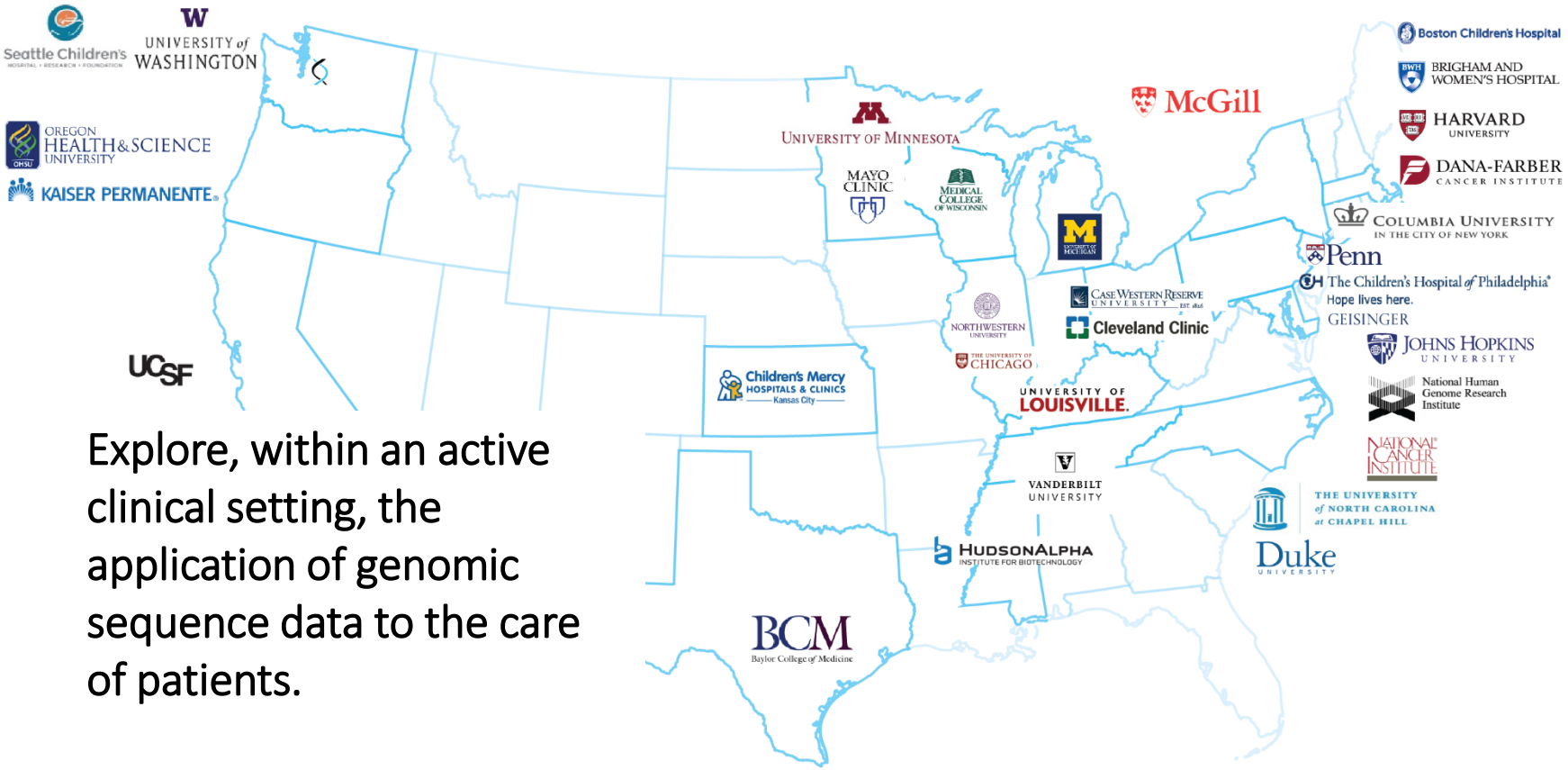
- Patient/consent issues
- Need for evidence base
  - When it helps
  - How best to do it
  - What do all those variants mean?
- Lack of practice guidelines / Lack of insurance coverage
- FDA regulations?
- Lack of non-geneticist provider training
- Poor reimbursement for genetic services
- Fewer academic physicians?



Clinical Sequencing Exploratory Research

*Moving the **Genome** Into the **Clinic***

377 Researchers
31 Institutions
1 Consortium



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

Coordinating Center

Twitter #hail_CSER

cser Clinical Sequencing Exploratory Research

www.genome.gov/CSER
www.cser-consortium.org

National Human Genome Research Institute

Thank you, UW Next Medicine Team

Gail Jarvik
Debbie Nickerson
David Veenstra
Wylie Burke
Malia Fullerton
Michael Dorschner
Donald Patrick
Peter Byers
Dean Regier
Fuki Hisama
Peter Tarczy-Hornoch
Patrick Heagerty

Laura Amendola
Martha Horike-Pyne
Sue Trinidad
Bryan Comstock
David Crosslin
Daniel Kim
Jane Ranchalis
Josh Smith
Robin Bennett
Sara Goering
Carrie Bennette
Elizabeth Hopley

Amber Burt
Jerry Kim
Sara Carlson
Emily Turner
Brian Shirts
Adam Gordon
Elisabeth Rosenthal
Kelly Jones

Brian Browning
Barbara Evans, JD
Carlos Gallego
Chris Nefcy
Clinical review committee

Bryon Paeper
Jeff Furlong
Peggy Robertson
Katie Igartua
Debbie Olson

Mari Tokita
Jimmy Bennett
Colin Pritchard
Tom Walsh
Wendy Raskind

Funded by NIH,NHGRI & NCI (U01HG006507, U01HG006375, 5T32GM007454), WA State Life Sciences Discovery Fund (265508, NWIGM); EVS data supported by NHLBI

NHGRI's Genomic Medicine Research Program

Program	Goal	Σ $M	Years
eMERGE II	Use biorepositories with EMRs and GWA data to incorporate genomics into clinical research and care	31.1	FY11-14
eMERGE-PGx	Apply PGRN's validated VIP array for discovery and clinical care in ~9,000 patients	9.0	FY12-14
cser (Clinical Sequencing Exploratory Research)	Explore infrastructure, methods, and issues for integrating genomic sequence into clinical care	66.5	FY12-16
RoR	Investigate whether/when/how to return individual research results to ppts in genomic research studies	5.7	FY11-13
ClinGen	Develop and disseminate consensus information on variants relevant for clinical care	25.0	FY13-16
IGNITE (Implementing GeNomics In practicE)	Develop and disseminate methods for incorporating patients' genomic findings into their clinical care	32.3	FY13-16
NSIGHT	Explore possible uses of genomic sequence information in the newborn period	10.0	FY13-16
UDN	Diagnose rare and new diseases by expanding NIH's Undiagnosed Diseases Program	67.9	FY13-17