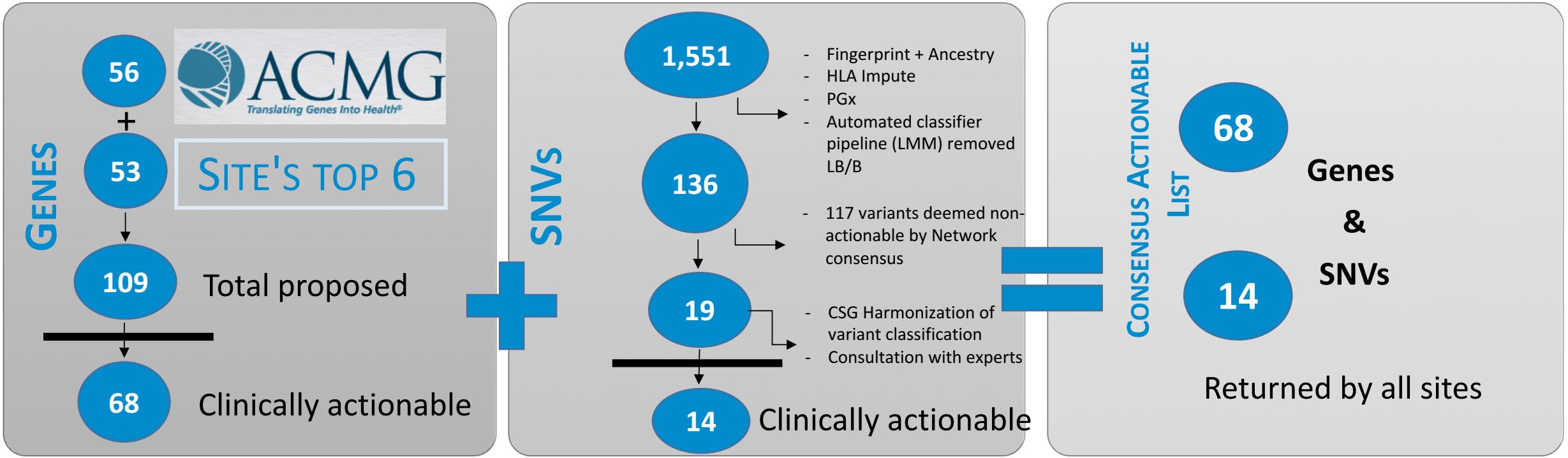
Evidence Generation for Genomic Medicine

Questions:

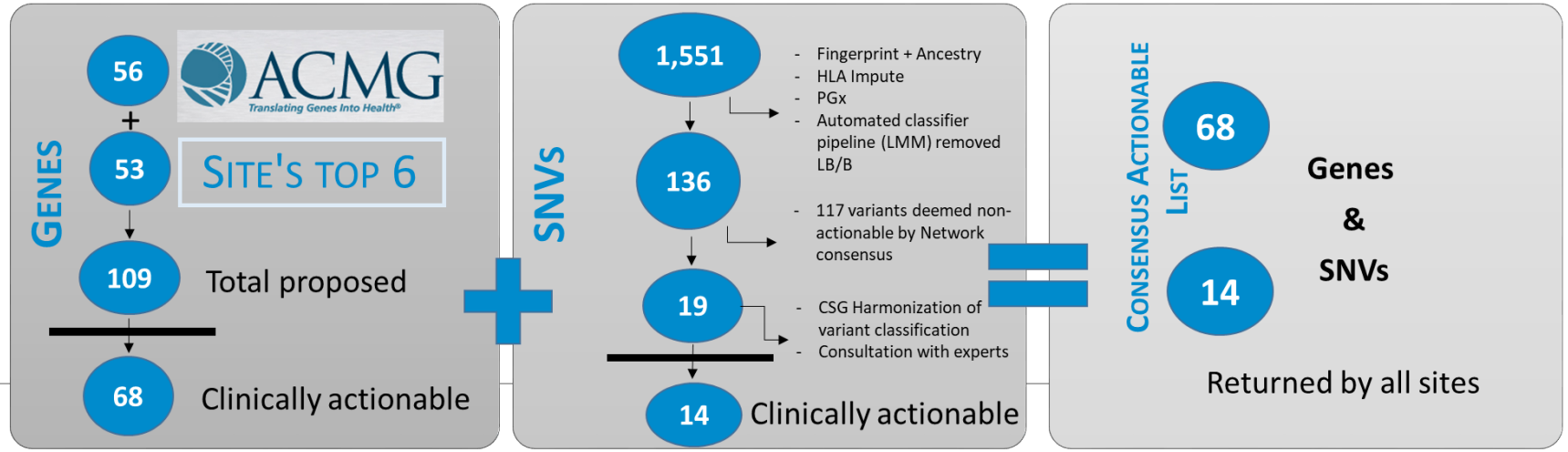
1. What methods can the eMERGE network develop and/or adopt to assess utility, validity, cost-effectiveness, quality of life, etc. of genetic/genomic testing?
2. How can eMERGE integrate other information (e.g., family history, physical and/or psycho-social environmental factors, etc.) with genetic/genomic testing results to improve our understanding of genomic medicine?

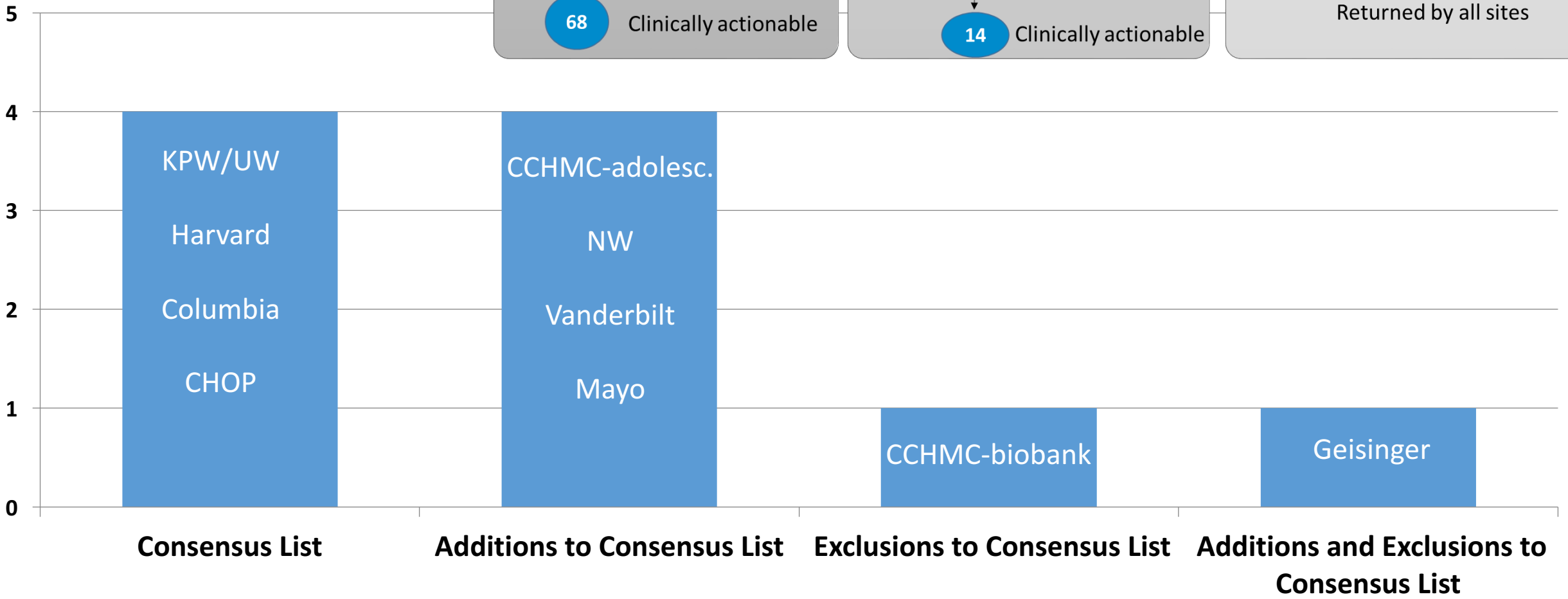
Deliverable: Development of an eMERGEseq Platform



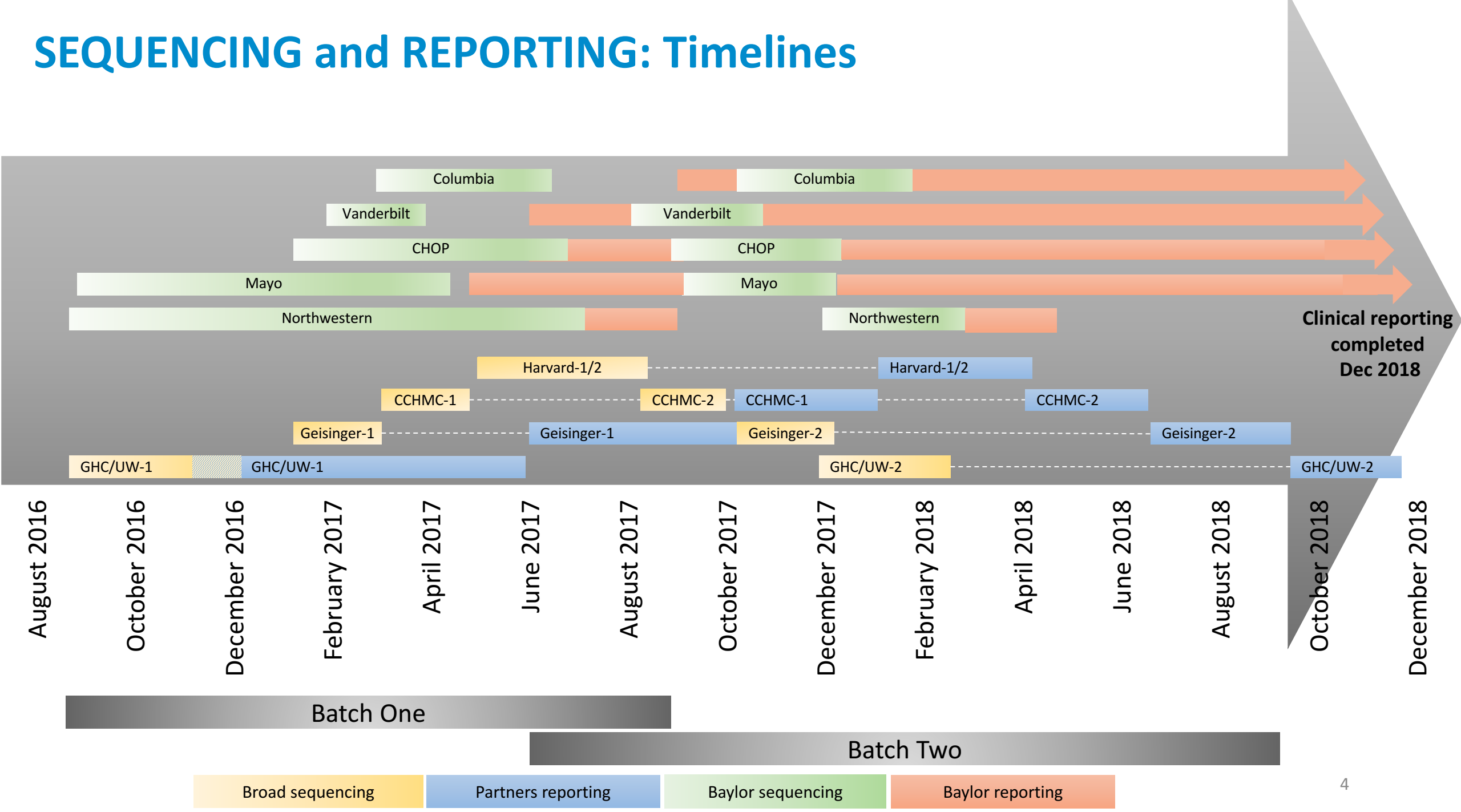
- Clinical reports are generated on the "Consensus Actionable List" and any specific genes or SNVs requested by individual sites
- *To date:* 14,077 samples sequenced and 3,716 reports issued

Network actionability and site reporting preferences





SEQUENCING and REPORTING: Timelines



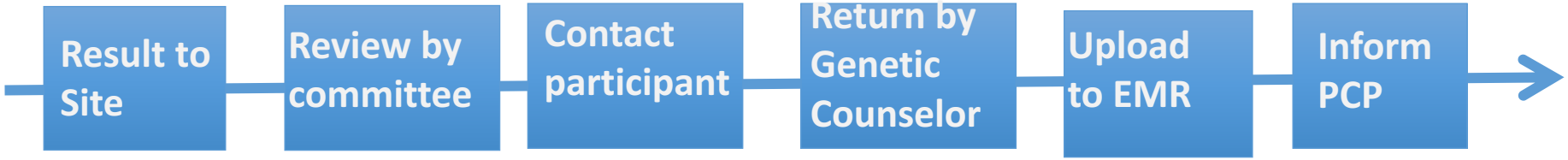
Process of Return

No two sites are the same

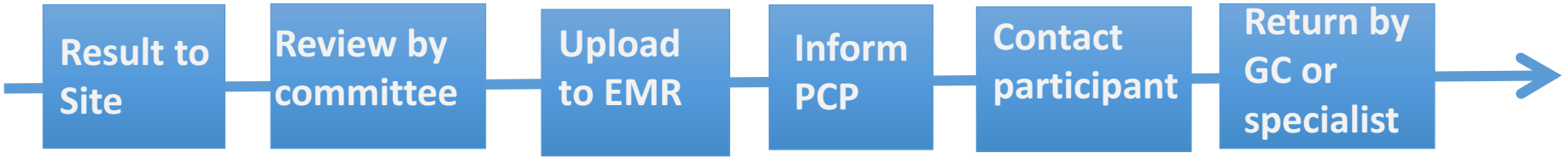
ALL (9/9) return the 68 common set of genes plus institutional genes/SNVs

MOST (7/9) follow this protocol

2/9 sites have returned results



Minority (2/9) follow this protocol



Rephenotyping by physical exam/lab/tests inform Pathogenicity and Penetrance: Seattle IFs (CRC primary)

Gene	Disorder	N participants
MYBPC3	hypertrophic cardiomyopathy	8 (4LP)
*HFE**	hemochromatosis	7
BRCA2	breast/ovarian cancer	4
SCN5A	Brugada, Romano-Ward, dilated cardiomyopathy	3 (3LP)
MYH7	cardiomyopathy	2 (2LP)
RYR1	malignant hyperthermia	2 (2LP)
*PALB2**	breast cancer	2
DSC2	Arrhythmogenic right ventricular cardiomyopathy	1 (1LP)
LDLR	Familial hyperlipidemia	1 (1LP)
BRCA1	breast/ovarian cancer	1 -> 0
MYL3	hypertrophic cardiomyopathy	1

*Not ACMG recommended

15 cardiomyopathy (10 LP) /1163

Either wrong or low penetrance

Clinically treated as P

Environmental measures: eMERGE Geocoding supplement

Factors	Source	Resolution	National/ Local
Demographics	Coordinating Center/Site EDW	Patient Level	National
SES	Census/ACS	Block Group Level	National
Built Environment	RUCA (rural-urban-commuting-area-codes	Tract Level	National
Traffic Volume	Google?		
Road Density	ArcGIS shapefiles	Block Group Level	National
Food Accessibility	Food Environment Atlas (USDA Economic Research Service)	County Level	National
Water Quality	NURE-HSSR database; Enviromapper?	Various	
Density of Parks	ArcGIS shapefiles	Block Group Level	National
Walkability	Walk Score Professional	Zip Code	National
Entropy Index	Census/ACS	Block Group Level	National
Crime			Local
Hospital Utilization	AHRF, HHS, HRSA	County Level	National

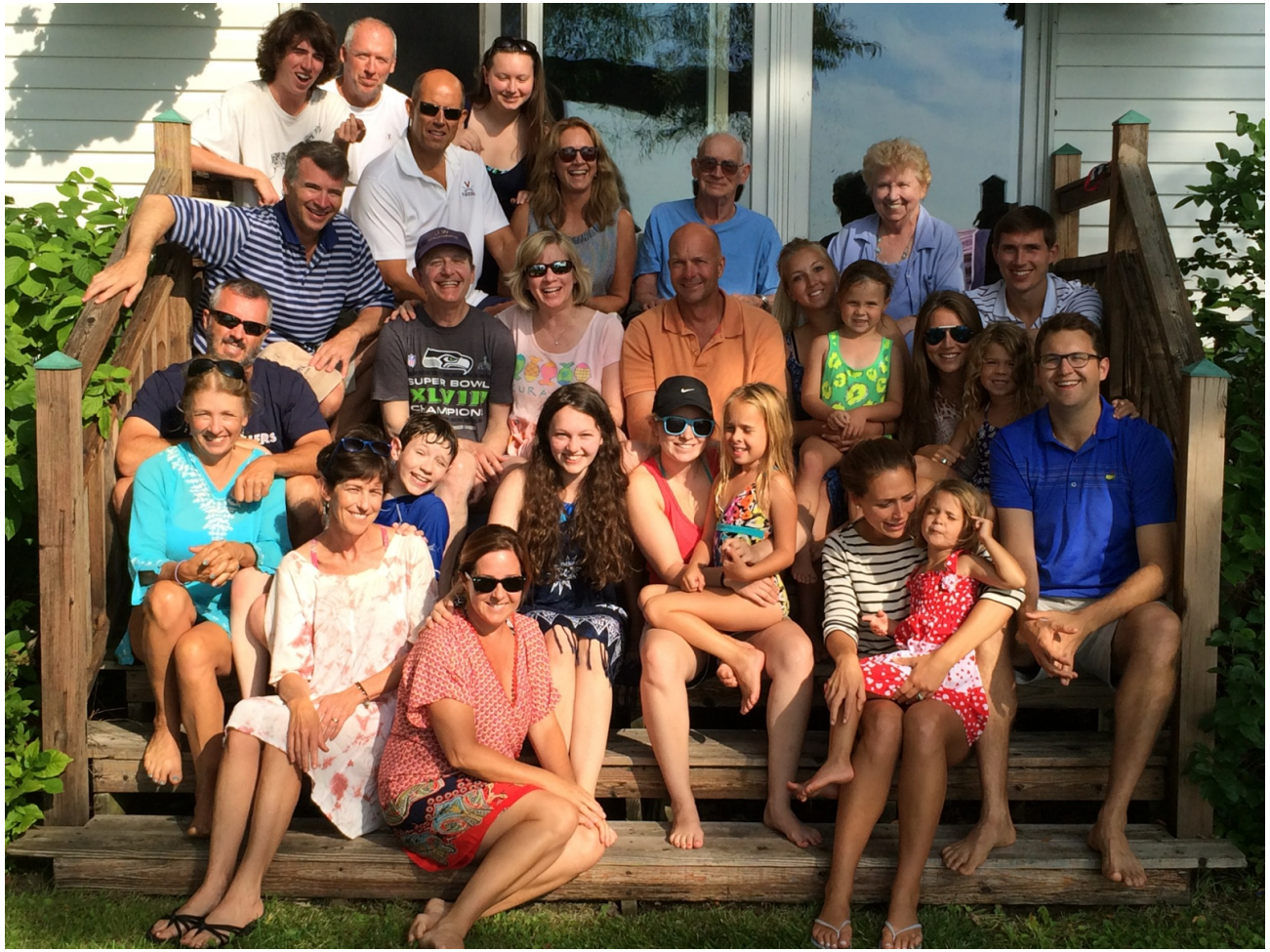
Slide courtesy of eMERGE CC

Family history data

- Very useful for stratifying analyses, identifying pathogenic variants, etc.
- Not captured well or systematically in most medical records
- Some sites may have clinical patient survey data on family history
- A standardized format would be useful

Family cascade testing and communication

- Used in pathogenicity assessment; important tool for estimating variant penetrance
- A major driver of cost effectiveness of genetic testing is follow-up testing of relatives
  - How do we spread the word?
- Need results early to be successful



Challenges and Opportunities

Challenge	Opportunities
Know variant pathogenicity and penetrance (even for ACMG genes!)	• Standardize what is returned (as possible) • Rephenotyping by EHR AND new PE • Family cascade testing for cosegregation • Pool data across sites • Reanalysis of sequence for path changes • Methods to share variant reclassifications
Add family history to analyses	• Standardize tool across sites
Add demographic data to analyses	• Geocoding
Cost-effect when family gets information/tested	• Family communication tools (Psycho-social data) • Cascade testing • More efficient return of results/counseling • Share negative reports
Data too late for much follow-up	• Generate sequence earlier: front load sequencing budget, use existing platform (medical exome, exome, genome)

eMERGE OUTCOMES WORKGROUP

Co-Chairs: Hakon Hakonarson (CHOP)
Josh Peterson (Vanderbilt)
Marc Williams (Geisinger)

eMERGE OUTCOMES WORKGROUP: Charter

Mission statement: The Outcomes workgroup will develop cross-site outcomes to track implementation and impact of eMERGE III sequencing. The workgroup will focus on answering the overarching question of whether returned eMERGE III-generated genomic results impact health care utilization and outcomes of importance to patients and families.

Outcome Types

(example pathogenic variant in *MLH1* associated with Lynch syndrome)

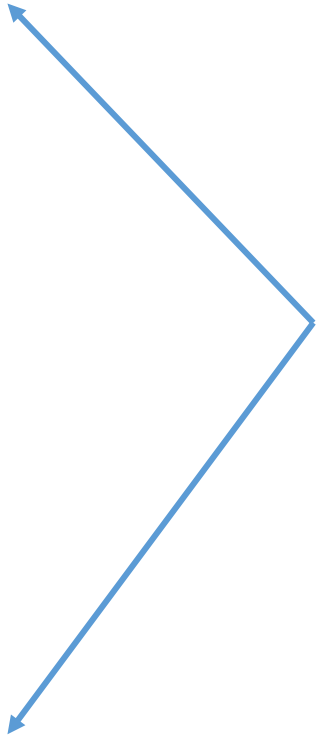
- ***Process Outcomes***
  - potential changes in health care utilization related to returning genetic information
    - Example: Colonoscopy ordered
- ***Intermediate or Surrogate Outcomes***
  - a biomarker indicating benefit or harm is more likely
    - Example: Positive FOBT
  - adherence to a recommendation
    - Example: Colonoscopy performed
- ***Clinical Outcomes***
  - the benefits or harms to a patient who receives an intervention
    - Example: Adenomatous polyp removed

Chain of evidence

- ***Evidence that a process or intermediate outcome has a direct impact on health outcomes of interest***
- ***Examples:***
  - Strong: Colonoscopy (intermediate) and colorectal cancer; LDLc <100 mg/dl (intermediate) and CAD
  - Intermediate: Prescribing beta-blocker (process) and sudden cardiac death (if adherence measured this is intermediate outcome)
  - Weak: CEA125 (intermediate) and ovarian cancer; Total body MR (intermediate) and Li-Fraumeni associated cancer mortality

eMERGE OUTCOMES WORKGROUP – Standard Data Collection Forms

Instrument name	Fields	View PDF
General Intake Form	17	
Return Of Result Information Form	29	
Aortopathy Outcomes	67	
Arrhythmia Outcomes	43	
Breast Cancer Outcomes - Women Only	27	
Cardiomyopathy Outcomes	25	
Colorectal Cancer and Polyposis Outcomes	24	
Cystic fibrosis transmembrane conductance regulator (CFTR)	38	
Ehlers Danlos Syndrome - Classical	32	
Ehlers Danlos Syndrome - Vascular	22	
Familial Hypercholesterolemia (FH)	15	
Generic Outcomes	11	
Ornithine Transcarbamylase Deficiency (OTCD) Outcomes	6	
Pediatric Familial Hypercholesterolemia (FH) Outcomes	17	
Tuberous Sclerosis Complex Outcomes	11	



Challenges

- Reliance on process and intermediate outcomes due to length of eMERGE 3
- One time point for outcomes assessment (6 months post-RoR)
- Timing of sequencing and reporting
- Attribution of outcome to RoR (rely on assertion by site)

Opportunities-Measure health outcomes

- Potential to follow some patients with RoR in eMERGE 4
  - Less straightforward that phenotype and GWAS efforts across eMERGE 1-3
- Identify conditions or genomic results where health outcomes are more likely to accrue in a four year time frame (or strong chain of evidence)
  - Pharmacogenomics for common drugs
  - Unrecognized genetic disorders (e.g. atypical Cystic Fibrosis, metabolic disorders, renal disease in dialysis patients)
  - Familial Hypercholesterolemia
- Get sequencing results faster to allow longer follow-up
- Develop and test methods to attribute outcomes to the Return of Results

Challenges

- Outcome collection approaches site-specific (in contrast to phenotypes)
- Manual processes required for cascade testing

Opportunities-Implementation and Dissemination

- Study variation in implementation and the impact on outcomes
  - R01 Dissemination and Implementation Lynch syndrome screening (Rahm-Geisinger and HCSRN)
  - If complete in eMERGE 3 can use to standardize implementation of RoR in eMERGE 4
- Study variation in implementation and the impact on outcomes
  - R01 Dissemination and Implementation Lynch syndrome screening (Rahm-Geisinger and HCSRN)
- Collaboration with pragmatic trials in IGNITE2 around certain conditions (2 approaches to evidence collection)
  - Need to use standard outcome measure
- Given public health impact of cascade testing make this a point of emphasis to develop and test methods
  - Could include legal and policy emphasis to inform novel approaches to contacting at risk relatives

Opportunities-Economic/Cost Effectiveness

- Add in economic outcomes
  - R01 (Vanderbilt, U Washington, Geisinger) developing and testing models to understand which outcomes drive cost-effectiveness and other outcomes of sequencing
  - Use this work to prioritize outcomes to collect in eMERGE 4