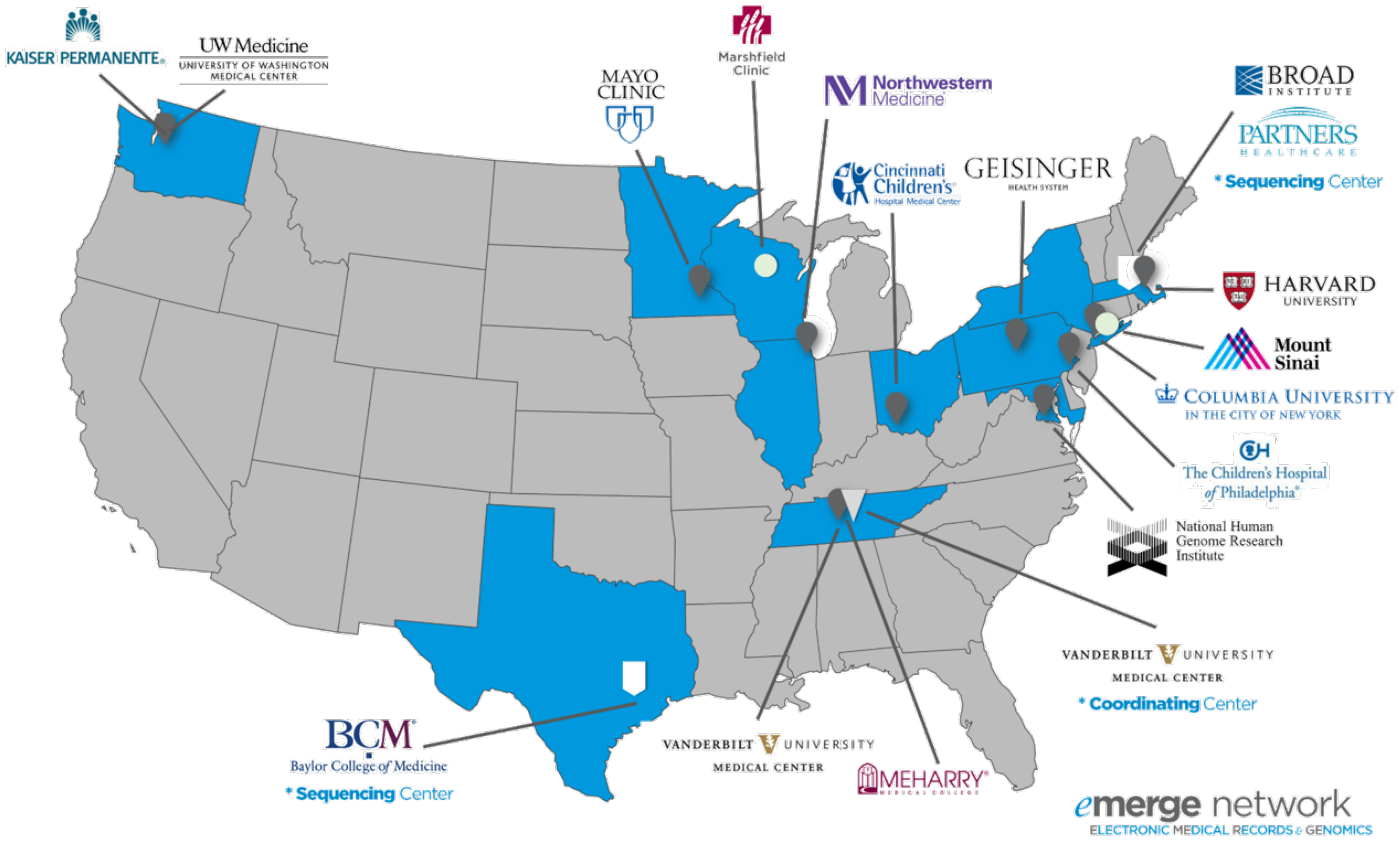
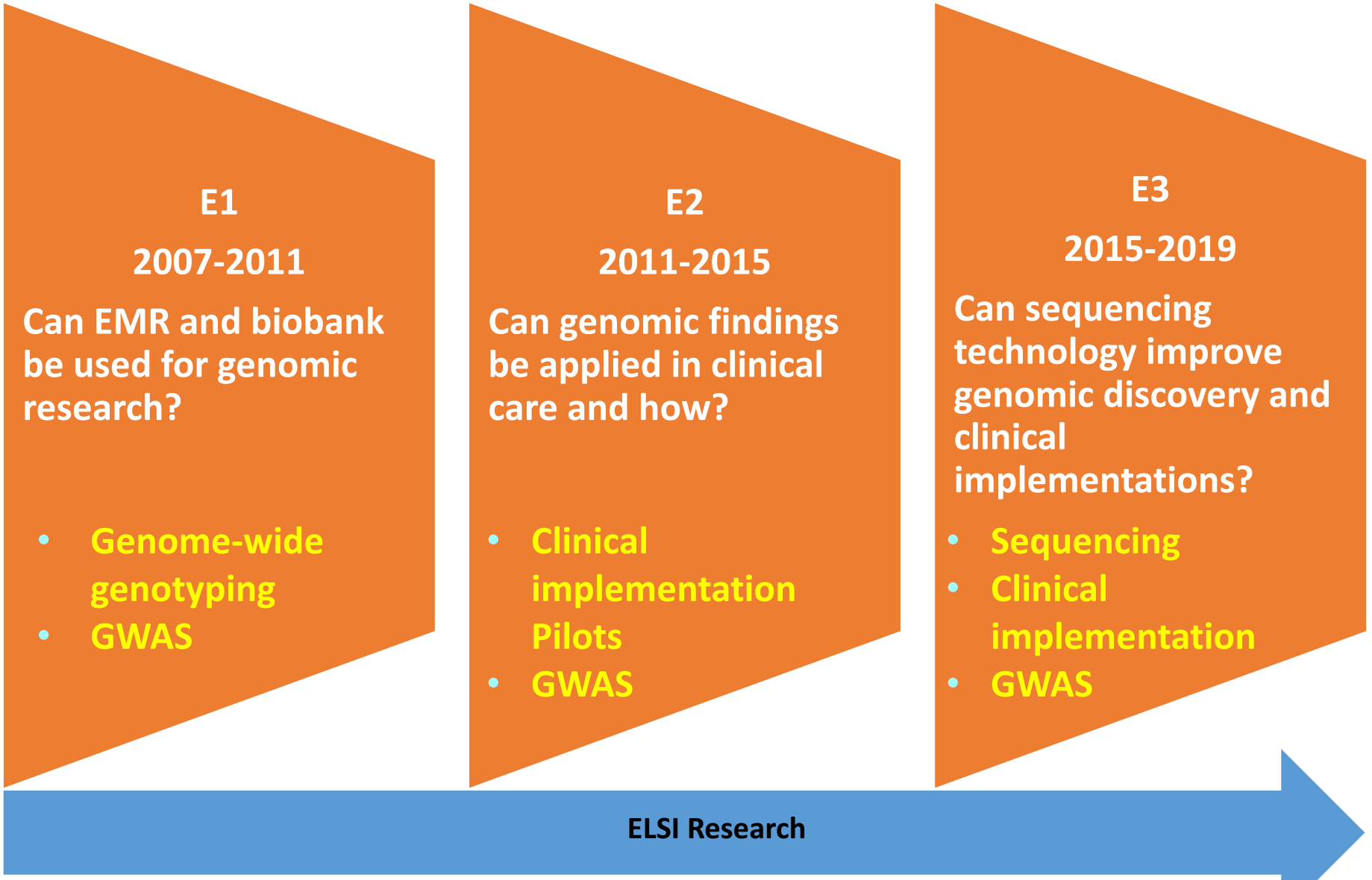
The eMERGE Network



eMERGE WORKGROUPS	
Clinical Annotation	EHR Integration
Genomics	Outcomes
PGx	Phenotyping
Return of Results/ELSI	
eMERGE SUPPLEMENTS	
Geocoding	Health Care Provider Survey
Phenotyping – OMOP Model	
eMERGE SUBGROUPS	
Familial Implications of ROR	HLA
Infobutton	ROR Legal Considerations
Participant Survey	Phenotype Variables

eMERGE PHASE III: SEPTEMBER 2015 – MAY 2019

eMERGE


E1
2007-2011
Can EMR and biobank be used for genomic research?
Genome-wide genotyping
GWAS
E2
2011-2015
Can genomic findings be applied in clinical care and how?
Clinical implementation Pilots
GWAS
E3
2015-2019
Can sequencing technology improve genomic discovery and clinical implementations?
Sequencing
Clinical implementation
GWAS
ELSI Research

*e*MERGE III: What do we do?

SPECIFIC AIMS *of the* eMERGE Network

1. Sequence and assess clinically relevant genes presumed to affect gene function in about 25,000 individuals
2. Assess the phenotypic implications of these variants
3. Integrate genetic variants into EMRs for clinical care
4. Create community resources

Impact: 110k genomic dataset

- Data on over 110,000 participants and informatics tools with which to harness the data

- eMERGE Record Counter
  - Drag and drop demographics, phenotypes, ICD codes to obtain preliminary cohort counts

- SPHINX (**S**equence and **PH**enotype **IN**tegration E**x**change)[+]
  - Search catalog by genes, drugs, rsID and pathways
  - For each gene view: SNVs, pathways, drug interactions
  - For each variant view: SNPid, category, frequencies
  - European, African, & Asian ancestry allele data

Set Name	Platform	Count
eI-eIII Merged*	GWAS	83,717
Exome chip	Exome	12,330
Whole exome	Sequencing	3,745
PGx	Sequencing	9,010
Whole genome	Sequencing	1,800
eMERGEseq	Sequencing	25,000
Total Current		**111,078**
Total Expected		**136,078**

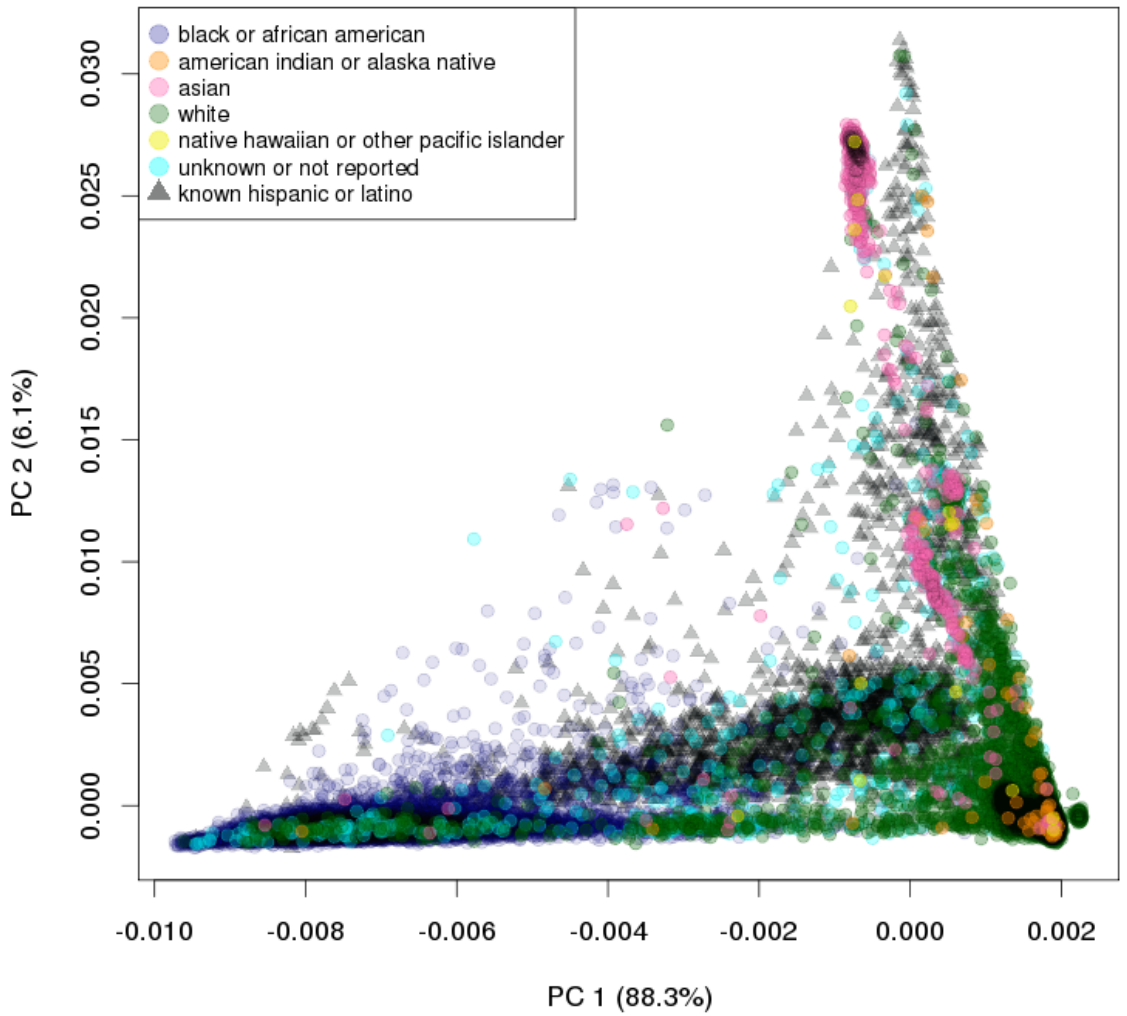
*eI-II: 55,029 samples; and eIII: 28,688 samples

[+]Rasmussen-Torvik LJ, Stallings SC, Gordon AS, Almoguera B, Basford MA, et al. *Design and Anticipated Outcomes of the eMERGE-PGx Project: A Multicenter Pilot for Preemptive Pharmacogenomics in Electronic Health Record Systems*. Clinical Pharmacology & Therapeutics. 2014 Oct; 96(4):482-9. **PMID: 24960519 PMCID: PMC4169732**

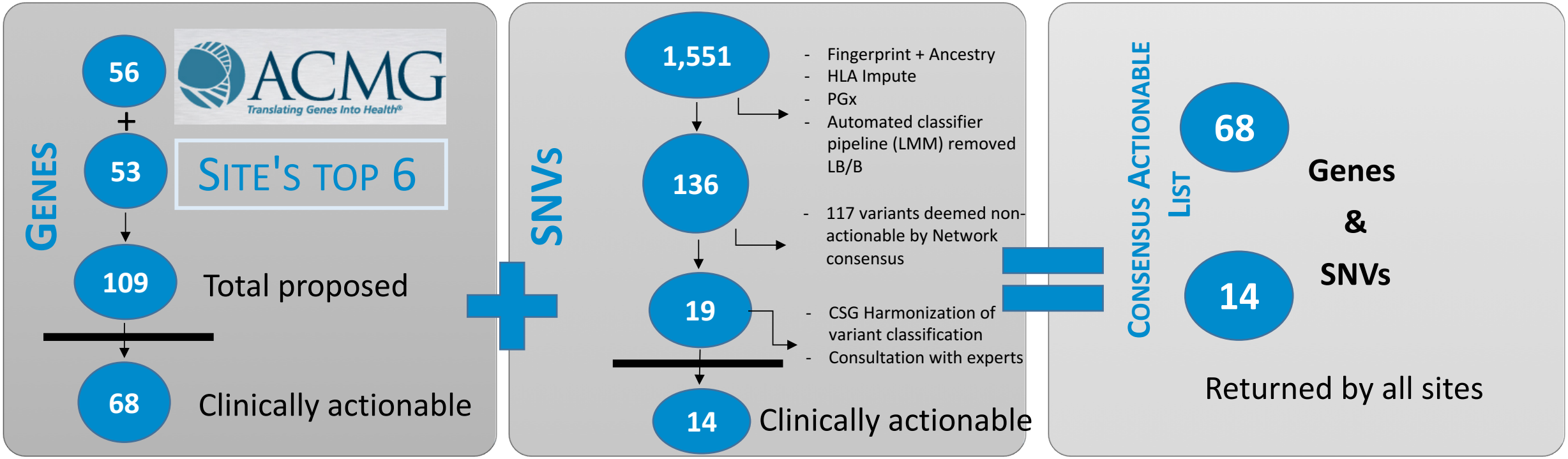
Deliverable: Imputation and merging of eI-III GWAS data

- Imputation of all eMERGE array data against the HRC reference using the Michigan Imputation Server
- HRC reference contains 39,235,157 SNPs, no indels, provides access to rare variation (low as 0.1%)
- 83,717 individuals in data set released to network
  - Principle components analysis (PCA) examined ancestry

PCA of eI-III imputation (Chr 1-22, n = 83717)



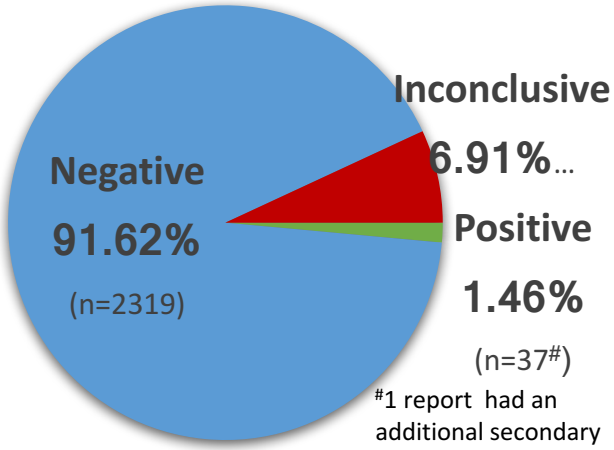
Deliverable: Development of an eMERGEseq Platform



- 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

Partners-Broad Interpretation and Reporting: Review of 5268 cases

Indication-based returnable results (n=2531)

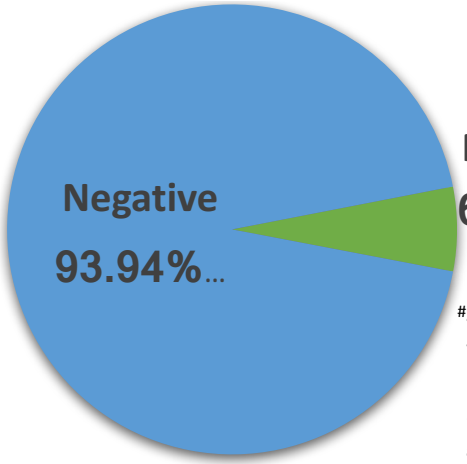


#1 report had an additional secondary finding

Indication	Total	Positive	Negative	Inconclusive
Colorectal cancer/Polyps	1165	24*	966	175
Ehlers-Danlos Syndrome	66	1	65	n/a
Abnormality of pain sensation	545	0	545	n/a
Pediatric migraine	443	0	443	n/a
Hyperlipidemia	258	12	246	n/a
Autistic Behavior	54	0	54	n/a
TOTAL	2531	13	2319	175

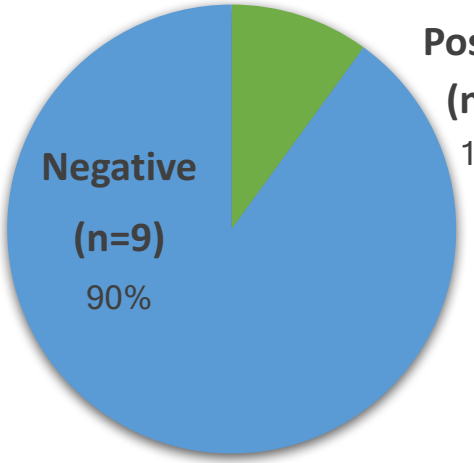
* 1 report had an additional secondary finding

Non indication-based consensus returnable results** (n=5268)



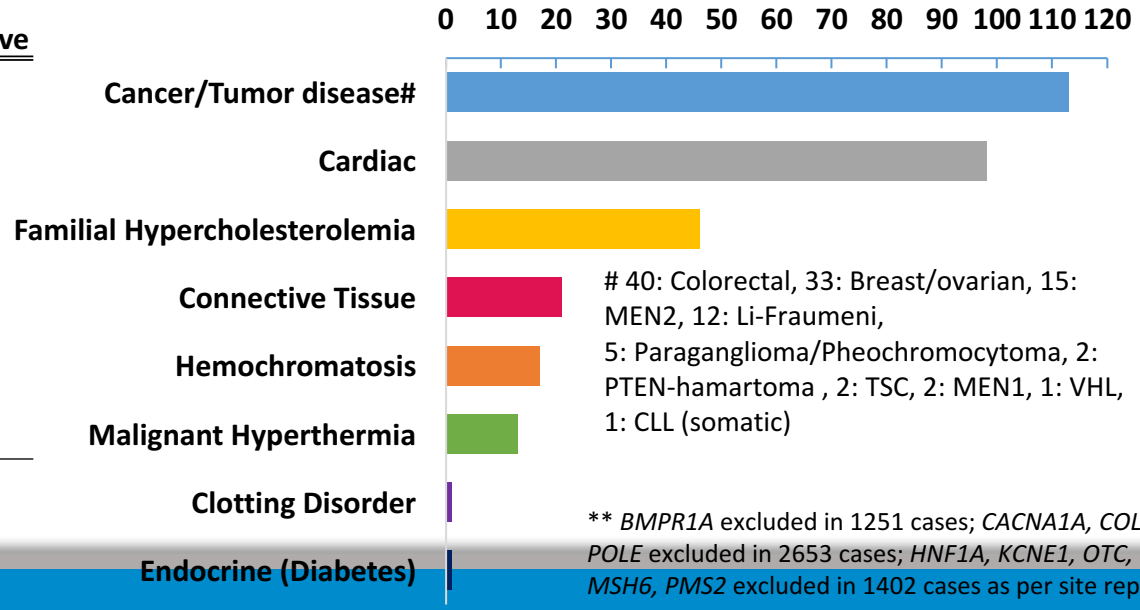
#4 reports had two pathogenic variants. Skewed positive rate due to one site with sample selection based on suspicious genotype (16% positive)

Non indication-based site-specific returnable results (n=10)



Path/Likely Path Variants in CCHMC-adolescent cohort specific genes	Total
CHEK2	1/10

Returnable findings per disease area

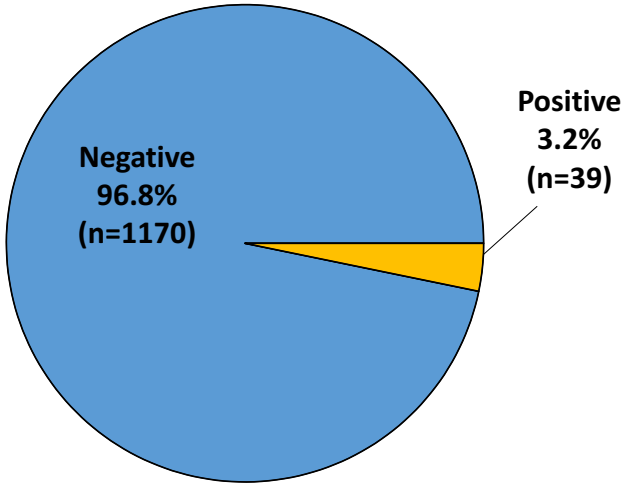


40: Colorectal, 33: Breast/ovarian, 15: MEN2, 12: Li-Fraumeni, 5: Paraganglioma/Pheochromocytoma, 2: PTEN-hamartoma , 2: TSC, 2: MEN1, 1: VHL, 1: CLL (somatic)

** *BMPR1A* excluded in 1251 cases; *CACNA1A, COL5A1, HNF1B, PALB2, POLD1, POLE* excluded in 2653 cases; *HNF1A, KCNE1, OTC, BRCA1, BRCA2, MLH1, MLH2 MSH6, PMS2* excluded in 1402 cases as per site reporting requirements

Interpretation & reporting: Baylor

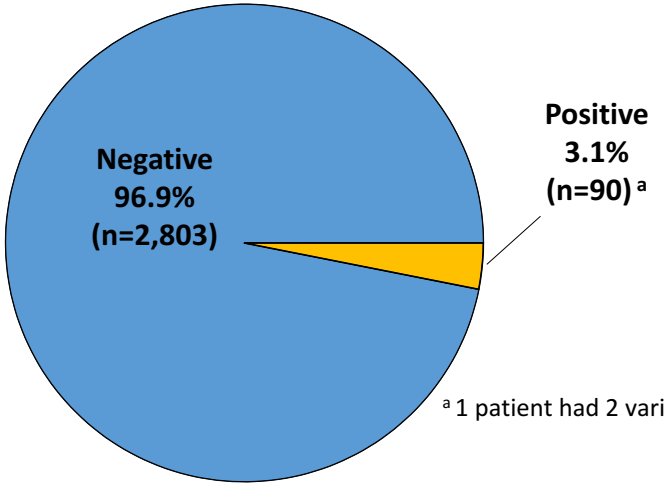
Indication based returnable results



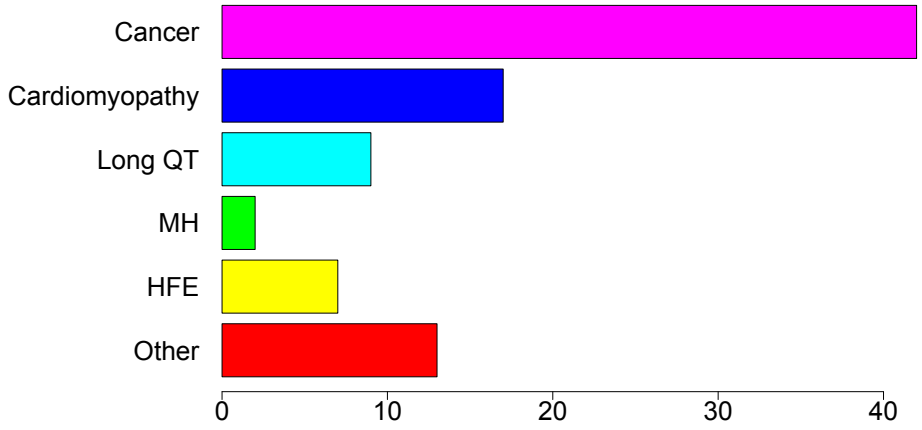
Indications	Total	Positive	Negative
Cardiomyopathy	1	1	0
Cardiac Arrythmia	31	0	31
Hyperlipidemia [a, b]	808	22	786
Colorectal Cancer	595	3	592
Breast/Ovarian Cancer[c]	72	16	56

[a] 298 patients had colorectal cancer and hyperlipidemia
[b] Hyperlipidemia includes FH, hypertriglyceridemia, hyperlipidemia and coronary artery disease indications.
[c] All returned genes belong to the 68 consensus except for CHEK2 in a breast cancer patient

Non indication based consensus returnable results

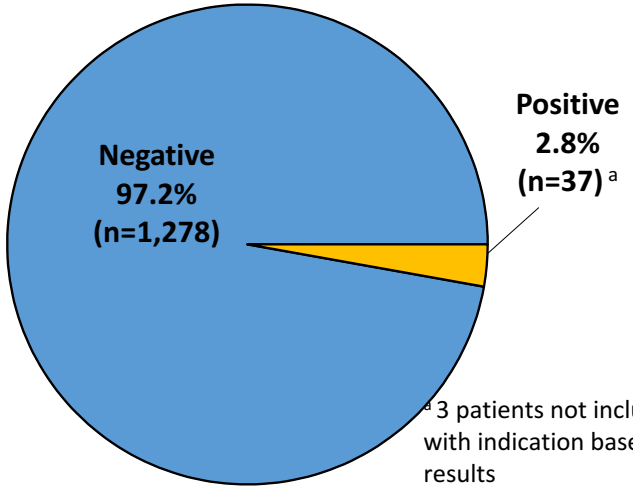


[a] 1 patient had 2 variants



Others include MEFV, HNF1A, CACNA1A, OTC,LDLR

Non indication based site-specific returnable results



[a] 3 patients not included with indication based results

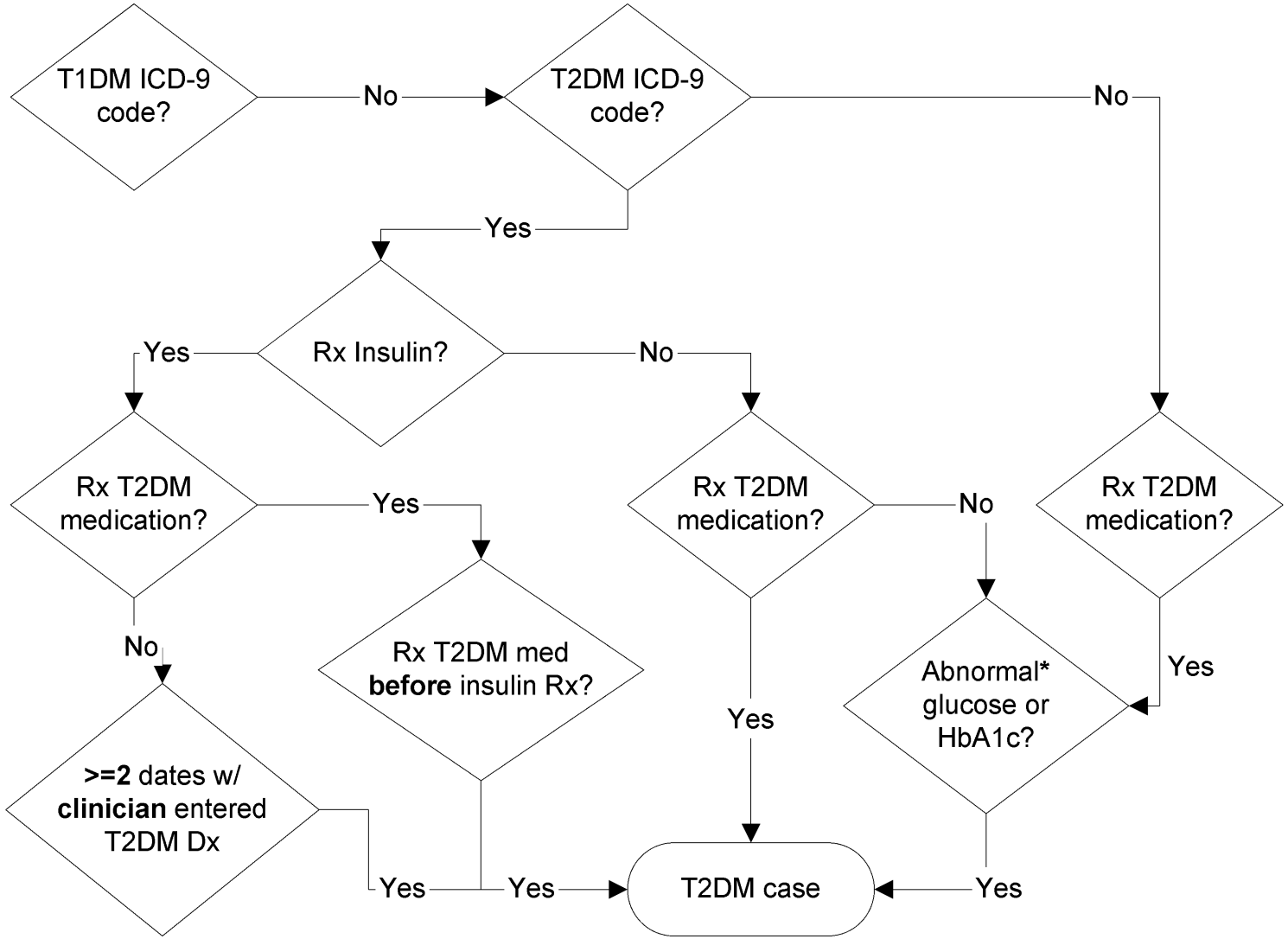
Path and Lpath variants in NU and Vanderbilt specific returned	Total
CHEK2	24
ATM	7
SERPINA1	3
MC4R	3
F11, FLG, KCNE2 (x1)	3

Impact: Electronic phenotyping & PheKB

- PheKB (**Phe**notype **K**nowledge**B**ase)
  - Collaborative environment to building and validating electronic algorithms
  - Computational algorithm library
    - 37 finalized, public phenotypes
- Demonstrated feasibility of use in Genomic Medicine
- Tools and process allowed for computational and algorithm development cross collaboration around the world

Kirby JC, Speltz P, Rasmussen LV, Basford M, Gottesman O, et al. *PheKB: a catalog and workflow for creating electronic phenotype algorithms for transportability.* J Am Med Inform Assoc. 2016 Nov;23(6):1046-1052. doi: 10.1093/jamia/ocv202. **PMID: 27026615 PMCID: PMC5070514.**

Type II Diabetes Case Algorithm



*** Abnormal lab=** Random glucose > 200mg/dl, Fasting glucose > 125 mg/dl, or hemoglobin A1c ≥6.5%.

Phenotype Development Workflow

Tool Support

Create

- Phenotype algorithm and data dictionary are in development
  - Share algorithm with project team
  - Standardize Phenotype Development
  - Standardize data collection

Tool Support: KNIME, eMERGE RecordCounter, eleMAP, PheKB

Validate

- Algorithm and Data Dictionary in review by validation site(s)
  - Share algorithm with validation team
  - Validate algorithm
  - Validate Data Dictionary

Tool Support: Dictionary/Dataset Validation, PheKB

Share

- Share and implement algorithm and data dictionary for multi-site data collection
  - Validate Dataset against Data dictionary

Tool Support: Dictionary/Dataset Validation, eMERGE RecordCounter, PheKB

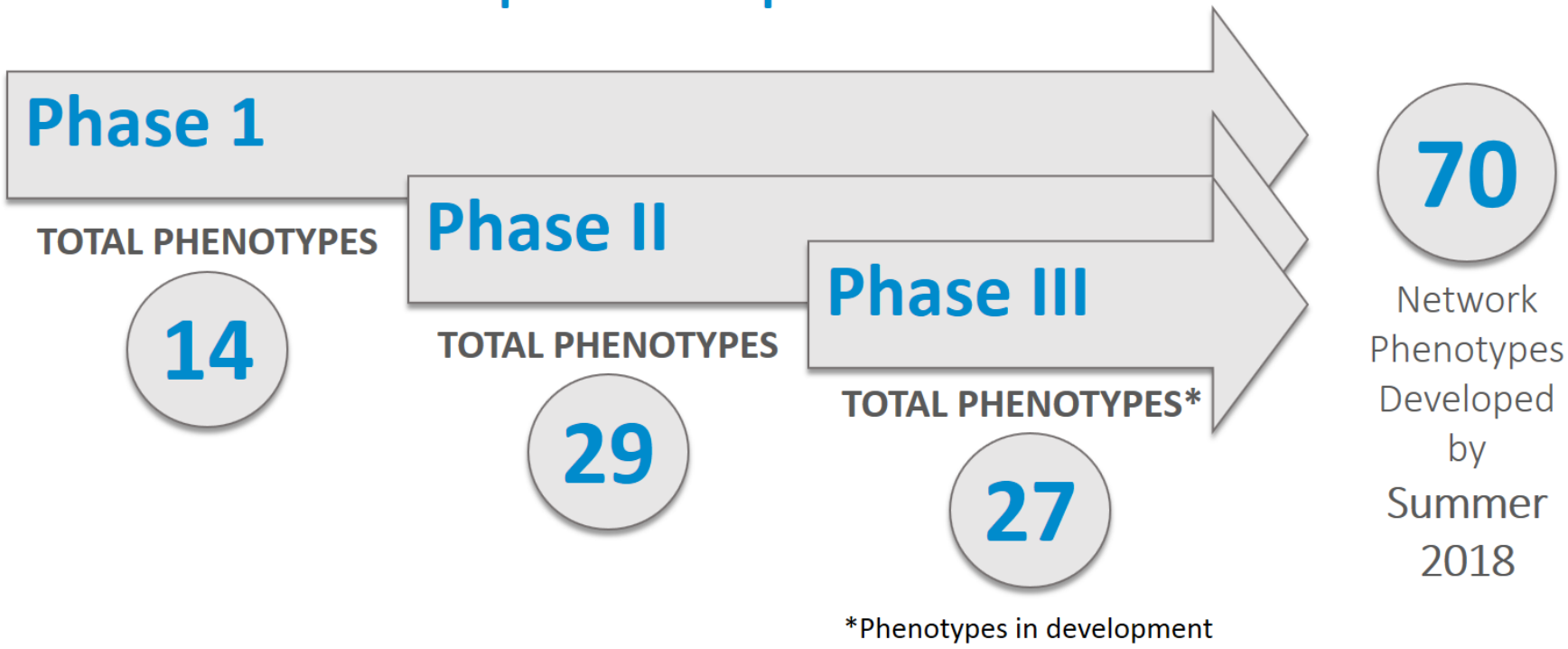
Publish

- Phenotype published and Algorithm is sharable to public

Tool Support: PheKB

Phenotypes

PHENOTYPES: Development & Implementation



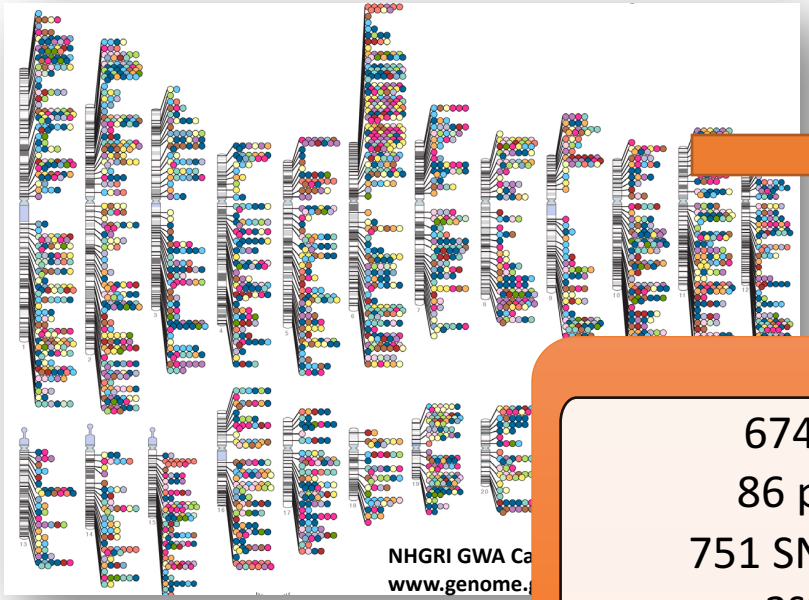
Impact: eMERGE PheWAS

- Developed methods for large scale genotype/phenotype analyses and implemented them across an entire collaborative Network

- Phenome-wide association studies (PheWAS)
  - 3144 SNPS present in NHGRI catalog (2012) in 13,835 individuals across 5 sites.
    - 1358 phenotypes analyzed for each SNP
  - Addition of Neanderthal PheWAS catalogue
  - Creation of Phecode mappings from ICD codes

Denny JC, Bastarache L, Ritchie MD et al. *Systematic comparison of phenome-wide association study of electronic medical record data and genome-wide association study data.* Nat Biotechnol. 2013 Dec;31(12):1102-10. **PMID: 24270849 PMCID: PMC3969265**

PheWAS of "all" NHGRI GWAS Catalog SNPs



3,144 SNPs with prior GWAS-discovered associations

674 SNPs with
86 phenotypes
751 SNP-phenotype associations

Test for replication of 751 associations using PheWAS

Replication Arm

3,144 SNPs

PheWAS for each SNP to discovery pleiotropy

Replication of novel associations

Discovery Arm

Denny *et al*, *Nat Biotech* 2013

Impact: eMERGE Pharmacogenomics *(PGx)*

SPHINX
A resource of the *e*MERGE Network

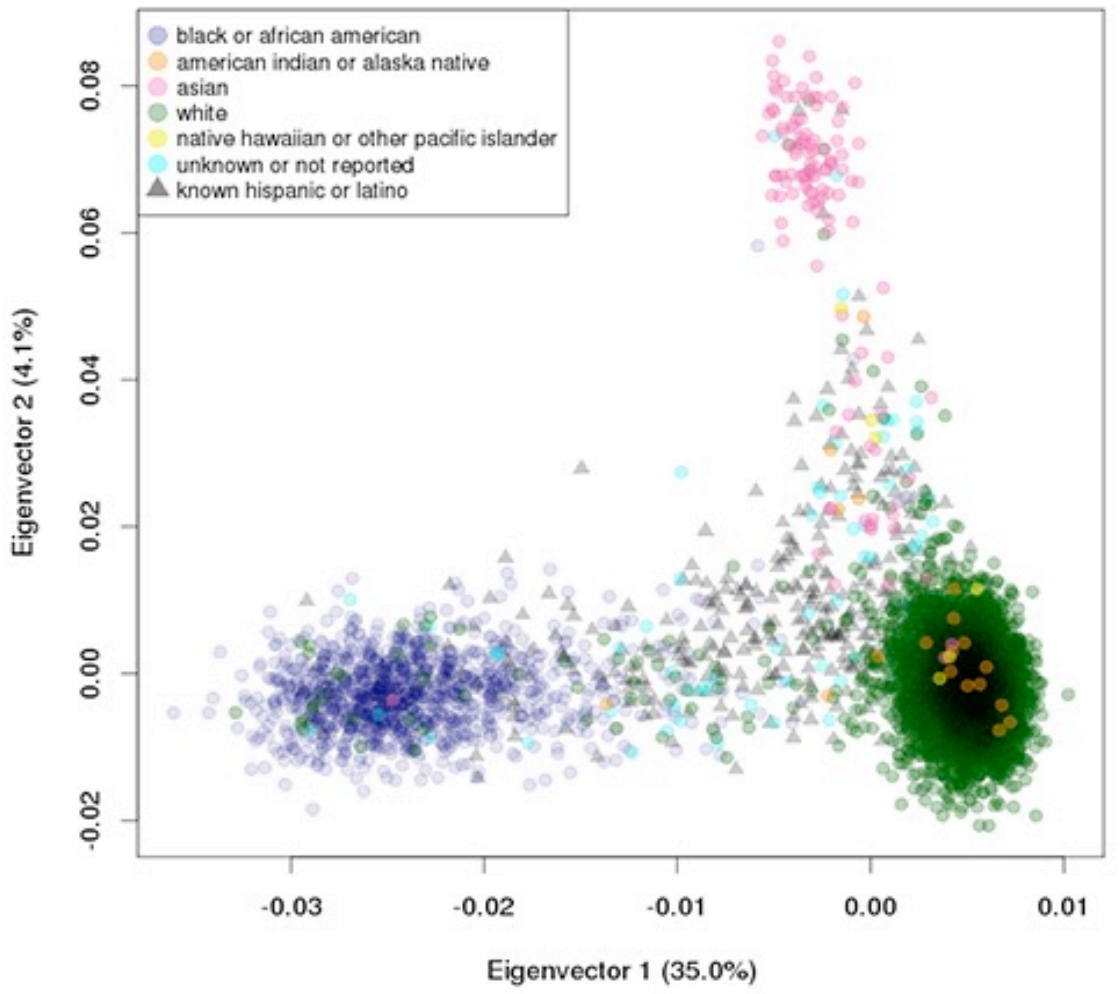
- Multi-site test of the concept that genetic sequence information can be coupled to electronic medical records (EMRs) for use in healthcare
- Genetic sequencing on a 9010 participant data set
  - Sequencing and phenotype data available on SPHINX
- 82 pharmacogenetic genes investigated
- Many more opportunities for research on these data
  - PGx SNVs on the eMERGE-Seq panel
- Sites continue to collect utilization and outcomes data

Bush WS, Crosslin DR, Owusu-Obeng A, Wallace J, Almoguera B. et al. *Genetic variation among 82 pharmacogenes: The PGRNseq data from the eMERGE network. Clin Pharmacol Ther. 2016 Aug;100(2):160-9. doi: 10.1002/cpt.350.* ***PMID: 26857349 PMCID: PMC5010878.***

Deliverable: PGRNseq multi-sample calling

- Original PGRNseq aligned to multiple references used by the original five sequencing centers
- All 9010 BAMs re-aligned to the same genome reference hs37d5.fa
- 9010 individuals in data set provided to the network for analysis
- Principle components analysis (PCA) examined ancestry

PCA: eMERGE PGRNseq data (N = 9010)



Impact: Return *of* genomic data *via* EMR

- Infrastructure and tools, in particular decision support tools, to enable genomic medicine

- InfoButton*
  - Explored use of infobuttons as a decision support tool to provide context specific links within the electronic health record (EHR) to relevant genomic medicine content
  - Assessed the coverage of content topics among information resources developed

- CDS_KB (**C**linical **D**ecision **S**upport **K**nowledge**B**ase)
  - Partnership with IGNITE network
  - Goal is to catalog and share CDS implementation artifacts and design considerations for genomic medicine programs from a broad community of institutions

*(Overby CL, Rasmussen LV, Hartzler A, Connolly JJ, Peterson JF, et al. *A Template for Authoring and Adapting Genomic Medicine Content in the eMERGE Infobutton Project*. AMIA Annu Symp Proc. 2014 Nov 14;2014:944-53. **PMID: 25954402 PMCID: PMC4419923.**)

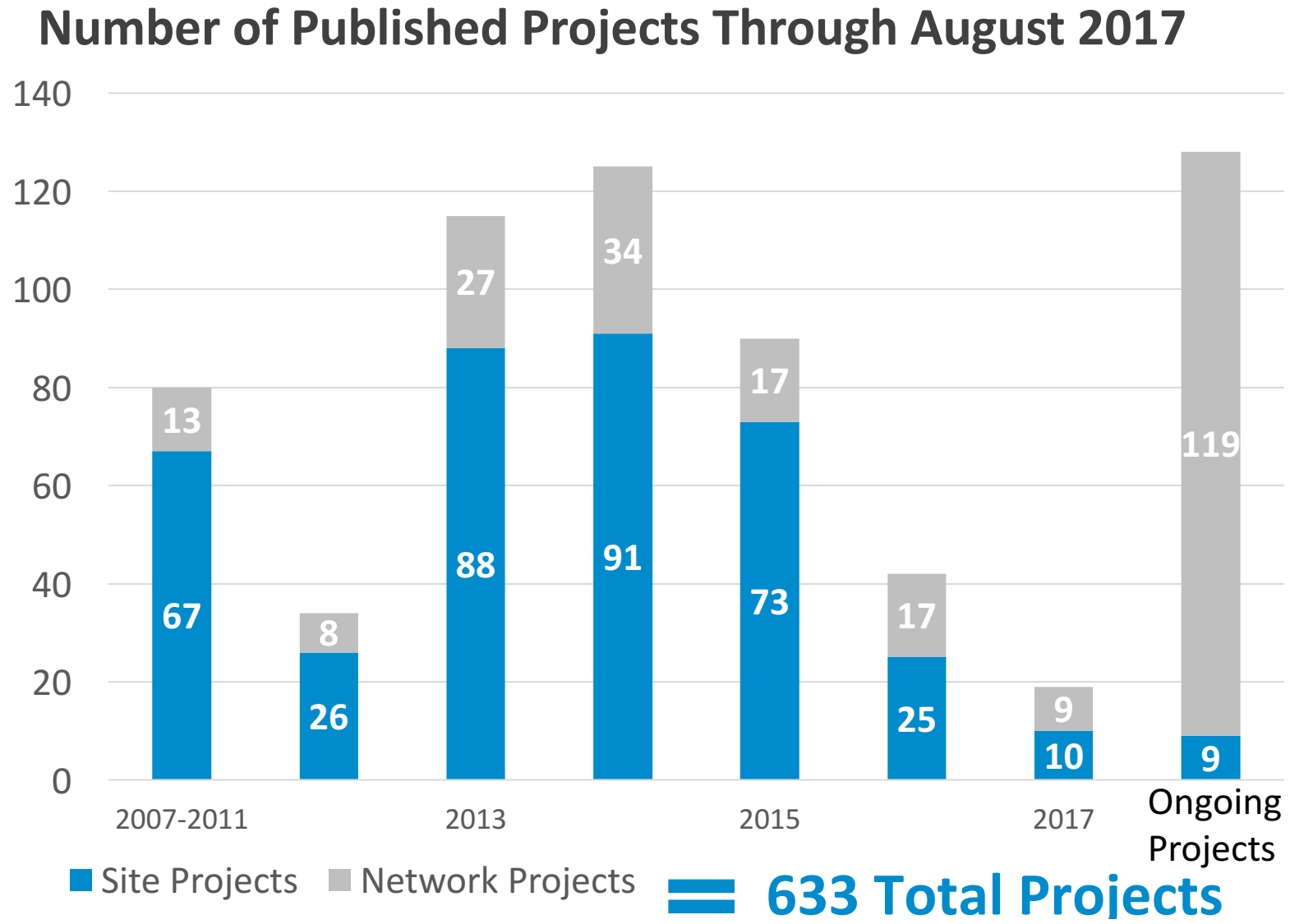
Impact: Network wide analyses 'DNAnexus'

- Utilization for sharing and managing genetic data in a cloud-based system

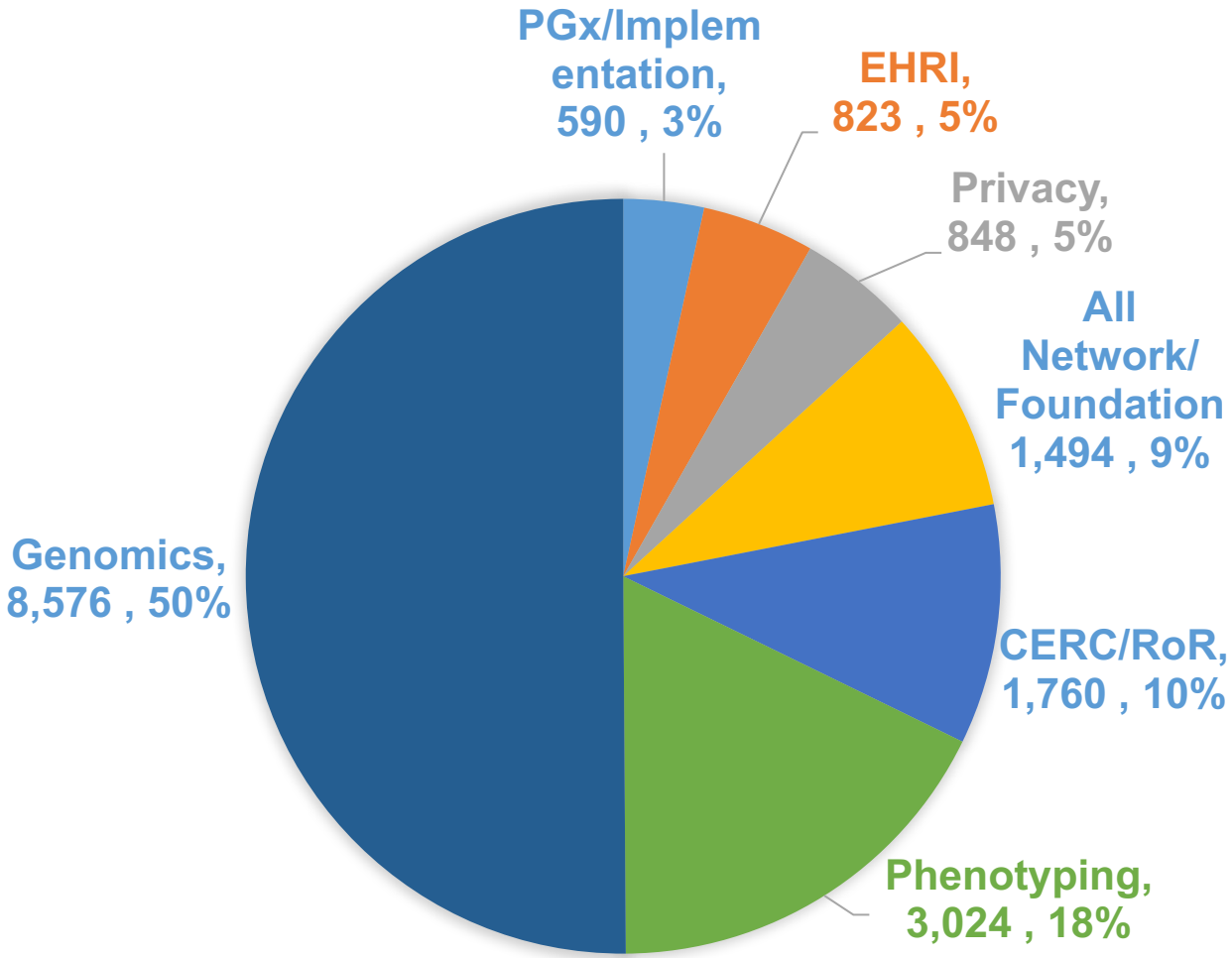
- Network seminar series demonstrating utility of the analysis pipeline and development of apps
  - Large scale analyses possible for all investigators, regardless of local computing power

- DNAnexus houses Network wide genetic datasets
  - GWAS
    - Including a subset of geocoded samples
  - PGRNseq
  - eMERGEseq

Impact: *e*MERGE Publications *2007-2017*



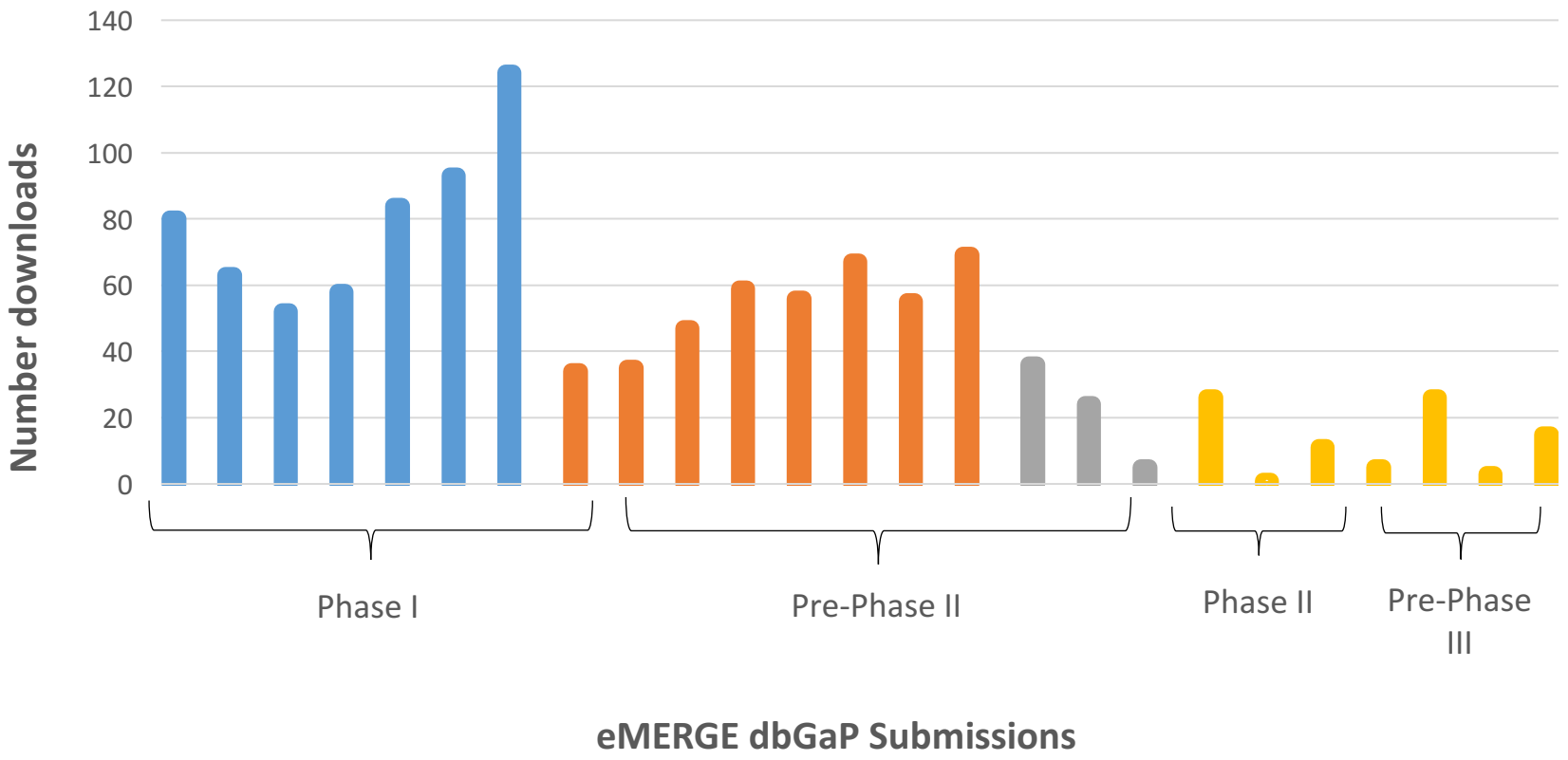
Citations of eMERGE Publications by Category



Cumulative Citation Counts: 17,115 (2007-March 2017)

Impact: dbGaP & Website analytics *2007-2017*

Data Reuse: # Downloads *of e* MERGE dbGaP Submissions as of August 2017



***> 1100** external downloads as of August 2017*

*e*MERGE Website

Average usage past 6 months

- 63.1% new visitors
- 1596 sessions/month
- 1043 users/month
- Views from 96 countries

PheKB Website

Average usage past 6 months

- 56.2% new visitors
- 1171 sessions/month
- 540 users/month
- Views from 76 countries

eMERGE Tools

PheKB
A **knowledgebase** for discovering phenotypes from electronic medical records

MyResults.org
An **informational tool** for educating patients about genetic test results

SPHINX
A **data exploration tool** for genetics-related drug response hypothesis generation

Infobutton Project template

***e*merge Model Consent Language**

PheWAS catalog

Additional Tools

GENOTYPING tools

PHENOTYPING tools

CDS tools

Natural Language Processing (NLP) Tools

*e*MERGE III: Future Deliverables

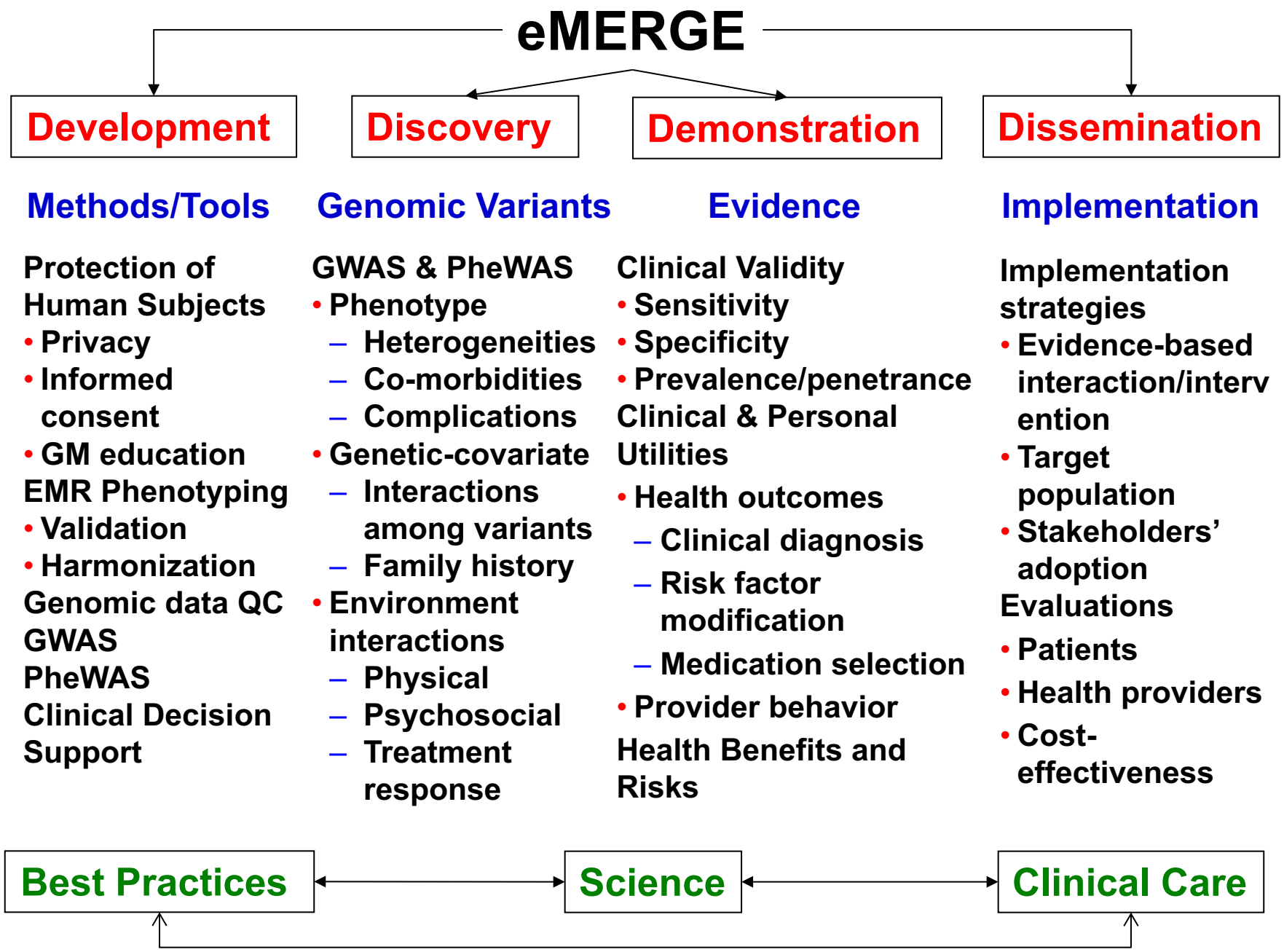
- dbGaP submissions
  - GWAS eI-III imputed set *(ready to submit)*
  - Interim (Fall 2017) and final eMERGEseq data

- Return of clinical results and EHR integration at all sites
  - Establishment of IT support for return of results processes based on data delivered through the network
  - Analysis of solutions, challenges and lessons learned
    - Manuscripts and methods documentation of Network-wide efforts
    - Sharing with CDSKB and standard bodies as appropriate

- Outcomes analysis for effect of return of results on patients and providers across sites
  - Compare differences in health outcomes and provider behaviors for return of negative and positive results
  - EHR and survey based methods for examining patient impacts and changes in care or awareness by providers

- Creation and deployment of 27 phenotypes, 8 deployed to date
  - 25 eI-III imputed GWAS
  - 13 PGRNseq
  - 24 eMERGEseq

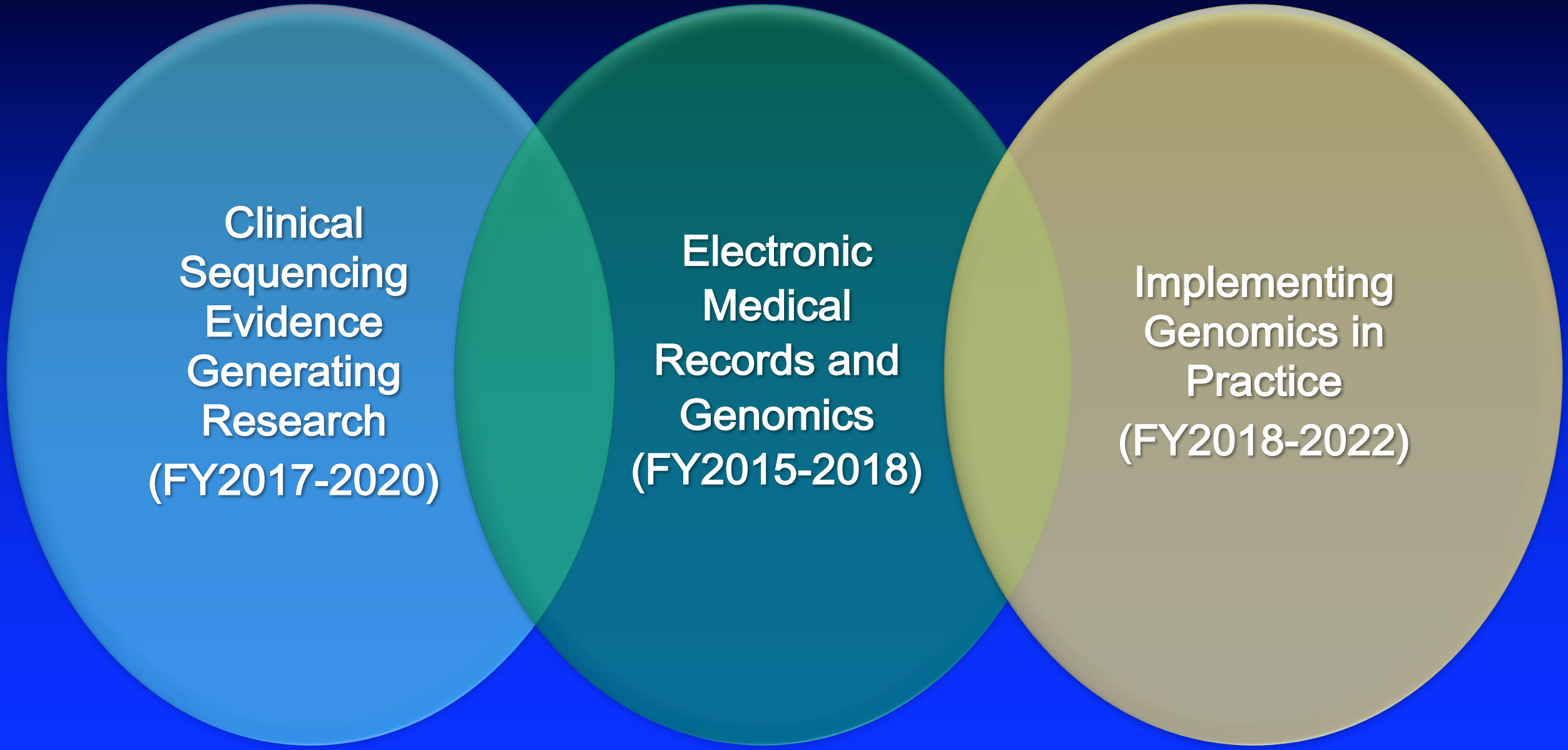
Questions??


eMERGE
Development
Discovery
Demonstration
Dissemination
Methods/Tools
Protection of Human Subjects
• Privacy
• Informed consent
• GM education
EMR Phenotyping
• Validation
• Harmonization
Genomic data QC
GWAS
PheWAS
Clinical Decision Support
Genomic Variants
GWAS & PheWAS
• Phenotype
– Heterogeneities
– Co-morbidities
– Complications
• Genetic-covariate
– Interactions among variants
– Family history
• Environment interactions
– Physical
– Psychosocial
– Treatment response
Evidence
Clinical Validity
• Sensitivity
• Specificity
• Prevalence/penetrance
Clinical & Personal Utilities
• Health outcomes
– Clinical diagnosis
– Risk factor modification
– Medication selection
• Provider behavior
Health Benefits and Risks
Implementation
Implementation strategies
• Evidence-based interaction/intervention
• Target population
• Stakeholders' adoption
Evaluations
• Patients
• Health providers
• Cost-effectiveness
Best Practices
Science
Clinical Care

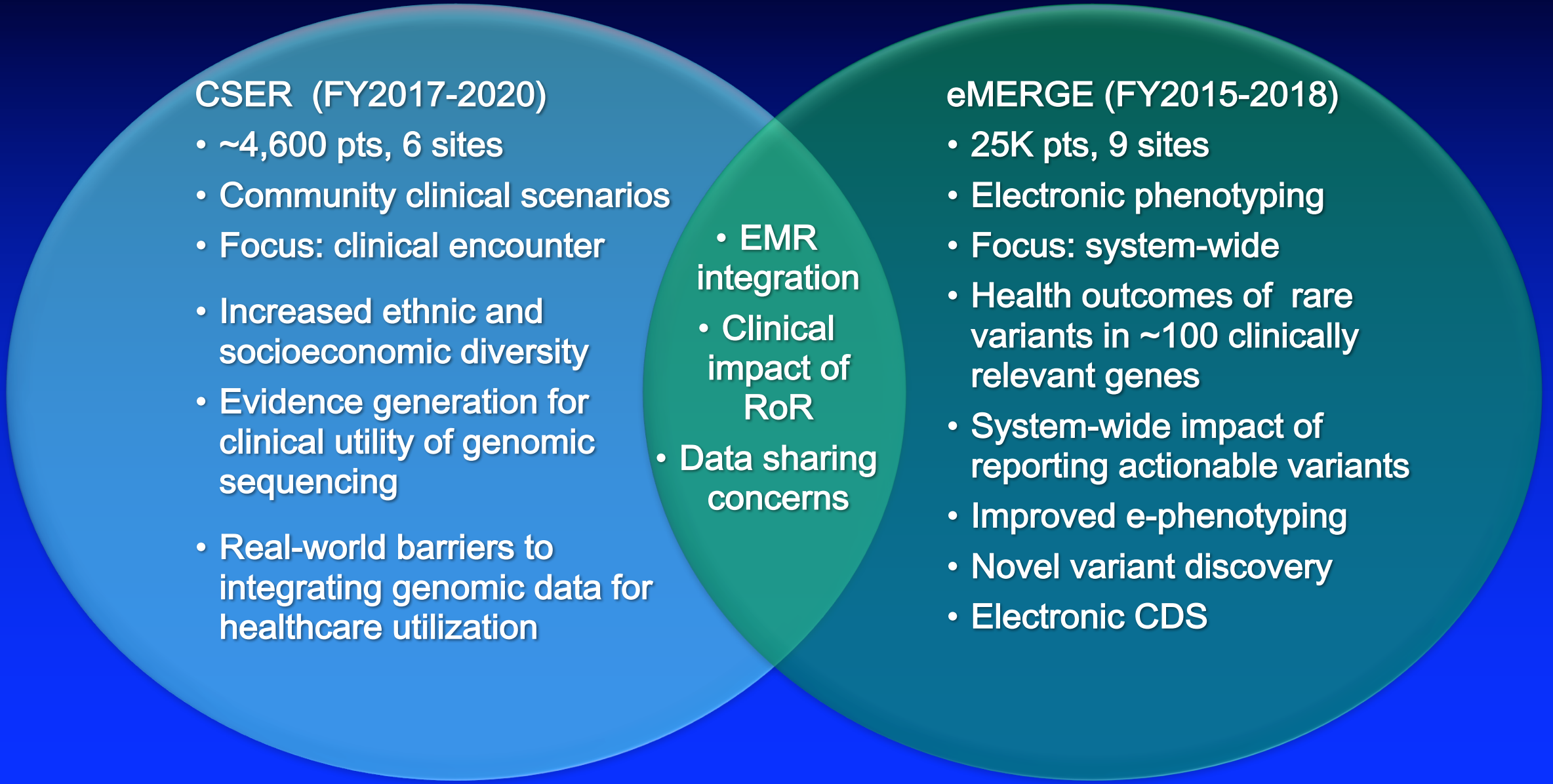
eMERGE Geocoding

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

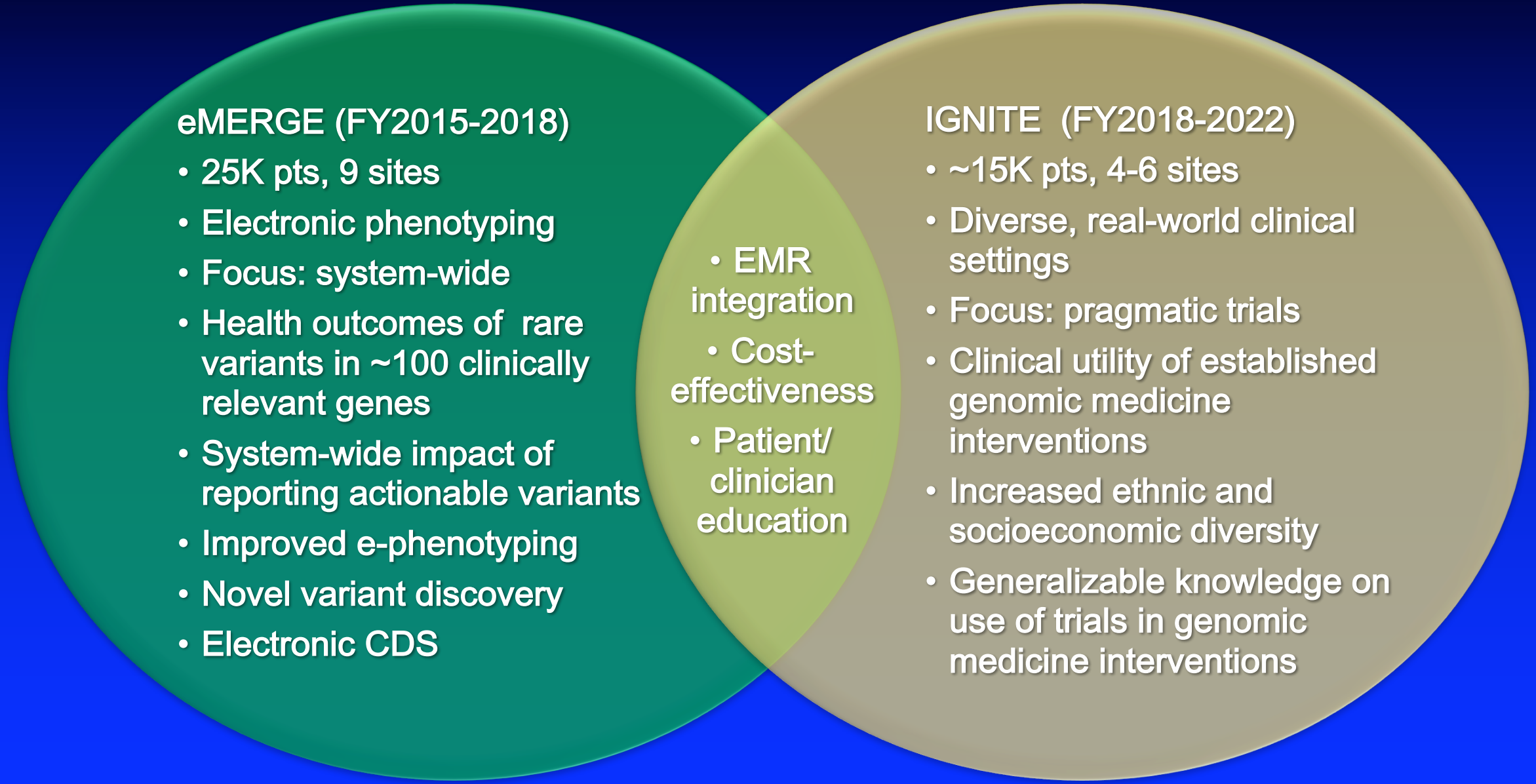
CSER, eMERGE, and IGNITE



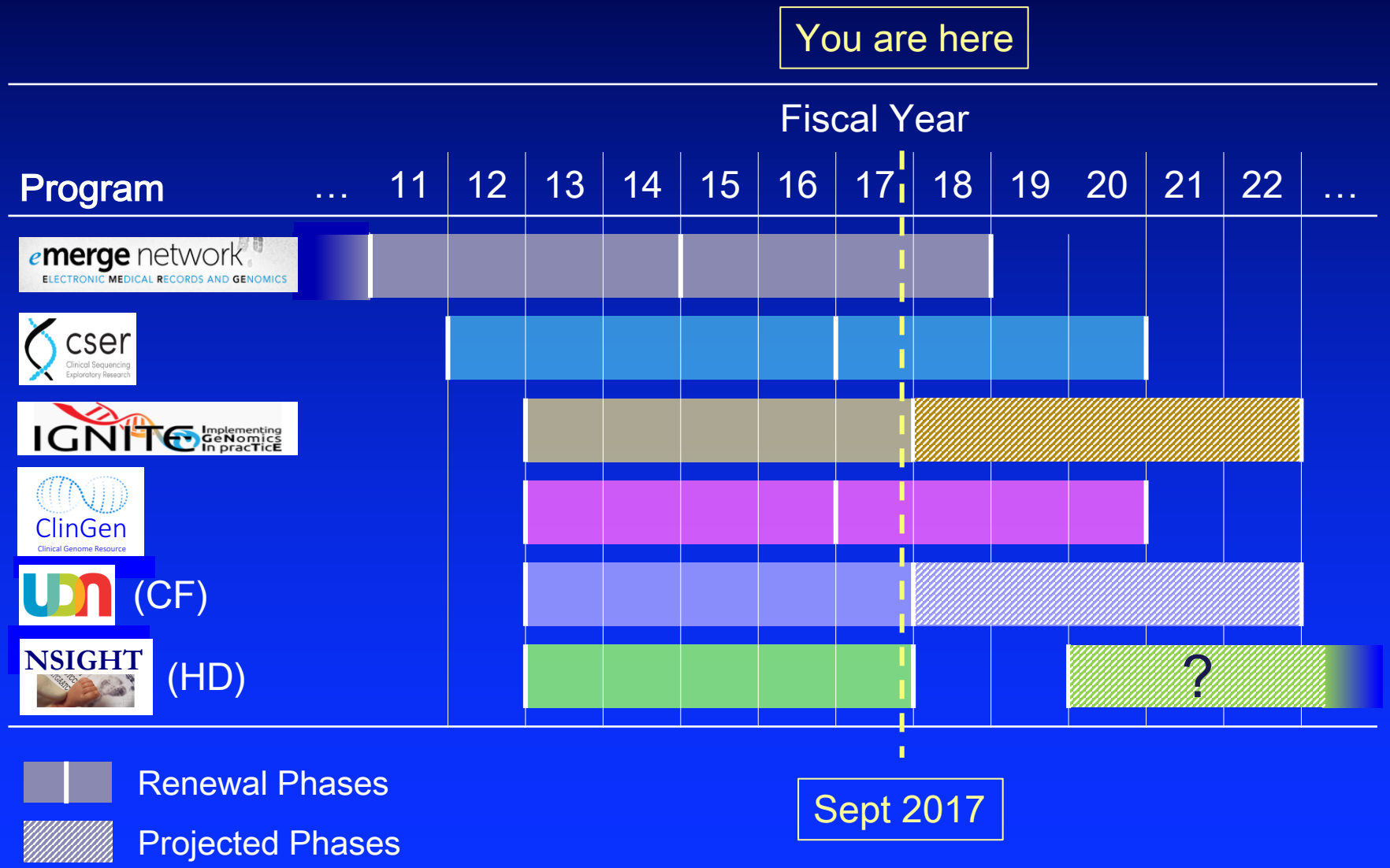
Commonalities and Complementarity of CSER and eMERGE



Commonalities and Complementarity of eMERGE and IGNITE



Timeline of NHGRI Genomic Medicine Programs



Resources

emerge network
ELECTRONIC MEDICAL RECORDS & GENOMICS

www.gwas.org

Manuscripts *(to date)*

https://emerge.mc.vanderbilt.edu/publications/

dbGaP *(published to date)*

https://emerge.mc.vanderbilt.edu/dbgap/

GWAS sequencing platforms *(eI-III)*

https://emerge.mc.vanderbilt.edu/wp-content/uploads/2015/02/Platform-Information-eMERGE.docx

TOOLS

PheWAS Resources

https://phewascatalog.org/

PheKB a knowledgebase for discovering phenotypes from electronic medical records

https://phekb.org/

CDS_KB
CLINICAL DECISION SUPPORT KNOWLEDGEBASE

https://cdskb.org/

SPHINX
A resource of the eMERGE Network

https://www.emergesphinx.org/