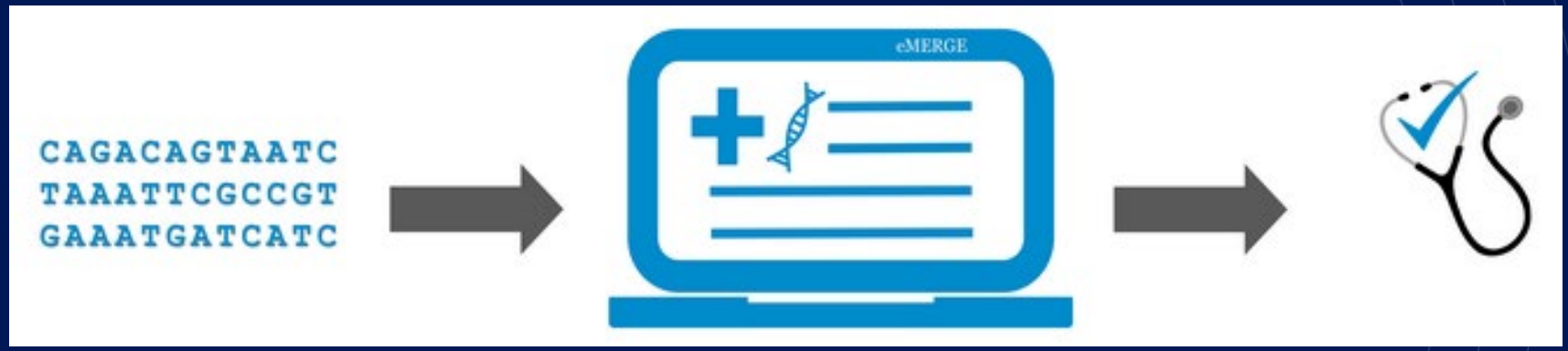


eMERGE Renewal– Genomic Risk Assessment and Management

National Advisory Council on Human Genome Research

Teri Manolio for eMERGE team: Jyoti Dayal, Zephaun Harvey, Deanna Ingersoll, Sheethal Jose, Rongling Li, Lisa Oken, Diane Patterson, Robb Rowley, Lisa Saletta, Ken Wiley

February 11, 2019

National Human Genome Research Institute

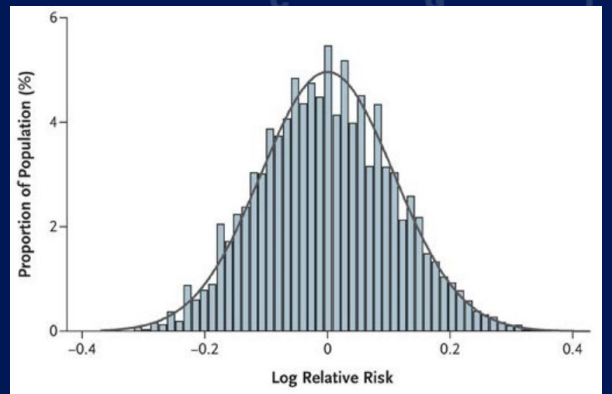
The Forefront of Genomics®

Purpose

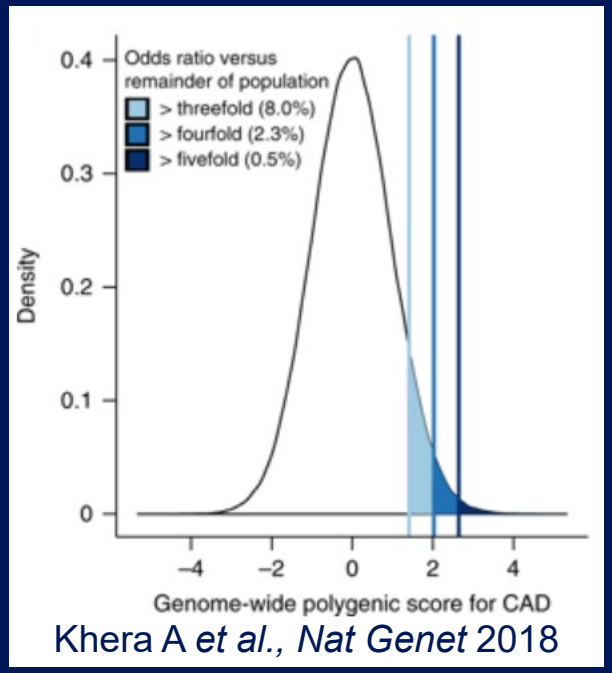
Use biorepositories linked to EMRs to develop, implement, and disseminate genomic risk assessment and management tools for clinical use

1. Calculate validated polygenic risk scores (PRS) for several complex diseases retrospectively using EMR-defined phenotypes in available datasets, and share their distributions, associations, and other characteristics

2. Develop EMR-based methods to communicate genomic risk profiles and relevant clinical recommendations based on PRS, family history, and other clinical data



Pharoah P *et al., NEJM* 2008



Khera A *et al., Nat Genet* 2018

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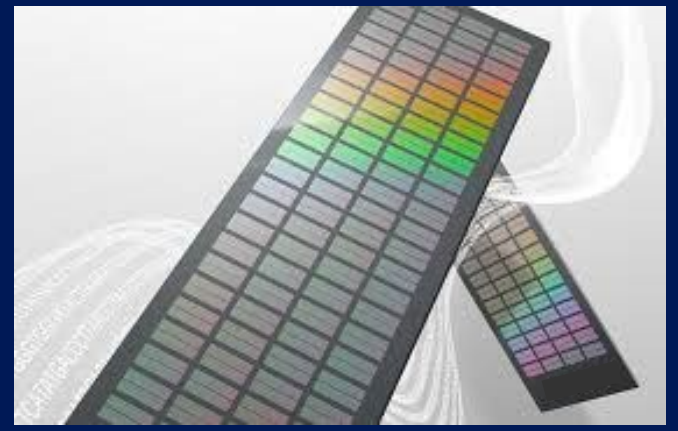
Purpose

Use biorepositories linked to EMRs to develop, implement, and disseminate genomic risk assessment and management tools for clinical use

3. Recruit and genotype 20,000 individuals of diverse ancestry, prospectively calculate their genomics-based risk for selected e-phenotypes, and provide risk estimates and management recommendations to them and their providers through EMR and/or patient portals

4. Use EMR-based methods to assess provider and patient uptake of risk-reduction recommendations and impact on related clinical outcomes



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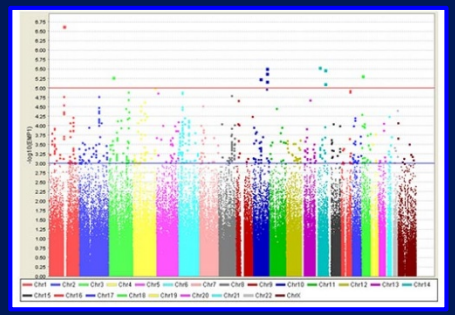
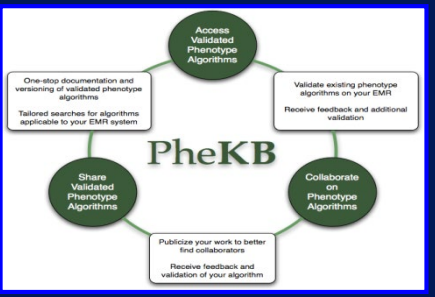
Purpose – continuing efforts

Continue to use biorepositories linked with EMRs for genomic research:

- Expand and enhance electronic phenotyping
- Identify genomic associations with e-phenotypes
- Develop and disseminate electronic clinical decision support (eCDS)
- Enable integration of genomic findings into EMRs for clinical research and care
- Disseminate methods, tools, and best practices to the scientific community





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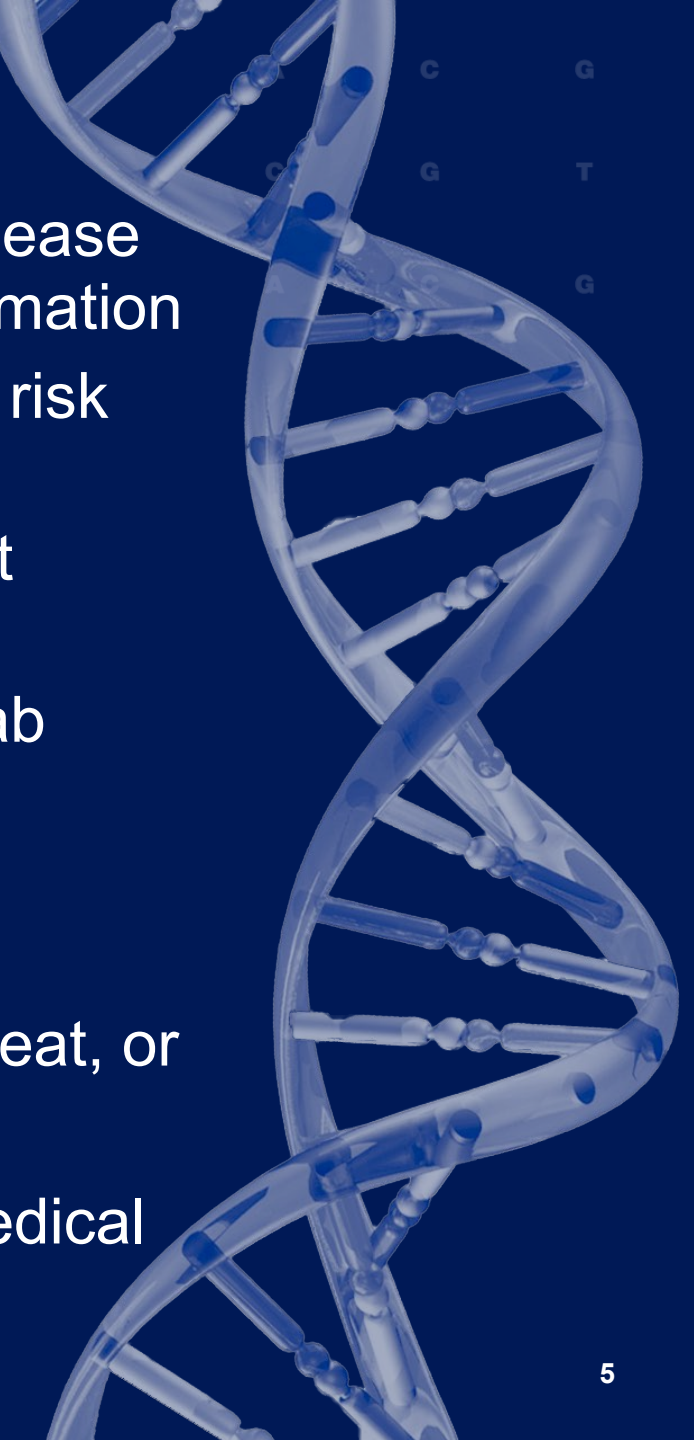
A few definitions…

- Genomic risk assessment: calculation of risk for complex disease from presence of risk alleles, family history, and clinical information
  - Polygenic risk scores (PRS): risk assessment based on risk allele frequencies
  - Family history (FHx): patient-driven, web-based tool that integrates with EMR such as IGNITE's MeTree
  - Clinical information: non-genomic information such as lab values, anthropometrics, habits, past medical history
- Risk management: implementation of further testing (mammography, bone density, specific gene panels) or interventions (drug treatment, surgical removal) to identify, treat, or prevent early disease
- Clinical risk estimation: non-genomic information such as medical history, physical findings, laboratory values



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A few (more) definitions…

- Diverse ancestry: non-European plus Hispanic/Latino ethnicity, per OMB Directive 15 categories (NOT-OD-15-089):
  - American Indian or Alaska Native
  - Asian
  - Black or African American
  - Hispanic or Latino
  - Native Hawaiian or Other Pacific Islander

- Under-served populations: per HRSA and NIMHD, "…areas or populations designated by HRSA as having too few primary care providers, high infant mortality, high poverty or a high elderly population"

https://data.hrsa.gov/tools/shortage-area/mua-find

eMERGE Phases (2007-2019)

Phase I
2007-2010

- Can EMR and biobank be used for genomic research?
  - Genome-wide genotyping
  - E-phenotyping
  - GWAS

Phase II
2011-2014

- Can genomic findings be applied in clinical care and how?
  - Clinical implementation pilots
  - Pediatrics, PGx
  - E-phenotyping
  - GWAS

Phase III
2015-2019

- Can sequence data in clinically relevant genes be used to assess penetrance and improve clinical care?
  - Sequencing
  - Clinical implementation
  - E-phenotyping
  - GWAS

ELSI Research

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Recent advances making study of genomic risk assessment and management feasible

- Clinically certified dense SNP arrays and imputation algorithms
- Consensus approaches to interpretation of actionable variants
- Professional guidelines for clinical use of actionable variants in high-risk individuals
- Polygenic risk scores (PRS) for multiple conditions, including atrial fibrillation, T2DM, ADHD, coronary disease, Alzheimer's disease, breast cancer
- Automated tools for systematic, patient-driven collection of FHx
- PGx variants predictive of altered response to commonly used drugs carried by nearly everyone

Gaps needing to be filled for clinical adoption of genomically-defined risk assessment and management

- Development and validation of EMR tools for:
  - Seamless integration of genomic risk estimates into EMRs
  - Delivery of recommended clinical actions in user-friendly manner using eCDS
- Predictability of EMR-derived phenotypes from PRS
- Estimation and validation of PRS in non-EA populations → GSP, MVP, PAGE, TOPMed
- Validation of PRS based on e-phenotypes in non-EA populations
- Assessment of uptake of risk reduction recommendations across a range of conditions
- Estimation of achievable changes in related clinical outcomes

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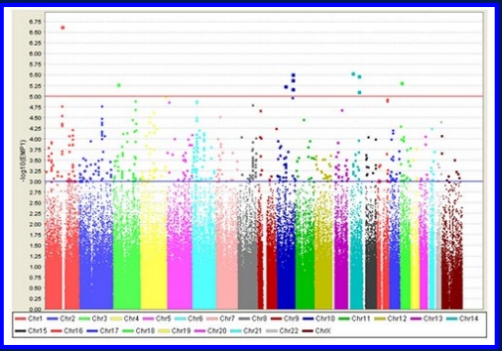
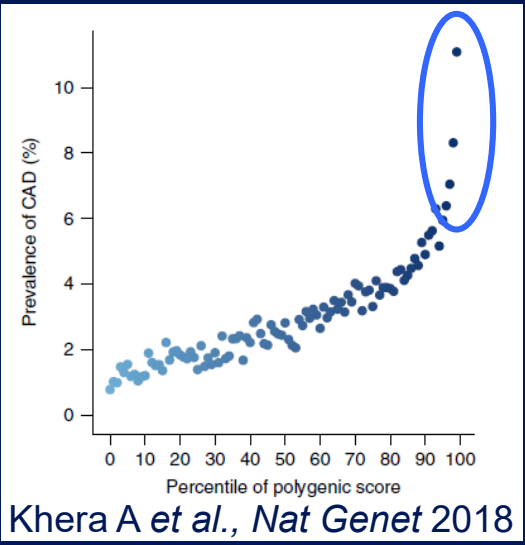
Objective: Retrospective validation and adaptation of PRS to EMR-defined phenotypes

- Use publicly available, densely imputed SNP data in 83K eMERGE participants and other studies to calculate PRS for ~20 complex diseases
- Identify appropriate thresholds (e.g., top 2% of risk; 2- to 3-fold increase over population as whole) for risk reduction recommendations based on current guidelines and budgetary constraints
- Determine distributions of risk across key demographic subgroups; modify thresholds as appropriate for differing allele frequencies or clinical characteristics



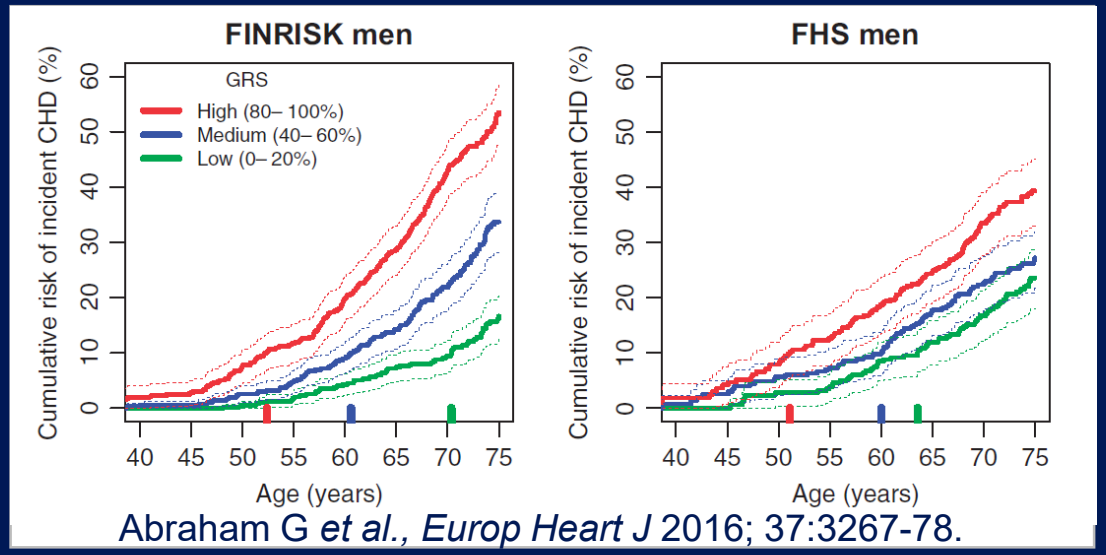
$$Y = \sum_{m=1}^{M_1} \beta_m X_m + \sum_{m=M_1+1}^{M} 0 \times X_m + \varepsilon$$



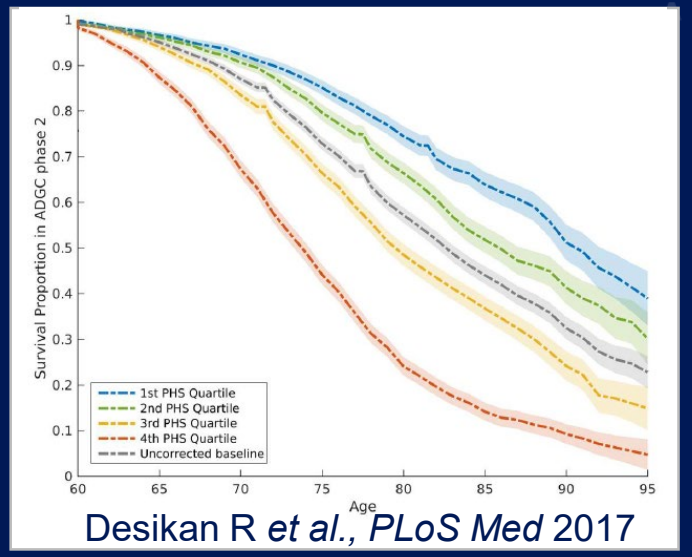
Khera A *et al., Nat Genet* 2018

NIH NHGRI

Objective: Retrospective validation and adaptation of PRS to EMR-defined phenotypes



Abraham G *et al., Europ Heart J* 2016; 37:3267-78.



Desikan R *et al., PLoS Med* 2017

- Compare risk predictions with specific e-phenotypes, modify thresholds or phenotypes as appropriate
- Select ~15 risk algorithms for prospective implementation
- Estimate as feasible added value of genomic information to risk estimates based on clinical (non-genomic) information

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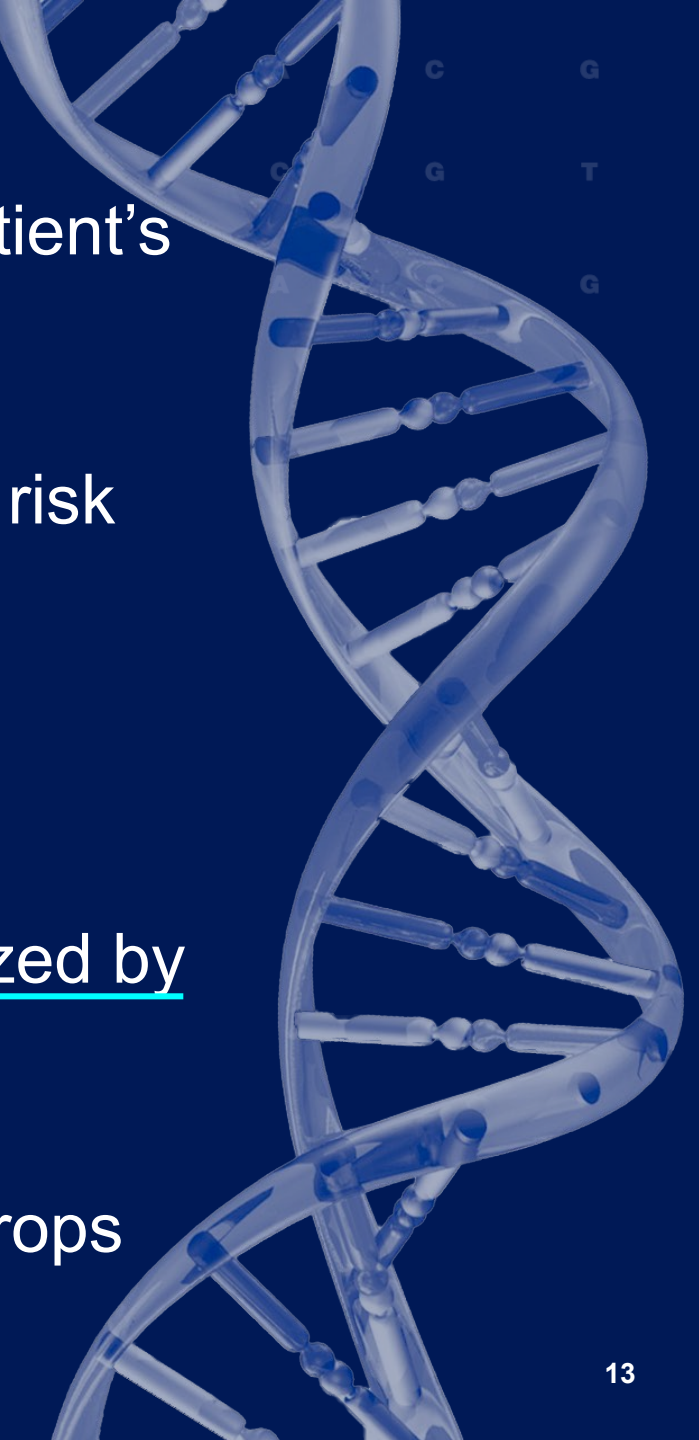
Objective: Prospective risk assessment and management using EMR tools

- Recruit 20,000 persons of diverse ancestry to undergo clinically certified dense SNP genotyping, FHx assessment, and clinical evaluation of risk
- Provide guideline-based risk estimates and clinical recommendations to providers and patients through EMR
- Arrange for follow-up testing and risk management of patients who exceed agreed-upon thresholds, as needed
- Quantify uptake of risk management recommendations (e.g., tests completed, treatments initiated); iterate approach as needed to reach ~50% uptake
- Disseminate and analyze rich dataset: estimating added value of genomic information to risk estimates based on non-genomic data

Risk Management

- Guideline-based interventions tailored to individual patient's estimated risk
- Guideline-based risk management recommendations delivered to patients exceeding agreed-upon levels of risk
- Design and components of genomic risk assessment, including the guideline-based risk reduction recommendations, to be proposed by each applicant
- Single network-wide protocol for risk assessment, risk management, and outcome ascertainment to be finalized by SC consensus
- Risk assessment and management to be updated as needed as new risk information accrues or if uptake drops significantly below 50%



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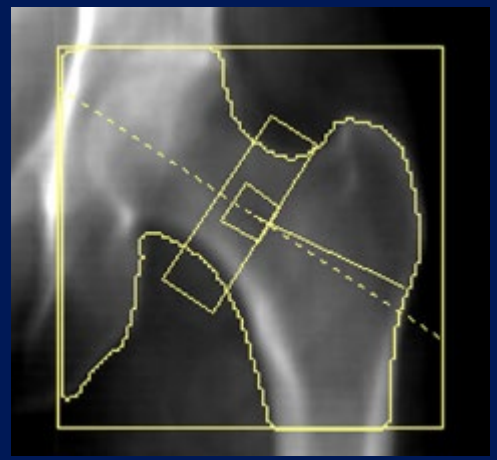
Data Collection and Outcome Measures

- Standard clinical risk factors (hypertension, obesity, health behaviors, etc.) extracted from EMRs at start and throughout
- Outcomes
  - Disease surveillance or screening consistent with guidelines
  - Drug selection and dosing c/w guidelines
  - Improvement in modifiable risk factors (cholesterol, blood pressure, bone density) after guideline-directed care
  - Other guideline-directed care such as drug treatment, surveillance practices, other health behaviors
- Cost and utilization of healthcare in high-risk group



Sample Size

- 20,000 patients screened for genomic risk (PRS, family hx, other risk assessment tools)
- 5,000 (25%) of patients at top 2% of risk for 1 or more of 15 complex diseases; 400 at top 2% for any single disease
- Place 95% CI around uptake proportion of 50% for each of disease
- For 400 persons at high risk of one disease, have 95% CI of ~ ± 5% [45.1,54.9]
- For subgroup comprising 20% of high-risk subgroup for each disease (80 persons), 95% CI = [39.0,61.0]

Criteria for Selection of Clinical Sites

- 6-10 Clinical Sites and CC, including subcontract for genotyping at CC
- Two Clinical Site FOAs, one each for ≥ 35% and ≥ 75% diverse ancestry or underserved populations
- Each CS able to recruit and follow ≥ 2,500 patients who have not previously received genomic information
- Able to implement e-phenotyping, eCDS, and outcome assessment in a comprehensive EMR
- Able to provide valid e-phenotypes for multiple outcomes
- Standard: collaborativeness, data sharing, productivity, expertise

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Budget Assumptions

- CLIA SNP genotyping @ $350
- Coordinating Center subcontracts for SNP genotyping
- 8 clinical sites recruiting 2,500 patients each
- Cost components can be divided into fixed (~ independent of sample size) and variable (directly proportional to sample size)
- Each high-risk patient incurs additional $1,250 in follow-up testing (assuming 20-30% paid by insurance, the remaining $1,000 borne by grant)
- Genotyping costs concentrated in years 2 and 3

Proposed Budget by Category (dollars in millions)

Cost Category	FY20	FY21	FY22	FY23	FY24	Total
Fixed Costs: Coord Ctr, Study Investigators, Informatics, etc.	4,536	4,633	4,633	4,633	4,501	22,936
Variable Costs: Recruitment/Consent, Genetic/Other Testing	3,480	6,478	6,471	4,112	270	20,811
Indirect Costs (58%)	3,836	5,023	5,019	4,666	2,767	21,311
Total Costs	**11,852**	**16,134**	**16,123**	**13,411**	**7,538**	**65,058**

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Proposed Budget by Site (dollars in millions)

Cost Category	FY20	FY21	FY22	FY23	FY24	Total
1 Clinical Site (DC)	756	1,001	1,000	924	525	4,206
1 Clinical Site (TC)	1,194	1,581	1,580	1,459	830	6,644
8 Clinical Sites (TC)	9,555	12,649	12,638	11,676	6,636	53,154
Coordinating Ctr (DC)	568	655	655	655	571	3,104
SNP Array Testing	1,400	2,450	2,450	700	0	7,000
Coordinating Ctr (TC)	2,297	3,485	3,485	1,735	902	11,904
Total Costs	**11,852**	**16,134**	**16,123**	**13,411**	**7,538**	**65,058**

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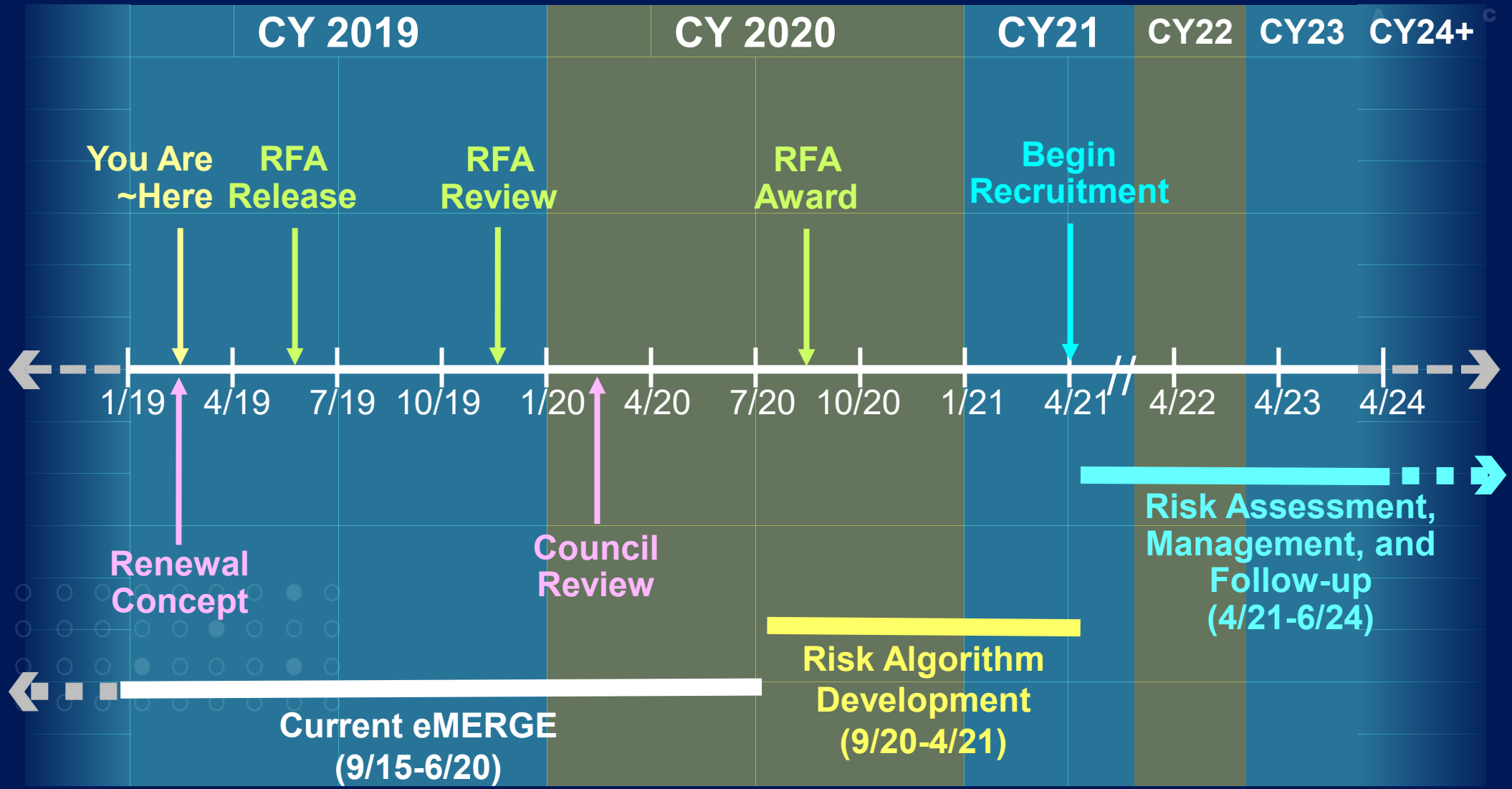
eMERGE Genomic Risk Assessment and Management Timeline



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Questions and Comments?

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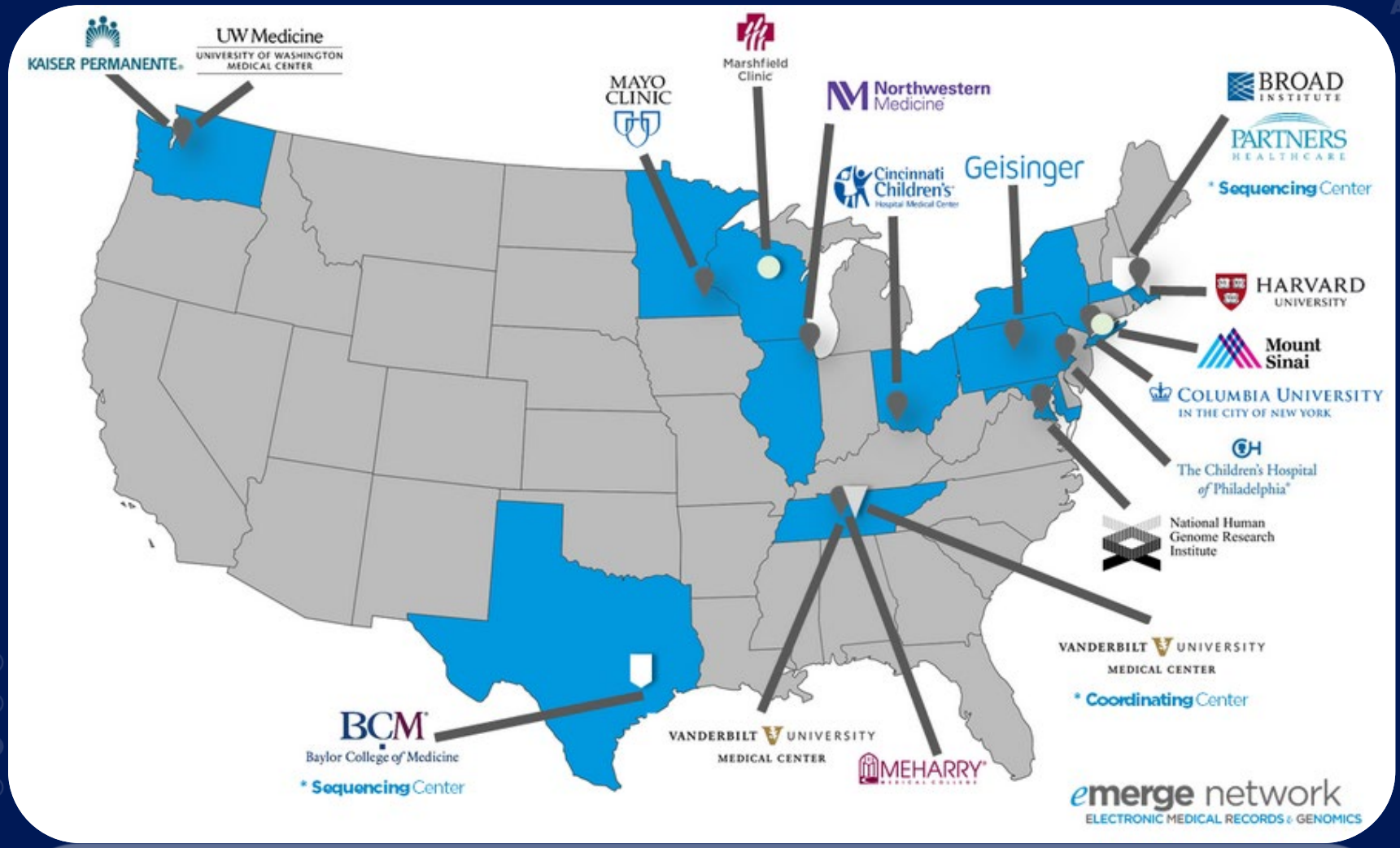
eMERGE Investigators 2014-2019



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