ECHO
Environmental influences on Child Health Outcomes

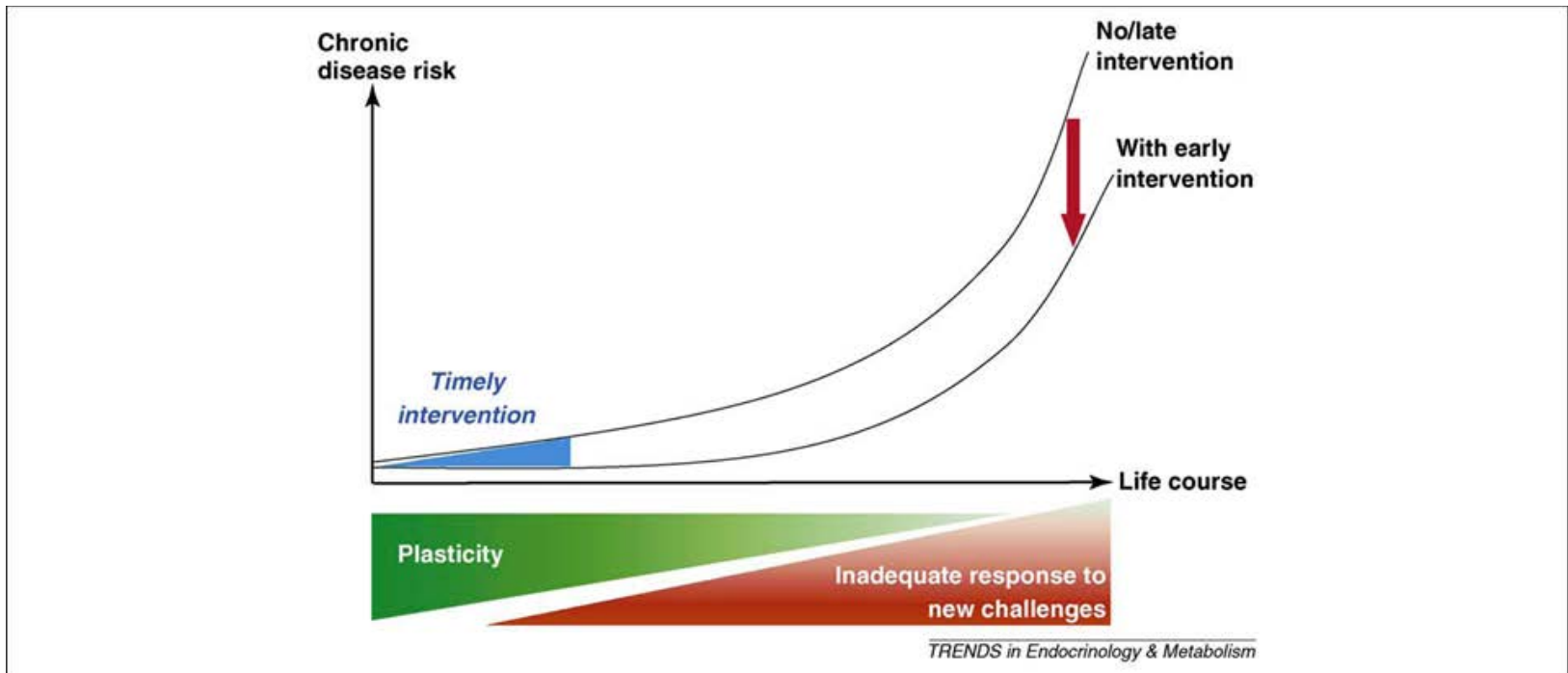Matthew W. Gillman, MD, SM

September 21, 2016

NICHD Advisory Council

Today

- Theory (1 slide)
- Goals
- Approach/organization
- Themes
  - Strategic
  - Scientific
- Components
  - What NIH funded (this morning)
- Discussion

Theory

TRENDS in Endocrinology & Metabolism

Goals

- Understand effects of early environmental exposures on child health and development

Goals

- Understand <u>effects</u> of early environmental exposures on child health and development
  - Effects: Observation (& intervention)

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  - Effects: Observation (& intervention)
  - Early: conception to age 5 y

Goals

- Understand effects of early <u>environmental exposures</u> on child health and development
  - Effects: Observation (& intervention)
  - Early: conception to age 5 y
  - Environmental exposures: Society to biology
    - Air pollution
    - Chemicals in our neighborhoods
    - Stress
    - Social networks
    - Behavior—sleep, diet, …
   - Biology—epigenetics, microbiota, …

Goals

- Understand effects of early environmental exposures on <u>child health and development</u>
  - Effects: Observation (& intervention)
  - Early: conception to age 5 y
  - Environmental exposures: Society to biology
  - Child health and development
    - High-impact conditions
    - 4 focus areas
      - Pre/peri/post-natal outcomes
      - Upper and lower airway
      - Obesity
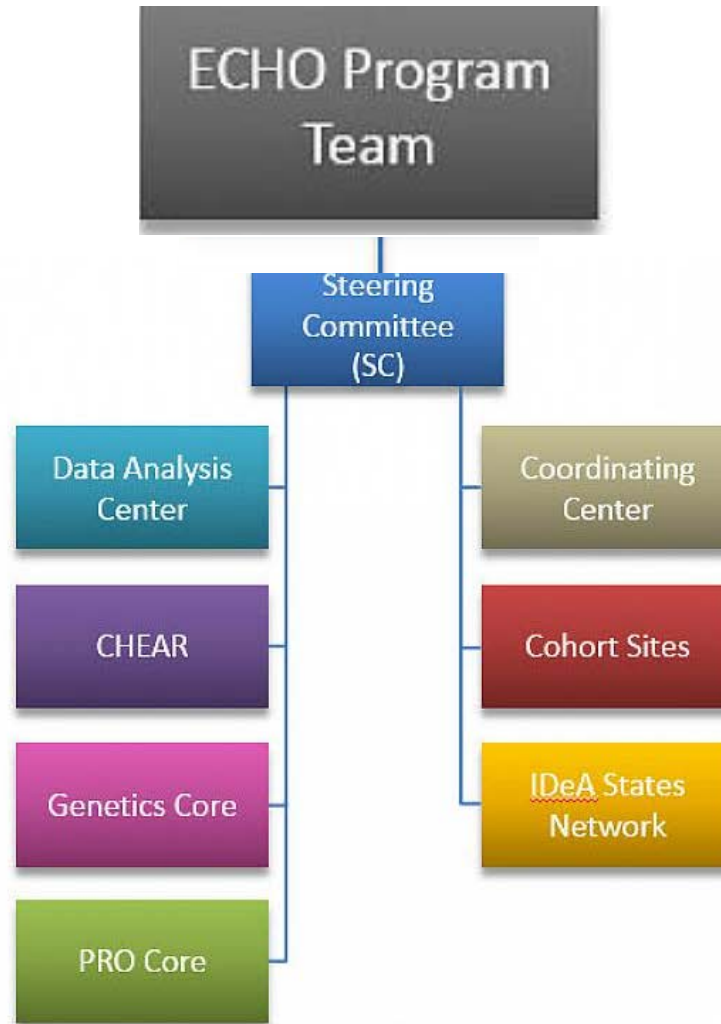   - Neurodevelopment
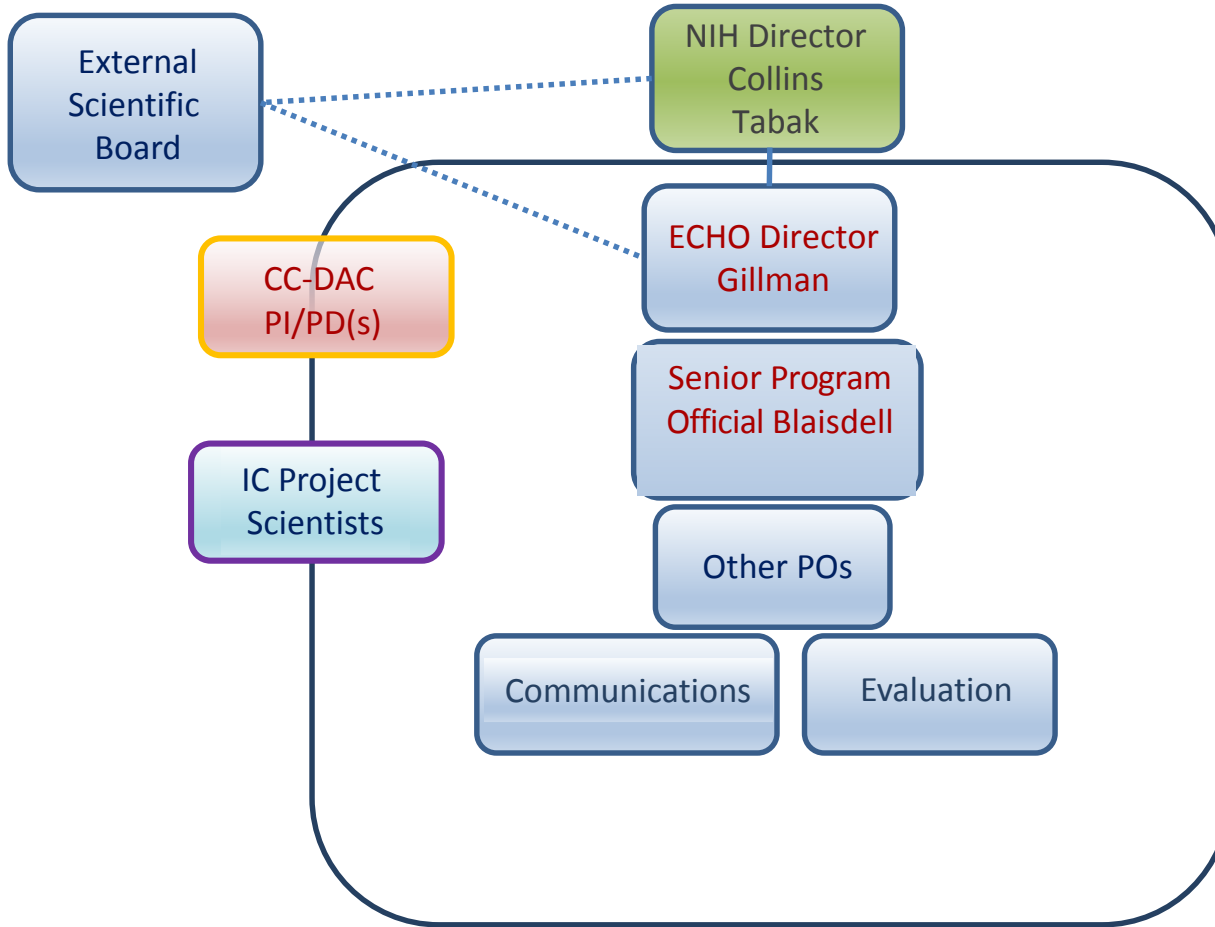
Approach

- Different from National Children's Study
- Extant cohorts
  - Individual cohort science
  - Synthetic cohort(s)
- Cooperative agreements
- Focus

ECHO Organization
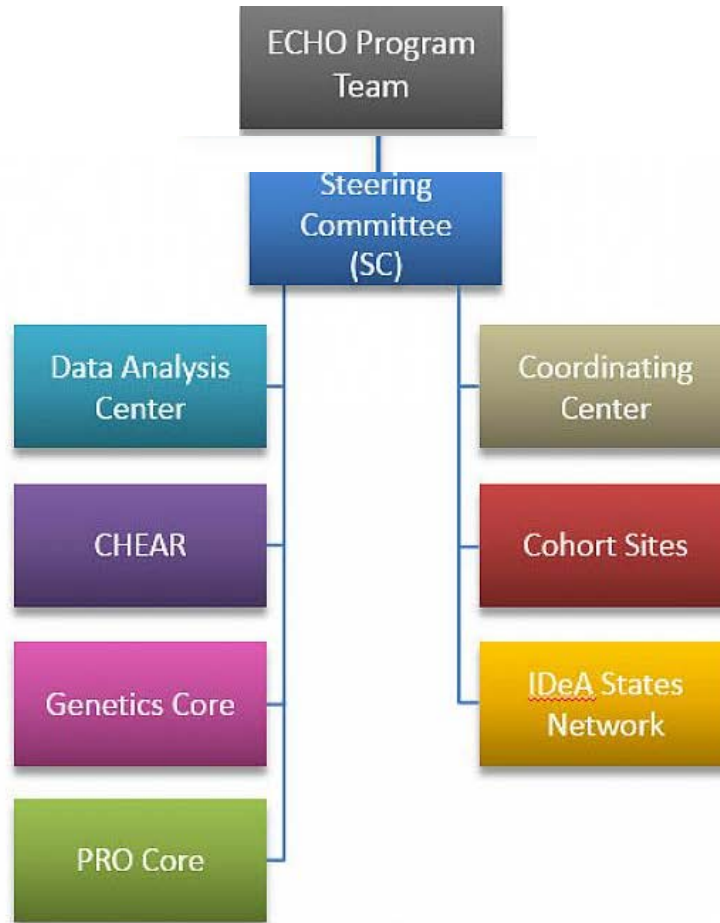
ECHO Organization

ECHO PROGRAM OFFICE

ECHO Funding

- $165m per year for 7 years
  - Annual appropriation
  - Exception
    - IDeA States Pediatric Clinical Trials Network
      - Funded for 4 years, up front

Tradeoffs/Challenges

- Alacrity v. patience
  - Need to hit the ground running, but
  - Need time to figure out best practices
- New (NCS) v. existing (ECHO) cohorts
  - No worrying about recruitment, but
  - Challenges in combining existing studies
    - Technical—harmonization
    - Sociocultural—"playing in the same sandbox"
- Many moving parts
  - Integrating IDeA States Pediatric Clinical Trials Network

ECHO Themes
Strategic & Scientific

ECHO Themes

Strategic

- Promote <u>interdisciplinary collaboration</u> so that whole is more than sum of parts.
- Innovations and consensus-building in <u>data harmonization, data sharing</u>
- <u>Rapid cycle program evaluation</u> to improve our program processes and outcomes in real time.
 - ECHO as Learning System

ECHO Themes
Scientific

- Synthetic cohort(s)
  - Whole is greater than sum of parts
    - Conduct <u>solution-oriented</u> observational studies of early environmental origins of common childhood conditions.
    - Combine <u>above and below the skin</u> pathways to pinpoint more precise potential levers of intervention.
    - Employ <u>sophisticated analytic techniques</u> to distinguish modes of intergenerational transmission.
    - Address early origins of child <u>health</u> as well as disease.
- Support infrastructure and training for <u>randomized trials in pediatrics</u> that link to ECHO themes.

Distinguishing modes of transmission critical for intervention design
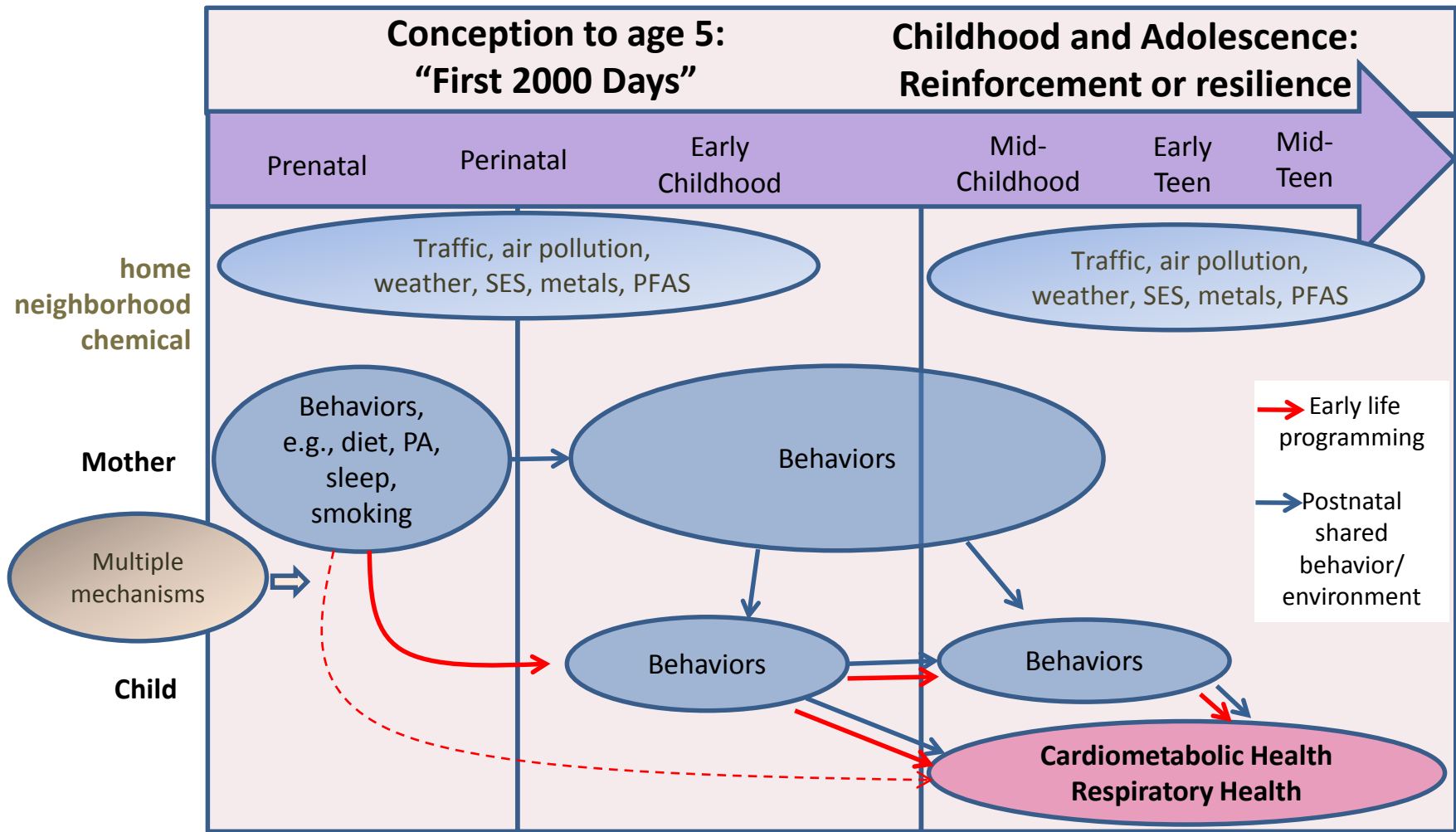
Adapted from figure by Emily Oken

Cross-cutting issues

- Heterogeneity
  - Geographic, social, demographic
- Explaining disparities
  - Racial/ethnic, socio-economic
- Replication
- Prevention
  - Primordial prevention
  - Risk stratification, "Precision prevention"

ECHO's Components

	Data Analysis Center	Mostly for cohorts	Coordinating Center	
FY16 supplements to FY15 funded centers	CHEAR	Cohort Sites	Dozens UG3/UH3
[RFP FY17]	Genetics Core	IDeA States Network	17 Clinical sites & DCOC
One	PRO Core		

Cohort Sites
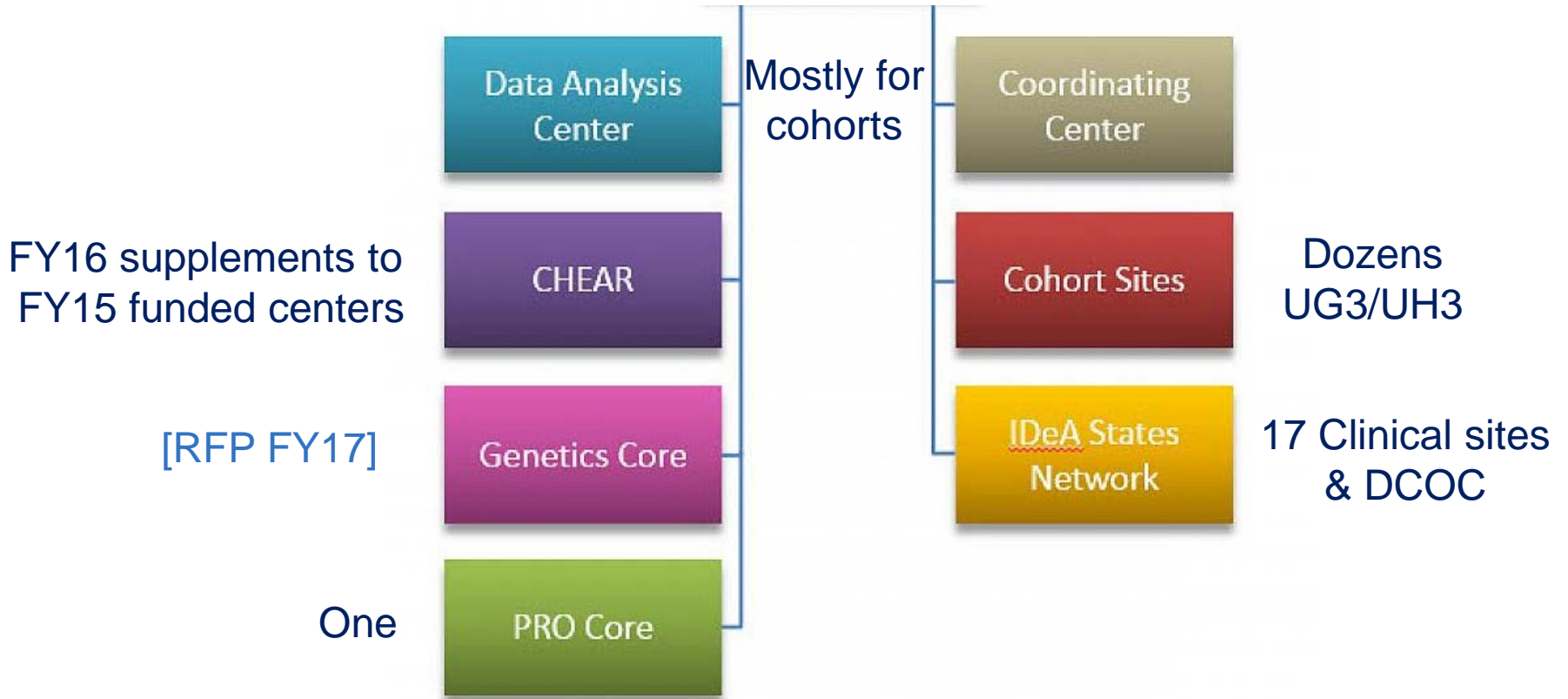
- To achieve greatest value for synthetic cohort(s)
  - Cohort hallmarks—quality measures, good retention
  - Maximize
    - Sample size overall and within the 4 focus areas
    - Diversity—race/ethnicity, sex, geography
  - Incorporate
    - Repeated touches early in life course
      - Pre/peri-conception—Moms & Dads
      - Pregnancy—U/S for fetal growth; real-time placenta
      - Infancy—body composition
    - Above/below skin exposures, pathways, covariates
      - From society to biology
    - Microbiome, metagenomics, epigenomics, metabolomics
    - Innovative analytic approaches

Cohort Sites

- To achieve greatest value for synthetic cohort(s), cont'd
  - Balance
    - Strengths of one-off studies against need to combine/synthesize
    - More mature and newer cohorts
  - Willingness/ability to participate in consortium
  - Overall costs within budget and per-study costs appropriate
- 35 applications funded
  - >35 individual cohorts
  - Institutions in ~38 states/DC/PR

Cohort Sites

|	Sample size (N)						
	Total	Asian	Black or Af-Am	AI/AN	Cauc.	Multi	Hispanic
35 Awardees	69492	3186 (5%)	11567 (17%)	2007 (3%)	45901 (66%)	6762 (10%)	17780 (26%)
Pre/peri/post-natal	15429						
Airways	40430						
Neurodevelopment	41310						
Obesity	38040						

- **DAC**
  - Create, maintain <u>database</u> and interfaces
  - Develop, conduct sophisticated statistical <u>analyses</u>
    - Data <u>harmonization</u> across disparate cohorts
  - Public <u>data sharing</u>
  - Data <u>security</u>
  - Johns Hopkins Univ/RTI
- **CC**
  - Policies, communication, coordination, QC
  - Opportunities and Infrastructure Fund
  - Managing biospecimens, biorepository
 - Duke Clinical Research Inst.

IDeA States Network

- **IDeA States Pediatric Clinical Trials Research Network**
  - Opportunity to enable children in rural and medically underserved locations to participate in clinical research
  - National network for pediatric clinical trials
    - NICHD/NIGMS
    - Support and infrastructure to establishing a teams of highly competent pediatric clinical trial professionals in IDeA states
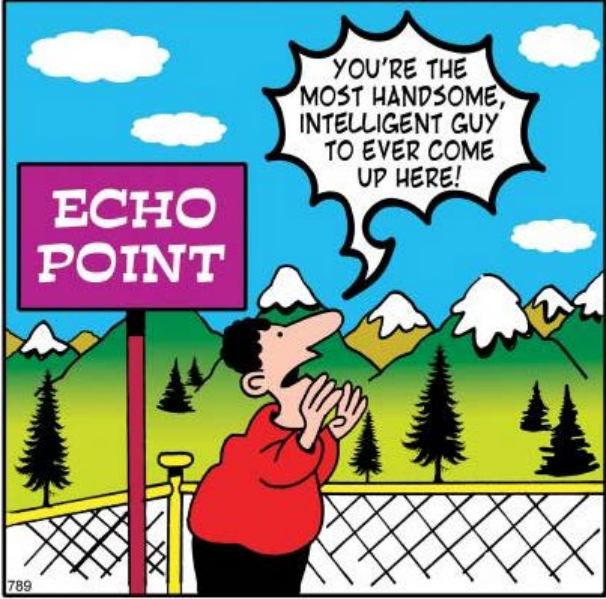   - Data Coordination and Operations Center
    - 17 Clinical Sites

CHEAR
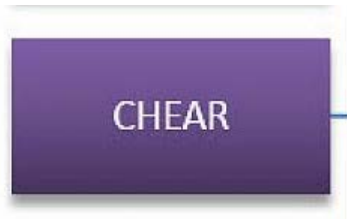
- Children's Health Exposure Analysis Resource
  - National Exposure Assessment Laboratory Network—6 sites
  - Data Repository, Analysis, and Science Center
  - Coordinating Center

- Funded in FY15 to serve academic community

- FY16 administrative supplements to support readiness for analyzing ECHO biospecimens
  - NIEHS
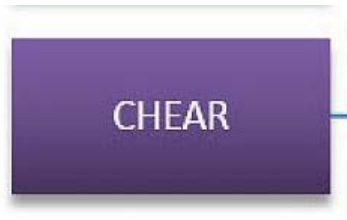
CHEAR unit	Function
CC	Integrate with ECHO workflow
DC	Integrate with ECHO data
WC	Targeted metals, organics
RTI	Primarily untargeted
UMN	Tobacco, nutrients
MSSM	Historical exposures (eg teeth)
Emory	Embed targeted in untargeted
UMI	Increase # analyses

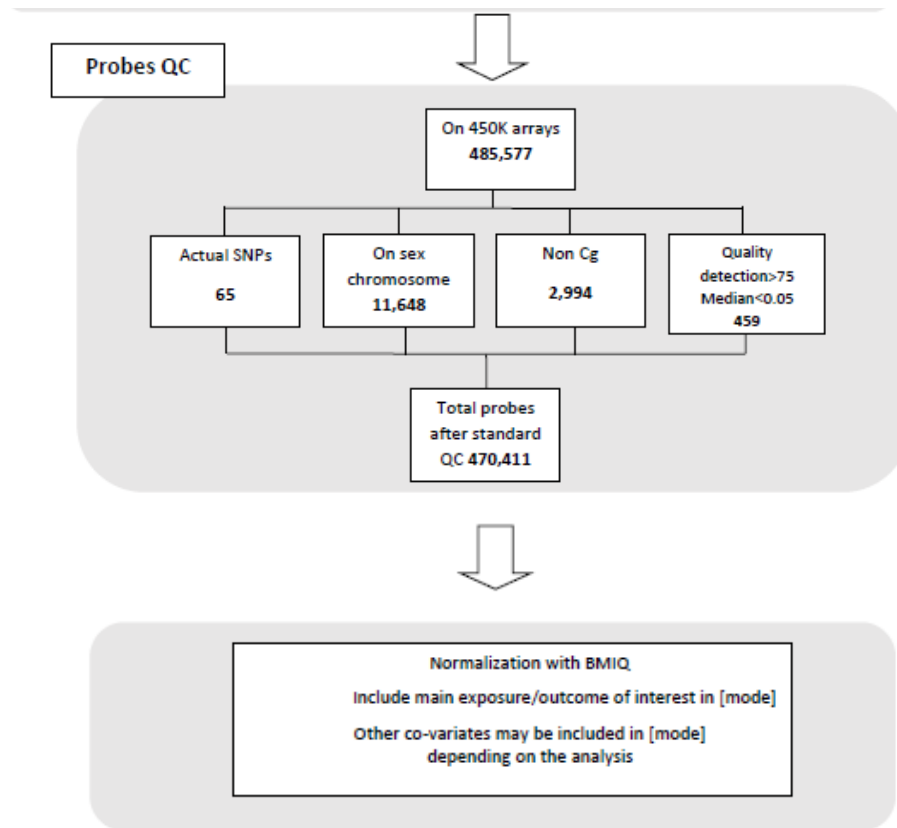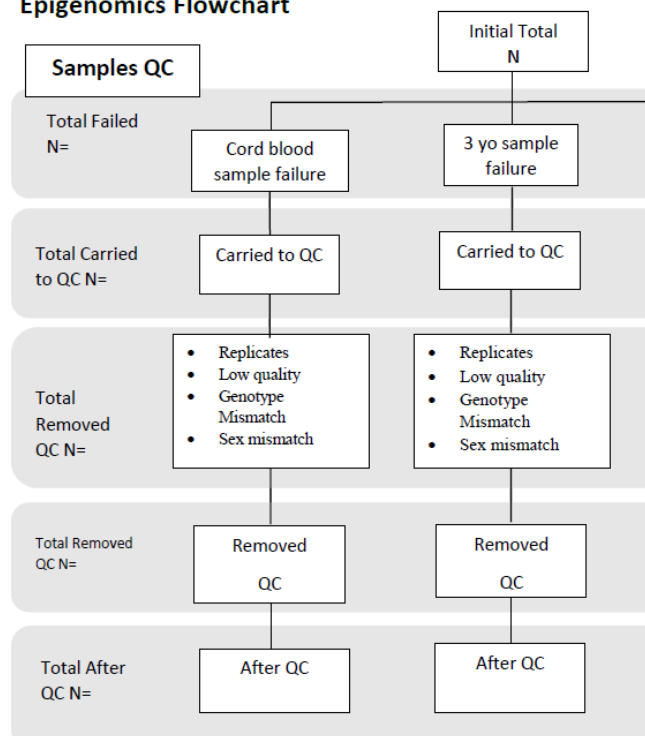PRO Core

- Development and validation of new instruments
- Provide research services and resources to all ECHO Components
  - Psychometric/medical expertise in patient (proxy)-reported measures
- In collaboration with
  - Validation of Pediatric Patient Reported Outcomes in Chronic Diseases (PEPR) Consortium
  - PROMIS, PhenX, Other NIH programs (e.g., Neuro-QOL, NIH Toolbox)
- Northwestern Univ

Epigenomics Flowchart

Samples QC

	Initial Total N	

Total Failed N=
Cord blood sample failure	3 yo sample failure

Total Carried to QC N=
Carried to QC	Carried to QC

Total Removed QC N=

Removed QC: Replicates, Low quality, Genotype Mismatch, Sex mismatch	Removed QC: Replicates, Low quality, Genotype Mismatch, Sex mismatch

Total Removed QC N=
Removed QC	Removed QC

Total After QC N=
After QC	After QC

Probes QC

**On 450K arrays
485,577**

Actual SNPs 65	On sex chromosome 11,648	Non Cg 2,994	Quality detection>75 Median<0.05 459

Total probes after standard QC 470,411

Normalization with BMIQ

Include main exposure/outcome of interest in [mode]

Other co-variates may be included in [mode] depending on the analysis

Analysis

Investigator Choice

Removal-Probes

Cross-reactive Probes

Outliers

SNPs under porobes

Ref: Chen et al. Other?

>3 IQR outside the 25th – 75th percentile

Getting the most updated SNP list

Removing direct SNPs under probe
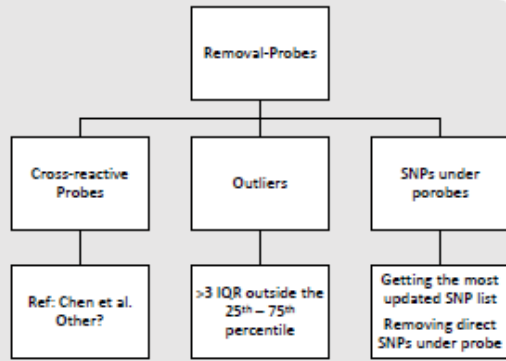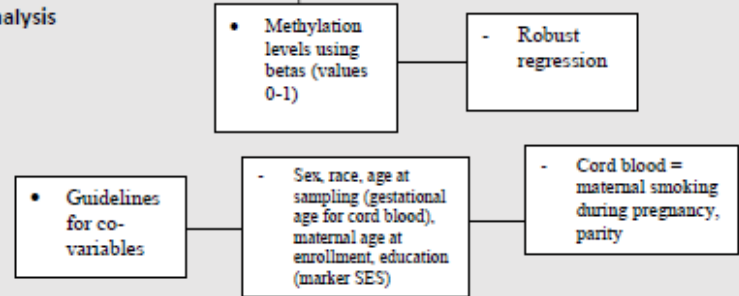
Batch Effect Adjustment = Combat

Additional co-variables that will be in your final regression model for the plan analysis

Cell Count Correction

Cell count estimated using Housman blood cells reference. Using 5out 6- leaving out granulocytes

Regression Analysis

- Methylation levels using betas (values 0-1)

- Robust regression

- Guidelines for co-variables

- Sex, race, age at sampling (gestational age for cord blood), maternal age at enrollment, education (marker SES)

- Cord blood = maternal smoking during pregnancy, parity

Multiple Test Correction

FDR

Interpretation

Annotation bioconductor package R

Cohort Sites

- 102 applications
  - 50 scored
  - Score [min, max; mean] 21, 61; 40
- Recommended applications
  - ECHO WG divided into focus areas for discussion
    - Each focus area group identified top 8-10
      - 26 applications to consider
  - Matt & smaller group married with goals and practices to create tapestry
    - Considered 4 alternate scenarios
    - Discussed with selected IC Directors
    - Final recommendation
      - Added 7 with compelling features to WG-recommended list
      - Total 33 = 31 scored + 2 ND

ECHO Themes
Strategic

- Provide generalizable guideposts/lessons for how to do science in 21st c.
  - Multiple stakeholders
  - Data sharing
  - Harmonization
  - Academic success
  - ECHO as learning system

Strategic

- Incorporate views of multiple stakeholders
  - Congress
  - NIH ICOs
    - ECHO Working Group
  - Investigators
  - Professional Societies
  - Participants, Advocacy Groups

Strategic

- Matching academic success with team science
  - Publication policies
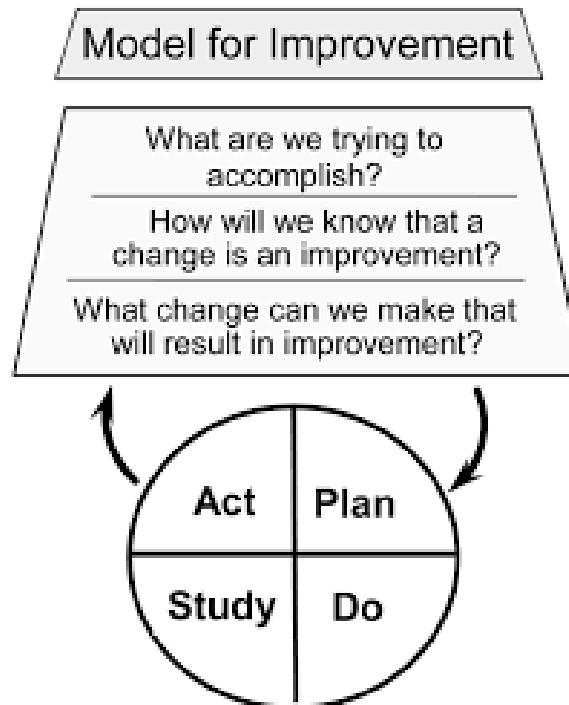 - Promotion policies?

Strategic

- Move the needle on Data Sharing
  - Among investigators
  - For public use
  - With individual participants

Strategic

- Harmonization
  - Squared-off pegs in rounded-off holes
  - Core elements for cohorts
    - Demographics
    - Typical early health and development
    - Genetic influences on early childhood health and development
    - Environmental factors
    - Patient/Person (parent and child) Reported Outcomes (PROs)
  - Bioinformatics is another area of harmonization

Strategic

- ECHO as learning system
  - Rapid cycle evaluation, Continuous Quality Improvement
  - For early wins and sustained impact

Model for Improvement

What are we trying to accomplish?

How will we know that a change is an improvement?

What change can we make that will result in improvement?

Act | Plan
Study | Do

ECHO Themes
Scientific

- Whole is greater than the sum of the parts
  - Questions
    - Solution-oriented
  - Design
    - Synthetic cohorts
      - What can everyone agree upon?
  - Analysis
    - To match conceptual models
    - Causality in observational studies
- Cross-cutting themes
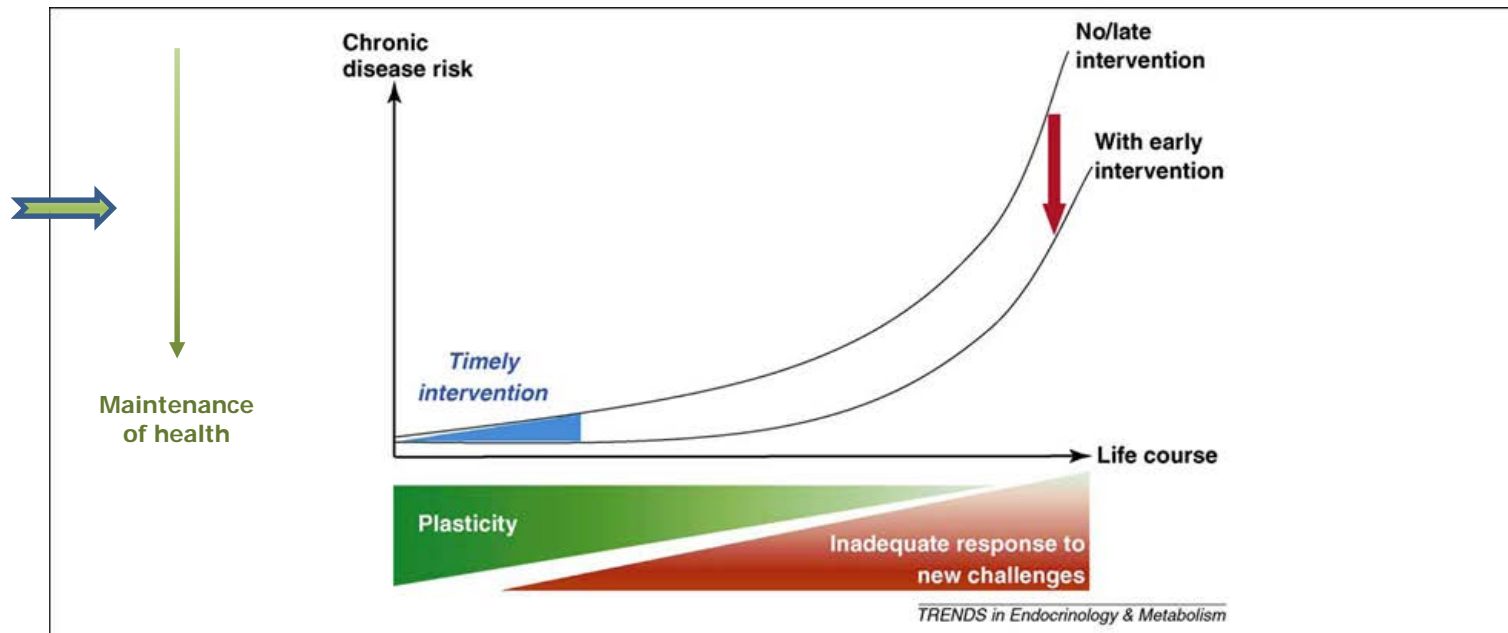
Solution-oriented Questions

- Questions in observational studies that lead to impactful interventions
- Maternal obesity, GWG, GDM
  - Interrelated
  - Interventions to date somewhat disappointing
  - Distinguishing them might lead to more precise interventions
  - Metabolomics could help

Solution-oriented Questions

- Environmental chemicals, air pollution
  - People are generally exposed to mixtures, not single moieties
  - Methodologies needed to examine mixtures

Synthetic Cohorts

- What can everyone agree upon?
  - Something that transcends perinatal, airways, neurodevelopment, obesity/cardiometabolic?
  - Child *health* rather than disease? (EC*H*O)

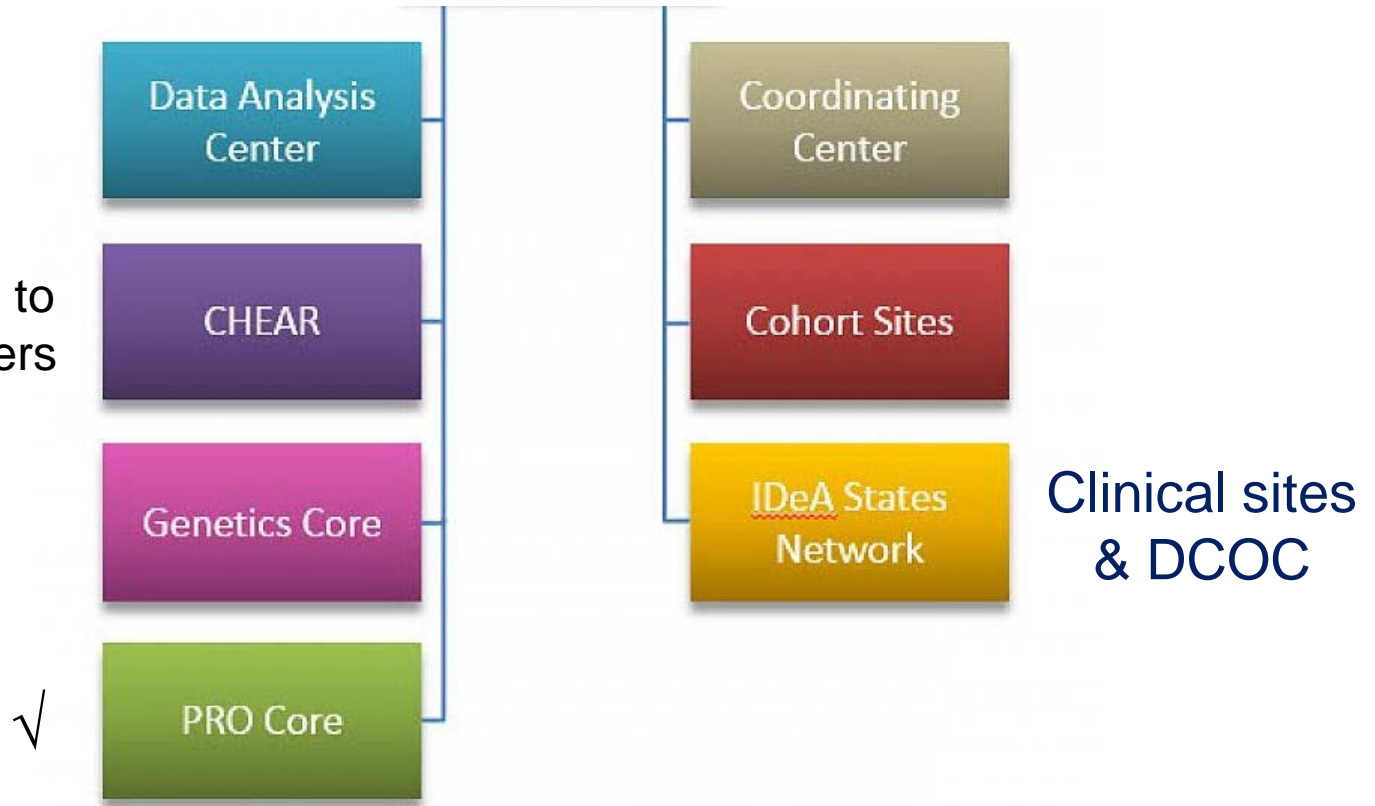TRENDS in Endocrinology & Metabolism

Analytic Methods to Mirror Solution-Oriented Questions

- Exposure mixtures
- Conceptual causal models
  - Intergenerational transmission
    - Biological ("fetal programming")?
    - Socio-cultural, e.g., shared family factors?

ECHO's Components

FY16 supplements to FY15 funded centers

Data Analysis Center

CHEAR

Genetics Core

√ PRO Core

Coordinating Center

Cohort Sites

IDeA States Network

Clinical sites & DCOC

Analytic Methods to Mirror Solution-Oriented Questions

- Exposure mixtures
- Conceptual causal models
  - Intergenerational transmission
    - Biological ("fetal programming")?
    - Socio-cultural, e.g., shared family factors?

- Trajectories of child health
  - Critical periods
- Shared vulnerability for > 1 outcome
- Unpacking complexity
  - Sophisticated approaches to mediation and time-varying confounding
  - Computational systems science simulation modeling