ECHO
Environmental influences on Child Health Outcomes

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NICHD Advisory Council
Today

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

• Understand effects of early environmental exposures on child health and development
Goals

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  – Effects: Observation (& intervention)
Goals

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

• Understand effects of early **environmental exposures** 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 child health and development
  – 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 Program Team
  - Steering Committee (SC)
    - Data Analysis Center
    - CHEAR
    - Genetics Core
    - PRO Core
  - Coordinating Center
    - Cohort Sites
    - IDEa States Network
ECHO Organization

ECHO Program Team

Steering Committee (SC)

Data Analysis Center
CHEAR
Genetics Core
PRO Core

Coordinating Center
Cohort Sites
IDeA States Network
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 **interdisciplinary collaboration** so that whole is more than sum of parts.
• Innovations and consensus-building in **data harmonization, data sharing**
• **Rapid cycle program evaluation** 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 solution-oriented observational studies of early environmental origins of common childhood conditions.
    • Combine above and below the skin pathways to pinpoint more precise potential levers of intervention.
    • Employ sophisticated analytic techniques to distinguish modes of intergenerational transmission.
    • Address early origins of child health as well as disease.

• Support infrastructure and training for randomized trials in pediatrics that link to ECHO themes.
Distinguishing modes of transmission critical for intervention design

Conception to age 5: “First 2000 Days”
- Prenatal
- Perinatal
- Early Childhood

Childhood and Adolescence: Reinforcement or resilience
- Mid-Childhood
- Early Teen
- Mid-Teen

Behaviors, e.g., diet, PA, sleep, smoking

Traffic, air pollution, weather, SES, metals, PFAS

Behaviors

Behaviors

Behaviors

Cardiometabolic Health
Respiratory Health

Early life programming
Postnatal shared behavior/environment

Mother
Child

Multiple mechanisms

home neighborhood chemical

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

FY16 supplements to FY15 funded centers

[RFP FY17]

One

Data Analysis Center

CHEAR

Genetics Core

PRO Core

Mostly for cohorts

Coordinating Center

Cohort Sites

IDEA States Network

Dozens UG3/UH3

17 Clinical sites & DCOC
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
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
<table>
<thead>
<tr>
<th></th>
<th>Sample size (N)</th>
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<tbody>
<tr>
<td></td>
<td>Total</td>
</tr>
<tr>
<td>35 Awardees</td>
<td>69492</td>
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<tr>
<td>Pre/peri/post-natal</td>
<td>15429</td>
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<tr>
<td>Airways</td>
<td>40430</td>
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<tr>
<td>Neurodevelopment</td>
<td>41310</td>
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<tr>
<td>Obesity</td>
<td>38040</td>
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• DAC
  – Create, maintain database and interfaces
  – Develop, conduct sophisticated statistical analyses
    • Data harmonization across disparate cohorts
  – Public data sharing
  – Data security
  – Johns Hopkins Univ/RTI

• CC
  – Policies, communication, coordination, QC
  – Opportunities and Infrastructure Fund
  – Managing biospecimens, biorepository
• 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
• 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
<table>
<thead>
<tr>
<th>CHEAR unit</th>
<th>Function</th>
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<tbody>
<tr>
<td>CC</td>
<td>Integrate with ECHO workflow</td>
</tr>
<tr>
<td>DC</td>
<td>Integrate with ECHO data</td>
</tr>
<tr>
<td>WC</td>
<td>Targeted metals, organics</td>
</tr>
<tr>
<td>RTI</td>
<td>Primarily untargeted</td>
</tr>
<tr>
<td>UMN</td>
<td>Tobacco, nutrients</td>
</tr>
<tr>
<td>MSSM</td>
<td>Historical exposures (eg teeth)</td>
</tr>
<tr>
<td>Emory</td>
<td>Embed targeted in untargeted</td>
</tr>
<tr>
<td>UMI</td>
<td>Increase # analyses</td>
</tr>
</tbody>
</table>
• 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
YOU'RE THE MOST HANDSOME, INTELLIGENT GUY TO EVER COME UP HERE!

YO! OY! OY!
Epigenomics Flowchart

Samples QC
- Total Failed N=
  - Cord blood sample failure
- Total Carried to QC N=
  - Carried to QC
- Total Removed QC N=
  - Replicates
  - Low quality
  - Genotype mismatch
  - Sex mismatch
- Total After QC N=
  - After QC

Initial Total N

Probes QC
- On 450K arrays 485,577
  - Actual SNPs 65
  - On sex chromosome 11,648
  - Non Cg 2,994
  - Quality data: 75% Median 0.05 439
- 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

- Cross-reactive Probes
  - Ref. Chen et al. Other?
  - SNP outside the 25th - 75th percentile
- Outliers
- SNPs under probes
  - 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 Sout 6-leaving out granulocytes

Regression Analysis
  - Methylation levels using betas (values 0-1)
  - Robust regression
  - Sex, race, age at sampling (gestational age for cord blood), maternal age at enrollment, education (marker SES)
  - Cord blood = maternal smoking during pregnancy, parity

Guidelines for co-variables

Multiple Test Correction
  - FDR

Interpretation
  - Annotation bioconductor package R
• 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 21\textsuperscript{st} 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
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? (ECHO)
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

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- Data Analysis Center
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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