ECHO
Environmental influences on Child Health Outcomes

NIH Advisory Committee to the Director

Matthew W. Gillman, MD, SM
8 December 2016

ECHO Overall Scientific Goal

Answer crucial questions about effects of broad range of early environmental exposures on child health and development
Why ECHO?

Why now?

A good start to life…
…can last a lifetime
To ensure a good start, need to understand potential risks…
To ensure a good start, need to understand potential risks… …and to whom they apply…

... then take action
ECHO Approach

- Focus on high-impact pediatric conditions
  - Pre/peri/postnatal outcomes
  - Obesity
  - Upper & lower airway
  - Neurodevelopment
  - Child health

ECHO Approach

Observational studies
Intervention trials
Meet Scientific Needs

- **Intervention trials**
  - Kids underrepresented in clinical trials
  - Especially hard-to-reach populations
    - Rural, medically underserved

- **Observational studies**
  - Ask solution-oriented questions
    - Questions that inform practice & policy
    - Inform, and informed by, trials
  - Sufficient number of participants for power, heterogeneity, generalizability
  - Include newer technology, biological pathways
  - Modern concepts of cause-effect relationships

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**FY16 Funding**

- ECHO Applications received: 162
- Cohort studies: 100
- Considered in detail by program to maximize:
  - Sample size overall & in focus areas
  - Diversity—race/ethnicity, sex, geography
  - Scientific impact
  - Engagement
- Presented to Council of Councils: 52
- Awarded: 35

Other components incl. IDeA States Pediatric Clinical Trials Network
Major Objective: Create ECHO-wide Cohort

- Start with multiple existing cohort studies
  - Increase likelihood of early successes
- Create data platform to conduct solution-oriented observational research
  - Standardized measures
    - Exposures
    - Parent/child-reported outcomes
    - Genes
- Goal >50,000 children
- Use
  - ECHO investigators
  - National research resource

ECHO-wide Cohort
Many people, many layers of data, many stages of life course
ECHO-wide Cohort
Integrating into whole

35 awards
74 PIs, 78 cohorts
-Majority started prenatally-

Cohort Prime Awardees
Cohort Sub-Awardees
On the way to >50,000...

Current:
~33,000 mothers
~46,000 children

Cohort Prime Awardees
Cohort Sub-Awardees

Diversity in geography, age, sex, social class, race/ethnicity
~46000 kids, currently

<table>
<thead>
<tr>
<th>Diversity Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asian</td>
</tr>
<tr>
<td>5%</td>
</tr>
<tr>
<td>Hispanic</td>
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</tbody>
</table>

Preliminary Data
ECHO Cohorts
2 Phases

• Phase I: 2 years
  – Pilot/feasibility
  – Engagement

  ↓ Meet milestones

• Phase II: Additional 5 years
  – Major scientific questions

Early Wins
Phase I

• Analyses on existing multiple-cohort data
  – Distributed data analysis approach
    • “Send programs to data”
  – Aggregate results
    • No sharing of individual-level needed yet
ECHO-wide Cohort Example
Phase I

- Factors during pregnancy and infancy that lead to childhood obesity

- Geographic data
  - Air pollution
  - Access to food/activity

NIH
Environmental influences on Child Health Outcomes (ECHO)
ECHO-wide Cohort Example
Phase I

- Factors during pregnancy and infancy that lead to childhood obesity
  - Geographic data
  - Biosamples
  - Self-report and sensors
Other Major Year 01 Goal

- IDeA States Pediatric Clinical Trials Network
  - Infrastructure and training in place to begin ≥1 clinical trial
Cohorts Address Wide-Ranging Questions
Phase II

- ECHO-wide cohort
  - Existing and new data
  - 2 levels
    - All cohorts: Broad level with common data elements
    - Subset with deeper measures
- Will have in hand
  - Pilot & feasibility results
  - New data collection protocol
    - Informed consent
    - Data & biospecimen sharing policies
ECHO-wide Cohort Example
Phase II

- Pre- and post-natal exposure to smoking, and trajectories of development of childhood wheezing and asthma
  - How much associations differ by
    - Maternal or child genetics
    - Socio-demographic factors
    - Sex of child
  - Mediated by
    - Immune development?
    - Functional changes in gut bacteria?

Getting the Work Done

- Foster culture of collaboration
  - Best practices to conduct team science in 21st c.
Getting the Work Done

• Foster culture of collaboration
• Investigators drive the science
  – Lead working groups

• Active involvement of NIH Institutes, Centers, and Offices
  – Ideas for measures, questions
  – Links with other NIH programs
  – Potential future co-funding

• Guidance by External Scientific Board
  – Reports to NIH Director via Council of Councils
Long-term

- Conduct innovative observational and intervention research
  - Answer crucial questions about child health and development
  - Inform programs, policies, and practices that improve health of children and adolescents

Enhance the health of our nation’s children for generations to come
Capitalizing on ECHO’s multiple support components

- Measurement of tobacco-related compounds
  - Children’s Health Exposure Analysis Resource (CHEAR)
- Valid covariate and outcome measures
  - Patient-reported Outcomes Core
    - NIH resources, e.g., PROMIS, PhenX, NIH Toolbox
- Genetics Core
Capitalizing on ECHO’s multiple support components

• State-of-science analyses involving exposure mixtures, confounding/mediation, combined outcomes
  – Data Analysis Center

• Special features, e.g., microbiome
  – NIH and cohort expertise

• Putting the operational pieces together
  – Coordinating Center

### ECHO v. NCS

<table>
<thead>
<tr>
<th></th>
<th>NCS</th>
<th>ECHO</th>
<th>Overcomes</th>
<th>Challenge</th>
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<tbody>
<tr>
<td>Cohorts</td>
<td>New</td>
<td>Existing</td>
<td>Recruitment issues</td>
<td>Data harmonization</td>
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<tr>
<td>Mechanism</td>
<td>Contracts</td>
<td>Cooperative agreements</td>
<td>Inflexibility</td>
<td>Engaging PIs in the commons</td>
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<td>Lead institute</td>
<td>NICHD</td>
<td>OD</td>
<td>Balkanization</td>
<td>Engaging all ICs</td>
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<tr>
<td>Components</td>
<td>~Single</td>
<td>Multiple, incl. IDeA States Network</td>
<td>No intervention component</td>
<td>Integration into whole</td>
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<tr>
<td>Leadership</td>
<td>Non-scientist</td>
<td>Scientist</td>
<td>Perceived lack of leadership</td>
<td>Following NIH processes</td>
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<tr>
<td>Outcomes</td>
<td>Agnostic</td>
<td>4 initially specified</td>
<td>Lack of focus</td>
<td>Bridging across silos</td>
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<tr>
<td>Phenotyping</td>
<td>More superficial</td>
<td>Deeper</td>
<td>Not enough biology, technology</td>
<td>Biospecimen ownership, measurement</td>
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<tr>
<td>Funding</td>
<td>Not initially appropriated</td>
<td>Line item in OD budget</td>
<td>Year-to-year uncertainty (?)</td>
<td>Still must prove worth</td>
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</table>
**ECHO Challenges & Responses**

<table>
<thead>
<tr>
<th>ECHO</th>
<th>Challenge</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohorts</td>
<td>Existing Data harmonization</td>
<td>Ontologies, new methods</td>
</tr>
<tr>
<td>Mechanism</td>
<td>Cooperative agreements Engaging PIs in the commons</td>
<td>PI-led working groups, UG3 milestones</td>
</tr>
<tr>
<td>Lead institute</td>
<td>OD Engaging all ICs</td>
<td>Project Scientists (Trans-NIH group)</td>
</tr>
<tr>
<td>Components</td>
<td>Multiple, incl. IDeA States Network Integration into whole</td>
<td>Working group membership, content overlap</td>
</tr>
<tr>
<td>Leadership</td>
<td>Scientist Following NIH processes Teamwork, incl. trusted deputy</td>
<td></td>
</tr>
<tr>
<td>Outcomes</td>
<td>4 initially specified Bridging across silos Add Child Health outcome</td>
<td></td>
</tr>
<tr>
<td>Phenotyping</td>
<td>Deeper Biospecimen ownership; measurement PI's develop policies: CHEAR, PRO &amp; Genetics</td>
<td></td>
</tr>
<tr>
<td>Funding</td>
<td>Line item in OD budget Still must prove worth Early win analyses</td>
<td></td>
</tr>
</tbody>
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**ECHO Cohorts**

**UG3 Milestones and Performance Metrics**

- **Cohort-specific**
  - Participant retention, accurate data
- **Collaborative**
  - Showing up, leadership, creating/agreeing to rules of the road, sharing data, participating in multi-cohort-wide analyses
- **Stretch Goals and Acceptable Goals**
  - Meet 100% Acceptable Goals to go to UH3
    - Achievable
ECHO-Wide Cohort
“Dynamic Cohort of Inception Cohorts”

Cohorts recruited at different points in the life course and in different eras with heterogeneity in retention within each and different follow-up schedules and different measures.
One Challenge
Phase I

- Harmonizing existing data

ECHO Funding

- $165m per year for 7 years
  - Annual appropriation
    - CC, DAC, PRO Core, Cohorts
      - NIAID
  - Exceptions
    - CHEAR funded for 4 years
      - NIEHS
    - IDeA States Pediatric Clinical Trials Network
      - Forward funded for 4 years
      - NIGMS, NICHD
    - Genetics Core FY'17
      - NIDCR, NHGRI developing
Working Across Disciplines

- What transcends perinatal, airways, neurodevelopment, obesity?
- Child *health* rather than disease (ECHO)
1 from each component,
2 from cohorts
1 from each component,
35 from cohorts
ECHO Themes

Strategy

• Provide best practices for how to do team science in 21st century
  • ECHO as Learning System
    • Promote transdisciplinary collaboration among many layers of stakeholders
    • Team science evaluation to improve our program processes and outcomes in real time
ECHO Themes
Strategy

• Provide best practices for how to do team science in 21st century
  • ECHO as Learning System
    • Promote transdisciplinary collaboration among many layers of stakeholders
    • Team science evaluation to improve our program processes and outcomes in real time
  • Innovations and consensus-building in data sharing, data harmonization, use of biospecimens, publication policies
    • Intellectual enterprises, potential publications
    • Needed to achieve our scientific aims
    • Our Cross-cutting working groups

The science of team science

Transdisciplinary approach

--K. Hall, NCI, and others
Move the Needle on Data Sharing

- Among investigators
- For public use
- With individual participants

“It’s just for genetics”
“[Institute’s] I’ve got 10 million variables in raw form and another 10,000 derived variables, and I’ve spent years cleaning them. No one else will understand how to use them, especially longitudinally.”
“I don’t want my data out there before my team—esp. my junior investigators—and I have a chance to analyze them.”
“NIH says I have to do it, so I will—but just the minimum necessary.”
Move the Needle on Data Sharing

• Need for nuanced approach
  – Adheres to the principles
    • We win when we all win
    • Big data are better than small
    • Publicly funded data are, in the end, public
  – Takes into account investigators’ fears
  – Plays by the rules
• Lessons learned from IC consortia

Cohorts “Demographic” Data (N = 84)

<table>
<thead>
<tr>
<th>Life course stage at enrollment of participants</th>
<th>N (%) cohorts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preconception</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Prenatal</td>
<td>48 (57%)</td>
</tr>
<tr>
<td>Infancy</td>
<td>27 (32%)</td>
</tr>
<tr>
<td>Toddler/early childhood</td>
<td>6 (7%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristic of participants</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mothers enrolled, N</td>
<td>~33000</td>
</tr>
<tr>
<td>Children enrolled, N</td>
<td>~46000</td>
</tr>
<tr>
<td>Age of children, y</td>
<td>Range 0 – 36</td>
</tr>
<tr>
<td>Minimum age, median</td>
<td>1.5</td>
</tr>
<tr>
<td>Maximum age, median</td>
<td>7.0</td>
</tr>
</tbody>
</table>
Solution-oriented Questions

• “So-what” questions in observational studies that lead to impactful interventions, policies, programs, practices
• Prevention
  – Primordial prevention?
  – Risk stratification, “Precision prevention?”

Analytic Methods to Mirror Solution-Oriented Questions

• Conceptual causal models
  – Intergenerational transmission
    • Biological (“fetal programming”)?
    • Socio-cultural, e.g., shared family factors?
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
  – Reversibility

• Shared vulnerability for > 1 outcome
  – Obesity & asthma
    • Each one causes the other, and
    • They have common underpinnings
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
• Shared vulnerability for > 1 outcome

• Unpacking complexity
  – Sophisticated approaches to mediation and time-varying confounding
  – Computational systems science simulation modeling

Cross-cutting issues

• Heterogeneity
  – Geographic, social, demographic (incl. sex)
• Explaining disparities
  – Racial/ethnic, socio-economic
• Replication
Solution-oriented Questions
From Kickoff Meeting—Use extant data

• To what extent do the following modifiable exposures in the pre- and peri-natal periods, individually and in combination, affect trajectories of linear growth during infancy (which predicts better later health)?
  – Hypertensive disorder of pregnancy
  – Gestational weight gain
  – Smoking
  – Infection of mom or baby
  – Pre- or postnatal steroids
  – Feeding type

• How do these associations differ according to genetic predisposition, preterm v. term, geography, sex, race/ethnicity?

All Components Under 1 Umbrella

• Ideas for integrating Cohorts and IDeA States Network
  – Test observations in intervention trials
    • And vice versa
  – Trials favor prevention or treatment of ECHO focus area conditions
  – IDeA States Network investigators members of cross-cutting working groups
    • Develop principles and policies for 21st c. team science
External Scientific Board
Requested Counsel

• Incorporating all ECHO components under one umbrella
• Attending to numerous strata of stakeholders
• Building a culture of collaboration and synergy
• Harmonizing data across disparate cohorts
• Capitalizing on expertise within as well as outside NIH
• Ensuring early and sustained successes
• Using funds wisely
• …Others?

External Scientific Board
Membership

• Working group of Council of Councils
  – 1 Council member
    • Children’s Environmental Health Network
  – 1 IDeA States Network Steering Comm. Chair
  – 3 Academic leaders
    • Genetics, toxic environment, neighborhood and social factors
    • NIH, NCS, FDA, CDC, IOM, Gates, etc.
  – 1 Parent, nominated by March of Dimes
  – 1 AI/AN representative, nominated by TCAC
  – 1 Big data maven?
“ECHO is like herding…lions”

ECHO

- Engender culture of collaboration
- Hit the scientific ground running
  - Show early successes
  - Become one of the nation’s pre-eminent research program in child health
ECHO Foci

- Outcome focus areas
  - Pre-, peri-, postnatal
  - Upper and lower airway
  - Obesity
  - Neurodevelopment
- 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)

ECHO—The Other Five FY’16 Components

Coordinating Center Data Analysis Center
Health Measurement Core
CHEAR ISPCTN DCOC
Strategic

- Harmonization
  - Squared-off pegs in rounded-off holes
  - Core data 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

**ECHO Cohorts**

**UG3 Milestones and Performance Metrics**

*Cohort-specific*

<table>
<thead>
<tr>
<th>Individual cohort-specific—NIH negotiates with each cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Item</strong></td>
</tr>
<tr>
<td>Enrollment (for some)</td>
</tr>
<tr>
<td>Re-contacted</td>
</tr>
<tr>
<td>Informed consent</td>
</tr>
<tr>
<td>Analyzable data including exposures of interest</td>
</tr>
<tr>
<td>Publications</td>
</tr>
</tbody>
</table>

- Enrolled (N)
  - +/- Followed in the interim
  - +/- Need to re-contact (%)
  - Retained/ enrolled (%)
  - Informed consent for ECHO-wide research (%)
ECHO Cohorts
UG3 Milestones and Performance Metrics

Collaborative

<table>
<thead>
<tr>
<th>Item</th>
<th>Metric</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Policies: publication, data sharing, biospecimen</td>
<td>Agreed (~signed)</td>
<td>September 2017</td>
</tr>
<tr>
<td>New ECHO multi-cohort data collection protocol</td>
<td>Submitted to IRB</td>
<td>September 2017</td>
</tr>
<tr>
<td>Participation in “early-win” collective analyses</td>
<td>1+</td>
<td>September 2017</td>
</tr>
<tr>
<td>Attendance</td>
<td>Steering Committee meetings (&gt;90%)</td>
<td>June 2018</td>
</tr>
<tr>
<td>Leadership</td>
<td>Leader of working group or its subcommittee</td>
<td>June 2018</td>
</tr>
<tr>
<td>Submission of participant-level data to Data Analysis Center</td>
<td>Enough for 1+ multi-cohort analyses</td>
<td>June 2018</td>
</tr>
<tr>
<td>ECHO multi-cohort publications</td>
<td>1+</td>
<td>June 2018</td>
</tr>
</tbody>
</table>

DOHaD Interdisciplinary Approach

Population-based Studies
- Cohort studies
- Randomized trials
- Biomarkers

Clinical Studies
- Tissue biopsies
- Molecular markers
- Small trials

Hypothesis testing

Animal Models
- Physiology
- Metabolism
- Genetic Susceptibility
- Epigenetic mechanisms

In Vitro Studies
- Isolated tissue studies
- Molecular markers
- Epigenetic mechanisms

Strategy

Thanks to Sue Ozanne
For maximal impact...

Need the right evidence...
Guiding Principles

• Teamwork
  – Working well together

• Impact
  – Research that has an impact on health

• Responsibility
  – Scientifically & ethically sound research

• Value
  – Return on investment in the eyes of Congress, NIH, investigators, and public

Developmental Origins of Health and Disease

• DOHaD emphasizes prenatal period and early childhood as important periods for development of chronic disease throughout life
Today

Cohort = group of participants followed over time