

# **AN OVERVIEW OF THE ECHO PROJECT IN MICHIGAN: OPPORTUNITIES FOR ENVIRONMENTAL RESEARCH IN CHILD HEALTH**

Nigel Paneth MD MPH

Departments of Epidemiology &  
Biostatistics and Pediatrics & Human  
Development

THE ECHO PROGRAM IS THE REPLACEMENT  
FOR THE FAILED  
NATIONAL CHILDREN'S STUDY

AFTER THE NCS WAS CANCELLED BY NIH,  
CONGRESS ASKED NIH TO COME UP WITH A  
ALTERNATIVE DESIGN FOR A NATIONAL  
CHILDREN'S STUDY

**A BRIEF HISTORY OF  
THE NATIONAL CHILDREN'S STUDY,  
AND ITS SUCCESSOR  
THE ECHO PROGRAM**

or

**THE RISE, FALL AND RISE AGAIN OF THE  
BIG STUDY OF CHILD HEALTH**

# NCS PHASE 1: 2000-2008: A WING AND A PRAYER

- In 2000, Congress passed the Children's Act, which authorized (but did not fund) a very large (N = 100,000 participants) study of child health for the purpose of uncovering early risk factors in the environment for childhood disease.
- However, the Bush administration did not allocate funds for the study, and for the following 8 years, only planning activities were conducted with limited resources.
- A complex and expensive study was designed, which **planned to recruit its subjects via door-to-door household recruitment in pregnancy**. This unprecedented manner of recruitment, which was viewed skeptically by many with experience in pregnancy research, was affirmed both by a special expert committee in 2004 and by the Institute of Medicine in 2006.

# MEANWHILE, BACK HERE IN MICHIGAN

- A group of investigators in Michigan met in 2002 to think about responding to the newly announced NCS, whenever it would start.
- We formed an alliance, representing five Michigan institutions, **MSU, U of M, WSU, HFHS, MDHHS**, and called ourselves MANCS, the Michigan Alliance for the NCS. Imagining that the study would want centers around the country, we thought we would be well positioned to be a lead center in the Mid-West.
- In 2004, a population-based design was announced, in which 100 counties were selected to represent the US; **5 of the counties were in Michigan** (Wayne, Macomb, Grand Traverse, Genesee, Lenawee)
- In 2007, we were awarded contracts totaling \$75 M to conduct the NCS in those 5 counties over the next 5 years.
- As it turned out, we were only permitted to recruit pregnancies for a short period of time in 2011, and only in Wayne County, but we managed that recruitment very successfully. \$65 M of the contract funds were unspent.

# PHASE 2: 2008-2015: FROM STAGNATION TO DISASTER

- With the election of President Obama, full funding for the NCS (\$165M/year) was initiated, and 40 centers (including MANCS) signed contracts to perform the study in their locations, via pregnancy recruitment in the sampled counties.
- A new administrative team was brought in, but it had little or no experience in epidemiologic studies
- Management was hectic, with many course changes.
- Most disturbingly, hypotheses were abandoned, the population-based sampling was changed to convenience sampling, and pregnancy recruitment was replaced by birth recruitment for 50% of the sample.
- One bright spot was that clinic-based pregnancy recruitment was *eventually* viewed as the best option for recruiting pregnancies

# PHASE 3: THE AXE FALLS

- Investigator discontent with the NCS across the country was channeled to congressional representatives, who required, in the 2013 allocation bill, that “**any new design for the NCS must be reviewed by IOM**”
- The IOM performed its review in 2014, and was harshly critical of the NCS, especially of its decision to abandon population sampling, and the halving of pregnancy sampling. One chapter of the report addressed management problems at NIH and recommended formal scientific oversight.
- Frances Collins appointed an advisory committee to recommend what to do, and the committee recommended the study be ended.
- The study spent \$1.3 billion dollars and enrolled some 4,000 – 5,000 pilot phase pregnancies across the nation. The advisory committee did not think investing in follow up of these children would be useful.
- In 2015, Congress asked NIH to provide **an alternative design** for a national children’s study.

# THE MICHIGAN ALLIANCE CONTINUES...

- After cancellation of the NCS, and in light of our success in pregnancy recruitment/follow-up in Wayne County, we continued as a coalition, seeking ways to conduct **a state version of the NCS in Michigan, based on recruiting a representative sample of pregnancies in our state.**
- We renamed ourselves **CHARM (which stands for Child Health Advances from Research with Mothers).**
- With local university resources and the Michigan University Research Corridor, we sampled the 83 hospitals in the LP of Michigan to obtain a stratified sample of 10 hospitals. We then sampled two referring clinics to each hospital. We refer to this planned statewide cohort as **MARCH (Michigan Archive for Research in Child Health).**
- We then began to seek funding, beginning with the Michigan Health Endowment Fund.



# THE MICHIGAN HEALTH ENDOWMENT FUND (MHEF)

- The State Health Care Corporation Reform Act requires BC/BS of Michigan to contribute up to \$1.56 billion over 18 years to a Health Endowment Fund whose purpose is to support efforts to improve the quality of health care while reducing costs, and to benefit the health and wellness through funding of programs for **minor children** and seniors, with special focus on
  - **infant mortality**
  - **behavioral health**
  - healthy aging
  - wellness and fitness programs
  - **access to healthy food**
  - technology enhancements
  - health related transportation needs
  - foodborne illness prevention
- <http://healthendowmentfund.org/about/>

# OUR SUPPORT FROM MHEF

- Working closely with our MDHHS partners, we obtained two grants from MHEF in 2016 to support pregnancy surveying in real time to improve maternal and child health outcomes in our state.
- One grant (one year) supports pregnancy recruitment in Detroit and Flint; the second grant (two years) supports pregnancy recruitment throughout the state
- We refer to these grants, which are not viewed as supporting research, but as supporting public policy development, **as MIM (Mothers in Michigan) 1 and 2.**
- These grants allowed us to begin the creation of the representative pregnancy cohort we feel is needed to study the origins of child health problems in our state.
- Our focus in MIM is on learning about the problems **women** face in pregnancy. We thus interview about stress, diet, health concerns, use of state programs, and we have a special focus on use of tobacco, alcohol and opioids.
- We also work closely **with MI-AIM (Michigan Alliance for Innovation on Maternal Health)** on maternal mortality/severe morbidity reduction, and ask questions and review medical records in support of their objectives.

## PHASE 4: THE ECHO PROGRAM, 2016 -

- In summer 2016, NIH defined the “alternative to the NCS” as a large study that would amalgamate “**extant cohorts**” of mothers and newborns, but “**expansion**” of extant cohorts was permitted.
- The study was named ECHO (Environmental Influences on Child Health Outcomes) and was to focus on four child health outcomes.
  - **Obesity**
  - **Neurodevelopment**
  - **Pregnancy outcomes**
  - **Asthma**
- NIH issued an RFA for cooperative agreements, to be managed from the Director’s Office (i.e. not in any one NIH institute)
- Congress allocated \$160M in 2016 for ECHO, about the same annual allocation as for the NCS
- In September, 2016, awards were made to 35 “pediatric cohorts” nationally, including to CHARM.

# STRUCTURE OF THE GRANT

- The grant is a UO1 – cooperative agreement – thus jointly managed by NIH and by investigators.
- The grant has two phases
  - UG3 – **two years – 9/2016 – 9/2018**. Pilot testing, instrument and data development, recruitment and retention feasibility, design of the main study.
  - UH3 – **five years – 9/2018-9/2023**. Carrying out the main study.
- Each cohort has to meet several metrics by **June 2018** to move on to the UH3 phase.

# THE MICHIGAN ECHO COHORTS

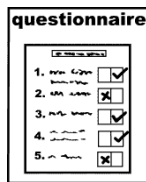
- We described three existing pregnancy cohorts in our NIH application – all convenience samples
  - **ARCH (Archive for Research in Child Health)** – 854 pregnancies recruited 2008 – 2016 in Lansing
  - **MMIP (Michigan Mother-Infant Pair Study)** – 133 pregnancies recruited since 2012 in Ann Arbor
  - **Pilot for MARCH (Michigan ARCH)** – 130 pregnancies 2016 - 2017 in Detroit, Flint, Grand Rapids and Traverse city enrolled in preparation for ECHO.
- Most importantly, we described our representative statewide sample (MARCH) as an **expansion of the ARCH cohort**. We plan to recruit at least 1,000 pregnancies in 20 clinics in our state.
- Because of the **water contamination in Flint**, we added Hurley hospital and its prenatal clinic as an extra recruitment location.

# WHAT IS ARCH?

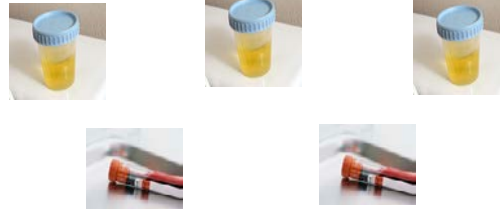
- The ARCH (Archive for Research in Child Health) recruited pregnancies in up to 3 Lansing prenatal clinics from 2008-2016, and follows the families by phone annually.
- The idea behind ARCH is that to really understand the origins of childhood diseases, we need more real-time information on pregnancy.
- In prenatal care, we archive medical and socio-demographic information about patients, but we discard biological material (blood, urine, placenta). The biological material is scientifically valuable, so why throw it away? Why not archive biological material in pregnancy so that it can be assessed later when children have problems?
- Supplement the above with interviews in pregnancy, and you have a database of important data to explore for risk factors for childhood diseases.
- ARCH was supported by MSU funds, and is low cost - using volunteer recruiters/interviewers, archiving specimens collected for clinical purposes, designed for work in community health settings.
- For the above reasons, collections are not as complete as we would wish
- With funds from a competitive MSU grant, a subset of ARCH (n = 125) had full developmental assessments at a mean age of five.

# ARCH DATA COLLECTION

## 1. Prenatal Clinic



SURVEY OF ACTIVITY,  
CONSENTS DIET, SES, OTHER  
ISSUES



3 URINES (EACH TRIMESTER)

2 BLOODS (1<sup>ST</sup> , LATE 2<sup>ND</sup>  
TRIMESTER)

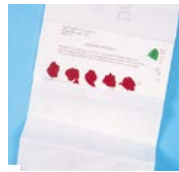
## 2. Delivery Hospital



SAMPLE OF  
PLACENTA,  
CORD, MEMBRANE



ACCESS TO  
NEWBORN BLOOD SPOT



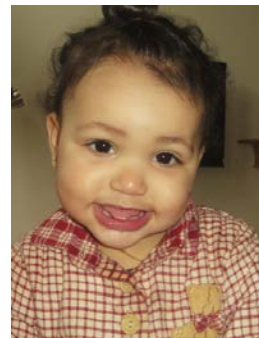
BIRTH  
CERTIFICATE



MEDICAL  
RECORDS

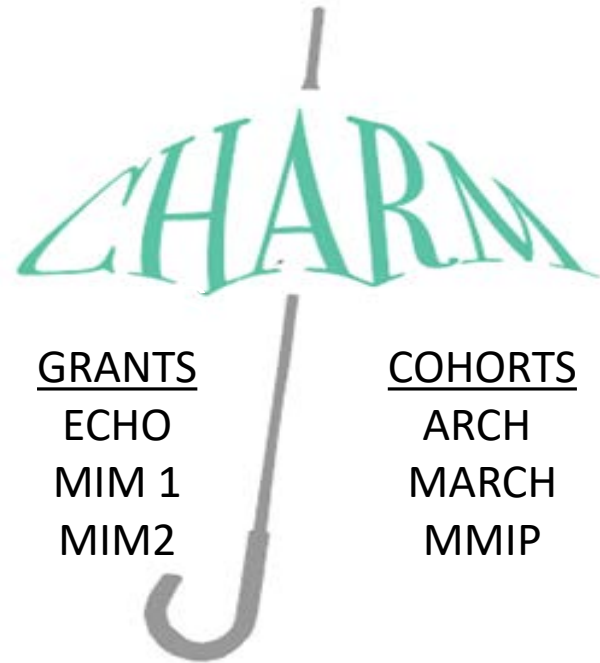
## 4. At Home

TELEPHONE INTERVIEW  
ABOUT CHILD HEALTH



Urines and bloods  
aliquotted and stored  
At -80C

# CHARM IS THUS THE UMBRELLA FOR SEVERAL COHORTS AND SEVERAL FUNDING SOURCES



CHARM is a coalition of researchers from our 5 institutions with many skills relevant to the study of maternal and child health. We may undertake additional studies, including trials generated by our observations, under the same umbrella.



# AIMS OF OUR ECHO PROJECT

We have one aim for each of three exposures: environmental chemicals, nutrients and infection/inflammation. These are first to be studied in the ARCH child development cohort (N = 125), and then on the larger cohorts supported by ECHO.

- AIM 1: To determine the effects of persistent organic pollutants (POPs) and heavy metals, assessed across two generations, on **cognitive outcomes**
- AIM 2: To assess the effect of maternal nutritional and weight status in pregnancy on **cognitive outcomes** and childhood obesity.
- AIM 3: To assess the effects of pregnancy viral infection and weight-associated inflammation in placenta and NDBS, on perinatal outcomes and behavior related to the **autism spectrum**

# MANAGEMENT STRUCTURE OF CHARM

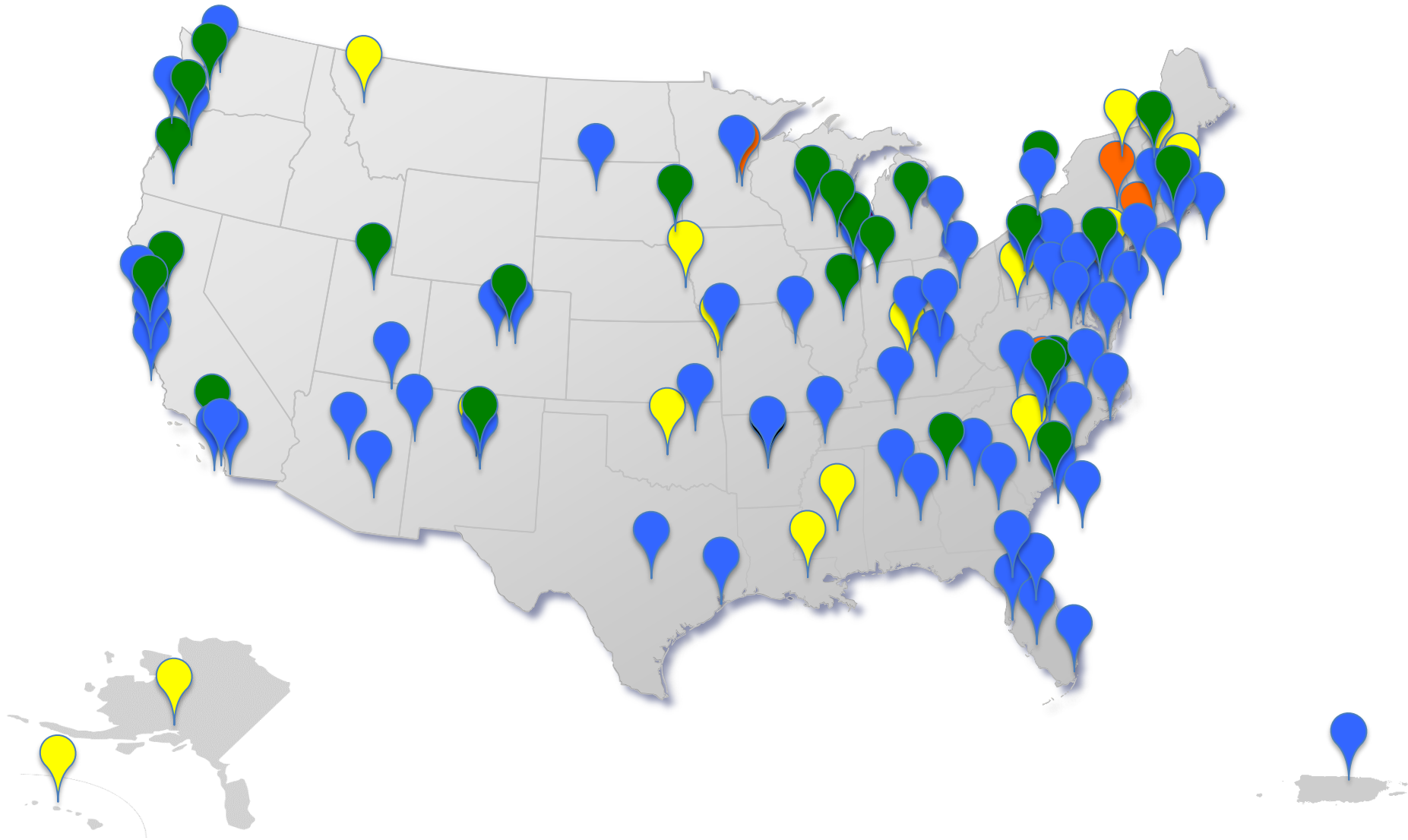
- Executive Committee (15 members, 3 from each institution)
- Advisory Council (16 members, 2 from each institution and 6 at-large members)
- Five institutions, each with an ECHO co-PI
  - HFHS – Charles Barone MD
  - MDHHS – Glenn Copeland MS
  - MSU – Nigel Paneth MD MPH (contact PI)
  - WSU – Douglas Ruden PhD
  - **UM – Michael Elliott PhD**
- Study Office at MSU
  - Tracy Thompson MPH (overall project direction)
  - Jean Kerver PhD (co-investigator; strategic advice and publications)
  - Julie Wirth PhD (protocols)
  - Kendall Cislo MPH (management consultant)

And our stellar graduate research assistants....

  - Alycinne Glazier MPH (biospecimens)
  - Shelby Atkinson (follow-up)
  - Teng-Fei Ma (data management)

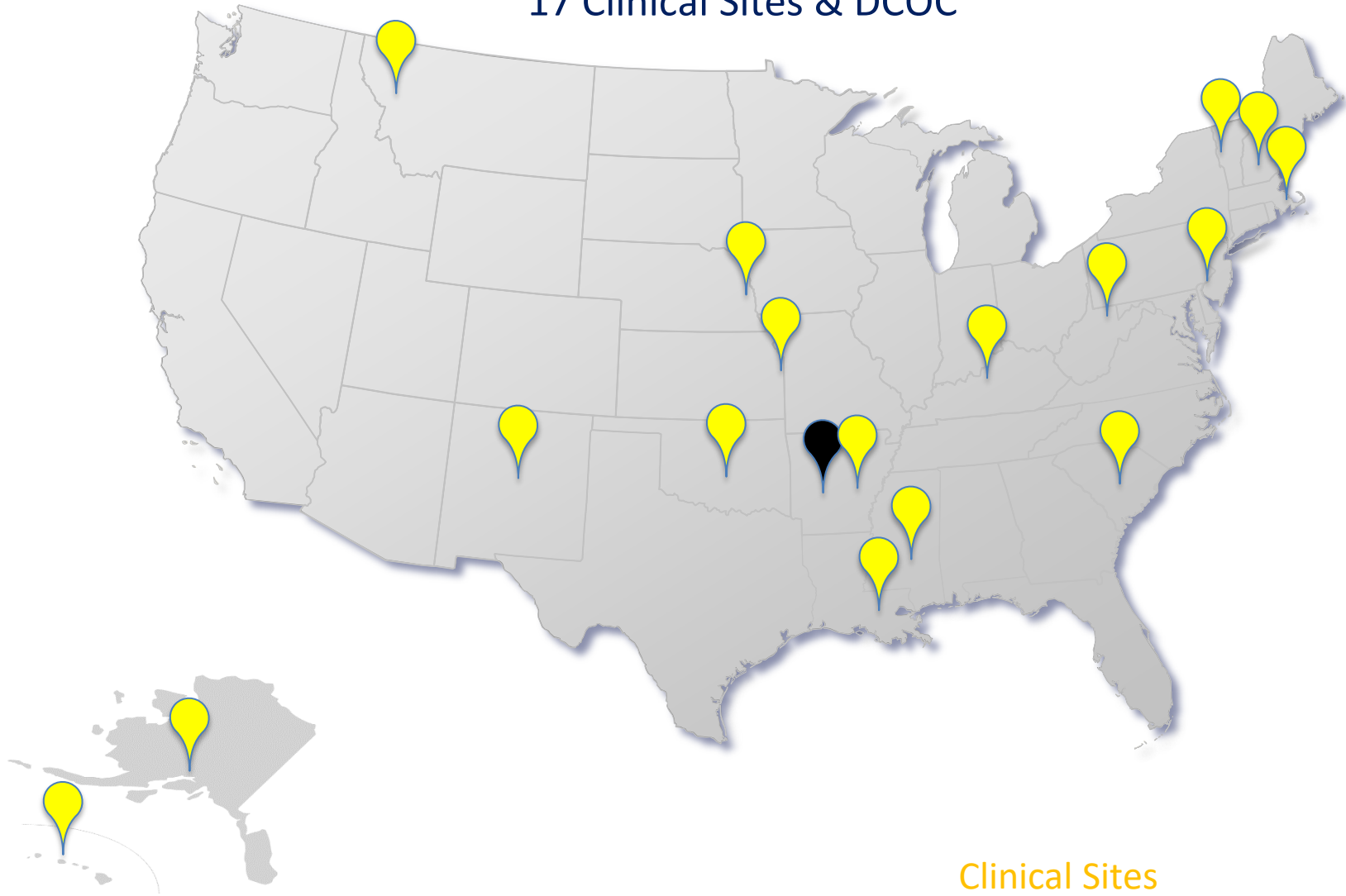
# THE NATIONAL ECHO PROGRAM

# ECHO—A Nationwide Program



# IDeA States Pediatric Clinical Trials Network

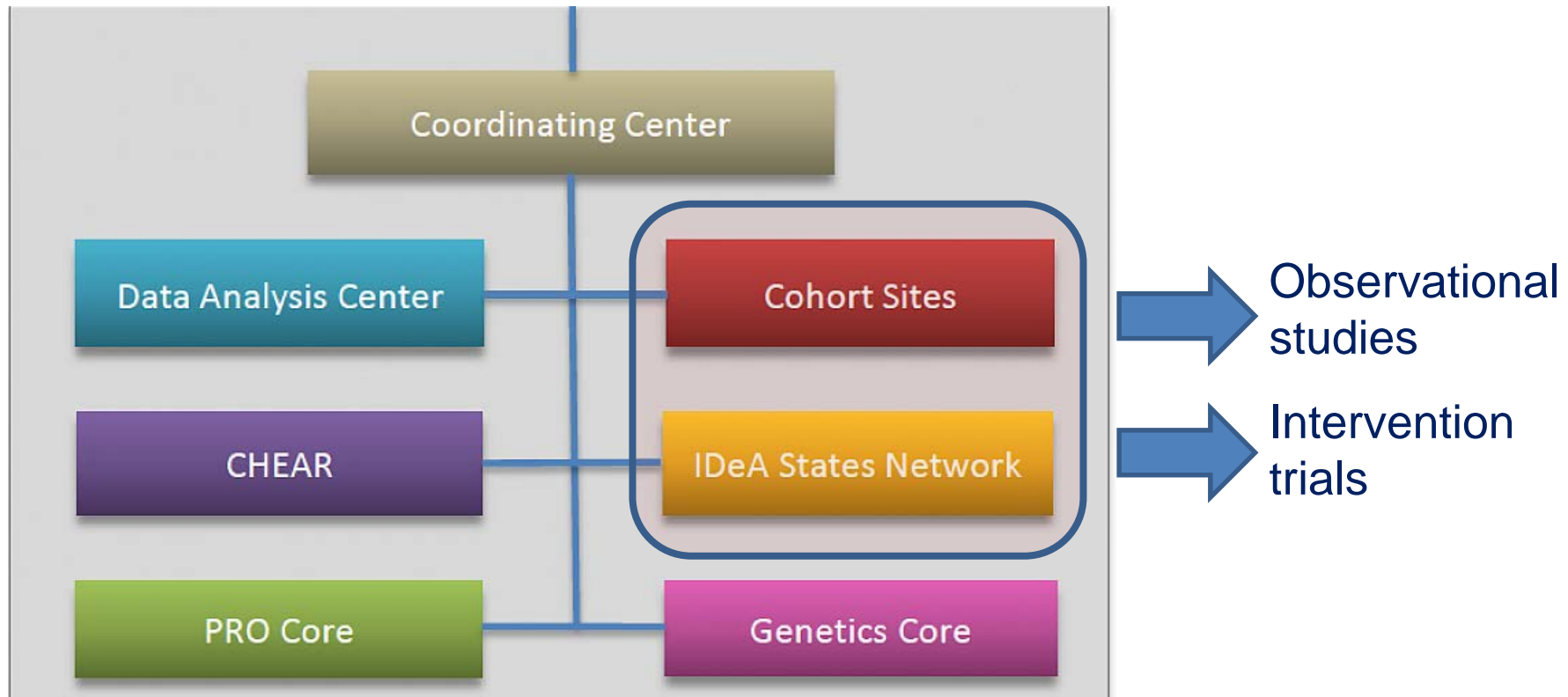
## 17 Clinical Sites & DCOC



Clinical Sites

Data Coordinating and Operations Center (DCOC)

# ECHO ORGANIZATION



# FIRST NATIONAL ECHO MEETING NOVEMBER, 2016



# ECHO focuses on early environmental exposures, broadly defined

- Early = Conception to age 5 y
- Broad = Society to biology
  - Physical and chemical
    - Air pollution
    - Chemicals in our neighborhoods
  - Societal factors—stress, maltreatment, etc.
  - Social factors—networks, SES, family dynamics, etc.
  - Medical factors—conditions, medications
  - Behavior—sleep, diet, physical activity, etc.
  - Biology—epigenetics, microbiota, etc.



# Major Objective: Create ECHO-wide Cohort

- A single data platform to conduct solution-oriented observational research
  - Harmonized existing measures
  - Standardized new measures
- 2 levels
  - All cohorts: common data elements
  - Some cohorts: deeper measures
- Goal >50,000 children
- Use
  - ECHO investigators
  - National research resource

# RETURNING TO MICHIGAN

THE DUAL PURPOSE OF CHARM

# THE DUAL PURPOSE OF CHARM

- Currently, we know about the pregnancy causes of child health from two sources:
  - Maternal interviews obtained when the child is diagnosed
  - Medical records of pregnancy
- But the ECHO program focuses on obtaining pregnancy information **when it occurs** so that we may better understand causes of childhood disease.
- Currently, we know about maternal health in pregnancy across our state from two population-based sources obtain after birth:
  - Birth certificates
  - PRAMS (Pregnancy Risk Assessment Monitoring System)
- But the MIM projects focuses on obtaining pregnancy information **when it occurs**, so that we may learn better how to help women during their pregnancies.

# AIM 1 IN MORE DETAIL

**To determine the effects of persistent organic pollutants (POPs) and heavy metals assessed across two generations, on cognitive outcomes**

We hypothesize that:

- a) in utero exposure to POPs/metals** will be associated with increased risk, especially in poor families;
- b) effects identified in hypothesis 1a will be mediated by epigenetic changes measured on NDBS;**
- c) grand-maternal exposure to POPS/metals** (measured on mother's blood spot when she was a newborn) will amplify the effects identified in 1a and 1b; and
- d) recent in utero lead exposure in Flint, MI, as assessed in NDBS, and in the shed teeth of exposed children,** will be associated with epigenetic changes and impaired cognitive outcomes.

# OUR ENVIRONMENTAL AGENDA

- Our two principal environmental laboratories are at WSU (Douglas Ruden) and U of M (Stuart Batterman), and we should have access to the national CHEAR laboratory system, which is linked to ECHO. (Dana Dolinoy directs the CHEAR laboratory at U of M).
- Our priority environmental chemicals are heavy metals (especially lead) and persistent organic compounds
  - Ruden lab – epigenetics and heavy metals
  - Batterman lab – POPs
- Our principal outcome of interest is neurodevelopment.
- Our matrices are:
  - Maternal serum, plasma, filter paper blood spot
  - Maternal urine
  - Newborn filter paper blood spot archived by MDHHS
  - ECHO will probably ask us to archive dyad **hair and toenails**
- We can also access **state geographic data** on ambient air and water pollution.

# ECHO DATA AVAILABLE NOW FOR ALL ECHO INVESTIGATORS

- Archived maternal serum, plasma, filter paper blood spots (up to twice in pregnancy) and urine (up to three times) on several hundred women beginning in first trimester.
- Archived newborn blood spot upon request (needs separate scientific review)
- All specimens aliquoted into 500 $\mu$ L vials for multiple testing.
- Maternal first-visit interviews on physical activity, nutrition, psychological state
- Birth certificate data (BW, GA, complication of pregnancy and labor)
- Medical record information can be obtained.
- > 80% contact with cohort to age 8.
- Modest telephone follow-up information, largely developmental milestones.
- Possible additional data from the MMIP project which includes cord blood.

# TWO SPECIAL FUNDING OPPORTUNITIES

ONE LOCAL  
ONE NATIONAL

# OUR LOCAL ECHO PROGRAM

- The VP's for research at UM, WSU and MSU have each pledged \$25,000/year for 7 years for an internal grant competition. In year 1, we also received \$25,000 from HFHS. This year's cap is \$37,500
- Year 1 awardees:
  1. Sarah Comstock, MSU – *Expansion of Microbiome Biospecimen Sample Collection in the Michigan ECHO Cohort to Investigate the Relationship between Maternal Pre-Pregnancy Obesity and the Maternal and Infant Microbiome/Resistome.*
  2. Paul Stemmer, WSU - *Identification and Quantitation of BTEX Exposures by Analysis of Adducts on Blood Proteins*
- Website for forms: [www.epi.msu.edu/CHARMstudy](http://www.epi.msu.edu/CHARMstudy)
- Deadlines:
  - Letter of Intent due: **November 15, 2017**
  - Application due: **Feb 15, 2018**
  - Funding to start: **April 1, 2018**
- Send letters and applications to [charmstudy@epi.msu.edu](mailto:charmstudy@epi.msu.edu)



# ECHO Opportunities and Infrastructure Fund (OIF)

- OIF is an annual grant funding opportunity. First RFA will be issued in 2017, and 4 more anticipated in years 3, 4, 6, and 7 of the ECHO Program. Each cycle will have a separate scientific focus.
- The RFA is for up to \$200,000 (including IDC) over one year for 10 awards. **Each center can submit only one application.**
- RFA deadline not yet final, but we anticipate **a release date of November 3** and a **due date of December 11.**
- Only early stage investigators (no R01 yet) at ECHO cohort funded institutions can apply. Collaboration across ECHO centers encouraged
- OIF this year focuses on new research tools and technologies useful to the ECHO program, specifically
  - Validation of measures
  - Integration of technology based measures
- Must address exactly how this proposal does not overlap any of the work currently funded by ECHO.
- Must include testable hypothesis or strong scientific rationale

# OIF APPLICATION FROM CHARM

- To put forth our most competitive application, our ECHO Study Office at MSU requests a letter of intent (LOI) from any investigator interested in applying for this opportunity by **October 31, 2017.**
- Please send letters to Study Office at [charmstudy@epi.msu.edu](mailto:charmstudy@epi.msu.edu) and include:
  - Name and biosketch of the early stage Investigator applying as PI
  - Names, affiliations of collaborators within our ECHO center in Michigan
  - Hypotheses or scientific rationale for the research proposed
  - New research, tools, or technologies introduced that would help the ECHO effort.
  - Describe any collaborations across ECHO centers.
- Please direct questions to: Tracy Thompson ([tthompson@epi.msu.edu](mailto:tthompson@epi.msu.edu))

# DATES REMINDER

- Letter of intent for the grant we submit from Michigan to **national ECHO** is **October 31<sup>st</sup>**. This short deadline is because the RFA will be announced **November 3<sup>rd</sup>**, and then we have five weeks (**till December 11<sup>th</sup>**) to get our Michigan application in. Cap is \$200K including IDC.
- The full RFA will not be available in advance, so please be guided in your letters of intent by the wording I gave in the slide above. High points:
  - Only early stage investigators
  - New research tools and technologies, especially validation of measures, integration of technology based measures
  - No overlap with funded ECHO work.
  - Testable hypothesis, strong scientific rationale
- Letter of intent for **our local grants program** is due **November 15<sup>th</sup>**. Cap is \$37,500, no IDC and no investigator salaries
- Send letters and applications to [charmstudy@epi.msu.edu](mailto:charmstudy@epi.msu.edu);
- Queries to [tthompson@epi.msu.edu](mailto:tthompson@epi.msu.edu)