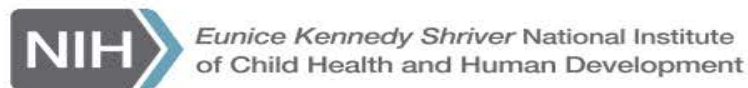


Inclusion of Pregnant and Lactating Women in Research

Diana W. Bianchi, M.D.
Director, NICHD



Presentation Overview

- The importance of including pregnant women in clinical research
 - PRGLAC
 - PregSource®
 - All of Us
 - Voice of the Participant
- Opioid use in pregnant and lactating women and NOWs
- 2018 NICHD Strategic Planning



NICHD and the Importance of Inclusion



“Sam and the Perfect World” by David Lenz, 2006



VIEWPOINT

Improving Public Health Requires Inclusion of Underrepresented Populations in Research

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Supplemental content

Advances in genomics have ushered in promising therapies tailored to the individual. Personalized medicine is promoted and has begun to positively influence care. For example, medications such as trastuzumab for the 30% of breast cancers that overexpress *ERBB2* and vemurafenib for patients with late-stage melanoma who carry the V600E variant have been beneficial.¹ Despite these advances, for many sectors of the population—children, older adults, pregnant and lactating women, and individuals with physical and intellectual disabilities—limited evidence-based therapies optimized to their specific medical needs exist. Combined, these groups comprise as much as 58% of the US population (eTable in the Supplement). Research focusing on or at the very least includes members of these groups is critically needed.

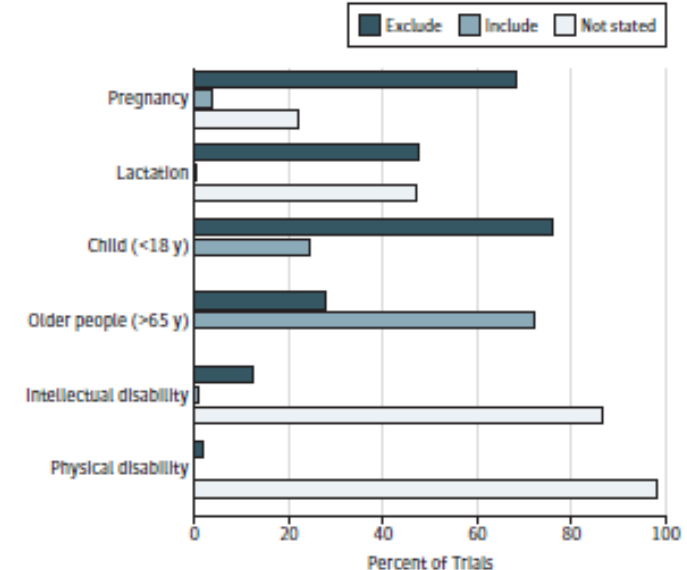
Until the initial passage of the Best Pharmaceuticals for Children Act in 2002, pediatric drug doses were based on extrapolation from adults. Importantly, body composition and metabolic processes change as children develop, resulting in different safety and efficacy

considerations are often prescribed with minimal evidence to support their use, especially psychotropic drugs with significant adverse effects.

Recently, discussions have arisen about the need for inclusion in research and elimination these gaps. In 2017, the National Institutes of Health (NIH) held a workshop, “Inclusion Across the Lifespan,” that highlighted current federal regulations that include protections for “vulnerable populations” (pregnant women, fetuses, neonates, prisoners, and children). Although these regulations were originally designed to protect these individuals, many investigators have called for reconsideration, opting to protect them *through* research, rather than *from* research. Inclusion will likely yield data that will benefit more people.

Many underrepresented populations encounter barriers to participation in research. In a review of 338 phase 3 and 4 NIH-funded actively recruiting studies in Clinicaltrials.gov, explicit exclusion was found in 68% for pregnant women, 47.3% for lactating women, 75.7%

Figure. Open NIH-Funded Phase 3 and 4 Studies as of October 19, 2017



Clinicaltrials.gov records (N=338) were reviewed. Exclusion for intellectual disabilities was based on IQ and defined intellectual disability or cognitive impairment; physical disabilities: exclusions for physical disabilities were inability to ambulate, extreme immobility, and paraplegia.

68% of studies explicitly exclude pregnant women
47% exclude lactating women

JAMA 2018; 319:337-8



eTable. Approximately 58% of the Total US Population Are Not Typically Included in Research Studies (Pregnant Women, Children, Older People, Those With Intellectual and Physical Disabilities)^a

	Approximate No. of People	Source
Total US population	325 000 000	http://www.worldometers.info/world-population/us-population
Pregnant women	6 300 000	http://www.statisticbrain.com/pregnancy-statistics
Children	73 000 000	https://www.childstats.gov/americaschildren/tables/pop1.asp
Age >65 y	46 200 000	https://www.census.gov/newsroom/facts-for-features/2016/cb16-ff08.html
Intellectually and developmentally disabled	6 500 000	http://www.specialolympics.org/Sections/Who We Are/What Is Intellectual Disability.aspx
Physically disabled	56 700 000	https://www.census.gov/newsroom/releases/archives/miscellaneous/cb12-134.html

^aThese numbers are approximate to provide a general impact; the numbers do not account for overlap between categories.



Pregnant women in studies at the NIH Clinical Center?



- Pregnant women have been historically excluded in clinical center studies
- A working group has been formed to examine benefits and risks of having healthy pregnant women participate in research protocols at the Clinical Center

21st Century Cures Act Update



SEC. 2041. TASK FORCE ON RESEARCH SPECIFIC TO PREGNANT WOMEN AND LACTATING WOMEN.

Specific topics to be addressed:

- Existing Federal efforts and programs to understand the health effects on pregnant and lactating women, and related birth and pediatric outcomes
- Research collaboration potential
- Ethical issues surrounding inclusion of pregnant and lactating women in clinical research
- Effective communication strategies with health care providers and the public
- 3 of 4 meetings have been completed
- Next meeting on May 14-15, 2018 will discuss recommendations
- Report to HHS due in September 2018

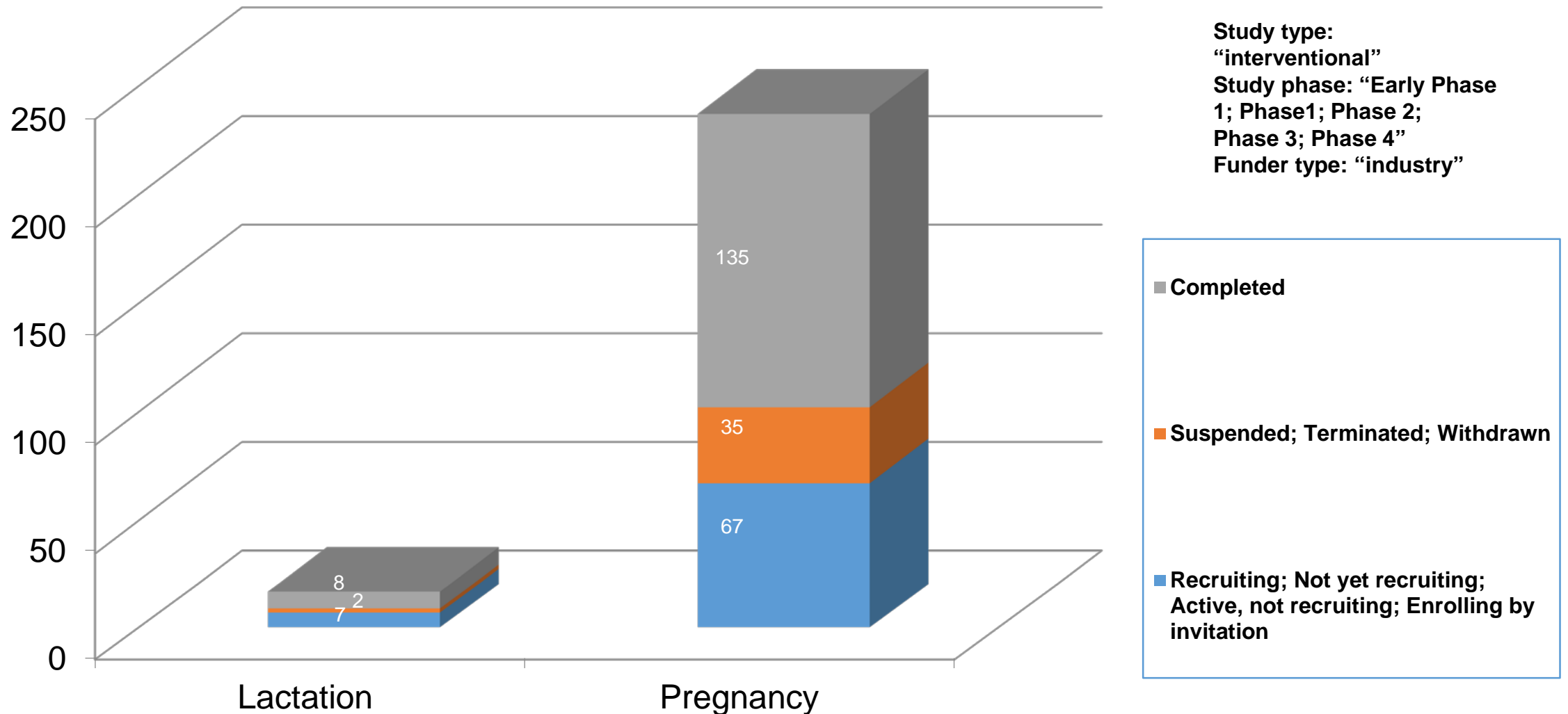


NICHD Pregnancy and Lactation Literature Analysis 2006-2017: Results for Pregnancy

- RCTs rare in almost all areas
- Exceptions:
 - Gestational diabetes
 - Hypertension
 - Preterm labor
 - Labor pain medication
 - Opioids and tobacco

	Condition	Basic	PK/PD	Pop/DB	RCT
Hypertension	Hypertension	127	9	18	40
Mental Health	Anxiety	16	0	3	2
	Bipolar	1	0	1	0
	Depression	21	4	21	4
	Schizophrenia	11	0	1	0
Pain	Labor Pain	5	0	7	49
	Headache/migraine	0	0	5	1
Preterm labor	Preterm labor	152	21	35	169
Substance Abuse	Alcohol	26	0	0	0
	Cocaine	6	0	1	0
	Meth/amph	10	3	1	0
	Opioids	22	3	9	25
	Tobacco	22	3	16	27

Status of Industry-Sponsored Interventional Trials in the US



Source: www.clinicaltrials.gov (Site accessed 09 Aug 2017)

Slide courtesy of Christina Bucci-Rechtweg, MD,
Novartis Pharmaceuticals Corporation



Research, Condition and Disease Categorization Codes

- RCDC is a database NIH has maintained since 2009 to categorize and report the amount of funding on more than 280 topics
- Data are generated using the following process:
 - Scientific experts develop definitions and lists of terms for each category
 - Sophisticated text mining is used to apply definitions to the NIH portfolio
 - Final curation and validation by scientific experts
- NIH does not budget by research category – used to **report** spending
- Categories are not mutually exclusive



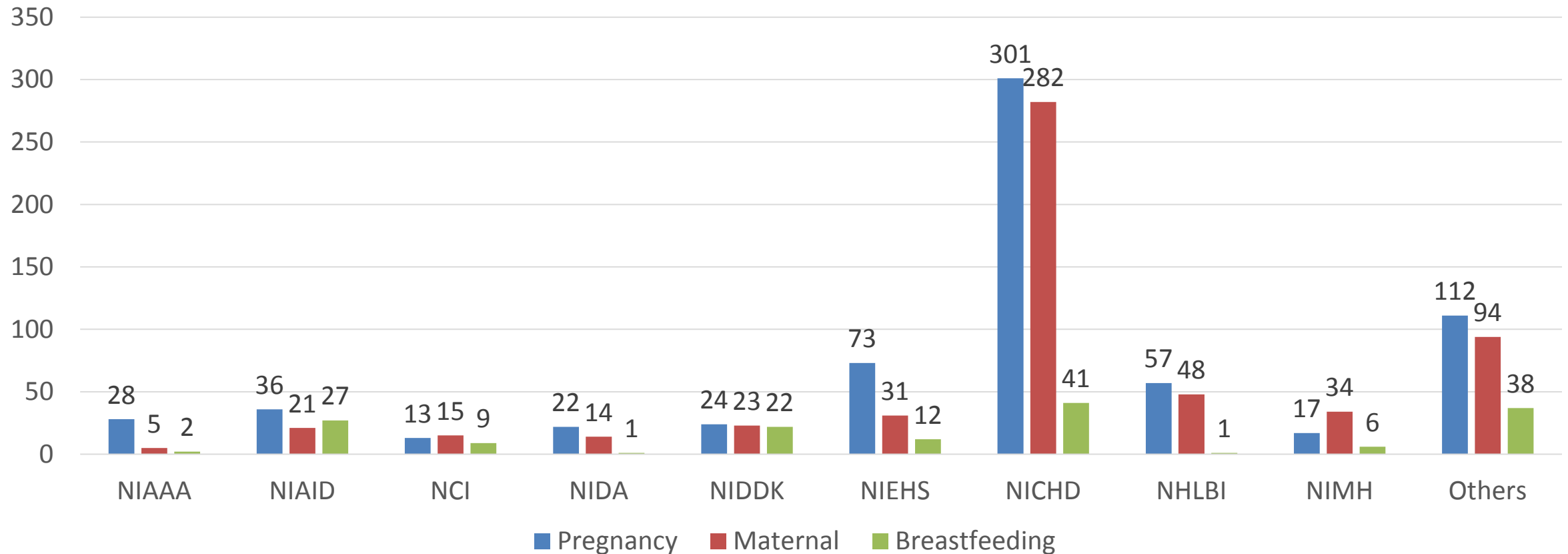
NIH Data Release for FY 2017

NEW RCDC Categories:

- Pregnancy
 - 683 projects, \$319 M total
 - 21 ICs + NIH OD
- Maternal Health
 - 567 projects, \$249 M total
 - 19 ICs + NIH OD
- Breastfeeding, Lactation, and Breast Milk
 - 159 projects, \$91.7 M total
 - 20 ICs + NIH OD

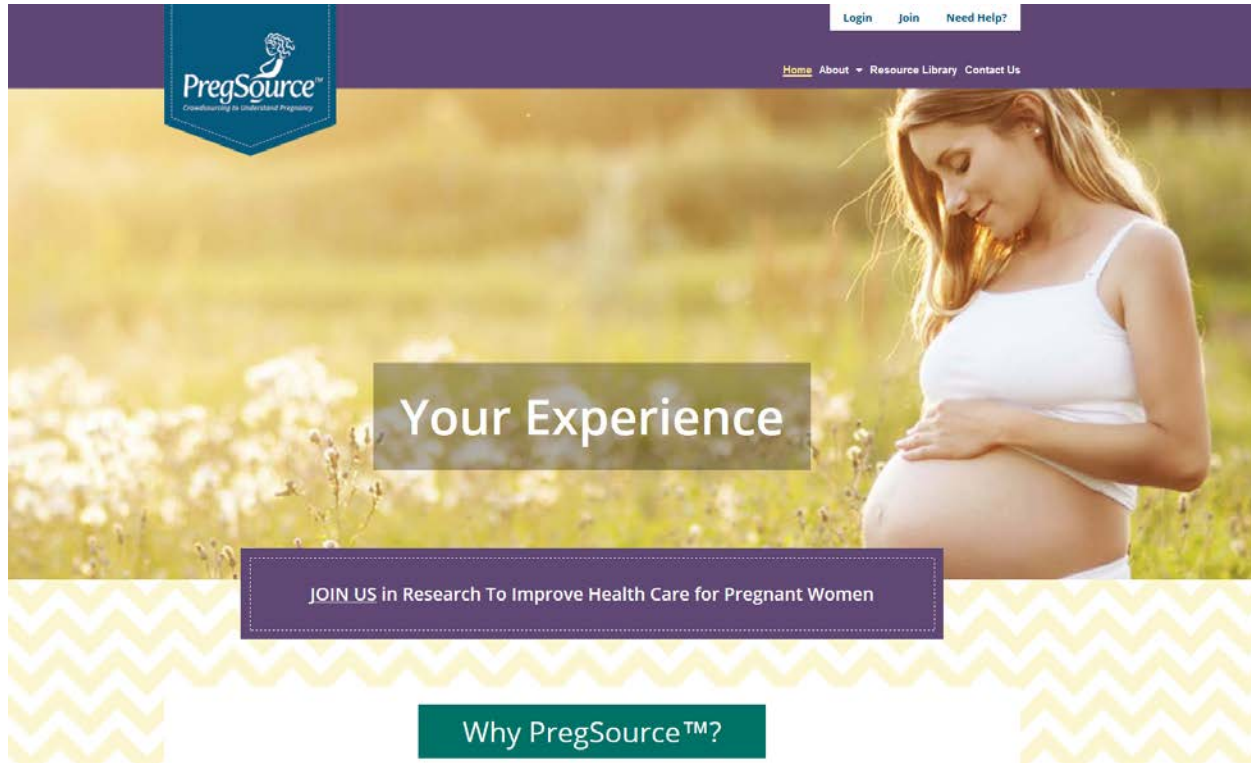


NIH-Funded Projects in Task-Force Related Categories, by NIH IC, FY 2017





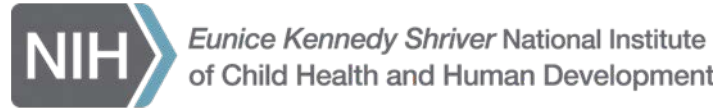
PregSource® Home Page



<https://PregSource.nih.gov>

- Pregnant women will provide information about their experiences in real-time:
 - Sleep
 - Nausea
 - Exercise
 - Weight
 - Medications
- Answers to these topics will help researchers build a more complete picture of normal pregnancy and develop strategies for improving maternal care

PregSource® Partners





Hello Test!

You are in **week 0** of pregnancy: **Pregnancy 1**
Your last visit to PregSource™ was: **October 27, 2017**



Questionnaires

To Do

- [During This Pregnancy](#)
- [My Latest Updates](#)
- [My Health History: Before This Pregnancy](#)
- [My Health History: Medications Before This Pregnancy](#)
- [Tell Us More About You](#)
- [My Health History: Prior Pregnancies](#)
- [Due Date and More About This Pregnancy](#)



15 My Progress

[Add My Latest Updates](#)
[Update My Due Date](#)



Messages

[You have 0 new message\(s\).](#)



Data, Facts, & Figures

[Show My Progress Trackers](#)
[Show Me All PregSource™ Data](#)
[Go to my Personalized Article Library](#)



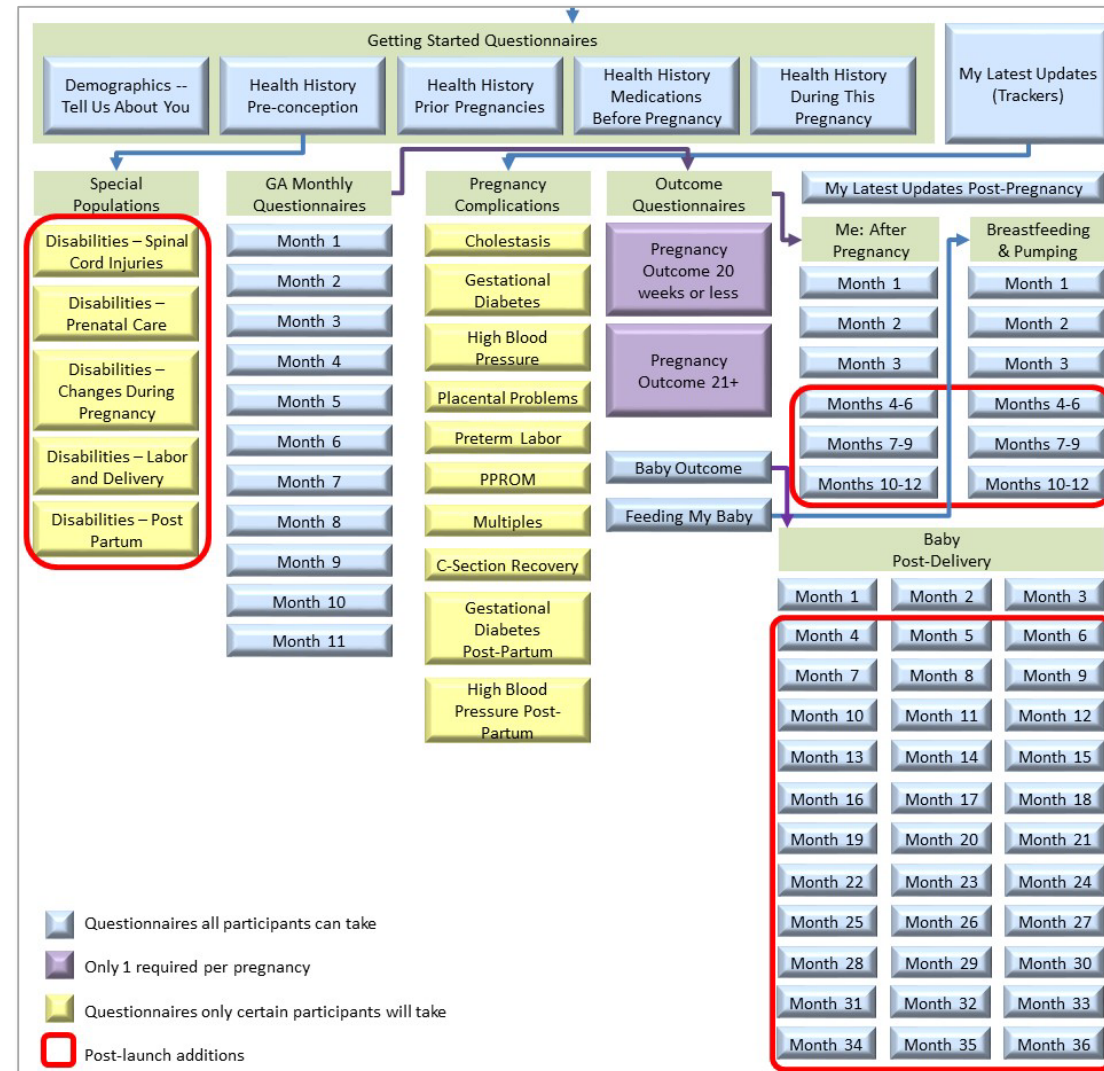
Change My Pregnancy Info

Current: Pregnancy 1 ([Change](#))
[Change My Pregnancy Info](#)
[Add a New Pregnancy](#)

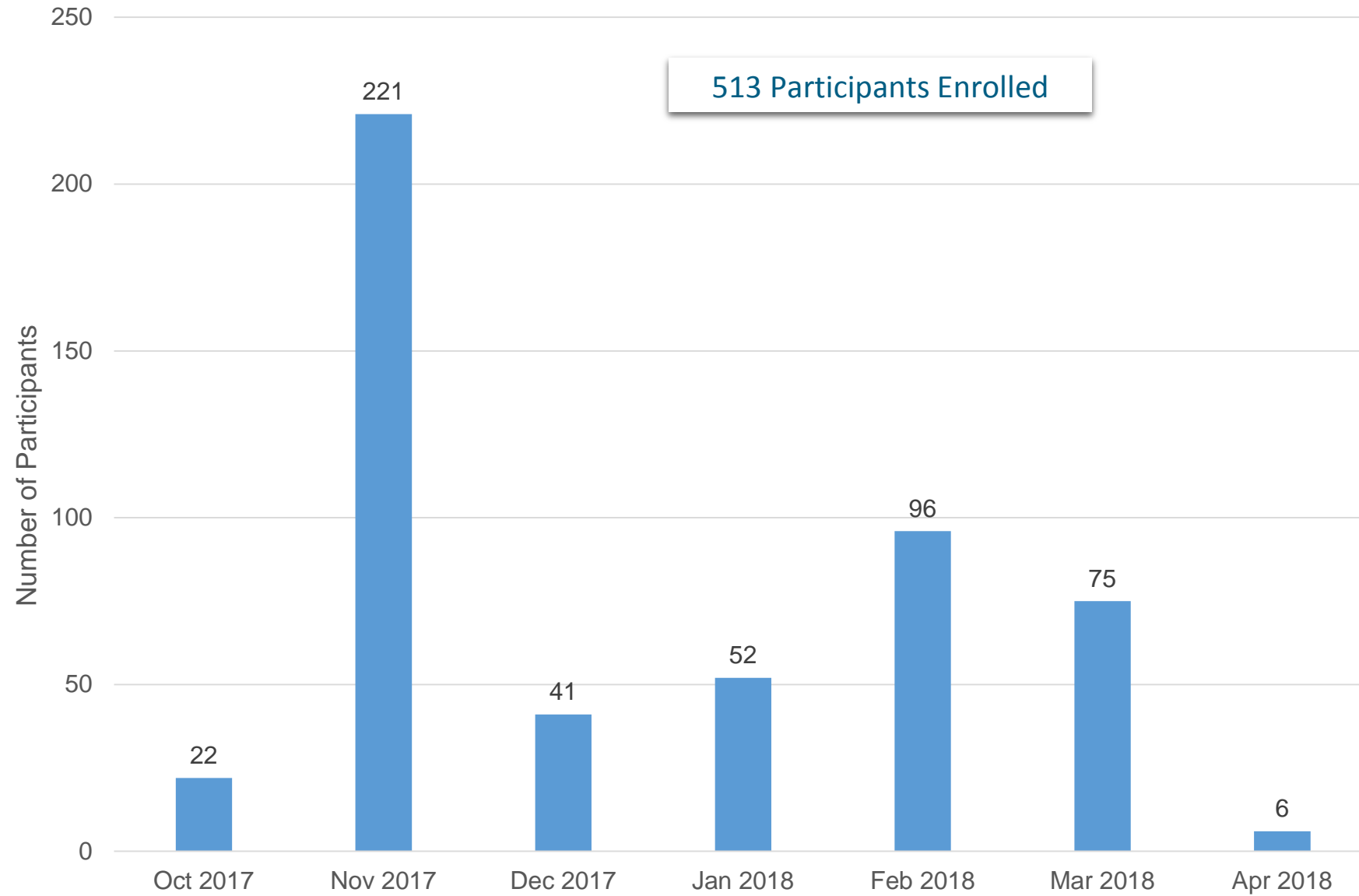


Questionnaires

- 41 questionnaires currently
- Plan to add:
 - Medication Tracker
 - Questionnaires on post-partum and infant health up to 36 months
 - Questionnaires for special populations/ topics (e.g., women with physical disabilities)
 - Spanish language translation
 - Develop professional portal for researchers
 - Mobile app



PregSource® Recruitment



As of April 11, 2018

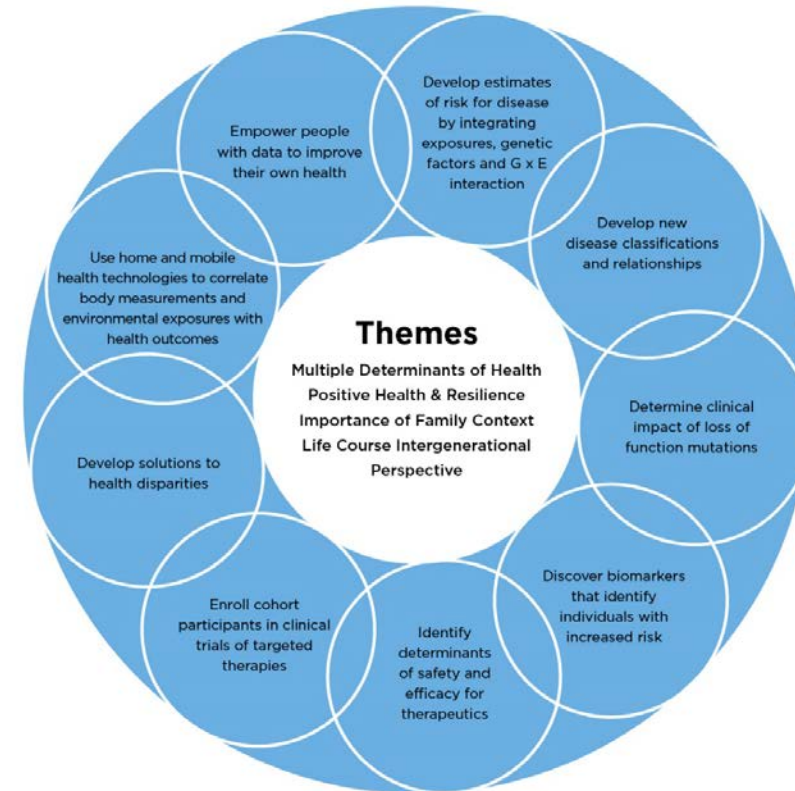


Inclusion of Children, Pregnant Women and People with Disabilities in *All of Us*



Opportunities Enabled Through the Enrollment of Children in the *All of Us* Research Program

The Child Enrollment Scientific Vision Working Group Report to the *All of Us* Research Program Advisory Panel
December 15, 2017

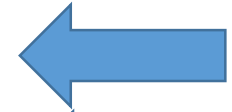


All of Us Research Program Child Enrollment Scientific Vision Working Group Report



Top Scoring *All of Us* Use Cases of Potential Interest to ORWH

Use Case	Votes	Use Case	Votes
1. What are the unique factors associated with early onset obesity in different ethnic and racial groups? (#4/650)	155	9. What risk factors predispose children to sepsis, and what interventions are most effective for prevention and treatment?	35
2. What microbiome characteristics of children exposed to antibiotics and different diets influence long-term health outcomes? (#5/650)	153	10. What is the genetic architecture of neurodevelopmental problems and how does it relate to health disparities?	33
3. What are the long-term effects and risks of opioid use disorder during pregnancy on maternal and child health? (#10/650)	120	11. What factors are involved in loss of fecundity in males and females?	29
4. Can Electronic Health Records (EHRs) be effectively utilized to facilitate clinical trials in pediatrics?	114	12. What genetic markers predict consequences of pregnancy associated hypertension & gestational diabetes for mothers & offspring?	26
5. How do genetic factors of ADHD influence treatment strategies? Can they affect success of treatment or the choice of therapy?	94	13. What genetic and environmental risk factors contribute to the development of pelvic organ prolapse (POP) as females age?	25
6. How are sleep characteristics associated with pediatric developmental conditions, disorders or chronic disease?	94	14. What is the effect of the individual's family and community network on health status and health behaviors?	23
7. What characteristics distinguish a healthy maternal pregnancy-microbiome from one that experienced microbial perturbations?	43	15. What are the characteristics of people who sustain traumatic injury who have optimal recovery compared to those who do not?	20
8. What are the genetic and environmental risk factors that contribute to the broader autism phenotype in adolescents and adults?	42	16. How can single accelerometers or smartphone based measures of gross activity characterize voluntary and involuntary movements?	19
17. What alternative methods of measurement for height & weight will be used in those who cannot use standard normative measures?			5



Inclusion of Participants and their Families



Kristine Ribas



Tara Shafer



Megan Connolly



Image from DS-Connect® promotional video

David and Kathleen Egan



Health and Fiscal Impact of Opioid Use During Pregnancy

- On average, women take between 3 – 5 prescription medications during pregnancy
- Increased prevalence of opioid use during pregnancy ≥ 5 times increase in NOWs
- In 2012, nearly 22,000 infants were born with NOWs in U.S.
- Nationwide costs: \$1.5 billion in hospital charges for treating infants with NOWs
- Infants with NOWs are taking up NICU beds that are needed for critically ill neonates
- In 2015, one Wisconsin county spent $>$ \$1 million (out of a \$9 million budget) on child welfare placements, largely as a result of parental opioid addiction





Prevention of NOWs Starts With Prenatal Care

- Many women using opioids receive little or no prenatal care
 - Those who do are reluctant to disclose substance use
- Screen pregnant women with opioid use disorder at intervals throughout pregnancy to optimize care
- Medication-assisted therapy is the standard of care
 - Methadone treatment: improved compliance with obstetric care, higher birth weights, and lower preterm birth and infant mortality rates
 - Buprenorphine treatment: decreased risk of overdose and improved neonatal outcomes
- Interest has increased in medically supervised withdrawal, but unclear whether this approach safe for the pregnant woman and her fetus



Neonatal Opioid Exposure and Withdrawal

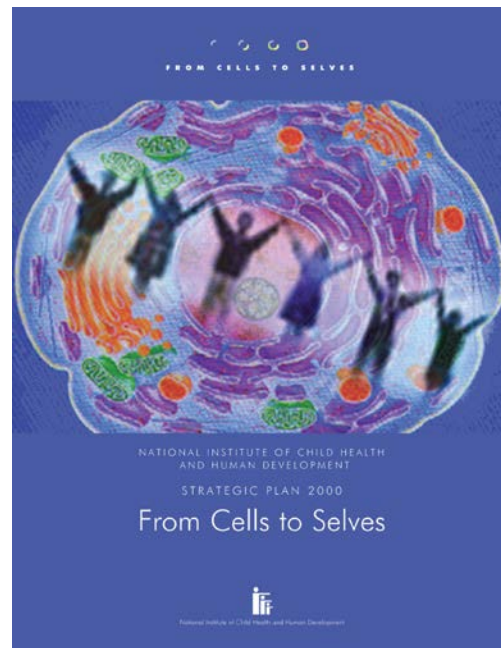


- Need to think about babies differently from adults
 - Pregnant women are not routinely screened for opioids
 - Babies do not die as a result of *in utero* exposure
 - Most babies are born in the hospital and are resuscitated if they do not breathe
 - Not all newborns exposed to opioids develop significant signs of withdrawal right away
- No consistent approaches to care for mothers and babies
 - Current treatments developed for heroin and methadone withdrawal
- Neonates with NOWs utilize resources
 - Occupy a significant number of NICU beds for long periods of time, social services, and local government expenses for foster family placement





The 2018 NICHD Strategic Planning Process



2000



2012

The 2018 NICHD Strategic Planning Process

- End goals: Determine scientific priorities for NICHD moving forward, align resources with priorities
- Work plan:
 - Developed a set of focus questions
 - NICHD planning subcommittee has met
 - Evidence based:
 - Incorporate impact analyses
 - Strategic Plan Work Group will include ~50 people, half from NIH and half from external communities
 - Stay tuned: 2018/2019 timeline
 - 2-day meeting October 2018
 - Updates to be posted on NICHD website



Summary

- Inclusion of pregnant and lactating women in clinical research is needed
 - Some progress: new RCDC codes, opportunity for recommendations to HHS secretary and Congress upon completion of PRGLAC, Clinical Center Working Group discussion
 - Inclusion of participants can put a “human face” on the need for research
- Opioid use screening and treatment is a major issue for women and children
- 2018 NICHD Strategic Planning is an opportunity to enhance partnership with ORWH



Thank You and Questions?