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Children's National Research Institute

Advisory Committee on Heritable Disorders in Newborns & Children
May 4, 2023

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Disclosure

- I have no conflicts of interest to disclose
- I have served as an ACHDNC committee member and the AAP liaison
- The opinions expressed herein do not reflect those of the NIH or Children's National Hospital

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Goals for the Presentation

- Illustrate the data gaps for the impact of false positives and uncertain prognoses with newborn screening
- Summarize active research projects aimed at filling these data gaps

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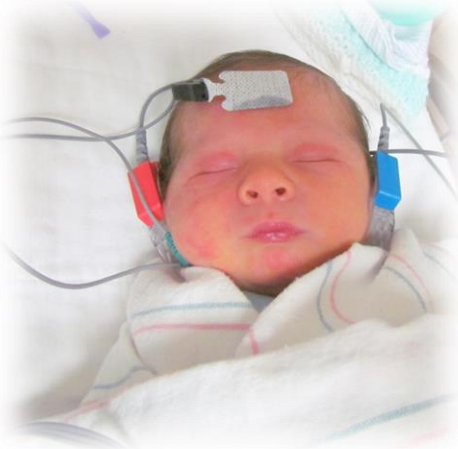

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NEWBORN SCREENING IS A SUCCESSFUL PROGRAM

AND

IT SHOULD CONTINUE

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ALL SCREENING HAS HARMS

AND IT IS UNETHICAL TO IGNORE THEM…

AND FAILING TO EXAMINE THEM COUNTS AS IGNORING THEM

"Rational Decision Making About Screening Requires A Consideration Of The Balance Between Benefits And Harms."

Harris RP, et al. The harms of screening: a proposed taxonomy and application to lung cancer screening. JAMA Intern Med. 2014 Feb 1;174(2):281-5.

Definition of Harm

- *"any negative effect perceived by patients or significant others resulting from screening compared with not screening."* (Harris et al 2014)

Harris RP, et al. The harms of screening: a proposed taxonomy and application to lung cancer screening. JAMA Intern Med. 2014 Feb 1;174(2):281-5.

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Domains of Harm

Harris et al. 2014

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Domains of Harm

- False Positive Results
- Uncertain Prognoses

Harris et al. 2014

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Domains of Harm

Physical

Psychosocial

Financial strain

Opportunity costs

- False Positive Results
- Uncertain Prognoses

Harris et al. 2014

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NBS collection

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NBS collection

Screening results

Within Range

Out of Range

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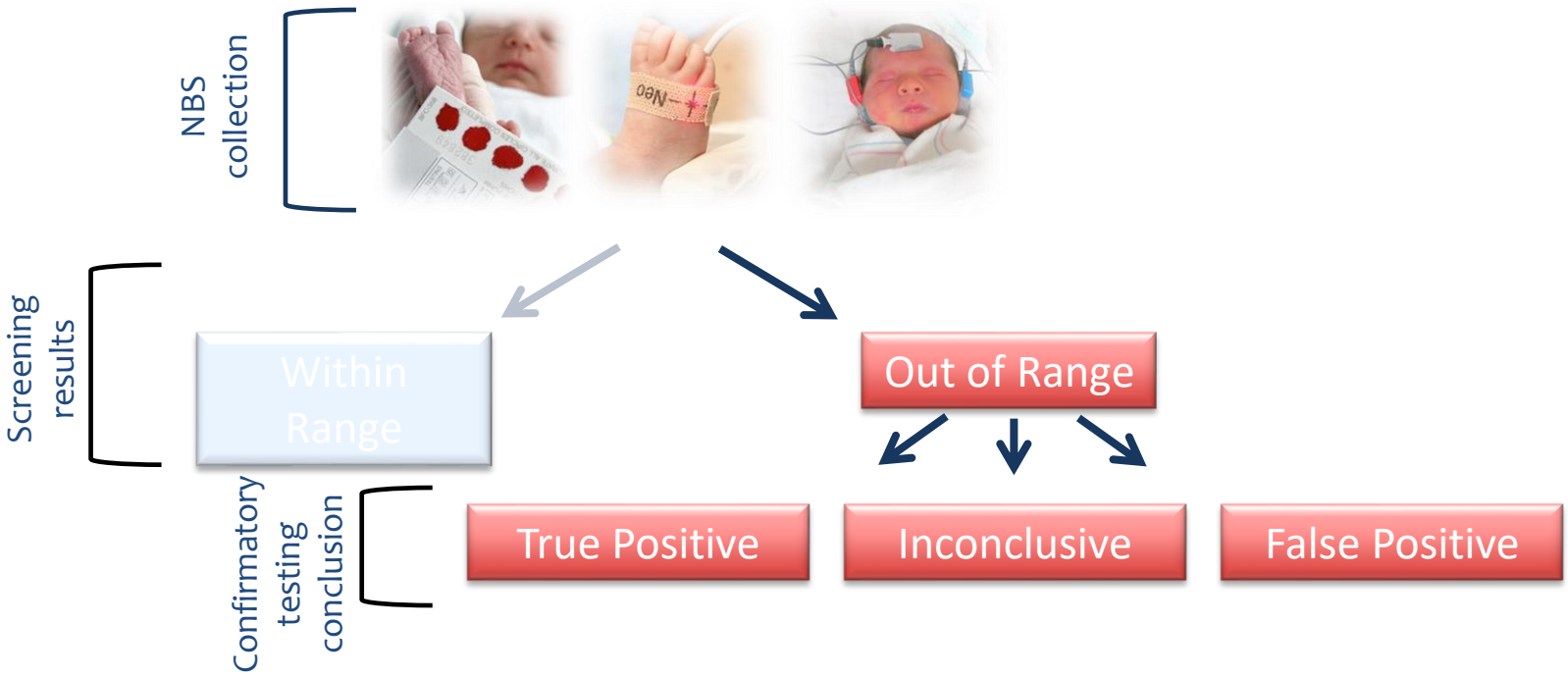

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NBS collection

Screening results

Within Range

Out of Range

Confirmatory testing conclusion

True Positive

Inconclusive

False Positive

Clinical management

None

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The PKU Anxiety Syndrome, 1968

Since July 1, 1966, we have seen a steadily increasing number of parents who are suffering from what we, at Bronx Municipal Hospital Center, have come to call "The PKU Anxiety Syndrome." This syndrome presents as acute and chronic anxiety ranging in degree from mild, periodic bouts to acute anxiety hysteria. It is present in parents who persist in their belief that their babies are or will become mentally retarded despite repeat negative tests and considerable reassurance and support from physicians. Our current, conservative estimate is that we are seeing two to four such families a month. In essence, these parents are saying, "The test that the big Board of Health laboratory did showed that my baby was mentally retarded. Then a doctor in a little cubicle in the Clinic did a test and said it was all right. He's reassuring—but I don't know. . . ."

REACTIONS TO THE THREATENED LOSS OF A CHILD: A VULNERABLE CHILD SYNDROME

Pediatric Management of the Dying Child, Part III

Morris Green, M.D., *and* Albert J. Solnit, M.D.

Departments of Pediatrics, Indiana University and Yale University School of Medicine

"So many people die who never died before."
(VIENNESE SAYING)

FOR MORE than six years, observations of pediatric patients in two regions of the country, Indianapolis and New Haven, have been made to examine the hypothesis that children who are expected by their parents to die prematurely often react with a disturbance in psycho-social development. The repetitive quality of the pathological reactions observed, the number of patients seen, and the relief which both child and parents experience when the problem becomes clarified through verbalization provide substantial clinical evidence that this hypothesis is a useful and significant one.

For purposes of presentation, these observations involve three patient groups: (1) children who are expected to die because they underwent a serious illness from which the parent did not believe the child would recover; (2) children who are expected to

tions in which this difficulty in the parent-child relationship, which we have termed a *vulnerable child syndrome*, is apparent in a more subtle or less clear fashion. The present report is concerned with the first group of children, i.e., those with a history of an illness or accident from which they were not expected to recover.

CLINICAL FEATURES

Table I summarizes some of the clinical data in 25 of these cases (16 boys and 9 girls). In most instances, the doctor had told the parents that the child was going to die, was likely to die, or would not live very long. In some cases the parents had been advised to contact an undertaker. For reasons not founded in reality, these children following recovery are considered by their parents to be vulnerable to serious illness or accident and destined to die during childhood. The parents have the feeling

Symptoms of Vulnerable Child

- Difficulty with Separation
- Infantilization
- Bodily Overconcerns
- School Underachievement

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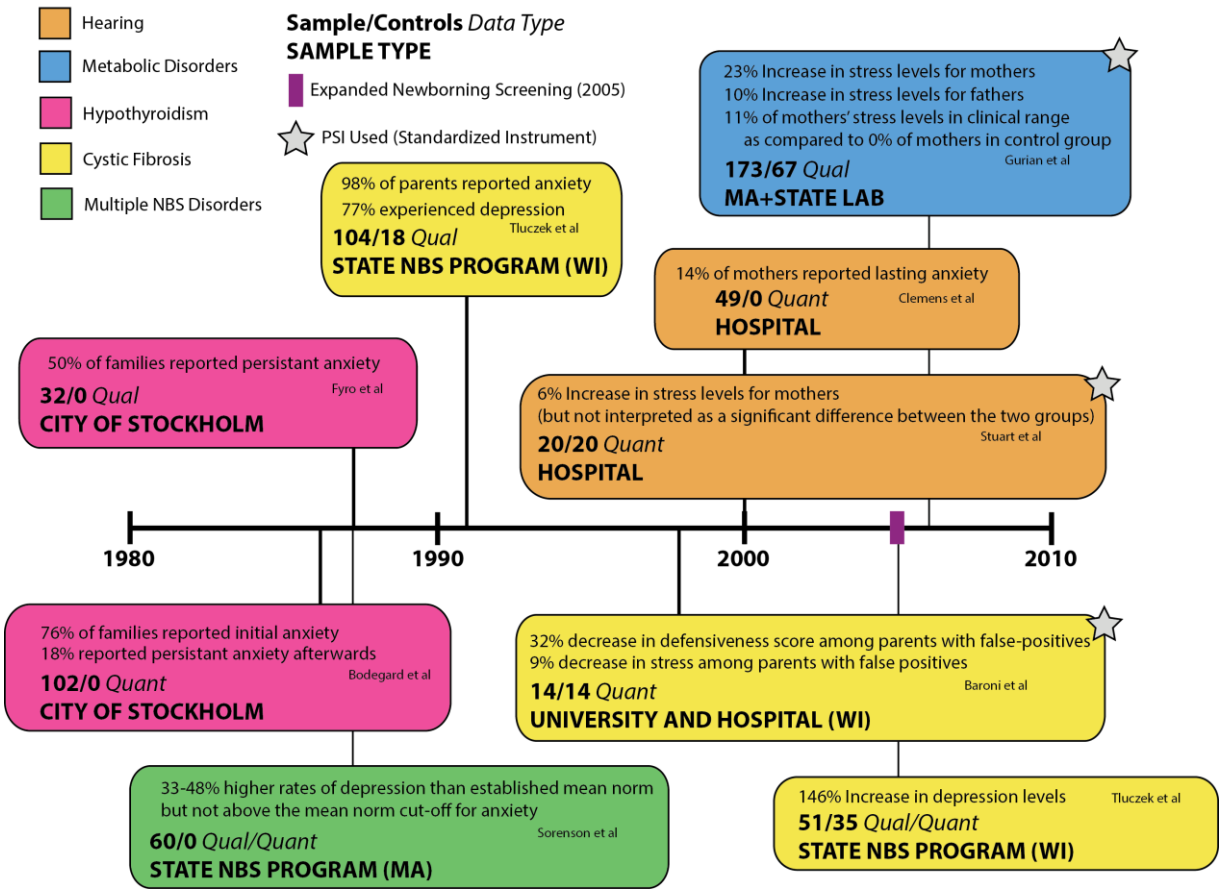
Studies of Psychological Effects of False Positive NBS Results on Parents



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QUALITATIVE	QUANTITATIVE
Hypothesis generating	Hypothesis testing
Rich details about experience	Lacking in detailed understanding
Cannot calculate prevalence	Can calculate prevalence
Not generalizable	Potentially generalizable (based on sample size and composition)
Interviews, focus groups	Questionnaires, administrative datasets

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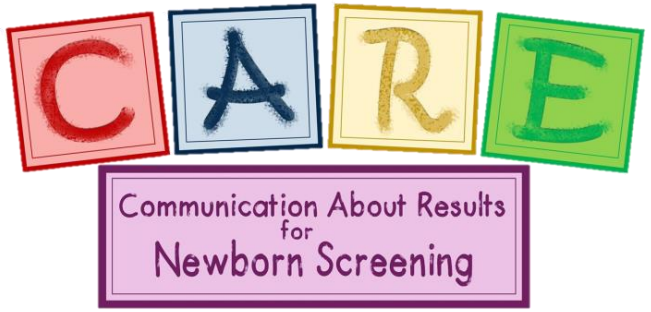

Unresolved Issues in NBS:

*Quantifying the Harms of a False Positive Result** *(R01HD095068)*

**funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development*

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Acknowledgments & Thank yous

- CARE NBS Team
  - CN Team: Beth Tarini, Brianne Miller, Anne Atkins, Norma-Jean Simon, Kelly Christensen, Xavier Marshall, John Barber, Aaron Goldenberg (Case)
  - VA Team: Christen Crews, Mary Lowe
  - IA Team: Emily Phillips, Carol Johnson, Sandy Daack-Hirsch, Knute Carter, Michelle Bargren

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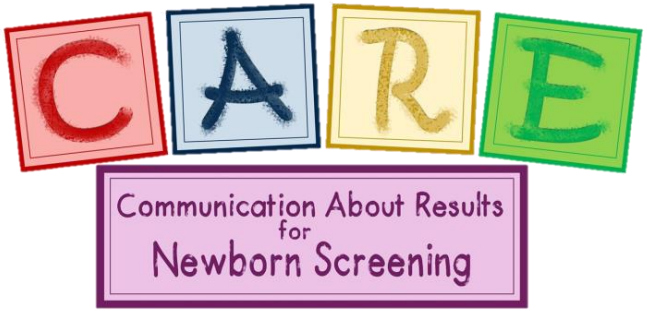

Multi-site prospective observational cohort study (until 2 years of age)

- Exposure group
  - parents/guardians of children who received a false positive NBS result
- Non-Exposure (Comparison) group
  - parents/guardians of children who have received a normal (within range) NBS result

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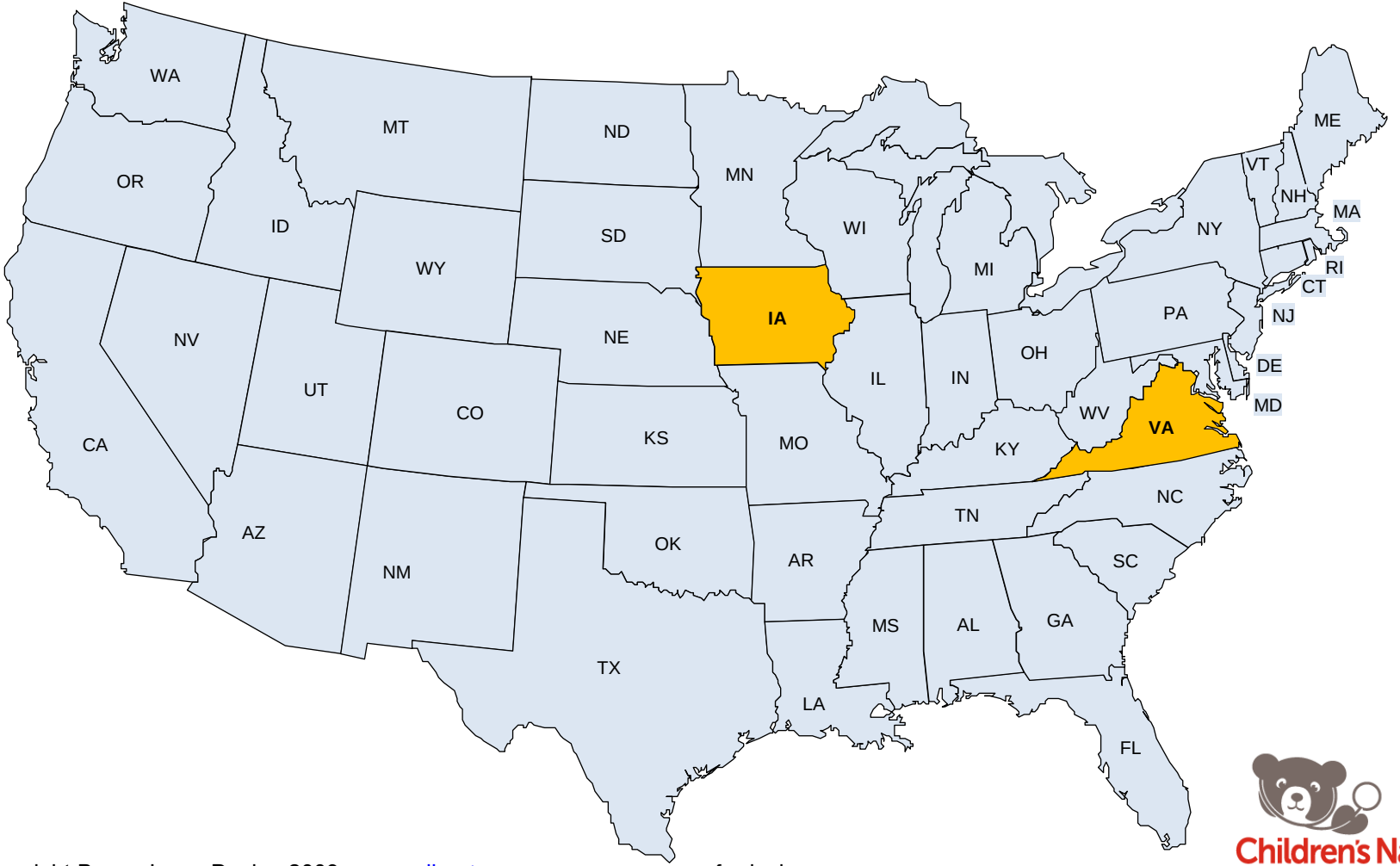

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Primary Outcome

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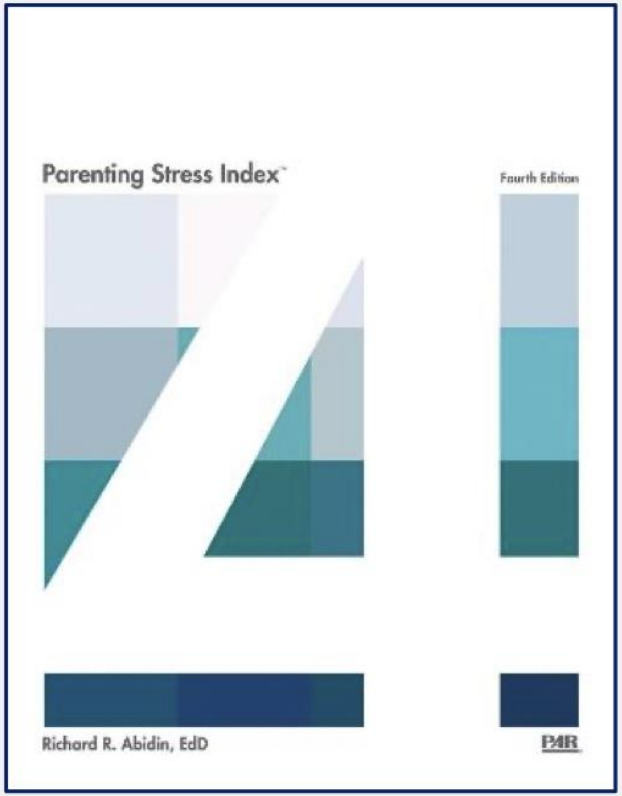

Validated 120 questions

Focuses on 3 major stress domains:

- child characteristics
- parent characteristics
- situational/demographic life stress

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Additional Measures

- Child Development
- Parent Anxiety
- Vulnerable Child Syndrome

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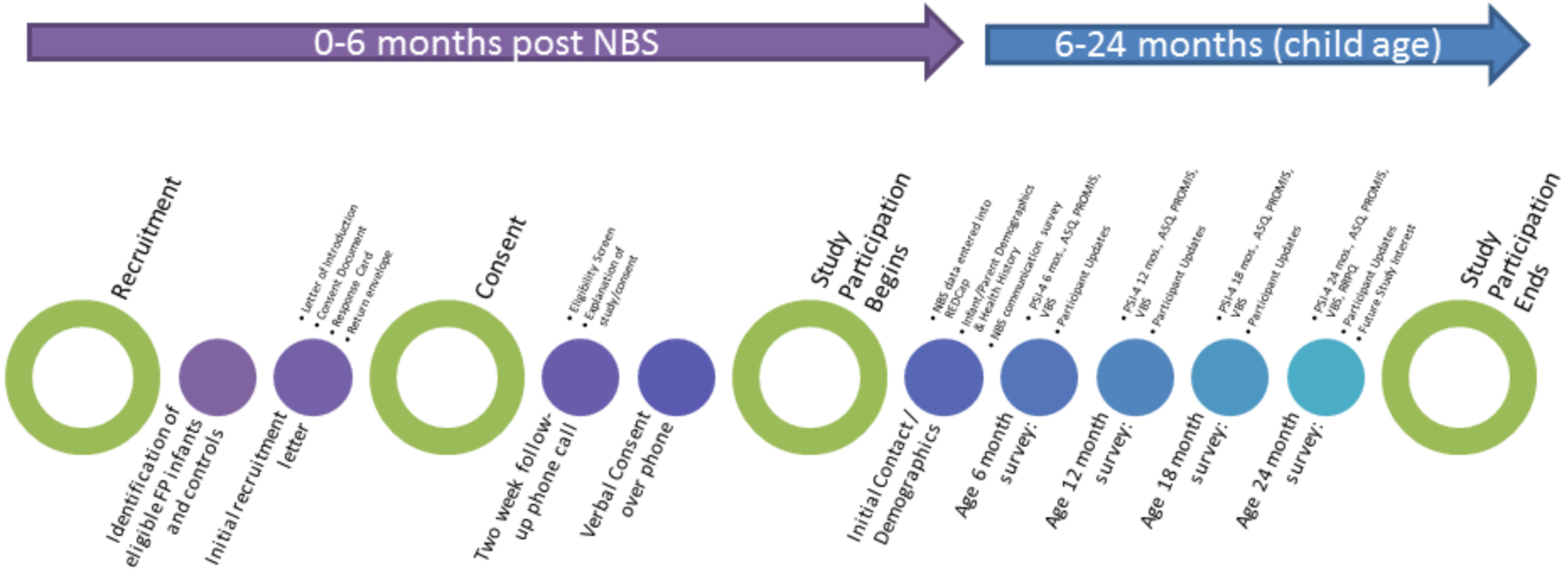
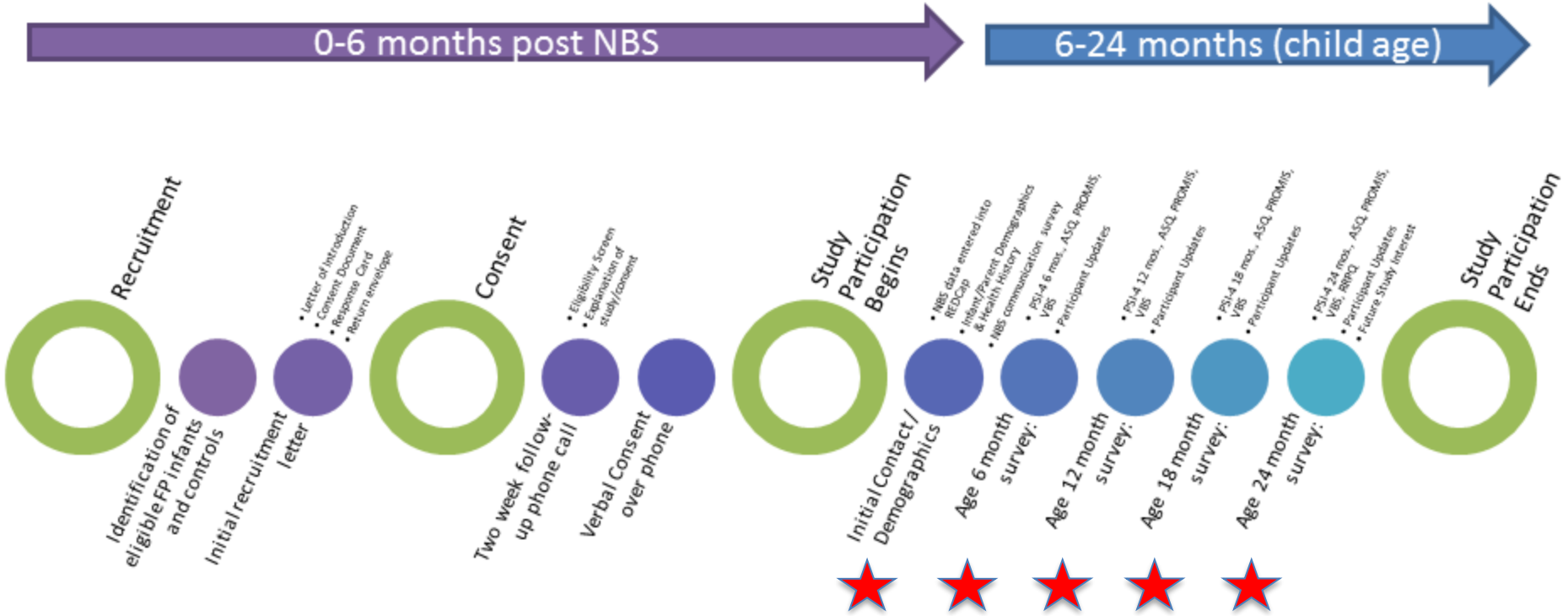


PSI-4: Parental Stress Index (PSI-4), long-form
ASQ: Ages & Stages Questionnaires: Social-Emotional Development Screening Tool (ASQ:SE-2)
PROMIS: PROMIS v.1.0 – Emotional Distress – Anxiety – Short Form
VBS: Vulnerable Baby Scale
RRPQ: Reactions to Research Participation Questionnaire



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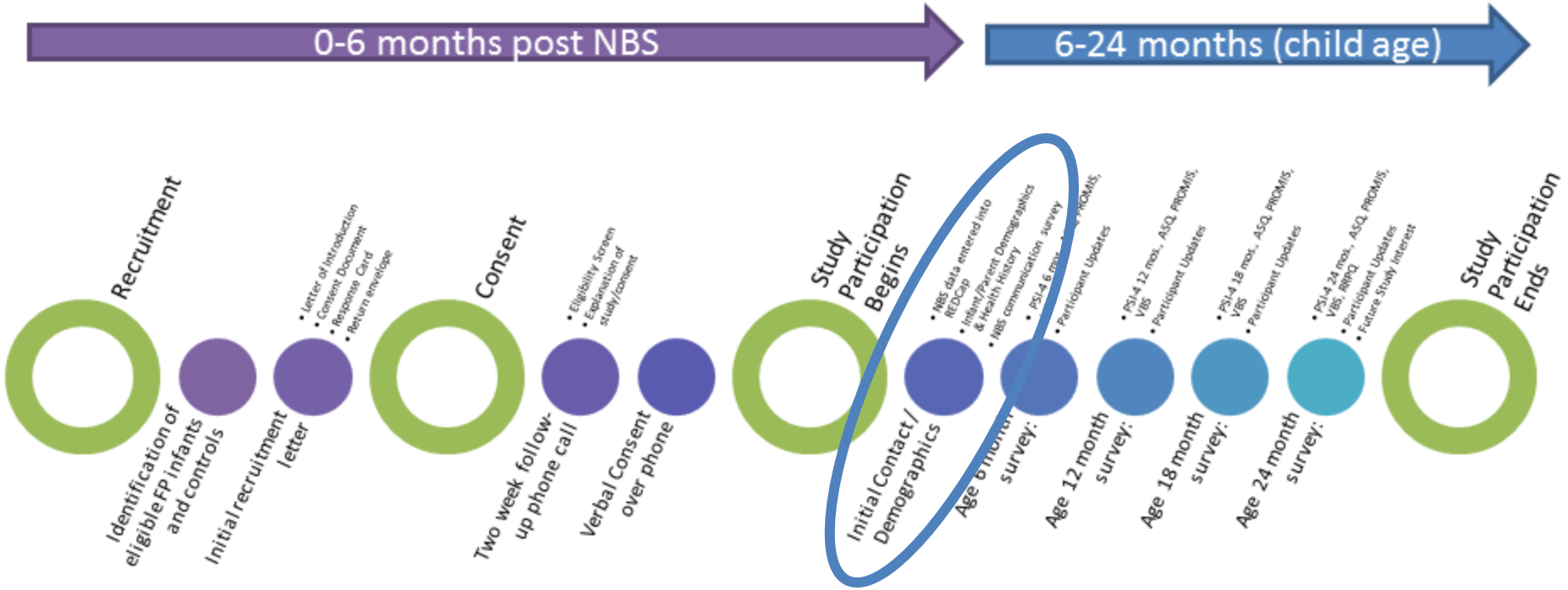

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Initial Survey

Parent Demographics	Child's Demographics	Pregnancy and Birthing Experience	Child's Health	Newborn Screening Experience	Household Demographics
• Relationship to child • Number of children • General health • Mental health • Pregnancy loss/ miscarriage • Insurance coverage • Comfort with medical forms • Country of birth	• Sex • Race/ Ethnicity	• Procedures/ Complications • Worry level during pregnancy • Where baby was born • Perceived difficulty of delivery • Perceived health of mother/infant during delivery	• Child Health Questionnaire • COVID-19 concerns • Diagnosed Conditions	• Introduction • In the Hospital • Hearing Screen • Congenital Heart Screen • Blood Spot Screen (heel prick test) • Results of the Blood Spot Screen	• Marital status • Number of caregivers in home • Annual household income, number of dependents • Education • Race/ Ethnicity • English proficiency/ languages spoken at home

Participant Demographics (N=998)

Demographics	Median (IQR)
Age (Parent)	31.9 years (28.5-35.5)
Age (Infant)	4.8 months (2.7-6.9)

	N	(%)
Dyads in Study	**N= 998**	
Dyad (parents in dyad)	343 (686)	(69%) ✓
Single Parent	312	(31%)
Sex of Participant	**N= 743**	
Male	343	(35%)
Female	654	(65%) ✓

	N	(%)
Biological Parent	984	(98.6%)
Marital Status	**N= 998**	
Married	786	(79%) ✓
Partnered but not married	136	(14%)
Separated	15	(1.5%)
Divorced	5	(0.5%)
Never married	55	(5.5%)
Number of Children	**N= 743**	
Only Child	273	(37%) ✓
One other child	254	(34%)
Two other children	126	(17%)
Three other children	60	(8.0%)
More than three	29	(3.4%)

Race and Ethnicity

Population Estimates – Census.gov

	N	(%)	Iowa	Virginia
Hispanic/Latino/Spanish?	**N = 998**			
Yes	94	(9.4%)	6.7%	10.2%
No	894	(89.6%)		
Race (Select all that apply*)				
White		(83.5%)	90.1%	68.8%
Black/African American		(8.7%)	4.3%	20.0%
American Indian or Alaska Native		(1.9%)	0.6%	0.6%
Asian		(5.4%)	2.8%	7.2%
Native Hawaiian or Pacific Islander		(0.6%)	0.2%	0.1%
Other		(3.3%)		
Born in the US?	**N = 998**			
Yes	858	(86%)		
No	138	(13.8%)	5.5%	12.5%

*participants could select more than one Race

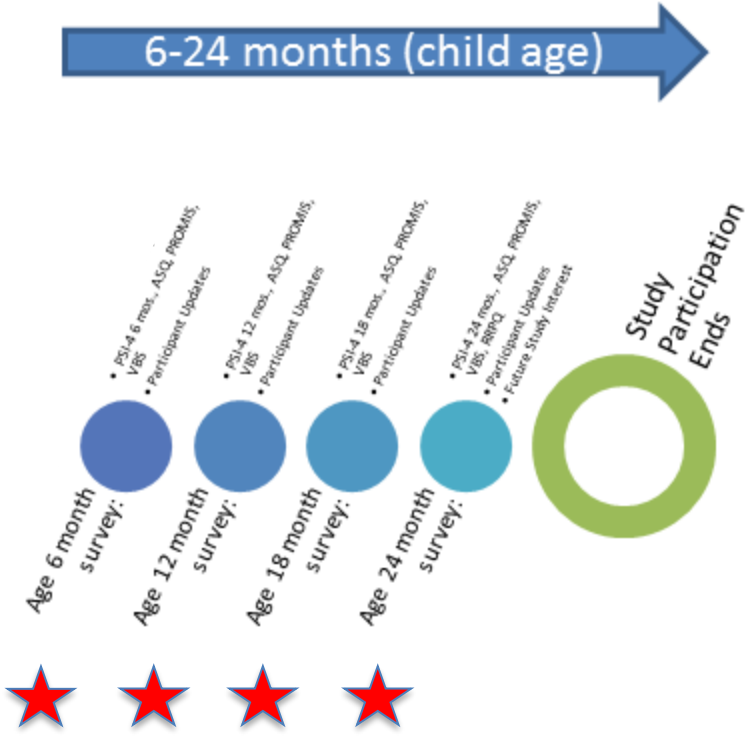
Language and English Proficiency

What languages are spoken in your home? (Select all that apply*)	**N**	**(%)**
English	937	(94%) ✔
Spanish	86	(8.6%)
French	11	(1.1%)
Chinese	15	(1.5%)
Tagalog	7	(0.7%)
German	8	(0.8%)
Vietnamese	3	(0.3%)
Korean	5	(0.5%)
Other	62	(6.2%)

How well do you speak English?		**N**	**(%)**
		N = 998	
	Do not speak English	21	(2.1%)
	Poorly	13	(1.3%)
	Well	46	(4.6%)
	Very well	917	(92%) ✔

How confident are you at filling out medical forms by yourself?	**N**	**(%)**
	N = 998	
Not at all	11	(1.1%)
A little bit	26	(2.6%)
Somewhat	94	(9.4%) ✔
Quite a bit	264	(26.5%)
Extremely	601	(60.2%)


UNDER CONSTRUCTION
CONTENT WILL BE AVAILABLE SOON


6-24 months (child age)
• PSI-4 6 mos., ASQ, PROMIS, VBS
• Participant Updates
• PSI-4 12 mos., ASQ, PROMIS, VBS
• Participant Updates
• PSI-4 18 mos., ASQ, PROMIS, VBS
• Participant Updates
• PSI-4 24 mos., ASQ, PROMIS, VBS, RRPQ
• Participant Updates
• Future Study Interest
Study Participation Ends
Age 6 month survey:
Age 12 month survey:
Age 18 month survey:
Age 24 month survey:

Domains of Harm

DRAFT

Physical

Psychosocial

- False Positive Results
- Uncertain Prognoses

Financial strain

Opportunity costs

Harris et al. 2014

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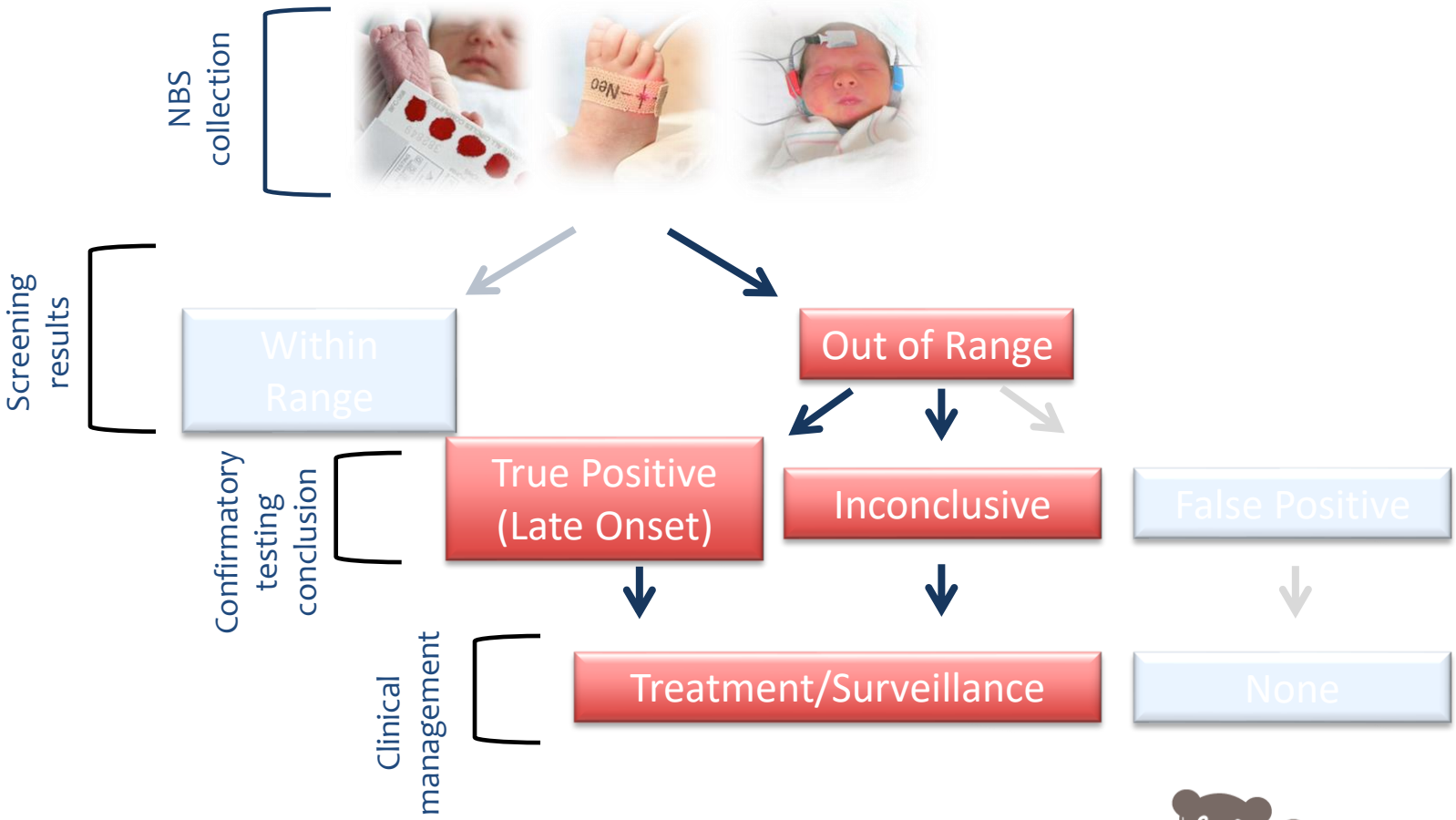

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"I'm fine; I'm just waiting for my disease" : The new and growing class of presymptomatic patients

Jennifer M. Kwon and Robert D. Steiner

Neurology 2011;77;522; Prepublished online July 13, 2011;
DOI 10.1212/WNL.0b013e318228c15f

Patients-in-Waiting: Living between Sickness and Health in the Genomics Era

Stefan Timmermans[1] and Mara Buchbinder[2]

Journal of Health and Social Behavior
51(4) 408–423

DOI: 10.1177/0022146510386794

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Available Published Peer-Reviewed Data

- Few studies
- Studies tend towards small, single center
- Majority qualitative

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Issues Raised

- Benefits of knowing
  - Avoidance of diagnostic odyssey
  - Reproductive benefits
  - Access to early treatment
- Harms of knowing
  - Anxiety and stress of waiting for disease
- Loss to follow-up

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*Emerging Challenges in NBS: Benefits and Harms of Receiving Uncertain Prognoses After NBS** *(R01HD106986)*

**funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development*

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Children's National Hospital
Study Team Members

Name	Title	Role
Beth Tarini, MD, MS, MBA	Associate Director, Center for Translational Research, Children's National Research Institute	Principal Investigator
Hiroki Morizono, PhD	Director, Biomedical Informatics	Data Manager
John Barber, MS	Senior Staff Biostatistician, Biostatistics and Study Methodology	Data Programmer
Anne Atkins, MPH	Clinical Research Coordinator	Research Coordinator
Brianne Miller, MPH	Clinical Research Coordinator	Research Coordinator
Kelly Christensen	Research Assistant	Research Assistant

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Case Western Reserve University Study Team Members

Name	Title	Role
Aaron Goldenberg	Professor, Research Director, and Vice Chair, Department of Bioethics and Medical Humanities	Principal Investigator
Marsha Michie	Associate Professor, Department of Bioethics	Co-Investigator
Roselle Ponsaran	Research Associate, Assistant Research Director, Department of Bioethics	Research Coordinator

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Iowa Study Team Members

Name	Title	Role
John Bernat, MD, PhD	Clinical Associate Professor, Stead Family Department of Pediatrics, Division of Medical Genetics & Genomics	Site PI
Knute Carter, PhD	Clinical Associate Professor, Biostatistics	Co-Investigator
Sandra Daack-Hirsch, PhD, RN, FAAN	Professor and Executive Associate Dean, College of Nursing	Co-Investigator
Katherine Mathews, MD	Professor of Pediatrics and Neurology, Vice Chair of Clinical Investigation, Department of Pediatrics	Co-Investigator
Carol Johnson	Supervisor, Iowa Newborn Screening Follow-Up Program	Co-Investigator
Emily Phillips, BSN, RN, CCRC	Nurse Coordinator, Iowa Newborn Screening Program	Recruitment Coordinator
Michelle Bargren, BSN, MSN, RN	Shorty Term Follow-up Nurse, Iowa Newborn Screening Program	Recruitment Coordinator

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Oregon

Name	Title	Role
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TBD		Research Assistant

Missouri

Name	Title	Role
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Julie Raburn-Miller	Missouri Department of Health and Senior Services	Collaborator
Lori Swartz	Missouri Department of Health and Senior Services	Collaborator

Tennesee

Name	Title	Role
Amanda Ingram	Coordinator, NBS Follow-Up, Tennessee Department of Health	Site PI

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Name	Title	Role
Tara Lavelle, PhD	Assistant Professor of Medicine, Tufts University	Co-Investigator
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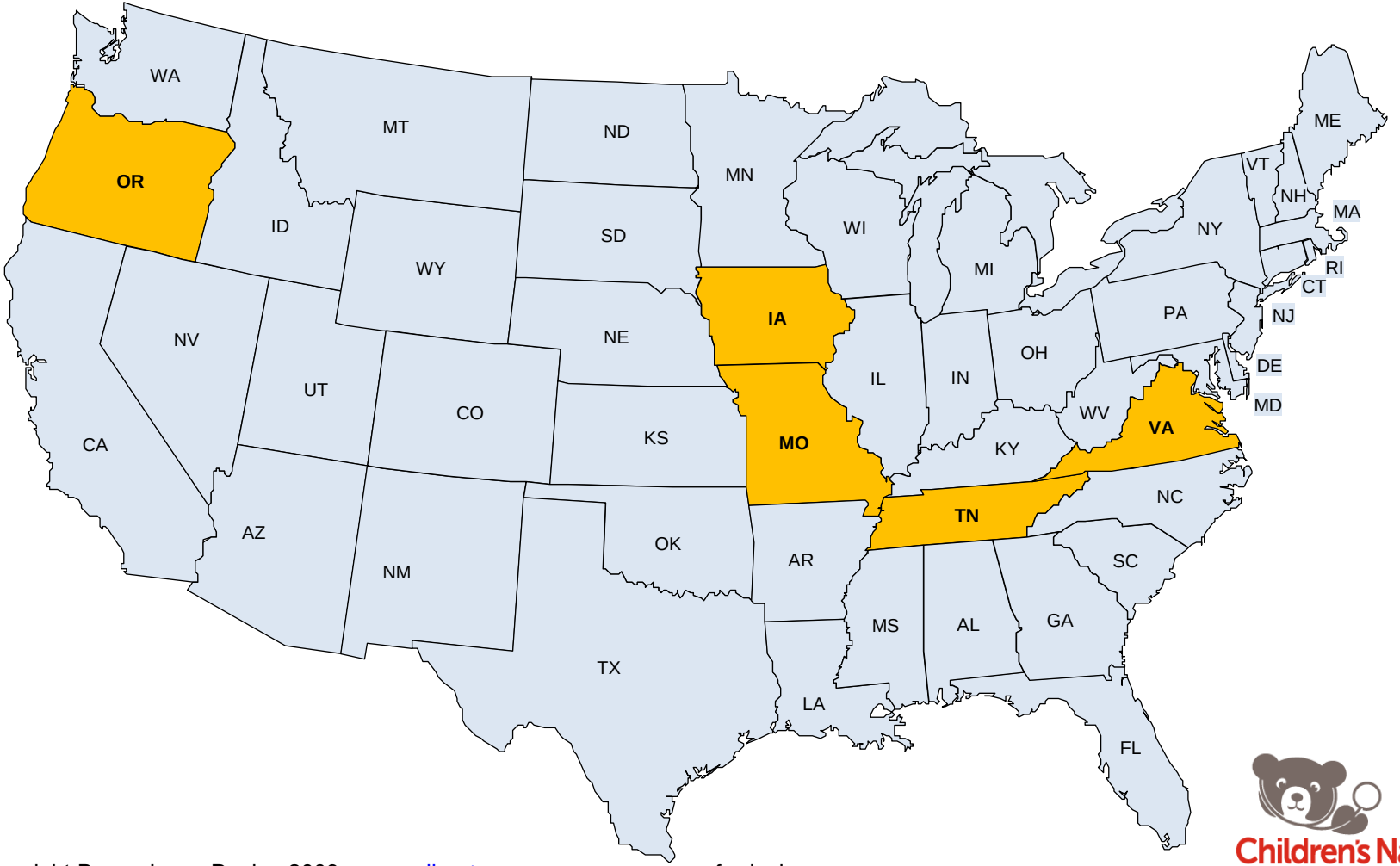
Norma-Jean Simon		Consultant
Natasha Bonhomme, BA	Founder, Expecting Health	Consultant
Lisa DeCamp, MD, MSPH	Associate Professor, University of Colorado School of Medicine and Children's Hospital Colorado	Consultant
Lindsay Cooper, MA	Spanish Language Research Coordinator	Consultant
Susan Berry, MD	Professor, Department of Pediatrics Faculty Member, Division of Pediatric Genetics and Metabolism, University of Minnesota	Advisory Committee
Melissa Wasserstein, MD	Professor, Dept. of Pediatrics and Dept. of Genetics, Chief, Department of Pediatric Genetic Medicine, Albert Einstein College of Medicine	Advisory Committee
Catherine Wicklund, MS	Director of the Graduate Program in Genetic Counseling at Northwestern University, Associate Professor in the Department of Obstetrics and Gynecology	Advisory Committee
Michele Gornick, PhD	Genetics Communication Expert	Advisory Committee



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Specific Aims

1. To determine the longitudinal scope and magnitude of benefits and harms on parents and their children who have received an uncertain prognosis after NBS. (Quantitative)

2. To elucidate the longitudinal experiences of parents and their children who have received an uncertain prognosis after NBS. (Qualitative)

3. To develop recommendations for NBS programs that will inform policies and practices to maximize benefit and minimize harm to children who receive an uncertain prognosis after NBS.

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Thank You!