



# PREMATURITY RESEARCH CENTERS

2018 Q1 UPDATE

# HEALTHY MOMS. STRONG BABIES.



## *Welcome to the Q1 Prematurity Research Center Update*

**P**reterm birth is an urgent health crisis for moms and families. In this country 1 in 10 babies is born prematurely each year. In the U.S. that's more than 380,000 babies, and world-wide, that number jumps to 15 million babies. The problem is more prevalent in some communities: Women of color have an up to 50 percent higher rate of preterm birth than white women. Their children can face a 130 percent higher infant death rate. But that's unacceptable, so we're taking action.

Because preterm birth has many possible causes, each of our six Prematurity Research Centers (PRCs) is charged with exploring a different research target that is likely to be crucial to the prevention of the problem as well as uncovering the underlying causes. Each PRC has its unique strengths, but it is through collaboration across disciplines and centers that we'll identify interventions in behavior and treatment that will help all moms and babies.

I hope you enjoy this update on our latest PRC research. Please accept my gratitude for your support and commitment as we fight this urgent health crisis together. We couldn't do it without you.

A handwritten signature in black ink, appearing to read 'Stacey D. Stewart'.

**STACEY D. STEWART**  
PRESIDENT  
MARCH OF DIMES

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**DR. LOU MUGLIA**

PROFESSOR OF PEDIATRICS  
AT THE UNIVERSITY OF  
CINCINNATI AND VICE  
CHAIR FOR RESEARCH,  
CO-DIRECTOR OF THE  
PERINATAL INSTITUTE AND  
DIRECTOR, CENTER FOR  
PREVENTION OF PRETERM  
BIRTH AT CINCINNATI  
CHILDREN'S HOSPITAL  
MEDICAL CENTER

# GENE DISCOVERY

## LINKS BETWEEN GENETICS AND PRETERM BIRTH

Preterm birth is still the world's gravest health problem for women and babies, affecting 15 million babies worldwide each year. One of the reasons preterm birth is such a difficult health problem to solve — perhaps the most difficult of all human health problems — is that in over 50 percent of preterm births, we don't know what caused them. And if you don't know the cause of a health problem, you're not going to be very effective developing interventions to stop it.

But there's also a lot we do know. For instance, we know that the single most important predictor of preterm birth is a previous preterm birth, whether the woman has already had one herself, or she comes from a family that has a strong history of preterm birth. That means there are important genetic indicators—ones we haven't recognized yet—that have a big impact on this problem.

*“Now, for the first time in history, we have a foundation secure enough to base future investigations on.”*

**LOUIS MUGLIA, M.D., PH.D.**  
OHIO COLLABORATIVE

### The largest genome-wide study of preterm birth ever conducted

While the technology to identify these genes has been available for the last 15 years or so, the stumbling block has been that we have never had a large enough data set to study. Now there is, for the first time in the history of human pregnancy.

Thanks to an unprecedented level of transdisciplinary and transcontinental collaboration, Dr. Louis Muglia and Dr. Ge Zhang of March of Dimes' Prematurity Research Center Ohio Collaborative in partnership with Dr. Bo Jacobsson of Sahlgrenska Academy, University of Gothenburg, Sweden and Norwegian Institute of Public Health, Oslo Norway and an

international team spearheaded an extraordinary breakthrough in the study of preterm birth. The group conducted the largest genome-wide study of preterm birth ever fielded, including more than 50,000 pregnancies. The results identified the locations of no less than six genes whose expressions play a significant role in causing the conditions that bring about preterm birth.

“The technology to perform this study has existed for the last 15 years or so. But we lacked the populations upon which to build a strong statistical foundation,” said Dr. Muglia. “In total, we analyzed over 50,000 pregnancies, and when you get into those kinds of numbers, you're establishing a foundation secure enough to base future investigations on. Now, for the first time in history, we have that foundation.”

### What comes next

We intend to collaborate very closely with the March of Dimes Prematurity Research Center University of Chicago-Northwestern-Duke because they're gene expression as well and are going to be an important partner. We're also going to be working with the Prematurity Research Center Stanford University School of Medicine to make this information, along with other findings, part of the GEnestation and other data repositories.

March of Dimes has supported Dr. Muglia's work since 2004 and was the driving force behind this latest breakthrough. But we were not the only ones who invested in his vision. The Gates Foundation was also instrumental in this funding as well as Scandinavian governments and philanthropic societies.

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PREMATURITY RESEARCH CENTER  
Ohio Collaborative



**PHILLIP BENNETT, M.D., PH.D.**  
PROFESSOR OF OBSTETRICS AND  
GYNECOLOGY, DIRECTOR OF THE  
INSTITUTE OF REPRODUCTIVE AND  
DEVELOPMENTAL BIOLOGY, DEPARTMENT  
OF SURGERY AND CANCER, IMPERIAL  
COLLEGE LONDON

# NEW CENTER IN LONDON

## INSIGHTS INTO LINKS BETWEEN MICROBIOLOGY AND PREMATURE BIRTH FROM OUR NEWEST PREMATURE RESEARCH CENTER

One of the most promising areas of inquiry in our search for the causes and preventions of premature birth is the interaction between the mom and her microbiome, the community of microorganisms in her body. We know that inflammation as a result of infection is responsible for at least 50 percent of all cases of premature birth. And typically, that infection triggers a complex series of actions and reactions in the microbiome. These include the activation of cells of the immune system, such as neutrophils, which can precipitate the physical transformations of collagen breakdown, cervical shortening, fetal membrane stretch, contractions and ultimately, premature labor and birth. Although we know some details about how that process works, up until now, we haven't known why. So, we've turned to some brilliant minds in microbiology and cell-cell communications for help.

### Adding expertise to the network

The expertise of Imperial College London in glycobiology, the study of sugar molecules that coat all cells, both human and bacterial, is unmatched by any other institution. This expertise in glycobiology is complementary to the research themes of other PRCs, including the microbiome (Stanford), physical changes in the structure of the birth canal and organs (University of Pennsylvania), and the genetics of premature birth (The Ohio Collaborative). It's an important new area of study because in the birth canal, these molecules perform a kind of "handshake" that either activates or deactivates immune responses that can in turn, either trigger or prevent premature birth.

### New researchers in London

Professor Phillip Bennett, M.D., Ph.D., is the center's principal investigator and has specialized in helping to prevent premature birth his entire career. Joining him to put the center together are Dr. David MacIntyre and Dr. Lynne Sykes from the Institute of Reproductive and Developmental Biology at Imperial College. Their team includes three world-renowned specialists in the glycosciences: Professor Anne Dell, Professor Ten Feizi and Dr. Stuart Haslam. Also on the team are experts in inflammation and immunology, Professor Marina Botto and Dr. Pascale Kropf, as well as some of the finest microbiologists, chemists,

mathematicians, obstetricians, gynecologists and researchers in the field of reproduction.

### A transdisciplinary approach

One of the motivating factors for Professor Bennett's team to join March of Dimes' PRC network was the transdisciplinary approach. "What normally happens in academia is that isolated university groups work in competition with each other. But what we found exciting was the concept of a research family," Professor Bennett said. "March of Dimes' model has some of the best universities in the world using their own individual expertise and skills to work together for a common cause—we find that to be a particularly attractive way of doing research."

March of Dimes believes the transdisciplinary approach to research will be profoundly important to understanding how premature birth happens and how to prevent the premature birth of 15 million babies worldwide each year. As always, we're limited only by resources, not ideas. More funding is vital for the research to continue.

March of Dimes' Prematurity Research Center at Imperial College London is supported by a grant from Ferring Pharmaceuticals. Together with a unique partnership with three major London hospitals: Queen Charlotte's Hospital, St. Mary's Hospital and Chelsea and Westminster Hospital, Imperial College London's team of physicians and top scientists will provide access to new and existing health data, an extremely diverse patient population and complementary research in a collaborative network.



PREMATURITY RESEARCH CENTER

Imperial College London



**KATE KEENAN, PH.D.**  
PROFESSOR OF PSYCHIATRY AND BEHAVIORAL  
NEUROSCIENCE UNIVERSITY OF CHICAGO

# RACIAL DISPARITY

## HOW MATERNAL STRESS AFFECTS PRETERM BIRTH DISPARITIES

One of the foundational beliefs of March of Dimes' initiative to end racial disparity and improve health equity is that all babies deserve a healthy start. But just when does that "start" begin? Grade school? Preschool? How about in the womb? A new study is looking at one well-known determining factor of disparity and health equity: stress. In particular, does the lifelong chronic and/or acute perinatal stress experienced by mothers in at-risk populations trigger both epigenetic changes and alterations of gene expression in their babies?

*“ We can intervene to improve children’s developmental trajectories. ”*

**KATE KEENAN, PH.D.**  
UNIVERSITY OF CHICAGO

African American women living in low income urban environments have both chronic and acute stress, both of which have been found to negatively affect perinatal outcomes, such as preterm birth, as well as infant health later on. They have acute stressors, like random community violence, on top of chronic stressors of housing, being the sole provider for their families, financial insecurity, and constant discrimination-related stress.

### Major research into how stress Affects birth outcomes

A major research effort at the Prematurity Research Center University of Chicago-Northwestern-Duke titled “Maternal Stress and Preterm Birth Disparities” includes a partnership with Dr. Kate Keenan, a clinical child psychologist whose work is focused on improving developmental outcomes for children in low-income environments. A component of the research effort—NAPS (Nutrition and Pregnancy Study) is a study of African American families with Medicaid insurance living in low-income neighborhoods on the south side of Chicago. The population has very strong base evidence for prenatal stress and its negative effect on birth outcomes and babies’ health.

“Psychologists have always been interested in health disparities, and how environments impact child development and health. And clinical child psychologists have always been interested in looking at critical developmental periods and the earliest point at which we can intervene to improve children’s developmental trajectories,” said Dr. Keenan. “This study combines those ideas to determine at what point we can intervene to help kids get a healthy head start in life. And we may find out that point is earlier than anyone realized. That’s something we’re really excited about.”

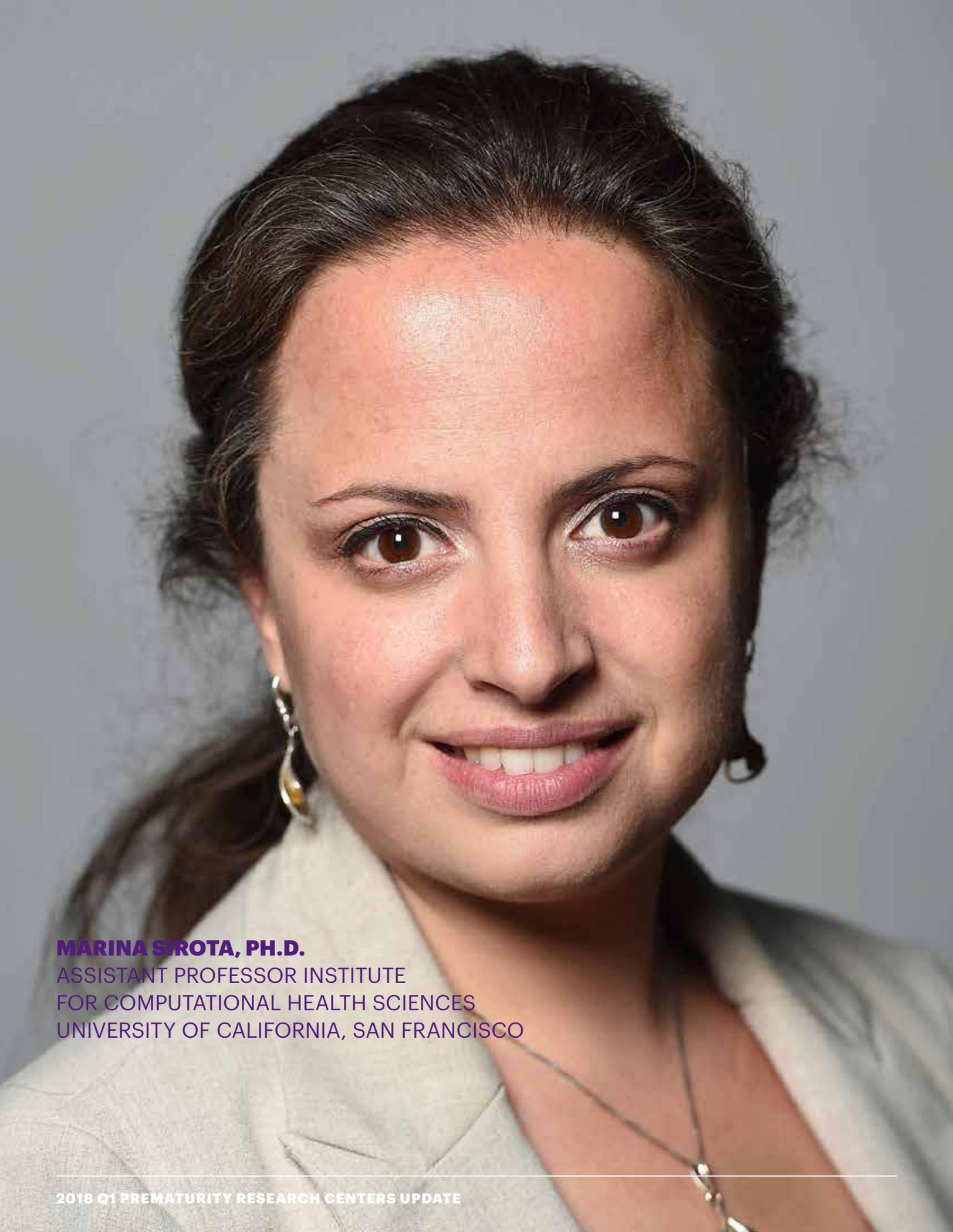
### Testing the diet hypothesis

The NAPS Study provides an opportunity to test hypotheses about how stress exposure leads to poor obstetric health and child outcomes. One component of NAPS includes having subjects take a supplement that contains Omega-3, an essential fatty acid only available through diet, known to be essential for aspects of brain function and potentially related to the integrity of the body’s response to stress. As an intervention, it’s both acceptable and feasible to administer.

The University of Chicago-Northwestern-Duke Prematurity Research Center will examine whether stress exposure increases the risk for premature birth through changes in the functioning of genes in cells at the maternal-fetal interface. The Center also will explore individual differences and potential modifiers of the association between stress exposure and preterm birth.

At March of Dimes, supporting research into a population of women who are at highest risk for preterm birth is essential to advancing the science and improving the lives of the countless moms and babies who need it most.

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PREMATURITY RESEARCH CENTER  
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**MARINA SIROTA, PH.D.**  
ASSISTANT PROFESSOR INSTITUTE  
FOR COMPUTATIONAL HEALTH SCIENCES  
UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

# DATA REPOSITORY

**THE PREMATURETY RESEARCH CENTERS DATA REPOSITORY IS ONE OF THE MOST IMPORTANT INNOVATIVE NEW TOOLS FOR COLLABORATIVE RESEARCH. NOW IT'S READY TO BECOME AN ENGINE OF DISCOVERY.**

From the time she was in high school, Marina Sirota was interested in the intersection of math and biology. Her timing was perfect. As an undergraduate at Stanford, she had an independently designed major: math and computer science curricula with an emphasis on machine learning and artificial intelligence, and a biology curriculum focused on genetics and genomics. As a graduate student, she again found herself in exactly the right place at the right time—working in the lab of a bioinformatics pioneer, Atul Butte, to develop the Prematurity Research Centers Data Repository.

*“The Prematurity Research Centers Data Repository is truly the backbone of the preterm birth research effort.”*

**MARINA SIROTA, PH.D.**  
STANFORD UNIVERSITY

## The backbone of our research effort

The Data Repository was launched in 2014, at the March of Dimes Prematurity Research Center (PRC) at Stanford University School of Medicine, integrating the work of researchers and clinicians from a broad range of disparate disciplines. More than 200 scientists, engineers, statisticians, sociologists and medical professionals work together to foster innovation that will accelerate discoveries of the unknown causes of preterm birth and new ways to prevent it. The Prematurity Research Centers Repository for Preterm Birth Research is truly the backbone of the research effort.

The Data Repository was designed to be both a catalog and catalyst. It provides the capability to ask new and important questions about preterm birth. Dedicated to enhancing research

collaboration and coordination, the Data Repository currently contains information from 13 studies, with individual molecular profiles on 365 patients, aggregated genetic data from more than 30,000 patients, and molecular measurements on more than 8,000 samples. More data is being added every day, and the Data Repository's contents were recently opened to all the other researchers studying preterm birth around the world, in an effort to encourage them to add their own findings to the Data Repository.

## Both collaboration and catalyst

Like most of the work it houses, the Data Repository is itself a synergistic collaboration between the Stanford PRC and several other entities and organizations. These include Northrop Grumman Health Solutions (NG), a partner of the National Institute of Allergy and Infectious Diseases (NIAID) Division of Allergy, Immunology, and Transplantation at the National Institutes of Health (NIH). Since 2004, NG has been working on the ImmPort database, a data sharing portal to ensure that NIH-funded discoveries serve as the foundation for future research.

The overarching goal of this effort is to enable new scientific discoveries from the rich molecular resources that have been funded by March of Dimes, and others, to advance the research in preterm birth. The resulting Data Repository, led by Marina Sirota and her team, is rapidly becoming a powerful tool to do just that.

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PREMATURITY RESEARCH CENTER  
Stanford University

Moms and babies in the U.S. are facing an urgent health crisis:

- In this country 1 in 10 babies is born prematurely each year
- Worldwide 15 million babies are born prematurely each year.
- Premature birth and its complications are the largest contributors to infant death in the United States and globally.
- More than 380,000 babies are born prematurely in the U.S. each year.
- In addition to the human toll, the societal cost of premature birth is more than \$26 billion in the U.S. per year.
- Women of color are up to 50 percent more likely to give birth prematurely and their children can face a 130 percent higher infant death rate.
- In this country black women have maternal death rates over three times higher than women of other ethnicities.
- More than 20 percent of premature babies are born to black women—that's 1 in 5 babies.
- Employers pay 12 times as much in health care costs for premature/low birthweight babies compared to babies born without these complications.

Because premature birth has many possible causes, each PRC is charged with exploring a different transdisciplinary research target that is likely to be crucial to the prevention of premature birth. The six March of Dimes Prematurity Research Centers are: Stanford University, the Ohio Collaborative, Washington University in St. Louis, the University of Pennsylvania, UChicago-Northwestern-Duke, and Imperial College London, in the UK.

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**DONATE TODAY**

For more information on how you can be a part of this effort please contact: 914.997.4492

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