March of Dimes Research Newsletter

January 2024

From the desk of our Chief Scientific Officer

Anecdotally, most New Year's resolutions don't make it past January. Whatever it is that you want to quit, start, or change, chances are it won't work if your first honest attempt happens the day after your resolution. Meaningful achievements happen gradually—with a lot of dedication, patience, and practice. It starts with hard work, becomes a routine, then a habit. And strong habits are hard to break.

I was never a big fan of New Year's resolutions, but not believing in them never stopped me from celebrating the end of one year and start of another. In fact, a big part of my celebration this year had to do with March of Dimes and all the work we've done in the research department and our scientists have done in their labs; the work that has made our operation smooth and reliable and the achievements of our scientists simply exhilarating.

With the foundation we've laid not only for the next 12 months, but for many years ahead, we've sailed past the zone of resolutions and into the zone of manifestation. Every day, we're achieving—and building on—incredible things.

I've said it to my team more than once and I'll say it to you now. We're making big, remarkable discoveries, and our investments into original scientific research are on a trajectory to form some of the most innovative, impactful, and transformative pregnancy-related tests, medicines, and approaches of the next decade and beyond.

To use a soccer metaphor, we're playing on a field we know well, we have the best players, we practice often, we watch reruns of our mistakes, and despite some losses and injuries, we never give up. We're passionate, we're experienced, we collaborate, and we win.

In 2024, we are well on our way. And moms and babies will reap the benefits in our lifetime.

Just last year, we launched a new March of Dimes Research Center for Advancing Maternal Health Equity at the University of Pennsylvania, where we're conducting vital research on how to narrow

Dr. Emre Seli
Chief Scientific Officer
March of Dimes

racial disparities in pregnancy and birth. The year prior, we launched a new Prematurity Research Center (PRC) at the University of California San Francisco, where lead investigator Dr. Marina Sirota is already using Artificial Intelligence, Machine Learning (AI/ML), drug repurposing and Electronic Medical Records (EMR) mining to make novel discoveries and connections about pregnancy outcomes.

During our annual PRC site visits, we checked in with our other California PRC, at Stanford, where scientists are using omics—or the totality of processes inside a cell—to identify biomarkers of preterm birth and preeclampsia, and machine learning to develop predictive models of preeclampsia. We went to Ohio, where researchers are doing exceptional work on the genetic and endocrine determinants of preterm birth, and to London, where our outstanding team is writing the blueprint on the powerful role of the vaginal microbiome in preterm birth and women's health overall.

Last year alone, our researchers used machine learning to predict specific prematurity-related diseases a baby will get even before birth, and to make two predictive models of preterm birth risk based on vaginal microbiome composition. They discovered that not all breastmilk is protective against prematurity-related illness necrotizing enterocolitis (NEC) because not all women have antibody receptors that bind to the bacteria thought to cause the condition. They used AI to discover that less sleep and physical activity in pregnancy is linked with preterm birth, and they uncovered that the simple presence of trees near a pregnant woman's home could significantly lower her risk of hypertensive disorders of pregnancy (HDP).

We also initiated a new research effort into the link between environmental factors and recurrent pregnancy loss (RPL), an effort led by our UCSF and Imperial College London PRCs, and launched MODCAST, our fascinating monthly research podcast.

We also set, early in the year, our research themes that guide all our inquiries: stress; structural, and systemic racism; cardiovascular issues; a lack of birth equity; and spontaneous, late preterm birth. Plus, we formalized our translational science research methodology that focuses our efforts on science that can be brought to clinical trial, tested, tried, and proven true—before being made clinically available to patients.
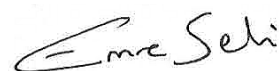
And just a handful of weeks ago, we hosted our annual Prematurity Research Center (PRC) Research Symposium, where PRC lead investigators and scientists from across our five PRCs came together virtually to present their groundbreaking work on preterm birth. The two-day meeting was an incredibly fruitful, collaborative working session aimed at spurring discoveries on a grand scale. From genomics and immunology, to microbiome and metabolism, to data modeling and crowdsourced research, the 2023 symposium covered a wide range of topics all focused on understanding, predicting, and preventing preterm birth.

So what's in store for the coming months? Other than some of the most exciting and groundbreaking, yet so far undisclosed, new research coming out of our PRCs, we will continue to probe pregnancy's biggest questions and find answers that lead to new tests and treatments for moms and babies. We'll also be unveiling our new research website, complete with all our areas of study, our scientists and their publications, in addition to our blogs, podcasts, newsletters, and news.

And best of all, you, like me, can expect some surprises, too, because when you've habituated yourself to the right processes and the right methodology with the right people, you're bound to run into some good luck.
No resolutions required.

With that, enjoy this first issue of the year where we update you on our latest discoveries, appearances, and our podcast.

Keep searching,

Dr. Emre Seli
Chief Scientific Officer

In case you missed it: recent blogs

When March of Dimes researchers publish new work, you hear about it right away on our blog page at marchofdimes.org/our-work/research/blog. Below are snippets of the latest pieces of research out of our dynamic group. Check out the blog page above to read them in full.

New study shows not all breastmilk protects against NEC

Not all breastmilk is created equal. At least that's what Dr. Timothy Hand, a March of Dimes researcher at the University of Pittsburgh, found when studying the link between breast milk and a life-threatening prematurity-related condition called necrotizing enterocolitis (NEC).

The findings were recently published in the Journal of Experimental Medicine. The report's lead author Dr. Chelseá B. Johnson-Hence and Dr. Hand showed that each mom passes on a unique set of antibodies to her baby. Unfortunately, some moms' breastmilk is low in antibodies that protect against NEC.

"This means that if a baby's parent happens to lack particular antibodies—such as those that fend off NEC, they're never going to receive that immunity," Dr. Hand said. "This could help explain why some babies get NEC and others don't."

In an interview with March of Dimes, Dr. Hand said the same would be true for a range of other illnesses. A baby's protection is significantly impacted by the antibodies delivered from breastmilk.

Dr. Hand's finding opens the door to the development of antibodies or therapeutics that could be added to breast milk or formula to boost immunity against NEC. NEC, which occurs when a baby's intestines become inflamed and infected, is a rare condition for babies overall, but a common one for babies born prior to 33 weeks' gestation.

Stanford PRC leaders pen eagerly awaited review on prenatal testing

A group of Stanford-affiliated researchers, including the lead investigator of the March of Dimes Prematurity Research Center (PRC) at the university, have published a major review paper on the state of noninvasive prenatal testing (NIPT), the now routine end-of-first-trimester screening test used by about half of all pregnant people in the U.S.

Published in August in The Annual Review of Biomedical Data Science, the paper chronicles the progression of NIPT since it became clinically available in 2011, charting the scientific advances, unresolved challenges, future possibilities, and ongoing ethical considerations of the technology.

The paper was penned by a group of global leaders in the field of prenatal diagnostics, including Stanford PRC Lead Investigator David Stevenson, PRC Investigator Gary Shaw, former Stanford PRC Collaborator and current Stanford Science Fellow Mira Moufarrej, Stanford Physicist Stephen Quake, and Diana Bianchi, the Director of the Eunice Kennedy Shriver National Institute of Child Health and Human Development.

It details how the test has evolved from analyzing cell-free DNA (cfDNA) to include analyzing cell-free RNA (cfRNA) and expanded from offering insights on the health of the fetus to the health of the mom, too.

"When this technology was first introduced, it wasn't fully understood or appreciated," said Dr. Moufarrej, the paper's corresponding author. "There was a focus on DNA testing to screen for conditions in the fetus, but not maternal health. Now we know that with one sample of maternal blood, we can get information on chromosomal and single gene disorders in the fetus, cancers, fibroids, autoimmune conditions, and infections in the pregnant individual and more recently a glimpse into due date and prenatal risks, too."

"These advances are remarkable," Dr. Moufarrej continued. "But with them, and future advances, come questions about who gets to make decisions with this powerful information, and in whose benefit are those decisions being made."

Less sleep, physical activity tied to preterm birth risk, Stanford Medicine AI model finds

Reduced sleep and physical activity in early and mid-pregnancy is associated with a significant increase in the risk for preterm birth, a new Artificial Intelligence (AI) model created by researchers at the March of Dimes Prematurity Research Center (PRC) at Stanford has found.

The findings, published recently in npj Digital Medicine, showed a nearly 50% increase in risk for those who slept and moved less. The risk of preterm birth was reduced by more than half for women who slept and moved more in later pregnancy.

The model used sleep and physical activity data from a wearable device on a pregnant woman to predict her gestational age and her risk of preterm birth. It could do both these things because from the start it used wearable data from 1,500 pregnant study participants to create the first ever standard, or "clock," for what is considered a normal amount of sleep and physical activity during pregnancy.

The study's most interesting moments came when the model substantially over or underestimated a woman's gestational age—in those cases, that woman saw her risk of preterm birth either dramatically increase or decrease.

"Based on this clock and data from the wearable, we showed that the AI model can tell us how pregnant people are," said lead study author Dr. Nima Aghaeepour, Associate Professor of Anesthesiology, Perioperative, and Pain Medicine, and of Pediatrics, at Stanford Medicine. "And we showed that when women diverge from this normal clock, when they move in a worse direction, when they are in early pregnancy, but the AI thinks they are in late pregnancy because of less movement and sleep, that is when bad things can happen."

The model found that women who aren't moving well and aren't sleeping enough have a 44% increased risk of preterm birth.

"We also showed the opposite," he said. "Women who the AI thinks are in early pregnancy because

they are moving and sleeping a lot but are actually in later pregnancy are protected from early labor risk." The model found that women who are moving well and sleeping a lot have a 52% reduced risk of preterm birth.

While the figures are striking, Dr. Aghaeepour said the devil is in the details. And those details are yet to be cracked open by his team.

Preeclampsia linked to fewer trees in neighborhoods, UPenn PRC finds

Researchers at the March of Dimes Prematurity Research Center (PRC) at the University of Pennsylvania (UPenn) have found that pregnant people who lived in urban neighborhoods with fewer trees were more than twice as likely to develop hypertensive disorders compared to those who lived around more trees.

The research, published recently in the American Journal of Perinatology, was led by UPenn PRC scientist and neonatologist Dr. Heather Burris and Dr. Max Jordan Nguemeni, an internal medicine resident at Brigham and Women's Hospital in Boston. It was also co-authored by UPenn Associate Professor of Emergency Medicine Dr. Eugenia South, a national expert on the impact of green spaces on health equity, with a focus on using green spaces to curb gun violence.

Drs. Burris and Nguemeni and their team found that study participants living in Philadelphia whose homes were within 100 meters of an area with less than 10 percent tree cover had more than twice the odds of developing hypertensive disorders of pregnancy (HDP) compared to participants whose homes were within 100 meters of a green area with more than 30% tree canopy.

This was true even when controlling for the Neighborhood Deprivation Index (NDI), which is calculated using factors like neighborhood income and education level.

Chief among HDP is preeclampsia, the most common and serious high blood pressure disorder of pregnancy, which disproportionally affects non-Hispanic Black pregnant people. Recent research has led scholars and scientists to

assert that lived experience—by way of overt and/or structural racism—plays a significant role in the development of the disease for non-Hispanic Black individuals.

Whether tree canopy comes in the form of parks, playgrounds, tree-lined streets, forested areas, or just trees, living near green spaces has long been thought to be beneficial to health. Now, the research by Drs. Burris and Nguemeni shows green spaces may help lower the risk of gestational hypertensive disorders like preeclampsia, the second leading cause of maternal death globally.

"Our findings suggest that investing in neighborhood greenspace may be a strategy to reduce HDP and improve perinatal health equity," Dr. Burris said. "While more research is needed to determine exactly how tree canopy cover decreases the chance of preeclampsia and other gestational blood pressure disorders, this work presents a natural intervention that may dramatically decrease the risk of one of the worst pregnancy outcomes."

MODCAST

Our research podcast MODCAST continues to release monthly episodes with a trio of new releases since the fall newsletter. Below is a brief summary of what you may have missed. To stay up to date with MODCAST, released on the last Wednesday of every month, subscribe and follow the podcast wherever you listen to podcasts: Apple, Spotify, Google, or other platforms. Or head over to marchofdimes.org/podcast to listen directly on our site. Happy listening!

Prof. David MacIntyre on Microbiome, Inflammation, and Targeted Diagnostics for Preterm Birth Risk

Dr. David MacIntyre
Professor of Reproductive Systems Medicine, Imperial College London

Microbiome, Inflammation, and Targeted Diagnostics for Preterm Birth Risk

Professor MacIntyre, one of the directors of the March of Dimes Prematurity Research Center at Imperial College London, discusses his team's new device that can, in under two minutes, identify the type of bacteria in a woman's vaginal microbiome and determine whether it's causing inflammation and could lead to preterm birth.

Dr. Nima Aghaeepour on Predicting Neonatal Complications with Machine Learning (AI)

Dr. Nima Aghaeepour

Predicting Neonatal Complications with Machine Learning (AI)
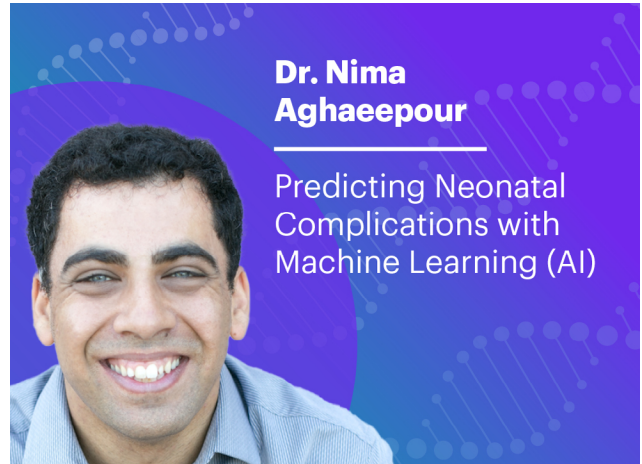
Dr. Nima Aghaeepour, a researcher at March of Dimes' Prematurity Research Center (PRC) at Stanford, discusses a Machine Learning (ML) model that predicts prematurity related newborn diseases weeks before they occur, including before a baby is even born.

Dr. Jay Greenspan and Dr. Liz Foglia on Hot Topics in Neonatology 2023 Conference Preview

Dr. Jay Greenspan and Dr. Liz Foglia

Hot Topics in Neonatology 2023 Conference Preview

Philadelphia neonatologists Dr. Jay Greenspan and Dr. Liz Foglia discuss three talks at the Hot Topics in Neonatology conference in Maryland: one on the lower limits of viability and the other two on racism in the NICU.

March of Dimes research in the news

2022-2023 March of Dimes Agnes Higgins Award

- **Health Professional Radio:** Dr. Erica P. Gunderson Named 2022-2023 March of Dimes Agnes Higgins Award Winner, 9/14/2023

Breast milk research

- **Health Professional Radio:** Dr. Timothy Hand: The Role of Breast Milk Antibodies in Shaping Infant Immunity, 10/5/2023

Industry coverage

- **Chief Healthcare Executive:** March of Dimes CEO: 'We're not prioritizing moms", 10/11/2023
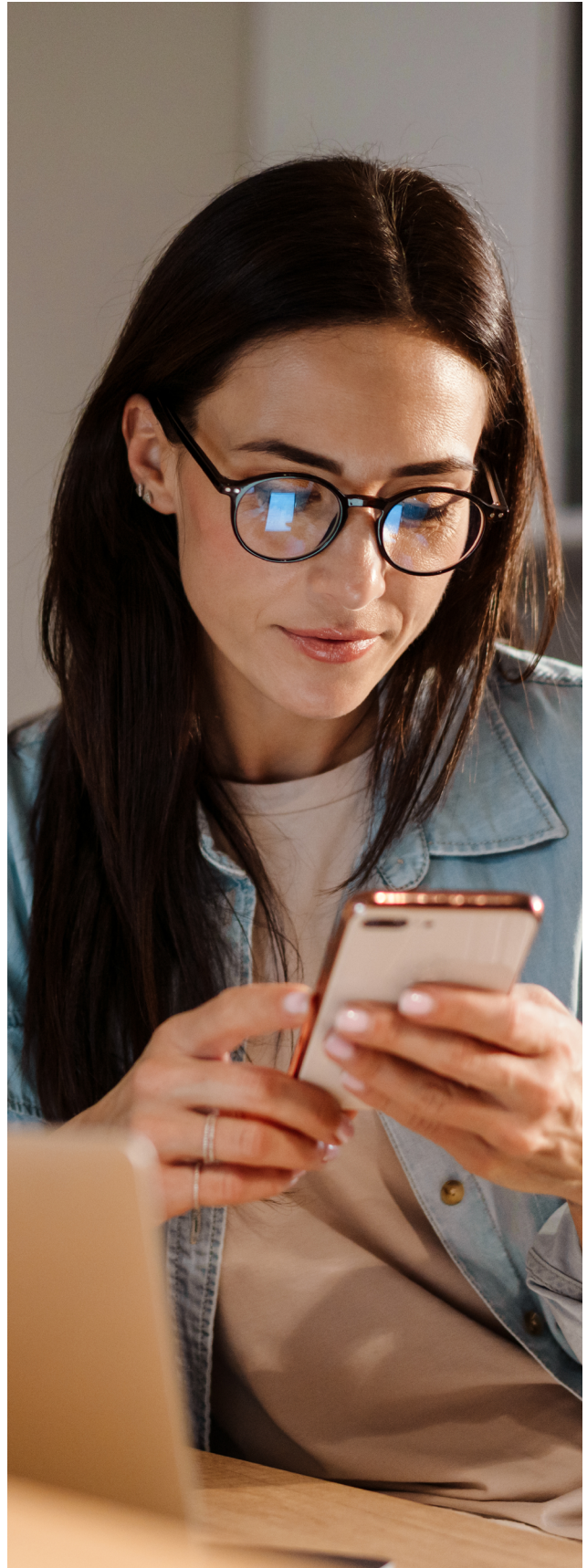
Dispatches from Jonathan Cherry

**Jonathan Cherry,** Senior Director
Research Operations

The second half of the year is primarily focused on our annual site reviews/visits to Prematurity Research Centers (PRCs), and the Annual PRC Research Symposium.

Our travels took us to Philadelphia, London, and Cincinnati to visit the PRCs in each of those locations. We also got updates from our Research Center for Advancing Maternal Health Equity and our Recurrent Pregnancy Loss (RPL) Research Group.

In September, we headed to Philadelphia to perform our annual site visit (ASV) and review of the UPenn PRC, and to get a peek at some of the findings from our newly launched Research Center for Advancing Maternal Health Equity (RCAMHE). The PRC group here has identified potential markers for preterm birth and interesting

new data that explains how the placenta, long seen as a byproduct of pregnancy, actually holds keys to unlock the mysteries of preterm birth. Closing out the day was a tour de force by the leader of the RCAMHE, Dr. Elizabeth Howell, who led us through the rationale and impact of the research center, and presented findings from the newly started PeliCaN project. This is a randomized controlled trial (RCT) for postpartum care in the NICU involving doula-midwife intervention for those most at-risk of developing complications postpartum.
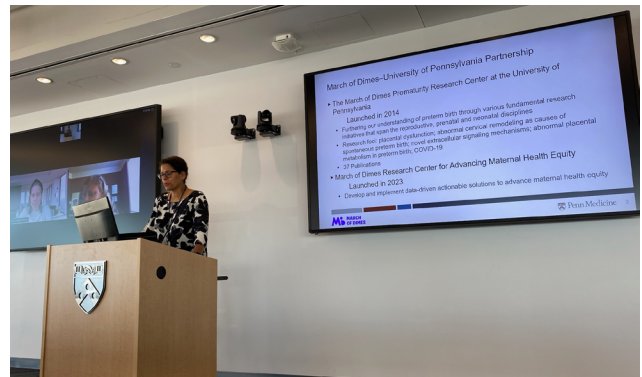

One week and several flights later, we landed in London for our ASV of the Imperial College London PRC. First, I'd like to share one of the interesting and important things about these site visits. Yes, they involve several staff, either in person or virtual, but they also require several volunteer reviewers. These reviewers are top-of-the-field, running significant research and medical institutions across the U.S. They give their time freely from their own schedule to make sure the March of Dimes research portfolio upholds the highest scientific rigor, and invests in research projects that will make a difference to moms and babies in our lifetime. I'm always impressed at their engagement, dedication, and focus. Their feedback, candid and pointed at times, helps us steward research funding to the most impactful projects.

The European PRC presented findings on the impact of microbiome on preterm birth, including several new and promising diagnostics and therapeutics to identify and treat those at risk of preterm birth. We also learned about links between blood group antigens, microbiota, and preterm birth that could lead to simple heuristics for physicians in the future. Of note were the presentations and discussions around a new treatment that could prevent preterm birth in cases where the microbiome plays a role. There's more to be done, but we're moving in the right direction.

A few weeks later, I traveled across Ohio to join the Ohio Collaborative PRC for their ASV. The Collaborative is composed of research teams from Cincinnati, Cleveland, and elsewhere around the state. We met at Cincinnati Children's Hospital Medical Center, and spent the day being wildly impressed by the work covering the genomics of preterm birth, immunological changes that trigger preterm birth, and the findings from the Black Birth Cohort out of Cradle Cincinnati.
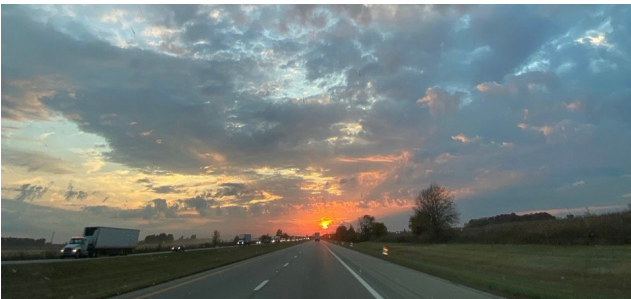
Some promising diagnostics to identify and stratify risk of preterm birth are in development; these could lead to some logical therapeutics through drug repurposing. Once again, the collaborative nature of the PRCs comes into play— the work is already underway to test in silico for interactions and candidates through the PRCs in California.

We just finished up our annual PRC research symposium. This event brings all of our PRC research groups together in one place to share ideas, findings, and expand our shared work.

We've been doing this in a virtual format several years now, and hope that next year we'll gather in person, perhaps at the March of Dimes HQ in Arlington. The researchers had lively discussions after each talk, finding new ways to work together to overcome obstacles others may face. After the sessions, we had a planning meeting for the coming year. Our watchwords for 2024 are integration and validation. We're focusing on streamlining how we test and validate biomarkers, for example, using precious research samples so that one test can answer many questions across the entire network.

And as always, thank you for your support, attention, and voice. Without it, we couldn't do what we do.

Jonathan Cherry,
Senior Director, Research Operations