March of Dimes Research Newsletter

October 2023

Dr. Emre Seli
Chief Scientific Officer
March of Dimes

From the desk of our Chief Scientific Officer

And somehow, it's already fall. For most people I know, at least those in a country with distinct changing seasons, autumn is beloved—a phase before year end when change is palpable, reflection is plentiful, and the future seems full of promise... and just a little bit of wonder.

Lately, as I walk the red and yellow leaf-covered sidewalks in Connecticut, where I live, my thoughts are filled with pride and excitement about how far we've come in the research department and how far we'll go—together.

You've probably heard me talk about the truly remarkable, impactful—and cool—work happening in our labs. Over the last few months, March of Dimes Senior Director of Research Operations Jonathan Cherry and I got to hear about it firsthand during our annual Prematurity Research Center (PRC) site visits in California.

As you'll read in Jonathan's dispatch in this issue, the visits were productive, illuminating, and exciting.

At our Stanford PRC, we heard about research focused on omics, or the totality of the processes and signals happening inside moms and babies (from proteins to genetic factors to epigenome and more). By profiling these different biomarkers, especially as they relate to immune response, our scientists are probing ways to predict and prevent preterm birth.

They're also using machine learning to make predictive models of immune responses associated with preeclampsia, and working on finding new roles for existing, pre-approved drugs to help prevent early labor (a process called drug repurposing).

At our University of California San Francisco (UCSF) PRC, the team updated us on their own drug repurposing efforts and the March of Dimes Database for Preterm Birth Research, which is a bank of every piece of molecular data that has come out of a PRC-funded study (comprising more than 40,000 experimental samples). As part of

UCSF's first DREAM Challenge, machine learning experts from around the world used March of Dimes' biorepository data to create two predictive models for preterm birth risk. You can read about that successful effort in this issue's research blog.

The UCSF team also updated us on their most recent AI4ALL graduate class, which was comprised of 28 high school students from under-represented backgrounds who learned about AI and machine learning through lectures and research projects over three weeks. This was UCSF's fifth year mentoring AI4ALL students, and the first year the program was supported by March of Dimes.
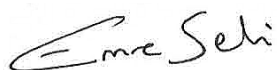
The trips were a great success—not only because our scientists showed us first-hand the impactful work they're doing with support from donors like you, but because we were able to meet face to face and connect over our shared passion for this work.

Several of our conversations focused on our newly launched research podcast, which we named MODCAST and release monthly. You can read more about it in this issue and listen anywhere you listen to podcasts (one of our episodes features the DREAM Challenge I mentioned above).

At the end of this issue, you'll read a story that you'll likely never forgot. It centers around Erika and Kris Young, who suffered a catastrophic loss last August when their daughter Sommer passed away less than two hours after birth following a sudden and inexplicable drop in heart rate. Donors to the March of Dimes Innovation Fund, the Youngs are doing everything they can to find answers. Their story is a stark reminder of why we are so dedicated to this work, and how much is left to be done.

We hope you enjoy this issue, and we thank you again for your enthusiastic support.

Keep searching,

Dr. Emre Seli
Chief Scientific Officer

Research dispatches from Jonathan Cherry

Jonathan Cherry, Senior Director Research Operations

These past few months have been busy. From coast to coast, we've been uncovering, translating, and spreading the word about the work of researchers focused on improving the health of moms and babies.

First, I awarded the Agnes Higgins Award in Maternal-Fetal Nutrition at the Pediatric Academic Societies meeting (PAS) in Washington, DC. This year's winner, Dr. Erica Gunderson, presented on her inspiring journey from public health nutrition to research into pregnancy and lactation. Following her curiosity and the ups and downs of working in research, she's established her work at Kaiser Permanente, focusing on cardiometabolic disease progression, breastfeeding, and health outcomes for those most at risk. Her career parallels Agnes Higgins, of the eponymous award, who dedicated her work to helping moms with nutrition so their children would be more likely to grow up healthy and strong. Her talk, her career, and her approach to making the world a better place is inspiring for new and established researchers and clinicians. Sometimes it's hard to see how you're making a difference until someone shows you. Dr. Gunderson's message encouraged folks to look forward and continue to blaze the trail, but also to look back at the path you've made for others to follow.

Often, we're invited to help the next generation of scientists, researchers, and clinicians understand how they can help us fight for the health of all moms and babies. That's why at the Birth Defects Research & Prevention (BDRP) meeting in July, I presented on March of Dimes' history, award and research priorities, and future goals. What we've discovered and doubled down on is collaborative and translational research. As a former bench researcher, I can appreciate what investigators are up against—it's complicated to work with folks across fields, but you can't always make the impact you need to on your own. The newest generation of researchers are more open to cross-domain research, including fields they have little experience in, to make an outsized impact. To be successful, this requires big-picture thinking, and an understanding of how to stack and lever up mechanisms across several funding sources. It's incredibly encouraging to be a part of these conversations, and I think I learn as much as I share in these meetings.

The work of BDRP has long been aligned with March of Dimes, and our presence and support of these groups is a signal that we're invested in the next generation of research and findings that will improve and save lives.

Not all our work takes us on the road for in-person meetings. I was a virtual participant in The NIH Workshop on Measuring and Predicting Reproductive Health: Advancing Technology and Fundamental Understanding in Maternal-Fetal Immunity. This two-day symposium gathered some of the best in the field of maternal-fetal immunology, and March of Dimes was well represented. Several of the participants are, or have been, researchers affiliated with March of Dimes. Now they're pushing the field forward to discover, understand, and share new ways to prevent preterm birth, predict risk for adverse outcomes, and advance reproductive health.

And then were all the site visits. A small cadre of our team traveled to review the scientific progress and work of two of our Prematurity Research Centers (PRCs), Stanford and UCSF. Stanford is home to one of our recent campaigns for Low

Dose Aspirin (LDA) that you may be hearing more about in another venue. They've taken a big swing at implementation, compliance, and the nuances of historical trust/mistrust between communities and healthcare systems. They've brought in partners across the spectrum, and are rolling out a state-wide effort to educate, implement, and track the impact of LDA. The findings from this could inform and shape national campaigns in the future.

That's only one part of the work being done at Stanford. They're also producing, testing, and refining risk-models for preterm birth, preeclampsia, and other complications.

This work is similar to the outputs from the UCSF team. Their group is what I like to think of as the hypothesis generators—they look for signals in the noise that can lead to interesting and useful findings. In partnership with other PRCs including the Ohio Collaborative, UPenn, and Imperial College London, the USCF group is testing the use of Electronic Health Records (EHR) and data to predict risk, direct early treatments, or place the right resources in place for patients before they have any clinical signs or outward symptoms. These models improve quality and access to care by reducing the time between diagnosis and treatment.

Another interesting project out of the UCSF group is drug repurposing. The team is taking a look at several over-the-counter medications that are safe during pregnancy and exploring in silico, individual, or combinations of drugs that could help prevent things like preeclampsia or post-partum hemorrhaging. Some surprising findings hold promise for treatments that could save lives and improve the health of moms and babies. This work certainly needs further testing but provides us with a low-risk high-impact outcome from our research portfolio.

Want to know more? Tune into MODCAST, our research podcast covering recent findings from our group in easy-to-understand language. The episodes are brief, but packed with goodies including researcher interviews. As we progress, we'd like your feedback. Would you like to follow us on the road? Maybe hear an interview, review, or report from the field? Drop us a line at research@marchofdimes.org or leave a comment in the podcast comments section and let us know.

The rest of the year has us completing our annual site reviews at the University of Pennsylvania, Imperial College London, and The Ohio Collaborative. These reviews are completed by experts in the field as a part of the contracts we have with these organizations, and are a way to make sure that your contributions to the research program at March of Dimes are yielding results that move the field toward tangible solutions for preterm birth and maternal and infant health. We'll also be convening a virtual research symposium at the end of November/early December on preterm birth—a method we use to gather contributors to our research portfolio in one venue to share and discover new ideas.

I'll also be representing research in a couple virtual and in-person events before the new year. In November, I'll be meeting with our National Collegiate Leadership Council. These are student leaders from around the country who have a passion for creating awareness and action on their collegiate campuses from coast to coast. They work through mission projects that will make a lasting impact in their community through mission activations, advocacy, and fundraising. I've also set up time to meet with folks in our local markets. And I'll attend some special events, where I'm happy to connect.

As always, thank you for supporting research. This is a big part of our legacy and history at March of Dimes. I'm honored to be a part of it, and to help move the mission forward.

Jonathan Cherry
Senior Director, Research Operations

Making connections at Pediatric Academic Societies (PAS) 2023. Agnes Higgins Award winner Dr. Erica Gunderson and Stanford PRC PI Dr. David Stevenson talk through the intricacies of maternal and infant cardiometabolic disease progression and incidence.

The BDRP Grant Development Workshop session was well attended and organized.

The UCSF PRC team presents research findings on the portfolio of projects during the annual PRC site review.

California Surgeon General Dr. Diana Ramos joins the Stanford PRC site review along with Dr. David Aronoff, Chair, Department of Medicine, Indiana University.

Have you heard? We launched a podcast

On a quiet day in the middle of June, a new podcast was born: MODCAST, March of Dimes' first research podcast.

Hosted by March of Dimes Director of Research Communications Olesia Plokhii, MODCAST features interviews with March of Dimes scientists, donors, and personalities about the most impactful maternal and infant health research conducted today.

MODCAST aims to bring scientists, doctors, donors, and families behind the laboratory doors for a fascinating look into the science that is changing, study by study, the story of moms and babies in the U.S.

In addition to March of Dimes scientists, MODCAST will dive into conversations with the field's most consequential researchers, no matter their affiliation, in an effort to foster openness, dialogue, and collaborative scientific discovery in the space.

From interviews with March of Dimes Chief Scientific Officer Dr. Emre Seli, to news analysis, to study discussions, and more, MODCAST is the leading source for today's preeminent research on moms and babies.

Episodes are released the last Wednesday of every month. Here's a summary of the first three episodes.

Dr. Emre Seli
Welcome to MODCAST: Why Research Matters

Episode 1
March of Dimes Chief Scientific Officer Dr. Emre Seli discusses the motivations behind the podcast, the research vision at March of Dimes, our belief in open, collaborative science, and our focus on translational research that makes a difference for moms and babies.

Drs. Sirota, Oskotsky, and Golob
Big Data Analysis and Preterm Birth Risk Prediction
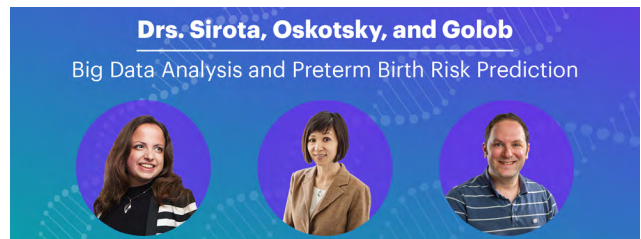
Episode 2
Dr. Marina Sirota, principal investigator at the March of Dimes Prematurity Research Center at UCSF, and colleagues Dr. Tomiko Oskotsky and Dr. Jonathan Golob, discuss using big data to launch a DREAM Challenge that succeeded in creating two predictive models for preterm birth risk.

Dr. Mira Moufarrej
Predicting Preeclampsia So We Can Prevent It

Episode 3
Stanford University Science Fellow Dr. Mira Moufarrej discusses what we know about preeclampsia, why Black women in the U.S. are disproportionately impacted, and a new blood test that could identify at-risk women in the first trimester.

Listen and subscribe wherever you listen to podcasts. Learn more: marchofdimes.org/podcast

DREAM completed: Scientists use massive data from March of Dimes repository for discovery

Scientists at the March of Dimes Prematurity Research Center (PRC) at the University of California San Francisco (UCSF) have submitted a paper detailing their DREAM Challenge, in which computational scientists from all over the world used publicly available microbiome data from across the PRC network and beyond to make predictive models on preterm birth—a testament to the organization's ardent belief in open science.

The challenge, which took place last summer and culminated in a trip to the DREAM Conference in Las Vegas for the winning teams in the fall of 2022, entailed using vaginal microbiome data from March of Dimes PRCs—Stanford, UCSF, Imperial College London, and University of Pennsylvania—as well as several other datasets that are part of the March of Dimes Database for Preterm Birth Research.

The publicly-facing database has been amassing data since its inception in 2015 by Dr. Marina Sirota, an associate professor in the Bakar Computational Health Sciences Institute and the department of Pediatrics at UCSF, as well as several colleagues. Dr. Sirota is also the principal investigator at the March of Dimes PRC at UCSF.

A vault of every piece of molecular data that has come out of a PRC, the database comprises 68 studies with more than 40,000 experimental samples from nearly 30,000 participants and more than 30 types of measurements.

It includes genomic, transcriptomic, immunological, microbiome, and other data that's available to the scientific community at large and accessible with a click of a mouse.

To date, the data has been downloaded more than 5,400 times and has enabled a number of research studies, including those for identifying new biomarkers and therapeutic strategies for preterm birth.

The database, co-directed by Dr. Sirota and Dr. Tomiko Oskotsky, a senior research scientist in Dr. Sirota's lab at UCSF, is the only public multi-omic data repository for preterm birth, and underscores March of Dimes' commitment to open science, collaboration, and accelerating the pace of research progress in the field of preterm birth.

"What drives March of Dimes research is not copyright, patent, or financial gain," said March of Dimes Chief Scientific Officer Dr. Emre Seli. "It's the ability to innovate, discover, and bring life-changing therapies to moms and babies in a smart and efficient manner."

"And the best way to do that is to open our data bank to doctors, scientists, and machine learning experts all over the world and tap into their collective brilliance to solve problems."

"That's why we've been doing this for nearly a decade already—because together, we believe we can go far."

The repository, which lives online perpetually, also ensures that the benefits of a research project are not limited to its immediate conclusions or a specific time frame. For example, data (often in the form of analytic findings from samples like blood, urine, or tissue) collected during a study period is accessible for years to come in the database, whereas it would be hard to access after a study concluded in a more traditional setting.

The database also makes it easier to do validation studies, which is the replication of a scientific study with a larger and more diverse population to ensure that its conclusions can be generalized to the wider population. The March of Dimes data biorepository makes validation easier because it contains data from a wide array of samples collected at different time periods. These can be used to test and validate a novel diagnostic approach quickly without having to take time and

resources to organize a large scientific study for sample collection.

But the most exciting—and powerful—aspect of the biorepository is its collaborative aspect: Discovery potential is increased exponentially by making data available to experts outside March of Dimes.

To this end, the PRC at UCSF has been involved in organizing several DREAM Challenges, which are open science competitions that seek to advance understanding of biology and disease. The competitions are open to biomedical researchers from academia and industry all over the world in hopes of crowdsourcing answers to some of science's most puzzling questions and spurring innovation through collaboration.

There have been numerous DREAM Challenges across the biomedical spectrum over the years, with the UCSF and Stanford PRCs being involved in organizing one other in the past.

In 2019, members of the two PRCs were involved in a challenge that sought to create predictive models on two things based on a pregnant woman's blood sample: the gestational age of her baby at the time of blood draw and the mom's risk of spontaneous preterm birth later in pregnancy. The challenge, which focused on gene and protein expression, was led by a Wayne State University team.

In the latest challenge held during the summer of 2022, based on vaginal microbiome data, machine learning experts all over the world submitted models that predicted risk for early preterm birth and preterm birth. The winning models were validated in silicon, and the PRC team at UCSF have shared their findings and learnings in a paper.

The paper, which is a collaborative effort with over 50 authors, details how investigators used vaginal microbiome to develop two predictive models for preterm birth. One for preterm birth (births before 37 weeks of pregnancy) and another for early preterm birth (births prior to 32 weeks of pregnancy).

The winning teams (one from Italy, one from Korea, and two from the U.S.) created fairly accurate predictive models. The early preterm birth model had an 87% accuracy, and the preterm birth model had a 69% accuracy—both scientifically significant scores.

The model creation is only part of the impressive work. Aggregating the data in a way that makes it useful for machine learning experts is another. To aggregate the data, UCSF scientists had to first gather data from nine smaller studies on the topic and combine them in a way where the data—comprised of more than 3,500 samples from more than 1,200 pregnant individuals—was useful. This was difficult because the studies investigated different regions of the same gene. (The gene, known as 16S, is commonly used to identify different species of bacteria in the microbiome). As a result, the data were coded differently.

With so much variability in the data, PRC scientists had to figure out how to harmonize, or make useful, the data; otherwise they'd be comparing apples to oranges, and the data would be unworkable.

To get around this, the PRC team leveraged an open-source tool called MaLiAmPi, developed by a close collaborator, Dr. Jonathan Golob, who's an Assistant Professor of Internal Medicine in the Division of Infectious Diseases at the University of Michigan. His tool harmonized the data, which has been placed in a visual atlas—the topic of a separate paper.

"By bringing together disparate pieces of data and unifying it all into one comprehensive dataset, which represents one of the largest and most geographically diverse encyclopedias of the vaginal microbiome in pregnancy, we were able to set the stage for machine learning experts to make reliable predictive models on the vaginal microbiome and preterm birth," said Dr. Sirota.

Dr. Oskotsky said the effort has resulted in vital learnings for those studying preterm birth.

"This work has allowed us to make some definitive statements about the vaginal microbiome and preterm birth: first, the makeup of the vaginal microbiome is a risk factor for preterm birth; and

second, we now have a predictive tool that can potentially identify women at risk."

Dr. Sirota said that discussions are already underway to gauge whether the models could be ready for clinical introduction in the future.

She said her team, in collaboration with Dr. Golob, Stanford PRC researcher Dr. Nima Aghaeepour, and others, is continuing to strengthen and improve the models by integrating more data like clinical and genetic risk factors, as well as markers of inflammation. In this way, the models may be able to predict risk factors for many more kinds of preterm birth, not just those related to microbiome.

She also said she's passionate about tapping into the repository data to make novel diagnostic and therapeutic predictions about preterm birth to improve the lives of moms and babies globally, as well as enabling experts around the world to do the same with the goal of speeding the pace of discovery in the field—together.

Dr. Marina Sirota
Associate Professor, Bakar Computational Health Sciences Institute and the Department of Pediatrics at UCSF; Principal Investigator, March of Dimes Prematurity Research Center at UCSF

Dr. Tomiko Oskotsky
Senior Research Scientist in Dr. Sirota's lab at UCSF

Dr. Jonathan Golob
Assistant Professor of Internal Medicine in the Division of Infectious Diseases, University of Michigan

March of Dimes research in the news

The Research and Marketing and Communications teams are partnering to ensure that our work is covered and recognized. Here are some recent highlights:

The March of Dimes Richard B. Johnston, Jr., MD Prize

- ***Health Professional Radio:*** Patricia Hunt receives March of Dimes prize for research on prenatal development and pregnancy's impact from age and environment, 6/28/2023

- ***Healio:*** Q&A: Impact of endocrine-disrupting chemicals on reproduction, pregnancy, 4/12/2023
  - Picked up by:
    - ***Deal Town***
    - ***Endocrine Today***

- ***Contemporary OB/GYN:*** Linking parental age and prenatal development, 4/4/2023
  - Picked up by:
    - ***Contemporary Pediatrics***
    - ***Medical World News***

- ***Medical World News:*** After Hours - a love for walking, 4/4/2023

2022-2023 March of Dimes Agnes Higgins Award

- ***San Francisco Business Times:*** Kaiser Permanente scientist wins national March of Dimes award for maternal health research, 6/23/2023

- ***Healio:*** Q&A: Breastfeeding has beneficial effects on cardiometabolic health, 5/26/2023
  - Picked up by:
    - ***Deal Town***
    - ***Medi-New***
    - ***Lifetechnology***
    - ***MedPub***

- ***Contemporary OB/GYN:*** Erica Gunderson, PhD, discusses link between lactation and maternal cardiometabolic health, 5/10/2023
  - Picked up by:
    - ***Newsbreak***
    - ***DNA Lady***

- ***Contemporary Pediatrics:*** Erica Gunderson, PhD, explains cardiometabolic health, childhood obesity link to breastfeeding, 5/9/2023
  - Picked up by:
    - ***Health Magazine***

Recurrent Pregnancy Loss (RPL) announcement

- ***Health Professional Radio:*** March of Dimes Builds on Recurrent Pregnancy Loss Research, 8/4/2023

- ***Contemporary OB/GYN:*** March of Dimes researches recurrent pregnancy loss, 6/16/2023

Breast Milk Research

- Contemporary OB/GYN: How breast milk antibodies impact infant immunity, 6/26/2023

110 minutes: Sommer Young's story

> **"** *This was a tragic loss for us. We want nothing more than to help Sommer make an impact and for other families to have a happier ending.*

Erika and Kris Young had surprisingly little trouble getting pregnant. Given their age and risk of birth complications, they conducted blood work and screening, and soon were thrilled to know they'd have a little girl who could grow to be strong, smart, and fierce.

But as time went on, the due date came and passed with no signs of labor. At this point, an induction was scheduled to help the baby along. On August 24, they went to the hospital for a stress test to make sure the baby was okay and to wait for a room to deliver. Baby's heart rate, movement, ultrasound, and mom all checked out fine.

The next day was time to deliver. It only took one pill to induce Erika into labor. With the contractions, though, came pain. Labor progressed unusually fast for a first-time mom. Erika was struggling, but the reality and excitement of the moment was incredible—they were going to have a baby.

Then, things changed. In the final moments of labor, the tracing report showed a sudden, large decline in the baby's heartbeat, and as Erika pushed her into the world, the delivery room became frantic with doctors from the NICU.

Sommer Vivienne Young was born on Thursday, August 25, 2022. She weighed 7 pounds, 3 ounces.

It was immediately clear that something was wrong: she was pale gray and limp. Kris remembered the distinct "thud" of the baby landing on Erika's chest. He says, "I had just a moment to look at her and to look Erika in the eyes before she was whisked away into the small baby bed monitoring station in the delivery room."

A dozen or more medical personnel flooded into the room. Kris looked down at his wife, who with tears in her eyes said, "I hope our baby is OK, Kris, I hope she's OK." "That sound reel replays in my head often," he says.

Sommer wasn't well. Her heart rate slowed and her situation worsened. Sommer Vivienne Young was alive for an hour and fifty minutes. She never opened her eyes or was able to take a breath on her own.

"We brought Sommer back to our delivery room, where we held and cuddled her for a few hours," Kris says. "I tried my best to hold her, appreciate her, love her, and soak in those moments."

Sommer would've celebrated her first birthday August 25. Erika and Kris Young connected with March of Dimes to express the importance of research so no other family experiences what they did.

"We wanted to have a legacy for Sommer," Erika says. While Sommer won't get a chance to live out the aspirations her parents had for her life, you can help her make an impact on families everywhere. Your donation to March of Dimes lets us continue fighting for the health of all moms and babies through our research, education, and advocacy.

You can also support, like the Youngs have, the March of Dimes Innovation Fund, which is investing in healthcare companies focused on solving maternal and infant health challenges.

The hospital and doctors who reviewed Sommer's case are still uncertain whether a possible lack of oxygen may have started in the second stage of labor or if a sudden, catastrophic, unexplainable event occurred as Erika pushed her out.

"This is part of why we're so committed to the March of Dimes Innovation Fund," Erika said. "We want to bring more and better technologies to pregnancy and delivery for doctors to have more information and so that other families don't have to live without answers when things go awry."