

# Can Big (Microbiome) Data Save the World? – Using AI and Microbiome Data to Predict Health Outcomes



Sirota  
Lab

Marina Sirota, PhD  
Associate Professor



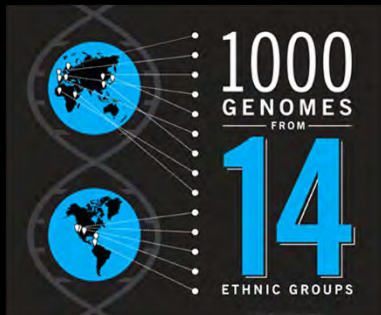
Bakar Computational Health  
Sciences Institute

BURROUGHS  
WELLCOME  
FUND

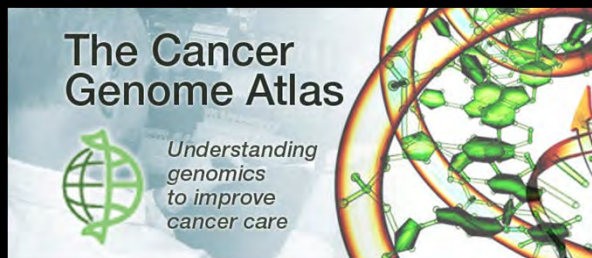


1

## Why Now?



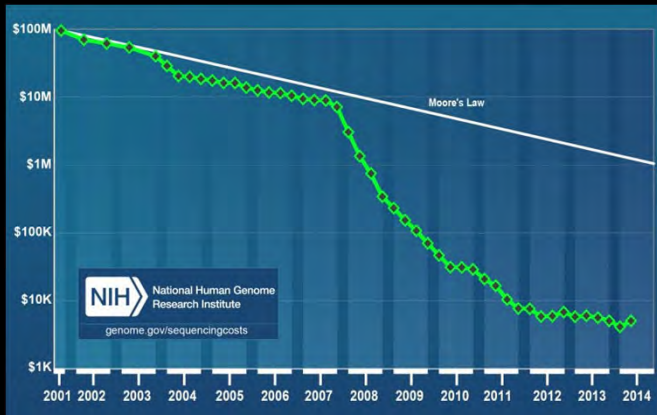
ENCYCLOPEDIA  
OF DNA  
ELEMENTS



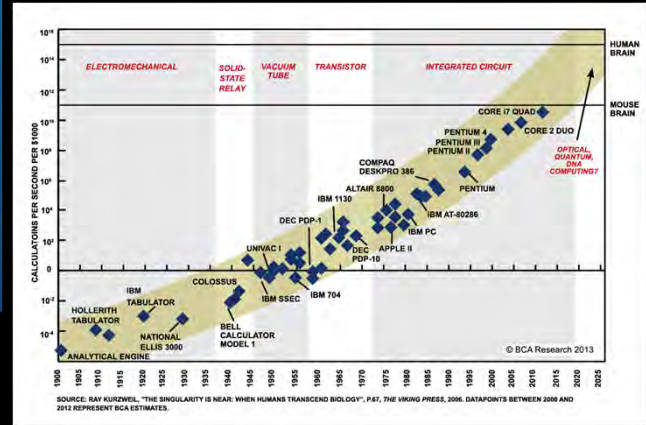
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# Moore's Law – Biology and Computation

Cost Per Genome

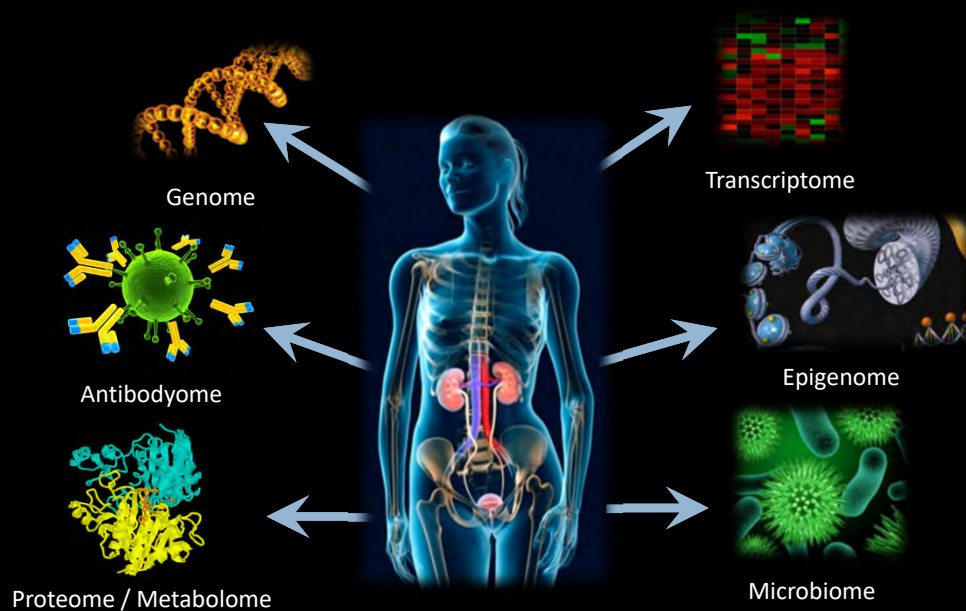


Cost of Computational Resources



3

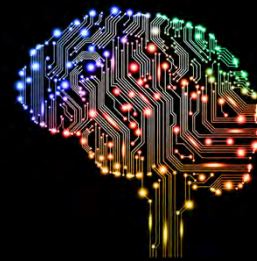
## Integrative Personal "Omics" Profiling



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# Artificial Intelligence

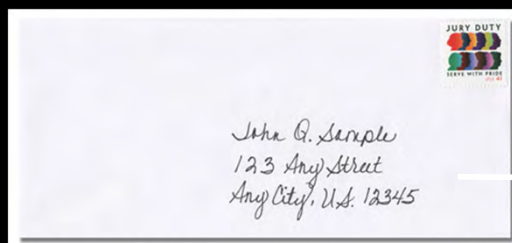
- A branch of computer science dealing with the simulation of intelligent behavior in computers – making predictions and decisions
- The capability of a machine to imitate intelligent human behavior
- Examples:
  - Visual perception
  - Speech recognition
  - Translation between languages
  - Decision-making



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# Machine Learning

- Computers are good at following instructions
- Example - run a spell checker on a document
- But what if the task is really complicated to describe?



John Q. Sample  
123 Any Street  
Any City, US, 12345

Eugene Davydov, PhD

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## Example: Digit Recognition

- Many tasks aren't easy to describe at the level of individual instructions
- We (humans) can recognize handwritten digits because we've seen many examples in our lifetimes

How can we write computer programs that can learn and get better from data?



Eugene Davydov, PhD

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## Machine Learning is Transforming Our Lives

- Machine learning (ML) is a type of artificial intelligence (AI) that provides computers with the ability to learn without being explicitly programmed
- Focuses on the development of computer programs that can change when exposed to new data

Recommender  
Systems

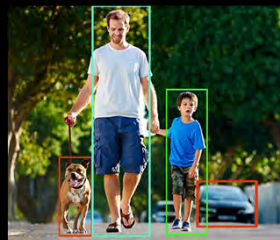
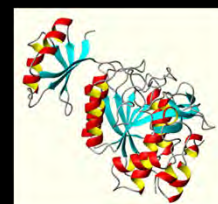


Image Processing

Biomedical  
Applications



Eugene Davydov, PhD

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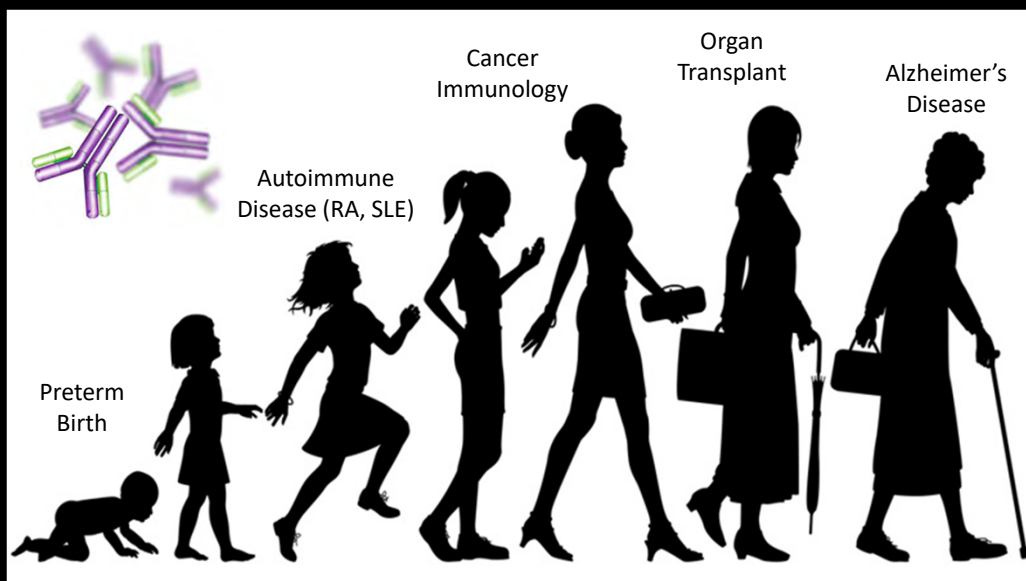
We have been so successful in transforming many everyday industries, but how can these data-driven approaches be applied in biomedicine?

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## Leveraging Computation to Understand Health and Disease Across the Lifespan...



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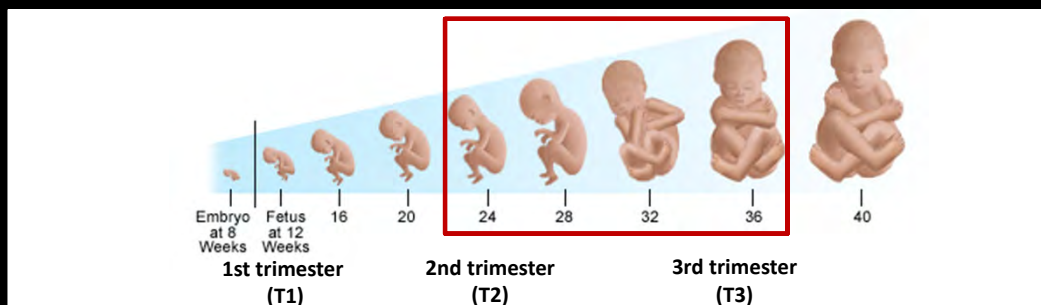
# Pregnancy and Preterm Birth



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## Why Study Preterm Birth?

Preterm birth (PTB) - live birth before week 37 of gestation



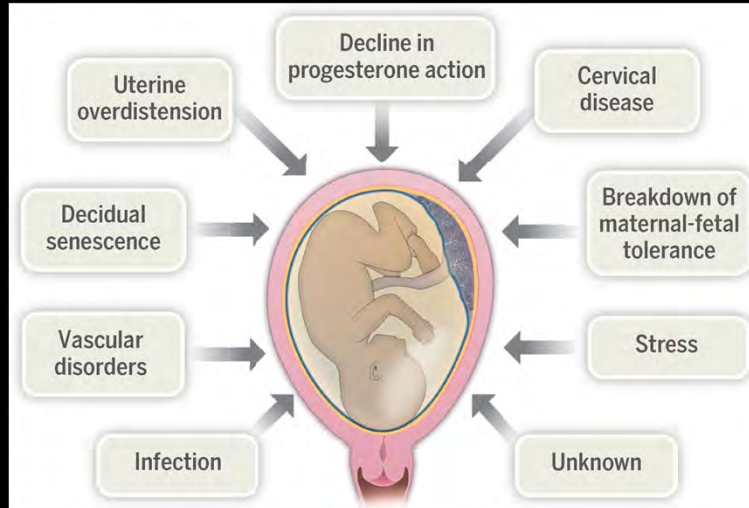
Worldwide, 15 million babies are born premature each year.

One million of these infants die within the first 28 days of life.

In nearly half of the cases of premature birth, there is no clear cause.

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## Many mechanisms have been associated with sPTB



Romero R, et al. *Science* (2014).

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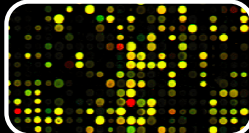
## Integrative Computational Approaches for Preterm Birth Research



- Elucidating Genetic and Environmental Determinants of Preterm Birth (**Scientific Reports, 2018; Env International, 2018**)
- Nadav Rappoport, Aolin Wang, Hongtai Huang, Dimitri Abrahamsson



- Microbiome Meta-Analysis in Preterm Birth (**Frontiers in Microbiology 2020**)
- Idit Kosti, Alennie Roldan, Tomiko Oskotsky, Alice Tang



- Transcriptomic Meta-Analysis in Preterm Birth (**Frontiers Immunology 2018, JCI Insight 2020, Cell Reports Medicine 2021**)
- Bianca Vora and Aolin Wang, Brian Le, Gaia Andreoletti



- Leveraging Electronic Medical Records to Study Preterm Birth (**On going, BiorXiv 2020**)
- Brian Le, Idit Kosti, Jackie Roger

Data Visualization Tools

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# Integrative Computational Approaches for Preterm Birth Research



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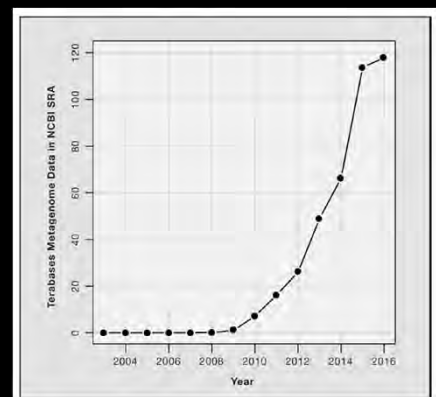
- Leveraging Electronic Medical Records to Study Preterm Birth (*On going, BiorXiv* 2020)
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Data Visualization Tools

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## Microbiome Meta-Analysis: Challenges and Opportunities

- Impossible to combine processed data, need to go back to the raw data
- Sample metadata is hard to get access to
- Lots of potential biases:
  - 16s vs. whole genome
  - Taxa vs. gene analysis
  - Sample prep differences
  - Variable regions of the 16s gene that were sequenced
  - Longitudinal vs. Case-Control



Stephen Nayfach and Katie Pollard, 2016

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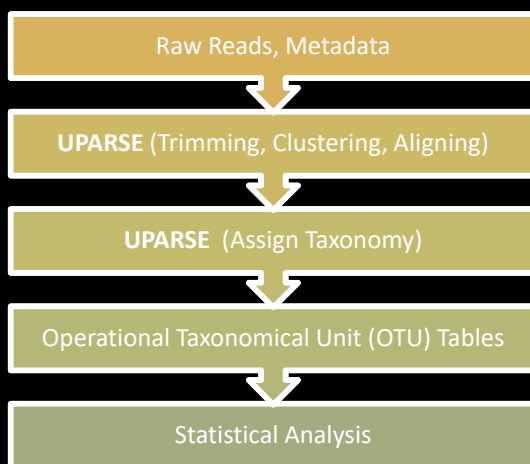
# Public Pregnancy Microbiome Data

	# of samples	Mother/ Baby	# of Subjects	# of body sites	# of Species	# of reads	Reference	Body sites	Type of Data	Time points
HMP	5,298	Controls	242	18	5385	30,336,944	The Human Microbiome Project Consortium	Mouth, Nose, Skin, Gut and Vagina	16s	Controls
Stanford PTB Longitudinal (MOD)	4,399	Mother	51	11	4694	656,308	DiGiulio et al.	Vagina, Gut, Saliva, and Tooth/Gum	16s, WGS	Weekly
Placenta Penn	69	Mother	6	5	2108	207,5881	Lauder et al.	Placenta, Vagina	16s	Delivery
Vaginal PTB	349	Mother	100	1	550	2,213,608	Romero et al.	Vagina	16s	Every 4 weeks until 24, every 2 weeks until the last prenatal visit
Placenta PTB	48	Mother	48	1	TBD	1,348,416	Aagard et al.	Placenta	16s, WGS	Delivery
Gut Microbiome in Pregnancy	972	Mother/ Baby	91	1	2339	112,8572	Koren et al.	Gut	16s	T1,T3,PP
Vaginal Pregnancy	TBD	Mother	42	1	TBD	TBD	MacIntyre et al.	Vagina	16s	T1,T2,T3,PP

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# Microbiome Meta-Analysis Pipeline

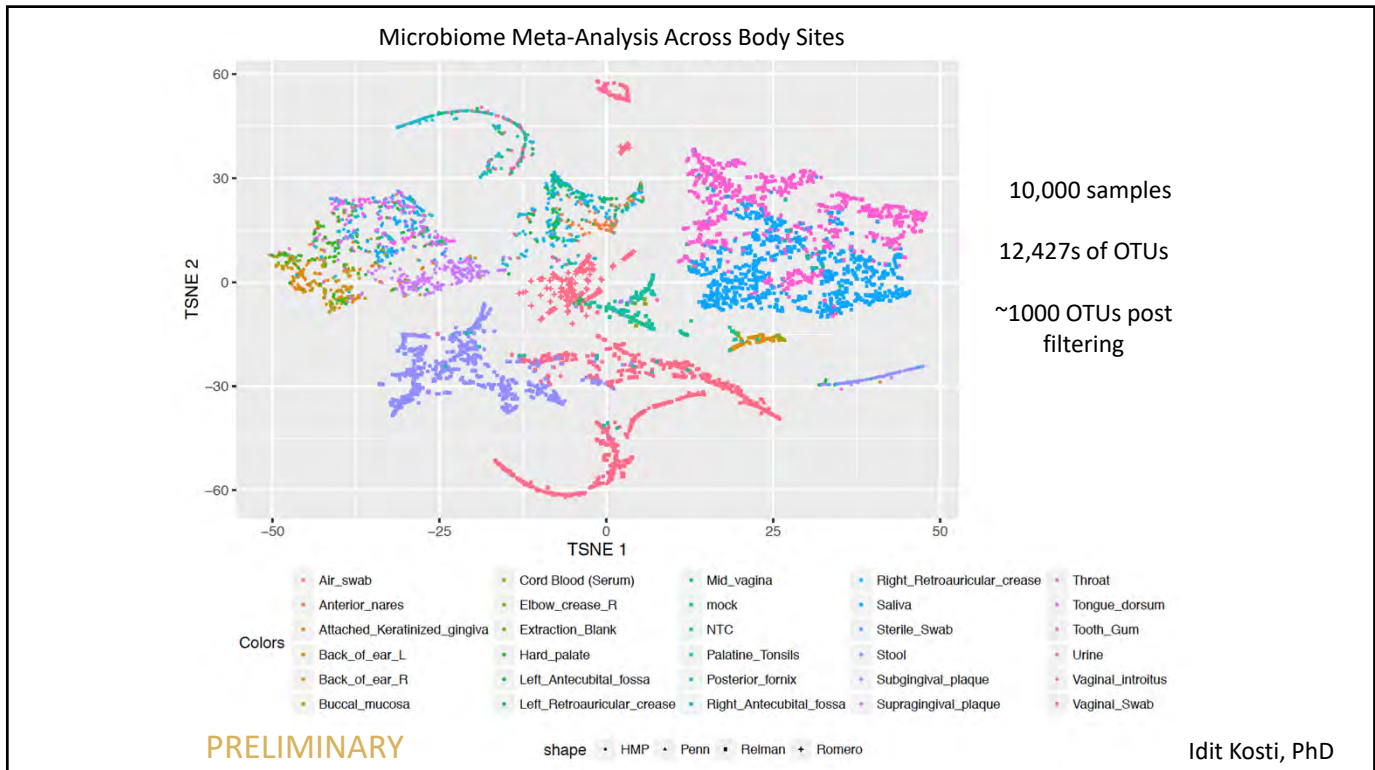
Is time consuming and computationally intensive



Study Name	Raw Reads Size
HMP	19.03GB
Stanford PTB Longitudinal (MOD)	8.98GB
Placenta Penn	991.2MB
Vaginal PTB	1.28GB
Placenta PTB	490.9MB
Gut Microbiome in Pregnancy	427.2MB

Idit Kosti, PhD

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Can we identify new microbial species associated with PTB in a longitudinal analysis leveraging public data?

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## Bacterial Vaginosis is a Known Risk Factor for PTB

- Bacterial vaginosis is a state of an overgrowth of anaerobic bacteria, replacing the normal vaginal Lactobacillus.
- Bacterial vaginosis has been shown to increase the risk for preterm birth.
- Several microbiome studies have been carried out but no meta-analysis to date.

Manns-James L., J Midwifery Womens Health, 2011

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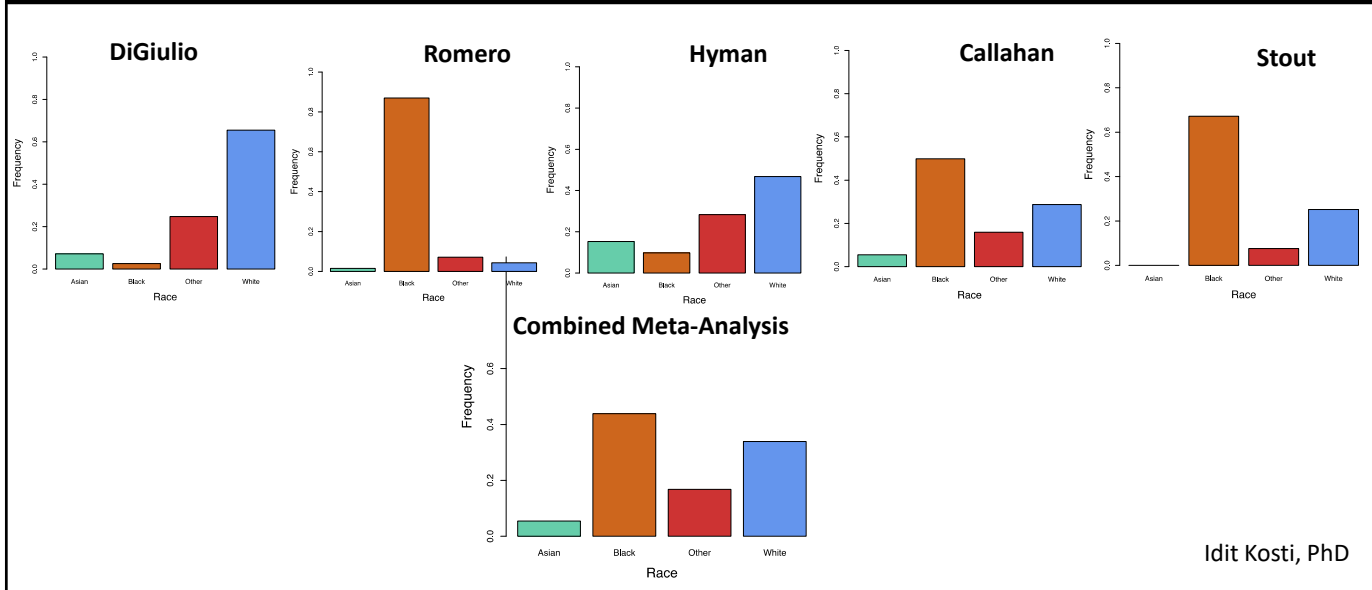
## Meta-Analysis Allows Greater Power

	Callahan et al.	DiGiulio et al.	Hyman et al.	Romero et al.	Stout et al
Total Number of Patients	135	37	82	87	74
PTB Patients	50	5	16	18	23
T1 Samples	42 (10 PTB)	21 (4 PTB)	37 (5 PTB)	6 (2 PTB)	14 (4 PTB)
T2 Samples	135 (50 PTB)	31 (4 PTB)	50 (10 PTB)	76 (17 PTB)	55 (18 PTB)
T3 Samples	123 (39 PTB)	36 (4 PTB)	46 (9 PTB)	60 (5 PTB)	59 (17 PTB)
Overall PTB Ratio	37%	12.5%	21%	17.33%	31.1%
Sampling Time Points	Once per week	Once per week	One per trimester	Once every 4 weeks (< 24 gestation weeks) Once every 2 weeks (> 24 gestation weeks)	Once per trimester

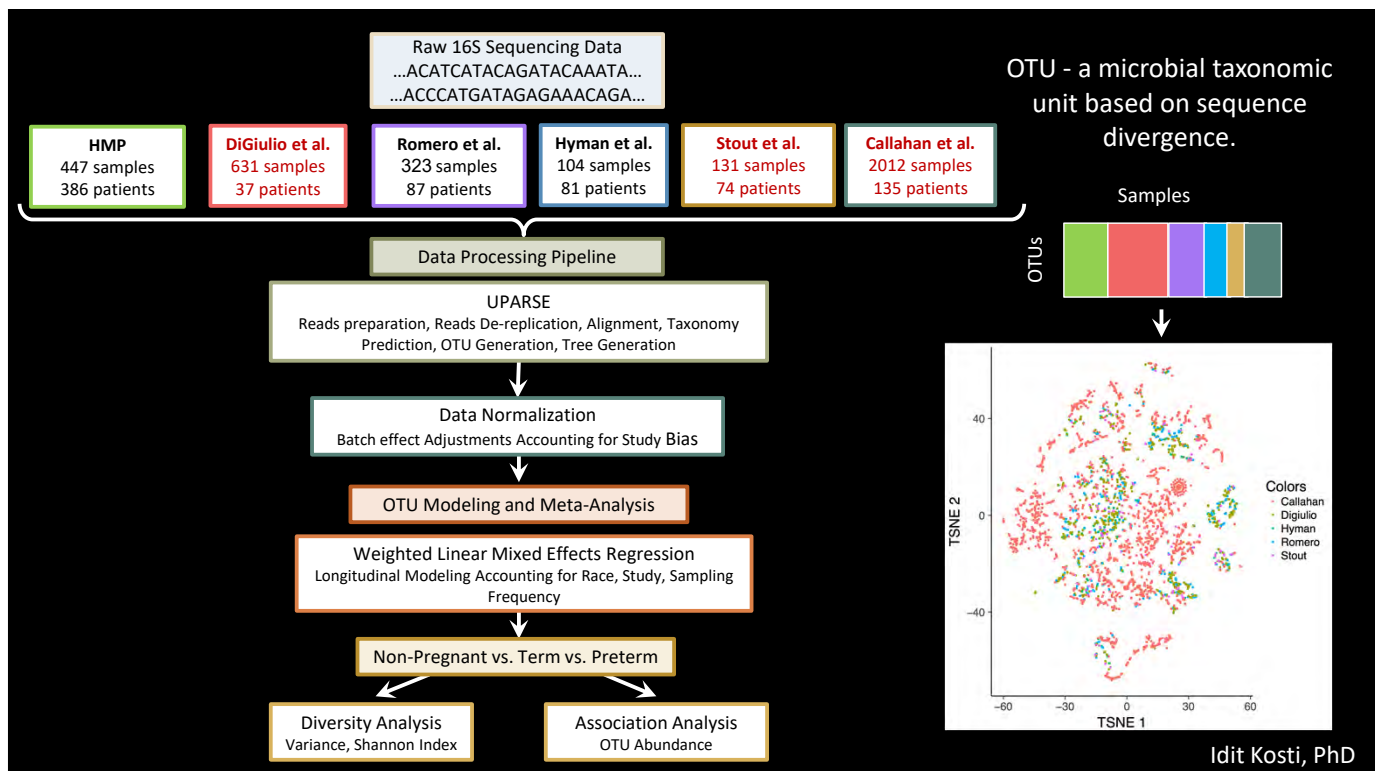
Over 3,000 samples and 350+ women

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# Why Meta Analysis? Better Balance Between Groups

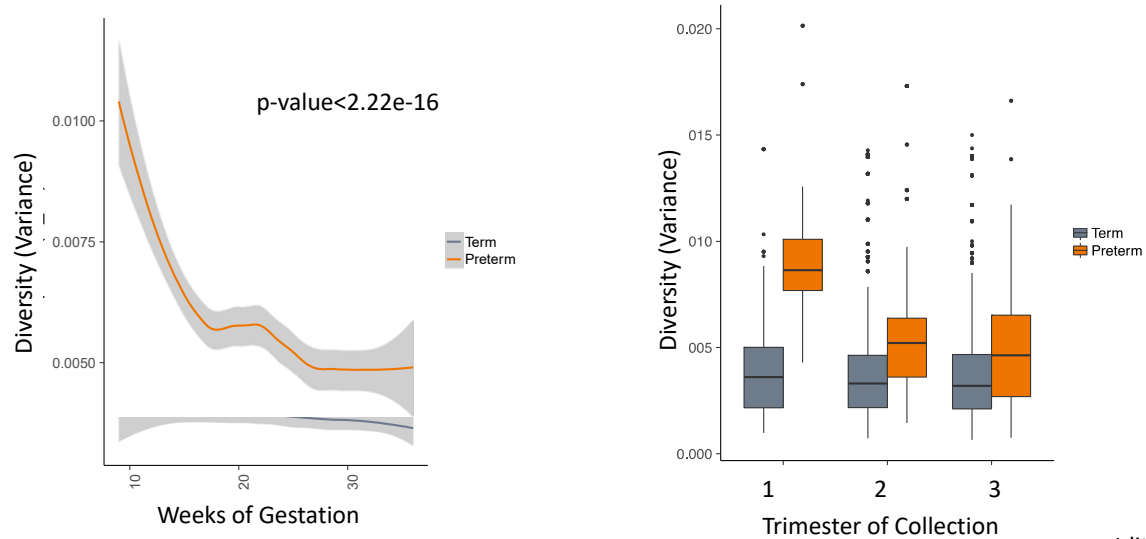


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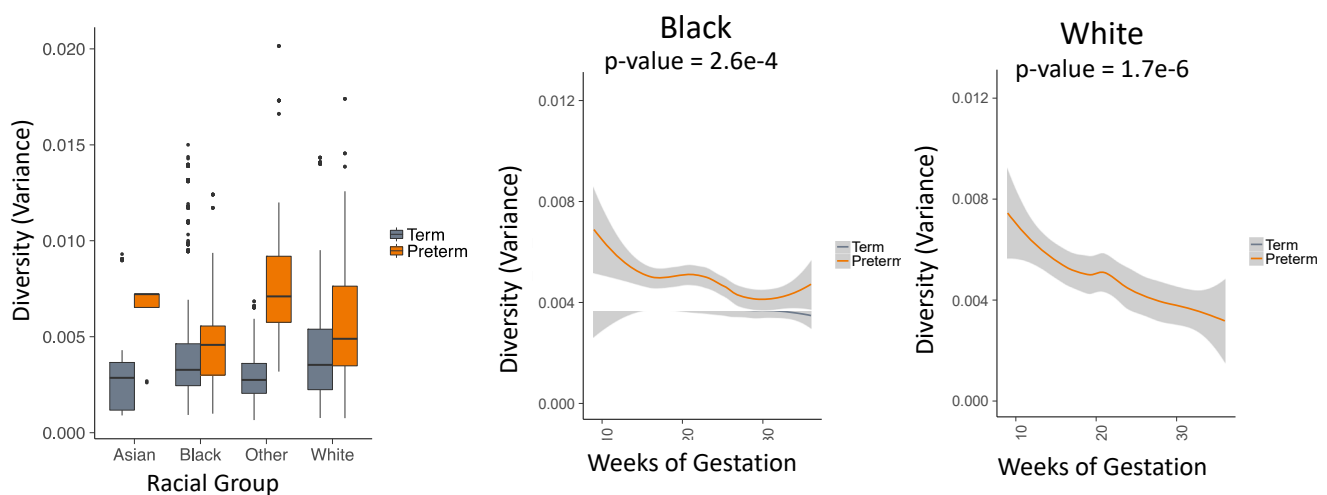
## Higher Diversity is Associated with PTB in the First Trimester (T1)



Idit Kosti, PhD

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## The Association Holds Across Racial Groups



Idit Kosti, PhD

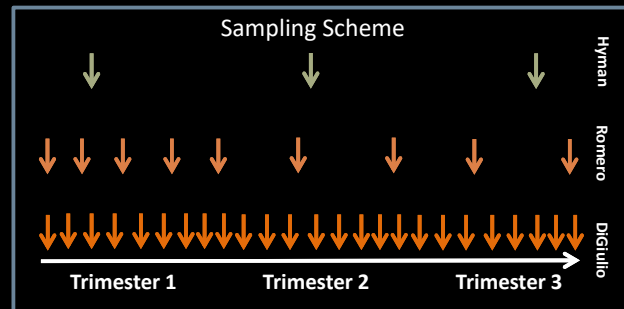
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# Linear Mixed Modeling

OTU Abundance  $\sim$  Trimester of Collection \* Outcome  
 + Race + (1 | SubjectID) + (1 | Source)

↑  
 White  
 Black  
 Asian  
 Other

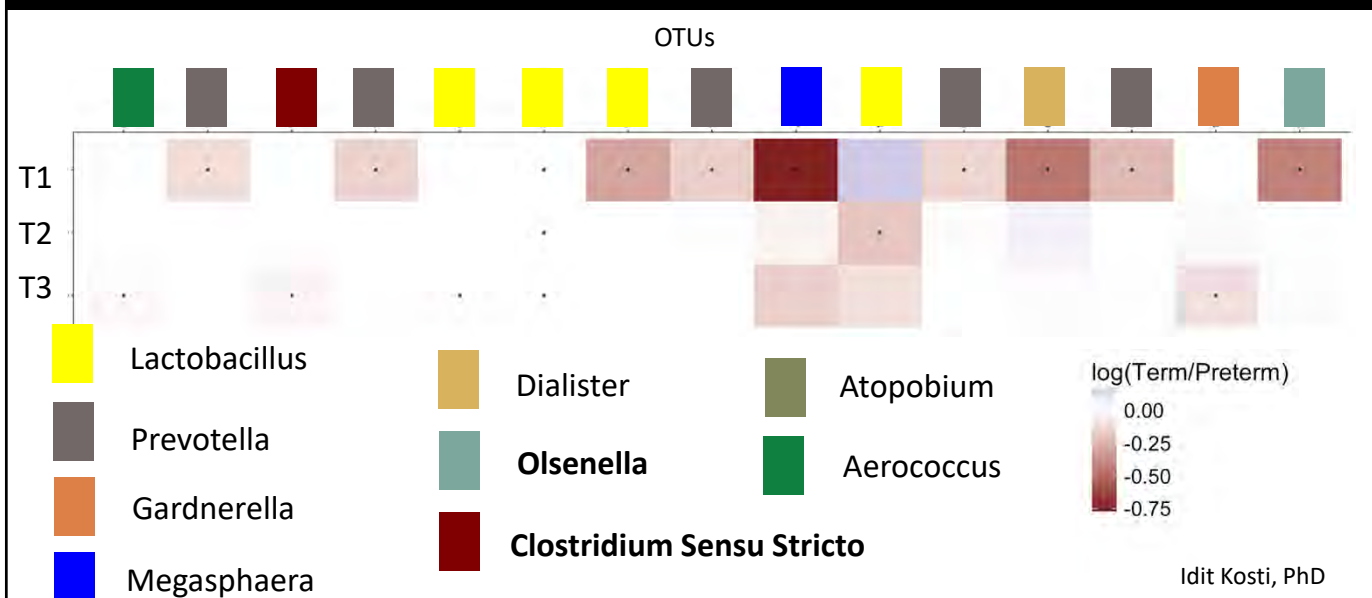
random effects



Idit Kosti in collaboration with Svetlana Lyalina  
 and Katie Pollard from the Gladstone Institutes  
 UCSF.

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## Specific Microbial Genera are Associated with PTB



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## Novel Bacterial Genera Identified by Meta-Analysis

OTU	Genera	Trimester	Adj. P-value	Bacterial Vaginosis	Associated with PTB
Otu875	Olsenella	1	<2.2e-16	✓	✗
Otu1238	Clostridium sensu stricto	3	1.58E-03	✗	✗

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## Summary

- We observe higher microbial diversity in women who deliver preterm, especially in the first trimester.
- We identify novel bacteria associated with preterm birth using a meta-analysis approach leveraging public data.
- First trimester vaginal sampling may help identify those at risk for preterm birth.

Kosti I, Lyalina S, ... Pollard K, Butte AJ, **Sirota M**. Meta-Analysis of Vaginal Microbiome Data Provides New Insights In Preterm Birth. *Frontiers in Microbiology*, 2020.

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# Meta-Analysis of Vaginal Microbiome Data Provides New Insights Into Preterm Birth

**Idit Kosti<sup>1,2</sup>, Svetlana Lyalina<sup>3</sup>, Katherine S. Pollard<sup>1,4,5,6</sup>, Atul J. Butte<sup>1,2†</sup> and Marina Sirota<sup>1,2\*†</sup>**

<sup>1</sup> Bakar Computational Health Sciences Institute, University of California, San Francisco, San Francisco, CA, United States, <sup>2</sup> Department of Pediatrics, University of California, San Francisco, San Francisco, CA, United States, <sup>3</sup> Integrative Program in Quantitative Biology, Gladstone Institutes, University of California, San Francisco, San Francisco, CA, United States, <sup>4</sup> Department of Epidemiology & Biostatistics, Institute for Human Genetics, University of California, San Francisco, San Francisco, CA, United States, <sup>5</sup> Quantitative Biosciences Institute, University of California, San Francisco, San Francisco, CA, United States, <sup>6</sup> Gladstone Institutes, San Francisco, CA, United States, <sup>†</sup> Chan Zuckerberg Biohub, San Francisco, CA, United States

Kosti et al, Frontiers in Microbiology, 2020.

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## The Goals of Creating a PTB Data Repository

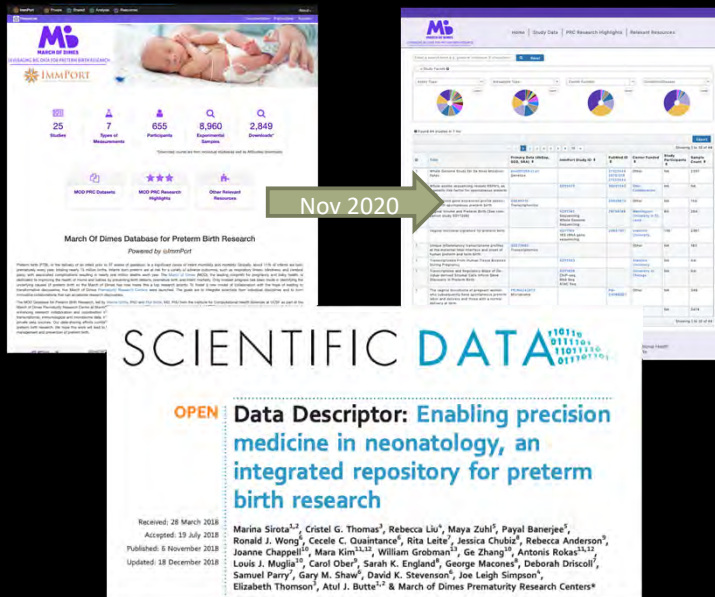
- Serve as a central data repository for omics data across the 6 MOD Transdisciplinary Centers
  - Transcriptomics, genomics, microbiome, proteome, CYTOF, methylation, metabolome, etc.
- Enable new scientific questions
- Enhance collaboration and coordination among centers
- Accelerate the pace of discovery

Tomiko Oskotsky, MD



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# MOD Biorepository Database: Brief Overview

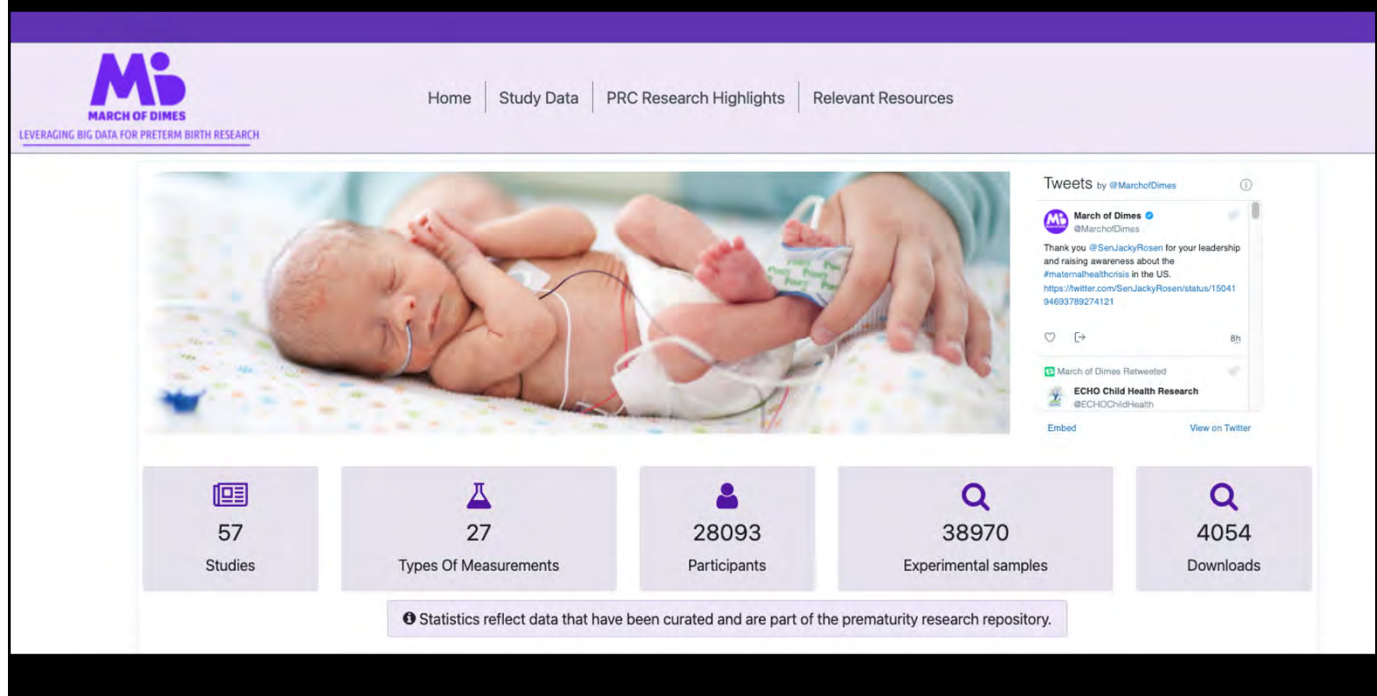


- Launched in 2017, spun out into an independent resource in 2020
- Regularly updated with publications, study data, and other preterm birth resources from MOD Prematurity Research Centers (PRCs) and other groups
- <https://pretermbirthdb.org>

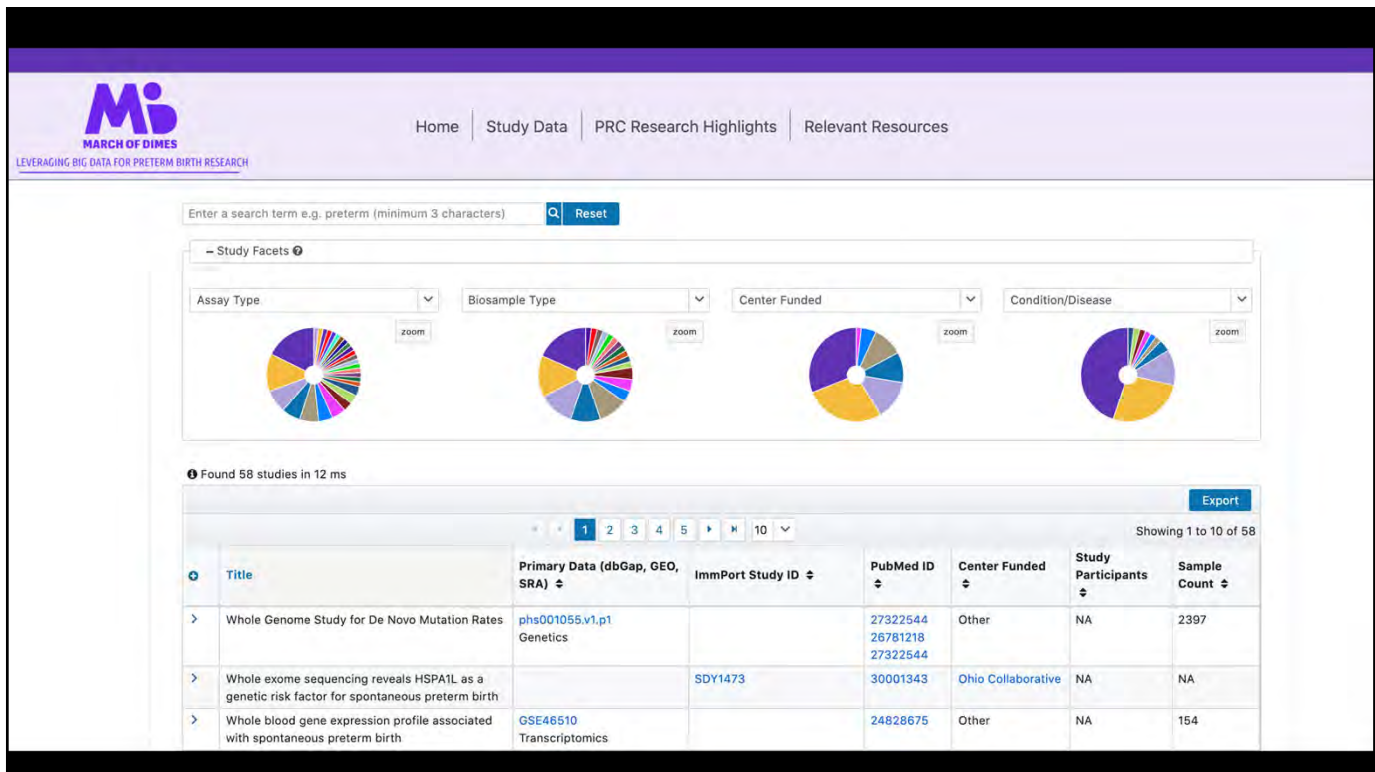
Sirota et al, Scientific Data 2018.

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<https://pretermbirthdb.org>



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## DREAM Challenges for PTB





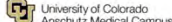




- The DREAM Challenges are crowdsourcing challenges examining questions in biology and medicine
- **Goal:** Bring computational community to MOD data resulting in rigorous, reproducible science and innovation
- **Question:** How can we predict those at higher risk of PTB (term vs. preterm or week of gestation) based on:
  - Transcriptomics Data, Microbiome Data, Multi-omics
  - Can use data in the repository for training, need datasets for testing!

Tomiko Oskotsky, Alennie Roldan, Jonathan Golob, Jake Albrecht, Gaia Andreoletti, Gustavo Stolovitzky, James Costello, Nima Aghaeepour, Adi Tarca, Roberto Romero, David MacIntyre, Phil Bennett, Yooni Li

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**Preterm Birth Prediction: Transcriptomics**  
DREAM Challenge

[Challenge Question](#)
[How to Participate](#)
[Updates and News](#)

There are 251 registered participants. Join them now!

[Click Here to Register](#)

## Overview

**SC1: Deadline Aug 15th**

A basic need in pregnancy care is to establish gestational age, and inaccurate estimates may lead to unnecessary interventions and sub-optimal patient management. Current approaches to establish gestational age rely on patient's recollection of her last menstrual period and/or ultrasound, with the latter being not only costly but also less accurate if not performed during the first trimester of pregnancy. Therefore development of an inexpensive and accurate molecular clock of pregnancy would be of benefit to patients and health care systems. Participants in **sub-challenge 1** (Prediction of gestational age) will be given whole blood gene expression data collected from pregnant women to develop prediction models for the gestational age at blood draw.

Another challenge in obstetrics, in both low and high-income countries, is identification and treatment of women at risk of developing the 'great obstetrical syndromes'. Of these, preterm birth (PTB), defined as giving birth prior to completion of 37 weeks of gestation, is the leading cause of newborn deaths and long-term complications including motor, cognitive, and behavioral impairment. Participants in **sub-challenge 2** (Prediction of preterm birth) will be given whole blood gene expression data collected from pregnant women to develop prediction models to determine the risk preterm birth.

Gaia Andreoletti, Adi Tarca, Gustavo Stolovitzky, James Costello, Nima Aghaeepour

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## DREAM Challenge for PTB: Microbiome

Total # of Studies	Total # of Participants	Total # of Term   Preterm Participants	Total # of Samples	Total # of Term   Preterm Samples
9	1323	911   412	5827	4422   1405

- **9 studies** incorporated into metadata analyses
- **1,323 participants** ~ 2:1 term:preterm participants (911 term / 412 preterm)
- **5827 samples** ~ 3:1 term:preterm samples (4422 term / 1405 preterm)

### Possible Sub-challenges

- 1: Prediction of gestational age
- 2: Prediction of preterm birth

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Study Accession ID	Center	Title	# of Participants	# of Term   PTB Participants	# of Samples	# of Term   PTB Samples	V Region Sequences
PRJEB21325	Imperial College London	Vaginal dysbiosis increases risk of preterm fetal membrane rupture, neonatal sepsis and is exacerbated by erythromycin. (Brown 2018)	116	21   95	158	23   135	V1 - V2
PRJEB30642	Imperial College London	Establishment of vaginal microbiota composition in early pregnancy and its association with subsequent preterm prelabor rupture of the fetal membranes.	98	35   63	254	78   176	V1 - V2
PRJNA242473	University of Maryland	The vaginal microbiota of pregnant women who subsequently have spontaneous preterm labor and delivery and those with a normal delivery at term	88	70   18	340	284   56	V1 - V3
PRJNA294119	Washington University	Early pregnancy vaginal microbiome trends and preterm birth	74	51   23	145	99   46	V1 - V3
PRJNA393472	Stanford University	Replication and Refinement of a Vaginal Microbial Signature of Preterm Birth	133	83   50	2134	1586   548	V4
PRJEB11895 & PRJEB12577	Imperial College London	The interaction between vaginal microbiota, cervical length, and vaginal progesterone treatment for preterm birth risk	154	121   33	154	121   33	V1 - V3
SDY465	Stanford University	Temporal and spatial variation of the human microbiota during pregnancy	40	33   7	1005	858   147	V3 - V5
JX871219 & JX871316	UCSF	Diversity of the Vaginal Microbiome Correlates With Preterm Birth	82	65   17	134	110   24	*Nearly* Complete Gene
PRJNA504518 (phs001739.v1.p1.)	University of Pennsylvania	Cervicovaginal microbiota and local immune response modulate the risk of spontaneous preterm delivery	538	432   106	1503	1263   240	V3 - V4

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master 6 branches 1 tag Go to file Add file Code

Jonathan Golob Major fix to filename bug 845169d 16 days ago 193 commits

- data Removed old test data 2 years ago
- maliampi-practice-data fixed test manifests 9 months ago
- modules Major fix to filename bug 16 days ago
- tests Cleaned up tests 7 months ago
- .dockerignore post pull commit 3 years ago
- .gitignore post pull commit 3 years ago
- LICENSE.txt Tidied up dada2 engine. Some permission shuffling 3 years ago
- README.md Fix documentation of manifest columns 2 months ago
- main.nf Added TrimGalore for PE and SE Illumina reads. last month

README.md

## MaLiAmPi

Maximum Likelihood Amplicon Pipeline: An amplicon (PCR / 16S) microbiome pipeline.

### Introduction

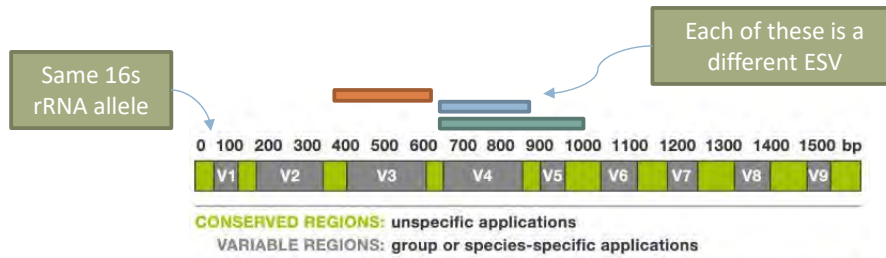
## MALIAMPI

- **Maximum Likelihood Amplicon Pipeline: An amplicon (PCR / 16S) microbiome pipeline.**
- Maliampi is a phylogenetic placement-based pipeline for handling 16S rRNA amplicons
- Leverage inherent ambiguity involved in any PCR / sequencing based approach, as well as rationally deal with the limits of the available references mapping between sequence-space and taxonomy.
- **A typical workflow:**
  - Create sequence variants
  - Make a reference package
  - Place on the reference package
  - Classify

Jonathan Golob, MD, PhD

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**Problem:** When combining 16S rRNA gene variable region ESVs from *different* studies, using different primers / sequencers / etc, the same organism will be split into different ESVs.



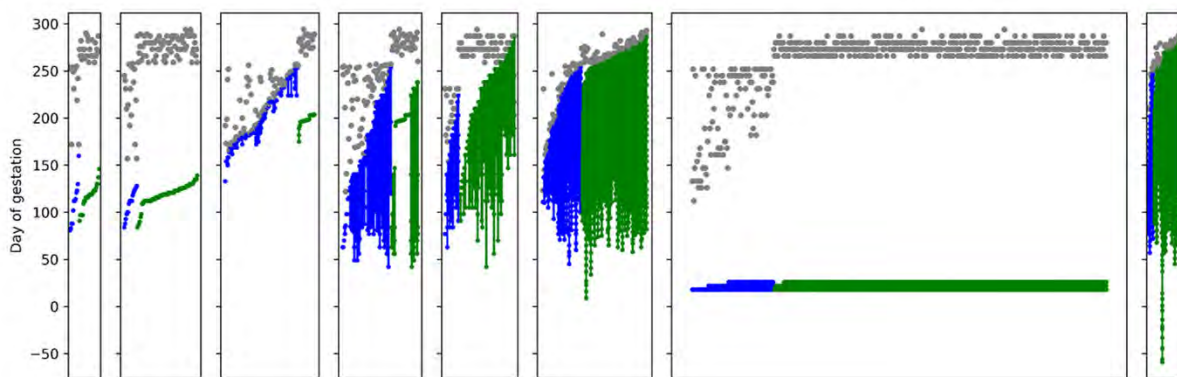
**Solution:** Phylogenetically place the ESVs onto a phylogeny of full-length 16S rRNA alleles possibly in the collection of specimens being analyzed.

Compare the weighted phylogenetic trees across conditions

Jonathan Golob, MD, PhD

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**Most studies have longitudinal collection of specimens from participants.** The time and frequency of collection vary by study. This is both an analytic challenge and opportunity.



Each block is a *study*.

Each column is a participant / pregnancy.

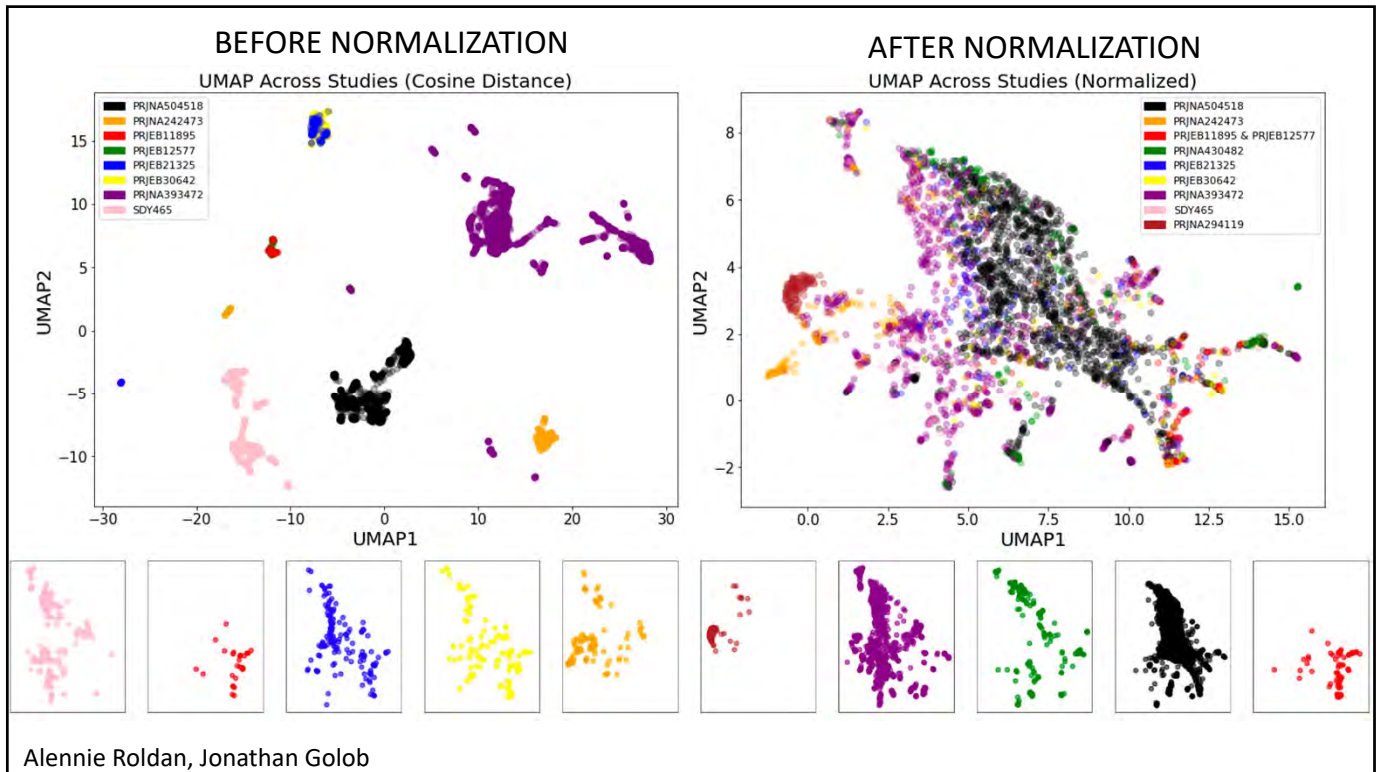
Grey: Gestational day of delivery

Blue: Specimen collected from pre-term pregnancy

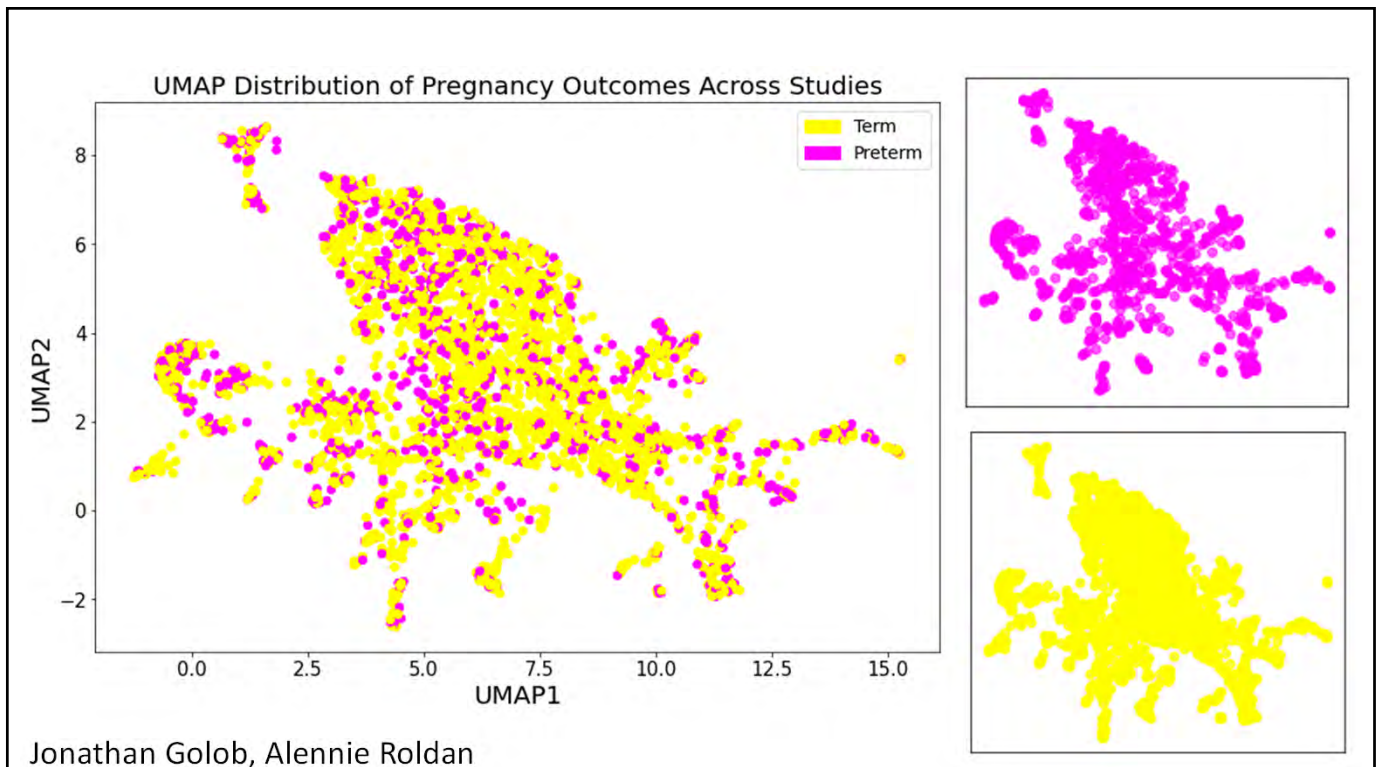
Green: Specimen collected from Term pregnancy

Jonathan Golob, MD, PhD

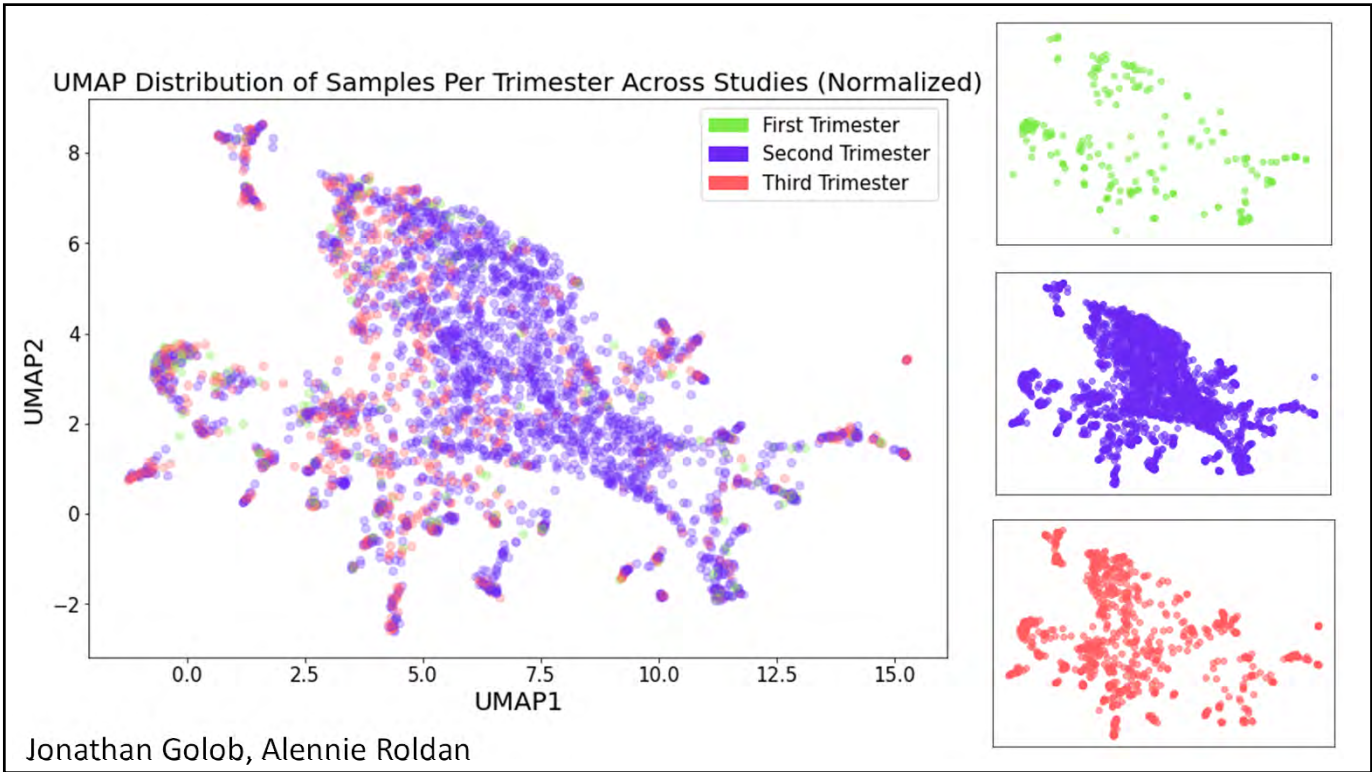
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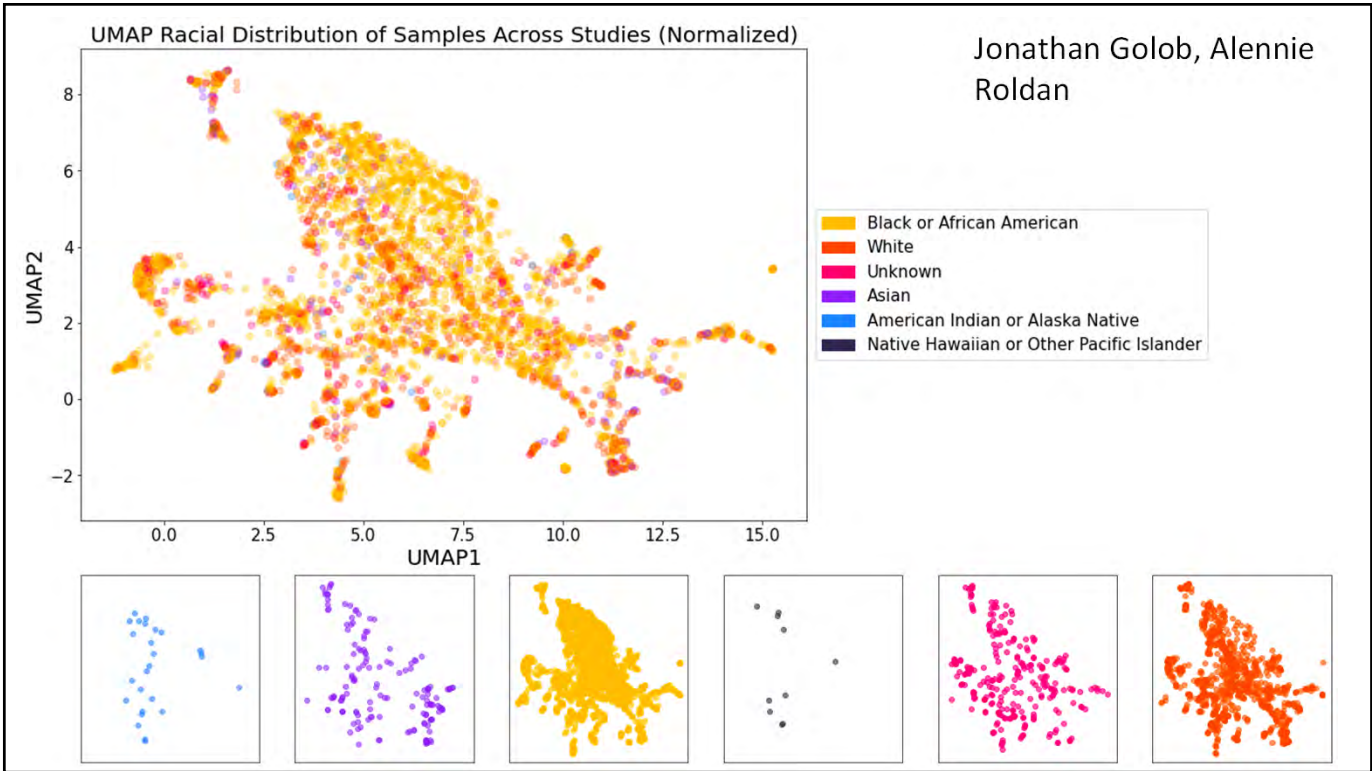
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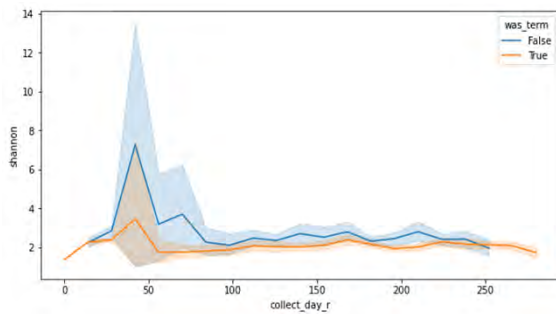


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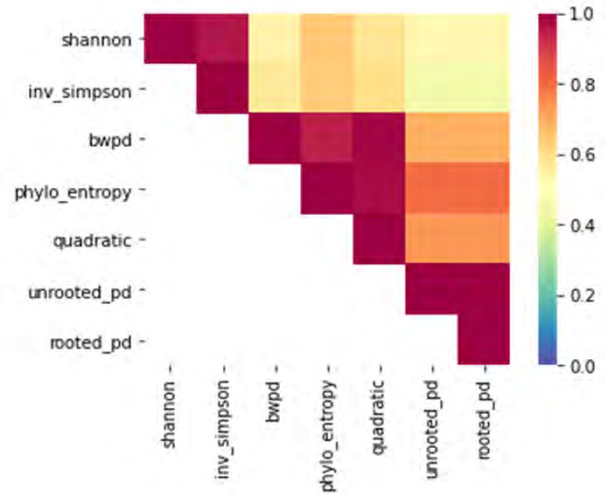


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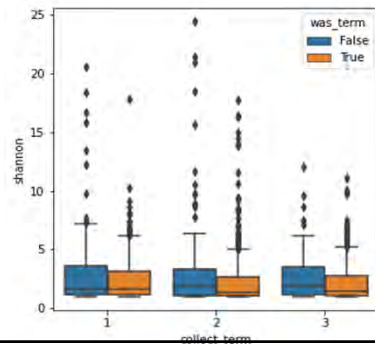
# Diversity Analysis is Consistent With Previous Findings



Rounded to nearest 2 wks, 95% Confidence Interval



Mann Whitney U Test:  
trim: 1 pval: 0.30  
trim: 2 pval: 2.9e-07  
trim: 3 pval: 0.00013

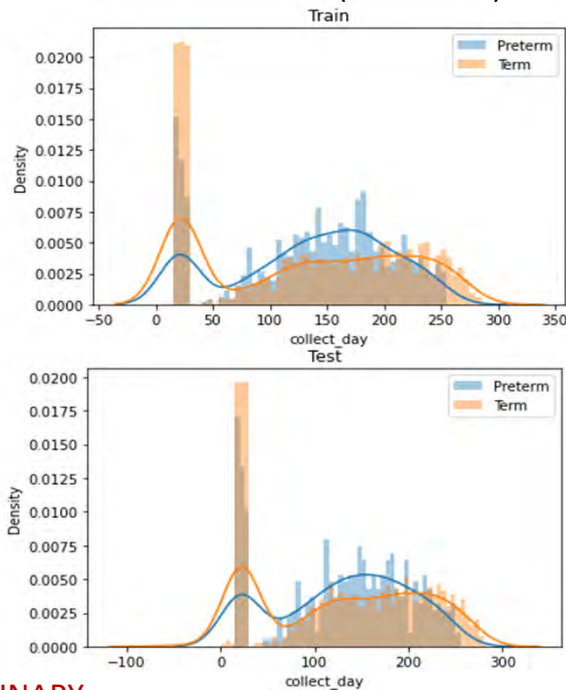


PRELIMINARY

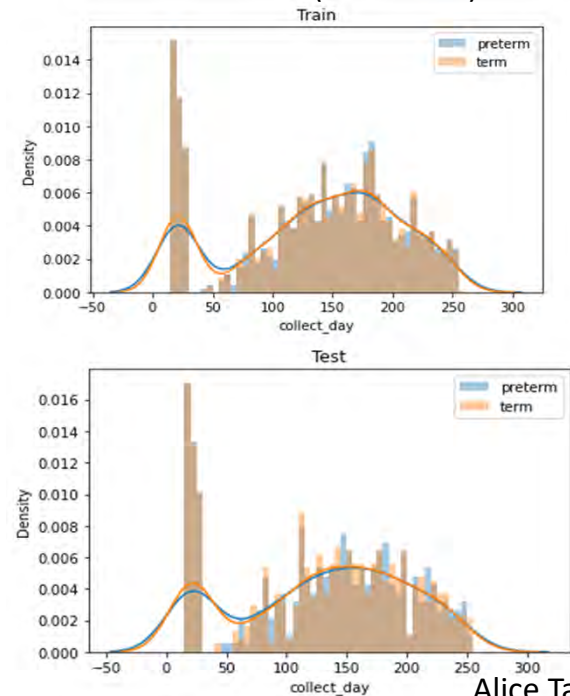
Alice Tang

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Unmatched (binsize = 5)



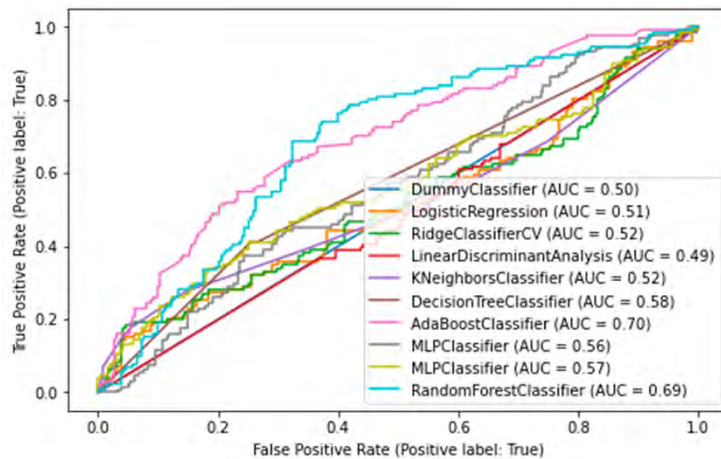
Matched (binsize = 5)



PRELIMINARY

Alice Tang

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**Term/Preterm Prediction.****Features: alpha diversity, phylotype, CST, family/genus****Random Forest top features**

Feature	Importance
unrooted_pd	0.015155
Megasphaera	0.014884
rooted_pd	0.014259
pt_00015	0.012659
Streptococcaceae	0.012314
collect_day	0.012055
bwpd	0.011706
Lactobacillaceae	0.011488
Lactobacillus	0.011327
phylo_entropy	0.011323
Sneathia	0.010947
quadratic	0.010646
pt_00001	0.010322
shannon	0.010175
Prevotella	0.010130
Prevotellaceae	0.010126
inv_simpson	0.010119
Finegoldia	0.009661
Veillonellaceae	0.009112
pt_00005	0.008631

**PRELIMINARY**

Alice Tang

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# Leveraging Microbiome Data for Education



X FVI

**Project TAs:**

Nana Afia Twumasi-Ankrah

Alice Tang

Eunice Leung

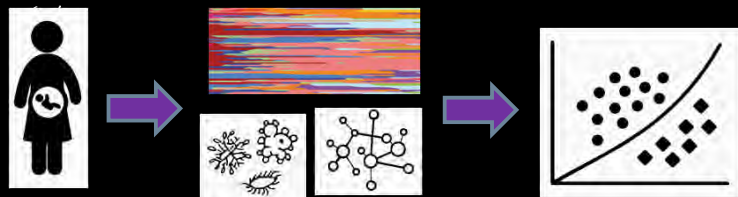
Alennie Roldan



- Program to empower and teach AI to under-represented and under-resourced high-school students + involvement with research projects. 50 alumni, over 200 applicants this year, 27 students admitted!
- Project: **Predicting Reproductive Health Outcomes Using Species Interactions And Microbiome Network**

**Goals of project:**

- Teach students about bioinformatics, microbiome, and reproductive health
- Utilize ML to predict pregnancy-related complications utilizing microbiome data and investigate how microbial interactions and networks modulate reproductive health
- Interpret and present findings with societal/health impact and equity in



Tomiko Oskotsky, MD

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# ***AI will change the world, Who will change AI?***



**Marina Sirota, PhD**

Associate Professor, Bakar Computational Health Sciences Institute, UCSF

**Tomiko Oskotsky, MD**

Research Scientist, Bakar Computational Health Sciences Institute, UCSF

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**UCSF**

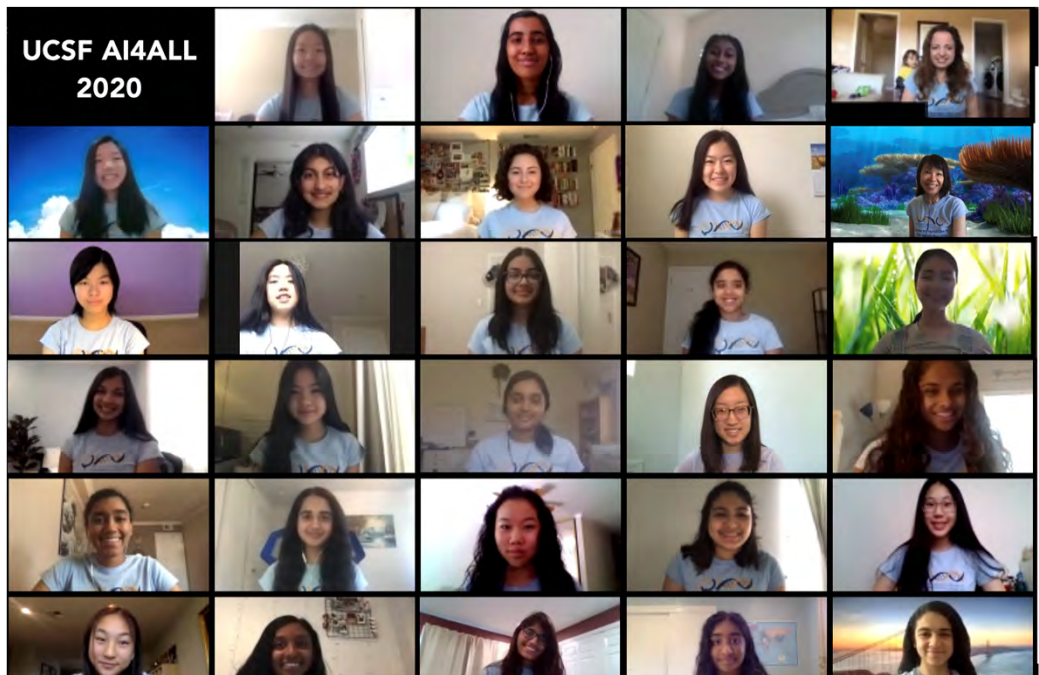
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## Class of 2019



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## Class of 2020



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## Over three weeks, our students...

- Learned about AI, Machine Learning, Clustering
- Learned how to code in Python
- Heard a number of faculty guest lecturers talk about their work applying AI in biomedicine
- Various Panels (Alumni, Undergrad, Grad, Industry)
- Attended a personal growth session focused on science communication
- Worked on 5 awesome research project



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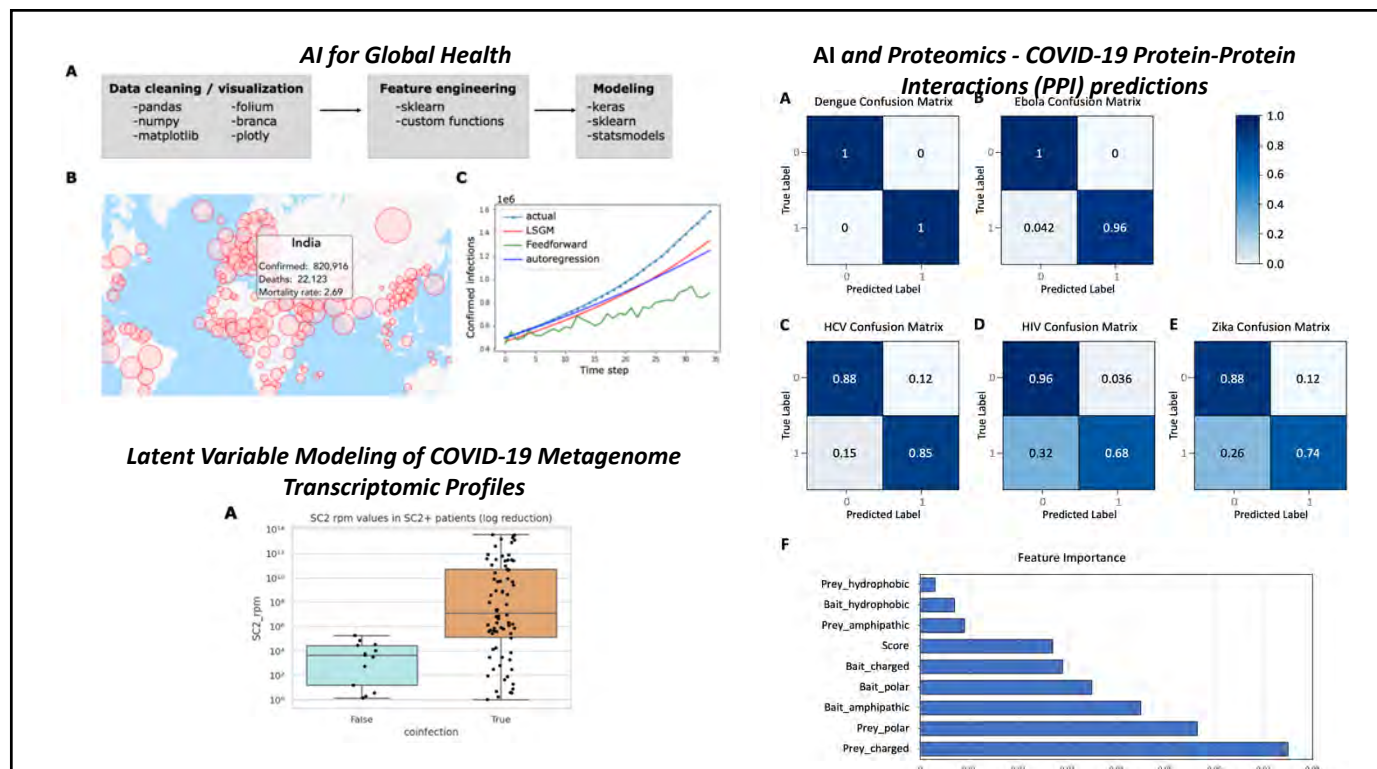
# 2020 Student Research Projects

- **Project 1: AI for Global Health - AI and COVID-19 Time Series Data**  
TAs: Jon Wang, Ishan Kanungo, and Jillian Burchard
- **Project 2: COVID-19 Protein-Protein Interactions (PPI) - AI and Proteomics**  
TAs: Snow Naing and Isha Karim
- **Project 3: COVID-19 Chest X-ray Classification - Computer Vision**  
TAs: Ina Chen, Tianna Grant, and Janice Yang
- **Project 4: Latent Variable Modeling of COVID-19 Host Transcriptomic Response**  
TAs: Will Connell, Ruchika Bajaj, and Claire Swadling
- **Project 5: PredictCOVID - AI and Electronic Medical Record (EMR) Data**  
TAs: Alice Tang and Bianca Vora

<https://www.youtube.com/watch?v=ulmjiHI7MDw&feature=youtu.be>

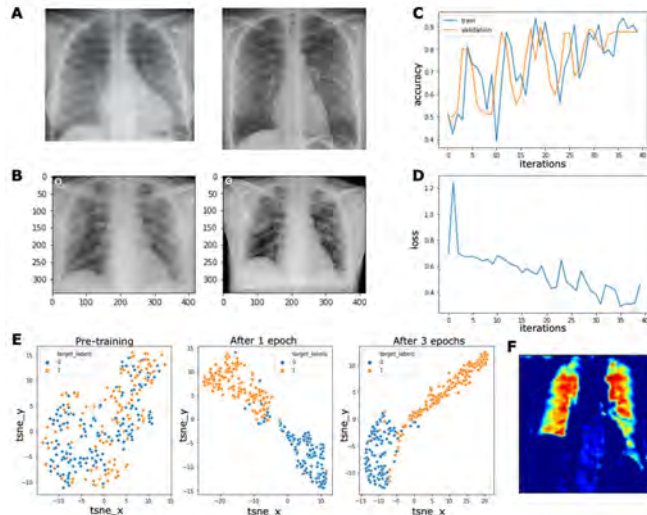


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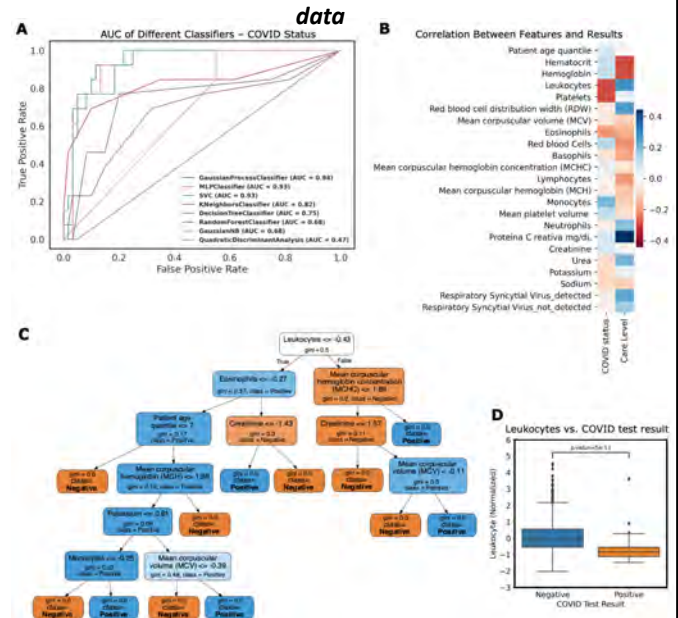


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### AI for Imaging Data - Computer Vision for COVID-19 Chest X-Ray Classification



### PredictCOVID - AI and Electronic Medical Record (EMR)



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## PLOS COMPUTATIONAL BIOLOGY

OPEN ACCESS PEER-REVIEWED

RESEARCH ARTICLE

### Nurturing diversity and inclusion in AI in Biomedicine through a virtual summer program for high school students

Tomiko Oskotsky , Ruchika Bajaj , Jillian Burchard , Taylor Cavazos , Ina Chen , William T. Connell , Stephanie Eanett , Tianna Grant , Ishan Kanungo , Karla Lindquist , Douglas Myers-Turnbull , Zun Zar Chi Naing , Alice Tang , Bianca Vora , Jon Wang , Isha Karim , Claire Swadling , Janice Yang , AI4ALL Student Cohort 2020 , Bill Lindstaedt, Marina Sirota  [ view less ]

Version 2

Published: January 31, 2022 • <https://doi.org/10.1371/journal.pcbi.1009719>

See the preprint

Article	Authors	Metrics	Comments	Media Coverage
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#### Abstract

Author summary

1. Introduction
2. Methods
3. Results

#### Abstract

Artificial Intelligence (AI) has the power to improve our lives through a wide variety of applications, many of which fall into the healthcare space; however, a lack of diversity is contributing to limitations in how broadly AI can help people. The UCSF AI4ALL program was established in 2019 to address this issue by targeting high school students from underrepresented backgrounds in AI, giving them a chance to learn about AI with a focus on

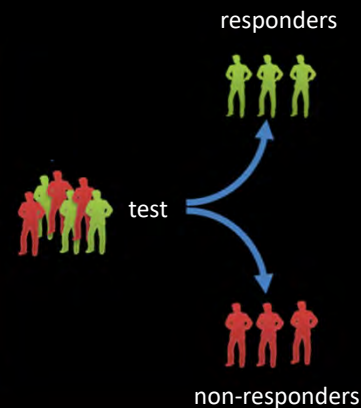
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## Summary

- Lots of (microbiome) data is available in the public domain – data sharing is vital!
- AI can be applied to build predictive models in disease
- Crowdsourcing approaches allow us to bring computational community to the data and interesting questions
- Case study: preterm birth
- Important to train the next generation of AI researchers!

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## Big Data → Precision Medicine



*"Doctors have always recognized that every patient is unique, and doctors have always tried to tailor their treatments as best they can to individuals. You can match a blood transfusion to a blood type — that was an important discovery. What if matching a cancer cure to our genetic code was just as easy, just as standard? What if figuring out the right dose of medicine was as simple as taking our temperature?"*

*- President Obama, January 30, 2015*

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# Acknowledgements

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Alice Tang

Zachary Cutts

Yaqiao Li

Sarah Woldemariam

Alennie Rodan

## UCSF

Tippi Mackenzie

Renan Sper

Scott Boyd

Sandra Nielson

Tony Capra

Abin Abraham

Tracey Woodruff

Amy Padula

Susan Lynch

Connie Ha

## STANFORD

David Stevenson

Ron Wong

Sota Iwatani

Cele Quaintance

Gary Shaw

Ivana Maric

Dan DiGiulio

David Relman

Ben Callahan

Nima Aghaeepour

Brice Gaudilliere

## PERATON

Elizabeth Thomson

Patrick Dunn

Kate Hypes

Ruth Monteiro

Zhiping Gu

Bryan Walters

## DREAM

Gustavo Stolovitzky

James Costello

Adi Tarca

Roberto Romero

Jonathan Golob

Jacques Ravel

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Sing Sing Way

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Thanks!

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<http://sirotalab.ucsf.edu>

We are hiring!