

Research at the Intersection of Translational Science and Women's Health

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Director

National Center for Advancing Translational Sciences

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April 12, 2023*



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An Overview

Thousands of Diseases

Disability-adjusted life years (DALYs) for diseases are **INCREASING** over time

Despite more tools and technologies

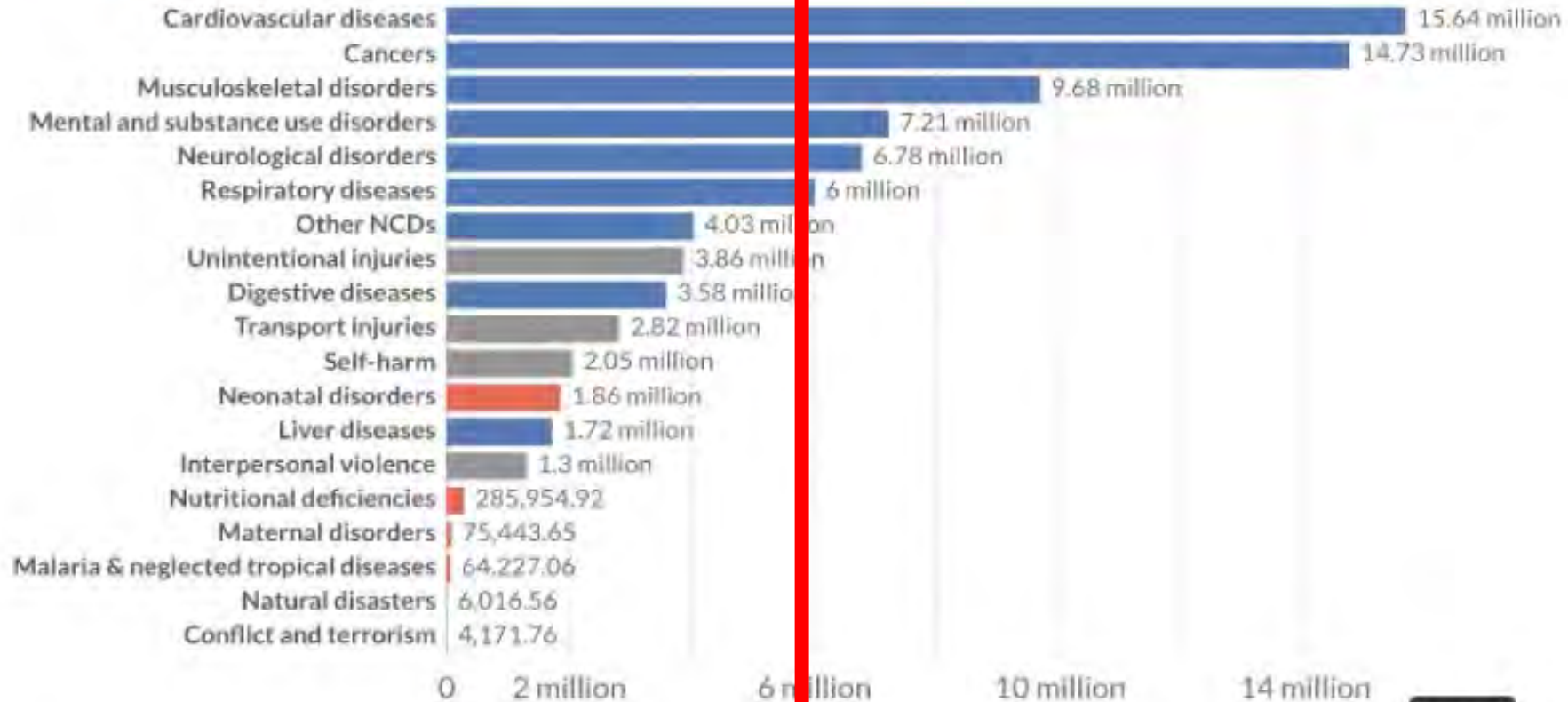
We are trending in the *wrong* direction

Burden of disease by cause, United States, 2017

Total disease burden, measured in Disability-Adjusted Life Years (DALYs) by sub-category of disease or injury. DALYs measure the total burden of disease – both from years of life lost due to premature death and years lived with a disability. One DALY equals one lost year of healthy life.

Our World in Data

Change country



Source: IHME, Global Burden of Disease

OurWorldInData.org/burden-of-disease

2017

C BY

1990

2017



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The Public Health Challenge

10,000

Diseases



and only

5%

Have
Treatments
or Cures



Time from early
development to the
medicine cabinet takes
10-15 years.

9

out of

10

Promising therapeutic candidates
that enter clinical trials fail.

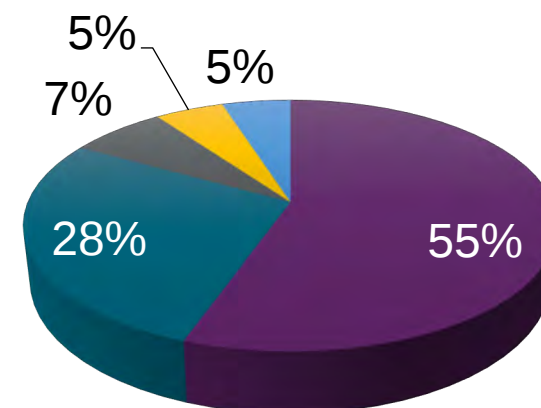


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Translational Problems in Drug Development

- The percentage of drugs entering clinical trials resulting in an approved medicine is less than **12%**
 - **55%** fail due to lack of efficacy
 - **28%** fail due to toxic effects in humans
- Average time to develop a drug takes **10-15 years**
- Average cost to develop a drug to market, including cost of failures is **\$2.6 billion**
- Current tools used for drug development involving **2-D cell culture** and **animal models** do not always predict human response
- “One size fits all” approach

Drug Failure Modes



Arrowsmith and Miller, *Nature Reviews Drug Discovery*, Volume 12, 569 (2013)

Cook et al., *Nature Reviews Drug Discovery*, Volume 13, 419 (2014)





NCATS' MISSION

**Turn research observations
into health solutions through
translational science**



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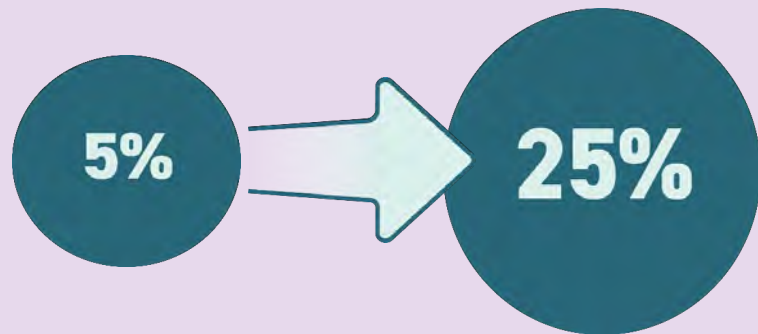
NCATS is Re-engineering the Translational Pipeline

NCATS is advancing translational science by addressing long-standing bottlenecks in the translational pipeline so that new treatments reach people faster.



NCATS Vision: Three Audacious Goals

More Treatments



**Five-Fold Increase
in Number of Diseases
with Treatments**

All People



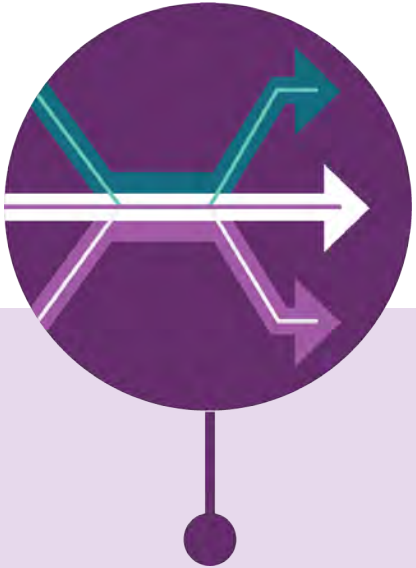
**Dramatically Increase
Inclusivity Across Every
Area We Support**

More Quickly



**Enable Diagnostics and
Therapeutics to Reach
People Twice as Fast**

Key NCATS Approaches



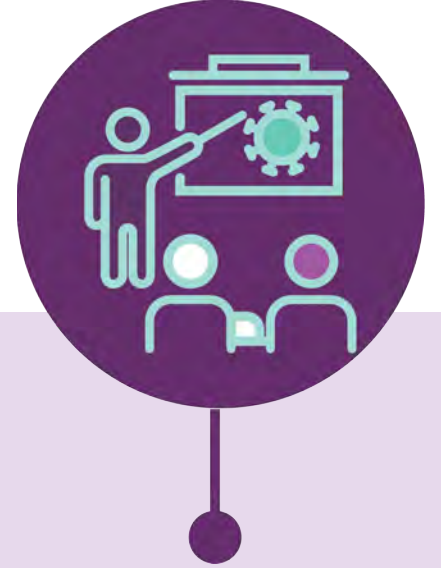
Understanding
what's similar
across diseases to
spur multiple
treatments at a
time



Developing models
that better predict a
person's reaction to
a treatment



Enhancing clinical
trials so the results
more accurately
reflect the patient
population



Leveraging real-
world data and data
science approaches
to address public
health needs

Translational Science

Translational Science is the field that generates scientific and operational innovations that overcome longstanding challenges along the translational research pipeline.



Prioritize initiatives that address unmet needs



Produce crosscutting solutions for common and persistent challenges



Emphasize creativity and innovation



Leverage cross-disciplinary team science



Enhance the efficiency and speed of translational research



Utilize boundary-crossing partnerships

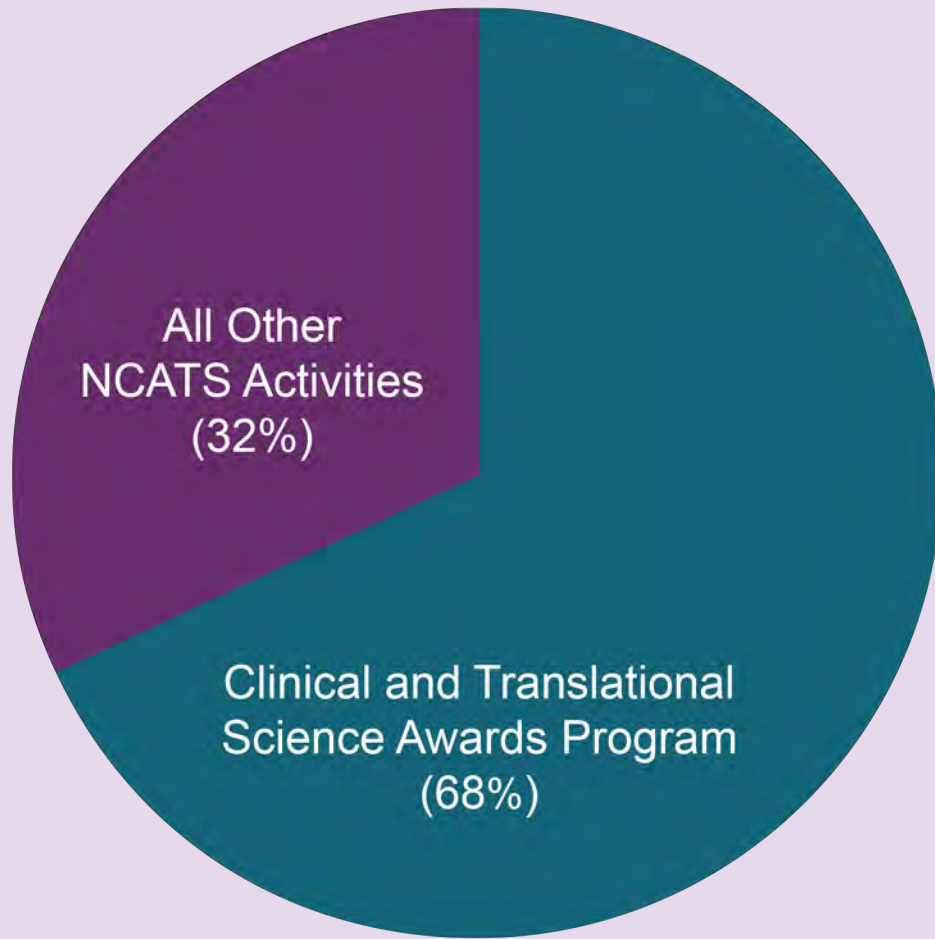


Use bold and rigorous research approaches



Advance diversity, equity, inclusion and accessibility in research

NCATS' Budget At-a-Glance



*Reflects Fiscal Year 2023 Enacted Appropriations
NCATS Budget: \$923,323,000*

Clinical and Translational Science Awards Program

Funds nationwide network of research institutions with consortium-wide resource centers and collaborative initiatives

All Other NCATS Activities

Supports intramural and extramural programs including drug repurposing, diagnostics, ethics and training

Stimulates transformative efforts and platform approaches through the Cures Acceleration Network

Enables patient-centric innovations for studying, treating and diagnosing rare diseases



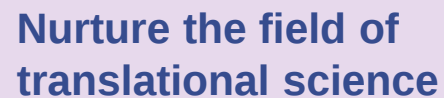
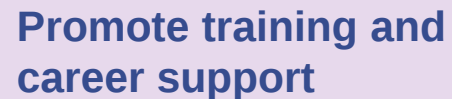
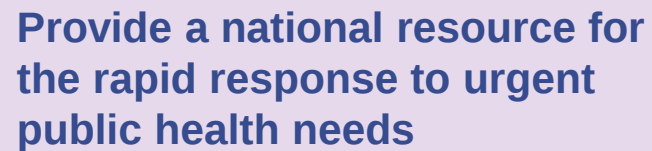
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Specific Efforts in Translational Science for Women's Health

Drugs and Medical Devices: Adverse Events and the Impact on Women's Health



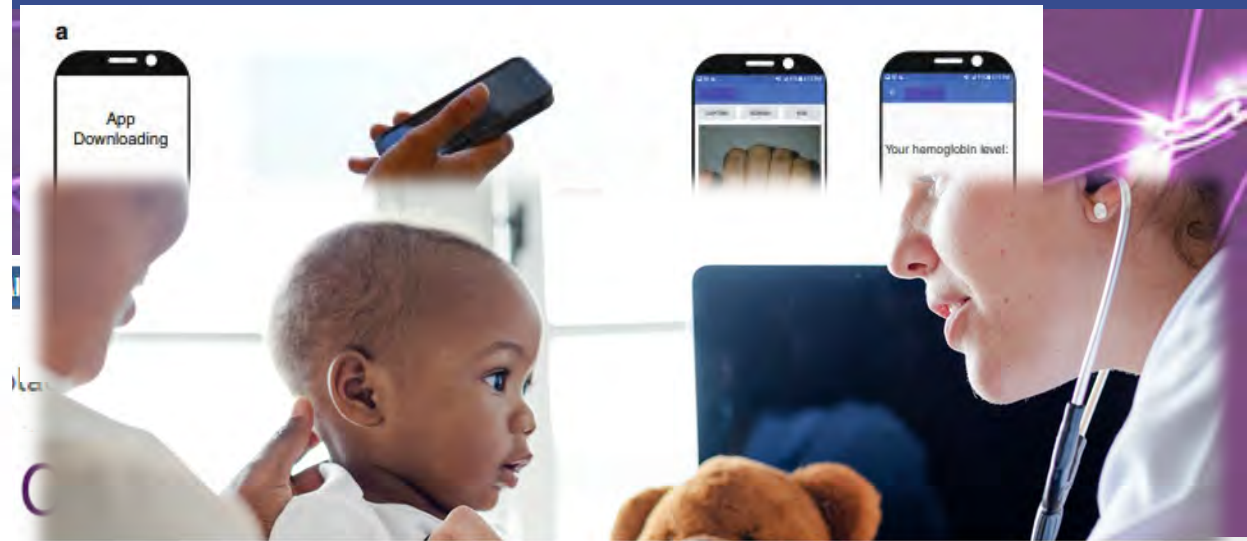
 CTSAProgram



Map of the United States showing the locations of 48 research sites. The sites are marked with black dots, many of which are surrounded by a purple glow. The dots are distributed across all 48 states, with a higher concentration in the Northeast and Midwest. The map includes state abbreviations and the names of Alaska (AK), Hawaii (HI), and Puerto Rico (PR).

January 2023

...Local strengths enable nimble, rapid, and robust responses to national public health



Supporting Pediatric Research on Outcomes and Utilization of Telehealth

Telehealth and Virtual Care Challenges (pre-COVID)

- Variation in services provided via telehealth and virtual care
- Lack of adequate research and reliable, generalizable data to support best practices, reimbursement, and provider adoption
- Different focus for different stakeholders: clinicians, payers, patients, hospitals, urgent cares, primary care

The N3C Data Enclave is a secure platform through which clinical data provided by our contributing members is stored. Data can only be accessed through a secure cloud portal hosted by N3C. Data cannot be downloaded or removed. N3C invites you to begin your journey with the Enclave and join the collaborative efforts of our partners to better understand and address the most pressing COVID-19 clinical questions.

Home > News > Researchers Shed Light on a Rare Genetic Disease in Children

Researchers Shed Light on a Rare Genetic Disease in Children

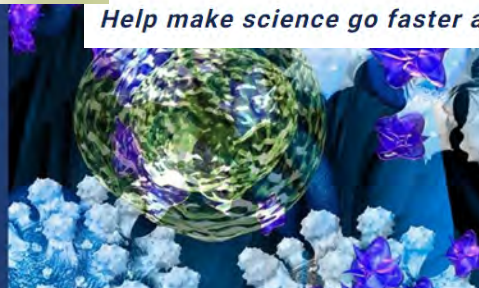
Findings could lead to better treatments for primary ciliary dyskinesia



Mobile health vehicles offer health resources, vaccine education and outreach opportunities through the Our Community, Our Health programs.

trial to test immune modulators for treatment of COVID-19

COVID-19 can trigger an immune response that causes inflammation that can lead to life-threatening conditions. ACTIV-1 will determine if regulating the immune response with immune modulators can reduce the need for ventilators and shorten hospital stays.



Help make science go faster and save lives

ACTIV-6

pressure. They had an average systolic blood pressure of 141 mmHg. The results were sustained over 12 weeks. In collaboration with the Vanderbilt University School of Medicine, a tool kit will be developed for use in research hubs locally or across the country.

CTSAs and Women's Health Research

CTSA Pilot Awards Promote Women's Health Research



- The Clinical and Translational Science (CTS) Pilot Award Program provides modest research support for new and innovative research projects to CTSA academic institutions
 - These provide valuable preliminary data to investigators planning more comprehensive studies and research applications.
- 11% of pilots (82 of 751) were solely focused on women's health research with an additional 4.3% (32) partially studying women's health, such as:
 - expanding knowledge about and evaluating services for incarcerated pregnant and postpartum women
 - improving cardiovascular risk prediction in women
 - an integrated smoking cessation and breastfeeding program to reduce cancer disparities



CTSAs and Cross-cutting Women's Health Research

Pain and Opioids

- [The Trial Innovation Network \(TIN\)](#) is an NCATS CTSA initiative that provides clinical trial infrastructure for the [HEAL Pain Management Effectiveness Research Network \(ERN\)](#) to speed scientific solutions to stem the national opioid public health crisis and improve pain management.
- The ERN program leverages the infrastructure of the TIN to support clinical trials that compare the effectiveness of existing non-addictive pain therapies as well as existing or novel approaches for pain prevention and management.
- Women's Health studies include:
 - One clinical trial seeking to address opioid overprescribing after cesarean delivery
 - A clinical trial determining the effectiveness of perioperative ketamine for prevention of post-mastectomy pain syndrome
 - ERN trials identifying better ways to manage chronic pain, a condition more prevalent in women.



TIN



HEAL research is seeking to optimize pain management for women after a C-section while reducing the number of leftover opioids and risk of opioid misuse. *Credit: Getty Images*



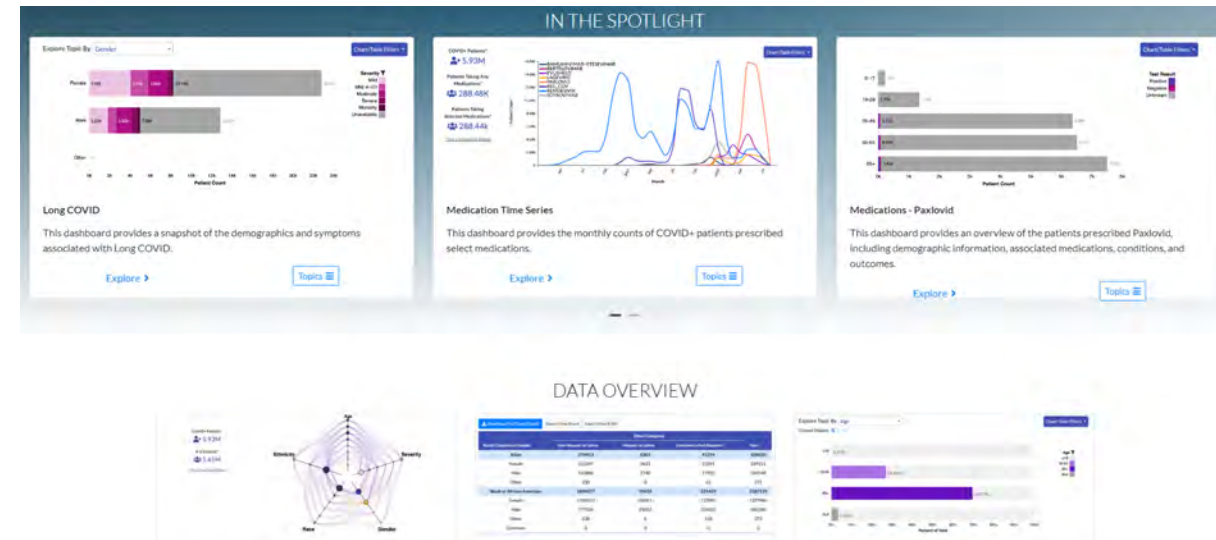
Towards a National Health Data Ecosystem: *National COVID Cohort Collaborative (N3C)*

The N3C data enclave is the largest collection of real-world COVID-19 data in the United States

- **Sites:** 77
- **Persons:** Over 17 million
- **COVID+:** Over 7 million
- **Rows of data:** 22.1 billion
- **Clinical observations:** 1.7 billion
- **Publications and preprints:** Over 117
- **Google citations:** Over 1,000
- **Informs public health questions**
 - Long-COVID risk
 - mAB effectiveness across variants
 - Paxlovid use

<https://covid.cd2h.org/dashboard/>

NCATS N3C Dashboard



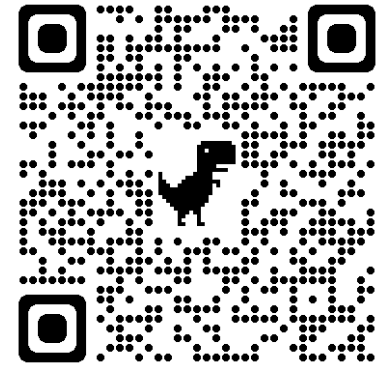
EHRs * CMS * Vaccine Data * Viral Variant Seq
Updated every 2 weeks



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Using the *National COVID Cohort Collaborative (N3C)* to Study the Impact of COVID-19 on Pregnancy

- The [National COVID Cohort Collaborative](#) (N3C) is being used to study COVID-19, identify potential treatments, and further validate existing therapies
- **The Pregnancy Clinical Domain Team** aims to leverage N3C data to gain insights into pressing COVID-19 questions around pregnancy.
 - These include understanding the incidence, timing, and severity of COVID-19 in pregnant women and the associated maternal and infant outcomes.
- One group used N3C to develop The Temporal Events Detector for Pregnancy Care (TED-PC) algorithm (Lyu et al., 2022; [PMID: 36315520](#))
 - TED-PC can determine the gestational week of clinical events in Electronic Health records (EHR) during pregnancy
 - TED-PC will be able to help evaluate the impact of COVID-19 on pregnancy.



N3C

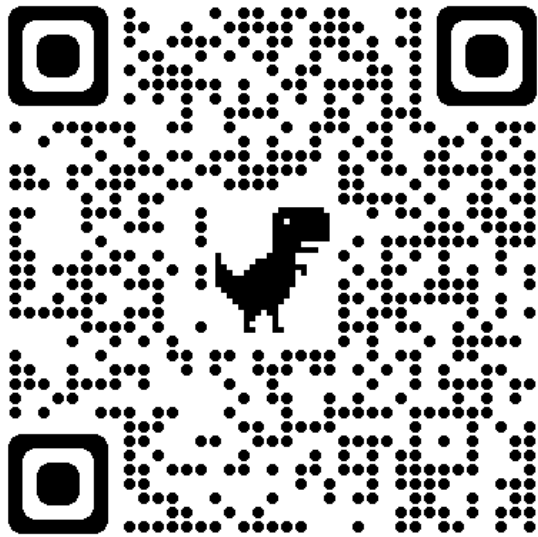
Findings from N3C: Sex Differences in Severe Outcomes in Patients with COVID-19

- Researchers evaluated association of comorbidities, inflammatory biomarkers, and severe outcomes in over 570,000 adult patients admitted for COVID-19 at hospitals or emergency rooms in 2020 and 2021

The top four fatal comorbidities in both sexes among patients hospitalized for COVID-19, were the same (moderate to severe liver disease, renal disease, metastatic solid tumor, and myocardial infarction) but **women had a higher magnitude of risk than men.**

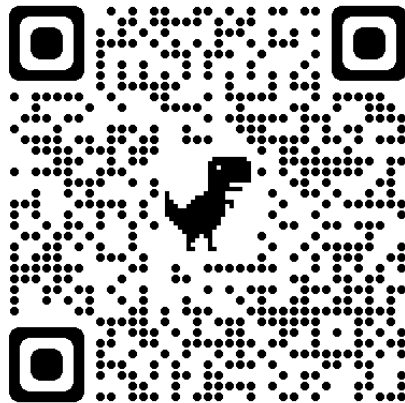
Similarly, abnormal levels of several proteins (including c-reactive protein (CRP), ferritin, procalcitonin, and NT proBNP, as well as increased neutrophil and platelet counts) were significantly associated with death in both sexes, **with the association being stronger in women than men.**

- [PMID: 36224551](https://pubmed.ncbi.nlm.nih.gov/36224551/) (Yoshida et al., 2022).

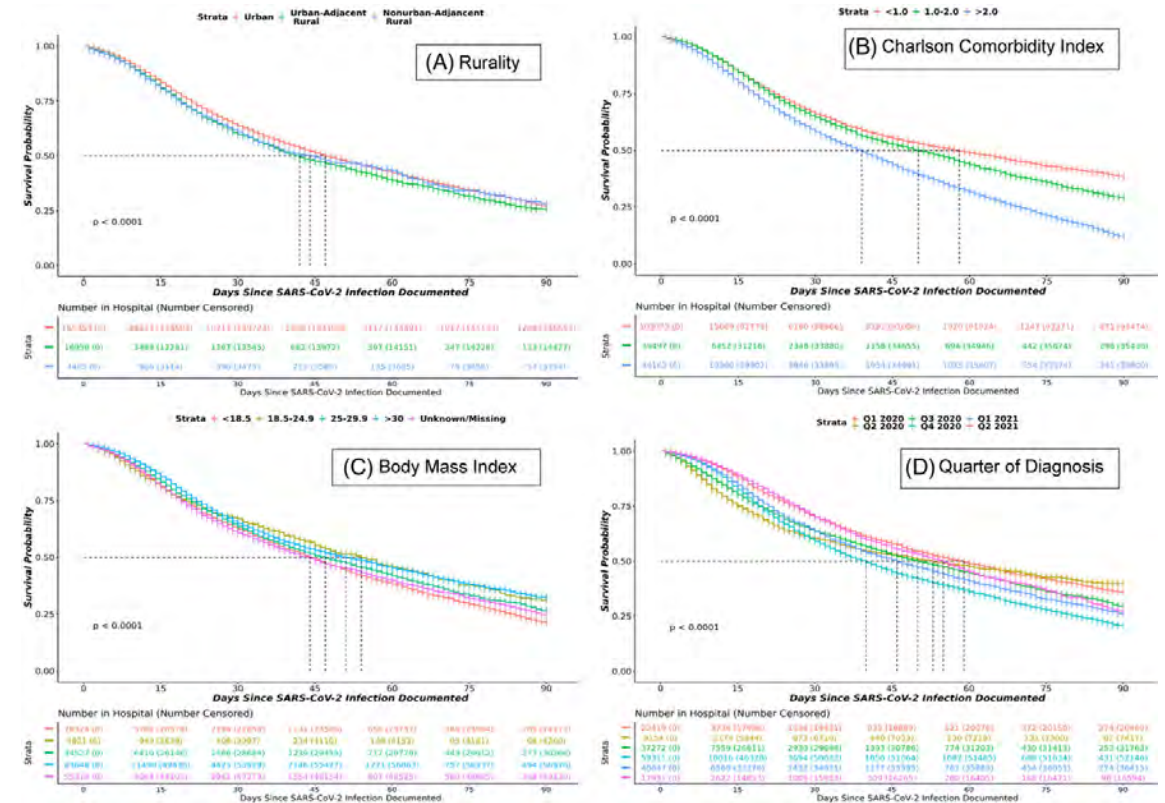


N3C Examples of Impact

- “Without the opportunity for CTRs to participate in N3C, rural Americans would be largely missing from a significant national health database.”
- Guidelines for HIV patients changed due to N3C analyses (CDC recommendations)
- Transplant guidelines changed due to N3C analyses (Canada)



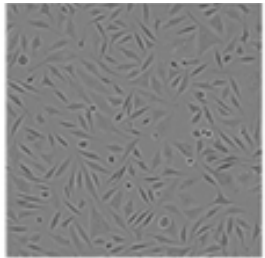
Higher hospitalization and mortality rates among SARS-CoV-2-infected persons in rural America – “Rural Penalty”



Revolutionizing Drug Development Approaches

(PhRMA, Biopharmaceutical Research Industry Profile, 2016)

2D Cell Lines



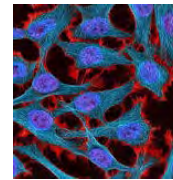
Human



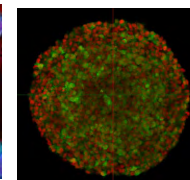
Mouse



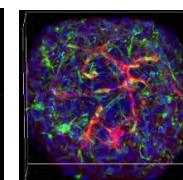
2D



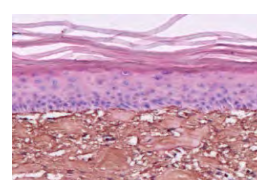
Spheroids



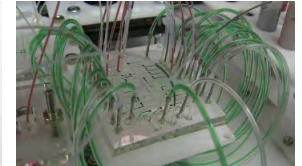
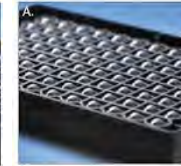
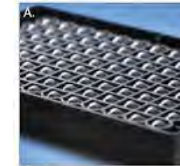
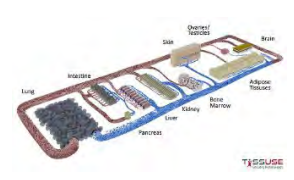
Organoids



Printed Tissues

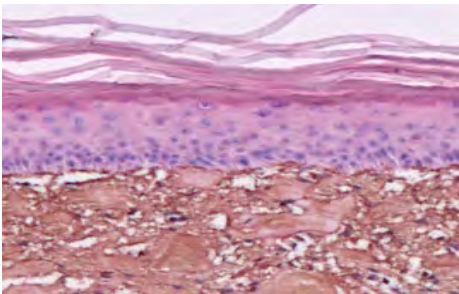
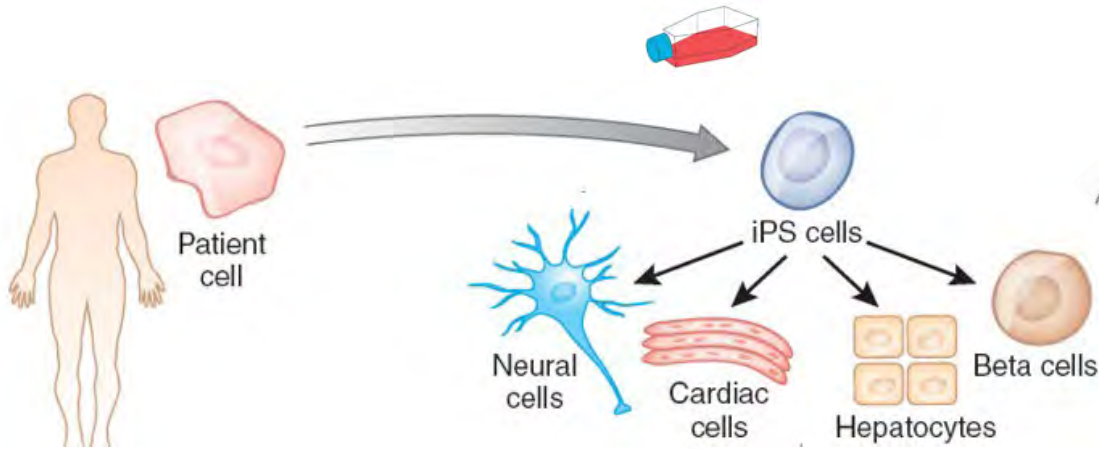


Organ-on-a-chip



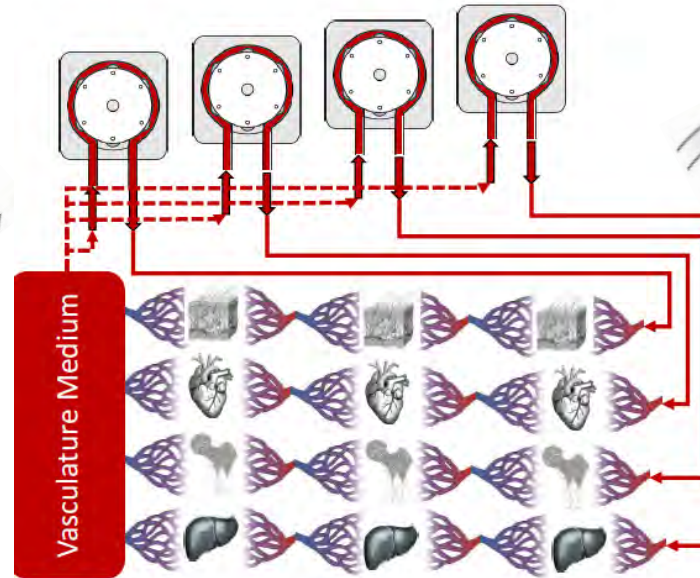
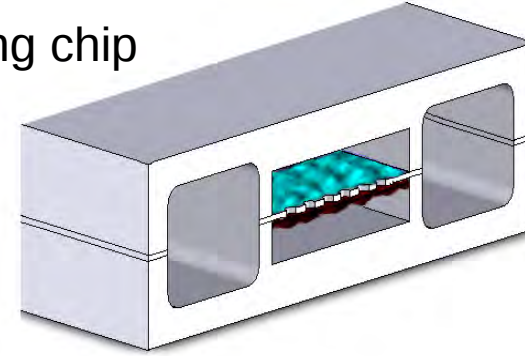
Need for new technologies and better predictive tools across the translational pipeline

Better predictive models

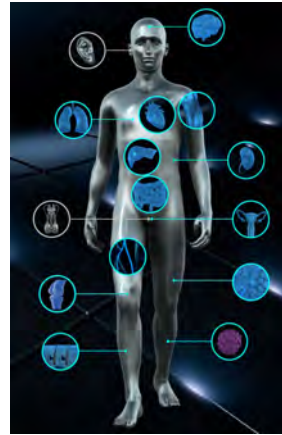


3D Bioprinted skin tissue

Lung chip



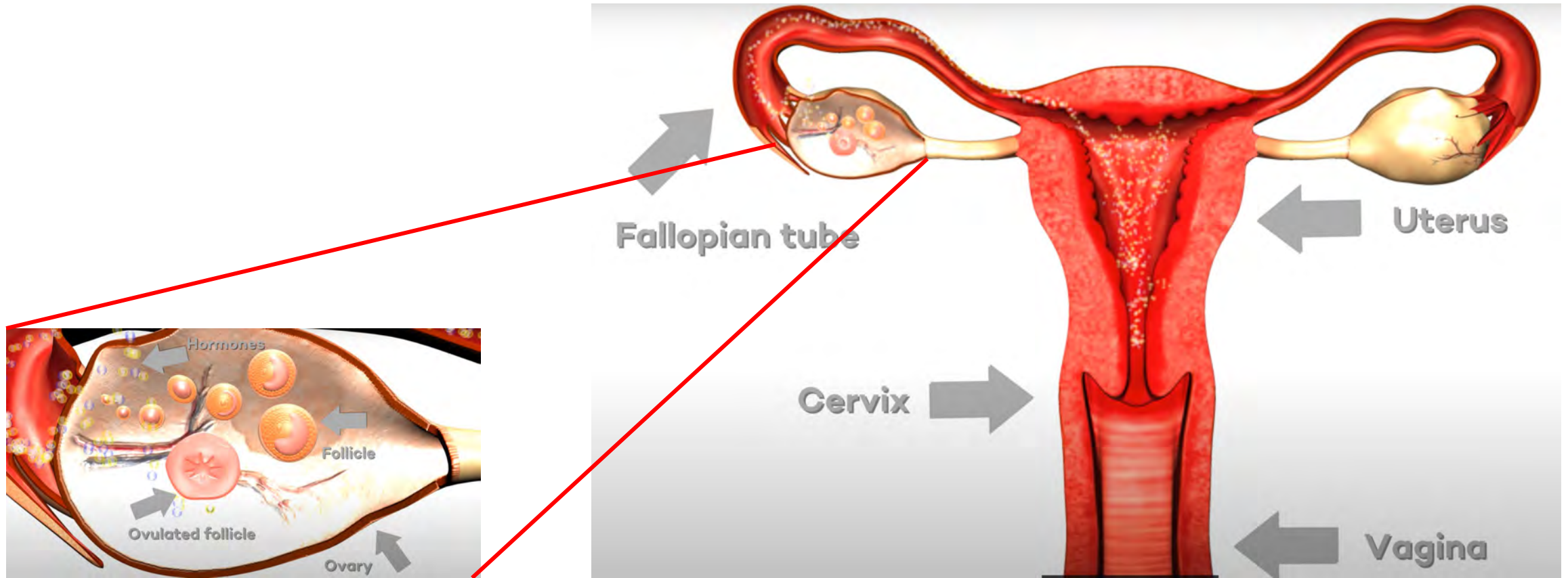
Multi-organ chip



Precision Medicine You-on-a-chip

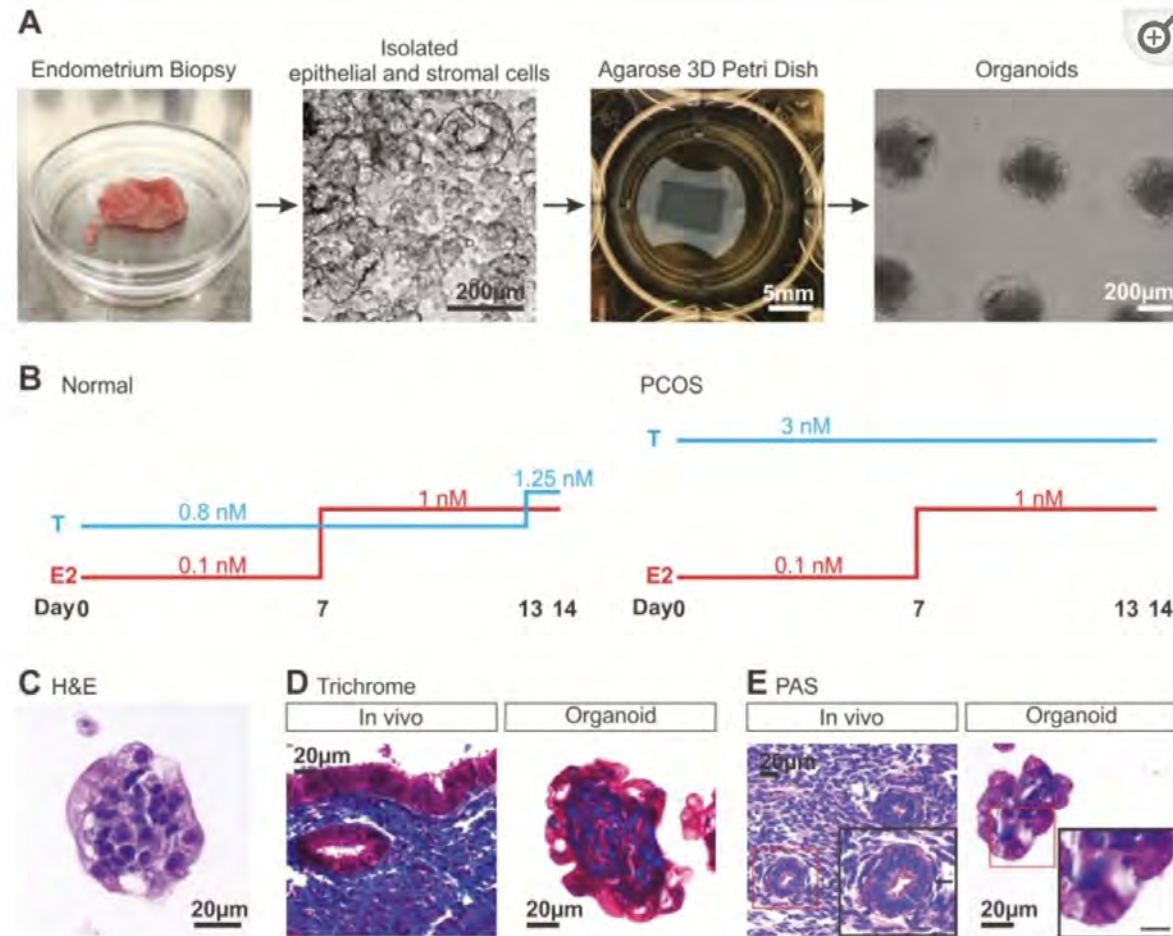
- Identify & test biomarkers
- Reduce trial risk
- Hone patient selection
- Explain variable treatment response

Modeling the Entire Female Reproductive Hormone System



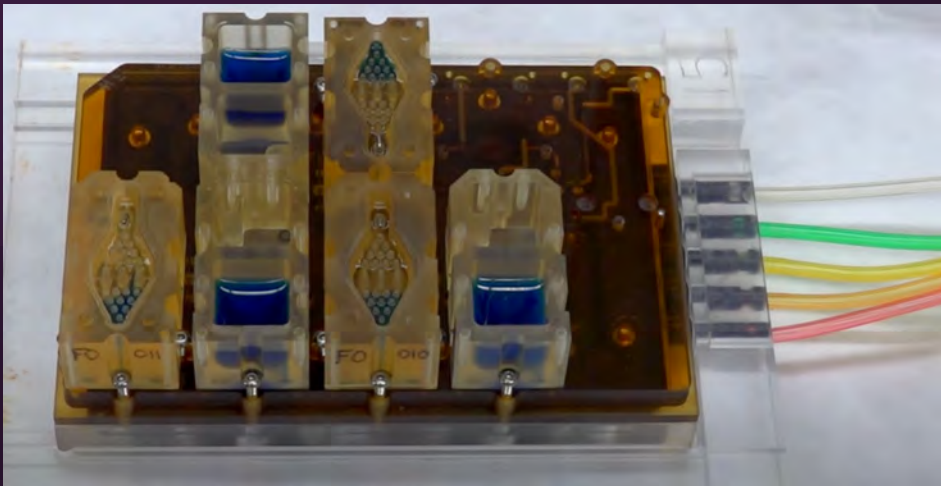
Teresa Woodruff, Ph.D Northwestern University on the ovaries; Joanna Burdette, Ph.D. (UIC), on the fallopian tubes; Julie Kim, Ph.D. (Northwestern), on the uterus; and Spiro Getsios, Ph.D. (Northwestern), on the cervix and vagina. Beth Sefton, Ph.D., at Northwestern, coordinates the work – TEAM SCIENCE!

3D Organoids



Generation of scaffold-free 3D endometrial organoids from human primary endometrial cells. **(A)** Endometrial epithelial and stromal cells were isolated from premenopausal endometrial tissues with benign pathology. Both stromal and epithelial cells were seeded into 1.5% agarose 3D Petri Dishes™ at a 1:3 ratio by volume and maintained in sex hormone-free medium for 7 days before downstream experiments. **(B)** Estradiol (E2) and testosterone (T) were added in a stepwise manner to the 3D cultures to mimic the levels of E2 and T during the follicular phase of a menstrual cycle. T levels were consistently higher (3 nM) in the polycystic ovarian syndrome hormone profile. After 14 days of normal hormone treatment, endometrial organoids were stained with **(C)** hematoxylin and eosin, **(D)** trichrome stain to detect collagen (blue), and **(E)** periodic acid-Schiff staining to stain mucosal substances (eg, mucins, glycoproteins; bright pink). Scale bar in inset of **(E)** is 10 µm.

Evatar

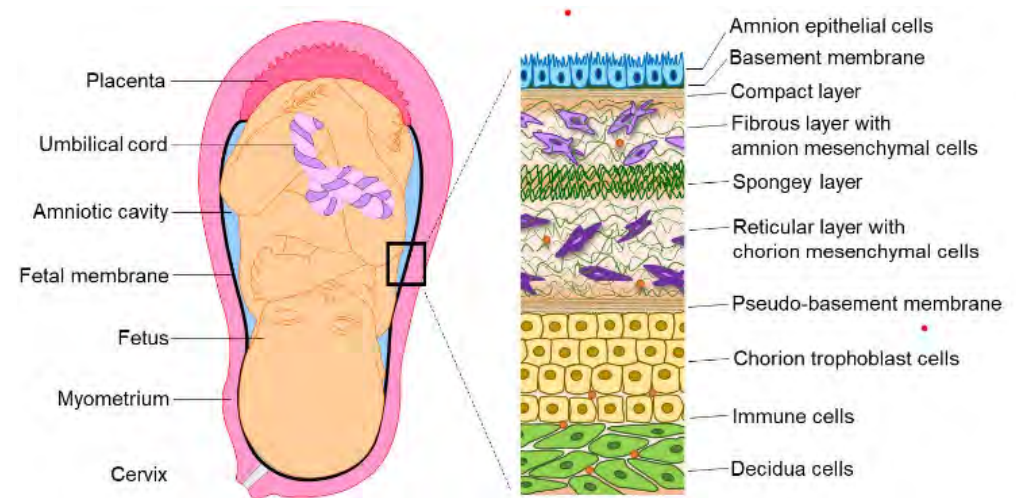


"This work is a remarkable advance for understanding female biology, and it will fill an important gap," said Janine A. Clayton, M.D., ORWH director. "It's a perfect example of how considering sex as a biological variable can help us develop individualized treatments and learn more about how females may metabolize drugs differently from males."

Teresa Woodruff, Ph.D Northwestern University on the ovaries; Joanna Burdette, Ph.D. (UIC), on the fallopian tubes; Julie Kim, Ph.D. (Northwestern), on the uterus; and Spiro Getsios, Ph.D. (Northwestern), on the cervix and vagina. Beth Sefton, Ph.D., at Northwestern, coordinates the work – TEAM SCIENCE!

Using 3-D Tissue Bioprinting and Tissue Chip to Improve Health in Pregnancy

- 3-D bioprinted interface tissue model that can mimic inflammation during pregnancy is being developed
- Up to 1,000 drug compounds that may reduce spontaneous preterm birth will be screened
- [1UH2TR004117-01](#)

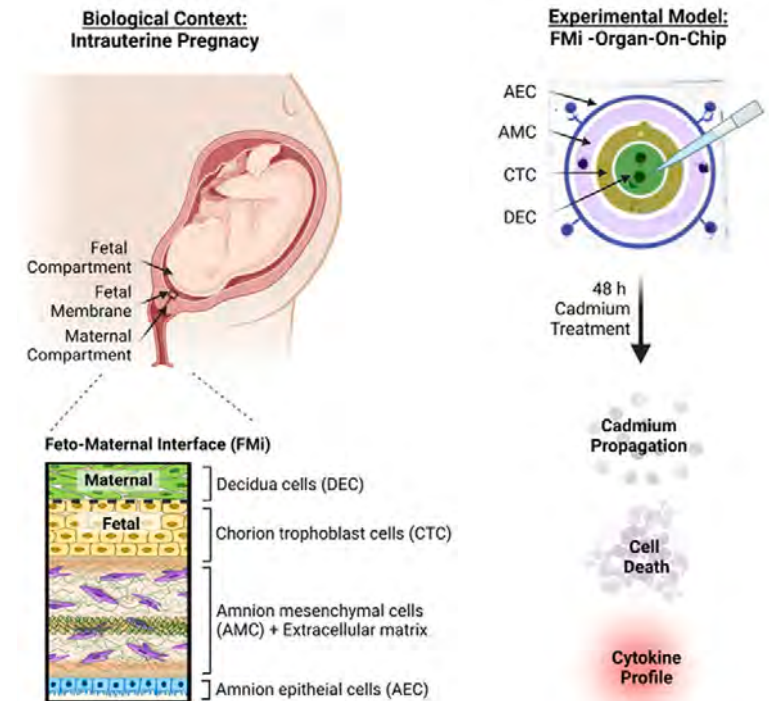


Intrauterine and fetal membrane anatomy. Richardson, L., & Menon, R. (2022). Fetal membrane at the feto-maternal interface: An underappreciated and understudied intrauterine tissue: Importance of the fetal membrane feto-maternal interface. *Placenta and Reproductive Medicine*, 1. <https://doi.org/10.54844/prm.2022.0104>



Using 3-D Tissue Bioprinting and Tissue Chip to Improve Health in Pregnancy

- The Maternal-Fetal Interface on a Chip aims to reproduce the structure, function, and responses of the fetal-maternal tissue interface (FMI), mimicking health and inflammation
- Reducing inflammation at the FMI could help maintain pregnancy and prevent spontaneous preterm birth.
- The goal is to offer a personalized FMI model to test potential treatments and streamline clinical trials.
- One study tested the effect of maternal exposure to cadmium (Cd), an environmental toxin, and found significant cell death in maternal cells, but minimal effect on fetal cells. ([PMID: 34391970](https://pubmed.ncbi.nlm.nih.gov/34391970/))



Kim S, Richardson L, Radnaa E, Chen Z, Rusyn I, Menon R, Han A. Molecular mechanisms of environmental toxin cadmium at the feto-maternal interface investigated using an organ-on-chip (FMI-OOC) model. J Hazard Mater. 2022 Jan 15;422:126759. doi: 10.1016/j.jhazmat.2021.126759. Epub 2021 Aug 2. PMID: 34391970; PMCID: PMC8595660.

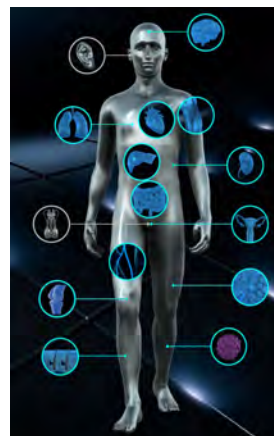


Physiological Changes under Prolonged Microgravity: Chips in Space

- **Early response (<3 weeks)**
 - Neurovestibular disturbances
 - Sleep disturbances
 - Bone demineralization
- **Intermediate (3 weeks to 6 months)**
 - Bone resorption
 - Muscle atrophy
 - Cardiovascular deconditioning
 - GI disturbances
 - Hematological changes
- **Long Duration (greater than 6 months)**
 - All of the above, and...
 - Declining immunity
 - Renal stone formation
- **Reverts to normal upon return to Earth**

Tissue Chips and Digital Twins: Technology and Platform Development on the Horizon

RCTs with prognostic digital twins overcome the limitations of external control arms



Precision Medicine You-on-a-chip

- Identify & test biomarkers
- Reduce trial risk
- Hone patient selection
- Explain variable treatment response

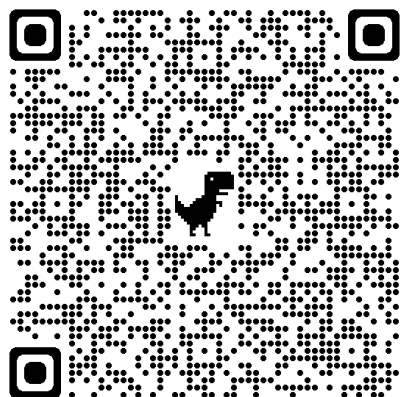
NASA's Artemis 3 mission: Landing humans on the moon

By Elizabeth Howell last updated November 16, 2022

NASA plans to land humans on the moon in 2025, for the first time in more than 50 years.



Artist's conception of SpaceX's Starship on the moon. Starship was selected to be NASA's human landing system for Artemis 3. (Image credit: SpaceX)



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Towards New Approach Methodologies: Human Cell-Based Physiological Systems for Women's Health

- Assess changes in metabolic activity of specific cell types
- Effects of exposure to hormonal treatment or chemical substances on aspects of reproduction and fertility
- Studies of diseases, causes, and adverse events occurring during pregnancy such as pre-eclampsia, infertility or preterm birth, endometriosis and infertility
- Allows the co-culture of different cell types under normal and disease states of the female reproductive tract and changes occurring during conception and pregnancy

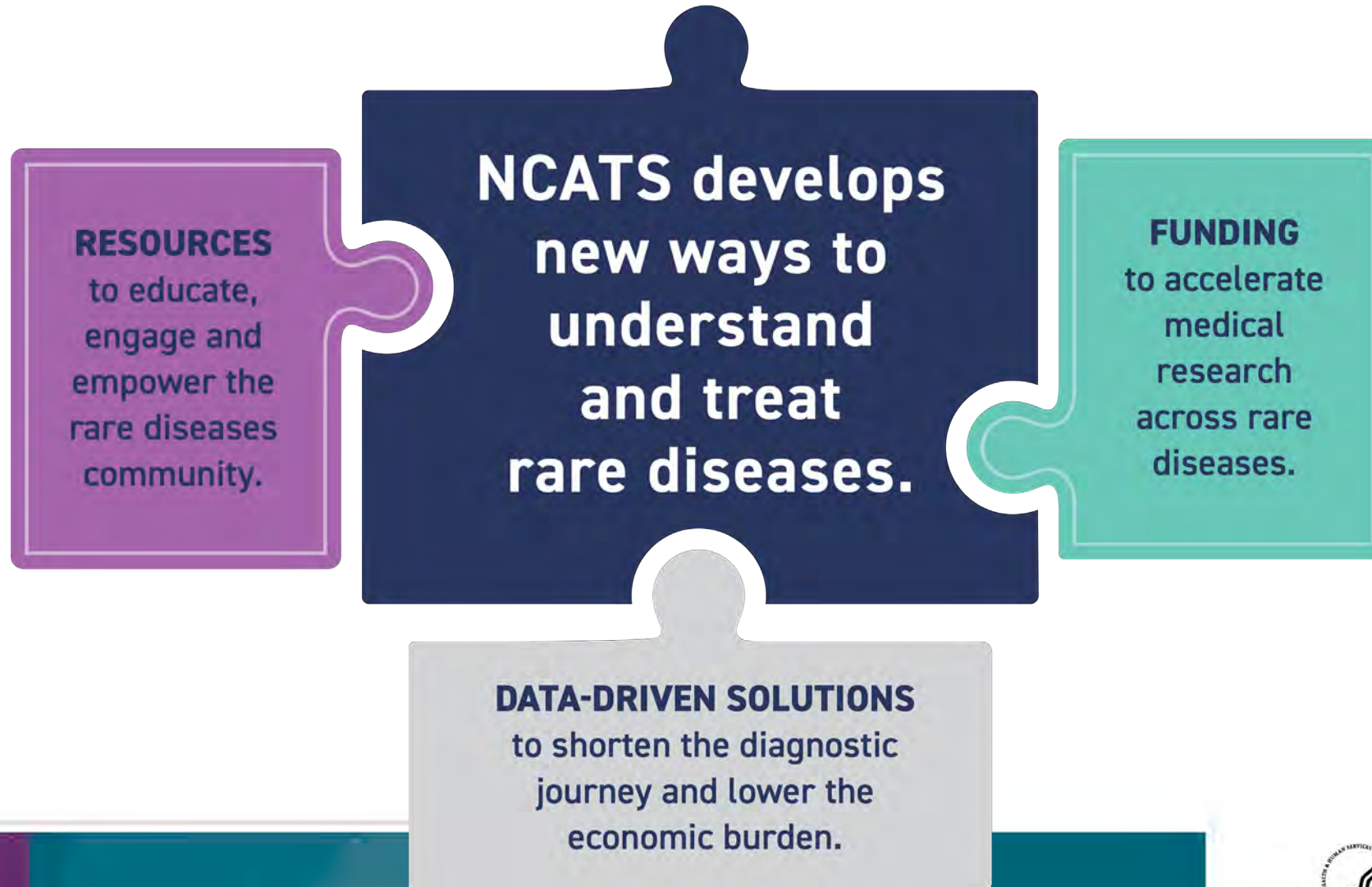


Small Molecule Therapeutics to Prevent Breast-to-Brain Metastasis

- Triple-negative (30%) and HER2+ (34%) breast cancers are more likely to metastasize to the brain
- Many therapeutic agents effective against breast cancer can't be used to treat brain metastases, because they cannot cross the blood-brain barrier.
- NCATS investigators are collaborating with researchers at the University of Manitoba, Winnipeg, to develop high-throughput screening approaches to identify molecules for treating breast-to-brain metastasis (Mark Henderson, [1ZIATR000405](#))
 - Developed the only current hematogenic HER+/ER α + breast-to-brain metastasis human cell model
 - Screened over 6,500 compounds, including about 2,500 cancer drugs
 - Identified a mechanism by which metastatic breast cancer cells use resident brain cells to avoid being killed by drugs that target the HER2 receptor



NCATS Has a Home for Rare Diseases



NCATS Study Suggests People with Rare Diseases Face Significantly Higher Health Care Costs

Individual medical costs for people with a rare disease are

3-5 TIMES

greater than for those who do not have a rare disease.

The medical costs of rare diseases have been underestimated.



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Yearly direct medical costs estimated at around

\$400 BILLION

are similar to those of cancer, heart failure and Alzheimer's disease.

Rare diseases are collectively common, affecting an estimated

**25-30
MILLION**

people in the United States.

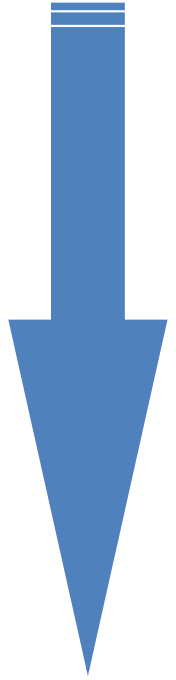
Source: The IDeaS Initiative: Pilot Study to Assess the Impact of Rare Diseases on Patients and Healthcare Systems



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Developing and Streamlining Delivery Approaches

Development



Clinical Trials

- 1) Somatic Cell Gene Editing – (SCGE)
 - 1) NIH Common Fund Program
 - 2) Moving to clinical studies for second phase
 - 3) Toolkit – data on performance of delivery technologies
- 2) Accelerated Medicines Program® – Bespoke Gene Therapy Consortium (BGTC)
 - 1) Enhancing vector manufacturing
 - 2) Enhancing gene expression
 - 3) Regulatory playbook
- 3) Platform Vector Gene Therapy – (PaVe-GT)
 - 1) Single AAV vector as a platform for multiple therapeutic genes
 - 2) Testing ability to increase efficiency to clinical trial start-up



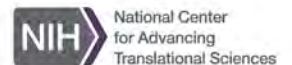
Advancement of Women in Biomedical Careers

- The Women Scientists Advisors (WSA) group within the Division of Preclinical Innovation (DPI) developed a new initiative in 2022
- Women scientists from DPI engage with the external Bethesda/DC-area community, particularly students in grades K-12.
- For grades 6-12, there are:
 - panel discussions
 - 1-on-1 “speed chatting” activities with opportunities for students to ask scientists about their careers, navigating higher education, how their science contributes to day-to-day life, and overcoming challenges.
- For students in K-5 there is:
 - “Translational Science in Action” role playing games, developed by WSA, where students pretend to be scientists approaching various scripted problems and learn science is about teamwork, curiosity, and persistence.

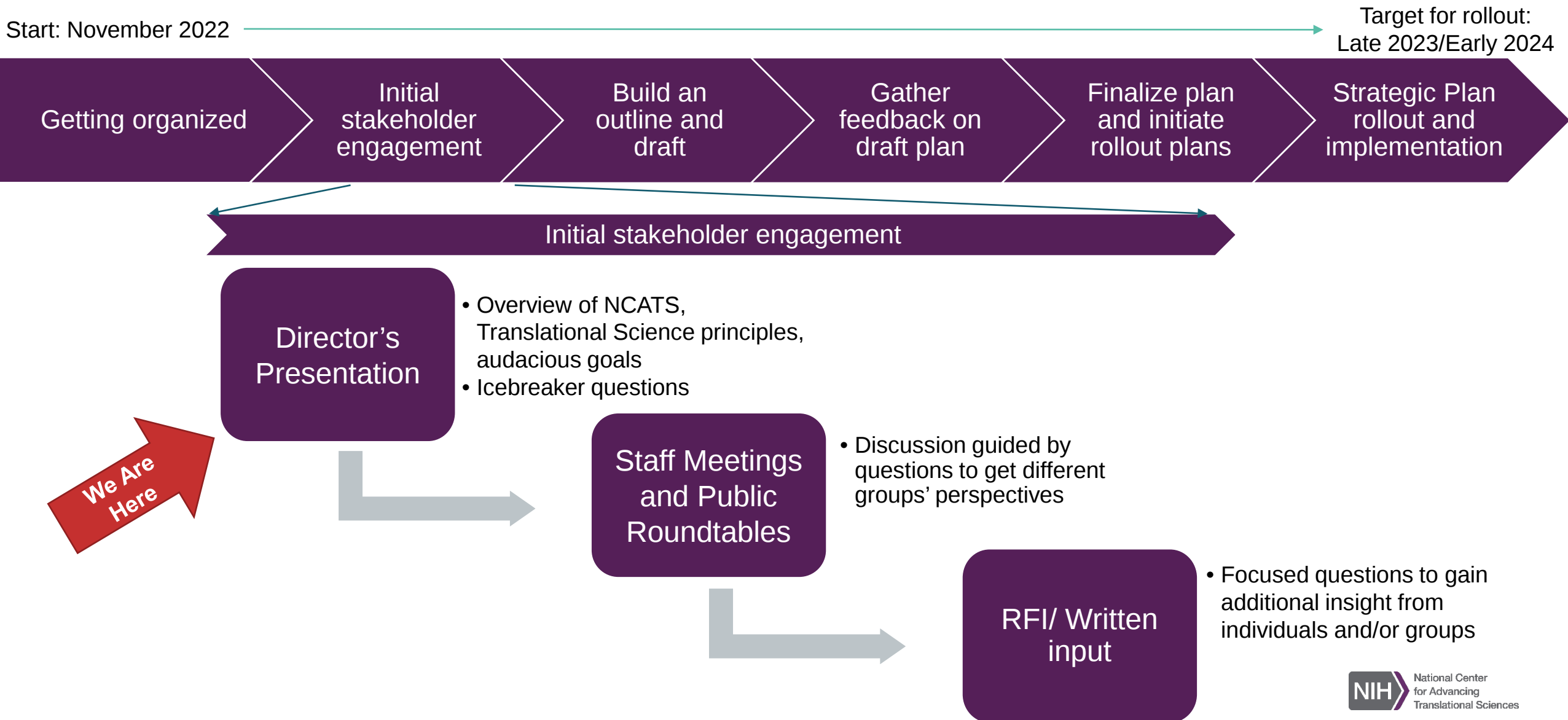


NCATS scientist Kelli Wilson takes local seventh graders on a tour of NCATS' laboratories during Frontiers in Science & Medicine 2018. Credit: Daniel Soñé Photography

This initiative increases visibility of women scientists, encourages development of students' scientific literacy while showing that science and scientists are relatable and anyone can have a job in science.



Strategic Planning Process: Stakeholder Engagement





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