WOMEN'S HEALTH *In Focus* AT NIH

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Data Science and Women's Health

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Director's Corner

Janine Austin Clayton, M.D., FARVO
Director, NIH Office of Research on Women's Health
NIH Associate Director for Research on Women's Health

Advances in data science are transforming the scale and pace of women's health research by allowing researchers to build sophisticated computational and mathematical models, detect patterns in large amounts of highly complex data, and responsibly integrate disparate data sources.

This issue highlights several areas where advances in machine learning, artificial intelligence, and computer hardware are transforming women's health research, including for conditions that disproportionately affect women, such as Alzheimer's disease, and for conditions that are female specific, such as endometriosis and preeclampsia.

In addition, the issue spotlights efforts at the National Institutes of Health (NIH) to develop, validate, and scale new and emerging technologies to reduce the need for animal testing and describes how these efforts might help advance women's health research. We also speak with Dr. Heather Desaire of the University of Kansas about building a team of scientists who can leverage big data to improve women's health, and with Dr. Donna K. Ginther of the University of Kansas about women's progress in scientific fields.

We conclude with a roundup of several exciting recent scientific findings concerning the use of estrogen receptor degraders to treat women with advanced breast cancer, the contribution of the fallopian microenvironment to the development of ovarian cancer, and sex-based metabolic differences in individuals with mild cognitive impairment.

We hope you will share this exciting issue of In Focus *with your colleagues. You can also subscribe to* In Focus *online.*

Janine Austin Clayton, M.D., FARVO
Director, NIH Office of Research on Women's Health
NIH Associate Director for Research on Women's Health

Data Science and Women's Health

The views and opinions expressed in the ORWH Quarterly publication are those of the interviewees and contributors; they do not reflect the official policy or position of the Office of Research on Women's Health (ORWH) or the National Institutes of Health (NIH), and their inclusion does not imply endorsement by ORWH or NIH.

Superficial similarities in health outcomes and disease symptoms can sometimes mask important sex differences. For example, although women and men often benefit from the same medications, women are 50% to 75% more likely to experience medication-related side effects.[1] Heart disease, schizophrenia, and autoimmune diseases affect both sexes but often present with different symptoms and follow different disease trajectories in men and women.[2,3,4] Women and men both develop Alzheimer's disease (AD), but women have approximately twice the lifetime risk for AD as men, and their higher risk is not merely because women on average live longer than men.[5]

To understand the roots of these sex differences, researchers need to look "under the hood," to examine how sex affects the complex, multidimensional cellular and physiological processes involved in these conditions. However, until recently, the sheer complexity of human cellular biology and physiology posed a nearly insurmountable barrier to studying sex differences at scale.

Advances in machine learning, artificial intelligence (AI), and data science are overcoming this barrier. These advances are opening the door to personalized medicine, including sex-specific diagnostics and therapies, and revealing new opportunities for prevention and treatment.

Machine Learning Models and Alzheimer's Disease

Jason H. Moore, Ph.D., Cedars-Sinai Medical Center

"A key advantage of machine learning is its ability to detect complex nonadditive interactions between multiple factors in a dataset, making it ideally suited to investigating context-dependent effects such as sex differences," says Jason H. Moore, Ph.D., Chair of the Department of Computational Biology at Cedars-Sinai Medical Center, who uses AI, machine learning, and systems biology approaches to analyze large biomedical datasets. Nonadditive interactions reflect combined impacts that are more than the sum of individual factors' impacts; they cannot be detected when individual factors are studied in isolation.

Although machine learning models excel at detecting nonadditive interactions, says Dr. Moore, more work needs to be done to improve the interpretability of these models, to home in on the important biomarkers for diseases like Alzheimer's disease, and to understand their biological effects.

AD is the most common age-related neurodegenerative condition. Approximately two-thirds of those living with AD are women, and the reasons for this female predominance are not well understood.[6]

Dr. Moore has constructed an open-source AD knowledge base (AlzKB). AlzKB integrates more than 20 sources of knowledge concerning genes, drugs, diseases, pathways and symptoms related to AD and contains an ontology that captures the semantic relationships between these data. Machine learning algorithms can use AlzKB to inform variable selection and model development and interpretation. This approach makes data analysis more computationally tractable, saving time and energy, and

renders the final model more interpretable because it is grounded in biology, says Dr. Moore. Researchers can also use AlzKB to direct AI-based tools to focus on aspects of the knowledge base relevant to specific AD risk factors, such as female sex.

Dr. Moore recently used AlzKB to search for novel genes and genetic pathways related to AD in the Alzheimer's Disease Sequencing Project, a National Institute on Aging-funded effort. "We designed an algorithm that explores genetic information far away from known AD genetic markers but that is predictive of AD. The resulting models performed as well as models that included known genetic risk factors for Alzheimer's, which was very exciting." Dr. Moore then connected the novel genetic pathways identified with U.S. Food and Drug Administration (FDA)-approved drugs to create a list of candidate novel AD treatments.

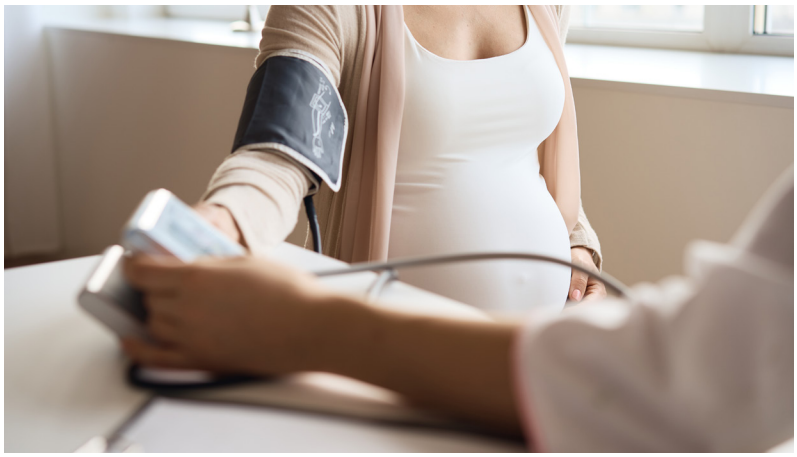
Building Computational Methods and Mathematical Models to Study Human Pregnancy and Lactation

Liat Shenhav, Ph.D., an Assistant Professor at the Institute for Systems Genetics and in the Departments of Microbiology and Obstetrics and Gynecology at the NYU Grossman School of Medicine, is using AI, machine learning, and other mathematical models to better understand the complex biological changes that take place during pregnancy and lactation.

Liat Shenhav, Ph.D., NYU Grossman School of Medicine

"My lab is conducting studies and participating in several large collaborations that collect data from around the world," says Dr. Shenhav. "We are especially focused on gathering data over time—what we call longitudinal data—and capturing a broad view of biological processes using state-of-the-art sequencing techniques and advanced imaging."

Most of the work in Dr. Shenhav's lab happens after data is collected. Her team develops and tests bespoke computational methods and mathematical models to uncover hidden patterns in these large, complex datasets.



One of Dr. Shenhav's projects examines how breastfeeding shapes the development of the infant microbiome—the community of microbes living in and on our body. Her team discovered that breastfeeding influences not only how quickly these microbial communities mature but also the sequence in which different microbes appear.[7] This gradual, orderly development was linked to a lower risk of childhood asthma.[7]

In another project, Dr. Shenhav's lab is designing custom algorithms to analyze high-resolution images of the retinal (back of the eye) to detect early warning signs of preeclampsia—a common and potentially dangerous pregnancy complication marked by elevated blood pressure and possible organ damage. Preeclampsia is believed to arise from problems with early placental development, particularly the failure to remodel key blood vessels the supply the growing fetus.[8]

"The placenta is fascinating. It's a temporary organ grown by the fetus that enables communication between the mother and baby," says Dr. Shenhav, "but it's very difficult to study directly during pregnancy. Instead, we study echoes of the placenta in other maternal organs, including the eye."

Dr. Shenhav's work aims to generate insights that could inform new clinical guidelines for both prenatal care and lactation—supporting healthier pregnancies, highlighting the benefits of human milk, and ultimately improving long-term health for women and children.

Expanding the Use of Existing Data to Improve Women's Health

Advances in data science are helping researchers address two other key barriers to understanding sex differences: (1) data silos (i.e., data housed in different, unconnected systems) and (2) dark data (i.e., data that once initially collected and analyzed remain dormant, despite containing valuable information for future research).

"Although we often we talk about a data gap in women's health, and that is indeed an issue, it's also true that we have many untapped data sources, albeit imperfect ones, that can help connect the dots and begin to address these data gaps," says Noémie Elhadad, Ph.D., an Associate Professor and Department Chair of Biomedical Informatics at Columbia University. Dr. Elhadad is using AI-based methods to collect new data and analyze existing data concerning several aspects of women's health, including endometriosis.

Noémie Elhadad, Ph.D., Columbia University

Endometriosis occurs when tissue similar to the uterine lining grows outside of the uterus, causing pain and heavy menstrual periods and potentially impairing fertility. Despite affecting up to 1 in 10 women of reproductive age, endometriosis research historically has been underfunded and understudied. As a result, women with endometriosis often must see four to five physicians and wait for an average of four to five years before receiving a diagnosis.[9]

To help reduce women's time to diagnosis, Dr. Elhadad developed a novel algorithm to search for proxy indicators of endometriosis across multiple electronic health records (EHRs) and medical claims datasets. She is now conducting a study at New York Presbyterian Hospital using this algorithm to identify reproductive-age women who may have endometriosis. Women identified as having a high likelihood of endometriosis are provided with referrals to a specialty gynecologist. Dr. Elhadad also provides them with access to a mobile phone app that she developed in 2017 to collect data regarding endometriosis symptoms and self-management strategies.

"In 2017, we did not yet understand that endometriosis is not merely a reproductive condition, but a chronic, systemic condition that is associated with inflammation, fatigue, and pain throughout the body, not just in the pelvic area," says Dr. Elhadad.

Rather than adopt a more traditional approach of surveying women with endometriosis about their symptoms, she developed a phone-based app that could capture contextual data about exercise, diet, and other lifestyle factors and potentially frequent fluctuations in symptoms. She then used AI-based methods to sift through the resulting rich contextual data. This research found that some women with endometriosis experience tinnitus (ringing in the ears) and difficulty urinating.[10] These types of symptoms seldom appear in medical charts, because doctors rarely ask about them, she notes. She is now conducting further analyses to develop personalized self-management strategies for women with endometriosis.

Overcoming Challenges Related to Confidentiality and Merging Data Across Sources

Although combining disparate sources of data can help researchers create population representative datasets and build sufficiently large samples for studying differences in health outcomes by sex and within hard-to-reach subpopulations, it can also raise challenges regarding privacy, confidentiality, and informed consent.

Raquel Hill, Ph.D., an Associate Professor of Computer Science at Spelman College, is developing policies that, in combination with advances in computer hardware and software, would enable researchers to aggregate data from multiple sources within a trusted environment without compromising individual privacy or data confidentiality.

Raquel Hill, Ph.D., Spelman College

This trusted environment would enable analysis of aggregate data without enabling unauthorized access to the data. Accomplishing this type of confidential computation requires (1) certified software to perform the analyses and (2) a trusted hardware environment that prevents unauthorized access, explains Dr. Hill. Computer central processing units (CPUs) can now meet these requirements by creating confidential protected areas of memory, called *enclaves*, within a computer's random access memory (RAM). These enclaves are sectioned off and protected from the rest of the operating system while the CPU performs computations on confidential data.

This new technology builds on cryptographic co-processors and trusted platform modules (TPMs) that were originally designed to allow for confidential data analysis, says Dr. Hill. However, cryptographic co-processors were limited in the types of analysis they enabled, whereas the enclave-based approach enables much greater flexibility. TPMs relied on a software co-root of trust, which introduced more vulnerabilities in the computational workflow, while the secure enclave approach ensures that only the CPU can access confidential data.

Since 1938, FDA has required testing in animal models of all medications for safety and scientific validity prior to testing in humans. Unfortunately, animal models do not always accurately reflect drug metabolism or safety in humans. Early-stage clinical trials in humans fail more often than not, because of species-specific differences in metabolism, biochemical pathways, immune responses, and other differences, says Danilo Tagle, Ph.D., Director of the Office of Special Initiatives at the National Center for Advancing Translational Sciences and Senior Scientific Advisor for Regulatory Science and Translational Research. An estimated 60% of human Phase I and II trials fail for lack of efficacy, and 30% fail because of toxicity.[11]

Danilo Tagle, National Center for Advancing Translational Sciences, NIH

In 2024, the NIH Common Fund launched the Complement in Animal Research in Experimentation (Complement-ARIE) program to reduce the reliance on animal models for preclinical testing by expanding the use of human-based new approach methodologies (NAMs), including:

- **Computational models** that simulate human biological pathways and systems, and drug metabolism and interactions;
- **Advanced cell-free in chemico assays** that assess how drugs and chemicals interact with other biological molecules; and
- **Microphysiological (organs-on-a-chip) systems** that use micro-engineered devices containing human cells to reproduce the structure and function of various human tissues.

Complement-ARIE will focus on the areas of greatest scientific needs, including better understanding the impacts of sex as a biological variable and improving research on pregnancy and development, says Dr. Tagle. Animal models often fail to recapitulate key aspects of women's health. Laboratory mice, for example, do not naturally menstruate and do not experience menopause or endometriosis.[12,13]

NAMs can help address this lack of suitable animal models. For example, researchers are now using NAMs such as organs-on-a-chip to study several women-specific conditions, including endometriosis, polycystic ovarian syndrome, ovarian cancer, and uterine cancer.[14,15,16]

Because the data needs for this initiative are enormous, Complement-ARIE will establish a data hub to house, annotate, and ensure interoperability of the datasets arising from this effort, says Dr. Tagle. The resulting publicly accessible database will adhere to the FAIR principles of Findability, Accessibility, Interoperability, and Reusability.

NIH is also creating a public-private partnership, including collaborations with FDA, the Environmental Protection Agency, and several international government entities, to develop a validation framework for using NAM-generated data to support advancing products into human clinical trials, adds Dr. Tagle.

SCIENTIST SPOTLIGHT

Heather Desaire, Ph.D., is a University Distinguished Professor of Chemistry at the University of Kansas. Her research focuses on the use of mass spectrometry to study a range of molecules, including glycoproteins and lipids. Dr. Desaire received her doctorate in chemistry from the University of California, Berkeley. She has received a William T. Kemper Award for Excellence in Teaching, an American Society for Mass Spectrometry Research Award, and a National Science Foundation Career Award. She currently serves as the Director for a Center of Biomedical Research Excellence at the University of Kansas, which was established to research the use of big data to improve women's health.

Heather Desaire, Ph.D., University of Kansas

What are your primary areas of research, and how has your research focus changed over time?

My training was in bioanalytical mass spectrometry, and when I first started my independent career, I became really interested using mass spectrometry to analyze the glycosylation on HIV vaccine candidates. To facilitate those studies, I collaborated heavily with software developers, since the mass spectrometry datasets we analyzed were very large and difficult to assign manually. Then, about seven years ago, I became interested in machine learning. So, I reserved all the time I could and didn't just learn about machine learning, but how to do it myself. Having that practitioner's knowledge has been key to seeing ways to leverage these tools in a space that I am familiar with (bioanalytical mass spectrometry). Now my research laboratory focuses most of its efforts working at the intersection of mass spectrometry (which provides the data) and machine learning, (which provides the analytics) to identify biomarkers of various diseases.

You serve as the Principal Investigator for the Administrative and Professional Development Core for the University of Kansas COBRE grant. What are the aims of this core program?

COBRE grants aim to build research infrastructure and a pipeline of NIH-funded researchers in states such as Kansas that are underrepresented in NIH's research portfolio. Our Center's primary goal is talent development, providing early-stage investigators (ESIs) and new investigators with the resources and skills that they need to successfully compete for external funding and sustain successful, productive research careers. We have multiple strategies to achieve these goals, including a formal mentoring program, skills training in grant writing, research support in data science, and establishing a community of researchers who are energized by the goal of advancing women's health research but who approach that challenge in a variety of ways.

Why is cross-disciplinary research on women's health so important? What are some examples of successful collaborations you have seen stem from the core program?

An example from our first center meeting springs to mind. One of our researchers, Amber Watts, who is studying the impact of exercise on menopause symptoms, was presenting. After she introduced her project, a somewhat off-topic conversation started about why some racial groups experience a higher incidence of hot flashes than others. Our natural scientists and social scientists proposed several divergent hypotheses. Some thought the underlying difference may be related to biochemical aspects, such as dietary differences resulting in different levels of inflammation; other theories were more social/psychological, that maybe women experience the same physical symptoms, but some groups are more likely to identify them as a problem. None of us knew whether the answer was already known, this was just a casual conversation, but it highlighted how a person's background and training can influence idea generation. We need this diversity of voices and ideas not only to advance women's health, but also to solve many problems in biomedicine.

What are some examples of how the core program is leveraging large biomedical datasets to improve women's health?

I could give you so many examples here. One study we are supporting, which I think has a lot of potential, is on detecting post-traumatic stress disorder (PTSD), which is twice as common in women as men. Jeff Girard and his team are using AI and computer vision to assess head movements and vocal pitch changes, and those changes are showing the potential to discriminate between someone suffering from PTSD and someone who also underwent a traumatic even but is not suffering PTSD. The disease currently requires significant clinical resources to effectively diagnose. This research could pave the way for an AI-assisted tool that could eventually facilitate diagnoses, saving cost and getting treatment to the people who need it more quickly.

What are some of the most persistent or key challenges in leveraging data science to improve women's health and how might they be addressed?

One issue that compels me is that women receive only about 20% of undergraduate computer science degrees in the United States, so data science is a male-dominated field. Yet women's health research is, understandably, a topic that typically energizes women more than men. Thus, the challenge is to figure out how to make sure those valuable skills and techniques in data science get applied to problems central to women's health. One obvious solution to this problem is fostering cross-disciplinary collaborations, where people with different expertise come

together. We certainly work to foster those interactions in our center. But another route toward the same goal, which might prove just as effective or even more effective, is to help people, faculty, students, postdocs, expand their knowledge, so a data scientist, with the right mentoring, could lead a project that focuses on sex disparities in sepsis treatment, for example. Or a faculty member with a background in ovarian cancer could develop a knowledge base in data science and effectively leverage those tools in her research. Some may question the feasibility of this second path, but I can point to myself as an example of the model working well. Researchers are knowledge workers, so developing new knowledge and skills is not only essential for success, but also a highly enjoyable aspect of the job.

What are some of your proudest accomplishments?
I think the thing that I am most proud of is my consistent modeling of a healthy work-life balance to my research group, colleagues, and community. Being a professor at a research institution, it's easy to feel like you need to work nonstop. But throughout the years I have found ways to advance research, keep my grants funded, while also prioritizing family time. It takes work to pull that off—it's a constant effort of "threading the needle," knowing what to say no to, knowing when "good enough is good enough" and when you need to go all out and give something 120% of your energy. I have homeschooled my daughter for the last nine years, while also working full time at this intense job. And my lab has a strong culture of productivity—of working hard when we're working, but not working all the time. Seeing my lab group becoming well equipped to handle the pressures of the world, being effective at their jobs, while also being happy because they have time for things other than their job, I think that brings me the most joy and pride.

What are the most significant barriers you have faced in your career and how have you addressed them?
I would not say that I have ever hit any single roadblock that prevented me from advancing my career. Instead, I think what I, and what research suggests a lot of other women academics in science, technology, engineering, and mathematics (STEM) face, is the "death by a thousand cuts" problem. Studies find that women get asked more frequently to serve in caregiving roles that take a lot of time but count for very little professionally, including academic advising, mentoring, helping other faculty, doing committee work, writing recommendation letters, being on dissertation committees, etc. I don't think this is done intentionally; rather, I think it happens because women are perceived to be more likely to say yes to helping out, and when a job needs to be done, the person looking to get the work done just wants to find someone to do it. Nevertheless, the outcome is often that women get asked a lot to do these kinds of things, not because it is their fair share of work, but because they are perceived as being more willing to do it. Likewise, studies show that men are more frequently put up for awards, invited for certain types of prestigious speaking engagements, and more likely to be groomed for leadership positions. So, I try to navigate these potential challenges by being careful about what I agree to take on, and by keeping my eyes open for opportunities that nobody suggested I consider.

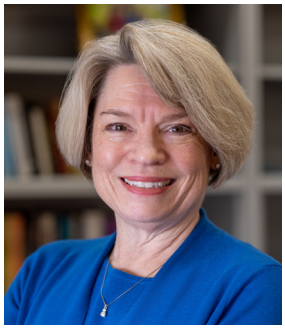
For example, when I was an Assistant Professor, my department suggested that I chair the committee for our department's next tenure track hire. This is one of the hardest service loads in our department, and I knew it would really cut down on the other things I wanted to do that year. So, I talked to my chair about it and made the case that this was not a reasonable ask for someone pre-tenure, pointing out that no other searches had been chaired by assistant professors since my arrival. As a result, somebody else was made chair of the search. This experience not only saved me considerable time to focus on my research, but also initiated a long process of establishing that I keep an eye on equitable distribution of workloads. I will do my share, for sure, but I will defend my time when the ask becomes unequitable.

What advice would you give to fledgling scientists or students considering a career in biomedical research?
A couple of things stand out. First, always invest in yourself. Learn new things that interest you; stay on top of new technology. Look for growth opportunities, both professional advances and expanding your domain-level expertise. The world is changing rapidly, and most people will have to be flexible and make changes in their careers, sometimes big changes. Knowing that will come, and that you can prepare for it by investing in yourself, is critical.

The other bit of advice is to think holistically about how your career fits into your life. (Although many young people starting out do a better job of doing this than people of my generation did, it is still important advice.) On that topic, people pursuing academic careers need to think about if and when they want to have kids and how to make the timing work. There is never going to be a "really good" time to have kids, and sometimes it is a matter of realizing that this "not great time" is workable. For example, one of my graduate students completed her PhD in less than four years this spring. She won our department's top research honor, and, on top of all that, she had a baby in February. I'm so proud of her. She is an example of someone who, with planning and determination, is successfully navigating the demands of career and family.

Progress for Women in Biomedical Careers: A Conversation with Donna K. Ginther

We spoke with Donna K. Ginther, Ph.D., Roy A. Roberts & Regents Distinguished Professor of Economics and Director of the Institute for Policy & Social Research at the University of



Donna K. Ginther, Ph.D., University of Kansas

Kansas and a Research Associate at the National Bureau of Economic Research, about her research on women's progress in fields related to science, technology, engineering, and mathematics (STEM).

What has driven your interest in studying women's progress in STEM-based fields?
Throughout my career, I have drawn on different data sources to develop a picture of what is happening in the scientific workforce and to understand how scientific careers evolve.

People who study labor economics typically know who employs different groups of workers and what they earn, but we seldom know what they produce. But the beauty of studying the scientific workforce is we can see what is produced. We can see the publications, the grants, and so we can observe productivity, and that has served as the guiding principle for my work, linking those measures of productivity to career outcomes. For example, we can observe that women do not publish as many papers as men, on average, but they tend to produce higher impact papers.

What has your research shown about women's progress over the past couple of decades in these fields?
Women's progress varies by field. In biomedicine, women are doing relatively well, compared to women in more math-intensive careers. Women currently earn about half of the degrees in biomedicine. The number of women entering academia drops around the postdoctoral period, but once women become professors, they are relatively successful. They are as successful as men at being promoted to Associate Professor and in obtaining NIH grants, and more successful at getting NSF grants.

In other fields, however, women's progress remains stalled. Women continue to be underrepresented in economics. Women Assistant Professors in economics are less likely to be promoted to Associate Professors and Full Professors than are men, even controlling for publications.

As an economist, I view each academic field as a separate labor market. For example, there is currently a high demand for people with training in computational biology, so people with that background have more job opportunities than someone with training in wet laboratory research.

What does the picture look like for women in math-intensive STEM fields?
Mathematical skills serve as a gatekeeper for many STEM-based careers. Individuals who do not take the requisite mathematical courses in high school cannot pursue math-intensive degrees in college. Gaps between men and women in mathematics begin as early as kindergarten, when girls may learn from their parents and their teachers that girls are not expected to do as well in mathematics as boys.

What are some of the reasons that, while women are receiving biomedical degrees at the same rate as men, they are pursuing biomedical academic careers less frequently?
First, the number of academic careers is flat or falling in most fields, and many people have to complete postdoctoral training prior to obtaining an academic position. So, one contributor may be that women do not want to postpone their eventual career and research independence for such a long period of time. The postdoctoral period coincides with the biological clock for women, which creates many challenges. The pay for postdoctoral fellows is low, and the chance of obtaining an academic job is low, so it can seem very risky to continue on the academic path when trying to balance having a career and having a family. Childcare is also very expensive, and even some grants that offer support for childcare do not fully cover the costs. In addition, some postdoctoral fellowships do not provide health insurance.

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NOTEWORTHY

Novel AI-Based Breast Cancer Risk Assessment Tool Receives FDA Clearance

Clairity Breast, a novel AI-based tool for assessing breast cancer risk from mammograms, received de novo clearance from FDA in early June.

Clairity Breast was developed by Clairity, a biotechnology startup founded in 2020 by Connie Lehman, M.D., a Professor of Radiology at Harvard Medical School and a breast imaging specialist at Massachusetts General Hospital.

Unlike current breast cancer risk assessments, which calculate risk based on family history, age, and life course factors such as age of first birth, Clairity Breast analyzes screening mammograms, using AI to scan for subtle, not detectable by humans changes to breast tissue that are associated with increased risk for breast cancer. The tool then delivers a five-year breast cancer risk estimate to providers.

New approaches to determining breast cancer risk are critical for identifying those in need of additional and/or more frequent screenings, such as by magnetic resonance imaging (MRI), in order to detect breast cancer in the early stages, when it is most treatable.

NOTEWORTHY

Approximately 370,000 women living in the United States are diagnosed with breast cancer each year, and 85% of these women have no family history of the disease.

Office of Autoimmune Disease Research in ORWH Launches NIH-Wide Strategic Plan for Autoimmune Disease Research

In July 2025, the Office of Autoimmune Disease Research in ORWH launched the *NIH-Wide Strategic Plan for Autoimmune Disease Research for Fiscal Years 2026–2030*. The plan aims to amplify autoimmune disease research being conducted across NIH and to promote innovation and collaboration on autoimmune disease research. The full plan is available online.

IN THE JOURNALS

Novel Estrogen Receptor Degrader Prolongs Progression-Free Survival in Women with Advanced Breast Cancer

(Original research by F-C Bidard, et al., New England Journal of Medicine, DOI: 10.1056/NEJMoa2502929)

Treatment with camizestrant, a novel therapeutic agent, can significantly extend progression-free survival in women with advanced breast cancer who have estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative tumors, finds a Phase III randomized clinical trial published in the June 2025 issue of the *New England Journal of Medicine*.[17]

First-line, standard of care treatment for women with these advanced tumors consists of an aromatase inhibitor, to block estrogen production, given in combination with cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor. Approximately 40% of these women will develop a mutation in the gene that encodes estrogen receptor 1 (*ESR1*). These mutations enable estrogen-independent activation of estrogen receptors, thereby creating tumor resistance to aromatase inhibitors. *ESR1* mutations result in disease progression at a median of six months from their first detection in the blood.

Camizestrant is a novel next-generation therapeutic that selectively degrades estrogen-receptors and acts as a complete estrogen receptor antagonist. Tumors that are resistant to aromatase inhibitors may therefore remain susceptible to camizestrant.

To test this hypothesis, François-Clément Bidard, M.D., Ph.D. (Institut Curie Paris and INSERM Centre d'Investigation Clinique) and colleagues randomly assigned women with advanced ER-positive, HER2-negative breast cancer who developed *ESR1* mutations to either to continue to receive an aromatase inhibitor in combination with a CDK4/6 inhibitor, or to receive camizestrant in combination with a CDK4/6 inhibitor.[17]

Women who received camizestrant with a CDK4/6 inhibitor experienced longer progression-free survival (median 16 months) than women who continued to receive an aromatase inhibitor (median 9.2 months).[17] Strikingly, women receiving camizestrant also experienced a more than three-fold longer period of time before reporting a decline in their global health status and quality of life (median of 23.0 months for those receiving camizestrant versus a median of 6.4 months for those receiving an aromatase inhibitor).[17]

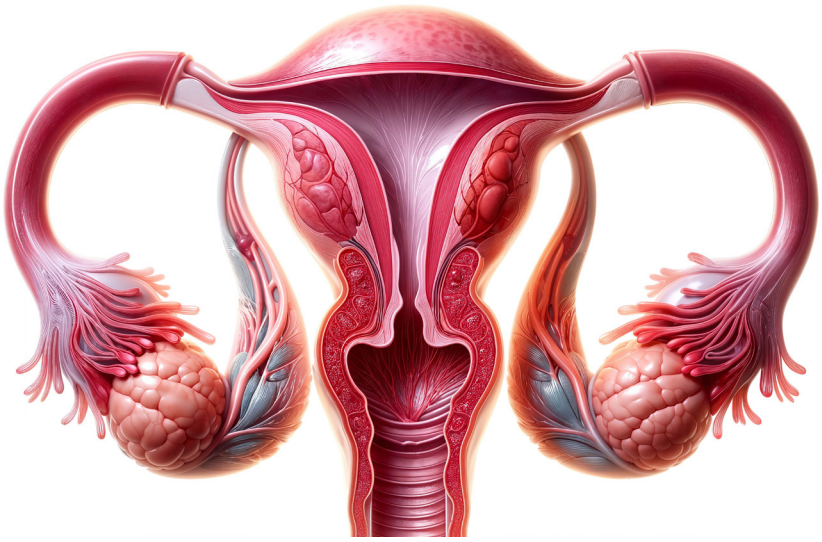
These results suggest a new approach to treating women with advanced breast cancer, highlighting the therapeutic value of switching to camizestrant for women who develop *ESR1* mutations. An ongoing Phase III trial is exploring the use of camizestrant as a first-line therapeutic, and future research may explore the effectiveness of camizestrant in combination with different CDK4/6 inhibitors.

Microenvironmental Changes Drive the Development of Ovarian Cancer in the Fallopian Tubes

(Original research by T. Kader and C.B. Hug et al., 2025. Cancer Discovery. DOI: 10.1158/2159-8290.CD-24-1366 and G.L. Garcia and T. Orellana et al., 2025. Cancer Discovery. DOI: 10.1158/2159-8290.CD-24-0805)

A series of studies shed new light on the origins of high-grade serous ovarian cancer (HGSOC), the most common ovarian cancer subtype, raising hopes for improving early detection and treatment of this highly aggressive cancer.

HGSOC causes few if any symptoms in its early stages. Most cases are diagnosed at an advanced stage of disease, when the cancer has spread beyond the ovary and treatment options are limited. The five-year survival rate for HGSOC that has spread to other local tissues is approximately 75%; for HGSOC that has spread to other organs, it is only 30%.[18] These rates have not improved substantially for decades.[18]



Poor understanding of how ovarian cancer develops has hindered early detection and treatment. Until recently, HGSOC was thought to develop from the ovarian surface epithelium. We now know, however, that the majority of HGSOC cases begin in the fallopian tubes, originating from precursor lesions derived from fallopian epithelial cells (FTE).[19]

"For years, pathologists overlooked small clusters of abnormal cells within the fallopian tube. When they noticed them, they dismissed them as rare anomalies rather than recognizing their recurring and meaningful presence. Ultimately, it took the fresh perspective of a graduate student armed with time, curiosity, and an unbiased mindset to see what others had missed."

A series of studies published in the June 2025 issue of *Cancer Discovery* reveal how these precursor lesions interact with surrounding cells and tissues to become cancerous. Tanjina Kader, Ph.D., and Clemens B. Hug, Ph.D. (Harvard Medical School) and colleagues used multi-omics to map the tumor-immune ecosystems during the development and progression of HGSOC.[20] Their analysis showed that the activation of interferon (IFN) signaling and chromosomal instability were critical early events in HGSOC progression; profound shifts in the immune microenvironment accompanied these changes. Early lesions were under active immune surveillance by type 1 conventional dendritic cells, natural killer cells, and tissue-resident memory CD8+ T cells.[20] As the lesions progressed, the presence of these immune cells significantly declined, and increases were seen in activated cytotoxic T lymphocytes.[20] With further progression, these activated cytotoxic T lymphocytes became increasingly nonfunctional and excluded from the microenvironment.[20] Drawing on these results, Kader, Hug, and colleagues postulate that early immune surveillance initially inhibits cancer development, but as the precursor lesions progress, they initiate changes such as upregulation of HLA-E that suppress immune surveillance.[20]

Geyon L. Garcia (University of Pittsburgh) and Taylor Orellana, M.D., (Hollings Cancer Center) and colleagues demonstrate that a type of epigenetically altered stromal cell found in the fallopian tubes, which they term high-risk mesenchymal stromal/stem cell (hrMSC), help transform FTE cells into serous tubal intraepithelial carcinomas (STIC) precursor lesions and HGSOC, by promoting DNA damage in FTE cells while fostering FTE cell survival.[21]

In an accompanying commentary, Maria Sol Recouvreux, Ph.D., and Sandra Orsulic, Ph.D., (University of California, Los Angeles) note that these findings suggest multiple potential pathways for intervention, such as (1) the development of drugs that target and disrupt tumor-promoting signaling between hrMSC and precursor lesions, (2) the use of immunotherapies to enhance early immune surveillance, and (3) the development of drugs that target or reverse early epigenetic changes in FTE.[22]

The National Cancer Institute and the U.S. Department of Defense contributed funding for this research.

Psychosis Is Associated with Distinct Sex-Specific Changes in Gene Expression in the Striatum

(Original research by Perez et al., 2025. Translational Psychiatry. DOI: 10.1038/s41398-025-03395-3)

The changes in gene expression in the striatum associated with psychosis appear to differ markedly between men and women, finds a new study of postmortem brain tissue by Megan S. Perez (University of Pittsburgh) and colleagues published in the June 2025 issue of *Translational Psychiatry*.[23]

Psychosis, a mental disorder characterized by disconnection from reality, is a hallmark of schizophrenia and a common symptom of bipolar disorder.[24] Studies estimate that each year anywhere from 15 to 100 people out of every 100,000 develop psychosis.[24] Symptoms of psychosis can include delusions, hallucinations, incoherent rambling, and agitation.[24]

Changes in the striatum, particularly in dopamine signaling, are a critical feature of psychosis.[23] The striatum contains three main subregions: the nucleus accumbens (involved in motivation and goal-directed behavior), the caudate nucleus (involved in anxiety, working memory, and conscious movement), and the putamen (involved in repetitive behavior and motor control).

To understand the changes in gene expression associated with psychosis, Perez and colleagues performed RNA sequencing on total RNA extracted from the nucleus accumbens, caudate, and putamen of 36 deceased individuals with psychosis and 59 unaffected deceased controls.[23]

Overall, individuals with psychosis exhibited changes in the pattern of ciliary-related pathways compared to controls.[23] In controls, ciliary-related gene expression was highest in the caudate, whereas in individuals with psychosis, it was highest in the nucleus accumbens.[23] Cilia are projections found on the surface of cells that help detect stimuli and regulate cell growth, migration, and differentiation.

Perez and colleagues also found several striking sex differences. Women with psychosis exhibited greater expression of genes involved in blood vessel growth and immune- and inflammation-related pathways, whereas men with psychosis exhibited lower expression of several immune-related pathways in the putamen and caudate.[23] Women with psychosis also exhibited lower expression of genes related to cellular respiration in the nucleus accumbens.[23] The expression of more than 600 genes exhibited opposing changes (e.g., upregulation versus downregulation) in men and women with psychosis compared to same-sex controls.[23]

These sex differences in gene expression in the striatum may contribute to known sex differences in the clinical presentation and outcomes associated with psychosis. For example, men tend to have earlier onset of psychosis, more severe "negative symptoms," such as social withdrawal and lack of emotional affect, and worse overall outcomes.[25,26] Future research will confirm these findings and examine how these sex differences may contribute to responses to medications and other clinical differences.

Multiple NIH Institutes and Centers funded this research.

Metabolome Profiling Discovers Multiple Sex Differences in Men and Women with Mild Cognitive Impairment

(Original research by R.D. Escarcega et al., 2025, Neurobiology of Disease, DOI:10.1016/j.nbd.2024.106747)

Several of the metabolic changes in blood associated with mild cognitive impairment (MCI) differ by sex, according to new research published in the November 2024 of *Neurobiology of Disease*.

IN THE JOURNALS

MCI is characterized by mild memory or thinking problems, and although it is less severe than dementia, it substantially increases the risk for developing AD and other forms of dementia. Changes in metabolism are associated with the risk for progressing from MCI to AD. Women are disproportionately affected by AD and have approximately double the lifetime risk for developing AD as men, for reasons that are not well understood.[6]

To assess how the metabolic changes involved in MCI may differ by sex, lead author, Rocio Diaz Escarcega, Ph.D., (McGovern Medical School at the University of Texas) and colleagues collected and analyzed metabolites in blood samples from 20 women and 20 men with MCI and 20 male and 2 female age-, sex-, and race-matched controls.[27] They discovered several sex differences in metabolite changes associated with MCI, the most pronounced of which were in lipid metabolism pathways.[27] Several lipid metabolites were higher in women with MCI than in men with MCI, including phosphatidyl choline lipids, lysophospholipids, long-chain fatty acids, and monoacylglycerols.[27] Notably, two bioactive monacylglycerols, 1-palmitoleoylglycerol and 1-arachidonoylglycerol, were higher in female than male participants with MCI but did not differ by sex in control participants.[27] Monoacylglycerols, a type of metabolite consisting of a glycerol molecule bound to a fatty acid, help regulate immunity and metabolism.[27]

These findings raise the possibility of identifying and validating sex-specific biomarkers for MCI and AD; they also underscore the importance of understanding sex-differential and sex-specific pathways involved in the development of MCI and AD.

UPCOMING EVENTS

64th Meeting of the Advisory Committee on Research on Women's Health (ACRWH)	October 7, 2025, 9:00 a.m.–4:00 p.m. EDT
Specialized Centers of Research Excellence (SCORE) on Sex Differences 2025 Annual Meeting Keynote and Capstone Addresses	November 3, 2025, 8:00 a.m.–5:00 p.m. EST
Building Interdisciplinary Research Careers in Women's Health (BIRCWH) Annual Meeting	November 4, 2025, 8:00 a.m.–5:00 p.m. EST

FUNDING OPPORTUNITIES

Women's Health Research (NOT-OD-24-079) Submission deadlines vary by awarding Institute, Center, and Office; please see the application and submission information table for more details.

Interventions to expand cancer screening and preventive services to ADVANCE health in populations that experience health disparities (R01, Clinical Trial Required) (PAR-25-098). The next deadline for new applications is October 5, 2025, for renewal/resubmission/revision applications (as allowed) is November 5, 2025, and for new/renewal/resubmission/revision applications (as allowed) related to AIDS is January 7, 2026.

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NIH Office of Research on Women's Health (ORWH)

6707 Democracy Boulevard, Suite 400, Bethesda, MD 20817

Phone: 301-402-1770 | ORWHinfo@mail.nih.gov

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