

INNOVATIONS

► in Women's Health

A QUARTERLY PUBLICATION of Women's Health Research at Yale



With a WHRY grant, Dr. Lauren Sansing (right) is exploring sex differences in response to stroke. Photo courtesy Yale Medicine

Age and Sex Differences in Treating Stroke

Understanding the response of brain cells offers a new treatment approach

One of the most important life-saving tools for someone experiencing a stroke, just might be a microscope. New research shows how the body responds on a cellular level during a common form of stroke, and how that response differs by age and in women and men.

This work may be the first step toward developing a first-of-its kind therapy for the second most common type of stroke, called an intracerebral hemorrhage (ICH), which occurs when a blood vessel in the brain ruptures.

“Early in my medical training, I saw how many patients we were admitting to the hospital with ICH for whom we could primarily offer supportive care.” It was that realization as a medical student that led Lauren Sansing, MD, the Academic Chief of Stroke and Vascular Neurology at Yale Medical School, to focus her research on treatment options for intracerebral hemorrhage. “By the time I finished my neurology rotation, it was pretty clear I had a fire in my belly to learn more about this disease,” Dr. Sansing said.

Continued on page 3...

In This Issue

- 1 Treating Stroke
- 4 Weaving Women's Health into the Medical School Curriculum
- 6 WHRY's Undergraduate Fellows Focused on the Future
- 8 Planned Giving for All
- 9 The Value of Diversity
- 10 Meet WHRY's New Communications Officer
- 11 Improving the Diagnosis of Heart Disease in Women

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Women's Health Research at Yale is tremendously grateful to the members of our Legacy Society who have included WHRY in their estate plans or have made planned gifts through a will or trust.

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Women's Health Research at Yale was founded in 1998 with initial funding from The Patrick and Catherine Weldon Donaghue Medical Research Foundation. Women's Health Research at Yale is a center within Yale School of Medicine. Yale University is a 501(c)(3) nonprofit organization.

Treating Stroke... (Continued from front cover)

In a study funded by Women's Health Research at Yale, Dr. Sansing set out to find the role age and sex differences play, if any, in this type of brain injury. Previous studies have shown that women experience more severe symptoms than men in response to ICH, yet little is known about how the basic biological response of brain cells and the immune system differ in women and men when a vessel ruptures.



Illustration of blood vessel rupture causing an intracerebral hemorrhage.

According to Dr. Sansing, "The main point of this study was to try and figure out, are there age and sex differences that can change the way key brain cells respond that make them either more helpful or more harmful?"

Her lab research focused on two types of cells: microglia and macrophages. Microglia are only found in the brain, while macrophages are found throughout the body. Both are essential in cleaning up damaged cells, including red blood cells from the bleed, and both can trigger an immune response designed to protect the body from disease.

"The first hypothesis [is] that perhaps older patients have worse outcomes because there is an enhanced inflammatory response with age," Dr. Sansing explained. In fact, her study found, as the brain

ages, the number of macrophages responding to a hemorrhage increase, and these cells secrete more chemokines, a protein that recruits greater inflammation in the brain.

However, this response does not change solely with age. Following up on her second hypothesis, that there are differences by sex, Dr. Sansing's research found that women can experience a greater immune response than men, and the sex difference in inflammatory response increases with age. In particular this response is from interferons – proteins also part of the immune system that the body uses to combat infections.

“*This could pave the way for the first clinical trial studying effects based on sex.*”

As Dr. Sansing explains, the presence of these interferons may be significant, especially for women. "They are also associated with conditions, such as mood disorders and depression. It causes me to wonder whether the specific interferon dependent response may make older women more susceptible to post-stroke depression and other cognitive challenges after brain injury."

So, where does this research lead us in the treatment of ICH?

"The first goal in terms of translating this is to test therapies that block these sex dependent

responses and see whether they improve outcomes in the model system. If I block the interferon response in aged females, does that actually make the aged females recover better or is this a bystander response and the real cause of disability is in a different pathway?" she theorized. Such a study could pave the way for the first clinical trial studying differential effects based on sex.

Dr. Sansing's study illustrates that sex differences occur at the molecular level and need to be understood. Moreover, as Dr. Sansing explains, it could be an important moment for the way researchers and drug makers approach biological diversity in clinical trials. "[I] wonder if some [therapies] have failed in clinical trials because we overlooked the biological differences found in age and sex, and certain therapies may need to be age and sex specific." ◀



ABOUT THE INVESTIGATOR

Dr. Lauren Sansing is an Associate Professor of Neurology and the Academic Chief in the Division of Stroke and Vascular Neurology at the Yale School of Medicine. Dr. Sansing's laboratory studies the responses of the immune system after acute brain injuries, such as stroke.



Associate Director for Medical Education in Women's Health, Dr. Kelsey Martin (left) interacts with WHRY undergraduate fellow Kayla Yup (right)
© Anthony DeCarlo

Weaving Women's Health into the Yale Medical School Curriculum

When Kelsey Martin, MD, meets a new patient her first goal is to get to know the person. This means inquiring about an individual's symptoms, medical history, and health behaviors. Also at the top of the list is their sex and gender because we now know these factors affect health and treatment outcomes.

"Medical research historically did not target the health of women beyond reproductive health and, as a consequence, data on women and the influence of sex and gender on health were not available to integrate into medical school teaching," said Carolyn Mazure, PhD, the director of Women's Health Research at Yale. "Now, science is catching up and we have data on women and on how sex and gender affect health and health care

that medical practitioners need to know."

Dr. Martin, as WHRY's new Associate Director for Medical Education in Women's Health, is focused on ensuring that Yale Medical School's year and a half-long preclinical curriculum, which is designed to teach the biology underlying health and disease, integrates women's health data and the role of sex and gender in health into medical education. "The goal is to incorporate key information into the curriculum that will prepare the clinicians and physician-scientists of the future," Dr. Martin said.

The medical school journey for Yale students begins with eight major courses, all have major themes that characterize multiple topics areas. The content to be

covered is extensive. Students explore the physiology and pathology found in every system of the body, and a partial list of topics range from cardiology, pulmonology, and endocrinology

Terminology

Sex: A classification used in the study of human subjects. Generally male or female, it is derived from the chromosomal complement XX for female, XY for male.

Gender: A classification used to refer to a person's self-representation, often influenced by societal expectations or how social institutions respond to their gender presentation.

to genetics, infectious disease, and neuroscience. There is a lot to teach and a lot to learn in a relatively short amount of time. To facilitate the process of integrating data on women and on sex and gender differences, two faculty already teaching within a course become "champions" in women's health – meaning they work with their teaching colleagues to help ensure that content on women's health, and sex and gender differences, is woven into the lectures and lessons.

WHRY's efforts to harmonize sex and gender differences within the already robust curriculum finds solidarity with likeminded efforts to include health data in relation to aging, LGBTQ+, disability, and other important topics. In fact, the concept of weaving new discoveries and data into core teaching is referred to as the "health equity thread." It is one way the medical school and leaders like Jessica Illuzzi, MD, the Deputy Dean for Education, and Michael Schwartz, PhD, the Associate Dean for Curriculum, are ensuring inclusivity.

The commitment is also evident in the medical school's newly created Health Equity Thread Advisory

Group, for which both Drs. Martin and Mazure are invited members. The 15-person group, chaired by Beverley Sheares, MD, and Douglas Shenson, MD, has Yale faculty and students, and New Haven and Connecticut based community members who actively promote health and social justice. The goal of the group is to develop best practices for training physicians to respond to inequities that affect health and disease.

To put this into perspective, surveys of medical schools in the U.S. and Canada have found that coverage of topics in which sex-and-gender-based data exist was lacking. A study of Yale Medical School's pre-clinical curriculum, led by WHRY, found that about a quarter of "teaching sessions raised the topic of sex or gender influences on physiology and pathophysiology or the experience of the patient in the health care environment." (Thande et al, 2019)

"By integrating empirical data as these pertain to sex and gender into our preclinical medical school curriculum, we'll be leading the development of really innovative education," Dr. Martin explained. "We're going to help our students

be leaders in their health care fields, and researchers uncovering new data on women and on sex and gender to help improve everyone's lives. ◀



Meet Dr. Kelsey Martin

Dr. Kelsey Martin is an Assistant Professor in Clinical Medicine (Hematology) at the Yale School of Medicine and an active clinician at the Smilow Cancer Hospital Care Center. Dr. Martin received her medical degree from the Royal College of Surgeons in Dublin, Ireland. She is a member of Yale's Committee on the Status of Women in Medicine, the Women Faculty Forum, and the American Society of Hematology.



Dr. Kelsey Martin discusses the health of women
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WHRY'S Undergraduate Fellows Focus on the Future

Each year, Women's Health Research at Yale mentors undergraduate students who are interested in pursuing a career in medicine and science. Through the WHRY fellowship these interests are infused with an appreciation for the role sex and gender differences have in medicine allowing them to integrate women's health into their academic pursuits.



Gillian Clouser '23

Majors: Molecular, Cellular, and Developmental Biology; Anthropology

Primary WHRY Mentor: Kelsey Martin, MD, Assistant Professor of Clinical Medicine (Hematology)

Project Topic: Clinical Care Career Development

“This fellowship is important to me because I have experienced the lack of knowledge and awareness that people have about how health issues of all kinds differentially affect women and men. I look forward to understanding medicine through observation in an active health care setting and appreciate the opportunity to learn more about women's health as I prepare for the next step in my career.”



Nandini Erodula '23

Major: History of Science, Medicine, and Public Health

Primary WHRY Mentor: Kelsey Martin, MD, Assistant Professor of Clinical Medicine (Hematology)

Project Topic: Medical School Curriculum Development

“I am incredibly excited to be a part of the WHRY Fellowship. This is a wonderful opportunity for me to hone skills that are necessary to conduct interdisciplinary research that bridge the gap in knowledge about conditions that specifically affect women. Through the Fellowship, under the mentorship of Drs. Martin and Mazure, I am researching and gaining greater understanding of how women's health education and sex and gender differences are being integrated into the medical school's curriculum.”



Yeji Lee '24

Majors: Sociology (Health and Society); Pre-Med

Primary WHRY Mentor: Sarah Yip, PhD, Associate Professor of Psychiatry; Sarah Lichenstein, PhD, Assistant Professor of Psychiatry

Project Topic: Connectome Research

“Through the WHRY Fellowship, I hope to bring attention to women's health and advocate for the elimination of inequalities in medicine and science. I hope to be part of the process to challenge a medical system designed by and for men and create a new era of healthcare. That involves gaining a deeper understanding of neurobiology and the effect reproductive hormones have on the neuropathology of drug addiction through my research on sex differences in opioid and cocaine addiction.”



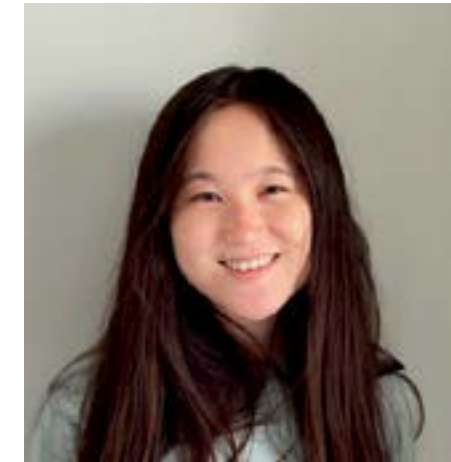
Sophia Silwal '24

Major: Neuroscience

Primary WHRY Mentor: Sarah Yip, PhD, Associate Professor of Psychiatry; Sarah Lichenstein, PhD, Assistant Professor of Psychiatry

Project Topic: Connectome Research

“The WHRY fellowship offers a great opportunity to investigate sex differences in all aspects of science and medicine. I am excited to learn from the experiences of my mentors and fellow students while also contributing to the discussion on sociopolitical and economic issues affecting science and medicine. I am excited to contribute meaningfully to the research in Dr. Sarah Yip's neuropharmacology lab, which seeks to explain the neural substrates that underly sex differences in impulsivity associated with addiction.”



Christina Lee '25

Major: Neuroscience

Primary WHRY Mentor: Marc Potenza, PhD, MD, Professor of Psychiatry, in the Child Study Center and of Neuroscience; Director, Center of Excellence in Gambling Research; Director, Yale Program for Research on Impulsivity and Impulse Control Disorders; Director, WHRY Women and Addictive Disorders Care

Project Topic: Addiction Research

“I am eager to learn about women's health in research, as well as gain a stronger understanding of how public health initiatives can use research to improve health outcomes for women. The effect of prenatal cocaine exposure on the brain is not fully understood, which can affect treatment options. To aid in changing that, I am working with Dr. Potenza through the WHRY fellowship to investigate gender-related differences in addiction and behavioral health.”



Kayla Yup '25

Majors: Molecular, Cellular, and Developmental Biology; History of Science, Medicine, and Public Health (Science Journalism)

Primary WHRY Mentor: Clare Flannery, MD, Associate Professor of Obstetrics, Gynecology, and Reproductive Sciences

Project Topic: Endocrinology Research

“As an aspiring science journalist, the WHRY fellowship is revealing to me how journalism and research should function as public services to advance collective awareness of women's health. I am thankful for this opportunity to interrogate sex/gender differences in science and medicine, including through my research on the role a high-fat diet has on reproduction. I am grateful to work with a community of researchers and clinicians at the forefront of disrupting the male-centric lens on research.”

Planned giving for all

By Daphne Foreman

Full disclosure, WHRY did not solicit this article: I initiated it. My presence as one of four members – so far – of the WHRY Legacy Society qualifies me to address this topic. My planned gift is in memory of my mother, Hilda, whose congestive heart failure I learned of seven days before she died. Symptoms were missed for months, if not years.

My view of planned giving is different from how charities and financial advisors often characterize it. The general assumption is that planned giving applies only to those with plenty of discretionary resources when, in fact, it's a great tool for anyone with a commitment to help a cause.

“

It's a great tool for anyone with a commitment to help a cause.

”

Traditional appeals for planned giving focus almost exclusively on

high-net-worth individuals – those for whom tax liability planning is essential. Strategic use of charitable gift annuities, charitable remainder trusts, and appreciated securities can help to manage capital gains taxes, ensure income keeps pace with inflation, and reduce estate tax liability. Yet, while these are important benefits, this sole perspective misses the passion behind the gift: the desire to benefit future generations.

My perspective is that planned giving can apply to all of us. So long as you are not insolvent, you have an estate. Which means you can plan a legacy.

Consider what you include in your will. Who or what are the beneficiaries of your life insurance policies or qualified retirement plan balances? My legacy gift to WHRY derives from permanent life insurance I sold to myself while working as a financial advisor, plus coverage my employer provides beyond what I “need.”

Appealing to any donor, including the midrange or smaller donor, isn't about reducing taxes. It's about love and wanting to change the world, which brings us back to my mom.

Hilda's income taxes were audited twice: both times because my parents' charitable contributions seemed out of proportion to their income. Now that's a philanthropist!

Smaller and mid-sized gifts can be powerful – especially when they're planned. Won't you join me? ◀



ABOUT THE AUTHOR

Daphne Foreman spent the 1980s at Yale: earning two master's degrees, from the School of Music and the School of Management. She also worked in the office of Athletic Director, Frank Ryan.

The Value of Diversity When Striving for Excellence



Dr. Darin Latimore (left) discusses diversity, equity, inclusion, and a sense of belonging at the Yale School of Medicine with Chenee Gallaher (right), Assistant Director of DEI for the School of the Environment.

What is diversity about?

Darin Latimore, MD, the medical school's Chief Diversity Officer and Deputy Dean for Diversity and Inclusion would say, “Excellence.”

WHRY's Council of community-based advisors recently spoke with Dr. Latimore about the Yale School of Medicine's plan to advance diversity, equity, inclusion, and a sense of belonging (DEIB). The Council's own DEIB Committee was eager to learn about the school's plan as WHRY initiates listening sessions on DEIB with leaders in women's health, health care and equity from inside academia and across the region.

WHRY's DEIB efforts and those of the medical school run in parallel to ensure women are recognized, the health of all women is studied, and sex and gender differences between and among women and men are targets of investigation. Our shared commitment to DEIB also

includes providing new knowledge of practical benefit so that health and health care is advanced for all communities.

Among the medical school's goals is recruiting and retaining an increasingly diverse faculty and student population while also initiating new programs that will ensure lasting change within the academic organization.

This work will undoubtedly open doors for women and minorities in medicine and academia. For example, changes include working with recruitment firms that have demonstrated success in attracting women and other underrepresented groups in medicine and science, building stronger relationships with Historically Black Colleges and Universities and Hispanic-serving institutions, and ensuring support for the immediate pipeline of residents and fellows.

Dr. Latimore stated, “The literature is very clear that diverse groups make better, more productive organizations,” and “diversity is about excellence.”

Advancing DEIB, while recognizing those who champion its ideals, is beneficial to the medical school and its research centers. In doing so, we can ensure women, and other underrepresented groups, play a pivotal role in transcending the current limits of science and medicine. ◀



Dr. Latimore highlighted elements of the medical school's strategic plan to illustrate how the school is building organizational excellence through DEIB.

How Can I Make a Legacy Gift?

Just as you would name a loved one, you can make WHRY a beneficiary of:



Will or Living Trust



Life Insurance



401K/IRA

Meet WHRY's New Communications Officer By Amanda Steffen

Breaking news! Women's Health Research at Yale has a new communications officer, and I am thrilled to become part of WHRY.

I have always been interested in writing and the nature of communication, and avidly pursued college degrees in journalism as well as telecommunications, which considers how to optimize the use of media. Over the last decade as a local news producer, most recently at NBC Connecticut, I enjoyed providing news through the spoken word and visuals. Yet perhaps my greatest joy was creating a new show – News at 7 – which was designed to examine the “why” behind the headlines, address what the community needs to know about how an event came to be, and what to do about it. As Dr. Mazure said, “This sounds a lot like what we do at WHRY.”

And it is. One of the center's five initiatives is to communicate. Every day for years our reporting informed audiences of what was happening in the world around them. Now in this new role, I am positioned and pleased to continue this work as it relates to advancing the health of women, understanding sex and gender

differences in health, and bringing health information of practical benefit to all.

For example, while reporting on the increased national use of opioid overdose deaths, it became clear that a crisis was looming and, of note, the rate of such deaths was increasing faster for women than men. Now, based on WHRY's work, I know that women are more likely than men to be prescribed opioids for a variety of conditions, usually pain syndromes. However, when compared to men who experience pain, women are still more likely to receive opioids and are more likely to become addicted after exposure to opioids. This new information allows me to explain at least part of the “why” about overdose deaths in women, as well as how sex and gender influence risk, outcomes, and how treatment interventions need to be developed to negotiate this continuing epidemic.

It also opens the door to thinking about how the opioid drug settlement funds should be spent. Last year, drug distributors and a manufacturer reached a multi-billion dollar settlement to end thousands of lawsuits over the way opioids were marketed and



the claim these companies misled doctors and patients about the addictive nature of opioids. As the first payments from that settlement arrive, based on the data indicating that these drugs affect women and men differently, it seems critical that states consider funding research on the sex and gender differences surrounding addiction.

As health care providers move forward with their life-saving care and investigators with their programs of research, WHRY is committed to research resulting in equitable health care. At its core, this type of public service is true of journalism as well, and I look forward to strengthening the partnership between science and reporting that can benefit us all. ◀

The Importance of Improving the Diagnosis of Heart Disease in Women



When women seek care for a possible heart attack, the standard is to test for an obstruction in the arteries leading to the heart. This test, however, was never designed to diagnose another cause of heart attack, which affects a greater number of women than men. It is known as microvascular disease and instead of an obstruction blocking blood flow, small vessels constrict or spasm which prevents adequate blood flow to the heart.

A WHRY-funded study made possible by the Wendy U. and Thomas C. Naratil Pioneer Award is changing the ways we diagnose, treat, and follow women experiencing heart-attack symptoms. Thanks to this grant, Dr. Samit Shah has demonstrated the effectiveness of expanding the standard angiogram to find this small vessel disease. The result is a more accurate diagnosis, fewer repeat hospitalizations, and better care.

The lasting benefits of the study's findings are not limited to testing and treatment. As part of the study, researchers are following up with women and have found that those who were given more accurate information regarding their symptoms reported an increased sense of well-being.

Here, a greater understanding of what is happening to our physical health, combined with clinical and community interventions, leads to

opportunities to improve mental health.

Foundational to all WHRY initiatives is a commitment to health equity, a world in which research and clinical practice provide the health information and, ultimately, the health care we need.

WHRY seeks you as a partner in this critical work. With your support, we can continue to discover and better understand the ways in which women and men differ in order to ensure that research, testing and treatment serves all. ◀

With my appreciation,

Barbara

Barbara M. Riley
Philanthropy Chair

NEWS YOU NEED TO KNOW

- States have received their first payment from the \$26 billion Opioid Settlement, which is the largest legal settlement since the Tobacco Settlement in 1998.
- Under the terms of the settlement, payments will be distributed over 18 years to states based on the severity of the crisis in each state. Johnson & Johnson must also increase transparency about their drugs by sharing clinical trial data.
- At least 16 states say they will consider funding research on non-opioid treatments for pain and health provider education on addiction risk factors. Nearly all states have expressed a need to pay special attention to pregnant and parenting women.

Hot off the Presses

A new book *Taking Care of You: The Empowered Women's Guide to Better Health* edited by Mary O'Connor, MD, and Kanwal Haq, MS, provides a comprehensive resource guide with chapters written by leading physicians and health experts from across the country. WHRY's Director, Carolyn Mazure, PhD, contributed a chapter which focuses on women and medical research. These are excerpts from Dr. Mazure's chapter.

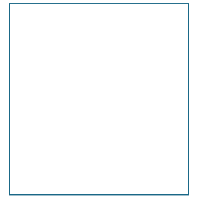
“I am often asked, ‘How could this happen in science -that women would be left out?’ My answer is that science is embedded in our culture and deeply influenced by societal views ... policies designed to protect women do not account for all of the lack of focus on studying women's health.”

“Reflecting on how recently women began to be studied, we can appreciate that we are in the infancy of learning about the health of women and have only touched the surface of learning about differences among women.”



Women's Health Research at Yale

► Better science, better lives ► ►



Women's Health Research at Yale is changing the landscape of medical research and practice by ensuring the study of women and examining health differences between and among women and men to improve the lives of everyone.

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What's Inside:



01 Age and Sex Differences in Treating Stroke

06 WHRY's Undergraduate Fellows Focus on the Future

04 Weaving Women's Health into the Medical School Curriculum

08 Planned Giving for All

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