



September 15, 2021

Janine Austin Clayton, M.D., FARVO
Director, NIH Office of Research on Women's Health (ORWH)
Associate Director for Research on Women's Health, NIH
6707 Democracy Boulevard Suite 400
Bethesda, MD 20817

Re: ORWH research efforts and priorities in preparation for the October 2021 Women's Health Consensus Conference

Dear Dr. Clayton:

Thank you for the opportunity to comment on NIH ORWH research efforts related to women's health, specifically, rising maternal morbidity and mortality rates, increasing rates of chronic debilitating conditions in women, and stagnant gynecological cancer survival rates, as you prepare for the October 2021 Women's Health Consensus Conference (WHCC). We commend the efforts of the ORWH to address these issues and encourage you to explore all gaps in women's health and advance more investment in research to bring new innovations to market meeting the needs of women across the lifespan.

The Women's Health Innovation Coalition (WHIC) is a group of innovators, investors, clinicians, analysts, and executives with the shared goal of advancing innovation in women's health. We source innovative solutions to address unmet needs in diseases, conditions, and indications that exclusively, predominantly, or differently impact the health of women. Through collaborative advocacy and policy efforts, we are working to drive initiatives that demonstrate women's health is not a niche market and to promote greater gender-relevant data transparency and public-private financial investment in R&D in women's health to spur innovation and better health outcomes.

We have identified eight areas of health that solely, predominantly, or differently impact women, requiring further government research investment and better education and awareness among patients and clinicians in order to advance scientific understanding and medical innovations:

- Cardiovascular Health
- Autoimmune and Immunological Diseases
- Oncology
- Aging and Bone Health
- Gynecological and Sexual Health

- Reproductive Health
- Cognitive and Brain Health
- Adverse Drug Events

Cardiovascular Health

Biological differences between females and males affect virtually every aspect of medicine and biomedical research, as women and men experience different biological reactions to health conditions, particularly in cardiovascular disease, Alzheimer’s disease, cancers, and mental health conditions.¹ Cardiovascular disease, in particular, affects one in sixteen women over the age of 20, is responsible for nearly one in five deaths annually for women, and women 55 and under are twice as likely to die from a heart attack than men.² Furthermore, women are seven times more likely to be misdiagnosed and discharged in the middle of a heart attack than men, as men and women present with different symptoms during cardiovascular distress and too many physicians continue to be trained to only see signs in white men.³ Women with cardiovascular disease are also more likely to report poorer patient experience, lower health-related quality of life, and poorer perception of their health when compared with men.⁴ This translates to unnecessary costs across the United States healthcare system, as unrecognized and inadequate treatment of cardiovascular diseases will surpass \$1 trillion by 2035.⁵

Autoimmune and Immunological Diseases

With 80 percent of all patients diagnosed with autoimmune diseases being women and 100 types of them predominantly affecting women, this area of health must be addressed.⁶ Specifically, approximately 80 to 95 percent of Sjögren’s syndrome, systemic lupus erythematosus (SLE), primary biliary cirrhosis, autoimmune thyroid disease and systemic sclerosis patients are women, and scientists have connected the dose of certain X chromosome –linked genes to the significant prevalence of autoimmune diseases in women.⁷ Part of this disparity can be attributed to many autoimmune disorders’ tendency to affect women during periods of extreme stress, such as pregnancy, or during period of hormonal change.⁸ There are few treatments available for many autoimmune diseases, which can be uncomfortable, painful and impact a woman’s ability to work and care for her family. Autoimmune diseases are also extremely costly, as the National Institutes of Allergy and Infectious Diseases has estimated that the cost of treating autoimmune disease in the U.S. is greater than \$100 billion annually. The figure is likely much higher, as the annual costs

¹ Brigham and Women’s Hospitals, “Sex-Specific Medical Research: Why Women’s Health Can’t Wait”, <https://www.brighamandwomens.org/assets/bwh/womens-health/pdfs/connorsreportfinal.pdf>

² Mayo Clinic, October 4, 2019: <https://www.mayoclinic.org/diseases-conditions/heart-disease/in-depth/heart-disease/art-20046167>

³ Coya Partners, 2020: <https://www.coyapartners.com/blog>

⁴ Victor Okunrintemi, Javier Valero-Elizondo, Benjamin Patrick, et. al, “Gender Differences in Patient-Reported Outcomes Among Adults with Atherosclerotic Cardiovascular Disease”, December 10, 2018, <https://www.ahajournals.org/doi/10.1161/JAHA.118.010498>

⁵ RTI International, “Cardiovascular Disease Costs will exceed \$1 Trillion by 2035”, February 14, 2017: <https://www.rti.org/news/cardiovascular-disease-costs-will-exceed-1-trillion-2035>

⁶ The Prevalence of Autoimmune Disorders in Women: A Narrative Review, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7292717/>

⁷ Tidsskr Nor Lægeforen 2017; doi: 10.4045/tidsskr.16.0935

⁸ Angum, Fariha et al. “The Prevalence of Autoimmune Disorders in Women: A Narrative Review.” Cureus vol. 12,5 e8094. 13 May. 2020, doi:10.7759/cureus.8094

of only seven out of the over 100 known autoimmune diseases are estimated to cost \$51.8 –70.6 billion annually.⁹

Oncology

Women bear the burden of inequitable oncological treatment options as well as disparities in specific cancers. For example, one in five people who are diagnosed with lung cancer have never smoked, yet non –smoking women are three times more likely to have the disease.¹⁰ Gender disparities are also pervasive in terms of treatment options, as a recent study showed that the odds of receiving radiation were 60 percent for women and 70 percent for men, and the odds for receiving intensive chemotherapy were 35 percent for women versus 46 percent for men.¹¹ In terms of mortality, the ratio of cancer deaths versus non –cancer deaths was 1.92 times higher for women than for men.¹² Cancers also disproportionately impact minorities and populations with social, environmental, and economic disadvantages that hinder access to healthcare. African American and Caucasian women have similar rates of breast cancer, yet African American women are more likely to die from the disease. Hispanic and African American women also have higher rates of cervical cancer than women of other ethnic groups, with African American women having the highest rates of death from cervical cancer.¹³ In addition, ovarian cancer is the only gender –specific cancer with greater than 50 percent mortality rate, and accounts for more deaths than any other cancer of the female reproductive system with Black women having a much higher 5 –year mortality rate (62 percent) vs. Caucasian women (54 percent).¹⁴

Aging and Bone Health

A women’s risk of bone fracture is equal to her combined risk of breast, uterine, and ovarian cancer, which is four times the rate of men. Of the ten million Americans with osteoporosis, approximately 80 percent are women and a proximately one in two women over age 50 will break a bone because of osteoporosis.¹⁵ Studies have shown that there are multiple reasons why women are more likely to get osteoporosis than men. Women tend to have smaller and thinner bones, and women’s estrogen, a hormone that protects bones, decreases when women reach menopause.¹⁶ This prevalence of bone diseases is not only dangerous for women but is also extremely costly. The annual cost of osteoporosis –related bone breaks is \$19 billion for patients, their families, and the healthcare system, and is expected to continue to rise. It is estimated that osteoporosis will be responsible for three million fractures, costing \$25.3 billion by the year 2025.¹⁷

⁹ American Autoimmune Related Diseases Association, “The Cost Burden of Autoimmune Disease: The Latest Front in the War on Healthcare Spending”, 2011, <http://www.diabetesed.net/page/files/autoimmune-diseases.pdf>

¹⁰ Brigham and Women’s Hospital, “Why Women’s Health Can’t Wait”, 2014, <https://www.brighamandwomens.org/assets/bwh/womens-health/pdfs/connorsreportfinal.pdf>

¹¹ Ibid

¹² Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA: A Cancer Journal for Clinicians 2017; 67(1):7–30

¹³ National Cancer Institute, “Cancer Disparities,” <https://www.cancer.gov/about-cancer/understanding/disparities>

¹⁴ American Cancer Society, <https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/cancer-facts-and-figures-for-african-americans/cancer-facts-and-figures-for-african-americans-2019-2021.pdf>

¹⁵ <https://www.nof.org/preventing-fractures/general-facts/what-women-need-to-know/>

¹⁶ National Osteoporosis Foundation “What Women Need to Know” <https://www.nof.org/preventing-fractures/general-facts/what-women-need-to-know/>

¹⁷ National Osteoporosis Foundation, “Osteoporosis Fast Facts,” <https://cdn.nof.org/wp-content/uploads/2015/12/Osteoporosis-Fast-Facts.pdf>

Gynecological and Sexual Health

Several gynecological conditions women face throughout their lives and especially as they age are often ignored with insufficient diagnostics and treatments. For example, the annual gynecological exam does not screen for ovarian cancer and 1 in 5 women have masses, yet few diagnostics can catch the cancerous tumors during the critical early stages, especially among women of color who are most often diagnosed too late and die sooner. In addition, more than 4,000 women enter menopause every day in the U.S., but only one in five OB/GYN residency programs provide menopause training to support them and nearly 80 percent of medical residents admit that they feel “barely comfortable” discussing or treating menopause.¹⁸ Also, 84 percent of women experience menopause symptoms, and more than one in ten (12 percent) say their symptoms can be severe or debilitating. Yet menopause is understudied and misunderstood by physicians and researchers alike with few treatments available for the impact on women that is so severe, many stay home or retire early when they are otherwise in the prime of their career. Most do not understand when symptoms are ignored or misdiagnosed during menopause years, they can lead to severe complications, preventable death, and avoidable and costly medical expenditures. Approximately 16–18 percent of post–menopausal women develop urinary incontinence, which can be a barrier to working and fully contributing to society.¹⁹ In fact, many women retire early just to avoid having to deal with menopause symptoms like incontinence and hot flashes at work. These conditions cost the U.S. healthcare system four times the costs of their non–symptomatic peers. Symptomatic women incur incremental healthcare spending of \$1,346 per person per year, and \$770 in productivity losses per menopausal woman per year. This cost can climb to \$6,500 per woman per year in extreme cases.²⁰ This is the same economic cost as uncontrolled hypertension.²¹ Globally, menopause–related productivity losses can amount to more than \$150 billion a year and if costs to the healthcare system are included, the total price tag of menopause could be higher than \$810 billion.²²

Reproductive Health

Disparities in maternal and reproductive health are also a major concern in the U.S. Studies document decades–long racial and ethnic disparities in several areas of reproductive health, including contraceptive use, care for sexually transmitted infections and the human papillomavirus (HPV) vaccination among younger women aged 18 to 25 years, as well as reproductive cancers, preterm deliveries, and maternal morbidity and mortality in all age groups.²³ Most women lack sufficient resources, information and access to care related to perinatal mood and anxiety

¹⁸<https://www.aarp.org>, Note this study also found 84 percent of women say that their menopausal symptoms interfere with their lives, including at work.

¹⁹Christina Tso, DNP, FNP–BC, CRP, and Wah Lee, DO, MS, “Postmenopausal Women and Urinary Incontinence”, January 10, 2018, <https://www.myamericannurse.com/postmenopausal-women-urinary-incontinence/>

²⁰ The Real Cost of Menopause <https://www.elektrahealth.com/real-cost-for-menopause> and Menopause: The Journal of The North American Menopause Society, Vol. 22, No. 3, pp. 260/266, DOI: 10.1097/gme.0000000000000320, The North American Menopause Society (2014).

²¹ Ibid.

²² Reenita Das, a partner and senior vice president for healthcare and life sciences at consulting firm, Frost & Sullivan, https://apple.news/AkFLvCBgGST6IKWENIXbf_w

²³ Obstetrics & Gynecology: February 2021 – Volume 137 – Issue 2 – p 225–233, doi: 10.1097/AOG.0000000000004224

disorders (PMADs), the number one complication resulting from pregnancy and childbirth. Half of perinatal women with a diagnosis of depression do not get the medical treatment that they need, resulting in poor patient outcomes and increased societal costs. The total annual societal costs incurred by PMADs, including maternal productivity loss (such as loss of work productivity and missing work), greater use of public sector services (such as welfare and Medicaid), and higher health care costs due to worsened maternal and child health, was \$14.2 billion in 2017. This equates to \$4.7 billion in productivity losses, \$2.9 billion in maternal health expenditures, \$3.3 billion in preterm births, and \$1.6 billion in child behavioral and developmental disorder spending.²⁴ These staggering costs and the devastating effects for mothers who suffer from PMADs must be discussed and addressed.

Cognitive and Brain Health

Cognitive and brain function is another health area in which significant disparities exist between men and women. Two-thirds of Alzheimer's patients over 65 are women and two-thirds of caregivers are women.²⁵ Moreover, despite clear biological differences in cognitive function, women are not proportionately represented throughout the research process, and female-specific cognitive diseases are not proportionately funded. In medical research for anxiety disorders, 90 percent of animal subjects are male, though women are twice as likely to be diagnosed with anxiety in their lifetime.²⁶ After accounting for the influence of race, age, and education, research has shown that there are sex differences in cognitive decline, as women have a significantly faster decline in global cognition and executive function, but not memory.²⁷ Although two-thirds of Alzheimer's patients are women 66 percent of animals used in Alzheimer's research are male or of an "unspecified gender," which are mostly male. There is also a stark disparity in funding allocation, as just 12 percent of the National Institutes of Health (NIH)'s 2019 budget of \$2.4 billion for Alzheimer's disease research went toward projects specifically focused on women. Not only does this hinder innovation, understanding, and treatment of Alzheimer's disease, it also results in severe economic consequences. If \$300 million had been shifted to the NIH's Alzheimer's budget to focus on women's brain health in that same year, it would have produced over \$930 million in economic benefits, including quality of life improvements, and reduced medical costs.²⁸ Ignoring women-focused research not only harms health outcomes, but it costs the U.S. economy nearly a billion dollars a year.

Adverse Drug Events

Adverse drug events are twice as common in women in 29 of the 30 FAERS categories and women are significantly more likely to be hospitalized secondary to an ADE.²⁹ While recent clinical

²⁴ Mathematica Policy Research, "Societal Costs of Untreated Perinatal Mood and Anxiety Disorders in the United States", April 29, 2019, <https://www.mathematica.org/download-media?MediaItemId={E24EE558-B67B-4BF6-80D0-3BC75DB12EB6}>

²⁵ Centers for Disease Control and Prevention, <https://www.cdc.gov/aging/caregiving/alzheimer.htm>

²⁶ Gender Differences in Anxiety Disorders: Prevalence, Course of Illness, Comorbidity and Burden of Illness, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3135672/>

²⁷ Levine DA, Gross AL, Briceño EM, et al. Sex Differences in Cognitive Decline Among US Adults. *JAMA Network Open*. 2021;4(2):e210169. doi:10.1001/jamanetworkopen.2021.0169

²⁸ Women's Health Access Matters, "Societal Impact of Research Funding for Women's Health in Alzheimer's Disease and Alzheimer's Disease Related Dementias," April 2021, https://thewhamreport.org/wp-content/uploads/2021/04/TheWHAMReport_ADRD.pdf

²⁹ Zucker, Irving, and Brian J Prendergast. "Sex differences in pharmacokinetics predict adverse drug reactions in women." *Biology of sex differences* vol. 11,1 32. June 5, 2020, doi:10.1186/s13293-020-00308-5

studies have included more women, for decades, the patients who participated in clinical trials for new drugs skewed heavily male. As a result, many drugs commonly prescribed to this day do not account for gender differences making them ineffective or causing patient harm. Today, most pre-clinical trials continue to exclusively use male mice and male animals even though sex differences are found at the cellular level. Few pre-clinical trials use both sexes to inform the next phase of studies in humans, and even if experiments do include female animals, the subgroup analyses by sex are not reported.³⁰ During the next phase of research when the clinical trial includes women, often for the first time, and always at a level far below the actual representation of women in prevalence rates for the disease for which the drug is being developed to treat, this underrepresentation is magnified with greater room for error and ADE occurrence. In sum, most, if not all these ADEs could be prevented with sufficient representation in clinical trials, improved data collection, correct and updated labeling, and application of this information to clinical practice. In the meantime, formats, definitions, and measures used for this reporting must include a means to associate medical errors with sex, race, and ethnicity to ensure more data is collected and clinicians are aware of additional considerations to make in prescribing treatments to patients.

Recommendations

With the continued failure to address so many women's health issues, we must increase NIH investment in advancing research in these areas. Women's health issues continue to be under-represented in terms of NIH resource allocation, with dire consequences. An analysis of NIH funding patterns found that in nearly three-quarters of the cases where a disease afflicts primarily one gender, the funding pattern favors males, in that either the disease affects more women and is underfunded, or the disease affects more men and is overfunded. Furthermore, the disparity between actual funding and that which is commensurate with burden is nearly twice as large for diseases that favor males versus those that favor females.³¹ A recent study of the funding of 18 different types of cancers by the National Cancer Institute found that gynecologic cancers (ovarian, cervical, uterine) ranked 10th, 12th and 14th, respectively, in funding normalized to years of life lost, whereas prostate cancer ranked 1st, yet 90 percent of prostate cancer patients survive.^{32,33} Furthermore, ovarian cancer is the only gender-specific cancer with a greater than 50 percent mortality rate, and accounts for more deaths than any other cancer of the female reproductive system. For comparison, prostate cancer has a 2 percent mortality rate, yet receives 50 percent more funding than ovarian cancer from the NIH.

Therefore, we ask that the NIH Office of Research on Women's Health prioritize all health conditions that solely, predominantly or differently impact women and for which we need to improve scientific understanding, investment, research, treatments, diagnostics and awareness. Cardiovascular health, autoimmune disease, oncology, aging and bone health, gynecological and sexual health, reproductive health, cognitive and brain health, and adverse drug reactions are all strong examples of such areas that could greatly benefit from this increased focus and research. We are eager to work with you in this endeavor and incentivize private investment to match NIH

³⁰ It is time to integrate sex as a variable in preclinical and clinical studies, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6056479/>

³¹ Arthur A Mirin, "Gender Disparity in the Funding of Diseases by the U.S. National Institutes of Health" July 30, 2021, <https://pubmed.ncbi.nlm.nih.gov/33232627/>

³² Arthur A. Mirin, *Journal of Women's Health*, Jul 2021.956–963, <http://doi.org/10.1089/jwh.2020.8682>

³³ <https://www.cancer.org/cancer/prostate-cancer/detection-diagnosis-staging/survival-rates.html>

investment, working in a concerted effort to advance women's health. Thank you for your consideration. Please contact us with any questions by emailing kbrown@G2Gconsulting.com.

Sincerely,

Members of the Women's Health Innovation Coalition

AOA Dx Inc. – Oriana Papin –Zoghbi, Co –Founder and CEO

Ascend BioVentures – Elaine Hamm, Ph.D., CEO

Aspira Women's Health – Valerie Palmieri, President and CEO

Aviation Medical, Inc. – Jill Schiaparelli, M.B.A., President and CEO

Avestria Ventures – Tracy Dooley, M.D., Partner

BIOMILQ – Katherine Richeson, Ph.D., Scientist

Bloomer Tech – Alicia Chong, Founder and CEO

Candelit Therapy – Lauren Elliot, Founder and CEO

CEFALY Technology – Jennifer Trainor McDermott, CEO

Curatio – Lynda Brown –Ganzert, Founder and CEO

Curio Digital Diagnostics – Shailja Dixit, CEO

Elektra Health – Alessandra Henderson, Co-Founder and CEO, and Jannine Versi, Co-Founder and COO

Elidah, Inc. – Gloria Kolb, Founder and CEO

FemmeBright Health – Julie Berg and Lisa Lechner, Co-Founders

FEMSelect Ltd. – Deborah Garner, Co-CEO

FemTech Collective – Megan Capriccio, Co-Founder and CEO

FemTech Focus – Brittany Barreto, Ph.D., Co-Founder and Executive Director

Femtech Insider – Kathrin Folkendt, Founder

FemTech Lab – Terri Harris, Head of Community

Foundation for Sarcoidosis Research – Mary McGowan, CEO

G2G Consulting – Liz Powell, Esq., M.P.H., Founder and President

Gabbi, Inc. – Kaitlin Christine, Founder and CEO

Gennev – Jill Angelo, Founder and CEO

Genome Medical – Lisa Alderson, CEO

Grace & Able – Sarah Dillingham, Founder and CEO

GynTools – Nimrod Lev, Co-Founder and CEO

Happify Health – Danielle Hamel, VP Kopa Commercialization

HealthyWomen – Martha Nolan, Senior Policy Advisor

Hera Health Solutions – Idicula Mathew, Co-Founder and CEO

HexoSkin – Heloise Auger, Biomedical Researcher

HLTH Foundation – Jana Guinen, Executive Director

IncelDx – Chris Meda, Chief Business Officer

InControl Health, Inc. – Laura Zumbrunnen, Co-Founder and CEO

Mitzi Krockover, M.D.

LactApp – Christi Gross, International Development Lead

Linked Inclusion – Angela Harris, Chief Marketing Officer

Lioness – Liz Klinger, Co-Founder and CEO

Lisa Health – Ann Garnier, Founder and CEO

Looms for Lupus – Estela Mata, President

Martell Diagnostic Laboratories – Michelle Edwards, CEO

Materna Medical – Tracy MacNeal, President and CEO

Maternal Mental Health Leadership Alliance – Adrienne Griffen, Executive Director and Jamie Belsito, Policy Director

Maternie – Meghan McCarthy, Founder

Natalist – Halle Tecco, M.B.A., M.P.H., Founder and Chief Women's Health Officer

Nest Collaborative – Amanda Gorman, Founder

Nixon Gwilt Law – Carry Nixon, Esq., Co-Founder and Managing Partner

Obseva – Elizabeth Garner, M.D., M.P.H., Chief Medical Officer

Oratel Diagnostics – Dorothee Goldman, Founder and CEO

Pandia Health – Sophia Yen, M.D. M.P.H., Co-Founder and CEO

Partum Health – Meghan Doyle, M.B.A., CEO

Denise Pines, Board Member of the Osteopathic Medical Board of California

Plenish Health – Joanna Strober, Esq., CEO

Pollie – Jane Sagui, Co-Founder and CEO

Posture Wings – Mary Fenske, CEO

Prima-Temp – Amy Wedeking Shannon, Chief Commercial Officer

Raydiant Oximetry – Neil Ray, M.D., Founder and CEO

Renalis – Missy Lavender, M.B.A., Founder and CEO

Kathryn M. Rexrode, M.D., M.P.H. – Chief of the Department of Medicine’s Division of Women's Health at Brigham and Women's Hospital and Associate Professor of Medicine at Harvard Medical School

Rhia Ventures – Elizabeth Bailey, Managing Director

Sana Health – Richard Hanbury, Esq., MBA CEO

SimpliFed – Andrea Ippolito, Founder and CEO

Society of Behavioral Medicine – Lindsay Bullock, C.A.E., Executive Director

SPARK Solutions for Growth – Rachel Braun Scherl, Managing Partner and Co-Founder

Springboard Enterprises – Kay Koplovitz, Chairman and Anna Consani, VP of Partnerships and Community

The 51 – Shelley Kuipers Co-CEO, General Partner & Growth Officer

Carolyn C. Thompson, M.D.

Univfy Inc. – Mylene Yao, CEO

Visana Health – Joe Connolly, Founder and CEO

Vital Start Health – Kirthika Parmeswaran, CEO

Watkins – Conti Products, Inc. – Allison Conti, Founder and CEO

Women’s Urology New York, PLLC – Dr. Angelish Kumar, Founder

Wu Consulting – Michelle Wu, Principal Consultant

ZIBRIO – Andrea Case Rogers, Chief Experience Officer