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September 15, 2021

RE: HealthyWomen's comments to inform the upcoming congressionally requested meeting titled "Advancing NIH Research on the Health of Women: A 2021 Conference"

Thank you for the opportunity to provide comments to help inform the discussion on women's health research to take place on October 20, 2021.

Founded in 1988, HealthyWomen is the leading nonprofit women's health information source with a mission of educating women ages 35 to 64 to make informed health choices. Throughout the years, we have informed consumers and healthcare providers about advances in women's health, from the latest information on diseases and conditions to various milestones pertaining to access to care. We ensure that women have accurate, balanced, evidence-based information so they can make informed decisions in partnership with their healthcare providers. We also educate our audience regarding innovations in research and science, as well as changes in policy that affect women's access to treatment and care so that women are prepared to self-advocate for better health outcomes.

One of HealthyWomen's greatest strengths is our nationwide group of women stakeholders, who provide us with testimonials about their extraordinary experiences advocating for themselves, fighting for their health and insisting on being heard so they can get the treatment best suited for them. Our comments in the three areas you requested will provide information on gaps and opportunities as well as our thoughts regarding the important direction we think that women's health research can take at NIH. We hope that our input can be taken into consideration for discussion at the Women's Health Consensus Conference in October.

1. Maternal mortality and morbidity

Maternal mortality rates in the U.S. are high compared to other high-income countries, and 52% of U.S. maternal deaths occur after the day of birth ([Commonwealth Fund 2020](#)). Black, American Indian and Alaskan Native women are [at greater risk](#) — almost threefold — of dying from pregnancy-related complications compared to white or Hispanic women. The causes for Black maternal mortality have been identified as cardiomyopathy, thrombotic pulmonary embolism and hypertensive disorders ([CDC media release](#)). Interestingly, cardiomyopathy and mental health conditions such as substance abuse and suicide were the leading causes of deaths between 43 days to one year postpartum (45%) (Petersen EE et. al 2019). Most of these deaths are considered preventable and have been attributed to lack of access or the poor quality of health care (Howell EA 2018). However, there is also a lack of understanding of what biological factors (genetic or hormonal) contribute to some of these conditions either during pregnancy or postpartum.

Challenges: Currently there are limitations to how accurately we are collecting or capturing data related to maternal mortality and morbidity within the U.S. This also includes the prevalence of conditions that affect mothers, such as cardiovascular conditions, perinatal mood disorders, preeclampsia, gestational diabetes and several other conditions. We gather most of our data on

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maternal mortality and morbidity from several governmental sources at the Centers for Disease Control and Prevention (CDC) including the National Vital Statistics Systems (NVSS), Pregnancy Mortality Surveillance System and the Maternal Mortality Review Information Application. The NVSS provides official reports on maternal mortality but has not published often. Although the most recent report published by NVSS was in 2018, it had not previously published a report since 2007. Further complicating matters is the fact that CDC data from the Pregnancy Mortality Surveillance System cannot be used to compare U.S. data with international data due to the different reporting criteria used by CDC — the CDC reports at one year postpartum versus international countries reporting 42 days postpartum. Most recently, the CDC has created the Maternal Mortality Review Information Application for which the data is populated by the maternal mortality review committees within each state to create a multistate reporting system. Thus, collecting accurate national data is challenging as a result of differences in how maternal deaths are collected, recorded and reported by each of these committees.

Opportunities: There is a need for a single national database for collecting and accurately reporting maternal mortality and morbidity data. Having a national database will allow for usage of proper definitions of conditions that affect mothers, collection of good quality data and the establishment of quality processes on how the data will be monitored and reported. We need to establish a proper funding mechanism for such a system and house it in an independent location that is central to all federal agencies. This database should allow for proper yearly reporting so we can monitor the progress made. The data elements need to be well established to include variables that allow us to study existing racial and ethnic disparities. A similar process to meet the need for high quality data and coordination of programs has been recently proposed for [maternal immunizations](#) by advocacy organizations.

HealthyWomen’s Real Women, Real Stories: [“When Postpartum Depression Hit, I Heard Only the Lies My Depression Told Me”](#)

“As a pharmacist, I understand medications for depression, but I still believed I was too defective for medicine to fix.”

2. Chronic Debilitating Conditions

There are several chronic debilitating conditions impacting women. However, we chose to focus on a few conditions that HealthyWomen feels deserve additional attention.

a. Chronic Pain

Chronic pain was declared a major public health crisis in the U.S. by the Institute of Medicine in 2010. Since then, several federal efforts have been made by the National Pain Strategy (NPS) to address chronic pain at multiple levels. However, not much progress has been made since the NPS was published a decade ago. According to the CDC, an estimated 20.4% of U.S. adults (50.0 million) had chronic pain and 8.0% of U.S. adults (19.6 million) had high-impact chronic pain in 2016 (Dahlhamer J et. al 2018). High impact chronic pain (HICP) has been described as pain that frequently limits life or work activities. Prevalence of both chronic pain and high-impact chronic pain, once age-adjusted, were significantly higher among women. Severe pain and more mental health and cognitive impairments were reported by persons with HICP than persons with chronic pain without disability. They were also more likely to report worsening health, more difficulty with self-care and greater healthcare use (Pitcher MH et. al

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2019). Certain chronic pain conditions are either sex-specific (such as endometriosis, fibroids or vulvodynia) or are conditions that disproportionately affect women (fibromyalgia, temporomandibular syndrome, osteoarthritis, rheumatoid arthritis, chronic back pain, migraine, complex regional pain syndrome). Several of these conditions can be very debilitating for women, and some of them have a bidirectional relationship with a number of mental health conditions and sleep disorders. However, the precise mechanisms underlying the bidirectional relationships are not well understood.

Below are some of the disparities in care for certain chronic pain conditions in women:

Fibroids: Fibroids are benign tumors, and risk factors for fibroids include ethnicity, race, age, family history, timing of last birth/delivery, premenopausal state, hypertension and diet. Based on ultrasonography, the estimated cumulative incidence of fibroids in women ≤ 50 years is significantly disproportionate. Women of color are also disproportionately affected: 80%-90% of Black women will be diagnosed with fibroids by age 50 compared to 70% of white women. Prevalence rates may actually be underestimated as a result of barriers in diagnosis, asymptomatic cases or lack of knowledge that may prompt additional screening measures. Disparity gaps persist among geographic regions of the U.S. and across racial and ethnic groups. For example, fibroids are not only more prevalent but also more severe among women of color, as studies show that more Black women undergo surgery for fibroids compared to non-Black women (VanNoy BN et. al, 2021; Eltoukhu H et.al 2014). In fact, data shows that Black women are nearly three times more likely to undergo hysterectomy for fibroid tumors than other racial groups of women (Eltoukhu H 2014). Black women have fibroids diagnosed at earlier ages, are more likely to be symptomatic, and are likely to have different responses to medical and clinical treatment than white women (Eltoukhu H 2014). Among women with equal access to care, there is a race-based difference in the outcome and response to fibroid treatment (VanNoy BN et. al 2021; Eltoukhu H et.al 2014; Marsh EE 2021).

HealthyWomen's Real Women, Real Stories: [“After My Hysterectomy, I'm Living My Best Life”](#)

“After living with the pain of fibroids for 17 years, treating them was the best gift I could give myself.”

Endometriosis: Endometriosis is a debilitating condition with features of chronic inflammation, but the biological cause is unclear (Mehedintu C 2014). It is one of the common gynecological conditions in premenopausal women and an estimated 1%-15% of women of reproductive age live with endometriosis (Mehedintu C 2014). Endometriosis has a profound impact on a woman's quality of life, relationships, fertility and livelihood, and the condition can cause intense pain. Asian women have a higher prevalence of endometriosis and are more likely to be diagnosed compared to white women, while Black women are less likely to be diagnosed with endometriosis compared to white women (Agarwal SK 2019). Diagnosing endometriosis is challenging since there are no proper diagnostic tools available, such as a blood test, and an invasive laparoscopy is usually needed to confirm the diagnosis (Mehedintu C 2014). Treatment is also complicated because of the lack of successful options, resulting in hysterectomies or oophorectomies (Mehedintu C 2014).

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HealthyWomen's Real Women, Real Stories: [“Endometriosis Made My Pregnancy High Risk”](#)
“I didn't realize that getting and staying pregnant would prove the most frightening experience of my life”

Rheumatoid arthritis: Rheumatoid arthritis (RA) is an autoimmune, chronic inflammatory disorder that can often cause pain, swelling and stiffness of the joints. More than 4 million U.S. women are affected by RA at a rate of 3:1 over men (Hemlick CG et.al 2008). For many, RA affects more than just the joints — it also damages a wide variety of body systems, including the skin, eyes, lungs, heart and blood vessels. While RA disproportionately affects women, it also unequally affects women of color. Epidemiology reports illustrate racial and ethnic disparities in clinical onset, disease severity, disease progression and patient health outcomes, putting Latino and Black Americans most at risk for greater disease activity levels and worsening functional status (Greenberg J et al. 2013). Although immediate intervention is critical to achieve remission for RA, it is common for six or more months to pass before women seek clinical evaluation (Kumar K et. al 2007). Research shows that more than 20% of individuals with RA are misdiagnosed, and among those misdiagnoses, roughly 90% are women (Santos-Moreno P. et al. (2017). Although many new treatments have been developed for RA in recent years, sadly they do not work for everyone the same way, necessitating the need for more personalized care (Favalli EG 2018). Sex and gender differences occur in RA onset, presentation and response to treatment. Comorbidities, including additional painful conditions, are frequently present in females. More research is needed to understand the influence of sex and the role of sex differences in disease etiology and treatments (Favalli EG 2018).

HealthyWomen's Real Women, Real Stories: [“Managing Chronic Pain Is a Mind-Body-Spirit Endeavor”](#)
“Living with pain for 23 years, I've learned that supporting others is essential to my health.”

Migraine: Migraine is a complex neurobiological disorder impacting multiple systems within the body. Migraine is also associated with several comorbid conditions including cardiovascular, neurological, mental health and various other medical conditions contributing to its complex pathophysiology. However, the underlying biology between migraine and its comorbidities is still relatively unknown. The global burden of migraine is disproportionately higher in women (18.9%) compared to men (9.8%), and the U.S. burden of migraine is highest among women ages 15 to 49 (GDBH collaborators; Buse DC et. al 2013). Migraine is ranked as the second most common cause of disability, impacting 1.04 billion individuals worldwide. Overall, females have a higher risk for headache and migraine across all race and ethnic groups compared to men. However, racial and ethnic disparities among women do exist in migraine disease: Prevalence data suggests that Native American women are at higher risk, followed by white women, followed closely by Hispanic women and Black women (Burch R et. al 2015). Asian women have the lowest prevalence of severe, frequent headache or migraine. Racial and ethnic disparities in access and quality of care for minority patients might lead to differences in diagnosis and treatment of headache and migraine.

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HealthyWomen's Real Women, Real Stories: "[How I Found New Relief From Migraine Disease](#)"

"I was plagued with migraine disease for decades and finally found relief with a new doctor, new diagnosis, new medication, and a new career."

For all of the above conditions, the following challenges and opportunities exist:

Challenges: Several challenges exist when it comes to understanding and diagnosing women's pain. Diagnosis is complicated by the fact that [women's pain is complex](#), as biological factors along with psychological and social factors influence how women experience pain. Racial trauma and childhood adverse experiences can also influence pain experience. The complex nature of women's pain makes treating chronic pain very challenging. Additionally, women typically experience [multiple chronic pain conditions](#) as well as several other comorbidities compared to men (Filligim RB et. al 2009). The more conditions women experience, the greater the sex difference. This indicates that there is a biological difference in how these conditions manifest in women compared to men. Currently, there is a knowledge gap when it comes to understanding the etiologies of several of these conditions. We also do not understand how acute pain translates to chronic pain. Although current research has made some advances in this area, we still have a lot to learn (Chapman CR et. al 2017).

Opportunities: Several research opportunities exist in trying to understand the biological mechanisms that contribute to women's pain. First and foremost, it is important to understand the role of gonadal hormones in influencing pain in women. Although the role of hormones has been established in the way females and males experience pain, the exact mechanisms by which hormones influence pain are poorly understood. Presence of gonadal hormone receptors in peripheral and central nervous tissues involved in nociceptive pain point to the role of hormones on pain experiences (Maurer AJ et. al 2016). These hormones also seem to influence neurotransmitters involved in the nociceptive pathways, but research studies are needed. With the emergence of new imaging modalities and their use in studying pain perception, we need more studies to understand the role of hormones in pain. Inflammation is also thought to play a key role in the pathophysiology of many chronic pain conditions. For example, a recent review has proposed the role of inflammasomes in the pathogenesis of endometriosis as well as the role of gonadal hormones in the inflammatory response in endometriosis (Garcia-Gomez E et. al 2020). The role of immune cells in pain signaling is a new area of research, but we need more sex differences research and reporting in this area (Rosen S et. al 2017). There is also a need for research to understand whether applying the biopsychosocial model to pain care will result in better patient outcomes. Understanding the social determinants of health and socioeconomic factors that influence the social domain of the biopsychosocial model of care may be an important driver to treatment and care. Racial disparities exist in chronic pain, and recently a conceptual model was proposed to show how epigenetics might explain some racial disparities in chronic pain: race, which is a social construct, can influence pain experience and related disability via the biological mechanisms of epigenetics (Aroke EN et al. 2019). However, more research is needed on race-based traumatic stress as well as adverse childhood experiences in chronic pain.

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b. “Long COVID”

In recent times, the COVID-19 pandemic has brought focus on [sex disparity](#) in coronavirus infections. Worldwide, we saw more men die from SARS-CoV-2 infection than women ([Global Health 50/50](#)). While gendered behavior was thought to contribute to the mortality rates, there are also underlying sex differences, such as higher levels of ACE2 receptors in men, along with gender differences that contribute to a male bias towards the infection. COVID-19 has also brought attention to sequelae of post-viral syndrome known as “Long COVID” that appears to disable and incapacitate patients, causing neurological symptoms such as fatigue, shortness of breath, brain fog and chronic pain. These symptoms seem to mimic other post-viral syndromes such as myalgic encephalomyelitis (ME)/ chronic fatigue syndrome (CFS), fibromyalgia and post-treatment Lyme disease (PTLDS).

Challenges: Several challenges have come forth since the COVID-19 pandemic emerged last year. We still do not fully understand how SARS-CoV-2 can cause sex differences in mortality and morbidity. We also don’t understand who is at risk and how they are at risk for “Long COVID.” Anecdotally, we have heard that more women are at risk for “Long COVID.”

Opportunities: Research studies are needed to better define the clinical presentation of the “Long COVID” condition (Orru G et. al 2021). We applaud the NIH for launching a new initiative to study “Long COVID”; however, we encourage NIH to examine the sex and gender disparities underlying “Long COVID” as well as conduct observational studies into the efficacy of vaccines on “Long COVID.” We further need to understand the sex differences in the immune response to SARS-CoV-2 that lead to sex disparity and severity in COVID-19 (Pradhan A et. al 2020). Since some of the symptoms of ME/CFS overlap with “Long COVID,” we need to understand the connection. It is possible that these patients may be diagnosed as ME/CFS based on the symptoms exhibited for greater than 6 months. Additionally, ME/CFS patients may also benefit from research on “Long COVID.”

HealthyWomen’s Real Women, Real Stories: [“I’ve Had COVID-19 Symptoms for 130 Days and Counting”](#)

“I was in despair when medical providers dismissed me — until I found the support of thousands of other COVID ‘long-haulers.’”

3. Stagnant Cervical Cancer Survival Rates

According to [CDC’s data visualization tool](#), there has been a slow decline in the incidence of cervical cancer deaths from 1999 to 2018 (age-adjusted death rate from 2.8 and 2.2). Although fewer new cases of cervical cancer have been reported from 1999 to 2018, this rate has also been low. This suggests that we have not seen much of an impact in the death rate since the introduction of HPV vaccine in 2006.

It is generally known that cervical cancer incidence and mortality rates are disproportionately higher in Hispanic women and non-Hispanic Black women compared to non-Hispanic white women because of existing disparities (Miller MJ et. al 2021). Lower screening rates for African Americans and Asian Americans are further increasing racial disparities. These rates have particularly decreased during the pandemic (Miller MJ et. al 2021). It’s interesting to note that a

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recent study published in 2020 pointed out that cervical cancer rates have dropped in girls between ages 12 to 29, suggesting that this drop in rate may be the result of increased HPV vaccination among this cohort (Mix JM et.al 2020). It has also been documented that screening rates observed for cervical cancer in recent times have decreased, especially in ages 21 to 29 (MacLaughlin KL et.al 2019).

One of the factors that could be preventing a substantial decrease could be lack of knowledge by patients on HPV and its cancer risk, preventing them from seeking out screenings. Patients are also not receiving a recommendation to get the vaccine from their physician (Suk R et. al 2019). Compounding this are social and health disparities, which have been exacerbated by the impact of the pandemic. This situation will only become worse with the growth of minority populations in the U.S. unless disparities and inequities in care are narrowed substantially.

Challenges: The multi-dose regimen of the HPV vaccine, like all vaccines with this component, immediately creates a problem with completion of the full regimen. It directly impacts women and families by requiring multiple doctor's office visits and, thus, higher copays and deductibles, more time off from work or out of school, and more transportation and caregiving issues. Additionally, older women are tested less frequently compared to younger women, especially women over 65 years of age who may not be screened after a recent Pap test. This is magnified by disparities and inequities created by differing standards of care depending on insurance coverage, including issues of deductibles and coinsurance. On top of all this now is COVID-19, increasing the need to understand how the pandemic is impacting our public health systems, how health care professionals are advising mothers, and what type of educational efforts are being made regarding the cancer risk and other risks of HPV.

Opportunities: The NIH could consider collaborating with CDC to develop a better understanding of the barriers to screening and HPV vaccine uptake among different demographics of women and to ensure that the science of HPV and cancer risks is understood. There is a need to examine how healthcare professionals are advising or not advising mothers for their daughters or women ages 18 to 29 with regard to receiving the HPV vaccine. There's an opportunity to create educational tools and resources targeted toward mothers that cover HPV and cervical cancer and their lifelong impact and how the HPV vaccine adds to long-term quality of life. Education among mid-life to older women on the need for regular screening should also be reinforced.

A well-designed campaign could be integrated into the healthcare system that engages and educates mothers on how they can positively impact the future of their daughters' lives through the HPV vaccine and screenings. There could also be a campaign for older women who are not screened regularly.

HealthyWomen's Real Women, Real Stories: ["My Life-Changing Cervical Cancer Diagnosis Inspired Me to Become an Advocate for Women's Health"](#)

"An unexpected diagnosis led me to a whole new perspective"

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We again thank you for the opportunity to offer input on "Advancing NIH Research on the Health of Women: A 2021 Conference." We look forward to continued collaboration. If we can be of further assistance, please contact Martha Nolan, J.D., Senior Policy Advisor, at martha@healthywomen.org or Monica Mallampalli, Ph.D., Senior Scientific Advisor, at monica@healthywomen.org.

Sincerely,

A handwritten signature in black ink that reads "Beth Battaglino". The signature is written in a cursive style with a large initial "B".

Elizabeth Battaglino, RN-C
CEO, HealthyWomen

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