



**Comments from the American Society of Hematology to
the National Academies of Sciences, Engineering, and Medicine (NASEM) Committee on
the Assessment of NIH Research on Women's Health
Submitted on April 3, 2024**

The American Society of Hematology (ASH) appreciates the opportunity to submit comments to the National Academies of Sciences, Engineering, and Medicine (NASEM) Committee on the Assessment of NIH Research on Women's Health regarding perspectives on gaps in women's health research, particularly across the institutes and centers at the National Institutes of Health (NIH).

ASH represents more than 18,000 clinicians and scientists worldwide committed to studying and treating blood and blood-related diseases. These disorders encompass malignant hematologic disorders such as leukemia, lymphoma, and multiple myeloma, as well as classical (or non-malignant) conditions such as sickle cell disease, thalassemia, bone marrow failure, venous thromboembolism (VTE), and hemophilia. In addition, hematologists are pioneers in demonstrating the potential of treating various hematologic diseases and continue to be innovators in the fields of stem cell biology, regenerative medicine, transfusion medicine, and gene therapy. ASH membership is comprised of basic, translational, and clinical scientists, as well as physicians providing care to patients.

The following are responses from ASH to the questions posed by the NASEM Committee:

What are the knowledge and research gaps in women's health and women's health research from your perspective? What are the barriers to filling these gaps?

From the hematology perspective, there are several areas of women's health research that would be potentially transformative to women's health if greater investment was made to fill existing research gaps, as follows:

- **The Hematologic Implications of Women's Reproductive Health.** There is a spectrum of issues (pathobiologic, social, and environmental) that need to be addressed regarding pregnancy for people with heart, lung, and blood diseases, including hematologic, cardiologic, and pulmonary complications of pregnancy even in people without underlying conditions. Increased research is needed into the lifespan of reproductive health, including menstruation, contraception, fertility/infertility, and menopause, all which have hematologic implications, such as thrombosis risks. The role of sex as a biological variable in medication studies is another critical research need, across specialties. One example is the failure of trials of anticoagulant and/or antiplatelet studies to consider heavy menstrual bleeding as an outcome. This emphasizes the importance of integrating sex as a biological variable in research to ensure comprehensive understanding and effective treatment strategies across diverse populations.
- **Iron Deficiency Anemia from Excessive Menstrual Blood Loss, and a Focus on Bleeding Disorders.** The World Health Organization estimates that 50% of women have anemia amenable to iron supplementation. However, more research is needed on the complex interactions between infections, inflammation, iron homeostasis and nutrient deficiencies that stymie the benefits of iron supplementation. Most research on hemophilia (which

predominantly impacts males) focuses on joint bleeding, yet reproductive bleeding remains a major concern for women with hemophilia and warrants investigation.

- **Assessing Hemorrhage and Thrombotic Risk in Patients (Including Transgendered Females) Receiving Hormonal Therapy.** A well-established but poorly understood link exists between hormone use (e.g., oral contraceptives [OC] and thrombosis). Globally, approximately 150 million OC users face a 2-5-fold risk of venous thromboembolism (VTE). While OCs are an essential therapeutic, the hematologic risk they pose warrants additional study to ensure we are providing appropriate care to patients.
- **Development of Effective Models to Assess the Association of OCs and VTE Risk.** Studies suggest mice do not recapitulate the effects of OC on thrombotic risk seen in humans. Innovative models and approaches to integrate multi-omics methodology with functional biology are needed to identify biomarkers and mechanisms of VTE risk in people taking OCs. Advancements in these models could significantly enhance our understanding of the complex association between OCs and VTE.
- **Addressing Knowledge Gaps in Reproductive and Sexual Health in Girls and Women with Sickle Cell Disease (SCD).** There is a critical need to address long-standing questions about the reproductive health of girls and women with SCD. There are many SCD-related reproductive risks and uncertainties across girls' and women's reproductive life span, with concerns about menstruation, contraception, fertility, and pregnancy. Girls and women with SCD are at risk for having SCD-related pain with menses and thrombotic complications with oestrogen-containing contraception. There are also many gaps in research related to pregnancy and SCD – this is underscored by the fact that women with SCD are at especially high risk of pregnancy related complications including death. In fact, women with SCD are 10 times more likely to die in childbirth than Black or African American women without SCD. Better understanding of these research gaps could significantly enhance our understanding and care of women with SCD, which could also help inform care for women with other bleeding disorders.

What should be the most important considerations NIH should use in prioritizing the research on women's health it supports?

Besides focusing on conditions that are unique to or occur predominantly in women, the NIH should focus on conditions that manifest differently in women than in men. As seen in the conditions that ASH believes require further study, certain conditions may occur in both sexes but still have sex-specific implications, like iron deficiency anemia and hemorrhage and thrombotic risks. NIH should consider prioritizing investment in these conditions and recognize that a comprehensive disease and treatment profile in men is not necessarily applicable to women.

Additionally, ASH recommends that NIH scrutinize its grant review process. All grant reviews for research related to women's health should include a subject matter expert with expertise in that area, to account for the women's health viewpoint.

From an equity perspective, what improvements may be made to NIH processes to advance health and gender equity in its research investments?

The lack of inclusion of women in clinical trials must be addressed across conditions and there are special considerations in hematology that should be considered and addressed by NIH. In bleeding disorders, the lack of inclusion of women in clinical trials of novel therapies for these disorders is a major impediment to improving outcomes and quality of life. Appropriate precautions are needed to avoid teratogenic effects, thrombosis in those using hormonal therapies or otherwise at risk of thrombosis, and iron deficiency anemia. Current challenges are the disparities in pregnancy complications and birth outcomes based on race, ethnicity, age, and other nonmodifiable risk factors; as well as environmental, and financial (i.e., potentially modifiable) risk factors.

Additionally, women who are immunocompromised due to treatment or autoimmune disorders should be included in clinical trials. Autoimmune hematologic disorders (e.g., immune thrombocytopenic purpura, thrombotic microangiopathies) are understudied, especially with respect to pregnancy. Often these patients are excluded from clinical trials pertinent to their care. Studies such as Amit, O., Barzilai, M., & Avivi, I. (2015). Management of Hematologic Malignancies: Special Considerations in Pregnant Women. *Drugs*, 75(15), 1725–1738. <https://doi.org/10.1007/s40265-015-0464-0> highlight considerations for managing hematologic malignancies during pregnancy. Guidance from these types of studies should be considered when developing inclusion and exclusion criteria for clinical trials. Finally, building capacity and promoting research in resource-limited settings needs to be addressed.

How can NIH training and education systems and programs be improved to build and maintain a robust women’s health research workforce? What are the barriers and opportunities within the current programs?

NIH has made efforts to support the physician-scientist workforce through programs to improve the postdoctoral training experience and grow the number of investigators across research career stages. ASH applauds NIH for these efforts and urges the agency to build upon these efforts. NIH should explore programs that specifically recruit physician-scientists focused on women’s health to grow this segment of the research workforce.

How do the structure, systems, and review processes of NIH affect the type of level of in women’s health research? How could these systems be strengthened and improved to better support advances in women’s health?

ASH is optimistic that NASEM’s work will help support more and better coordinated research in women’s health, including in the hematologic conditions outlined in this letter. The Society recognizes and applauds the NIH’s Office of Women’s Health Research’s (ORWH) work. However, we believe that more can be done. ORWH helps coordinate work across Institutes and Centers, but the Society recommends that increased transparency and opportunities for public input be included in this process. Strengthening alignment across Institutes and Centers and their diverse research areas is essential to foster a comprehensive approach, ultimately leading to more impactful advancements in women's health.