AMERICAN SOCIETY OF HEMATOLOGY
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December 26, 2023

Dr. Carolyn Mazure
Chair, White House Initiative on Women's Health Research
Office of the First Lady
1600 Pennsylvania Avenue, NW
Washington, DC 20500

Dear Dr. Mazure:

The American Society of Hematology (ASH) applauds President Joe Biden and First Lady Jill Biden for launching the first-ever White House Initiative on Women's Health Research ("Initiative"), which we believe has the potential to greatly advance research on hematological conditions unique to or more common in women.

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 Society thanks you for this opportunity to provide these comments on areas of research, which would be potentially transformative to women's health if greater investment is made. Specifically, we wish to highlight the following topic areas for potential study:

- **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.[1] 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 VTE.[i] 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 particular concerns about menstruation, contraception, fertility and pregnancy.[ii] Girls and women with SCD are at risk for having SCD-related pain with menses and thrombotic complications with oestrogen-containing contraception.[iii] [iv] 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 women without SCD.[v][vi] 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.

Several of these topic areas and research needs are addressed in ASH's portfolio of evidence-based clinical practice guidelines. Each guideline provides a description of the health problem in the introduction of the guideline as well as future research needs under each recommendation. For example, in ASH's *2018 guidelines for management of venous thromboembolism: venous thromboembolism in the context of pregnancy*, under recommendations 1 and 2: "The panel identified the following additional research need: more data are required regarding the safety of fondaparinux and the direct oral anticoagulants during pregnancy."

Diversity of Clinical Trials

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 as part of this Initiative. 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

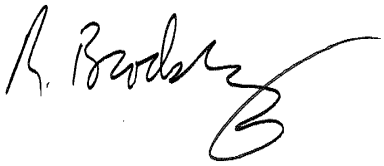
are excluded from clinical trials pertinent to their care. Studies such as Amit et al's (Management of hematologic malignancies: special considerations in pregnant women." Drugs 75.15 (2015): 172501738) highlight considerations for managing hematologic malignancies during pregnancy. Guidance from these 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.

Agency Coordination and Stakeholder Engagement

ASH is optimistic that the Initiative will address many of the hematologic conditions outlined in this letter as well as other women's health conditions. To ensure that stakeholders remain aware of and involved in the administration's work, the Society urges you to ensure that the offices of women's health across agencies better coordinate their efforts and increase collaboration when appropriate. The Department of Health and Human Services (HHS) Office of Women's Health is already responsible for running the HHS Coordinating Committee on Women's Health; this group should meet regularly and include representatives from the Department of Veterans Affairs and the Department of Defense who also are focused on women's health research. This expanded group should have public meetings and allow for stakeholder comment. Strengthening alignment across these diverse research areas is essential to foster a comprehensive approach, ultimately leading to more impactful advancements in women's health. The Biden administration's dedication to fostering better collaboration within the government will provide for a future where women's health research receives the attention and resources it deserves.

Thank you for considering these comments. Should you have any questions or wish to discuss these issues further, please contact Suzanne M. Leous, MPA, ASH's Chief Policy Officer, at *sleous@hematology.org* or 202-412-7531.

Sincerely,



Robert A. Brodsky, MD
President, 2023

Mohandas Narla, DSc
President, 2024

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