AMERICAN SOCIETY OF HEMATOLOGY
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ASH Recommendations to the NIH's RFI on its Strategic Plan for Research on the Health of Women

The National Institutes of Health (NIH) through this request for information (RFI), aims to update its current Strategic Plan for Women's Health Research FY 2019-2023 by addressing the following:

i. Research opportunities in the plan that should be modified to account for recent scientific advances.
ii. Emerging research needs and opportunities that reflect the changing landscape of the study of the health of women that should be added to the plan.
iii. Cross-cutting scientific themes (for example, multidisciplinary research, and/or utilizing data science, natural language processing, and artificial intelligence) or research-related themes that should be common to all future strategic goals and objectives (such as considerations of sex, gender, and age on health and disease, and health disparities).

Below are ASH's recommendations in response to NIH's request (also submitted electronically through the NIH's RFI submission site):

1) **Research opportunities in the NIH Strategic Plan for Women's Health Research FY 2019-2023 that should be modified to account for recent scientific advances.**
ASH believes several of the overarching goals of this strategic plan are relevant to the field of hematology. The Society commends the NIH for outlining a goal specifically aimed at training and supporting the careers of female investigators, which will be crucial for retaining female researchers in the workforce. ASH, however, recommends that the strategic plan clearly outline ways in which NIH will support work-family balance for women during pregnancy and afterwards (e.g., childcare resources). Highlighting efforts to enhance training, leadership, and mentorship for females especially those from underrepresented backgrounds is key.

Furthermore, to ensure the goals in this strategic plan are comprehensive and applicable to hematology and other medical disciplines, the Society suggests the following points of clarification and/or inclusion.

- **Clearly articulate goals that focus on transgendered individuals.** While the document references the value of research focused on sex and gender differences, there is no clear language specifying the importance of conducting research in transgendered females. Additionally, focused research on the effects of hormones (endogenous or exogenous) for cis and trans women is crucial for effective therapy development.
- **Prioritize the inclusion of pregnant individuals and females of reproductive age in clinical trials.** ASH suggests a slight revision to overarching goal #2 on page 11 to state the following "Advancing rigorous research (basic through clinical) that is relevant to the health of females throughout the reproductive lifespan."
- **State how the institutes are implementing (or plan to implement) NIH's policy on sex as a biological variable and inclusion of women in clinical trials cited on page 8**. ASH recommends transparency in the implementation of these policies as it will provide additional guidance for investigators applying for NIH grants.
- **Highlight NIH's strategy to enhance access to (and disseminate information on) research related to women's health in lay-friendly language**.

2) **Emerging research needs and opportunities that reflect the changing landscape of the study of the health of women that should be added to the plan.**

- Women's health is significantly impacted by hematology, and as such ASH recommends focused opportunities in the following areas:
    - **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 (Pasricha S.R et al. Iron Deficiency. Lancet. 2021 Jan 16;397(10270):233-248). However, studies are 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, ~150 million OC users face a 2-5-fold risk of venous thromboembolism (VTE) (Solymoss S. Risk of venous thromboembolism with oral contraceptives. CMAJ. 2011 Dec 13;183(18):E1278-9). While OCs are an essential therapeutic, the hematologic risk they pose warrants additional study.
    - **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.
    - **Inclusion of immunocompromised women (due to treatment or autoimmune disorder) 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 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): 1725-1738) highlight considerations for managing hematologic malignancies during pregnancy. Guidance from these types of studies should be considered when developing clinical trial inclusion/exclusion criteria.

3) **Cross-cutting scientific themes (for example, multidisciplinary research, and/or utilizing data science, natural language processing, and artificial intelligence) or research-related themes that should be common to all future strategic goals and objectives (such as considerations of sex, gender, and age on health and disease, and health disparities).**

- ASH recommends that the NIH consider the following cross-cutting scientific themes that will be relevant for the advancement of women's health research and clinical care both for hematologic diseases and other disease disciplines:
    - **Development of effective prediction models that could be used to predict disease risk, identify potential research gaps in care, and discern the implications of sex or gender on disease onset/progression.**
    - **Leveraging patient generated health data (e.g., menstrual apps) to study/ identify women at higher risk for bleeding disorders or development of anemia.** Taking advantage of such technologies (i.e.,

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women's health and fitness applications) that aren't currently being used in this manner could be valuable to understanding disease risk and development. Funding opportunities from the National Institute of Biomedical Imaging and Bioengineering focused on applications for women's health could further this aim.

- **Using machine learning models effectively to enhance precision medicine in women.** For example, can machine learning be used to predict what treatment protocols are likely to succeed in female patients based on their distinct attributes? For such predictions to happen, sex and gender will need to be included as part of machine learning models and biases that can sometimes occur in these models will need to be mitigated.
- **Implementation of tools to automate the analyses of sequencing results and pathology slides will reduce bias and further advance women's research and would be of great interest to the hematology field.**

ASH would like to thank the NIH for the opportunity to comment on this important subject and looks forward to serving as a resource for the Office of Research on Women's Health at NIH on this issue. Please contact the ASH's Deputy Director, Scientific Affairs, Alice Kuaban, MS, at akuaban@hematology.org for any additional information.

Sincerely,

Jane N. Winter, MD
ASH President