

Sex Differences Research, Precision Medicine, and the Future of Women's Health

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Abstract

The National Institutes of Health's (NIH) commitment to improving health outcomes for women and men through rigorous science has been compromised by the lack of basic science evidence obtained from female animals. To correct this limitation, in June 2015 the NIH announced expectations that "sex," as a biological variable, be included into research design and analysis in studies of vertebrate animals and humans (NOT-OD-15-102). Scientists must take the responsibility to implement this directive. However, in doing so, there is a risk that attention could be restricted to only studies of direct comparison between female/women and male/men. By contrast, understanding how sex influences health and disease needs to take a programmatic approach that includes the study of sex-specific conditions. A programmatic approach will assure the advancement of knowledge to improve women's health.

Introduction

ATTENTION TO WOMEN'S HEALTH has evolved from a limited focus on reproductive and breast health to encompassing all aspects of health from birth through old age.¹ In the era of individualized and precision medicine, innovative medical, surgical, pharmacological, regenerative, and genetic technologies are available to improve the health of women. Application of these technologies increases the potential to better diagnose and treat conditions, both acute and chronic, that are specific to women, occur more frequently in women than men, or that present with different symptoms and outcomes for women compared to men. To address the evolving definition of women's health, health care and academic research institutions have established women's clinical and research centers that encompass holistic approaches to women's health and include gynecological, reproductive, and obstetric services, as well as other medical subspecialties (e.g., cardiology, gastroenterology, immunology, hematology, endocrinology, nephrology, neurology, rehabilitation medicine, nutrition, and psychiatric services). Many of these centers were developed as a result of government-funded initiatives promoted by the Office on Women's Health in the Department of Health and Human Services (i.e., the Centers of Excellence in Women's Health) and by the Office of Research on Women's Health (ORWH) at the National Institutes of Health (i.e., the

Specialized Centers of Research on Sex Differences), and the training program Building Interdisciplinary Research Careers in Women's Health (BIRCWH).

Critical to the future advances in women's health is continued research into all aspects of female physiology and pathophysiology to provide the evidence base for practice guidelines and to educate the next generation of basic science investigators, clinical investigators, and healthcare providers. The National Institutes of Health's (NIH) commitment to improving health outcomes for women and men through rigorous science has been compromised by the lack of basic science evidence obtained from female animals.^{2,3} To correct this limitation, in June 2015 the NIH announced expectations that "sex," as a biological variable, be included into research design and analysis in studies of vertebrate animals and humans (NOT-OD-15-102). Scientists must take the responsibility to implement this directive. However, caution is needed in how this directive is interpreted by scientists and study sections who review grant applications. There is a risk that their interpretation may restrict attention to studies involving the direct comparison between female/women and male/men ignoring the contribution of sex-specific conditions. Understanding how sex influences all aspects of health and disease needs to take a programmatic approach that includes the study of sex-specific conditions.

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Legislation reintroduced into the United States House of Representatives in the form the “Research for All Act” (H.R. 2101) codifies the NIH support for the Specialized Centers of Research on Sex Differences. Passage of this bill will assure that these Specialized Centers of Research will continue. However, enthusiasm for the act also must be tempered on two fronts. First, the language of the final bill should not be restrictive, but rather flexible so that the Centers can expand their research scope to follow scientific discoveries. Second, in the need to increase understanding of the physiological processes that differ between women/females and men/males, it is possible to ignore those processes related to sex-specific conditions (i.e., those related to reproduction). The exclusion of the study of sex-specific conditions may actually slow progress in understanding women’s health across the life-span. Said another way, because there are sex-specific conditions, there are sex differences in all physiological processes. So, have we come full circle? Women’s health, viewed through the lens of sex differences, incorporates research into reproductive health and the physiological processes directed by the XX chromosomal complement, including hormonal changes accompanying puberty, pregnancy, and menopause that have lifelong consequences. Genomic analysis is a strategic part of the national Precision Medicine Initiative (www.nih.gov/precisionmedicine).⁴ Implied but not stated in the publically available web material is the inclusion of sex as a variable in specific studies. However, inclusion of the sex chromosomes in genome-wide association studies (GWAS) analysis to date is sparse,⁵ and we hope this new Precision Medicine Initiative will increase attention to the contribution of the sex chromosomes to health and disease. Investigators in women’s health research are developing statistical packages that consider the sex chromosomes and X chromosome inactivation in GWAS. Including analysis of the X chromosome is critical to understand sex differences and to ensure the success of the national precision medicine initiative.

An Integrated Approach to Women’s Health: A Case Example

The future of women’s health requires development of models to sustain basic and clinical research and educational initiatives in women’s health in the absence of, or in spite of, specific government directives. Women’s health must become a natural part of the culture of clinical practice, discovery science, and medical/health education.

Mayo Clinic has embraced individualized (precision) medicine as a strategic investment in the future of health care. The strategy is an evidence-based practice built on basic discoveries of the root causes of disease.⁶ By definition, a cornerstone of precision care is to recognize the contribution of biological sex (as dictated by the complement of sex chromosomes) and of gender (that includes cultural and environmental influences that define feminine and masculine).^{7,8}

Some women’s health clinics and research centers focus on specific patient subsets and activities that reflect the clinical and research expertise of their faculties. The Specialized Centers of Research on Sex Differences funded by the NIH in association with ORWH represent a model for the development of interdisciplinary teams. These Centers act as cata-

lysts to discovery and advancement of knowledge to improve the quality of care for women by incorporating both sex differences and sex-specific conditions. This approach also can be applied more broadly in other research and clinical areas not typically considered “women’s health.” For example, ongoing research in women’s health and sex-based medicine at Mayo Clinic crosses multiple specialties. These programs include collaborations between engineers, primary care providers, and oncologists to develop imaging modalities that can better detect breast cancers in women with dense breasts that are not easily identified by conventional mammography.⁹ Gynecological surgeons partner with oncologists and molecular scientists to develop non-invasive and sensitive tests to detect endometrial cancer.¹⁰ Epidemiologists partner with gynecologists and internists to identify health disparities related to uterine fibroids in ethnic minorities,^{11,12} risks of overall mortality, and chronic diseases in women who have undergone oophorectomy,¹³ and conditions of pregnancy such as hypertension, preeclampsia, eclampsia, and gestational diabetes that affect lifelong risk for cardiovascular disease in women.¹⁴ However, in addition to these more typical women’s health arenas, cardiologists partner with basic scientists and surgeons to investigate sex differences in the etiology of valvular calcification and heart disease,¹⁵ and with neurologists to evaluate how the autonomic nervous system contributes to the etiology of postural orthostatic hypotension and fibromyalgia.¹⁶

With the aging of the population, investigation of sex-specific molecular pathways associated with age-related diseases such as sarcopenia are being pursued to understand how interventions may slow these processes.¹⁷ Radiologists are working with neurologists to develop improved methods to detect sex-specific alterations in brain structures associated with cognitive decline.¹⁸ These initiatives are probably not unique to our organization but most likely reflect similar activities at other academic medical centers. These projects share an understanding that there are sex differences in the physiological processes under investigation and that these differences impact women’s health. Thus, sex and hormonal status are key biological variables for organ and tissue transplantation, regenerative medicine, and pharmacogenomic programs. The support for sex-specific as well as sex-different initiatives will require dedicated medical services and patient-specific biorepositories. For example, sex-specific clinical databases can be developed within existing women’s health clinics such as the Data Registry on Experiences of Aging, Menopause, and Sexuality (DREAMS) developed by the Mayo Clinic Women’s Health Clinic. The DREAMS project was designed to study, for example, the effects of caffeine intake on menopausal symptoms,¹⁹ women’s views of menopause and the symptoms experienced, and the association of recent physical and mental abuse with menopausal symptoms. Similar clinical initiatives provide resources to junior investigators in women’s health to develop longitudinal studies of women as they age.

It Doesn’t Stop with Research

Discoveries from research related to women’s health and concepts of sex and gender differences in physiology and pathophysiology must become embedded into the material used to train future scientists and health care providers. The

ORWH sponsored BIRCWH programs support early career investigators in women's health. Programs such as the BIRCWH need to be sustained and expanded to create a critical mass of investigators leading and catalyzing research teams in women's health.

Community, academic, national, and global partnerships are developing innovative educational materials and curricula to train the next generation of women's health scientists and healthcare providers.²⁰ Opportunities are available to develop and test these curricular materials focusing on sex- and gender-based evidence in all phases of health care education through projects supported in part by the NIH, the ORWH, the American Medical Women's Association, the Canadian Institutes of Health Research, the European Gender Medicine program, the Society for Women's Health Research, the Organization for the Study of Sex Differences, and the Sex and Gender Women's Health Collaborative. Utilization of these educational materials will stimulate future research, facilitate translation of discoveries into patient care, and ultimately will reduce health disparities for women by improving their care.

Summary

Patient-centered, precision medicine defines 21st century health care. Viewing the patient through a sex and gender lens is a first step toward personalizing care. However, personalized healthcare must be based on evidence derived from research designed to study how sex and hormonal status influence health across the life-span. The Mayo Clinic approach to translation of women's health research into clinical practice is embodied by innovative technologies driving discovery in regenerative medicine, organ and tissue transplantation, and pharmacogenomics. This approach may serve as a model by which other academic institutions can expand their women's health research programs. Ongoing initiatives in healthcare education are required to assure that future healthcare providers, researchers, and educators recognize that sex matters when making decisions about prevention, diagnosis, disease management, and patient outcomes. A plan to successfully integrate sex difference research and precision medicine should include research of sex-specific conditions.

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