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Sex and sensitivity: the continued need for sex-based biomedical research and implementation

Candace M Tingen^{1*}, Alison M Kim^{1*}, Pei-Hsuan Wu² & Teresa K Woodruff^{1,2}

The phrase 'women's health research' embraces women as part of the biomedical research engine while categorizing women as separate. Before personalized medicine can become a reality, we must first ensure that basic physiological differences between the sexes are clearly delineated. In this article we argue that research into sex differences should be encouraged at the most fundamental levels of the biomedical sciences. Moreover, appropriate representation of both sexes as participants in clinical studies is still critically needed. Academic and governmental organizations must continue to articulate strong policy in order to ensure inclusion and analysis of sex as a critical variable. Focused attention on sex as a contributing factor to health, disease and therapeutic activity will increase our fund of knowledge regarding our everyday health, increase the pace of clinical research and ensure a healthier population.

Developments in research and technology, such as decoding the sequence of the human genome, have paved the way for the personalized medicine revolution. In personalized medicine, "each patient is an individual with unique biology, not some biological everyman"; a tailored care plan allows "the ability to approach each patient as the biological individual that he or she is, thereby radically changing our paradigms and improving efficacy" [1]. This individual-specific approach brings attention to genetic risk profiles, environmental factors, life and family circumstances, patient values and decision-making styles that can affect health and is supported by some of today's most influential leaders, including the current head of the NIH, Dr Francis Collins, and President Barack Obama.

We believe that sex-based medicine is the next step in offering true personalized medicine because sex is an important determinant in the experience of health, the diagnosis and treatment of disease and the quality of life after a medical intervention, and is implicitly good for both sexes (reviewed in [101]). There is a strong correlation between sex and the incidence, prevalence, symptoms, ages at onset and severity of disease as well as the reaction to drugs. A review of the current literature reveals significant sex differences in many diseases that are unrelated to reproduction, such as certain mental disorders (e.g., major depressive disorder, schizophrenia, autism, eating disorders and attention-deficit hyperactivity disorder),

autoimmune diseases (e.g., rheumatoid arthritis, lupus and multiple sclerosis), asthma and several types of cancer [2,102,103]. We must keep in mind these biological differences from the onset of, and throughout, development and administration of all drug and technology design phases.

Sex-based science & medicine are good for all

As we recognize new biomedical breakthroughs and think about the future of women's healthcare, we believe that sex-based medicine is implicitly good for both sexes and that sex-based development of new technologies will improve healthcare and cut costs for all. We have recently published an article arguing that sex differences research centers that encourage representation from both sexes in clinical studies are still critically needed [3]. In that short piece, we briefly mention the levels of biomedical research, production and education at which sex differences research is most urgently needed, and most readily able to be implemented. However, we believe this argument benefits from further elaboration on both the current deficits and potential opportunities for sex differences research. Herein, we contend that a sex-based approach is vital at four separate checkpoints in the pipeline of biomedical discovery and dissemination: biomedical research; medical education and clinical diagnosis; the development of therapeutics and diagnostics; and patient access to healthcare.

¹Department of Obstetrics & Gynecology, Feinberg School of Medicine, Northwestern University, Chicago, IL 60611, USA

²Department of Biochemistry, Molecular Biology & Cell Biology, Northwestern University, Evanston, IL 60208, USA

*Author for correspondence:

Tel.: +1 312 503 2504

Fac: +1 312 503 0219

tkw@northwestern.edu

*These authors contributed equally to this work

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- sex difference

Sex-based differences in biomedical research

With the recent push for women's health research and an NIH mandate for appropriate inclusion of both sexes in government-funded studies, the scientific community has accumulated enough evidence regarding fundamental physiological and behavioral disparities between the sexes to merit the integration and prioritization of sex-based considerations into research design (FIGURE 1). In mice, hundreds of genes have been demonstrated to have different expression levels in males and females in a number of tissues [4], indicating that there is an inherent difference between the sexes at the most basic level of our biological makeup. These inherent variances are complicated by differential changes in hormone levels and accompanying physiological responses to these changes in men and women, although not all sex differences are attributed solely to hormones. The etiology of sex-based differences extends beyond the sex chromosomes to phenomena such as imprinting, in which the males and females uniquely modify the genomes inherited by their progeny (reviewed in [5]). Diseases such as Prader–Willi Syndrome and Angelman Syndrome have been attributed to anomalies in genomic imprinting, demonstrating the potential impact of these imprinting differences [6]. Together, the identification and understanding of sex-based characteristics, particularly in the

diseased state, remains a great need in research at all levels, from the single cell to animal models to human subjects [7].

Sex-based differences in medical education & clinical diagnosis

The utility of sex-based research is undermined if the results of these endeavors are not directly translated to the clinic. Clinicians' awareness of and sensitivity to sex-based differences in physiology and behavior should be honed in medical school to extend into their individual practices. Awareness of this educational need has been growing, with more medical schools urged to revise their curricula to be more inclusive of women's health. In 1996, the American Board of Internal Medicine released a set of recommendations for medical educators based on "the belief that internists should be trained to provide comprehensive care to men and women based on an awareness of the influences of gender ... on an individual's health" [8]. Unfortunately, an independent survey conducted a decade later concluded that few medical schools had fully incorporated sex-based education into their curricula, nor did they offer courses or clerkships in women's health [9]. As our understanding of sex differences continues to expand past the reproductive system, sex-based medicine must become a primary consideration for all clinicians in their interactions with and treatment of patients.

Others have argued that practicing physicians also lack appropriate and up-to-date knowledge of the scientific literature, thereby compromising their ability to accurately diagnose their patients in a sex-based manner [10]; for example, a recent survey revealed that only one in five physicians were aware that more women than men die from cardiovascular disease each year [11]. It is well documented that female and male patients are affected disparately by diseases outside the realm of reproduction, in conditions such as cardiovascular disease [12], stroke [13] and diabetes [14]. Not only do these illnesses present differently in men and women, but these sex-based differences extend to disease management and prognosis as well [15–17].

Aside from the biological, sex-based disparities, there are also behavioral, gender-based disparities between male and female patients and the manner in which physicians interact with them. A linguistics study found that among patients with chest pain, female patients tended to describe their emotional state more than their physical suffering compared with male patients, who directly communicated their illness and their interest in

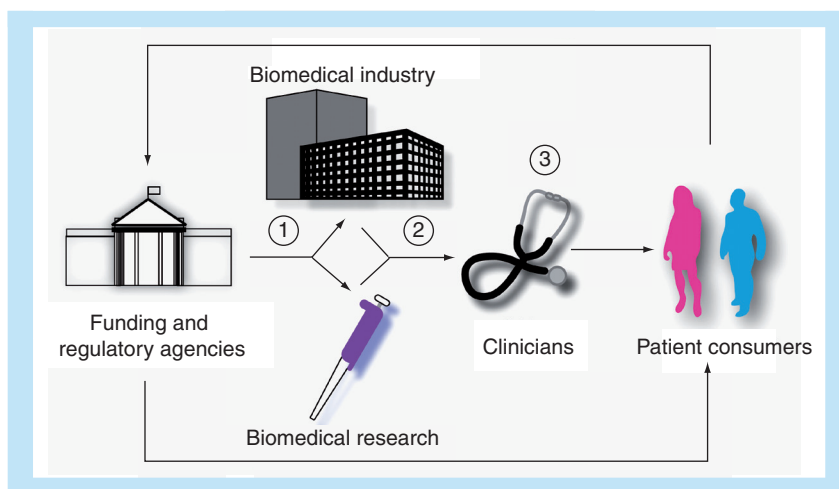


Figure 1. Blueprint for inclusion and explanation of sex differences in biomedical research. Research into sex differences can be promoted by each of the primary participants in biomedical research as follows: **(1)** regulatory and funding agencies extend their requirement for sex inclusion from humans to preclinical animal studies; **(2)** journals require their authors (i.e., scientists in biomedical research and industry) to address sex-based differences in research design and data analysis where appropriate, or clearly designate and justify a single-sex study; and **(3)** clinicians continue their education in sex differences research via surveys of the literature and participation in physician education initiatives, in order to better treat and educate patient consumers.

treating it [18]. There is also evidence of gender bias on the clinician's part when treating female patients; for example, some studies show that complaints from female patients are more likely to be perceived as emotional rather than organic [18]. The Task Force on Women's Health Issues (US Public Health Service) argued that attributing women's health concerns to overanxiousness while accepting men's concerns as normal would risk ineffective treatment of both genders [19].

Even when there is a clearly defined sex-based difference in disease manifestation and risk, as in cardiovascular disease, physicians were prone to assigning female patients to a lower risk category, although their calculated risk was actually similar to those male patients [11]. These observations emphasize the importance of continued education for even experienced clinicians, as physiological and behavioral differences between males and females have become better defined with time. This way, clinicians may apply emerging knowledge into their practice to enhance and tailor patient care in a sex- and gender-based manner. The movement for health provider education is growing through organizations such as the Women and Heart Disease: Physician Education Initiative, which was established by the New York State Department of Health, the New York Chapters of the American College of Physicians, and the American College of Obstetricians and Gynecologists to promote physician awareness of sex-based risk factors in cardiovascular disease [20]. This organization has recently tested a pilot program in which physicians in an obstetrics and gynecology office participated in an educational session on hypertension and subsequently demonstrated improved rates of referral and patient counseling on sex-based cardiovascular risk factors, illustrating the effectiveness of continuing education for clinicians [21].

Sex-based differences in the development of diagnostics & therapeutics

As previously discussed, a number of diseases present differently in men and women, suggesting that protocols for diagnosis and treatment also require customization based on the sex of the patient. We have already discussed differential gene expression in males and females, as discovered in animal models. These variables are further confounded by disease states and a single disease can induce variable physiological reactions based on one's sex; for example, male and female patients with non-small-cell lung cancer were shown to have differential activation of signaling

pathways [22]. Such observations have dire consequences on the utility of biomarkers, which may need to be used selectively based on the sex of the patient. The same is true of therapeutics, if the disease is manifested differently in females and is therefore improperly targeted with an inappropriate treatment method.

Sex should be a prominent consideration not only when defining the therapeutic target, but also the therapeutic mechanism; for example, drug efficacy is influenced by the number of factors including body weight, body composition, and metabolism. However, despite the fact that women weigh less with a higher percentage of body fat than men [23], and sex-specific differences in enzyme activity have been described [24–26], drug doses are often not corrected for these parameters. Even among drugs that have a greater than 40% difference in pharmacokinetics between males and females, sex-specific recommendations for drug dosage were absent on the product labels [23]. This may partially explain why females have a higher risk for adverse drug reactions than their male counterparts [27]. Sex-dependent effects of therapeutics should be better advertised not only to the patient-consumer, but also to the clinician.

Sex-based differences in patient access to healthcare

The debate over healthcare reform in the USA is one of the dominant discussions in American politics; its passage will clearly affect every citizen, but may be disproportionately important for women. Women are the largest consumers of healthcare in the USA; in their reproductive years, women visit their primary care physician significantly more often than men and have more diagnostic testing ordered [28]. This increased use is associated with increased costs, but women also have increased costs for services that they use at the same rate as men, including specialty clinic and emergency department visits [28]. The cost of healthcare is particularly important for women because women tend to have lower incomes [29], and therefore end up spending a higher percentage of their total income on health services [30]. Insurance coverage is also significantly different between men and women. Among workers, women are less likely to be eligible for their employer's sponsored health plan because they are more likely than men to work part-time and have lower incomes [31]. Even among those covered by employer-sponsored insurance, women are less likely to be insured through their own job and more likely to be insured as a dependent on their spouse's plan [31]. This makes women much

more susceptible to losing coverage owing to death of a spouse or divorce. In the circumstance of loss of employer-provided insurance, women encounter greater difficulty obtaining individually purchased insurance owing to the practice of gender rating, an insurance company practice where women are charged higher premiums than similarly aged men with the same health history, supposedly due to the increased use of the healthcare system by women. Indeed, women's premiums can be up to 2.5-times higher than men's if maternity coverage is included, and nearly twice as high, excluding maternity benefits [32]. The recent Affordable Healthcare for America Act passed by Congress specifically disallows gender rating, but only for individuals and small businesses (less than 100 employees). Plans offered by larger businesses are not prohibited from charging women more for the same coverage [104]. Probably as a result of all of these factors, approximately half of women are either uninsured or underinsured [33], a clear factor in the decision to avoid seeking medical care or filling out needed prescriptions owing to cost [34]. In fact, women are much more likely than men to avoid healthcare because of cost, to have problems paying their medical bills, and to accrue medical debt [33]. It is clear that any measures enacted that make insurance more affordable by capping premiums or restricting the ability of insurance companies to deny coverage will help both men and women, but could have more impact on women because of their current deficits in income, insurance coverage and ability to pay for healthcare.

Future perspective

Emerging from our discussion of sex-based medicine are a number of opportunities that can improve the health of all people. There are specific changes that may be implemented easily and immediately by each of the primary stakeholders in the process of scientific discovery and communication, which are listed below, in order to promote sex-based research and medicine:

- The distributors of scientific knowledge, namely, scholarly journals;
- The funding agencies and regulatory bodies charged with support and oversight of scientific endeavor;
- The producers of scientific content, the scientific and clinical researchers.

As the distributors of scientific content, scientific journals serve as the gatekeepers that uphold a standard of scientific review and communication

before knowledge is communicated to the wider research and medical communities and to the general public. For this reason, we recommend that scientific journals and their editorial staff require authors to address sex-based differences in their research designs and analyses where appropriate, or provide justification for pursuing a single-sex study. Furthermore, if an outcome is measured in a single sex, that outcome should be designated and communicated as such. A simple change in how we present preclinical and clinical research findings in journals will enhance the sex-specific scientific literacy of practitioners and ensure that the general public is informed regarding the limits of our knowledge. Second, we strongly support a change in public funding agency policy that will extend the current requirement for sex-inclusion in human trials to preclinical animal studies. If funding is limited or there is clear parity between the sexes in a particular end point, the applicant would identify and address these issues in the grant proposal. Implementation of a requirement for inclusion or explanation is particularly important for the US FDA, which oversees pharmaceutical studies; where appropriate, all clinical trials should represent both sexes equally in their study designs and sex should always be included as a variable in data analysis and interpretation. Understanding sex-based variables will improve the efficiency, application and cost-effectiveness of large pharmaceutical studies. With the recommended change in funding agency policy – including that of the NIH, the National Science Foundation and the Medical Research Council, among others – all investigators funded by taxpayer dollars would be asked to consider the sex-based aspects of their proposed research and the potential impact on anticipated outcomes. Finally, and perhaps the most challenging change to implement, is an improvement in the education of clinicians and researchers regarding the value of sex-based research. This important literacy initiative can be incentivized through an increase in funding and publication opportunities for sex-based research, as well as the application of penalties for opting out. We anticipate that these systematic changes will result in a significant and important shift in the way research is done, advance the analysis of basic and clinical research findings, promote more rapid translation of these findings to the clinic, and improve patient care by providing medicine that takes into account sex as a determinant in health and disease.

Executive summary

- Studying sex-based differences in basic science and clinical practice is the first step in personalized medicine. Sex-based differences must be analyzed in four areas: biomedical research; medical education and clinical diagnosis; the development of therapeutics and diagnostics; and patient access to healthcare.

Sex-based differences in biomedical research

- Biological sex differences come from more than just sex chromosomes and hormones; they also extend to the gene expression patterns across the genome.

Sex-based differences in medical education & clinical diagnosis

- Clinicians are not always properly educated regarding differences in the presentation of disease in women. They are also more likely to underestimate the risk of disease and attribute patient-reported symptoms to anxiety or emotion in women as compared with men.

Sex-based differences in the development of therapeutics & diagnostics

- The presentation of disease differs based on sex. Pharmacokinetics are also sex-specific owing to differences in body weight, fat distribution and metabolism, but sex-specific drug dosages are often absent from drug labels.

Sex-based differences in patient access to healthcare

- Women are the primary users of medical care in the USA. Despite lower incomes, women pay more for medical care, are less likely than men to be covered by their employer's plan, are more likely than men to have only the unstable coverage of a spouse's employer, and pay more for private insurance.

Future perspective for change

- In order to address these sex and gender disparities, we propose that scientific journals require sex differences to be analyzed and addressed or for the exclusion to be explained, that funding and regulatory agencies implement these same requirements for patent or grant proposals, and that researchers and clinicians make the effort to educate themselves regarding sex differences in biomedicine.

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- **Great resource for showing the real benefits of the Affordable Healthcare for America Act for women specifically; it also points out places where reproductive rights were overlooked or excluded from the reform.**