OPINION

Sex, equity, and science

Teresa K. Woodruff[1]

Women's Health Research Institute, Northwestern University, Chicago, IL 60611

It's clear that 2014 has the potential to be a big year for realizing equality in women's health research and care.

First came an announcement from the National Institutes of Health (NIH) on new partnerships that are being formed between the NIH, drug companies, and nonprofit organizations to target intractable diseases such as Alzheimer's disease, type 2 diabetes mellitus, rheumatoid arthritis, and lupus (1). The formation of these unconventional partnerships suggests that it is no longer business as usual at the NIH under the direction of Dr. Francis S. Collins and taking aim on stubborn diseases is something we welcome. Perhaps most importantly, the diseases in the NIH crosshairs disproportionately impact women. Nearly two-thirds of Americans with Alzheimer's are women (2), 90% of adults with lupus are women (3), and women are three times as likely to suffer from rheumatoid arthritis than men (4). It is therefore critical that drug development—from bench to bedside, from in vitro studies with cells and model systems to clinical trial design—include females. The NIH insists on reporting the sex of human subjects by grantees; the next step is to ask for the same kind of attention to be placed on animal research.

Therefore, we were equally thrilled by a second statement from Dr. Collins published in *Nature* that "crucial experimental design elements are all too frequently ignored including. . .the effect of sex differences" (5). This deliberate attention to sex differences by the NIH director will go a long way toward encouraging the basic science community to focus on sex as an important variable in the earliest steps of the discovery process. If we can learn where sex matters during the initial developmental phases of the scientific research pipeline, we will reduce costs in the later testing phases, reduce the risk of adverse events, and improve the efficacy of drugs based on a "personalized" approach (6).

These issues seem like "no brainers"; however, very little is known about how sex matters in developing drugs and designing medical devices. Why? Because women are not equally included in basic science studies or in preclinical research, and where they are included, the impact of sex on outcomes is rarely analyzed. Despite calls for action and a growing body of literature on the broad influence of sex on biological function—from heart to liver to bone—statistics of female inclusion in laboratory or clinical investigations have moved barely or not at all (7, 8).

Indeed, the January 2014 issue of the *Journal of Women's Health* published an analysis (9) of the inclusion of women in postapproval medical device studies based on US Food and Drug Administration (FDA) draft guidelines (10). Their study revealed that only 14% of device studies included sex as a key outcome measure and only 4% included a subgroup analysis for female participants. This may seem shocking, but this lack of sex-based analysis has been well known for many years despite repeated efforts to advocate for its inclusion in study design (7). Although no formal mandates have yet been issued, the FDA is now drafting an Action Plan to be released this year that emphasizes the importance of recognizing the unique clinical needs of women by the medical device industry (11).

Attention to sex differences by the NIH director will go a long way toward encouraging the basic science community to focus on sex as an important variable in the earliest steps of the discovery process.

Comparable oversight is needed in the realm of drug development. As a case in point, adverse events reported for Ambien recently skyrocketed, largely because the drug has a delayed clearance rate in women compared with men. The FDA finally took concrete action on Ambien and created the first ever sex-specific labeling that recommends a lower dose for women. Given that the removal of drugs and medical devices from the market after approval largely results from adverse events in women (women have a nearly twofold greater risk of developing adverse drug reactions than men) (12, 13), this action by the FDA is welcome news and shines a spotlight on the larger issue of the need for sex-based research in drug development.

Teresa K. Woodruff.

Fueling the conversation on sex differences in research can only get us so far; government support is essential to restore health in the cases of the stubborn diseases targeted by Francis Collins above, to ensure that the FDA tests devices in both sexes and that drugs are approved based on efficacy and pharmacology that is right for men and women. President Obama's State of the Union Address alluded to increased funding for research to "undo the damage done by last year's cuts to basic research," and Congress agreed to increase funding for public health services. Both are positive advances that can provide opportunities to accelerate sex-based research. Just as we have called for equity of pay and rights for women in the workforce, so must we call for sex and sex

Author contributions: T.K.W. wrote the paper.

[1]E-mail: tkw@northwestern.edu.

parity in research design and execution. It is time that researchers, providers, industry, and citizens advocate for processes aimed at improving the quality of basic science and clinical outcomes by including sex in study design and drug testing.

We welcome 2014 and the attention on sex as a critical part of biomedical research by thought leaders, funders, and governmental agencies. Ensuring that basic and clinical science accounts for the physiological differences in men and women will lead to better science, better preventive and therapeutic options, and better health care for all.

ACKNOWLEDGMENTS. This work is endorsed by the Leadership Council of the Women's Health Research Institute of Northwestern University.

1 Kolata G (2014) An unusual partnership to tackle stubborn diseases. *New York Times*, February 5, p A14.
2 Alzheimer's Association (2012) Alzheimer's disease facts and figures. Available at http://www.alz.org/downloads/facts_figures_2012.pdf. Accessed February 24, 2014.
3 Office on Women's Health US Department of Health and Human Services (2014) Lupus fact sheet. Available at http://www.womenshealth.gov/publications/our-publications/fact-sheet/lupus.html. Accessed February 24, 2014.
4 Centers for Disease Control and Prevention (2010) NHIS arthritis surveillance. Arthritis prevalence in women and men. Available at http://www.cdc.gov/arthritis/data_statistics/national_nhis.htm. Accessed February 24, 2014.
5 Collins FS, Tabak LA (2014) Policy: NIH plans to enhance reproducibility. *Nature* 505(7485):612–613.
6 Soldin OP, Chung SH, Mattison DR (2011) Sex differences in drug disposition. *J Biomed Biotechnol* 2011:187103.
7 Kim AM, Tingen CM, Woodruff TK (2010) Sex bias in trials and treatment must end. *Nature* 465(7299):688–689.
8 Woodruff TK, Kibbe MR, Paller AS, Turek FW, Woolley CS (2014) 'Leaning in' to support sex differences in basic science and clinical research [published online before print February 7, 2014]. *Endocrinology*, 10.1210/en.2014-1068.
9 Pinnow E, Herz N, Loyo-Berrios N, Tarver M (2014) Enrollment and monitoring of women in post-approval studies for medical devices mandated by the Food and Drug. *J Womens Health (Larchmt)*, 10.1089/jwh.2013.4343.
10 Food and Drug Administration (2011) Draft guidance for industry and food and drug administration staff: Evaluation of sex differences in medical device clinical studies. Available at http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm283453.htm. Accessed February 24, 2014.
11 McMurry-Heath M (2013) Considering women's needs in developing medical devices: Here's "HoW." Available at http://blogs.fda.gov/fdavoice/index.php/2013/08/. Accessed February 24, 2014.
12 Tharpe N (2011) Adverse drug reactions in women's health care. *J Midwifery Womens Health* 56(3):205–213.
13 American Association for Justice (2013) Unequal harm: The disproportionate damage to women from dangerous drugs and medical devices. Available online http://www.justice.org/cps/rde/xbcr/justice/AAJ_Unequal_Harm.pdf. Accessed February 24, 2014.