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Commentary

Why "sex as a biological variable" conflicts with precision medicine initiatives

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Policies that require male-female sex comparisons in all areas of biomedical research conflict with the goal of improving health outcomes through context-sensitive individualization of medical care. Sex, like race, requires a rigorous, contextual approach in precision medicine. A "sex contextualist" approach to gender-inclusive medicine better aligns with this aim.

In recent years, biologists and women's health advocates in the field of "sex-based biology" have aligned their work with the goals of precision medicine.[1] Attending to sex, they argue, is part and parcel of both an individualized approach to patient care and a precise approach to gender-specific medicine. This is most clear in the literature supporting the NIH's Sex as a Biological Variable (SABV) policy requiring the inclusion of male and female materials in preclinical research. Dr. Janine Clayton of the NIH Office of Research on Women's Health (ORWH), a leading advocate of the much-debated mandate, has characterized the policy as "one step toward the more individualized approach to human health that is the trajectory of medical practice and the aim of the Precision Medicine Initiative."[1]

Precision medicine advocates aim to account for individual variability using large multidimensional genomic, environmental, and lifestyle datasets.[2] Policies that require male-female sex comparisons in all areas of biomedical research are in tension with the goal of improving health outcomes through context-sensitive individualization of medical care. As critics of SABV mandates, including ourselves, have argued, an intensive focus on documenting sex differences risks producing decontextualized results with little relevance to human health.[3] For example, early claims that excess male COVID-19 mortality was due to biological sex differences obscured within-sex differences in mortality, such as the fact that Black women died at higher rates than white women and white men, and neglected important social candidate causes, such as patterns of occupational exposure, compliance with masking and hand-washing advice, and access to healthcare.[4]

A one-size-fits-all approach to sex also comes at the expense of the rigor and precision at which precision medicine aims. In a recent reanalysis of 147 articles identified by Nicole C. Woitowich and colleagues[5] as conforming to best practices for sex-based biology, Yesenia Garcia-Sifuentes and Donna L. Maney[6] showed that over 70% of papers claiming to find differences in treatment responses between males and females did not perform the statistical comparisons that would be necessary to demonstrate that a sex difference existed. Similarly, a reanalysis of a headline-making paper purporting to show sex differences in immune response to COVID-19 demonstrated that the evidence overwhelmingly pointed to null findings of sex similarity.[7] Furthermore, researchers who study sex differences rarely specify how they operationalize sex. All too commonly, researchers assert sex differences based on aggregations of data by physician- or patient-reported "sex" or "gender" without specification and actual analysis of underlying variables that account for these differences, and an *a priori* study design suitable to doing so. These results replicate long-standing concerns that methodological shortcomings render sex comparisons in biomedical research spurious at worst and unintelligible at best,[8] resulting in a "catalogue of differences"[9] with little relation to real-life, embodied health disparities. As epidemiologist Janet Rich-Edwards and colleagues warn, "without careful methodology, the pursuit of sex difference research, despite a mandate from funding agencies, will result in a literature of contradiction."[10]

Precision medicine visionaries understand these issues well when it comes to race. For example, in a recent high-profile perspective in *Cell*, Joshua Denny, director of the NIH's "All of Us" initiative, and NIH Director Francis Collins sketched an expansive vision for the future of "Precision Medicine in 2030."[11] Race, they argued, is just the sort of crude category that precision medicine is poised to deflate. As they write, the use of race as a variable "conflates a plethora of social, cultural, political, geographic, and biological factors together and can perpetuate systemic racism." A precision medicine approach, by contrast, would eschew race-categorization, engaging instead in the "routine collection of social determinants of health in both research and clinical care in combination with more precise measures of environmental influences, habits, and genetic ancestry," yielding "more rational, etiology-based adjustments" and "better risk stratification and

treatments." Denny and Collins link precision medicine with the aim of reducing the use of overly crude biological classifications such as race in biomedical research and in the clinic. In doing so, they join a chorus of scientists and philosophers who have shown that race, as a biological category, is at best a bad proxy variable and at worst a reproduction of social hierarchy.[12]

Similarly, there are better approaches to the analysis of sex-related variables in biomedical research, ones that align well with the aims of precision medicine. For example, in contrast to mandates to disaggregate and compare data by binary male and female sex, a "sex contextualist" framework recognizes the pluralism and context-specificity of sex as a biomedical research variable.[13] What this means in practice is defining and analyzing sex-related biological variables within well-specified contexts, including individual life history, social and physical environment, laboratory and technological constraints, species, strain, developmental stage or age, and level of biological analysis. This reflects what biologists already well know: that factors associated with sex-differentiated biological pathways cut across many different forms of biological organization, from chromosomes to tissues, hormones, and organs.

These multiple instantiations of "sex" do not align in simple or predictable ways. In some cases, such as karyotype, sex may be well understood as a categorical variable, whereas in other contexts, such as measuring gonadal hormone levels, it may vary continuously.[14] Furthermore, some sex-associated traits, such as hormone levels, vary over the life of an individual, and are highly mutable, as for instance by exogenous supplementation, diet, and social roles.[14] Sex contextualism recognizes that male-female comparisons, in many cases, are insufficient or unnecessary to detect sex-related variation, and that findings of sex differences in one context may not be generalizable to another. On this view, sex-related variables are not omnirelevant, but emerge as relevant or not within the context of a research program or other pragmatic aim.

When we closely attend to the empirics of sex/gender systems across species, research questions, and laboratory experimental set-ups, we see that researchers by necessity make choices among many options for operationalizing sex in clinical and preclinical research, and for integrating consideration of biological and social variables in our understandings of health and behavior. This means that scientists and policymakers must grapple with the responsibility and the challenge of discriminating among these options. Importantly, discharging this responsibility begins with taking the causal relevance of any particular dimension of sex to be an empirical question, rather than an *a priori* assumption. Like race, sex-associated variables must be subjected to high standards for rigorous causal inference and judicious norms for proxy variable choice. As biocultural anthropologist L. Zachary DuBois and evolutionary biologist Heather Shattuck-Heidorn write, "there are unnecessary and potentially inaccurate linkages made when binary categories of sex are exclusively drawn on to interpret sex-associated biology…. When used in this way, the *categories themselves* are interpreted as *proxy for pathways* and thus biological differences are concluded to be "sex-based," as opposed to driven by some other mechanism."[14] A contextualist approach avoids begging the question of the relationship between biological variables and "sex-associated" outcomes, which may actively mislead researchers in pursuit of sex-specific prevention and treatment interventions.

Taking seriously the social consequences of sex-based classification, such as the stigmatization of allegedly "abnormal" testosterone levels that depart from binarized expected values, also means that the "inclusion" of sex in biomedicine carries more ambivalent ethical weight than advocates allow.[14] As scientific journals begin to adopt publication guidelines informed by science funding mandates, a contextualist approach can help researchers evaluate both the pursuitworthiness and the epistemic merits of sex-based biology in ways that better capture the material, epistemological, and social complexities of rigorous scientific practice, and which vary appropriately across research contexts.

Precision medicine initiatives such as the "All of Us" program will structure scientific research and funding priorities for decades to come. From our vantage as scholars of sex and gender science, the promise of precision medicine hinges on the rigor and criticality with which aims of precision are applied to crude categories such as male and female sex. Notwithstanding, of course, vital concerns about privacy, ethics, and equity,[2,15] a precision approach to biomedical research could bring a positive realignment of sex and gender science: shifting away from blunt and often uninterpretable "sex" categories and toward contextually specified use of sex-related biological variables, integrated with the study of gender-related social and environmental variables. We caution that superficial attempts to incorporate considerations of sex into precision medicine could result, as SABV policies have, in the proliferation of decontextualized and uninterpretable claims of biomolecular differences tagged as "male" or "female." Treating sex as a binary biological variable, uncoupled from research context, its social dimensions, and from intersecting demographic and environmental variables, is anything but precise.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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