

Gender and the Genome: A New Journal for the 21st Century

Marianne J. Legato, MD, PhD (hon.c.), FACP^{1,2}

“Moving forward in science is as much unwinding the distorted thinking of the past as it is putting a clearer idea on the table.”¹

—Craig Venter

THE NUMBER OF E-MAIL solicitations for contributions to freshly minted journals is at an all time high. How do we defend proposing another? Because *Gender and the Genome* fills a unique niche in 21st century medical publishing. It has a specific well-defined mission—a mission that reflects and integrates two scientific developments that have revolutionized our ability to understand and to manipulate the human phenotype: the development of gender-specific medicine (GSM) in the last decades of the 20th century and, in the first decades of the 21st century, arguably the greatest achievement in the history of mankind: decoding the structure of the human genome. Both are transformative, exponentially expanding developments and demand the integration of the two into a coherent approach to biomedical investigation.

What Does Sex Have to Do with It?

It is curious that while the conviction that men and women are different is arguably as old as human life itself, an effective exploration of HOW different is less than two decades old. After the observation that specific diseases often had a different prevalence in men and women, the effort to explore WHY those differences exist was seldom if ever pursued; most often clinical investigators attributed them to a vaguely defined impact of sexually dimorphic hormonal profiles.

The social and political forces that developed as a result of the two great wars of the 20th century forced American clinical investigators for the first time to examine the colossal and completely unsubstantiated assumption that apart from reproductive physiology, men and women were identical. The early 1990s saw the first systematic efforts to include women in clinical investigation and to compare data obtained in studies that included both sexes. Progress was uneven; investigators balked at the idea of testing women directly because of their presumed vulnerability and that of any fetus conceived during the course of a clinical trial as well as marked differences in the timing and prevalence of accompanying comorbidities in the two sexes. Although it has been a slow process to consider sex in research protocols

and continues to require urging from eminent scholars² and the National Institutes of Health itself³ to consider the impact of sex on experimental data, the importance of its impact on normal function and in the experience of disease is now incontrovertible. GSM continues to evolve into a genuine and ever more complex discipline: the mechanisms underlying sexual dimorphism are continually amplified by a flourishing international confederation of scholars. The term has never been a euphemism for women’s health: it is the science of how normal human physiology and the experience of disease differ as a function of biological sex.

An explanation for the sexual dimorphism in the human phenotype is partially explained by the completely unexpected finding that biological sex modifies genetic expression.⁴ In one of the most important articles of the decade, Yang *et al.* showed that thousands of genes exhibited sexual dimorphism in the liver, adipose tissue, muscle, and perhaps most significantly, in the brain. Thousands of the genes identified were involved in tissue-specific biological functions and/or pathways relevant to common diseases and showed tissue-specific chromosomal enrichment. A significant portion of sexually dimorphic genes were located on sex chromosomes, but some were carried on autosomes as well. The authors themselves were astonished by their data:

We saw striking and measurable differences in more than half of the genes’ expression pattern between males and females. We didn’t expect that. No one has previously demonstrated this genetic gender gap at such high levels.

The new information that the genome itself is significantly modified by biological sex demanded immediate consideration of whether those differences were clinically significant. That process, unfortunately, has been unacceptably slow. While we suspect that the reasons for this are complex, in part, it is probably a reluctance to change what seems to be a “good enough” way to care for patients. In any case, pursuing the therapeutic consequences of gender-specific characteristics has lagged far behind their discovery. Despite the peak–trough nature of the rate of all progress gender-specific investigation and its application to the human condition have produced a spectacular, if uneven, impact on the prevention and treatment of disease.

In recent decades, our understanding of the components involved in phenotypic expression has expanded significantly:

¹Emerita Professor of Clinical Medicine, Columbia University, New York, New York.

²Adjunct Professor of Medicine, The Johns Hopkins University School of Medicine, Baltimore, Maryland.

we have begun to unravel the mechanisms by which environment, age, and hormones impact function through epigenetic modification of genes themselves. As Gillian Einstein reminds us, “the world writes on the body.”⁵ The important insight that sex, developmental age, hormones, and the environment all interact to produce the unique phenotype of each individual makes the old vigorously fought debate about which of our characteristics is the hard-wired consequence of biological sex and what is the consequence of what we experience moot. In fact, the machinery of our genome is constantly being modified. No matter how Herculean the effort, it is virtually impossible to define definitively the precise role of the many elements that produce those modifications. Thus, the science of epigenetics is an important new frontier that makes clear *that the old and artificial division between biological sex and external factors such as experience and developmental age, so intensely debated in the past, is obsolete*. The two are inextricably interwoven and have a common language: the molecular modification of genes and the elements that regulate their expression. A recent commentary in *Nature* by Leppert and Patel stresses the role of the environment in producing the complexities of personal vulnerability to and the experience of disease, in this case, kidney cancer:

To address the ‘why’ questions, the knowledge gap must be filled by epidemiological and risk-factor research.⁶

Trumping Darwinian Evolution

“...it is easier to construct a new organism using the information encoded in DNA than it is to fix an aging, malfunctioning one.”⁷

—Marshall Nirenberg

The second sea change in the direction of our interest and efforts in biomedical investigation has been to explore, augment, and transform—the nature of created life and to manufacture entirely novel entities, both biological and mechanical and/or a combination of the two. Arguably, the most significant achievement in the history of mankind, deciphering the genetic code, has opened the door to a revolutionary expansion of our opportunities to explore and to change the precise nature of living beings.

Our ability to alter the very structure of DNA itself *signals the end of Darwinian evolution* as the only factor producing the changes in living species that populate our planet. We no longer simply have to witness modification of living forms through the process of natural selection but can intervene in increasingly precise ways to alter and/or produce entirely novel forms of life. Effective and affordable mechanisms to do this such as the CRISPR-Cas 9 gene editing technology are now available and are being perfected and exploited by the private sector.⁸

With the expansion of our revolutionary new power, many biomedical researchers—and the journals they are establishing—are concentrating on the nanoscience of molecular biology. Investigations once restricted to the whole patient/animal model can now be extended to the exploration of the protean role of the sex chromosomes themselves in regulating normal physiology. Predictably, the fact that genomic expression is profoundly impacted by biological sex has not been considered in the design and the implica-

tions of these new interventions—we are taking the first baby steps into an exploration of how, when, and why to alter the genome. Designing protocols that will test the consequences of these interventions in males compared with females will be an important next step if the data are to be applied accurately to patient care. As these investigations expand in depth and sophistication, it will be important to involve the collaboration of clinicians involved in patient care as well as molecular biologists and engineers.

Augmenting Living Beings with Technology and Exploring Artificial Intelligence

The relevance of GSM to the scientific revolution of the 21st century is not confined to genomic manipulation: engineers are producing an explosion of mechanical devices not only meant to augment humans’ functional ability but also to create increasingly more competent machines to assist human life on this planet and ultimately on extraterrestrial sites. It is a new world, in which molecular biologists, engineers, and clinical investigators can and are collaborating to improve and perfect the human condition in ways that we had never before imagined. Given our experience with clinical research before the awareness of the importance of sex in normal biological function and the experience of disease, it is predictable that engineers as a whole have not yet begun to consider the impact of biological sex on their investigations. For example, engineers and their biomedical collaborators must test whether there will be sexually dimorphic responses to technological interventions intended to improve function that are merged with/implanted in humans in the creation of a cyborg.

The concept of how sexual dimorphism affects the design of free standing machines with artificial intelligence and how such machines are accepted and used by the humans who utilize them are also important to consider. In a comprehensive review of the current research on gender characteristics in robotic design, Nomura points out that gendering of robots by simply designing sex-specific voices and names affects the interaction between humans and the machine.⁹ It is clear that robots’ acceptance by men compared with women is impacted not only by the robot’s characteristics and behavior but also by the sex-specific aspects of acceptability in the two sexes. For example, a game between a robot and a human had two possible outcomes. In one version, the two competed against each other for competitive scores. In the other, they cooperated for a total score. While women did not prefer one outcome over the other, men preferred the competitive task.

What Gender and the Genome Will Publish

We are casting a wide-flung net for our journal, asking not only for reports of original research but also for commentary from legal experts and ethicists about the new technology of altering created life and generating entirely new species. This first issue, for example, reports the roundtable discussion of a group of world class scientists and legal experts who considered the potential issues and challenges involved in modifying the human genome. The rapidly expanding complexity and power of artificial intelligence present an important subject for our next roundtable: a consideration of the issues of design and the legal rights of robots and of

machines, some of which have intelligence that matches and even surpasses our own.¹⁰ The increasing efforts, many of which are being pursued not only by the federal government but also by private entrepreneurs, to equip humans for space travel and the colonization of distant planets¹¹ will also demand close attention to the differences in males and females that will dictate how we prepare them for such adventures.

Our aim is to make this journal one of the most original and exciting in science. Its concentration on radically new technology, commentary on the ethical and legal aspects of what the biomedical investigators and engineers are doing, and considerations of the most effective ways to translate their achievements into the improvement and prolongation of human life on earth and ultimately to prepare us for extraterrestrial existence will make it unique.

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Address correspondence to:
Marianne J. Legato, MD, PhD (hon.c.), FACP
 903 Park Avenue
 Suite 2A
 New York, NY 10075

E-mail: mjl2@cumc.columbia.edu