COVID, SEX DISCRIMINATION, AND MEDICAL RESEARCH

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INTRODUCTION

When I read that men are nearly twice as likely to die from COVID-19 as women,[1] I thought of science fiction books that

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1 Roni Caryn Rabin, *In N.Y.C., the Coronavirus is Killing Men at Twice the Rate of Women*, N.Y. TIMES (Apr. 7, 2020), https://www.nytimes.com/2020/04/07/health/coronavirus-new-york-men.html [https://perma.cc/X35Y-V6NC]; *see also Provisional COVID-19 Death Counts*, CTRS. FOR DISEASE CONTROL & PREVENTION, https://data.cdc.gov/NCHS/Provisional-COVID-19-Death-Counts-by-Sex-Age-and-S/9bhg-hcku/data [https://perma.cc/V7SF-S7YK] (last updated Aug. 19,

posit pandemics that wipe out men. Only men. Since the publication of Joanna Russ's 1975 novel, *The Female Man*,[2] novelists have imagined gender-specific pandemics. In Russ's novel, the female survivors live in a utopia once all those nasty men are out of the way. In Mario Bellatin's *Beauty Salon*, the government, through inaction, fails to stem a pandemic affecting only men.[3]

Such scenarios could plausibly exist, given that men and women are biologically different.[4] The innate differences between the sexes are encoded into the cells themselves,[5] leading to differing natures of men's and women's immunological and hormonal systems. As a result, women and men differ in how certain diseases manifest and how they respond to treatments.[6]

With the striking difference in mortality rates, understanding women's biological reactions to COVID-19 might actually provide the best bet for a treatment for COVID-19, but the medical research system has traditionally been biased toward research on men. In the project we undertook and report in this Article, we analyzed the burgeoning medical research literature about COVID-19 and found that the historical failure to take women's symptoms and needs into account continues to this day. Our project also illustrates what the societal costs are of that failure.

Part I of this Article analyzes the history of sex discrimination in medical research. Part II discusses the regulatory attempts in the 1990s to enroll women in more medical studies to rectify the disproportionate focus on men in medical research and why those efforts fell short. It also analyzes recent policies designed to encourage precursor research on female animals and female cells. Part III addresses the differing effects of COVID-19 on men and women. It demonstrates how, in the course of research on COVID-19,

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2020) (proportion calculated by dividing the sum of all U.S. deaths of men due to coronavirus for the age groups under 44 (3,177) and the sum of all U.S. deaths of women due to coronavirus for the age groups under 44 (1470). Data was updated on Aug. 19, 2020 and covers the span of Feb. 1, 2020 to Aug. 15, 2020).

2 JOANNA RUSS, THE FEMALE MAN (Beacon Press 1986) (1975).

3 MARIO BELLATIN, BEAUTY SALON (2009).

4 Sabra L. Klein, *Immune Cells Have Sex and So Should Journal Articles*, 153 ENDOCRINOLOGY 2544, 2546 (2012).

5 *Id.* at 2545.

6 *Id.* at 2546.

women's symptoms and needs are again being ignored even though understanding women's response to COVID-19 might hold the key to a treatment. Part IV argues that more stringent regulations are necessary, not just to benefit women, but to benefit us all. It also points out that the context in which medical research is undertaken must be taken into account if we are to vanquish this global pandemic.

I
THE HISTORY OF MEDICAL RESEARCH ON WOMEN

The National Institutes of Health ("NIH"), with its vast 300-acre campus in Bethesda, Maryland,[7] is the largest funder of medical research in the United States.[8] Almost every medical technology from cancer drugs to the artificial heart got its start with NIH funding.[9] Founded in 1887,[10] the focus of the NIH's research for the first century was men, leading to the development of diagnostic and treatment technologies that benefited men and—in some instances—created risks when they were subsequently used on women.[11] A study of heart disease—the leading cause of death among women[12]—was undertaken on 22,000 men and no women.[13] A federal study on health and aging proceeded for twenty years with only male

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7 Steve Hendrix, *At the NIH, White-Tailed Deer Get Sterilized in Luxurious Surgery Rooms*, WASH. POST (Dec. 24, 2014), https://www.washingtonpost.com/local/at-the-nih-white-tailed-deer-get-sterilized-in-luxurious-surgery-rooms/2014/12/24/0b4eb23e-8ae0-11e4-8ff4-fb93129c9c8b_story.html [https://perma.cc/PJ32-HWRC].

8 *Grants & Funding*, NAT'L INST. OF HEALTH, https://www.nih.gov/grants-funding [https://perma.cc/YGC8-XPU5] (last visited Sept. 4, 2020) ("NIH is the largest public funder of biomedical research in the world.").

9 *FDA Approval of First Totally Implanted Permanent Artificial Heart*, NAT'L INST. OF HEALTH, https://www.nih.gov/news-events/news-releases/fda-approval-first-totally-implanted-permanent-artificial-heart [https://perma.cc/QW2S-JBPS] (last visited Sept. 5, 2020).

10 Rachel Silver, *National Institutes of Health (NIH) Founded – 1887*, IMARC RESEARCH (May 2, 2014), https://www.imarcresearch.com/blog/bid/344355/national-institutes-of-health-nih-founded-1887 [https://perma.cc/A8KW-TCK8].

11 *See* WOMEN AND HEALTH RESEARCH: ETHICAL AND LEGAL ISSUES OF INCLUDING WOMEN IN CLINICAL STUDIES 1–2 (Anna C. Mastroianni, Ruth Faden & Daniel Federman eds., 1994).

12 Rebecca Dresser, *Wanted: Single, White Male for Medical Research*, 22 HASTINGS CTR. REP. 24 (Jan.–Feb. 1992).

13 Natalie Davis Spingarn, *Women's Ill Treatment by Doctors: Authors Indict Male-Controlled Medicine for Blindness, Bias, and Boorishness*, WASH. POST, Jan. 31, 1995, at Z13.

subjects.[14] An NIH-funded study of the relationship between obesity and breast cancer included only men.[15]

Sex discrimination pervades even animal research. A 2009 survey of research on animals across ten disciplines showed "a male bias in 8 of the 10 fields surveyed," reporting a male-only to female-only study ratio as skewed as 5.5:1 and that sex was "omitted in 22-42% of articles in neuroscience, physiology, and interdisciplinary biology journals, and in more than 60% of immunology reports."[16]

Because of biological differences between men and women, women's health needs are not being met by medical research. But we also disadvantage men because understanding women's unique responses to disease could help in the developments of cures.

The dangers from male-centered research are profound. Women's hormones are different than men's, causing some drugs to have enhanced effects in women[17] and some to have diminished effects.[18] Even though women consume approximately 80% of medications in the U.S.,[19] drug research

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14 Dresser, *supra* note 12.

15 *Id.*; Karen H. Rothenberg, *Gender Matters: Implications for Clinical Research and Women's Health Care*, 32 HOUS. L. REV. 1201, 1208 (1996).

16 Annaliese K. Beery & Irving Zucker, *Sex Bias in Neuroscience and Biomedical Research*, 35 NEUROSCIENCE & BIOBEHAVIORAL REVS. 565, 567 (2011).

17 Simona Pace et al., *Androgen-Mediated Sex Bias Impairs Efficiency of Leukotriene Biosynthesis Inhibitors in Males*, 127 J. CLINICAL INVESTIGATION 3167, 3171 (2017) ("We provide evidence that androgens cause these sex differences in vivo and in vitro, and we show that androgens impede the agonist induced, tight assembly of the 5-LO/FLAP complex at the nuclear membrane of human and murine leukocytes. Conclusively, females should benefit more from anti-LT therapy than males."); *see also* Amy Westervelt, *The Medical Research Gender Gap: How Excluding Women from Clinical Trials Is Hurting Our Health*, GUARDIAN (Apr. 30, 2015, 3:32 PM), https://www.theguardian.com/lifeandstyle/2015/apr/30/fda-clinical-trials-gender-gap-epa-nih-institute-of-medicine-cardiovascular-disease [https://perma.cc/DGQ3-JRUJ] ("The inclusion of more women in clinical trials has resulted in evidence that some lung cancer treatments work better for women than men.").

18 For example, doctors typically only prescribe a uniform dosage of Adderall to women across the month, despite the fact that women's bodies react differently to the drug throughout the month—meaning there are times of the month where the drug may be less effective, or not effective at all, when bioavailability is low. *What Are The Side Effects Of Adderall?*, AM. ADDICTION CTRS., https://americanaddictioncenters.org/adderall/side-effects [https://perma.cc/YGL5-P6EQ] (last updated Feb. 3, 2020).

19 Londa Schiebinger, *Women's Health and Clinical Trials*, 112 J. CLINICAL INVESTIGATION 973, 974 (2003).

is still predominantly conducted on men[20] and doesn't analyze how drugs act over the course of a woman's menstrual cycle.[21] Consequently, drugs can reach the market that are actually harmful to women. In fact, eight of the ten dangerous drugs removed from the market between 1997 and 2000 caused greater harm and fatalities for women.[22] A wide range of medications, including some antihistamines, gastrointestinal drugs, antibiotics, and antipsychotics trigger potentially fatal heart arrhythmia more often in women than men.[23] Similarly, says Stanford professor Londa Scheibinger, medications administered after a heart attack to diminish blood clots, "while beneficial to many men, may cause significant bleeding problems in women."[24]

On the other hand, some treatments may be beneficial to women, but never brought to market if the testing is done primarily on men.[25] Let's say that a drug study enrolls 1,000 people, 100 of whom are women. What if it offers no benefit to the 900 men, but all 100 women are cured? The researchers will abandon the drug, judging that it is only 10% effective. If a follow-up study focused on women, it could lead to a new drug that benefits women.

When Paula Johnson, now president of Wellesley College, was a Harvard Medical School professor, she and her colleagues pointed out that

> [t]he science that informs medicine—including the prevention, diagnosis, and treatment of disease—routinely

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20 *Id.* at 973 ("Until 1988, clinical trials of new drugs by the US Food and Drug Administration (FDA) were routinely conducted predominately on men . . . .").

21 Dresser, *supra* note 12, at 27 ("Antiseizure and antidepressant drugs may require different doses over the menstrual cycle to achieve the desired effect, and the failure to calibrate asthma medication to this cycle may contribute to the existing premenstrual rise in asthma deaths.").

22 Suk Kyeong Lee, *Sex as an Important Biological Variable in Biomedical Research*, 51 BMB REP. 167, 167 (2018) ("During the time period from 1997 to 2000, ten prescription drugs were withdrawn from the market by the US Food and Drug Administration (FDA). Eight of the withdrawn drugs caused greater health risks in women.").

23 Roni Caryn Rabin, *The Drug-Dose Gender Gap*, N.Y. TIMES (Jan. 28, 2013, 6:02 PM), https://well.blogs.nytimes.com/2013/01/28/the-drug-dose-gender-gap/ [https://perma.cc/PM6E-C74S].

24 Schiebinger, *supra* note 19, at 974.

25 *Id.* ("[D]rugs developed for men and untested on women may be dangerous for women, drugs that are potentially beneficial to women may be eliminated in early phases of clinical testing when the test group does not include women and no benefits are manifest in male subjects.").

> fails to consider the crucial impact of sex and gender. . . . Once clinical trials begin, researchers frequently do not enroll adequate numbers of women or, when they do, fail to analyze or report data separately by sex. This hampers our ability to identify important differences that could benefit the health of all.[26]

Understanding sex differences in diseases not only affects the availability of diagnostics and treatments, it also affects the decisions that insurers and government agencies make about funding health care and other services for women.[27] The original definition of AIDS did not recognize the way the disease progressed in women.[28] Men suffered from skin lesions due to Kaposi sarcoma,[29] while women faced esophageal candidiasis and cervical dysplasia.[30] Without proper research, women did not receive adequate treatment. And because the disease definition was based on male symptoms, women were unable to receive federal funding for AIDS-related treatment and services.[31] As Tasleem Padamsee pointed out in her recent

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26 PAULA A. JOHNSON ET AL., MARY HORRIGAN CONNORS CTR. FOR WOMEN'S HEALTH & GENDER BIOLOGY AT BRIGHAM & WOMEN'S HOSP., SEX-SPECIFIC MEDICAL RESEARCH: WHY WOMEN'S HEALTH CAN'T WAIT 5 (2014).

27 *See, e.g.*, OFFICE OF TECH. ASSESSMENT, OTA-BP-H-89, *The CDC AIDS Definition: Implications of the CD4 Lymphocyte Count*, *in* THE CDC'S CASE DEFINITION OF AIDS: IMPLICATIONS OF PROPOSED REVISIONS II.1–II.2 (1992).

28 Mary Anne Bobinski, *Women and HIV: A Gender-Based Analysis of a Disease and Its Legal Regulation*, 3 TEX. J. WOMEN & L. 7, 16 (1994).

29 OFFICE OF TECH. ASSESSMENT, OTA-BP-H-89, *supra* note 27.

30 Janet L. Mitchell, John Tucker, Patricia O. Loftman & Sterling B. Williams, *HIV and Women: Current Controversies and Clinical Relevance*, 1 J. WOMEN'S HEALTH 35, 36–37 (1992).

31 When the AIDS outbreak occurred, the Centers for Disease Control in the U.S. Department of Health and Human Services created a definition of AIDS. James W. Curran & Harold W. Jaffe, *AIDS: The Early Years and CDC's Response*, 60 CTRS. FOR DISEASE CONTROL & PREVENTION MORBIDITY & MORTALITY WKLY. REP. 64 (2011), https://www.cdc.gov/mmwr/preview/mmwrhtml/su6004a11.htm [https://perma.cc/A8W5-HD2V]. It included conditions that are almost exclusive to men infected with AIDS, including "pneumocystis carinii pneumonia, Kaposi's sarcoma, esophageal candidiasis, toxoplasmosis of the brain, and HIV wasting syndrome." Tasleem J. Padamsee, *Fighting an Epidemic in Political Context: Thirty-Five Years of HIV/AIDS Policy Making in the United States*, 33 SOC. HIST. OF MED. 1001, 1018 (2018); *see also* OFFICE OF TECH. ASSESSMENT, OTA-BP-H-89, *supra* note 27. It did not include cervical cancer, candidiasis, and other symptoms commonly experienced by infected women. Susan Blumenthal & Negar Avaregan, *A World Without AIDS for American Women*, AMFAR (June 20, 2014, 11:37 AM), https://www.amfar.org/world-without-aids-for-american-women/ [https://perma.cc/ZRE8-YBTL]. Unless a person suffered from one of the abovementioned conditions, he or she was not considered to have AIDS under the definition. CDC, *Revision of the CDC Surveillance Case Definition for Acquired Immunodeficiency Syndrome*, 36 CTRS. FOR DISEASE CONTROL & PREVENTION

article, *Fighting an Epidemic in Political Context: Thirty-Five Years of HIV/AIDS Policy Making in the United States*, "an official AIDS diagnosis was needed to qualify for most federal assistance program[]s, yet the existing clinical definition omitted important manifestations characteristic of groups other than gay men."[32]

II
THE REGULATORY ATTEMPTS TO ADDRESS THE GENDER GAP IN MEDICAL RESEARCH

A major turning point in the fight for female inclusion in medical research was the "aspirin study,"[33] in which researchers in 1989 concluded, after monitoring participants for an average of five years, that taking baby aspirin daily would prevent heart attacks.[34] The study included 22,071 men as subjects, but no women.[35] The study results thus offered no guidance as to whether aspirin would have a similar effect on women, or whether it might actually harm women.[36] The failure to include women in this landmark study, along with a U.S. Government Accounting Office report about the vast under-inclusion of women in pharmaceutical research,[37]

MORBIDITY & MORTALITY WKLY. REP. 1S, 4S (1987), https://www.cdc.gov/mmwr/preview/mmwrhtml/00000948.htm [https://perma.cc/35B5-4SGR]; OFFICE OF TECH. ASSESSMENT, OTA-BP-H-89, *supra* note 27. The definition had been criticized because the majority of the conditions necessary to qualify only occur in white, homosexual men. OFFICE OF TECH. ASSESSMENT, OTA-BP-H-89, *supra* note 27, at II-2; *see* Padamsee, *supra.* The definition failed to include symptoms most commonly associated with women and injected drug users, and thus disqualified them from receiving Medicaid funding. OFFICE OF TECH. ASSESSMENT, OTA-BP-H-89, *supra* note 27, at II.6. This meant that the needs of women with AIDS were not addressed and they could not access treatment. *Id.*

32 Padamsee, *supra* note 31.

33 MARY HORRIGAN CONNORS CTR. FOR WOMEN'S HEALTH & GENDER BIOLOGY AT BRIGHAM & WOMEN'S HOSP, THE NIH REVITALIZATION ACT OF 1993, https://www.brighamandwomens.org/assets/BWH/womens-health/pdfs/1993-nih-revitalization-act.pdf [https://perma.cc/NL3N-S6WG] (last visited Aug. 30, 2020).

34 Steering Committee of the Physicians' Health Study Research Group, *Final Report on the Aspirin Component of the Ongoing Physicians' Health Study*, 321 NEW ENG. J. MED. 129, 129 (1989).

35 *Id.*

36 *Id.*

37 U.S. GEN. ACCOUNTING OFFICE, GAO/HRD-93-17, WOMEN'S HEALTH: FDA NEEDS TO ENSURE MORE STUDY OF GENDER DIFFERENCE IN PRESCRIPTION DRUG TESTING 11 (1992) (53% of drugs were not tested to determine if women reacted differently than men).

prompted the introduction of legislation designed to remedy the problem.[38]

On June 10, 1993, the NIH Revitalization Act of 1993 was passed in an attempt to include more women in clinical trials and medical research.[39] The statute focused on the inclusion of women in NIH-funded research, meaning that privately-funded researchers were not bound by the statute.[40] The statute provided that, for any clinical research conducted in the future, the NIH Director shall ensure that "women are included as subjects."[41] Any proposed research "conducted or supported by any agency of the [NIH]" that failed to specify how the research would comply with the NIH guidelines could be rejected by the NIH Director.[42]

Under the statute, it was permissible to exclude women as subjects if there existed "substantial scientific data demonstrating that there is no significant difference between" men and women.[43] However, to show that the groups were comparable, it would seem that researchers would have to report comparison data, which they were not doing.

The statute provided that from 1995 onward, the Director

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38 MARY HORRIGAN CONNORS CTR. FOR WOMEN'S HEALTH & GENDER BIOLOGY AT BRIGHAM & WOMEN'S HOSP., *supra* note 33. The guiding force behind this legislation was NIH researcher Dr. Florence Haseltine, MD, PhD, who mobilized the women in Congress. Ruth Macklin, *Women's Health: An Ethical Perspective*, 21 J. L. MED. & ETHICS 23, 24 (1993).

39 National Institutes of Health Revitalization Act of 1993, 42 U.S.C. § 492B(a)(1-2) (1993); Carolyn M. Mazure & Daniel P. Jones, *Twenty Years and Still Counting: Including Women as Participants and Studying Sex and Gender in Biomedical Research*, 15 BMC WOMEN'S HEALTH 1, 1 (2015).

40 42 U.S.C. § 492B(e)(2); Mazure & Jones, *supra* note 39. Similar mandates were adopted by the Food and Drug Administration which covered privately-funded drug research. The FDA approach is addressed in Allison Whelan's article in this symposium. Allison M. Whelan, *Unequal Representation: Women in Clinical Research*, 106 CORNELL L. REV. 87 (2021).

41 42 U.S.C. § 492B(a)(1)(A-B).

42 42 U.S.C. § 492B (e)(2). The statute also provided exemptions to the requirement that NIH-funded researchers include women in clinical trials. 42 U.S.C. § 492B(b)(1-3). There are three instances listed in which NIH-funded researchers would not be bound to include women as subjects in their research: (1) where it is "inappropriate with respect to the health of the subjects;" (2) "inappropriate with respect to the purpose of the research," and (3) "inappropriate under such other circumstances as the Director of NIH may designate." *Id.* However, to combat the likelihood that researchers would try to claim exemptions from statutory requirements due to the cost associated with testing on women (and more subjects per study generally), the statute provided that "costs of such inclusion in the trial is not a permissible consideration in determining whether such inclusion is appropriate." 42 U.S.C. § 492B(d)(2)(A)(i).

43 42 U.S.C. § 492B(d)(2)(B)(i-ii).

of NIH "may not approve any proposal of clinical research" backed by federal funding unless that proposal "specifies the manner in which the research will comply" with the standards within the statute.[44] To ensure compliance for federally-funded research, the statute also prompted "advisory council[s] of each national research institute [to] prepare biennial reports" which would explain how that institute has complied with the statute.[45]

Despite these legal mandates, medical research continued to be undertaken primarily on male subjects.[46] Male-centric studies were particularly prevalent in research involving "biology, neuroscience, physiology, pharmacology, and behavior."[47] The consequences to women have been tragic. Between 1997 and 2000, the FDA recalled ten prescription drugs from the market, eight of which were pulled because of the health risks they posed to women.[48]

Even if perfect implementation of the 1993 statute had occurred, and women had been entered into clinical trials in the same proportion as their proportion of the population, it would not have done enough to ensure that the diagnostics and treatments that were developed benefitted, rather than harmed, women. Inclusion of women in clinical trials is a remedy that occurs too late in the process. Women need to be considered much earlier in the pipeline. The development of diagnostics, drugs, and other treatments needs to give due consideration to women's immune systems, hormones, and genetics. This requires policy changes at the level of basic research on cells and on animals.

Studying the effects of drugs on female mice allows researchers to pick up on early indicators of drug success or failure that may not be visible in a human trial.[49] Furthermore, the results of studies on mice determine which drugs move

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44 42 U.S.C. § 492B(e)(2).

45 42 U.S.C. § 492B(f).

46 Brian J. Prendergast, Kenneth G. Onishi, & Irving Zucker, *Female Mice Liberated for Inclusion in Neuroscience and Biomedical Research* 40 NEUROSCIENCE & BIOBEHAVIORAL REVS. 1, 2 (2014).

47 Beery & Zucker, *supra* note 16, at 567.

48 Lee, *supra* note 22, at 167.

49 Rae Ellen Bichell, *A Fix For Gender-Bias in Animal Research Could Help Humans*, NPR (Feb. 10, 2016, 3:23 PM), https://www.npr.org/sections/health-shots/2016/02/10/464697905/a-fix-for-gender-bias-in-animal-research-could-help-humans [https://perma.cc/6E3B-ZENB].

forward to a human trial.[50] Leaving female mice out of testing can mean that certain drugs that are harmful to women are approved for the general public and that certain drugs with the potential to help women never make it to market.[51]

Research on the cellular level is equally important. Cellular differences can render some drugs useless for women if those drugs do not target the appropriate receptors and cells.

For example, recent studies show that women respond differently to pain than men.[52] In a report discussing the importance of studying sex differences in neurological disorders, including pain, researchers noted that the sex of cells can affect the likelihood of some diseases and the lack of research on sex differences impedes our understanding of such disorders.[53] By reporting differences in sex in research, the results would have "a significant impact on the public health of both sexes."[54]

In 2000, the U.S. General Accounting Office produced another report focused on NIH.[55] The report acknowledged that progress was being made to include women as subjects in clinical trials,[56] primarily because researchers were more likely to receive federal funding if their research included women.[57] However, the report also found that the clinical trials often did not analyze differences in results by sex.[58] Even a majority of medical studies in cells and non-human animals still did not disaggregate or analyze sex-based data or findings.[59]

By 2008, a study found that female life expectancy in the United States was falling for the first time since 1918 as compared to life expectancy in Japan, Australia, New Zealand,

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50 *Id.*

51 *Id.*

52 Mazure & Jones, *supra* note 39, at 5.

53 *Id.* at 7.

54 *Id.*

55 U.S. GOV'T ACCOUNTABILITY OFFICE, HEHS-00-96, WOMEN'S HEALTH: NIH HAS INCREASED ITS EFFORTS TO INCLUDE WOMEN IN RESEARCH 1 (2000), https://www.gao.gov/assets/230/229100.pdf [https://perma.cc/F2U8-6LWF]; Mazure & Jones, *supra* note 39, at 3–4.

56 U.S. GOV'T ACCOUNTABILITY OFFICE, HEHS-00-96, *supra* note 55, at 7; Mazure & Jones, *supra* note 39, at 4.

57 U.S. GOV'T ACCOUNTABILITY OFFICE, HEHS-00-96, *supra* note 55, at 7; Mazure & Jones, *supra* note 39, at 4.

58 U.S. GOV'T ACCOUNTABILITY OFFICE, HEHS-00-96, *supra* note 55, at 13; Mazure & Jones, *supra* note 39, at 7–8, 13.

59 Klein, *supra* note 4, at 2544.

and Western Europe.[60] This may be due, in part, to the lack of effective research on disease in women, female mice, and female cells. In 2014, ten Democratic members of the Senate and House of Representatives—all of whom were women—wrote a letter to the Comptroller General.[61] The letter recognized that over twenty years had passed since the NIH Revitalization Act was adopted and it requested further changes be implemented to increase inclusion of women in clinical research.[62]

As a result of the political pressure, the NIH introduced new internal policies with an application date of 2016 to broaden the scope of female study participant requirements, building on the standards of the existing 1993 statute.[63] The new guidelines required inclusion of women, female animals, and female cells at the clinical and preclinical levels[64] or extensive justification if they were not to be included.[65] The 2016 guidelines, which apply to NIH-funded research, provide that "[r]esearchers working with animal models should consider if and how the female estrous cycle is relevant for experimental design and analysis" and include animals at different stages of the estrous cycle in preclinical trial stages.[66] The guidelines also recommend using sex as a biological variable at the preclinical level to understand molecular and cellular differences between the sexes.[67]

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60 Mazure & Jones, *supra* note 39, at 5.

61 Letter from Kelly Ayotte et al., to The Honorable Margaret Hamburg, M.D., U.S. Commissioner of Food and Drugs (Apr. 30, 2014); *see also* Press Release, Dianne Feinstein, Senator, Senators Fight for Women's Health in Medical Trials (Apr. 30, 2014), https://www.feinstein.senate.gov/public/index.cfm/press-releases?ContentRecord_id=f42d96ad-9fdc-45ff-b3e9-60ea8f43acee [https://perma.cc/M32K-4TZ2].

62 Kelly Ayotte et a., *supra* note 61; *see also* Feinstein, *supra* note 61.

63 *See Including Women and Minorities in Clinical Research Background*, NAT'L INSTS. OF HEALTH, https://orwh.od.nih.gov/research/clinical-research-trials/nih-inclusion-policy/including-women-and-minorities-clinical [https://perma.cc/B5WT-GMWU] (last visited Aug. 30, 2020) (explaining that researchers are required to explain how they take into account certain variables, including sex, in their research, as well as provide "strong justification" from scientific literature or data if researchers choose to solely study one sex).

64 *Id.*

65 *Id.*

66 NIH GUIDE NOTICE, NOT-OD-102, CONSIDERATION OF SEX AS A BIOLOGICAL VARIABLE IN NIH-FUNDED RESEARCH, https://orwh.od.nih.gov/sites/orwh/files/docs/NOT-OD-15-102_Guidance.pdf [https://perma.cc/SYE9-QXX9] (last visited Sept. 3, 2020) (companion reference).

67 *Id.*

"Just like randomization, blinding, sample size calculations, and other basic design elements, consideration of sex is a critical component of rigorous experimental design," notes the NIH. "For studies using both sexes, [the researcher should] develop a data analysis plan that, at a minimum, provides for the collection of data disaggregated by sex."[68]

Research on COVID-19 provides a case study for whether the scientific guidelines for inclusion of women in studies has been met.[69] Even though COVID-19 is a novel pandemic, the amount of literature about the disease is exploding.[70] By May 13, 2020, there were more than 23,000 papers published on COVID-19[71] with the number of articles doubling every twenty days.[72] According to a *Science* article written by Jeffrey Brainard, this is "among the biggest explosions of scientific literature ever."[73]

Even though tens of thousands of studies about COVID-19 have been undertaken,[74] only a few analyze the difference in symptoms between

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68 *Id.*

69 The NIH policies apply only to federally-funded research and not all COVID-19 research is federally-funded. But the norms of gender fairness apply to all research. And a surprising amount of private company research related to COVID is, in fact, federally-funded, including a $9 billion federal allocation to seven companies for vaccine research. Karen Weintraub & Elizabeth Weise, *Federal Spending on COVID-19 Vaccine Candidates Tops $9 Billion, Spread Among 7 Companies*, USA TODAY (Aug. 8, 2020, 8:00 AM), https://www.usatoday.com/story/news/health/2020/08/08/feds-spending-more-than-9-billion-covid-19-vaccine-candidates/5575206002/ [https://perma.cc/V8SY-63TH].

70 *See* Jeffrey Brainard, *Scientists Are Drowning in Covid-19 Papers. Can New Tools Keep Them Afloat?*, SCIENCE (May 13, 2020, 12:15 PM), https://www.sciencemag.org/news/2020/05/scientists-are-drowning-covid-19-papers-can-new-tools-keep-them-afloat [https://perma.cc/3H6Y-CVMD].

71 *Id.*

72 *Id.*

73 *Id.*

74 *See, e.g.*, Ye Yi, Philip N.P. Lagniton, Sen Ye, Enqin Li & Ren-He Xu, *COVID-19: What Has Been Learned and To Be Learned About the Novel Coronavirus Disease*, 16 INT'L J. BIOLOGICAL SCI. 1753 (2020); W. Guan et al., *Clinical Characteristics of Coronavirus Disease 2019 in China*, 382 NEW ENGL. J. MED. 1708 (2020); Alamin Alkundi, Ibrahim Mahmoud, Abdelmajid Musa, Saima Naveed & Mohammed Alshawwaf, *Clinical Characteristics and Outcomes of COVID-19 Hospitalized Patients with Diabetes in the United Kingdom: A Retrospective Single Centre Study*, 165 DIABETES RES. & CLINICAL PRAC. 1 (2020); Marie E. Killerby et al., *Characteristics Associated With Hospitalization Among Patients With COVID-19—Metropolitan Atlanta, Georgia, March–April 2020*, 69 MORBIDITY & MORTALITY WKLY. REP. 790, (2020); *The COVID-19 Sex-Disaggregated Data Tracker*, GLOBAL HEALTH 5050, https://globalhealth5050.org/covid19/sex-disaggregated-data-tracker/ [https://perma.cc/YLA4-6EMR] (last visited Jan. 19, 2021); WORLD HEALTH

ORG., REPORT OF THE WHO-CHINA JOINT MISSION ON CORONAVIRUS DISEASE 2019 (COVID-19) (2020), https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf [https://perma.cc/W9DD-548D]; Jian-Min Jin et al., *Gender Differences in Patients With COVID-19: Focus on Severity and Mortality*, 8 FRONTIERS PUB. HEALTH 1 (2020); Gavin Y. Oudit & Mark A. Pfeffer, *Plasma Angiotensin—Converting Enzyme 2: Novel Biomarker in Heart Failure with Implications for COVID-19*, 41 EUROPEAN HEART J. 1818 (2020); Safiya Richardson et al., *Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area*, 323 JAMA 2052 (2020); WORLD HEALTH ORG. EUR., COVID-19 WEEKLY SURVEILLANCE REPORT DATA FOR THE WEEK OF 20–26 JUL 2020 (July 26, 2020), https://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19/weekly-surveillance-report [https://perma.cc/KE7Y-G9LS]; Rabin, *supra* note 1; Zhonghua Liu Xing Bing Xue Za Zhi, *The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronavirus Diseases (COVID-19) in China, 2020*, 41 CHINESE CTR. DISEASE CONTROL & PREVENTION 145 (2020) (article in Chinese); Annemarie B. Docherty et al., *Features of 20133 UK Patients in Hospital With Covid-19 Using the ISARIC WHO Clinical Characterisation Protocol:Prospective Observational Cohort Study*, 369 BMJ 1 (2020); Carlos del Rio & Preeti N. Malani, *COVID-19—New Insights on a Rapidly Changing Epidemic*, 323 JAMA 1339 (2020); Timothée Klopfenstein et al., *Diarrhea: An Underestimated Symptom in Coronavirus Disease 2019*, 44 CLINICS & RES. HEPATOLOGY & GASTROENTEROLOGY 282 (2020); Cristina Menni et al., *Real-Time Tracking of Self-Reported Symptoms to Predict Potential COVID-19*, 26 NATURE MED. 1037 (2020); Samuel J. Pleasure, Ari J. Green & S. Andrew Josephson, *The Spectrum of Neurologic Disease in the Severe Acute Respiratory Syndrome Coronavirus 2 Pandemic Infection*, 77 JAMA NEUROLOGY 679 (Apr. 10, 2020); Shamika Ravi & Mudit Kapoor, *COVID-19 Trends From Germany Show Different Impacts By Gender and Age*, BROOKINGS (May 1, 2020), https://www.brookings.edu/blog/techtank/2020/05/01/covid-19-trends-from-germany-show-different-impacts-by-gender-and-age/ [https://perma.cc/UZ68-UGAP]; Monica Webb Hooper, Anna María Nápoles & Eliseo J. Pérez-Stable, *COVID-19 and Racial/Ethnic Disparities*, 323 JAMA 2466 (2020); Cato T. Laurencin & Aneesah McClinton, *The COVID-19 Pandemic: A Call to Action to Identify and Address Racial and Ethnic Disparities*, J. RACIAL & ETHNIC HEALTH DISPARITIES 1 (2020); CDC COVID-19 Response Team, *Characteristics of Health Care Personnel With COVID-19—United States, February 12–April 9, 2020*, 69 MORBIDITY & MORTALITY WKLY. REP. 477 (2020); Ibrahim Y. Hachim et al., *The Molecular Basis of Gender Variation in Mortality Rates Associated With the Novel Coronavirus (COVID-19) Outbreak*, PREPRINTS (2020); Serge Rozenberg, Jean Vandromme & Martin Charlotte, *Are We Equal in Adversity? Does Covid-19 Affect Women and Men Differently?*, 138 MATURITAS 62 (2020); Fei Zhou et al., *Clinical Course and Risk Factors for Mortality of Adult Inpatients With COVID-19 in Wuhan, China: A Retrospective Cohort Study*, 395 LANCET 1054 (2020); Ruth Sneep et al., *Early Epidemiological and Clinical Analysis of the First 200 Patients With COVID-19 Admitted via the Emergency Department in Kings College Hospital, London: A Retrospective Cohort Study*, LANCET (2020); Christopher M. Petrilli et al., *Factors Associated with Hospital Admission and Critical Illness Among 5279 People With Coronavirus Disease 2019 in New York City: Prospective Cohort Study*, 369 BMJ 1 (2020); Jeremy A. W. Gold et al., *Characteristics and Clinical Outcomes of Adult Patients Hospitalized with COVID-19—Georgia, March 2020*, 69 MORBIDITY & MORTALITY WKLY. REP. 545 (2020); Eboni G. Price-Haywood, Jeffrey Burton, Daniel Fort & Leonardo Seoane, *Hospitalization and Mortality Among Black Patients and White Patients With Covid-19*, 382 NEW ENGL. J. MED. 2534 (2020).

men and women.[75] The failure to consider sex differences also plagues the research on COVID vaccines. Women experience worse side effects after the COVID-19 vaccine than men, including ones that are life-threatening.[76] For example, all of the anaphylaxis reactions to the Moderna vaccine occurred in women and 94% of the anaphylaxis reactions to the Pfizer vaccine occurred in women.[77] In fact, when the CDC analyzed data from the first 13.7 million vaccine doses given to Americans,[78] it found that 79.1% of the reports of side effects came from women, even though only 61.2% of the vaccines had even been administered to women.[79] If the side effects on women versus men had been studied during the development of the vaccines, research could have been conducted to determine whether a smaller dose of a vaccine or a different type of vaccine would have been more appropriate for women.

The fact that, in 2020 and 2021, researchers would blindly assume women's bodies behave like men's is troubling. By failing to disaggregate symptoms by sex, researchers are failing to take seriously existing policies. More importantly, they are missing out on the opportunity to better understand—and to better treat and prevent—the further spread of the global pandemic.

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75 Jian-Min Jin et al., *supra* note 74(noting the gender differences for fever, cough, and diarrhea as symptoms of COVID-19). There is also anecdotal evidence of differing symptoms for men and women. For example, Tom Hanks and Rita Wilson had different COVID symptoms. *See* Hadley Freeman, *Tom Hanks on Surviving Coronavirus: 'I had Crippling Body Aches, Fatigue and Couldn't Concentrate'*, GUARDIAN (July 6, 2020, 1:00 AM), https://www.theguardian.com/film/2020/jul/06/tom-hanks-on-surviving-coronavirus-i-had-crippling-body-aches-fatigue-and-couldnt-concentrate [https://perma.cc/VN34-6LVR].

76 Melinda Wenner Moyer, *Women Report Worse Side Effects After a Covid Vaccine*, N.Y. TIMES (March 8, 2021), https://www.nytimes.com/2021/03/08/health/vaccine-side-effects-women-men.html [https://perma.cc/HH5H-N23N].

77 Tom T. Shimabukuro, Matthew Cole & John R. Su, *Reports of Anaphylaxis After Receipt of mRNA COVID-19 Vaccines in the US—December 14, 2020-January 18, 2021*, 325 JAMA 1101 (2021).

78 Julianne Gee et al., *First Month of COVID-19 Vaccine Safety Monitoring—United States, December 14, 2020-January 13, 2021*, 70 CDC MORBIDITY AND MORTALITY WKLY REP. 283, 284 (February 26, 2021).

79 *Id.*

III
THE DIFFERENTIAL EFFECT OF COVID-19 ON WOMEN AND MEN

A coronavirus is a common virus that causes an infection in an individual's nose, sinuses, or upper throat.[80] Most coronaviruses are not dangerous.[81] In December 2019, however, there was an outbreak in China of what was later identified as SARS-CoV-2, a new type of coronavirus.[82] This outbreak spread around the world. This coronavirus disease, otherwise known as COVID-19, primarily spreads through saliva or nose discharge.[83] At the outset of this pandemic, scientists thought that COVID-19 was only a respiratory virus.[84] Subsequent research has revealed, however, that the virus can affect other organs, including the heart,[85] liver,[86]

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80 Geng Li et al., *Coronavirus Infections and Immune Responses*, 92 J. MED. VIROLOGY 424, 425 (2020) ("The [corona]viral infections are generally associated with upper respiratory tract infections, of which the signs and symptoms commonly include fever, headache, and cough; some patients may have lower respiratory tract infection."); Neha Pathak, *Coronavirus and Covid-19: What You Should Know*, WEBMD (Aug. 17, 2020), https://www.webmd.com/lung/coronavirus [https://perma.cc/KBA4-RAWK].

81 Pathak, *supra* note 80.

82 Guan et al., *supra* note 74, at 1709; Pathak, *supra* note 80.

83 *Coronavirus*, WORLD HEALTH ORG., https://www.who.int/health-topics/coronavirus#tab=tab_1 [https://perma.cc/3EFW-8S4Q] (last visited Aug. 17, 2020); *see also* Guan et al., *supra* note 74, at 1713 ("Conventional routes of transmission of SARS- CoV, MERS-CoV, and highly pathogenic influenza consist of respiratory droplets and direct contact, mechanisms that probably occur with SARS-CoV-2 as well. Because SARS-CoV-2 can be detected in the gastrointestinal tract, saliva, and urine, these routes of potential transmission need to be investigated.").

84 Julie Steenhuysen, *Scientists Just Beginning to Understand the Many Health Problems Caused by Covid-19*, HUFFPOST (June 27, 2020, 12:56 PM), https://www.huffpost.com/entry/scientists-just-beginning-to-understand-the-many-health-problems-caused-by-covid-19_n_5ef77886c5b6acab28426268?ncid=engmodushpmg00000004 [https://perma.cc/3NHU-ETCV] ("

> 'We thought this was only a respiratory virus. Turns out, it goes after the pancreas. It goes after the heart. It goes after the liver, the brain, the kidney and other organs. We didn't appreciate that in the beginning,' said Dr. Eric Topol, a cardiologist and director of the Scripps Research Translational Institute in La Jolla, California.

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85 *See* Peter Libby, *The Heart in COVID-19: Primary Target or Secondary Bystander?*, 5 JACC BASIC TO TRANSLATIONAL SCI. 537, 540–42 (2020) ("Although we are early in our experience with this novel coronavirus disease, most patients affected by COVID-19 encountered by cardiologists may have more secondary cardiac involvement then primary infective . . . . It behooves us to consider the multiple mechanisms of cardiac injury in patients with COVID-19."); Steenhuysen, *supra* note 84.

86 Dinesh Jothimani, Radhika Venugopal, Mohammed Forhad Abedin,

kidney,[87] and the nervous system.[88] Older adults and people of any age who have a serious underlying medical condition appear to be at a higher risk for developing a more severe case of COVID-19.[89]

COVID-19 has many physiological impacts. According to the Centers for Disease Control and Prevention, the most common reported symptoms of COVID-19 include fever, cough, shortness of breath or difficulty breathing, chills, muscle pain, sore throat, and a loss of taste or smell.[90] The

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Ilankumaran Kaliamoorthy & Mohamed Rela, *COVID-19 and Liver*, 73 J. HEPATOLOGY 1231, 1237 (2020) ("COVID-19 causes pneumonia, but hepatic dysfunction can occur in severe cases and is associated with fatal outcome. Cases of severe acute liver injury has been reported with higher mortality."); Steenhuysen, *supra* note 84.

87 Ki Ryang Na et al., *Acute Kidney Injury and Kidney Damage in COVID-19 Patients*, 35 J. KOREAN MED. SCI. 1, 7 (2020) ("SARS-CoV-2 can affect not only the lungs but also other organs, as well as cause organ failure in other organs, including the kidney."); Steenhuysen, *supra* note 84.

88 Igor J. Koralnik & Kenneth L. Tyler, *COVID-19: A Global Threat to the Nervous System*, 88 ANNALS NEUROLOGY 1, 9 (2020) ("Although we are only starting to grasp the complexity of SARS-CoV-2 biology, it is already apparent that COVID-19 causes a global threat to the entire nervous system.").

89 Andrew Clark et al., *Global, Regional, and National Estimates of the Population at Increased Risk of Severe COVID-19 Due to Underlying Health Conditions in 2020: A Modelling Study*, 8 LANCET GLOBAL HEALTH e1003, e1003 (2020) ("Emerging evidence from China, Europe, and the USA has shown a consistently higher risk of severe COVID-19 in older individuals and those with underlying health conditions.") (citing CDC COVID-19 Response Team, *Preliminary Estimates of the Prevalence of Selected Underlying Health Conditions Among Patients with Coronavirus Disease 2019—United States, Centers for Disease Control and Prevention, February 12-March 28, 2020*, 69 MORBIDITY & MORTALITY WKLY. REP. 382, 382 (2020); *Characteristics of COVID-19 Patients Dying in Italy: Report Based on Available Data on March 20th, 2020*, INSTITUTO SUPERIORE DI SANITÀ, https://www.epicentro.iss.it/coronavirus/bollettino/Report-COVID-2019_20_marzo_eng.pdf [https://perma.cc/EZG4-RT4A] (last visited June 8, 2020); Andrew Clark et al., *supra* ("

> The share of the population at increased risk [of COVID-19] was highest in countries with older populations, African countries with high HIV/AIDS prevalence, and small island nations with high diabetes prevalence. Estimates of the number of individuals at increased risk were most sensitive to the prevalence of chronic kidney disease, diabetes, cardiovascular disease, and chronic respiratory disease.

"); *see also* Amitava Banerjee et al., *Estimating Excess 1-Year Mortality Associated With the COVID-19 Pandemic According to Underlying Conditions and Age: A Population-Based Cohort Study*, 395 LANCET 1715, 1715 (2020) ("Age and underlying conditions combined to influence background risk, varying markedly across conditions."); *What is Coronavirus? Who is Affected?*, SCRIPPS (Apr. 29, 2020), https://www.scripps.org/news_items/6882-what-is-coronavirus-who-is-affected [https://perma.cc/2LBW-HWW9].

90 *Symptoms of Coronavirus*, CTRS. FOR DISEASE CONTROL & PREVENTION,

virus can cause patients to experience respiratory distress,[91] blood clots,[92] extreme inflammation that attacks multiple organ systems,[93] and neurological complications.[94] COVID-19 also manifests certain central nervous system symptoms.[95] These manifestations include dizziness,[96] headaches,[97] impaired consciousness,[98] acute cerebrovascular disease,[99] ataxia,[100] and seizures.[101] Other neurological manifestations include taste impairment,[102] smell impairment,[103] vision impairment,[104] and nerve pain.[105] This list is not exhaustive. Other less commonly reported symptoms include nausea, vomiting, and diarrhea.[106]

A. Gendered Analyses of the Incidence of and Effects of COVID-19

How do sex differences affect a person's risk of contracting COVID and dying from the disease? One might expect that men would have a higher rate of prevalence than women because men travel more than women and would thus be expected to contract COVID-19 at a higher rate.[107] Further,

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https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html [https://perma.cc/L2B9-SYGJ] (last updated Dec. 22, 2020); *Covid-19 Basics*, HARV. HEALTH PUBL'G, https://www.health.harvard.edu/diseases-and-conditions/covid-19-basics [https://perma.cc/MY9R-Y6GA] (last updated Jan. 21, 2020).

91 Steenhuysen, *supra* note 84.

92 *Id.*

93 *Id.*

94 *Id.*

95 Ling Mao et al., *Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China*, 77 JAMA NEUROLOGY 683, 684 (2020).

96 *Id.* at 686.

97 *Id.*

98 *Id.*

99 *Id.*

100 *Id.*

101 Ling Mao, *supra* note 95, at 686.

102 *Id.*

103 *Id.*

104 *Id.*

105 *Id.*

106 Xi Jin et al., *Epidemiological, Clinical, and Virological Characteristics of 74 Cases of Coronavirus-Infected Disease 2019 (COVID-19) with Gastrointestinal Symptoms*, 69 GUT 1002, 1005 (2020); *see also* CTRS. FOR DISEASE CONTROL & PREVENTION, *supra* note 90.

107 Sharon Begley, *Who Is Getting Sick, and How Sick? A Breakdown of Coronavirus Risk by Demographic Factors*, STAT (Mar. 3, 2020),

studies indicate that men generally wash their hands less frequently, which could lead to a higher transmission rate.[108] Additionally, according to a March 2020 poll by *Gallup*, women are more concerned about COVID-19 than men[109] by a 62% to 58% margin.[110] Men might be more at risk of contracting COVID-19 because they are less concerned about the virus[111] and thus may tend to increase their exposure to environments where they could contract it.[112]

On the other hand, one might also expect that women would have a higher COVID-19 prevalence than men because more women work in front-line healthcare jobs, and there are social reasons to expect that women are more likely to be exposed to and contract COVID-19.[113] A higher percentage of women (52%) than men (48%)[114] have been declared essential workers, and women are more likely than men to be on the front lines of health care and in jobs, like grocery store workers, that have a direct and constant exposure to the

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https://www.statnews.com/2020/03/03/who-is-getting-sick-and-how-sick-a-breakdown-of-coronavirus-risk-by-demographic-factors/ [https://perma.cc/A58U-BV4X] ("It's possible the apparent sex imbalance reflects patterns of travel and contacts that make men more likely to be exposed to carriers of the virus, not any inherent biological differences.").

108 Adam Moeser, *COVID-19's Deadliness for Men Is Revealing Why Researchers Should Have Been Studying Immune System Sex Differences Years Ago*, CONVERSATION (June 9, 2020, 8:20 AM), https://theconversation.com/covid-19s-deadliness-for-men-is-revealing-why-researchers-should-have-been-studying-immune-system-sex-differences-years-ago-138767 [https://perma.cc/8EZR-L8ER] ("

> A number of factors can interact with biological sex to increase or decrease one's susceptibility to COVID-19. Another major factor is gender, which refers to social behaviors or cultural norms that society deems appropriate. Males may be at increased risk for severe disease, because in general, they tend to smoke and drink more, wash their hands less frequently and often delay seeking medical attention.

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109 Justin McCarthy, *U.S. Coronavirus Concerns Surge, Governments Trust Slides*, GALLUP (Mar. 16, 2020), https://news.gallup.com/poll/295505/coronavirus-worries-surge.aspx [https://perma.cc/HE5R-MA8Y].

110 *Id.*

111 *See id.*

112 *See id.*

113 Campbell Robertson & Robert Gebeloff, *How Millions of Women Became the Most Essential Workers in America*, N.Y. TIMES (Apr. 18, 2020), https://www.nytimes.com/2020/04/18/us/coronavirus-women-essential-workers.html [https://perma.cc/86A6-5KR5]

114 *See id.*

public.[115] Women make up 77% of the essential health care workforce and 73% of the COVID-infected health care workers.[116]

In fact, these social factors tend to balance each other out and, consequently, the prevalence of COVID-19 in men and women appears to be about equal.[117] What is striking, though, is that nearly every country in the world is reporting higher COVID-19 mortality rates in men than in women.[118] Emerging research suggests that, while women and men have a similar prevalence of the COVID,[119] men are up to 2.4 times more likely to die from COVID-19 than women.[120] According to the WHO-China Joint Mission Report, men have a 4.7% mortality rate,[121] while women have a 2.8% mortality rate.[122] In Italy, of the proportion of deaths of those with confirmed COVID-19 cases, 13.3%[123] were men, compared with 7.4% women.[124] In New York City men with the virus are dying at almost twice the rate of women.[125]

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115 While police officers (a mainly male profession) are also on the front lines, there are four times as many registered nurses than there are police officers. (And this does not even consider the large number of women who are nurse assistants and home health care aides.). *See id.*

116 *See id.*

117 Jian-Min Jin et. al., *supra* note 74. There is some indication that men are slightly more likely to get COVID-19 than women. The WHO China Joint Mission found that, among the 55,924 laboratory confirmed cases, 51.1% were male. WORLD HEALTH ORG., *supra* note 74. In Italy, for every 11 female cases, there were about 14 male cases. *See* Catherine Gebhard, Vera Regitz-Zagrosek, Hannelore K. Neuhauser, Rosemary Morgan & Sabra L. Klein, *Impact of Sex and Gender on COVID-19 Outcomes in Europe*, 11 BIOLOGY OF SEX DIFFERENCES 1, 3 (2020) (citing *Sex, Gender, and COVID-19*, GLOBAL 5050, https://globalhealth5050.org/covid19/ [https://perma.cc/HNW3-5H3S] (last visited Feb. 4, 2020)) (chart presents data as of April 2, 2020). In Atlanta, Georgia, researchers reported the characteristics of 220 COVID-19 hospitalized and 311 non-hospitalized patients. Killerby et. al., *supra* note 74, at 790 (June 26, 2020). The researchers found that of the hospitalized group, 51.8% were men and 48.2% were women. *Id.* at 792. However, they found that of the non-hospitalized patients, 36.7% were male and 63.3% were female. *Id.*

118 *COVID-19 Sex-Disaggregated Data Tracker*, *supra* note 74.

119 Jian-Min Jin et. al., *supra* note 74; WORLD HEALTH ORG., supra note 74; *see also* Gebhard, *supra* note 117; Killerby et. al., *supra* note 74, at 790.

120 Jian-Min Jin et. al., *supra* note 74.

121 WORLD HEALTH ORG., *supra* note 74.

122 *Id.*

123 Gebhard, *supra* note 117.

124 *Id.*

125 Rabin, *supra* note 1. (As of April 7, 2020, in New York City there had been 43 COVID-19 deaths for every 100,000 men, compared with 23 deaths for every 100,000 women).

This gender gap in COVID-19-related deaths pervades all age groups.[126] For example, COVID-19 deaths in women and men under the age of 44 in the United States are approximately 1 to 2 respectively.[127] Additionally, Germany reports that the mortality rate is higher for men than it is for women in all age groups.[128] At the early stage of the pandemic, the mortality rate of men was only slightly higher than women in Germany.[129] However, the difference has grown significantly, and now the mortality rate of men across all age groups is50% greater than it is for women.[130]

Men having a higher rate of death during a pandemic is not novel.[131] In fact, research on the 1918 Spanish influenza pandemic revealed that non-elderly adult men died at a higher rate than women.[132] Additionally, during the SARS outbreak, men died at higher rates than women,[133] even though more

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126 Jian-Min Jin et. al., *supra* note 74 (concluding that "[w]hile men and women have the same [COVID-19] prevalence, men with COVID-19 are more at risk for worse outcomes and death, independent of age."); *see also* Rabin, *supra* note 1.

127 *Provisional COVID-19 Death Count*, CTRS. FOR DISEASE CONTROL & PREVENTION, https://data.cdc.gov/NCHS/Provisional-COVID-19-Death-Counts-by-Sex-Age-and-S/9bhg-hcku/data [https://perma.cc/74JL-H4S5] (updated Aug. 19, 2020) (proportion calculated by dividing the sum of all U.S. deaths of men due to coronavirus for the age groups under 44 (3,177) and the sum of all U.S. deaths of women due to coronavirus for the age groups under 44 (1470). Data was updated on Aug. 19, 2020, and covers the span of Feb. 1, 2020 to Aug. 15, 2020.

128 Ravi & Kapoor, *supra* note 74; *see also* Richard V. Reeves & Tiffany N. Ford, *COVID-19 Much More Fatal for Men, Especially Taking Age Into Account*, BROOKINGS (May 15, 2020), https://www.brookings.edu/blog/up-front/2020/05/15/covid-19-much-more-fatal-for-men-especially-taking-age-into-account/ [https://perma.cc/MGQ6-BJUM].

129 Ravi & Kapoor, *supra* note 74; *see also* Reeves & Ford, *supra* note 128.

130 Ravi & Kapoor, *supra* note 74; *see also* Reeves & Ford, *supra* note 128.

131 Andrew Noymer & Michel Garenne, *The 1918 Influenza Epidemic's Effects on Sex Differentials in Mortality in the United States*, 26 POPULATION AND DEVELOPMENT REV. 565, 566 (2000) ("The male death rates in 1918 far exceed the female death rates among adults. Among the elderly in both years, there is a slight female excess death rate. Among children and adults, there is a slight male excess death rate in 1917. But in 1918, males were at a much greater disadvantage in terms of flu mortality.").

132 *Id.*

133 J. Karlberg, D.S.Y. Chong & W.Y.Y. Lai, *Do Men Have a Higher Case Fatality Rate of Severe Acute Respiratory Syndrome than Women Do?*, 159 AMERICAN J. OF EPIDEMIOLOGY 229, 229 (2004) ("Using data from early March to September 22, 2003, the authors found that males had a significantly ($p < 0.0001$) higher case fatality rate than females did, 21.9% versus 13.2%."); *see also*, *Why the New Coronavirus May Kill More Men than Women*, ADVISORY BOARD (Feb. 25, 2020), https://www.advisory.com/daily-briefing/2020/02/25/men-

women were infected by the disease.[134]

Given that social factors may act on both women and men to increase their chance of being infected with COVID, it is not surprising that the prevalence of COVID for men and women is similar. However, social trends do not explain why men are dying at a higher rate than women.[135] To do that, we need to turn to biological factors.

B. Biological Differences Influencing Reactions to COVID

Women with COVID-19 may have a lower mortality rate because of various biological differences between men and women. These include immunological differences,[136] hormonal differences,[137] and genetic differences.[138]

1. *Immunological Differences*

The difference in men and women's immune systems may be a factor in why COVID-19 is less harmful to women.[139] Women have a more responsive immune system than men do,[140] leading one researcher to opine, "women are not the 'weaker sex' when it comes to immunity."[141]

Immunological differences between men and women are thought to be based in the different amounts and activities of different types of cells.[142] Mast cells—cells that act as first

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coronavirus.

134 ADVISORY BOARD, *supra* note 133.

135 Bob Curley, *Why COVID-19 Is Hitting Men Harder Than Women*, HEALTHLINE (May 11, 2020), https://www.healthline.com/health-news/men-more-susceptible-to-serious-covid-19-illnesses [https://perma.cc/NA2D-5Z4P].

136 *Id.*

137 Moeser, *supra* note 108.

138 Oudit & Pfeffer, *supra* note 74, at 1818.

139 Curley, *supra* note 135.

140 *See* Shani Talia Gal-Oz et. al., *ImmGen Report: Sexual Dimorphism in the Immune System Transcriptome*, 10 NATURE COMMUNICATIONS 1, 2 (2019) ("

> The mammalian immune system displays widespread sexual dimorphism—the difference between males and females. In general, females are healthier than males, and they have better outcomes for illnesses caused by infectious diseases, sepsis, trauma, or injury [citation omitted]. At the molecular level, the immune responsiveness of females is higher than that of males, as it is manifested by higher levels of immunoglobulins IgM and IgG and stronger humoral and cell-mediated immunity [citation omitted].

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141 Curley, *supra* note 135.

142 *See* Klein, *supra* note 4.

responders to pathogens and arrange immune system responses to help clear pathogens[143]—initiate a more active immune response in females.[144] According to Dr. Adam Moeser, an immunologist and associate professor at Michigan State University, "[t]his may actually help females fight off infectious diseases better than men."[145]

Women have higher levels of immune cells such as monocytes, macrophages, and dendritic cells than men do.[146] Women also produce more cytokines than men.[147] Men have lower CD3+ and CD4+ cell counts,[148] lower CD4+ to CD8+ cell ratios,[149] and lower helper T responses than women.[150] These cell differences are linked to immune responses, with higher active cell counts thought to result in greater immune responses.[151]

While researchers are aware that immunological functions decline as both animals and humans age,[152] studies have also shown that women experience slower immune system aging as compared to men.[153] Immunological degradation is linked closely to the decreasing performance of T cells,[154] which are integral to the body's ability to recognize foreign invaders to the body and thus kick off an immune response.[155] A Japanese study found a statistically significant decline with age in T cell activity and TCPI—a composite measure of immune function with respect to different levels of distinct T cell types.[156] But there was a lesser rate of decline for women than men, meaning that women conserved more immunological function

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143 Moeser *supra* note 108 (citing Emily Mackey et. al., *Sexual Dimorphism in the Mast Cell Transcriptome and the Pathophysiological Responses to Immunological and Psychological Stress*, 7 BIOLOGY OF SEX DIFFERENCES 1, 1-2 (2016)).

144 *Id.*

145 *Id.*

146 Klein, *supra* note 4.

147 *Id.*

148 *Id.*

149 *Id.*

150 *Id.*

151 *See, e.g.*, *id.*

152 Katsuiku Hirokawa et. al., *Slower Immune System Aging in Women Versus Men in the Japanese Population*, 10 IMMUNITY & AGING 19, 19 (2013).

153 *Id.*

154 *Id.*

155 *Id.*

156 *Id.*

as they aged than did men.[157]

At a system-wide level, infections such as the common cold, the flu,[158] or COVID-19[159] trigger the body's attack mode, which in turn causes inflammation as the body works harder to fend off the illness.[160] Specifically, the body's innate immune cells called macrophages produce pro-inflammatory cytokines (a type of signaling protein released by immune cells).[161] This process is referred to as the activation of the peripheral immune system.[162]

One important finding about how a coronavirus infection advances to a deadly disease is the cytokine storm.[163] Normally, if cytokines are released in the appropriate quantity, they stimulate a healthy immune response to an invading disease.[164] However, if these signaling cascades are overproduced, the constant activation of the immune system

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157 *Id.*

158 Kate Streit, *A Sick Neuroscientist Explains How the Flu Affects Your Brain*, SIMPLEMOST (Feb. 19, 2018), https://www.simplemost.com/how-flu-affect-brain/ [https://perma.cc/6CUS-3QAQ].

159 U. of Minn., *A New Approach to Averting Inflammation Caused by COVID-19*, MEDICAL EXPRESS (May 12, 2020), https://medicalxpress.com/news/2020-05-approach-averting-inflammation-covid-.html [https://perma.cc/MAD6-XZDY].

160 Adriana Barton, *Why 'Brain Fog' From the Common Cold Isn't All in Your Head*, THE GLOBE AND MAIL (Nov. 17, 2017), https://www.theglobeandmail.com/life/health-and-fitness/health/why-brain-fog-from-the-common-cold-isnt-all-in-your-head/article36812938/ [https://perma.cc/EY2C-MMBL].

161 Miriam Merad & Jerome C. Martin, *Pathological Inflammation in Patients With COVID-19: A Key Role for Monocytes and Macrophages*, 20 NATURE REVS. IMMUNOLOGY 355, 355 (2020).

162 Robert Dantzer, Jason C. O'Connor, Gregory G. Freund, Rodney W. Johnson & Keith W. Kelley, *From Inflammation to Sickness and Depression: When the Immune System Subjugates the Brain*, 9 NATURE REVS. NEUROSCIENCE 46, 46 (2008).

163 Dina Ragab et al., *The COVID-19 Cytokine Storm; What We Know So Far*, 11 FRONTIERS IN IMMUNOLOGY 1, 2 (2020).

164 *See id.* ("

> The immune system has an exquisite mechanism capable of responding to various pathogens. Normal anti-viral immune response requires the activation of the inflammatory pathways of the immune system; however, aberrant or exaggerated response of the host's immune system can cause severe disease if remains uncontrolled (25). Cytokines are an essential part of the inflammatory process. Cytokines are produced by several immune cells including the innate macrophages, dendritic cells, natural killer cells and the adaptive T and B lymphocytes.

"); Jennifer R. Tisoncick, et. al., *Into the Eye of the Cytokine Storm*, 76 MICROBIOLOGY & MOLECULAR BIOLOGY REVS. 16, 17 (2012).

turns deadly: in certain coronavirus patients, a "cytokine storm," or an over-activity of the cytokine signaling protein, induces inflammation causing harm to many organs, including the lungs, which in some patients leads to the condition known as acute respiratory distress syndrome ("ARDS").[165] ARDS is the serious condition which leads to a low oxygen saturation level and is a major cause of mortality in COVID-19 patients.[166]

Dr. Akiko Iwasaki and her team at the Yale School of Medicine studied the differences between men's and women's immune responses to COVID-19.[167] They found that women's immune systems mounted a more robust T cell activation (a good thing) than men's immune systems, but early in the disease had higher levels of inflammatory cytokines (a bad thing).[168] Men's systems, though, have an overall higher inflammatory cytokine response (a bad thing) than women.[169] This overproduction of cytokines can result in a cytokine storm that attacks various organs.[170] The Iwasaki study also found that men developed less T-cell immunity (a bad thing) than women.[171]

Ultimately, this study suggests immunological answers to the question of why women fare better with a coronavirus infection than men.[172] This conclusion is especially salient

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165 Ragab et al., *supra* note 163 ("

> This increase in cytokines results in influx of various immune cells such as macrophages, neutrophils, and T cells from the circulation into the site of infection with destructive effects on human tissue resulting from destabilization of endothelial cell to cell interactions, damage of vascular barrier, capillary damage, diffuse alveolar damage, multiorgan failure, and ultimately death. Lung injury is one consequence of the cytokine storm that can progress into acute lung injury or its more severe form ARDS (27). ARDS leading to low oxygen saturation levels is a major cause of mortality in COVID-19. Although the exact mechanism of ARDS in COVID-19 patients is not fully understood, the excessive production of pro-inflammatory cytokines is considered to be one of the major contributing factors [citation omitted].

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166 Ragab et al., *supra* note 163, at 3.

167 Takehiro Takahashi et al., *Sex Differences in Immune Responses to SARS-CoV-2 That Underlie Disease Outcomes*, MEDRXIV at 1 (June 26, 2020), https://www.medrxiv.org/content/10.1101/2020.06.06.20123414v2.full.pdf (preprint) [https://perma.cc/WK5H-QFJH].

168 *Id.* at 11.

169 *Id.*

170 *Id.*

171 *Id.*

172 *See* Takahashi et al., *supra* note 167, at 11.

because by recognizing the inherent differences between male and female immune systems with respect to COVID-19, immunological therapies that boost T cells might be an effective way to treat male patients,[173] whereas female patients might benefit from drugs that can dampen an early overproduction of cytokines.[174]

2. *Hormonal Differences*

Hormonal differences may also play a role in the sex differences as it relates to COVID-19. Sex hormones are important to the development of cellular immunity.[175] Women have a faster and more effective immune response to tissue injury than men,[176] and scientists believe that this is due in part to women's higher levels of estrogen.[177] Estrogen is directly linked to cytokine production,[178] cell activation,[179] and cell proliferation,[180] all of which contribute to the intensity of an immune response.[181] Researchers hypothesize that female sex hormones could explain the sex differences in COVID-19 severity.[182] Along those lines, a study revealed that activating the estrogen receptor in female mice offered them protection against SARS-CoV.[183] The fact that sex hormones

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173 *Id.*

174 *Id.*

175 Sumathi Sankaran-Walters et al., *Sex Differences Matter In The Gut: Effect On Mucosal Immune Activation And Inflammation*, 4 BIOLOGY SEX DIFFERENCES 1, 2 (2013).

176 *Id.*

177 *Id.*

178 *Id.*

179 *Id.*

180 *Id.*

181 *See* Sankaran-Walters et al., *supra* note 175.

182 Roni Caryn Rabin, *Can Estrogen and Other Sex Hormones Help Men Survive COVID-19*, N.Y. TIMES, (May 7, 2020), https://www.nytimes.com/2020/04/27/health/coronavirus-estrogen-men.html [https://perma.cc/C5HA-YMHB].

183 Rudragouda Channappanavar et al., *Sex-Based Differences in Susceptibility to Severe Acute Respiratory Syndrome Coronavirus Infection*, 198 J. IMMUNOLOGY 4046, 4046 (2017) ("

> To investigate these differences, we infected male and female mice of different age groups with SARS-CoV and analyzed their susceptibility to the infection. Our results showed that male mice were more susceptible to SARS-CoV infection compared with age-matched females . . . . Furthermore, ovariectomy or treating female mice with an estrogen receptor antagonist increased mortality, indicating a protective effect for estrogen receptor signaling in mice infected with SARS-CoV. Together, these data suggest that sex differences in the susceptibility to SARS-CoV in

can play a role in protecting against coronaviruses prompted the launch of two clinical trials in the United States.[184]

Researchers also hypothesize that male sex hormones actually make men more susceptible to COVID-19.[185] Faranak Fattahi, a stem cell biologist at University of California, San Francisco, found that male hormones, including testosterone, actually enable SARS-CoV-2—the coronavirus that causes COVID-19—to infiltrate human cells.[186] She posits that the virus activates dihydrotestosterone, a hormone that aids puberty in men and the development of male characteristics.[187] Dihydrotestosterone, an active form of testosterone, then initiates a process that activates the enzyme TMPRSS2.[188] This enzyme makes human cells more receptive to coronavirus.[189]

3. *Genetic Differences Between Men and Women*

Genetics may also play a role in the sex differences in response COVID-19.[190] Another reason why women have a stronger immune system relates to their extra X chromosome.[191] X chromosomes contain more genes encoding immune responses[192] and, while most of these genes are made

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> mice parallel those observed in patients and also identify estrogen receptor signaling as critical for protection in females.

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184 *See* Rabin, *supra* note 182.

185 Zaniar Ghazizadeh et al., *Androgen Regulates SARS-CoV-2 Receptor Levels and Is Associated With Severe COVID-19 Symptoms in Men*, BIORXIV 2 (May 2020) ("[Study] findings provide important insights on the mechanism of increased disease susceptibility in male COVID-19 patients and identify androgen receptor inhibition as a potential therapeutic strategy."); *see also*, Peter Fimrite, *Why Men Get Sicker: Male Hormones May Help Coronavirus Infiltrate Human Cells*, SAN FRANCISCO CHRONICLE (July 9, 2020), https://www.sfchronicle.com/health/article/Unwelcome-mat-Male-sex-hormones-appear-to-help-15395442.php [https://perma.cc/FM88-6GKD].

186 Fimrite, *supra* note 185 (citing Zaniar Ghazizadeh et al., *supra* note 185).

187 *Id.*

188 *Id.*

189 *Id.*

190 Moeser, *supra* note 108.

191 Claube Libert, Lien Dejager, & Iris Pinheiro, *The X Chromosome in Immune Functions: When A Chromosome Makes the Difference*, 10 NATURE REVS. IMMUNOLOGY 594, 594 (2010) ("The X chromosome is partly responsible for the hyperresponsiveness of the female immune system. Females carry two X chromosomes, one from each parent, whereas males carry one X chromosome inherited from the mother and one Y chromosome from the father."); *see also* Curley, *supra* note 135.

192 Libert et al., *supra* note 191 ("

> The X chromosome has numerous genes which, directly or indirectly, are involved in immunity, and naturally occurring

randomly inactive to avoid duplicate copies of proteins being made, some immune genes escape inactivation.[193] This leads to a doubling in the number of possible immune-related genes.[194] For men, who only have one copy of the X chromosome, a mutation in any one of the immune genes on the single X chromosome could be disastrous, while women have a redundant copy which may afford them protections.[195]

> variations in one gene copy might result in two distinct alleles with different regulatory and response capacities. For females, this means additional physiological diversity: not only do heterozygous females avoid the effects of deleterious gene-mutations, they also benefit from added diversity when facing new immune challenges, such as microbial infections.

"); Moeser, *supra* note 108.

193 Libert et al., *supra* note 191 ("

> To avoid double dosage of proteins in females, one of the X chromosomes is randomly silenced during X chromosome inactivation, which occurs in the early stages of female embryogenesis; however, the pseudoautosomal regions of the X chromosome escape inactivation [figure omitted]. The process of X chromosome inactivation results in female cellular mosaicism: in a female, approximately half of the cells express genes derived from the maternal X chromosome and the other half express genes derived from the paternal X chromosome. Thus, deleterious or disadvantageous mutations that occur in an X chromosome-linked gene will result in the functional loss of the protein in all cells in a male but in only half of cells in a female.

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194 Libert et al., *supra* note 191 ("

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195 Libert et al., *supra* note 191 ("

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Another contributing factor could be that men have higher concentrations of angiotensin-converting enzyme 2 (ACE2) in their blood:[196] it has been suggested that ACE2 enables the coronavirus to infect healthy cells.[197]

C. Emerging Studies That Use Research on Women to

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male but in only half of cells in a female.

"); *see also* Moeser, *supra* note 108 ("

> Biological females have two copies of the X chromosome, which contains more immune genes. While the genes on one X chromosome are mostly inactive, some immune genes can escape this inactivation, leading to double the number of immune-related genes and thus double the quantity of certain immune proteins compared with biological men who have only one X chromosome. Sex hormones such as estrogen and testosterone can also impact the immune response. In one study, researchers showed that activating the estrogen receptor in female mice provided them protection against SARS-CoV. And there is an approved clinical trial that will examine the effects of estrogen patches on the severity of COVID-19 symptoms.

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196 Oudit & Pfeffer, *supra* note 74, at 1819 (In the [study] cohort, patients with higher concentrations of ACE2 were more often men, had atrial fibrillation, higher heart rate, and lower systolic blood pressure, which was largely confirmed . . . In the current study, male sex was the strongest predictor of elevated plasma ACE2 concentrations in both cohorts."); *see also*, Moeser, *supra* note 108 ("

> There is also evidence that males and females have different quantities of certain receptors that recognize pathogens or that serve as an invasion point for viruses like SARS-CoV-2. One example is the quantity of angiotensin converting enzyme 2 (ACE2) receptors, which SARS-CoV-2 binds to in order to infect cells. While there is currently no conclusive evidence for a role of ACE2 receptors impacting sex differences and the severity of COVID-19 disease, it remains a potential contributing factor.

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197 Oudit & Pfeffer, *supra* note 74, at 1820 ("

> The underlying factor linking the multiple organ systems affected by the virus is the ubiquitous tissue expression of ACE2, the receptor mediating SARS-CoV-2 binding and entry into cells . . . When faced with the rapidly expanding COVID-19 pandemic and in the absence of definitive data, the results of [another study] obtained in heart failure patients in the pre-COVID-19 period offer supporting evidence to continue ACE inhibitors or ARBs in patients at risk for SARS-CoV-2 infection.

"); *see also* Moeser, *supra* note 108 ("

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Guide COVID-19 Treatments

Given the evidence that sex differences influence the differing reactions to COVID-19 between men and women, it is crucial that more studies that explore sex differences be undertaken. Understanding women's immune, hormonal, and genetically-mediated responses to COVID is likely to be the best way to understand the disease and find a cure. A few clinical studies are beginning to take these sex differences into account in research about treatments.[198]

Medical researchers in Long Island, New York and Los Angeles, California are undertaking clinical trials where they will dose men with female sex hormones for limited durations.[199] Their hypothesis is that female hormones—namely estrogen and progesterone—could be playing a part in protecting women against COVID-19.[200] At the Renaissance School of Medicine at Stony Brook University, New York, in a study led by Dr. Sharon Nachman, doctors are treating COVID-19 patients with estrogen in an effort to strengthen men's immune responses.[201]

Another sex hormone trial is in the works in Los Angeles.[202] At Cedars-Sinai Medical Center, doctors will be treating male patients with the female hormone progesterone[203] that has anti-inflammatory properties.[204] Progesterone can potentially prevent overreactions of the immune system.[205] Dr. Sara Ghandehari, a pulmonologist and intensive care physician at Cedars-Sinai in Los Angeles, is the principal investigator for

198 *See Progesterone for the Treatment of COVID-19 in Hospitalized Men*, U.S. NATL. LIB. MEDICINE, https://clinicaltrials.gov/ct2/show/NCT04365127 [https://perma.cc/8G3B-JECN] (last updated April 28, 2020) (ClinicalTrials.gov entry for Cedars-Sinai progesterone COVID-19 trial); Rabin, *supra* note 182.

199 Rabin, *supra* note 182.

200 Jamie Ducharme, *Why is COVID-19 Striking Men Harder than Women?*, TIME (May 1, 2020), https://time.com/5829202/covid-19-gender-differences/ [https://perma.cc/8NL9-QXFU].

201 Rabin, *supra* note 182; *see also Stony Brook Researchers Look for New Ways to Combat Coronavirus*, RENAISSANCE SCH. OF MED. STONY BROOK UNIV., https://renaissance.stonybrookmedicine.edu/COVID_Research [https://perma.cc/6JLJ-JSTN] (accessed Aug. 23, 2020) ("Stony Brook researchers are fast-tracking a number of research studies, including these clinical trials . . . [including] [t]he use of the estrogen patch for treatment of COVID-19.").

202 U.S. NATL. LIB. MEDICINE, *supra* note 198; Rabin, *supra* note 182.

203 Rabin, *supra* note 182; *see also* U.S. NATL. LIB. MEDICINE, *supra* note 198.

204 Rabin, *supra* note 182; *see also* U.S. NATL. LIB. MEDICINE, *supra* note 198.

205 Rabin, *supra* note 182.

the progesterone study.[206] According to her, 75% of the hospital's intensive care COVID-19 patients are men.[207] Dr. Ghandehari's hypothesis is that the hormone will prevent the overreaction of the immune system and reduce the likelihood of acute respiratory distress syndrome.[208] However, it is worth noting that current data shows that women with COVID-19 have better survival rates than men even in the 80-plus age group, where hormone levels in both sexes are actually equal.[209] In fact, across all age ranges, the gender gap in death rates is large.[210]

IV
POLICY RECOMMENDATIONS

The devastating effects of the global pandemic of COVID-19 may have been largely avoided if women had not been excluded for so long from medical research. That exclusion led to an inadequate understanding of the bases for immune responses. This is particularly tragic given that during previous pandemics, including the 1918 Spanish flu and the SARS outbreak,[211] it was clear that there was something biologically different about women that enhanced women's survival rates.

Given the historic and seemingly abiding male-centric

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206 *Id.*; *see also* U.S. NATL. LIB. MEDICINE, *supra* note 198.

207 Rabin, *supra* note 182.

208 *See id.* ("

> The researchers in Los Angeles are pinning their hopes on progesterone rather than estrogen because research has shown that the hormone reduces pro-inflammatory immune cells, and supports those that fight inflammation, Dr. Ghandehari said. The hypothesis is that progesterone will prevent or dampen a harmful overreaction of the immune system, called a cytokine storm, and will reduce the likelihood of acute respiratory distress syndrome.

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209 Moeser, *supra* note 108.

210 Reeves & Ford, *supra* note 128; WORLD HEALTH ORG., *supra* note 74 ("The [crude fatality ratio] is higher among males compared to females (4.7% vs. 2.8%).").

211 Noymer & Garenne, *supra* note 131 ("

> The male death rates in 1918 far exceed the female death rates among adults. Among the elderly in both years, there is a slight female excess death rate. Among children and adults, there is a slight male excess death rate in 1917. But in 1918, males were at a much greater disadvantage in terms of flu mortality.

"); Karlberg, *supra* note 133 ("Using data from early March to September 22, 2003, the authors found that males had a significantly ($p < 0.0001$) higher case fatality rate than females did, 21.9% versus 13.2%.").

approach to clinical research, we are concerned that the development of COVID-19 treatments will again focus on men. There is a danger that researchers will use the knowledge gained on women to help men, such as by giving female hormones to men, as is being done in several of the proposed studies, rather than also exploring a different strategy of treatment to benefit women.

Policy changes are needed to reduce sex discrimination in medical research in order to vanquish COVID-19. First, any scientific reporting—whether to the World Health Organization or to the Centers for Disease Control – should disaggregate symptoms by sex (and also by pregnancy status). Any proposal for funding from the National Institutes of Health or for drug approval from the Food and Drug Administration should be required to indicate what previous research was undertaken on female cells, female animals, and women and how their responses differed, if at all, from male responses. The penalties for not doing so should be severe—including, for example, a multi-year suspension of the researchers and their organizations from being able to get any federal funding or get any treatment approved.

Second, we need to be concerned about the gendered context in which research funding and the research enterprise takes place. We need to involve more women in medical research by ensuring that women get a fair shake in education, promotion, NIH grants and private funding. The impressive work on immunological, hormonal, and genetic sex differences in response to infectious diseases that is discussed in this Article has been undertaken primarily by female researchers. Yet female researchers only make up 39% of tenure-track faculty and 23% of tenured faculty.[212] Male graduate students applying to be laboratory managers are more likely to be chosen over equally-qualified female graduate students and more likely to be offered higher salaries and more mentoring.[213]

The scandalous treatment of female researchers continues at all stages of their careers. The NIH awards over

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212 NAT'L INST. OF HEALTH, GENDER INEQUALITY TASK FORCE REPORT (May 2018) https://diversity.nih.gov/programs-partnerships/gender-inequality-task-force-report [https://perma.cc/GE5N-SACN].

213 Corinne A. Moss-Racusin, John F. Dovidio, Victoria L. Brescoll, Mark J. Graham & Jo Handelsman, *Science Faculty's Subtle Gender Biases Favor Male Students*, 109 PROC. OF THE NAT'L ACAD. SCI. U.S. 16474, 16474 (2012).

$40,000,000,000 in funding each year.[214] But a 2018 study found that first-time male grantees received an average grant of $165,721 in grants, compared to $126,615 for similarly-situated women.[215] "The difference is just about $40,000—arguably enough to make or break a project, or a career," noted Colleen Flaherty in *Inside Higher Ed.*[216] Women lose out in private funding as well. Female innovators receive less than 2% of the money men receive from venture capitalists,[217] even though women's start-ups earn more than men's.[218]

At high emotional and physical costs, the COVID-19 pandemic has provided many lessons for our society. We have seen how unprepared our medical system was and we've learned how, once again, people of color are being disproportionately disadvantaged.[219] But there is an additional important lesson emerging from COVID-19—that remedying sex discrimination in medical research is not only necessary to achieve justice, but may also point our way out of a pandemic.

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214 DEP'T OF HEALTH AND HUM. SERVS., FY 2021 BUDGET IN BRIEF 54, https://www.hhs.gov/sites/default/files/fy-2021-budget-in-brief.pdf [https://perma.cc/GUT8-JFXZ] (last visited Nov. 28, 2020).

215 Diego F. M. Oliveria, Yifang Ma, Teresa K. Woodruff & Brian Uzzi, *Comparison of National Institutes of Health Grant Amounts to First-Time Male and Female Principal Investigators*, 321 JAMA 898 (2019) (research letter).

216 Colleen Flaherty, *Smaller Pots for Women*, INSIDE HIGHER ED (Mar. 6, 2019), https://www.insidehighered.com/news/2019/03/06/new-study-nih-funding-says-women-get-smaller-grants-men [https://perma.cc/M3AG-YAHU].

217 Valentina Zarya, *Venture Capital's Funding Gender Gap Is Actually Getting Worse*, FORTUNE (Mar. 13, 2017), http://fortune.com/2017/03/13/female-founders-venture-capital/ [https://perma.cc/3WUE-TZ7H].

218 *Female Founders Outperform Their Male Peers*, FIRST ROUND, http://10years.firstround.com/ [https://perma.cc/834A-8FEM]; Kimberly Weisul, *When It Comes to Revenue, Women Entrepreneurs Are Pummeling the Guys*, INC. (June 6, 2018), https://www.inc.com/kimberly-weisul/boston-consulting-group-female-founders-higher-revenues.html [https://perma.cc/42PL-ZDVQ].

219 Price-Haywood, *supra* note 74; *see also Coronavirus Disease 2019—Racial & Ethnic Minority Groups*, CTRS. FOR DISEASE CONTROL & PREVENTION (June 4, 2020), https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/racial-ethnic-minorities.html [https://perma.cc/JV66-2KKG].