

PAULA:

Leading out from that, we're going to move to our first panel. So our first panel is entitled Sex and Gender Differences, Understanding the Biological and Social Determinants of Health. Our moderator today is Dr Chloe Bird. And Dr Bird is the director of the Center for Health Equity Research at Tufts Medical Center and the Sara Murray Jordan Professor of Medicine at the Tufts University School of Medicine and senior sociologist at Rand. Chloe, if you want to start coming up to the stage and I'll ask the other panelists to come forward. Thank you all very much.

CHLOE BIRD:

Good morning. Thank you, Paula, for starting us off wonderfully. Before I begin introducing the panel, I want to point to a place that you can listen from. Today, it's clear that researchers are developing and advancing personalized medicine, including genetically targeted treatments. It's a great time to be engaged in science. And yet the question of the day is, how are we doing in terms of advancing the evidence base on women's health and in terms of their health care? You may be wondering, how bad could it be? Paula pointed to a lot of progress. I liked the point of 50% of the scientists said they always test for sex and gender differences. Interestingly, when we look at the NIH portfolio, NIH found themselves that in fiscal 2019, 11% of studies said they would answer questions as whether or not the results held for women. And clearly, the goal isn't 50% good science and 50% evidence-based medicine. Recently, Lori, Frank and I oversaw a study commissioned by Women's Health Access Matters, and we looked at the return on investment of doubling NIH funding for studies that do, in fact, say they're going to answer questions on women's health in Alzheimer's disease, 12% said they would.

And we found assuming a 100th of a percent improvement would come out of one years of investment, it would take another \$288 million and produce a 224% return on investment. It would, in fact, more than pay for itself. It's not too expensive. The results are more striking for coronary artery disease. 4.5% of the studies said they would answer questions on women's health. It would take a \$20 million investment to double that. And we found a 9,500% return on investment. For lung cancer, \$6 million would produce another 1,200% return on investment. Clearly, that's not going to get us to the day where the research is actually systematically doing complete work and answering questions on women's health. We have a long way to go. Does it really matter or are we doing good enough already? I want you to consider the coronary artery disease where in her team's work on doing a systematic review of the literature on the basic science. My colleague, Iris Jaffrey, found there were differences in the pathways.

There were differences in plaque, in burden, in morphology that are to the extent that the drug development that ignores that, it's not even possible and the panel today will point to this. It's not even possible to have effects in women where they've used a knockout gene, and they know what happens when a gene is not present. So we have an opportunity to be doing the science, to be changing the way that we're doing the work, and avoid the kinds of errors that mean you underestimate. You either think something works in the whole population and go out and try to treat women, or, as we've often done in science assumed that it didn't work in anybody when in fact a treatment could work in men. So we have a huge opportunity today, and I want you to listen to from what's possible because it's clear from our work that it's not that it's going to cost more to do good science. What's costing us billions is not knowing how to cure for women. So we'll start with Janine Clayton, who I assume everyone does, in fact, already know is the associate director for research on women's health at NIH and director of the Office of Research on Women's Health.

Thank you for being here, Janine.

JANINE CLAYTON:

Thank you so much, Dr Bird. And thank you to the academies for this amazing day that you've planned. I entitled my talk Raising the Bar, Putting Science to Work for the Health of Women. You heard from Dr Johnson, who so eloquently outlined the history of women's health research, both at NIH and in our country. And I do want to make sure that I mention that the then NIH director, Dr Bernadine Healy, the so far only woman director of NIH, appointed Dr Vivian Pinn, the first full-time director of ORWH in 1991 after the office was founded in 1990. The office was founded because women were being excluded from NIH-supported clinical research, and members of the Congressional Caucus for Women's Issues essentially demanded that NIH create this new office. And it was in 1993 that the NIH Revitalization Act, as Dr Johnson outlined, put forward that women and underrepresented racial and ethnic groups must be included in NIH-supported research. So let's think about that word inclusion. So what does ORWH do?

At NIH, we serve as the focal point for women's health research. We work collaboratively with the 27 institutes and centres at NIH, each of whom does women's health research and supports women's health research in the context of their mission areas. Our goal is to expand that research, make sure that women are included, and advance women in STEM, because we imagine a world we're all women which all women receive evidence-based diagnostics treatment and care tailored to their own circumstances, goals and needs. We imagine a world where sex and gender are integrated across the biomedical research continuum from the beginning to the end, and a world where all women in science reach their full potential. So what are the programs that we put forward in order to make that happen? The first effort that Dr Pinn led was the development of the Birch program, building interdisciplinary research careers in women's health. And the purpose of that program is to expand the cadre of women's health researchers, the people doing that research.

And over 750 scholars have now been trained across the country, and the majority of them have remained in research and the majority have actually achieved leadership positions. In addition, to make sure that we were able to test for sex differences in the context of conditions that are relevant to the health of women, we created the Specialized Centers of Research Excellence on Sex Differences, which remains NIH's only centre-level program focused on sex differences across all diseases and organ systems. And the NIH working Group on Women in Biomedical Careers addresses the policies and practices and programs needed in order to support women in STEM. In 2016, NIH put forward this policy on Sex as a Biological Variable. It essentially states that we expect that sex as a biological variable will be factored into research designs, analyses, and reporting for vertebrate animal and human studies and that strong justification has to be provided for single-sex studies. Incorporating consideration of sex and gender for human studies across the research continuum, from the lab to the clinic.

Advance rigour, relevance, discovery, innovation, and equity because we all want to get to that centre with healthy people. So if we consider sex in those pre-clinical studies, those in vitro studies, those animal models. And as we translate that into first in human for through phase one, two and three clinical trials, where the definitive results of phase three clinical trials inform regulatory decision-making and clinical care. And then of course, in performing those trials, we need to report the results by sex, and we need to publish those results in journals and journal editors and publishers play a key role there so that those publications can lead to new hypotheses and new studies. It's essential that we integrate consideration of sex and gender to inform and improve the health of women into our interprofessional

health education at the undergraduate level, at the graduate level, medical students and dentists, pharmacists, and then we can consider delivering sex and gender-informed health care.

And of course, all of this evidence should inform policy making. The health of women today is considered far much more than reproductive health. Women's health constitutes everything that affects a woman, from head to toe, inside and out, across her life course. In the context of where she works, lives, and plays, external environments, societal contexts, whether that's a toxic relationship or a toxic exposure, the life course must be considered. You heard from Dr Johnson about pregnancy-induced hypertension, increasing the risk for cardiovascular disease as we get older, NHLBI funded studies found that that is within three years of the pregnancy-induced hypertension, not 20 years later. And we already knew that gestational diabetes is associated with a type two diabetes risk. So how can we take that stress test of pregnancy and bridge the chasm between pregnancy care and postpartum care, because we do know that women have more chronic conditions and spend more years of their lives disabled with poor quality of life despite the fact that women do live longer than men in general.

How can we take advantage of midlife health and menopause, which is a clear inflection point for the increased risk of chronic disease? And I like to call it our last best chance to prevent those chronic diseases. So we combined sex and gender, that biology and social construct in an R01 on intersections of sex and gender for health and disease. And we address these issues of chronic diseases because the US Congress asked us to look at three particular areas, maternal morbidity and mortality. And you saw the data. The levels are increasing. And I will add that the levels have increased above the levels for white women, for Hispanic women for the first time ever in the United States. So we looked at maternal mortality, stalled cervical cancer survival rates and chronic debilitating conditions because women in the US are sicker than ever. And Congress decided that we... and it should form an Office of Autoimmune Disease Research, supporting that in FY 22, and that was formed within ORWH.

And we collaborated with the Gates Foundation on an effort that I'll talk about in a moment. So I mentioned inclusion and remembering that word. And so I want you to think now about intention. We need to intentionally integrate considerations of sex and gender across the biomedical research continuum, whether that means focusing, as we have, on understudied, underreported and underrepresented populations of women in our U3 program, or setting the next NIH-wide strategic plan for women's health research. Of course, NIH-supported research has had incredible advances, whether it was the Women's Health Initiative, the Swan study, microfluidic studies, the basic science work that led to Jak inhibitors, or the basic science work that led to the first-ever treatment for postpartum depression. Discovery is critical to innovation and the improvement of the health of women. Yet gaps exist, 8% of people have an autoimmune disease, and 80% of those people are women. Women who experienced a heart attack are less likely to receive, in addition to waiting longer, they're less likely to receive guideline-based treatment and less guideline-based diagnostics and less invasive treatments.

And the CDC recently reported that 20% of women report mistreatment while receiving maternity care. And primary prevention of cancer is more difficult and challenging in women, and we still have ways to go to fully implement sex as a biological variable. So as a group, we partnered with the Gates Foundation to create a Women's Health Opportunity map that crosses sectors and countries and disciplines and powered by partnerships, we identified 50 high-return opportunities to advance global women's R&D. So I'm going to end with a couple of highlights of the interprofessional education opportunities that we

provide that are listed on slide here. And I'm so appreciative for the time to be here with you today. Thank you so much.

CHLOE BIRD:

Thank you, Dr Clayton. Now, I'd like to introduce Dr Carolyn Mazure, who is the Spungin and Bildner professor of women's health research at Yale. A professor of psychiatry and psychology and director of women's health research. She also established and built the Center for Women's Health Research at Yale, which is now celebrating 25 years. Thank you.

CAROLYN MAZURE:

Thank you, Dr Bird. I appreciate the introduction. So today I'm going to focus on who we study and why. And I'm going to try to use that as a context or a backdrop to look at opportunities for discovery and pivot off some of the comments my colleagues have made. So one of the major points I'd like to make with this slide is simply that by the late 1990s, the scientific community was really undergoing a sea change, and those of us in the room who back in that time were writing R01s were very well aware of the fact that the NIH had changed the requirement. It was a key change, and that's one of the points that I want to bring home today. The capacity to make change. The reason, as Dr Johnson said, for optimism. So here we are in the late 1990s, we have the NIH change, women are to be included. At the same time as this is being acknowledged, there's still this continuing debate that in some circles exists today, as others are pointing out about whether there is real value in studying the biology of women beyond reproductive health.

And at this juncture, I want to turn to the incredible importance of the IOM and a whole variety of ways. So in response to this debate, the IOM, in 1999, convened a committee on Understanding the biology of Sex and Gender Differences. And they were charged with evaluating the science at that juncture and then coming to a conclusion about whether or not sex-based differences, both in vertebrate animals as well as in cells were relevant to human biology. If they made a difference in clinical care and in medicine. So as they concluded, and Dr Johnson showed you the book that really came from this committee. They concluded that there was certainly sufficient knowledge. They promoted this idea of sex as a biological variable and they conceptualized sex as generally dimorphic and gender as a continuum. So here we are in 2001, 20-plus years ago, they were ahead of their time, they were anticipating this. They knew about this. They wanted us to think about this. They formally recognized genetic and physiologic etiology as well as environmental and experience as affecting health outcomes, and they recommended sex and gender as the terms to use.

And I'll show you their definitions in one second. But they wanted us to think about sex and gender in order to aid and endorse research in both of these areas, both the biology and the social psychology cultural effects on health. So here we are now, by the start of the 21st century, and we're looking at what I consider landmark policy and guidance indicating, first of all, research participants should include women. Second, the influence of biological sex and social experience of gender affect health outcomes and have to be studied. And thirdly, and very importantly, to remarks that you've already heard today, these concepts need to continue to evolve. And that is happening. Not only we have to keep up with this, we have to be part of this. As Dr. Johnson was talking to us about that. So here are the definitions, both given by the IOM back in 2001, but also definitions updated by NASEM in 2022. What you'll notice as you compare those definitions or two things, in my opinion. First, the great similarity between the two.

But second, where the difference lies and the major difference lies in thinking more dimensionally about these concepts. They are not binary, they are dimensions. They're continuum. And so I would encourage you to focus on that as you think about your science, as you think about categorization of people. Today I am talking about women and men and using that as a general binary. But we have to engage in a discussion about what we're going to call people, what the language means, and how that relates to the biology. And it seems to me that one of the things we can do is get very excited about studying the variation in way in which people identify now and understand that intersection. So now we see, as a consequence of these policies and guidances that I've been mentioning, the growth of clinically relevant data. So in terms of the optimism scale, I would propose to you that there is a lot of reason for optimism because there's a reason for opportunity. And just as an example, here's a list of just some particular disorders in which now we have clinically relevant data by comparing women and men.

SPEAKER:

It's not just in the epidemiology, it's not just in the prevalence and incidence of disease. It's the way in which it presents. It's the way in which diseases progress. It's also affects the treatment of disease and there are many studies now in the last 3 to 5 years showing that. Where also and you'll hear more, fortunately, from Dr. Paige in a moment about the contribution of basic science in terms of sex and gender. And I think principally sex and cell signaling, sex and gene regulation, how those concepts really are important for us as we consider this field. But the reason I show this graphic is I went on and I did a PubMed search for these topics. And if you look at the way in which there's been this tremendous uptick in the interest in this area and the publication in this area, this is happening because people are getting findings and they are interested in knowing how these findings relate to the greater biology. However, there is so much more to do. So as you've heard a bit about today, and it's worth repeating compared to other developed economies, we're lagging behind.

The Commonwealth Fund did a study in 2022 showing that US women of reproductive age have the highest rate of death from avoidable causes. Maternal mortality is built into that, but it is not exclusively mortality as a function of childbirth or maternal position. Women overall at the US, in the US are at higher risk for a variety of different disorders. Co-occurring disorders are more common in women. Psychosocial stressors are more common in women. Living in poverty is more common in women, and Dr. Zhao and others have pointed to the importance of social factors. These social factors make a difference, and these data are our call to action. And what I like to talk about when I talk about this, particularly at home with the scientists that I work with, is the concept that we have seen the capacity of science to change. These guidelines, these landmark policy changes have helped us think about making those changes in our work, and we can do it. Back in the 1990s when we were troubling about how are we going to write an RR1 and include women and men?

We figured it out and we can figure this out and so what's exciting about the future is we can change this. We've shown that it can be done, and we can show that it advances science and most importantly, improves outcomes. And everybody thrives as women do better, families do better, children do better, and the society improves. Thank you. (APPLAUSE) Next, we have Dr. David Page, who's a member of the Whitehead Institute, a Professor of biology at Massachusetts Institute of Technology and an investigator at Howard Hughes Medical Institute. Thank you.

DAVID C. PAGE:

Hey. Thank you, Dr. Bird, and I want to thank all my fellow panel members and Paula and Victor and

Karen for launching this and leading this discussion, which is a wonderful one of women's health from cells to society. OK, We've talked about science. I'm going to flip into my role as a professor with you here and invite you all to spend a few minutes exploring my favourite pair of chromosomes. On the left. I didn't say anything. On the left, stately and statuesque. The X chromosome and to its right, with its head down, the demure, diminutive Y chromosome. Now, truth be told, I've spent most of my career defending the honour of the little one in the face of innumerable insults to its character and its future prospects. So, I have no right taking the stage at a symposium on women's health. But my new obsession and it really is an obsession, is the X chromosome, which I will argue today is as misunderstood as the Y chromosome ever was. So let's start correcting that misunderstanding right here, right now.

So, the members... Let me see. Am I doing... It's not. What am I doing wrong? Yeah.

SPEAKER:

The x. The x. The x. The x.

DAVID C. PAGE:

Here? I'll get it I'll get it. Hey, there we go. Put joy. We rehearsed this well, don't you think? Let's see. Here, Hellen, I'm going to see if I can work this thing. I don't know, do you want to?

HELLEN:

(INAUDIBLE). You just. Tell me.

DAVID C. PAGE:

I don't know, let's see. Okay, well, we'll see how this goes, right? It's... The members of our species are said to have sex chromosomes of two kinds. And while that's true in conventional genetic parlance, epigenetically speaking... Yeah, that was good. Human somatic cells have sex chromosomes of three kinds. This is my real lesson for the day. There are three kinds of sex chromosomes that we have in our somatic cells. There's the Xa, the active X chromosome, Xi the so-called inactive X chromosome. Do you remember learning about the Barr body? OK? Hands. Barr body, OK. That's the Xi. Barr body is another name for the Xi, inactive X and then there's the y. And the amazing thing is that these three epigenetically distinct kinds of sex chromosomes can coexist in the same somatic cell. Not in our germ cells that make eggs and sperm, but these three kinds of chromosomes can coexist in the same somatic cell in various combinations. So, I have a pop quiz to offer to you. What is the name of the syndrome where an individual's cells have one Xa, one Xi and a Y chromosome?

SPEAKER:

The Klinefelter syndrome.

DAVID C. PAGE:

The Klinefelter syndrome, OK? We'll work on that, Paula. Don't worry. That's right. Right. But typically, typically, human somatic cells come in two varieties. One X plus one Xi or one Xa plus one Y. Now the amazing thing, what I really want to point out to you here is that one X is present in somatic cells of both sexes. And actually, after extensive epigenetic characterization, my colleagues and I find no difference between the Xas in female and male cells. So, while the Xa is often referred to, at least in my experience, it's often referred to as a female chromosome. The Xa is no more female than any of the 44 autosomes in each of our cells. So the chromosomes then, that differ between the sexes, between females and males are actually Xi versus Y. So the other 45 chromosomes are genetically and epigenetically

equivalent in females and males. Only the 46th chromosome differs. So we traditionally say, and this has been said for as long as I've been alive, for sure. We traditionally say that females are XX and males are XY.

But now one could say that females are Xi and males are Y. Just let you... Let that sink in a little bit. Now, but wouldn't this just be semantics? Isn't Xi genetically inactive? After all, it's the inactive X chromosome and the Y chromosome, isn't it of no importance outside the testes? Well, indeed, the old understanding of the human X and Y, which is to say, what's taught in most universities and medical schools today, the old understanding is that the Y chromosome functions only in testes and that in female cells, the second X chromosome, the XY, is silent. And if you think through the implications of those two things, you arrive at the conclusion that outside the gonads XX and XY cells are functionally, maybe even morally equivalent, that both XX and XY cells would then be functionally Xo, outside the gonads. But it turns out these are very outdated understandings. And so what we now know is that there are ten different genes on the Y chromosome that are expressed across the body and virtually every cell type and these regulate expression of thousands of autosomal genes.

And there are hundreds of genes that are expressed from the so-called inactive X chromosome. And amazingly, these include X-specific versions of the Y chromosomes, broadly expressed global regulators, so that throughout the body then, that XY is not equal to XX. And we now understand that at a chromosomal and biochemical level. So, stated differently the old understanding and apologies for the bathroom gendered, which I note is present throughout this building. The old understanding was that whether one is XX or XY, mattered only in the nether regions, only in the gonads, whose sex hormone exports were thought to drive all biological sex differences across the body. So today, we supplement this gonad-centric view of XX and XY biology with an understanding that the first X chromosome Xa, is shared between and does not differentiate the sexes. And instead, biological differences between females and males stem from the long-neglected Xi and Y chromosomes, which we now understand are active in every cell type of the body, including the gonads.

So in closing, the scientific quest then, is and it's a massive quest is to discover the molecular bridges that connect the human sex chromosomes and specifically Xi versus Y to sex differences in health and disease across the body. I would assert that all biologically based differences, those that are not due to social or environmental determinants, that all biologically based differences trace their origins to the sex chromosomes. So the task is to connect the 46th chromosome, Xi or Y to sex differences across the breadth of human biology and medicine. And I would argue that the first task, and one of special interest to women's health is to understand the underestimated and far from inactive Xi. Thank you very much. Alright. (APPLAUSE)

SPEAKER:

Now we have Dr. Elissa Epel, Professor and Chair of the Department of Psychiatry and Behavioral Sciences at the University of California, San Francisco and director of Aging, Metabolism and Emotions Center. Thank you.

ELISSA EPEL:

Thank you so much. I'm so delighted to speak with you today with an update on the science of stress. How individuals and groups interact with and react to the environment. We heard a little bit about the exposures, the social environment from Dr. DeSalvo, Dr. Clayton, and social chronic stress illuminates our understanding of lifespan women's health. So I'm going to give you a very quick view of how stress is

different, how it's reflected in the neurobiological reactivity in the body in critical periods. And the most exciting part in interventions at critical periods, which, as you'll see, we have the evidence, we have the data for and there's really a call to action here. So the stress exposome is the world of exposures of both social stressors and environmental stressors. And they get under the skin to affect health for everyone men and women. But look at these stressors and you will see these are gendered stressors in that they're much more common, intense and systemic in women's lives.

Traumatic events, caregiving stress, crime and violence, exposure, financial strain, poverty, work stress with low control. And then there's these physiological stressors that either we eat or get under the skin. Food insecurity drives, processed food intake, which interacts with the stressed organism to synergize into early metabolic disease. We have, of course, poor air quality, pollution, chemicals. We now have frequent climate stressors, excessive heat, poor air quality from wildfire smoke. We now have climate trauma. We know that exposure to wildfires six months later leaves an imprint on brain function that looks like post-traumatic stress disorder. So how does stress affect the brain in women versus men? The neurobiology of stress in women shows us that there's more neuroplasticity. There are greater and prolonged stress reactions. And that means that for women, acute stress can become chronic stress responses more easily. That helps explain the mental health disparity, the pro-inflammatory burden of diseases early in life for women.

In rats, it's very clear. Acute stress and chronic stress affect female rats with a more exaggerated profile, and we know that this is due to estrogen. So in rats, you could say simply this explains the greater mental health burden. In humans, it's so much more complex. We know that hormones are intricately involved in mental and physical health, in general protection, and we have so much to gain by developing that science and translating it to application. We know chronic stress affects not just function, but the structure of the brain, damage to dendritic spines, prefrontal cortex in the hippocampus. And so when we think of the implications of these sex differences, it's that acute becomes chronic much more easily. Now, what about in the body? We now know with very, I would say, high resolution, that both early traumatic stress and chronic stress gets into the skin to promote accelerated biological aging. Looking at most of the hallmarks of aging. So here I'm showing you research by our group and others showing that chronic stress accelerates systemic inflammation early in life, telomere shortening, mitochondrial enzyme dampening, and the epigenetics of accelerated aging.

When does this start? How early? This starts in the womb. We also now know that for women, exposure to severe stress during pregnancy predicts accelerated biological aging on day one of offspring. The research on telomeres is accelerating. There's now many studies showing that stress, trauma, air pollution, heat stressors predict shorter telomeres on day one of life and of course, maternal health as well. Sex differences in most studies, you can't make sense of them. The samples are too small. The results are inconsistent. Clearly, there's sex differences in transmission. So I want to just tell you briefly about this amazing opportunity we've had to study women from ten years old to midlife, 40 years old, black and white women. You can see the early team and our current team. We've looked at... This study tells the story of social determinants of health very clearly. Education tracks and predicts accelerated cell aging, with one of the biggest effects. But more so, grandparent education tracks across to accelerate the aging of grandchild epigenetic clocks.

Now, we've been going in to look at early life stress in this prospective cohort and how it predicts midlife early aging in women in black and white women. And what we have found is that early trauma predicts



accelerated aging, systemic inflammation, the epigenetic aging and telomere shortening through speeding up onset of reproductive development through early puberty. So this is a really important pathway set early in life that accelerates women's aging. The excessive morbidity that we see throughout women's life could be explained by this. Now let me tell you a fun fact. Stress researchers were turning away from just looking at what makes us sick about stress, what happens during reactivity because there's a whole other side that we've ignored. What happens at rest? How quickly do we recover? How much time do we spend in restoration mode? So we have just published a large review showing the biology of rest, leisure and deep rest sleep and what happens in our body during meditation mindfulness, mind body practices.

There's a very solid literature showing that these are states we rarely get to, but they are the other half of the equation. They repair from the stress damage that many people experience chronically. What do we know from this? We know that women get less deep rest. They have 50% more insomnia, lower quality sleep, and less leisure time. So, men get, on average, five or more hours of leisure a week. So, this is just another half of the equation we want to think about when we think about structural factors, health behaviors, and what is filtering down to our cells. So, I'm very excited to talk to you about pregnancy interventions, which are such a critical period for women's health, for future cardiovascular disease, but also for two generations for offspring health. And there are group prenatal interventions that provide education and social support, like centering pregnancy. Centering pregnancy is one of the only interventions that can reduce preterm birth and other complications. And so for offspring.

And so we know pregnancy interventions in the healthcare system work. We've been optimizing a pregnancy health intervention to reduce social stress and improve nutrition through choices and mindful eating. And I wanted to show you really briefly what we found. This is one of our cohorts after the intervention, eight weeks of training, reducing stress, increasing restorative time, increasing the amount of time that they're giving to themselves and the baby for deep rest and reparation, sending different signals to the baby's developing brain. So, what have we found? In eight weeks early in pregnancy, we reduced risk for diabetes, we reduced impaired glucose tolerance, we reduced depression. But we followed them eight years later with my colleague Nicki Bush. We now know that the women report lower weight and significantly lower depression still. How is that on return on investment? So, this is a very short intervention during pregnancy that's affecting two generations, so that infants also benefit more resilient stress reactivity and less visits, six less doctor's visits in the first year of life.

So, what are the implications? All this added together, I've pointed to the excessive embedding of social and systemic stressors that women are exposed to the exaggerated neurobiological reactivity. In addition, we have these development periods. We can think of them as vulnerability, but there are periods of opportunity of neuroplasticity, of resilience if we can intervene at these periods. And so, of course, pregnancy is a time when we can intervene intergenerationally and pro-social policies are something that we really want to think about. Policies that help with physical, with resources, with healthcare for women and families. But what do I mean by pro-social? Nice. Just not, not just nice. The United Nations is promoting the universal values of pro-social qualities. This is compassion, dignity, individual rights, kindness, generosity, altruism, sharing resources. This is the fundamental way we are wired as social mammals. This is what promotes healthy communities. So, rather than just focusing on reducing risk and what makes us sick, we need to promote pro-social values.

They're the undergirding of the policies that we are all dying to have implemented. They're the undergirding of what we hear from Don Berwick about the moral determinants of health. So, we my colleagues and I, Laura Kubzansky, Richie Davidson, we just put out a commentary in nature behavior showing this emerging data that prosociality improves health and wellness from the individual to the social level. And so prosocial policies, I hope we'll get to discuss more. Thank you.

CHLOE:

So, first I'd like to ask about what you think is possible in making advances an example of something that's been done, that highlights what's possible? I don't know if everybody here is aware this morning Dr. Claudia Goldin Economist won the Nobel Prize for economics for her work on women's labor force participation. It's been a long time coming. But I think that's a great harbinger of what's possible out of work that actually investigates and looks beyond what we've thought worked, what we thought we knew from studying men or from studying men and adding women. As Pratt Schroeder would say, we add women in stir. We're kind of at the women's history month level of women in science and women in medicine. So, you can give a few examples, but we're gonna turn into some great examples. What's something where it really made a difference? And we'll start with Janine. In how an area thought about problems?

JANINE:

Thanks for that question, Chloe. I'd like to cite Louise McCullough's work on stroke. We know that actually women fare more poorly than men do after stroke. And her animal model, mouse model, rodent model, she observed that PARP1 inhibitors might work. She had data to suggest that. So, then she did an in vitro work where she removed the neurons and exposed them in their cell death model to PARP1 inhibitor, which reduced cell death, which is an improvement in the male mice only, and not in the female mice. In fact, it worsened and she showed her data when it was combined, you could not see any effect when the data were not disaggregated. So, to answer your question, we could identify therapeutics that might work in one sex and not the other. And we could avoid harm by understanding the potential sex specific effects if we consider sex as a biological variable from the beginning.

CHLOE:

You Carolyn.

CAROLYN:

Thanks, Chloe. Yeah, I have another example that I think would be of interest. So, one of the things that my center has done over the last 25 years is really try to focus on disorders and conditions of high morbidity and mortality in women, because you're more likely to find a positive effect there if you can make an intervention and show difference. And one of the areas in which we work is cardiovascular disease. And we have an interventionalist that I talk with frequently about the nature of his work. And what he tells me is that down in the ED, when people come in presenting for heart attack, of course, we all know that the major cause of heart attacking women and men is a blocked artery. And yet he often sees women who don't have a blocked artery and yet have the symptoms for heart attack. And so he got quite interested in that. Came to us, we fund pilot studies because we think it's very important to take innovative clinical ideas and turn them around and see if there's something we can do with them that's really gonna make a difference.

And he had this idea that while he was doing the angiogram, that he was gonna do anyway on everybody to see if he could locate a blockade, a blockade, he would then, if he didn't find blockage in a

major coronary artery, he would do an acetylcholine challenge. And he was able to show vasospasm as well as show a microvascular disease. And as a consequence of that, he has, and we know that microvascular disease is more common in women than men. It can be suffered by men, but more common in women. And he was able to show then consequently, that he could correctly diagnose women who had histories of having stents placed, even though they didn't have blockage of women undergoing, in fact all sorts of repair in invasive procedures. And this is now a procedure being used in our ED. He's publishing this material. We're looking to get the information out more widely. And it's using an accepted procedures, but it's working. I think, at that interface between the question of high morbidity mortality in women and clinical care.

CHLOE:

David, bring us back to the XI (LAUGHS)

DAVID:

I will, and I'm thinking I've a lot of... But I'll bring it back to an illustration that connects to an aspect of life that we've talked about a lot this morning. And that's pregnancy and maternity. And of course one challenging dimension of human reproduction is our rather high rate of miscarriage, of spontaneous abortion. And it turns out that it may not be widely known speaking about the sex chromosomes, that 99% of XO fetuses, abort spontaneously. Turner syndrome survivors are very, very uncommon. And so I'll just pose to you the question of, so why is it... I'll ask each of you, why is it that I survived (LAUGHS) as a fetus? And I will offer the answer as that. It's because in addition to that, XA, you added, (LAUGHS) you carried either an XI or it turns out a Y. So, a curious thing is we're coming to understand that during fetal development, that fetal survival actually requires in nearly all or perhaps all cases, the presence of a second sex chromosome. And in some sense, the XI and the Y are serving as equivalent providers of viability during pregnancy.

There are also other conditions that I've just been musing about lately. It turns out there are some trisomies that we hear very little about things like trisomy 13 and trisomy 18 that are compatible with survival to birth. But when we think about sex differences, there are amazingly there's a much higher frequency of trisomy 13 and 18 among females than among males. And what is the difference? Why do females survive, have a better survival with trisomy 13 and 18? My guess is the answer will again, be XI. But many questions to be framed with respect to pregnancy and fetal viability.

ELISSA EPEL:

I'll talk about a pregnancy from a macro angle (LAUGHTER) which is thinking about lead policies and what that means biologically. So, we have amazing examples of antecedent pregnancy leave, this acknowledgement that there is biological work going on that's incompatible with rushing and daily stress. And of course, there are countries that have maternity leave for a year. Again, acknowledging these are critical neuroplastic periods that need to be supported. And so even, you know, work policies that provide flexibility and shorter leave, I know that... Sorry more flexibility just within a day as well, have a huge difference to mental health. The idea that people with low resources and moonlighting and very few degrees of freedom are going to be able to access different employee wellness programs and gyms. It doesn't happen. We can't even get our socially disadvantaged employees to read their email about any benefits. So, the messages and the communications aren't even getting there. So, I think work should be a source of improved health purpose and meaning, and not a detraction from health and particularly during pregnancy.

CHLOE:

Thank you. Another category I'm interested in is the diseases where we've overfit to a model of men. And certainly we can think of a lot of areas of cardiovascular disease where often what women get told is you don't have the disease, and in fact it may be you just don't have what a disease looks like in men. Are there any areas that, that are in your work that are of interest or are making progress and understanding? It certainly runs a continuum. Do you wanna take this one, Janine? You're nodding.

JANINE:

I think Carolyn gave the quintessential example, which is the microvascular disease. And maybe I could just extend that to say that the coronary angiogram is the gold standard for detecting obstructive coronary artery disease, because obstructive coronary artery disease is the male pattern of disease, predominant male pattern of disease. So, the idea that we develop our gold standards based on a pattern that we look at and we study is really important. And why we spent time on talking about history today is because we are behind in terms of studying women's health because women weren't included till 1993. So, we're playing catch up and trying to complete this basis. So, this is how that plays out. Where now we do have the acetylcholine challenge. We have MRI where we can detect microvascular disease, but we're still saying that that's atypical because we're comparing it. And I would argue that we just need to understand how heart disease occurs in men and in women. And it may or may not be different.

In fact, there's some gendered behaviors around a heart disease where more feminine approaches to the occurrence of the disease was associated with better outcomes even in men. So, then I'll end with just saying it's not just the gold standard diagnostic intervention, it's every single test that we use to diagnose a disease. So, we know hemoglobin and hematocrit are different for males and females, and we don't think any other thing of that. We know that bone density is different for males and females, but did you know that hemoglobin A one C might be different? Did you know that the systolic blood pressure above which you might have consequences is probably lower in women than in men? And that's from our score study. So, just pulling it together how these things that we've all talked about, what are the practical implications?

CAROLYN:

So, just to elaborate on something that Elissa was talking about in regard to stress, and you were kind enough to cite one of the recent studies that we did in this regard. What we find generally is in civilian populations, when you look at the effect of a stress, what you're really looking at are whether or not people are having functional symptoms. And those symptoms usually fall in the area of mental health. So, are people getting anxious? Are people unable to do their job? Are there other symptoms of PTSD or depression or anxiety? In the literature in general, when you look at reaction to stress, real life events, adverse events, what you find is that women are more likely to score higher on measures of stress like anxiety symptoms, depressive symptoms, et cetera. What we did studying a large cohort in New York City at the start of the COVID-19 pandemic, was to take baseline data on their reports of what stress was like doing their job and compared it over time. And what we found were two things that I think are relevant to this discussion.

Number one, yes, we found that women reported more symptoms. Two, we found that if you looked at co-occurring stressors in the lives of women and men, that sex difference disappeared entirely. It was eliminated. And what that means, basically, is that women have a greater stress burden on a daily basis.

And as a function of that, they score higher when they're asked about their stress level referable to a specific stressor, implying that women are less resilient, more vulnerable to stress is a term you'll often see in the literature, not quite the case. It's actually that women bear more stress burden before they actually start to report symptoms. And I think that's part of why we're so intrigued by this interface between biology and social experience. Tony Lewis down at Emory is doing beautiful work, very elegant work where she's studying black populations in terms of daily stressors of discrimination and the report of perceived stress and how that relates to hypertension. And she's finding a clear correlation between the two.

But what she's finding is it's worse for women than it is for men. So, everywhere you look, whether it's in an interaction between racial identity and identified sex or gender, or you're just looking broadly at sex and gender, you find these kinds of differences.

CHLOE:

You wanna do it.

DAVID:

Yeah, let me pick up from Ellen. You set me up there. Got my mind thinking about the interaction between biology and social engagement. And so let me put on the table. Autism, an autism spectrum disorder. As I'm sure you know, the diagnosis of autism or autism spectrum disorder is made about four times as often in young males as in young females. And there's great debate about the degree to which this might be due to diagnostic bias. And I suspect that diagnostic bias plays some role in that four to one male to female diagnostic ratio. But it's probably, it is my sense that's not a sufficient explanation. It may be a partial explanation. And there's been tremendous studies have been done in recent decades into the genetic basis of autism and much has been learned. And what's been found broadly speaking, is that a great variety of genetic variations can contribute to the risk of autism. And the amazing thing is, so you might think, well, maybe is autism in females and males, are they different disorders?

Well, that's a question that I think will live and be not fully answered for a long time. But if you look at the genetic level, it appears that the genetic variations that predisposed to autism in males and females are fundamentally the same. That is, they're being drawn from the same universe of genetic variations that predispose males and females to autism. However, for a female to be diagnosed with autism requires a greater sampling of that universe of genetic variations. In other words, females with a diagnosis of autism tend to have a greater genetic burden, if you will, than than males. And this has led to the concept of a female protective effect in autism and autism spectrum disorder. And we don't know the contours or the identity of that female protective effect in detail, but let me offer one possible explanation that is XR...

DAVID C. PAGE:

You shouldn't be surprised to hear me say that, but alright, alright, alright.

ELISSA EPEL:

Yeah, just piggybacking on to Karen's point about this sex difference and stress. So, Victor made the point earlier that there is no health equity without social equity and the social determinants that we will never beat the effects of social determinants, education... Age is always gonna be the best predictor of aging and mortality. But beyond that, we've got the most robust predictor which is the social determinants. And so there's a lot that goes into describing the social determinants, the 80% that Mike

McGinnis shows us, that's not genetics, but that is social and behavioral. So, the way I think about stress is that it tells the story of the social determinants and behavior in an umbrella way, in that it's not the only factor, but it is a gateway. It is how behaviour starts falling apart, as well as the integrity of cellular aging. So, we know that 30% of the adult population feels extreme stress on a daily basis. And then you break it down and say, who? What subgroups? Who's reporting stress?

That sounds kind of low. Look at young women and it's 60%. And the who is at... And add any marginalized socialized identity and you get higher and higher stress levels. And so it is a response to the embedded social stress and systemic stressors and white men are always lowest. It's not easy to be white men now and they're still not low in levels of stress. So, I just wanted to point out that's how I think it's packed into this pathway of social determinants.

CHLOE E BIRD:

Thank you. I wanna take some questions from the audience. If you can come to the mic, please try to limit or eliminate the preamble so that we can get a few questions. And you can come up and tell us your preamble after the fact.

ELISSA EPEL:

State your name.

CHLOE E BIRD:

And state your name. Here on the right.

JOHN QUACKENBUSH:

So, good morning. And I wanna thank the panel so much for the really great discussion and David mentioned genetics. And there's an interesting thing that if you look at Genome-Wide Association Studies and I apologize for the preamble, but not a single GWAS study accounts for X and Y, right? And the question is why? And the answer is because there's a lack of quantitative methods for dealing with this kind of molecular data, right? Don Demayo and I applied for eight years in a row before getting a grant to be able to develop quantitative methods for inferring gene regulatory networks that account for the X and Y chromosomes. So, one of the things I wanna applaud you for is bringing this to our attention. But really, I wanna encourage you, as you think about this going forward, to really consider the need to make an investment in the quantitative side of dealing with the data and in particular, the molecular data.

CHLOE E BIRD:

Thank you. On the left.

RITA REDBERG:

Thanks, I'm Rita Redberg, a cardiologist from UC San Francisco and great keynote and panel and so glad to hear Women's Health featured. I wanted to pick up on a point that I have been thinking about too. And the representation. Well, there were a lot of points there, but the one I'll pick up on is the representation of women in drug and device trials, which Dr Johnson mentioned in her keynote and some of you mentioned, and Janine knows, you know, the NIH when Bernadine put out the guidance. The guidance didn't really make a difference in the GAO show that women were still not being represented and being excluded from clinical trials. I can say I participated in FDA workshops in the 90s on how to have more women in device trials, and the FDA has put out a number of guidances, but the

numbers have changed very little. There's been some improvement, for sure, but women are sorely underrepresented, particularly in cardiology. And so I'm wondering if it's time we do have FDA leadership at this meeting to actually do what the NIH did and have it as a requirement.

And I understand that means that it could either be bigger trials, could have more women in than men in the trials for a change. But I would just like to get some feedback and feasibility of that because it is very discouraging for 30 years to see so little progress in the number of women. And I don't wanna come back to this meeting and not see progress.

CHLOE E BIRD:

I certainly was discussing that with Iris Jaffe, who heads our cardiovascular basic research at Tufts. And it's cheaper to do the research. At the same time, if we do a study whether in humans or in animals, that's all males or we don't have the data to break it down sufficiently otherwise, and then go back five years later and study female mice in a different lab, we don't know if we don't get the same results because of some other factors. We've got to do the head-to-work and get the answers from the beginning. On the right.

LESLIE BENET:

This is a paired talk. I'm also UCSF, Leslie Benet and I wanna talk about 30 years ago. 30 years ago, I spoke at the NIH menopause workshop of what we know about menopause and drug pharmacokinetics and pharmacodynamics, the answer was nothing. And this coming Wednesday morning, the FDA Office of Women's Health is doing menopause again. And you can all it's a public workshop you can get off. And I'm speaking at that meeting today even on Wednesday also, what do I know, 30 years later, that drugs decrease in menopause in terms of its kinetics and dynamics in most women. The only thing I know in 30 years is giving estrogen and progestin replacement doesn't change it. We need to have some real studies of drugs in postmenopausal women.

CHLOE E BIRD:

Thank you. That's a question that I got many people asking me if we were gonna be able to address. Do you wanna speak to that?

JANINE AUSTIN CLAYTON:

Thank you for sharing that. Just briefly, we did focus on menopause and optimizing midlife health of women this year at the Annual Vivian Pinn Symposium, where we recognized National Women's Health Week. So, we do have all of that material available online on a new menopause page. Absolutely more research needs to be done. It's a critical health inflection point, and I'm glad that you'll be able to participate in that FDA session later this week.

CHLOE E BIRD:

You know, I'm gonna take the question on the left, but then after that, I wanna know if we have any online questions. So, if a staffer can get my attention or come up to the mic and bump. We do have one down here. OK, please, sir.

GEORGE HILL:

Good morning. My name is George Hill from Vanderbilt University School of Medicine. I really, Dr Johnson, I really appreciate your talk. As we say, you knocked it out of the park. And I really appreciate you mentioning Serena, because in the African-American community, as you know, what happened to

her is real and I just thank you for it. And Janine, I appreciate you mentioning Vivian. Vivian Pinn, who has led the fight for women's health for so, so long. Dr Johnson brought up the point and it never left your talk about race and black women. And I wondered if someone on the panel could comment on what are some areas now that would be helpful to emphasize in research for addressing the health disparities when it comes to black women. Stress has been touched on, but what are some of the other areas that might be researched?

CHLOE E BIRD:

Thank you. Janine, go first and then we'll definitely come back to you.

JANINE AUSTIN CLAYTON:

So, good afternoon, Dr Hill. Great to see you. So, I can highlight some ways that we are offering funding opportunities for this area that I wanna make sure this audience is aware of. And that's our understudied, underreported, and underrepresented populations of women or U3 funding opportunity. So, where we specifically include race as one of factors that might be associated with understudied women, as one of the ways to be able to get funding. But as you know, NIMHD the National Institute for Minority Health and Health Disparities is leading in that space. And I would say stay tuned to some things that are coming out of their shop as well.

CHLOE E BIRD:

Add to this.

ELISSA EPEL:

I don't think we know how to measure stress in African Americans and especially African-American women. I think we have a self-report of race discrimination and racism, and we get a little bit of percent variance. But the systemic racism, stigma, assaults, and impoverished resources from a life span, we can never measure that. And in our study. So, yes, stress is part of it and we haven't shown that well with the way we measure it. But in our study of black and white girls, what we see is that the black girls are more resilient. As girls, they have lower perceived stress. They have happier families, they have more family cohesiveness. And although they have more external stressors, when we measure what happens to them, their mental health is better for years until midlife. And we start to see the pre-diabetes, a health condition that also promotes systemic inflammation and depression. I was last here on this stage eight years ago, I think, with James Jackson, who was really on to understanding those race differences with social affordances and understanding, you know, turning to things like stress-eating and how that was protecting mental health at the cost of later physical health.

GEORGE HILL:

Thank you.

JANINE AUSTIN CLAYTON:

Chloe, can I just add one thing? So, George, I also wanna make sure that you know about the IMPROVE Initiative. IMPROVE stands for Implementing a Pregnancy Outcome Vision for Everyone. It is an NIH-wide initiative that I co-led with Dr. Diana Bianchi and Dr. Shannon Zenk. And the centerpiece of that initiative is Maternal Health Centers of Excellence, which were recently launched and that initiative specifically calls out health disparities experienced by African Americans and other women. So, in the maternal morbidity and mortality space. So, we wanna make sure you're aware of that as well.



CHLOE E BIRD:

Please. We were talking about representation of those on the phone.

NOAH DUFF:

We have a question from the virtual audience related to nomenclature. So, "Do publications use the term 'sex and gender' correctly? And how can we promote that they do."

CHLOE E BIRD:

Certainly not using it all exactly the same. Do you wanna take a step in on Carolyn?

CAROLYN M MAZURE:

Sure. So, there's a very rich history to the derivation of both of those terms, and in more contemporary times, we've seen it conflated so that sometimes you'll read an article in sex and gender will be used interchangeably in the same article, or one article will use sex to describe a sociologically based study or a psychosocial study, et cetera, et cetera. And I think really it depends on several different areas of responsibility. One, as scientists, as researchers, as authors, we have to be clear about what we're saying. If we're unclear or that you want to make the comment that there should be greater clarity. I do this now in all of my papers. I always ensure that in the discussion section, there is a short paragraph describing why I use those terms and give a reference as to where somebody could pursue it further. I also think journal editors obviously have a lot of responsibility here to require the correct terms, and also to require the inclusion of individuals. And I still get papers to review where inclusion is not where it should be.

So, I would say journal editors also have to up their game in some regards. Nature has done a beautiful job of trying to do that, in my view. A variety of journals lance it. Others have taken responsibility and said, "Look, looking back at our work, we haven't been that clear about it and we're gonna be clear going forward." So, I think that's one way to do it.

CHLOE E BIRD:

Alright. On the right.

OMAILDA VELAZQUEZ:

Thank you. Good morning. My name is Omailda Velazquez from Miami. I appreciate the insights from Dr Johnson and this great panel. Two specific questions. One is, as a vascular surgeon, I'm very intrigued by this connection between acetylcholine and the cardiovascular and chest pain syndromes and acetylcholine and depression. And we've known for a long time that chronic stress is a factor in both cardiovascular complications, chest pain syndromes, whether atypical or not, as well as depression. Is there a role, according to the panel, to have programmatic funding for these revealing connections that begin to fill in the blanks or put together the puzzle of things that we've known for decades I never quite understood? That's my first question, the acetylcholine and its receptor's connection to both atypical chest pain and depression in women.

CHLOE E BIRD:

Thank you. Do you wanna take this, Janine?

JANINE AUSTIN CLAYTON:

Well, I can't speak to that specific topic. I would say the one that I mentioned specifically is to connect sex and gender in the context of a disease, whether there is a gendered aspect to that mental health

piece, that's one angle that you might. But I think that what you're highlighting is that we need a whole-person health approach from head to toe, and that is a little bit more challenging to find opportunities that are integrative and interdisciplinary. But, ORWH has been supporting interdisciplinary research from the outset. That's actually one of Dr. Pinn's guiding principles. So again, our other newest funding opportunity is an R01 and R21 on chronic diseases that are understudied in women and that just came out last year. Another receipt date this year. So, there may be opportunities there as well.

OMALDA VELAZQUEZ:

My second question is on the Xi versus X and I wonder whether we understand a little or need to understand a lot more about what happens when the Xi gets exposed to testosterone, and when the X gets exposed to estrogen. What are the epigenetic changes? Which ones of those changes might be of benefit health-wise, and which ones may have some risks that we need to be prepared to prevent?

DAVID C. PAGE:

It's a great question. I think it's directed to me, and it's a great question and one that will take a few years to answer. Not on this stage, but by the research community. I think you... Let me paraphrase your question or generalize it and say that as we think about differences in gene expression across the whole genome and across all the many cell types of our bodies, there is a fundamental question when we or others observe male-female biases in gene expression, we say our first question is, is that due to sex hormones circulating throughout the body, or is that due to a cell-autonomous action of the Xi versus Y within that cell type? And in very few cases do we know the answer today. So that is a big fund... You've just touched upon an enormously fundamental question that needs to be asked of every cell type in the body across the lifespan. Who's in charge? The sex hormones, the sex chromosomes, or are they actually speaking to each other? What I would say is that we've been looking at this just superficially of late.

It does not appear that the X chromosome is terribly much under the influence of the sex hormones. That might seem ironic, but it does seem as if these are two different currencies that are playing out simultaneously. I'll point out, despite the fact that one of the great ironies is that the X chromosome is the home to the gene that encodes the androgen receptor. (LAUGHS)

CHLOE E BIRD:

On your first point, I just wanted to add. You're spot on that there are many critical questions that show up around studying sex and gender about recognizing and treating these. And one of the interesting pieces, when NIH looked at the studies that did, in fact, say they were going to look at something around women's health, they were disproportionately funded by special emphasis panels. So, the way we have the machine set up is to produce exactly the results we're getting, which is undervaluing work that studies a question in women that we think we already understand in men, or that actually takes a... That is innovative. It's often seen as devalued, as not innovative, and as if we already know a lot more than we know. So, thank you for bringing that up. Do we have another question for the audience?

NOAH DUFF:

Just one final question.

CHLOE E BIRD:

Alright.

NOAH DUFF:

And then we'll conclude.

SAMUEL SILVERSTEIN:

If you wanna have a huge impact on this topic, which you ought, you ought to note that neither Kandel's Textbook of Neuroscience, the most widely used textbook in neuroscience in all medicine, Albert's Textbook of Cell Biology, the most widely used Cell Biology textbook. I don't believe Harrison's Textbook of Medicine or Campbell's Textbook of Biology has a chapter, a single chapter on womens, on the distinction between male and female biology, or terms of health. There's no better place to start than in middle and high school and carry it all the way through professional development. And I hope that all of you will lobby the authors of these and many other textbooks to include a chapter on the very important topic you've brought to the floor today.

CHLOE E BIRD:

Thank you. I believe we're gonna have to adjourn to lunch now. Did you have anything to add, Karen?

KAREN B DESALVO:

Listen, I just wanna thank you. Thank you, Dr Bird. Thank you to the entire panel. Can we give a round of applause for them? (APPLAUSE) That was an extraordinary from chromosome to society. Very much appreciate it. We're gonna take a break until 1:30 Eastern time. There's lunch in the tent for those that are here in person. Please stop by the in the rotunda. The students are there with their posters on solutions for women who are unhoused. I'm sure they'd appreciate some visitors. Thank you. I'll see you at 1:30 Eastern time.

CHLOE E BIRD:

Great job.