Genomic Response to the Social Environment: Implications for Health Outcomes

June 24, 2020

Workshop Summary

Workshop Goals

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Dr. Gill welcomed participants and acknowledged funding support from the National Institutes of Health (NIH) Office of Disease Prevention (ODP) and the NIH Office of Behavioral and Social Sciences Research (OBSSR) as well as colleagues across NIH Institutes, Centers, and Offices who participated in planning the workshop. Although it has long been recognized that the social environment can influence the risk, manifestation, and trajectory of disease and associated symptoms, the underlying biological mechanisms remain largely understudied. This transdisciplinary event will address the relationship among genomics (e.g., epigenomics, gene expression, microbiome, telomeres), the social environment, and health outcomes across conditions, populations, and the lifespan. Discussions will include an exchange of ideas to advance a social genomics research strategy that illuminates genetic influences on disease burden and to inform future interventions.

Overview of the Day and Introduction of Keynote Speakers

Lois Tully, PhD
Program Director, NINR

Dr. Tully provided an overview of the workshop agenda and introduced the keynote speakers, Drs. Janice Kiecolt-Glaser and Steve Cole. She encouraged participants to engage in thoughtful discussion about potential next steps toward integrating a social genomics approach into personalized strategies that prevent, modify, or buffer adverse social environments and lead to better health outcomes.

Lovesick: How Couples' Relationships Influence Health

Janice Kiecolt-Glaser, PhD
Director, Institute for Behavioral Medicine Research
Distinguished University Professor
Institute for Behavioral Medicine Research
The Ohio State University College of Medicine

Dr. Kiecolt-Glaser presented an overview of research on how couples' relationships affect health, including the interplay between depression, stress, inflammation, and immune response. Married people have better health outcomes than the unpartnered, but the presence of a spouse is not necessarily protective. A troubled marriage is itself a prime source of stress and depression; studies have shown that marital distress amplifies risk for major depressive disorder and depressive symptomology.

A number of studies have explored the health consequences of providing care for a spouse who has Alzheimer's Disease (AD). A study that measured antibody response to vaccines found that caregivers could not maintain the same protective antibody response as non-caregiver controls, stress and depression were associated with poorer responses, and aging magnified the effects of stress on immune response. Multiple labs have shown stress-related alterations in both antibody and T-cell responses to viral and bacterial vaccines including hepatitis B, influenza, pneumococcal pneumonia, rubella, meningitis C conjugate, and tetanus.

A study that measured impact of stress on wound healing showed that caregivers took 24 percent longer to heal and reported greater pain than non-caregiver controls. Infection and wounds trigger the inflammatory response, which is critical to resolving infections and repairing tissue damage, the immediate response to pathogens or wounding. Dr. Kiecolt-Glaser noted that the wound healing studies lacked power to detect racial and ethnic disparities.

Stress and depression fuel inflammation. Disease/disorders linked to heightened inflammation include cardiovascular disease (CVD), osteoporosis, arthritis, type 2 diabetes, cancer, periodontal disease, and AD, as well as frailty and functional decline. A longitudinal community study found that caregivers' average rate of increase in interleukin 6 (IL-6)—a pleotropic cytokine associated with pro- and anti-inflammatory effects—was four times that of non-caregiver controls. Based on the health correlates of inflammation, one might expect premature mortality in caregivers. Another study found that being a caregiver who is experiencing mental or emotional strain is an independent risk factor for mortality among elderly spousal caregivers; those who report strain associated with caregiving are 63 percent more likely to die in the immediate after effects of spousal loss than are non-caregiver controls.

Dr. Kiecolt-Glaser noted that couples' interactions have an impact on their health. For example, marital distress and depression fuel poor health behaviors that promote inflammation (e.g., sedentary behavior, poor sleep, smoking, alcohol abuse, unhealthy diet). Studies of mentally and physically healthy newlywed couples demonstrated that hostile behavior elevates epinephrine (adrenaline) and norepinephrine (found in the inflammation pathway) during conflict. Poorer immune function was observed the morning after conflict, suggesting that hostile marital behavior is bad for the immune system. A study of marital interactions and wound healing found that production of IL-6, interleukin-1β $(IL-1β)$, and tumor necrosis factor-α (TNF-α) was lower at wound sites following marital conflicts than after a social support task. Time to healing was one day longer after the conflict visit than after the social support visit. Blister wounds in highly hostile couples healed two days later than wounds in less hostile couples.

Couples' fights at home are more negative and last longer than those studied in the lab. A troubled marriage is uniquely stressful, providing regular acute stressors (arguments) that heighten chronic relationship stress. Distressed families experience roughly twice as many tensions per day as non-distressed families.

Discussion

- Participants discussed whether differences in stressors are observed between married or otherwise committed couples versus partners where the commitment is less clear.

- Psychosocial stressors associated with the COVID-19 pandemic and their potential impact on outcomes were discussed. An escalation of loneliness has been reported due to the combination of social isolation, economic stresses, and personal stresses. Prior studies detected differences in immune function between lonelier medical students versus their less lonely counterparts; those who had better social connections were more resilient, and those that were already disadvantaged (for example, in terms of marital or other stresses) were at increased risk.

- Unique relationships emerge during times of challenge. Consider individuals who, out of necessity, have bonded within their communities and/or families and are strengthening bonds while spending more time together. With more positive relationships, other positive outcomes could emerge.

- COVID effects are greatest in people who are most disadvantaged. Scientists at Columbia University reported seeing a disproportionate effect of COVID on minority and low-income populations. Researchers might want to explore how to reduce or relieve chronic stress that exacerbates chronic health conditions.

Social Regulation of Human Gene Expression
Steve Cole, PhD
Professor of Medicine and Psychiatry and Biobehavioral Sciences
Norman Cousins Center for Psychoneuroimmunology and Jonsson Cancer Center
University of California, Los Angeles (UCLA) School of Medicine

Dr. Cole presented on relationships between risk factors, the world of social epidemiology, and biological impact at the level of genome function. He began with a small molecular epidemiologic study that found that loneliness is an environmental factor that increases expression of inflammatory genes and reduces expression of genes involved in antiviral defense. Follow-up studies have shown that this is a response not only to social isolation but also to a variety of negative life experiences such as extended periods of insecurity, threat, uncertainty, or worry.

Many of these effects are mediated, in large part, in innate immune cells, particularly myeloid lineage cells (i.e., monocytes, neutrophils, dendritic cells) that are produced in the bone marrow. They traffic through the blood to healthy tissue sites for long-term surveillance or to damaged tissue environments where they attempt to eradicate the threats to cellular health and well-being. Myeloid lineage cells are exquisitely sensitive to signaling from the fight-or-flight division of the autonomic nervous system. Sympathetic nerve fibers release norepinephrine, which can interact with beta-adrenergic receptors on the myeloid cells to activate signal transduction machinery and biochemical response pathways that stimulate RNA transcription from inflammatory genes and suppress transcription from interferon genes. This myeloid cell molecular profile is a major driver of disease processes and especially bad program to run in the midst of the COVID-19 epidemic.

Myeloid lineage cells have a short lifespan and must be regenerated in huge numbers. In adverse environmental conditions, the release of norepinephrine induces the hematopoietic stem cells to reduce production of lymphoid lineage cells and increase output of myeloid lineage cells. This alteration of the prevalence of particular types of cells in the white blood cell pool has a variety of implications. In the brain, these cells contribute to neurodegenerative disease; precipitate atherosclerosis in damaged blood vessels; cause pneumonia, asthma, and other airway diseases in the lungs; precipitates tumor metastasis and progression and alters cytokine production in the lymph nodes in a way that undermines antiviral responses. In wounded tissue, these monocytes interfere with the conversion of initial inflammation into a subsequent wound healing response.

Additional studies have found correlations between changes in gene expression and adverse life experiences. For example, investigators have detected differences between gene expression in resected breast tumor tissue from patients with low levels of social support versus samples from patients with high levels of social support.

Dr. Cole outlined a pathway for translating these findings into interventions. Effects of social risk factors can be mapped by combining observational studies of at-risk populations with genomic methods to identify correlations; conducting experiments of causal effects on these gene expression profiles; and building cellular and animal models to detail specific molecular pathways through which these transformations take place. Mechanistic models can help identify molecular targets for translation into protective interventions—using them as biomarkers to assess impact of behavioral interventions and as targets for pharmacologic interventions to block these effects.

This work raised questions about the kinds of psychological, social, or cultural factors that might block these effects. Can one identify individuals in adverse circumstances who do not show this molecular fingerprint of distress and sympathetic nervous system activity? What are the characteristics of people who seem to be protected from this genomic response?

Taking these questions a step further, Dr. Cole asked the question: How should we live? In positive psychology, there are two broad theories about well-being: hedonic (derived from pursuit of positive emotions like happiness and satisfaction) and eudaimonic (derived from the pursuit of virtues such as helping others). Gene expression of individuals with high levels of hedonic well-being had similar or even worse profiles than those with modest levels of well-being. By contrast, a number of studies have found that people who report a greater sense of eudaimonic well-being show more favorable gene expression profiles (i.e., lower expression of inflammatory genes, higher expression of genes involved in innate antiviral responses).

Cole described a UCLA study in which gerontologists designed an intervention to help older adults be more active and reduce isolation by serving as teachers' aides for at-risk children in South-Central LA K–3 schools. Participants experienced a notable decline in expression of inflammatory genes and upregulation of antiviral genes. Results indicate that the correlation between eudaimonic well-being and favorable gene expression profiles can be protocolized and implemented in community settings.

Other randomized controlled experiments have also documented effects of pro-social behavioral interventions on inflammatory and antiviral gene expression, verifying a causal effect in humans. In other words, changing pro-social and/or helping behavior to enhance eudaimonic well-being has favorable impact on gene expression.

The neurobiological mechanisms of pro-social interventions are an active topic of research. Several research teams have hypothesized that the sympathetic nervous system can be functionally inhibited by caregiving due to its activation of the parasympathetic nervous system. A particular set of reward-related regions in the brain seem to be essential to this kind of caregiving behavior (particularly the ventral striatum and septal areas). Similar favorable changes have been observed in gene expression in the circulating immune cell pool when activity of this neurobiological circuitry is stimulated in animals.

Discussion
- Participants discussed prenatal and neonatal stress exposures, including a study of early stress experienced by preterm infants in a neonatal intensive care unit (NICU), and whether early negative programming can be reversed. Dr. Cole expressed the opinion that early adversity does not lock in for life or intergenerational life and encouraged researchers to continue their work with interventions. He cited a 2011 study led by Dr. Steve Suomi that randomized monkeys to adverse early rearing followed by a return to their natal colonies; within six months of their reintroduction to a stable social environment, 95 percent of the adversity-impacted genes reverted to a normal level of expression, but the remaining 5 percent did show indications of persistent negative programming.

- Dr. Cole defined loneliness as a sense of disconnection from others that is distinct from physical isolation. Lonely people who are nevertheless socially secure and show high levels of eudiamonic well-being tend to show favorable gene expression. Although he has not seen evidence that parental loneliness affects gene expression in their offspring, it seems likely that loneliness can be transferred "culturally" or "perceptually" between generations if parents perceive the world as a dangerous place populated by untrustworthy people. By natural extension, one would expect to see distinctions between individualistic cultures like that of the United States and cultures with a greater sense of community found in Asia.

- Robust literature suggests that mindfulness activities, e.g., yoga, tai chi, breath control, produce small but statistically significant favorable effects on threat-related gene expression profiles.

- Gene expression profiles have not yet reached the point where they can be used in clinical care. That will require data from ongoing large population health studies quantifying how transcriptional profiles predict disease incidence or progression of prevalent diseases.

Session 1: Social Genomics State of the Science – Epigenomics and Gene Expression
Moderator: William Elwood, PhD
NIH Office of Behavioral and Social Sciences Research

Dr. Elwood briefly introduced the OppNet initiative, a trans-NIH program that accelerates discovery in basic mechanisms and processes that underlie health behaviors. He invited workshop participants to visit https://oppnet.nih.gov/funding for information about funding opportunities.

Intergenerational Impact of Genetic and Psychological Factors on Blood Pressure (InterGEN) Study
Jacquelyn Y. Taylor, PhD, PNP-BC, FAHA, FAAN
Professor of Nursing
Director, Center for Research on People of Color
Columbia University School of Nursing

Dr. Taylor described InterGEN, an NINR-funded longitudinal study that aims to delineate independent and interaction effects of genomic and psychological environment (GXE interaction) factors on blood pressure (BP) among 250 African American (AA) mother-child dyads over a two-year period. Psychological factors include perceived racial discrimination, maternal mental health (i.e., depression), and mothers' parenting behavior.

The average age of mothers enrolled in the study was 31 years, average BP was 114/72 (normal), and average body mass index (BMI) was 29.7 (obese); 22 percent reported they were current smokers, 20 percent reported having a hypertension (HTN) diagnosis, and most had at least a high school diploma or some college. The average age of children was 3.7 years, BP was 91/59 (normal for this age), and 46 percent were the youngest children in their households. Seven children were born outside of the United States.

Four interview/data collection visits were conducted over the course of the study. Saliva was collected for DNA analysis at the first interview. Physiological measurements included BP, height, weight, BMI, percent body fat, and percent body water; health and birth histories were collected. Mothers answered questions on parenting stress, parent behavior, parenting styles, experiences of discrimination, race-

related events, experiences of trauma (mother and child), stress overload, coping strategy, and symptoms of depression. Mothers born outside of the United States completed an acculturation measure.

The study was guided by a conceptual model adapted from Bronfenbrenner's Ecological Systems Theory, which takes into account genetic components as well as environmental factors. The analysis plan included multivariate linear regression models, linear mixed models, multivariate mixed models for different interactions, correction for antihypertension medication use, and assessment of ancestry informative markers. (For details on study methods, see design and methods for recruitment and psychological measures and design and methods for complex DNA analysis.)

InterGEN study findings on epigenomic and psychological environment factors affecting BP can inform implementation studies that focus on earlier identification of root causes (e.g., stress, discrimination) and interventions. Specific findings (see publications) include:
- An association between social determinants of health, perceived discrimination, and BMI on symptoms of depression (*Archives in Psychiatric Nursing*, forthcoming).
- Influence of discrimination and coping style on BP.
- A significant association between perceived racial discrimination and DNA methylation.
- A positive association of stress and coping with DNA methylation and BP-related genes.
- A significant association between parenting stress and DNA methylation.
- A significant association of obesity with DNA methylation age acceleration in mothers.

Dr. Taylor outlined future plans that include repeating the DNA methylation analysis over time and application of Horvath's new DNA methylation age acceleration analysis methods to children enrolled in the study.

Genomic Basis of Human Wound Chronicity

Chandan K. Sen, PhD
Distinguished Professor and J. Stanley Battersby Chair
Professor and Vice-Chairman (Research), Department of Surgery
Executive Director, Indiana University Health Comprehensive Wound Center
Associate Dean, School of Medicine
Indiana University

Dr. Sen delivered a presentation from the viewpoint of a wound care provider who, along with his team, established Indiana's first comprehensive wound center (CWC) with a primary goal of providing care that reduces wound chronicity and the incidence of amputation. On average, wounds that present at the CWC are several years old; the patient's family physician has sent them to the Center for specialized care.

Current practice focuses on local factors (e.g., debridement, dressings), and some wounds eventually close; some shrink; and some close and then reopen.

Dr. Sen's approach aims to understand the systemic and local factors that are responsible for the chronicity of the wound to inform interventions that achieve much better outcomes and reduce the number of amputations. For example, a study of samples from 84 chronic wound patients at the CWC identified single nucleotide polymorphisms (SNPs) that are associated with wound chronicity. Evidence in the literature links these mutations to genes that impair healing when they become nonfunctional.

Blister studies conducted in 2005 showed that myeloid cells have an overall suppressive effect on gene expression. Dr. Sen's lab has run single-cell sequencing on chronic wound edge tissue and found genes

showing similar expression patterns in stress and severe chronic wounds. Whole-genome differential methylation (nucleotide level) analysis of wound tissue revealed that patient chronic wound edges are hypermethylated, which leads to gene silencing. Dr. Sen noted that a recent publication from his lab found that epithelial-to-mesenchymal transition is required not only to close the wound but also to perfuse the wound; Dr. Cole made similar observations in his earlier presentation.

In animal models of wound ischemia, applying a DNA methyl transfer inhibitor (DNAMTi 5-azacytidine) quickly changes the course of healing. Dr. Sen is doing CRISPR/Cas9 genome editing of methylation status; this work should inform efforts to determine how to change the course of healing.

Bereavement Stress and Gene Expression: Does It Go Both Ways?

Mary-Frances O'Connor, PhD
Associate Professor, Director of Clinical Training
Psychology Department
University of Arizona

Sociogenomics work demonstrates that gene expression and plasticity are related to environmental (social) factors. Dr. O'Connor highlighted the importance of communicating to the public what social genomics research means, which some geneticists and science writers have begun to do through blog posts.

Bereavement is a unique social stress that involves an attachment relationship rather than an affiliation relationship. It is linked to the widowhood effect (broken heart phenomena) wherein spouses are nearly twice as likely to die during the immediate after-effects following death of their spouse. Although the majority of bereaved persons are resilient, grief disorders or depression may arise for others, and the psychological stress in response to a bereavement event may have an impact on an individual's health.

Dr. O'Connor conducted a small case control study, Divergent gene expression responses to complicated grief and noncomplicated grief, that explored how bereavement modulates immune function gene expression. About half of the bereaved subjects had complicated grief (CG), an umbrella term for prolonged, severe grief. The study found that CG and noncomplicated grief (NCG) differed markedly in their expression, particularly expression of Type I interferon-related transcripts; NCG widow(er)s showed substantial upregulation compared with nonbereaved controls. Bereavement-related distress was linked to differential transcription factor activation and gene expression involved in innate antiviral responses. The study's limited sample size may explain the lack of nuclear factor kappa B (NF-κB) activity differences indicated between the bereaved and nonbereaved.

Decreased expression of antiviral response in CG subjects may be linked to resistance to infectious disease. Other studies have shown that older widows have significantly lower influenza vaccine response compared with nonbereaved controls, and the odds of dying from infections, sepsis, influenza, or pneumonia are higher for widow(er)s. This unique response to bereavement among those with a CG diagnosis is evident in morbidity and mortality indices; for example, bereavement stress is seen in cardiovascular, endocrine, and immune responses to grief, resulting in greater morbidity and mortality.

Neuroepigenetics is the study of how the brain encodes information to form long-lasting memories that lead to stable changes in behavior. Social experiences like pair bonding and trauma memories are known to create neuroepigenetic change. For example, studies of prairie voles indicate that initial mating induces a specific histone H3 acetylation in the nucleus accumbens of the brain, enhancing its transcription and producing higher oxytocin receptor (OTR) mRNA and protein expression that facilitates partner preference formation. After pair bonding, vole behavioral changes indicate partner preference (i.e.,

attachment). Blocking this change at this specific locus prevents pair bonding, which suggests that epigenetic modification shapes the neural systems that modulate bonding behavior.

The "gone-but-not-forgotten" hypothesis suggests that relationships create biological fingerprints in the brain so that when a partner dies, the brain "misses" them in a real biological sense. Activity-dependent molecular mechanisms (e.g., histone modification, DNA methylation) dynamically regulate the gene expression required for memory formation. Attachment includes a perseverative belief in the existence of the attachment figure, even in the figure's absence. Bereavement is the low probability experience of an attachment figure dying. One source of information says the person is alive (encoded in epigenetic modifications of neurons), and another source of information says the person is deceased (episodic and, eventually, semantic memory). The mismatch of these two sources of information causes grief, confusion, and stress.

Dr. O'Connor is interested in exploring clinical interventions that help reconcile the conflicting sources of information and reduce the stress of the paradox and whether gene transcription changes associated with grief revert under psychological treatment. Although studying epigenetics in specific regions of human brains is challenging, it is not impossible. Good translational studies between animal and human neuroscience are planned.

Discussion

- Participants suggested a potential intersection between Dr. O'Connor's bereavement work and Dr. Sen's work with amputees. Dr. O'Connor suggested that the loss of a limb leads to a type of grief stress similar to the loss of an attachment relationship; in both situations, the brain takes time to catch up with the new reality. Dr. Sen speculated that this may be more severe for amputees because their limbs have been present for their entire lives, whereas over time, the attachment figure goes away and comes back.

- Resilience in handling stress depends on care and support that the bereaved individual receives.

- Participants discussed caregiver self-care needs. The caregiver needs to know how to care for the patient and develop coping skills to address his/her own grief.

- A participant reported that NIH is working with the Department of Defense on a limb loss and preservation registry. She asked for input on what measures to use and what variables to collect in support of research in this area.

- Participants discussed potential differences in bereavement when the spouse's death is sudden and/or violent. Dr. Connor responded that sudden or violent death is predictive of psychological response in the first few months; it is not a long-term predictor. For soldiers, death of a brother-in-arms can result in CG or post-traumatic stress disorder (PTSD).

- Participants asked whether the InterGEN study identified any differences in gene expression associated with parity. Dr. Taylor responded that a parity analysis has not been conducted. Previous studies have shown that number of children affects parenting stress and blood pressure. She is interested in looking at how parity, age differences, and developmental stages of children affect parental stress.

Session 2: Social Genomics State of the Science – Microbiome and Telomeres
Moderator: Catherine M. Bender, PhD, RN, FAAN

Professor, Nursing and Clinical and Translational Science Institute
Nancy Glunt Hoffman Endowed Chair in Oncology Nursing
University of Pittsburgh School of Nursing

Dr. Bender summarized her research focus on changes in neurocognitive function with cancer and cancer therapy. She and her longtime collaborator, Dr. Yvette Conley, led a series of studies examining biological mechanisms underlying these changes. Currently, they are leading a randomized controlled trial to examine the influence of aerobic exercise on neurocognitive function and brain health in women with breast cancer.

The Social and Behavioral Determinants of the Vaginal Microbiome in Black Women
Elizabeth J. Corwin, PhD, RN, FAAN
Vice Dean for Strategy & Innovation in Research
Anna C. Maxwell Professor of Nursing Research
Columbia University School of Nursing

African American (AA) women report significantly greater exposure to multiple stressors and experience a significantly higher rate of preterm birth (PTB) compared with white women. Biological indicators have been identified in AA women that correlate or associate with increased stress, such as shortened telomeres, exaggerated inflammation, and hypothalamic-pituitary-adrenal (HPA) axis dysregulation. Dr. Corwin's presentation focused on whether life stressors also are associated with dysbiosis (i.e., increased diversity and presence of organisms associated with pathogenesis or infection) of the vaginal microbiome.

Healthy vaginal microbiota reduces bacterial vaginosis (BV), sexually transmitted infections, and urinary tract infections that lead to ascent of pathogens into the pregnant uterus and create inflammatory reactions that contribute to PTB. Protection is attributed to dominance by *Lactobacillus* spp. that produce lactic acid and bacteriocidal compounds and can block expression of certain gene transcriptions and receptor uptake. Without *Lactobacillus* dominance, organisms common in BV and risk factors for PTB (e.g., *Gardnerella vaginalis, Prevotella, Bacteroides, Fusobacterium, Mycoplasma hominis*) are able to colonize.

Studies have identified variations in vaginal microbiota by race. *L. crispatus* is the most common among non-Hispanic white (NHW) women and remains dominant as vaginal diversity decreases as pregnancy progresses. AA women are more likely to have the less protective *L. iners* as well as diverse other organisms such as *Gardnerella*, *Prevotella*, and other BV-associated bacteria (BVAB) that increase during pregnancy. In AA women, early-pregnancy vaginal microbiota may be the most important rather than changes across pregnancy.

Factors contributing to predominance of different *Lactobacillus* species across races are unknown. Health disparity researchers recommend looking within the disparity population to identify risk and protective factors.

For the Microbiome and Preterm Birth in AA Women study (R01NR014800), women were recruited from two socioeconomically different hospital clinics in Atlanta: Grady Memorial Hospital, the area's "safety net" hospital, and Emory prenatal clinics that see women from a wide range of educational and economic backgrounds. Prenatal data collection occurred between 8 and 14 weeks and between 24 and 30 weeks gestation, including questionnaire measures of stress, diet, health and sexual behaviors, and hygiene; blood for inflammation, chronic stress exposure, nutrients; and oral, vaginal, and rectal swabs

for microbiome (16S rRNA gene sequencing). Post-delivery data collection was conducted via vigorous medical record abstraction for pregnancy complications and outcomes.

Compared with Emory subjects, Grady subjects were younger; more likely not to be in a relationship, and, if in a relationship, not as likely to be cohabitating and less likely to be married. Highest level of educational attainment was lower for Grady subjects (72 percent high school or equivalent and 28 percent some college) in comparison with Emory subjects (27 percent high school or equivalent and 73 percent some college). Nearly 100 percent of Grady subjects receive Medicaid, whereas 48 percent of Emory subjects receive Medicaid and 52 percent have private insurance. No differences were observed in prior number of births, risk or experience of prenatal infection, or antibiotic use. Birth outcomes were markedly different; risk of PTB was 19 percent for Grady patients (high) and 9 percent for Emory patients.

Self-reported stress behaviors, perceived stress, depression scores, anxiety, and stressful life events were similar for both patient groups. However, Grady subjects reported significantly higher adverse childhood experiences and significantly higher likelihood of emotional or physical abuse.

Dr. Corwin summarized the overall composition of microbiota from a subsample (n=158) of first-visit collections. Overall, *Lactobacillus* dominates in 46 percent of the population, primarily *L. iners*, and 54 percent have diverse microbiota. *Lactobacillus* was detected in 64 percent of the Emory group and 38 percent of the Grady group. Sociodemographic and behavioral factors associated with *Lactobacillus* dominance in this subsample include cohabitation status (married or not) and type of insurance.

Dr. Corwin summarized preliminary findings from this ongoing study. There is significant variability in the rate of PTB within the population. Nearly all women in the study population show taxa dominated by *Lactobacillus iners* with some BVABs. The only variable associated with overall microbial composition is being married/cohabitating. Compared with non-cohabitating women, women living with partners were more likely to engage in vaginal sex, less likely to douche or use sprays or creams, and more likely to have a *Lactobacillus*-dominant vaginal microbiome. Women not living with their partners were more likely to harbor *Megasphaera spp*. and *Lachnospiraceae* (BVAB2).

Living with a partner may be associated with social and behavioral changes that are conducive to *Lactobacillus* predominance, and partnership status may be an important consideration in future studies. Potential mechanisms by which this occurs remain unknown. Frequent contact with the same partner could support behaviors that drive the stability of the vaginal microbiome. Having a partner can be stabilizing for a number of reasons, including financial security and emotional support. Recommendations include avoiding douching and limiting the number of sexual partners.

Discussion
- Participants asked how systemic (viral) infections such as COVID-19 affect the vaginal microbiome. Dr. Corwin responded that systemic infections are associated with inflammation, fevers, and other factors that influence pregnancy outcomes. Chronic stress can increase systemic inflammation as well.

Effects of Health Determinants on Telomere Length: Acculturation and Adverse Childhood Experiences

Rita H. Pickler, PhD, RN, FAAN
FloAnn Sours Easton Professor of Child and Adolescent Health
Director, PhD & MS in Nursing Science Programs
The Ohio State University College of Nursing

Dr. Pickler presented an overview of telomeres and provided examples of effects of health determinants on telomere length (TL). Telomeres are a region of repetitive nucleotide sequences that act as protective caps at the end of chromosomes, keeping gene content from truncating during cell division.

Average TL declines from 11 kb at birth to less than 4 kb in older adults and shorten at a faster rate in men than in women. It is not known whether short telomeres are a sign of cellular aging or whether they contribute to the aging process themselves. Premature or unexpected shortening is affected by many factors. Oxidative stress-mediated DNA damage is an important cause of telomere shortening due to free radicals, which explains the difference between the estimated loss by division or end replication and actual telomere shortening rate. Shortening due to free radicals has a greater absolute effect on length than shortening by end replication.

Meta-analyses have shown that increased perceived psychological distress is associated with small decreases in TL. Extremely short and long telomeres have been associated with neurodegenerative diseases, dementia and other cognitive impairments, diabetes, CVD, and cancer risk. Although shorter telomeres are associated with increased cancer risk, cancer cells themselves have elongated telomeres as the result of reactivated telomerase that occurs in almost 90 percent of all cancers.

Determinants of health are non-medical factors that directly influence health, including values, attitudes, knowledge, and behaviors, and also may refer to external sources of influence such as family, neighborhood, and social network. A large body of literature over the past several decades has shown that health across the lifespan is strongly linked to social disadvantage.

Research has replicated the association between stress and shortened TL; however, it is unclear whether shortening contributes mechanistically to the later adverse effects of chronic stress or is simply a biomarker of these effects. Researchers have proposed that physiological correlates of stress increase oxidative burden on the cell that damages the telomere and accelerates telomere attrition; other studies point to depressed telomerase, but the evidence supporting either hypothesis is not strong.

Acculturation—the process of social, psychological, and cultural change stemming from trying to balance two cultures while adapting to the new cultural environment—leads to changes in culture, religious practices, and healthcare. Individual-level outcomes of acculturation include acculturative stress that arises from maintaining language and brokering between native and host differences. Individuals who abandon their heritage cultural identity and acquire the host cultural identity or the converse may be at greater risk for poorer health outcomes.

A secondary analysis of relationships among cellular senescence-measured TL, acculturation, depression, discrimination, and stress in Hispanic Mexican American women during pregnancy was performed. Data were collected at 22 weeks gestation, a critical window for development of the neuroendocrine system in the fetus. Two latent factors accounted for more than 70 percent of the variance in length: (1) Anglo orientation and acculturation and (2) total scores for depression, discrimination, and perceived stress. Acculturation had significant negative effects on TL, and negative affectivity had a smaller indirect negative effect on TL. More acculturated pregnant Hispanic Mexican American women had shorter telomeres compared with newly immigrated pregnant Hispanic Mexican American women.

Dr. J. Ruiz, the principal investigator of the study on TL in Hispanic Mexican American pregnant women, is planning a study of a mastery lifestyle intervention that targets areas of greatest concern (i.e., depression, anxiety, perceived stress, acculturative stress and coping) from early pregnancy through post-delivery. The project would explore intervention effects on neuroendocrine risk factors of PTB and birth outcomes.

Adverse childhood events (ACEs; i.e., stressful or traumatic experiences such as abuse, neglect, and household order) are associated with a wide range of long-term poor health outcomes and have cumulative effects. ACEs have been linked to biomarkers including TL, and there is evidence that adversity type and timing significantly affect TL.

A proposed study will focus on ACEs and TL in adolescence, a period when the areas of the brain responsible for emotion regulation and stress responsivity undergo organization. Compared with younger children, adolescents experience greater autonomy and spend more time with peers, which may increase the likelihood of exposure to adverse social and physical environments. The study will examine patterns of ACEs occurring across childhood and adolescence and their effect on adolescent biological stress, psychological distress, and TL; relationships between biological stress and TL and psychological distress and TL; and the extent to which biological stress and psychological distress mediate the relationship between patterns of ACEs and adolescent TL. Study results will inform development of interventions targeting individual and contextual exposure patterns placing youth at risk for cellular senescence.

Dr. Pickler concluded that many social, psychological, and environmental factors are associated with TL and illness. Although oxidative damage appears to be the main condition that can destabilize telomere dynamics, more research is needed to identify other factors affecting TL and understand how telomeres interact with other factors to determine human health.

Discussion
- Participants discussed the time course of when TL effects are observed and how that might inform timing of interventions. Dr. Pickler noted the need for large cohort studies that include collection of many biomarkers across ages in order to understand how these markers change over time. Hopefully, the adolescent study will enable investigators to look at the historic record of ACEs and compare that to TL.

- Dr. Pickler pointed to ample evidence showing that poverty is the single greatest predictor of poor health outcomes. Individual interventions can help manage health and appraise stressful situations. In reality, an enormous social intervention is needed to change the living conditions into which children are born and mature. Until that day, efforts will focus on teaching individuals how to avoid unhealthy situations—telling young people about exposures and strengthening their own sense of well-being so that they can make good decisions.

- DNA methylation is another measure of aging that may complement TL.

Moderated Discussion
Panelists and participants discussed a wide range of topics presented during the workshop. Key areas of interest included the following:

- **Collaborative, multidisciplinary team science approaches** are needed to advance the science— sociology, psychology, biological sciences, and nursing. Nurses are well poised to lead investigations in social environments. Social scientists are needed to look at how social factors such as racism affect health outcomes. Historians help us learn from the past; for example, the roots of systemic racism and what happened during the flu epidemic of 1918.

- **Clinicians need to be engaged** in recognizing early indicators of chronic or acute stress and different risk factors before adverse health patterns are established.

- **Local health officials** (e.g., county, city) and other lay communities should be invited to attend and participate in workshops.

- **The community should be asked to determine the health problems of greatest concern** to them, and members of the community should be included on the research team.

- **Partnerships should be established with multiple institutions that have strong, positive relationships with the communities they serve**. It is important to recognize that relationships with communities take a long time to build.

- **Multi-institutional research can help ensure diversity** of samples needed to answer important scientific questions.

- **Existing tools and measures need to be validated in multiple populations.**

- **Artificial intelligence and machine learning approaches** can be used to support analysis of diverse social environmental data from different sources.

- **Longitudinal studies that include multiple molecular aging markers** (e.g., TL, DNA methylation, P16 cell senescence) are needed.

- **Current findings should be confirmed** in larger or different cohorts.

- **Standardized collection methods and analysis plan designs** are needed for microbiome studies.

- Research projects should be developed that **combine biological measures and interventions**.

- It is important to **be inclusive of marginalized, understudied populations** (e.g., LGBTQ).

- **Male partners should be included** in pregnancy, birth, and aging studies.

- **Minority populations**, particularly those who suffer from health disparities across multiple common chronic illnesses, would benefit from continued social genomics research.

- Research is needed on **intergenerational disease risk** (e.g., pregnant women and their offspring) and offers the possibility of exploring the development of the biobehavioral system in its entirety.

Closing Remarks

Dr. Tully thanked presenters and participants for their contributions toward advancing the field and setting the stage for future directions.