Menopause is a universal experience for midlife women. The average age for menopause is 51 years, although the normal age range for this transition spans over a decade. With the decline in estrogen production, many women past the age of 40 are experiencing symptoms associated with menopause. Given the large number of women in the menopausal age range in the US, and the unique health care needs of these women, there is a pressing need for education of both patients and their providers, regarding the potential benefits of selecting, and management of these symptoms and mitigation of health risks associated with menopause. Vasomotor symptoms are the most common symptom of menopause and occur in up to three-fourths of the women at some time during the menopause transition. These can be severe and disruptive to life, in about one-third of the patients who experience them. Despite that, current evidence suggests that majority of these women are not treated. Not only do untreated vasomotor symptoms contribute to poor quality of life, they have thought to have long-term health effects, including an increase in risk for cardiovascular disease and potentially osteoporosis.

Even though hormone therapy is effective for management of vasomotor symptoms and other symptoms of menopause, there has been hesitance in using it, both in the patients and the providers. This is essentially due to the results of the Women’s Health Initiative study, that brought out concerns regarding increased cardiovascular and breast cancer risk with hormone therapy use. However, subgroup analyses of those data and newer evidence suggest that hormone therapy use is essentially safe in recently postmenopausal women. Moreover, hormone therapy use in recently postmenopausal women may, in fact, lead to multiple health benefits, including a reduced risk of diabetes, osteoporosis, all-cause mortality, and potentially reduction in the risk of coronary artery disease.

In addition to hormone therapy, there are other effective prescription medications available for patients who are not candidates for hormone therapy use for any reason, as they are less efficacious than hormone therapy.

Vasomotor Symptoms 101: Hormone Therapy and Alternatives

An Steiner, MD, FACOG, NCMP, Obstetrics and Gynecology, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA

The most common complaint associated with menopause is that of vasomotor symptoms (VMS), affecting about 80% of menopausal women. Data from the Penn Ovarian Aging study and The Study of Women’s Health Across the Nation have shown that VMS are bothersome to about 10-15% of women and never completely resolve in about 9%. Management of VMS is a shared decision based on symptom severity, personal preference, medical history and risk assessment, and treatment objectives. Treatment options may include lifestyle changes, non-FDA approved treatments including CBT, compounded hormones, and botanicals; off label use of FDA approved medications such as SSRI/SNRIs, gabapentin, oxybutynin, combined oral contraceptives, and clonidine. Many improved medications such as an SSRI and hormone therapy. There are risks and benefits to each of these. In addition, a number of promising and innovative therapies are being studied but are not yet approved or to market. The use of hormone therapy in menopause has been shown to be effective in the treatment of VMS in multiple studies including Utian W et al, Fert Steril 2001. It’s use in women who have their uterus requires hormonal protection to prevent endometrial neoplasia. There are a number of medications which effectively protect the endometrium, both on and off label. The initiation and continued use of hormone therapy in menopause requires ongoing vigilance, with continued shared decision making and evaluation of risk/benefit. Discussion, medical history evaluation, as well as use of cardiovascular risk assessment tools may be useful. The route of delivery of hormone therapy may mitigate some risk as in the use of transdermal versus oral hormone therapy. Case studies are useful in decision making learning.

Genitourinary Syndrome of Menopause 101: How To Diagnose and Treat

Susan Kellogg-Spadt, PhD, CRNP, IF, GSI, CSC. Female Sexual Medicine, Drexel University, Bryn Mawr/Philadelphia, PA

For an estimated 60-75% of menopausal women, genital comfort and sexual quality of life can be compromised by the signs and symptoms that accompany Genitourinary Syndrome of Menopause (GSM). GSM is a chronic progressive condition that results from depletion of estrogen in the genitourinary tissues. Signs of GSM include: dryness, pallor and loss of elasticity of the vagina, introital stenosis, atrophy of the clitoris, labia, prepuce, urethra. Vaginal dryness, burning, irritation, dysuria and dyspareunia are both associated with GSM. The goal of GSM treatment is to restore comfort, maintain genitourinary and sexual function. First line GSM therapies include: use of over-the-counter vaginal lubricants which can temporarily reduce friction during sexual activity and long-acting vaginal moisturizers which can be inserted several times weekly. Maintaining moisture to the vulva and introitus may mitigate some of the symptoms associated with the use of vaginal dilitators, which are useful to gradually increase or maintain vaginal vault size. Many women also require therapy to address shortened, painful muscles of the pelvic floor, that can preclude comfortable intercourse. In this case, women are referred to a course of pelvic floor muscle therapy. For symptoms which do not respond to first line interventions, local low-dose vaginal estrogen therapy (ET) in the form of creams, inserts, tablets, and rings have been approved for the treatment of vulvovaginal atrophy associated with GSM. These work by enhancing thickness and elasticity of the vaginal epithelium and improving local blood flow. A 2016 Cochrane review reported that the efficacy of these formulations was similar and found no increased risk of endometrial hyperplasia with any of the local therapies. Additional evidence of the safety and efficacy associated with local estrogen therapy for GSM was suggested by a series of post-marketing studies. No statistical difference was found between local estrogen and placebo in terms of tamoxifen-associated breast cancer risk outcomes (including: MI, CVA, DVT, PE) or invasive cancers (including colorectal, breast, ovarian and endometrial). Despite being safe and effective options which results in improving underlying physiologic alterations, VMS local vaginal estrogen therapy cannot be an underutilized treatment option for women who suffer with GSM. There are additional non-estrogen alternatives approved for treatment of GSM/dyspareunia symptoms. Ospemifene, an oral selective estrogen-receptor modulator (SERM) with agonistic vaginal effects, is approved to treat moderate to severe dyspareunia associated with GSM. A dehydroepiandrosterone vaginal insert (prasterone) used daily has been approved for the same indication. Personal preference and reimbursement issues are factors in shared decision making with a woman when initiating therapy for GSM. Laser technology is an emerging technology for treatment of GSM and dyspareunia. Laser appear to induce wound healing, stimulate collagen and elastin and restore vaginal pH. The results of a recent multicenter, randomized, trial of vaginal laser therapy vs estrogen cream for the treatment of GSM suggested that laser therapy and estrogen cream produced similar effects on all global PT scores, female sexual function scores; incidence of adverse effects and in sustained efficacy at 6 months. While promising, larger, blinded, long-term, randomized, sham-controlled studies are needed to evaluate the safety and efficacy of this procedure. Cancer therapy with tamoxifen and other endocrine therapies either induce GSM and sexual dysfunctions or exacerbate existing ones. Laser therapy, off-label use of local low-dose vaginal estrogen or on-label intravaginal prasterone (which has no contraindications for use with breast cancer survivors) have been proposed as potential treatment options, with decisions made in conjunction with a woman’s oncology provider. Moreover, women who suffer with distressing symptoms of GSM can benefit greatly from an informed discussion of the physiologic basis of their symptoms, shared decision making regarding efficacy and safety of behavioral, nonhormonal, hormonal and laser therapy treatment options.

Bone Health 101: Diagnosis and Treatment of Osteoporosis

Andrea J. Singer, MD, FACP, CCD. Obstetrics & Gynecology and Medicine, MedStar Georgetown University Hospital, Washington, DC

Osteoporosis is a costly, major public health problem. In the US, 10 million individuals have osteoporosis and another 44 million have low bone mass placing them at risk for fractures, which can be devastating, life altering events. Roughly one in two women aged 50 years or older will suffer an osteoporotic fracture in her lifetime. Fractures are responsible for a substantial clinical burden, which for the individual includes changes to overall health and quality of life, impairments in mobility as well as social and physical functioning, and an increased risk of mortality, especially following hip and vertebral fractures. There is an increased risk of additional fractures, which is highest in the first 1-2 years following the prevalent fracture but persists for many years and can compound morbidity. Despite the significance of osteoporotic fractures, their magnitude and importance are underestimated, and osteoporosis itself remains underdiagnosed and undertreated. A comprehensive approach to diagnosing osteoporosis includes a detailed medical and family history, physical examination, and an appropriate, bone mineral density (BMD) assessment, vertebral fracture imaging to detect prevalent fractures, and focused studies to evaluate for secondary causes of bone fragility. While osteoporosis has classically been defined by BMD with a T-score of ≤2.5 at the lumbar spine or hip, or a T-score ≤−1.3 at radius, BMD is not the sole determinant of fracture risk or need for treatment. Indeed, current guidelines have expanded the clinical diagnosis of osteoporosis to include not only BMD criteria, but also the following categories: low-trauma fracture of the hip or spine regardless of BMD; low trauma fracture of the proximal humerus, pelvis or distal radius in people with low bone mass (T-score between -1 and -2.5); and low bone mass (T-score between -1 and -2.5) with a 10-year hip fracture risk ≥2% or a 10-year major osteoporosis-related fracture risk ≥20% based on the US adapted FRAX model (or TBS adjusted FRAX risks where available). Nonpharmacologic interventions to preserve bone strength are regarded as part of a treatment plan. These include adequate intake of calcium, vitamin D and protein; regular weight-bearing, muscle strengthening, and balance exercises; cessation of tobacco use and reduction of excessive alcohol intake; and falls risk assessment and prevention. Current medications build bone and/or decrease bone breakdown and dramatically reduce prevalent incident fractures. All osteoporosis agents effectively treat but do not cure the disease. Osteoporosis is therefore a chronic disease which requires long-term management if fractures are to be avoided. Even if improved or normal BMD is achieved, osteoporosis and elevated risk for fracture are still present. Current FDA-approved medications for prevention and/or treatment of osteoporosis include the antiresorptive agents: estrogen, progesterin, estrogen/bazedoxifene, estrogen agonist/antagonist (raloxifene), selective estrogen receptor modulators (SERMs); bisphosphonates (alendronate, ibandronate, risedronate, zoledronate); and the RANK ligand inhibitor denosumab; and the osteoblastic stimulators: teriparatide, abaloparatide, and romosozumab. Therapeutic agents should be assessed based on fracture efficacy, site(s) of fracture prevention (ie, spine, hip, and/or nonvertebral), onset of effect, magnitude of effect, duration of use parameters, and the balance of benefits and risks in terms of lifestyle impact. Treatment should be started in women aged 50 years or older who have one or more risk factors for osteoporosis, including a fracture of the proximal humerus, pelvis or distal forearm in the setting of low bone
Sexual problems are common in women. Despite their frequency and impact, female sexual dysfunctions (FSDs) are substantially undetected in clinical settings and often undetected even when recognized. FSDs are chronic sexual conditions in the domains of sexual desire, arousal, orgasm, and pain. A biopsychosocial assessment is vital for identifying potentially modifiable factors associated with personal distress. FSD may be lifelong or acquired and situational. The most frequently reported factors are related to mood, self-esteem, self-assessed health, anxiety, low educational level, partner sexual problems, sexual abuse, marital difficulties, stress, antidepressants, poor health, cancer, urinary incontinence, and chronic diseases such as diabetes, neurological diseases, and pain. A biopsychosocial assessment is vital for identifying potentially modifiable factors and guiding multidisciplinary interventions. Screening is best initiated by a universalizing and normalizing ubiquity statement followed by an open-ended inquiry. All phases of the sexual response cycle and sexual pain should be evaluated. Self-administered questionnaires include the Decreased Sexual Desire Screener; the Sexual Desires Scale; Revised; and the Female Sexual Function Index (FSFI), a well validated instrument that provides an overview of important data presented in the recent AHA statement on menopause and CVD as outlined in this abstract. Reproductive aging includes 7 stages, yet not all women experience each of these 7 stages. Moreover, the duration of each of these stages varies between women, and each stage is characterized by variable changes in the menstrual pattern, hormonal levels, and menopause-related symptomatology, underscoring the complexity of studying the MT and its potential for health-related sequelae. Several MT characteristics beyond the dynamic changes associated with MT and/or GMS are linked to CVD risk. These include the type of menopause, menopause stage, menopause-related symptoms. Earlier age at menopause and iatrogenically induced menopause during the premenopausal period are both associated with higher CVD risk. The perimenopause stage begins with the onset of intermenstrual cycle irregularities or other menopause-related symptoms such as vasomotor symptoms. However, it has not been shown to be effective in the management of depressive disorders in postmenopausal women. Menopausal hormone therapy has not been shown to significantly improve measures of cognitive function over several years of use. An approach to assessment and initial treatment for mood changes and cognitive complaints will be discussed.

PRE-MEETING SYMPOSIUM

2020 AHA Statement on Menopause and CVD Risk
Samar R. El Khoudary, PhD, MPH, BPharm, FAHA. Epidemiology and Translational Science Institute, University of Pittsburgh, Pittsburgh, PA
Cardiovascular disease (CVD) is the leading cause of death in women, yet only 56% of women are aware of this fact. Women develop coronary heart disease (CHD) several years later than men, with a notable increase in CHD risk during midlife, a period coinciding with the menopause transition (MT). This observation led to the hypothesis that the MT contributes to the increase in CVD risk. In 2020, the AHA published the first scientific statement discussing the contemporary literature on menopause and CVD risk with the intent of increasing awareness of the significant adverse cardiovascular metabolic and adverse metabolic effects when administered to perimenopausal women with depression, with or without concomitant vasomotor symptoms. However, it has not been shown to be effective in the management of depressive disorders in postmenopausal women. Menopausal hormone therapy has not been shown to significantly improve measures of cognitive function over several years of use. An approach to assessment and initial treatment for mood changes and cognitive complaints will be discussed.
APOs have a pre-existing subclinical vascular condition that is simply unmasked during pregnancy that increases their CVD risk, or whether APOs result in de novo vascular endothelial damage that results in subsequent CVD. In a cohort of women with evidence of ischemia and no obstructive coronary disease, we found that women with APOs had abnormally low microvascular coronary flow reserve up to 30 years after the index pregnancy, raising the hypothesis that the APOs may be related to dysfunction of the microvasculature. Further, the microvascular abnormalities, and their consistency and frequency, is thought to impair tissue function and increase the expression of inflammatory markers. In addition, there are significant differences in the clinical presentation of CVD; the VIRGO (Variation in Recovery: Role of Gender in Outcomes of Young AMI Patients) study demonstrated that women with ST elevation myocardial infarction were more likely than men to present without chest pain (odds ratio, 1.51; 95% confidence interval, 1.03–2.22). Women were also more likely to present with asymptomatic ST segment elevation. Risk factors for CVD in women have been identified, but as we will see, the prevention and treatment is complex and difficult due to the presence of comorbidities, elevated risks of macrovascular outcomes (coronary heart disease, cerebrovascular disease, and peripheral arterial disease) and adverse changes in body fat distribution, lipids, and vascular health. Women with premature (before age 40) or early menopause (age 40 to 45 years) have substantially increased risk of CVD. Early menopause and atherosclerosis have been associated with menopause transition and female hormone regulation. We are currently working to determine how this occurs and the role of the hypothalamic-pituitary-adrenal (HPA) axis in these processes. We are also interested in the role of neurokinin B (NKB) and dynorphin (KDNY) in female hormone regulation of hot flashes and sleep disturbances. At the heart of our work lies a population of estrogen-sensing kisspeptin neurons that are functionally and anatomically conserved in mammalian females, from rodents to humans. These neurons are part of the reproductive hypothalamic-pituitary axis, and are coined for the signature expression of genes that encode: kisspeptin, neurokinin B and dynorphin (KDNY). KDNY neurons are robustly activated under low estrogen conditions, such as menopause, and play a critical role in fertility via GnRH neurons of the reproductive axis. We are interested in the elaborate pattern of axonal projections from KDNY neurons, which extend to many postynaptic targets aside from GnRH. KDNY projections suggest that they may disseminate estrogen status beyond the reproductive axis. Using the power of mouse genetics and modern tools in neuroscience, we can artificially manipulate KDNY neurons to understand their functional significance. Based on prior observations that KDNY projections to the preoptic area of the hypothalamus, it was proposed that KDNY neurons may be involved in menopausal vasomotor hot flashes. To test this hypothesis, we used a combination of optogenetic and chemogenetic techniques to artificially activate KDNY neurons in mice. Acute stimulation of KDNY neurons was sufficient to evoke a flush (rise in skin temperature and drop in core temperature). KDNY-evokedflushes were robustly diminished by the inducing a pharmacological blockade against neurokinin B into the preoptic area. This work was the first to demonstrate a role for KDNY neurons outside of their canonical role in the neuroendocrine reproductive axis. Because KDNY neurons project broadly throughout the hypothalamus and beyond, we believe that they have to potential to mediate a wide range of behavioral and physiological outcomes in response to fluctuations in estrogen and progesterone. We are currently working to determine whether KDNY neurons play a role in the dynamic regulation of skin temperature that occurs when transitioning from a wake to sleep state and whether this transition is influenced by steroid hormone status.

**Stress and HPA–Axis Dysregulation in Hot Flashes and Menopausal Sleep Disturbance**

Fiona Baker, PhD. Human Sleep Research Program, SRI International, Menlo Park, CA

Sleep disturbances and hot flashes are common symptoms of the menopausal transition and can have a major impact on quality of life, mood, productivity, and health, particularly in women who suffer severe and persistent symptoms. An underlying factor that can exacerbate sleep problems and hot flashes is stress. Indeed, abnormalities in the stress response systems are hypothesized to reflect an underlying biological mechanism for sleep and hot flash disturbances. Recent research provides evidence that stressful life events predict poorer sleep quality in midlife women. Also, stress can act as a trigger for hot flashes in midlife women. We aim to investigate these relationships further, and we and others have used experimental stress paradigms to determine effects of stress on night-time sleep and autonomic nervous system responses, and hot flashes in perimenopausal women.

**Ischemia with No Obstructive Coronary Artery Disease**

Puja K. Mehta, MD, FACC, FAHA. Emory Women’s Heart Center and Emory Clinical Cardiovascular Research Institute, Emory University School of Medicine, Atlanta, GA

Women with chest pain who have evidence of myocardial ischemia on stress testing usually undergo coronary angiography to evaluate for obstructive coronary artery lesions. However, a large proportion of patients suspected of having ischemic heart disease are found to have no obstructive coronary artery disease (INOCA), a finding that is more prevalent in women. Cardiovascular disease risk factors such as hypertension, diabetes, smoking, inflammation, etc. contribute to INOCA, which is a diagnosis that is associated with major adverse cardiovascular events, such as myocardial infarction and heart failure.

Coronary vascular dysfunction is implicated as a major pathophysiological mechanism contributing to adverse events in INOCA. This includes dysfunction in the larger epicardial vessels as well as coronary microvascular dysfunction. Invasive coronary function testing can help diagnose abnormal coronary vascular reactivity and impairment in microcirculatory flow. Women may be more susceptible to coronary endothelial dysfunction due to mechanistic factors such as inflammation, autonomic dysfunction, and neuro-endocrine disruption, as well as mental stress susceptibility. Therapies that target cardiac risk factors, atherosclerosis, and angina are used to manage INOCA, although it remains underdiagnosed and undertreated.
vagal activity in perimenopausal women with and without insomnia. Stress anticipation effects on vagal activity extended into the first few hours of sleep, and even longer for women with insomnia, suggesting a greater sensitivity to stress in this group. Anticipation of stress did not increase the frequency of physiological hot flashes during the night, however, during an acute experimental psychosocial stress procedure in the morning, one third of women experienced a hot flash. Findings on physiological HPA-axis and cardiovascular reactivity to acute experimental stress in midlife women with insomnia are ambiguous, with some indicating blunted cardiovascular responses, and others showing no difference compared with controls. Further study is needed, considering factors like menopausal stage, history of chronic stress, and comorbid symptoms like depression, to establish the role that develops in the context of menopause in characterized by altered stress reactivity either as a pre-existing factor or as a consequence of insomnia, which could potentially be an important factor in the etiology of the disorder. Clinical trials that have investigated efficacy of relaxation techniques for alleviating menopausal symptoms have produced mixed findings, however, a recent study showed that a combined program of relaxation and stress management reduced stress, and improved sleep and psychological symptoms in a group of peri- and postmenopausal women. Further, clinical trials of cognitive behavioral therapy for insomnia in midlife women have shown consistent improvements in sleep and hot flash related interference. These findings show non-pharmacological therapies tailored for midlife women are effective for the management of menopausal-related sleep disturbances.

Downstream Effects of Menopausal-related Sleep Interruption on Mood State and Metabolism
Hadine Joffe, MD, MSc. Brigham & Women’s Hospital, Harvard Medical School, Boston, MA
Sleep interruption is highly prevalent in women across and after the menopause transition, affecting half of women in midlife. Menopausal sleep disturbance is characterized by repeated middle-of-the-night interruption with brief awakenings as well as altered sleep stage transitions and cortical arousal, which together translate to diminished sleep consolidation and less refreshing sleep. Nighttime hot flashes (or night sweats) are the primary cause of this sleep interruption. However, other mechanisms also disrupt sleep in some midlife women — including changes in gonadal steroids, the wake-promoting neuropeptide orexin, sleep apnea, periodic limb movement, stress, depression, anxiety, and environmental stimuli. While shortening of total sleep hours is known to adversely affect health outcomes, the impact on the health of the menopause-pattern of interrupted sleep occurring within a normal total sleep duration is less well understood. Accumulating experimental data in humans show that menopause-pattern sleep interruption has adversely consequences on metabolic health, daytime wellbeing, and mental health. Each of these adverse effects represents a common health problem that is strongly linked with menopause. Metabolic changes involving reduction in use of fats as a nutrient may lead to body fat gain that is common as women traverse menopause. This specific type of disrupted sleep reduced sleep quality and increases daytime sleepiness, which may affect neurocognitive function. Disruption of mental health includes diminution of positive affect, heightening of negative affect, and increases in depressive symptoms. Demonstration that disrupted sleep adversely affects metabolic and neuropsychological wellbeing provides evidence that sleep is causally linked with these health changes. While the mechanisms through which these effects may occur are not fully understood, changes in cortisol suggest that perturbation of the hypothalamic-pituitary-adrenal axis may contribute to adverse health consequences of menopause-pattern sleep interruption. Other explanatory pathways are under active investigation. Taken together, this accumulating evidence highlights the central role of menopausal-related sleep disruption as a highly modifiable target for health interventions in the midlife years. The health of aging women has been shown to be linked to menopause-pattern sleep disruption. The clinical importance of menopause-related sleep problems in midlife women is highlighted by the following recommendations for practitioners:

- Evaluate menopause-related sleep problems as a comorbid condition in women with primary or secondary insomnia.
- Assess for potential contributors other than menopause, such as hormone therapy, antidepressants, and other medical conditions.
- Consider the use of sleep hygiene and behavioral interventions for sleep disruption.
- Consider the use of pharmacological interventions for sleep disruption, including non-habitforming agents.

PLENARY SYMPOSIUM #2
Breast Cancer Risk Assessment for Women’s Health Clinicians
Lisa C. Larkin, MD, FACP, NCMP, IF. Ms.Medicine, Cincinnati, OH
Breast cancer is the most common cancer in US women with more than 250,000 new cases each year and more than 40,000 deaths. In the US 12% of women or nearly 1 in 8 will develop breast cancer and breast cancer prevention is a public health imperative. Increased genetic testing and identification of mutation carriers is an essential first line tool for evaluating risk and appropriate patients should be referred for genetic testing. It is estimated that only ~5% of those carrying genetic mutations associated with hereditary risk have been identified. Carriers particularly predisposed to estrogen receptor positive disease (ie, BRCA2, CHEK2 and ATM) may be more strongly motivated toward risk reduction and there are nuanced management issues surrounding risk-reducing medications in both BRCA1 and BRCA2 carriers given recommended early surgical menopause. Other high-risk women include those that have received therapeutic thoracic radiation to the chest between the ages of 10 and 30, women with benign atypical lesions (atypical hyperplasia and lobular carcinoma in situ), women with extreme breast density and women with an estimated lifetime risk of 20% or greater as defined by models that are largely dependent on family history. Guidelines for preventive medication from the United States Preventive Services Task Force (USPSTF) and the American Society of Clinical Oncology (ASCO) recommend using short term risk estimation to assess whether the benefits of preventive medications likely outweigh the risks in the absence of contraindications. Four medications are recommended for preventive purposes: tamoxifen, raloxifene, exemestane and anastrozole. Recently, the option of low-dose tamoxifen has gained appeal in women with intraepithelial neoplasia and personalized genomic risk estimation using the polygenic risk score has been shown to increase the uptake of chemoprevention. Health care professionals should be expert in managing side effects of these medications to promote and maintain optimum quality of life and improve medication compliance. High risk women intolerant of the vasomotor symptoms of menopause or unable to tolerate those associated with estrogen medication should understand the data regarding medical and non-medical use and limited studies of estrogen in combination with bazedoxifene. Promotion of lifestyle modification is important for all women for breast cancer risk reduction and overall health; the strongest breast cancer risk data exists for obesity and excessive alcohol use. Obesity, unhealthy dietary patterns, and physical inactivity, which disproportionally affect minority populations, have been shown to have a major impact on outcomes across the breast cancer continuum. There is a great need in women’s health to partner with patients in optimizing health and promoting breast cancer prevention. References: Medication Use to Reduce Risk of Breast Cancer – US Preventive Services Task Force Recommendation Statement. JAMA, 2019;322(9):857-867. Visvanathan K, Fabian C, Bantuag E et al. Use of Endocrine Therapy for Breast Cancer Risk Reduction; ASCO Clinical Practice Guideline Update. J Clin Oncol, 37:3152-3165. DeCensi A, Pintoni M, Guerrieri-Gonzaga A et al. Randomized Placebo Controlled Trial of Low-Dose Tamoxifen to Prevent Local and Contralateral Recurrence in Breast Intraepithelial Neoplasia. J Clin Oncol, 37:1-9. Bandera E, Alfano C, Qin B et al. Harnessing Nutrition and Physical Activity for Breast Cancer Prevention and Control to Reduce Racial/Ethnic Health Disparities. Asco.org/edbook. 2021.
Adapting Menopause Care to Telehealth and Virtual Medicine

Gloria A. Bachmann, MD, MMS. Obstetrics, Gynecology and Reproductive Sciences, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ

Due to the pandemic and social distancing, telehealth is being adopted by many menopause practitioners who were not previously utilizing it. As a result, patients with climacteric symptoms have often managed via virtual visits and face-to-face visits. Although a negative event prompted our adoption of telehealth, it has reaped benefits for clinicians and patients, including easier access to professional health services by the patient. According to data provided to the CDC (http://www.cdc.gov/violenceprevention/pdf/intimate-partner-violence-508.pdf), utilization of virtual visits are obvious; remote encounters mitigate the need for leaving home and travel; incur fewer costs and; avoid direct physical contact between provider and patient. Through electronic means clinicians can, in many scenarios, diagnose, treat, and provide preventive interventions without a hands-on physical exam and the need to space patients visits in order to avoid contact in the waiting area or have patients wait outside. Most clinicians, having now utilized telemedicine, can more clearly note the benefits of virtual health services, which encompass Internet and web applications, phones, wearable activity trackers, interactive voice response systems, and virtual reality sets. Despite our recent acknowledgment of these modalities, several earlier precursors allowed distant transmission of information without individuals being physically together. The first remote system that alerted individuals to imminent harm were smoke signals, which was used from 1450 BCE. A more advanced system that may not be obsolete is the telegraph system invented by Polybius, with a specific pattern of smoke designated for each letter of the alphabet. In 1876 Bell invented the telephone, an invention which continues to be one of the major ways patients and clinicians communicate. The radio was introduced in 1895 and the telegraph in 1926. In 1939, Atanasoff and co-invented the computer, which was the predecessor to the Internet, an indispensable part of the healthcare record and medical communication today. By the 1950s, there were some instances of hospital-based telemedicine utilization and in the 1960s closed-circuit television link was established, with first use in cardiac consultation. Also, during the 1960s telemedicine began to emerge mainly in urban communities and was useful for medical emergencies. An example is the partnership in 1967 between Jackson Memorial Hospital and a fire department, who transmitted electrocardiographic rhythms over the radio in rescue situations. The benefits of telehealth and virtual medicine are continually emerging with many directed in their use specifically for low-risk menopausal women who are up to date with mammogram and cervical cancer screenings. Consultation for management of menopause symptoms and vaginal atrophy can often be done in this manner. Discussions regarding bone health, weight management, bladder issues, other pelvic floor concerns and of course follow up can be done this way. Telephone based cognitive behavioral therapy, recommended Internet-delivered tools such as applied relaxation techniques, and wearable activity sensors are among the virtual interventions utilized in midlife and older women’s healthcare. Obstacles to virtual clinical practice and care should be addressed with patients including limited access to the Internet, smartphones, tablets, or computers; lack of familiarity with technology; and lack of privacy to discuss personal health matters, such as menopause. Telehealth encounters now have an appropriate opportunity to go beyond, based on the level of acuity or necessity to conduct an in-person physical examination or diagnostic testing. Telehealth and virtual medicine, which is generally well accepted by clinicians and patients, is here to stay. Over time, more and more interventions for menopausal women will emerge using a virtual platform for the delivery of patient care.

Collateral Damage of COVID-19 in Women and Methods to Manage

Vikki Pedigo, WHNP-BC, NNP-BC. Integrative Medicine, Vanderbilt University Medical Center, Nashville, TN

The COVID-19 pandemic has profound and wide reaching psychosocial ramifications. We have learned from past pandemics that the elevated stress levels experienced during a pandemic may result in increased incidences of depression, anxiety, and symptoms of posttraumatic stress disorder. The Household Pulse Survey reveals that our current COVID-19 pandemic follows the pattern or previous pandemics, with approximately 47% of women reporting symptoms of anxiety and/or depression compared to 38% of men in December of 2020, an increase from an overall adult baseline of 10.8% in 2019. In addition, rates of suicide ideation, attempts, and self-harm have increased compared to pre-pandemic rates. The weight of the pandemic is not experienced equally throughout the population, with a greater toll on women and disadvantaged and marginalized people. Intimate partner violence has been reported at increased rates in many countries, including the US. Risk factors for intimate partner violence that have increased in the pandemic include social isolation, fear of dying, loss of loved ones, and difficulties in accessing services. Healthcare providers need to be aware of the context in which patients are experiencing the pandemic including indicators of vulnerability, they must support the therapeutic relationship, and appropriately screen and consult for COVID-19 associated stressors, secondary adversities, and psychosocial effects. Healthcare providers and systems should strive to provide trauma-informed care utilizing the principles of safety, choice, collaboration, trustworthiness and empowerment. Validated screening tools may be used to identify and assess symptoms along with symptom severity and distress. Healthcare providers need to be prepared to normalize help-seeking behavior, provide appropriate psychoeducation, provide resources for immediate mental health needs and/or community or online mental health and social services. The stress and trauma that can impact women may be associated with increased psychosocial needs. Healthcare providers are important to identify and support women in these difficult times.

Osteoporosis Screening in Women in Their 50s: FRAX and Beyond

Carolyn J. Crandall, MD, FACP, NCMP. Medicine, University of California Los Angeles

Osteoporosis, defined as bone mineral density (BMD) T-score ≤ -2.5 by dual-energy x-ray absorptiometry (DXA) or fragility fracture, is common among postmenopausal women. The incidence increases with age; at age 65 years, the United States Preventive Services Task Force (USPSTF) recommends evaluating for any risk factor of smoking, parental hip fracture, excess alcohol, low body weight. If any of these risk factors are present, then the clinician should use a formal clinical risk assessment tool to determine which women should receive a BMD test. There are five formal clinical risk assessment tools recommended by the USPSTF: Fracture Risk Assessment Tool (FRAX), Simple Calculated Osteoporosis Risk Estimation (SCORE), Osteoporosis Risk Assessment Instrument (ORAI), Osteoporosis Index of the United States (OS-IOUS), and Osteoporosis Risk Estimation (ORIE). The ORIE has been validated in a study that has evaluated these tests for prediction of BMD T-score in the osteoporotic range (≤-2.5) or for prediction of fracture are based on the Women’s Health Initiative. The studies have compared OSTE, SCORE, and FRAX in young postmenopausal women. For identifying postmenopausal women with BMD T-score ≤ -2.5, which is the goal of osteoporosis screening (i.e. to identify candidates for pharmacologic therapy), OSTE and SCORE work better than FRAX, and OSTE is simplest (formulated based on age and body weight). Tools with more risk factors do not have better discrimination (AUC) to identify T-score ≤ -2.5 than tools with fewer risk factors. Change in BMD (baseline to 3 years) in young postmenopausal women (not taking osteoporosis medication) does not add meaningfully to distinguish between women who do, and women who do not, experience subsequent fracture. There are public health consequences of the cost and risk of BMD testing that is not required to perform a formal risk assessment tool for BMD testing in younger postmenopausal women. For young postmenopausal women, use the USPSTF screening strategy (assessing clinical risk factors, and then using one of the five recommended formal clinical risk assessment tools to decide who should receive BMD testing). The benefit of BMD measurement is that it allows for treatment of bone disease. The risk of BMD testing is that it may result in unnecessary treatment and therapy. The risk-benefit of osteoporosis drug therapy in healthy postmenopausal women less than 65 years are unclear.

Osteoporosis in Special Populations

Kendall F. Moseley, MD. Endocrinology, Diabetes, Metabolism, Johns Hopkins University School of Medicine, Baltimore, MD

Osteoporosis is most commonly diagnosed in the context of postmenopausal declines in estrogen with resultant bone loss and skeletal fragility. However, the pathophysiology and evolution of low bone density is often more complex and can occur at many different time points in a woman’s lifecycle. To understand the origins of osteoporosis in special populations, it is helpful to first consider the natural history of bone. Women acquire bone in the first two to three decades of life. That is, bone formation rates surpass that of bone resorption, resulting in a net gain of bone density. In the next phase of bone metabolism, skeletal remodeling is in steady state, or balanced formation and resorption, with overall bone density maintained. Over the perimenopause period, bone loss can occur as a rate as high as 1-2% per year, subsequently followed by a period of slower decline thereafter. With this in mind, one can appreciate how a single deleterious health event or accumulation of health challenges in one’s lifetime and cycle of bone loss could have lasting effects leading up to the point of diagnosis and beyond. The risk-benefit of osteoporosis drug therapy in healthy postmenopausal women less than 65 years are unclear.
management strategy. The evaluation begins with a thorough history and focused
of expected ovulatory dysfunction in the perimenopausal period, it is still important
formation and anovulatory or oligo-ovulatory bleeding patterns. Despite this background
to disordered follicular growth, impaired follicle rupture, resulting in ovarian cyst
ovarian reserve declines in the early to mid-40s, FSH levels rise, and inhibin B levels
a classification system in 2007, which was further revised in 2011, to classify specific
treatment. The International Federation of Gynecology and Obstetrics (FIGO) created
bleeding that is abnormal in quantity, duration, or schedule. Given the breadth of the
Abnormal uterine bleeding (AUB) is a common presenting problem for women
Medicine, Baltimore, MD
Department of Gynecology and Obstetrics, Johns Hopkins University School of
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magnification that can be considered “sonomicroscopy.” There is abundant information
sampling has called this into question as a reliable method of evaluation when such
higher frequency in closer proximity to the pelvic structures and yields a degree of image
secretory phase and then is shed as a menses. Thus estrogen causes the endometrium to
endometrium consists of a basalis and a functionalis. Estrogen stimulates the functionalis
to proliferate. After ovulation the production of progesterone (or in sequential HT the
addition of a progestogen) causes this estrogen primed functionalis to be converted to a
secretory phase and then is shed as a menses. Thus estrogen causes the endometrium to
thicken when viewed with transvaginal ultrasound (TV US). However, in those patients who are cycling, endometrial thickness measurements by TV US will be extremely time
sensitive and need to be performed as soon as possible after the bleeding cycle ends.
Several decades ago blind endometrial biopsies, originally developed for endometrial
dating as part of an infertility work up, quickly became the standard of care for evaluating
patients with abnormal uterine bleeding. This was done on very little scientific data. However, recently improved understanding about the limitations of blind endometrial
sampling has called this into question as a reliable method of evaluation when such
blind biopsies are negative for hyperplasia or cancer. TV US employs transducers of higher frequency in closer proximity to the pelvic structures and yields a degree of image
magnification that can be considered “sonomicroscopy.” There is abundant information
about the reliability of a thin distinct endometrial echo (not “stripe”) on TV US to
exclude significant pathology in patients with abnormal uterine bleeding. (However, a
thick endometrial echo in non-bleeding patient should not automatically be assumed to
be pathologic or in need of further invasive evaluation). In addition, not all uteri lend
themselves to a meaningful TV US examination. The axial uterus, coexisting fibroids, adenomyosis, or abnormality in anatomy can result in an inability to adequately visualize an
endometrial echo on TV US. In such cases, the installation of saline known as saline
infusion sonohysterography, or SIS, will allow better visualization of the endometrial
cavity. Structural abnormalities will require further tissue evaluation whereas the lack of any
endometrial echo indicates anovulation or atrophy in truly menopausal patients. Finally, new disposable hysteroscopes that can be easily adapted to an office setting may allow for “point of care” diagnosis in our patients with abnormal uterine bleeding.

Medical Management of Menopausal Bleeding
Chanel I. Cross, MD. Division of Reproductive Endocrinology and Infertility,
Department of Gynecology and Obstetrics, Johns Hopkins University School of
Medicine, Baltimore, MD
Abnormal uterine bleeding (AUB) is a common presenting problem for women
throughout their reproductive lifespan and into perimenopause. AUB is defined as
bleeding that is abnormal in quantity, duration, or schedule. Given the breadth of the
definition, reserve declines in the early to mid-40s, as suggested by the addition of
ovulatory dysfunction in the perimenopausal period, it is still important to
approach AUB systematically to exclude concurrent issues that may influence the
management strategy. The evaluation begins with a thorough history and focused
physical examination. Appropriate laboratory and imaging studies should be ordered,
and typically include a complete blood count, TSH, HCG and transvaginal ultrasound. If
counseling, as suggested by the history, a thorough evaluation for coagulopathy is indicated. In accordance with the American College of Obstetricians and Gynecologists, endometrial sampling is indicated in women over the age
of 45 with AUB, and in women under age 45 with other risk factors for endometrial
intraepithelial neoplasia. Treatment should be directed at the source of bleeding and can
include expectant, medical and surgical management when appropriate. As previously
outlined, ovulatory dysfunction is the predominant cause of AUB during perimenopause,
and hormonal treatments are the mainstays of improving the regularity of the bleeding
pattern. Medical approaches including combined oral contraceptives, progesterone
only contraceptives, and the levonorgestrel intrauterine releasing system are commonly
used. In contrast, postmenopausal bleeding (PMB) is defined as any unexpected vaginal
bleeding that occurs after the final menstrual period. For patients with medical therapy, PMB refers to any bleeding that occurs outside of the expected cyclic bleeding in response to hormone withdrawal. The most common cause of PMB is atrophy; however endometrial cancer must also be considered. Over 90% of patients with endometrial cancer will present with PMB, and approximately 14% of patients with PMB will have endometrial cancer. Given these statistics, it is imperative that any patient presenting
with PMB undergo a prompt evaluation for causes of bleeding to exclude underlying
malignancy. Evaluation includes a detailed personal and family history, review of
medications and supplements, and physical examination. Low risk patients presenting
with their initial bleeding episode, can be screened with transvaginal ultrasonography or
endometrial biopsy. Patients with recurrent bleeding, or who have multiple risk factors
for endometrial cancer, should have endometrial sampling. If malignancy is diagnosed,
prompt referral to a gynecologic oncologist is warranted. If atrophy is diagnosed,
expectant management or localized estrogen therapy may be considered. Breakthrough
bleeding (BBT) is a common complaint for patients receiving postmenopausal hormone
therapy and is most common during the first 6 months of treatment. Managing BBT
can be difficult, but strategies include changing from continuous to cyclic therapy or
increasing the dose of progestin.
Menopause and the Voice 

It is common for women to notice vocal changes around the time of menopause, which may include deepening of the voice, a more raspy or hoarse sound quality, and the quicker onset of fatigability. No studies support the majority of available lactobacillus formulations or probiotic as an adjunctive therapy in women with BV. BC recur in up to 30% of cases of and twice-weekly suppository metronidazole vaginal gel can be considered. 1. Workowski KA, Barchmann LH, Chan PA, et al. CDC Sexually Transmitted Infections Treatment Guidelines, 2021 MMWR Recomm Rep July 23 2021; 70 (4); 1-187.

How to Win at Losing: Hair Loss in Midlife Women

Alison J. Bruce, MB, ChB; Dermatology, Mayo Foundation for Medical Education and Research, Rochester, MN

Hair loss in middle aged females is common. Normal hair cycle includes anagen (growth phase) lasting 2-4 years with individual variation. This is followed by catagen (transitional phase) lasting 2-3 weeks, and finally telogen (resting) during which time the terminal hair detaches from the papilla and sheds (3 months) until re-entering anagen. Common causes for hair loss include non-scarring alopecia – androgenetic alopecia and telogen effluvium; and scarring alopecias – frontal fibrosing alopecia and central centrifugal cicatricial alopecia. Androgenetic alopecia was the traditional term to describe progressive loss of terminal hairs on the frontal and/or vertex scalp in both sexes. This was considered an androgen-dependent hereditary trait, hence the terminology. More recently, female pattern hair loss is preferred, since this distinguishes the differing clinical features between sexes, and reflects the lack of evidence to support a hormonal etiology. Although hormonal and genetic predisposition may be relevant, the mechanism through which these factors play a role is unclear since most patients do not have abnormal serum androgens. Women typically report progressive ponytail thinning, increasing scalp visibility, and easy shedding of hair. Women have a lifetime risk of midlife hair loss, with up to 30% of women affected, with reports varying from 10-20% by 50 years of age, and 50% of women affected by 65 years of age. Help is available for those women affected, with treatments ranging from regular hair care measures to medical therapies. Hair loss prior to noting their female pattern hair loss. Usually there is preservation of the terminal hair. Women with facial hair, diffuse thinning, or scarring can also develop midlife hair loss. Women with male-pattern (Androgenetic) hair loss frequently develop significant thinning or balding, with women affected by 50-60% of women by age 50, and 80% of women affected by age 60. Non-scarring alopecia due to temporary alteration in the hair cycle. This cycle shift results in fewer anagen hairs, with increased shedding as proportionally more hairs enter telogen. This increased shedding in hair density is a decrease in telogen hair density. Drug therapies include non-steroidal anti-inflammatory drugs, and spironolactone. Newer therapies like platelet rich plasma (PRP) have been shown to be effective in improving hair density and hair growth. Other therapies include topically applied 5% minoxidil and may take at least 3 months before noticing benefit. Finasteride is a 5-alpha reductase inhibitor FDA approved for male hair loss. As an off-label indication, it may be effective even though higher doses are required. Addition therapies include topical minoxidil containing OCP, and minoxidil. In elite voice professionals even small changes can drastically change the perceived pitch of the voice. An f0 difference of more than 1% can be detected by experienced listeners (e.g. opera, theater, and concert audiences). Controlling for age-related changes the difference in f0 between menopausal women without hormone therapy and those on hormone therapy was found to be 7.4%. For singers, voice actors, and professional presenters, voice changes of this magnitude can be career-ending. Unfortunately, there are relatively few studies providing specific on therapeutic options. For Premenstrual Voice Syndrome, which usually starts 4 – 7 days prior to menses, the use of combined oral contraceptive has been successful in improving midlife voice quality. For Menopause Voice Syndrome, estrogen therapy has been shown to reverse most of the observed voice changes and results in improvement in 73% of affected women at one year of therapy. It is imperative that these women follow otorhinolaryngology recommendations to improve voice quality in vocal folds, remodeling of surrounding tissues, and dehiscence of the larynx resulting in a reduction in vocal range and a loss of high frequencies. Vocal changes during menopause can be due to other causes as well. Inflammation, infection naphotic lesions of the larynx, GERD, drugs, and adrenal and thyroid disorders are just some of the conditions that can lead to altered vocal quality. Certain steroids (dexamethasone, testosterone, tibolone) are known to cause vocal changes which may be permanent, even after withdrawal of the drug. The perceived pitch of the voice is called the fundamental frequency, the “f0”. An f0 difference of more than 1% can be detected by experienced listeners (e.g. opera, theater, and concert audiences). 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pregnancy increase in migraine frequency. Estradiol can cross the blood brain barrier, ovulation. Estradiol levels falling dramatically at birth also can explain some of the post-

During the menstrual cycle itself, estradiol levels have a precipitous drop just prior to

Pure menstrual migraine and menstrually-related migraine are in the International

After childbirth, and during the menopausal transition (MT) and perimenopausal periods.

we have new or worsening headache during the perimenopausal period. After menopause, migraine incidence and prevalence drops considerably, thought to be due to stability of estradiol levels. Interestingly, women who experience pure menstrual migraine and menstrually-related migraine often have better prognoses post-menopause. Alternatively, surgical menopause (with or without oophorectomy) has been shown to worsen migraine, thought to be due to abrupt hormonal fluctuations.

Treatment Options for Midlife Migraines

Carolyn A. Bernstein, MD\(^1\), \(^2\)Neurology, Harvard Medical School, Boston, MA; \(^3\)Neurology, Brigham and Women’s Hospital, Boston, MA

Menopause is a common medical condition, affecting as many as 38 million people in the US. One out of every five households includes a person with migraine; it is the third most common cause of missed days of work. Women are three times as likely to have migraines as men; part of this may be explained by hormonal fluctuation that women experience although there are likely differences in brain pain expression in women compared to men. Migraines often present in puberty and then may worsen during the menopause transition. Despite the high frequency of the condition, there are no specific evidenced guidelines for treating migraines in midlife other than standard of care. This lecture will review medication and complementary and alternative options, focusing on best practice, unifying therapies, and shared decision making. A review of migraine pathophysiology will be followed by discussion of newer targeted biologics and the lecture will conclude with case-based examples.

PLENARY SYMPOSIUM #10

How to Advise of the Risks and Benefits of Hormone Therapy During Menopause

Jewel M. Kling, MD, MPH, NCMP, FACP. Women’s Health Internal Medicine, Mayo Clinic, Scottsdale, AZ

Menopause symptoms are common in midlife women, and include but are not limited to vasomotor symptoms, sleep disturbance, and sexual problems, which can negatively impact quality of life. Hormone therapy (HT) is the most effective treatment for the vasomotor symptoms of menopause and has a role in the prevention of osteoporosis, but many women go untreated. Various myths persist about the risk profile of HT. Since the Women’s Health Initiative (WHI) trial results in 2002, it has become clear that the risks of HT are low for healthy women within ten years from menopause or less than age 60. Taken together, the benefits are likely to outweigh the risks in view of HT’s efficacy for symptom management. Discussing the risks and benefits of HT by system (cardiovascular, brain, breast, bone, etc.) will empower healthcare practitioners to counsel their patients appropriately and provide an individualized and informed approach to HT prescribing.

Vasomotor Symptom Management: What’s on the Horizon?

Stephanie S. Faubion, MD, MBA, FACP, NCMP. Women’s Health, Mayo Clinic, Jacksonville, FL

Vasomotor symptoms are prevalent, experienced by about 75% of women in the menopause transition. Further, symptoms last a mean of 7-10 years, longer in women whose symptoms begin in perimenopause. There are associations of vasomotor symptoms with not only poorer quality of life, sleep problems and negative mood, but also with lower bone density and subclinical cardiovascular disease. Several therapies, both hormone and nonhormone, are under investigation for vasomotor symptom management. Some of these are approved for other indications and others are novel compounds that are not yet government approved. Oxybutynin is an antimuscarinic, anticholinergic agent used for management of overactive bladder symptoms and hyperhidrosis which also has been found to reduce vasomotor symptom frequency and severity. Although there are concerns regarding dementia risk with longer-term use, short term use may provide symptom relief for women with significant or bothersome vasomotor symptoms. Neurokinin 3 receptor antagonists are in phase 3 clinical trials for treatment of vasomotor symptoms and represent a promising nonhormone therapy for women who are unable or unwilling to receive menopause therapy. These agents appear to rapidly and effectively reduce vasomotor symptom frequency and severity. The effects of NK3 inhibitors on weight, cardiovascular, bone, brain or sexual health remain unknown, and long-term safety and efficacy have yet to be established. Estetrol (E4) is a naturally occurring estrogen with selective action in tissues and is produced by the body in response to rapid changes in female hormone levels. E4 may show reduced vascular and hot flash thermal frequency and severity as well as improvements in the vaginal maturation index. E4 has recently been approved in the US and Canada for use as a contraceptive and is under investigation for vasomotor symptom management. These promising therapies have the potential to provide women with a greater number of options for vasomotor symptom management.
NAMS/PFIZER WULF H UTIAN ENDOWED LECTURE

Promises and Challenges of Gene Editing in the Age of CRISPR
Neville Sanjana, PhD 1,2. Biology, New York University, New York, NY; New York Genome Center, New York, NY

We have developed advanced tools to manipulate the written word, digital information, and computer code. But, until recently, we have had few tools for easy manipulation of DNA — the programming language of all living things. In this talk, I will explore the scientific frontiers in DNA manipulation using a new tool called CRISPR that is transforming biomedical science. I will explain how CRISPR is used to precisely modify genomes, including human genomes, and what are the broader implications of this new capability. This includes the ability to address pressing global problems, including food security through engineered plants, battling infectious diseases like malaria, and designing new cellular therapies for cancer. I will also present an example of genome editing in action from our lab’s research at the New York Genome Center and NYU. In our work, we take advantage of the easy programmability of CRISPR to target not just one or two genes but all of the approximately 20,000 genes in the human genome. In this manner, we can efficiently “hunt” for genes responsible for SARS-CoV-2 (COVID-19) infection and, using this information, engineer new therapeutic strategies. For more about Dr. Sanjana’s research, please visit: http://sanjanalab.org.

NAMS/KENNETH W KLEINMAN ENDOWED LECTURE

Death, Dying, and Dignity: The Art of End-of-Life Care
Leslie J. Blackhall, MD, MTS. Palliative Care, University of Virginia School of Medicine, Charlottesville, VA

All of us are born and all of us die. Most of us will not die suddenly, we will die of chronic, progressive, life limiting illnesses. Most hospitalized patients suffer from these illnesses: cancer, heart disease, COPD, and dementia. Unfortunately, care for patients who are approaching the end of life is often scattered, ineffective, and distressing to patients, providers, and family members, despite the best intentions of all involved. For the past 40 years we have attempted to improve care at end of life by encouraging open and honest communication between patients and providers and the use of advance care directives to allow people to choose quality of life instead of aggressive life-prolonging care. Despite the increase in education surrounding ethics, death and dying, and despite the increased availability of hospice and palliative care services, many, if not most people with life limiting illnesses still spend the end of life going in and out of emergency departments, hospitals, ICUs and nursing homes getting care that does not improve their quality of life and often does not improve their length of life. What if the frame we have used to consider end of life is wrong? What if, instead of looking at death as something extrinsic to life, something with causes that can continually fought back, we saw it as intrinsic, something that is built in to being human. Instead of seeing end of life care as a matter of “choice” and “communication,” this talk will ask what it would be like to view end of life as part of the continuum of care, and ask what the best medical care is for those whose illnesses are no longer responding to disease specific therapies. As Atul Gawande put it “what should medicine do when it can’t save your life?”