MENOPAUSE 101 COURSE

Menopause Basics

Gloria A. Richard-Davis, MD, MBA, MSCP, FACOG. Division of Diversity, Equity, and Inclusion, Department of Obstetrics and Gynecology, University of Arkansas Medical Sciences, Little Rock, AR

Menopause is a natural biological process that marks the end of a woman's reproductive years. Menopause effects every woman if she lives long enough. It usually occurs between the ages of 45 and 55, with the average age being around 51. During menopause, a woman's ovaries gradually produce less estrogen and progesterone, leading to the cessation of menstrual cycle. Certain medical interventions like surgery or certain medical conditions can also induce menopause earlier than the typical age range. The incidence of menopause varies based on demographic factors such as genetics, socioeconomic status, and lifestyle choices. About 5,000 women per day, 2 million per year enter menopause. It is estimated of 61 million women will be post menopause by 2030. Understanding the reproductive stages of a woman life outlined in STRAW in important in help her become aware and manage her reproductive life. Most women will live a significant part of their life post-menopausal. It is imperative that providers understand the physiological, psychological and socio-economic impact on women's quality of life in their post menopause phase. Physiologically, menopause is characterized by a decline in hormone production, resulting in various symptoms such as hot flashes, night sweats, mood changes, vaginal dryness, and sleep disturbances. While these symptoms are common, their intensity and duration can vary widely among individuals. Racial and ethnic differences can influence the experience of menopausal symptoms and their treatment. Studies have shown that some ethnic groups may have different frequencies and severities of symptoms With the changing demographics in the US and globally, it is imperative that providers have an increase in knowledge about the racial and cultural differences in how women experience menopause. Study of Women Across the Nation (SWAN) has added much to our body of knowledge in understanding the of racial and ethnic differences in menopause symptoms. SWAN has documented the duration of symptoms are longer than previously believed and the duration is affected by race, ethnicity and other factors. Overall, the SWAN study has provided valuable insights into the multifaceted nature of menopause and its impact on women's health. Research emphasizes the importance of personalized care and understanding the diverse experiences women undergo during this life stage.

Vasomotor Symptoms 101

Nanette F. Santoro, MD. Obstetrics and Gynecology, University of Colorado School of Medicine, Aurora, CO

Vasomotor symptoms (VMS) affect the vast majority of individuals who will traverse menopause in addition to those who take endocrine ablation therapy for a variety of diseases. VMS cause significant disruption of quality of life, impact sleep, and may have long-term consequences for cardiometabolic health. Knowledge gained through a number of epidemiological studies of the menopause transition confirm a high prevalence of VMS and have identified participant factors associated with them. VMS are prevalent even before the menopause transition, with overall greater prevalence among populations of color. VMS increase in prevalence during the early menopause transition and peak prevalence occurs in the year before and after the final menstrual period in studies of naturally menopausal women. Surgically menopausal women are believed to have a more severe and prolonged experience with VMS. Longitudinal studies of the menopause transition indicate that the median duration of VMS is 7.4 years, however sociodemographic predictors impact greatly on duration. For example, African American women have an overall longer duration of VMS, over a decade on average, and an even longer duration for African American women with a BMI <25 kg/m^2. VMS are effectively treated with hormone therapy. However, risks and benefits for each individual woman need to be assessed and reassessed, as some risks (eg, breast cancer) accrue over time and some women will develop a contraindication to hormone therapy (eg, DVT). Other treatments for VMS have largely been discovered when women with a contraindication to hormone use took a medication for a different reason and noted that their VMS improved. Systematic study of these medications then ensued. In this manner, the SSRI/SNRI class of medications, gabapentin, clonidine, and oxybutynin were found to improve VMS symptoms in many women. However, these nonhormone alternatives are not as effective as hormone therapy. New to the science of VMS and new to the market, selective neurokinin 3 (NK3) receptor antagonists have been discovered and developed as effective treatments for VMS. Because they target the NK3 receptor proximal to the estrogen mediated pathway, they abrogate hot flashes on a par with hormones in terms of effectiveness.

Genitourinary Syndrome of Menopause 101

Caroline Mitchell, MD, MPH. Obstetrics, Gynecology, and Reproductive Biology, Harvard Medical School, Boston, MA

Over 50% of women experience genitourinary syndrome of menopause (GSM), which can have a significant negative impact on quality of life. GSM encompasses vaginal dryness, vulvovaginal irritation, dyspareunia, dysuria, and urinary urgency, among other symptoms. In this presentation we will discuss the presentation and evaluation of GSM, as well as how to distinguish this from other conditions that occur after menopause. Treatment for GSM can range from simple changes to personal care habits, to nonhormonal, over-the-counter interventions, to prescription therapies. This talk will review the range of treatment options for different presentations of GSM, including topical estrogens and non-estrogen hormonal therapies.

Sexual Function 101

James A. Simon, MD, CCD, MSCP, IF, FACOG. Department of Obstetrics and Gynecology, George Washington University, IntimMedicine Specialists, Washington, DC

Pleasurable sexual activity is sought-after in men, women, and couples* of all ages, being associated with better health and longevity. Even in the oldest old (men and women ≥ 80 years) sexual activity continues. While heterosexual activities commonly change with aging, other alterations in physical capabilities (i.e., erectile dysfunction, arthritic restrictions, and other pain syndromes) couples continue to enjoy sex well into their 9th decade. Practitioners of all backgrounds have many barriers to addressing these problems in today's healthcare environment including their own insecurities, pressures of time, lack of knowledge, etc., patients also present roadblocks to care. While sexual problems are common in women of all ages, they seem to become less distressing in partnered women as they age. Less frequently, those problems escalate by their severity, duration or both to a medical dysfunction causing personal or interpersonal distress. All the sexual dysfunctions (desire, arousal and orgasmic, as well as sexual pain [the latter to be covered in part elsewhere in this course]) increase prior to and at the time of menopause. While the pattern of change varies greatly by the diagnosis, and consistent with the underlying pathophysiology, desire problems are typically the most common presenting complaint with the average practitioner encountering 8.4 (ob/gyn) and 4.5 (primary care) women per week noting low or absent sexual desire. Utilizing a biopsychosocial model for approaching patients with sexual problems or dysfunctions is critical to successful resolution. As such, a multidisciplinary approach is usually required, unless the practitioner has had special training (i.e., psychology or psychiatry). While this lecture will focus on biological approaches to treatment, consistent with The Society's membership, psychosocial interventions which eliminate or reduce personal or interpersonal relationship challenges, whether primary to the sexual problem or a result of it, are often required. Further, pain syndromes, commonly associated with sexual problems/dysfunctions especially during the peri and menopausal years must be reduced or eliminated as well. Problems of vulvodynia, vestibulodynia, genitourinary syndrome of menopause (GSM), deep pelvic pain, and pelvic floor dysfunction both hypertonic and hypotonic, typically must be resolved before desire concerns can be adequately addressed. Desire problems are also the most easily attended to with existing therapies, both off-label (e.g., systemic testosterone) and FDA-approved (e.g., flibanserin, bremelanotide). Understanding the evolutionary triggers for sexual activity (midcycle ovulation for procreation) form the cornerstone for understanding the available treatment approaches. In the perimenopause and following menopause these historical biological triggers are lost and many women's sexual desire changes from spontaneous sexual thoughts and fantasies to a more responsive pattern of desire. Recognizing concomitant underlying medical problems and their treatments which might be interfering in the normal sexual response is a common initial approach to care. Once these potential causes of sexual problems are eliminated, thoughtful selection of an evidence-based therapy frequently results in improvement of symptoms. Screening approaches fit for today's high-volume practices and an evidence-based process-of-care documents are available. Remembering the partner in both a psychosocial and physical context is also critical to partner women. *In this lecture, I will use the gender specific language commonly used in the published literature. I recognize and accept that there are many who identify differently from the gender and/or specific pronouns and relationship types used here. Nothing in my choice of language is meant to comment upon or criticize those that define themselves differently.

Mood, Sleep and Cognitive Function

Pauline M. Maki, PhD. Psychiatry, Psychology, and Obstetrics and Gynecology, University of Illinois at Chicago, Chicago, IL

Disruptions in mood, sleep, and cognitive function reliably occur during the menopause transition and persist in the postmenopause for many women. These symptoms commonly co-occur and are associated with reduced quality of life. Clinical guidelines describe the perimenopause as a window of vulnerability for elevated depressive symptoms though most women who experience major depressive episodes (MDE) in the perimenopause are women with a history of major depressive disorder (MDD). As such, MDE in these women represents a recurrence of prior MDD, and treatment is guided by the antidepressant treatments that improved mood in the past (eg, SSRIs, psychotherapy, or both). Some women do experience a new onset of MDD in the perimenopause due to individual sensitivity to hormonal fluctuations, particularly with stressful life events. Those women may be vulnerable to a rebound of depressive symptoms after withdrawal from hormone therapy (HT). Vasomotor symptoms (VMS) are associated with elevated depressive symptoms but appear to play less of a role in MDD. VMS-related awakenings also contribute to mood symptoms. In women whose mood has declined with life stressors (eg, relationship stress, children leaving), psychotherapy is recommended. Estrogen therapy (ET) has been shown to improve MDD symptoms in perimenopausal women with MDD, though ET is not FDA-approved for that indication and ET is ineffective in treating MDD in postmenopausal women. This window of efficacy for ET is consistent with accumulating evidence that hormonal fluctuations in the perimenopause contribute to depressed mood. During the menopause transition, about 60% of women experience sleep disturbance and 5-30% experience clinical insomnia disorder, with higher rates of subclinical and clinical insomnia among women with VMS. Cognitive behavioral therapy for insomnia (iCBT) is effective in improving sleep in midlife women. VMS, mood symptoms, and hormonal changes play important roles in subclinical and clinical sleep disturbance at menopause. Sleep disturbance, depressed mood, VMS, and hormonal changes contribute to both cognitive complaints and declines in performance on cognitive tests, particularly memory tests. In fact, there is a reliable decline in memory for words, stories and other verbal materials in the perimenopause that persists into the postmenopause for some women. There are no large randomized clinical trials of hormone therapy (HT) or oral contraceptives on cognitive outcomes

in the perimenopause or among women with bothersome VMS. Randomized trials reliably show neutral effects of HT on cognition in the early postmenopause. In the late postmenopause, effects of HT on cognition vary by formulation; estradiol has neutral effects and combination conjugated equine estrogen plus medroxyprogesterone acetate has negative effects. Lifestyle modifications (eg, exercise, Mediterranean diet) and treatment of cardiovascular risk factors can help women optimize cognitive health at midlife and beyond.

Hormone Therapy: Yes, No, Maybe? Treatment in Medically Complex Patient

Stephanie S. Faubion, MD, MBA, FACP, NCMP, IF. 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. Menopausal hormone therapy (HT) is the most effective treatment for vasomotor symptoms, and evidence supports its use in healthy women who are less than 60 years of age and within 10 years of menopause onset at the time of initiation. However, decision making is more complex in women with one or more chronic medical conditions which may alter the benefit to risk balance of HT use. This clinical scenario is a common one given that 80% of women over the age of 55 years have at least one chronic medical condition. Further, 2 in 3 women over age 40 and 3 in 4 women over age 60 have overweight or obesity. While some of the more common conditions including obesity, hypertension, dyslipidemia, and diabetes are not contraindications to the use of HT, decision making to use HT for vasomotor symptoms in this setting is more nuanced and requires individualization. The transdermal route of administration of estrogen may provide less risk than the oral route by avoiding first-pass hepatic metabolism which is known to increase coagulation factors, sex hormone-binding globulin, C-reactive protein, and triglycerides. Because of this, a transdermal route of administration of estrogen is preferred in women with cardiovascular disease risk factors and certain other conditions. Women who are at high risk for cardiovascular disease (10-year ASCVD risk ≥ 10%) are generally advised to avoid systemic hormone therapy. It is important clinicians are aware that HT may be considered in women with chronic medical conditions with individualized risk assessment, shared decision making, and risk factor modification.

MEDICAL BREAST AND GENETICS 101 COURSE

Risk Assessment

Lisa C. Larkin, MD, FACP, NCMP, IF. Ms.Medicine, Cincinnati, OH

Breast cancer is the most common cancer in women globally with enormous associated morbidity, mortality, and economic impact. To date, early detection of breast cancer with a one size fits all, age-based screening approach has been the focus, while population prevention efforts have been largely ignored. It is imperative that we change the paradigm and shift our efforts to breast cancer prevention. As with other diseases, prevention of disease starts with risk assessment and identification of individuals at high risk. For breast cancer, prevention requires improved identification of individuals who carry a hereditary cancer mutation associated with increased breast cancer risk, and identification of individuals who are at high risk due to non-genetic, established modifiable and non-modifiable factors. This presentation will provide an overview of modifiable and non-modifiable risk factors for breast cancer, including lifestyle, review available validated risk assessment models, and provide a framework for incorporating breast cancer risk assessment into clinical practice. Breast cancer genetics will be discussed later in the symposium.

Breast Cancer Screening: Average and High Risk

Holly J. Pederson, MD, MSCP. Medical Breast Services, Cleveland Clinic, Lerner College of Medicine, Cleveland, OH

The aim of breast cancer screening is to detect cancer at its earliest, most treatable Stage. Screening mammography in average risk patients has been shown to reduce mortality from breast cancer by 20-40% in all age groups (from age 40). Screening guidelines, however, continue to evolve and major organizations such as the National Comprehensive Cancer Network, the American College of Radiology, the American Cancer Society, the Society of Breast Imaging, and the United States Preventive Task Force have released sometimes conflicting guidelines, creating confusion for patients and providers. Further, it is critical that processes are in place in both the clinical and the screening setting to identify high risk patients so that they may receive further counseling and recommendations. Areas of controversy include the age at which screening should begin, the age at which it should cease, and the interval between studies (one to three years). Generally, patients are offered screening mammography at either 40, 45, or 50, every year or every other year, with cessation at 74 or when the patient's comorbid conditions preclude benefit from screening. Generally, mammography performs better in older women with a higher sensitivity, specificity, cancer detection rate and positive predictive values. In older women, overall health status should be considered as well as patient preference. There seems general agreement to offer annual screening from age 45-55, with mammograms every 1-2 years from 56-74. Options for supplemental screening in women with dense tissue should be presented to patients as well, though recommendations in this domain also lack clear guidance. Shared decision-making is key. High risk patients are defined as those with identified hereditary risk (with pathogenic or likely pathogenic variants found in highly penetrant or moderately penetrant genes), untested first degree relatives of highly penetrant gene mutation carriers, patients with family history, extremely dense breast tissue, a history of benign atypical biopsies such as atypical hyperplasia and LCIS, survivors of childhood cancers such that therapeutic radiation was received between the ages of 10 and 30 years, and those with an estimated lifetime risk for the development of breast cancer of 20% or greater. Full sequence magnetic resonance imaging (MRI) is the most sensitive screening method for breast cancer, reducing mortality in high risk patients by an additional 20%. MRI, however, often results in false positive findings, sometimes false positive biopsies, and there remain issues around access and affordability. Screening recommendations for patients at increased risk are more consistent amongst major organizations than those recommendations for the average risk patient. Typically, MRI is added annually in addition to the annual screening mammogram (tomosynthesis preferred), often in an alternating fashion. Pregnancy Associated Breast Cancer occurring during pregnancy, while breastfeeding, or within one year of delivery affects 1/3,000 – 1/10,000 pregnancies. Delay in diagnosis is common and tumors may be more aggressive. Continuation of screening through pregnancy and lactation should be discussed with all patients, but particularly those at increased risk. During pregnancy, screening mammography is safe; the radiation dose of a standard four view mammogram is <0.03 mGy (with a toxic dose being >50 mGy). MRI is contraindicated during pregnancy as the gadolinium dye may cross the placenta and is teratogenic in animals. During lactation, both MRI and mammography are safe; there is no need to interrupt breastfeeding. It is critical to remember that symptomatic patients either during pregnancy or lactation should have a comprehensive evaluation beginning with an ultrasound, but diagnostic imaging should be performed as indicated. Finally, in 2021, the American College of Radiology issued transgender screening guidelines. In average risk transfeminine (male-to-female) individuals 40 years of age and older with a past or current hormone use equal to or greater than 5 years, annual screening mammography should be discussed and offered. Mammography is recommended in higher-than-average risk patients, with age at initiation informed by the risk factors.

Breast Density and Supplemental Screening: A Comprehensive Overview

Laura H. Dean, MD. Cleveland Clinic, Cleveland, OH

Breast density has emerged as a significant factor in breast cancer screening and diagnosis, leading to increased interest in supplemental screening methods. This presentation aims to provide a comprehensive overview of breast density and its impact on breast cancer detection. The definition of breast density will be described, as well as the association with breast cancer risk. Finally, the limitations of mammography in dense breasts will be discussed. Dense breast tissue is common, with approximately 50% of screened women falling into the category of having either heterogeneously dense or extremely dense tissue. Numerous studies demonstrate at least a moderate association of mammographic density and breast cancer risk. Women in the extreme density group are 4- to-6 times more likely to develop breast cancer than women with fatty breasts. Radiologists interpreting mammograms understand the challenges and limitations of cancer detection for women with dense breast tissue, as dense fibroglandular tissue can obscure a cancer on mammography. This results in an increased risk of interval and higher stage cancers for women with dense tissue. Masking of cancer by dense tissue has become a political issue. Advocacy efforts over the last decade have resulted in legislation in the United States which now mandates patient notification of breast density along with mammography results. Various supplemental screening techniques have been developed, that can aid in detecting breast cancers missed by mammography in women with dense breasts. These include ultrasound, magnetic resonance imaging (MRI), tomosynthesis, contrast enhanced mammography, and molecular breast imaging (MBI). Each of these supplemental modalities has its own effectiveness and limitations. There are challenges and considerations in implementing each of these supplemental screening approaches, including cost, accessibility, and evidence-based guidelines. There is an emerging role of artificial intelligence (AI) in breast cancer screening, especially for women with dense breasts. AI algorithms can analyze mammographic images and improve the accuracy of cancer detection in dense breasts. There are no specific screening guidelines that differ for patients with dense tissue. Screening mammography remains the gold standard for breast cancer screening, with the addition of supplemental modalities depending on patient risk factors and overall individual goals of screening.

Evaluating Basic Breast Complaints

Zahraa AlHilli, MD. Department of General Surgery, Cleveland Clinic, Cleveland, OH

The evaluation of basic breast complaints is an important foundation in the management of breast disease. This assessment involves thorough history taking and risk assessment as well as examination and utilization of imaging work-up and in some cases pathology diagnosis. This presentation aims to provide a structured approach to efficiently diagnose and manage basic breast complaints commonly seen in the breast clinic.

Benign Breast Disease and Management

Zahraa AlHilli, MD. Department of General Surgery, Cleveland Clinic, Cleveland, OH

The management strategies of benign breast disease involve the accurate diagnosis, appropriate risk assessment, and an individualized treatment of a large spectrum of presentations seen and managed in the breast clinic. Benign breast disease includes a range of presentations including non-proliferative lesions (ex. cysts) and proliferative lesions without atypia (ex. fibroadenoma, papilloma, radial scar) and with atypia (atypical hyperplasia). This presentation will address the overall work-up of these lesions and focus on the contemporary management strategies and controversies related to some of these lesions.

Risk Reducing Medications for Breast Cancer: Chemoprevention

Juliana M. Kling, MD, MPH, NCMP, FACP. Division of Women's Health Internal Medicine, Mayo Clinic Alix School of Medicine, Scottsdale, AZ

National guidelines including the National Comprehensive Cancer Network (NCCN), the United States Preventive Services Task Force (USPSTF) as well as the American Society of Clinical Oncology recommend consideration for the initiation of endocrine therapy for women with an elevated risk for breast cancer as a tool to prevent breast cancer.

Women are considered a high risk for breast cancer if they have received thoracic radiation administered prior to 30 years of age, have a ≥1.7 percent five-year risk for breast cancer (using the Breast Cancer Risk Assessment Tool/Gail model), a history of atypical hyperplasia or lobular carcinoma in situ. Options that can be considered for risk reduction include the selective estrogen receptor modulators, tamoxifen or raloxifene, or the aromatase inhibitors (AIs), anastrazole or exemestane. Of these options, tamoxifen and raloxifene are the only ones approved by the US Food and Drug Administration (FDA) for primary prevention against breast cancer. However, there are large studies that have demonstrated efficacy in both anastrazole and exemestane in reducing breast cancer risk in high-risk women. Taken together, research shows these reduce breast cancer risk by 50 – 65%. SERM's can be used in both pre and postmenopausal women, whereas the aromatase inhibitors can only be used in postmenopausal women. In addition to menopausal stage, other criteria that help with selection include risks and side effects. SERMs can increase risk of venous thromboembolism and endometrial cancer, and can cause significant hot flashes, particularly in premenopausal women. AI's can increase the risk of osteoporosis and joint pain. Typically, it is recommended to obtain a bone density prior to initiation of an AI. The benefits outweigh the risks of these medications more in younger women at the highest risk of developing breast cancer, and those without a uterus. Uptake of these medications is suboptimal, likely for multiple reasons including lack of knowledge in primary care and clinical settings, as well as concern for side effects. Learning more about these valuable tools can help facilitate appropriate clinical implementation, ultimately leading to reductions in breast cancer risk for high-risk women.

Genetics 101

Cameron Friedman, MS, CGC. Genetics, MetroHealth Medical Center, Cleveland, OH

A clinician's ability to identify patients who should be referred for cancer genetic counseling and genetic testing to screen for potential pathogenic germline mutations in cancer susceptibility genes is vital. These results can impact medical management recommendations and screening frequency. Currently, 5-10% of all cancers are considered to be hereditary, due to an underlying genetic risk factor. These mutations are usually involved with tumor suppressor genes which can impact cell growth and DNA repair. A widely known example is mutations in the *BRCA1/2* genes, which infer the highest risk for developing breast and ovarian cancers. For patient's harboring these mutations, they should be offered essential increased surveillance and surgical interventions. The National Comprehensive Cancer Network (NCCN) provides general guidelines and management principles for these patients and characteristics associated for a genetics referral. Cancer genetic counseling plays a necessary role in patient understanding of different genetic concepts, explaining and clarifying various types of results, obtaining informed consent, facilitating psychosocial support, and assisting with genetic testing coordination for other at-risk family members. As cancer genetics knowledge and technology continue to advance, appropriate referrals for cancer genetic testing become crucial in guiding screening, medical management, and personalized medicine approaches.

Management of the Gene-Positive Patient

Allison W. Kurian, Md, MSc. Stanford University, Stanford, CA

Genetic testing is increasingly used, as guidelines for genetic risk evaluation have broadened and testing costs have fallen. Thirteen genes are recognized as associated with an increased risk of developing breast cancer, and ten with an increased risk of ovarian cancer; many of these confer elevated risks of additional cancers including pancreatic, colorectal, and endometrial. Options for management of breast cancer risk include prophylactic bilateral mastectomy, intensive screening incorporating breast magnetic resonance imaging, and risk-reducing medication, with the choice between these options depending on magnitude of genetic risk, other health conditions and patient preference. Ovarian cancer risk is managed by bilateral salpingo-oophorectomy, with considerations including age at surgery and a two-staged procedure of pre-menopausal salpingectomy followed by oophorectomy after menopause. Other organ-specific screening strategies, such as endoscopic ultrasound and magnetic resonance cholangiopancreatography for pancreatic cancer, may be warranted depending on the affected gene and family cancer history.

OPENING SYMPOSIUM

Cell-Free DNA: A Paradigm Shift in Cancer Screening

Mylynda B. Massart, MD, PhD[1,2]. [1]Family Medicine, UPMC Primary Care Precision Medicine Center, Pittsburgh, PA; [2]Research Inclusivity and Community Partners Cores, Clinical and Translational Science Institute, Institute for Precision Medicine, University of Pittsburgh, Pittsburgh, PA

A paradigm shift is occurring in cancer screening. Clinicians have long been frustrated with late-stage diagnosis of cancer and limited screening guidelines as well as numerous barriers to achieving successful screening rates. With the advancement of cell-free liquid biopsy technology, medicine is poised to make significant changes in how we screen for cancer, a large advancement in the number of cancers screened, and in the accessibility of cancer screening. Although the technology is new and not yet covered by insurance, it is exciting to learn about the potential opportunities to supplement current USPSTF cancer screening guidelines with this new emerging precision medicine technology. Come learn about how cell-free liquid biopsies and DNA methylation patterns can help to detect cancer earlier and the data demonstrating higher positive predictive values than our current standard of care screening.

Breast Cancer Screening in the Era of Precision Medicine: What's New in Radiomics, Genomics, and Artificial Intelligence?

Emily F. Conant, MD, FSBI. Radiology, University of Pennsylvania, Philadelphia, PA

Mammography is currently the most effective test for the detection of breast cancer, but it is far from perfect. While mammographic screening false-negative rates are relatively low, there is a significant number of false positive studies necessitating additional imaging and often, biopsies. While digital breast tomosynthesis has helped improve both the sensitivity and specificity of mammographic screening, increased breast density and/or "breast complexity" is associated with a high false negative rate as well as a higher risk of developing breast cancer. By incorporating such image-derived data ("radiomics") to quantitatively reflect image-derived biomarkers, more personalized approaches to screening may be implemented with the goal of improving screening outcomes. In this talk, we will review the added benefit of incorporating of image-derived risk factors such as breast density and complexity based on deep learning and artificial intelligence algorithms. Results from more "personalized screening" strategies that include such radiomics data as well as demographic and genetic data in risk assessment algorithms will be presented. Conant EF, Talley MM, Parghi CR, Sheh BC, Liang SY Pohlman S, Rane A, Jung YS, Stevens LAS, Paulus JK, Alsheik N. Breast Cancer Mammographic Screening in Routine Practice: Multisite Study of Digital Breast Tomosynthesis and Digital Mammography Screenings. Radiology 2023 May;307(3):e221571. doi: 10.1148/radiol.221571. PMID: 36916891 Eriksson M, Czene K, Vachon CV, Conant EF, Hall P. A Clinical Risk Model for Personalized Screening and Prevention of Breast Cancer. Cancers (Basel). 2023 Jun 19;15(12):3246. doi: 10.3390/cancers15123246. PMID: 37370856 Eriksson M, Czene K, Vachon C, Conant EF, Hall P. Long term Performance of an Image-based Short-term Risk Model for Breast Cancer J Clin Oncol. 2023 May 10;41(14):2536-2545 PMID: 36930854 Gastounioti A, Desai S, Ahluwalia VS, Conant EF, Kontos D. Artificial intelligence in mammographic phenotyping of breast cancer risk: a narrative review. Breast Cancer Res. 2022 Feb 20;24(1):14. doi:10.1186/s13058-022-01509-z. PMID: 35184757 Eriksson M, Conant EF, Kontos D, Hall P. Risk assessment of breast cancer in population-based screening. J Clin Oncol. 2022 Jul 10;40(20):2279-2280. PMID: 35544593 Eriksson M, Destounis S, Czene K, Zeiberg A, Day R, Conant EF, Schilling K, Hall P. A Risk Model for Digital Breast Tomosynthesis to Predict Breast Cancer and Guide Clinical Care. Sci Transl Med. 2022 May 11;14(644). doi: 10.1126/scitranslmed.abn3971. PMID: 35544593 Haas JS. The Complexity of Achieving the Promise of Precision Breast Cancer Screening. J Natl Cancer Inst. 2017 Jan 27;109(5):djw301. doi: 10.1093/jnci/djw301. PMID: 28130476

Personalizing Treatment for Early-Stage Breast Cancer

Allison W. Kurian, MS, MSc. Stanford University, Stanford, CA

Breast cancer is the most common malignancy and the second most common cause of cancer death among women in the United States. While the incidence of breast cancer has increased over time, mortality has fallen due to a combination of mammography screening and effective treatment. The advent of precision oncology, with routine molecular and genomic characterization of breast tumors, has enabled targeted therapies. Breast tumors were first subtyped by their expression of three therapeutic targets – estrogen receptor, progesterone receptor, and HER2 – which confer eligibility for anti-hormonal and HER2-directed treatments along with or instead of cytotoxic chemotherapy. Currently, tumors are evaluated for responsiveness to immune-activating therapies (such as the immune checkpoint inhibitor pembrolizumab) and germline mutation-targeted treatments (such as the poly(ADP-ribose polymerase inhibitor olaparib) which can increase cure rates and save lives. However, these emerging targeted therapies confer unique toxicities, such as autoimmune disease, which must be considered in the care of breast cancer survivors.

Detection of Minimal Residual Disease After Treatment of Early Stage Breast Cancer: Cell-Free DNA and Beyond

Amy S. Clark, Md, MSCE. Division of Hematology/Oncology, Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

The majority of the approximately 250,000 women diagnosed annually with breast cancer have curable disease at diagnosis. Unfortunately, despite advances in biologic understanding of the disease and treatment options, one third of early stage breast cancer patients will experience a recurrence. Local recurrences remain potentially curable however distant recurrences are not. Once the breast cancer has spread outside of the breast and regional lymph nodes, the cancer is treated as a chronic disease requiring lifelong treatment. Risk of recurrence is estimated based on several clinicopathologic factors and is highest for the first 5 years after diagnosis. Pathophysiologically, breast cancer spreads by "seed cells" that escape the primary breast tumor into the blood stream. These seed cells can either immediately become a metastatic site in an organ or become dormant, living in the bone marrow. The goal of adjuvant therapy is to prevent recurrence and kill these seed cells. Existence of these cells after completion of adjuvant therapy greatly increases the risk of breast cancer recurrence; these cells are considered minimal residual disease. Breast cancer minimal residual disease is a continuum of dormant tumor cells to replicating tumor cells that circulate and grow in organs to become a frank metastatic site. Dormant tumor cells, also called disseminated tumor cells (DTCs), live in the bone marrow and can be detected via bone marrow aspirate. Stage for stage, patients who have detectable DTCs have a higher rate of breast cancer recurrence than their counterparts without detectable DTCs. DTCs stay alive using autophagy and hide from the immune system. For reasons that are only partially understood, these cells wake up activating specific protein cascades such as the CDK 4/6/Rb pathway and/or the PI3K/Akt pathway and re-enter the cell cycle. Once this re-activation has occurred, they leave the bone marrow and enter the circulating blood where they can move to different organs and continue to grow- becoming a metastatic site. At this time, cancer tumor DNA (also called cell free DNA, cfDNA) can be measured in the blood of patients and can be

detected prior to development of frank metastatic disease. Current clinical trials aim to identify patients with DTC and/or cfDNA and provide treatment to eliminate them in order to determine whether more patients can be cured from breast cancer.

New Strategies for Ovarian Cancer Detection

Mitchell Clark, MD, FRCSC. Division of Gynecologic Oncology, Department of Obstetrics, Gynecology, and Reproductive Sciences, Yale University School of Medicine, New Haven, CT

Ovarian cancer continues to account for the greatest proportion of gynecologic cancer related morbidity and mortality despite its relatively lower prevalence compared to other pelvic malignancies. The overall poor outcomes are typically related to lack of effective screening and delays in diagnosis related to non-specific symptoms at early-stage disease. This talk will seek to address the current standards in work up and diagnosis of the most common types of ovarian cancer while addressing the current limitations in screening based on the available large trials completed both in the U.S and other countries. Unfortunately, despite multiple types of assays, combinations of ultrasound and serum biomarkers and panel testing, results remain disappointing for an effective screening tool. Until a test is developed, identifying women at the highest risk based on personal and family history is critical in improving survival. We will discuss strategies to triage women into low and high-risk categories and how genetic testing can guide counseling regarding risk reducing strategies for those women at the highest risk. Significant ongoing research is being conducted to address gaps in our understanding of how to develop safe and effective screening and we will discuss the current state of research ongoing to address this need.

Colorectal Cancer Screening in 2023

Cynthia M. Yoshida, MD, AGAF. Division of Gastroenterology and Hepatology, University of Virginia Health System, Charlottesville, VA

Colorectal cancer (CRC) is highly preventable with screening, yet nearly one-third of screen-eligible Americans are unscreened. It is estimated that over half of this year's projected 52,550 CRC related deaths in our country can be attributed to missed screening opportunities. The American Cancer Society National Colorectal Cancer Roundtable set a goal to reach 80% (or more) screened in every community and to eliminate barriers to screening. CRC screening rates vary by geography with the highest rates in the northeastern US and lowest rates in the west. And there are many disparities with CRC screening rates lowest among American Indian/Alaska Natives, those with less than a high school education or who lack health insurance, and among recent immigrants. Screening options recommended by the U.S. Preventive Services Task Force (USPSTF) include annual fecal immunohistochemical test (FIT) or high-sensitivity guaiac fecal occult blood test (gFOBT); multi-target stool DNA test (mt-sDNA) every three years; CT colonography (CTC) every five years; flexible sigmoidoscopy (FS) every five years; or colonoscopy screening every ten years. There are no head-to-head randomized controlled trials to demonstrate that any test is superior in lowering CRC incidence or mortality thus the USPSTF does not provide a tiered or ranked list of screening strategies. All of these screening options can be utilized by average risk adults, however people with a high risk for colorectal cancer (eg, those with a personal or family history of CRC or advanced polyps, a family history of a genetic syndrome linked to CRC, or a history of inflammatory bowel disease) should be screened with colonoscopy. FIT/gFOBT, mt-sDNA, CTC and FS are all 'two step screening tests' – a positive result requires a follow-up colonoscopy for screening benefits to be achieved. Stool-based tests (FIT and mt-sDNA) are to be used for average-risk CRC screening; providers should avoid inappropriate use (eg, for blood in stool or in lieu of colonoscopy in patients with a history of polyps). Using shared decision making and offering screening options allows patients to determine which test is feasible/preferable and increases the likelihood that the screening test will be completed. The 2021 USPSTF now recommends that CRC screening begin at age 45 (B recommendation). Only 20% of 45-49 year olds are up-to-date with CRC screening; twenty million in this age group still need to be screened. Several surveys suggest that younger adults in this age group may prefer non-invasive stool-based testing. The rationale for lowering the screening age to forty-five was in part due to the increasing incidence of early age onset CRC in adults younger than fifty years which accounts for 10% of CRC cases and is projected to more than double by 2030. Data from the American Cancer Society and the National Cancer Institute indicates that young adults born in 1990 are two times more likely to develop colon cancer and four times more likely to develop rectal cancer than those born in 1950. It is imperative that healthcare providers educate the public about this epidemic and to have a low threshold to refer young patients with symptoms (eg, abdominal/back pain, change in bowel habits, blood in stool) for a colonoscopy. 2023 marks a turning point in CRC screening with several new blood-based and novel imaging modalities on the horizon. CRC is the only cancer for which screening has been proven to reduce cancer deaths. If all healthcare providers join the collective mission to increase screening to 80% in our individual 'communities' we can further reduce colorectal cancer cases and deaths.

Cervical Cancer Screening in 2023

Mark H. Einstein, MD, MS, FACS, FACOG[1,2]. [1]Department of Obstetrics, Gynecology, and Reproductive Health, Clinical Research Institute, Rutgers New Jersey Medical School, Newark, NJ; [2]New Jersey Alliance for Clinical and Translational Science, Rutgers Biomedical and Health Sciences, Newark, NJ

Due to an explosion of molecular markers for clinical use for cervical cancer prevention as well as long term cohort studies, there has been a broadly changing landscape of cervical cancer prevention, not only in the US, but across the globe in places that have organized screening programs. As US cervical cancer screening and management guidelines get generated it often leads to different types of workflows for an office and it ultimately leads to different management for the patients. Most of the management changes that have happened over the last 10-15 years have really been to be more precise with picking up those who are at risk for having pre-cancerous disease or worse versus those who are not at risk for having pre-cancerous disease or worse. Nearly all the updated changes have led to less unnecessary colposcopy. Many of these markers are molecular so they are not based on a 'human' read and many of them are agnostic to the hormonal status or menopause status of the patient, unlike cervical cytology. There have also been some disturbing trends of an increasing risk of cervical cancer as women grow older. Recommendations for cervical cancer screening to end at age 65 differs from the disturbing trends of increased cancer incidence in older women. This talk will address some of the nuances and some of the data-driven approaches to the management of cervical cancer screening including issues with postmenopausal patients and why some of the molecular markers that are related and integrated into cervical cancer screening and management are highly relevant to menopausal patients. We will discuss how you as a provider can improve the care of your patients by increasing the surveillance and management of the patients who are most at risk while decreasing unnecessary colposcopy and giving reassurance to those least at risk through following evidence-based guidelines.

PLENARY SYMPOSIUM #1

The Etiology of Medical Misinformation

Jevin D. West, PhD[1,2]. [1]University of Washington, Seattle, WA; [2]Center for An Informed Public, Seattle, WA

The surgeon general declared misinformation a health threat. Throughout the pandemic, false rumors of treatments and vaccine side effects spread widely on social media. Doctors, nurses, and other medical staff are spending more and more of their time in the clinic addressing medical conspiracies. In this talk, I will provide examples of medical misinformation, how we may have got here, and the potential health impacts of this growing problem. I will also discuss potential interventions, with a special focus on the role of medical professionals in reducing the spread of misinformation.

Combating Disinformation in Menopause Care

Monica M. Christmas, MD, FACOG, NCMP. University of Chicago Medicine and Biological Sciences, Chicago, IL

Social media outlets such as Facebook, Instagram, Tik Tok, and Twitter have become a mainstay for people looking for services, healthcare professionals, and medical education. According to Statista, there are 4.9 billion social media users as of April 2023 with the average person visiting seven different sites per month. A survey distributed by the American Osteopathic Association (AOA) on social media usage and sharing of health information found almost half of adults surveyed would like to follow their healthcare providers on social media and felt social media was an appropriate means to contact their providers regarding their personal health concerns. In addition, 32% of those surveyed acknowledged adopting a health-related behavioral change based on information obtained via social media. Approximately 80% of internet users look for guidance on healthcare online. This is alarming because misinformation and miscommunication is often propagated through social media outlets by sensationalizing or misrepresenting research findings, and through self-proclaimed "experts" and lay influencers often motivated by increasing "followers" and monetary gain. Despite the risks, the use of social media to disseminate medical information may have significant benefits when it comes to improving access to care, online support, and promotion of research. The exponential increase in virtual medical communities geared to education and telehealth, along with professional medical organizations and individual health professionals pivoting to a virtual platform illustrates the overwhelming demand from patients. However, protecting patients from disinformation is of utmost importance and requires widespread collaboration from the healthcare community and social media outlets. Interventions geared towards enhancing credibility include requiring disclosure of conflicts of interest, verification of source credibility, mandate credentials be listed, and fine entities promoting false information. Other studies have found interventions geared toward notifying the public of misinformation are helpful in reducing the spread. This can be done formally through the platform or informally by peers. For example, warnings stating "this tweet may contain misinformation" have been shown to be effective, as well as campaigns encouraging users to refute false and misleading information. Professional organizations, like The Menopause Society, play a major role in disputing falsehoods and broadly sharing evidence-based information. In addition, healthcare professionals should take a more proactive role in directing patients to credible, evidenced-based, peer-reviewed websites. Despite the ubiquitous nature of menopause and potential adverse impact on women, their work, and our society, much is still unknown. Women go to social media in search of answers. It is imperative we help individuals assess the credibility of information and include them in the research process. Ensuring that research is relevant, and patient focused is particularly important for conditions such as menopause, where the aim of care is to empower and support women to manage their own health and minimize the impact of symptoms. Menopause Priority Setting Partnership (MAPS) is a global initiative which will allow those with lived experience of menopause to identify their priority research questions to direct a new, patient-focused research agenda. Their needs, priorities, views, and values will inform the research questions that will be translated into a global research agenda in menopause. Inclusion of women in the research process helps to garner trust and ensures that new research is acceptable and culturally appropriate to the priority population.

Conveying Scientific Information to Menopausal Patients Through Compelling and Understandable Messaging

Susan D. Reed, MD, MPH, MS, NCMP. Department of Obstetrics and Gynecology, University of Washington School of Medicine, Seattle, WA

"Women have been misled about menopause" stated a NYT article published Feb 1, 2023, describing some perimenopausal women's struggles with menopause and the role of hormone therapy in relieving symptoms.[1] Expert opinion suggests that only 25% of patients *seek medical treatment* for VMS (UpToDate, accessed August 2023), and a US online survey of several thousand women in the late transition or early postmenopause showed that only 72% had *ever talked with their provider* about menopause (Healthy Women Survey, personal communication). When asked why women opted not to use MHT or stopped using MHT, over 50% felt that it was too risky. Knowledge disparities exist: Hispanic and Black women had less awareness of menopause treatment options compared to white women. Among postmenopausal women surveyed, other sources of information about menopause included: health information websites (83%), magazines or newspapers (50%), family and friends (45%), books (40%), social media networks (22%), online blogs or message boards (20%). Another large international online survey of patients and their providers showed that among providers, only 65% prescribed treatments for VMS (73% MHT and 31% SSRI/SNRIs), 57% reported they had patients with VMS who were eligible for MHT but were hormone averse; 91% reported MHT was effective.[2] In that study, up to 30% of patients surveyed felt they had contraindications to MHT. How can this be and how did this happen? The answer is complex and the blame cannot be placed on any single constituency. Reasons include: ● Researchers – never trained to speak in a language that the public can understand and until very recently not mandated by federal funding agencies to disseminate their research findings. ● Congress and NIH - federal funding for menopausal research is abysmally low – up to 85% of half the world's population experience bothersome menopausal symptoms, suggesting "a high cultural tolerance for women's suffering. Menopause is not regarded as important."[1] ● Media – alarm and risk are the mantra – the message can become oversimplified and lost, categorizing MHT as "good" or "bad." This can lead to misunderstanding of the truth which is often nuanced.[3] ● Clinicians – not always practicing evidence-based medicine and not reliably providing credible evidence-based bite size messages for our patients. ● Patients – lured in and hooked on the glitter and glitz of social media, confused by the volumes of conflicting misinformation. Let's all join in this call to action. Professional organizations play a major role in disputing falsehoods and disseminating evidence-based information using compelling and understandable language. We must be proactive, guiding patients, colleagues, trainees and the public to trustworthy, evidenced-based, websites. Some examples to consider: ● **The Menopause Society** (*MenoNotes*) https://www.menopause.org/publications/consumer-publications/-i-menonotes-i- ● **NIH** https://www.nia.nih.gov/health/what-menopause, https://medlineplus.gov/menopause.html ● **SWAN** (Menopause FAQs) https://www.swanstudy.org/fact-sheets/ ● **MsFLASH** (Mymenoplan) https://mymenoplan.org/ ● **Endocrine Society** (Menopause Map) https://www.endocrine.org/menopausemap/signs-and-symptoms/index.html ● **Mayo Clinic** https://www.mayoclinic.org/diseases-conditions/menopause/symptoms-causes/syc-20353397 ● **ACOG** (Menopause FAQ) https://www.acog.org/womens-health/faqs/the-menopause-years ● **UpToDate** INFORMATION FOR PATIENTS and society guideline links to The Menopause Society, ES, IMS, ISSWSH, USPSTF https://www.uptodate.com/contents/menopause-beyond-the-basics References 1. https://nytimesineducation.com/women-have-been-misled-about-menopause/ 2. Stute P. Maturitas 2022 Jun 23;164:38-45. Stute P, Cano A, Thurston RC, Small M, Lee L, Scott M, Siddiqui E, Schultz NM. Evaluation of the impact, treatment patterns, and patient and physician perceptions of vasomotor symptoms associated with menopause in Europe and the United States. *Maturitas*. 2022 Oct;164:38-45. doi: 10.1016/j.maturitas.2022.06.008. Epub 2022 Jun 23. Erratum in: *Maturitas*. 2023 Mar;169:55. PMID: 35785563. 3. https://www.whi.org/md/news/nyt-response

PLENARY SYMPOSIUM #2

Lessons From the Study of Estrogen Receptor Pharmacology in Breast Cancer Will Impact the Development of New Menopausal Medicines

Donald P. McDonnell, PhD. Department of Pharmacology and Cancer Biology, Duke University School of Medicine, Durham, NC

Whereas the debate continues as to beneficial and detrimental effects of estrogens (with or without progestins), when used as hormone therapy in the climacteric patient there remains considerable interest in identifying targetable nodes in the estrogen receptor (ER) signaling pathway(s) that can be exploited in the development of new therapeutics for a wide range of estrogenopathies. Outside of cancer the focus has been on developing Selective Estrogen Receptor Modulators (SERMs), drugs whose ER agonist or antagonist activities are influenced by tissue/cell context, and which can be used to mimic the actions of estrogens in some tissues (e.g., bone and CNS). However, most of the ER modulator discovery efforts of late have been in the realm of breast cancer and are focused primarily on the development of Selective Estrogen Receptor Downregulators (SERDs) with the goal of eliminating ER expression within cancer cells to achieve absolute inhibition of estrogen signaling. Workfrom our group has resulted in the identification of the first clinically useful oral SERD, etacstil, a drug which established the utility of eliminating ER expression as a therapeutic approach in patients with metastatic breast cancer (MBC). Whereas the development of this drug was discontinued, it encouraged others to adopt this therapeutic approach. The SERM/SERD hybrid elacestrant emerged from discovery efforts in our laboratory and was recently approved for the treatment of MBC. We also repurposed the SERM lasofoxifene as a treatment for breast cancer and it is demonstrating considerable efficacy in patients whose metastatic tumors express activating ER (ESR1) mutations. Notwithstanding these successes, it is surprising that the majority of SERDs and SERMs that have been evaluated in the setting of MBC, even those which exhibited considerable efficacy in preclinical models of breast cancer, have failed to achieve their clinical endpoints. This, we interpret as highlighting deficiencies in the animal models of MBC and to an incomplete understanding of how modulation of ER action impacts tumor pathobiology. We do have a clear understanding of the biochemical mechanisms that enable ER within specific cells to distinguish between SERDs and SERMs. Specifically, it has been determined that subtle differences in the structure of ligands can result in significant changes in the surface topography of ER, which enables the differential presentation of protein-protein interaction surfaces to engage functionally distinct coregulator proteins to achieve different phenotypic outputs. What has been overlooked is how the actions of ER-ligand complexes in different cells combine to determine the overall pharmacological output of a drug. This puts in context the results of our recent work in animal models of breast cancer which has revealed that the anti-tumor efficacy of ER modulators is determined in large part by their cancer cell extrinsic actions. Notably we have identified important roles for ER signaling in regulating the activity of macrophages, NK cells, eosinophils, and dendritic cells, most of which are regulated differentially by different SERMs and SERDs. We have also made the surprising finding that modulating ER action in the brain impacts the pharmacology of ER ligands in orthotopically implanted tumors in animal models. Thus, SERM/SERD efficacy is influenced by the extent to which these drugs cross the blood brain barrier and by their relative agonist/antagonist/degrader activity in the brain. The importance of ER action in immune cells and in the brain and how they impact the overall pharmacology of SERMs and SERDs will be discussed as will be how this information will inform the discovery of the next generation of ER modulators for cancer and hormone therapy.

Tissue Selective Estrogen Complexes (TSECs) in Clinical Practice: An Update

Hugh S. Taylor, MD. Department of Obstetrics, Gynecology, and Reproductive Sciences, Yale School of Medicine, New Haven, CT

The use of estrogens and progestins have long dominated menopausal hormone therapy (MHT). The risk of breast cancer has been the major factor limiting patient acceptance of MHT. Recent advances have strived to eliminate that risk even in the presence of a uterus. Instead of use of a progestin, selective estrogen receptor modulators (SERMs) have been combined with an estrogen to create the TSEC. Importantly SERMS offer far more tissue specificity than estrogens and can counteract estrogens in some tissues. These combinations allow for the benefits of estrogens where needed, ie, for control of vasomotor symptoms (VMS), vaginal atrophy and bone loss with the potential for mitigating some risks. The TSEC containing conjugated equine estrogens (CE) with bazedoxifene (BZA) has recently been reintroduced. BZA/CE is effective in relieving hot flashes as well as preventing loss of bone. BZA/CE also improves lipid parameters and induces a higher rate of amenorrhea than placebo in menopausal women. Importantly, BZA/CE does not have stimulatory effects on breast as demonstrated by no change in mammographic density. Similarly, this combination has a much more favorable effect on breast cancer cells in vitro and in mouse models of breast cancer. TSECs may provide a better way to administer estrogens without some of the deleterious effects of estrogen/progestin combinations.

PLENARY SYMPOSIUM #3

Precision Osteoporosis Treatment for Postmenopausal Women

E M. Lewiecki, MD, FACP, FACE. New Mexico Clinical Research & Osteoporosis Center, Albuquerque, NM

Osteoporosis is a lifelong progressive systemic skeletal disease characterized by low bone density and poor bone quality, resulting in low bone strength and increased risk of fracture. The treatment of osteoporosis should consider factors that include the patient's age, bone density, fracture risk, and personal preference. Universal recommendations are for healthy lifestyle, good nutrition, adequate intake of calcium and vitamin D, and avoidance of falls. Pharmacological therapy to reduce fracture risk is indicated for patients at high risk of fracture, with more aggressive treatment advised for patients at higher risk of fracture. All patients should be evaluated for factors contributing to skeletal fragility and fall risk, with interventions to address risk factors that are identified. Although most patients with osteoporosis are not currently being recognized or treated, and any treatment is better than none, the NAMS 2021 position statement on the management of osteoporosis in postmenopausal women provides guidance on choosing initial treatment. For women at moderate fracture risk, consider treatment with raloxifene or a bisphosphonate (alendronate, risedronate, ibandronate, or zoledronate); for high fracture risk, consider a bisphosphonate or denosumab, and for very high fracture risk, consider an anabolic agent (teriparatide, abaloparatide, or romosozumab). Each of these medications has its own provide of expected benefits and possible risks that must be understood by the healthcare provider and the patient. An example of moderate risk is a 62-year-old woman with lumbar spine T-score -2.6 and no other risk factors. A 68-year-old woman with femoral neck T-score -2.8, mother with a hip fracture, and personal history of a wrist fracture at age 60 years would be considered at high risk. An example of very high risk is a 72-year-old woman with femoral neck T-score -3.0, humerus fracture at age 68 years, and two recent vertebral fractures. Having a recent fracture greatly increases the risk of subsequent fractures in the following 1-2 years ("imminent fracture risk"), so that initiation of treatment with a robust therapeutic agent that will produce a rapid improvement in bone strength is urgently indicated. Head-to-head clinical trials in high-risk patients have shown that anabolic drugs reduce fracture risk more than bisphosphonates. The sequence of therapy is important, with anabolic therapy followed by and antiresorptive medication being associated with a great increase in bone density

than anabolic therapy started after antiresorptive. A "real world" study of US Medicare claims data has found that patients treated with denosumab have fewer fractures than those treated with alendronate. Recent meta-regression studies have clearly shown that larger increases in bone density in clinical trials with a broad range of medications are associated with greater reduction idea that the goal of treatment is achievement of an acceptable level of fracture risk and that treatment that is mostly likely to achieve that goal is best suited for initial therapy. Response to therapy is necessary but not always sufficient in reaching that goal. For patients started on treatment because of a T-score equal to or less than -2.5, a T-score greater than -2.5 may be an appropriate treatment target, with greater increases better than smaller one. For one drug, denosumab, reaching a T-score of -1.5 or better has been associated with greatest reduction of fracture risk. The treatment target that appears to have the greatest clinical target for Final treatment decisions must be individualized.

Bone Quality: What Is It and How to Measure It

Marcella D. Walker, MD. Medicine, Division of Endocrinology, Columbia University Irving Medical Center, New York, NY

Osteoporosis is characterized by low bone mineral density (BMD) and deteriorated bone microarchitecture, which predisposes to fragility fractures. Fragility fractures occur with no trauma or trauma equivalent to a fall from a standing height or less. Whether a bone fractures, is related in part to its strength or resistance to fracture when a force is applied. The majority of the bone's strength, 60-75%, is accounted for by bone mass. Dual energy x-ray absorptiometry or DXA is the gold standard for assessing bone mass and evaluating fracture risk. BMD measured by DXA powerfully predicts risk of future fracture. For each standard deviation decrease in BMD, there is a two-to-three-fold increased risk of fracture. Osteoporosis is defined, densitometrically, as a BMD less than or equal to 2.5 standard deviations below the mean of a young adult reference population (T-score). DXA has many advantages. It is widely available, inexpensive, can be acquired quickly, and associated with low radiation exposure. Yet, it is widely recognized that most women who sustain fragility fractures do not have osteoporosis, but rather have low BMD defined by T-scores of -1.1 to -2.4. This relates, in part, to osteopenia being more common than osteoporosis. Additionally, other aspects of bone quality, other than BMD, are independently associated with fracture. These include the bone's microstructure (internal trabecular network and cortex), bone remodeling (rates of bone formation and resorption), matrix properties (collagen cross linking, mineral to matrix ratio, etc.), bone size and geometry, and microdamage (small cracks) among others. Traditionally, invasive tetracycline-labeled iliac crest bone biopsy was required to analyze these aspects of bone quality. However, recent advances have led to the ability to measure some indices of bone quality non- or minimally invasively. These include vertebral fracture assessment (VFA), the trabecular bone score (TBS), high resolution peripheral quantitative computed tomography (HRpQCT), bone turnover markers (BTMs) and impact microindentation (IMI) among others. VFA, a low radiation lateral spine film that can be obtained on a densitometer, detects silent spine fractures. Such fractures if atraumatic are diagnostic of osteoporosis and associated with the development of future fractures. TBS, an indirect measure of spine trabecular microarchitecture obtained from the DXA spine image, predicts fracture independently of BMD. It was FDA-approved in 2012 as an adjunct to BMD measurement for fracture risk stratification. HRpQCT, while not FDA-approved, provides assessment of the bone's internal microstructure non-invasively with a resolution of ~60 microns. Bioengineering techniques applied to images provide integrative measures of bone strength, which may be more strongly associated with incident fractures than BMD obtained by DXA. BTMs refer to collagen breakdown products and other molecules released from bone cells during bone formation and resorption. They provide insight into bone remodeling and predict rates of bone loss and fracture, but substantial variability limits their clinical use. IMI measures the distance a probe extends into the tibial bone cortex. It correlates with the bone's ability to resist development of cracks. IMI was FDA-approved in 2021. The exact significance of this measure and its application in the clinical setting is unclear, but some data suggest it provides information independent of BMD and is associated with fracture. These technologies have been applied in the research setting to better understand clinical conundrums such as the increased risk of fracture in patients with type 2 diabetes mellitus (T2DM). Such technologies indicate that while patients with T2DM tend to have high BMD measured by DXA compared to those without T2DM, measures of bone quality show increased cortical porosity, low bone turnover, low TBS and low bone material strength measured by IMI. These impairments may explain high rates of fractures in patients with T2DM. Clinical evaluation of skeletal health should utilize several measurements of bone quality including BMD by DXA, TBS in those with osteopenia and VFA or spine imaging to evaluate for vertebral fractures in those in whom their presence would change management.

PLENARY SYMPOSIUM #4

Menopause 201: Management of Women with Complex Medical Conditions

Cynthia A. Stuenkel, MD, NCMP. UC San Diego School of Medicine, La Jolla, CA

Of the myriad complex medical conditions that present in postmenopausal women, one of the most challenging as a factor in selecting treatment for menopausal symptoms is a history of cardiovascular disease (CVD), which includes coronary artery disease, myocardial infarction, stroke, and venous thromboembolic disease. Furthermore, screening tests increasingly utilized in those considered for primary prevention can reveal an elevated coronary artery calcium (CAC) score, associated with mortality rates equivalent to those individuals with stable secondary prevention-level risk. From a population standpoint, rates of CVD are increasing in the premenopausal population, so the number of women approaching menopause with a positive CVD history or elevated risk will also be increasing. Finally, the prevalence of congestive heart failure is on the rise. From a safety standpoint, the Food and Drug Administration labeling considers CVD to be an absolute contraindication to menopausal hormone therapy (MHT). Current consensus MHT treatment recommendations advise that women with a calculated 10-year risk $\geq$ 10% should also avoid systemic MHT. Awareness of the considerable evidence regarding the relative and absolute risks of increased CVD outcomes in clinical trials of MHT in women with a history of CVD underscores these recommendations. Fortunately, a growing list of pharmacological agents have been approved for treatment of vasomotor symptoms. Techniques such as cognitive behavioral therapy and hypnosis can also be effective. In the unlikely event that a woman remains unacceptably symptomatic with a substantial negative impact on quality of life in spite of these therapeutic options, it would be appropriate to first rule out other conditions that might mimic vasomotor symptoms. Considerations for additional treatment options could then be discussed.

Premature Menopause

Ekta Kapoor, MBBS, FACP, MSCP. Mayo Clinic, Rochester, MN

Natural menopause occurs at the mean age of 52 years. Loss of ovarian follicular activity (spontaneously or induced) before the age of 40 years resulting in permanent cessation of menses constitutes premature menopause. It results in loss of fertility and premature deficiency of female reproductive hormones, particularly estrogen. In addition to causing symptoms, the premature estrogen loss increases risk for osteoporosis, cardiovascular disease, and cognitive decline in affected women. The prevalence rate is estimated to be about 3%, with potentially higher rates in regions with a low Human Development Index. The premature loss of ovarian follicles may be iatrogenic or spontaneous (mediated by genetic factors, autoimmunity, and in rare cases, toxic environmental exposures, or infections). Iatrogenic causes include pelvic surgery (bilateral oophorectomy, ovarian cystectomy, and hysterectomy), pelvic radiation, and chemotherapy (extent of gonadotoxicity determined by the agent, dose, duration of use, and pre-existing ovarian reserve). Women typically present with primary or secondary amenorrhea, infertility, or a combination. They may also present with menopause symptoms—hot flashes, sleep disturbances, mood changes, anxiety, and cognitive complaints. Premature menopause can be a devastating diagnosis with a profound psychological impact in young women, particularly if fertility is desired. The women with spontaneous premature menopause require a thorough history and physical examination and laboratory evaluation for establishing the diagnosis and ascertaining the etiology of menopause. Initial laboratory testing includes a serum pregnancy test, follicle-stimulating hormone (FSH), thyroid-stimulating hormone (TSH), and prolactin levels. If FSH level is elevated, testing should be repeated in 4 to 6 weeks. A persistently elevated FSH more than 40 IU/L confirms the diagnosis of ovarian insufficiency, although some guidelines use lower thresholds of 30 IU/L or 25 IU/L. Genetic testing should be offered to all women, particularly those with a family history of ovarian insufficiency and those aged younger than 30 years at the time of onset of symptoms. It is recommended to screen for the common autoimmune associations, particularly adrenal insufficiency, Hashimoto's thyroiditis, and type 1 diabetes. Ovarian antibody testing is not indicated because of poor sensitivity and specificity. The goals of management include counseling and psychological support, hormone replacement therapy (HRT), symptom control, assistance with fertility if desired, and reduction in long-term health risks. Patients who desire childbearing should be referred to a reproductive endocrinologist. Unless a true contraindication exists, estrogen replacement is recommended for restoration of the hormonal milieu to that of a premenopausal woman, even in the absence of symptoms of estrogen deficiency. Despite strong observational evidence demonstrating benefit on long-term bone and cardiovascular health outcomes in women with premature menopause, HRT is underutilized because of fear of adverse effects based on the clinical trials findings in women after natural menopause. However, the risks of hormone therapy use in women after natural menopause are not applicable and should not be extrapolated to these young women. Randomized, controlled trial data informing HRT decision-making in premature menopause are sparse, and specific consensus guidelines are lacking, but experts recommend use of HRT at least until the age of natural menopause (with the possibility of longer use as dictated by symptoms and risk-benefit considerations) and use of higher doses of estrogen to approximate premenopause hormone levels (estradiol patch delivering 100 μg/d or oral estradiol 2 mg/d or equivalent doses of other forms of estrogen). Long-term studies on the appropriate progestogen regimen for endometrial protection in women on high doses of estrogen are not available, but the general principle is to use higher doses of progestogens (≥200 mg of micronized progesterone or equivalent doses of other progestogens). Testosterone therapy may be a consideration in those with hypoactive sexual desire disorder, particularly after bilateral oophorectomy. All women should receive counseling regarding adherence to healthy lifestyle choices for cardiovascular risk reduction.

Genitourinary Syndrome of Menopause in Breast Cancer Survivors

Tami Rowen, MD, MS. Obstetrics, Gynecology, and Gynecologic Surgery, University of California San Francisco School of Medicine, San Francisco, CA

The most recent data from the United States shows that over 230,000 cases of breast cancer were diagnosed in 2020 and over 40,000 died, these numbers are projected to increase based on current trends. The data looks far worse for black non-Hispanic women, who have a 25% increased mortality rate, with higher risk disease developing at younger ages. Currently there are over 4 million people living with a history of breast cancer. Genitourinary syndrome of menopause (GSM) is very common amongst all women and those assigned female at birth who have a history of breast cancer. GSM is highly influenced by age at diagnosis and treatment types. When treating GSM it's important to keep in mind that it causes more than just sexual problems, it can cause

urinary frequency and infections and vaginal bleeding. Long-term treatment with aromatase inhibitors worsens the problem in women who have hormone positive breast cancer and will already be in menopause. Treatment for GSM involves local lubricant, moisturizers, and hormones. Each of these products has a different goal in terms of sexual activity, comfort, and long-term vulvovaginal health. For moisturizers and lubricants, it's important to note that there is no requirement that they match the pH and osmolality of the natural vagina, and thus all products are not equal. Most patients are willing to try lubricant and moisturizers but are far more concerned about hormones, which are most effective in improving overall vulvovaginal health, but of most concern for those with a hormone sensitive cancer. There have been numerous studies that have raised controversy over both the efficacy of vaginal hormones as well as whether local hormones cause significant increase in systemic estradiol. These studies have been challenged by their short-term data points as well as laboratory variation in measurement of systemic estradiol. Other data suggests that the greatest risk of elevated systemic estradiol levels occurs for women on aromatase inhibitors. The Menopause Society has published comprehensive guidelines on the management of GSM in hormone sensitive breast cancer survivors and those at high risk of breast cancer. The key points of the paper are that there is no data that looks at the main outcome of interest, that is the recurrence of breast cancer. Most data are on systemic levels on estradiol and symptomatic relief of GSM. Women with lower risk disease are the safest to consider topical hormone therapy, and this also includes those on aromatase inhibitors. The safest formulations are vaginal tablets and the ring, and there may be a role for local prasterone. Many patients also ask about vaginal lasers, but the newest data has shown that there is no benefit to lasers over placebo. Most importantly, it's critical to understand the oncology literature and guidance and for all providers to work with a patient's oncologist in coming p with an appropriate treatment plan for GSM treatment.

PLENARY SYMPOSIUM #5

Updates in the Management of Hypertension and Dyslipidemia in Midlife Women

Beth L. Abramson, MD, MSc, FRCPC, FACC[1,2]. [1]Medicine, University of Toronto, Toronto, ON, Canada; [2]Division of Cardiology, St. Michael's Hospital, Toronto, ON, Canada

Cardiovascular (CV) disease remains a leading cause of death and disability in postmenopausal women. A woman's CV risk increases after menopause. Women with premature menopause (<40y) have increased risk of CV events. In women <age 40, estrogen withdrawal, leads to changes in body fat distribution, reduced glucose tolerance, abnormal lipids, higher blood pressure (BP), increased sympathetic tone, endothelial dysfunction, and vascular inflammation. CV risk factors such as hypertension and dyslipidemia become more pronounced after menopause and can lead to ischemic heart disease (IHD), stroke, and heart failure (HF). MHT (menopausal hormone therapy) is an important treatment for women who suffer menopause symptoms, but there is no evidence for primary or secondary prevention of all-cause mortality, CVD, non-fatal myocardial infarction, angina, or revascularization. In general, MHT is safe for short-term use in terms of CVD risk – meaning about 5 years. The Women's Health Initiative found that women who used MHT for an average of 5-1/2 years did not have increased CVD events over 18 years of follow-up. A Cochrane review found that MHT initiated within 10 years of menopause lowered coronary heart disease in postmenopausal women. In addition, it found there was a reduction in all-cause mortality and no increased risk of stroke. However, there was an increased risk of venous thromboembolism. Therefore, other means of managing CV risk are needed in our female patients. Aggressive identification and modification of risk factors, with diet and exercise and in some women medication, is still the most effective means of reducing CVD risk. The elimination of hypertension could lead to a ~ 40% reduction in CVD mortality in women. It is estimated that women without hypertension live approximately 5 years longer than those with hypertension. Hypertension prevalence progressively increases with age, reaching about 56% for those aged 55 to 64 years. Specifically, 65% of women aged 65 to 74 years and 81% of women aged 75 years and older have hypertension. Women should be screened at all appropriate clinical visits to assess CV risk or response to treatment. BP greater than 130/80 mm Hg on two or more readings over two or more occasions confirms a diagnosis of hypertension. Accurate measurement of BP is essential to establishing a diagnosis. Nonpharmacologic therapies can reduce BP and may result in 5 mm Hg to 10 mm Hg improvement. Proven strategies include weight loss in patients with hypertension who are overweight or obese (estimated 1 mm Hg reduction for each 1 kg weight loss), sodium reduction (goal, <1,500 mg/d), increased potassium intake, increased physical activity (goal, 150 min/wk of moderate-level exertion), and moderation of alcohol intake with one or fewer drinks daily recommended for women. In order to reduce future risk of hypertension in specific groups of women at higher risk, focused intervention aimed at weight loss after gain in pregnancy and in those with obesity at midlife should be instituted. Sex differences exist in pharmacokinetic and pharmacodynamic properties of antihypertensive medications but do not appear to alter therapeutic response. First-line therapy as dictated in current guidelines for management of hypertension in adults is advised. Lipid lowing therapies are also proven effective in women to reduce CV events. This needs to be reinforced, given patient concerns from reading noncredible sources and lay literature which can lead to non-evidence-based decision making. Clinical trials included women to show that statins, in addition to PCSK=9 I, and IPE, are effective in lowering long term CV risk with minimal side effect profile. The HOPE-3 trial showed that low-dose statin therapy, is superior to placebo in reducing long-term CV events in an intermediate-risk population, which included women over 60 with 2 risk factors, and women over 65 with one risk factor. Assessment and management of CV risk factors are crucial in the care of our female patients, at midlife and beyond. Evidence based and guideline directed therapy is available and should be reinforced reduce death and disability in women.

The Skinny on Weight Management in Midlife

Maria D. Hurtado, MD, PhD[1,2]. [1]Division of Endocrinology, Diabetes, Metabolism, and Nutrition, Department of Medicine, Mayo Clinic, Jacksonville, FL; [2]Precision Medicine for Obesity Program, Division of Gastroenterology and Hepatology, Department of Medicine, Mayo Clinic, Rochester, MN

Weight gain in midlife women is a common occurrence that predisposes them to develop overweight or obesity. Weight gain is the result of changes related to aging, menopause, and lifestyle. On one hand, aging is associated with decreased energy expenditure and physical activity, two important culprits for weight gain, even in the setting of stable dietary habits. On the other hand, the hormonal changes of menopause, characterized by decreased estrogen levels, influence body adiposity distribution and contribute to increased central adiposity. Weight gain and changes in body fat distribution have negative health ramifications such as the development of cardiometabolic diseases, mechanical complications, cancer, changes in cognition and mental health, and worsening menopause symptoms. In clinical practice, efforts should focus on early counseling and anticipatory guidance on the importance of dietary changes and physical activity to mitigate weight gain during midlife. While counseling women on weight loss has favorable weight outcomes with minimal adverse events, currently, there is a lack of specific recommendations on interventions in midlife women. Weight management in midlife women should not be different than in the general population. Comprehensive lifestyle interventions remain the backbone of any treatment plan for weight gain prevention or weight loss, and should include medical nutrition therapy, exercise, and behavioral interventions. For midlife women, there are special considerations in relation to macronutrient dietary content and the type of exercise. While effective, lifestyle modification-induced weight loss is often followed by weight regain due to compensatory changes in appetite and energy expenditure. Therefore, in many cases, anti-obesity medications and/or surgical interventions are considered in conjunction with lifestyle changes.

Reproductive Risk Factors for Cardiovascular Disease in Women

Michael Honigberg, MD, MPP, FACC[1,2]. [1]Cardiology Division, Department of Medicine, Massachusetts General Hospital, Boston, MA; [2]Broad Institute of MIT and Harvard, Cambridge, MA

Beyond conventional risk factors for cardiovascular disease, women face an added burden of sex-specific risk factors. Key stages of a woman's reproductive history may influence or reveal short- and long-term cardiometabolic and cardiovascular trajectories. Early and late menarche, polycystic ovary syndrome, menstrual irregularity, infertility, adverse pregnancy outcomes (e.g., hypertensive disorders of pregnancy [preeclampsia, gestational hypertension], gestational diabetes, preterm delivery), and absence of breastfeeding are all associated with increased future cardiovascular disease risk. Recent data indicate shared genetic architecture between the hypertensive disorders of pregnancy and cardiovascular disease, partly explaining the excess cardiovascular risk observed in affected women across the life course. In addition, the menopause transition represents a period of accelerated cardiovascular disease risk, with timing (e.g., premature menopause), mechanism, and symptoms of menopause, as well as treatment of menopause symptoms, each contributing to this risk. Heightened cardiovascular disease risk associated with premature age of menopause extends to a diverse set of cardiovascular conditions (e.g., coronary artery disease, ischemic stroke, heart failure, atrial fibrillation, and aortic valve stenosis) and does not appear to be fully explained by postmenopausal sex hormone deficiency. Differences in conventional cardiovascular disease risk factors (e.g., hypertension, hypercholesterolemia, diabetes) explain some, but not all, of the observed associations between reproductive history and later-life cardiovascular disease; further research is needed to elucidate unique sex-specific disease mechanisms toward improved prediction, prevention, and treatment. History of adverse pregnancy outcomes and premature age of menopause are now incorporated in multi-society guidelines as "risk-enhancing factors" to refine risk assessment for coronary heart disease and stroke and guide allocation of primary prevention statin therapy. Overall, a history of reproductive risk factors represents an opportunity for comprehensive risk factor screening, refinement of cardiovascular disease risk assessment, and implementation of primordial and primary prevention to optimize long-term cardiometabolic health in women.

PLENARY SYMPOSIUM #6

2023 Nonhormone Therapy Position Statement

Chrisandra L. Shufelt, MD, MS, FACP, MSCP. Division of General Internal of Medicine, Women's Health Research Center, Mayo Clinic, Jacksonville, FL

While menopause hormone therapy remains the most effective treatment for vasomotor symptoms and should be considered in women at or around the time of menopause without contraindications, some women may not choose to or not be candidates for hormone therapy. Healthcare providers need to be aware of the nonhormone options for vasomotor symptoms that are supported by science. The current evidence-based clinical recommendations of nonhormone options were published by The Menopause Society in its 2023 Nonhormone Therapy Position Statement. This statement was updated from the 2015 position statement, and recommended treatments include cognitive-behavioral therapy, clinical hypnosis, selective serotonin reuptake inhibitors/serotonin-norepinephrine reuptake inhibitors, gabapentin, oxybutynin, weight loss, stellate ganglion block, and the new, first-in-class FDA-approved medication, fezolinetant. Therapies that were not recommended for the treatment of vasomotor symptoms included the use of

paced respiration, supplements/herbal remedies, cooling techniques, avoiding triggers, exercise, yoga, mindfulness-based intervention, relaxation, suvorexant, soy products, cannabinoids, acupuncture, calibration of neural oscillations, chiropractic interventions, clonidine, dietary modification, and pregabalin. These evidence-based recommendations ensure personalized and individualized care options alongside continued shared decision-making for the patient.

Neural Pathways of NK3R Inhibition in Vasomotor Symptoms

Victor M. Navarro, PhD. Harvard Medical School; Brigham and Women's Hospital; Harvard Graduate Program in Neuroscience, Boston, MA

Kiss1 neurons of the arcuate nucleus, also termed KNDy neurons because they co-express kisspeptin, neurkinin B (NKB) and dynorphin A (Dyn), have been implicated in the control of pulsatile GnRH release and the onset of vasomotor symptoms (VMS), aka hot flushes. The autosynaptic release of the excitatory NKB and the inhibitory Dyn on KNDy neurons leads to the pulsatile release of kisspeptin onto GnRH neurons, which is mirrored by GnRH pulses. This mechanism is enhanced in the absence of circulating sex steroids, leading to the increase in frequency and amplitude of LH pulses. Coincidentally, the onset of hot flushes occurs as circulating sex steroid levels decrease, *e.g.* during menopause. Recent studies have demonstrated that when KNDy neurons become hyperactive during natural or surgical menopause, they release NKB onto NKB receptor (NK3R) expressing neurons of the medial preoptic area (MnPOA), thus inducing a hot flush that often coincides with a pulse of LH. However, the whole mechanism underlying this effect remains to be elucidated. This finding has led to the development of pharmaceutical approaches to target KNDy neurons and either prevent their activation (using NK3R antagonists) or induce their inhibition (using peripherally restricted Kappa agonists), thus leading to the development of the first effective non-steroidal treatments to reduce hot flushes, which has enormous clinical implications. Preliminary data from our lab is offering new insights into additional populations of NK3R-expressing neurons regulating hot flushes and the cellular and molecular mechanisms participating in the role of KNDy neurons in thermoregulation both in humans and rodent models.

PLENARY SYMPOSIUM #7

Skin Changes in Aging

Ellen Gendler, MD. NYU Langone Medical Center, New York, NY

Women become aware of changes in their skin as they approach menopause, and these frequently become more profound once menopause has begun. These skin changes are of concern to many women, and we need to be honest and realistic with our patients about achieving their skin goals. It is incumbent on those of us who provide healthcare to women to address these issues as early as possible, even before menopause, in order to stave off some of the unpleasantness associated with aging skin. I will review the physiology of the skin aging process and discuss important ways to address the changes, both topically and procedurally, giving an honest and informative session on what we can do to help women maintain healthy and beautiful skin as they age.

Rheumatologic and Musculoskeletal Issues at Midlife

Lisa A. Mandl, MD, MPH. Weill Cornell Medical College, New York, NY

Musculoskeletal pain is common among women at midlife. It is reported in > 50% of women at menopause, and pain is the primary complaint in over 20%. However, musculoskeletal pain should not be dismissed as "normal ageing;" it is important to make a diagnosis, as many treatable rheumatic and musculoskeletal conditions commonly present in this age cohort. In addition, midlife is a time when interventions can be made to slow the progression of osteoarthritis, the most common joint disease in the world and a leading cause of disability. This talk will highlight some of the musculoskeletal and rheumatic conditions which impact women in their 40s-60s, provide flags for diagnosis, and review evidence based therapeutic approaches.

PLENARY SYMPOSIUM #8

Breast Cancer Risk Estimation and Risk-based Screening

Karla Kerlikowske, MD. Department of Veterans Affairs and Departments of Medicine and Epidemiology and Biostatstics, University of California San Francisco, San Francisco, CA

Introduction Breast cancer risk estimation and risk-based breast cancer screening strategies are guided by the population being evaluated, proposed intervention, and outcome trying to prevent. Five-year invasive breast cancer risk is used to identify women in a general population at higher risk than women their same age and race/ethnicity to consider screening at a younger age and/or offer primary prevention. Advanced cancer (prognostic pathologic stage IIA or higher) occurs in about 22% of routinely screened women diagnosed with breast cancer, with advanced cancer rates more than 2-fold greater in Black compared to White women. Identifying women at increased advanced cancer risk and providing them with targeted screening strategies could improve the effectiveness of breast imaging services and reduce breast cancer mortality. Calculating six-year cumulative advanced cancer risk can inform the most effective screening interval and whether supplemental imaging should be considered. Knowledge of personal and clinical risk factors associated with invasive and advanced cancer informs risk prediction and primary prevention. **Objectives** To describe the Breast Cancer Surveillance Consortium (BCSC) v3 5-year invasive breast cancer risk prediction model and the cumulative 6-year advanced breast cancer risk prediction model and their applications in risk-based screening and primary prevention. **Methods** The BCSC (https://www.bcsc-research.org/) is a cohort of women undergoing breast imaging in seven breast imaging registries across the United States. Women in the BCSC undergoing mammography were used to create and validate the BCSC 5-year invasive cancer risk calculator (https://tools.bcsc-scc.org/BC5yearRisk/)[1] and 6-year cumulative advanced cancer risk model (https://tools.bcsc-scc.org/AdvBC6yearRisk/).[2] Advanced cancer is defined as American Joint Commission on Cancer prognostic pathologic stage IIA or higher because it most accurately predicts breast cancer death.[3] **Results** Will present: Goals of risk-based breast cancer screening Types of breast cancer risk models Risk factors for invasive cancer and advanced breast cancer Risk prediction for deciding when to start screening and initiate primary prevention Risk prediction for deciding screening interval and supplemental imaging Reducing breast cancer risk factors with a high population attributable risk **Summary** Heterogeneously or extremely dense breasts and overweight/obesity are the strongest and most prevalent clinical risk factors for invasive and advanced breast cancer among routine screeners, with prevalence of risk factors varying by race and ethnicity. Calculating 5-year invasive breast cancer risk can guide when to start screening and initiate primary prevention with selective estrogen receptor modulators or aromatase inhibitors. Calculating advanced breast cancer risk can guide patient/provider discussions on screening interval and supplemental imaging among women undergoing routine screening. Women at low/average risk of advanced breast cancer may undergo biennial screening mammography while those at intermediate or high advanced cancer risk may consider annual screening with or without supplemental imaging. Risk factor reduction should focus on shifting overweight and obese women to normal weight to reduce invasive and advanced breast cancer risk. **References** 1. Gard CC, Tice JA, Miglioretti DL, et al. Extending the Breast Cancer Surveillance Consortium model of invasive breast cancer. *J Clin Oncol*, under review. 2. Kerlikowske K, Chen S, Golmakani MK, et al. Cumulative advanced breast cancer risk prediction model developed in a screening mammography population. *J Natl Cancer Inst.* 2022;114(5):676-685. 3. Kerlikowske K, Bissell MCS, Sprague BL, et al. Advanced breast cancer definitions by staging system examined in the Breast Cancer Surveillance Consortium. *J Natl Cancer Inst.* 2021;113(7):909-916.

Exogenous Hormones and the High-Risk Patient

Holly J. Pederson, MD, MSCP. Medical Breast Services, Cleveland Clinic, Cleveland Clinic Lerner College of Medicine, Cleveland, OH

Addressing the hormonal needs of individuals at increased risk of breast cancer can be a challenge. Observational, prospective, and case-control data support the safety of hormonal contraception in women, often with the added benefits of ovarian and endometrial cancer risk-reduction. Most data on menopausal hormone therapy (HT) in the highest-risk patients comes from studies of patients with pathogenic variants in *BRCA1* and *BRCA2* who undergo early surgical menopause. The benefits of risk-reducing salpingo-oophorectomy are not minimized by HT, while its use mitigates accelerated osteoporosis and cardiovascular disease. In other patients at increased risk, such as with family history, studies in patients on HT have shown little risk with significant benefits. The concern regarding exogenous hormone exposure is understandable. Estrogens have been shown to promote the development of mammary cancer in animal models. Progestogens stimulate the RANK ligand pathway, causing breast cancer in mice, and progestogens may stimulate breast cancer development in *BRCA1* carriers. It has also been shown in both the Breast Cancer Surveillance Consortium and the Nurses' Health Study that serum estradiol levels were most strongly associated with the development of estrogen receptor-positive breast cancer. Two large meta-analyses and a population-based study have examined combined hormonal contraceptives in *BRCA* carriers and have shown no increase in breast cancer risk. Although women with a family history are at higher risk for the disease, most will not develop it, and most of those that do will be over age 50. In a large collaborative group analysis from 52 studies including more than 150,000 women, there was no increase in breast cancer with oral contraceptive use in those with family history. In *BRCA* carriers undergoing early surgical menopause for ovarian cancer risk reduction, hormone therapy, if not contraindicated, is not only safe but recommended. BRCA carriers who undergo surgical menopause before the age of 45 years have a 50% to 55% reduction in BC risk (particularly BRCA2 carriers), and use of HT does not negate this risk reduction. BC risk tends to be lower in women who receive estrogen alone, compared with estrogen plus a progestogen (OR, 0.62; 95% CI, 0.29-1.31). In one prospective study of 872 BRCA1 carriers who were followed for a mean of 7.6 years after oophorectomy (done at an average age of 43.4 y), no increase in BC risk was seen with the use of HT. Data continues to mature. For gene-negative women at increased risk due to family history of breast cancer, HT does not appear to increase that risk. A large case-control study conducted in Southern California showed that the relative risk for BC with EPT use did not vary with alcohol use, parity, history of benign breast disease, or family history. It also appears that the use of HT may be associated with decreased mortality in those that do develop breast cancer. A recent study of 121,435 women with BC from 67 studies looked at their risk factors and survival by tumor subtype. Use of exogenous hormones, both oral contraceptive pills and menopausal hormone therapies, were associated with reduced all-cause mortality regardless of tumor subtype. For most women, HT is generally safe, especially within the first 5 years of use. In patients with early surgical menopause or when initiated within 10 years of menopause, it improves quality of life and reduces all-cause mortality and risks of coronary artery disease and osteoporosis. Micronized progesterone is likely safer than synthetic progestogens, both in terms of breast cancer risk and the development of thromboembolic complications. Women at increased risk for breast cancer both early and later in life should be offered reassurance around the use of premenopausal and postmenopausal hormonal therapies. The absolute risks associated with these therapies are low, even in the very high-risk

patient, and the benefits are often substantial. Consideration should be given to personal and family history of cardiovascular disease, stroke, venous thromboembolic disease, and breast cancer when individualizing recommendations. Shared decision-making is key.

PLENARY SYMPOSIUM #9

Postmenopause Orgasmic Dysfunction

Lauren Streicher, MD, NCMP. Obstetrics and Gynecology, Northwestern University, Chicago, IL

Disorders of orgasm in postmenopausal women represent the second most frequently reported women's sexual dysfunction after sexual desire disorders. Acquired orgasmic dysfunction includes women who at one time achieved orgasm without difficulty but are no longer able to do so despite appropriate arousal and stimulation. Physiologically, orgasmic function is determined by several biologic factors including genital sensation, genital blood flow, pelvic floor muscle integrity, and an intact neurologic pathway. Hormonal influence (estrogen and testosterone) is not an absolute requirement but facilitates orgasm by increasing libido and also genital vasodilatation. Neurotransmitters, both serotonergic and noradrenergic pathways, play a significant role. Orgasmic dysfunction may also be a downstream effect of hypoactive desire disorder, dyspareunia, or climacteric symptomatology. Healthy clitoral hemodynamics is essential for normal orgasmic function and is often compromised in the postmenopause population due to aging and comorbidities such as diabetes and vascular disease. Decreased nerve-stimulated clitoral and vaginal blood flow with diffuse fibrosis of the clitoris, decreased clitoral engorgement secondary to impaired capillary engorgement, clitoral neuropathy and higher vibratory perception threshold are all contributing factors to postmenopause orgasmic dysfunction. There are currently no FDA-approved medications for the treatment of postmenopause orgasmic dysfunction. Elimination of sexual pain and increasing arousal are critical in the treatment of orgasmic dysfunction. Treatment options include off-label use of hormone therapy and various vasodilators to maximize clitoral blood flow. Increasing vibratory stimulation is useful given the higher vibratory threshold in a postmenopause population. While there is no data regarding the systemic or local use of cannabis to facilitate orgasm, many women are self-treating, and it is incumbent on the clinician to be aware of its use.

Not All Vulvodynia Is Genitourinary Syndrome of Menopause

Andrew T. Goldstein, MD, FACOG[2,1]. [1]George Washington University School of Medicine, Washington, DC; [2]The Centers for Vulvovaginal Disorders, Washington, DC

Vulvodynia, defined as chronic vulvar pain of an unknown etiology, has a lifetime prevalence of up to 16% of women[1]; and a recent study showed a point prevalence of 4% in menopausal women.[2] Vulvodynia was once considered a medical "black box." There was no way to peer inside this box to figure out the cause(s) of the pain; therefore, there were few efficacious treatments. However, over the past two decades there has been considerable progress in determining the underlying pathophysiology of several (often overlapping) conditions that we label as "vulvodynia." Using this new knowledge, in 2015 ISSWSH, ISSVD, and IPPS sponsored and convened a consensus conference to develop a new vulvodynia nomenclature that identified different subcategories of vulvodynia (vestibulodynia, clitorodynia, etc.) as well as "associated factors" (hormonal, neuroproliferative, inflammatory, etc.) that could be used to differentiate specific types of vulvodynia to guide both research and treatment.[3] For example, a woman might have a "hormonally associated vestibulodynia" or a "generalized vulvodynia secondary to overactive pelvic floor muscles." The consensus group published a subsequent paper in 2019 on the descriptors of vulvodynia.[4] Concurrently, over the past two decades a diagnostic and treatment algorithm for vulvodynia has been developed that can help guide clinicians' treatment of women suffering from vulvodynia (www.vulvodynia.com/publications).[5] This lecture will use two case studies to illustrate how the new nomenclature and the diagnostic algorithm can help clinicians find effective treatments for their patients suffering from vulvodynia. References: 1. Guidozzi F, Guidozzi D. Vulvodynia - an evolving disease. *Climacteric*. 2022 Apr;25(2):141-146. 2. SD Mitro, SD Harlow, JF Randolph, BD Reed, Chronic vulvar pain in a cohort of post-menopausal women: atrophy or Vulvodynia? *Women's Midlife Heal.* 2 (2016) 3. Bornstein J, Goldstein AT, Stockdale CK, et al. Consensus vulvar pain terminology committee of the International Society for the Study of Vulvovaginal Disease (ISSVD); International Society for the Study of Women's Sexual Health (ISSWSH); International Pelvic Pain Society (IPPS). 2015 ISSVD, ISSWSH, and IPPS Consensus Terminology and Classification of Persistent Vulvar Pain and Vulvodynia. *J Sex Med.* 2016;13(4):607-12. 4. Bornstein J, Preti M, Simon JA, et al. International Society for the Study of Vulvovaginal Disease (ISSVD), the International Society for the Study of Women's Sexual Health (ISSWSH), and the International Pelvic Pain Society (IPPS). Descriptors of Vulvodynia: A Multisocietal Definition Consensus (International Society for the Study of Vulvovaginal Disease, the International Society for the Study of Women Sexual Health, and the International Pelvic Pain Society). *J Low Genit Tract Dis.* 2019;23(2):161-163. 5. Andrew T. Goldstein. An Overview of the Evaluation of Dyspareunia, Vulvovaginal Pain, and Pelvic Pain. In *Female Sexual Pain Disorders 2nd edition.* Andrew Goldstein, Caroline Pukall, Irwin Goldstein (Editors). Blackwell-Wiley, 2021.

What's Your Pelvic Floor Plan?

Karen Connor, PT, DPT, PRPC, Clinical Specialist. University Hospitals, Cleveland, OH

The pelvic floor should be a part of all assessments for female sexual function. What should we be looking for? Mobility! A pelvic floor needs to move and can be impacted by either underactivity or overactivity. Muscle restrictions such as trigger points or spasm can cause pain and limit pleasure. In addition, recognizing the pelvic floor as part of a larger force transfer and stabilization system challenges us to look at other muscles and structures that surround and support the pelvic floor – hips, low back, the glute complex. It takes a village for a healthy pelvic floor.

PLENARY SYMPOSIUM #10

Unveiling the Role of Insulin, Hormones, and Exercise

Fernanda G. de Felice, PhD. Center for Neuroscience Studies, Departments of Biomedical and Molecular Sciences and Psychiatry, Queens University, Kingston, ON, Canada

The development of effective therapeutic strategies for Alzheimer's disease (AD) must take into consideration the ample spectrum of this disease, which has been associated with changes in a wide range of networks including neurotransmitter systems, neurotrophic factors, immune system, neuroendocrine system, and epigenetics. We have been investigating the influence of the periphery-to-brain communication in health and disease, with a focus on decrease hormonal signaling in AD. Our studies have been focusing on the understanding of mechanisms by which insulin resistance develops in AD and how physical exercise may slow down AD progression and bring about positive outcomes for patients. We have been studying FNDC5/irisin, a hormone produced by the muscle upon exercise, is decreased in AD brains. FNDC5/irisin corrects synapse and memory defects in AD mouse models and was found to mediate the beneficial effects of exercise in memory in mice. Our study indicates the existence of an interesting muscle-brain axis. Determination of physical exercise protocols capable of modulating the muscle-brain axis in humans can lead to optimized strategies to preserve overall brain health and cognition.

The Female Aging Brain: What Do We Know About Alzheimer's Prevention?

Jessica Caldwell, PhD, ABPP/CN. Department of Neurology, Cleveland Clinic, Las Vegas, NV

Recent research in the fields of women's health, dementia, and Alzheimer's disease presents new opportunities for countering risk and supporting resilience in women's cognitive aging. Women represent two-thirds of individuals currently diagnosed with Alzheimer's disease, and this disparity is impacted by factors related to both biological sex and the social construct of gender. Some sex-based risks to women are unchangeable, such as women's up to 4 times greater dementia risk due to having copies of the apolipoprotein epsilon 4 allele (ApoE E4). At the same time, other sex- and gender-influenced risks are treatable or amenable to change. For example, women are twice as likely as men to be physically inactive and at twice the risk for depression, both of which are malleable risks for dementia and Alzheimer's disease. Women also experience greater brain-based impact of several avoidable or treatable chronic diseases, including sleep apnea and diabetes. Another area of interest is stress effects on sex-based dementia risk. Women have greater odds of experiencing certain kinds of stressors and show sex-specific short and long-term stress responses in the brain and periphery, which in turn may have detrimental effects on memory system function and structure. Beyond these factors, menopause represents a sex-specific dementia risk factor of high current interest. Estrogen directly supports memory and neural plasticity in memory systems. Both monthly fluctuations in estrogen across the menstrual cycle and loss of estrogen at menopause have been associated with measurable changes in brain activity, brain micro- and macro-structure, and memory performance on standardized tests. Some women's brains may recover poorly from the typical menopause transition, placing them at greater dementia risk. In addition, early and surgical menopause present risk for poor cognitive aging. Despite the daunting nature of women's added dementia risk, understanding these sex-and gender-based risks more deeply can help direct interventions for women's resilience in cognitive aging. This is key, as research shows up to 40% of current cases of dementia and Alzheimer's disease may have been avoided with changes to lifestyle, beginning in early adulthood and continuing throughout the lifespan. To date, evidence points toward critical preventive roles for exercise, stress management, and treating or helping women to avoid risks such as smoking, heavy drinking, diabetes, hypertension, and depression. Intellectual and social engagement have also shown important roles in resilience. Mechanistic and intervention work on these resilience-supporting behaviors is ongoing, and the potentially brain-health supporting role of menopausal hormone therapy remains under investigation. Given the complex and challenging nature of changing lifestyle, support for women's healthy aging requires an early, partnership-based approach, one that appreciates the intersection of sex- and gender-based risks with those risks related to race, ethnicity, and socioeconomic status. Women's health providers have unique opportunities to support resilience through educating patients about protecting their brain health through the life span. Taking this proactive approach may significantly reduce the future public health burden of dementia.

Amyloid-based Therapies for Mild Cognitive Impairment: Will They Make a Difference?

Victor W. Henderson, MD. Departments of Epidemiology & Population Health and of Neurology & Neurological Sciences, Stanford University, Stanford, CA

Memory symptoms and cognitive concerns are increasingly common in midlife and older age and may represent mild cognitive impairment (MCI). Underlying causes vary, but MCI is often due to early pathological changes of Alzheimer's disease. In this disorder, a key initiating pathological event is the abnormal accumulation of the amyloid-beta protein, which is deposited in the brain as a core component of neuritic plaques. Amyloid-beta itself probably has only minor effects on memory and thinking, but it may set the stage for downstream neuronal damage and progressive dementia. Three new anti-amyloid biologic agents have attracted attention and controversy. Aducanumab

received limited FDA approval in 2021; lecanemab received full FDA approval in 2023; and donanemab will likely follow suit. All three are monoclonal antibodies directed against amyloid-beta and administered by intravenous infusion. Each of these drugs was tested in large, phase-3 randomized clinical trials in people with MCI or mild dementia plus biomarker evidence for amyloid (usually based on a positive amyloid-PET scan). These infusion therapies worked: they very effectively removed amyloid from the brain. However, for all three drugs, average clinical outcomes declined for patients in active treatment arms as well as for patients in placebo arms. Moreover, average effects on cognition in the phase-3 trials fell below thresholds for clinical meaningfulness. For the first time ever, there are now approved treatments for MCI and mild dementia associated with an Alzheimer biomarker. These anti-amyloid monoclonal therapies are expensive, require biweekly or monthly intravenous infusions for up to 18 months, and have occasional, serious side-effects (brain swelling and bleeding). Despite controversy, these precision therapies will be of enormous interest to people with mild cognitive symptoms and their physicians.

KEYNOTE ADDRESS

Women Have Been Misled About Menopause

Susan Dominus. Staff Writer, The New York Times, New York, NY

In February of 2023, the *New York Times* Magazine ran a cover story that I wrote about menopause; within mere minutes of its going live, I was receiving texts from friends telling me that their friends, women I didn't know, were circulating it on their group chats. The enthusiasm grew over subsequent days and weeks; ultimately, the article generated more than 3,000 online comments, an unusually high number, with women reflecting in their own stories the thesis of the article: That for some women, life leading up to and after menopause can be devastating and confusing, with too few options for relief up for discussion, and too little discussion of the subject, period. In this talk, I'll share some thoughts about why the article was written in the first place, what the response has been and what I hope comes of the conversation that was already well underway when I first started digging into this fascinating and important field of medical care.

THE MENOPAUSE SOCIETY/PFIZER WULF H UTIAN ENDOWED LECTURE

Ovarian Hormones and Cognitive Health: The Past and The Future

Kejal M. Kantarci, MD, MS[1,2]. [1]Mayo Clinic Women's Health Research Center, Rochester, MN; [2]Mayo Clinic Alzheimer's Disease Research Center, Mayo Clinic, Rochester, MN

Early termination of the Women's Health Initiative (WHI) hormone therapy trial because of an increased risk of cerebrovascular events, breast cancer, and dementia in the combined estrogen plus progestin arm in women 65 and older, led to discussions on whether hormone therapy given to recently postmenopausal women would have similar risks. Supporting this concept, among women starting hormone therapy aged between 50 years and 55 years in the WHI Memory Study of Younger Women (WHIMS-Y) there was no influence of hormone therapy on cognitive function. Two other randomized trials tested the effects of estrogen and progestogen treatment on cognitive function in women who started treatment shortly after menopause; in both trials, cognitive function was not affected by hormone therapy compared with placebo. One of these trials, the Kronos Early Estrogen Prevention Study (KEEPS) was a randomized double-blind placebo-controlled trial, which tested the hypothesis that hormone therapy in the form of oral conjugated equine estrogen or transdermal 17β-estradiol administered to women within 3 years of menopause onset with good cardiovascular health would slow the progression of atherosclerosis. The secondary goal of KEEPS was to investigate the cognitive and mood effects administered early after the onset of menopause. Although a lower frequency of depression and anxiety was observed in the group treated with oral conjugated equine estrogen compared to placebo, the effects were neutral for cognitive outcomes in comparison to placebo during the 4 years of follow-up in KEEPS. Observational studies have reported conflicting findings on the risks and benefits of hormone therapy with respect to cognitive function, but recent observational studies from large national registries have shown an association between hormone therapy and dementia. However, there may be confounding factors and biases associated with observational studies looking for treatment effects and therefore the evidence from observational studies should not be used in shared decision making about use of hormone therapy for menopausal symptoms. Randomised clinical trials provide the strongest evidence on the effect of hormone therapy on dementia risk. Although decades of follow-up may be needed to determine the risk of dementia for a clinical trial conducted during midlife, brain imaging biomarkers might help to identify the effects of hormone therapy on dementia pathophysiology at an earlier stage, making assessment of its influence on dementia risk in trials of recently postmenopausal women feasible.

THE MENOPAUSE SOCIETY/KENNETH W KLEINMAN ENDOWED LECTURE

Embracing Intersectionality in Women's Experiences of Midlife Healthcare and Employment

Andrey M. Elegbede, PhD, MA, PCC, ELI-MP-CLDS, CTDS, CPDS, CWDS. Mayo Clinic Comprehensive Cancer Center, Mayo Clinic, Rochester, MN

Menopause is a nearly universal experience of the 3.9 billion women in the world, including those who are critical drivers in the global economy. As of 2023, 47% of women 15 years of age and over were active in the global workforce - 57.3% in the United States – with retained or increasing engagement in middle and later ages (46-65) when menopause is typically experienced. Symptoms of midlife health changes are often - at least through a western cultural lens – medicalized and associated with decreased job satisfaction and productivity levels, unrealized advancement opportunities, as well as increased likelihood of early retirement, leaving the workforce, and risk of unemployment. While the COVID19 pandemic increased flexibility and individualized employment options, work sector policies and procedures have been slow to consider midlife health challenges, including comprehensive paid leave, accommodations for health limitations, flexibility work schedules, and caregiver supports. This experience is magnified for women who hold historically marginalized and minoritized identities, particularly when considering intersectionality. Intersectionality, a term coined by Kimberlé Crenshaw, is rooted in the research and activism of women of color, extending at least as far back as 1851 with Sojourner Truth's "Ain't I A Woman" speech at the Ohio Women's Rights Conference in Akron, Ohio. The concept recognizes that systems of privilege and oppression are not just issues of race and ethnicity, or just issues of gender, but rather are multidimensional and include concurrent issues of gender, ability, age, immigration status, religious affiliation, etc. The concept further attempts to address the unique experiences that exist at the intersection of multiple identities. Using this framework, we can facilitate a better understanding of the menopausal experience and address changing needs and expectations in and out of the workplace environment. Reignited and expanded social change movements have elevated expectations that different identities matter, are valued, and must be accommodated in patient care and health and employment equity efforts. The next generation will (rightly) expect more. They are accustomed to fighting for their rights, and they have seen the impact of social justice efforts in their communities. Additionally, projections for older women's engagement in the workforce through 2031 are that numbers will increase significantly, and that future economic growth will depend, in large part, on the engagement of older women. Our professions must prepare to meet future needs and expectations of women's healthcare, in part because the next generation will demand it but also because it will be necessary for continued economic growth and opportunity, employment satisfaction and retention, and workforce diversification. Integrating both anthropological and executive coaching methodologies, this lecture will review systemic inequalities that impact of lives of individuals experiencing menopause, explore intersectionality as a framework for understanding how identity(ies) shape life experience and opportunity, and ultimately facilitate application of an intersectional lens to enact change and improve healthcare delivery and systemic employment supports for women in midlife.