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. This is usually characterized by the permanent cessation of menstruation, and it is considered to occur when there has been no menstruation for 12 consecutive months. The average age for menopause is between the ages of 45 and 55, with the average age being around 51. Menopause is a normal part of the aging process and is a natural part of a woman's lifespan.

Sexual Function 101

James A. Simon, MD, CCD, MSCP, IF, FACOG. Department of Obstetrics and Gynecology, University of Illinois at Chicago, Chicago, IL

Sexual Function 101

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

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in the perimenopause or among women with bothersome VMS. Randomized trials reliably show neutral effects of HT on cognition in the early perimenopause. In the late perimenopause, 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 Patients

Stephanie S. Faubion, MD, MBA, FACP, FACPM, 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 quality of life, sleep symptoms and an agitated 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 globalin, C-reactive protein, and triglycerides. Because of this, a transdermal route of administration of estrogen is preferred for women with cardiovascular disease 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. Latkin, MD, FACCP, NCMP, IF. Ms.Clinicencei, 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 genetic, established modificable 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 additional diagnostic workup. There is a lack of controversy including 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 prevent further screening. Factors that may increase risk 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 40 to every year every 1-2 years, anytime from 56-74. Options for non-standard 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 or likely pathogenic genetic 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 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 year of delivery, or within 18 months of delivery, is a special case. MRI is the screening modality of choice 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 globalin, C-reactive protein, and triglycerides. Because of this, a transdermal route of administration of estrogen is preferred for women with cardiovascular disease 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.

Breast Density and Supplemental Screening: A Comprehensive Overview

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

Breast density is 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 its 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 breast tissue visualization and the importance of mammographic analysis. MRI, tomosynthesis, contrast enhanced mammography, and molecular breast imaging (MBI) are all valuable tools for breast cancer diagnosis, especially for women with dense breasts. Each of these modalities can analyze cancer distribution in a structured manner and can provide additional information that will 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

Zahra A. Hill, 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 physical examination, as well as imaging and evaluation 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

Zahra A. Hill, 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.
Women are considered a high risk for breast cancer if they have received thoracic radiation administered prior to 30 years of age, have a ≥7.5 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 anastrozole 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. SERM’s 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

Caryn 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. Cancer screening frequency can currently vary, 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 BRCAl/2 genes, which infer the development of 250,000 breast and ovarian cancers. For patients who harbor a germline mutation, these 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. Kurvey, 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 that confer 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 surgical stage and history of blood clotting disorders, breast cancer history, or a family history of 1 per 250,000 women. Options for breast cancer risk: a narrative review. Breast Cancer Res. 2022 Feb 28;24(1):14. doi: 10.1186/s13058-022-01590-2. PMID: 35809332 Gargiulo P, Aghi M, Almog Y, Conomos MP, Kaittanis D, Kontos E, Karam S, Kontos D. Artificial intelligence in mammography. J Natl Cancer Inst. 2020 Dec 1;112(23):1523-1532. doi: 10.1093/jnci/djaa246. PMID: 32230924

OPENING SYMPOSIUM

Cell-Free DNA: A Paradigm Shift in Cancer Screening

Mylinda B. Massart, MD, PhD 1,2,3, Family Medicine, UPMC Primary Care Precision Medicine Center, Pittsburgh, PA; 1Research 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. Coming from 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?

J gave, MD, FSHR, Breast Imaging, Thomas Jefferson University Hospital, Philadelphia, PA


Personalizing Treatment for Early-Stage Breast Cancer

Allison W. Kurvey, MD, 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

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

Women are considered a high risk for breast cancer if they have received thoracic radiation administered prior to 30 years of age, have a ≥7.5 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 anastrozole 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. SERM’s 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.
detected prior to development of frank metastatic disease. Current clinical trials aim to identify patients with DTC and/or cDNA 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 L. Milas, MD, 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 deaths. This mortality despite its relatively lower prevalence is due to several 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 diagnostic testing. Some 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 screening opportunities are unclaimed. It is estimated that over half of this year’s projected 25,520 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 the highest risk group 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 immunochemical 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 colorectal cancer or a family history of colorectal cancer). Screening 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 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 that has been proven to reduce cancer deaths at 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, FACOG1, 2. Department of Obstetrics, Gynecology, and Reproductive Health, Clinical Research Institute, Rutgers New Jersey Medical School, Newark, NJ; 5. New Jersey Alliance for Clinical and Translational Science, Rutgers Biomedical Health Sciences, New Brunswick, 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 ongoing activity. As US cervical cancer screening and management 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.

The Etiology of Medical Misinformation

Jevin D. West, PhD, 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, we will provide examples of medical misinformation, examine if they have got here, and the potential health impacts of 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

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**Conveying Scientific Information to Menopausal Patients Through Compelling and Understandable Messaging**

Susu J. Oyebode, MS, NCMP, Department of Obstetrics and Gynecology, University of Washington School of Medicine, Seattle, WA

“Women have been misled about menopause” stated a NY Times article published Feb 1, 2023, describing some perimenopausal women’s struggles with menopause and the role of hormone therapy in menopause symptoms. Epistemological studies suggest 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 (HealthyWomen Survey, personal communication). When asked why women did not 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 contradictions 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 federal funding for breast cancer research experience bothersome vasomotor symptoms, and the high cultural tolerance for women’s suffering. Menopause is not regarded as important.2 • Media – alarm and risk are the mantra – the message can become oversimplified and not reliable in predicting evidence-based 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 key role in disseminating 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 (MenoSite) https://www.menopause.org/professionals/consumer-publications/1-somenotions-1 • 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://www.cdc.gov/nchs/data/hestat/est2020_12.pdf 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: 35785653. 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 ER Modulators (SERMs) and SERDs for diseases where 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 use of high-throughput Estrogen Receptor Ligands (ERLs) with the goal of eliminating ER expression within cancer cells to achieve absolute inhibition of estrogen signaling. Work from our group has resulted in the identification of the first clinically useful oral SERD, etacitul, 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 estradiol emerged from discovery efforts in our laboratory and was recently approved for the treatment of MBC. Studies on the SERM/SERD (elacestrant) for the treatment of breast cancer are encouraging, 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 targets. This is despite the fact that we now have a good understanding of the animal models of MBC and to an incomplete understanding of how modulation of ER action impacts tumor pathology. We do have a clear understanding of the biochemical mechanisms that enable ER within specific cells to distinguish between SERDs and SERMs. Specifically, ER agonist/antagonist/degrader 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 antitumor efficacy of ER modulators is determined to a 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 risk even in the presence of a uterus. Instead of use of a progestin, selective estrogen receptor modulators (SERMs) are 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**

Thomas J. Raczewski, 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 fractures. The treatment of osteoporosis is based on clinical risk factor assessment, 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 moderate risk, consider a bisphosphonate or denosumab; for low 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 of these patients have shown that anabolic drugs reduce the risk of vertebral fractures compared to bisphosphonates. The sequence of therapy is important, with anabolic therapy followed by and antiresorptive medication being associated with a greater 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-analyses clearly show that the 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 in 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 increase in fracture risk. 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 architecture (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 microarchitectural measures 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 relationships of the bone mass 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 it does provide a more direct measure of bone architecture and its ability to resist fracture. These techniques have been applied in the research setting to better understand clinical comorbidities such as the increased risk of fracture in patients with type 2 diabetes mellitus (T2DM). Such techniques 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 measures 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, NCPM. UC San Diego School of Medicine, La Jolla, CA
Of the many medical and non-medical conditions that affect 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 cholesterol levels will continue to increase. A growing number of women are making lifestyle behavioral changes such as increasing their physical activity and weight loss, which has led to a decrease in prevalence of metabolic syndrome. However, despite the decrease in prevalence of metabolic syndrome, 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. These include drugs with anxiolytic, anti-depressant or cognitive-behavioral therapy and hypnosis and 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, FACP. 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. Premature menopause may be iatrogenic (related to drug therapy determined by the agent, dose, duration of use) or idiopathic. Such causes may be associated by genetic factors, autonomy, 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 treatment) and natural menopause. Premature menopause is associated 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 FSH levels (25 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 thyroid autoimmunity, 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 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 women with premature menopause. HRT is a non-controlled trial data informed decision-making. Premenopause is a pathologic condition and decisions informing use of HRT 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 progestagen 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 risk will also be reduced. Finally, the prevalence of menopause due to 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 ≥ 10% should 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. These include drugs with anxiolytic, anti-depressant or cognitive-behavioral therapy and hypnosis and can also be effective. Premature Menopause

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. Treatment based on current guidelines for a breast cancer includes surgery, axillary lymph node evaluation, and hormone therapy. Hormone therapy in breast cancer patients has been shown to reduce recurrence and mortality, yet patients can experience serious adverse effects including hot flashes, and other symptoms. The hypothesis that hormone therapy would benefit these 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 risk of breast cancer with both who have a history of breast cancer and those without. 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 are treated with aromatase inhibitors in menopause. Treatment for GIM 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 will want 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 GIM 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 GIM. 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 up with a appropriate treatment plan for GIM treatment.

PLENARY SYMPOSIUM #5

Updates in the Management of Hypertension and Dyslipidemia in Midlife Women
Beth L. Abramson, MD, MSc, FRCPC, FACC 1,2 1Medicine, University of Toronto, Toronto, ON, Canada; 2Division 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 (<45y) have increased risk of CV events. In women aged 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 thrombembolism. Therefore, other means of managing CV risk are needed in our female patients. Aggressive identification and modification of CV risk factors (weight 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 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 lowering therapies are also proven effective in women to reduce CV events. This needs to be reinforced, given patient concerns from media sources and lay literature which can lead to non-evidence-based decision making. Clinical trials included women to show that statins, in addition to PCSK9-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 based decision making. Clinical trials included women to show that statins, in addition to

PLENARY SYMPOSIUM #6

2023 Nonhormone Therapy Position Statement
Chirsandra 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 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 nonhormonal treatments included cognitive-behavioral therapy, clinical hypnosis, selective serotonin reuptake inhibitors/serotonin-norepinephrine reuptake inhibitors, gabapentin, oxybutynin, weight loss, stellate ganglion blocks and the new, first-in-class FDA-approved medication, fexiletinoid. Therapies that were not recommended for the treatment of vasomotor symptoms included the use of

The Skinny on Weight Management in Midlife Women
Beth L. Abramson, MD, MSc, FRCPC, FACC 1,2 1Medicine, University of Toronto, Toronto, ON, Canada; 2Division of Cardiology, St. Michael’s Hospital, Toronto, ON, Canada
Over 60 with ≥ 2 risk factors, and women over 65 with one risk factor. Assessment and profile. The HOPE-3 trial showed that low-dose statin therapy, is superior to placebo in
paced respiration, supplements/herbal remedies, cooling techniques, avoiding triggers, exercise, yoga, mindfulness-based intervention, relaxation, suvorveyx, soy products, cannabidiol, and clinical evaluation of neural oscillations, brain imaging, diet and lifestyle, 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 Primary Care Program in Neuroscience; Boston, MA

Kiss1 neurons of the arcuate nucleus, also termed KNDy neurons because they co-express kisspeptin, neuropeptide 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 autonomic 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 NK3 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-hormonal treatments for VMS. Future work will need to target the 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 changes become more pronounced 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 changing their skin goals. It is incumbent on those of us who provide treatments that can help women to address these issues as early as possible, even before menopause, in order to stave off some of the unpleasantries 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. Manoli, 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 aging”; 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 40th-60th, 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 Biostatistics, 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 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 clinical risk factors associated with invasive and advanced cancer informs risk prediction and primary prevention.

Objectives To describe the Breast Cancer Surveillance Consortium (BCSC) v 3.5 invasive breast cancer risk prediction model and the cumulative 6-year advanced breast cancer risk prediction model and their applications in risk-screening and primary prevention. Methods The BCSC (https://www.bcsc-research.org/) is a cohort of women undergoing breast imaging in 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/) and 6-year cumulative advanced cancer risk model (https://tools.bcsc-scc.org/AdvBC6yearRisk/). Advanced cancer risk model defined as American Joint Commission on Cancer staging T4b or N3b or M1 or stage IIA or higher because it most accurately predicts breast cancer death. 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 model which to use when to start screening Interventions for deciding screening interval and supplemental imaging Reducing breast cancer risk factors with a high population attributable risk Summary Heterogeneously or extremely densely 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 and their applications in risk-based screening and primary prevention. J Natl Cancer Inst. 2021;113(7):909-916.
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 Organic Dysfunction**

Lauren Stanchier, 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 is frequently reported who at one time experienced an orgasm without that ability 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 recruitment, clitoral neuropathy, and higher vibratory perception threshold are all contributing factors to postmenopause organic dysfunction. There are currently no FDA-approved medications for the treatment of postmenopause organic dysfunction. Elimination of sexual pain and increasing arousal are critical in the treatment of organic 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 compounds 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.1,2.1. George Washington University School of Medicine, Washington, DC; ‘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; and a recent study showed a point prevalence of 4% in menopausal women.1 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.1 For example, a woman might have a “hormonally associated vestibulodynia” or a “generalized vulvodynia secondary to overactive pelvic muscles.” The consensus group published a subsequent paper in 2019 on the descriptors of vulvodynia.2 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). We will use these case studies to illustrate how the new nomenclature can guide clinicians’ treatment of women suffering from vulvodynia. References: 1. Guidozi F, Guidozi 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 Health. 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 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 Foundation for the Study of Women’s Sexual Health (IFSSH), 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’s Sexual Health, and the International Pelvic Pain Society). J Low Genit Tract Dis. 2019;32(2):163. 5. Andrew T. Goldstein, An Overview of the Evaluation of Dyspareunia, Vulvodynia, Vulvodynia 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 spasms 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, neurotrophic factors, immune system, neuroendocrine system, and epigenetics. We have been investigating the influence of the peripheral-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 counteracting risk and supporting resilience in women’s local use of campuses to facilitate orgasm, many women are self-treating, and it is incumbent on the clinician to be aware of its use.

**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

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 higher 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 menopausal transition, placing them at greater risk for developing clinical cognitive impairment present 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 ultimately have been avoided by choices to change 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 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.

**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 middle 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. This plaques, with their negative impact on memory and thinking, but it may set the stage for downstream neuronal damage and progressive dementia. Three new anti-amyloid biological agents have attracted attention and controversy. Aducanumab
KEYNOTE ADDRESS

Women Have Been Misled About Menopause

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 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

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 minimized 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 enacting change and improve healthcare delivery and systemic employment supports for women in midlife.

THE MENOPAUSE SOCIETY/PFIZER WULF H UTIAN ENDOWED LECTURE

Ovarian Hormones and Cognitive Health: The Past and The Future
Kejal Kantarci, MD, MS 1, Mayo Clinic Women’s Health Research Center, Rochester, MN; 2Mayo 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 to 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.