

Plenary Symposium #1—Presidential Symposium *“Digital Medicine & Informatics—The Future is Now!”*

Meaningful Use of Electronic Health Records

Judy Murphy, RN, FACMI, FHIMSS, FAAN. US Department of Health & Human Services, Washington, DC

The final requirements for Meaningful Use Stage 1 and 2 are behind us. These requirements focused on electronic data capture and information exchange to enable Stage 3, which is all about improving patient outcomes. As the country approaches \$15 billion in incentive payments, we are only beginning the journey to a truly transformed health care system. Exemplar health systems have led the way, with many others following the trail that has been blazed. As we push into Stage 3 and beyond, what should we be doing to maintain a patient-centric view that enables safe and efficient medication therapy? How do we move the needle in interoperability and health data exchange? How do we ensure that patients become and remain engaged? From her position as Deputy National Coordinator for Programs and Policy, Judy Murphy is uniquely qualified to answer these and many other questions. Attendees will have the opportunity to learn the latest news on EHR adoption and to learn what the ONC is doing to ensure that the EHR is a tool to enable patient-centric care.

Learning Objectives:

At the conclusion of this presentation, participants should be able to:

- Select and utilize EHRs and other digital medicine technology more effectively in clinical practice

Plenary Symposium #1—Presidential Symposium

“Digital Medicine & Informatics—The Future is Now!”

Perils & Prospects of Practicing Medicine in a Digital Era

Kent Bottles, MD. PYA Analytics, Knoxville, TN

Dr. Kent Bottles, Chief Medical Officer of PYA Analytics, Lecturer at The Thomas Jefferson University School of Population Health, and Social Media Adviser to the American College of Physician Executives, will provide an overview to the digital medicine revolution that is currently transforming the American clinical delivery system. The convergence of wireless sensors, genomics, imaging, electronic medical records, mobile connectivity and bandwidth, the Internet, social networking, and cloud computing create opportunities and challenges to how we practice medicine. How much is hype and how much is real? When will all this happen? Dr. Bottles will answer these questions and provoke you into considering how you deliver medical care.

Learning Objectives:

At the conclusion of this presentation, participants should be able to:

- Understand the various definitions of digital medicine
- Appreciate how social media sites like Twitter and Facebook can be leveraged by medical practices
- Discuss the pros and cons of electronic medical records
- Implement disruptive technology into their medical practice

Plenary Symposium #1—Presidential Symposium *“Digital Medicine & Informatics—The Future is Now!”*

Beyond Personal Health Records: The Emergence of Patient Powered Research Networks

Sally Okun, RN, MMHS. PatientsLikeMe, Inc., Cambridge, MA

Established in 2004, PLM has been an early pioneer as a patient-powered research network. Today, over 200,000 members have reported their real-world experiences on more than 1,500 diseases, ranging from rare conditions such as amyotrophic lateral sclerosis (ALS) to more prevalent ones like depression, fibromyalgia, multiple sclerosis, and psoriasis. Members create health profiles using clinically relevant and research-based data collection tools to monitor how they're doing between doctor or hospital visits, document the severity of their symptoms, identify triggers, note how they are responding to new treatments, and track side effects. At its core, PLM is a clinical research platform that has generated over 30 peer-reviewed publications. PLM research professionals have completed studies with real-world data that have helped refute and preempt traditional randomized clinical trials, modeled Parkinson's Disease, validated epilepsy quality measures, shed new light on medication adherence in patients with multiple sclerosis (MS) and organ transplants, and added and validated patient reported outcomes in psoriasis, autism and MS research. In 2012 the first “dose effect curve for friendship” was reported showing that epilepsy patients who connect on PLM have better outcomes (Wicks P et al. *Epilepsy & Behavior*. 2012;29:16-23) This is especially significant given that over one third of our patients with epilepsy report never having met another person with the disease prior to joining PLM. In 2013 PLM launched the Open Research Exchange (ORE), funded by a grant from the Robert Wood Johnson Foundation. The ORE seeks to inform the development of novel Patient-Reported Outcomes instruments (PROs) to more granularly and comprehensively measure disease and wellness in populations. This system allows for the rapid authoring, deployment, and feedback on new instruments in our online cohorts. We anticipate generating initial instruments via this process by the end of 2013. To achieve a continuously learning health system a new fourth aim of prepared and involved people will be essential. We will explore how patient focus is helping to drive a new era of health care in which people can benefit in real time from the information they share while contributing to a new way of measuring health.

Learning Objectives:

At the conclusion of this presentation, participants should be able to:

- Describe recent and emerging digital medicine technologies, their use, and potential to enhance patient care, patient communication, and clinical research

Keynote Address

“Going Full Frontal: Rewiring Frontal Brain Networks to Restore Cognitive Health”

Going Full Frontal: Rewiring Frontal Brain Networks to Restore Cognitive Health

Sandra B. Chapman, PhD. The University of Texas at Dallas, Dallas, TX

In the past century, the human lifespan has doubled. The average life expectancy in the United States is over 78, and one in three infants born today is predicted to live to 100 years. The downside of these longer life years is that little has been done to strengthen cognition and lengthen one's years of brain health. We each want to live a long life, but only if we still have our minds functioning and are able to make our own decisions. Our brain's frontal lobes and their complex system of connections are the last of the brain regions to develop, with dramatic changes and remodeling extending well into our twenties. On the flipside and downside, these frontal regions of our brain that support our mental independence are the first to decline with age. The majority of healthy adults experience declines in cognitive function that reportedly emerges as early as the mid 40s. This slippage occurs in areas mainly controlled by the frontal lobe and its rich connections throughout the brain such as planning, decision-making, memory, new learning, and problem-solving. Until recently, age-related cognitive decline was viewed as a consequence of living longer rather than a brain condition to be addressed and solved. Recent scientific discoveries now show that our brains retain immense capacity to be modified and strengthened as we age inducing biological changes in brain function and structure as well as behavioral improvements. The brain's potential to reorganize and rewire by birthing new neurons and creating new neural pathways is commonly referred to as neuroplasticity. This innate ability makes our brain the most modifiable organ in our entire body. Thus, in the absence of disease, cognitive decline is happening as a result of non-action; in aging, loss of brain health is not a fait accompli. Brain imaging technology is providing ways to characterize neural/brain health in real time. Mentally challenging activities can alter the brain at all levels of organization from brain metabolism and blood flow, increased brain activity and efficiency, to expanding the physical connections across brain regions. Scientific discoveries show that mental exercise increases the brain's blood flow across major brain regions. Humans lose approximately 2% of their brain blood flow every decade beginning in their 20s. This pattern can be reversed – increasing brain blood flow by 8% or more - with complex mental activity. The bottom-line is that staying mentally active helps to prevent and reverse brain decline in aging. This powerful evidence of neural plasticity suggests that engaging in complex mental activities may serve to maintain and lengthen brain span and perhaps slow the rate of cognitive decline. Just as we cannot ignore our body's health until late life, we have to attend to our brain's health early, often and continually. Whether we experience brain hits from chemotherapy, hormonal changes, sleep problems, or general anesthesia — to mention a few — science is now showing the brain can rebound given mental training. We are complicit in our own brain decline by failing to keep our frontal lobe as fit as we can and should. You are never too young or too old to adopt healthy brain habits that strengthen the brain's capacity to think smarter. Our cognitive brain health does not have to deteriorate; our best brain years can be ahead of us. Without brain health, we do not have health.

Learning Objectives:

At the conclusion of this presentation, participants should be able to:

- Counsel patients and caregivers on lifestyle, nutritional, and pharmacologic approaches to preventing and treating Alzheimer's disease and dementia

Plenary Symposium #2

“Hot Flashes—More Than a Minor Annoyance”

Supported in part by grant funding from: Noven Women's Health

When is a Hot Flash Not Just a Hot Flash?

Rebecca C. Thurston, PhD. University of Pittsburgh, Pittsburgh, PA

Vasomotor symptoms (VMS, or hot flashes, night sweats) are common menopausal symptoms, experienced by upwards of 70% of women during the menopause transition. VMS have long been understood to have important implications for quality of life, sleep, and mood during the menopause transition. However, aside from signaling a changing hormonal milieu, they have generally been conceived as having few implications for physical health. Emerging data have called that assumption into question. For example, in both the Heart and Estrogen/progestin Replacement Study (HER) and the Women's Health Initiative (WHI) randomized trials of hormone therapy (HT) for the primary or secondary prevention of coronary heart disease, women with VMS, and in the case of the WHI, older women with VMS, were at the highest risk of coronary heart disease with HT use. Data from the Study of Women's Health Across the Nation (SWAN) showed higher subclinical CVD, including elevated carotid intima media thickness, elevated aortic calcification, and lower flow mediated dilation among women with VMS and compared to those without VMS, controlling for CVD risk factors and estradiol levels. Several lines of research from epidemiologic and laboratory investigations have investigated potential mechanisms that may link VMS to CVD risk, including blood pressure, lipids, endothelial function, inflammation and hemostasis, and cardiac vagal control. However, positive findings of CVD risk associated with VMS are not universal. Data from women with exceptionally low CVD risk profiles do not find these links, and recent data from the observational WHI cohort underscored the importance of the timing of VMS relative to the menopause transition. Ongoing work from our laboratories is considering physiologically-measured VMS in relation to CVD risk. Data on links between VMS and CVD risk will be reviewed, and potential mechanisms linking VMS to CVD risk will be considered. How best to conceptualize any VMS-CVD relations (e.g. as causal to CVD risk or as a marker of underlying CVD risk) will be emphasized, and clinical implications of this work will be discussed.

Learning Objectives:

At the conclusion of this presentation, participants should be able to:

- Identify and help patients manage health risks associated with vasomotor symptoms

Plenary Symposium #2

“Hot Flashes—More Than a Minor Annoyance”

Supported in part by grant funding from: Noven Women’s Health

Behavioral Interventions for Hot Flashes

Gary Elkins, PhD, ABPP. Baylor University, Waco, TX

Due to concerns over increased cancer risks, side effect profiles as well as growing interest in non-pharmacological treatment options, behavioral interventions for hot flashes are being increasingly studied and utilized. To date, a number of behavioral interventions treating hot flashes have been investigated to include, Yoga, Paced Respiration, Cognitive Behavioral Therapy, Mindfulness-Based Stress Reduction, Psychoeducation, Relaxation Therapy, & Clinical Hypnosis. Though research into most of these interventions is still in the nascent stages, the results are generally positive. There are concerns, however, over the methodological quality of much of the published research. Additional, adequately powered and placebo-controlled or comparative therapy studies are critically needed. There is promise that a behavioral intervention for hot flashes is feasible, acceptable and effective, however. Results of a recent large-scale, randomized and structured attention controlled trial of clinical hypnosis to treat hot flashes in post-menopausal women has shown effect sizes matching or exceeding the best results from non-hormonal pharmaceutical trials, showing an average of 70% reduction in hot flashes after 5, weekly sessions of hypnosis and the daily practice of self-hypnosis at home. Hypnosis is a mind-body intervention that involves the induction of a deeply relaxed state and suggestions for therapeutic effect. Hypnosis for hot flashes involves the use of imagery and suggestions for coolness and comfort as well as suggestions for increased control over hot flashes. The risks associated involved with a behavioral intervention for hot flashes are minimal and infrequent, potentially involving feelings of disappointment, embarrassment, and troublesome feelings. However, hypnosis is a personnel-intensive intervention and currently not widely available. Guided self-hypnosis and audio formats hold potential for greater dissemination, but more research is needed. The benefits for a behavioral intervention for treating hot flashes are myriad. Results show that these interventions show positive effects not only for the reduction of the frequency, severity and duration of hot flashes, but also in anxiety, sleep, and quality of life.

Learning Objectives:

At the conclusion of this presentation, participants should be able to:

- Describe behavioral interventions for hot flashes, including self-hypnosis, and the evidence base for each
- Discuss risks and benefits of behavioral interventions for hot flashes with patients
- Implement evidence-based behavioral interventions for hot flashes in practice or refer patients appropriately

Plenary Symposium #2

“Hot Flashes—More Than a Minor Annoyance”

Supported in part by grant funding from: Noven Women’s Health

Beyond Hormone Therapy: Innovative Options for Treatment of Hot Flashes

JoAnn V. Pinkerton, MD, NCMP. University of Virginia, Charlottesville, VA

Hormone therapy remains the gold standard pharmaceutical treatment for moderate to severe bothersome menopausal hot flashes for the majority of women. Nonhormonal options for the treatment of hot flashes among women at risk for complications of hormone therapy, including those with a history of breast or uterine cancer or who are at elevated risk for venous thrombosis are needed. Despite several medications which have shown efficacy in reduction of hot flashes in women meeting FDA standard of 7 hot flashes per day or 50 per week, only one agent has been approved for vasomotor symptoms of menopause. In a randomized clinical trial (RCT) of 568 women, 7.5 mg of mesylate salt of paroxetine (LDMP), well below the dose of paroxetine typically used to treat depression, resulted in approximately nine fewer hot flashes per week compared with women receiving placebo.[11] After 24 weeks of therapy, 47.5% of women treated with LDMP improved compared to 36.3% on placebo. Adverse events were generally similar between LDMP and placebo. Potentially effective drug therapies which are sometimes used off label include the antihypertensive clonidine, selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), and gabapentin (TABLE 1).^{2,4} In large, randomized, controlled trials, the following agents were modestly more effective than placebo: desvenlafaxine,⁵ low-dose paroxetine salt,⁶ escitalopram,⁷ and gastroretentive gabapentin. Participants in these trials included women with both spontaneous and surgically induced menopause. Concerns about risks compared to benefits or need for additional trials prevented FDA approval of desvenlafaxine and gastroretentive gabapentin. . Benefits of these nonhormonal prescription therapies (FDA approved or used off label) need to be weighed carefully against side effects, because the reduction in absolute hot flashes is modest and there are no large RCT comparing them to hormone therapy. Adverse events have included nausea, dizziness, somnolence, excess sweating, need to taper on and off medication and concern about P450 interaction with SSRIs for women on tamoxifen Many small trials have assessed other medications and complementary and alternative therapies regarding management of menopausal symptoms. Most, however, are limited by small numbers of enrolled participants and shorter study duration (≤12 weeks). In addition, enrolled participants have variable numbers of hot flashes, often less than 14 per week.

Nonhormonal treatment of vasomotor symptoms

Treatment	Study Design*	Findings
Complementary/alternative medicines (black cohosh, St. John’s Wort, red clover, acupuncture, exercise)	Duration: 4-52 wk; OI and RPL trials; entry criteria for most trials: >14 hot flashes/wk	Mixed results, mostly with no sustained improvement
SSRIs** (paroxetine, fluoxetine, sertraline, citalopram, escitalopram)	Duration: 4-36 wk; RPL trials with all agents; N = 20-90 in active arms; entry criteria for most trials: >14 hot flashes/wk	Reduction in vasomotor symptoms (frequency, composite scores): 28%-55%
SNRIs** (venlafaxine, desvenlafaxine)	Duration: 12-52 wk; RPL trials with all agents; N = 20-65 in VEN; N = 120-200 in DVS; Entry criteria >14 hot flashes/wk for VEN; >50/wk for DVS	Reduction in VMS (frequency, composite scores): 35%-58% for VEN, 55%-68% for DVS
Gabapentin**	Duration: 4-12 wk; RPL trials; N = 20-100; entry criteria for most trials: >14-50 hot flashes/wk	Reduction in vasomotor symptoms (frequency, composite scores): 50%-70%

***All studies of menopausal, nondepressed women.**

****Treatment is off label.**

Learning Objectives:

At the conclusion of this presentation, participants should be able to:

- Offer a full range of treatment options for vasomotor symptoms based on patients’ individual risks and preferences

Plenary Symposium #3

“When Ovaries Retire Too Soon”

Primary Ovarian Insufficiency: Etiology and Diagnosis

Marcelle I. Cedars, MD. UCSF School of Medicine, San Francisco, CA

Primary ovarian insufficiency (POI) suggests a failure of the ovary with respect to oocyte and estradiol production. This diagnosis can be devastating for the individual. Thus, accurate, early and thoughtful diagnosis and care are required. However, up to 50% of women given this diagnosis will have some intermittent ovarian function, with 5-10% ultimately conceiving. So the terms premature “failure” or menopause are discouraged in favor of POI. POI rarely presents as amenorrhea but rather is most commonly first identified in a woman with irregular cycles. Given that menstrual irregularity is a common finding in women, the presentation of any menstrual irregularity (oligomenorrhea or polymenorrhea), following establishment of regular cycles, should be approached with a high degree of suspicion and POI should be excluded in all such women. The diagnosis is confirmed, in a woman under 40 years of age, with oligo/amenorrhea lasting 4 months and FSH is the menopausal range on two occasions at least one month apart. Given the significance of this diagnosis, particularly in women with amenorrhea, following exclusion of pregnancy, all should be evaluated for POI. Once diagnosed, attempt should be made to understand the etiology. Medical conditions and/or treatments (such as chemotherapy/radiation) should be queried. In the absence of significant medical history, the etiology is most frequently unknown. But all patients should have the exclusion of associated (causal) genetic and autoimmune etiologies. This testing includes karyotype (especially for women under 30 years of age), Fragile X mutation, and screening for autoimmunity with anti-adrenal and anti-21-hydroxylase antibodies.

Learning Objectives:

At the conclusion of this presentation, participants should be able to:

- Diagnose primary ovarian insufficiency and differentiate it from menopause
- Order appropriate tests to exclude causal genetic and autoimmune etiologies

Plenary Symposium #3 *“When Ovaries Retire Too Soon”*

Primary Ovarian Insufficiency and Early Menopause: Effects on Risks for Cardiovascular Disease and Fracture

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

For a woman who experiences menopause before the average anticipated age, compromised fertility and its myriad ramifications often dominate her immediate concerns. Once the dust has settled, however, on exploring potential parenthood options, questions regarding long-term health implications arise. Prevailing dogma suggests that women with premature ovarian insufficiency (POI) or early menopause (between ages 40 and 45 years) are expected to be at increased risk for mortality, cardiovascular disease, osteoporosis, psychosexual dysfunction, cognitive decline, neurological disease, and compromised quality of life. Careful review of the body of evidence generating these concerns, largely composed of observational studies that include a significant proportion of women with surgical menopause, reveals the challenge in drawing firm conclusions about risk. Methodological discrepancies abound: participant numbers vary from a few hundred to tens of thousands, the specified age of menopause might depend upon patient recall decades later with attendant inaccuracies, designated age cut-offs for risk stratification vary from study to study, surgical menopause may not be confirmed by medical records, women with surgical menopause may be combined with women who have experienced early natural menopause, rates of hormone therapy use may not be adjusted, and comparison groups and duration of follow up are inconsistent. Furthermore, selected cardiovascular endpoints range from cardiovascular disease to cardiovascular mortality to coronary heart disease, myocardial infarction, all-cause mortality, post-infarction angina, measures of left ventricular function, coronary artery calcification, carotid intima-media thickness, metabolic syndrome, Framingham risk score, atrial fibrillation, and stroke. Contrary to conventional wisdom, not all studies, particularly those published recently, report increased cardiovascular disease risk in women with early menopause. From the standpoint of bone health, similar concerns about an increase in osteoporosis with early or premature menopause prevail, although in some recent analyses, fracture rates in women with surgical menopause have not exceeded those with natural menopause, also calling this concern into question. Although the use of hormone therapy in appropriate candidates for treatment of vasomotor symptoms, vaginal symptoms, and enhancement of quality of life is nearly universally endorsed, whether the proposed risks of early menopause, particularly cardiovascular disease and osteoporosis, merit specific preventive strategies remains an essential question in the clinical management of these women.

Learning Objectives:

At the conclusion of this presentation, participants should be able to:

- Cite the increased health risks in women with primary ovarian insufficiency
- Assess and manage these risks in women with primary ovarian insufficiency

Plenary Symposium #4

“Cancer Survivorship—With, Through & Beyond”

Cancer Survivorship and Women’s Health: What Are the Challenges?

Patricia A. Ganz, MD. UCLA Schools of Medicine & Public Health, Los Angeles, CA

During the past three decades there have been dramatic advances in the detection and treatment of various cancers, such that worldwide there are now millions of women who are living more than five years after their cancer diagnosis with no evidence of disease. The human cost of this success can be considerable, including physical, psychological and social consequences. Cancer survivors want to continue in the workplace and with their pre-diagnosis life, wishing to restore a sense of normalcy after completion of cancer treatments. However, sometimes persistent symptoms such as pain, fatigue, depression and cognitive difficulties will make it impossible for this to occur. In this presentation, I will review what is known about long-term and late effects of cancer treatments, which women are more likely to experience some of them, and strategies that should be considered to prevent as well as address these survivorship difficulties in this large population of patients. Specific concerns related to women’s health, such as premature menopause, fertility preservation, gynecological and menopause-related symptoms, and bone health will be addressed. High quality survivorship care must attend to these issues, and the cancer care team needs to work collaboratively with primary care providers and women’s health specialists to manage ongoing symptoms and the late effects of treatment.

Learning Objectives:

At the conclusion of this presentation, participants should be able to:

- Identify the most common cancer sites among female cancer survivors
- Cite the cancer treatment exposures that lead to common long-term and late effects of treatment
- Manage common cancer survivorship problems

Plenary Symposium #4

“Cancer Survivorship—With, Through & Beyond”

Reclaiming Sexual Health for Cancer Survivors

Michael L. Krychman, MDCM. The Southern California Center for Sexual Health & Survivorship, Los Angeles, CA

Sexual problems are common in cancer survivor. This may be due, in part, to the emotional impact of the diagnosis, but is often compounded by treatments like surgery, radiation therapy, chemotherapy, hormonal medications, each of which can have sexuality-altering side effects. Survivorship programs and sexual rehabilitation medicine is a subspecialty emerging in both the oncologic and general medicine settings, to address the intimacy concerns that are paramount for survivors. Physiological removal of sex organs whether it is the breasts, vulva or gynecological organs can impact a woman's hormonal function as well as impact her sexual self esteem and perception of womanhood. Radiation therapy can cause skin thickening and contractures as well as changes in texture and color of the exposed tissues. Chemotherapy-induced effects, including early menopause, can lead to hot flashes, sleep disturbances, mood changes, and vaginal atrophy; all of which may negatively impact sexual pleasure. Relationship dynamics can change once a woman has a cancer diagnosis. The partner, who may transition into the role of caregiver or primary wage earner, may have difficulty adjusting to altered familial roles. The treatment paradigm is often multifaceted. Identifying and treating simultaneous chronic medical conditions can be helpful in restoring sexual functioning. Identifying and altering medications such as antihypertensive or anti depressants that can affect sexual responsiveness may also be important. Maintenance of a well-balanced diet, engaging in mild to moderate aerobic exercise, discontinuation of tobacco or illicit drugs and minimizing alcohol consumption can contribute to overall wellness, and re-invigorate sexual response. Managing stress and hectic schedules while making time for structured sexual exercises can be paramount in the comprehensive management for sexual complaints. Comprehensive sexual health programs

often include: private couples counseling, programs of guided imagery, meditation, deep-muscle relaxation, acupuncture, referral to pain management specialists. For many cancer survivors, systemic hormonal treatment may not be acceptable as treatment, and alternatives either prescriptive or those using behavioral techniques maybe acceptable solutions. Local treatments with minimally-absorbed vaginal estrogen preparations, such as the Conjugated Equine Estrogen (Premarin Vaginal cream ®) or 17β-estradiol tablets, (Vagifem ®), have recently gained attractiveness within the oncology community but still may pose some difficulties due to the lack of clinical safety as it pertains to their minimal systemic absorption. Investigational medications like vaginal DHEA and newer approved medications like the non-estrogen, Ospemifene, hold promise for women who decline hormonal therapy or for those who want a safe effective oral treatment for moderate to severe dyspareunia, a symptom of VVA due to menopause. Care and consultation with between the survivor and her oncological team should be aimed at discussing individualized treatment plans that minimize risk while maximize sexual wellness. Nonhormonal vaginal moisturizers (i.e.: Replens ®), and water-based vaginal lubricants (i.e.: Astroglide®, K-Y Jelly®) maybe helpful to address both vulvar and vaginal dryness and irritation. Commercially available vibrators/self stimulators can also be helpful for women who benefit from extra stimulation to erotic areas of the vagina and clitoris. Sexual dysfunction, during or following cancer therapy, is a very complex group of disorders and can compound an already stressful life event. A comprehensive sexual medicine evaluation combined with sexual rehabilitation therapeutics promotes healthy sexual functioning by fostering open communication, validating sexual thoughts and feelings, and rectifying biologic abnormalities. Treatment plans are often seen as the ingredients where an individual is encouraged to create her own individualized recipe for sexual and sensual success. Adapted from a previously published article by the author and Dr Susan Kellogg, published in *Coping* 2009.

Learning Objectives:

At the conclusion of this presentation, participants should be able to:

- Provide and coordinate sexual health counseling and care in women who are cancer survivors

Plenary Symposium #4

“Cancer Survivorship—With, Through & Beyond”

Oncofertility

Mitchell P. Rosen, MD, HCLD. University of California, San Francisco, San Francisco, CA

According to 2011 Surveillance Epidemiology and End Results (SEER), 123,000 young adult women ages 18-44 are diagnosed with cancer every year in the US. Furthermore, an additional 6000 children and adolescents are treated for cancer each year. Many of these children and young adult women will face adverse reproductive health outcomes. Treatment for most cancer types in reproductive age women can involve removal of the reproductive organs or potentially gonadotoxic treatments like chemotherapy and/or radiotherapy. Early loss of ovarian function not only puts patients at risk for menopause-related complications at a very young age but is also associated with loss of fertility. Studies of reproductive compromise in young women undergoing cancer treatment have focused on the resumption of menses immediately post-treatment and therefore have underestimated the extent of long-term gonadotoxicity. More recently, it has been shown that chemotherapy is not only associated with acute ovarian failure, but also with the more remote outcomes of infertility and early menopause in women whose menses have resumed after treatment. The overall incidence of acute ovarian failure on average in women exposed to chemotherapy is 3-13%; infertility is 30-60% and early menopause between 9-28%. However, in high-risk groups, the chances of any of these sequelae are much higher. The variance in outcomes may be influenced by ovarian reserve, genetic susceptibility, age at treatment, time elapsed since treatment, and treatment type. As a consequence of the increase in the number of patients surviving cancer, greater attention has been focused on the delayed effects that cancer treatments can have on the quality of patients' future life. Recent studies have shown that the loss of potential fertility due to iatrogenic causes – i.e., the loss of a potential child – has a profound impact on young women. For some it may be even more stressful than the cancer diagnosis. Therefore, patients diagnosed with cancer should be counseled about their reproductive risks and given the opportunity to preserve fertility prior to treatment when possible. And, if the patient presents after gonadotoxic treatment and desires to become a biological parent, she can still be given options to improve her chances of building a family. Multiple strategies have emerged that aim to preserve fertility and offer to cancer survivors with significant reproductive compromise the chance to achieve parenthood. These include embryo and oocyte cryopreservation, cortical and whole ovary cryopreservation, ovarian transplantation, ovarian transposition, and gonadotropin releasing hormone agonist protection (during chemotherapy). Special considerations are taken to minimize risk for patients with hormone receptor positive cancers and to reduce the chance of vertical transmission in patients with hereditary disease. Currently, embryo and mature oocyte cryopreservation following in vitro fertilization are the only techniques endorsed by the American Society of Reproductive Medicine (ASRM), while the other methods are still considered investigational. Ovum donation and adoption remain viable options for many women. As we strive to improve young cancer survivors' quality of life, future research will be aimed at: 1) better identifying patients who are at risk for post-treatment reproductive compromise and 2) expanding the breadth and quality of options available preserve one's chances of biological motherhood and to reduce the untoward effects of iatrogenic early menopause.

Learning Objectives:

At the conclusion of this presentation, participants should be able to:

- Recognize the importance and the potential challenges of fertility preservation in women with cancer
- Assess women's risks of reproductive impairment from cancer treatment
- Counsel women with cancer on fertility preservation and refer appropriately

Plenary Symposium #5 *"Your Aging Brain & You"*

Bioenergetics in Relation to Menopause & Dementia

Roberta D. Brinton, PhD. University of Southern California, Los Angeles, CA

Estrogen is a fundamental regulator of the metabolic system of the female brain and body (Rettberg et al., *Frontiers in Neuroendo* 2013). Within the brain, estrogen regulates glucose transport, aerobic glycolysis, and mitochondrial function to generate ATP (Brinton, *TINS* 2008, *TIPS* 2009). In the body, estrogen protects against adiposity, insulin resistance, and type II diabetes, and regulates energy intake and expenditure (Rettberg et al., *Frontiers in Neuroendo* 2013). During menopause, decline in circulating estrogen is coincident with decline in brain bioenergetics and shift towards a metabolically compromised phenotype (Yao et al., *Neurobio of Aging* 2012). Our preclinical discovery research has shown that: 1) decline in brain glucose uptake occurs early in the process of female brain aging; 2) decline in brain glucose uptake is paralleled by decline in glucose transporter expression in neurons and rise in glial associated glucose transporters; 3) decline in brain glucose uptake and neuronal glucose transporter expression are paralleled by decline in key metabolic enzymes required for glucose metabolism; 4) decline in glucose metabolism is paralleled by increases in alternative substrate supply (ketone bodies) and associated transporters (MCT2 and MCT4); and lastly 5) these changes in brain glucose supply and the system required for glucose transport and metabolism precede development of mitochondrial dysfunction. These changes in the systems required for substrate supply for production of ATP to support energetic demand temporally map onto the earliest phase of reproductive transition. The decline in brain glucose uptake and neuronal glucose transport preceded the shift to alternative, less efficient fuels, which was coincident with the age of reproductive senescence (Ding et al., *Plos One* 2013; Yao et al., *Mol Aspects Med.* 2011) Clinical parallels to preclinical data are evident (reviewed in (Rettberg et al., *Frontiers in Neuroendo* 2013). In premenopausal women, differences in glucose metabolism coincided with phase of the menstrual cycle. In normal aging, CMRglu declines with age, with the most significant declines occurring in the prefrontal cortex. In the menopausal female brain, this age-related decline in glucose metabolism in prefrontal cortex has been detected, as well as a decline in glucose metabolism in the posterior cingulate that was specific to estrogen deprivation. Multiple FDG-PET imaging studies in neurologically normal persons at risk for Alzheimer's disease, including those with a maternal history of Alzheimer's, present with significant hypometabolism in brain prior to development of pathology. Deficit in brain glucose metabolism is an early indicator of and hallmark for the disease. In at-risk populations, decline in cerebral glucose utilization appears decades prior to the onset of clinical diagnosis of Alzheimer's, precedes brain atrophy and correlates with degree of cognitive impairment and pathological burden. Estrogen regulation of the bioenergetic system of the brain and body provides a strategy for identifying women appropriate for and efficacy of hormone therapy intervention. Further, estrogen regulation of metabolism serves as a rationale for biomarkers for early identification of women at risk for neurodegenerative diseases such as Alzheimer's. This research is funded by NIA 2R01AG032236 and NIA 5P01AG026572 to RDB.

Learning Objectives:

At the conclusion of this presentation, participants should be able to:

- Describe the aging process in the female brain
- Describe the research on biomarkers that may allow risks of neurodegenerative disease, such as Alzheimer's, to be identified early in women

Plenary Symposium #5

“Your Aging Brain & You”

Sex Differences in Alzheimer’s Disease

Pauline M. Maki, PhD. University of Illinois at Chicago, Chicago, IL

Alzheimer’s disease (AD) is now the sixth leading cause of death in the United States, with approximately 5.4 million individuals with the disease. Of the top 10 leading causes of death in the United States, AD shows the greatest sex difference, with more women than men dying from the disease. Age-adjusted mortality rates from AD between 1999 and 2008 show that 20% more women than men died of the disease. There is debate about whether this sex difference in the prevalence of AD is due to the greater longevity of women compared to men. In light of the sex difference in AD prevalence, investigators have examined how sex-specific factors such as menopause and sex-related factors such as lifestyle factors might alter a woman’s risk for the disease. There is mixed evidence about the impact of age at menopause on risk for AD, but early removal of the ovaries before the natural onset of the menopause increases the risk for AD by 70%. Treatment with estrogen therapy offsets that risk. The impact of hormone therapy on the risk of AD is hotly debated, though three observational studies support the view that early use of hormone therapy confers benefits. Sex differences in psychological conditions and lifestyle factors might contribute to sex differences in AD. A history of major depression increases the risk of AD, and compared to men, women have a two-fold higher risk of major depression. There is evidence that cardiovascular exercise decreases risk for AD. Worldwide, compared men, women engage in less exercise. Higher levels of education and intellectually demanding occupations are associated with a decreased risk of AD. Educational and occupational levels are lower in elderly women compared to men, though education levels are rising generally in younger generations. There is mixed evidence concerning sex differences in the prevalence of Mild Cognitive Impairment (MCI), a preclinical stage of AD, though a recent study from the Mayo Clinic found that men convert from normal aging faster than women. This sex difference in the risk of MCI was interpreted as suggesting that women might transition from normal cognition directly to dementia at a later age but might transition more abruptly. Meta-analyses indicate that after diagnosis of AD, women show a more rapid decline in all cognitive domains. Mice models of AD and human neuroimaging studies of AD patients show sex differences in brain structure. Lastly, and importantly, women also take on a greater burden of caring for patients with AD.

Learning Objectives:

At the conclusion of this presentation, participants should be able to:

- Describe sex differences in the prevalence and incidence of Alzheimer’s disease
- Discuss how reproductive aging and hormone therapy might influence the risk for Alzheimer’s disease
- Describe sex differences in risk factors for Alzheimer’s disease

Plenary Symposium #5 *"Your Aging Brain & You"*

Strategies for Healthy Brain Aging

Victor W. Henderson, MD, MS. Stanford University, Stanford, CA

A major concern of baby boomers (and now Gen Xers) is maintaining cognitive skills and avoiding dementia during transitions to midlife and thence to older adulthood. Both mild cognitive impairment and dementia are increasingly prevalent with advancing age. A distinction can be made between age-related cognitive decline and mild cognitive impairment, with the latter presumed to be due to pathological changes that lead to Alzheimer's disease and to other forms of dementia. Genetic factors, such as variations in the gene that encodes apolipoprotein E, are linked to risk of both mild cognitive impairment and Alzheimer's disease; interestingly, relative risks conferred by possession of the apolipoprotein epsilon-4 allele appear to differ between women and men. Genetic antecedents cannot be altered, but other risk factors are potentially amenable to remediation. These particularly include factors associated with vascular disease but also exogenous hormone exposures (hormone exposures), diet and dietary supplements (including phytoestrogens), depression, physical activity, and mental activity. In many instances, benefit is thought to accrue through enhanced cognitive reserve — building capacity, efficiency or redundancy in brain areas and nerve pathways used during cognitive performance. For some factors, there is now substantial evidence for a role in risk reduction, and there is a lot that we can advise our patients to do now. However, many interventions intended to remediate cognitive aging and to forestall the development of mild cognitive impairment and dementia have not been subject to rigorously designed randomized clinical trials. The fact that some answers are not known with certainty should not deter clinical recommendations, but at the same time we need to advocate for better data upon which to base our recommendations.

Learning Objectives:

At the conclusion of this presentation, participants should be able to:

- Cite the differences between age-related cognitive decline, mild cognitive impairment, and dementia
- Recognize that Alzheimer's disease is the most common cause of dementia and suspect the disease in cases of mild cognitive impairment
- Assess patients' risk of cognitive decline, mild cognitive impairment, and dementia
- Advise patients how to modify these risks

NAMS/Pfizer Wulf H. Utian Endowed Lecture “Sex Differences in Cardiovascular Repair”

Sex Differences in Cardiovascular Repair

Doris A. Taylor, PhD, FAHA, FACC. Texas Heart Institute at St. Luke’s Episcopal Hospital, Houston, TX

Historically, the lack of appreciation for the impact of sex on cardiovascular outcomes has allowed for women’s health in the cardiovascular arena to be largely ignored. In fact, cardiovascular disease is the number one cause of death in both women and men. Although female sex does appear to be associated with cardioprotection, aging and menopause are major risk factors for cardiovascular disease. In fact, specific cardiovascular diseases, such as heart failure with preserved ejection fraction, occur more frequently in women than men by a proportion of 2:1¹. As our current population ages, the number of women living with cardiovascular disease is ever increasing, imposing a major economic burden on global health care systems. Therefore, a better understanding of the effects of gender on disease progression, pharmacogenomics, therapeutic and environmental responses may allow for the development of gender-specific therapeutics. Aging is associated with a reduced capacity for the heart to repair itself. Since stem cells aid in mediating endogenous repair, cardiovascular disease might be, in part, a failure of stem-cell mediated cardiac repair. Indeed, we found that as both men and women age, there is a decrease in the frequency of blood circulating stem cells that express the stem cell marker, CD34 which differs between the sexes, decreasing at a much earlier age in males than females. This is mimicked in animal models of atherosclerotic disease where a sex-difference decrease in CD34+ cells with age is inversely correlated with progression of disease. These cells play an important role in mediating new blood vessel growth after myocardial ischemic episodes due to coronary artery disease. Aging is also associated with altered inflammatory responses, and patients with multiple risk factors for cardiovascular disease development demonstrate a significant increase in inflammation. Sex differences in inflammation also exist and the functionality of progenitor cells is higher in middle-aged women than in middle-aged men. In fact, we found that delivery of female reparative

inflammatory cells into male mice having atherosclerotic disease, results in an increase in male reparative cell number and response suggesting that female inflammatory cells may confer protection. Indeed, we found that stem cells from female mice exposed to ischemia, exhibit decreased apoptosis, decreased cytokines and growth factors such as tumor necrosis factor (TNF), interleukin-6 (IL-6), and increased vascular endothelial growth factor (VEGF) expression. Other studies have shown that female stem cells offer greater protection after ischemia/reperfusion injury than do male cells. Clinical studies have shown that hearts from women are protected against ischemia/reperfusion injury with a decrease in TNF, IL-1 and IL-6 inflammatory cytokines. The heart itself may also differ in men and women. For example, during pregnancy women must functionally compensate for an increase in blood volume and for rapid reduction in blood volume after delivery. The inability to compensate for these changes can cause heart failure associated pregnancy². Interestingly, we have found that extracellular matrix of female hearts is actually stiffer than male hearts which may be related to gender-specific hormones. Indeed, administration of estrogen limits undesirable extracellular matrix remodeling in blood volume overloaded hearts³. The mechanisms for these sex differences are unclear. Since menopause is a major risk factor cardiovascular disease development, it is postulated that hormones such as estrogen play an important role in mediating these sex differences. However, the use and efficacy of replacement hormone therapy in post-menopausal women has proven controversial and in some trials, ineffective reducing the incidence of disease. This suggests that gender-specific hormones may not be the only mechanism for sex differences in disease outcomes. Interestingly, prepubescent male and female children also have differences in their inflammatory cytokine responses suggesting that the X chromosome, itself and genes escaping X chromosome inactivation may contribute to sex differences. A greater understanding of sex differences in cardiovascular disease will inevitably lead to therapeutics limiting disease progression and decreasing mortality for women.

Learning Objectives:

At the conclusion of this presentation, participants should be able to:

- Cite the sex differences in cardiovascular regenerative repair and the treatments these discoveries may bring for women with cardiovascular disease

Plenary Symposium #6

“Musculoskeletal Update: The Dynamic Duo”

Supported in part by grant funding from: Amgen Inc., Warner Chilcott

Sarcopenia—The Neglected Factor

Neil C. Binkley, MD. University of Wisconsin, Madison, WI

Sarcopenia and osteoporosis are defined respectively as age-related declines in quantity and quality of muscle and bone. These diseases have shared pathogenic mechanisms and adverse health consequences. Sarcopenia is appropriately receiving increased interest as a contributor to disability, falls and fractures. However, in addition to low muscle and bone quantity/quality, both absolute and relative fat excess, ie, obesity and sarcopenic obesity, also contribute to disability, falls and fractures. Historically, efforts to reduce fracture risk have focused on a single component, osteoporosis. Rather than such singular focus, an opportunity exists to combine clinical factors into a syndrome of increased risk, thereby allowing improved identification of older adults at risk for disability, falls and fractures. We suggest that such a combination be termed dysmobility syndrome, analogous to the approach taken with metabolic syndrome. A score-based approach to dysmobility syndrome diagnosis is proposed. Further evaluation of this approach in large population-based and prospective studies is warranted. Clinical recognition of the roles of sarcopenia and obesity as factors increasing “osteoporotic” fracture risk is needed.

Learning Objectives:

At the conclusion of this presentation, participants should be able to:

- Assess multiple risks for disability, falls, and fractures in women, including osteoporosis, sarcopenia, and obesity

Plenary Symposium #6

“Musculoskeletal Update: The Dynamic Duo”

Supported in part by grant funding from: Amgen Inc., Warner Chilcott

Old and Possibly New Therapies for Osteoporosis—How to Choose?

Michael McClung, MD, FACE, FACP. Oregon Osteoporosis Center, Portland, OR

In the absence of studies directly comparing the fracture protection efficacy of drugs, the choice among treatment options is based on a combination of contraindications, strength of evidence of efficacy, tolerability and concerns about safety as well as cost and patient preference. The primary goal in treating osteoporosis is to reduce the risk of serious fragility fractures in patients at moderate to high fracture risk. For treatment, multiple choices among several classes of drugs are available. Only rarely would drugs be used in combination. Estrogen is neither approved nor recommended for long term of patients with osteoporosis. Calcitonin, raloxifene, oral and intravenous bisphosphonates and denosumab are anti-remodeling drugs with varied evidence of efficacy, different safety concerns and different routes of administration. All but calcitonin are useful, having general or niche roles as treatment options. Teriparatide, due in part to its significant expense, is generally reserved for treatment for 1-2 years in patients with very high risk of spine fracture. Its effect on hip fracture risk is uncertain. Teriparatide may have particular benefit in patients with glucocorticoid induced osteoporosis. Preventing bone loss in early menopausal women with low bone mass, even if fracture risk is low, is a separate objective of osteoporosis therapy. Estrogen has its major role here, especially in patients who derive benefit of menopausal symptoms relief. However, the salutary skeletal effects of estrogen abate quickly upon discontinuing treatment; there is no long-term benefit from short-term estrogen therapy. Raloxifene may blunt but does not prevent bone loss in these settings. Denosumab is effective but long-term treatment is required to achieve lasting benefit. Teriparatide is not usually considered. Because of their unique pharmacology, long acting bisphosphonates (alendronate or zoledronic acid) is an attractive strategy for these patients. These drugs can continue to prevent bone loss for several years after a relatively short therapy (2-3 years) interval of treatment, during which time, the risk of atypical femoral fracture is very low. Two new agents are in late stage development. Odanacartib, an inhibitor of cathepsin K, inhibits osteoclastic bone resorption without affecting other osteoclast functions and without significantly decreasing bone formation. Significant increases in long bone cortical thickness are observed in animals with odanacartib. If such changes occur in our patients, this agent may provide substantial benefits to reduce nonvertebral fracture risk. It could become a first-line therapy for most patients with osteoporosis as well as an option in patients who have been on long-term bisphosphonate therapy. Monoclonal antibodies that inhibit sclerostin, the osteocyte-derived inhibitor of bone formation, restore bone mass and bone structure to normal in monkeys with ovariectomy-induced osteoporosis. Early clinical studies document a robust anabolic effect without an accompanying increase in bone resorption as is seen with teriparatide. Perhaps this drug will be a treatment for patients with severe osteoporosis, followed by an anti-resorptive agent to consolidate and maintain the gains achieved. We have very effective and quite safe therapies to treat postmenopausal osteoporosis. Despite limited evidence of comparative efficacy, individualized treatment decisions can be made to optimize effectiveness of these treatments in daily practice.

Learning Objectives:

At the conclusion of this presentation, participants should be able to:

- Cite the risks and benefits of current options for treating postmenopausal osteoporosis
- Be able to choose among options to prevent rapid bone loss in recently estrogen-deficient women
- List emerging osteoporosis treatment options and describe their risks and benefits

Plenary Symposium #6

“Musculoskeletal Update: The Dynamic Duo”

Supported in part by grant funding from: Amgen Inc., Warner Chilcott

DXA Testing & Screening: How Early, How Often?

Jane A. Cauley, DrPH, University of Pittsburgh, Pittsburgh, PA

The average age of the world's population is increasing at an unprecedented rate and this increase is changing the world. From 2010 to 2040, the world's population 65 years of age or older will double from about 506 million in 2008 to 1.3 billion by 2040, accounting for 14% of the world's population; the proportion age 80 or older is projected to double from 2010 until 2050. The US 2010 census showed that 57% of those 65 or older are women and of those 85 or older, 67.4% of them are women. These demographic changes will lead to an increased number of women with osteoporosis and osteoporotic fractures. To alleviate the public and private burden of osteoporosis, assessment of risk and reduction of individual risk is critical. Of importance identification of women with low bone mineral density (BMD) who had a high risk of fracture. Treatment of these women will likely reduce burden. In 2011, the US Preventive Services Task Force (USPSTF) recommended routine screening for women age > 65 years. The USPSTF recommended BMD testing for women age 50-64 years whose predicted 10 year risk of major osteoporotic fracture using FRAX without BMD is >9.3%, similar to the risk of fracture in a 65 year old white women. However, it is currently unknown if these USPSTF recommendations are appropriate for younger women. The USPSTF noted that evidence about optimal intervals for repeated screening is lacking. However, analysis from a large cohort of white women age 65 and older noted that the optimal interval for BMD testing for women with normal BMD was 16.8 years and for women with osteoporosis, 4.7 years. The presentation will review the current evidence on optimal screening and rescreening strategies for postmenopausal women.

Learning Objectives:

At the conclusion of this presentation, participants should be able to:

- Review the current evidence on optimal bone density screening and rescreening intervals
- Screen or rescreen patients based on current best evidence

MsFLASH Research Network

“MsFLASH Research Network: Latest Findings”

The MsFLASH Research Network: Latest Findings

Andrea Z. LaCroix, PhD¹, Hadine Joffe, MD, MSc², Lee S. Cohen, MD³, Katherine M. Newton⁴, Susan D. Reed, MD, MPH⁵, Katherine A. Guthrie⁶, Kristine E. Ensrud⁷. ¹Fred Hutchinson Cancer Research Center, Seattle, WA; ²Brigham & Women’s Hospital, Boston, MA; ³Massachusetts General Hospital, Boston, MN; ⁴Group Health Research Institute, Seattle, WA; ⁵University of Washington, Seattle, WA; ⁶University of Minnesota, Minneapolis, MN; ⁷VA Healthcare System, Minneapolis, MN

Estrogen therapy (ET) is the gold standard treatment for hot flashes and night sweats (vasomotor symptoms, VMS), but some women are unable or unwilling to use it because of associated risks. The serotonin norepinephrine reuptake inhibitor (SNRI) venlafaxine is used widely as a non-hormonal alternative pharmacologic treatment for VMS. While clinical impression is that venlafaxine is less effective than ET, no previous clinical trials have simultaneously included treatment groups of ET, venlafaxine and placebo, limiting the ability to address this important clinical question. This session will feature the results from the recently completed MsFLASH double-blind, randomized controlled trial which quantifies the individual effects of low-dose oral estradiol and venlafaxine vs. matching placebo for relief of VMS, as well as several other common menopause-related symptoms including insomnia, perceived sleep quality, vaginal discomfort, and sexual dysfunction. We will report the results of a randomized, placebo controlled trial that enrolled 339 peri- and postmenopausal women with ≥ 2 bothersome VMS per day (mean 8.1 ± 5.3 /day) to treatment with low-dose oral 17-beta-estradiol 0.5-mg/day (n=97), low-dose venlafaxine XR 75-mg/day (n=96), or placebo (n=146) for 8 weeks. 94% of women were adherent to study medication and completed 8-week VMS diaries. Intent-to-treat analyses compared change in VMS frequency, the primary outcome, between each active intervention and placebo. Dr. Joffe will present the primary VMS outcome results of the trial. Dr. Newton will present the results for treatment effects on insomnia symptoms as measured by the Insomnia Severity Index and perceived sleep quality as measured by the Pittsburgh Sleep Quality Index. Dr. Reed will present the results for treatment effects on vaginal symptoms and sexual function, as well as preliminary findings related to the postmenopausal vaginal microbiota and the vaginal microbiome. Finally, Dr. Guthrie will present the results of a joint analysis of the three MsFLASH randomized controlled trials comparing treatment effects of 6 interventions vs. placebo on VMS frequency, severity and bother: escitalopram, aerobic exercise, yoga, Omega-3 supplementation, low dose estradiol and venlafaxine. These findings will allow practitioners to counsel women with menopause symptoms on how these treatments compare with respect to relief of VMS.

Learning Objectives:

At the conclusion of this presentation, participants should be able to:

- Summarize the results of the MsFLASH trials
- Counsel patients on the effectiveness and safety of alternatives to hormone therapy based on the evidence from the MsFLASH trials

Plenary Symposium #7

“Lessons from KEEPS, ELITE, MsFLASH Trials: Do the Findings Guide Clinical Practice?”

The Early versus Late Intervention Trial with Estradiol: A Randomized Trial to Test the Timing Hypothesis of Hormone Therapy

Howard N. Hodis, MD and Wendy J. Mack, PhD, for the ELITE trial group
Atherosclerosis Research Unit, Departments of Medicine and Preventive
Medicine, Keck School of Medicine of the University of Southern California,
Los Angeles, CA

The hormone therapy (HT) “timing hypothesis” has been proposed to explain differences in outcomes of coronary heart disease,^{1,2} cognition and dementia^{3,4} between randomized controlled trials and observational studies, in which different populations of women were studied, average age 64 years and >12 years postmenopausal versus 30-55 years of age and <6 years postmenopausal, respectively. The timing hypothesis posits that HT benefits and risks depend on the temporal initiation of HT relative to the time-since-menopause and/or age, which in turn is related to the health of the underlying vasculature.^{5,6} The divergent results between the atherosclerosis progression sister trials Estrogen in the Prevention of Atherosclerosis Trial (EPAT)⁵ and the Women’s Estrogen Lipid-Lowering Hormone Atherosclerosis Regression Trial (WELL-HART)⁶ provided early clinical trial support for this hypothesis. While EPAT demonstrated a reduction of subclinical atherosclerosis progression with HT in postmenopausal women without clinical cardiovascular disease, WELL-HART demonstrated a null effect in postmenopausal women with documented coronary artery atherosclerosis.^{5,6} Experimental animal studies^{7,8} replicate these divergent effects of HT on atherosclerosis. With completion of EPAT and WELL-HART, a new randomized controlled trial was proposed to the National Institutes of Health (NIH) in early 2002 entitled the Early versus Late Intervention Trial with Estradiol (ELITE). Since initiation of ELITE, data supporting the timing hypothesis has grown considerably over the past decade.^{1,9} Meta-analyses of the cumulated trial data show that the effect of HT on CHD and total mortality is null when HT is initiated in women >60 years of age and/or >10 years-since-menopause whereas, in women who initiate HT when <60 years of age and/or <10 years-since-menopause, there is a 32% reduction in CHD and 39% reduction in total mortality relative to placebo.¹⁰⁻¹³ The magnitude of CHD and total mortality reduction for women <60 years of age and/or <10 years-since-menopause when randomized to HT is similar to observational studies of populations of women who initiated HT at or near the time of menopause. ELITE remains unique and timely as the only randomized trial specifically designed to test the timing hypothesis of HT in relation to atherosclerosis progression and cognitive change in postmenopausal women. ELITE is a 2x2, double-blinded, placebo-controlled trial in which 643 women were randomized according to their time-since-menopause (<6 years, n=271 or ≥10 years, n=372) upon entry into the trial. The primary atherosclerosis outcome is progression of common carotid artery intima-media thickness over 5-6 year duration of oral 17β-estradiol 1 mg per day with or without 4% vaginal progesterone gel versus placebos. A broad spectrum of cognitive skills was assessed using a comprehensive battery of 14 neuropsychological tests. The secondary atherosclerosis end points included contrast and non-contrast coronary computed tomography assessed as participants completed the trial. Baseline and trial results will be presented.

Learning Objectives:

At the conclusion of this presentation, participants should be able to:

- Describe the findings of the Early versus Late Intervention Trial with Estradiol (ELITE)
- Incorporate findings from ELITE into clinical decision making about hormone therapy

Plenary Symposium #7

“Lessons from KEEPS, ELITE, MsFLASH Trials: Do the Findings Guide Clinical Practice?”

MsFLASH: Do the Findings Guide Clinical Practice?

Lee S. Cohen, MD. Massachusetts General Hospital and the MsFLASH Network, Boston, MA

Hot flashes and night sweats (VMS) are the cardinal symptoms of menopause. Although VMS and other menopause-related symptoms adversely affect the well-being of women, data supporting a singular clear choice of therapy with high likelihood of symptom improvement are few. Estrogen therapy (ET) has been the gold standard for treatment of menopausal symptoms, particularly VMS, and at this time, only one treatment other than ET has been approved by the FDA for the indication of menopause-related VMS. The last decade has demonstrated large numbers of women who are either unable or unwilling to use hormonal treatments because of associated risks and thus alternative therapeutic options with clear evidence of efficacy are needed. The MsFLASH network (Finding Lasting Answers to Symptoms and Health) was established to conduct systematic randomized trials of novel and/or understudied interventions postulated to alleviate vasomotor and other menopausal symptoms. Three randomized controlled trials examining six different interventions for relief of VMS and associated menopausal symptoms have been conducted. These have included: 1) a randomized, double-blind, placebo-controlled clinical trial designed to evaluate effectiveness of the selective serotonin reuptake inhibitor escitalopram in reducing vasomotor symptom frequency and severity; 2) a 3 x 2 factorial design to test two behavioral interventions (yoga, exercise), and omega-3 supplementation for improvement of vasomotor symptom frequency and both respectively, and 3) a double-blind randomized three-arm trial of the serotonin-norepinephrine reuptake inhibitor venlafaxine and low-dose oral estradiol versus placebo for reducing vasomotor symptom frequency, severity or both. Results of the first two trials revealed the following: 1) efficacy of 10-20 mg/day of escitalopram for reduction of VMS compared to placebo and 2) failure of both behavioral interventions (yoga and exercise) as well as treatment with omega-3 fatty acid supplementation to demonstrate efficacy compared to a wait-list control group or placebo respectively. Results and implications of the third trial in which venlafaxine and low dose estradiol were tested against placebo with respect to ability to reduce hot flash frequency (primary outcome) as well as other menopausal symptoms will be reviewed. The question of whether MsFlash findings inform clinical practice will be discussed. While the results of MsFLASH trials may not point to a “best agent” to be used for management of VMS, network efforts do highlight the importance of applying rigorous methods to the study of menopausal symptoms which when untreated, compromise quality of life. Delineation of those interventions which following rigorous testing support efficacy versus those interventions whose efficacy is supported more by clinical lore than systematic study helps the clinician in practice offer a spectrum of choices to patients seeking lasting answers to bothersome menopausal symptoms.

Learning Objectives:

At the conclusion of this presentation, participants should be able to:

- Describe the findings of the MsFLASH trials
- Incorporate findings from the MsFLASH trials into clinical decision making about hormone therapy alternatives

Plenary Symposium #7

“Lessons from KEEPS, ELITE, MsFLASH Trials: Do the Findings Guide Clinical Practice?”

The KEEPS Trial: Do the Findings Guide Clinical Practice?

JoAnn E. Manson, MD, DrPH, NCMP. Harvard Medical School, Boston, MA

The Kronos Early Estrogen Prevention Study (KEEPS), which included 727 women ages 42-58 and within 3 years of their final menstrual period, was designed to evaluate the effects of oral and transdermal estrogen in newly menopausal women over 4 years of follow up. KEEPS evaluated two 2 formulations — oral conjugated equine estrogens (o-CEE) at a daily dose of 0.45 mg and transdermal estradiol (t-E2) in a weekly patch at a dose of 50 µg/d (both with the addition of cyclic oral micronized progesterone, 200 mg daily for 12 days each month) — compared to placebo. The primary endpoint was progression of atherosclerosis measured by carotid intima-medial thickness (CIMT). Secondary endpoints were atherosclerosis progression measured by coronary artery calcium (CAC); cognitive function and mood/affective outcomes; cardiometabolic risk factors/biomarkers; quality of life outcomes (vasomotor symptoms, sleep, sexual function); and bone mineral density (in a subset). Regarding vascular health, KEEPS had neutral results for both CIMT and CAC, although there was a nonsignificant trend toward less CAC in both hormone therapy (HT) arms compared with placebo. Due to extremely low rates of atherosclerosis progression in these newly menopausal women over 4 years, the statistical power for these aims was low. For both interventions, HT produced many favorable effects, including significant improvement in hot flashes, night sweats, and sleep disturbances; preservation of BMD; and improvement in sexual function in terms of pain and lubrication. For t-E2, there was also improvement in libido. There were neutral effects on cognition overall, but some evidence for a cognitive benefit of o-CEE in a subset of women who had good cardiovascular health at baseline. o-CEE was also found to improve mood and depressive symptoms. Neither form of HT increased blood pressure (BP) and o-CEE had the expected first-pass liver effects on lipids—reduction in LDL and increase in HDL cholesterol and triglycerides. With o-CEE, there was also an increase in C-reactive protein. Lipids were generally unchanged with t-E2, while glucose tolerance improved and insulin resistance declined. Because t-E2 had favorable effects on insulin resistance and did not raise triglycerides or CRP, it may be a better choice than oral estrogen for an obese patient or a woman with metabolic syndrome who has significant vasomotor symptoms and chooses to take HT. Transdermal estrogen may also have advantages for women with concerns about low libido. In contrast, oral estrogen may have advantages for newly menopausal women with symptoms related to mood or memory. The KEEPS trial helps to inform clinical decision-making about HT and assists in individualizing care of menopausal women, but many of the findings are preliminary and require confirmation in other studies.

Learning Objectives:

At the conclusion of this presentation, participants should be able to:

- Describe the main findings of the Kronos Early Estrogen Prevention Study (KEEPS)
- Compare the results for oral and transdermal estrogen therapy
- Incorporate findings from KEEPS into clinical decision making about hormone therapy

Plenary Symposium #8

“Menopause & Sleep—More Zzzs Please”

Sleep & Menopause: Etiology & Treatment Approaches

Hadine Joffe, MD, MSc. Brigham & Women’s Hospital, Boston, MA

Sleep disturbance is a core symptom of the menopause transition. Women are more likely to experience problems sleeping in general and specific sleep disorders in particular during the perimenopause and postmenopause than during their reproductive years. Common causes of sleep disturbance linked with the menopause transition include hot flashes, sleep apnea, insomnia, depression and restless legs/periodic limb movement disorder. Other factors include age-related sleep changes and medical conditions. These conditions can co-occur and may be difficult to disentangle. Evaluation of sleep disturbance in midlife women involves ascertaining the nature of the sleep disturbance (e.g., fall or staying asleep, snoring or gasping, kicking, unrefreshing sleep) and obtaining an overnight sleep study where indicated. Treatment considerations vary with the type of the sleep disturbance and include therapies targeting nighttime hot flashes, sleep hygiene, cognitive behavioral therapy for insomnia, hypnotic agents and treatments for primary sleep disorders of sleep apnea. Dr. Joffe will review data bearing on the leading causes of sleep disturbance during the menopause transition and treatment options for these conditions.

Learning Objectives:

At the conclusion of this presentation, participants should be able to:

- List the most common causes of sleep disturbance in women during the menopause transition
- Evaluate and treat sleep disturbances related to the menopause transition

Plenary Symposium #8

“Menopause & Sleep—More Zzzs Please”

Sleep Loss, Sleep Apnea & Metabolic Consequences

Esra Tasali, MD. University of Chicago, Chicago, IL

Diabetes is a rising epidemic in the U.S., largely attributed to the alarming increase in overweight and obesity. Despite substantial resources applied to implement lifestyle interventions such as healthy diet and exercise, the economic and public health burden of diabetes and obesity remains enormous. In parallel with the epidemics of diabetes and obesity, voluntary sleep curtailment has become an increasingly prevalent behavior in modern society. Today, as many as one-third of American adults report obtaining less than 7 hours of sleep. Substantial evidence from population studies suggest that individuals reporting short habitual sleep durations are at increased risk of developing diabetes and obesity. Short-term laboratory studies in healthy subjects have revealed that sleep loss is associated with adverse metabolic consequences. Current epidemiologic and clinical evidence suggest a strong link between sleep apnea and metabolic disorders such as insulin resistance, glucose intolerance and type 2 diabetes. This lecture will review the current evidence for a link between alterations in glucose metabolism and sleep apnea. The talk will also discuss the findings from the experimental laboratory studies examining the metabolic effects of reduced sleep duration and quality.

Learning Objectives:

At the conclusion of this presentation, participants should be able to:

- Cite the evidence that links sleep disturbances with risks of altered glucose metabolism and diabetes
- Counsel patients on these risks

NAMS/Kenneth W. Kleinman Endowed Lecture
“Liability Issues for Prescribers of Compounded Drug Products”

Liability Issues for Prescribers of Compounded Drug Products

Bruce Patsner, MD, JD. University of Houston Law Center, Houston, TX

Healthcare providers who prescribe drugs (or vaccines or medical devices) for patients always run the risk of being sued even when the manufacturer of the product is protected from liability in state or federal court by legislation (as is the case with some medical devices and most childhood vaccines). Failing to adequately warn about potential side effects, or prescribing the wrong dose or wrong drug are established liability concerns for clinicians, but worrying about the purity/potency or manufacturing defects are not, at least for commercially manufactured drug products. The widespread publicity and media coverage surrounding the deaths caused by the Massachusetts compounding pharmacy’s products have added an additional layer of counseling that clinicians must provide to their patients for compounded prescription drugs, whether they are supposed to be sterile or not. What should patients be told about prescription drugs....indications, side effects, and ALL other risks from the product?

Learning Objectives:

At the conclusion of this presentation, participants should be able to:

- Outline the liability risks of prescribing compounded products
- Counsel patients appropriately on the risks of compounded and prescription products to minimize liability

Plenary Symposium #9

“Proceedings from the ISSWSH/NAMS Consensus Conference on Vaginal Atrophy Terminology”

What’s in a Name? The Need for a New Nomenclature for Vulvovaginal Atrophy

David J. Portman. Ohio State University College of Medicine, Columbus, OH

The term vulvovaginal atrophy (VVA) is often used to describe the constellation of vulvar and vaginal signs, symptoms, and pathology associated with decreased estrogen levels associated with menopause. Frequently used by clinicians, this term is often used interchangeably, and perhaps imprecisely, with atrophic vaginitis. The two terms represent clinically different conditions. Further, the term vulvovaginal atrophy is not well received by patients because of the negative connotations of the word atrophy. To standardize and destigmatize the nomenclature, as well as the diagnosis, a Consensus Conference was held to discuss potential alternative nomenclature, review the latest scientific data, and devise a practical, concise staging tool for clinicians based on consistent anatomic and physiologic changes. Recent survey data regarding patient perception of VVA and its impact were reviewed. Before discussing nomenclature and developing the tool, experts discussed key topics related to vaginal health. Committee members comprised experts representing The North American Menopause Society and the International Society for the Study of Women’s Sexual Health. The selection of Committee members and the key topics used by the Committee to develop the nomenclature and the tool will be discussed.

Learning Objectives:

At the conclusion of this presentation, participants should be able to:

- Critique the terminology for vaginal atrophy based on the current and proposed mechanisms of genitourinary changes in menopause

Plenary Symposium #9

“Proceedings from the ISSWSH/NAMS Consensus Conference on Vaginal Atrophy Terminology”

New Nomenclature and a New Staging Tool for Vulvovaginal Atrophy

Margery L. Gass, MD, NCMP. Cleveland Clinic Lerner College of Medicine of Case Western Reserve University School of Medicine, Cleveland, OH

The ISSWSH/NAMS Consensus Conference members discussed a variety of terms to replace the term vulvovaginal atrophy (VVA). They took into consideration the genitourinary organs that undergo anatomic changes in the presence of low estrogen, as well as the constellation of signs and symptoms seen clinically. In addition, they considered how the public and how women affected by the condition might perceive the proposed terms. The Committee ultimately reached consensus on a recommendation, which will be presented for discussion by those attending this plenary session. The thought process and key factors in selecting a term to replace VVA will be described. In addition to proposing new terminology for VVA, the Consensus Conference members drafted a staging tool for clinicians, which will be presented and discussed. The staging tool is intended to serve as an aid for clinicians who prefer a checklist form of evaluation and documentation. The tool could also serve as a research screening tool for studies on VVA that are designed to track improvements in certain parameters. The tool allows changes in such vulvovaginal features as elasticity, lubrication, tissue integrity, and specific aspects of anatomy, such as introital stenosis and urethral changes to be categorized as normal, mild, moderate, or severe.

Learning Objectives:

At the conclusion of this presentation, participants should be able to:

- Assess the usefulness and accuracy of a proposed tool to diagnose and stage genitourinary anatomic changes

Plenary Symposium #10 *“Nutrition in the 21st Century”*

The Impact of a Probiotic Strain on the Structure and Function of the Human Gut Microbiota

Claire M. Fraser, PhD. University of Maryland, Baltimore, MD

The gut is colonized by trillions of microbes (the “microbiota”) that play an essential role in metabolic homeostasis. The two most abundant bacterial phyla in the large intestine are the gram-negative Bacteroidetes and the gram-positive, low-percentage-GC Firmicutes. Efforts to understand the role of the gut microbiota in health and disease have used 16S rRNA profiling to describe disease-associated dysbiosis (e.g., in obesity, T2DM, metabolic syndrome) and diet-induced changes in the composition of the gut microbiota. Consumption of probiotic bacteria has been heralded as a means to promote digestive health, alleviate a range of deleterious conditions including atopic dermatitis and gastroenterological diseases, and presumably reverse dysbiotic microbiota to restore gut mucosal homeostasis. In vitro studies to delineate the molecular mechanisms of probiotic species have indicated modulatory capabilities for strain-specific and molecule-specific benefits to the host, which include shifts in anti-inflammatory cytokine profiles and stabilization of epithelial tight junctions. However, extrapolation of these mode-of-action studies to in vivo behavior is complicated by a multitude of factors, largely by the complex, reciprocal interaction of the host with the resident microbiota along the gastrointestinal tract. The majority of randomized clinical trials (RCTs) to evaluate the in vivo health benefits of probiotic species have focused on a collection of clinical measurements from the human host, yet few studies have focused on the impact of probiotic consumption on the resident gastrointestinal microbiota at a community-wide scale. The most comprehensively studied probiotic, *Lactobacillus rhamnosus* GG ATCC 53103 (LGG), has exhibited clinical benefits from a variety of cohort studies and is thought to act by (i) competitive colonization advantage through the use of mucus-binding pili, (ii) putative bacteriocin activity identified via bacteriocin-like genomic architecture, and (iii) soluble effector signaling proteins that elicit anti-inflammatory cytokines and activate MAPKs. A major challenge to assess the impact of probiotics on the resident gut consortia is the ability to measure both compositional and functional components on a community-wide scale. We have characterized the structure and functional dynamics of the gut microbiota associated with consumption of the single-organism probiotic, *Lactobacillus rhamnosus* GG ATCC 53103 (LGG), from a study of twelve healthy elderly individuals. The gut microbiota of the elderly provides a unique system to study the fitness landscape of the presumptive healthy, aging microbiota and assess the community stability and dynamics. We found that while the community composition and structure was not modified due to probiotic intake, community-wide transcriptional changes were evident. Furthermore, we provide key insight into the role of a single-organism probiotic on the structure and function of the resident gut microbiota.

Learning Objectives:

At the conclusion of this presentation, participants should be able to:

- Outline the tools and approaches to study the human microbiota
- Describe the composition of the human gut microbiota
- Evaluate the advantages and limitations of probiotic therapies in humans

Plenary Symposium #10

“Nutrition in the 21st Century”

Application of Nutrigenomics Toward Personalized Dietary Recommendations

Johanna W. Lampe, PhD, RD. Fred Hutchinson Cancer Research Center, Seattle, WA

Nutrigenomics has been defined as the study of the effects of diet and food constituents on gene expression. It has also been described as the influence of genetic variation on response to diet. Taken together, the interaction of genetic polymorphisms and dietary exposure on gene expression has the capacity to influence a myriad of pathways critical to health. We now have the technologic capabilities to collect large amounts of genetic, epigenetic, transcriptomic, metabolomic, and gut microbiome data. These ‘omics’ data have the potential to transform our approach toward individual nutrition counseling by allowing us to recognize and embrace the metabolic, physiologic and genetic differences among individuals. An ultimate goal would be to integrate these multi-dimensional data so as to characterize the health status and disease risk of an individual and to provide personalized dietary recommendations to maximize health and minimize disease risk. To this end, we need accurate and predictive systems-based measures of health that incorporate molecular signatures of genes, transcripts, proteins, metabolites, and microbes. Observational studies have provided insights into the associative interactions between genotypes or phenotypes and diet and their impact on disease risk. Suhre et al (Nat Genet, 2011) conducted an analysis of genotype-dependent metabolic phenotypes using a genome-wide association study (GWAS) and non-targeted metabolomics in a sample of 1768 individuals. They identified 37 genetic loci associated with blood metabolite concentrations, of which 25 showed effect sizes that accounted for 10–60% difference in metabolite levels per allele copy. Their results provided important functional insights into chronic disease-related associations that have been reported in previous studies. However, fewer experimental studies in humans have addressed the effects of genotype or phenotype and diet and the impact on risk factors for disease risk. We can use dietary interventions that test carefully controlled diets in well-characterized study populations and that monitor system-wide responses (ideally using more than one omics platform) to generate the data necessary to characterize phenotypes under controlled conditions. For example, Heinzmann et al (J Proteom Res, 2012) used metabolomics to study the stability of phenotypic response to diet through sequential dietary challenges and showed that inter-individual differences tended to be greater than differences within an individual in response to dietary modulation. In another study, Niculescu et al (J Nutr Biochem, 2007) reported differential lymphocyte gene expression by bacterial metabolic phenotype in postmenopausal women receiving a soy isoflavone supplement; greater increases in estrogen-responsive genes were observed in women harboring the gut bacteria capable of converting the isoflavone daidzein to equol. A growing number of studies such as these are contributing to the characterization of comprehensive phenotypic profiles. Thus, given the availability of the necessary tools, we will ultimately be able to provide personalized dietary recommendations. However, in order to develop effectively these recommendations, we need to understand better what contributes to the phenotypic complexities of individuals and their responses to the complexities of their diets.

Learning Objectives:

At the conclusion of this presentation, participants should be able to:

- Personalize dietary recommendations for patients now and in the future based on discoveries in nutrigenomics

Plenary Symposium #11

“Bioidentical Hormones—What Are the Issues?”

Bioidentical Hormone Therapy—What, Why & How?

Jan L. Shifren, MD, NCMP. Harvard Medical School, Boston, MA

“Bioidentical hormone therapy (bioHT)” is a marketing term, rather than a medical term, so there is no universally accepted definition. For a woman with bothersome menopausal symptoms and concerns about potential HT risks, “bioHT” may mean a formulation of hormones with all of the benefits and no risks, as it’s “natural” and contains no package insert with a black box warning. For a “bioHT” practitioner, it may mean a way of helping menopausal women disenfranchised with the medical establishment, while providing a steady source of income. For a clinician or pharmacist practicing within the current standard of care, an FDA inspector, or lawyer for a woman with endometrial cancer associated with its use, “bioHT” may mean something quite different! “BioHT” typically involves the prescription of ‘natural’ hormones (estradiol, estrone, estriol, progesterone, and testosterone) custom compounded in a topical cream (or oral tablet) for an individual patient based on her symptoms and blood or salivary hormone levels. There is some evidence supporting the use of estradiol and progesterone instead of other forms of estrogen and progestogen for menopause symptoms. Research also supports the use of transdermal instead of oral estrogen administration. In contrast, there are no quality data supporting the use of custom compounded HT formulations for the majority of women and well documented concerns regarding the safety, purity, dose consistency and bioavailability of these products. In addition, HT dosing should be guided by a woman’s symptoms and there are no data to support the use of blood or saliva measurements to improve treatment efficacy. Government approved formulations of estradiol for menopausal symptoms are currently available as an oral tablet, skin patch, topical gel, topical spray and vaginal ring. Low doses of estradiol for use in the vagina to treat vaginal dryness and dyspareunia are available as a vaginal tablet, cream, and ring. Progesterone is available as an oral capsule. Current concerns with “bioHT” relate principally to custom compounding. If “bioHT” is defined as HT formulations that utilize hormones chemically identical to those naturally produced by the ovaries during a woman’s reproductive years with principally transdermal administration, then a clinician practicing within current standards of care can provide “bioHT” formulations to women with menopausal symptoms using only high quality government approved products.

Learning Objectives:

At the conclusion of this presentation, participants should be able to:

- Differentiate bioidentical hormone therapy from custom-compounded hormone therapy
- List the documented concerns about the safety, purity, dose consistency and bioavailability of custom-compounded hormones and explain these to patients in counseling
- Counsel patients on the risks and benefits of custom-compounded and FDA-approved hormone therapy formulations

Plenary Symposium #11

“Bioidentical Hormones—What Are the Issues?”

Compounded vs FDA Approved: Is There a Controversy? Fact vs Fiction Erika Schwartz, MD. Age Management Institute, New York, NY

The history of compounding is recorded in 754 AD. The Food and Drug Administration started in the late 19th century. Franklin Roosevelt signed the Food, Drug, and Cosmetic Act 1938. (www.fda.gov) Compounded drugs are omnipresent in the practice of medicine from hospital medications in IVs, chemotherapy, pain to pediatric medications to transdermals. The initial controversy started in the wake of the publication of the results of the Women’s Health Initiative. (Writing Group for the Women’s Health Initiative Investigators 2002 “Risks and Benefits of Estrogen Plus Progesterin in Healthy Postmenopausal Women: Principal Results From the Women’s Health Initiative Randomized Controlled Trial”. JAMA 288 (3): 321–333) Since Premarin and Provera, studied by the WHI appeared to carry high risk some physicians opted to start using human identical hormones. Compounding was initially the primary source for human identical hormones (17-beta estradiol, progesterone) not included in the WHI but heavily studied for decades. The most destructive controversy was started in 2007 by a TV actor and marketer, who misrepresented the human identical alternatives 17-beta estradiol and progesterone as novel and superior options in the form of compounded “bioidentical hormones”. (Kantrowitz B; Wingert P (2006-11-13). “A Real Somers Storm: At war over Suzanne Somers’s book on ‘bioidenticals’”. Newsweek.) As a result, six years of confusion and controversy hurt women and polarized the physicians they needed most. Estradiol and progesterone are human identical hormones in use in the conventional medicine for decades. All hormones do not behave the same in the human body. Numerous studies have shown that (E3N, KEEPS, PEPI, RUTH, Danish Study, etc). The term “bioidentical” initially used by non-physicians, alternative groups and the media was discarded as “marketing term” by conventional medical world creating more fractionation and discord. Compounding was trashed in an article by Boothby and Doering in 2008 (Boothby LA, Doering PL (August

2008). “Bioidentical hormone therapy: a panacea that lacks supportive evidence”. Curr. Opin. Obstet. Gynecol. 20 (4): 400–7 containing much misinformation leading to further confusion and fragmentation. The incorrect identification of saliva testing with compounding furthered the discord. (Rosenthal, MS (2008). “The Wiley Protocol: an analysis of ethical issues”. Menopause 15 (5): 1014–22.) Bioidentical hormones is a term used to describe human identical hormones- 17 beta estradiol, progesterone, micronized testosterone, human insulin, etc. All hormone preparations are synthetic compounded or FDA approved. Many exist in preparations that are both FDA approved since the late 1980s and compounded since the 1800s. All hormones do not behave the same in the human body. (International Menopause Society- 2011- PEPI, KEEPS, RUTH, E3N, Danish Study, etc) Compounding is part of individualized medicine. It creates formulations either not available in FDA approved products or formulated to meet specific needs; testosterone for women, transdermal preparations tolerated or absorbed better by the patient. Saliva testing should not be equated to compounding or “bioidentical hormones”. The connection between the two is misleading. The use of estriol is limited to a small group of physicians and is not available in FDA approved formulations. (www.fda.org). It should not be equated to the term “bioidentical hormones”. Safety profile is as important in FDA approved and compounded products and is not the responsibility of clinicians. Compounding- customization – there will always be a need to customize drugs and the case of “bioidenticals” is not different. (Fugh-Berman, A; Bythrow J (2007) “Bioidentical Hormones for Menopausal Hormone Therapy: Variation on a Theme”. Journal of General Internal Medicine 22 (7): 1030–4) Individualized medicine requires compounding. It behooves physicians to become familiar with the use of compounding through education and cooperation. Cost and reimbursement- Just like FDA approved medication, compounded hormones vary in cost and insurance coverage. With better understanding of the facts this controversy will be resolved and both FDA approved and compounded human identical hormones will coexist.

Learning Objectives:

At the conclusion of this presentation, participants should be able to:

- Explain why there is controversy over bioidentical hormones
- Clearly appraise the issues and nomenclature at the core of the controversy
- Differentiate scientific evidence from media hype, alternative stances, and special interests
- Base hormonal management of patients’ menopause symptoms on best practices and not polarized positions

Plenary Symposium #11

“Bioidentical Hormones—What Are the Issues?”

Is the Truth About Compounding Knowable?

Bruce Patsner, MD, JD. University of Houston Law Center, Houston, TX

I'm going to contrast the counseling/costs for bioidentical hormone replacement therapy (BHRT) products for menopause with that for commercial hormone therapy (HT) products, using FDA guidance documents as a map. We're also going to go over some typical (and atypical) promotional claims and websites as well as who and how they are currently being regulated.

Learning Objectives:

At the conclusion of this presentation, participants should be able to:

- Contrast the counseling/costs for bioidentical hormone replacement therapy products for menopause with those of commercial hormone therapy products
- Assess websites and promotional claims for bioidentical hormone replacement therapy products
- Review the current regulations that apply to these claims and websites