

## 2017 Hormone Therapy Position Statement of The North American Menopause Society

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Hormone therapy (HT) is the most effective treatment for hot flashes, night sweats, and sleep disruption caused by menopause; it also prevents bone loss and fractures. Risks of HT differ depending on type, dose, duration of use, route of administration, timing of initiation, and whether a progestogen is needed. HT is safe for most menopausal women under 60 or within 10 years of menopause, using the lowest dose and safest route for relief of symptoms. Longer duration may be more favorable for ET than for EPT, based on the WHI RCTs. For women who initiate HT more than 10 or 20 years from menopause onset or when aged 60 years or older, the benefit-risk ratio appears less favorable, because of greater absolute risks of CHD, stroke, VTE, and dementia. Low-dose vaginal ET is recommended when needed for GSM symptoms. **Recommendation:** NAMS encourages practitioners to find the appropriate type, dose, formulation, and duration of HT use, with individualized shared decision making based on evidence-based information and the unique health risks of the individual woman and with ongoing surveillance and periodic reassessment. Following the release of the controversial WHI trial results 15 years ago, many women who could have benefited from HT went without the help they needed. The NAMS HT Advisory Panel reviewed WHI results and 13 year follow-up, newer randomized trials and observational data; this review was not limited to a single study, product, time period, or country and included the effects of HT on cardiovascular disease (CVD), metabolic syndrome, and diabetes; cancers including breast, endometrial, lung, colon, and ovary; osteoporosis and fracture prevention; mood and cognition; vasomotor symptoms including sleep disruption; liver and gallbladder; musculoskeletal, osteoarthritis and joints; special senses (skin, eyes, ears); genitourinary issues; quality-of-life (QOL), risk stratification, and economic issues. Key points summarize findings with areas of scientific uncertainty identified. Clinical Guidelines are provided with the level of evidence graded to provide strength and quality of evidence. **Breast Cancer:** For women with a uterus, progestogens protect against estrogen-stimulated uterine cancer. The risk (rare, <1/1000) of breast cancer appears associated with the combination of estrogen and progestogen or longer durations of estrogen alone. No increased risk was seen with conjugated estrogen alone during the 7 years in the WHI study, but some studies suggest increased risk after 15 or 20 years. **CVD:** Data suggest reduced risk of CHD in women who initiate HT aged younger than 60 years and/or within 10 years of menopause onset, but not in women who initiate HT older than age 60 or more than 10 or 20 years, from menopause onset. **Special Populations:** *Early menopause:* For women with POI or premature surgical menopause without contraindications, HT is recommended until at least median age of menopause (52 y). Observational studies suggest benefits appear to outweigh the risks for effects on bone, heart, cognition, GSM, sexual function, and mood. (Level II). *Family history (FH) of breast cancer:* Observational evidence suggests that use of HT does not alter the risk for breast cancer in women with FH of breast cancer; FH should be assessed when counseling regarding HT. (Level II). *BRCA-positive women without breast cancer:* BRCA-positive women without breast cancer are at higher genetic risk of breast cancer, primarily estrogen-receptor negative. For those with surgical menopause (oophorectomy), benefits of estrogen to decrease health risks caused by premature loss of estrogen need to be considered. (Level II). After appropriate counseling in women without contraindication, systemic HT may be offered until the median age of menopause based on limited observational studies; longer use should be individualized. (Level II). *Extended use:* The recommendation using the Beers criteria to routinely discontinue systemic HT after age 65 is not supported by data. Decisions regarding continuation of HT beyond the age of 60 should be individualized with appropriate evaluation and counseling about potential benefits and risks and with ongoing surveillance. (Level III).

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## Plenary Symposium 1—Presidential Symposium

### *Social Media and Technology: Driving the Direction of Women’s Health*

#### **The Impact of Media on Medicine and Consumer Education**

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The landscape has changed in how consumers get their health information. In addition, the highly complex information in medicine and science separates health journalism from other forms of journalism. It is clear that knowledge translation is complex and begs the cooperation of scientists and journalists alike. In *The Elements of Journalism*<sup>1</sup> the authors point out that the so-called “discipline of verification is what separates journalism from entertainment, propaganda, fiction, or art.” The authors go on to add: never add anything that was not there, never deceive the audience, be as transparent as possible about your methods and motives, rely on your own original reporting, and exercise humility. They also emphasize that there is a skill required in the translation of knowledge to the consumer. But the question remains, is the reporter of science and medicine always skilled and trained in these areas? In 2002, Melinda Voss looked at newspapers and the key role in disseminating information and shaping perceptions about health, research, and policies.<sup>2</sup> Voss pointed out that inadequate or misleading reporting constitutes a public health threat that can jeopardize individual health and lead to harmful health policies. In her study, surveys were mailed to 165 reporters at 122 newspapers in 5 Midwest states. The association of training, newspaper size, and experience with reporter’s self-perceived reporting ability was assessed. The response rate was 69.6% and 66-85% of the reporters assessed 4 tasks vital to sound health reporting as “sometimes difficult” to “nearly always difficult.” Respondents with less experience reported higher difficulty in perceived ability. Reporters may have difficulty understanding complex health issues and interpreting statistics because they are inadequately trained. Vincent Covello of the Center for Risk Communication at Columbia University states that the media has a pervasive impact on public perceptions of risk. “Research has shown that strong beliefs about risk, once formed, change very slowly and are extraordinarily persistent in the face of contrary evidence.” Therefore, the way in which we report, the language we use, and the knowledge translation become critical for the consumer in making that first impression. The media world is changing and social media has revolutionized how we communicate. It’s no longer enough to ask “how can the media help communicate messages” but better to find ways to harness the power of online communication to make sure consumers get correct information and as much information as they need to navigate. According to Pewinternet, 31% of mobile phone owners have used their phone to look for health information<sup>3</sup> and their analyst forecast indicated that 500 million people would be using mHealth apps by 2015.<sup>4</sup> Yet, few apps actually have anything to do with health.<sup>5</sup> What is clear to me after decades of reporting health and medicine is the importance of knowledge translation done in understandable language on whatever media platform we can examine. Indeed medicine does not work in sound bites but that is often all that is remembered or heard. As healthcare providers and scientists we often speak in a language that is understood by only our own community and, as such, can be an invitation to misinterpret. It is critical to recognize it is the responsibility of all of us, not the media alone, to educate the consumer. 1. Kovach B, Rosenstiel T, *The Elements of Journalism: What Newspeople Should Know and the Public Should Expect*. 3rd ed. New York, NY: Three Rivers Press; 2014. 2. Voss M. Checking the Pulse: Midwestern reporters’ opinions on their ability to report healthcare news. *Am J Public Health* 2002;92:1158-1160. 3. Fox S, Duggan M. Mobile health 2012. Pew Research Center Website. Available at: <http://www.pewinternet.org/2012/11/08/mobile-health-2012/>. Accessed February 1, 2016. 4. Research2Guidance. mHealth app developer economics 2014. Available at: <http://mhealththeconomics.com/mhealth-developer-economics-report/>. Accessed February 1, 2016. 5. Melnick M. In the candy store of iPhone apps, users treat health apps like broccoli. *Time*. October 21, 2010. Available at: <http://healthland.time.com/2010/10/21/in-the-candy-store-of-iphone-apps-users-treat-healthapps-like-broccoli/>. Accessed February 1, 2016.

## Plenary Symposium 1—Presidential Symposium *Social Media and Technology: Driving the Direction of Women's Health*

### Mobile Health Technologies in Clinical Care and Research

Claudio N. Soares, MD, PhD, FRCPC, MBA<sup>1,2</sup>. <sup>1</sup>Department of Psychiatry, Queen's University School of Medicine, Kingston, ON, Canada; <sup>2</sup>University of Toronto, St. Michael's Hospital, Toronto, ON, Canada

Mobile Health Technologies (M-Health) are here to stay as part of a novel era in clinical care and cutting-edge research. In recent years remote biosensors have already become useful tools for the management of multiple and complex medical conditions—from the use of ‘smart shirts’ for patients with chronic obstructive pulmonary disease to the development of wristbands that detect potentially deadly seizures and alert wearers and caregivers. Remote monitoring is diminishing traveling costs and reducing the burden incurred by multiple visits to health care services. But there are other enticing applications for m-health technologies, particularly with the use of smartphones. The smartphone penetration in North America is currently 70% with more than 250 million users. Smartphones have an almost continuous presence in patients’ everyday lives, allowing data collection in a personalized manner with minimal effort and at a relatively low cost. Phone sensors already capture temporal and geographic mobility patterns, speech and vocal markers and physiological measures. Real-time assessments (also known as ecological momentary assessments, EMAs) allow the characterization of fluid changes in people’s moods, behaviors and activities over time. These assessments produce an invaluable amount of data for clinical and research purposes. They also reduce the effects of recall bias or random physiological and behavioral changes due to heightened sensitivity to in-person interviews (the so-called white coat effect).<sup>1</sup> We are entering the era of *digital phenotyping* in which a ‘*real-time, moment-by-moment quantification of the individual-level human phenotype*’ can be construed using data from personal digital devices.<sup>2</sup> The premise here is that individuals leave behind a footprint of their health status through their use of technologies, including but not limited to mobile devices, wearable technologies, use of social media and online communities. In the recent article *Smartphone Psychiatrist*,<sup>3</sup> Tom Insel (former NIMH director and co-founder of Mindstrong Health) praised the potential use of smartphones to track daily behaviors that reflect mental health. “A phone can sense the beginning of a crisis and trigger an appropriate treatment response.” Like his start-up, many other companies are testing a variety of phone-based data-collection-and-analysis systems. In the near future, he says, mega-data could lead us to the characterization of repetitive semantic structures or key words/phrases which in turn could become indicative of emotional or cognitive states—a relapse into a depressive state after a period of wellness, a psychotic episode or an early sign of cognitive deterioration. Despite the ‘technological hype’ this field still faces skepticism and barriers for greater adoption by end-users (healthcare agencies, researchers, clinicians and patients). There are important questions around privacy and confidentiality of information gathered; reliability and usefulness of mega-data collected (real data versus noise); and credibility of mobile applications currently available in the market. In a recent survey, there were more than 1,500 ‘depression’ apps available in the marketplace; surprisingly, only 5% of those had credible links to medical centers, universities and institutions.<sup>4</sup> It is critical to recognize that clinicians and researchers can no longer remain bystanders or afford being laggards in the adoption of these novel technologies. Instead, we need to find our way to the driving seat. 1. Marzano L, Bardill A, Fields B, Herd K, Veale D, Grey N, Moran P. The application of mHealth to mental health: opportunities and challenges. *Lancet Psychiatry*. 2015;2(10):942-8. 2. Onnela JP, Rauch SL. Harnessing Smartphone-Based Digital Phenotyping to Enhance Behavioral and Mental Health. *Neuropsychopharmacology*. 2016;41(7):1691-6. 3. Dobbs D. The Smartphone Psychiatrist. Available at: <https://www.theatlantic.com/magazine/archive/2017/07/the-smartphone-psychiatrist/528726/>. Accessed July 20, 2017. 4. Shen N, Levitan MJ, Johnson A, Bender JL, Hamilton-Page M, Jadad AA, Wiljer D. Finding a depression app: a review and content analysis of the depression app marketplace. *JMIR M health U health*. 2015;3(1):e16.

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## Plenary Symposium 1—Presidential Symposium

### *Social Media and Technology: Driving the Direction of Women’s Health*

#### **Improving Patient Engagement and Outcomes Through Novel Technology**

Carlos Rodarte. Volar Health, LLC, Cambridge, MA

Clinical encounters are often structured for efficiency and not always centered on the *person*. As a result, there is little concern for everyday behaviors, individual aspirations, support structure, home life, and other aspects of “real life.” Those developing health technologies need to go a step further than understanding the clinical exchange — in order to solve a patient’s problems, they must truly understand the patient’s everyday experiences. In today’s world, technology is all around us. In the last five years alone, patients now have access to more smartphone apps, wearables, and Internet-of-Things devices than ever before. However, better health outcomes are not always achieved. What are the technologies being developed that are actually making an impact on patient engagement? Improving health outcomes? How are they being developed? What is the impact of these technologies on the broader healthcare ecosystem? From chatbots employing natural language processing (NLP) to Artificial Intelligence (AI) approaches, such as machine learning-based decision support systems (ML-DDS), there are a number of examples of how technology is being incorporated into the delivery of care. Further, the role of “digital biomarkers” is only growing and helping us understand health status, disease progression, and treatment effectiveness. Companies that are the most successful in developing new technologies are shifting their perspective from the belief that we are simply building *products* and *services*, but rather, designing whole-life experiences to promote positive behaviors. The days of deciding what is best for an individual, without asking the individual are gone. This presentation will explore methods to gather “real life” data, approaches to consider when designing healthcare experiences, and showcase a diverse set of novel patient engagement solutions being utilized by health systems, providers, and payors.

## Keynote Address

### ***Minimally Invasive Gynecologic Surgery: What the Menopause Practitioner Needs to Know***

#### **Minimally Invasive Gynecologic Surgery: What the Menopause Practitioner Needs to Know**

Arnold P. Advincula, MD, FACOG, FACS. Columbia University Medical Center, New York, NY

Since the advent of the first laparoscopic-assisted vaginal hysterectomy in the late 1980's, minimally invasive surgical techniques have had a significant impact on women's health. Although technological innovation has occurred by leaps and bounds over the last couple of decades, so have the complications and controversies related to those advancements. This presentation will address the risks and benefits of undergoing minimally invasive gynecologic surgery during the menopausal years. Relevant surgical device controversies and the implications on clinical decision making for postmenopausal women will be discussed.

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## Plenary Symposium 2

### ***Addressing Vaginal Health and Pelvic Pain***

*Supported by grant funding from Amag Pharmaceuticals and Endoceutics, Inc.*

#### **Treating Vulvovaginal Atrophy/Genitourinary Syndrome of Menopause: Lubricants, Moisturizers, and Vaginal DHEA**

Nick Panay, BSc, MBBS, MRCOG, MFSRH. West London Menopause and PMS Centre at Queen Charlotte's and Chelsea Westminster Hospital, London, United Kingdom

Vaginal dryness and pain are common symptoms, occurring in up to 50% of postmenopausal women as a result of Vulvovaginal Atrophy (VVA)/ Genitourinary Syndrome of Menopause (GSM). The impact of vaginal dryness and pain on interpersonal relationships, quality of life, daily activities, and sexual function can be significant, but the impact is frequently underestimated. Furthermore, barriers exist to treatment-seeking and this problem is often underreported and undertreated. Greater education about VVA/GSM and the range of available treatments is essential to encourage more women to seek help for this condition. Alternatives to vaginal estrogen are particularly important in women with a past history of hormone dependent malignancy e.g. breast cancer. Personal lubricants and moisturizers are effective at relieving discomfort and pain during sexual intercourse for women with mild to moderate vaginal dryness, particularly those who have a genuine contraindication to estrogen or who choose not to use estrogen. However, there are notable differences between different commercially available products. In order to optimize effectiveness and minimize adverse effects, women should be advised to choose a product that is optimally balanced in terms of both osmolality and pH, and is physiologically most similar to natural vaginal secretions. A series of clinical recommendations for the use of vaginal lubricants and moisturizers, either on their own or in combination with systemic or topical hormone therapy, will be presented. Information will also be presented on the efficacy and safety of intravaginal dehydroepiandrosterone (DHEA) when used to treat VVA/GSM symptoms. The US Food and Drug Administration recently approved Intrarosa (prasterone) to treat women experiencing moderate to severe pain during sexual intercourse (dyspareunia), one of the key symptoms of VVA/GSM. The potential clinical roles of this product will then be put into context of all the currently available therapeutic options.

## Plenary Symposium 2

### *Addressing Vaginal Health and Pelvic Pain*

*Supported by grant funding from Amag Pharmaceuticals and Endoceutics, Inc.*

#### **Physical Therapy and Pelvic Muscle Health and Function in Menopause**

Denise Hartzell Leggin, PT, MBA, WCS. University of Pennsylvania Health System, Radnor, PA

During the female lifecycle of puberty, adolescence, early adult life, mid adult life, and late adult life the body undergoes significant changes. Menopause is a normal physiologic event occurring from 40-58 years of age. However, menopause can be induced at an earlier age due to surgery, iatrogenic, or related to medical treatment such as chemotherapy or pelvic radiation. According to the Center of Disease Control(CDC) and US Government Census, female life expectancy is 81 years (2015) compared to male life expectancy of 77; 41% of the female population is older than 45 (2012), 8.5% of women are older than 65 (2015). Estimates forecast that by 2030, worldwide, 13.4% of the population will be women over age 65. With these numbers, 80% of women can experience 1/3 of their life with menopausal symptom complaints (NAMS 2015). According to the CLOSER survey (NAMS Dec 2011-Feb 2012), the top five postmenopausal symptoms include: night sweats, weight gain, hot flashes, and vaginal/urinary symptoms. In 2014, ISSWSH and NAMS adopted Genitourinary Syndrome of Menopause (GSM) as providing more conclusive symptoms experienced during menopause (including vaginal, sexual, voiding symptoms). Although this is opinion, GSM terminology may permit more open discussion of symptoms with those experiencing such symptoms and their healthcare provider. Pelvic floor dysfunction (PFD) may coexist with menopausal symptoms. Bump (1998), defined pelvic floor dysfunction (PFD) to include a variety of clinical conditions: urinary incontinence, anal incontinence, pelvic organ prolapse, sensory and emptying dysfunction of the lower urinary tract, pelvic pain and sexual dysfunction. PFD is likely to exist from a mechanism that is difficult to attribute to one specific mechanism and pathophysiological process. Therefore, a multidisciplinary approach may need to be considered. The role of the pelvic floor as a musculoskeletal complex and its functional role has been studied and validated since at least 1975 by Vreeken. Diendl (1993) has established the role of pelvic floor function in SUI. Diendl looked at wire EMG in nulliparous women on continence. The pubococcygeus muscle was active at rest; but increased during intraabdominal pressure; and decreased during voiding. Ruth Sapsford in 2004, found that pelvic floor muscle activity changes with seated static posture (i.e. less tone with slumped and more active with erect/increased lordosis posture). Paul Hodges (2007) demonstrated the role of pelvic floor muscles contributing to core stability for postural control and respiration (with Sapsford). Abdominal and/or pelvic surgery due to POP, endometriosis, gynecological function should be considered. Abdominal pain due to adhesions have been reported in 63-97% (Arung W, 2013) of women following single or multiple abdominal surgeries such as Cesarean section, laproscopic procedures, GI surgery, etc. Interestingly, 1/3 of these surgeries require re-admittance for surgery due to pelvic pain, with 20% occurring within first year following their first surgery. Physical therapy and manual therapy may be adjunctive for pelvic pain. In February 2011, histological data on early manual therapy interventions on visceral and soft tissues in rats resulted in less post-surgical adhesions. As with other skeletal muscles, the pelvic floor is affected by the normal physiological changes of aging such as decrease in strength. When we superimpose the female hormonal changes, the complexity of involvement of functional role of this muscle group on stability, support, continence and sexual appreciation; we can appreciate how dysfunction of the pelvic floor may contribute to functional impairment. Verbal instruction of pelvic muscle contraction alone has been demonstrated as ineffective 50% of the time (Bump). This 30 minute talk will briefly discuss the multidisciplinary approach to decision making and considerations for referral to Physical Therapy based on comorbidities such as medical/surgical history, gynecological/birthing history, GI function, and occupational/social activities with patient's subjective complaints.

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## Plenary Symposium 3

### *Hormone Therapy*

*Supported in part by grant funding from TherapeuticsMD*

#### **Selecting Progestogens: Breast, Cardiovascular, and Cognitive Outcomes**

James H. Liu, MD, NCMP. Case Western Reserve University School of Medicine, UH MacDonald Women's Hospital, Department of Obstetrics and Gynecology, Cleveland, OH

The primary reason for use of progestogens as a critical component of hormone therapy is the prevention of endometrial hyperplasia and carcinoma in those women with a uterus. Endogenous progestogens are derived from a 21-carbon structure with progesterone being the prototype. Synthetic progestogens derived from the 21-C skeleton include medroxyprogesterone acetate, megestrol acetate, and drospirenone while those derived from a 19-C structure (19-nortestosterone) include levonorgestrel, desogestrel, and norethindrone (i.e. norethisterone). Progestogens exert their biological effects through binding of two isoforms of the progesterone receptor, PR-A and PR-B within target tissues. The tissue phenotype response is based upon the ratio of PR-A to PR-B within the specific tissue. Thus, the breast, brain, liver, and vascular endothelium may respond differently to the same progestogen. The progestogen effects on non-endometrial tissue can be classified as "off-target effects." The 19-C derived progestogens have increased androgenic side effects such as acne, hirsutism, and weight gain. Liver metabolism of lipoproteins will be altered with an increase in LDL, reduction of HDL, and a decrease in triglycerides levels. Sex-hormone binding globulin will be reduced which may alter bioactive estrogen and testosterone levels. The androgenic activity is greatest for levonorgestrel whereas norethindrone may have weak estrogenic activity. In reproductive-aged women, estrogen in conjunction with progesterone stimulates increased breast mitotic activity. However, in epidemiological menopause studies of hormone therapy, evidence suggests that micronized progesterone has a lower breast cancer risk than those containing other synthetic progestogens. Sequential use of micronized progesterone does not seem to alter cardiovascular effects of estrogen. However, oral micronized progesterone can be associated with "premenstrual" mood and cognitive changes. Sleepiness can occur due to conversion of progesterone to  $20\alpha$ -hydroxyprogesterone, a natural soporific. This derivative may also be breast protective since it has been shown to be an aromatase inhibitor in breast tissue in vitro.

## Plenary Symposium 3 *Hormone Therapy*

*Supported in part by grant funding from TherapeuticsMD*

### **Hormone Therapy: No Sweat for Menopause Symptoms**

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

Vasomotor symptoms (VMS) are highly prevalent, affecting up to 85% of women traversing the menopause. Recent data suggest that VMS—consisting of hot flashes and night sweats—can persist for more than 10 years total duration. Menopausal hormone therapy with estrogen alone or estrogen plus progestin is nearly 100% effective in relieving VMS, and there are currently no available non-hormonal alternatives that have comparable efficacy. Vaginal dryness and dyspareunia due to genitourinary syndrome of menopause (GSM) are also very amenable to estrogen treatment, and other, approved medications do not appear to have comparable efficacy. For most women, therefore, the fastest and most efficient means to symptom relief is via hormone therapy. The degree of relief obtained by hormones are also the ‘gold standard’ against which all other treatments are measured, particularly for these two conditions. It is therefore critical to balance the benefits against the potential risks of hormone therapy. For many women, short-term treatment of 5 years or less poses minimal risks, especially for women who are in their 50’s. As women age, and background risks for disease increases, the benefit/risk equation needs to be more carefully balanced, or non-hormonal alternatives need to be considered. Ideally, symptomatic menopausal women can be treated for several years, and periodically attempt to wean off of hormones. For those with VMS who are fortunate, and do not have long-lasting symptoms, withdrawal from hormone therapy may be relatively straightforward, as symptoms will not return at the same level of intensity as they were at initial presentation and withdrawal will be easy. For those with persistent or prolonged symptoms, non-hormonal alternatives may be tried or hormone use can be extended. For vaginal symptoms, withdrawal of estrogen is likely to result in a reappearance of symptoms at the same intensity as before; therefore, for sexually active women, continued hormone use may be necessary and indicated. Other symptoms attributed to menopause, such as poor sleep and adverse mood, are less clearly related to hormone withdrawal, and may be more readily treated with condition-specific therapies.

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## Plenary Symposium 4

### *Evaluation of Uterine Bleeding and Adnexal Masses*

#### **Evaluation of Postmenopausal Bleeding: What Is the Standard of Care?**

Steven R. Goldstein, MD, FACOG, CCD, NCMP. New York University School of Medicine, New York, NY

Cancer of the endometrium (EM) is the most common type of gynecologic cancer in the United States. In 2017, an estimated 60,050 cases of this cancer will occur with an estimated 10,470 deaths. Vaginal bleeding is the presenting sign in more than 90% of postmenopausal (PM) patients with EM carcinoma. The majority of patients with postmenopausal vaginal bleeding (PMB) experience bleeding secondary to atrophic changes of the vagina or endometrium. However, depending on age and risk factors 1–14% will have EM cancer. Thus the clinical approach to PMB requires prompt and efficient evaluation to exclude or diagnose carcinoma. SHORTCOMINGS OF BLIND ENDOMETRIAL SAMPLING In 1991, after a single study by Stovall et al in women with known carcinoma reported 97.5% accuracy, blind EM sampling became the standard approach to patients with PMB. This was widely publicized, marketed and promoted and was rapidly accepted as, “standard of care.” In a similar study, however, Guido et al performed blind EM sampling in 65 patients with known carcinoma in the operating room just prior to their hysterectomy. They missed 11/65 cancers (sensitivity only 83%) but, upon opening all those uteri, they reported that when the cancers occupied 50% or more of the EM surface the biopsy was 100% accurate. Similar studies in women with known carcinomas yielded false negative rates of 16% and 32%, respectively. As a result, in 2012, ACOG, in its Practice Bulletin, acknowledged the primary role of EM sampling in such patients is to determine if carcinoma or premalignant lesions are present. The bulletin goes on to state that, “EM biopsy has high overall accuracy in diagnosing EM cancer when an adequate specimen is obtained and when the EM process is global. If the cancer occupies less than 50% of the surface area of EM cavity the cancer can be missed by blind individual biopsy. Therefore, these tests are only an endpoint when they reveal cancer or a typical complex hyperplasia.” This has tremendous ramifications for clinical practice. Certainly, healthcare providers, especially in low resource areas, can begin the evaluation with a blind biopsy but if the results do not indicate cancer or atypical hyperplasia the evaluation is not complete, especially if bleeding persists. Thus, the concept of distinguishing global from focal pathologies is becoming increasingly understood and important. Transvaginal ultrasonography (TV U/S) has been explored as an alternative technique to indirectly visualize the EM. The earliest reports comparing TV U/S measurement of EM thickness in women with PMB with EM sampling consistently found that an EM thickness of less than or equal to 4–5 mm in these patients reliably excluded EM cancer. Since that time a number of confirmatory multicenter trials have been completed. Because TV U/S in patients with PMB has an extremely high negative predictive value, it is a reasonable first approach to such patients. It is not possible to complete a meaningful TV U/S examination with a reliable measurement of EM thickness in all patients. An axial uterus, obesity, coexisting myomas, adenomyosis, or previous uterine surgery can contribute to difficulty in obtaining reliable TV U/S assessment of EM thickness and texture. Failure to adequately identify a thin, distinct EM thickness in a PM woman with bleeding should trigger some alternative method of evaluation, like saline infusion sonohysterography (SIS) or hysteroscopy, preferably in an office setting. Since there has been widespread use of TV U/S to exclude pathology in PM women with bleeding, some clinicians have inappropriately extrapolated this information to assume that a thick echo discovered incidentally is abnormal and requires investigation. Data indicates that 13% of asymptomatic PM women will have an endometrial polyp. In a large multicenter trial in which 1152 polyps in non-bleeding PM women were removed only 1 contained a cancer, yet the serious complication rate from such removals is reported as 3.6%! Thus, an EM measurement greater than 4 mm incidentally discovered in a PM patient without bleeding need not routinely trigger evaluation, although, an individualized assessment based on patient characteristics and risk factors is appropriate.

## Plenary Symposium 4 *Evaluation of Uterine Bleeding and Adnexal Masses*

### **Adnexal Masses in Menopausal Women—Surgery or Surveillance?**

Frederick R. Ueland, MD. University of Kentucky, Lexington, KY

Ovarian tumors in menopausal women require a thoughtful evaluation, because ovarian cancer is the leading cause of gynecologic cancer death in the U.S. and the mean age at diagnosis is 63 years. Ovarian cancer has a high mortality rate due in part to late stage presentation, as two thirds of women are diagnosed with stage III or IV cancer where the estimated 5-year survival is only 30%. In contrast, women diagnosed with stage I disease have an overall survival exceeding 90%. So the early identification of ovarian cancer has a decisive impact on patient outcome, particularly for menopausal women where the likelihood of malignancy is higher. It has been estimated that 200,000 surgeries are performed each year in the U.S. for a suspected pelvic mass. Since there are approximately 20,000 new cases of ovarian cancer identified each year, roughly 10 surgeries are performed to treat one ovarian cancer. But surgery is not risk-free as complications occur in up to 15% of gynecologic procedures. Surgical complications are also more likely to occur when performed by low volume surgeons, and it is estimated that 80% of gynecologic surgeons in the U.S. are low volume. It is no longer suggested that all postmenopausal ovarian tumors be surgically removed. Symptomatic masses or tumors at high risk for malignancy require surgery; however, asymptomatic low risk tumors can be safely monitored without surgical intervention. Consensus groups have recommended that women who experience certain symptoms might be at increased risk of ovarian cancer, including: bloating, pelvic or abdominal pain, early satiety, and urinary urgency or frequency. Not surprisingly, vague and nonspecific symptoms can represent a variety of conditions, and the majority of these women will not have ovarian cancer. If symptoms are from ovarian cancer, it likely represents an advanced stage. When persistent symptoms are present, recommendations include a complete physical exam, a transvaginal ultrasound, and if abnormal, biomarker testing. Physical examination is an important part of any gynecologic evaluation; however, it is not a reliable way to identify and classify tumors as benign or malignant. Pelvic examination is consistently less accurate than transvaginal ultrasound in detecting ovaries and defining ovarian dimensions, particularly in larger women, older women, or women with an enlarged uterus. Transvaginal ovarian ultrasound should include measurements of tumor volume, tumor structure, and blood flow. There is consensus that unilocular and simple septate tumors are very unlikely to be malignant and when asymptomatic, and regardless of age, should be followed without surgery. Ovarian tumors that are at increased risk for malignancy exhibit solid and cystic morphology, have papillary growths, or are mostly solid and secondary testing is recommended. Secondary testing may include serum biomarker testing (CA125, OVA1, ROMA, Overa) or serial ultrasonography. Serial ultrasound can document the physiologic behavior of an ovary by measuring changes in tumor size and morphology over time. By identifying tumors that do not worsen over time, it is possible to safely reduce the number of surgeries performed for benign abnormalities. Ovarian surveillance requires an objective system like the Kentucky Morphology Index to measure a tumor's risk of malignancy. When secondary testing suggests that an ovarian tumor is at high risk for malignancy, referral to a gynecologic oncologist is recommended. Unfortunately, as few as 1 in 3 women with ovarian cancer in the United States are referred to a gynecologic oncologist for their primary surgery. The following is recommended for evaluating an ovarian tumor in a menopausal woman: 1) perform an ultrasound with morphology indexing. 2) Determine if the tumor is at low, intermediate, or high risk of malignancy. 3) A *low* risk ovarian tumor should have a follow-up ultrasound in 6-12 months. An *intermediate* risk tumor should undergo secondary testing with a serum biomarker or serial ultrasound. A woman with a *high* risk tumor should be referred to a Gynecologic Oncologist for surgical removal.

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## **Plenary Symposium 5**

### ***Lesbian Health and Sexuality***

#### **Lesbian Sexuality and Fluidity**

Lisa M. Diamond, PhD. University of Utah, Salt Lake City, UT

The past decade has seen profound changes in the scientific understanding of sexual orientation and its expression over the life course, but little of this information has “trickled down” into clinical practice. This presentation will review the most important changes in our understanding of the expression of same-sex sexuality in women across the life course, and the newly understood phenomenon of “fluidity,” which refers to the widespread capacity for longitudinal change in sexual attractions at different stages of life and within different intimate relationships. I will review research on the prevalence of same-sex sexuality and sexual fluidity and I will discuss the implications of this emerging body of work for future clinical practice on women’s mental and physical health over the life course.

## Plenary Symposium 5 *Lesbian Health and Sexuality*

### **Caring for the Midlife Lesbian Woman**

Patricia A. Robertson, MD. University of California School of Medicine, San Francisco, Department of Obstetrics, Gynecology, and Reproductive Science, San Francisco, CA

Lesbian and bisexual women are considered a medically underserved population in the United States by the Institute of Medicine and the National Institutes of Health. Between 5% - 10% of female patients are lesbian or bisexual in orientation but the majority may not be “out” to their care provider. Although most patients would like their health care provider to know their sexual orientation, the patients may not be sharing that part of their lives spontaneously in a medical setting, so it is important that clinicians are comfortable directly asking their patients about identity/sexual behavior as part of the patient interview. One study concluded that sexual minority women reported greater satisfaction with their health care provider when the clinician assessed or knew their sexual orientation. The medical setting should be welcoming to all sexual minority patients, from front desk staff (there are training videos as well as consultants who can be trained) to having a selection of diverse reading materials for the waiting room. Approximately 70% of midlife lesbian women are partnered/married: they are less likely to have children than heterosexual women, and some lesbian women have been estranged from their family of origin so many have families “of choice.” Many lesbian women do not have advanced directives. Compared to heterosexual women, lesbian women have an increased incidence of smoking, past alcohol use, depression, asthma, obesity, breast cancer, and cardiovascular disease, exposure to violence during their lifetime, an equivalent incidence of interpersonal violence, and a decreased incidence of sexual dysfunction, and poor diets with high glycemic indices. Lesbian women choose less interventions when faced with a terminal diagnosis than heterosexual women. Lesbian women have different concerns with hysterectomies and breast cancer in terms of partner issues compared to heterosexual women. Care providers should consider being an advocate for this sexual minority group by supporting the inclusion of the sexual orientation question in research studies, being a compassionate listener with patients whose children are in the process of coming out, and being an engaged clinician who keeps up with the emerging research in this area, and improves the health care of lesbian and bisexual women by applying this research to their health care.

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## NAMS/Pfizer Wulf H Utian Endowed Lecture

### *Menopause, Estrogens, and Lipoprotein Particles*

#### **Menopause, Estrogens, and Lipoprotein Particles**

Ronald M. Krauss, MD<sup>1,2</sup>. <sup>1</sup>UCSF, Oakland, CA; <sup>2</sup>Children's Hospital Oakland Research Institute, Oakland, CA

Despite advances in its prevention and management, cardiovascular disease (CVD) remains the leading cause of death in both women and men in the US. Multiple lines of evidence have established that low density lipoproteins (LDLs) play a causal role in the disease process and guidelines for CVD prevention have emphasized the benefit of LDL lowering therapy. It is well established that CVD risk is lower in premenopausal women than in men of comparable age but that this protection is lost in the years following menopause. While the basis for the age-related increase in CVD risk in women is multifactorial, increased plasma levels of LDL-cholesterol (LDL-C) have been implicated. LDL-C is the amount of cholesterol that is transported on LDL particles. However, there are multiple distinct subclasses of these particles ranging from larger, more lipid-enriched to smaller, lipid-depleted LDL, also designated small, dense LDL (sdLDL). An increase in sdLDL is a key component of the atherogenic dyslipidemia of metabolic syndrome along with increased triglyceride and reduced HDL-C. Notably, due to the relatively low cholesterol content of sdLDL, total plasma LDL-C is typically not elevated in this syndrome. There is evidence however that sdLDL have properties that render them relatively atherogenic, including lower LDL receptor binding affinity and hence longer plasma residence time than larger LDL as well as greater oxidative susceptibility and binding to arterial wall proteoglycans. Moreover, the LDL-C measurement also includes the cholesterol contained in intermediate density lipoproteins (IDLs), a class of particles distinct from LDL that are generated from lipolytic "remnants" of triglyceride-rich lipoproteins (TRLs). TRL remnants are highly atherogenic, and the combined elevation of LDL and TRLs is a prevalent trait strongly associated with CVD risk. Using the technique of ion mobility to directly measure concentrations of LDL and other lipoprotein particles we have demonstrated that in both women and men, plasma LDL-C is more strongly correlated with IDL than with LDL particles and is also significantly correlated with TRLs. Notably, in a stepwise regression model over 48% of the variance in LDL-C was explained by IDL vs. only ~2% by LDL particles. The non-specificity of the LDL-C measurement is particularly relevant with regard to the lipoprotein particle changes that we have found to underlie both the increases in LDL-C with age in women (n=372) and the reductions in LDL-C that result from postmenopausal hormone use. As shown in previous studies, there was an increase of LDL-C in the peri- and postmenopausal years (40-60). However, levels of LDL, IDL, and TRL particles increased linearly from ages 30-70 without a noticeable change in slope at perimenopause. Moreover, the age-related increases in these particles were significantly greater in women than men, such that levels were lower than in men before age 40 and higher than in men after age 55-60. Although there was no significant change in HDL-C with age, there was an increase in HDL particle concentration from 30-50 yr, primarily in smaller vs. larger HDL particles that are less strongly associated with CVD protection. Consistent with previous studies, users of postmenopausal hormones (both unopposed estrogen and combination estrogen-progestin) in a subgroup of this cohort (ages 57-88, n=35) exhibited significantly lower LDL-C than nonusers (n=139): 140±2.6 vs. 124±6 mg/dL, mean±SEM, p=0.001, as well as higher triglycerides (p=0.014) and borderline higher HDL-C (p=0.09). Notably, the lower LDL-C was accounted for by reduced cholesterol content of IDL and larger LDL particles, without a reduction in total IDL or LDL particle number. In contrast, levels of sdLDL particles were significantly higher in hormone users. In summary, greater age-related increases in LDL, IDL, and TRL particles in women vs. men may contribute to increased CVD risk in older women and loss of CVD protection compared to men at premenopausal ages. In addition there appear to be menopause-related increases in cholesterol content of IDL and large LDL particles that can be reversed by hormone therapy. While it is possible that this hormonal effect favorably impacts CVD risk, concomitant increases in sdLDL and triglyceride levels may have offsetting effects that limit the CVD benefit of estrogen therapy.

## Plenary Symposium 6 *Cardiovascular Disease Risk Factors*

### **Dyslipidemia and the Postmenopausal Woman: Calculating Cardiovascular Disease Risk**

Beth L. Abramson, MD, MSc, FRCP, FACC<sup>2,1</sup>. <sup>1</sup>Cardiac Prevention Centre and Women's Cardiovascular Health, St. Michael's Hospital, Toronto, ON, Canada; <sup>2</sup>University of Toronto, Toronto, ON, Canada

The overall female population is aging. Women in Canada can expect to live on average nearly 83 years, approximately 5 years longer than men. Women spend at least one third of their lives postmenopause. Cardiovascular disease (CVD) is a leading health threat for postmenopausal women. Traditional risk factors for CVD include: age, sex, dyslipidemia, diabetes, smoking, and a family history of premature CVD. Menopause is an important milestone and may be one of the first times a woman seeks medical advice around issues of long-term CVD prevention. Many of the risk factors for the conditions prevalent among older women are modifiable through changes in lifestyle; while others will need medication. The INTERHEART study examined modifiable risk factors and determined the main risks for CVD are modifiable and for women 94% of CVD risk can be attributed to modifiable factors. Factors identified in this study as contributing substantially to increased CVD risk include diabetes mellitus, hypertension, abdominal obesity, current smoking, and psychosocial stress. Each of these risks can be reduced through appropriate choices, interventions, or both. Despite overall health care improvements, risk of heart disease in women continues to be underestimated. CVD remains the leading cause of death and an important contributor to illness and disability among women: half of all postmenopausal women will have CVD, and a third will die from it. Health behavior interventions remain a cornerstone of chronic disease prevention in women, including CVD prevention, and should be highlighted during health care visits. Observational studies show a relationship between serum cholesterol levels and cardiovascular disease (CVD), and dietary measures to lower these levels are an important part of disease prevention. A diet low in sodium and simple sugars, with substitution of unsaturated fats for saturated and trans fats, as well as increased consumption of fruits, vegetables, and fibers is recommended. Evidence from the Nurses' Health Study suggests that replacing dietary saturated fat and trans fatty acids with nonhydrogenated, monounsaturated, and polyunsaturated fats may be more effective in reducing the CVD risk than reducing overall fat intake in women. Recent AHA statements support the importance of addressing dietary fat in prevention of CVD. Blood pressure generally increases after menopause. Menopause-related hormonal changes can lead to weight gain and make blood pressure more reactive to salt in diet, which, in turn, can lead to higher blood pressure. Blood pressure should be assessed in women at all appropriate visits in order to screen for hypertension (HTN), assess CVD risk, and monitor antihypertensive treatment if applicable. Reversible risks for developing HTN include obesity, poor dietary habits, high sodium intake, sedentary lifestyle, and high alcohol consumption. Close attention to these factors should occur when assessing menopausal and postmenopausal women. A composite CV risk assessment in the postmenopausal woman should be part of the health exam. CCS Dyslipidemia Guidelines state that women  $\geq 50$  years of age or postmenopausal, and those with additional risk factors such as current cigarette smoking, diabetes, and arterial hypertension, have a full lipid profile screening done every 1 to 3 years. A CV risk assessment using the "10 Year Risk" provided by the Framingham model (the Framingham Risk Score, FRS) should be completed every 3 to 5 years for women age 50 to 75. If there is a positive family history of premature CVD (ie, first degree relative  $<55$  years for men;  $<65$  years for women) the age parameters should be modified. A risk assessment may also be completed whenever a patient's expected risk status changes. The Reynolds Risk Score, an alternative tool that takes into account both hsCRP and family. This session will review CV risk assessment and Risk reduction strategies.

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## Plenary Symposium 6

### *Cardiovascular Disease Risk Factors*

#### **Polycystic Ovary Syndrome—Is the Cardiometabolic Risk Increased After Menopause?**

Anuja Dokras, MD, PhD. University of Pennsylvania, Philadelphia, PA

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in reproductive age women with a prevalence of approximately 10%. It is typically defined by the presence of irregular menses and hyperandrogenism. These features typically improve by the fourth decade of life such that most women regain menstrual regularity and serum androgen levels decrease. In addition, ultrasound appearance of polycystic ovaries also normalizes with advancing age. However, young women with PCOS have an increased prevalence of cardiovascular disease (CVD) risk factors such as obesity, impaired glucose tolerance, diabetes, dyslipidemia and metabolic syndrome compared to age matched controls. These metabolic risks are higher in the hyperandrogenic phenotypes compared to the non-hyperandrogenic phenotype suggesting a potential role for androgens. This is supported in some studies in reproductive age women where high serum androgen levels are associated with increased CVD risk factors. Although other CVD biomarkers such as hsCRP, homocysteine and plasminogen activator inhibitor 1 antigen are also increased in PCOS, only a few longitudinal studies have examined the persistence of these risk factors during the menopause transition and in the menopause. Cross sectional studies demonstrate increased subclinical atherosclerosis, measured by carotid intima media thickness and coronary artery calcium scores, in young women with PCOS. These findings are independent of obesity and are supported by few population based studies that include post-menopausal women with a retrospective diagnosis of PCOS. However, the association between serum androgens and subclinical atherosclerosis in large population based studies including post-menopausal women in the general population show mixed results. These findings suggest that other hormonal or biological factors rather than isolated hyperandrogenism might contribute to increased CVD risk in PCOS. The few studies examining the risk of cardiovascular events and stroke in this population are also inconsistent. Limitations to assessing the precise overall CVD burden and its etiology in women with PCOS include small cross sectional studies, lack of longitudinal data in prospectively phenotyped subjects and limited use of gold standard androgen assays. Current guidelines recommend screening all women with PCOS for hypertension, glucose intolerance, dyslipidemia and obesity at the time of diagnosis and at frequent intervals. Future studies should focus on determining the precise risk of CV mortality and morbidity in this population after menopause.

## Plenary Symposium 7 *Migraines and Mood Disorders in Midlife Women*

### **Migraines in Midlife Women**

Jelena M. Pavlovic, MD, PhD. Albert Einstein College of Medicine/  
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Migraine is a chronic disorder with episodic attacks manifested by headaches of long duration (4-72 hours) characterized by moderate to severe pain and associated symptoms, such as photo- and phonophobia, nausea and vomiting. Migraine is at least three times more common in women than in men and is the 4<sup>th</sup> leading cause of disability in women. The annual prevalence of migraine among women of all ages is 18%. Onset of migraine increases at menarche, with peaks in prevalence in the early 40s, and a decline after menopause. Abundant population data suggest that hormonal factors may trigger headache attacks and influence onset and remission. Changes in estrogen presumably lead to increased migraine attack occurrence at the time of menses as well as to worsening of migraine during the menopausal transition. Menstrual migraine (MM) occurs in association with menstruation, specifically from plus or minus two days of menstruation onset. It is important to note that nomenclature for days of MM varies from common gynecological nomenclature for menses, with the onset of menses referred to as day 1 and the period of peri-menstrual migraine referred to as day -2 to +3 (+/-2 days from the first day of bleeding). Women whose migraines occur only peri-menstrually are categorized as Pure Menstrual Migraine (PMM). This is a relatively rare condition, which affects 7%–12% of women who are of reproductive age. In contrast to PMM, the majority of women with migraine experience migraine headaches both peri-menstrually and at other times of the month. This condition is defined as Menstrual Related Migraine (MRM), and is estimated to affect up to 73% of women. When migraines appear not to be related to menstruation they are classified as Non-Menstrual Migraine (nMM). Clinic based studies support the commonly held notion that peri-menstrual migraine attacks are more severe, long-lasting and refractory to both acute and prophylactic treatment. It is likely that peri-menstrual attacks may differ from non-menstrual attacks due to different pathophysiologic mechanisms. Menstrually related attacks may have a typical duration of several hours, but in some cases head pain can last several days and may be extremely severe and poorly responsive to analgesics. The predictability of peri-menstrual attacks in women of reproductive age allows for effective short-term treatment of migraine while minimizing exposure to medication. While there are extensive data on migraine during women's reproductive years, there has been a paucity of studies focusing on migraine through the menopausal transition. Majority of available knowledge stems from clinical observation supported by epidemiological studies that migraine generally worsens during the menopausal transition and improves post-menopause. However, studies from headache centers show a conflicting picture where migraine either persists, or even worsens through menopause. Furthermore, the type of menopause matters as well, with surgically induced menopause associated with worse migraine outcomes than natural menopause. The prevalence of migraine during particular stages of menopausal transition has not been well characterized as detailed menopause related data are scarce in migraine research settings. Also, little is known about potential mechanism of migraine transformation under the influence of changing sex hormones typical of menopausal transition and the eventual remission of migraine in menopause.

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## Plenary Symposium 7

### *Migraines and Mood Disorders in Midlife Women*

#### **Treatment of Mood Disorders in Midlife Women**

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Department of Obstetrics & Gynecology, Gainesville, FL

Over 1.3 million women become menopausal each year in the United States. In addition to vasomotor symptoms, women may also suffer from mood symptoms. Risk factors for mood disorders in midlife women include: history of depression, history of premenstrual dysphoric disorder, history of postpartum depression, low socioeconomic status, race, and social stressors. Despite these known risks, research is still lacking in recognizing additional risk factors that may identify at-risk women before their symptoms become severe. There are several theories that identify possible causes of mood disorders, they include: abrupt hormone fluctuations, domino theory, and empty nest syndrome. Regardless of the “cause” of perimenopausal mood disorders, there are several options of pharmacologic management. Medications felt to be most beneficial are HRT and antidepressants, specifically serotonin-norepinephrine re-uptake inhibitors (SNRIs). Alternative therapies can also be utilized including acupuncture and herbal supplements, however, care must be taken to verify safety.

## Plenary Symposium 8 Advances in Breast Imaging

Supported in part by grant funding from Hologic

### Summary of Outcomes of Tomosynthesis Screening at the University of Pennsylvania

Emily F. Conant, MD. Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

Screening mammography, despite ongoing controversy regarding the risk-benefit ratio, remains the mainstay of early breast cancer detection. However, screening with conventional 2-D digital mammography continues to generate many false-positives while also failing to detect some clinically significant cancers. In 2-D digital mammography (DM), both false-positives and false-negatives are caused by the same issue: the breast is a 3-dimensional structure viewed as a 2-dimensional image. Digital breast tomosynthesis (DBT) is an extension of DM that allows the volume of breast tissue to be viewed in a 3-D format, reducing the effect of superimposition of normal anatomic structures that both obscure cancers causing false negatives (the “masking effect”) and also cause normal breast tissue to appear suspicious, prompting unnecessary false positives and potentially, biopsies. There is growing concern that mammographic screening may cause “overdiagnosis” of some cancers, specifically in situ cancers that may not be harmful yet are treated aggressively. Several screening studies have shown that DBT reduces false-positive recalls while simultaneously improving cancer detection, specifically, invasive cancers, not in situ cancers. Most evidence on the improved outcomes achievable with DBT has come from first-round screening in either limited prospective trials<sup>1-3</sup> or retrospective studies.<sup>4-6</sup> Questions remain whether the improved outcomes are sustainable over multiple rounds of screening and whether synthetic 2D imaging as a method to reduce the x-ray dose of DBT will have similarly outcomes. Here we present the screening outcomes from multiple years of breast cancer screening with DBT as well as early data utilizing synthetic 2D imaging in screening with DBT.<sup>7,8</sup> **References:** 1. Skaane P, Bandos AI, Eben EB, Jepsen IN, Krager M, Haakenaasen U, Ekseth U, Izadi M, Hofvind S, Gullien R. Two-view digital breast tomosynthesis screening with synthetically reconstructed projection images: comparison with digital breast tomosynthesis with full-field digital mammographic images. *Radiology*. 2014;271(3):655-63. 2. Ciatto S, Houssami N, Bernardi D, Caumo F, Pellegrini M, Brunelli S, Tuttobene P, Bricolo P, Fanto C, Valentini M, Montemezzi S, Macaskill P. Integration of 3D digital mammography with tomosynthesis for population breast-cancer screening (STORM): a prospective comparison study. *Lancet Oncol*. 2013;14(7):583-9. 3. Gilbert FJ, Tucker L, Gillan MG et al. The TOMMY trial: a comparison of TOMosynthesis with digital MammographY in the UK NHS Breast Screening Programme--a multicentre retrospective reading study comparing the diagnostic performance of digital breast tomosynthesis and digital mammography with digital mammography alone. *Health Technol Assess* 2015; 19: i-xxv, 1-136. 4. Friedwald SM, Rafferty EA, Rose SL, Durand MA, Plecha DM, Greenberg JS, Hayes MK, Copit DS, Carlson KL, Cink TM, Barke LD, Greer LN, Miller DP, Conant EF. Breast cancer screening using tomosynthesis in combination with digital mammography. *JAMA* 2014 Jun 25;311(24):2499-507. 5. McCarthy AM, Kontos D, Synnestvedt M, et al. Screening outcomes following implementation of digital breast tomosynthesis in a general-population screening program. *J Natl Cancer Inst* 2014; 106(11): dju316 doi: 10.1093/jnci/dju316. 6. McDonald, ES, Oustimov, A, Weinstein, SP, Synnestvedt, M, Schnell, M, Conant, EC. Effectiveness of Tomosynthesis in Combination with Digital Mammography: Outcomes Analysis from Three Years of Breast Cancer Screening. *JAMA Oncology* 2016; 2(6): 1-7. 7. Conant EF, Beaber EF, Sprague BL, et al: Breast cancer screening using tomosynthesis in combination with digital mammography compared to digital mammography alone: a cohort study within the PROSPR consortium. *Breast Cancer Res Treat* 2016; 156(1): 109-16. 8. Zuckerman SP, Conant EF, Weinstein SP, Synnestvedt M, Korhonen KE, McDonald ES. Early Implementation of Synthesized 2D in Screening with Digital Breast Tomosynthesis: A Pictorial Essay of Early Outcomes. *Radiol* 2016; 281(3):730-736.

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## Plenary Symposium 8

### *Advances in Breast Imaging*

*Supported in part by grant funding from Hologic*

#### **Molecular Breast Imaging: Functional Imaging to Unveil the Hidden Cancer Reservoir in Dense Breasts**

Deborah J. Rhodes, MD. Mayo Clinic, Rochester, MN

Breast density notification legislation, active in over 30 states, informs women of potential tumor masking by density on mammography and recommends discussion of additional screening with providers. The benefit of additional screening depends on the likelihood that cancers will be missed on mammography [false negative rate (FNR)], information neither routinely nor accurately provided to women. Studies of mammography performance have historically under-represented FNR by relying on subsequent mammography plus clinical follow-up to determine FNR, which in turn determines sensitivity. This reporting method inflates mammography performance by: 1) not accounting for cancers that remain clinically and mammographically occult over the measurement period; and 2) counting any tumor detected by mammography in a woman undergoing regular screening even if advanced at diagnosis (and likely present but undetected during previous mammograms). Using this method, the Breast Cancer Surveillance Consortium (BCSC), a multi-site U.S. registry linking mammography data to tumor registry and pathology data, reports a mammography sensitivity of 84% with little variance across density categories. However, numerous studies comparing more sensitive supplemental technologies to mammography in dense breasts reveal a reservoir of previously undetected cancer, with reported mammography sensitivities in these studies ranging between 25 and 50%. Although rates of cancer localized to the breast increased markedly since the advent of mammography screening (much of which is DCIS and may represent overdiagnosis), rates of advanced cancer (the most lethal cancers) have not declined with mammography, signaling an opportunity to reduce breast cancer mortality through earlier detection of advanced cancers with other imaging techniques. Supplemental screening with whole-breast screening ultrasound has been found to increase cancer detection modestly; however, operator dependence and high false positive rates have limited dissemination. Tomosynthesis, while effective in reducing false positive findings, contributes a marginal increase in cancer detection (approximately 1.2 additional cancers per 1000 screened) likely due to continued masking of tumors by density even with 3-dimensional x-ray images. In contrast, when a functional imaging test, such as MRI, is added to mammography, the cancer detection rate is increased by 14.2 cancers per 1000 screened. Furthermore, when MRI is repeated over annual screens, the reservoir of advanced cancers diminishes because cancers previously obscured by density over multiple mammographic screens have been eliminated. MRI screening is currently limited to high-risk patients due to high cost; abbreviated MRI is under study as a supplemental tool in dense breasts, but cost and access will likely remain concerns. At approximately one-tenth the cost of MRI, Molecular Breast Imaging (MBI) is a functional breast imaging tool utilizing dual-head solid state gamma cameras which allow for improved sensitivity and thus administration of a lower radiation dose (below background levels) relative to earlier breast-specific gamma imaging devices. The patient receives an injection of Tc-99 sestamibi, which is preferentially taken up by breast tumors regardless of breast density. In three single-institution studies conducted in women with dense breasts, the addition of MBI increased cancer detection by 7.5 to 8.8 cancers per 1000 screened. The sensitivity of mammography was 25% compared to 81% for MBI. While most MBI-only detected cancers were small and node negative, consistent with early detection, MBI also detected node positive and large cancers (> 4 cm) that were mammographically occult, suggesting potential to eliminate the advanced cancer reservoir masked on mammography by density. Recall rates for MBI are low (additional 6-8%) and positive predictive values of MBI-prompted biopsy are between 20 to 33%. In women with dense breasts, MBI is a low-cost, well-tolerated supplemental screening option offering a low rate of false positive findings while increasing cancer detection almost four-fold relative to 2D mammography, alone. A recently opened, multi-year, multicenter trial comparing MBI to tomosynthesis in women with dense breasts will provide important new data to inform women's decisions regarding supplemental screening.

**NAMS/Kenneth W Kleinman Endowed Lecture**  
*US Women's Health Policy in 2017: What's Changed, What's Next?*

*Speaker's abstract  
not received in time  
for publication*

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## Plenary Symposium 9

### *Musculoskeletal Health Concerns*

#### **Dysmobility Syndrome: The Future of Fracture Risk Reduction**

Neil C. Binkley, MD. University of Wisconsin School of Medicine and Public Health, Madison, WI

Fractures in older adults reduce independence/quality of life, engender major healthcare cost, and increase mortality risk. Despite availability of multiple therapies to reduce risk for future fracture, few patients are treated even following hip fracture. This failure to intervene following fracture has recently been termed a “crisis in the treatment of osteoporosis.” Clearly, approaches of the past aimed at reducing fracture risk, primarily by diagnosing osteoporosis and initiating bone-active medications, have failed. As such, a different approach is required; such a change in focus is proposed here. Briefly, the dysmobility syndrome concept recognizes fracture as the clinical outcome of consequence and emphasizes that osteoporosis is only one part of a syndrome leading to what is currently called “osteoporosis-related” fracture. The dysmobility syndrome relationship with falls and fractures is analogous to metabolic syndrome and its association with cardiovascular disease. Other proposed components of the dysmobility syndrome include sarcopenia, obesity, diabetes, and potentially multiple other factors that increase risk for falls with attendant increased fracture risk. A small, but increasing body of literature finds a preliminary, score-based approach to the diagnosis of dysmobility syndrome to be associated with falls, fractures and overall mortality. In summary, the dysmobility syndrome concept moves the field, and also, importantly, older adults at risk for fracture, beyond a singular focus on osteoporosis to more appropriately focus on a comprehensive approach to fracture risk reduction. This comprehensive approach emphasizes nutrition (overall caloric intake, protein, calcium, and vitamin D), exercise, falls risk reduction and pharmacologic treatment only if needed.

**Plenary Symposium 9**  
*Musculoskeletal Health Concerns*

*Speaker's abstract  
not received in time  
for publication*

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## Plenary Symposium 10

### *Improving Evidence for Millions of Women: The MsFLASH Vaginal Health Trial*

#### **Improving Evidence for Millions of Women: The MsFLASH Vaginal Health Trial**

Andrea Z. LaCroix, PhD<sup>1</sup>, Susan D. Reed<sup>2</sup>, Katherine A. Guthrie<sup>3</sup>, Caroline M. Mitchell<sup>4</sup>, Susan J. Diem<sup>5</sup>. <sup>1</sup>University of California, San Diego, San Diego, CA; <sup>2</sup>University of Washington School of Medicine, Seattle, WA; <sup>3</sup>Fred Hutchinson Cancer Research Center, Seattle, WA; <sup>4</sup>Massachusetts General Hospital, Boston, MA; <sup>5</sup>University of Minnesota, Minneapolis, MN

**BACKGROUND:** Bothersome postmenopausal vaginal symptoms are prevalent and adversely affect quality of life, including sexual function. Up to 40% of postmenopausal women have vaginal symptoms presumed to be related to vaginal atrophy. Despite this high prevalence of genitourinary syndrome of menopause (GSM), evidence based information to guide treatment choices is limited. Minimal data supports efficacy of nonprescription treatments for vaginal dryness and symptoms, and their comparative efficacy versus estrogen therapy is virtually unknown. Microbiologic, inflammatory and hormonal mechanisms likely underlie GSM manifestation; their impact in determining treatment response is uncertain. **METHODS:** The MsFLASH network conducted a multicenter trial comparing popular treatments for bothersome vaginal symptoms and sexual dysfunction, and created a biorepository of specimens to allow future translational, mechanistic research on the etiology of vaginal symptoms. Recruitment was via mass mailing and Facebook advertisements. A 3-arm, randomized, controlled, double-blind, clinical trial (N=302) compared the effects of: 1) estradiol vaginal tablet (Vagifem®) + placebo gel vs. placebo tablet + placebo gel; and 2) hydrophilic moisturizing vaginal gel (Replens®) + placebo tablet vs. placebo gel + placebo tablet. The primary outcome was change from baseline to 12 weeks in severity of the most bothersome symptom (MBS) - dryness, itching, irritation, soreness and pain with penetration. Secondary outcomes included: a) composite vaginal symptom score; b) sexual function (Female Sexual Function Index); c) treatment satisfaction; d) menopause quality of life (MenQOL); and e) objective measures of GU atrophy (pH, vaginal maturation index and epithelial thickness). **RESULTS:** Mass mailing and Facebook ads were both effective recruitment methods, although costs and participant retention varied by method. Women were randomly assigned to receive Vagifem (N= 102), Replens (n=100) or placebo (N=100). Study continuation was high: 293 women provided week 12 data (95%Vagifem, 99% Replens, 97% placebo). No meaningful differences in baseline characteristics were observed between treatment groups. Mean age was 61 (SD 4) years and 88% were white. The mean MBS score was 2.5 (SD 0.6); pain with sexual activity 61%, vaginal dryness 21%, vulvar or vaginal itching 7%, vulvar or vaginal irritation 6%, and vulvar or vaginal pain or soreness 5%. Baseline mean FSFI score was 15.5 (SD 6.4). Intervention results on the primary and selected secondary outcomes will be presented. **CONCLUSIONS:** Recruitment via Facebook for a vaginal health trial in postmenopausal women was successful, although not necessarily less expensive than mailing. The MsFLASH Vaginal Health Trial comparing hormonal and nonhormonal products will provide valuable evidence to guide treatment decisions for women with GSM.