Precision hormone therapy: gaps and opportunities

Yu Jin Kim[1], Roberta Diaz Brinton[1,2,3,*]

[1] Center for Innovation in Brain Science, University of Arizona, Tucson, AZ 85721, USA; [2] Department of Pharmacology, College of Medicine, University of Arizona, Tucson, AZ 85724, USA; [3] Department of Neurology, College of Medicine, University of Arizona Tucson, AZ 85724, USA

ABSTRACT

During the decades of medical prescribing of hormone therapy (HT) use has increased or decreased based on medical and scientific advances in clinical assessments, changes in formulation and mechanistic insights. While the selection and clinical assessment of HT efficacy can be personalized through the physician/patient interaction, a major gap has been application of precision medicine methods to advance the optimization of HT. Precision medicine has emerged as a promising approach to optimize pharmaceutical care by a priori considering patient-specific characteristics, including genetic risks, physiological health, age, gender, environmental constraints and lifestyle factors. There are 39 HT products approved by regulatory agencies in the U.S. (FDA), Canada (HPFB), and Europe (EMA) composed of 13 potential estrogen- or progestogen-types of steroids, over 12 different dosage forms, and administered via 4 different routes of administration resulting in multiple pharmacokinetic profiles. Despite the array of differences among FDA, HPFB, and EMA approved products, there is comparable efficacy in treating menopausal symptoms whereas long-term health metrics has greater variability. Individual differences have become increasingly evident and have been sufficient to influence clinical prescribing away from regulated to unregulated products. In an attempt to personalize HT, the customization of compounded bioidentical hormone products has increased, although these products are unregulated and adverse outcomes under-reported. Personalized clinical care powered by precision medicine analytics has the potential to advance optimization of HT through combining the safety and efficacy of FDA, HPFB, and EMA approved products with big data analytics of health outcomes to deliver the personalized approach sought by both physicians and patients. Challenges and opportunities to achieving precision medicine for HT are considered.

KEYWORDS

Precision medicine, Hormone therapy, Menopause, FDA, HPFB, EMA, Compounded hormones, Bioidentical hormone formulations.

Introduction

Since inception in 1942, hormone therapy (HT) has benefited from a personalized approach through physician/patient interactions to arrive at an optimal formulation and dose to treat menopausal symptoms. This very personalized approach has generated decades of data that can be combined with 21st century genomic technologies to create a precision medicine approach to HT. Personalized clinical care powered by precision medicine analytics has the potential to advance HT to optimize both efficacy and safety [1,2].

Precision medicine is best exemplified by selection of cancer treatments which has pioneered personalized precision medicine by combining the genetics of cancer patients with genomic technologies and big data acquired from millions of patient records to screen treatments against the patient's own tumor cells.

In contrast, HT for menopausal symptoms poises a much more complex challenge as HT is a whole body/multi-organ intervention that requires consideration of patient-specific characteristics including genetic variability, physiological health, age, gender, environment, and lifestyle (Figure 1) [2,3].

HTs approved by the U.S. Food and Drug Administration (FDA), the Health Products and Food Branch (HPFB) of Health Canada, and the European Medicines Agency (EMA) are well characterized thereby providing a well characterized set of therapeutic interventions. Big data and computational systems biology analytics can be utilized to analyze medical records to detect patterns and associations between variables listed above and the short and long-term health outcomes associated with specific HTs.

In considering precision HT, we first provide a historical perspective followed by an analysis of the current state of the field concluding with near term opportunities to advance development of precision HT.

Article history
Received 3 Dec 2019 – Accepted 24 Jan 2020

Contact
Roberta Diaz Brinton; rbrinton@email.arizona.edu
Center for Innovation in Brain Science, University of Arizona, 1230 N Cherry Avenue, Tucson, AZ 85721, USA

Historical perspective on drivers of precision Hormone Therapy

HT was first introduced in the 1940s with transition to greater use in the late 1960s 4. The use of HT increased again after 1988 when the FDA approved estrogen therapy to prevent postmenopausal osteoporosis [4]. Based on a national pharmacy claims database, the prevalence of women using HT was 21.6, 21.4, and 20.9 % in 2000, 2001, and 2002 respectively, among women aged 50 years and older [5]. Observational cohort studies of HT users suggested decreased mortality of coronary heart disease by 20-40% and reduced risk of Alzheimer's disease [4].

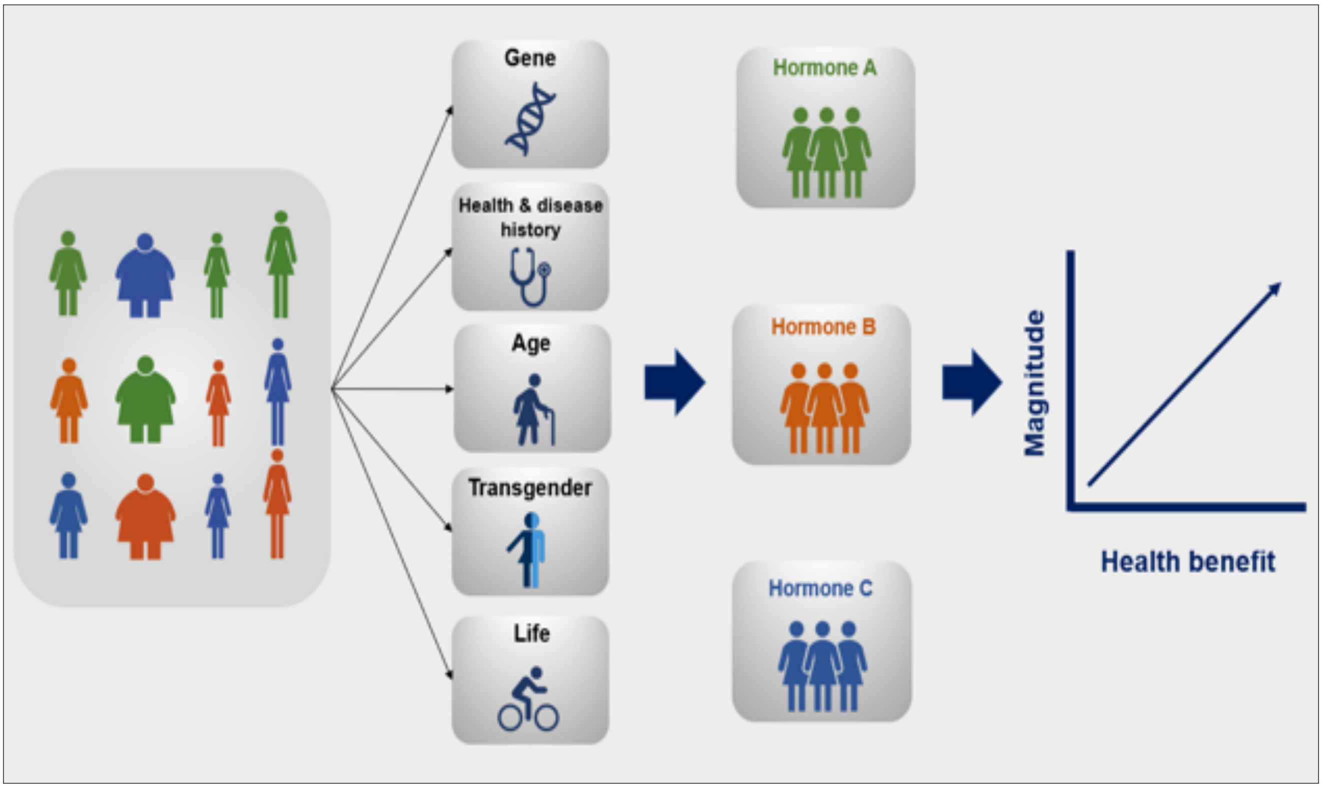
HT has consistently reduced menopausal symptoms whereas the association with longer term health outcomes has illuminated the urgent need of a precision medicine approach to HT. As the number of women using HT use increased, adverse effects became more apparent in the mid 1970s [4]. Data emerged indicating increased risks of breast cancer, uterine cancer, and stroke in estrogen therapy users [4]. Thereafter, a progestogen was combined with estrogen therapy to prevent uterine cancer. However, studies suggested a decrease in the attenuating effect of HT on cardiovascular disease when estrogen therapy was combined with a progestogen [4].

Increased concern regarding safety of HT drew the attention of the National Institute on Health (NIH) and the FDA which identified a need for large randomized clinical trials of HT [4]. The Women's Health Initiative (WHI) was one of the outcomes of those concerns. The WHI clinical trials recruited 16,608 healthy postmenopausal women aged 50 to 79 years with an intact uterus at baseline in 1993-1998 for HT trials, and participants received 0.625 mg of oral conjugated equine estrogens (CEE) with 2.5 mg daily medroxyprogesterone acetate (MPA) or placebo [6,7]. The HT trials also included 10,739 women who were post-hysterectomy at baseline and received either unopposed estrogen therapy consisting of 0.625 mg of CEE daily or placebo [7]. The initial purpose of the clinical trials was to determine whether HT prevented from heart disease, breast and colorectal cancer, and osteoporotic fractures in postmenopausal women [8].

A turning point in HT use in women occurred following the report of WHI outcomes in 2002 [8]. Initial findings from the WHI study were unexpectedly negative, indicating that overall health risks exceeded benefits in the combined CEE and MPA group who had on average 5.2-years of follow-up. Outcomes of these analyses were that the combination of CEE and MPA should not be initiated or continued for the primary prevention of coronary heart disease as well as identified risks of cardiovascular disease and breast cancer [6,9]. These findings derived from a single HT formulation and dosage were generalized to all formulations and doses.

Following the initial report, additional studies were conducted to investigate the association of HT with multiple outcomes including venous thromboembolic (VTE) events [10,11], cognitive function [12-18], stroke [19], and age-related diseases [20,21]. A lower oral dose (0.3 mg) of CEE reduced the risk of stroke relative to the higher dose (0.625 mg) [22]. Increased risks of dementia and cognitive impairment during and after HT were closely associated with occurrence of type 2 diabetes [23]. HT was beneficial for women who are at risk of osteoporotic fractures and low bone mineral density [6]. Overall, the impact of the WHI has been sustained and remains a factor in considering HT by women and their physicians.

Figure 1 Personalized factors for precision hormone therapy to optimize medical and pharmaceutical care based on individual-specific characteristics including genetic, health, age, and life information.



Factors Influencing Precision Hormone Therapy

Age and response to HT

The impact of age on HT response is illustrated in two studies. In a randomized longitudinal study of postmenopausal women with a mean age of 57.7 year, impact of HT on an indicator of aging, telomere length, was investigated [24]. Outcomes of these analyses on a biomarker of aging biology indicated that APOE-e4 carriers had marked telomere attrition during the 2-year study window which was equivalent to approximately one decade of additional aging compared to non-carriers. Further analyses revealed a modulatory effect of HT on the association between APOE status and telomere attrition. APOE-e4 carriers who continued HT during the 2 year trial sustained telomere length and did not exhibit signs of aging, whereas women who discontinued HT telomere length shortened consistent with accelerated aging [24]. Women who did not carry the APOE4 allele exhibited no protective effect of HT on telomere length [24]. The impact of HT in APOE4 positive women in the Nurses' Health Study indicated that cognitive function in 70–81 year old APOE4 carriers currently using HT was associated with a slight increase in rate of decline [25]. Transdermal estrogen therapy was advantageous for women at risk of VTE, as the first pass metabolism of oral estrogen-only HT increases resistance to activated protein C, which is a natural anticoagulant [26].

Although benefits of HT in symptomatic peri to menopausal women were well documented, the negative outcomes from WHI in postmenopausal women resulted in a dramatic decrease in HT use from 21.6% in 2000 to 8.8% in 2009 in women aged 50 years and older [5]. Prescription claims for US commercial health insurance indicated that the age-standardized annual prevalence of oral estrogen prescriptions was 83 per 1,000 women in 2007, and decreased to 42 per 1,000 women in 2015 [27]. The majority of the WHI-Memory study population was older than 60 years with only 20% of enrolled women aged 50-60 years and less than 5% were 54 years of age [4]. Thus, it is important to note that WHI-Memory study findings were based on ~ 75% of women who were 10+ years post menopause and thus quite different from age of women (45-55 years of age) for whom HT is typically prescribed. Despite the advanced age of women receiving HT, the WHI findings resulted in the discontinuation of HT use in all age groups including younger postmenopausal women [28].

To assess differences in HT use before and after the WHI, Crawford *et al*. [28] analyzed survey data collected from 3,018 midlife women in a prospective cohort study conducted between 1996 and 2013 from the Study of Women's Health Across the Nation. They divided participants into four age groups: 42-49.5 years, 49.6-53 years, 53.1-57.1 years, and 57.2 years and older. Overall, HT initiation decreased from 8.6% (pre-WHI) to 2.8% (post-WHI). Based on their analysis, the percent of HT initiation was the highest in 49.6 and 57.1 years age groups before the WHI, but were the age groups with largest decrease after the WHI [28].

Currently, FDA advises women to use HT for the shortest time (generally less than five years or not beyond age 60 years) and at the lowest dose possible to treat menopausal symptoms [29,30]. Collectively, the data indicate that age, a critical variable for precision HT [31], significantly impacted response to HT. Thus, extrapolation of outcomes of HT initiated in older women, such as in the WHI, to younger perimenopause to early menopausal women, who may benefit from HT, is problematic as multiple molecular pathways in multiple organ systems change across the menopausal transition [31-33].

Hormone therapies approved by regulatory agencies

There are 39 HT products approved by regulatory agencies in the U.S. (FDA), Canada (HPFB), and Europe (EMA) composed of 13 potential estrogen- or progestogen-types of steroids, over 12 different dosage forms, and administered via 4 routes of administration, resulting in multiple pharmacokinetic profiles (Table 1).

Impact of progestins

Different types of progestogens have been utilized in combined HT with estrogen, which include progesterone naturally secreted by ovary and placenta, and progestins (synthetic forms of progesterone) such as MPA, dydrogesterone, norethindrone/norethisterone, norethisterone acetate, and levonorgestrel [34]. It has been reported that the type of progestogens in HT is one of the critical factors to be optimized, as they have shown different effects on risks associated with HT, such as breast cancer and cardiovascular diseases. Previous studies demonstrated a relative low risk of breast cancer [35,36] and VTE [37] by using dydrogesterone. On the contrary, a relative high risk of VTE was observed among MPA users as compared to norethisterone/norgestrel users [11].

One of the potential reasons for different effects of progestogens on the risk of breast cancer risk may be explained by their different binding affinity to steroid receptors expressed in breast cancer cells, including estrogen receptor (ER), androgen receptor (AR), glucocorticoid receptor (GR), mineralocorticoid receptor (MR), and progesterone receptor (PR) [38]. In addition, different biological activities of metabolites of progesterone and progestins may contribute to proliferation or apoptosis of breast cancer cells. An example are the opposing actions of two different progesterone metabolites, 5α-dihydroprogesterone and 3α-dihydroprogesterone, on mitosis, apoptosis, and expressions of B-cell lymphoma 2 (Bcl-2), Bax (an effector of apoptosis in breast cancer), and p21 (a potent cyclin-dependent kinase inhibitor) in human breast cell lines [39].

Different progestogens exert different cellular and neurobiological outcomes [40-41]. MPA exacerbates glutamate-induced neurotoxicity in primary hippocampal neural cultures, regardless of its formulation types and chemical structures (crystalline MPA versus a pharmaceutical formulation, Depo-Provera®) whereas progesterone promoted neuroprotection [40]. The impact of progesterone and MPA on glycolysis, oxidative stress, and mitochondrial function in neural tis-

Table 1 Hormone medicines commercially available in U.S., Canada, and Europe for the treatment of menopausal symptoms (Drugs@FDA, www.menopause.org, www.ema.europa.eu, and www.medicines.org.uk).

BRAND	GENERIC NAME	DOSAGE FORM	ROUTE	STRENGTH
ESTROGEN ALONE				
Alora®	Estradiol	Patch	Transdermal	0.025, 0.05, 0.075 and 0.1 mg/day
Climara®	Estradiol	Patch	Transdermal	0.025, 0.0375, 0.05, 0.06, 0.075, or 0.1 mg/day
Delestrogen®	Estradiol valerate	Injection (shot)	Intramuscular	10, 20, and 40 mg/ml
Divigel®	Estradiol	Gel	Transdermal	0.25, 0.5, and 1 g
Elestrin™	Estradiol	Gel	Transdermal	0.52 or 1.04 mg
Estrace®	Estradiol	Cream	Vaginal	0.1 mg
Estraderm®	Estradiol	Patch	Transdermal	0.025 and 0.1 mg per patch
Estraderm® MX	Estradiol	Patch	Transdermal	0.75, 1.5, 2.25, and 3 mg
Estradot®	Estradiol	Patch	Transdermal	0.39 mg estradiol in 2.5 cm2 patch
Estragyn™	Estrone	Cream	Vaginal	0.1% (w/w)
Estring®	Estradiol	Insert	Vaginal	2 mg
EstroGel®	Estradiol	Gel	Transdermal	0.06% (1.25 mg/activation)
Evamist™	Estradiol	Spray	Transdermal	One spray daily containing 1.53 mg estradiol
Femring™	Estradiol acetate	Ring	Vaginal	0.05 and 0.1 mg/day
Linoladiol®	Estradiol	Cream	Topical	Linoladiol N: 0.1 mg/g Linoladiol HN: 0.05 mg estradiol/4 mg corticosteroid prednisolone per gram
Menest®	Esterified estrogen	Tablet	Oral	0.3, 0.625, 1.25, and 2.5 mg
Menostar® (only used to prevent osteoporosis)	Estradiol	Patch	Transdermal	14 mcg/day
Minivelle™	Estradiol	Patch	Transdermal	0.0375, 0.05, 0.075, and 0.1 mg/24 hr
Oesclim®	Estradiol	Patch	Transdermal	25, 37.5, 50, 75, and 100 mcg/24 hr
Ogen® 5	Estropipate	Tablet	Oral	6 mg
Osphena® (not estrogen only)	Ospemifene	Tablet	Oral	60 mg
Premarin®	Conjugated estrogens	Tablet	Oral	0.3, 0.45, 0.625, 0.9, and 1.25 mg
Premarin®	Conjugated estrogens	Cream	Vaginal	0.625 mg/gm
Premarin®	Conjugated estrogens	Injection (shot)	Intravenous/intramuscular	25 mg/vial
Vagifem®	Estradiol	Tablet	Vaginal	10 mcg
Vivelle-Dot®	Estradiol	Patch	Transdermal	0.025, 0.0375, 0.05, 0.075, and 0.1 mg/day
PROGESTIN ALONE				
BRAND	**GENERIC NAME**	**DOSAGE FORM**	**ROUTE**	**STRENGTH**
Duphaston®	Dydrogesterone	Tablet	Oral	10 mg
Prometrium®	Micronized progesterone	Capsule	Oral	100, 200 and 300 mg
Provera®	Medroxyprogesterone acetate	Tablet	Oral	2.5, 5, and 10 mg
Crinone®	Progesterone	Gel	Vaginal	4 and 8%
COMBINATION OF ESTROGEN AND PROGESTIN				
BRAND	**GENERIC NAME**	**DOSAGE FORM**	**ROUTE**	**STRENGTH**
Activella®	Estradiol/norethindrone acetate	Tablet	Oral	1 mg/0.5 mg and 0.5 mg/0.1 mg
Angeliq®	Estradiol/drospirenone	Tablet	Oral	0.5 mg/0.25 mg and 1 mg/0.5 mg
Climara Pro™	Estradiol/levonorgestrel	Patch	Transdermal	0.045 mg/0.015 mg per 24 h
Combipatch®	Estradiol/norethindrone acetate	Patch	Transdermal	0.05 mg/0.14 mg and 0.05 mg/0.25 mg per 24 h
Estalis®	17ß-estradiol/norethindrone	Patch	Transdermal	0.05 mg/0.14 mg and 0.05 mg/0.25 mg
Femhrt®	Ethinyl estradiol/ norethindrone acetate	Tablet	Oral	0.0025 mg/0.5 mg, 0.005 mg/1 mg
Femoston®	Estradiol hemihydrate/ dydrogesterone	Tablet	Oral	1 mg/10 mg and 2 mg/10 mg
Prempro™	Conjugated estrogen/ medroxyprogesterone acetate	Tablet	Oral	0.625 mg/2.5 mg, 0.625 mg/5 mg, 0.45 mg/1.5 mg, and 0.3 mg/1.5 mg
Premphase®	Conjugated estrogens/ medroxyprogesterone acetate	Tablet	Oral	0.625 mg of conjugated estrogen and 5 mg of medroxyprogesterone acetate

sue was progestin specific [41]. In contrast to progesterone, MPA diminished glycolytic and oxidative phosphorylation protein and activity, and reduced estradiol-induced enhancement of mitochondrial respiration in hippocampal neurons and glia, which eventually exacerbate oxidative damage and neurodegeneration [41].

Alternatives to progestins

As an alternative to progestogen therapy for women with an intact uterus, Duavee® (approved by the FDA in 2013) is a combination product containing conjugated estrogens and bazedoxifene which is a selective estrogen receptor modulator used for the prevention of osteoporosis. The efficacy and safety of this combination was evaluated in five phase 3 Selective estrogens, Menopause, And Response to Therapy (SMART) trials [42]. Further, bazedoxifene was reported to inhibit the proliferation of endocrine-resistant breast cancer cells [43]. The combination of conjugated estrogens plus bazedoxifene reduced vasomotor symptoms and osteoporosis-related fractures, increased vulvar/vaginal atrophy without increasing indicators of cardiovascular disease or endometrial and breast cancer in postmenopausal women in the SMART studies [44-49].

Treatment Regimen

Treatment regimen (cyclic versus continuous) of combined HT has been addressed as one of the factors impacting HT-associated breast cancer risk [50]. Cyclic HT with the combinations of 17β-estradiol and progesterone is suggested to be more effective than their continuous use, because a cyclic exposure to progesterone closely mimics the natural female hormone pattern, inducing gene expression profiles to be consistent with the ovary intact brain [50]. Another study presented that cyclic progesterone reduced β-amyloid levels and enhanced 17β-estradiol effects in a transgenic mouse model of Alzheimer's disease [51]. It has been also suggested that progesterone administration in cyclic regimens does not affect a risk of breast cancer [52]. Cyclic or continuous MPA with estrogen inhibited vasodilatation by 50%, however, there was no diminished estrogen-induced vasodilatation by nomegestrol acetate [53].

Non-hormone therapies for menopausal symptoms

In addition to hormone-based therapies, there are two FDA-approved non-hormone drugs to treat menopausal symptoms : (1) Brisdelle™ (approved in 2013), an oral capsule form of paroxetine, a selective serotonin reuptake inhibitor indicated for the treatment of moderate to severe vasomotor symptoms due to menopause [54] and (2) Osphena® (approved in 2013), an oral tablet of ospemifene, an estrogen agonist/antagonist indicated for the treatment of moderate to severe dyspareunia and vulvar and vaginal atrophy due to menopause [55].

Bioidentical and compounded HTs

Patient and physician interest in bioidentical and compounded medicines has grown as an alternative option of FDA-approved hormone medicines. The bioidentical hormone drug contains active ingredient(s) with the same chemical structure of human hormones. In 2018, the FDA approved the first bio-identical oral hormone combination of 17β-estrogen and progesterone, Bijuva, indicated for women with a uterus for the treatment of moderate to severe vasomotor symptoms associated with menopause [56].

Alternatively, compounded hormone formulations are not regulated by the FDA and are generated by compound pharmacies that often, but not consistently, contain United States Pharmacopeia (USP)-grade steroids [57]. Compounded HT is formulated as capsules, creams, gels, lotions, trochs, and suppositories (Table 2) [57,58]. These formulations are not approved nor regulated by the FDA [57]. Further, the FDA does not regulate production processes, number of users nor track adverse outcomes. Although there is a lack of verification regarding safety of compounded steroid therapies, women select compounded hormone drugs because of increased public concern regarding risk factors of the current FDA-approved HTs and unawareness that compounded hormone drugs are not approved by the FDA [59,60].

Because the number of compounded drug users is not officially tracked, surveys serve as a proxy to characterize the demographics of the compounded drug users. The North American Menopause Society (NAMS) conducted an Internet-based consumer survey in 2015. An age of participants in the survey was between 40 and 84 years. Among 3,725 women enrolled and eligible for the survey, 28% of the women were current or past HT users, and 31% used compounded hormone drugs and the majority (69%) were FDA-approved hormone medicine users.

One of the interesting observations in this survey was that the percent of compounded hormone users was highest (41%) in early age group (40-49 years) and the compounded hormone users tended to be younger than the FDA-approved hormone users. The percent of women who selected FDA-approved HT was higher than the compounded users in all age groups, but the percent was the highest in the oldest age group. Furthermore, almost one-third of the women were not sure whether the HTs they used was approved by the FDA [59].

Another large internet survey conducted by Harris Interactive Inc also reported that 86% of women surveyed (aged 45-60 years) were unaware that compounded drugs were not approved by the FDA [60]. These survey results stress two important gaps: (1) the need for public education regarding

Table 2 Common compounded hormone drugs [57,58]

ACTIVE INGREDIENT	Estriol Combination of estradiol and estriol Combination of estrone, estradiol, and estriol Progesterone Testosterone Dehydroepiandrosterone (DHEA)
ROUTE AND DOSAGE FORM	Oral capsule Topical cream, gel, lotion, and troche Vaginal suppository

the use of compounded hormone drugs, and (2) the necessity for a verification process for compounded hormone drugs in terms of safety and efficacy. With growing interest in compounded hormone drugs, the FDA announced an agreement with the National Academics of Science, Engineering & Medicine (NASEM) for two studies to examine the clinical utility of patients treated with compounded hormone products, and the safety and effectiveness of multi-ingredient compounded topical pain creams [61].

Due to uncertainties regarding safety, the American College of Obstetricians and Gynecologists' Committee on Gynecologic Practice and the Practice Committee of the American Society for Reproductive Medicine cautioned against the use of compounded hormone formulations [62].

Advancing Precision Hormone Therapy Opportunities

Genetic factors influencing clinical use of HT:

Genetics can determine response to HT and provide a technologically feasible strategy to achieve precision HT. One well described impact of formulations relevant to precision HT is the induction of venous thromboembolism (VTE) in women carrying the Factor V Leiden (rs6025) gene variant with oral estrogen therapy [63,64].

In non-carrier HT users, the relative risk for VTE is increased 2- to 4-fold relative to non-users of HRT. In contrast, HT users with Factor V Leiden genetic variant showed an increased risk for VTE between 7- to 15-fold relative to non-carriers and nonusers [64,65].

Hepatic first-pass metabolism that occurs with oral administration of estrogen induces liver clotting factors leading to VTE, which can be avoided by transdermal administration [63,65]. The study by Laliberté *et al.* [26] showed a comparison of the risk of VTE between oral- and transdermal-estradiol administration. They conducted a claims analysis using the Thomson Reuters MarketScan database from January 2002 to October 2009, which included participants aged 35 years or older and newly used transdermal or oral estrogen-alone therapy. Each group included 27,018 women, and 115 transdermal-estradiol users developed VTE, which was a significantly lower incidence compared to oral-estradiol users (164 women) [26]. The benefit of transdermal administration for estradiol therapy was associated with the avoidance of hepatic first-pass metabolism of estradiol. Orally administered estradiol undergoes first-pass metabolism, and it has been known that estrone, a major metabolite of estradiol, can affect thrombin generation, a marker of hypercoagulability which is used to determine thrombotic risk associated with HT [10,11,66,67]. Thus, a transdermal route has been suggested as a safe option for women at a high risk of VTE compared to an oral route.

In addition, biomarkers relevant to cardiovascular disease was proposed by Manson [1], which includes lipids (e.g. serum LDL cholesterol, LDL/HDL ratios, triglyceride, 27-OH-cholesterol, and apolipoprotein), inflammatory markers (e.g. high-sensitivity C-reactive protein, interleukin-6, tumor necrosis factor α, and leukocyte count), adipokines (e.g. adiponectin, leptin, and retinol binding protein-4), endothelial marker (e.g. E-selectin, P-selectin, ICAM, and VCAM), glucose tolerance markers (e.g. fasting glucose, insulin, HOMA-IR, and IGF-1), matrix metalloproteinases, hemostatic markers (e.g. D-dimer, factor VIII, von Willebrand factor, homocysteine, fibrinogen, and tissue factor pathway inhibitor or acquired activated protein C resistance), sex steroid hormone level, and sex hormone binding globulin level [1].

Genetics associated with breast cancer are a well documented consideration of HT use. To reduce the risks of breast and ovarian cancers, bilateral prophylactic oophorectomy is selected among BRCA1/2 mutation carriers [68]. In particular, BRCA1/2 mutations play a critical role in increased breast and ovarian cancer risks [69-71]. However, HT is prescribed for women suffering from menopausal symptoms after surgery [72]. There has been discussion whether HT mitigates the protective effect of bilateral prophylactic oophorectomy on decreased risks for breast or ovarian cancer. However, studies have demonstrated that short-term use of HT does not reduce the protective effect of oophorectomy surgery in breast cancer patients [69]. Furthermore, the use of HT was reported to decrease breast cancer risk in postmenopausal women with a BRCA1 mutation [70]. A recent study suggested that a combined treatment of mifepristone, a selective progesterone receptor modulator, and progesterone exerted anti-proliferative effect on ovarian mesenchymal stem/stromal cells of healthy female BRCA1/2 carriers *in vitro* [73].

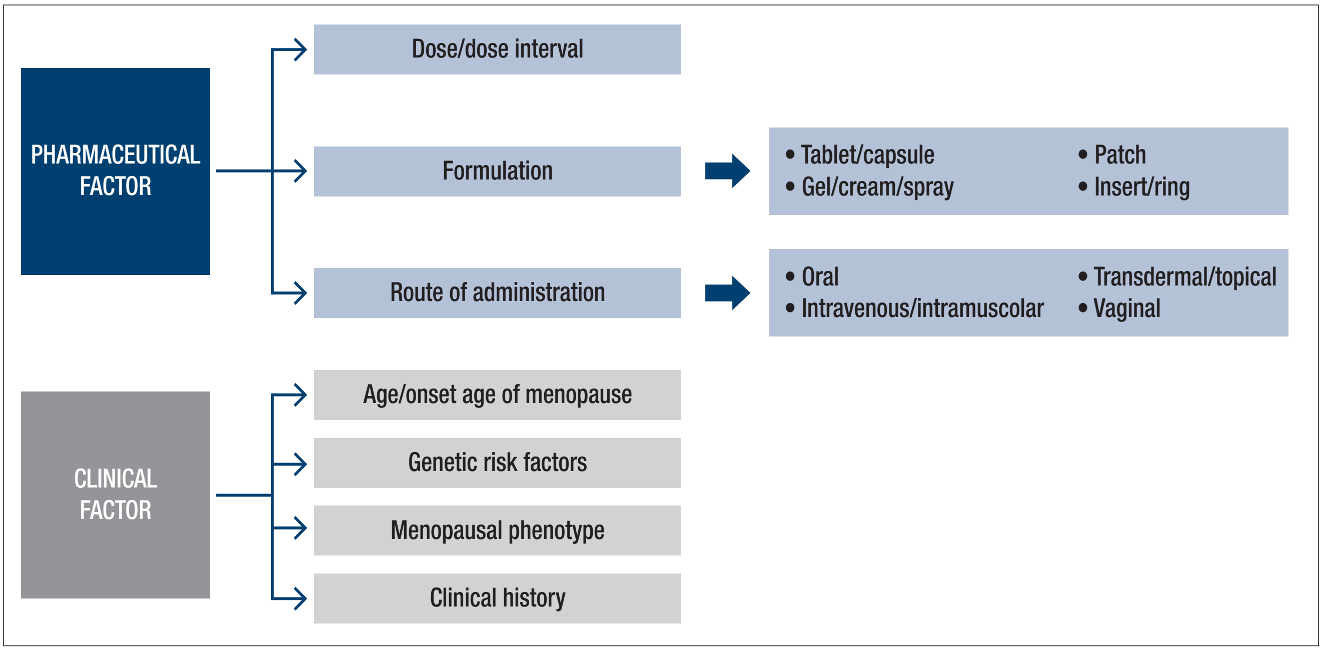
In addition to BRCA 1/2 mutations, common markers associated with breast cancer tumors are the estrogen receptor (ER), the progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) [74]. In addition to these receptors, a host of other genes associated with increased risk for breast or ovarian cancer includes: (1) PALB2, ATM, CHEK2, and MSH6 for a risk for breast cancer, and (2) MSH6, RAD51C, TP53, and ATM for a risk for ovarian cancer [71].

Cytochrome P450 (CYP) enzymes are involved in metabolic conversion of estrogens, which are relevant to individual's response to drugs [75]. Estradiol and estrone are metabolized by irreversible hydroxylation catalyzed by the NADPH-dependent CYP enzymes. Genetic polymorphisms in genes encoding CYP1A1, CYP1B1, CYP17A1, and CYP19A1 can impact estrogen metabolism and therefore impact downstream consequences [75]. Risk of breast cancer was significantly affected by genetic polymorphisms in CYP1B1 [76].

Clinical conditions impacting response to HT:

Estrogen plays a critical role in the bioenergetic system of the brain and promotes glucose transport, aerobic glycolysis, and mitochondrial function [33,77-79]. In addition to regulating expression of glucose transporters, estrogen promotes the insulin-sensitive glucose transporter [33]. Type 2 diabetes is a risk factor for dementia and in particular Alzheimer's disease [78]. Espeland and colleagues investigated the effect of

Figure 2 Pharmaceutical and clinical factors for the development of precision HT.



HT on brain volumes and incidence of cognitive impairment in postmenopausal women based on type 2 diabetes status [79]. Outcomes of their analyses indicated that increased risk of cognitive impairment occurred among menopausal women with type 2 diabetes or emerging diabetes which was paralleled by changes in gray matter (total and hippocampal) volume [79,80].

Conclusion

From a clinical perspective, precision HT is critical to delivering personalized medicine for management of menopausal symptoms and bridging the gap between health span and life span in postmenopausal women. Achieving precision HT requires inclusion of multiple factors including age, genetic risk factors, symptomatic phenotype and clinical history (Figure 2).

From a pharmaceutical perspective, determining the optimal HT depends on the molecular constituents, dose, treatment regimen, formulation and route of administration. Much of the data required to achieve precision HT is available but with varying degrees of accessibility. Barriers to achieving precision HT can be overcome by increasing access to electronic medical records for medical informatic and computational systems biology analysis. Outcomes of these analyses could form the foundation of an algorithm decision making tree [30] which incorporates genetic risk factors, patient clinical data with, pharmaceutical data on different HTs to optimize HT.

Remarkably, the patient and physician goal of personalized HT aligns with the currently available data and analytic technologies to achieve precision HT. Development of precision HT will significantly advance womens' health while also creating a foundation on which to advance precision contraceptive medicine and male HT.

References

1. Manson JE. The role of personalized medicine in identifying appropriate candidates for menopausal estrogen therapy. Metabolism. 2013;62 Suppl 1:S15-9.
2. Taylor HS. Precision menopausal medicine. Menopause. 2017; 24:482-3.
3. Bardakjian T, Gonzalez-Alegre P. Towards precision medicine. Handb Clin Neurol. 2018;147:93-102.
4. Lobo RA. Hormone-replacement therapy: current thinking. Nat Rev Endocrinol. 2017;13:220-31.
5. Steinkellner AR, Denison SE, Eldridge SL, Lenzi LL, Chen W, Bowlin SJ. A decade of postmenopausal hormone therapy prescribing in the United States: long-term effects of the Women's Health Initiative. Menopause. 2012;19:616-21.
6. Rossouw JE, Anderson GL, Prentice RL, et al.; Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA. 2002;288:321-33.
7. Stefanick ML, Cochrane BB, Hsia J, Barad DH, Liu JH, Johnson SR. The Women's Health Initiative postmenopausal hormone trials: overview and baseline characteristics of participants. Ann Epidemiol. 2003;13(9 Suppl):S78-86.
8. DeNeui T, Berg J, Howson A. Best practices in care for menopausal patients: 16 years after the Women's Health Initiative. J Am Assoc Nurse Pract. 2019;31:420-7.
9. Anderson GL, Limacher M, Assaf AR, et al; Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA. 2004;291:1701-12.
10. Bagot C, Marsh M, Whitehead M, et al. The effect of estrone on thrombin generation may explain the different thrombotic risk between oral and transdermal hormone replacement therapy. J Thromb Haemost. 2010;8:1736-44.
11. Sweetland S, Beral V, Balkwill A, et al. Venous thromboembolism risk in relation to use of different types of postmenopausal hormone therapy in a large prospective study. J Thromb Haemost. 2012;10:2277-86.
12. Resnick SM, Maki PM, Rapp SR, et al; Women's Health Initiative Study of Cognitive Aging Investigators. Effects of combination estrogen plus progestin hormone treatment on cognition and affect. J

Clin Endocrinol Metab. 2006;91:1802-10.

13. Wroolie TE, Kenna HA, Williams KE, et al. Differences in verbal memory performance in postmenopausal women receiving hormone therapy: 17β-estradiol versus conjugated equine estrogens. Am J Geriatr Psychiatry. 2011;19:792-802.
14. McCarrey AC, Resnick SM. Postmenopausal hormone therapy and cognition. Horm Behav. 2015;74:167-72.
15. Wharton W, Baker LD, Gleason CE, et al. Short-term hormone therapy with transdermal estradiol improves cognition for postmenopausal women with Alzheimer's disease: results of a randomized controlled trial. J Alzheimers Dis. 2011;26:495-505.
16. Espeland MA, Shumaker SA, Leng I, et al; WHIMSY Study Group. Long-term effects on cognitive function of postmenopausal hormone therapy prescribed to women aged 50 to 55 years. JAMA Intern Med. 2013;173:1429-36.
17. Valen-Sendstad A, Engedal K, Stray-Pedersen B, et al. Effects of hormone therapy on depressive symptoms and cognitive functions in women with Alzheimer disease: a 12 month randomized, double-blind, placebo-controlled study of low-dose estradiol and norethisterone. Am J Geriatr Psychiatry. 2010;18:11-20.
18. Gleason CE, Dowling NM, Wharton W, et al. Effects of hormone therapy on cognition and mood in recently postmenopausal women: findings from the randomized, controlled KEEPS–Cognitive and Affective Study. PLoS Med. 2015;12(6):e1001833.
19. Canonico M, Carcaillon L, Plu-Bureau G, et al. Postmenopausal hormone therapy and risk of stroke: impact of the route of estrogen administration and type of progestogen. Stroke. 2016;47:1734-41.
20. Nicoletti A, Arabia G, Pugliese P, et al. Hormonal replacement therapy in women with Parkinson disease and levodopa-induced dyskinesia: a crossover trial. Clin Neuropharmacol. 2007;30:276-80.
21. Bove R, White CC, Fitzgerald KC, et al. Hormone therapy use and physical quality of life in postmenopausal women with multiple sclerosis. Neurology. 2016;87:1457-63.
22. Grodstein F, Manson JE, Colditz GA, Willett WC, Speizer FE, Stampfer MJ. A prospective, observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. Ann Intern Med. 2000;133:933-41.
23. Espeland MA, Brinton RD, Hugenschmidt C, et al; WHIMS Study Group. Impact of type 2 diabetes and postmenopausal hormone therapy on incidence of cognitive impairment in older women. Diabetes care. 2015;38:2316-24.
24. Jacobs EG, Kroenke C, Lin J, et al. Accelerated cell aging in female APOE-ε4 carriers: implications for hormone therapy use. PLoS One. 2013;8:e54713.
25. Kang JH, Grodstein F. Postmenopausal hormone therapy, timing of initiation, APOE and cognitive decline. Neurobiol Aging. 2012;33:1129-37.
26. Laliberté F, Dea K, Duh MS, Kahler KH, Rolli M, Lefebvre P. Does the route of administration for estrogen hormone therapy impact the risk of venous thromboembolism? Estradiol transdermal system versus oral estrogen-only hormone therapy. Menopause. 2011;18:1052-9.
27. Weissfeld JL, Liu W, Woods C, et al. Trends in oral and vaginally administered estrogen use among US women 50 years of age or older with commercial health insurance. Menopause. 2018;25:611-4.
28. Crawford SL, Crandall CJ, Derby CA, et al. Menopausal hormone therapy trends before versus after 2002: impact of the Women's Health Initiative Study results. Menopause. 2018;26:588-97.
29. U.S. Food and Drug Administration. Menopause. (Aug 22, 2019). Available at: https://www.fda.gov/consumers/womens-health-topics/menopause.
30. Martin KA, Barbieri RL. Treatment of menopausal symptoms with hormone therapy. Up-to-date, Crowley Jr WF (Jun 5, 2017) Available at: https://www.uptodate.com/contents/treatment-of-menopausal-symptoms-with-hormone-therapy.
31. Brinton RD. The healthy cell bias of estrogen action: mitochondrial bioenergetics and neurological implications. Trends Neurosci. 2008;31:529-37.
32. Brinton RD. Neuroendocrinology: oestrogen therapy affects brain structure but not function. Nat Rev Neurol. 2016;12:561-2.
33. Rettberg JR, Yao J, Brinton RD. Estrogen: a master regulator of bioenergetic systems in the brain and body. Front Neuroendocrinol. 2014;35:8-30.
34. VAN Heertum K, Liu J. Differential Effects of Progestogens Used for Menopausal Hormone Therapy. Clin Obstet Gynecol. 2018;61:454-62.
35. Fournier A, Mesrine S, Dossus L, Boutron-Ruault MC, Clavel-Chapelon F, Chabbert-Buffet N. Risk of breast cancer after stopping menopausal hormone therapy in the E3N cohort. Breast Cancer Res Treat. 2014;145:535-43.
36. Fournier A, Berrino F, Clavel-Chapelon F. Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study. Breast Cancer Res Treat. 2008;107:103-11.
37. Vinogradova Y, Coupland C, Hippisley-Cox J. Use of hormone replacement therapy and risk of venous thromboembolism: nested case-control studies using the QResearch and CPRD databases. BMJ. 2019;364:k4810.
38. Moore NL, Hanson AR, Ebrahimie E, Hickey TE, Tilley WD. Anti-proliferative transcriptional effects of medroxyprogesterone acetate in estrogen receptor positive breast cancer cells are predominantly mediated by the progesterone receptor. J Steroid Biochem Mol Biol. 2020;199:105548.
39. Wiebe JP, Beausoleil M, Zhang G, Cialacu V. Opposing actions of the progesterone metabolites, 5alpha-dihydroprogesterone (5alphaP) and 3alpha-dihydroprogesterone (3alphaHP) on mitosis, apoptosis, and expression of Bcl-2, Bax and p21 in human breast cell lines. J Steroid Biochem Mol Biol. 2010;118(1-2):125-32.
40. Nilsen J, Morales A, Brinton RD. Medroxyprogesterone acetate exacerbates glutamate excitotoxicity. Gynecol Endocrinol. 2006; 22:355-61.
41. Irwin RW, Yao J, Ahmed SS, Hamilton RT, Cadenas E, Brinton RD. Medroxyprogesterone acetate antagonizes estrogen up-regulation of brain mitochondrial function. Endocrinology. 2011;152:556-67.
42. Umland EM, Karel L, Santoro N. Bazedoxifene and conjugated equine estrogen: a combination product for the management of vasomotor symptoms and osteoporosis prevention associated with menopause. Pharmacotherapy. 2016;36:548-61.
43. Lewis-Wambi JS, Kim H, Curpan R, Grigg R, Sarker MA, Jordan VC. The selective estrogen receptor modulator bazedoxifene inhibits hormone-independent breast cancer cell growth and down-regulates estrogen receptor α and cyclin D1. Mol Pharmacol. 2011;80:610-20.
44. Mirkin S, Komm BS. Tissue-selective estrogen complexes for postmenopausal women. Maturitas. 2013;76:213-20.
45. Gallagher JC, Palacios S, Ryan KA, et al. Effect of conjugated estrogens/bazedoxifene on postmenopausal bone loss: pooled analysis of two randomized trials. Menopause. 2016;23:1083-91.
46. Lobo RA, Pinkerton JV, Gass ML, et al. Evaluation of bazedoxifene/conjugated estrogens for the treatment of menopausal symptoms and effects on metabolic parameters and overall safety profile. Fertil Steril. 2009;92:1025-38.
47. Kagan R, Komm BS, Ryan KA, Lavenberg J, Yu C-R, Pinkerton JV. Timing and persistence of effect of conjugated estrogens/bazedoxifene in postmenopausal women. Menopause. 2016;23:1204-13.
48. Pinkerton JV, Harvey JA, Lindsay R, et al; SMART-5 Investigators. Effects of bazedoxifene/conjugated estrogens on the endometrium and bone: a randomized trial. J Clin Endocrinol Metab. 2014; 99:E189-98.
49. Pinkerton JV. Tissue-selective Estrogen Complex for Menopausal Hormone Therapy. Clin Obstet Gynecol. 2018;61:463-9.
50. Zhao L, Morgan TE, Mao Z, et al. Continuous versus cyclic progesterone exposure differentially regulates hippocampal gene expression and functional profiles. PLoS One. 2012;7:e31267.
51. Carroll JC, Rosario ER, Villamagna A, Pike CJ. Continuous and cyclic progesterone differentially interact with estradiol in the regulation of Alzheimer-like pathology in female 3xTransgenic-Alzheimer's disease mice. Endocrinology. 2010;151:2713-22.
52. Campagnoli C, Clavel-Chapelon F, Kaaks R, Peris C, Berrino F. Progestins and progesterone in hormone replacement therapy and the risk of breast cancer. J Steroid Biochem Mol Biol. 2005;96:95-108.

53. Sitruk-Ware R. Progestins and cardiovascular risk markers. Steroids. 2000;65:651-8.
54. U.S. Food and Drug Administration. Brisdelle: Highlights of prescribing information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/204516s004lbl.pdf.
55. U.S. Food and Drug Administration. Osphena: Highlights of prescribing information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/203505s000lbl.pdf.
56. U.S. Food and Drug Administration. Bijuva: Highlights of prescribing information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210132s000lbl.pdf.
57. Thompson JJ, Ritenbaugh C, Nichter M. Why women choose compounded bioidentical hormone therapy: lessons from a qualitative study of menopausal decision-making. BMC Womens Health. 2017;17:97.
58. Sood R, Shuster L, Smith R, Vincent A, Jatoi A. Counseling postmenopausal women about bioidentical hormones: Ten discussion points for practicing physicians. J Am Board Fam Med. 2011;24:202-10.
59. Gass ML, Stuenkel CA, Utian WH, LaCroix A, Liu JH, Shifren JL; North American Menopause Society (NAMS) Advisory Panel consisting of representatives of NAMS Board of Trustees and other experts in women's health. Use of compounded hormone therapy in the United States: report of the North American Menopause Society Survey. Menopause. 2015;22:1276-84.
60. Pinkerton JV, Santoro N. Compounded bioidentical hormone therapy: identifying use trends and knowledge gaps among US women. Menopause. 2015;22:926-36.
61. U.S. Food and Drug Administration. Compounding research. (Jun 24, 2019). Available at: https://www.fda.gov/drugs/human-drug-compounding/compounding-research.
62. Committee on Gynecologic Practice and the American Society for Reproductive Medicine Practice Committee. Committee opinion No. 532: compounded bioidentical menopausal hormone therapy. Obstet Gynecol. 2012;120(2 Pt 1):411-5.
63. Sitruk-Ware R. Hormonal contraception and thrombosis. Fertil Steril. 2016;106:1289-94.
64. Kujovich JL. Factor V Leiden thrombophilia. Genet Med. 2011;13:1-16.
65. Gomes MP, Deitcher SR. Risk of venous thromboembolic disease associated with hormonal contraceptives and hormone replacement therapy: a clinical review. Arch Intern Med. 2004;164:1965-76.
66. Olié V, Canonico M, Scarabin PY. Risk of venous thrombosis with oral versus transdermal estrogen therapy among postmenopausal women. Curr Opin Hematol. 2010;17:457-63.
67. Modena MG, Sismondi P, Mueck AO, et al; TREAT. New evidence regarding hormone replacement therapies is urgently required: transdermal postmenopausal hormone therapy differs from oral hormone therapy in risks and benefits. Maturitas. 2005;52:1-10.
68. Rebbeck TR, Lynch HT, Neuhausen SL, et al.; Prevention and Observation of Surgical End Points Study Group. Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. N Engl J Med. 2002;346:1616-22
69. Rebbeck TR, Friebel T, Wagner T, et al; PROSE Study Group. Effect of short-term hormone replacement therapy on breast cancer risk reduction after bilateral prophylactic oophorectomy in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. J Clin Oncol. 2005;23:7804-10.
70. Eisen A, Lubinski J, Gronwald J, et al; Hereditary Breast Cancer Clinical Study Group. Hormone therapy and the risk of breast cancer in BRCA1 mutation carriers J Natl Cancer Inst. 2008;100:1361-7
71. Lu H-M, Li S, Black MH, et al. Association of breast and ovarian cancers with predisposition genes identified by large-scale sequencing. JAMA Oncol. 2019;5:51-7.
72. Böös JN, Von Schoultz B, Carlström K. Elective ovarian removal and estrogen replacement therapy--effects on sexual life, psychological well-being and androgen status. J Psychosom Obstet Gynaecol. 1993;14:283-93.
73. Ponandai-Srinivasan S, Lalitkumar PG, Garcia L, et al. Mifepristone mediates anti-proliferative effect on ovarian mesenchymal stem/stromal cells from female BRCA1-/2- carriers. Acta Obstet Gynecol Scand. 2019;98:250-61.
74. Allred DC. Issues and updates: evaluating estrogen receptor-alpha, progesterone receptor, and HER2 in breast cancer. Mod Pathol. 2010;23 Suppl 2:S52-9.
75. Samavat H, Kurzer MS. Estrogen metabolism and breast cancer. Cancer Lett. 2015;356(2 Pt A):231-43.
76. MARIE-GENICA Consortium on Genetic Susceptibility for Menopausal Hormone Therapy Related Breast Cancer Risk. Genetic polymorphisms in phase I and phase II enzymes and breast cancer risk associated with menopausal hormone therapy in postmenopausal women. Breast Cancer Res Treat. 2010;119:463-74.
77. Brinton RD, Yao J, Yin F, Mack WJ, Cadenas E. Perimenopause as a neurological transition state. Nat Rev Endocrinol. 2015;11:393-405.
78. Carcaillon L, Brailly-Tabard S, Ancelin ML, et al. High plasma estradiol interacts with diabetes on risk of dementia in older postmenopausal women. Neurology. 2014;82:504-11.
79. Espeland MA, Brinton RD, Manson JE, et al; WHIMS-MRI2 Study Group. Postmenopausal hormone therapy, type 2 diabetes mellitus, and brain volumes. Neurology. 2015;85:1131-8.
80. Ley SH, Ardisson Korat AV, Sun Q, et al. Contribution of the Nurses' Health Studies to uncovering risk factors for type 2 diabetes: diet, lifestyle, biomarkers, and genetics. Am J Public Health. 2016;106:1624-30.

Acknowledgement: *This work was supported by NIH grants R37AG053589, 1R01AG057931 and P01-AG026572 to RDB.*