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Corporate Reimbursement Policy

Hormonal Testing in Adult Females AHS – G2161 **"Notification"**

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Description of Procedure or Service
This policy only addresses coverage of hormonal testing in adult females (age 18 years and older)

A multitude of hormones fluctuate throughout a woman's lifetime. Estrogens, especially estradiol or E2, as well as follicle stimulating hormone (FSH) and luteinizing hormone (LH), are involved in the regulation of menstrual cycle in females. During the menopausal transition, known as perimenopause, anti-Müllerian hormone (AMH) and inhibin B levels fall (Stuenkel et al., 2015). Whenever a woman over the age of 40 ceases menstruation without any outside intervention or cause for at least twelve consecutive months, it is a natural menopause; menopause prior to the age of 40 is abnormal and referred to as primary ovarian insufficiency (POI) or premature ovarian failure. Estrogen deficiency from menopause is linked to an increase of bone loss (osteoporosis), a change in body composition, reduction in collagen, and an increased risk of cardiovascular disease (Casper, 2020). Polycystic Ovary Syndrome (PCOS) is due to a dysregulation of testosterone in females presenting in a variety of metabolic, reproductive, and psychological features (Teede et al., 2018)..

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

BCBSNC will provide coverage for hormonal testing in adult females when it is determined the medical criteria or reimbursement guidelines below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When hormonal testing in adult females is covered

1) Reimbursement is allowed for measurement of serum follicle stimulating hormone (FSH), luteinizing hormone (LH), anti-Müllerian hormone (AMH), and/or estradiol (E2) in the following situations:
    a. Women under the age of 40 with primary ovarian insufficiency, including cases of amenorrhea and oligomenorrhea; OR

   b. Women under the age of 60 prior to initiating adjuvant chemotherapy for cancer treatment.
2) Reimbursement is allowed for testing for serum total testosterone* (See Note 1) in symptomatic females being evaluated for conditions associated with androgen excess (e.g., polycystic ovary syndrome and functional hypothalamic amenorrhea). The technology used for testing should be sensitive enough to detect the low concentrations normally found in females.
3) Reimbursement is allowed for testing for serum testosterone* (See Note 1) in gender-dysphoric/gender-incongruent persons at baseline, during the treatment and for the therapy monitoring every three months for transgender females on gender-affirming hormone therapy.
4) Reimbursement is allowed for measurement of serum prolactin, LH, FSH, growth hormone (GH), thyroid stimulating hormone (TSH), and adrenocorticotropic hormone (ACTH) in the following situations:
   a. For the diagnosis and management of pituitary adenoma
   b. Diagnosis of hypopituitarism

When hormonal testing in adult females is not covered

1) Reimbursement is not allowed for measurement of serum FSH, LH, AMH, and/or estradiol in the following situations:
   a) To predict final menstruation for women over the age of 40; OR
   b) To determine need for or use of contraceptives; OR
   c) To determine menopause status for women over the age of 40; OR
2) Reimbursement is not allowed for measurement of serum AMH in the following situations
   a) To diagnose polycystic ovary syndrome; OR
   b) To assess fertility; OR
   c) TO predict pregnancy loss
3) Reimbursement is not allowed for measurement of serum FSH, LH, AMH, and/or estradiol to assess or monitor hormone therapy.
4) Reimbursement is not allowed for measurement of serum estrone or estrone
5) Reimbursement is not allowed for testing for serum testosterone for the identification of androgen deficiency in women. (see note 2 for signs and symptoms)
6) Reimbursement of testing of inhibin A and inhibin B for the diagnosis of perimenopause or menopause in women aged over 45 years.
7) Salivary testing of estrogen, progesterone, estradiol, estrone, estrone sulfate, FSH, LH, and/or AMH for screening, diagnosis, and or monitoring of menopause is considered investigational.
8) Salivary testing of estrogen, progesterone, estradiol, estrone, estrone sulfate, FSH, LH, and/or AMH for monitoring and/or assessing hormone therapy is considered investigational.
9) Reimbursement is not allowed for serum testing of dihydrotestosterone levels in females is considered investigational except in testing for 5-alpha reductase deficiency for individuals with ambiguous genitalia, hypospadias, or microphallus.

NOTE 1: Due to considerable variability in serum total testosterone testing, the Centers for Disease Control and Prevention (CDC) developed a standardization program for total testosterone assays (Hormone Standardization [HoSt]/Testosterone). An assay certified by the CDC's HoSt/Testosterone program is standardized to within ±6.4% of the CDC total testosterone reference standard. It is **STRONGLY RECOMMENDED** that serum total testosterone testing be performed on an assay that has been certified by the CDC HoSt/Testosterone program (Bhasin et al., 2018). A list of CDC-certified assays is available on the HoSt website (CDC, 2020).

NOTE 2: Signs and symptoms of androgen deficiency in women include decrease in or loss of libido, unexplained fatigue, decrease in lean body mass, loss of pubic hair, dysphoria, osteopenia, and/or osteoporosis (Mathur & Braunstein, 2010).

Policy Guidelines

Estrogens, including estradiol, are sex steroid hormones that can affect transcription via two classes of pathways. In the classical estrogenic pathway, the hydrophobic estrogen diffuses through the cell membrane to bind to the activating estrogen receptors that dimerize to subsequently bind the estrogen responsive elements in the nucleus to target transcription. In the non-classical pathway, the estrogen binds to separate plasma membrane receptors to initiate a signaling cascade, such as through MAPK or inositol, to ultimately affect transcription. Regardless of the activation pathway, a neuroprotective effect on the central nervous system (CNS) occurs. Estradiol concentration rises and falls throughout the ovarian continuum. An increase in estrogen levels in the presence of the protein hormone inhibin initiates negative feedback to decrease the concentration of follicle stimulating hormone (FSH). At the end of the cycle, estradiol and progesterone concentrations decrease to eliminate the negative feedback inhibition of the hypothalamic-pituitary-gonadal (HPG) axis and to increase the levels of FSH (Del Rio et al., 2018).

Menopause is the transition from regular to irregular menstrual cycles. Other clinical manifestations include "hot flashes, sleep disturbances, mood symptoms, and vaginal dryness" as well as lipid composition changes and bone loss; hot flashes are the most predominant symptom with up to 80% of women experiencing them (Casper, 2020). To date, no reliable method has been established and verified to predict the final menstrual period. "The diagnosis of the menopausal transition is made in women over 45 years based upon irregular menstrual cycles and menopausal symptoms such as hot flashes, mood changes, or sleep disturbance. We suggest no further diagnostic evaluation. Although serum FSH is often measured, it offers no additional information, and may be misleading. Menopause may be diagnosed clinically as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. We do not recommend further diagnostic evaluation for women in this group (Casper, 2020)."

Salivary hormone level testing is often highly recommended by advocates and compounders of bioidentical hormones as a means of offering individualized therapy (Boothby, Doering, & Kipersztok, 2004). However, individualized testing and monitoring is only indicated when a narrow therapeutic window exists for a drug or a drug class. Steroid hormones, such as estrogen and progesterone, do not meet these criteria and, thus, do not require individualized testing, but they can be used for other research studies (ACOG & ASRM, 2012; Conaway, 2011). For instance, a study conducted by Mernone, Fiacco, and Ehlert (2019) utilized saliva samples of estrogen, testosterone, progesterone, and dehydroepiandrosterone sulfate (DHEAS) as measures of sexual functioning among a sample of middle-aged and older females to conclude that, although aging and menopause negatively affect sexual functioning, other factors, such as optimism, emotional support, and relationship satisfaction, can correlate positively with healthy sexual functioning.

Analytical Validity

A 2014 study by Handelsman et al. investigated the validity of five commercially available direct immunoassays for estradiol and compared them to the liquid chromatography–mass spectrometry (LC-MS) reference method. This study included 101 samples from healthy men and utilized the Siemens ADVIA Enhanced Estradiol assay, Siemens IMMULITE 2000 Estradiol assay, Roche cobas Estradiol II assay, Abbott ARCHITECT System Estradiol assay, and Beckman Coulter Access Estradiol assay. Three of the assays detected E2 in all samples, while the Siemens IMMULITE 2000 Estradiol assay detected E2 in only 53% of the samples and Beckman Coulter Access Estradiol assay detected E2 in 72%. "All 5 assays had positive biases, ranging from 6% to 74%, throughout their ranges" (Handelsman et al., 2014).

The Centers for Disease Control and Prevention (CDC) reviewed estradiol and testosterone testing in 2014 (Vesper, Botelho, & Wang, 2014). The positive bias identified by steroid analyte testing indicates "that the assay is measuring other compounds in addition to the analyte and lacks specificity." The CDC also report that the imprecision of estradiol testing for commercial

immunoassays "ranges from 1.2% to 42.6% CV [coefficient of variation] at concentrations from 18 to 846 pg ml^{-1} (66 pmol l^{-1})." Conclusions state that "although technologies for steroid hormone measurement have advanced significantly, measurement variability within and across laboratories has not improved accordingly… Within-assay variability for current assays is generally high, especially at low analyte concentrations" (Vesper et al., 2014). Immunoassays have been used to study FSH, E1, and E2 levels in the urine and serum of pre- and postmenopausal women; a total of 92 women (31 premenopausal and 61 postmenopausal) participated in this study (Onizuka et al., 2019). FSH, E1 and E2 levels were similar in both urine and serum samples, suggesting that only one type of sampling method should be used in the future. "There were correlations in the levels of FSH, E1 and E2 between urine and serum in both postmenopausal ($r = 0.96$ for FSH, $r = 0.91$ for E1, $r = 0.80$ for E2) and premenopausal ($r = 0.98$ for FSH, $r = 0.92$ for E1, $r = 0.90$ for E2) women. It is indicated that the correlations were stronger in the premenopausal group compared with the postmenopausal group, especially for FSH (Onizuka et al., 2019)." These results show that correlations in FSH, E1, and E2 are found in both premenopausal and postmenopausal women, and that the levels of these hormones are similar in both urine and serum samples.

Hormones like AMH, FSH, LH, free androgen index (FAI), prolactin, estradiol, testosterone, and others have been used for the clinical diagnosis of polycystic ovary syndrome (PCOS). In a study done by Khashchenko et al. (2020) with a sample of 130 girls with PCOS by the Rotterdam criteria, cutoffs for the most significant hormone indicators of PCOS diagnosis in adolescents were identified. "The levels of AMH > 7.20 ng/mL and FAI > 2.75 [ng/mL] showed the highest sensitivity (76.0% and 75.0%) and specificity (89.0 and 93.0%, respectively) for PCOS diagnostics in adolescence. Moreover, we determined that levels of testosterone > 1.15 nmol/L, androstenedione > 11.45 ng/mL, and LH/FSH ratio > 1.23 also showed high sensitivity of 63.2–78.2% and specificity of 84.4–93.7% in PCOS diagnosis in the studied sample of girls (Khashchenko et al., 2020)." The combined use of either four thresholds (AMH, FAI, testosterone, androstenedione, LH/FSH ratio as previously stated) yielded a diagnostic accuracy of 90.2-91.6% in predicting PCOS in adolescents (Khashchenko et al., 2020).

In 2016, the Endocrine Society published guidelines concerning hypopituitarism. As part of this extensive guideline, they characterized common automated immunoassays of a variety of hormones, including FSH, LH, and estradiol. The Endocrine Society reports that all three tests show variability between assays; however, the imprecision of the three hormone tests were considerably different (Fleseriu et al., 2016). FSH has 8.1% variability within the method and 8.9% between methods. LH has 7.7% variability within the method and, similar to FSH, has 8.9% between methods. Estradiol, on the other hand, is significantly worse with 16.9% variability within the method and 64.9% variability between methods (Fleseriu et al., 2016).

Clinical Utility and Validity

A 2013 study of urinary FSH testing of 209 women between the ages of 30-44 was conducted since decreased ovarian reserve had been associated with an increase in serum FSH (Steiner et al., 2013). The urinary FSH concentration was corrected using creatinine. The authors note that the women who had initial urinary FSH concentrations under 7 ml U/mg creatinine had a "nonsignificant reduction in the probability of pregnancy"; however, the same was true for women with elevated FSH levels above 12 ml U/mg creatinine. "Using the most recent or maximum urinary FSH value did not strengthen the association. In the general population, urinary FSH levels appear to be nonlinearly associated with fertility; however, broad CIs [confidence intervals] indicate a lack of statistical significance. Repetitive testing appears to be of little benefit (Steiner et al., 2013)."

Alipour, Rasekhjahromi, Maalhagh, Sobhanian, and Hosseinpoor (2015) compared the sensitivity and specificity of AMH to FSH in diagnosing premature ovarian failure or primary ovarian insufficiency (POI). Their study consisted of 96 women who had both AMH and FSH serum levels measured at day 3 of their menstrual cycle using an electrochemiluminescence

immunoassay. AMH was more sensitive (80%) than FSH (28.57%) with statistically equal specificities (78.89% versus 78.65%, respectively). The researchers conclude, "AMH serum level is more sensitive than FSH serum level. Also, AMH has more negative predictive value. Besides, this hormone can be measured at any time of menstrual cycle, against FSH. AMH seems to be more useful in early diagnosis of POF [premature ovarian failure]" (Alipour et al., 2015).

Polycystic ovary syndrome (PCOS) is defined by the presence of hyperandrogenism and ovarian dysfunction; however, the clinical and biochemical manifestations can vary considerably between different females. "Clinically, diagnosing a woman as having PCOS implies an increased risk for infertility, dysfunctional bleeding, endometrial carcinoma, obesity, type 2 diabetes mellitus (DM), dyslipidemia, hypertension, and possibly cardiovascular disease (CVD). Furthermore, it has important familial implications, principally, but not exclusively, for her sisters and daughters" (Azziz et al., 2009). Some estimates place the rate of occurrence as 8-13% of reproductive-aged women with up to 70% of those affected being undiagnosed (NHMRC, ASRM, & ESHRE, 2018). Treatment of PCOS can depend on the clinical manifestations and may include life-long therapies, such as the use of insulin sensitizers (Azziz et al., 2009). Recently, Bozdag, Mumusoglu, Coskun, Yarali, and Yildiz (2019) investigated whether AMH levels were an appropriate tool to diagnose PCOS; 392 serum samples taken from a group of women were used in this study. The researchers based diagnostic criteria on guidelines published by the National Institutes of Health, Rotterdam-2003 and Androgen Excess, and PCOS Society. Four patient phenotypes were identified in this study: phenotype A (patients with hyperandrogenism, ovulatory dysfunction and PCOM), phenotype B (patients with hyperandrogenism and ovulatory dysfunction), phenotype C (patient with hyperandrogenism and PCOM), and phenotype D (patients with ovulatory dysfunction and PCOM); results revealed that "AMH has poor to fair validity to diagnose PCOS among an unselected group of women, except for patients bearing all features of the syndrome (Phenotype A)" (Bozdag et al., 2019).

A 2011 study reported that AMH can be used to predict the initial onset of menopause even though it is a reported 20-year span of variability. This study was limited in scope and included data from only 257 females. After 11 years, only 48 of the women were postmenopausal. Even the study's authors noted the limitation in merely predicting an age-range: "Using age and AMH, the age range in which menopause will subsequently occur can be individually calculated" (Broer et al., 2011). Another more recent, long-term cohort study addressed the use of AMH in predicting the onset of menopause. This study included 265 women beginning in 1992 with the last reported follow-up in 2013. The researchers note that the use of serum AMH can decrease the estimated age-range of onset of menopause from 20 years to 10.1 years. This study also discovered another limitation on the use of AMH: "The observed predictive effect of AMH became less strong with increasing age of the woman" (Depmann et al., 2016). Through an extensive literature search, Moolhuijsen and Visser (2020) concluded that AMH could predict time of onset of menopause with certain limitations; the measurement was limited in precision on an individual level and produced conflicting results among women of late reproductive age. However, in The Study of Women's Health Across the Nation (SWAN study), Finkelstein et al. (2020) found that combined with age and BMI, AMH still had use and had a better predictive value for predicting the final menstrual period than FSH.

A longitudinal study followed 2,434 premenopausal women for a total of 20 years, collecting data every five years to determine how efficient AMH levels as a screening tool could be used "for the duration of the female reproductive lifespan" (de Kat et al., 2019). AMH was measured in plasma samples via the picoAMH assay. Based on the results, the researchers determined that "knowledge of the AMH decline rate does not improve the prediction of menopause. Based on the low discriminative ability and underestimation of the risk of early menopause, the use of AMH as a screening method for the timing of menopause cannot currently be advocated (de Kat et al., 2019)." The results of this study may contradict the data reported by Broer et al. (2011) and Depmann et al. (2016).

A 2018 study indicated that both serum estrone (E1) and estrone sulfate (E1S) are elevated in normal postmenopausal women as compared to women with vulvovaginal atrophy (VVA). Serum E1 and E1S were 14.5% and 16.9% higher, respectively, in normal postmenopausal women as compared to women with moderate-to-severe VVA. The authors do not conclude that the use of serum E1 or E1S levels can be directly indicative of VVA; on the other hand, "Such data indicating a lower estrogenic and androgenic global exposure in women diagnosed with VVA offers an opportunity for the local intravaginal administration of DHEA to replace the deficiency in endogenous DHEA" (Ke et al., 2018).

Another study by Palinska-Rudzka et al. (2019) measured serum AMH levels in 66 young women with breast cancer and lymphoma and compared these results with 124 healthy controls; measurements were taken both one and five years after chemotherapy, as well as once before chemotherapy. Results showed that "Reproductive-age women with malignancy have lower serum AMH than healthy controls even before starting chemotherapy. Pre-chemotherapy AMH was significantly associated with long-term ovarian function in women with breast cancer. At key time points, AMH measurements could be used as a reproductive health advisory tool for young women with cancer" (Palinska-Rudzka et al., 2019).

This was corroborated in a study of 144 premenopausal women who were undergoing breast cancer treatment. Li et al. (2020) concluded that "AMH is an efficient marker for predicting postchemotherapy ovarian function exclusively in premenopausal female patients with breast cancer aged >35 years," after finding that chemotherapy-induced amenorrhea was associated with prechemotherapy AMH levels, E2 levels, and FSH levels, but recovery of menstruation was only associated with prechemotherapy AMH levels and not E2 or FSH levels. A significant drop in AMH was only seen among those who were >35 years, demonstrating how early onset of menopause could be dictated by AMH postchemotherapy in specific populations (Li et al., 2020).

State and Federal Regulations, as applicable
Estradiol testing has been approved by the FDA in a wide array of methodologies. A search of the FDA-approved device database on 10/14/2020 yielded 56 different records for the keyword "estradiol". Likewise, the FDA has approved 22 devices for measuring follicle stimulating hormone (FSH) and 24 devices for luteinizing hormone (LH). The Access AMH anti-müllerian hormone test system by Beckman Coulter, Inc. was approved by the FDA in 2017. On 10/24/2018, the FDA released a news release stating that they will allow Ansh Labs to market their PicoAMH ELISA test as an aid to determine menopausal status by measuring AMH in a patient's blood. Diagnostics Biochem Canada, Inc., has an FDA-approved estrone radioimmunoassay (RIA), and Diagnostic Systems Laboratories, Inc., has both an estrone RIA and estrone sulfate RIA approved by the FDA (FDA, 2020).
Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

Policy Statement(s)
Guidelines and Recommendations

Choosing Wisely—an ABIM initiative—and Choosing Wisely UK (AAP, 2017; ASRM, 2015; FSRH, 2016)
The American Society for Reproductive Medicine (ASRM) recommends, "Don't obtain follicle-stimulating hormone (FSH) levels in women in their 40s to identify the menopausal transition as a cause of irregular or abnormal menstrual bleeding. Menstrual bleeding patterns for women after age 40 are less predictable than in younger years due to the normal menopausal transition…During this time, blood levels of FSH vary both from woman to woman and from day to day in the same woman. An FSH level does not predict with the transition to menopause will

occur, diagnose that it has begun or provide reassurance that contraception is no longer necessary. If there are no other causes of irregular or abnormal bleeding, the treatment for these women will not change based on the FSH level" (ASRM, 2015).

The section on endocrinology from the American Academy of Pediatrics (AAP) recommends to "avoid ordering LH and FSH and either estradiol or testosterone for children with pubic hair and/or body odor but no other signs of puberty (AAP, 2017). Premature adrenarche is usually the diagnosis and does not involve activation of the pituitary-gonadal axis but is due to an early increase in adrenal androgens. DHEA-S levels are elevated for age but do not alter the management of this common and generally benign condition."

2016 FSRH [as part of Choosing Wisely UK (FSRH, 2016)]: "If a woman over the age of 45 years with typical symptoms of menopause, such as hot flushes and sweats and if her periods have become irregular, much lighter or have stopped, further bloods [sic] tests to check hormone levels are not usually necessary."

Endocrine Society (ES) (Fleseriu et al., 2016; Gordon et al., 2017; Santoro et al., 2016; Stuenkel et al., 2015)

The ES's 2015 (Stuenkel et al., 2015) guideline concerning the treatment of the symptoms of menopause recommends "diagnosing menopause based on the clinical criteria of the menstrual cycle" (Recommendation 1.1 Level 2++). In Recommendation 1.2 (Level 2++), they state that "if establishing a diagnosis of menopause is necessary for patient management in women having undergone a hysterectomy without bilateral oophorectomy or presenting with a menstrual history that is inadequate to ascertain menopausal status, we suggest making a presumptive diagnosis of menopause based on the presence of vasomotor symptoms (VMS) and, when indicated, laboratory testing that includes replicate measures of FSH and serum estradiol." They do note that for young women (under the age of 40) with primary ovarian insufficiency (POI) "a tentative diagnosis" can be given for persistent FSH elevation (Stuenkel et al., 2015). Regarding AMH, "Sex steroids, gonadotropins, inhibin B, or anti-Mullerian hormone measurements do not further inform the diagnosis, do not indicate precisely when the final menstrual period will occur, and will not influence management unless a woman is seeking fertility" (Stuenkel et al., 2015).

The ES in 2016 issued guidelines concerning the use of hormone replacement in females afflicted with hypopituitarism (Fleseriu et al., 2016). In recommendation 1.14 (Level 1++), they state, "In the presence of oligomenorrhea or amenorrhea, we recommend measuring serum estradiol (E2), FSH, and LH. Clinicians should exclude other causes of menstrual irregularities related to impaired ovulation (hyperprolactinemia, hyperandrogenism, and thyroid disease), particularly if no other pituitary hormone deficits are present. In cases of amenorrhea, clinicians should also exclude pregnancy." In recommendation 1.16 (Level 1 +++), they "recommend that in postmenopausal women, the absence of high serum FSH and LH is sufficient for a diagnosis of gonadotrope dysfunction (provided the patient is not on hormonal replacement therapy [HRT])"; however, they do not recommend in testing with GnRH (Gonadotropin Releasing Hormone) because it "offers no useful diagnostic information" (Recommendation 1.15, Level 2++). It should be noted that the Endocrine Society does state that "clinicians should consider differences among assays and use the same assay for serial and longitudinal measurements" when testing estradiol. Within the remarks concerning estrogen hormone replacement in premenopausal women, they note that "measuring serum E2 [estradiol] levels is [sic] not beneficial; moreover, some estrogens are not detected by the assays" (Fleseriu et al., 2016).

Also, in 2016, the ES released guidelines concerning custom-compounded bioidentical hormone therapy (BHT), comparing BHT alongside menopause hormone therapy (MHT) (Santoro et al., 2016). First, MHT is regulated by the FDA whereas BHT is not as of time of publication. Within Table 1, they note that BHT requires extensive pretreatment testing (either serum and/or salivary) of hormone levels but that the FDA-approved MHT requires no pretreatment testing. "Furthermore, there is no evidence that monitoring compounded HT [hormone therapy] with serial salivary or blood testing is effective, except in the case of thyroid hormone. Finally, no

evidence supports the popularized notion that custom-compounded bioidentical hormones have fewer risks when compared with Food and Drug Administration (FDA)-approved hormone treatments." They also say that biochemical testing of hormone levels is "rarely needed" for MHT whereas BHT requires "routine salivary or blood testing to monitor and adjust doses…." (Santoro et al., 2016). Concerning estrone (E1), "it could be argued that the most physiologic estrogen in a postmenopausal woman is E1 because that is the molecular estrogen species that circulates in the bloodstream of postmenopausal women in the greatest quantity" (Santoro et al., 2016).

Testosterone testing in addition to other endocrine laboratory tests is recommended as part of an initial endocrine assessment for women with clinical hyperandrogenism in the evaluation of suspected Functional Hypothalamic Amenorrhea (FHA) (Gordon et al., 2017).

The American College of Obstetricians and Gynecologists (ACOG, 2012, 2017, 2018a, 2018b, 2019a, 2019b)

ACOG addressed testing hormone levels for women using hormone replacement therapies in 2012 and reaffirmed their findings in 2020. "Although more sensitive testing is becoming available through the use of mass spectrometry, there are few indications for the measurement of hormone levels to ascertain success of therapy when treating a postmenopausal woman with hormones. If treatment is initiated for symptom control, subjective improvement in symptoms is the therapeutic end point, and there is no need to assess hormone levels. Hormone therapy should not be titrated to hormone levels (serum, urinary, or salivary)" (ACOG, 2012).

ACOG also released guidelines regarding hormone therapy in primary ovarian insufficiency. It was stated that "Primary ovarian insufficiency is a pathologic condition that should not be considered a hastening of natural menopause" and therefore "Although women with primary ovarian insufficiency share common health risks with naturally menopausal women, the approach to health maintenance in these women is distinct" (ACOG, 2017). These guidelines were reaffirmed in 2019.

In 2018, the ACOG released guidelines on the clinical management of polycystic ovary syndrome (PCOS). In its suggested evaluation of patients with PCOS, the ACOG recommends having a physical, laboratory testing, and an ultrasound examination to confirm the polycystic ovaries. With regards to hormone testing, it includes "documentation of biochemical hyperandrogenemia" by "total testosterone and sex-hormone binding globulin or bioavailable and free testosterone," but notes to conduct testing that would exclude other causes of hyperandrogenism, such as thyroid dysfunction and hyperprolactinemia. ACOG includes TSH, prolactin, and 17-hydroxyprogesterone as hormones to measure to exclude other causes. The ACOG (2018b) also acknowledges that "there is no standardized testosterone assay in the United States and the sensitivity and reliability in the female ranges are often poor."

Regarding Müllerian Agenesis, ACOG writes that the initial evaluation of a patient without a uterus "may include the following laboratory tests: testosterone level, FSH level, and karyotype" (ACOG, 2018a).

In 2019, ACOG released a guideline regarding the "screening and management of the hyperandrogenic adolescent". In it, they state that the diagnosis of hyperandrogenism can be based on clinical symptoms or measurement of serum androgens. However, they recommend against monitoring serum androgens.

ACOG recommends identifying clinical symptoms of androgen excess during the initial evaluation. In the proposed algorithm for evaluation, ACOG recommends two separate batteries of hormone tests depending on type of menses. For regular menses, ACOG lists free and total testosterone, DHEAS (dehydroepianandrosterone sulphate), and 17OHP (17-α-hydroxyprogesterone) as hormones that may be tested. For irregular menses, ACOG lists prolactin, LH, FSH, TSH, and the three previously mentioned hormones. ACOG also notes that

PCOS may be one of the diagnoses if both androgen excess and irregular menses are identified (ACOG, 2019b).

ACOG also published a guideline titled "The Use of Antimüllerian Hormone [AMH] in Women Not Seeking Fertility Care" in 2019. In it, they make the following recommendations:

- "Serum antimüllerian hormone level assessment generally should not be ordered or used to counsel women who are not infertile about their reproductive status and future fertility potential."
- "Although serum antimüllerian hormone levels are a known predictor of ovarian response to exogenous gonadotropin stimulation in infertile women undergoing assisted reproduction cycles, the use of antimüllerian hormone in women with presumed fertility is limited by a lack of international assay standards and differing assay methodologies."
- "A single serum antimüllerian hormone level assessment obtained at any point in time in a population of women with presumed fertility does not appear to be useful in predicting time to pregnancy."
- "The use of antimüllerian hormone levels as a predictor of the onset of menopause is unsuitable for clinical practice at this time."
- "Currently, serum antimüllerian hormone levels are not part of the accepted diagnostic criteria for polycystic ovary syndrome (PCOS)."
- More data on the use of serum antimüllerian hormone levels to predict postchemotherapy fertility and to guide fertility counseling in these patients are needed.
- "Routine antimüllerian hormone testing for prediction of pregnancy loss is not recommended." (ACOG, 2019a)

Faculty of Sexual & Reproductive Healthcare (FSRH, 2019)
The United Kingdom's FSRH amended its guidelines concerning contraception in women over the age of 40 in 2019. When addressing the question "When is contraception no longer needed?", they recommend that "most women do not require measurement of their serum hormone levels to make the diagnosis" of the onset of menopause as defined by "a clinical diagnosis made retrospectively after 1 year of amenorrhoea." This recommendation falls under the category of "Good Practice Point based on the clinical experience of the guideline development group." For women over the age of 50 on progestogen-only contraception, including depot medroxyprogesterone acetate (DMPA) with a recommendation grade "D" they state that "if needed,... [the patient] can have serum follicle-stimulating hormone (FSH) measurements undertaken to check menopausal status." They also do not recommend hormonal testing for women on combined hormonal contraception/contraceptives or hormone replacement therapy because "measuring these hormones does not give accurate information on which to base advice regarding menopausal status and when to stop contraception" (Grade D) (FSRH, 2019).

Society of Obstetricians and Gynaecologists of Canada (SOGC) (Reid et al., 2014; SOGC, 2020)
The SOGC in Managing Menopause do not recommend measuring estradiol or FSH to determine the onset of menopause. "An adequate independent biologic marker for the event does not exist, and there is no place for performing serial measurements of the serum concentration of estradiol or FSH in an attempt to specify whether the final menstrual period has passed" (Reid et al., 2014).

In 2020, the SOGC also reaffirmed their 2014 statement with regards to ordering hormone panels to diagnose menopause: "Don't routinely order hormone levels including estradiol, progesterone, follicle-stimulating hormone and luteinizing hormone in postmenopausal women or after a hysterectomy, either to diagnose menopause or to manage hormone therapy" (SOGC, 2020). Rationale for this recommendation lied in that "relying on elevated FSH to make a diagnosis may result in women being denied effective therapy for disruptive symptoms" (SOGC, 2020).

2014 North American Menopause Society (NAMS) (Shifren & Gass, 2014)
NAMS recommends using either a paper or electronic menstrual calendar to determine the onset of menopause (Level 1). Also, as a Level 1 recommendation, they state, "Although determinants of ovarian reserve, including levels of antimüllerian hormone (AMH), cycle day-3 FSH and estradiol, and ovarian antral follicle count, are available, their clinical use is best confined to counseling women seeking fertility rather than predicting time to menopause." They recommend (Level 1) evaluating any woman under the age of 40 for primary ovarian insufficiency (POI) who misses three or more consecutive menstrual cycles with the baseline evaluation including "assays for human chorionic gonadotropin (hCG), FSH, estradiol, prolactin, and thyroid-stimulating hormone (TSH). The diagnosis of POI is confirmed by two elevated FSH levels drawn at least 1 month apart." Also, they do not recommend using hormone testing to determine menopause status (Level II recommendation). Under the section concerning Premature Menopause and Primary Ovarian Insufficiency, with a level II recommendation, they state, "Further assessment of ovarian reserve with an AMH level and/or vaginal ultrasound determination of antral follicle count can be helpful in counseling and management" (Shifren & Gass, 2014).

Cancer Care Ontario (CCO) & American Society of Clinical Oncology (ASCO) (Dhesy-Thind et al., 2017)
The 2017 guideline issued jointly by CCO and ASCO concerning the use of adjuvant bisphosphonates and bone-modifying agents as possible breast cancer therapies states in Recommendation 5, "In women age ≤ 60 years with a previous hysterectomy and ovaries left in place, luteinizing hormone, follicle-stimulating hormone, and serum estradiol should be in the postmenopausal range and measured prior to initiation of any systemic therapy to receive adjuvant bisphosphonates." They specifically note that for women under the age of 60, "hormone levels and the absence of menses are unreliable indicators of menopause during treatment with tamoxifen (Dhesy-Thind et al., 2017)."

The Endocrine Society (ES)-Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons (Hembree et al., 2017, 2018a, 2018b)
Testosterone levels monitoring is suggested at baseline and every 6-12 months during suppression of puberty treatment protocol in gender-dysphoric/gender-incongruent persons. The laboratory monitoring of testosterone levels is also suggested at baseline and every 6-12 months during induction of puberty protocol. Measurement of serum testosterone levels is suggested every 3 months until levels are in the normal physiologic male range during the monitoring of transgender males on gender-affirming hormone therapy. Testosterone testing is also needed midway between injections for monitoring of testosterone enanthate/cypionate injections, alternatively peak and trough levels could be measured to ensure levels remain in the normal male range. For parenteral testosterone undecanoate, testosterone should be measured just before the following injection. For transdermal testosterone, the testosterone level can be measured no sooner than after 1 week of daily application (at least 2h after application). For monitoring transgender females on gender-affirming hormone therapy, measurement of serum testosterone is indicated every 3 months (Hembree et al., 2017, 2018a, 2018b).

The Endocrine Society (ES)-Polycystic Ovary Syndrome (PCOS) (Legro et al., 2013)
Relative to the diagnosis of PCOS, the ES identifies three criteria that may be evaluated: androgen excess, ovulatory dysfunction, and polycystic ovaries. Two of the three criteria are sufficient for diagnosis, and if both clinical criteria are met, they do not recommend testing for androgen excess. Androgen excess is characterized by elevated serum androgen levels such as elevated total, bioavailable, or free serum testosterone levels. Considering that serum testosterone levels are variable and poor standardization of the assays, Task Force recommends familiarity with local assays and does not define an absolute level that is diagnostic of PCOS or other causes of hyperandrogenism (Legro et al., 2013).

International PCOS Network/National Health and Medical Research Council (NHMRC)/Centre for Research Excellences in Polycystic Ovary Syndrome

(CREPOS)/American Society for Reproductive Medicine (ASRM)/European Society of Human Reproduction and Embryology (ESHRE) (NHMRC et al., 2018; Teede et al., 2018)
The International PCOS Network released their extensive guidelines in 2018. Concerning the screening and diagnostic assessment of PCOS, they have the following recommendations (NHMRC et al., 2018; Teede et al., 2018):

- "Calculated free testosterone, free androgen index or calculated bioavailable testosterone should be used to assess biochemical hyperandrogenism in the diagnosis of PCOS." [Evidence-based recommendation (EBR), strong recommendation]
- "High-quality assays such as liquid chromatography–mass spectrometry (LCMS) and extraction/ chromatography immunoassays, should be used for the most accurate assessment of total or free testosterone in PCOS." [EBR, conditional recommendation]
- "Androstenedione and dehydroepiandrosterone sulfate (DHEAS) could be considered if total or free testosterone are not elevated; however, these provide limited additional information in the diagnosis of PCOS." [EBR, conditional recommendation]
- "Direct free testosterone assays, such as radiometric or enzyme-linked assays, preferably should not be used in assessment of biochemical hyperandrogenism in PCOS, as they demonstrate poor sensitivity, accuracy and precision." [Clinical consensus recommendation]
- "Reliable assessment of biochemical hyperandrogenism is not possible in women on hormonal contraception, due to effects on sex hormone-binding globulin and altered gonadotrophin-dependent androgen production." [Clinical practice point (CPP)]
- "Where assessment of biochemical hyperandrogenism is important in women on hormonal contraception, drug withdrawal is recommended for months or longer before measurement, and contraception management with a non-hormonal alternative is needed during this time." [CPP]
- "Assessment of biochemical hyperandrogenism is most useful in establishing the diagnosis of PCOS and/or phenotype where clinical signs of hyperandrogenism (in particular hirsutism) are unclear or absent." [CPP]
- "Interpretation of androgen levels needs to be guided by the reference ranges of the laboratory used, acknowledging that ranges for different methods and laboratories vary widely. Normal values are ideally based on levels from a well phenotyped healthy control population or by cluster analysis of a large general population considering age and pubertal specific stages." [CPP]
- "Where androgen levels are markedly above laboratory reference ranges, other causes of biochemical hyperandrogenism need to be considered. History of symptom onset and progression is critical in assessing for neoplasia, however, some androgen-secreting neoplasms may only induce mild to moderate increases in biochemical hyperandrogenism." [CPP]
- "Serum AMH levels should not yet be used as an alternative for the detection of PCOM [polycystic ovarian morphology] or as a single test for the diagnosis of PCOS." [EBR]

The following statement is used to justify their recommendations:

"Total testosterone alone can identify 20 - 30% of women with PCOS as having biochemical hyperandrogenism, while measures of unbound or free testosterone will identify 50 - 60%. Laboratory calculated values are recommended. High quality assays provide a more accurate diagnosis and the additional associated cost was deemed important and justified after considering all elements of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework. Access issues were also acknowledged. Given the challenges in assessing biochemical hyperandrogenism, whilst androgen measures are useful to detect biochemical hyperandrogenism where PCOS is suspected, these are likely to be most useful in diagnosis of PCOS in adolescents and women who demonstrate minimal to no features of clinical

hyperandrogenism (e.g. hirsutism). Clarity around standardised assessment for biochemical hyperandrogenism provided by the guideline is likely to be valued" (NHMRC et al., 2018). It should be noted that in the 200+ pages of the International guidelines they do not mention testing the serum levels of dihydrotestosterone.

National Institute for Health and Care Excellence (NICE, 2019)
The NICE updated their 2015 guidelines on the diagnosis and management of menopause in 2019. It recommends to not use AMH, inhibin A, inhibin B, estradiol, antral follicle count, and ovarian volume to "diagnose perimenopause or menopause in women aged over 45 years." NICE guidelines also stated: "Do not use a serum follicle-stimulating hormone (FSH) test to diagnose menopause in women using combined oestrogen and progestogen contraception or high-dose progestogen," and to consider using an FSH test for menopause diagnosis only "in women aged 40 to 45 years with menopausal symptoms, including a change in their menstrual cycle" and "in women aged under 40 years in whom menopause is suspected" (NICE, 2019).

British Menopause Society (BMS, 2019)
The BMS published a guideline regarding bioidentical HRT [hormone replacement therapy]. The guideline calls attention to a recent type of hormone therapy, called "compounded bioidentical hormone replacement therapy" [cBHRT]. The guideline notes that the primary difference between this type of HRT and "regulated bioidentical hormone replacement therapy" [rBHRT] are the regulatory agencies that oversee and approve each type.

The BMS remarks that cBHRT prescribers purport that they can determine the exact requirements [of hormone therapy] of any individual woman. However, the BMS states that "this costly practice has never been substantiated through rigorous research, it is not recommended by the menopause societies and it is largely unnecessary (BMS, 2019)."

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 82024, 82397, 82642, 82670, 82679, 82681, 83001, 83002, 83003, 83520, 84146, 84402, 84403, 84410, 84443, 86636, S3650, S3652

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

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Specialty Matched Consultant Advisory Panel 6/2020

Policy Implementation/Update Information

1/29/18	New policy developed. BCBSNC will provide coverage for hormonal testing in females when it is determined to be medically necessary because the medical criteria and guidelines in this policy are met. Medical Director review 1/1/2019. Policy noticed 1/29/2019 for **effective date 4/1/2019**. (an)

10/1/19 References and policy guidelines updated. Reviewed by Avalon 2nd Quarter 2019 CAB. Medical Director review 8/2019. Coding table removed and codes listed. Added code 82024, 82642, 83003, 84146, 84443. Note 1 added to when not covered for symptom clarity. "for individuals with ambiguous genitalia, hypospadias, or microphallus" added to when not covered #7. When covered #4 added. (eel)

10/1/19 Policy Statement revised to read: BCBSNC will provide coverage for hormonal testing in females when it is determined the medical criteria and guidelines below are met. Wording revised in When Covered section. "Medically Necessary" changed to "Reimbursement is allowed…" Wording revised in the Not Covered section. "Not Medically Necessary" changed to read "Reimbursement is not allowed…" Notification given 10/1/2019 for effective date 12/2/2019. (an)

2/11/20 Reviewed by Avalon 4th Quarter CAB. No changes to policy. (eel)

7/14/20 References updated. Specialty Matched Consultant Advisory Panel review 06/17/2020. No changes to policy statement. (eel)

2/9/21 Annual review by Avalon 4th Quarter 2020 CAB. Title changed from Hormonal Testing in Females to Hormonal Testing in Adult Females. Items 2a-c and 6 added to Not Covered section. Note 1 moved to Note 2 and Note 1 added to not covered section. "This policy only addresses coverage of hormonal testing in adult females (age 18 years and older)" added to Description section. CPT codes 82397, 82681, and 86636 added. Description, Policy Guidelines, and References updated. Medical Director review 1/2021. Notification given **02/09/2021** for effective date **04/20/2021**. (bb)