Patient Name : **TEST PATIENT**
Date of Birth : December 27, 1966
Sex : F
Collected : May 11, 2015
Lab id : 3389105
Referring Physician: Dr TEST TOCTOR

MICRO SAMPLE ASSAYS

DRIED URINE	Result	Range	Units
Advanced Hormones, Dried Urine			
Dried Urine Hormone Comments	Please refer to PDF attached.		

Patient Name: TEST TEST **Samples Collected** Urine - 00.00 Urine - 00:00 Urine - 00:00 Urine - 00:00

TEST NAME	RESULTS | 12/03/18	RANGE
Urinary Estrogens		
Estradiol	0.44	0.15-0.75 µg/g Cr Postmenopausal
Estrone	1.42	0.64-2.56 µg/g Cr Postmenopausal
Estriol	<dl L	0.28-1.17 µg/g Cr Postmenopausal
E3/(E1+E2)	N/A	>0.3 (> median value)
2-OH Estradiol	0.31	0.08-0.31 µg/g Cr Postmenopausal
2-OH Estrone	0.68	0.25-1.00 µg/g Cr Postmenopausal
4-OH Estradiol	0.06	0.03-0.12 µg/g Cr Postmenopausal
4-OH Estrone	0.08	0.06-0.22 µg/g Cr Postmenopausal
16α-OH Estrone	0.05 L	0.10-0.41 µg/g Cr Postmenopausal
2-OH (E1 + E2)/16-α-OH E1	17.8 H	1.47-8.17 Postmenopausal
2-MeO Estradiol	0.05	0.02-0.07 µg/g Cr Postmenopausal
2-MeO Estrone	0.14	0.06-0.29 µg/g Cr Postmenopausal
2-MeO E1/2-OH E1	0.21	0.19-0.36 Postmenopausal
4-MeO Estradiol	<dl L	<0.04 µg/g Cr
4-MeO Estrone	<0.01	<0.04 µg/g Cr
4-MeO E1/4-OH E1	N/A	0.03-0.38 Postmenopausal
4-MeO E2/4-OH E2	N/A	0.14-0.73 Postmenopausal
Bisphenol A	2.32	1.5-4.5 µg/g Cr Postmenopausal

TEST NAME	RESULTS | 12/03/18	RANGE
Urinary Progestogens		
Pregnanediol	50 L	465-1609 µg/g Cr Premeno-luteal or PgRT
Allopregnanolone	2.50	2.23-14.87 µg/g Cr Premeno-luteal or PgRT
Allopregnanediol	11.01 L	14.65-76.71 µg/g Cr Premeno-luteal or PgRT
3α-Dihydroprogesterone	0.35 L	0.67-2.03 µg/g Cr Premeno-luteal or PgRT
20α-Dihydroprogesterone	0.93 L	3.93-11.62 µg/g Cr Premeno-luteal or PgRT
Deoxycorticosterone	3.31 H	0.69-2.23 µg/g Cr Premeno-luteal or PgRT
Corticosterone	18.08 H	3.19-9.59 µg/g Cr Premeno-luteal or PgRT
Pgdiol/E2	147.06 L	1000-1500 (Optimal Luteal Only)
Urinary Androgens		
DHEA	29.74	8.63-37.28 µg/g Cr Postmenopausal
Androstenedione	4.15	2.07-7.94 µg/g Cr Postmenopausal
Androsterone	282	152-482 µg/g Cr Postmenopausal
Etiocholanolone	548	239-777 µg/g Cr Postmenopausal
Testosterone	5.70 H	0.66-2.89 µg/g Cr Postmenopausal
Epi-Testosterone	1.44 H	0.39-1.32 µg/g Cr Postmenopausal
T/Epi-T	3.96 H	0.5-3.0
5α-DHT	2.16 H	0.26-0.98 µg/g Cr Postmenopausal
5α,3α-Androstanediol	6.68	2.32-8.17 µg/g Cr Postmenopausal
Urinary Glucocorticoids		
Total Cortisol	52.02 H	13.23-39.26 µg/g Cr Postmenopausal
Total Cortisone	57.02	23.32-59.61 µg/g Cr Postmenopausal
Cortisol/Cortisone	0.91 H	0.5-0.7
Tetrahydrocortisol	626	281-711 µg/g Cr Postmenopausal
Tetrahydrocortisone	1328	551-1474 µg/g Cr Postmenopausal
Urinary Free Diurnal Cortisol		
Free Cortisol	17.54	7.8-29.5 µg/g Cr (1st Morning)
Free Cortisol	64.89	23.4-68.9 µg/g Cr (2nd Morning)

TEST NAME	RESULTS | 12/03/18	RANGE
Urinary Free Diurnal Cortisol		
Free Cortisol	15.59	6.0-19.2 µg/g Cr (Evening)
Free Cortisol	4.18	2.6-8.4 µg/g Cr (Night)
Urinary Free Diurnal Cortisone		
Free Cortisone	51.19	31.6-91.6 µg/g Cr (1st Morning)
Free Cortisone	119.07	63.3-175.8 µg/g Cr (2nd Morning)
Free Cortisone	64.55	30.6-88.5 µg/g Cr (Evening)
Free Cortisone	23.71	15.5-44.7 µg/g Cr (Night)
Urinary Diurnal Melatonin MT6s		
Melatonin	27.86	18.0 - 40.9 µg/g Cr (1st Morning)
Melatonin	10.40	7.3 - 31.9 µg/g Cr (2nd Morning)
Melatonin	0.88	0.7 - 2.2 µg/g Cr (Evening)
Melatonin	0.85 L	1.7 - 11.1 µg/g Cr (Night)
Urinary Creatinine		
Creatinine (pooled)	0.99	0.3-2.0 mg/mL
Creatinine	0.98	0.3-2.0 mg/mL (1st morning)
Creatinine	1.55	0.3-2.0 mg/mL (2nd morning)
Creatinine	1.03	0.3-2.0 mg/mL (Evening)
Creatinine	0.99	0.3-2.0 mg/mL (Night)

<dL *= Less than the detectable limit of the lab.* ***N/A*** *= Not applicable; 1 or more values used in this calculation is less than the detectable limit.* ***H*** *= High.* ***L*** *= Low.*

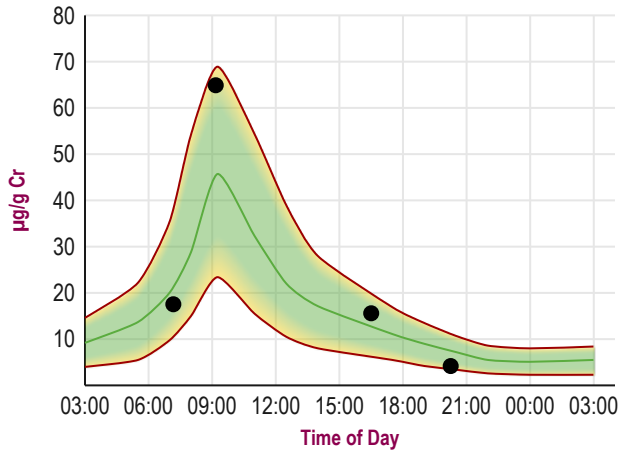
Therapies

Graphs

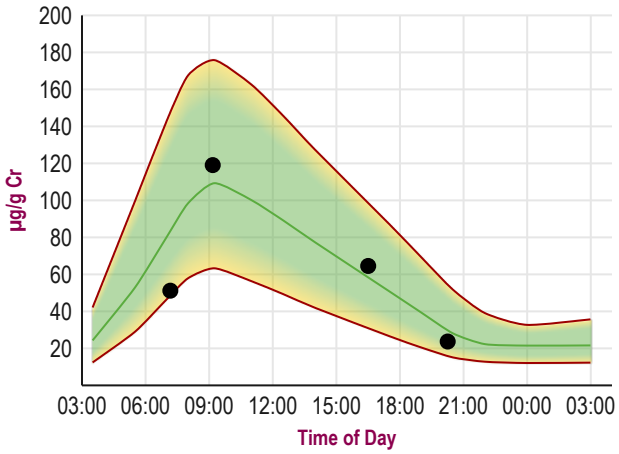
Disclaimer: Graphs below represent averages for healthy individuals not using hormones. Supplementation ranges may be higher. Please see supplementation ranges and lab comments if results are higher or lower than expected.

Average ▼▲ Off Graph

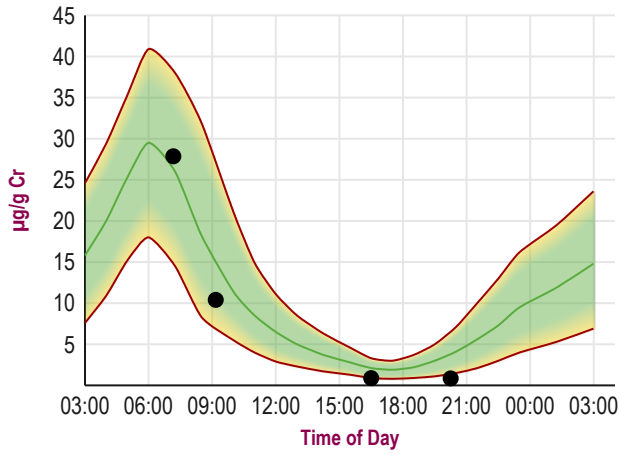
Urinary Free Cortisol



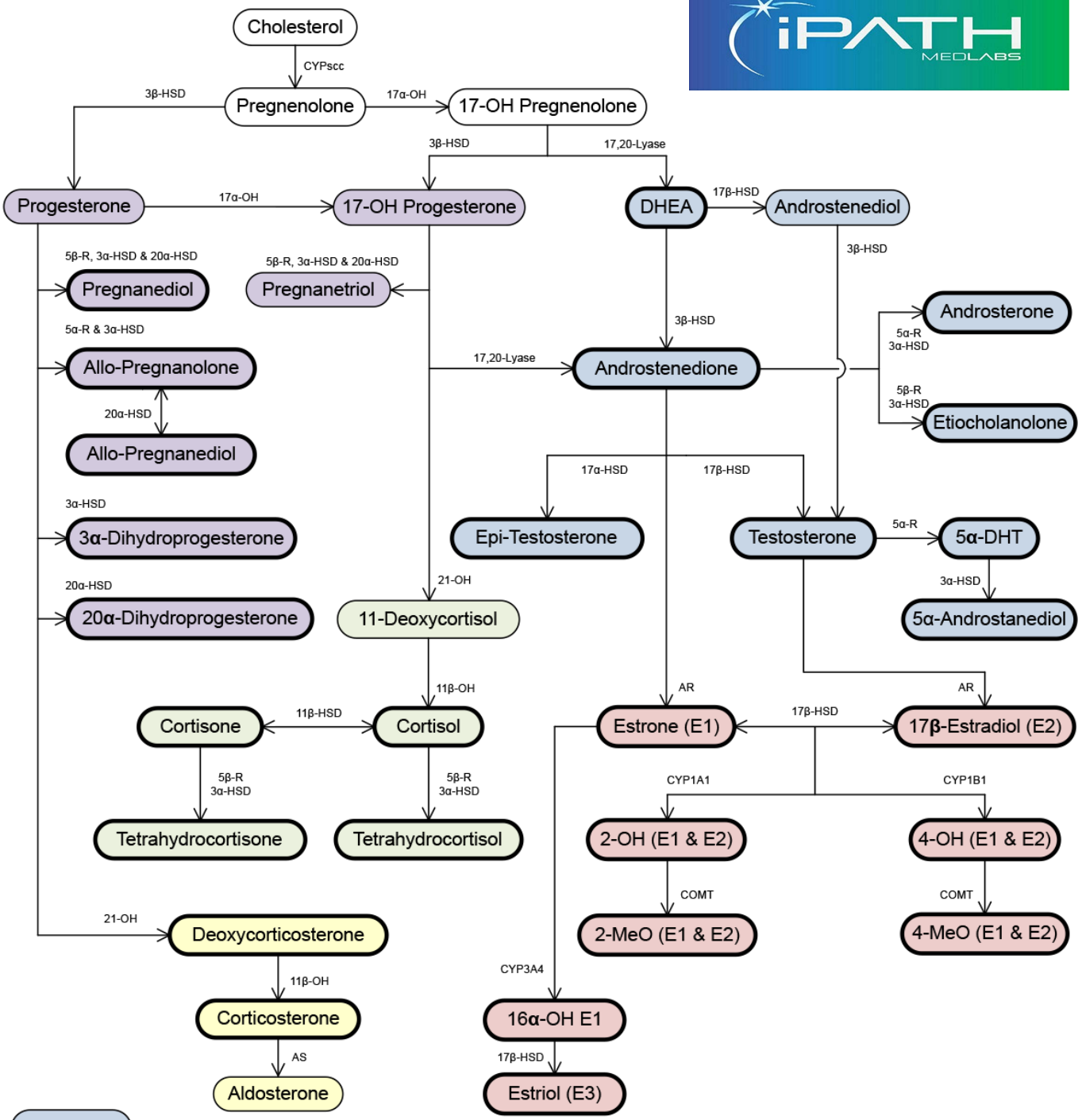
Urinary Free Cortisone



Urinary Melatonin (MT6s)



The Steroid Hormone Cascade



Androgens

Estrogens

Glucocorticoids

Mineralocorticoids

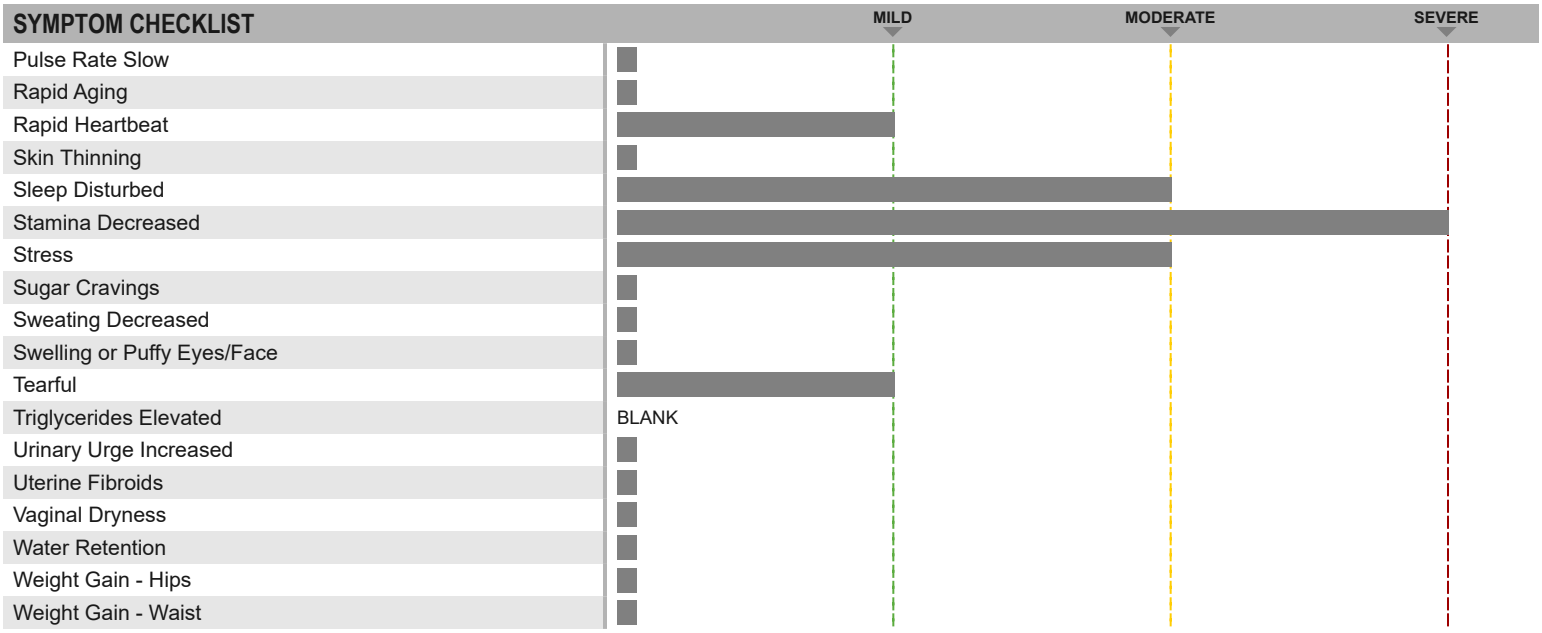
Progestogens

Enzyme Abbreviations

(5α-R) 5α-Reductase
(5β-R) 5β-Reductase
(11β-OH) 11β-Hydroxylase
(17α-OH) 17α-Hydroxylase
17,20-Lyase (same enzyme as 17α-OH)
(21-OH) 21-Hydroxylase
(3α-HSD) 3α-Hydroxysteroid dehydrogenase
(3β-HSD) 3β-Hydroxysteroid dehydrogenase
(11β-HSD) 11β-Hydroxysteroid dehydrogenase
(17α-HSD) 17α-Hydroxysteroid dehydrogenase
(17β-HSD) 17β-Hydroxysteroid dehydrogenase
(20α-HSD) 20α-Hydroxysteroid dehydrogenase
(AR) Aromatase
(AS) Aldosterone Synthase
(CYP) Cytochrome p450 (scc, 1A1, 1B1 & 3A4)
(COMT) Catechol-O-Methyl-Transferase

SYMPTOM CATEGORIES	RESULTS | 12/03/18
Estrogen / Progesterone Deficiency	30%
Estrogen Dominance / Progesterone Deficiency	25%
Low Androgens (DHEA/Testosterone)	46%
High Androgens (DHEA/Testosterone)	13%
Low Cortisol	49%
High Cortisol	32%
Hypometabolism	39%
Metabolic Syndrome	2%

SYMPTOM CHECKLIST	MILD	MODERATE	SEVERE
Aches and Pains	■	■	
Acne			
Allergies	■	■	
Anxious	■		
Bleeding Changes			
Blood Pressure High			
Blood Pressure Low	■	■	■
Blood Sugar Low			
Body Temperature Cold			
Bone Loss			
Breast Cancer			
Breasts - Fibrocystic			
Breasts - Tender			
Chemical Sensitivity			
Cholesterol High			
Constipation	■	■	■
Depressed	■	■	
Fatigue - Evening	■	■	■
Fatigue - Morning	■	■	■
Fibromyalgia	■	■	■
Foggy Thinking	■	■	■
Goiter	■		
Hair - Dry or Brittle			
Hair - Increased Facial or Body	■		
Hair - Scalp Loss			
Headaches	■	■	
Hearing Loss			
Heart Palpitations	■		
Hoarseness	■	■	
Hot Flashes			
Incontinence			
Infertility			
Irritable	■	■	■
Libido Decreased	■	■	
Memory Lapse	■	■	
Mood Swings	■	■	■
Muscle Size Decreased			
Nails Breaking or Brittle			
Nervous	■	■	■
Night Sweats	■		
Numbness - Feet or Hands			



Lab Comments

PARENT ESTROGENS (ESTRADIOL-E2, ESTRONE-E1, ESTRIOL-E3)

The parent estrogens are lower than the median of the reference ranges seen in postmenopausal women, Low levels of these estrogens are consistent with self-reported symptoms of estrogen deficiency (e.g. hot flashes, night sweats, vaginal dryness, sleep disturbances, etc.). Consider estrogen replacement therapy, balanced with natural progesterone, assuming no contraindications (e.g. breast or uterine cancer). Adequate estrogen is necessary for maintaining healthy skin, bones, nerves (raises pain threshold) and brain function (helps create neurotransmitters), and in concert with progesterone helps maintain optimal tissue sensitivity to insulin (prevents insulin resistance).

HYDROXYLATED (CATECHOL) ESTROGENS (2-OH E2 & E1, 4-OH E2 & E1, 16-OH E1) and 2-OH/16-OH RATIO

The hydroxylated estrogens are either low or within normal reference ranges for a postmenopausal woman, inferring a lower risk for breast cancer.

The hydroxylation of estradiol and estrone represent the first phase of metabolism and elimination of these estrogens via urine. Following hydroxylation at the 2-, 4-, or -16 position, the estrogens undergo further modification (methylation, sulfation, glucuronidation) that increases their solubility and excretion in urine. The sulfate and glucuronide groups are removed by enzyme hydrolysis, which allows for measurement of the different types of hydroxylated estrogens, in addition to methylation of the hydroxyl groups (see below). The 2- and 4-hydroxylated E1 and E2 are referred to as catechol estrogens.

Research and clinical studies show that the 2-hydroxylated estrogens (2-OH E2 and 2-OH E1) are a safer pathway of hydroxylation than the 4-hydroxyestrogens (4-OH E2 and 4-OH E1), which bind to and damage DNA, leading to mutations that are associated with increased breast cancer risk. For reviews see: Cavalieri EL, Rogan EG Future Oncol 6(1): 75-79, 2010; and Lee, JR, Zava DT What Your Doctor May Not Tell You About BREAST CANCER: How Hormone Balance Can Help Save Your Life: Chapter 7.

2-hydroxylated estrogen metabolism is increased with cruciferous vegetables and extracts of them. The most commonly used are indole-3-carbinol (I3C) and its metabolite diindolylmethane (DIM). Iodine also increases the 2-hydroxylation of estrogens, with a slight increase in 4-hydroxylation (Stoddard FR et.al. Int J Med Sci 5: 189-196, 2008). The more dangerous 4-hydroxylated estrogen metabolism is enhanced by exposure to environmental toxins, mostly petrochemical-based products but also heavy metals, that induce 4-hydroxylation pathway enzymes (1B1), and cause formation of Reactive Oxygen Species (ROS) that co-oxidize the catechol estrogens to quinones.

16-hydroxyestrone is another pathway of estrone metabolism and is a precursor to estriol (see Steroid Hormone Cascade). Early clinical research in humans suggested that a high urinary level of 16-hydroxyestrone relative to 2-hydroxylated estrogens (i.e. a low 2-OH E1 + 2-OH E2/16-OH E1 ratio), was associated with an increased risk of breast cancer in premenopausal women, but not in postmenopausal women. This has remained controversial and newer research suggests that while higher levels of 16-hydroxy estrone may indeed be slightly associated with increased breast cancer risk in premenopausal women, higher levels are, paradoxically, associated with a decreased risk in postmenopausal women (Huang J et.al. Analytica Chimica Acta 711: 60-68, 2012). Overall, more recent studies have not shown the 2/16 ratio to be useful for predicting breast cancer risk.

METHYLATION OF HYDROXYESTROGENS

The methylated forms of the 2-OH-estrogens (2-MeO-E2 and 2-MeO-E1) are within range, suggesting adequate methylation of these estrogens. In contrast, 4-MeO-E2 is lower than the median of the reference range and its precursor, 4-OH-E2, is higher than median of the reference range, resulting in a low ratio of 4-MeO-E2/4-OH-E2 . Poor methylation and higher levels of the more dangerous 4-hydroxyestrogens (4-OH-E2 and 4-OH-E1) are associated with a higher breast cancer risk (Cavalieri EL, Rogan EG Future Oncol 6(1): 75-79, 2010).

The 2- and 4- hydroxyl estrogens are methylated by the enzyme Catechol-o-Methyl Transferase (COMT), which renders these catechol estrogens inert and harmless (Cavalieri EL, Rogan EG Future Oncol 6(1): 75-79, 2010). In the methylated form the catechol estrogens are rapidly excreted in urine. However, if methylation pathways are defective due to low levels of COMT, or lack of precursors of methylation (i.e. vitamins B6, B12, folate, betaine), then the 2- and 4-hydroxyl estrogens can take a more insidious and dangerous pathway of metabolism, which is oxidation to 4-estrogen quinones. Estrogen quinones, especially the 4-quinone of estradiol and estrone are highly electrophilic and bind to DNA forming adducts that lead to permanent mutations in the DNA. Many studies have shown that high urinary levels of the 4-hydroxy estrogens (4-OH-E2 and 4-OH-E1) are associated with increased breast cancer risk if they are not inactivated by methylation or by glutathione sulfation. The 2- and 4-hydroxy estrogens are converted to their more dangerous oxidized quinone forms under oxidizing conditions in the cell, and this occurs rapidly in the presence of oxidized lipids, especially those from trans-hydrogenated fats. These estrogen quinones, like all oxidized and electron-hungry molecules in the body are inactivated when bound to glutathione, the most ubiquitous antioxidant in the body. However, if glutathione is low, due to insufficient levels of minerals (selenium, iodine) and vitamins (C and E), these highly reactive and toxic 4-quinone estrogens are less likely to be detoxified (inactivated) and have potential to damage cells/DNA in close proximity to their formation (i.e. the breast cell/DNA).

RATIO OF 2- and 4-METHYLATED HYDROXYESTRONE/HYDROXYESTRONE

The ratios of the 2- and 4-hydroxylated estrogens to their methylated counterparts is evaluated to determine what predominate species of estrogen is forming (i.e. the less dangerous 2- or the more dangerous 4-hydroxylated estrogen) and if the levels of any of the hydroxylated estrogens are high, are they being adequately methylated, which renders them biochemically inert. A good methylation index is associated with the ratio value towards the upper end, or higher, of the reference range. This is particularly true for the 4-hydroxylated estrogens, which if not methylated properly are associated with increased risk for conversion to more dangerous estrogen quinones (not measured) that can potentially damage DNA causing mutations and lead to a higher risk of developing cancer. Even if higher levels of 4-hydroxylated estrone or estradiol are present, adequate methylation (higher ratio) render them potentially less harmful.

The type of hydroxyl-estrogen formed, 2- or 4-estradiol or -estrone, and their degree of methylation is associated with breast cancer risk. Increased levels of 4-hydroxy estrone or 4-hydroxy estradiol are associated with increased breast cancer risk. In contrast, formation of the 2-hydroxylated estrogens is associated with a lower breast cancer risk; however, very high levels of 2-hydroxylated estrogens, if not associated with concomitant methylation are also associated with increased risk.

BISPHENOL A (BPA)

Bisphenol A (BPA) is within reference range. BPA is an endocrine disrupting chemical (EDC) derived from plastics used for making bottles, wraps for foods, and linings for food cans. BPA is not retained in the body for a prolonged period of time and is rapidly excreted into urine. High urinary levels of BPA indicate recent exposure to plastics that released excessive amounts of BPA into food or beverages consumed in the past 24-48 hr.

BPA acts as an EDC by binding to a activating both membrane and nuclear estrogen receptors in a manner similar to estradiol. Thus by mimicking the actions of endogenous estrogens, high levels of BPA can contribute to symptoms of estrogen dominance. High BPA levels have been associated with increased risks for many different health issues, including diabetes, breast cancer, and prostate cancer. When BPA levels are elevated, identification of its source and reducing exposure is worth considering.

PROGESTERONE METABOLITES (PREGNANEDIOL, PREGNANES AND PREGNENES)

Pregnanediol (PgDiol) and the pregnane (allopregnanolone and allopregnanediol) and pregnene metabolites (3-alpha-dihydroxyprogesterone and 20-alpha-dihydroprogesterone) categories of progesterone metabolites are low, or lower than the median, of the expected reference ranges for a postmenopausal woman supplementing with topical progesterone. This indicates that the topically delivered progesterone is not converting to these down-stream progesterone metabolites, as seen in premenopausal women during luteal phase of the menstrual cycle, or in postmenopausal women using oral progesterone (levels usually higher than premenopausal range). When progesterone or any other steroid hormones are delivered topically, very little of them passes through the liver (first-pass effect) and therefore are not metabolized or excreted by the kidneys into urine. Topically delivered progesterone does NOT result in a significant increase in venipuncture serum and urine levels of progesterone, but results in a striking increase in salivary, capillary blood (finger stick dried blood spot), and tissue levels of progesterone (for details see Du…Zava et.al. Menopause 20 (11), 1169-1175, 2013), indicating that urine progesterone metabolites are NOT reflective of tissue uptake of progesterone following topical progesterone delivery.

One of the pregnane metabolites of progesterone is allopregnanolone, which is well studied and a known anxiolytic neurosteroid that binds to brain GABA receptors, resulting in a calming and sleep-inducing effect. Higher levels of this progesterone metabolite are associated with a lower incidence of PMS in premenopausal women and better sleep patterns in both premenopausal and postmenopausal women supplementing with exogenous oral or topical progesterone. The pregnane-mediated metabolism of progesterone, via the 5a-reductase pathway, is increased during pregnancy and is induced by estradiol. The 5a-reductase enzyme is also much higher in breast tumors. Not unexpectedly, more of this anxiolytic

progesterone metabolite is formed with oral progesterone supplementation, and less so with topical progesterone. In some individuals who convert large amounts of progesterone to allopregnanolone, the sleep-inducing effect can be overwhelming. Therefore, if progesterone causes excessive drowsiness, you are likely a high pregnane metabolizer, and it is best to use it only before bed. If the low allopregnanolone, as reported herein, is associated with sleep disturbances, it may be worthwhile to consider oral progesterone, as this usually results in higher production of this anxiolytic progesterone metabolite.

Women who are at increased risk of developing breast cancer (mid-forties and older, high estrogens relative to progesterone, high stress levels and associated high cortisol particularly at night, low night melatonin, poor diet, and sedentary lifestyle), should evaluate how they metabolize progesterone (pregnene or pregnane pathways) before considering use of a pharmacological progesterone dose (> 50 mg). While neither oral nor topical progesterone therapy have been shown to be associated with higher breast cancer risk, excessive production of the pregnane metabolites, including allopregnanolone, has been associated with increased growth of mammary tumors in animals and human breast cancer cell lines in tissue culture, particularly those that are negative for estrogen and progesterone receptors (Wiebe JP, Cancer Res 60: 936-943, 2000).

PROGESTERONE METABOLITES: MINERALCORTICOID PRECURSORS

Deoxycorticosterone (DOC) and corticosterone (CC) are higher than reference range for a premenopausal woman (luteal phase). Both DOC and CC are down-stream metabolites of progesterone.

DOC is a weak mineralcorticoid and DOC and CC are precursors to the more potent mineralcorticoid aldosterone (see Steroid Hormone Cascade). This might suggest that aldosterone, a more potent mineralcorticoid, could be low (expect low blood pressure) if these metabolites are not converted to aldosterone by aldosterone synthetase, and instead are converted to phase II metabolites and excreted into urine. Alternatively, this could suggest that aldosterone is elevated (expect high blood pressure).The conversion of progesterone to DOC varies by up to 20-fold among women (MacDonald Endocrine Reviews 12: 372-401, 1991) p. 390), as can the side effects seen in some women during the luteal phase or those supplementing with progesterone. Adverse reactions to higher progesterone levels that occur during the luteal phase of the menstrual cycle, pregnancy, or with progesterone replacement therapy may involve high conversion to DOC.

ANDROGEN PRECURSORS (ANDROSTENEDIOL, DHEA)

The androgen precursors, androstenedione and DHEA, are within normal reference ranges. In premenopausal women about half of the androstenedione is derived from the ovaries and the other half from the adrenals. At menopause, most of the androstenedione derives from the adrenal glands. DHEA is synthesized in the adrenal glands and is rapidly sulfated to DHEA-sulfate (DHEAS) to extend its half-life in blood. Androstenedione is converted into the androgens, testosterone and Epi-testosterone in near equal amounts in most individuals, or into estrone. More conversion to the estrogen, estrone, occurs in individuals with higher amounts of adipose (fat) tissue. DHEA is an androstenedione precursor and is commonly used as a supplement to raise testosterone levels in women.

DHEA METABOLITES: (ANDROSTERONE, ETIOCHOLANOLONE)

Etiocholanolone and androsterone are within expected reference ranges. These hormones are downstream metabolites of DHEA and androstenedione (see Steroid Hormone Cascade). As a precursor molecule, DHEA is metabolized to androstenedione, which is then converted to etiocholanolone or androsterone through 5-beta or 5-alpha reductase enzymes, respectively. Androsterone, because it is created from the same enzyme (5 alpha reductase) that converts testosterone to dihydrotestosterone, provides a good secondary marker of 5 alpha reductase activity. This enzyme also converts progesterone to 5 alpha dihydroprogesterone (5a-DHP), a precursor to the neuroactive steroid allopregnanolone (5 alpha, 3 alpha tetrahydroprogesterone). Higher levels of etiocholanolone are believed to lower cancer risk by inhibiting glucose utilization, essential for tumor growth.

ANDROGENS AND METABOLITES (TESTOSTERONE, EPI-TESTOSTERONE, AND 5-ALPHA-DIHYDROTESTOSTERONE)

Testosterone (T) is higher than the reference ranges for a postmenopausal woman. This is likely a result of higher levels of precursors (DHEA and androstenedione). A higher level of T is also seen in women supplementing with DHEA or topical testosterone (none indicated). Epi-testosterone (Epi-T), the inert epimer of T, is also higher than the reference range for a postmenopausal woman, suggesting that T is derived from a precursor (DHEA or androstenedione) and not from topical T therapy. Higher T, relative to Epi-T (> 3.0), is expected with T therapy. Endogenously, Epi-T and T are synthesized in about equal amounts from androstenedione, a down-stream metabolite of DHEA. With endogenous production, the T/Epi-T ratio is about 1, and ranges from about 0.5-2. When testosterone is supplemented the T rises in proportion to dosage, but Epi-T remains the same, reflecting endogenous production.

The more potent metabolite of T, 5-alpha-dihydrotestosterone (DHT) is also higher than reference range for a postmenopausal woman. DHT is formed from testosterone within target cells via the enzyme 5 alpha reductase, and there binds to androgen receptors to activate androgen-specific gene sites. High T (as seen in these test results), and particularly high levels of the more potent androgen DHT, can be associated with increased facial and body hair, acne, loss of scalp hair, and oily skin and hair. These adverse side effects are more problematic when androgen antagonists are low (i.e. estrogens, progesterone, cortisol). Androgens (T and DHT) are important for strengthening structural tissues such as muscles, bone, connective tissue, and skin. They also play an important role in the brain to increase the level of neurotransmitters such as dopamine, which are important for mood elevation and sex drive.

TOTAL GLUCOCORTICOIDS (F, E, THF, THE)

Total cortisol (F) and cortisone (E), and their down-stream metabolites, tetrahydrocortisol (THF) and tetrahydrocortisone (THE), are within the high-normal to high reference ranges.

The total levels of these four glucocorticoids are determined from the average of four urine collections throughout the day and are very similar to the 24 hour urine values. To appreciate baseline and supplemented cortisol levels it is more appropriate to test cortisol levels throughout the day (following cortisol therapy) by the urinary free cortisol test (UFC-see below).

Excessive cortisol levels resulting from prolonged and excessive adrenal cortisol synthesis outside the normal reference ranges may eventually lead to adverse health issues. While a high cortisol is a normal and healthy response to an acute stressor, a persistently high cortisol resulting from chronic stressors or excessive cortisol therapy can lead to distinct symptoms, dysfunctions, and eventually to disease. Chronically elevated cortisol may include memory problems, depression, loss of muscle mass (gluconeogenesis), weight gain mostly in the waist, glucose dysregulation. Insulin resistance and metabolic syndrome. Also a consequence and cause of chronically elevated cortisol are the diseases of aging such as diabetes, cardiovascular disease, cancer, and bone loss. High cortisol can also disrupt normal thyroid function, lowering TSH release from the pituitary and increasing the intracellular conversion of T4 to reverse T3, an inactive form of T3 unable to activate thyroid receptors. If thyroid symptoms are problematic consider high cortisol as a contributing factor.

For additional information about strategies for supporting adrenal health and reducing stress(ors), the following books are worth reading: "Adrenal Fatigue", by James L. Wilson, N.D., D.C., Ph.D.; "The Cortisol Connection", by Shawn Talbott, Ph.D.; "The End of Stress As We Know It" by Bruce McEwen; "Awakening Athena" by Kenna Stephenson, MD.

URINARY FREE CORTISOL (F) AND FREE CORTISONE (E)

Urinary free cortisol (F) and free cortisone (E) are following a normal circadian rhythm and are within/near normal reference ranges throughout the day. This individual has self-reported a significant problem with sleep disturbances, which can be caused by abnormally high or low cortisol during normal sleeping hours. Because cortisol and its downstream inactive metabolite, cortisone, are within normal ranges self-reported sleep disturbances are not likely caused by cortisol excess or deficiency, or abnormal conversion of cortisol to cortisone (seen as low F/high E or high F/low E). However, this does not exclude other stressors or hormonal imbalances as a contributor to sleep disturbances. For example, excessive exercise, consumption of caffeine-containing beverages, or imbalances in hormones such as estrogens or androgens (testosterone or DHEA) resulting from stress, aging, hormone supplementation, and/or medications (none indicated, or hormones tested), may contribute to sleep disturbances.

For additional information about adrenal dysfunction and its relationship to stress and sleep the following books and journal articles are worth reading: "Adrenal Fatigue", by James L. Wilson, N.D., D.C., Ph.D.; "The Cortisol Connection", by Shawn Talbott, Ph.D.; "The End of Stress As We Know It" by Bruce McEwen; "The Role of Stress and the HPA Axis in Chronic Disease Management" by Thomas Guilliams, PhD.

MELATONIN METABOLITE 6-SULFATOXYMELATONIN (MT6s)

The melatonin metabolite MT6s is within normal reference range throughout most of the day, but fails to increase as evening progresses into nighttime. Low melatonin at night can contribute to self-reported sleep problems. If melatonin supplementation is not helpful for sleep issues, consider that other hormonal imbalances may be responsible (e.g. elevated night cortisol) and, if so, treated with lifestyle modifications (stress reduction) and/or hormone therapy.

When melatonin is within normal range but sleep issues are problematic, this condition may, more likely, be related to excessive stress(ors) or to other hormonal imbalances (low or high) in estrogens (necessary for REM sleep, excessive levels can be over stimulating), progesterone (metabolite allopregnanolone binds GABA receptors and has a calming effect), cortisol (low or high levels can disrupt sleep) and/or low thyroid. If any of the symptoms of estrogen, progesterone, cortisol, or thyroid hormones appear to be imbalanced, consider testing them and correcting imbalances to facilitate better sleep.

In a healthy individual the circadian rhythm of melatonin is inversely related to cortisol, i.e. melatonin levels rise with darkness and peak about 2-3 am, while cortisol falls to a nadir at this time of day. With morning and onset of light exposure, melatonin drops rapidly and cortisol begins to rise, peaking about 30 min to 1 hr after waking and exposure to light. By mid-afternoon melatonin reaches a nadir and then gradually begins to rise again with nightfall and less light exposure. Cortisol continues to fall as melatonin rises again, when both hormones reach their nadir and peak, respectively, about 2-3 am. Melatonin synthesis by the pineal gland is controlled by light exposure, while cortisol synthesis is controlled by the hypothalamic-pituitary axis in response to stressors.

The circadian patterns of melatonin are easily tracked with collections of urine timed throughout the day and measurement of 6-sulfatoxymelatonin (MT6s), a stable metabolite of melatonin and surrogate marker of melatonin synthesis. MT6s levels in urine lag about 2-3 hours behind active circulating levels of melatonin found in blood and saliva, which makes early morning first void MT6s measurements convenient for determining melatonin's average synthesis during the dark-hours of the early morning.

Melatonin, produced by the pineal gland in the brain and released into the circulation, rapidly enters tissues throughout the body where it carries out its restorative properties. Melatonin synthesis decreases with aging and calcification of the pineal gland, the latter of which can result in very low production of melatonin.

Melatonin is known to have many different beneficial effects in the body. It helps slow the aging process, is a potent anti-oxidant, inhibits formation and growth of tumors such as breast and prostate cancers, and helps regulate the synthesis of the sex-hormones estradiol and progesterone (melatonin increases progesterone and decreases estrogens). Low melatonin caused by pineal calcification has been associated with many different dysfunctions and diseases such as immune dysfunction, neurodegenerative disorders (Alzheimer's disease, senile dementia), pain disorders, cardiovascular disease, cancers of the breast and prostate, and type 2 diabetes (Hardeland R. Aging and Disease 3 (2): 194-225, 2012). Low melatonin is also thought to contribute to obesity in people with insomnia or those who do night shift work.

Low night time melatonin levels (mostly seen as low first morning void MT6s levels as this reflects overnight production of melatonin) are seen commonly in breast and prostate cancer patients. The WHO's International Agency for Research on Cancer has concluded that "shift work that involves circadian disruption is probably carcinogenic to humans," because of the suppression of melatonin production by exposure to light during the night.

Because of its established role in the regulation of the circadian rhythm, treatment with exogenous melatonin has been found useful in people with circadian rhythm sleep disorders, such as delayed sleep phase disorder, jet lag, shift worker disorder, and the non-24-hour sleep-wake disorder most commonly found in totally blind individuals; however, its utility for the treatment of chronic insomnia is not established and remains controversial.

If melatonin is taken as a supplement (available OTC) to correct low levels or treat a condition, the timing and dosage are important to its effectiveness, especially as a sleep aid. Response to supplemental melatonin can be very individual. For optimal benefit it is best to work with a health care provider familiar with melatonin dosage and timing. Excessive dosing can result in spillover of melatonin into daylight hours, excessive sleepiness during the day, and disruption of the normal melatonin-cortisol circadian rhythms. This will be seen as very high levels of MT6s in the first and second urine voids, and often carry-over into the evening when levels should be low. Consider dosage reduction if MT6s levels are excessive throughout the daylight hours and this is associated with persistent sleepiness during the day. While MT6s is an excellent surrogate marker for melatonin levels in the circulation, oral melatonin supplementation results in much higher MT6s levels in urine that are NOT reflective of active circulating bioavailable levels of melatonin, as measured by saliva or blood testing. Most (50-70%) of the melatonin delivered as an oral supplement is rapidly metabolized by the liver and kidney and excreted into urine as MT6s; much less is released as melatonin into the systemic circulation and bioavailable to tissues.

For more general information about melatonin please see: http://www.nlm.nih.gov/medlineplus/druginfo/natural/940.html

Creatinine is within range throughout the day reflecting normal concentration of urine.