NutriPATH
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TEST PATIENT
Sample Test Name
Sex : F
Date Collected : 00-00-0000
111 TEST ROAD TEST SUBURB
LAB ID: 00000000 UR#:0000000

TEST PHYSICIAN
DR JOHN DOE
111 CLINIC STREET
CLINIC SUBURB VIC 3000

MICRO SAMPLE ASSAYS

DRIED URINE	Result	Range	Units
Intermediate 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 | 12/04/18	RANGE
Urinary Estrogens		
Estradiol	0.14 L	0.15-0.75 µg/g Cr Postmenopausal
Estrone	0.62 L	0.64-2.56 µg/g Cr Postmenopausal
Estriol	0.16 L	0.28-1.17 µg/g Cr Postmenopausal
E3/(E1+E2)	0.25 L	>0.3 (> median value)
2-OH Estradiol	0.10	0.08-0.31 µg/g Cr Postmenopausal
2-OH Estrone	0.24 L	0.25-1.00 µg/g Cr Postmenopausal
4-OH Estradiol	0.01 L	0.03-0.12 µg/g Cr Postmenopausal
4-OH Estrone	0.03 L	0.06-0.22 µg/g Cr Postmenopausal
16α-OH Estrone	0.06 L	0.10-0.41 µg/g Cr Postmenopausal
2-OH (E1 + E2)/16-α-OH E1	5.67	1.47-8.17 Postmenopausal
2-MeO Estradiol	0.04	0.02-0.07 µg/g Cr Postmenopausal
2-MeO Estrone	0.04 L	0.06-0.29 µg/g Cr Postmenopausal
2-MeO E1/2-OH E1	0.18 L	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	0.33	0.03-0.38 Postmenopausal
4-MeO E2/4-OH E2	N/A	0.14-0.73 Postmenopausal
Bisphenol A	2.21	1.5-4.5 µg/g Cr Postmenopausal

TEST NAME	RESULTS | 12/04/18	RANGE
Urinary Progestogens		
Pregnanediol	51 L	56-220 µg/g Cr Postmenopausal
Allopregnanolone	1.20	0.3-1.31 µg/g Cr Postmenopausal
Allopregnanediol	6.11	1.38-6.75 µg/g Cr Postmenopausal
3α-Dihydroprogesterone	0.98 H	0.19-0.77 µg/g Cr Postmenopausal
20α-Dihydroprogesterone	0.64	0.60-5.53 µg/g Cr Postmenopausal
Deoxycorticosterone	1.00	0.37-1.97 µg/g Cr Postmenopausal
Corticosterone	6.35	2.32-9.88 µg/g Cr Postmenopausal
Pgdiol/E2	425 L	1000-1500 (Optimal Luteal Only)
Urinary Androgens		
DHEA	17.93	8.63-37.28 µg/g Cr Postmenopausal
Androstenedione	3.41	2.07-7.94 µg/g Cr Postmenopausal
Androsterone	356	152-482 µg/g Cr Postmenopausal
Etiocholanolone	621	239-777 µg/g Cr Postmenopausal
Testosterone	2.01	0.66-2.89 µg/g Cr Postmenopausal
Epi-Testosterone	0.96	0.39-1.32 µg/g Cr Postmenopausal
T/Epi-T	2.09	0.5-3.0
5α-DHT	1.07 H	0.26-0.98 µg/g Cr Postmenopausal
5α,3α-Androstanediol	5.03	2.32-8.17 µg/g Cr Postmenopausal
Urinary Glucocorticoids		
Total Cortisol	20.96	13.23-39.26 µg/g Cr Postmenopausal
Total Cortisone	30.24	23.32-59.61 µg/g Cr Postmenopausal
Cortisol/Cortisone	0.69	0.5-0.7
Tetrahydrocortisol	471	281-711 µg/g Cr Postmenopausal
Tetrahydrocortisone	1683 H	551-1474 µg/g Cr Postmenopausal
Urinary Free Diurnal Cortisol		
Free Cortisol	20.90	7.8-29.5 µg/g Cr (1st Morning)
Free Cortisol	37.16	23.4-68.9 µg/g Cr (2nd Morning)

TEST NAME	RESULTS | 12/04/18	RANGE
Urinary Free Diurnal Cortisol		
Free Cortisol	13.98	6.0-19.2 µg/g Cr (Evening)
Free Cortisol	4.38	2.6-8.4 µg/g Cr (Night)
Urinary Free Diurnal Cortisone		
Free Cortisone	49.82	31.6-91.6 µg/g Cr (1st Morning)
Free Cortisone	210.85 H	63.3-175.8 µg/g Cr (2nd Morning)
Free Cortisone	33.87	30.6-88.5 µg/g Cr (Evening)
Free Cortisone	21.90	15.5-44.7 µg/g Cr (Night)
Urinary Diurnal Melatonin MT6s		
Melatonin	39.98	18.0 - 40.9 µg/g Cr (1st Morning)
Urinary Creatinine		
Creatinine (pooled)	1.32	0.3-2.0 mg/mL
Creatinine	1.40	0.3-2.0 mg/mL (1st morning)
Creatinine	0.17 L	0.3-2.0 mg/mL (2nd morning)
Creatinine	1.36	0.3-2.0 mg/mL (Evening)
Creatinine	0.61	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

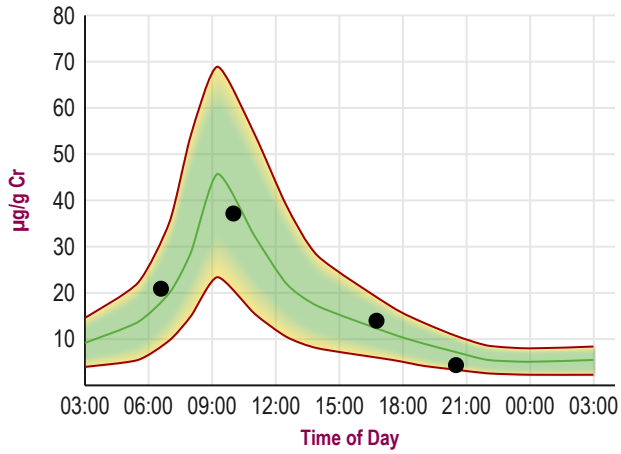
None Indicated

Graphs

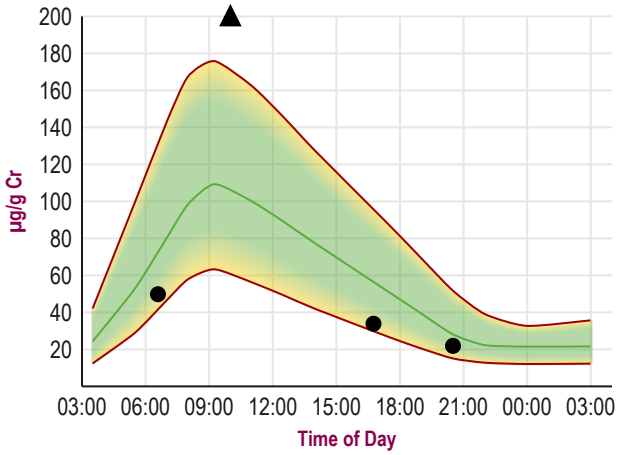
Disclaimer: Graphs below represent averages for healthy individuals not using hormones. Supplementation ranges may be higher. Please see supplementation ranges and lab comments if results are higher or lower than expected.

Average ▼▲ Off Graph

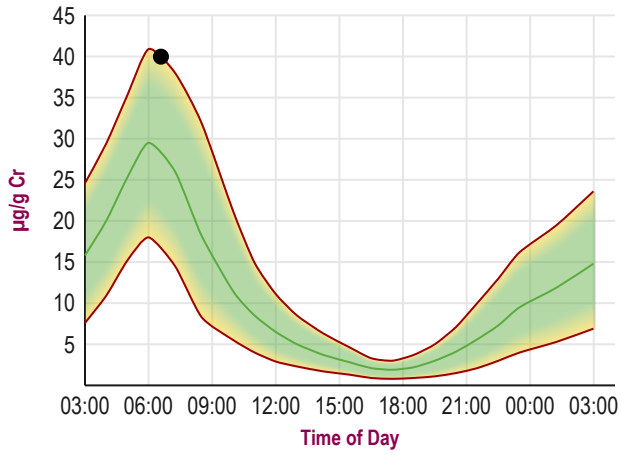
Urinary Free Cortisol



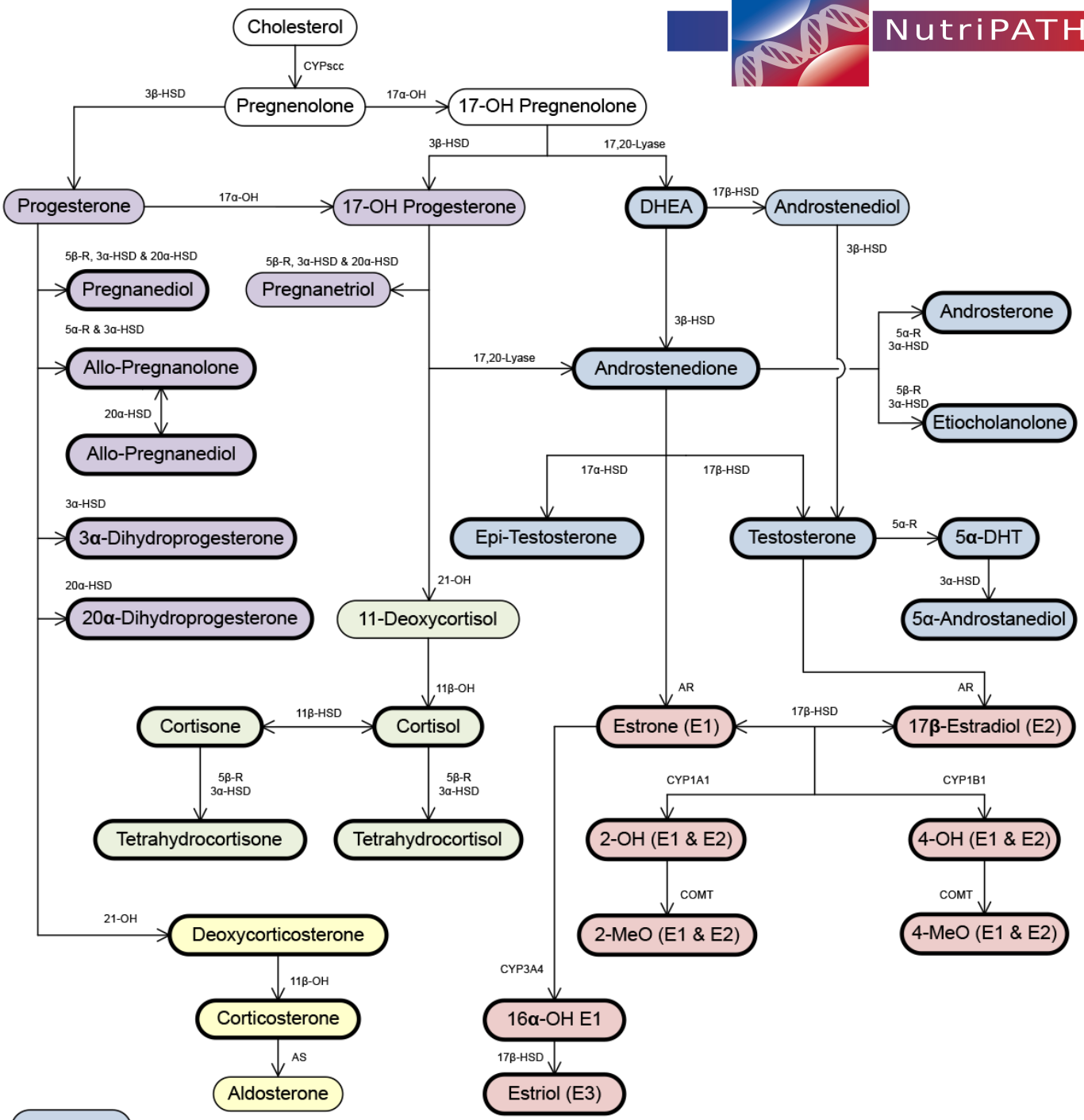
Urinary Free Cortisone



Urinary Melatonin (MT6s)



The Steroid Hormone Cascade

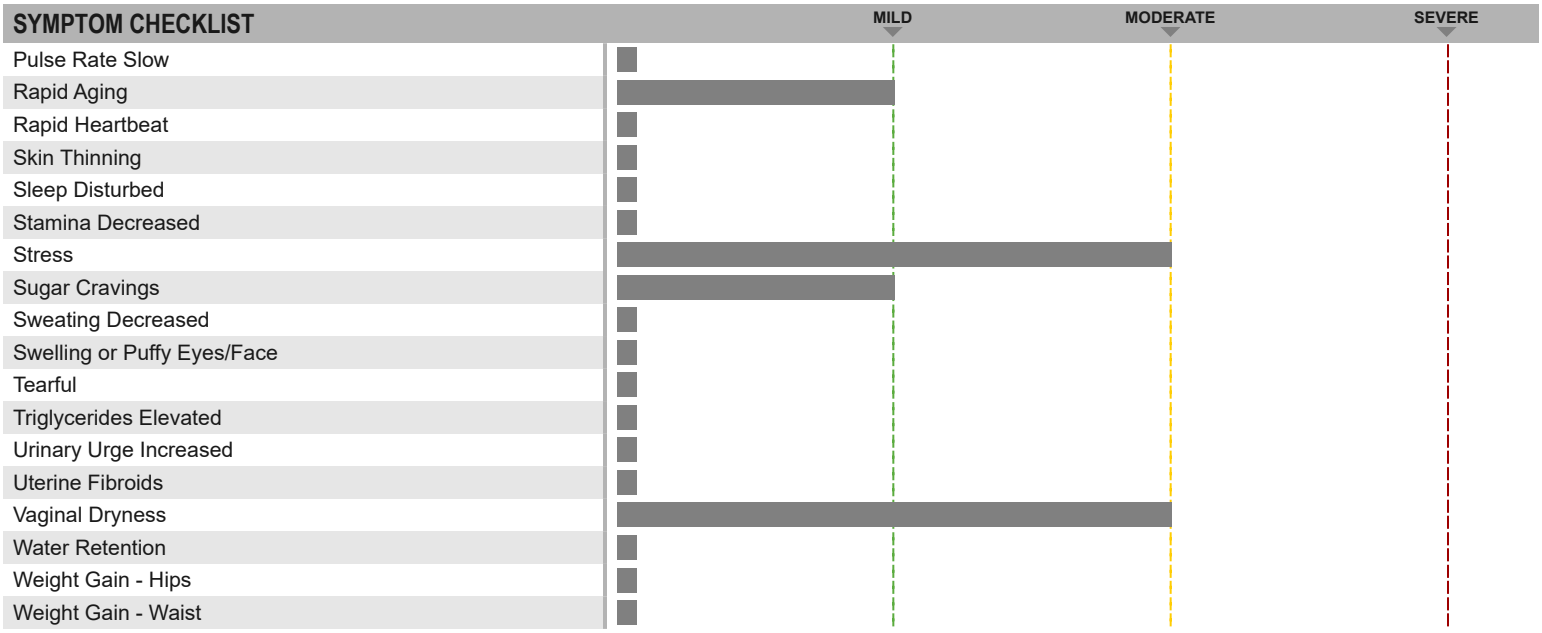


Enzyme Abbreviations

(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 | 12/04/18
Estrogen / Progesterone Deficiency	16%
Estrogen Dominance / Progesterone Deficiency	10%
Low Androgens (DHEA/Testosterone)	22%
High Androgens (DHEA/Testosterone)	11%
Low Cortisol	10%
High Cortisol	22%
Hypometabolism	13%
Metabolic Syndrome	4%

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)

Estradiol, estrone, and estriol are all low or lower than the median of the reference ranges for a postmenopausal woman. This is usually equivalent to a serum estradiol of < 25 pg/ml or a salivary estradiol of < 1 pg/ml. Low estrogens often contribute to symptoms of estrogen deficiency such as vasomotor symptoms (hot flashes and night sweats), vaginal dryness, incontinence, and long term effects on bone loss, insulin resistance, and cardiovascular risk. Use of small amounts of estrogens (physiologic dosing to bring estrogens to low premenopausal levels) is worth considering assuming no contraindications, particularly if estrogen deficiency symptoms are problematic. Estrogen therapy that achieves premenopausal levels of estrogens should always be balanced with progesterone, the natural estrogen antagonist.

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

The hydroxylated estrogens are low or lower than the median reference ranges for a postmenopausal woman. While this might infer a lower risk for estrogen-sensitive cancers (e.g. breast cancer), it might also increase risk for adverse symptoms of estrogen deficiency and long term adverse effects on health (e.g. bone loss, cardiovascular disease).

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- and 4-hydroxyestrogen are low or within low-normal reference ranges for a postmenopausal woman. The low levels of some are often due to low levels of precursor hydroxylated estrogens. If any of the hydroxyestrogens (2-OH-E2, 2-OH-E1, 4-OH-E2, and 4-OH-E1) are within normal range or high, and their methylated metabolites (2-MeO-E2, 2-MeO-E1, 4-MeO-E2, and 4-MeO-E1) are low, this indicates poor methylation of the hydroxyestrogens.

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 this form the methylated catechol estrogens are rapidly excreted in urine. However, if methylation pathways are inadequate due to low levels of COMT or lack of precursors of methylation (i.e. vitamins B6, B12, folate, betaine) the 2- and 4-hydroxyl estrogens can take a more insidious and dangerous pathway of metabolism, which is oxidation of the hydroxyl (catechol) groups to 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 these 4-quinones of estradiol and/or estrone 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), the 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). Neither the quinone estrogens nor their interaction with DNA is measured-only the precursor hydroxyl-estrogens and their methylated metabolites.

RATIO OF 2- and 4-METHYLATED HYDROXYESTRONE/HYDROXYESTRONE
The ratios of 2- and 4-methylated hydroxyestrone are within expected mid reference ranges or higher, indicating that methylation of the hydroxyestrogens is adequate.

The ratio of 2- and 4-hydroxy estrone 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 these estrogen species is 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 damage DNA causing mutations and potentially 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)

Pregnanediol is lower than the expected reference range for a postmenopausal woman. Pregnanediol is a metabolite of progesterone that is excreted into urine. In menopausal women a small amount of progesterone is produced primarily in the adrenal glands. Serum levels are much lower than seen during the luteal phase of the menstrual cycle of premenopausal women, when progesterone is produced in large amounts by the ovaries. Levels of pregnanediol closely parallel those of progesterone in serum, making pregnanediol a good surrogate marker of circulating levels of progesterone.

Progesterone therapy is often helpful when estradiol levels are normal to elevated, urinary pregnanediol is low, and symptoms of estrogen imbalance (both estrogen deficiency and dominance) are problematic.

PROGESTERONE METABOLITES: MINERALCORTICOID PRECURSORS

Deoxycorticosterone (DOC), a weak mineralcorticoid and precursor to the more potent mineralcorticoid aldosterone, are within or near normal reference ranges for a postmenopausal woman. The conversion of progesterone to DOC varies by up to 20-fold among women (MacDonald Endocrine Reviews 12: 372-401, 1991) p. 390). Adverse reactions to higher progesterone 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 (T), Epi-testosterone (Epi-T), 5-alpha-Dihydrotestosterone (DHT)

Testosterone and Epi-Testosterone (Epi-T) are within expected ranges for a postmenopausal woman. DHT, the more potent down-stream metabolite of T, is slightly higher than range for a postmenopausal woman, but within range for a premenopausal woman. If symptoms of androgen deficiency are problematic, consider androgen replacement therapy (e.g. testosterone or DHEA). DHEA therapy usually increases T levels by about 50%.

Endogenously, Epi-T and T are normally synthesized in about equal amounts from androstenedione. With endogenous production, the T/Epi-T ratio is about 1, and ranges from about 0.5-2. A higher ratio usually indicates exogenous T therapy.

TOTAL CORTISOL (F)

Total cortisol (F) is within the expected reference range. Total F is determined from the average of four urine collections throughout the day and is equivalent to a 24 hour total F urine value.

While 24 hr and 4-spot total cortisol urine tests provide useful information about the adrenal glands average capacity to synthesize cortisol and downstream metabolites in a day, they provide no information about the diurnal synthesis of cortisol throughout the day. In healthy individuals cortisol synthesis should be high in the morning, drop progressively throughout the day, and be at the lowest level during the night while sleeping. Deviations from this pattern are associated with symptoms typical of adrenal dysfunction, poor health and disease. Thus, total glucocorticoid production, while important, should be viewed in light of the diurnal cortisol pattern, which can be determined by testing cortisol 4x throughout the day in saliva, or in the four urine samples used here to determine total cortisol.

Adrenal dysfunction can include many of the self-reported signs/symptoms such as anxiety, nervous-irritability, self-perceived stress, excessive fatigue, and sleep disturbances. Chronic abnormal cortisol levels (both high and low, or not showing a normal circadian rhythm) might also include memory problems, depression, loss of muscle mass, and weight gain in the waist. High cortisol is closely associated with insulin resistance and metabolic syndrome, as are the diseases of aging such as diabetes, cardiovascular disease, cancer, and bone loss. When cortisol remains high these symptoms/conditions/syndromes/diseases progressively become more problematic over time. Excessive chronic high cortisol lowers synthesis of testosterone, growth hormone, thyroid hormones and their tissue receptors. If symptoms of adrenal imbalance are problematic despite normal total cortisol levels seen in these test results, consider testing the diurnal pattern of cortisol.

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; "The Role of Stress and the HPA Axis in Chronic Disease Management" by Thomas Guilliams, PhD.

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

Urinary free cortisol (F) is following a normal circadian rhythm and is within/near normal reference ranges throughout the day. In contrast with F, cortisone (E), the inert metabolite of cortisol, is elevated in the second urine void but within/near normal ranges the remainder of the day. Normal F but high E in the second urine void indicates that cortisol synthesis is high at this time, but is being rapidly converted to cortisone via 11-beta hydroxysteroid dehydrogenase type II (see Steroid Hormone Cascade). (11-beta HSD-II) (for review see: Seckl JR and Chapman KE Eur J Biochem 249, 361-364, 1997). This cortisol-metabolizing enzyme is expressed in tissues such as the kidneys, liver, lungs, colon, and salivary

glands. It plays an key role in preventing excess buildup of cortisol in tissues, especially the kidneys, where it activates the mineralocorticoid receptor at high levels.

Higher cortisol and/or cortisone synthesis is usually caused by excessive stressors. Persistent stressors and chronic high cortisol production by the adrenal glands over a prolonged period (months/years) can lead to excessive breakdown of normal tissues (muscle wasting, thinning of skin, bone loss) and immune suppression. It can also lead to suppression of TSH and lower tissue conversion of T4 to T3 by thyroid deiodinases.

High cortisol or cortisone, particularly if either is elevated at night, are associated most commonly with symptoms and conditions such as sleep disturbances, vasomotor symptoms (hot flashes and night sweats despite normal or high estrogen levels), fatigue, depression, weight gain in the waist, bone and muscle loss. Because chronic stressors and associated high cortisol can have adverse effects on health and wellbeing, it is important to develop strategies to identify and eliminate or reduce the stressors or consider bioidentical hormone replacement therapies, foods, and/or nutritional supplements that help control excessive accumulation of cortisol. For additional information about adrenal dysfunction and strategies for adrenal support and lowering stress/cortisol levels the following books and journal articles are worth reading: "The Role of Stress and the HPA Axis in Chronic Disease Management" by Thomas Guilliams, PhD; "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.

MELATONIN METABOLITE 6-SULFATOXYMELATONIN (MT6s)

The urine melatonin metabolite MT6s is within normal reference range in the first morning void. MT6s in the first morning void is representative of the average melatonin produced throughout the night, which is usually a 6-8 hr interval without light. The first void should have the highest level of melatonin since it usually represents the longest period of darkness, which is necessary for melatonin synthesis. Melatonin is produced by the pineal gland in the brain where it is released into the circulation and rapidly enters tissues throughout the body to carry out its restorative properties. Melatonin synthesis decreases with aging; calcification of the pineal gland, which has been associated with cancers such as breast cancer, 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 a susceptibility to obesity in people with insomnia or those who do night shift work. 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. Melatonin levels tend to be low and have flat circadian rhythms in individuals with cancers of the breasts and prostate.

If sleep issues are problematic melatonin may be helpful. However, when morning melatonin is within normal range sleep issues may be caused by hormonal imbalances (e.g. high or low levels of estrogens, testosterone, and/or cortisol) or other medications that interfere with sleep. Treatment with 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 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, causing 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 urine void and thereafter throughout the day if testing diurnal melatonin levels. For more information about melatonin see: http://www.nlm.nih.gov/medlineplus/druginfo/natural/940.html.