P:1300 688 522
E:info@nutripath.com.au
A:PO Box 442 Ashburton VIC3142

Please refer to PDF report attached

Practitioner:	RACHEAL LEE (NPINS)
	14 ORANA STREET
	AIRLIE BEACH QLD
	QLD
	4802
Request id:	3809317
Patient:	NICOLE GORDON
	166 SMITHS LANE
	BOHENA CREEK NSW
	NSW
	2390
Date of Birth:	15-Aug-1989
Sex:	F

TEST REPORT

 # 2022 04 21 123 U

Ordering Provider:
NutriPath

Samples Received
04/21/2022

Report Date
04/27/2022

Samples Collected
Urine - 04/05/22 07:50
Urine - 04/05/22 10:00
Urine - 04/05/22 18:00
Urine - 04/05/22 22:00

Patient Name: Nicole Gordon
Patient Phone Number:

Gender	Last Menses	Height	Waist
Female	03/19/2022	161 cm	Unspecified
DOB	**Menses Status**	**Weight**	**BMI**
8/15/1989 (32 yrs)	Pre-Menopausal	101 kg	39.0

TEST NAME	RESULTS | 04/05/22	RANGE
Urinary Estrogens		
Estradiol	1.45	0.78-1.79 µg/g Cr Premeno-luteal or ERT
Estrone	6.85 H	2.27-5.22 µg/g Cr Premeno-luteal or ERT
Estriol	2.94 H	0.78-1.98 µg/g Cr Premeno-luteal or ERT
E3/(E1+E2)	0.35	>0.3 (> median value)
2-OH Estradiol	1.13 H	0.17-0.70 µg/g Cr Premeno-luteal or ERT
2-OH Estrone	4.62 H	0.70-2.54 µg/g Cr Premeno-luteal or ERT
4-OH Estradiol	0.38 H	0.10-0.18 µg/g Cr Premeno-luteal or ERT
4-OH Estrone	0.60 H	0.17-0.47 µg/g Cr Premeno-luteal or ERT
16α-OH Estrone	1.55 H	0.35-1.07 µg/g Cr Premeno-luteal or ERT
2-OH (E1 + E2)/16-α-OH E1	3.71	1.29-5.49 Premeno-luteal or ERT
2-MeO Estradiol	0.07	0.03-0.08 µg/g Cr Premeno-luteal or ERT
2-MeO Estrone	0.89 H	0.26-0.68 µg/g Cr Premeno-luteal or ERT
2-MeO E1/2-OH E1	0.19 L	0.21-0.38 Premeno-luteal or ERT
4-MeO Estradiol	0.05 H	<0.04 µg/g Cr
4-MeO Estrone	0.04	<0.04 µg/g Cr
4-MeO E1/4-OH E1	0.07	0.05-0.13 Premeno-luteal or ERT
4-MeO E2/4-OH E2	0.13	0.10-0.29 Premeno-luteal or ERT
Bisphenol A	<dl L	1.11-3.74 µg/g Cr Premeno-luteal

TEST NAME	RESULTS | 04/05/22	RANGE
Urinary Progestogens		
Pregnanediol	1408	465-1609 µg/g Cr Premeno-luteal or PgRT
Allopregnanolone	6.39	2.23-14.87 µg/g Cr Premeno-luteal or PgRT
Allopregnanediol	42.24	14.65-76.71 µg/g Cr Premeno-luteal or PgRT
3α-Dihydroprogesterone	2.86 H	0.67-2.03 µg/g Cr Premeno-luteal or PgRT
20α-Dihydroprogesterone	6.36	3.93-11.62 µg/g Cr Premeno-luteal or PgRT
Deoxycorticosterone	1.97	0.69-2.23 µg/g Cr Premeno-luteal or PgRT
Corticosterone	5.80	3.19-9.59 µg/g Cr Premeno-luteal or PgRT
Pgdiol/E2	971.03 L	1000-1500 (Optimal Luteal Only)
Urinary Androgens		
DHEA	498.94 H	15.82-129.17 µg/g Cr Premeno-luteal or DHEAT
Androstenedione	29.43 H	3.93-13.53 µg/g Cr Premeno-luteal or ART
Androsterone	1188 H	248-937 µg/g Cr Premeno-luteal or ART
Etiocholanolone	1309 H	330-960 µg/g Cr Premeno-luteal or ART
Testosterone	2.16	1.22-3.97 µg/g Cr Premeno-luteal or ART
Epi-Testosterone	7.07 H	2.01-4.66 µg/g Cr Premeno-luteal
T/Epi-T	0.31 L	0.5-3.0
5α-DHT	0.78	0.28-1.52 µg/g Cr Premeno-luteal or ART
5α,3α-Androstanediol	15.07 H	2.98-13.10 µg/g Cr Premeno-luteal or ART
Urinary Glucocorticoids		
Total Cortisol	26.31	12.26-33.12 µg/g Cr Premeno-luteal
Total Cortisone	40.17	23.27-50.88 µg/g Cr Premeno-luteal
Cortisol/Cortisone	0.65	0.5-0.7
Tetrahydrocortisol	564 H	214-546 µg/g Cr Premeno-luteal
Tetrahydrocortisone	1221 H	437-1184 µg/g Cr Premeno-luteal
Urinary Free Diurnal Cortisol		
Free Cortisol	10.65	7.8-29.5 µg/g Cr (1st Morning)
Free Cortisol	48.82	23.4-68.9 µg/g Cr (2nd Morning)
Free Cortisol	12.87	6.0-19.2 µg/g Cr (Evening)

TEST NAME	RESULTS | 04/05/22	RANGE
Urinary Free Diurnal Cortisol		
Free Cortisol	4.31	2.6-8.4 µg/g Cr (Night)
Urinary Free Diurnal Cortisone		
Free Cortisone	47.29	31.6-91.6 µg/g Cr (1st Morning)
Free Cortisone	213.03 H	63.3-175.8 µg/g Cr (2nd Morning)
Free Cortisone	160.69 H	30.6-88.5 µg/g Cr (Evening)
Free Cortisone	56.43 H	15.5-44.7 µg/g Cr (Night)
Urinary Diurnal Melatonin MT6s		
Melatonin	37.24	18.0 - 40.9 µg/g Cr (1st Morning)
Melatonin	19.31	7.3 - 31.9 µg/g Cr (2nd Morning)
Melatonin	<dl L	0.7 - 2.2 µg/g Cr (Evening)
Melatonin	3.30	1.7 - 11.1 µg/g Cr (Night)
Urinary Creatinine		
Creatinine (pooled)	0.49	0.3-2.0 mg/mL
Creatinine	0.85	0.3-2.0 mg/mL (1st morning)
Creatinine	0.25 L	0.3-2.0 mg/mL (2nd morning)
Creatinine	0.20 L	0.3-2.0 mg/mL (Evening)
Creatinine	0.36	0.3-2.0 mg/mL (Night)

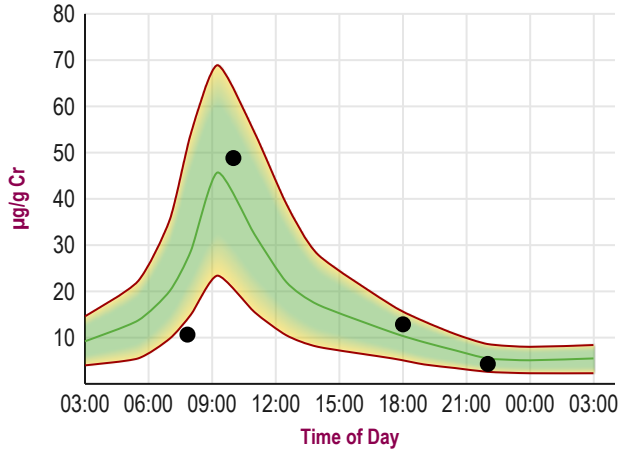
<dl *= Less than the detectable limit of the lab.* ***N/A*** *= Not applicable; 1 or more values used in this calculation is less than the detectable limit.* ***H*** *= High.* ***L*** *= Low.*

Therapies

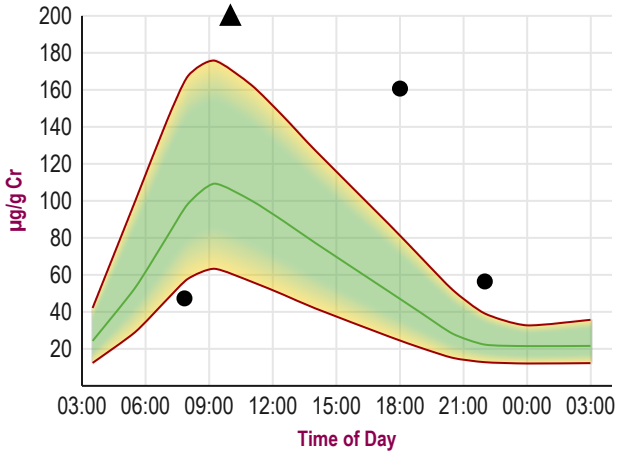
None Indicated

Graphs

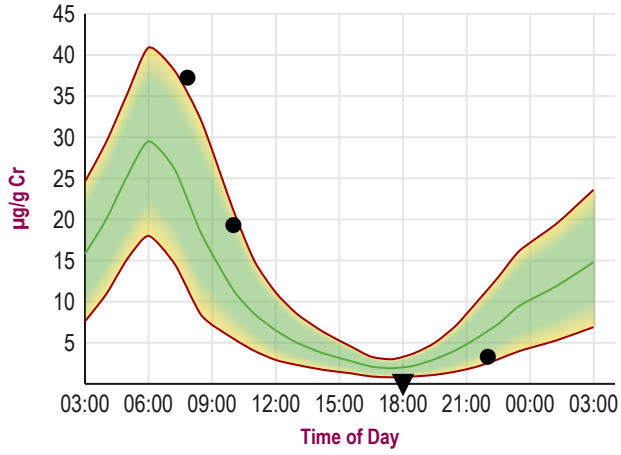
Urinary Free Cortisol



Urinary Free Cortisone



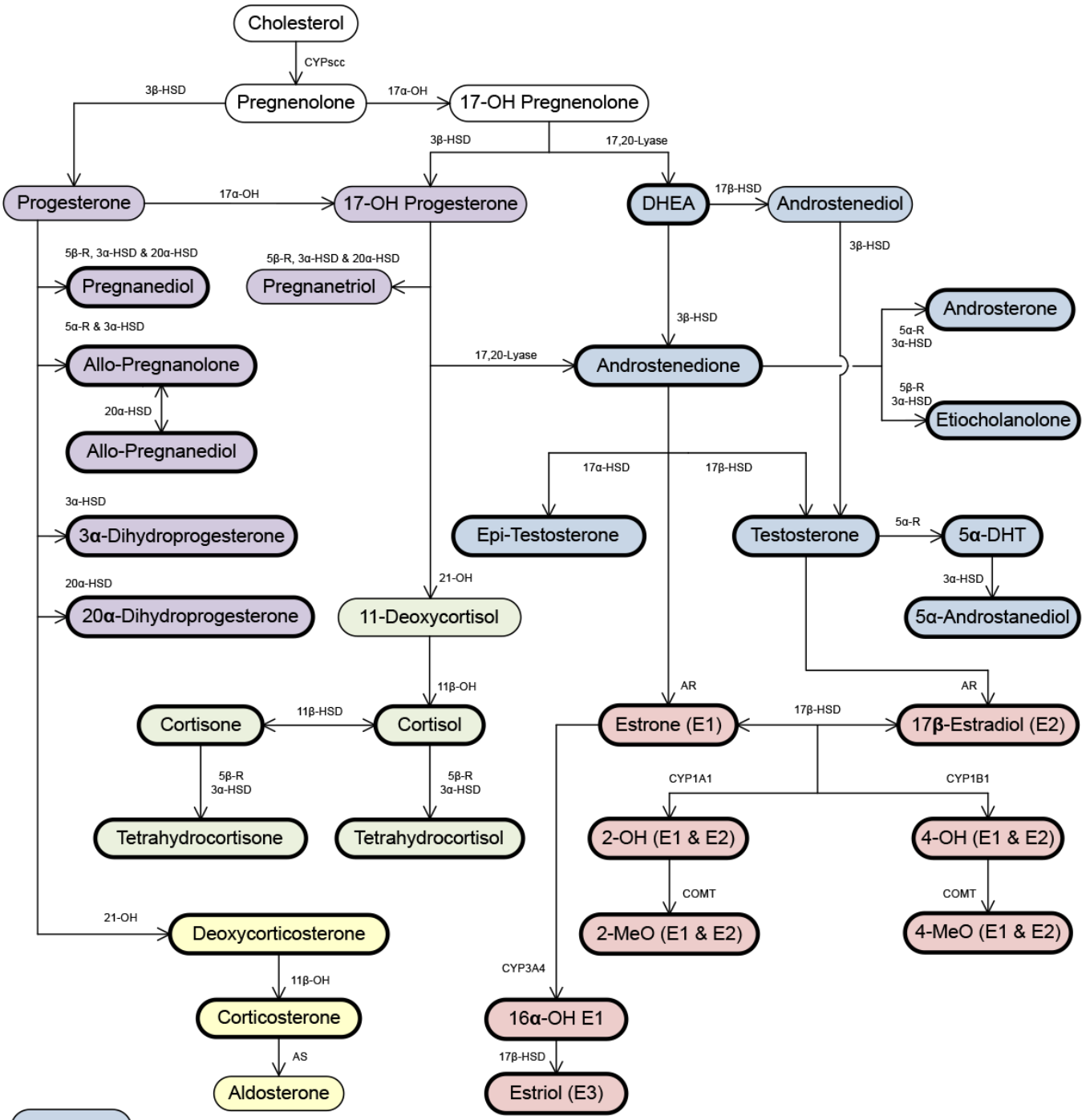
Urinary Melatonin (MT6s)



TEST NAME	WOMEN
Urinary Estrogens	
Estradiol	0.15-0.75 µg/g Cr Postmenopausal; 0.78-1.79 µg/g Cr Premeno-luteal or ERT
Estrone	0.64-2.56 µg/g Cr Postmenopausal; 2.27-5.22 µg/g Cr Premeno-luteal or ERT
Estriol	0.28-1.17 µg/g Cr Postmenopausal; 0.78-1.98 µg/g Cr Premeno-luteal or ERT
E3/(E1+E2)	>0.3 (> median value)
2-OH Estradiol	0.08-0.31 µg/g Cr Postmenopausal; 0.17-0.70 µg/g Cr Premeno-luteal or ERT
2-OH Estrone	0.25-1.00 µg/g Cr Postmenopausal; 0.70-2.54 µg/g Cr Premeno-luteal or ERT
4-OH Estradiol	0.03-0.12 µg/g Cr Postmenopausal; 0.10-0.18 µg/g Cr Premeno-luteal or ERT
4-OH Estrone	0.06-0.22 µg/g Cr Postmenopausal; 0.17-0.47 µg/g Cr Premeno-luteal or ERT
16α-OH Estrone	0.10-0.41 µg/g Cr Postmenopausal; 0.35-1.07 µg/g Cr Premeno-luteal or ERT
2-OH (E1 + E2)/16-α-OH E1	1.47-8.17 Postmenopausal; 1.29-5.49 Premeno-luteal or ERT
2-MeO Estradiol	0.02-0.07 µg/g Cr Postmenopausal; 0.03-0.08 µg/g Cr Premeno-luteal or ERT
2-MeO Estrone	0.06-0.29 µg/g Cr Postmenopausal; 0.26-0.68 µg/g Cr Premeno-luteal or ERT
2-MeO E1/2-OH E1	0.19-0.36 Postmenopausal; 0.21-0.38 Premeno-luteal or ERT
4-MeO Estradiol	<0.04 µg/g Cr
4-MeO Estrone	<0.04 µg/g Cr
4-MeO E1/4-OH E1	0.03-0.38 Postmenopausal; 0.05-0.13 Premeno-luteal or ERT
4-MeO E2/4-OH E2	0.14-0.73 Postmenopausal; 0.10-0.29 Premeno-luteal or ERT
Bisphenol A	1.5-4.5 µg/g Cr Postmenopausal; 1.11-3.74 µg/g Cr Premeno-luteal
Urinary Progestogens	
Pregnanediol	56-220 µg/g Cr Postmenopausal; 465-1609 µg/g Cr Premeno-luteal or PgRT
Allopregnanolone	0.3-1.31 µg/g Cr Postmenopausal; 2.23-14.87 µg/g Cr Premeno-luteal or PgRT
Allopregnanediol	1.38-6.75 µg/g Cr Postmenopausal; 14.65-76.71 µg/g Cr Premeno-luteal or PgRT
3α-Dihydroprogesterone	0.19-0.77 µg/g Cr Postmenopausal; 0.67-2.03 µg/g Cr Premeno-luteal or PgRT
20α-Dihydroprogesterone	0.60-5.53 µg/g Cr Postmenopausal; 3.93-11.62 µg/g Cr Premeno-luteal or PgRT
Deoxycorticosterone	0.37-1.97 µg/g Cr Postmenopausal; 0.69-2.23 µg/g Cr Premeno-luteal or PgRT
Corticosterone	2.32-9.88 µg/g Cr Postmenopausal; 3.19-9.59 µg/g Cr Premeno-luteal or PgRT
Pgdiol/E2	1000-1500 (Optimal Luteal Only)
Urinary Androgens	
DHEA	8.63-37.28 µg/g Cr Postmenopausal; 15.82-129.17 µg/g Cr Premeno-luteal or DHEAT
Androstenedione	2.07-7.94 µg/g Cr Postmenopausal; 3.93-13.53 µg/g Cr Premeno-luteal or ART
Androsterone	152-482 µg/g Cr Postmenopausal; 248-937 µg/g Cr Premeno-luteal or ART
Etiocholanolone	239-777 µg/g Cr Postmenopausal; 330-960 µg/g Cr Premeno-luteal or ART
Testosterone	0.66-2.89 µg/g Cr Postmenopausal; 1.22-3.97 µg/g Cr Premeno-luteal or ART

TEST NAME	WOMEN
Urinary Androgens	
Epi-Testosterone	0.39-1.32 µg/g Cr Postmenopausal; 2.01-4.66 µg/g Cr Premeno-luteal
T/Epi-T	0.5-3.0
5α-DHT	0.26-0.98 µg/g Cr Postmenopausal; 0.28-1.52 µg/g Cr Premeno-luteal or ART
5α,3α-Androstanediol	2.32-8.17 µg/g Cr Postmenopausal; 2.98-13.10 µg/g Cr Premeno-luteal or ART
Urinary Glucocorticoids	
Total Cortisol	13.23-39.26 µg/g Cr Postmenopausal; 12.26-33.12 µg/g Cr Premeno-luteal
Total Cortisone	23.32-59.61 µg/g Cr Postmenopausal; 23.27-50.88 µg/g Cr Premeno-luteal
Cortisol/Cortisone	0.5-0.7
Tetrahydrocortisol	281-711 µg/g Cr Postmenopausal; 214-546 µg/g Cr Premeno-luteal
Tetrahydrocortisone	551-1474 µg/g Cr Postmenopausal; 437-1184 µg/g Cr Premeno-luteal
Urinary Free Diurnal Cortisol	
Free Cortisol	7.8-29.5 µg/g Cr (1st Morning); 23.4-68.9 µg/g Cr (2nd Morning); 6.0-19.2 µg/g Cr (Evening); 2.6-8.4 µg/g Cr (Night)
Urinary Free Diurnal Cortisone	
Free Cortisone	31.6-91.6 µg/g Cr (1st Morning); 63.3-175.8 µg/g Cr (2nd Morning); 30.6-88.5 µg/g Cr (Evening); 15.5-44.7 µg/g Cr (Night)
Urinary Diurnal Melatonin MT6s	
Melatonin	18.0 - 40.9 µg/g Cr (1st Morning); 7.3 - 31.9 µg/g Cr (2nd Morning); 0.7 - 2.2 µg/g Cr (Evening); 1.7 - 11.1 µg/g Cr (Night)
Urinary Creatinine	
Creatinine (pooled)	0.3-2.0 mg/mL
Creatinine	0.3-2.0 mg/mL (1st morning); 0.3-2.0 mg/mL (2nd morning); 0.3-2.0 mg/mL (Evening); 0.3-2.0 mg/mL (Night)

The Steroid Hormone Cascade

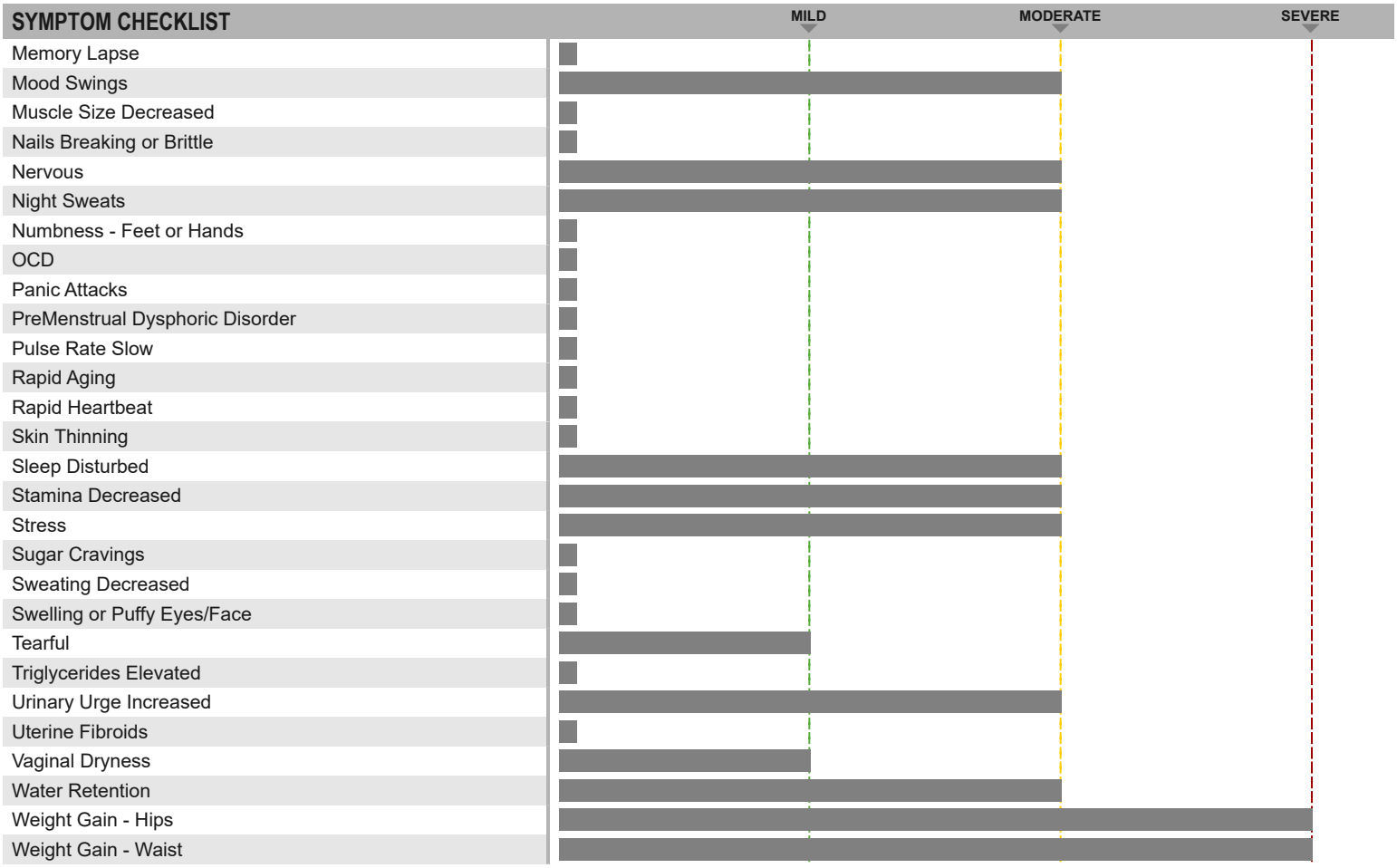


Enzyme Abbreviations

(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 | 04/05/22
Estrogen / Progesterone Deficiency	32%
Estrogen Dominance / Progesterone Deficiency	37%
Low Androgens (DHEA/Testosterone)	27%
High Androgens (DHEA/Testosterone)	9%
Low Cortisol	23%
High Cortisol	35%
Hypometabolism	17%
Metabolic Syndrome	27%

SYMPTOM CHECKLIST	MILD	MODERATE	SEVERE
Aches and Pains			
Acne			
ADD/ADHD			
Addictive Behaviors			
Allergies			
Anxious			
Autism Spectrum Disorder			
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			
Developmental Delays			
Eating Disorders			
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			
Mania			



Lab Comments

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

The parent estrogens are within (or near) the reference ranges seen in premenopausal women. However, symptoms are characteristic of both estrogen excess and deficiency. This suggests that although estrogens were within normal range on the day of testing, they likely fluctuate erratically throughout a 28 day menstrual cycle from high to low, precipitating symptoms of both estrogen deficiency and dominance. This is common in women who are transitioning into menopause when symptoms of both estrogen deficiency (mostly hot flashes and night sweats) and excess are more problematic. When estrogens are within the mid-normal reference intervals, or slightly higher, it is important that they are well balanced with progesterone to prevent excessive proliferation of estrogen sensitive tissues such as the breasts and uterus. Progesterone also helps prevent wide fluctuations in estrogens that occur during the transition to menopause.

If symptoms of estrogen imbalance are problematic (as seen in this individual) consider progesterone restoration therapy as this often helps accelerate estrogen clearance and balance symptoms of both estrogen deficiency and excess. If this is not helpful, consider means to lower the estrogen burden further, or investigate other hormonal imbalances that may be causing symptoms (e.g. low androgens, low or high cortisol, and/or low thyroid).

In the premenopausal patient estradiol should be well balanced with progesterone (optimal PgDiol/E2 ratio = 1300-2000 ug/g Cr during the luteal phase of the menstrual cycle. It is important to note that this optimal ratio only applies to endogenous pregnanediol that is produced during the luteal phase of the menstrual cycle, and not in women treated with exogenous oral, topical or vaginal progesterone. Exogenous oral progesterone results in urinary PgDiol levels higher than range (high Pgdiol/E2 ratio), while topical and vaginal progesterone result in levels lower than range (low Pgdiol/E2 ratio). For a more complete explanation see Progesterone and Metabolites below.

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

The hydroxylated estrogens (2-OH-E2, 2-OH-E1, 4-OH-E2, 4-OH-E1), referred to as catechol estrogens, are all within the upper quadrant of the reference ranges, or higher.

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 positions, 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 that formed elsewhere in the body but were excreted in urine.

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 are considered more toxic as they bind to DNA causing 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.

The safer 2-hydroxylated estrogen metabolism is increased, relative to the 4-hydroxylation pathways, with cruciferous vegetables and extracts of them. The most commonly used are indole-3-carbinol (I3C) and its metabolite diindolylmethane (DIM). Eating a healthy diet of plants with beneficial phytochemicals (e.g. leafy vegetables with color, soy foods, flax, foods high in antioxidants such as turmeric) also helps prevent toxic estrogen metabolism. 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 much more reactive quinone estrogens. The 4-quinone estrogens, if not inactivated by glutathione, can potentially bind to and damage DNA leading to mutations that increase lifetime risk for cancer.

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 associated with a decreased risk in postmenopausal women (Huang J et.al. Analytica Chimica Acta 711: 60-68, 2012). A meta-analysis of nine studies investigating the relationship of the urinary 2/16 ratio have NOT shown it to be useful for predicting breast cancer risk (Obi N et.al. Int J Women's Health 3: 37-51, 2011).

METHYLATION OF HYDROXYESTROGENS

The methylated forms of the 2- and 4-hydroxyestrogens are within normal reference ranges, or elevated, for a premenopausal woman. Methylation of the hydroxyl estrogens is beneficial as this renders them inert, and prevents them from oxidizing further to more dangerous estrogen quinones that can form adducts with DNA, causing mutations that can lead to increased cancer risk

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 (4-Quinone-E2) and estrone (4-Quinone-E1) are highly electrophilic and bind to DNA, forming adducts that lead to permanent mutations. 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 the 4-hydroxylated estrogens are notinactivated by methylation, or the 4-quine estrogens are inactivated 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 more efficiently 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. Nevertheless, clinical studies investigating estrogen metabolites have shown that high levels of 4-hydroxylated estrogens (4-OH-E2 and 4-OH-E1) and/or low levels of their methylated forms are associated with increased breast cancer risk.

In contrast to the more toxic 4-hydroxylated estrogens, 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, but less so than with the 4-hydroxylated estrogens.

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-PgDiol, Allopregnanolone-AlloP)

The progesterone metabolites, pregnanediol (PgDiol) and allopregnanolone (AlloP), are within expected reference ranges for premenopausal women. PgDiol is a metabolite and surrogate marker of serum progesterone. AlloP is another progesterone metabolite that freely enters the brain from the bloodstream through the blood brain barrier and serves as a neuroactive steroid. AlloP binds to GABAa receptors in the brain and has a calming (anxiolytic) and sleep-inducing effect at high concentrations. Only high levels of AlloP, achieved at peak of an optimal luteal phase, during pregnancy, and with progesterone therapy, have the anxiolytic effects on GABAa receptors in the brain. In a small percentage (about 5-10%) of premenopausal women AlloP at physiological levels has a paradoxical effect and causes anxiety (anxiogenic) and other symptoms characteristic of premenstrual dysphoric disorder (PMDD). This is thought to be due to individual differences in the subunit structure of GABAa receptors in the brain.

PROGESTERONE METABOLITES

The urinary progesterone metabolites are within, or near, normal reference ranges seen in premenopausal women. The urinary progestogen metabolites included encompass the primary urinary metabolite, pregnanediol (Pgdiol), and four other more minor metabolites that belong to the pregnane (Allo-pregnanolone, Allo-pregnanediol) and pregnene (3a-dihydroprogesterone, 20a-dihydroprogesterone) categories. In postmenopausal women the level of pregnanediol is expected to be much lower than in premenopausal women (mean values 81 and 1324 µg/g creatinine, respectively). The mean and range levels for urinary pregnanediol established in premenopausal women during the early follicular and mid-luteal phases of the menstrual cycle are 152 µg/g creatinine (range 92-346) and 1324 µg/g creatinine (range 579-1700), respectively. Thus, about a 10-fold increase in Pgdiol is expected during the progression from the follicular to the luteal phase of the menstrual cycle. The urinary ranges of pregnanediol during the luteal phase are equivalent to a range of about 3-25 ng/mL progesterone in blood (capillary whole blood, venous serum or plasma) and about 50-250 pg/mL in saliva. Optimal luteal ovarian production of progesterone is reflected in all three body fluids (urine, blood, salivary), which is roughly > 1300 µg PgDiol/g creatinine in urine, > 10 ng Progesterone/mL in blood, and > 100 pg Progesterone/mL in saliva.

While the level of urinary pregnanediol is optimal for a premenopausal woman, the ratio of pregnanediol to estrradiol (PgDiol/E2) is low, indicating an overall dominance of estradiol relative to progesterone. This occurs commonly in women approaching menopause (perimenopause) from about age 45-55, and is associated with symptoms of both estrogen dominance and deficiency, as the estrogen levels fluctuate erratically from high to low throughout a menstrual cycle. Progesterone therapy is often helful as it helps reduce the estrogen burden and desensitizes estrogen sensitive tissues such as the breasts and uterus by down-regulating estrogen receptors. However, when estradiol is too excessive progesterone is less effective and other means to lower the estrogen burden should be considered before using progesterone.

PROGESTERONE METABOLITES: MINERALCORTICOID PRECURSORS

Deoxycorticosterone (DOC) and cortiscosterone (CC) are within/near the expected reference ranges for a premenopausal woman. DOC and CC are downstream metabolites of progesterone and progesterone therapy, particularly oral progesterone, usually increases DOC and CC beyond reference ranges.

DOC is a weak mineralcorticoid and precursor to the more potent mineralcorticoid aldosterone. 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)

DHEA(S) is very high which suggests excessive synthesis by the adrenal glands or DHEA supplementation (none indicated). With 5-25 mg DHEA supplementation, urinary DHEA-S increases from a postmenopausal baseline (7.85-28.8 ug/g Cr) to 10.89-65.37 ug/g Cr. Urinary DHEA levels are proportionately higher with higher dosing. Little or no increase in urinary DHEA-S is seen with topical DHEA supplementation. Oral DHEA results in a slight increase in androstenedione from baseline: 1.98-4.75 ug/g Cr vs 2.02-7.36 ug/g Cr.

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/ANDROSTEINE METABOLITES: (ANDROSTERONE-ANDROS, ETIOCHOLANOLONE-ETIO)

Androsterone (Andros) and etiocholanolone (Etio) are higher than reference ranges. Both are downstream metabolites of androstenedione, which is a metabolite of DHEA (see Steroid Hormone Cascade). High DHEA contributes to high levels of these downstream metabolites. DHEA is converted to androstenedione via 3 beta-HSD and then into etiocholanolone by 5-beta-reductase. DHEA is metabolized to androstenedione and then to androsterone by 5-alpha-reductase (see Hormone Cascade).

High DHEA and its downstream metabolites is usually a result of oral DHEA therapy, Congenital Adrenal Hyperplasia (CAH), or more rarely an adrenal tumor.

ANDROGENS AND METABOLITES

Testosterone (T), and its more potent metabolite, 5-alpha DHT (DHT) are within the mid to high expected reference range for a premenopausal woman. Epi-testosterone (Epi-T), on the other hand, is much higher than the reference range. This is unusual since T and Epi-T are usually produced in equal amounts from androstenedione, a down-stream metabolite of DHEA.

While Epi-T and T are normally created in about equal amounts and the ratio of T/Epi-T is usually about 1 (normal range 0.5-3), T and DHT can be much lower than Epi-T, resulting in a very low T/Epi-T ratio. Low urinary T and DHT occurs more frequently in men and women of Asian and Indian (Asian Continent) descent due to deletion polymorphisms in testosterone glucuronidation. This results in less glucuronidation of testosterone and consequently less of the T-glucuronide conjugate excreted in urine, despite normal levels of T in serum (Jakobsson J J Clin Endocrinol Metab 91: 687-693, 2006; Strahm E. Br J Sports Med 43: 1126-1130, 2009). T levels in saliva and capillary blood (Dried Blood Spots-DBS) would also be within normal range despite the "apparent" low T seen in urine. When T and DHT are low and Epi-T is higher than range, especially if symptoms of high androgens are problematic, testing of blood or saliva may provide a more accurate result of the true circulating level of testosterone.

Physiological levels of 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. T is also a precursor to estradiol via the enzyme aromatase.

High androgens in premenopausal women often indicate Polycystic Ovarian Syndrome (PCOS), which is closely associated with obesity, insulin resistance, and metabolic syndrome. Testosterone serves as a precursor to estrogens via aromatase. If estrogens are high and symptoms problematic consider testing saliva, DBS, or serum for total testosterone.

5-ALPHA 3-ALPHA ANDROSTANEDIOL (ADIOL)

The downstream metabolite of DHT, 5-alpha 3-alpha androstanediol (Adiol), is within the high-normal to high reference range. Elevated Adiol is usually associated with higher levels of DHT and androsterone, as well as their precursors DHEA, androstenedione, and testosterone. Adiol is considered a neuroactive steroid that passively enters the brain from the bloodstream through the blood brain barrier. Thus, levels in body fluids outside the brain (blood, urine, saliva) are likely reflective somewhat of levels available to the CNS. Some researchers have suggested that high Adiol, resulting from high testosterone therapy, through its activation of the pleasure/reward dopaminergic pathways, is responsible for addictive effects of high dose androgens (Frye CA. Pharmacol Biochem Behav 86: 347-367, 2007).

Adiol binds to GABAa and dopaminergic receptors in the brain. It has a similar anxiolytic (calming) effects, albeit weaker than allopregnanolone, the 5-alpha 3-alpha metabolite of progesterone. Adiol also interacts with the dopaminergic pathways in the brain and is associated with the dopamine pleasure and reward pathway. Thus, high levels of Adiol are more likely to be associated with conditions/symptoms (addiction, pleasure-thrill seeking behaviors) common to high dopamine and over-activation of the dopaminergic neurons.

TOTAL GLUCOCORTICOIDS (F, E, THF, THE)

Total cortisol (F) and cortisone (E), and their down-stream metabolites, tetrahydrocortisol (THF) and tetrahydrocortisone (THE), are within/near the normal 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 (see below).

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) 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 several times throughout the day indicating that cortisol synthesis is high, 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 melatonin metabolite, 6-sulfatoxymelatonin (MT6s), is within normal reference ranges throughout the day, and showing a normal circadian rhythm. This suggests that sleep issues self-reported by this individual may be more likely 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 thyroid. Many of the listed symptoms suggest some these hormones could be out-of-balance. Testing them and correcting any imbalances is worth considering as a means to help with sleep issues.

In a healthy individual the circadian rhythm of melatonin is inversely related to cortisol. Melatonin levels in blood, urine, and saliva 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. While melatonin and cortisol levels are inversely related during the light-dark cycles of the day, neither directly controls the synthesis of the other. 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 at night during sleep. Sleep disturbances, or high cortisol during the night do not necessarily control melatonin synthesis by the pineal gland; this is regulated by light exposure. Stress during the dark hours may result in insomnia and more light exposure, which would lower melatonin synthesis.

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, regulates the immune system, 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 excessive light exposure during the dark hours, or calcification of the pineal gland caused by aging, 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 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 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 late afternoon when levels should be low. MT6s is an excellent surrogate marker for endogenous melatonin production, but not for oral supplementation with melatonin. Oral melatonin supplementation results in much higher MT6s levels in urine that are NOT reflective of active circulating levels of melatonin in the bloodstream and bioavailable to tissues

throughout the body. Most of the melatonin taken as a supplement is rapidly metabolized by the liver (first-pass effect) and kidney and excreted into urine as MT6s. To accurately determine circulating levels of melatonin with exogenous melatonin supplementation, it is necessary to test melatonin in blood or saliva. Fifty to seventy percent of melatonin in the bloodstream is bioavailable (compare with only 2-3% bioavailability of sex-steroid hormones like estradiol, progesterone, and testosterone) making saliva a viable option for testing bioavailable melatonin.

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