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)
	SHOP 6/115 SHINGLEY DRIVE
	AIRLIE BEACH QLD
	QLD
	4802
Request id:	4044652
Patient:	LORRAINE WADLEY
	10 THUNDER CIRCUIT
	HARRISON ACT
	ACT
	2914
Date of Birth:	11-Aug-1969
Sex:	F

TEST REPORT

 # 2024 11 19 078 U

Ordering Provider:
NutriPath

Samples Received
11/19/2024

Report Date
11/26/2024

Samples Collected
Urine - 11/09/24 07:02
Urine - 11/09/24 08:57
Urine - 11/09/24 17:15
Urine - 11/09/24 21:36

Patient Name: Lorraine Wadley
Patient Phone Number:

Gender	Last Menses	Height	Waist
Female	10/20/2024	151 cm	98 cm
DOB	**Menses Status**	**Weight**	**BMI**
8/11/1969 (55 yrs)	Pre-Menopausal - Irregular	76 kg	33.3

TEST NAME	RESULTS | 11/09/24	RANGE
Urinary Estrogens		
Estradiol	15.47 H	0.78-1.79 µg/g Cr Premeno-luteal or ERT
Estrone	73.03 H	2.27-5.22 µg/g Cr Premeno-luteal or ERT
Estriol	1.86	0.78-1.98 µg/g Cr Premeno-luteal or ERT
E3/(E1+E2)	0.02 L	>0.3 (> median value)
2-OH Estradiol	0.63	0.17-0.70 µg/g Cr Premeno-luteal or ERT
2-OH Estrone	4.82 H	0.70-2.54 µg/g Cr Premeno-luteal or ERT
4-OH Estradiol	0.44 H	0.10-0.18 µg/g Cr Premeno-luteal or ERT
4-OH Estrone	1.51 H	0.17-0.47 µg/g Cr Premeno-luteal or ERT
16α-OH Estrone	1.45 H	0.35-1.07 µg/g Cr Premeno-luteal or ERT
2-OH (E1 + E2)/16-α-OH E1	3.76	1.29-5.49 Premeno-luteal or ERT
2-MeO Estradiol	0.26 H	0.03-0.08 µg/g Cr Premeno-luteal or ERT
2-MeO Estrone	2.43 H	0.26-0.68 µg/g Cr Premeno-luteal or ERT
2-MeO E1/2-OH E1	0.50 H	0.21-0.38 Premeno-luteal or ERT
4-MeO Estradiol	0.13 H	<0.04 µg/g Cr
4-MeO Estrone	0.04	<0.04 µg/g Cr
4-MeO E1/4-OH E1	0.03 L	0.05-0.13 Premeno-luteal or ERT
4-MeO E2/4-OH E2	0.30 H	0.10-0.29 Premeno-luteal or ERT
Bisphenol A	<dl L	1.11-3.74 µg/g Cr Premeno-luteal

TEST NAME	RESULTS | 11/09/24	RANGE
Urinary Progestogens		
Pregnanediol	1364	465-1609 µg/g Cr Premeno-luteal or PgRT
Allopregnanolone	12.51	2.23-14.87 µg/g Cr Premeno-luteal or PgRT
Allopregnanediol	47.66	14.65-76.71 µg/g Cr Premeno-luteal or PgRT
3α-Dihydroprogesterone	4.18 H	0.67-2.03 µg/g Cr Premeno-luteal or PgRT
20α-Dihydroprogesterone	4.41	3.93-11.62 µg/g Cr Premeno-luteal or PgRT
Deoxycorticosterone	1.12	0.69-2.23 µg/g Cr Premeno-luteal or PgRT
Corticosterone	11.89 H	3.19-9.59 µg/g Cr Premeno-luteal or PgRT
Pgdiol/E2	88.17 L	1000-1500 (Optimal Luteal Only)
Urinary Androgens		
DHEA	10.14 L	15.82-129.17 µg/g Cr Premeno-luteal or DHEAT
Androstenedione	3.04 L	3.93-13.53 µg/g Cr Premeno-luteal or ART
Androsterone	384	248-937 µg/g Cr Premeno-luteal or ART
Etiocholanolone	465	330-960 µg/g Cr Premeno-luteal or ART
Testosterone	1.60	1.22-3.97 µg/g Cr Premeno-luteal or ART
Epi-Testosterone	3.58	2.01-4.66 µg/g Cr Premeno-luteal
T/Epi-T	0.45 L	0.5-3.0
5α-DHT	0.27 L	0.28-1.52 µg/g Cr Premeno-luteal or ART
5α,3α-Androstanediol	5.20	2.98-13.10 µg/g Cr Premeno-luteal or ART
Urinary Glucocorticoids		
Total Cortisol	31.97	12.26-33.12 µg/g Cr Premeno-luteal
Total Cortisone	38.41	23.27-50.88 µg/g Cr Premeno-luteal
Cortisol/Cortisone	0.83 H	0.5-0.7
Tetrahydrocortisol	613 H	214-546 µg/g Cr Premeno-luteal
Tetrahydrocortisone	1225 H	437-1184 µg/g Cr Premeno-luteal
Urinary Free Diurnal Cortisol		
Free Cortisol	9.81	7.8-29.5 µg/g Cr (1st Morning)
Free Cortisol	50.58	23.4-68.9 µg/g Cr (2nd Morning)
Free Cortisol	11.68	6.0-19.2 µg/g Cr (Evening)

TEST NAME	RESULTS | 11/09/24	RANGE
Urinary Free Diurnal Cortisol		
Free Cortisol	9.31 H	2.6-8.4 µg/g Cr (Night)
Urinary Free Diurnal Cortisone		
Free Cortisone	48.40	31.6-91.6 µg/g Cr (1st Morning)
Free Cortisone	235.03 H	63.3-175.8 µg/g Cr (2nd Morning)
Free Cortisone	48.33	30.6-88.5 µg/g Cr (Evening)
Free Cortisone	43.06	15.5-44.7 µg/g Cr (Night)
Urinary Diurnal Melatonin MT6s		
Melatonin	31.18	18.0 - 40.9 µg/g Cr (1st Morning)
Melatonin	16.12	7.3 - 31.9 µg/g Cr (2nd Morning)
Melatonin	2.01	0.7 - 2.2 µg/g Cr (Evening)
Melatonin	1.61 L	1.7 - 11.1 µg/g Cr (Night)
Urinary Creatinine		
Creatinine (pooled)	1.11	0.3-2.0 mg/mL
Creatinine	1.89	0.3-2.0 mg/mL (1st morning)
Creatinine	0.27 L	0.3-2.0 mg/mL (2nd morning)
Creatinine	2.21 H	0.3-2.0 mg/mL (Evening)
Creatinine	1.18	0.3-2.0 mg/mL (Night)

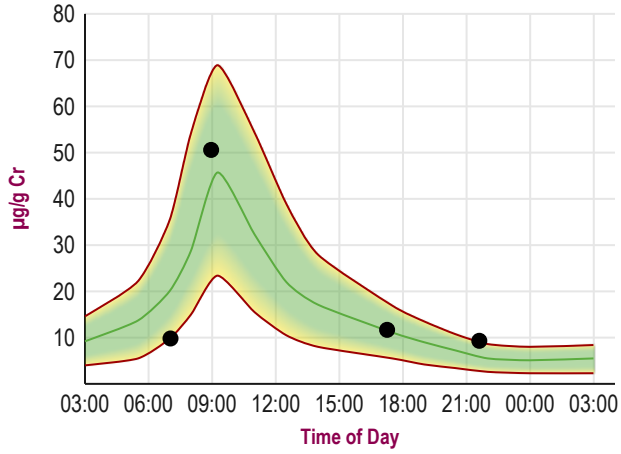
<dl *= Less than the detectable limit of the lab.* ***N/A*** *= Not applicable; 1 or more values used in this calculation is less than the detectable limit.* ***H*** *= High.* ***L*** *= Low.*

Therapies

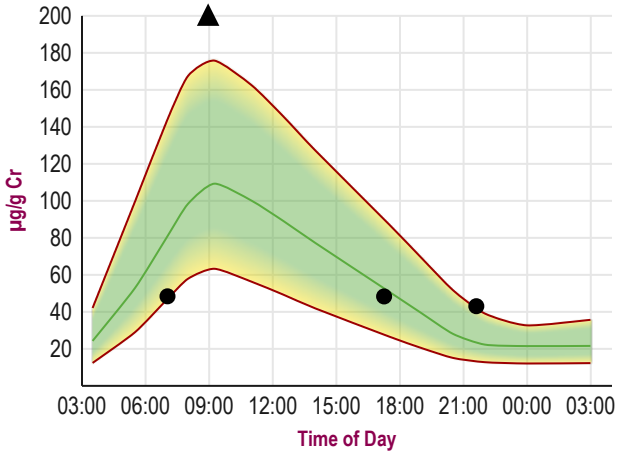
oral Estradiol (Pharmaceutical) (12 Hours Last Used); oral Progesterone (Pharmaceutical) (12 Hours Last Used)

Graphs

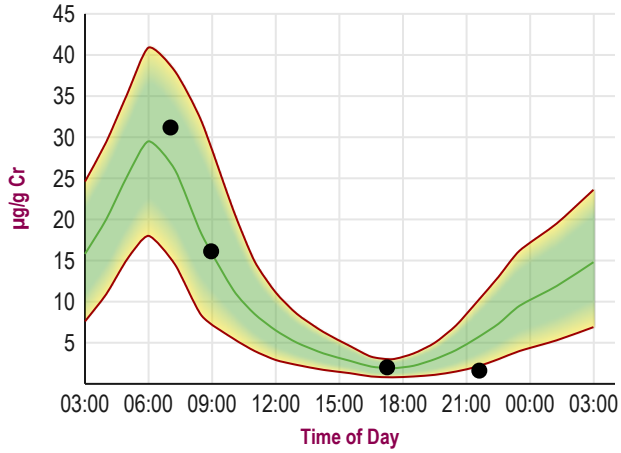
Urinary Free Cortisol



Urinary Free Cortisone



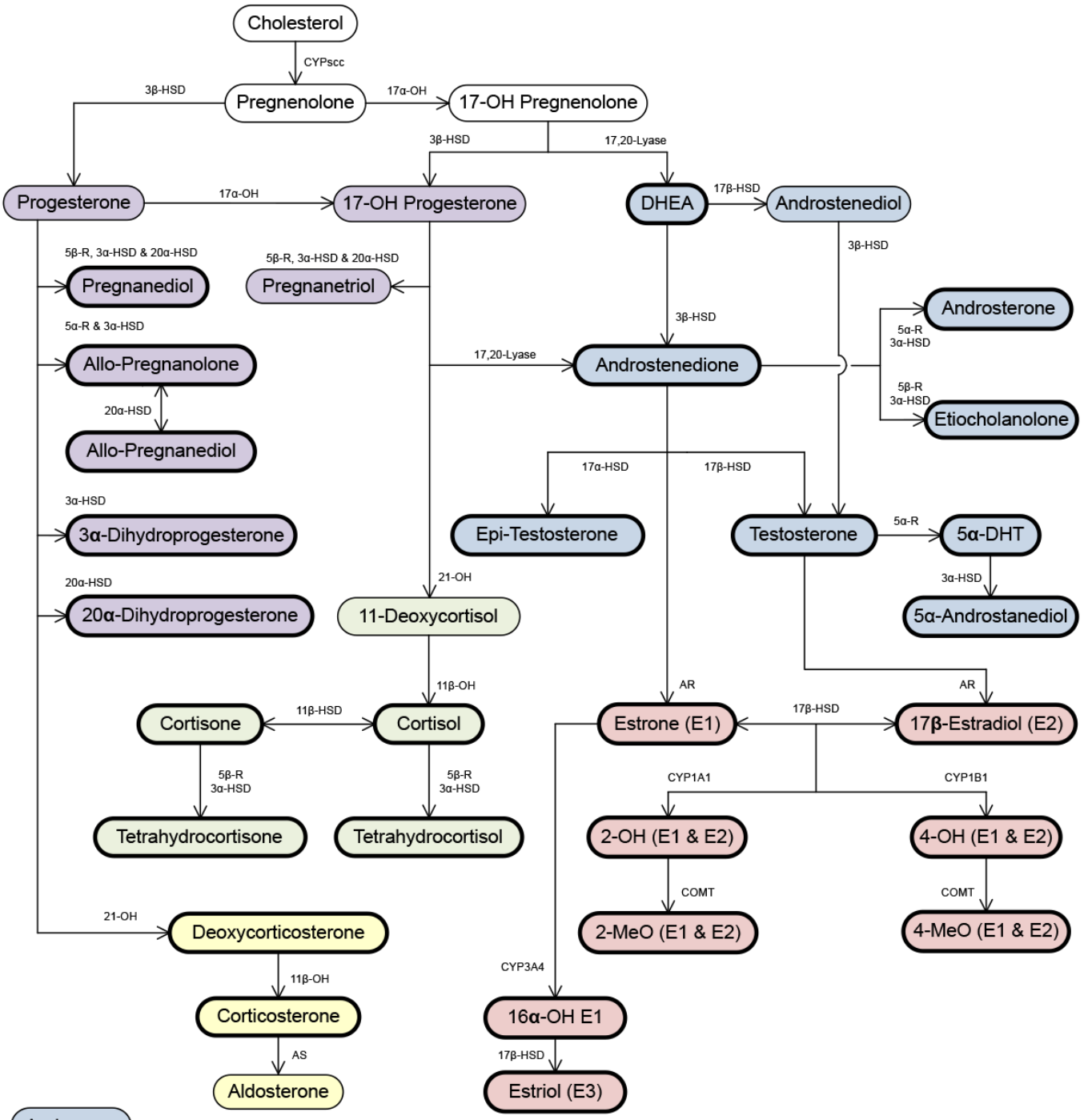
Urinary Melatonin (MT6s)



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 | 11/09/24
Estrogen / Progesterone Deficiency	44%
Estrogen Dominance / Progesterone Deficiency	49%
Low Androgens (DHEA/Testosterone)	47%
High Androgens (DHEA/Testosterone)	52%
Low Cortisol	40%
High Cortisol	38%
Hypometabolism	49%
Metabolic Syndrome	36%

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)

Urinary estradiol and estrone are much higher than urine reference ranges for a postmenopausal woman on oral estradiol therapy and are much higher than ranges seen during the luteal phase of premenopausal women. Estriol, a downstream product of estrone, is within normal range seen in postmenopausal women, indicating that very little estrone is being converted to the more inert estriol. High estradiol and estrone and low to normal estriol results in a very low estriol to estradiol + estrone ratio, which at least with endogenous estrogen production is considered a higher risk for breast cancer. This is not likely the case with oral estrogen therapy.

Very high urinary estradiol and estrone are due to the mode of estrogen delivery (oral) and the type of body fluid used to monitor the estrogens (urine). With oral dosing estradiol is absorbed into the hepatic vein from the GI tract where it passes through the liver and is metabolized mostly to inert sulfate and glucuronide estradiol and estrone conjugates, as seen in these results. These inert estrogens then enter the bloodstream and are rapidly eliminated in urine and bile. The total urinary excreted estrogen conjugates are then tested for estradiol by mass spectrometry following enzymatic removal of the sulfate and glucuronide conjugates in the laboratory. It is important to keep in mind that the urine estrogen conjugates are not biologically active in the circulation and are not representative of the free estrradiol circulating in the bloodstream.

Only about 5-10 percent of the estrogens delivered orally actually enter the systemic circulation as the parent estrogen (e.g. estradiol, estrone, estriol). For example, for a 1 mg (1000 micrograms) oral dose of estradiol or a 50:50 biestrogen (0.5 mg estradiol + 0.5 mg estriol) only about 25-50 micrograms of estradiol and estriol enter the systemic circulation as estradiol and estriol and are available to target tissues throughout the body. Most of the estradiol (approximately 98-99%) is bound up in the bloodstream by Sex Hormone Binding Globulin (SHBG), which itself is induced by oral, but not topical, estrogen therapy. Of this small fraction of "active" E2 and E3 in the circulation, only about 2% can enter tissues (bioavailable), bind cellular receptors, and induce an estrogen response. For this reason, a more accurate way to determine the true bioavailable fraction of orally delivered estradiol is to measure it in saliva. This is true also for orally delivered progesterone.

Very high urinary estrogens, and their catechol metabolites, are usually very high with oral estrogen delivery; however, the high estrogen is NOT usually associated with symptoms of estrogen excess (dominance), especially if the estrogen is complemented with a progestogen. If symptoms of estrogen dominance are, or become, problematic despite apparent high levels of these estrogens determined by urine testing, then the bioavailable fraction of these hormones is more than likely within physiological range. However, if symptoms of estrogen dominance are

problematic this likely indicates that the high urinary estrogens are reflective of high bioavailable estrogens that are not well balanced with progesterone.

It is also important to note that oral estrogens can lower the bioavailability estradiol itself as well as that of other hormones (progesterone, testosterone, cortisol, thyroid hormones) by increasing the hepatic production of hormone binding globulins, which include estrogen-androgen binding globulin, SHBG (Sex Hormone Binding Globulin), Cortisol Binding Globulin (CBG), and Thyroid Binding Globulin (TBG). These estrogen-inducible hepatic proteins are released into the bloodstream where they bind tightly and sequester the active hormone, reducing their tissue bioavailability. SHBG binds very tightly to testosterone, and less tightly to estradiol, reducing bioavailability of these hormones to tissues. Very high SHBG resulting from oral estrogen therapy can result in normal, or even high, serum, and urine, levels of testosterone, but very low levels of bioavailable testosterone. Thus, symptoms of androgen deficiency may be problematic despite normal androgen levels. High oral estrogen dosing can also be problematic because the high circulating levels of estrogens can down-regulate androgen receptors in target tissues and lead to symptoms of androgen deficiency. This is even more problematic when androgens such as testosterone, or its more potent metabolite, DHT, are low. Oral estrogens also lower the bioavailability of thyroid hormones (T3 and T4) by increasing the hepatic production of thyroid binding globulin. For this reason, thyroid therapy often needs to be increased with estrogen therapy.

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

The hydroxylated estrogens are all higher than the reference ranges with exception of 2-OH-E2, which is within normal reference range. Higher levels of the 4-hydroxyestrogens (4-OH-E2 and 4-OH-E1) infer a higher lifetime risk for breast cancer if the 4- hydroxyestrogens are not adequately methylated (see Methylated Hydroxyestrogens below) and eliminated.

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 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 may cause 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, 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-hydroxyestrogens (2-MeO-E2 and 2-MeO-E1) are higher than reference ranges and the ratio of the methoxyestrogens to the catechol estrogens (2-MeO-E2/2-OH-E2 and 2-MeO-E1/2-OH-E1) is high (beneficial). While the more toxic 4-OH-E2 is well methylated and the ratio of 4-MeO-E2/4-OH-E2 is within range (beneficial), 4-OH-E1 is not well methylated and the ratio of 4-MeO-E1/4-OH-E1 is lower than reference ranges. Adequate methylation of the hydroxyestrogens, and an associated high ratio of 4-hydroxylated estrogens to 4-methoxyestrogens (i.e. 4 MeO-E2/4-OH-E2 and 4-MeO-E1/4-OH-E1) is considered beneficial as this indicates the 4-hydroxyestrogens are rendered inert preventing them from oxidizing further to more dangerous 4-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.

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 a premenopausal woman. PgDiol is a metabolite and surrogate marker of serum progesterone. While Pgdiol is within expected luteal range, it is low relative to estradiol (low PgDiol/E2 ratio). This is often results in symptoms of estrogen dominance. Progesterone therapy to help balance and raise the PgDiol/E2 ratio often helps if symptoms of estrogen imbalance are problematic.

AlloP is another progesterone metabolite that is active as a neurotransmitter in the brain. AlloP that forms outside the CNS and circulates in the bloodstream freely enters the brain through the blood brain barrier. In the brain AlloP binds to GABAa receptors where it has a calming (anxiolytic) and sleep-inducing effect. 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: MINERALCORTICOID PRECURSORS

Deoxycorticosterone (DOC) is within reference range but corticosterone (CC) is higher than reference range. 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 mineralocorticoid aldosterone (see Steroid Hormone Cascade). Elevated CC might suggest that aldosterone could be low (expect low blood pressure) if these metabolites are not converted to aldosterone by aldosterone synthetase, and are accumulating instead (see http://omim.org/entry/203400). This is thought to be caused by a metabolic defect in aldosterone synthesis, which leads to accumulation of the precursor CC, low aldosterone, and associated symptoms of hypoaldosteronism (low blood pressure and faintness with standing up, frequent urination, salt wasting, hearing problems, fatigue, poor exercise tolerance and painful muscles and joints). Cortisol and down stream metabolites are usually within normal range with this defect in aldosterone synthesis.

Alternatively, a high CC could suggest that aldosterone is elevated (expect high blood pressure) if high CC is rapidly converting to aldosterone by aldosterone synthetase. Progesterone supplementation may result in higher levels of downstream DOC, CC, and/or aldosterone. In women the conversion of endogenous progesterone, and particularly high dose exogenous progesterone therapy, to DOC varies by up to 20-fold (MacDonald Endocrine Reviews 12: 372-401, 1991) p. 390), with higher conversion associated with higher risk for adverse symptoms (e.g. water retention, headaches, increased blood pressure).

ANDROGEN PRECURSORS (ANDROSTENEDIOL, DHEA)

The androgen precursors, androstenedione and DHEA, are lower than normal reference ranges for a premenopausal woman.

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.

Consider DHEA supplementation if low androgen symptoms are problematic. 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: TESTOSTERONE (T); EPI-TESTOSTERONE (EPI-T); DIHYDROTESTOSTERONE (DHT)

Testosterone (T) and its inert epimer, Epi-testosterone (Epi-T), are within expected ranges for a premenopausal woman. The downstream and more potent metabolite of T, dihydrotestosterone (DHT) is lower than reference range, indicating low 5-alpha reductase (5aR) activity (converts T to DHT) or inhibition of 5aR by plant antagonists (e.g. saw palmetto), pharmaceutical androgen antagonists (e.g. Finesteride), or natural progesterone..

T and Epi-T are created in about equal amounts from androstenedione, a downstream metabolite of DHEA (see Steroid Hormone Cascade). The ratio of T/Epi-T should be about 1 under normal circumstances. When testosterone is supplemented with any delivery system except topical, the T/Epi-T ratio increases, which reflects an increase in the exogenous testosterone, but not Epi-T, which represents endogenous production.

If symptoms of androgen deficiency are, or become, problematic, androgen therapy (DHEA or testosterone) is worth considering, assuming no contraindications. DHEA therapy increases both DHEAS and testosterone levels in women, but may also increase estrogens, which need to be countered with natural progesterone if increased by androgens.

5-ALPHA 3-ALPHA ANDROSTANEDIOL (ADIOL)

The downstream metabolite of DHT, 5-alpha 3-alpha androstanediol (Adiol), is within expected reference range. Adiol is considered a neuroactive steroid that can passively enter the brain from the bloodstream through the blood brain barrier.

Adiol binds to GABAa receptors in the brain and has a similar anxiolytic (calming) effect, albeit weaker than allopregnanolone. It also interacts with the dopaminergic pathways in the brain and is associated with the dopamine pleasure and reward pathway. Thus, low levels of Adiol are more likely to be associated with conditions/symptoms common to low dopamine, and high levels with high dopamine. Fibromyalgia and chronic fatigue syndrome (CFS) are common in individuals with low dopamine, as are symptoms of brain fog, achy muscles, and excessive fatigue.

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 CORTISONE (E)

Urinary free cortisol (F) and cortisone (E) are within/near expected reference ranges throughout the day and are following a normal circadian rhythm. A normal daily output of cortisol is essential to maintain normal metabolic activity, help regulate steady-state glucose levels (important for brain function and energy production), and optimize immune function. When cortisol levels are within normal range under situations of excessive stress this usually indicates that the adrenal glands are overworking to keep up with the demands of the stress(ors). These conditions are most commonly caused by one or more of the following: psychological stress (emotional), physical insults (surgery, injury), diseases (cancer, diabetes), chemical exposure (environmental pollutants, excessive medications), and/or pathogenic infections (bacteria, viruses and fungi).

When these stressors persist, or become worse, over a period of time this can lead to adrenal exhaustion, low cortisol levels, and symptoms

which often overlap with those of high cortisol (e.g. fatigue, sleep disturbances, low thyroid symptoms) or are more characteristic only of low cortisol (e.g. allergies-immune dysfunction, chemical sensitivity, and sugar craving due to hypoglycemia). For additional information about strategies to support adrenal health and reduce stress(ors) that can lead to high or low cortisol, the following books are worth reading: "Adrenal Fatigue; The 21st Century Stress Syndrome", 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

Urinary creatinine is within normal reference ranges throughout the day, based on testing diurnal 2x, 4x, or 6x urine collections.
Creatinine values slightly lower than range usually indicate overly dilute urine from excessive water intake shortly before collection, or not spacing collection of multiple urine samples by at least 2 hr (most problematic in second morning urine collection). Creatinine slightly higher than range is usually due to inadequate hydration.
Extreme low or high values may be caused by kidney or other metabolic disorders (e.g. metabolic syndrome and diabetes).