Accession # 00280402
Male Sample Report
123 A Street
Sometown , CA 90266

Ordering Provider:
Precision Analytical

DOB: 1966-05-06
Age: 50
Gender: Male

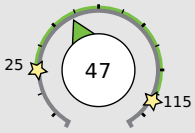
Collection Times:
2016-10-01 06:01AM
2016-10-01 08:01AM
2016-10-01 06:01PM
2016-10-01 10:01PM

Hormone Testing Summary

Key (how to read the results):

Sex Hormones

Estradiol(E2)



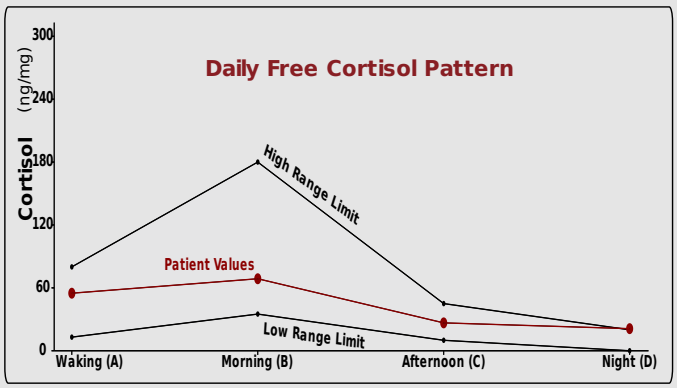
Testosterone

Testosterone

Age	Range
18-25	50-115
26-40	40-95
41-60	30-80
>60	25-60

Adrenal Hormones

See pages 4 and 5 for a more complete breakdown of adrenal hormones



Total DHEA Production

Age	Range
20-39	3000-5500
40-60	2000-4000
>60	1000-2500

Total DHEA Production
(DHEAS + Etiocholanolone + Androsterone)

24hr Free Cortisol
(A+B+C+D)

cortisol metabolism

Metabolized Cortisol (THF+THE)
(Total Cortisol Production)

Free cortisol best reflects tissue levels. Metabolized cortisol best reflects total cortisol production.

The following videos (which can also be found on the website under the listed names along with others) may aid your understanding:
DUTCH Complete Overview Estrogen Tutorial Male Androgen Tutorial Cortisol Tutorial

PLEASE BE SURE TO READ BELOW FOR ANY SPECIFIC LAB COMMENTS. More detailed comments can be found on page 9.

Accession # 00280402
Male Sample Report
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Sex Hormones and Metabolites

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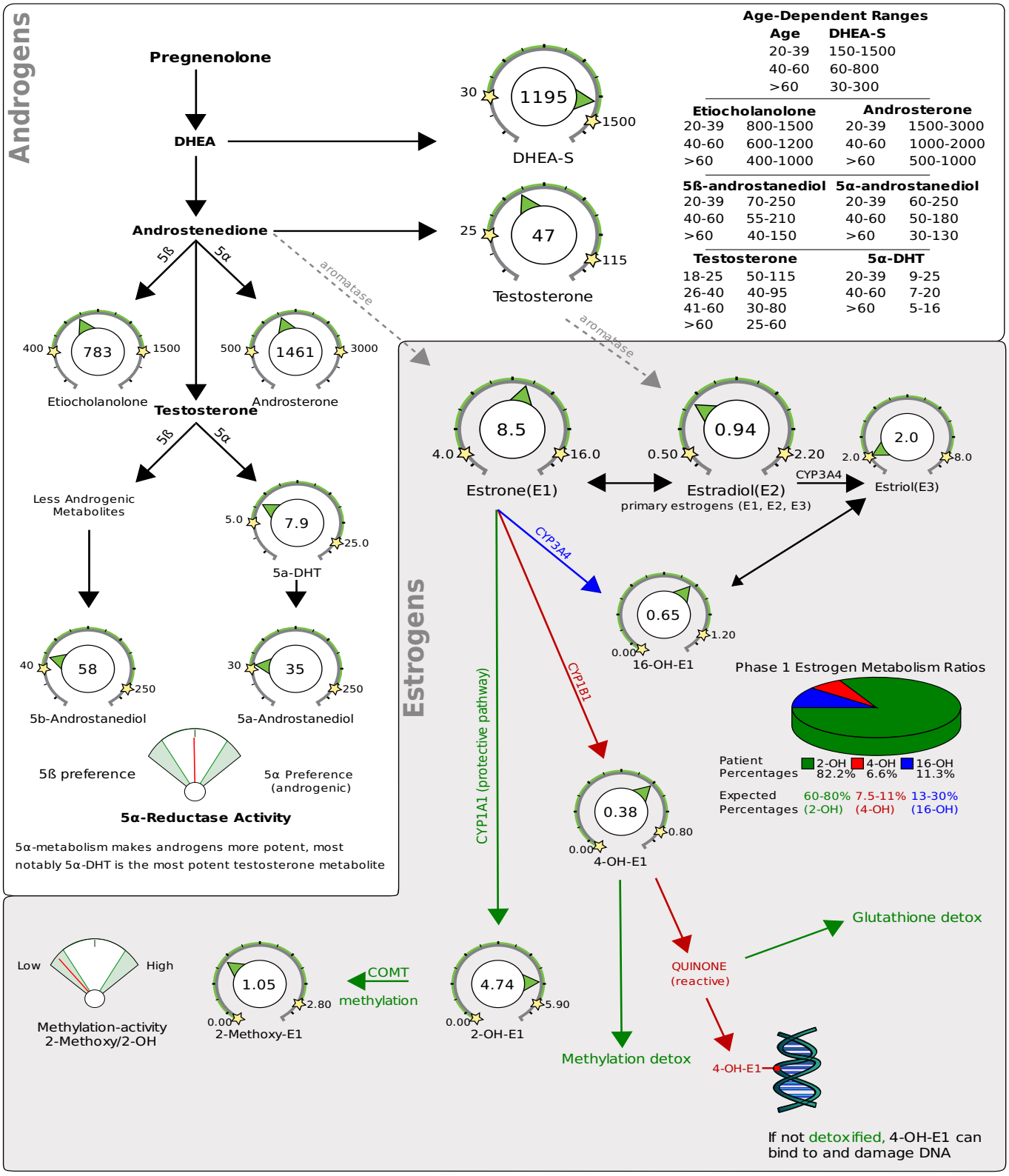
2016-10-01 10:01PM

Category	Test		Result	Units	Normal Range
Progesterone Metabolites (Urine)					
	b-Pregnanediol	Low end of range	107.0	ng/mg	75 - 400
	a-Pregnanediol	Low end of range	40.0	ng/mg	20 - 130
Estrogens and Metabolites (Urine)					
	Estrone(E1)	Within range	8.5	ng/mg	4 - 16
	Estradiol(E2)	Within range	0.94	ng/mg	0.5 - 2.2
	Estriol(E3)	Low end of range	2.0	ng/mg	2 - 8
	2-OH-E1	High end of range	4.74	ng/mg	0 - 5.9
	4-OH-E1	Within range	0.38	ng/mg	0 - 0.8
	16-OH-E1	Within range	0.65	ng/mg	0 - 1.2
	2-Methoxy-E1	Within range	1.05	ng/mg	0 - 2.8
	2-OH-E2	Within range	0.28	ng/mg	0 - 0.6
	4-OH-E2	Within range	0.1	ng/mg	0 - 0.3
	2-Methoxy-E2	Within range	0.5	ng/mg	0 - 0.8
	Total Estrogen	Within range	19.14	ng/mg	10 - 34
Androgens and Metabolites (Urine)					
	DHEA-S	Within range	1195.0	ng/mg	30 - 1500
	Androsterone	Within range	1461.0	ng/mg	500 - 3000
	Etiocholanolone	Within range	783.0	ng/mg	400 - 1500
	Testosterone	Within range	46.8	ng/mg	25 - 115
	5a-DHT	Low end of range	7.9	ng/mg	5 - 25
	5a-Androstanediol	Low end of range	35.4	ng/mg	30 - 250
	5b-Androstanediol	Low end of range	57.7	ng/mg	40 - 250
	Epi-Testosterone	Low end of range	35.6	ng/mg	25 - 115

Hormone metabolite results from the previous page are presented here as they are found in the steroid cascade. See the Provider Comments for more information on how to read the results.



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Male Sample Report
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Adrenal

Ordering Provider:
Precision Analytical

DOB: 1966-05-06
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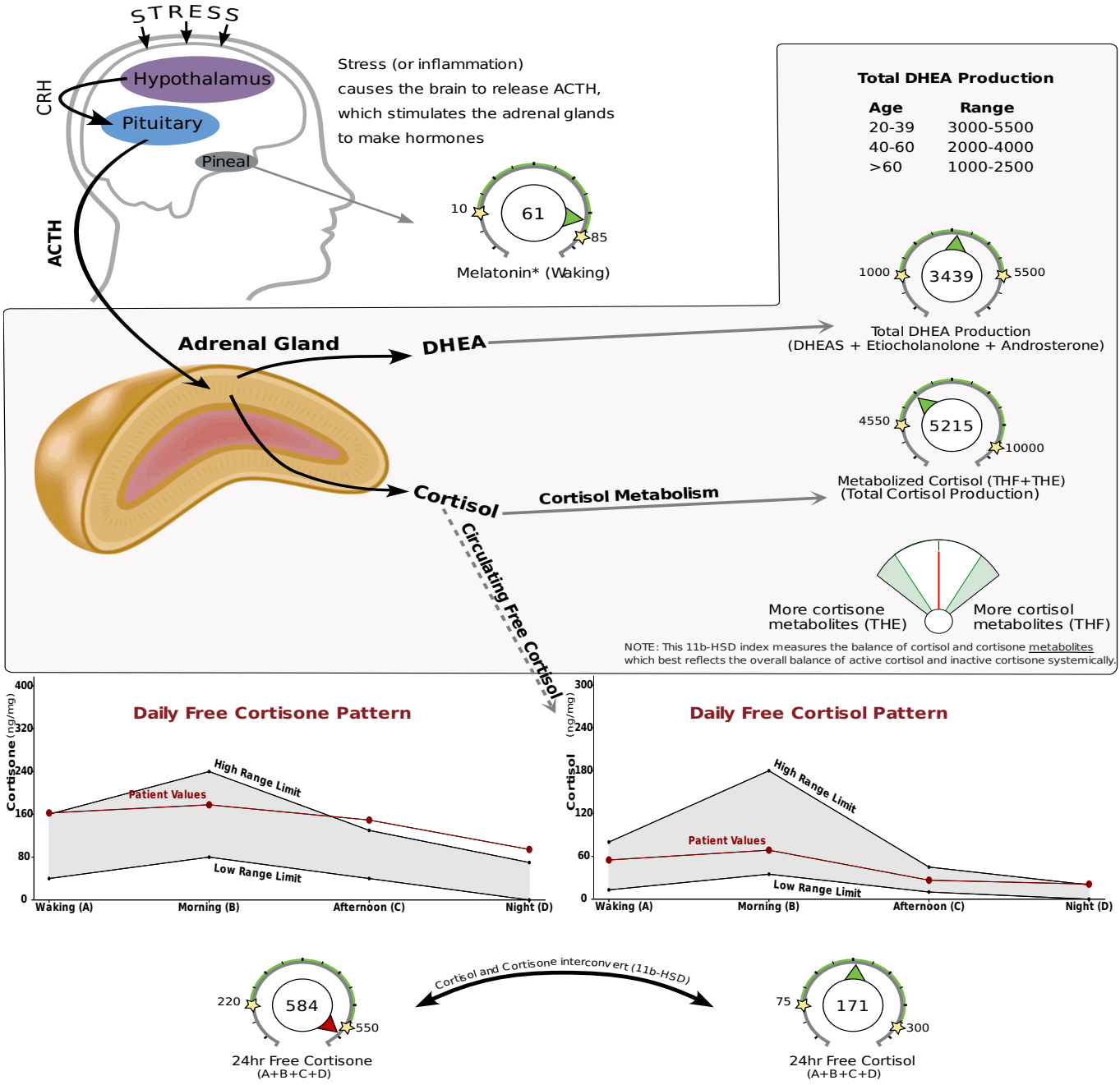
Gender: Male

Collection Times:
2016-10-01 06:01AM
2016-10-01 08:01AM
2016-10-01 06:01PM
2016-10-01 10:01PM

Category	Test		Result	Units	Normal Range
Creatinine (Urine)					
	Creatinine A (Waking)	Within range	1.1	mg/ml	0.3 - 3
	Creatinine B (Morning)	Within range	0.93	mg/ml	0.3 - 3
	Creatinine C (Afternoon)	Within range	0.9	mg/ml	0.3 - 3
	Creatinine D (Night)	Within range	1.13	mg/ml	0.3 - 3
Daily Free Cortisol and Cortisone (Urine)					
	Cortisol A (Waking)	Within range	54.9	ng/mg	13 - 80
	Cortisol B (Morning)	Within range	68.7	ng/mg	35 - 180
	Cortisol C (Afternoon)	Within range	26.6	ng/mg	10 - 45
	Cortisol D (Night)	Above range	21.1	ng/mg	0 - 20
	Cortisone A (Waking)	Above range	162.6	ng/mg	40 - 160
	Cortisone B (Morning)	Within range	177.8	ng/mg	80 - 240
	Cortisone C (Afternoon)	Above range	149.3	ng/mg	40 - 130
	Cortisone D (Night)	Above range	94.4	ng/mg	0 - 70
	24hr Free Cortisol	Within range	171.3	ng/mg	75 - 300
	24hr Free Cortisone	Above range	584.1	ng/mg	220 - 550
Cortisol Metabolites and DHEA-S (Urine)					
	a-Tetrahydrocortisol (a-THF)	Within range	419.0	ng/mg	175 - 700
	b-Tetrahydrocortisol (b-THF)	Low end of range	1961.0	ng/mg	1750 - 4000
	b-Tetrahydrocortisone (b-THE)	Low end of range	2835.0	ng/mg	2350 - 5800
	Metabolized Cortisol (THF+THE)	Low end of range	5215.0	ng/mg	4550 - 10000
	DHEA-S	Within range	1195.0	ng/mg	30 - 1500



The first value reported (Waking "A") for cortisol is intended to represent the "overnight" period. When patients sleep through the night, they collect just one sample. In this case, the patient did not report waking up during the night to collect a sample, so the "Waking (A)" cortisol and cortisone values should accurately represent the entirety of the overnight period.
The first value reported (Waking "A") for cortisol is intended to represent the "overnight" period. When patients sleep through the night, they collect just one sample. In this case, the patient woke during the night and collected (see the top of the report for the times collected). We call this value "A1" and the value from the sample collected at waking "A2." These values are used to create a "time-weighted average" to create the "A" value. The individual values are listed here for your use:
The middle-of-the-night "A1" sample registered a cortisol value of 9.9ng/mg.
The waking "A2" sample registered a cortisol value of 87.1ng/mg.
These two values are averaged together, taking into account the amount of time each one represents, to create the "A" value of approximately 54.9ng/mg that you will see on the report.
In this particular case, this A2 value is larger than the sample (collected two hours after waking) expected to have the highest cortisol value. Cortisol levels typically rise sharply *after* waking thanks to the cortisol awakening response. In a case like this where the waking sample (A2) shows higher levels, this cortisol awakening response may have happened while the patient was in bed before rising.

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Organic Acid Tests (OATs)

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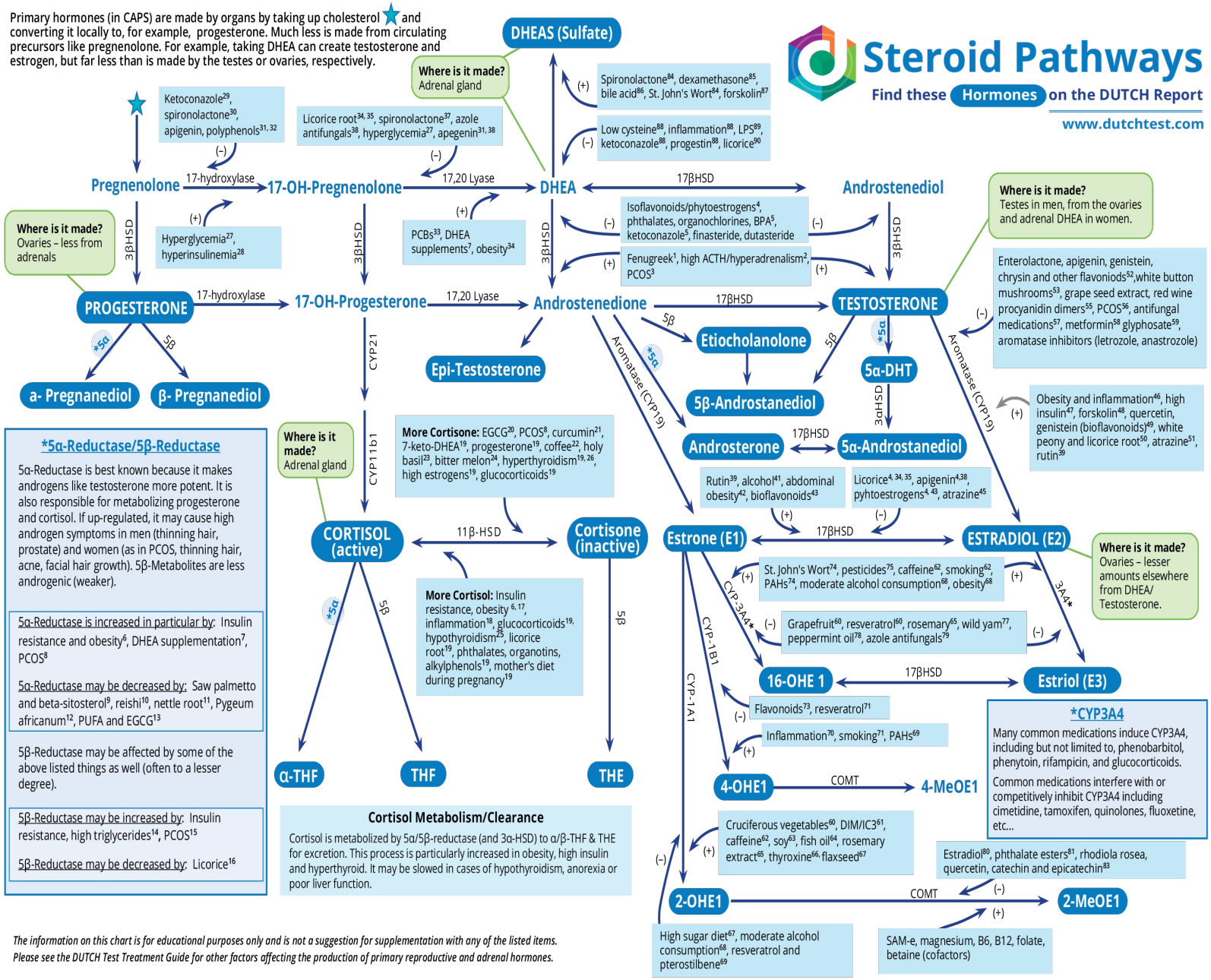
Collection Times:
2016-10-01 06:01AM
2016-10-01 08:01AM
2016-10-01 06:01PM
2016-10-01 10:01PM

Category	Test		Result	Units	Normal Range
Nutritional Organic Acids					
Vitamin B12 Marker (may be deficient if high) - (Urine)					
	Methylmalonate (MMA)	Within range	1.4	ug/mg	0 - 3.5
Vitamin B6 Markers (may be deficient if high) - (Urine)					
	Xanthurenate	Within range	0.8	ug/mg	0.2 - 1.9
	Kynurenate	Within range	3.5	ug/mg	1 - 6.6
Glutathione Marker (may be deficient if low or high) - (Urine)					
	Pyroglutamate	Low end of range	44.1	ug/mg	38 - 83
Neurotransmitter Metabolites					
Dopamine Metabolite - (Urine)					
	Homovanillate (HVA)	Low end of range	5.3	ug/mg	4 - 16
Norepinephrine/Epinephrine Metabolite - (Urine)					
	Vanilmandelate (VMA)	Low end of range	3.1	ug/mg	2.5 - 7.5
Melatonin (*measured as 6-OH-Melatonin-Sulfate) - (Urine)					
	Melatonin* (Waking)	Within range	61.2	ng/mg	10 - 85
Oxidative Stress / DNA Damage, measured as 8-Hydroxy-2-deoxyguanosine (8-OHdG) - (Urine)					
	8-OHdG (Waking)	Within range	2.8	ng/mg	0 - 8.8



Precision Analytical (Dawn Huo, Ph.D., Lab Director)
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Male Sample Report
FINAL REPORT
01/28/2021

Clinical Support Overview

Thank you for choosing DUTCH for your functional endocrinology testing needs! We know you have many options to choose from when it comes to functional endocrinology evaluation, and we strive to offer the best value, the most up-to-date testing parameters and reference ranges, and the greatest clinical support to ensure the most accurate results.

Please take a moment to read through the Clinical Support Overview below. These comments are specific to the patient's lab results. They detail the most recent research pertaining to the hormone metabolites, treatment considerations, and follow-up recommendations. These comments are intended for educational purposes only. Specific treatment should be managed by a healthcare provider.

Alert comments:

How to read the DUTCH report

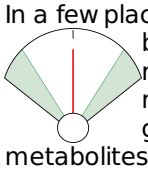
This report is not intended to treat, cure or diagnose any specific diseases. The graphic dutch dials in this report are intended for quick and easy evaluation of which hormones are out of range. Results below the left star are shaded yellow and are below range (left). Results between the stars and shaded green are within the reference range (middle). Results beyond the second star and shaded red are above the reference range (right). Some of these hormones also change with age, and the age-dependent ranges provided should also be considered.

Low Example

Normal Example

High Example

In a few places on the graphical pages, you will see fan-style gauges. For sex hormones, you will see one for the balance between 5a/5b metabolism as well as methylation. For adrenal hormones, you will see one to represent the balance between cortisol and cortisone metabolites. These indexes simply look at the ratio of hormones for a preference. An average or "normal" ratio between the two metabolites (or groups of metabolites) will give a result in the middle (as shown here). If the ratio between the metabolites measured is "low" the gauge will lean to the left and similarly to the right if the ratio is higher than normal.



Patient or Sample Comments

Throughout the provider comments you may find some comments specific to your situation or results. These comments will be found in this section or within another section as appropriate. Comments in other sections that are specific to your case will be in **bold**.

Note: The dates listed on the samples imply that they were older than our allowed 3 weeks when they were received. The instructions ask that patients freeze or refrigerate samples if they are to be held. If that is not the case, the free cortisol and cortisone levels may drop somewhat over time if the samples are too old. Other hormones tested are stable for more than 12 weeks at room temperature. Samples that are refrigerated or frozen are stable for months.

Androgen Metabolism

- **Androgen Metabolites: DHEA**

DHEA and androstenedione are made almost exclusively by the adrenal gland (although a smaller amount is made in the testes). These hormones appear in urine as DHEA-S (DHEA-Sulfate), androsterone and etiocholanolone.

DHEA peaks for men in their 20’s with a slow decline expected with age. DHEA mainly circulates throughout the body as DHEA-s, with interconversion to active DHEA as it reaches various tissues. DHEA is a weak androgen and will predominately convert to androstenedione, which will then convert to testosterone or aromatize to estrone. DHEA-s is made by sulfation, has a much longer half-life than DHEA and lacks a diurnal rhythm, which is why it is considered the best way to assess DHEA levels in the body. DHEA-s levels can be affected both by the total production as well as by the body’s ability to sulfate DHEA.

The best way to assess the total production of DHEA is to add up these three metabolites. As DHEA production decreases quite significantly with age, we provide the age-dependent ranges.

The Total DHEA Production (page 1) was about 3,439ng/mg which is within the overall range and also within the age-dependent range for this patient. This implies that the adrenal glands are producing appropriate DHEA levels.

- **Androgen Metabolites: Testosterone**

The DUTCH test measures the total of testosterone glucuronide and testosterone sulfate. These conjugates of testosterone are formed mostly from bioavailable testosterone that undergoes phase 2 metabolism to make it ready for urine excretion.

Testosterone glucuronide is mostly made by the UGT2B17 enzyme, which also makes the glucuronide forms of

5a-DHT and 5b-androstanediol. Genetic variants of this enzyme reduce the urinary levels of these hormones without affecting serum levels. The genetic variants of UGT2B17 vary in the population from 7-80% (variation dependent on genetic ancestry, with the highest rates in those of Asian descent). Heterozygous individuals show milder reductions in urinary testosterone than homozygous. For this reason, low and very low levels of urinary testosterone should be confirmed with serum testing before treatment is applied. Serum testing can include free and total testosterone and SHBG.

The testes make most of the male's testosterone. Levels tend to be their highest at around 20 years of age and start to decline when men get into their 30's. Levels continue to drop as men age. Testosterone is needed for building bones and muscle mass, regulating body fat distribution and in the production of sperm and red blood cells. Testosterone is also important for libido and downstream production of modest amounts of estrogen.

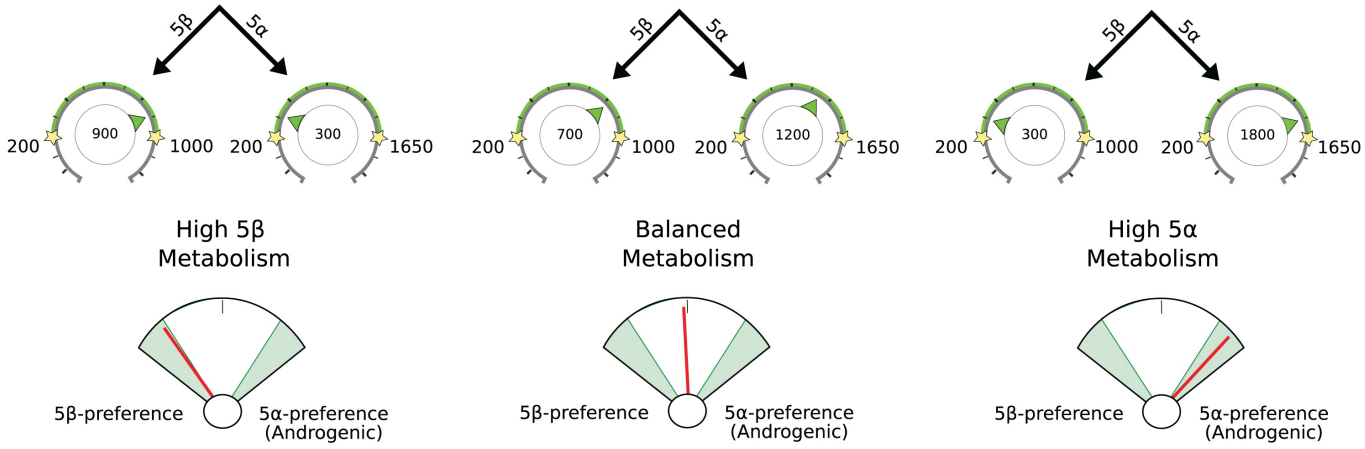
Age dependent ranges are provided for all androgens as some decline is seen with age. Testosterone levels in healthy men vary widely so it is suggested that these ranges be interpreted with caution and consideration of symptoms. In addition, because estrogen also supports libido, erections and healthy weight management, estrogen levels should be considered along with the testosterone levels when assessing symptoms.

- **Andogen Metabolites: 5a-reductase versus 5b-reductase**

5a-reductase converts testosterone into 5a-DHT (DHT), which is even more potent (~3x) than testosterone. High levels of DHT can lead to symptoms associated with too much testosterone (thinning scalp hair, acne, etc.) and may also be associated with prostate issues in older men. However, 5aDHT plays an integral role in supporting bone, muscle and connective tissue integrity and improving brain health through the upregulation of dopamine, which can improve mood and libido.
Metabolites created down the 5b-pathway are significantly less androgenic than their 5a counterparts.

The fan-style gauge below the hormones shows the 5a or 5b preference based on the balance between etiocholanolone (5b) and androsterone (5a) as well as 5a-androstanediol and 5b-androstanediol. The gauge shows the relative ratio of 5a to 5b products but does not express the absolute value of DHT or if 5a-reductase inhibition is or is not indicated. Consider symptoms and look at the total androgen levels if high androgen symptoms are a concern.

Example of how to read fan-style gauge for 5a-reductase activity:



You will also see levels of epi-testosterone, which is not androgenic like testosterone. It happens to be produced in about the same concentrations as testosterone (this is an approximate relationship). This can be helpful when assessing the validity of urinary testosterone testing in an individual patient. If epi-testosterone is much higher than testosterone, serum testosterone assessment should considered before initiated therapy for low testosterone. Epi-testosterone is suppressed when exogenous testosterone is given, which can serve as a proxy for assessing endogenous testosterone production which can be obscured by the exogenous hormone administration.

Estrogen Metabolism

When evaluating estrogen levels, it is important to assess the following:

- **The status (low, normal or high?) of estrogen production:**

Levels of the primary estrogen, estradiol (the strongest estrogen), as well as "total estrogens" may be considered.

- **Phase I Metabolism:**

Estrogen is metabolized (primarily by the liver) down three phase I pathways. The 2-OH pathway is considered the safest because of the anti-cancer properties of 2-OH metabolites. Conversely, the 4-OH pathway is considered the most genotoxic as its metabolites can create reactive products that damage DNA. The third pathway, 16-OH creates the most estrogenic of the metabolites (although still considerably less estrogenic than estradiol) - 16-OH-E1.

When evaluating phase I metabolism, it may be important to look at the ratios of the three metabolites to see which pathways are preferred relative to one another. It may also be important to compare these metabolites to the levels of the parent hormones (E1, E2). If the ratios of the three metabolites are favorable but overall levels of metabolites are much lower than E1 and E2, this may imply sluggish phase I clearance of estrogens, which can contribute to high levels of E1 and E2.

The pie chart will assist you in comparing the three pathway options of phase I metabolism compared to what is "normal." 2-OH metabolism can be increased by using products containing D.I.M. or I-3-C. These compounds are found (or created from) in cruciferous vegetables and are known for promoting this pathway.

- **Methylation (part of Phase II Metabolism) of estrogens:**

After phase I metabolism, both 4-OH and 2-OH (not 16-OH) estrogens can be deactivated and eliminated by methylation. The methylation-activity index shows the patient's ratio of 2-Methoxy-E1 / 2-OH-E1 compared to what is expected. Low methylation can be caused by low levels of nutrients needed for methylation and/or genetic abnormalities (COMT, MTHFR). The COMT enzyme responsible for methylation requires magnesium and methyl donors. Deficiencies in folate or vitamin B6 or B12 can cause low levels of methyl donors. MTHFR genetic defects can make it more difficult for patients to make sufficient methyl donors. Genetic defects in COMT can make methylation poor even in the presence of adequate methyl donors.

Progesterone Metabolism

Male progesterone is synthesized in the testes and, to a lesser degree, in the adrenal glands. It’s role in men’s health is not well understood, although progesterone is known to be involved in sperm activation. In healthy men, progesterone is positively correlated to markers of inflammation.

Metabolites of progesterone are measured in urine, including 5b-pregnanediol and 5a-pregnanediol. 5b-pregnanediol is inactive in the body but is the major metabolite of progesterone. 5a-pregnanediol is often a metabolite of more interest, as it can cross the blood brain barrier and up-regulate GABA activity and is considered neuroprotective to the brain. Both taken together represent the major metabolic end points for progesterone and can be used to represent total progesterone production.

The patient's progesterone metabolites are in range indicating normal production.

DUTCH Adrenal

The HPA-Axis refers to the communication and interaction between the hypothalamus (H) and pituitary (P) in the brain down to the adrenal glands (A) that sit on top of your kidneys. When cortisol is needed in the body, the hypothalamus releases cortisol releasing hormone (CRH) and the pituitary responds by releasing adrenocorticotropic releasing hormone (ACTH), which is the signal to the adrenal gland to release cortisol, DHEA and DHEA-s. It is these adrenal hormones that are assessed on the DUTCH test to understand the patient’s HPA axis.

The cortisol awakening response is a complex interaction between the HPA axis and the hippocampus, where ACTH normally surges right after waking leading to the day’s highest levels of cortisol. This signal is considered by researchers to be separate from the regular circadian rhythm (the smooth transition from lower cortisol at night to modestly higher cortisol in the morning) and to reflect the person’s anticipation of stress during the day, some psychosocial factors such as depression or anxiety and their metabolic state. The waking surge in cortisol helps with energy, focus, morning blood sugar and immune regulation.

As the day progresses, ACTH declines and subsequent cortisol decreases throughout the day, so it is low at night for sleep. This cycle starts over the next morning.

Free cortisol provides negative feedback to CRH & ACTH. When free cortisol is too low, ACTH will surge. ACTH will also surge when a physical or psychological stressor occurs.

Only a small fraction of cortisol is "free" and bioactive. The “free” cortisol is what the person feels in terms of energy and focus. Free cortisol is also what feeds back to the hypothalamus and pituitary gland for ACTH and cortisol regulation. The free cortisol daily pattern is very useful for understanding cortisol and its interaction with the patient’s symptoms throughout the day. However, because only a fraction of the cortisol is bioactive, when considering treatments that affect the whole HPA axis, including DHEA, it is essential to measure metabolized

cortisol to get a bigger picture.
In urine, we can measure both the total metabolized cortisol (THF) and total metabolized cortisone (THE) excreted throughout the day. These two components better represent the total cortisol production from the adrenal glands than the free cortisol alone. Outside of the HPA axis, metabolism of cortisol occurs with the help of thyroid hormone in the liver. A significant amount of cortisol is also metabolized in adipose tissue.

To best determine total adrenal production of cortisol throughout the day it is important to assess both metabolized cortisol and free cortisol.

When evaluating cortisol levels, it is important to assess the following:

- **The daily pattern of free cortisol throughout the day, looking for low and high levels:**

Abnormal results should be considered along with related symptoms. Remember that with urine results, the "waking" sample reflects the night's total for free cortisol. The sample collected two hours after waking captures the cortisol awakening response, which is typically the time with the most cortisol secretion.

- **The sum of the free cortisol as an expression of the overall tissue cortisol exposure:**

This total of four free cortisol measurements is the best way to assess the total of free cortisol throughout the day, and this result correlates reasonably well to a true 24-hour urine free cortisol. Do be aware that this measurement does not consider transitory shifts in cortisol in the late morning or early afternoon. This number is calculated from the simple addition of the 4 points, so if a single point is very high or very low, it may skew the number up or down especially if it is the morning "B" point, as it is weighted more heavily in the reference range.

- **The total level of cortisol metabolites:**

This total of four free cortisol measurements is the best way to assess the total of free cortisol throughout the day, and this result correlates reasonably well to a true 24-hour urine free cortisol. Do be aware that this measurement does not consider transitory shifts in cortisol in the late morning or early afternoon. This number is calculated from the simple addition of the 4 points, so if a single point is very high or very low, it may skew the number up or down especially if it is the morning "B" point, as it is weighted more heavily in the reference range.

Overall cortisol levels are appropriate as both free and metabolized cortisol levels are within range. If the diurnal pattern of the free cortisol is as expected, this implies normal HPA-Axis cortisol production.

- **A potential preference for cortisol or cortisone (the inactive form):**

Looking at the comparison between the total for free cortisol and free cortisone is NOT the best indication of a person's preference for cortisol or cortisone. The kidney converts cortisol to cortisone in the local tissue. This localized conversion can be seen by comparing cortisol (free) and cortisone levels. To see the patient's preference systemically, it is best to look at which *metabolite* predominates (THF or THE). This preference can be seen in the fan style gauge. This is known as the 11b-HSD index. The enzyme 11b-HSD II converts cortisol to cortisone in the kidneys, saliva gland and colon. 11b-HSD I is more active in the liver, fat cells and the periphery and is responsible for reactivating cortisone to cortisol. Cortisol and cortisone are then metabolized by 5a-reductase to become tetrahydrocortisol (THF) and tetrahydrocortisone (THE) respectively.

Nutritional Organic Acids

Organic acids are the metabolic byproducts of cellular activity in the body. Organic acid production varies by the individual and can be influenced by foods, environmental toxins, medications or supplements, nutrient status, genetics and more. Organic acids begin to build up when a nutrient cofactor or mineral is not present for a specific reaction to occur. As a response, byproducts (organic acids) build up and can be measured in urine. On the DUTCH test, the organic acids we measure were chosen due to their specific roles in the metabolism and function of enzymes required for hormone and adrenal health and function. As industry standard dictates, the organic acids are measured from the waking sample.

Methylmalonate (MMA)

Methylmalonic acid is a metabolic byproduct of the Citric Acid Cycle (Krebs cycle). Methylmalonic acid requires adenosylcobalamin for conversion to succinyl-CoA and onto ATP synthesis. If someone does not absorb enough B12 from their diet due to low B12-rich food consumption, low stomach acid, has an autoimmune disorder impacting Intrinsic Factor in the gut (required for B12 absorption), or has an MUT enzyme SNP (required for conversion of MMA to Succinyl coA, dependent on adenosylcobalamin) then MMA will build up. Vitamin B12 is required for COMT activity (estrogen methylation, dopamine breakdown) and PNMT activity (the enzyme that takes norepinephrine to epinephrine), but is also critical for memory, energy production (ATP synthesis), gait and more. When MMA is high, consider supporting B12 through foods, digestive support or supplementation.

Xanthurenate & Kynurenate

Xanthurenate and kynurenate are metabolic byproducts in the production of tryptophan to NAD in the liver. If either xanthurenate or kynurenate build up in the urine, it can indicate a need for vitamin B6. This need is amplified if BOTH markers are elevated, and often indicates a more severe deficiency of vitamin B6. Vitamin B6 is critical as a co-factor to over 100 important reactions that occur in the human body and is stored in the highest concentration in muscle tissue.
Tryptophan is converted to NAD by the liver and one of the steps in this pathway requires B6. When B6 is insufficient, xanthurenate is made instead. Xanthurenate can also bind to iron and create a complex that increases DNA oxidative damage resulting in higher 8-OHdG levels. If both the xanthurenate and 8OhdG levels are elevated, there is likely an antioxidant insufficiency.
Kynurenate may also become elevated when patients are B6 deficient because of a different, possibly less B6 dependent pathway. While there is always some tryptophan going down the kynurenine pathway towards NAD, and possibly xanthurenate, this process is up regulated by inflammation, estrogen and cortisol elevations. If levels of estrogen or cortisol are high, it may exacerbate kynurenic acid and increase the need for vitamin B6. As the Xanthurenate and Kynurenate pathways lead to biomarkers with other influence in the body, elevations in these markers may not always agree.

Pyroglutamate

Pyroglutamate is an intermediate in glutathione recycling and production. Glutathione requires the amino acids cysteine, glycine and glutamate for production. If the body cannot convert pyroglutamate forward to glutathione, it will show up elevated in the urine. High pyroglutamate is an established marker for glutathione deficiency. Remember that glutathione is one of the most potent antioxidants in the human body and is especially important in getting rid of toxins including the reactive quinone species formed by 4-OH-E1 and 4-OH-E2. This reactive species can damage DNA if not detoxified by either methylation or glutathione.
Some have reported that low pyroglutamate may also be indicative of a need for glutathione; however, this is not established in the scientific literature.
Note: Pyroglutamate in the urine can also be elevated with Italian cheese consumption. Italian Cheeses (parmesan, etc.) may transiently increase pyroglutamate because they use a thermophilic lactobacilli to ripen the cheese- which our gut breaks down into pyroglutamate. This is not clinically significant and only reflects that they ate this style of cheese (if applicable).

Neurotransmitter Metabolites

Neurotransmitters are chemical signals produced by neurons in tissues throughout the body that act as chemical messengers that influence mood, cortisol, heart rate, appetite, muscle contraction, sleep and more. Measuring neurotransmitters directly is difficult because of their instability, and their direct urinary measurements are controversial with respect to how well they reflect the body's level of these neuro-hormones.

Each of the neurotransmitters assessed on the DUTCH test (dopamine, norepinephrine/epinephrine) can be assessed indirectly by measuring their urine metabolites (HVA and VMA respectively). While these metabolites are not a perfect reflection of what is going on in the brain, the scientific literature does affirm their use for a good representation of overall levels of these neurotransmitters in the body.

Homovanillate (HVA)

Homovanillate (HVA) is the primary metabolite of dopamine, a brain and adrenal neurotransmitter that comes from tyrosine (with BH4 and iron as co-factors). Dopamine goes on to create norepinephrine and epinephrine (adrenaline).

Low levels of dopamine are associated with depression, addictions, cravings, apathy, pleasure seeking behaviors, increased sleepiness, impulsivity, tremors, low motivation fatigue and low mood.
High levels of dopamine are associated with agitation, insomnia, mania, hyperactivity, hyper-focus, high stress, anxiety and addictions/cravings/pleasure seeking (to maintain high levels).
High HVA can be caused by the use of the following supplements, foods or medications within 72 hours of collecting urine samples: tyrosine, phenylalanine, mucuna, quercetin, bananas, avocados as well as parkinson's medications. If these are being used, the HVA on the DUTCH test may not accurately reflect circulating dopamine levels and should be disregarded.

Vanilmandelate (VMA)

Vanilmandelate (VMA) is the primary metabolite of norepinephrine and epinephrine (adrenaline). The adrenal gland makes cortisol and DHEA (from the adrenal cortex) as well as norepinephrine and epinephrine (from the adrenal medulla). When adrenal hormone output is low, VMA levels may be low. If HVA levels are significantly higher than VMA, there may be a conversion problem from dopamine to norepinephrine. This case can be

caused by a copper or vitamin C deficiency.
The enzymes COMT (methylation of catechols) and MAO are needed to make HVA and VMA from dopamine and norepinephrine respectively. If these enzymes are not working properly, HVA and/or VMA may be low in urine, when circulating levels of dopamine and/or norepinephrine/epinephrine may not be low.

Low levels of norepinephrine/epinephrine are associated with addictions, cravings, fatigue, low blood pressure, low muscle tone, intolerance to exercise, depression, and loss of alertness.

High levels of norepinephrine and epinephrine are associated with feelings of stress, aggression, violence, impatience, anxiety, panic, excess worry/hypervigilance, insomnia, paranoia, increasing tingling/burning, loss of memory, pain sensitivity, high blood pressure and heart palpitations.

Melatonin (measured as 6-OHMS)

Melatonin is considered one of our sleep hormones. It is made predominately by the pineal gland in response to darkness and is stimulated by melanocyte stimulating hormone (MSH). A low MSH is associated with insomnia and an increased perception of pain. Mold exposure can inhibit MSH as well. The majority of our melatonin production comes from the pineal gland, but melatonin is also made in the gut, and to a lesser extent in the bone marrow, lymphocytes, epithelial cells and mast cells.

The DUTCH test uses the waking (A) sample to test melatonin. The urine sample given on waking reflects overnight hormone production and metabolism. This sample can be used to assess melatonin throughout the night. When patients take a middle of the night sample, both the middle of the night and waking samples are tested and the highest number in ng/mg creatinine is reported.

8-OHdG (8-Hydroxy-2-deoxyguanosine)

8-OHdG (8-Hydroxy-2-deoxyguanosine) is a marker for estimating DNA damage due to oxidative stress (from ROS creation). 8-OHdG is considered pro-mutagenic and is a biomarker for various cancer and degenerative disease initiation and promotion states. It can be increased by chronic inflammation, increased cell turnover, chronic stress, hypertension, hyperglycemia/pre-diabetes/diabetes, kidney disease, IBD, chronic skin conditions (psoriasis/eczema), depression, atherosclerosis, chronic liver disease, Parkinson's (increasing levels with worsening stages), Diabetic neuropathy, COPD, bladder cancer, or insomnia (to name a few). Studies have shown higher levels in patients with breast and prostate cancers. When levels are elevated it may be prudent to eliminate or reduce any causes and increase the consumption of antioxidant containing foods and/or supplements.

Urine Hormone Testing - General Information

What is actually measured in urine? In blood, most hormones are bound to binding proteins. A small fraction of the total hormone levels are "free" and unbound such that they are active hormones. These free hormones are not found readily in urine except for cortisol and cortisone (because they are much more water soluble than, for example, testosterone). As such, free cortisol and cortisone can be measured in urine and it is this measurement that nearly all urinary cortisol research is based upon. In the DUTCH Adrenal Profile the diurnal patterns of free cortisol and cortisone are measured by LC-MS/MS.

All other hormones measured (cortisol metabolites, DHEA, and all sex hormones) are excreted in urine predominately after the addition of a glucuronide or sulfate group (to increase water solubility for excretion). As an example, Tajic (Natural Sciences, 1968 publication) found that of the testosterone found in urine, 57-80% was testosterone-glucuronide, 14-42% was testosterone-sulfate, and negligible amounts (<1% for most) was free testosterone. The most likely source of free sex hormones in urine is from contamination from hormonal supplements. To eliminate this potential, we remove free hormones from conjugates. The glucuronides and sulfates are then broken off of the parent hormones, and the measurement is made. These measurements reflect the bioavailable amount of hormone in most cases as it is only the free, nonprotein-bound fraction in blood/tissue that is available for phase II metabolism (glucuronidation and sulfation) and subsequent urine excretion.
Disclaimer: the filter paper used for sample collection is designed for blood collection, so it is technically considered "research only" for urine collection. Its proper use for urine collection has been thoroughly validated.

Reference Range Determination (last updated 12.20.2018)

We aim to make the reference ranges for our DUTCH tests as clinically appropriate and useful as possible. This includes the testing of thousands of healthy individuals and combing through the data to exclude those that are not considered “healthy” or “normal” with respect to a particular hormone. As an example, we only use a premenopausal woman’s data for estrogen range determination if the associated progesterone result is within the luteal range (days 19-21 when progesterone should be at its peak). We exclude women on birth control or with any conditions that may be related to estrogen production. Over time the database of results for reference ranges has grown quite large. This has allowed us to refine some of the ranges to optimize for clinical utility. The manner in which a metabolite’s range is determined can be different depending on the nature of the metabolite. For example, it would not make clinical sense to tell a patient they are deficient in the carcinogenic estrogen metabolite, 4-OH-E1 therefore the lower range limit for this metabolite is set to zero for both men and women. Modestly elevated testosterone is associated with unwanted symptoms in women more so than in men, so the high range limit is set at the 80th percentile in women and the 90th percentile for men. Note: the 90th percentile is defined as a result higher than 90% (9 out of 10) of a healthy population.

Classic reference ranges for disease determination are usually calculated by determining the average value and adding and subtracting two standard deviations from the average, which defines 95% of the population as being “normal.” When testing cortisol, for example, these types of two standard deviation ranges are effective for determining if a patient might have Addison’s (very low cortisol) or Cushing’s (very high cortisol) Disease. Our ranges are set more tightly to be optimally used for Functional Medicine practices.

Below you will find a description of the range for each test:

Male Reference Ranges (Updated 08.21.2019)

	Low%	High%	Low	High		Low%	High%	Low	High
b-Pregnanediol	10%	90%	75	400	Cortisol A (waking)	20%	90%	13	80
a-Pregnanediol	10%	90%	20	130	Cortisol B (morning)	20%	90%	35	180
Estrone (E1)	10%	90%	4	16	Cortisol C (~5pm)	20%	90%	10	45
Estradiol (E2)	10%	90%	0.5	2.2	Cortisol D (bed)	20%	90%	0	20
Estriol (E3)	10%	90%	2	8	Cortisone A (waking)	20%	90%	40	160
2-OH-E1	0	90%	0	5.9	Cortisone B (morning)	20%	90%	80	240
4-OH-E1	0	90%	0	0.8	Cortisone C (~5pm)	20%	90%	40	130
16-OH-E1	0	90%	0	1.2	Cortisone D (bed)	0	90%	0	70
2-Methoxy-E1	0	90%	0	2.8	Melatonin (6-OHMS)	20%	90%	10	85
2-OH-E2	0	90%	0	0.6	8-OHdG	0	90%	0	8.8
4-OH-E2	0	90%	0	0.3	Methylmalonate	0	90%	0	3
2-Methoxy-E2	0	90%	0	0.8	Xanthurenate	0	90%	0	2.1
DHEA-S	20%	90%	30	1500	Kynurenate	0	90%	0	9.3
Androsterone	20%	80%	500	3000	Pyroglutamate	10%	90%	43	85
Etiocholanolone	20%	80%	400	1500	Homovanillate	10%	95%	4.8	19
Testosterone	20%	90%	25	115	Vanilmandelate	10%	95%	2.8	8
5a-DHT	20%	90%	5	25					
5a-Androstanediol	20%	90%	30	250	**Calculated Values**				
5b-Androstanediol	20%	90%	40	250	Total DHEA Production	20%	80%	1000	5500
Epi-Testosterone	20%	90%	25	115	Total Estrogens	10%	90%	10	34
a-THF	20%	90%	175	700	Metabolized Cortisol	20%	90%	4550	10000
b-THF	20%	90%	1750	4000	24hr Free Cortisol	20%	90%	75	300
b-THE	20%	90%	2350	5800	24hr Free Cortisone	20%	90%	220	550

% = population percentile: Example - a high limit of 90% means results higher than 90% of the women tested for the reference range will be designated as "high."

Provider Notes:

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