Accession # 00280397
Male Sample Report
123 A Street
Sometown, CA 90266

Ordering Physician:
Precision Analytical

DOB: 1967-08-09
Age: 50
Gender: Male

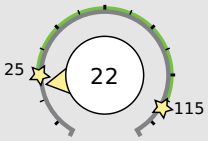
Collection Times:
2017-08-09 06:01AM (S)
2017-08-09 06:31AM (S)
2017-08-09 07:01AM (S)
2017-08-09 05:01PM (S)
2017-08-09 10:01PM (S)
2017-08-09 06:01AM (U)
2017-08-09 08:01AM (U)
2017-08-09 05:01PM (U)
2017-08-09 10:01PM (U)

Hormone Testing Summary

Key (how to read the results):

Sex Hormones

Estradiol(E2)



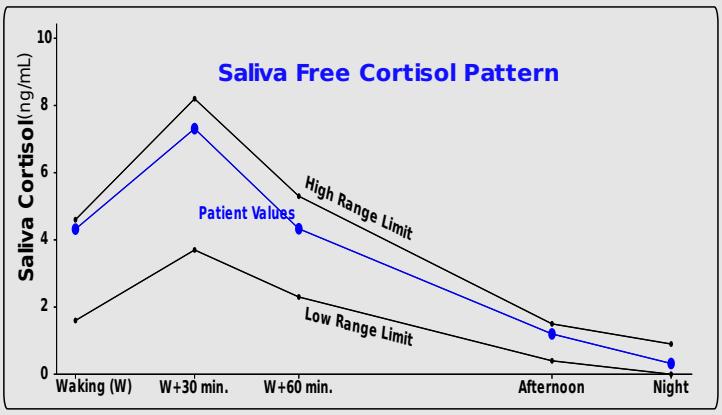
Testosterone

Testosterone

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

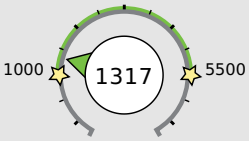
Adrenal Hormones

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)

Saliva Cortisol Total
(Sum of 5 values)

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 Plus Overview (quick overview) Estrogen Tutorial Male Androgen Tutorial Cortisol/CAR Tutorial

PLEASE BE SURE TO READ BELOW FOR ANY SPECIFIC LAB COMMENTS. More detailed comments can be found on page 8.

The Cortisol Awakening Response (CAR) was 2.99ng/mL (expected range 1.5-4.0) or 69.2% (range 50-160%). See page 5 for more details.

dutchplus
COMPLETE WITH CORTISOL AWAKENING RESPONSE

Accession # 00280397
Male Sample Report
123 A Street
Sometown, CA 90266

PRECISION ANALYTICAL INC.
SIMPLY · BETTER · TESTING

Sex Hormones and Metabolites

Ordering Physician:
Precision Analytical

DOB: 1967-08-09
Age: 50
Gender: Male

Collection Times:
2017-08-09 06:01AM (S)
2017-08-09 06:31AM (S)
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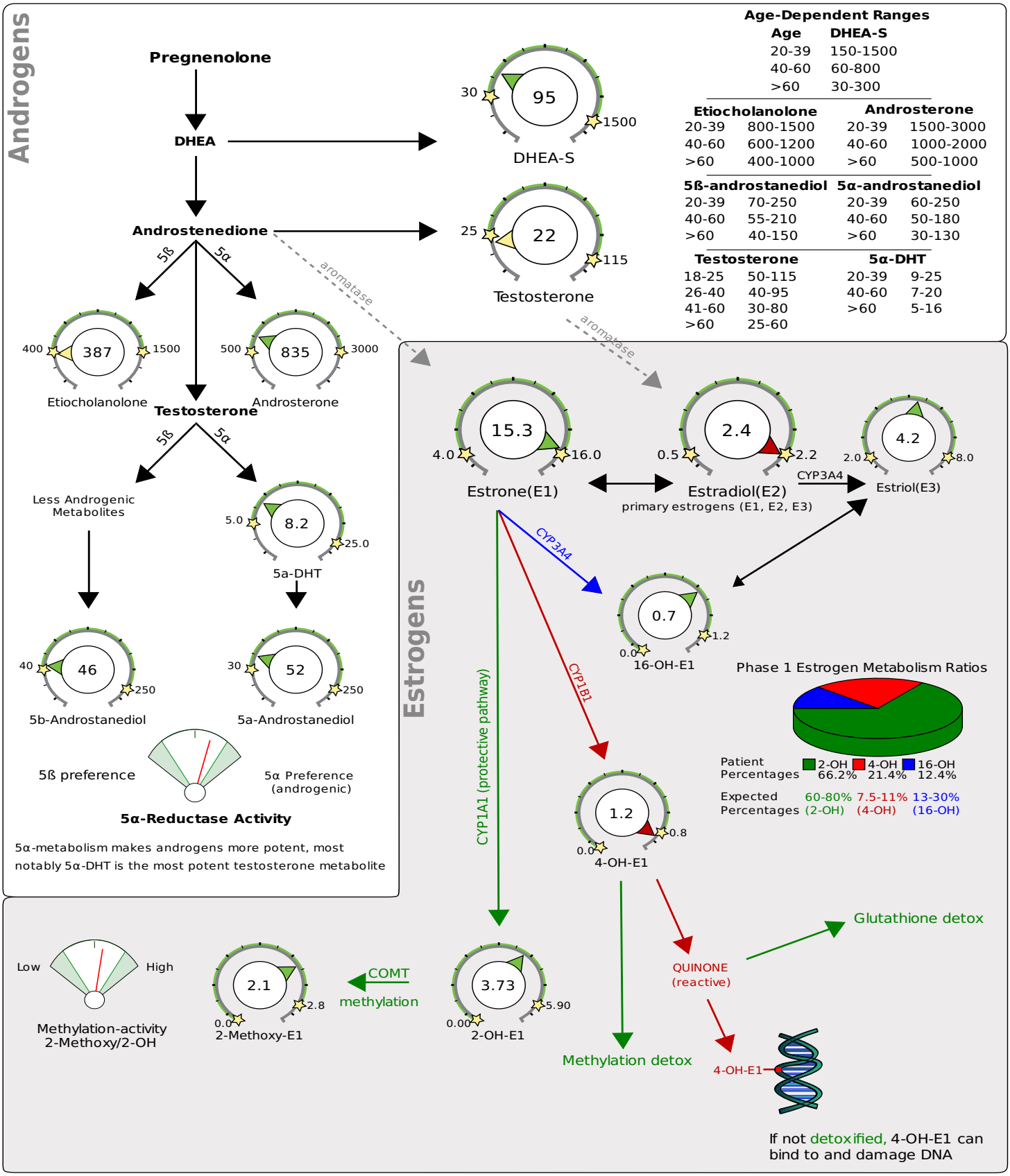
2017-08-09 10:01PM (U)

Category	Test		Result	Units	Normal Range
Progesterone Metabolites (Urine)					
	b-Pregnanediol	Low end of range	110.0	ng/mg	75 - 400
	a-Pregnanediol	Low end of range	40.0	ng/mg	20 - 130
Estrogens and Metabolites (Urine)					
	Estrone(E1)	High end of range	15.3	ng/mg	4 - 16
	Estradiol(E2)	Above range	2.4	ng/mg	0.5 - 2.2
	Estriol(E3)	Within range	4.2	ng/mg	2 - 8
	2-OH-E1	Within range	3.73	ng/mg	0 - 5.9
	4-OH-E1	Above range	1.2	ng/mg	0 - 0.8
	16-OH-E1	Within range	0.7	ng/mg	0 - 1.2
	2-Methoxy-E1	Within range	2.1	ng/mg	0 - 2.8
	2-OH-E2	Above range	0.61	ng/mg	0 - 0.6
	4-OH-E2	Within range	0.1	ng/mg	0 - 0.3
	2-Methoxy-E2	Within range	0.3	ng/mg	0 - 0.8
	Total Estrogen	High end of range	30.3	ng/mg	10 - 34
Androgens and Metabolites (Urine)					
	DHEA-S	Low end of range	95.0	ng/mg	30 - 1500
	Androsterone	Low end of range	835.0	ng/mg	500 - 3000
	Etiocholanolone	Below range	387.0	ng/mg	400 - 1500
	Testosterone	Below range	21.6	ng/mg	25 - 115
	5a-DHT	Low end of range	8.2	ng/mg	5 - 25
	5a-Androstanediol	Low end of range	52.0	ng/mg	30 - 250
	5b-Androstanediol	Low end of range	46.0	ng/mg	40 - 250
	Epi-Testosterone	Low end of range	38.1	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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COMPLETE WITH CORTISOL AWAKENING RESPONSE

Accession # 00280397
Male Sample Report
123 A Street
Sometown, CA 90266

PRECISION ANALYTICAL INC.
SIMPLY · BETTER · TESTING

Adrenal

Ordering Physician:
Precision Analytical

DOB: 1967-08-09
Age: 50
Gender: Male

Collection Times:
2017-08-09 06:01AM (S)
2017-08-09 06:31AM (S)
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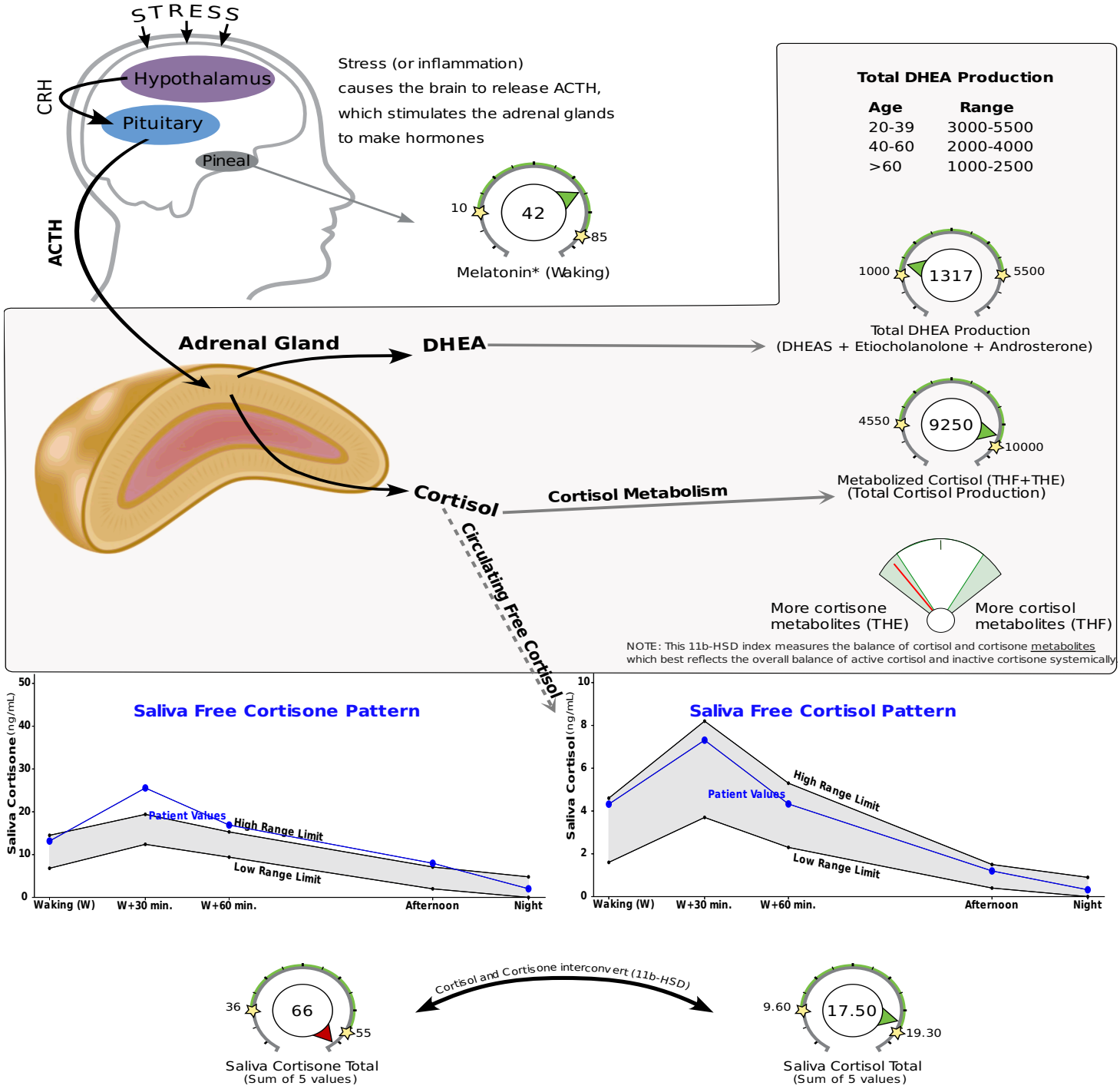
2017-08-09 10:01PM (U)

Category	Test		Result	Units	Normal Range
Free Cortisol and Cortisone (Saliva)					
	Saliva Cortisol - Waking (W)	High end of range	4.32	ng/mL	1.6 - 4.6
	Saliva Cortisol - W+30 min.	High end of range	7.31	ng/mL	3.7 - 8.2
	Saliva Cortisol - W+60 min.	Within range	4.33	ng/mL	2.3 - 5.3
	Saliva Cortisol - Afternoon	Within range	1.2	ng/mL	0.4 - 1.5
	Saliva Cortisol - Night	Within range	0.32	ng/mL	0 - 0.9
	Saliva Cortisone - Waking (W)	High end of range	13.16	ng/mL	6.8 - 14.5
	Saliva Cortisone - W+30 min.	Above range	25.57	ng/mL	12.4 - 19.4
	Saliva Cortisone - W+60 min.	Above range	16.9	ng/mL	9.4 - 15.3
	Saliva Cortisone - Afternoon	Above range	7.98	ng/mL	2 - 7.1
	Saliva Cortisone - Night	Within range	2.02	ng/mL	0 - 4.8
	Saliva Cortisol Total	High end of range	17.50	ng/mL	9.6 - 19.3
	Saliva Cortisone Total	Above range	65.63	ng/mL	36 - 55
Creatinine (Urine)					
	Creatinine A (Waking)	Within range	0.45	mg/ml	0.3 - 3
	Creatinine B (Morning)	Within range	0.41	mg/ml	0.3 - 3
	Creatinine C (Afternoon)	Within range	0.9	mg/ml	0.3 - 3
	Creatinine D (Night)	Within range	0.88	mg/ml	0.3 - 3
Cortisol Metabolites and DHEA-S (Urine)					
	b-Tetrahydrocortisol (b-THF)	Within range	2800.0	ng/mg	1750 - 4000
	a-Tetrahydrocortisol (a-THF)	Within range	450.0	ng/mg	175 - 700
	b-Tetrahydrocortisone (b-THE)	Above range	6000.0	ng/mg	2350 - 5800
	Metabolized Cortisol (THF+THE)	High end of range	9250.0	ng/mg	4550 - 10000
	DHEA-S	Low end of range	95.0	ng/mg	30 - 1500



The Cortisol Awakening Response (CAR) is the rise in salivary cortisol between the waking sample and the sample collected 30 (as well as 60) minutes later. This "awakening response" is essentially a "mini stress test" and is a useful measurement in addition to the overall up-and-down (diurnal) pattern of free cortisol throughout the day. **This patient shows a waking cortisol of 4.32 and an increase to 7.3 after 30.0 minutes. This is an increase of 2.99ng/mL or 69.2%.** Expected increases differ depending on the methods used. Preliminary research shows that 50-160% or 1.5-4.0ng/mL increases are common with samples collected 30 minutes after waking. These guidelines are considered research only. **This patient shows a salivary cortisol of 4.33 measured 60 minutes after waking. This is an increase of 0.01ng/mL or 0.23% compared to the waking sampe.** To date, data suggests that expected results may be 0-70%, and this guideline is considered for research only.

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COMPLETE WITH CORTISOL AWAKENING RESPONSE

Accession # 00280397
Male Sample Report
123 A Street
Sometown, CA 90266

PRECISION ANALYTICAL INC.
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Organic Acid Tests (OATs)

Ordering Physician:
Precision Analytical

DOB: 1967-08-09
Age: 50
Gender: Male

Collection Times:
2017-08-09 06:01AM (S)
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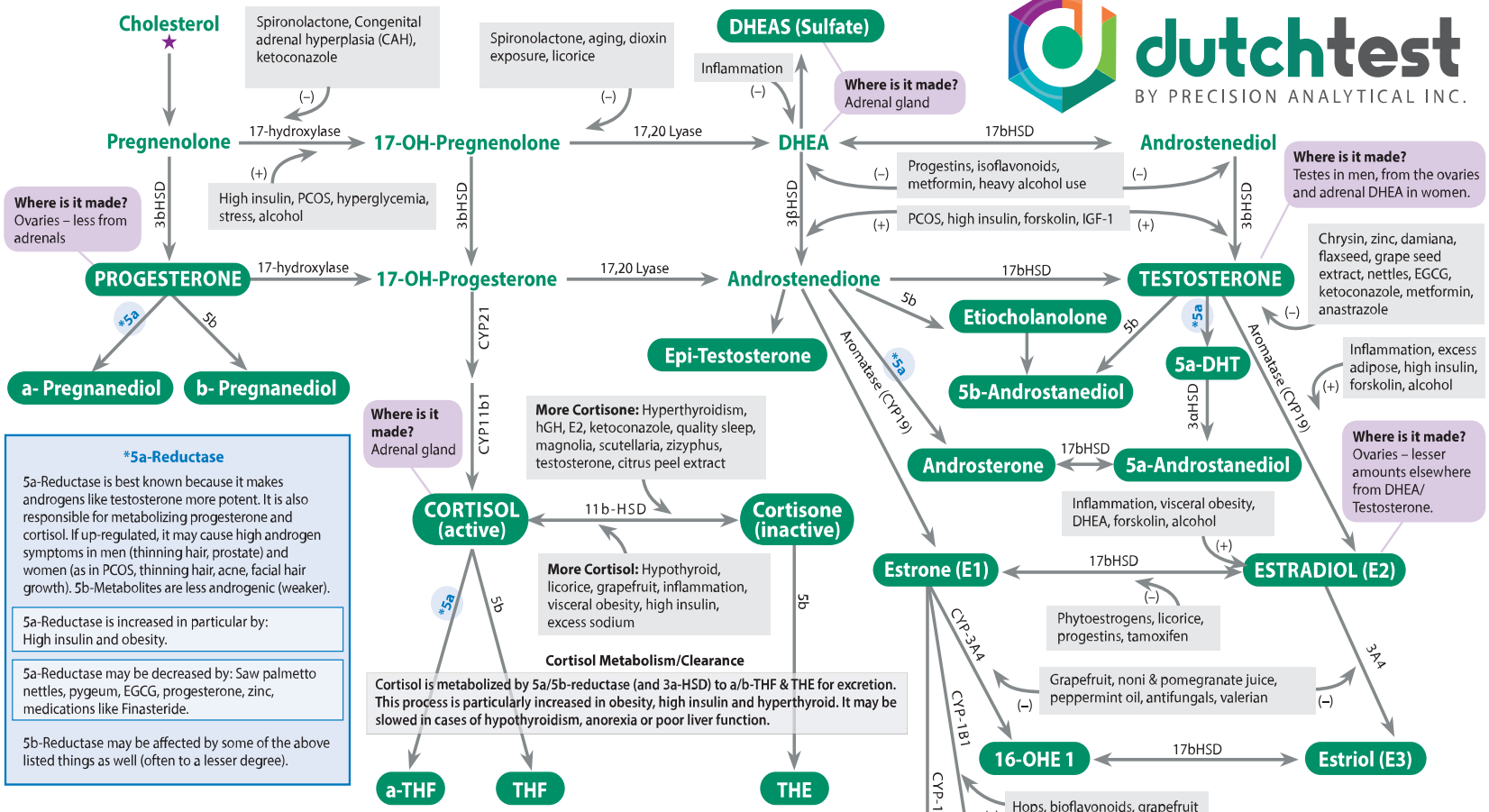
Category	Test		Result	Units	Normal Range
Nutritional Organic Acids					
Vitamin B12 Marker (may be deficient if high) - (Urine)					
	Methylmalonate (MMA)	Within range	1.2	ug/mg	0 - 3
Vitamin B6 Marker (may be deficient if high) - (Urine)					
	Xanthurenate	Above range	6.8	ug/mg	0 - 2.1
Glutathione Marker (may be deficient if low or high) - (Urine)					
	Pyroglutamate	Below range	23.2	ug/mg	43 - 85
Neurotransmitter Metabolites					
Dopamine Metabolite - (Urine)					
	Homovanillate (HVA)	Low end of range	5.6	ug/mg	4.8 - 19
Norepinephrine/Epinephrine Metabolite - (Urine)					
	Vanilmandelate (VMA)	Within range	4.8	ug/mg	2.8 - 8
Serotonin Metabolite - (Urine)					
	5-Hydroxyindoleacetate (5HIAA)	Above range	16.0	ug/mg	3 - 10
Melatonin (*measured as 6-OH-Melatonin-Sulfate) - (Urine)					
	Melatonin* (Waking)	Within range	42.4	ng/mg	10 - 85
Oxidative Stress / DNA Damage, measured as 8-Hydroxy-2-deoxyguanosine (8-OHdG) - (Urine)					
	8-OHdG (Waking)	Within range	4.0	ng/mg	0 - 8.8

Steroid Pathways

Find these Hormones on the DUTCH Complete

Primary hormones (in CAPS) are made by organs by taking up cholesterol ★ and converting it locally to, for example, progesterone. Much less is made from circulating precursors like pregnenolone. For example, taking DHEA can create testosterone and estrogen, but far less than is made by the testes or ovaries, respectively.



*5a-Reductase

5a-Reductase is best known because it makes androgens like testosterone more potent. It is also responsible for metabolizing progesterone and cortisol. If up-regulated, it may cause high androgen symptoms in men (thinning hair, prostate) and women (as in PCOS, thinning hair, acne, facial hair growth). 5b-Metabolites are less androgenic (weaker).

5a-Reductase is increased in particular by: High insulin and obesity.

5a-Reductase may be decreased by: Saw palmetto nettles, pygeum, EGCG, progesterone, zinc, medications like Finasteride.

5b-Reductase may be affected by some of the above listed things as well (often to a lesser degree).

Cortisol Metabolism/Clearance

Cortisol is metabolized by 5a/5b-reductase (and 3a-HSD) to a/b-THF & THE for excretion. This process is particularly increased in obesity, high insulin and hyperthyroid. It may be slowed in cases of hypothyroidism, anorexia or poor liver function.

Other factors affecting the production of primary reproductive and adrenal hormones:

- Increased Cortisol: stress, inflammation, Cushing's Disease, obesity
- Decreased Cortisol: glucocorticoid use, opioid use, Addison's Disease, Accutane, chronic marijuana use
- Increased DHEA: PCOS, acute stress, Bupropion (Wellbutrin), Alprazolam (Xanax), ADD meds
- Decreased DHEA: aging, rapid weight loss, Venlafaxine/Mirtazapine, opioids, glucocorticoids, hormonal birth control, antipsychotic meds, estrogens, diabetes meds
- Increased Testosterone: PCOS, HCG, HGH, L-Dopa, Climiphene Citrate (Clomid)
- Decreased Testosterone: obesity, opioids, hormonal birth control, acute illness, aging, high insulin, steroid use
- Increased Estrogens: PCOS, inflammation, pregnancy, DHEA/testosterone supplementation
- Decreased Estrogens: hormonal birth control, ovarian failure (menopause), opioids, anorexia, underweight
- Increased Progesterone: pregnancy, pregnenolone supplementation (increases urine progesterone metabolites, not actual circulating progesterone), Vitex (chaste tree berry)
- Decreased Progesterone: hormonal birth control, stress, high insulin, opioids, NSAID use >10 days, anovulation, luteal phase defect, high prolactin, underweight, hypothyroid, hormonal IUD (Mirena)

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DutchTest.com

Male Sample Report
FINAL REPORT
09/12/2018

Precision Analytical (Raymond Grimsbo, Lab Director)
3138 Rivergate Street #301C
McMinnville, OR 97128

Provider Notes

How to read the DUTCH report

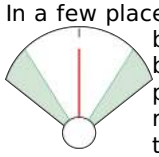
This report is not intended to treat, cure or diagnose any specific diseases. The graphic dutch dials in this report are intended for quick and easy evaluation of which hormones are out of range. Results below the left star are shaded yellow and are below range (left). Results between the stars and shaded 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

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

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

DHEA and androstenedione are made almost exclusively by the adrenal gland (although a smaller amount is made in the ovaries). These hormones appear in urine as DHEA-S (DHEA-Sulfate), androsterone and etiocholanolone. The best way to assess the total production of DHEA is to add up these three metabolites. This total can be seen on the first page of the DUTCH Complete (and DUTCH Plus). DHEA production decreases quite significantly with age. Age-dependent ranges can be seen on the graphical page of results.

The Total DHEA Production (page 1) was about 1,317ng/mg which is within the overall range but is below the range for the patient's age-dependent range. This implies that the adrenal glands are not producing appropriate DHEA levels for the patient's age. Low DHEA is associated with depression, diabetes, heart disease, inflammation and immune disorders. It can be caused by hypothyroidism. It can cause fatigue, low mood and low libido. Supplementing DHEA in women often raises both testosterone and estrogen, which may or may not be desirable here. DHEA may increase with adaptogens such as maca and rhodiola, which improve overall adrenal output.

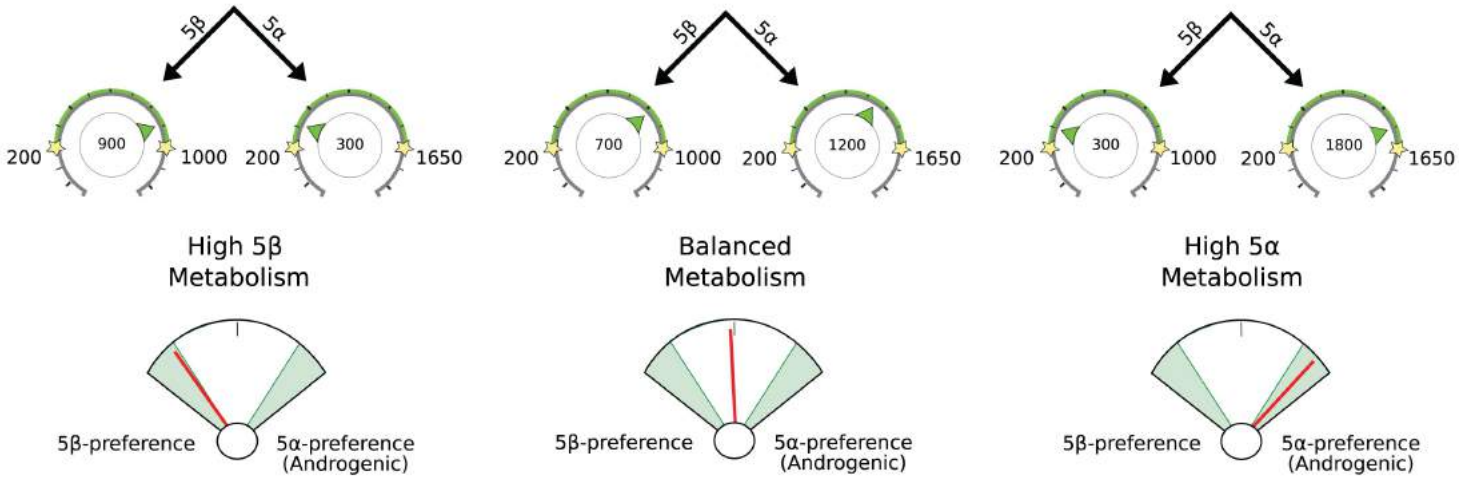
- **The status (low, normal or high?) of testosterone:**

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. Consider the appropriate age-dependent range for your patient. In older men, you can also consider the 18-25 year-old group to approximate what levels may have been when the patient was young and relatively healthy.

- **The metabolic preference for the 5a (5-alpha) or 5b (5-beta) pathway:**

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. Metabolites created down the 5b-pathway are significantly less androgenic than their 5a counterparts. In the examples below, the example on the left shows a patient with 5b-metabolism preference. A patient with a pattern like the example on the right may have high androgen symptoms even though testosterone is in the normal range because of the likely preference for turning a lot of his testosterone into DHT. 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.

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 to assess testosterone therapy and rare cases where testosterone may have other complexities.

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 levels are of marginal value in men, although deficiency can be associated with some clinical conditions such as depression, fatigue, and low libido.

Progesterone metabolites have limited relevance in male patients, but may be worth considering in some patients with abnormal results. In this case, both progesterone metabolites are within the normal range.

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 a physical or psychological stressor occurs, the hypothalamus tells the pituitary to make ACTH, a hormone. ACTH stimulates the adrenal glands to make the stress hormone, cortisol and to a lesser extent DHEA and DHEA-S. Normally, the HPA-axis production follows a daily pattern in which cortisol rises rather rapidly in the first 10-30 minutes after waking (this is the C.A.R.) in order to help with energy, then gradually decreases throughout the day so that it is low at night for sleep. The cycle starts over the next morning. Abnormally high activity occurs in Cushing's Disease where the HPA-axis is hyper-stimulated causing cortisol to be elevated all day. The opposite is known as Addison's Disease, where cortisol is abnormally low because it is not made appropriately in response to ACTH's stimulation. These two conditions are somewhat rare. Examples of more common conditions related to less severely abnormal cortisol levels include fatigue, depression, insomnia, fibromyalgia, anxiety, inflammation and more.

Only a fraction of cortisol is "free" and bioactive. This fraction of cortisol is very important, but levels of metabolized cortisol

best represent overall production of cortisol therefore both should be taken into account to correctly assess adrenal function.

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

- **The overall up-and-down pattern of free cortisol throughout the day, looking for low and high levels:** Abnormal results should be considered along with related symptoms.
- **The sum of the free cortisol as an expression of the overall tissue cortisol exposure:** This total of five free cortisol measurements is the best way to assess the total of free cortisol throughout the day, but do be aware that it is heavily weighted towards the morning production since three of five measurements are made within the first hour of the day.
- **The total level of cortisol metabolites:** We call this calculation "Metabolized Cortisol" which is the sum of a-THF, b-THF and b-THE. While free cortisol is the best assessment for tissue levels of cortisol, it only represents 1-3% of the total produced. The majority of cortisol results in a urine metabolite and the total of these metabolites best represents the total glandular output of cortisol for the day. When overall production is much higher than free cortisol levels, cortisol clearance may be increased (as seen in hyperthyroidism, obesity, etc.) The most common reason for sluggish cortisol clearance (assumed when free cortisol levels are much higher than metabolized cortisol) is low thyroid.
- **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 saliva gland converts cortisol to cortisone in the local tissue. This localized conversion can be seen by comparing cortisol 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 gauge below metabolized cortisol. 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. Both are then metabolized by 5a-reductase to become tetrahydrocortisol (THF) and tetrahydrocortisone (THE) respectively.
- **The Cortisol Awakening Response (CAR):** The unique feature of the DUTCH Plus is the inclusion of the CAR assessment. The response to waking adds one more piece to HPA-axis function. In some cases overall levels of free cortisol may be normal, but the response to stress may be under or overactive. Reasons for a lower CAR might include: an underactive HPA Axis, excessive psychological burnout, seasonal affective disorder (SAD), sleep apnea or poor sleep in general, PTSD, and "chronic fatigue" patients. An elevated CAR can be a result of an over-reactive HPA axis, ongoing job-related stress (anticipatory stress for the day), glycemic dysregulation, pain (ie. waking with painful joints or a migraine), and general depression (not SAD). Scientific literature points to the magnitude of the morning cortisol increase as being connected to HPA-axis health whether the overall production of cortisol is low, normal or high.

Nutritional Organic Acids

The following three organic acids are functional markers for vitamin deficiency. These compounds essentially back up in human biochemistry when a key nutrient is missing. These three metabolites have fairly straightforward interpretations. When the markers are elevated, it is likely that the patient's cellular levels of the related nutrient may be insufficient.

Methylmalonate (MMA)

Methylmalonate (also known as methylmalonic acid or MMA) is a functional marker of vitamin B12 (also known as cobalamin) deficiency. When cellular levels of B12 are low either from deficiency or due to a B12 transporter gene mutation, levels of MMA increase. This marker is considered superior to measuring serum B12 levels directly. A 2012 publication by Miller showed that 20% of those tested had a genetic defect in the protein that transports B12 to cells. These patients may have a functional B12 deficiency even if serum levels of B12 are normal.
If levels of MMA are elevated, it may be advisable to increase B12 consumption. Common foods high in B12 include beef liver, sardines, lamb, wild caught salmon, grass-fed beef, nutritional yeast and eggs. Vitamin B12 levels can also be increased through supplementation of B12 (taken as cobalamin, methylcobalamin, hydroxycobalamin, or adenosylcobalamin). Symptoms of a vitamin B12 deficiency include: fatigue, brain fog, memory problems, muscle weakness, unsteady gait, numbness, tingling, depression, migraines/headaches and low blood pressure.

Xanthurenate

Xanthurenate (also known as xanthurenic acid) is a functional marker of vitamin B6 (also known as pyridoxine). Vitamin B6 is a critical co-factor to over 100 important reactions that occur in the human body and is stored in the highest concentrations in muscle tissue. Tryptophan is readily converted to NAD by the liver. One of the steps in this pathway requires B6. When there is insufficient B6, xanthurenate is made instead.
In this case xanthurenate is elevated, which implies a vitamin B6 deficiency. Not only is xanthurenate an indicator of a lack of B6, it is also harmful to the human body. It complexes with insulin and decreases insulin sensitivity. In fact, rats fed xanthurenate will actually develop diabetes because of the effects on insulin. You may consider B6 supplementation in this case. Food high in B6 include turkey breast, grass-fed beef, pinto beans, avocado, pistachios, chicken, sesame and sunflower seeds.
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. If levels of estrogen or cortisol are high, it may exacerbate xanthurenate elevations and increase the need for B6.
Xanthurenate can also bind to iron and create a complex that increases DNA oxidative damage resulting in higher 8-OHdG levels. If both markers are elevated, there is likely an antioxidant insufficiency.

Pyroglutamate

Pyroglutamate (also known as pyroglutamic acid) is a functional marker of glutathione deficiency. Pyroglutamate is a step in the production/recycling of glutathione. If the body cannot convert pyroglutamate forward, it will show up elevated in the urine. High pyroglutamate is an established marker for glutathione deficiency.
Glutathione is one of the most potent anti-oxidants in the human body. It 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.

Neurotransmitter Metabolites

The neurotransmitters dopamine, norepinephrine and serotonin are important for human health. Measuring neurotransmitters directly (direct testing of serotonin, for example) is difficult because of their instability and their urinary measurements are controversial with respect to how well they reflect the body's levels of these neuro-hormones. Each of these three neurotransmitters can be assessed indirectly by measuring their urine metabolites. While these metabolites are not a perfect reflection of what's going on in the brain, the scientific literature does affirm their use for a good representation of overall levels of these neurotransmitters.

Homovanillate (HVA)

Homovanillate (also known as HVA) is the primary metabolite of dopamine, a brain and adrenal neurotransmitter that comes from tyrosine (with BH4 and iron as co-factors) and goes on to create norepinephrine (noradrenaline) and epinephrine (adrenaline).
Low levels of HVA can be due to low levels of dopamine or poor conversion of dopamine to HVA. The latter may be due to insufficient levels of SAM, Magnesium, FAD and NAD which are needed to metabolize dopamine. Low circulating dopamine may be due to insufficient BH4, iron or tyrosine. It may also be seen when adrenal function is generally low. Low dopamine levels may be associated with addictions, cravings and pleasure seeking (to boost levels) in addition to sleepiness, impulsivity, tremors, less motivation, fatigue and low mood.
Elevated HVA may be caused by generally increased adrenal hormone output or because of a copper or vitamin C deficiency (which are needed for dopamine conversion to norepinephrine). Elevations may also be caused by a number of medications or supplements including: MAO inhibitors, quercetin, tyrosine, DL-phenylalanine (DLPA), L-dopa, macuna, dopamine medication (Levodopa, Sinemet, Methyldopa), SNRI medication (Wellbutrin), tricyclic antidepressants, amphetamines, appetite suppressants, and caffeine. Bananas also contain dopamine. Elevated dopamine may be associated with loss of memory, insomnia, agitation, hyperactivity, mania, hyper-focus, high stress and anxiety as well as addictions, cravings and pleasure seeking (to maintain high levels).

Vanilmandelate (VMA)

Vanilmandelate (also known as VMA) is the primary metabolite of norepinephrine and epinephrine (adrenaline). The adrenal gland makes cortisol and DHEA as well as norepinephrine and epinephrine. When adrenal hormone output is generally 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) and MAO are needed to make VMA from norepinephrine. If these enzymes are not working properly, VMA may be low when circulating norepinephrine and/or epinephrine are not low. Low levels of norepinephrine and epinephrine may be associated with addictions, cravings, fatigue, low blood pressure, low muscle tone, intolerance to exercise, depression, loss of alertness.
When the body is under physical or psychological stress, VMA levels may increase. Because dopamine gets converted to norepinephrine and ultimately to VMA, the list of medications and supplements that increase HVA may also increase VMA. Elevated levels may be associated with feeling stressed, aggression, violence, impatience, anxiety, panic, worry, insomnia, paranoia, increased tingling/burning, loss of memory, pain sensitivity, high blood pressure and heart palpitations.
If VMA and HVA are both extremely high, it may be necessary to rule out a neuroblastic tumor.

5-Hydroxyindoleacetate (5HIAA)

5-Hydroxyindoleacetate (also known as 5HIAA) is the primary metabolite of serotonin. Serotonin is often thought of as the "antidepressant" neurotransmitter (because common antidepressants aim to increase levels) however it is important to note that 90% is made in the gut and just 1% in the brain. In the gut, serotonin is required for gut motility and activates smooth muscle activity. In the brain, the dorsal raphe nucleus (DRN) in the brain stem contains the largest serotonergic nucleus. There is also a large portion of serotonin innervation in the forebrain (cerebrum, thalamus, hypothalamus, pituitary and limbic system). Approximately 40% of the DRN contains estrogen receptors demonstrating the tight relationship estrogen has with serotonin and the brain. The Estrogen Receptor Beta (ERb) upregulates mRNA of tryptophan hydroxylase which is the rate limiting step to making 5-HTP (a precursor to serotonin). If estrogen is low, it's possible less 5-HTP will be made.

Elevated 5HIAA implies increased serotonin turnover or the consumption of related compounds. High levels are often seen in people using SSRI antidepressants like Prozac because it increases available serotonin, which is metabolized to 5HIAA. People taking supplements like 5-HTP will usually have very high levels. Because metabolism from 5-HTP to serotonin metabolites may happen in the gut, these high levels may not represent circulating (or brain exposure) serotonin levels. Certain foods (butternuts, black walnuts, plantain, pecans, pineapple, banana) can also contain serotonin. If these variables are ruled out, it may be necessary to rule out a carcinoid tumor as well if levels are VERY high. These types of tumors make very high levels of serotonin, but they are very rare.

Melatonin (measured as 6-OHMS)

Melatonin is not technically an adrenal or sex hormone however it is highly involved in the entire endocrine system. It is

made in small amounts in the pineal gland in response to darkness and stimulated by Melanocyte Stimulating Hormone (MSH). A low MSH is associated with insomnia, an increased perception of pain, and mold exposure. Pineal melatonin (melatonin is also made in significant quantities in the gut) is associated with the circadian rhythm of all hormones (including female hormone release). It is also made in small amounts in the bone marrow, lymphocytes, epithelial cells and mast cells. Studies have shown that a urine sample collected upon waking has levels of 6-Hydroxymelatonin-sulfate (6-OHMS) that correlate well to the total levels of melatonin in blood samples taken continuously throughout the night. The DUTCH test uses the waking sample only to test levels of melatonin production.
Low melatonin levels may be associated with insomnia, poor immune response, constipation, weight gain or increased appetite. Elevated melatonin is usually caused by ingestion of melatonin through melatonin supplementation or eating melatonin-containing foods. Elevated melatonin production that is problematic is rare, but levels can be higher in patients with Chronic Fatigue Syndrome and may be phase shifted (peaking later) in some forms of depression.

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

8-OHdG (8-hydroxy-2-deoxyguanosine) results can be seen on page 6 of the DUTCH Complete (or DUTCH Plus) report. It is a marker for estimating DNA damage due to oxidative stress (ROS creation). 8-OHdG is considered pro-mutagenic as it is a biomarker for various cancer and degenerative disease initiation and promotion. 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. 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.
The reference range for 8-OHdG is a more aggressive range for Functional Medicine that puts the range limit at the 80th percentile for each gender. A classic range (average plus two standard deviations) would result in a range of 0-6ng/mg for women and 0-10ng/mg for men. Seeking out the cause of oxidative stress may be more crucial if results exceed these limits.

Reference Range Determination (last updated 11.15.2017)

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 06.06.2018)

	Low%	High%	Low	High
b-Pregnanediol	10%	90%	75	400
a-Pregnanediol	10%	90%	20	130
Estrone (E1)	10%	90%	4	16
Estradiol (E2)	10%	90%	0.5	2.2
Estriol (E3)	10%	90%	2	8
2-OH-E1	0	90%	0	5.9
4-OH-E1	0	90%	0	0.8
16-OH-E1	0	90%	0	1.2
2-Methoxy-E1	0	90%	0	2.8
2-OH-E2	0	90%	0	0.6
4-OH-E2	0	90%	0	0.3
2-Methoxy-E2	0	90%	0	0.8
DHEA-S	20%	90%	30	1500
Androsterone	20%	80%	500	3000
Etiocholanolone	20%	80%	400	1500
Testosterone	20%	90%	25	115
5a-DHT	20%	90%	5	25
5a-Androstanediol	20%	90%	30	250
5b-Androstanediol	20%	90%	40	250
Epi-Testosterone	20%	90%	25	115
a-THF	20%	90%	175	700
b-THF	20%	90%	1750	4000
b-THE	20%	90%	2350	5800
% = 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."				

	Low%	High%	Low	High
Saliva Cortisol Waking (W)	20%	90%	1.6	4.6
Saliva Cortisol (W+30 min.)	20%	90%	3.7	8.2
Saliva Cortisol (W+60 min.)	20%	90%	2.3	5.3
Saliva Cortisol (Afternoon)	20%	90%	0.4	1.5
Saliva Cortisol (Night)	0	95%	0	0.9
Saliva Cortisol (2-3 am)	0	90%	0	0.9
Saliva Cortisone Waking (W)	20%	90%	6.8	14.5
Saliva Cortisone (W+30 min.)	20%	90%	12.4	19.4
Saliva Cortisone (W+60 min.)	20%	90%	9.4	15.3
Saliva Cortisone Afternoon	20%	90%	2	7.1
Saliva Cortisone Night	0	95%	0	4.8
Melatonin (6-OHMS)	20%	90%	10	85
8-OHdG	0	90%	0	8.8
Methylmalonate	0	90%	0	3
Xanthurenate	0	90%	0	2.1
Pyroglutamate	10%	90%	43	85
Homovanillate	10%	95%	4.8	19
Vanilmandelate	10%	95%	2.8	8
5-Hydroxyindoleacetate	10%	95%	3	10
Calculated Values				
Total DHEA Production	20%	80%	1000	5500
Total Estrogens	10%	90%	10	34
Metabolized Cortisol	20%	90%	4550	10000
Saliva Cortisol Total	20%	90%	9.6	19.3
Saliva Cortisone Total	20%	90%	36	55

Provider Notes: