Laboratory Interpretations:

When “WNL” Isn’t Good Enough

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Suzanne Keyes “declare(s) no conflicts of interest, real or apparent, and no financial interests in any company, product, or service mentioned in this program, including grants, employment, gifts, stock holdings, and honoraria.”

Information is known to be accurate at the time of presentation. The compounder is encouraged to consult reference compendia and current USP documentation as information is subject to change.
OBJECTIVES

Upon completion of this module, the participant shall be able to:

• Describe how normal lab reference ranges are derived
• Define the different definitions of health
• Discuss the clinical significance of particular lab tests
• Begin using certain tests as useful biomarkers of disease
• Argue as to why standard labs are simply prolonging diagnosis of chronic disease and not preventing it
“NORMAL” IS JUST ONE SYMPTOM FROM DISEASE

Suzanne Heyes, Pharm.D.
The Conventional Path

Health → Symptom → MD → Specialists → More Disease → Rx/Surgery → Rx/Surgery → Death

If unaddressed, triggers continue to create more disease
The Functional Path
HOW DID WE DETERMINE WHAT IS “NORMAL”
What Is A Reference Range?  

• A reference range is *a set of values* that includes upper and lower limits of a lab test *based on a group of otherwise healthy people*.

• The values in between those limits may *depend on* such factors as *age, sex, and specimen type* (blood, urine, spinal fluid, etc.) AND can also be *influenced by circumstantial situations* such as fasting and exercise.

*These intervals are thought of as "normal ranges or limits."*
How “WNL “ Is Determined

Three important things to know about reference ranges:

• A normal result in one lab may be abnormal in another: You must use the range supplied by the laboratory that performed your test to evaluate whether your results are "within normal limits." While accuracy of laboratory testing has significantly evolved over the past few decades, some lab-to-lab variability can occur due to differences in testing equipment, chemical reagents used, and analysis techniques.

• Consequently, for most lab tests, there is no universally applicable reference value. This is the reason why so few reference ranges are provided in the test information on this website, Lab Tests Online.
• **A normal result does not promise health:** While having all test results *within normal limits* is certainly a good sign, *it’s not a guarantee*. For many tests, *there is a lot of overlap among results from healthy people and those with diseases*, so there is still a chance that there could be an undetected problem. Lab test results in some people with disease fall within the reference range, especially in the early stages of a disease.

• **An abnormal result does not mean you are sick:** *A test result outside the reference range may or may not indicate a problem*. Since many reference values are based on statistical ranges in healthy people, you may be one of the healthy people outside the statistical range, especially if your value is close to the expected reference range. However, the abnormal value does alert your healthcare provider to a possible problem, especially if your test result is far outside the expected values.
“...Our lab, like almost all labs, sets the normal result range for a particular test so that 95% of our healthy patients fall within the normal range. That means that 5% of our healthy patients fall outside of the normal range, even when there is nothing wrong with them. **Thus an abnormal test does not necessarily mean that there is something wrong with you.** Statistically if you have 20 or 30 individual tests run as part of a panel, chances are 1 or 2 will be slightly outside the normal range. Part of what you see your doctor for is to interpret whether or not these changes are meaningful...”
NOW WHAT??
...as a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity...
The definition of health is contradicted by the very manner in which it is determined.

Suzanne Feyes, Pharm.D.
Properly Prescribed Drugs

- Cause about 1.9 million hospitalizations a year

- Another 840,000 hospitalized patients are given drugs that cause serious adverse reactions for a total of 2.74 million serious adverse drug reactions

- 128,000 people die from drugs prescribed to them.
As long as we limit our interpretation of health to:

• *skewed normal ranges*
• *looking at the wrong biomarkers*
• *prescribing drugs without determining the root cause* and
• *treating disease without identifying and removing triggers*

we have a prescription for disaster that culminates in almost 130,000 deaths that could have possibly been avoided
Functional Endocrinology

A unique and progressive way to understand and interpret the results of a variety of tests to get an overall picture of the health of the body and how well it and all the organs are working.
You can't connect the dots looking forward; you can only connect them looking backwards.

- Steve Jobs
Create a picture for your patient and practitioner by putting the pieces together

- The SAD
- Sugar
- Chronic Disease
- Insulin
- Inflammation

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CONNECT THE DOTS
## My Standard Orders

<table>
<thead>
<tr>
<th>Test</th>
<th>Test</th>
<th>Test</th>
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<tbody>
<tr>
<td>free T3</td>
<td>Lipid Panel</td>
<td>Erythrocyte <em>(or RBC)</em> zinc</td>
</tr>
<tr>
<td>reverse T3</td>
<td>Apolipoprotein Evaluation</td>
<td>Vitamin B12, Folate</td>
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<tr>
<td>free T4</td>
<td>SHBG</td>
<td>Vitamin D3 25(OH)</td>
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<tr>
<td>TSH <em>(thyroid stimulating hormone)</em></td>
<td>Glycoprotein Acetylation</td>
<td>Vitamin D3 1,25(OH)</td>
</tr>
<tr>
<td>TBg <em>(thyroid binding globulin)</em></td>
<td>hsCRP</td>
<td>Ferritin, iron, TIBC, %Sat</td>
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<td>anti TPO antibodies <em>(thyroid peroxidase)</em></td>
<td>Homocysteine</td>
<td>Erythrocyte <em>(or RBC)</em> magnesium</td>
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<tr>
<td>anti Tg antibodies <em>(thyroglobulin)</em></td>
<td>CBC w/ differential</td>
<td>Insulin</td>
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<tr>
<td>tTG *(IgG, IgA) <em>(tissue transglutaminase)</em></td>
<td>CMP</td>
<td>Leptin</td>
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<td>MMA <em>(prn)</em></td>
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<td>A1c</td>
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<td>Uric Acid</td>
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HYPOTHALAMUS

PITUITARY

ADRENAL

STRESS

T4
(Inactive / storage hormone)

B2, B12, C, Iodine, Tyrosine

Selenium, Fe+

REVERSE T3

T3
(active hormone)

B2, B12, C, Iodine, Tyrosine

Zinc, B12, Mg+

~95% of T4 & T3 is unavailable & bound to TBG at any given time

Thyroid STIMULATING Hormone

Receptor tissue

A, D

Thyroxine BINDING Globulin

Thyroid

RELEASING Hormone

Corticotropin RELEASING Hormone

Adrenocorticotropin RELEASING Hormone

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Free $T_3$:

- Decreased in acute illness and starvation
- Often “normal” in hypothyroidism even when T4 is low
- Affected by several meds (propranolol, amiodarone, steroids)
- Free T3 is generally considered to provide a more reliable indication of true thyroid status

(T3 Uptake):

- T-uptake or Resin thyroid uptake
- Useful in combination with the total portions to measure the indirect free index level
- Heavily relied upon historically, particularly before direct free T4 / free T3 assays became available

https://www.auburn.edu/~deruija/endo_thyroidfts.pdf
Reverse T3

• Sits on cell receptor like T3 but acts as a gatekeeper blocking the effects of T3

• Serves as a disposal path for T4

• Can produce Euthyroid Sick Syndrome (LOW free T3, HIGH rT3 - also known as Reverse T3 pooling - “WNL” T4 & TSH)

• Natural breaking system when the body is compromised

• Production levels is affected by too much or too little cortisol

• Chronic caloric restriction, chronic inflammation and chronic illness or infections (including SIBO) increase reverse T3 to increase
Free $T_4$\textsubscript{5}

- More sensitive of an \textit{indicator of disease development} than free T3 therefore \textit{used to confirm dx}

- Free T4 is \textit{not affected by changes in concentrations of binding proteins}. Thus such conditions as pregnancy, or estrogen and androgen therapy \textit{do not affect} the FT4.

(Total $T_4$)\textsubscript{5}

- Used to \textit{complement TSH} assays

- \textit{Dependent on thyroid transport hormones} (specifically TBG & albumin)

- \textit{Usually elevated in hyperthyroidism}, but it misses 5% of cases that are due to triiodothyronine (T3) toxicosis

[https://www.auburn.edu/~deruija/endo_thyroidfts.pdf](https://www.auburn.edu/~deruija/endo_thyroidfts.pdf)
Thyroid Binding Globulin

• One of 3 proteins produced by the liver to transport thyroid through the blood (*pre-albumin and albumin are the other two*)

• Reversibly binds T3 and T4

• Useful in differential diagnosis of patients presenting with significantly abnormal levels of total thyroid hormone levels but no other clinical signs or symptoms of thyroid disease.

• *Increase proportionately as estrogen increases*

• Individual health status including pregnancy and certain medications (androgens and glucocorticoids) influence TBG levels

http://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/84382
Thyroglobulin is the protein precursor of thyroid hormone and is **not secreted into the systemic circulation under normal circumstances**

However, *follicular destruction* through inflammation (thyroiditis and autoimmune hypothyroidism), hemorrhage (nodular goiter), or rapid disordered growth of thyroid tissue, as may be observed in Graves disease or follicular cell-derived thyroid neoplasms, *can result in leakage of Tg into the blood stream*

This results in the **formation of autoantibodies** to Tg (anti-Tg) in some individuals.

Thyroglobulin is **made by normal well differentiated benign thyroid cells or thyroid cancer cells**. Although thyroglobulin levels may be elevated in patients with thyroid cancer, a **large number of benign thyroid conditions may also be associated with elevated levels of thyroglobulin**, hence an increased thyroglobulin alone in a patient not known to have thyroid cancer is not a sensitive or specific test for the diagnosis of thyroid cancer.

http://www.thyroid.org/patient-thyroid-information/ct-for-patients/vol-7-issue-2/vol-7-issue-2-p-7-8/
Anti-Thyroglobulin Ab

• Since thyroglobulin plays a significant role in thyroid synthesis, storage and release of thyroid, autoantibodies bind thyroglobulin

• In combination with anti TPO Ab, TgAb are considered the disease markers for Hashimoto’s Thyroiditis and Grave’s Disease

• In autoimmune hypothyroidism, 30-50% will have detectable anti-thyroglobulin antibodies, whereas 50-90% will have detectable anti-TPO antibodies

http://www.mayomedicallaboratories.com/testcatalog/Clinical+and+Interpretive/84382
**Thyroid Peroxidase**

- The enzyme responsible for iodinating tyrosine
- Stimulated by iodine and found in thyroid follicle cells where it converts T4 to T3
- Progesterone appears to both improve the signaling mechanisms of thyroid receptors as well as stimulate TPO production

**Anti-TPO or TPO Ab**

- The formation of antibodies against TPO is most common in Hashimoto’s (present in up to 95% of patients and in approximately 85 percent of Graves' disease cases)
- Initially, the higher the level, the more hyperthyroid symptoms will appear as the thyroid cells are destroyed and stored thyroid dumps in the blood
- Ab MAY appear decades before changes in TSH are detected BUT ...
- Th1 / Th2
• Most people with thyroid resistance also have leptin resistance (as Leptin levels increase and your brain slows down your metabolism, your body will start to convert Free T4 into Reverse T3)

• Known as the “satiety hormone”, leptin controls appetite

• Produced by fat cells and leptin resistance occurs in obesity when the brain is flooded with the hormone and eventually becomes resistant to its affects

• Leptin suppresses TSH and T4 to T3 conversion

• THYROID PROFILE in Leptin Resistance: Low-Normal TSH; Low Free T4; Mid-High Free T3; High rT3
• Made in the liver, SHBG transports sex steroids through the blood stream to target tissues
• T4 increases SHBG and an increased SHBG causes a decreased CBG.
• A decreased CBG causes fatty liver, chronic pain, decreased BP and chronic fatigue. SHBG, therefore can be used as an indirect indicator of thyroid function
• **Increased in:**
  hepatitis, hyperthyroidism (T4&T3 act indirectly on the liver to stimulate SHBG production); exo/endo estrogens; high cortisol, heart disease and in the presence of low protein, high fiber, breast/testicular cancers, smoking, caffeine, anorexia, significant weight loss, pregnancy
• **Decreased in:**
  obesity, IR, DM, hypothyroidism, metabolic syndrome, insulin resistance, diabetes, sleep apnea, kidney disease, obesity, alcohol intake & low estradiol
• With less SHBG available over time, the supplemental doses of testosterone are more rapidly excreted by the body and don't have an opportunity to build up in the blood and get to the tissues.
• **PCOS pts are characterized by low SHBG**
• Because *T4 increases SHBG*, if thyroid replacement is given and SHBG does not increase proportionally, it *may be an indication of thyroid resistance*

• **FROM LIFE EXTENSION:** SHBG levels have an important relationship with nearly every biomarker of cardiovascular disease, from C-reactive protein (CRP) to arterial calcification. *Low SHBG is also associated with elevated triglycerides and low-density lipoprotein (LDL).*

Calcification of blood vessels, an early finding in cardiovascular disease, is also associated with lower SHBG levels, especially in women.

• *Low SHBG in women is associated with higher levels of C-reactive protein* (CRP), an important marker of inflammation and cardiovascular risk

• In men, low SHBG indicated an increased risk of death from cardiovascular disease. In both men and women, *low SHBG levels are strongly correlated with obesity.*
Medications Affecting SHBG Levels

• Meds that INCREASE SHBG:
  tamoxifen, carbamazepine, clomiphene, phenytoin, rifampin

• Meds that DECREASE SHBG:
  Omegas EPA/DHA, Testosterone and Vitamin D3
  *DHEA may decrease SHBG in postmenopausal women*
Apolipoproteins are found on the surface of lipoproteins and regulate lipid metabolism. The two apolipoproteins that are of clinical interest are apo B and apo A1.

Apolipoprotein A1 is the primary protein associated with HDL whereas APO B is associated with LDL cholesterol.

Their combined evaluation is a predictive value that is superior to that of serum lipid fractions.

Apolipoprotein-related Mortality RISk (AMORIS) study found that apo B was a stronger predictor of risk of fatal MI than LDL cholesterol. Apo A1 was found to be protective for risk of fatal MI.


ApoB/apoA1 is an effective predictor of coronary heart disease risk in overweight & obesity
Min Lu, Qun Lu, Yong Zhang, and Gang Tian

The Apolipoprotein B/Apolipoprotein A-I Ratio as a Potential Marker of Plasma Atherogenicity
Anastasiya M. Kaneva,1 Natalya N. Potolitsyna,1 Evgeny R. Bojko,1 and Jon Ø. Odland2
Values of apoB>120 mg/dL and apoA-I<120 mg/dL have been proposed as the cut-off points defining a high cardiovascular risk [21, 22].

Apo B/Apo A-1 ratio
“The apo B/apo A-1 ratio could be a simple, robust, precise indicator of great value in health screening and during lipid-lowering therapy.”

An odds ratio of 1 implies that the event is equally likely in both groups.
A ratio of apo B/apo A-1 of 0.7 or lower would be considered lower risk, whereas a ratio of 0.8 or higher would represent an elevated risk

Abstract

**Background:** Apo B and Apo A-I, are structural and functional components of lipoprotein particles that serve as transporters of cholesterol. The apo B/apo A-I ratio reflects the cholesterol transport and has been shown to be strongly related to risk of Myocardial infarction, stroke and other Cardiovascular manifestations.

**Materials and Methods:** Forty five participants with Cardiovascular Disease (CVD) and forty four healthy participants were included from different locations of Kathmandu valley, Nepal. Fasting blood samples were collected from ante-cubital vein and serum samples were used for lipid parameters.

“...shown to be strongly related to risk of MI, stroke and other cardiovascular manifestations.”

“**Conclusion:** Apo B/apo A-I ratio seems to have better predictive value than that of classical lipid parameters in cardiovascular risk assessment.”
Glycoprotein Acetylation

• Glycoprotein acetylation (GlycA) has been shown to **predict risk of cardiovascular disease and all-cause mortality**

• GlycA marked the levels of a myriad of **inflammatory cytokines in circulation**

• A recent study completed by experts from the Intermountain Medical Center Heart Institute in Salt Lake City discovered that two new biomarkers such as glycoprotein acetylation (GlycA) and C-reactive protein (CRP) both are **associated with an increased risk of heart attack or stroke**

http://www.cell.com/cell-systems/abstract/S2405-4712(15)00145-3

Homocysteine is a chemical in the blood that is produced when the amino acid methionine is broken down.

Elevated levels of homocysteine show an increased risk for atherosclerosis, and venous thrombosis.

Elevations in HC may be caused by a deficiency of B vitamins and folate. Increased homocysteine is also seen in people with kidney disease, low levels of thyroid hormones, psoriasis, and with certain medications.

It has been recognized that some people have a common genetic variant (called methylenetetrahydrofolate reductase, abbreviated MTHFR) that impairs their ability to process folate. This defective gene leads to elevated levels of homocysteine in some people who inherit MTHFR variants from both parents.

http://circ.ahajournals.org/content/111/19/e289
Vitamin D3 1,25(OH)

• DHVD levels are the most accurate to predict the body's actual vitamin D content. 1,25(OH) is the most potent form of vitamin D

• **INC'd in:** autoimmune disease, inflammation (*The active secosteroid hormone 1,25-dihydroxyvitamin-D (1,25D) often reaches excessive levels in normocalcemic patients suffering from chronic Th1 INFLAMMATORY illnesses*), sarcoidosis, malignancies, hyperparathyroid (*could be secondary to low D intake or low calcium*)

• **DEC'd in:** hypoparathyroid, chronic renal disease

• Test when pts 25(OH) won't increase with supplementation; suspect a genetic SNP in the VDR or in autoimmunity
Along with a high %sat & high serum iron, increased ferritin correlates with **MTHFR SNPs and hemachromatosis (genetic trait where the body simply loads too much iron)**

> 90 (women) or 100 (men) *may indicate inflammation*

Ferritin is the last to show a deficiency

Serum ferritin above 100 ng/ml has been associated with decreased cardiovascular fitness and increased incidences of: atherosclerosis, type 2 diabetes, cancer gout and accelerated aging including osteoporosis and sarcopenia (muscle wasting) due to oxidative stress.

Elevated ferritin *can indicate INSULIN RESISTANCE* and **FATTY LIVER**

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2570219/
• Elevated insulin is associated with central obesity

• *Hyperinsulinaemia is the earliest subclinical metabolic abnormality, which precedes insulin resistance* in obese children

• It’s been shown that individuals with a “*WNL* OGGT” may still have an abnormal insulin response

• Insulin *should return* to optimal levels within 2 hours post prandial

*https://www.nature.com/articles/srep36270*
Recent studies show that fructose-induced uric acid generation causes mitochondrial oxidative stress that stimulates fat accumulation independent of excessive caloric intake.

MTHFR 677T: a significant association between hyperuricemia (SUA ≥ 7mg/dL) and MTHFR 677T allele carriers was observed.

http://diabetes.diabetesjournals.org/content/62/10/3307
WHY IS SUGAR SO CRITICAL?

• Normally crosses the BBB
• Implicated in Alzheimer’s (type III diabetes) d/t loss of insulin sensitivity
• Drives inflammation
• Reduces T4 to T3 conversion
• Depletes dopamine
• Insulin stimulates PCSK9
**PCSK-9**

LDLR bound to PCSK9 is digested in the lysosome. LDL-C is incorporated into the cell.

LDLR Recycling
Statins May Stimulate Atherosclerosis and Heart Failure

• Statins may be causative in coronary artery calcification and can function as mitochondrial toxins that impair muscle function in the heart and blood vessels.

• Thus, the epidemic of heart failure and atherosclerosis that plagues the modern world may paradoxically be aggravated by the pervasive use of statin drugs.

More on Statins

- The Archive of Internal Medicine that showed a **strong link between statin use and diabetes**

- That study followed nearly 154,000 women in the Women’s Health Initiative and found that post-menopausal women taking certain types of statins had a **48% greater risk of developing type 2 diabetes**

- A total of 8,749 non-diabetic participants, aged 45–73 years, were followed up for 5.9 years. New diabetes was diagnosed in 625 men by means of an OGTT, HbA1c ≥6.5% (48 mmol/mol) or glucose-lowering medication started during the follow-up. Insulin sensitivity and secretion were evaluated with OGTT-derived indices.

- **Conclusions/interpretation:** *Statin treatment increased the risk of type 2 diabetes by 46%, attributable to decreases in insulin sensitivity and insulin secretion.*

50% of heart attacks leading to sudden death happen in patients with normal cholesterol.
Remember that “to ARGUE” does not imply distain, disgust or anger...

argue
/ˈärgyoo/ 

verb

1. give reasons or cite evidence in support of an idea, action, or theory, typically with the aim of persuading others to share one’s view. "defense attorneys argue that the police lacked “probable cause” to arrest the driver"

synonyms: contend, assert, maintain, insist, hold, claim, reason, allege; More
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22) http://diabetes.diabetesjournals.org/content/62/10/3307