Casual Friday Presents

SLE – Lupus, Part 2

A BIOGENETIX CLINICAL PRESENTATION

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Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with multisystemic involvement. The condition has several phenotypes, with varying clinical presentations from mild mucocutaneous manifestations to multiorgan and severe central nervous system involvement. Several immunopathogenic pathways play a role in the development of SLE. Hargraves described the lupus erythematosus (LE cell) in 1948. Several pathogenic autoantibodies have since been identified. Despite recent advances in technology and understanding of the pathological basis and risk factors for SLE, the exact pathogenesis is still not well known. Diagnosis of SLE can be challenging, and while several classification criteria have been posed, their utility in the clinical setting is still a matter of debate. Management of SLE is dictated by organ system involvement. Despite several agents shown to be efficacious in treating SLE, the disease still poses significant morbidity and mortality risk in patients.[1]

https://www.ncbi.nlm.nih.gov/books/NBK535405/

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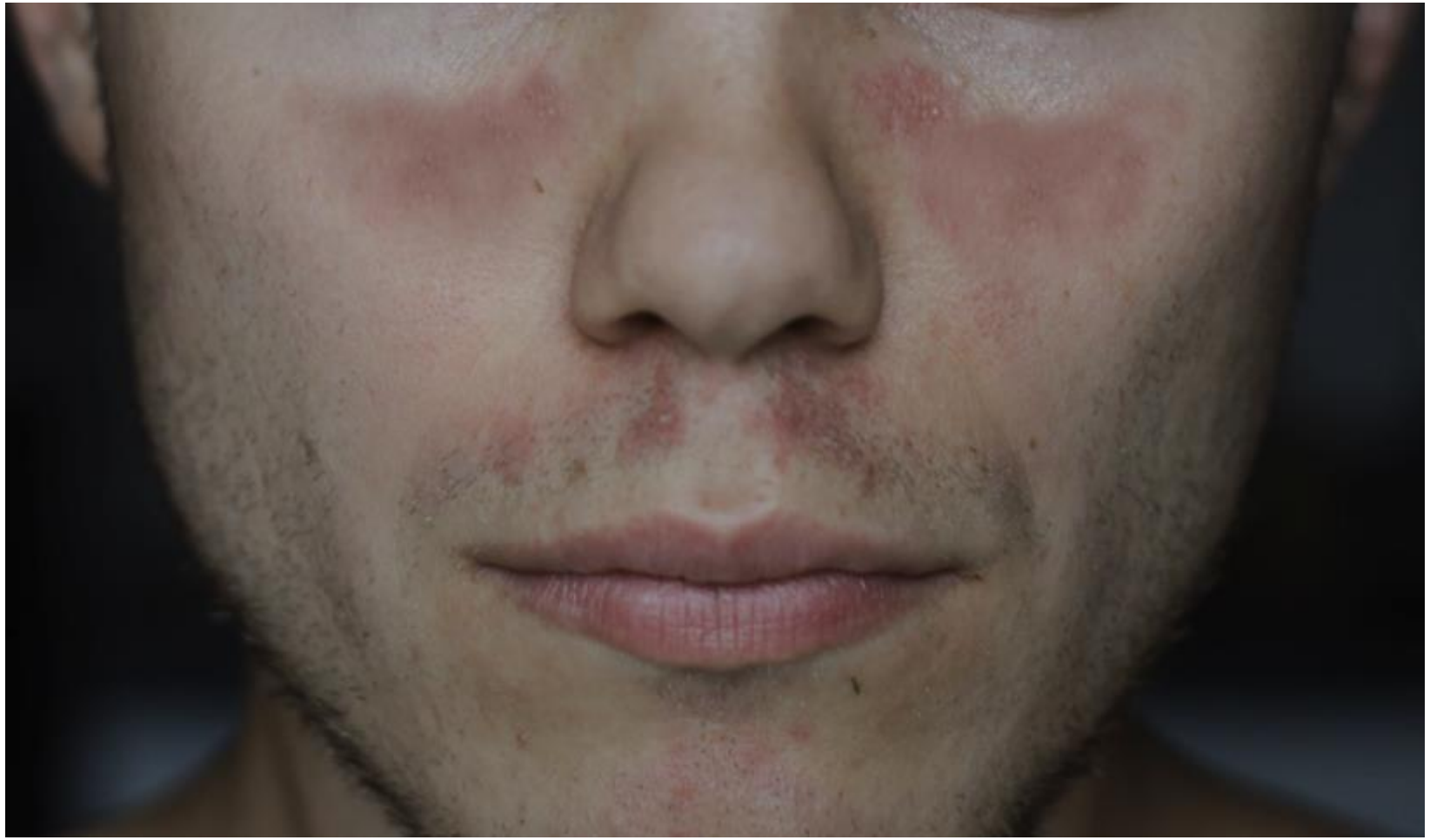
Constitutional symptoms are seen in more than 90% of patients with SLE and are often the initial presenting feature. Fatigue, malaise, fever, anorexia, and weight loss are common. While more than 40% of patients with SLE may have lupus flare as a cause of fever, infections must always be ruled out first, given the immunocompromised state of these patients. Further, SLE is an infrequent cause of fever of unknown origin.[11]

Acute cutaneous lupus erythematosus (ACLE) may be localized or generalized. The hallmark ACLE lesion is the malar rash or the butterfly rash, an erythematous raised pruritic rash involving the cheeks and nasal bridge. The rash may be macular or papular and spares the nasolabial folds (photoprotected).

Subacute cutaneous lupus erythematosus (SCLE) rash is a photosensitive, widespread, nonscarring, nonindurated rash. SCLE may be either papulosquamous resembling psoriasis or an annular/polycystic lesion with central clearing and peripheral scaling.

Discoid lupus erythematosus (DLE) is the most common form of chronic cutaneous lupus erythematosus (CCLE). DLE may occur with or without SLE and can be localized (only head and neck) or generalized (above and below the neck). The lesions are disk-shaped erythematous papules or plaques with adherent scaling and central clearing. DLE heals with scarring and can be associated with permanent alopecia when present on the scalp.

Acute Cutaneous Lupus Erythematosus (ACLE)



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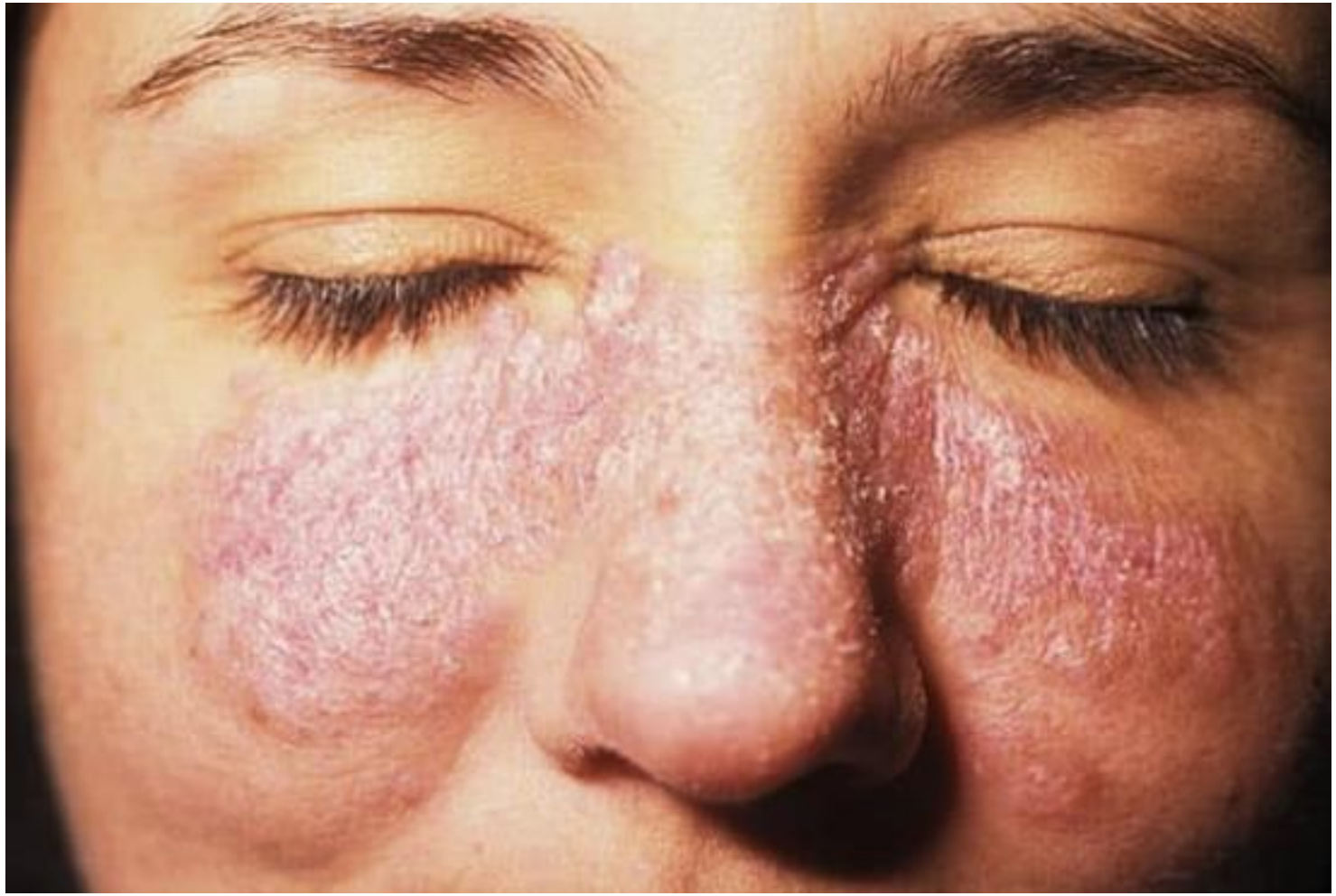
Acute Cutaneous Lupus Erythematosus (ACLE)



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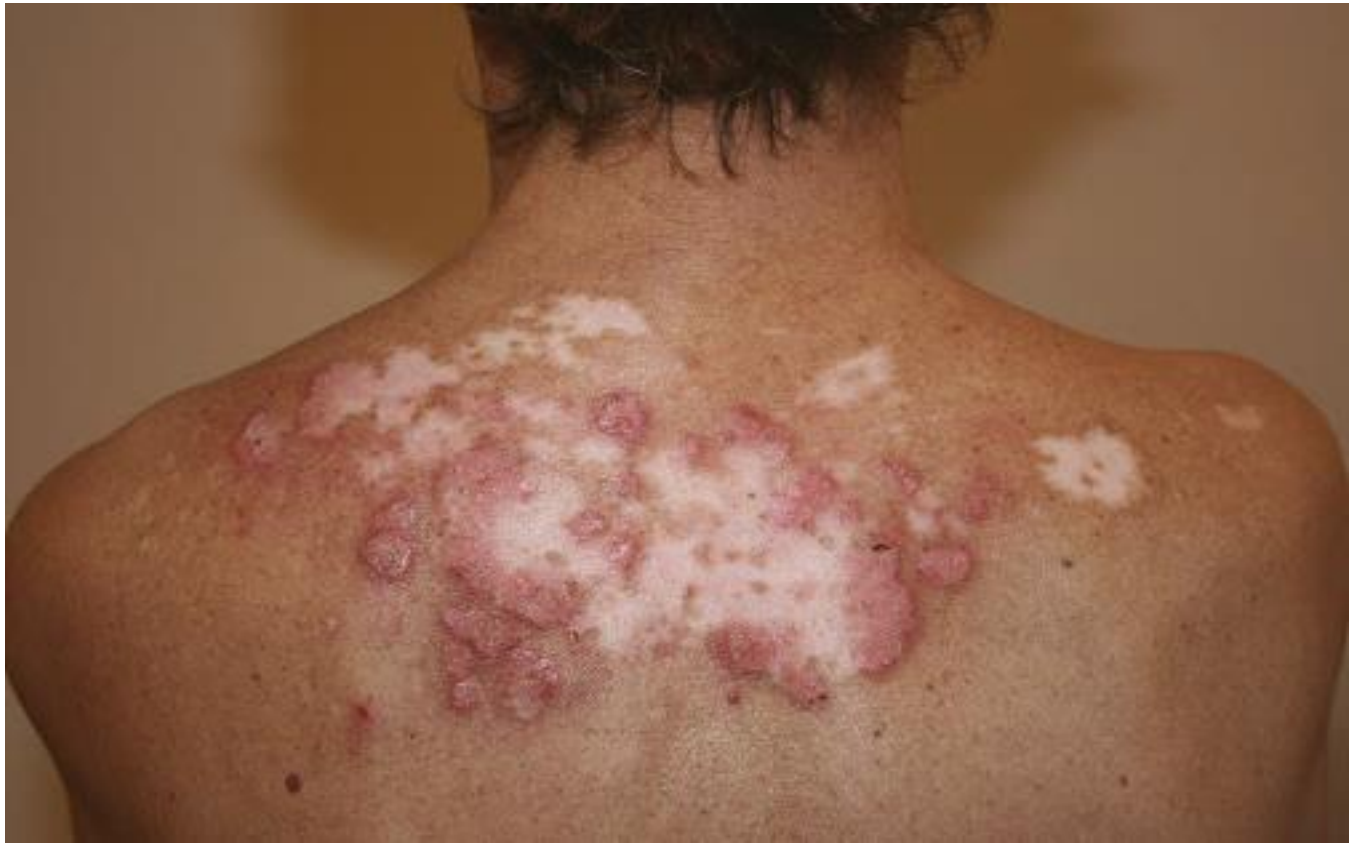
Discoid Lupus Erythematosus (DLE)



https://www.chandigarhayurvedcentre.com/wp-content/uploads/2021/10/Discoid-Lupus-erythematous.jpg

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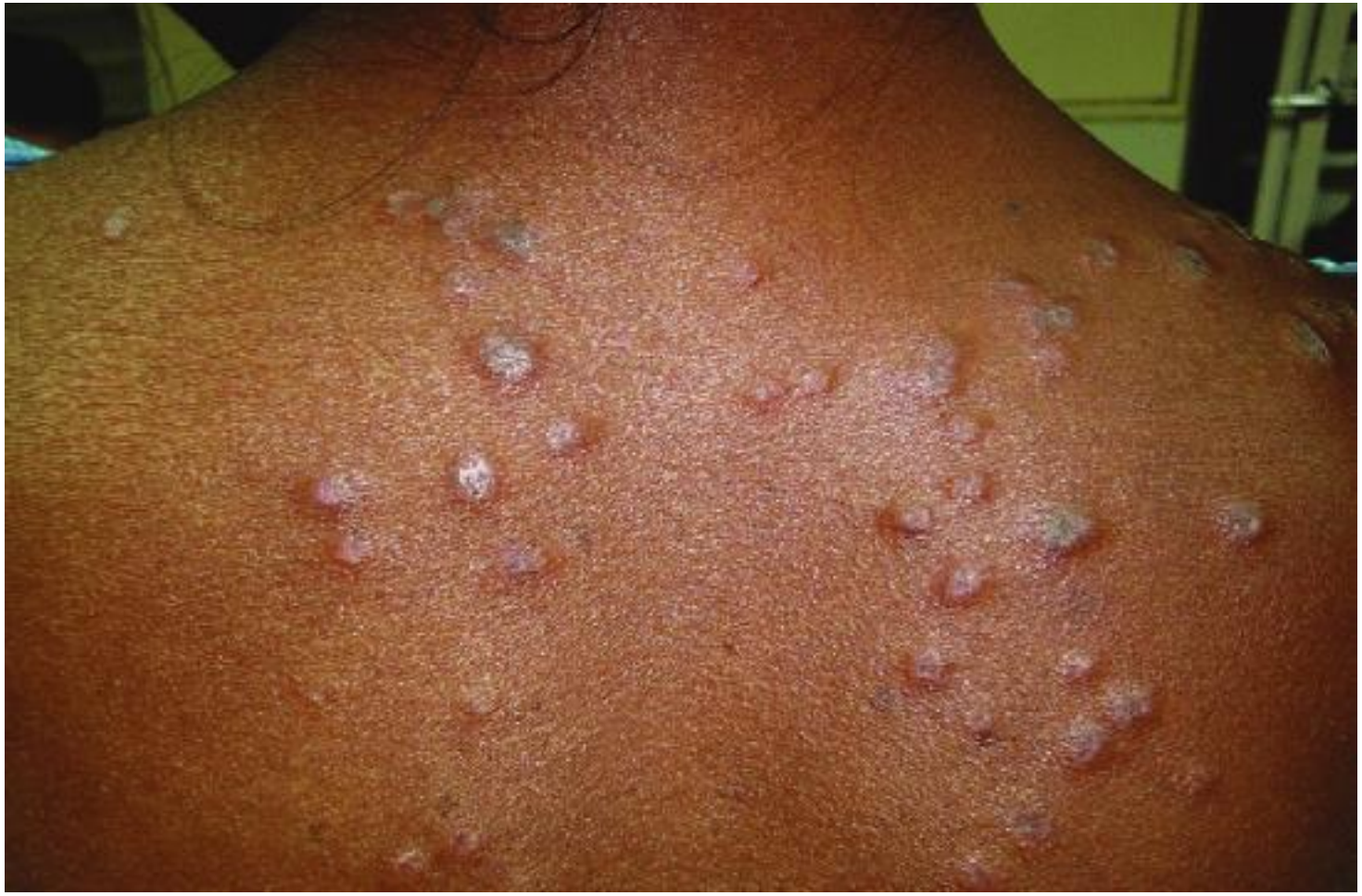
Papulosquamous Rash in SLE



https://www.researchgate.net/publication/338551795/figure/fig3/AS:847136925184001@1578984590229/A-case-of-SLE-with-papulosquamous-rash.png

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Antinuclear antibodies (ANA) are the hallmark of the disease and shall be the initial test performed. Immunofluorescence assay is considered the gold standard test for ANA. Although other detection methods such as enzyme-linked immunosorbent assay (ELISA) and multiplex assays are widely available, they lack sensitivity. A positive ANA is seen in more than 97% of cases of SLE. However, it can also be seen in several other disorders and a significant proportion of the healthy population, and have a specificity of only 20%. Hence, a positive ANA does not confirm SLE diagnosis, but a negative ANA makes it significantly less likely. ANA negative SLE has been rarely described, although it is primarily due to methodical error. Those cases have either a positive ANA on immunofluorescence or a positive Anti-Ro (SSA) antibody.

Several patterns of ANAs have been reported, including speckled, homogenous, centromere, cytoplasmic, nucleolar, and dense fine speckled patterns. With the availability of more specific ANAs targeting specific antigens, the staining patterns of ANAs are not considered significant enough by themselves. ANAs with a dense, fine speckled pattern (anti-DFS70) are considered least pathological, and patients with ANAs with this pattern rarely develop systemic autoimmune diseases. The speckled pattern is seen when ANAs are directed against the antigens such as SSA, SSB, Smith, ribonucleoprotein. The homogenous pattern is associated with ANAs targeted at histones, chromatin, and dsDNA, while the centromere pattern is associated with Anti-centromere antibodies seen in limited systemic sclerosis. [17]

Antibodies to deoxyribonucleic acid (DNA) can be primarily divided into two groups: those reactive with denatured, single-stranded (ss)DNA and those identifying native, double-stranded (ds)DNA. Notably, anti-ssDNA antibodies are considered non-specific and may be seen either as a laboratory error or in the healthy population. Anti-double-stranded deoxyribonucleic acid (dsDNA) antibodies have more than 95% specificity for SLE but are found in only about 60% to 70% of SLE patients. Thus a negative anti dsDNA does not rule out the diagnosis of SLE. The Farr radioimmunoassay test is considered the gold standard for detecting anti-dsDNA antibodies, although it is not frequently used. ELISA tests are available, but they have a high risk of giving a false positive test. The immunofluorescence test by using the *Crithidia luciliae* method can confirm the presence of anti-Ds-DNA antibodies. Anti-dsDNA antibodies can also be seen in drug-induced lupus, primarily secondary to anti-TNF agents and interferon-alpha. Rarely low titers of anti-dsDNA antibodies have been reported in rheumatoid arthritis and Sjogren syndrome. In SLE, anti-dsDNA antibodies can correlate with disease activity and the development of lupus nephritis. However, this may not always be true as some patients have elevated anti-dsDNA antibodies in the setting of minimally active or inactive lupus.

Anti-Ro (SSA) and anti-La (SSB) antibodies target ribonucleoprotein particles. Anti-Ro and Anti-La antibodies are seen in up to 90% of cases of Sjogren syndrome but can be seen in SLE as well (anti-Ro in up to 50% and anti-La in up to 20% of the cases). In SLE, they may be associated with secondary Sjogren syndrome and keratoconjunctivitis sicca, subacute cutaneous lupus, photosensitivity, congenital heart block, and neonatal lupus.[18]

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Complements C3 and C4 shall be checked in patients with SLE or suspicion of SLE, and low complement levels indicate complement consumption and may correlate with disease activity. Markers of inflammation such as erythrocyte sedimentation rate and C-reactive protein may be elevated. Complete blood counts, liver function tests, and renal function tests, including serum creatinine, urinalysis, and urine protein quantification (24-hour urine protein, or spot urine protein/creatinine ratio), shall be checked to assess organ involvement. Synovial fluid aspiration reveals an inflammatory fluid. Joint radiographs may demonstrate peri-articular osteopenia, deformities, or subluxation but rarely show erosions. Chest imaging with computed tomography (CT) scan, cardiac workup including echocardiography (trans-esophageal when suspecting Libman-Sacks endocarditis), CNS work up with magnetic resonance imaging (MRI), and/or lumbar puncture shall be pursued if specific organ involvement is suspected. Renal biopsy shall always be performed if suspicion of lupus nephritis. Skin biopsies can be considered, especially if atypical presentation.[19]

https://www.ncbi.nlm.nih.gov/books/NBK535405/

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TABLE 1: DIFFERENCES BETWEEN DRUG-INDUCED LUPUS ERYTHEMATOSUS AND SYSTEMIC LUPUS ERYTHEMATOSUS

Clinical Features	Systemic Lupus Erythematosus	Drug-Induced Lupus
Age (years)	20-40	50
Female:Male	9:1	1:1
Onset of symptoms	Gradual	Abrupt
Symptom severity	Mild to severe	Generally mild
Constitutional symptoms	83%	50%
Arthralgia and arthritis	90%	95%
Pleuropericarditis (procainamide)	50%	50%
Hepatomegaly	5%-10%	15%-20%
Cutaneous involvement	54%-70% (malar, discoid rash, oral ulcers)	<5%-25%
Renal disease	32%-53%	Photosensitivity, purpura
Central nervous system disease	20%-32%	5%-10%
Hematologic abnormalities	Common	<5%
Serologic factors		
Antinuclear antibody	>95%	>95%
Antihistone	60%-80%	90%-95%
Anti-double stranded DNA antibodies	50%-70%	<5%
Anti-Smith	20%-30%	Rare
Hypocomplementemia	50%-60%	<5%

https://www.pharmacytimes.com/view/drug-induced-autoimmune-diseases

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Causal and associated relationship with SLE

Antihypertensives
Calcium channel blockers
Diltiazem, verapamil, nifedipine
Angiotensin-converting enzyme inhibitors
Thiazide diuretics
Hydrochlorothiazide
Beta blockers
Acebutolol
HMG-CoA reductase inhibitors (statins)
Interferon alpha and beta
Antifungals
Terbinafine, griseofulvin
Antiplatelets
Ticlopidine
Nonsteroidal anti-inflammatory drugs
Piroxicam, naproxen
Antidepressants
Bupropion
Others
Lansoprazole, tamoxifen, leflunomide, docetaxel
Biologicals
Efalizumab, etanercept, infliximab, interferon-beta

- Estrogens, oral contraceptives
- Danazol
- Mesalazine
- Reserpine
- Griseofulvin
- Clonidine
- Hydroxyurea
- Gemfibrozil
- Allopurinol
- Quinine
- Minoxidil
- Calcium channel blockers
- Amiodarone
- Spironolactone
- Clozapine
- Tocainide
- Zafirlukast
- Omeprazole

Although DILE has a more favorable prognosis than SLE, prompt diagnosis and discontinuation of the offending agent are critical. Once mainly associated with cardiovascular drugs, DILE is now associated with more drug classes, including TNF blockers and interferons. Because these agents are used to manage autoimmune disorders, diagnosing DILE can be challenging. The challenge is being able to differentiate a true drug-induced lupus from an exacerbation of preexisting lupus or the unmasking of a second autoimmune disease.[1]

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Current Pharma Intervention

•**NSAIDs** These anti-inflammatory medications relieve some lupus symptoms by reducing the inflammation responsible for the stiffness and discomfort in your muscle, joints, and other tissues. NSAIDs are milder than many other lupus drugs and may be taken either alone to treat a mild flare or in combination with other medications.

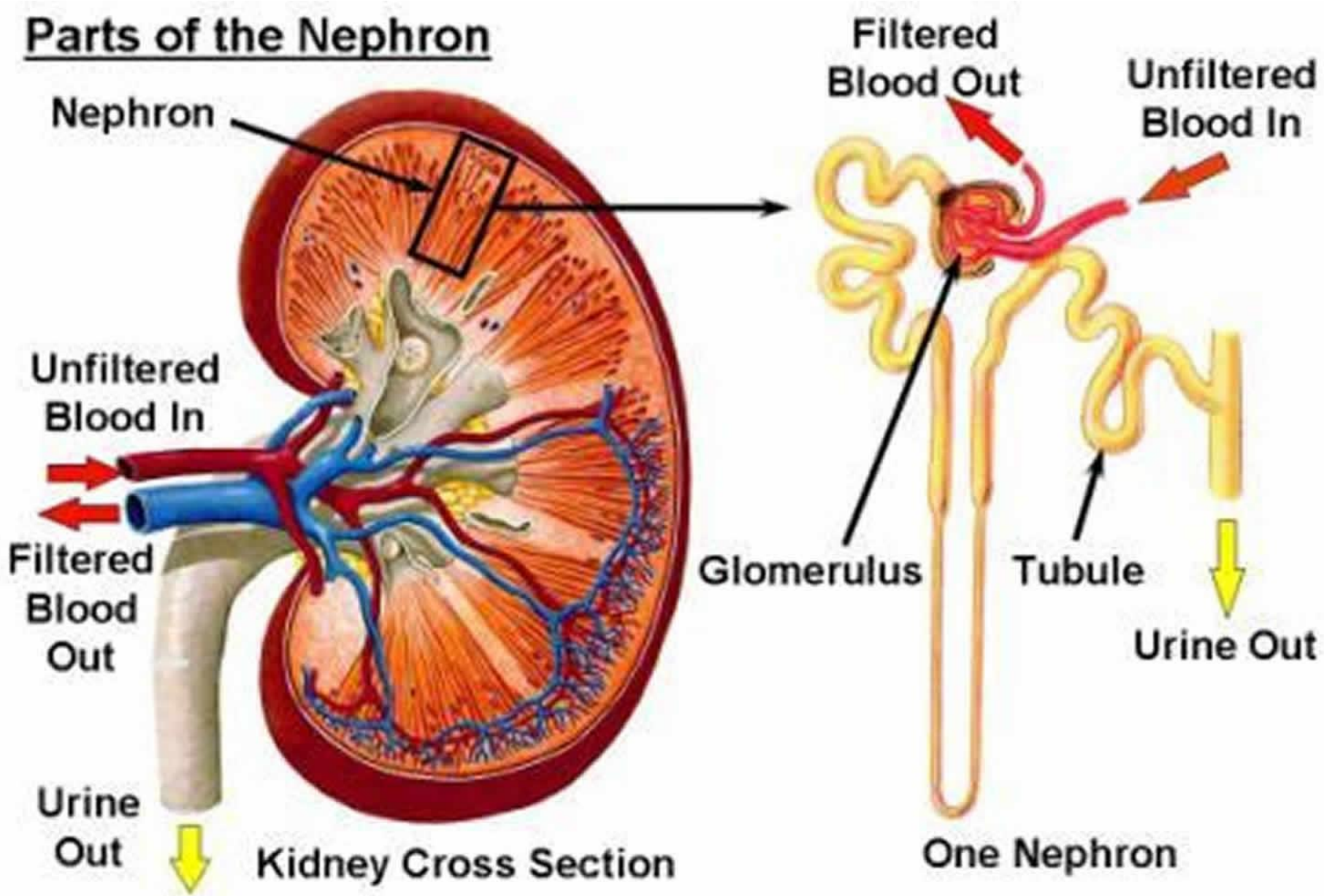
•**Anti-Malarial Drugs** Plaquenil and other anti-malarials are the key to controlling lupus long term, and some lupus patients may be on Plaquenil for the rest of their lives. For this reason, you can think of anti-malarials as a sort of "lupus life insurance."

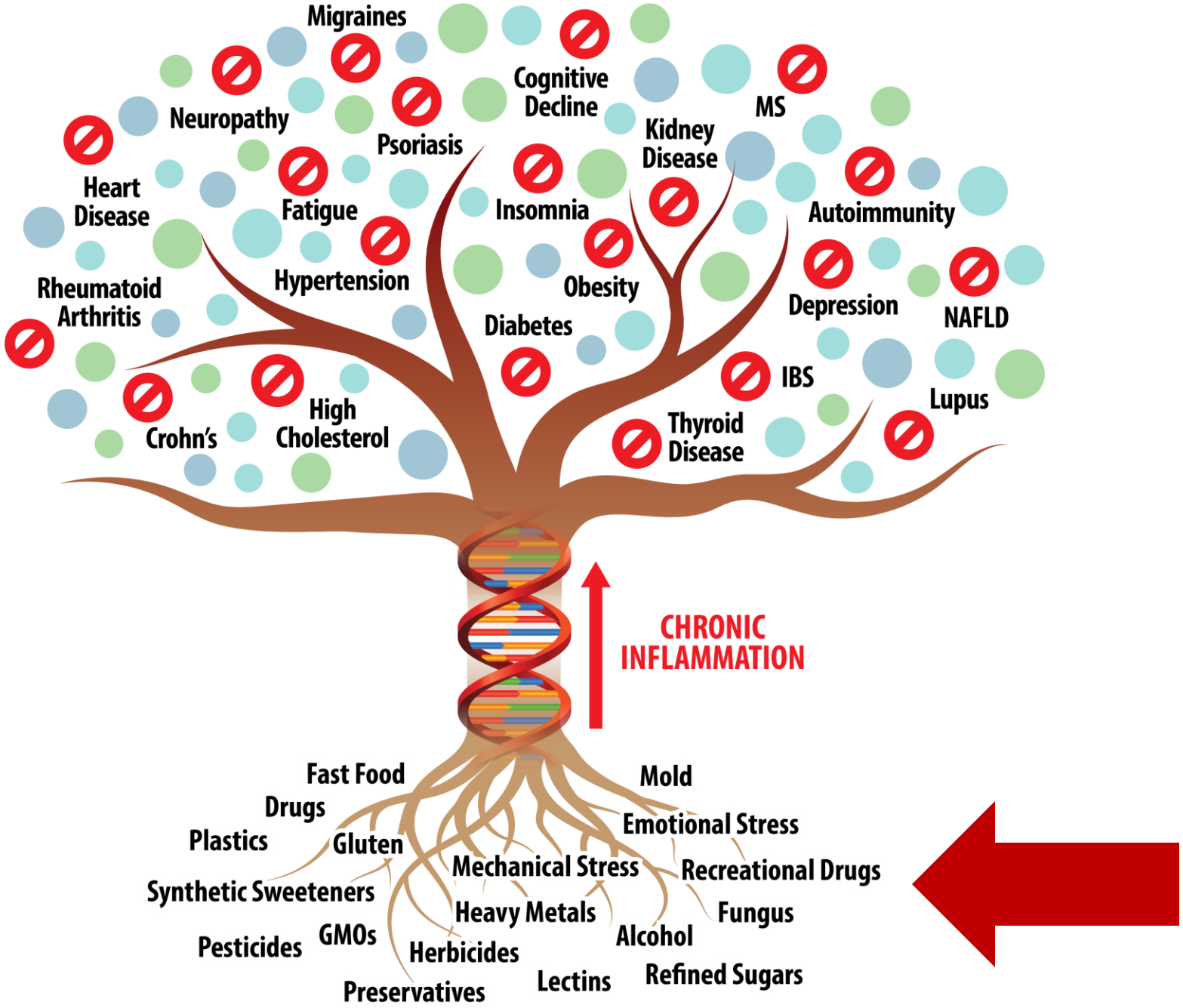
•**Steroids** Synthetic cortisone medications are some of the most effective treatments for reducing the swelling, warmth, pain, and tenderness associated with the inflammation of lupus. Cortisone usually works quickly to relieve these symptoms. However, cortisone can also cause many unwelcome side effects, so it is usually prescribed only when other medications—specifically NSAIDs and anti-malarials—are not sufficient enough to control lupus.

•**Immunosuppressive Medications** Immunosuppressives are medications that help suppress the immune system. Many were originally used in patients who received organ transplants to help prevent their bodies from rejecting the transplanted organ. However, these drugs are now also used for the treatment of certain autoimmune diseases, such as lupus and rheumatoid arthritis.

•**DHEA** DHEA is a mild male hormone that is effective in treating some of the symptoms of mild to moderate lupus, including hair loss (alopecia), joint pain, fatigue, and cognitive dysfunction (e.g., difficulty thinking, memory loss, distractibility, difficulty in multitasking). DHEA can also be effective against osteoporosis.

https://www.hopkinslupus.org/lupus-treatment/lupus-medications/




Migraines
Neuropathy
Psoriasis
Cognitive Decline
MS
Kidney Disease
Heart Disease
Fatigue
Insomnia
Autoimmunity
Rheumatoid Arthritis
Hypertension
Obesity
Depression
NAFLD
Diabetes
IBS
Lupus
Crohn's
High Cholesterol
Thyroid Disease
CHRONIC INFLAMMATION
Fast Food
Drugs
Plastics
Gluten
Synthetic Sweeteners
Pesticides
GMOs
Herbicides
Preservatives
Lectins
Refined Sugars
Heavy Metals
Mechanical Stress
Alcohol
Mold
Emotional Stress
Recreational Drugs
Fungus

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Immunology

Test Name	Result	Reference Range	Lab
ANA SCREEN, IFA, W/REFL TITER AND PATTERN			CB
ANA SCREEN, IFA	**POSITIVE**	NEGATIVE	
ANA IFA is a first line screen for detecting the presence of up to approximately 150 autoantibodies in various autoimmune diseases. A positive ANA IFA result is suggestive of autoimmune disease and reflexes to titer and pattern. Further laboratory testing may be considered if clinically indicated. For additional information, please refer to http://education.QuestDiagnostics.com/faq/FAQ177 (This link is being provided for informational/ educational purposes only.)			
ANTINUCLEAR ANTIBODIES TITER AND PATTERN			CB
ANA TITER	**1:80 H**	titer	
A low level ANA titer may be present in pre-clinical autoimmune diseases and normal individuals. Reference Range <1:40 Negative 1:40-1:80 Low Antibody Level >1:80 Elevated Antibody Level			
ANA PATTERN	**Nuclear, Speckled**		
Speckled pattern is associated with mixed connective tissue disease (MCTD), systemic lupus erythematosus (SLE), Sjogren's syndrome, dermatomyositis, and systemic sclerosis/polymyositis overlap. AC-2,4,5,29: Speckled International Consensus on ANA Patterns (https://doi.org/10.1515/cclm-2018-0052)			
Physician Comments:			

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Test Name	In Range	Out Of Range	Reference Range
THYROID PANEL WITH TSH			
THYROID PANEL			
T3 UPTAKE	29		22-35 %
T4 (THYROXINE), TOTAL	8.4		5.3-11.7 mcg/dL
FREE T4 INDEX (T7)	2.4		1.4-3.8
TSH	1.49		mIU/L
			Reference Range
			1-19 Years 0.50-4.30
			Pregnancy Ranges
			First trimester 0.26-2.66
			Second trimester 0.55-2.73
			Third trimester 0.43-2.91
LIPID PANEL, STANDARD			
CHOLESTEROL, TOTAL	153		<170 mg/dL
HDL CHOLESTEROL	56		>45 mg/dL
TRIGLYCERIDES	87		<90 mg/dL
LDL-CHOLESTEROL	80		<110 mg/dL (calc)
LDL-C is now calculated using the Martin-Hopkins calculation, which is a validated novel method providing better accuracy than the Friedewald equation in the estimation of LDL-C. Martin SS et al. JAMA. 2013;310(19): 2061-2068 (http://education.QuestDiagnostics.com/faq/FAQ164)			
CHOL/HDLC RATIO	2.7		<5.0 (calc)
NON HDL CHOLESTEROL	97		<120 mg/dL (calc)
For patients with diabetes plus 1 major ASCVD risk factor, treating to a non-HDL-C goal of <100 mg/dL (LDL-C of <70 mg/dL) is considered a therapeutic option.			
HS CRP		**3.4 H**	mg/L
Reference Range			
Optimal <1.0			
Jellinger PS et al. Endocr Pract.2017;23(Suppl 2):1-87.			
For ages >17 Years:			
hs-CRP mg/L	Risk According to AHA/CDC Guidelines		
<1.0	Lower relative cardiovascular risk.		
1.0-3.0	Average relative cardiovascular risk.		
3.1-10.0	Higher relative cardiovascular risk. Consider retesting in 1 to 2 weeks to exclude a benign transient elevation in the baseline CRP value secondary to infection or inflammation.		
>10.0	Persistent elevation, upon retesting, may be associated with infection and inflammation.		

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COMPREHENSIVE METABOLIC PANEL		
GLUCOSE	71	65-99 mg/dL Fasting reference interval
UREA NITROGEN (BUN)	18	7-20 mg/dL
CREATININE	0.78	0.50-0.96 mg/dL
EGFR	113	> OR = 60 mL/min/1.73m2
BUN/CREATININE RATIO	SEE NOTE: Not Reported: BUN and Creatinine are within reference range.	6-22 (calc)
SODIUM	139	135-146 mmol/L
POTASSIUM	4.3	3.8-5.1 mmol/L
CHLORIDE	103	98-110 mmol/L
CARBON DIOXIDE	21	20-32 mmol/L
CALCIUM	9.9	8.9-10.4 mg/dL
PROTEIN, TOTAL	8.0	6.3-8.2 g/dL
ALBUMIN	4.7	3.6-5.1 g/dL
GLOBULIN	3.3	2.0-3.8 g/dL (calc)
ALBUMIN/GLOBULIN RATIO	1.4	1.0-2.5 (calc)
BILIRUBIN, TOTAL	0.5	0.2-1.1 mg/dL
ALKALINE PHOSPHATASE	92	36-128 U/L
AST	29	12-32 U/L
ALT	16	5-32 U/L
HEMOGLOBIN A1c	5.5	<5.7 %

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MAGNESIUM	2.0		1.5-2.5 mg/dL
PHOSPHATE (AS PHOSPHORUS)	4.7		3.0-5.1 mg/dL
URIC ACID	4.8		2.4-6.6 mg/dL
LD		**228 H**	100-200 U/L

Results slightly increased due to hemolysis.

GGT	14		6-26 U/L
T4, FREE	1.2		0.8-1.4 ng/dL
T3, FREE	3.3		3.0-4.7 pg/mL
T3, TOTAL	108		86-192 ng/dL
THYROID PEROXIDASE AND THYROGLOBULIN ANTIBODIES			
THYROGLOBULIN ANTIBODIES	<1		< or = 1 IU/mL
THYROID PEROXIDASE ANTIBODIES	1		<9 IU/mL
FIBRINOGEN ACTIVITY, CLAUSS	268		175-425 mg/dL
CBC (INCLUDES DIFF/PLT)			
WHITE BLOOD CELL COUNT	8.9		4.5-13.0 Thousand/uL
RED BLOOD CELL COUNT	4.27		3.80-5.10 Million/uL
HEMOGLOBIN	13.8		11.5-15.3 g/dL
HEMATOCRIT	41.7		34.0-46.0 %
MCV	97.7		78.0-98.0 fL
MCH	32.3		25.0-35.0 pg
MCHC	33.1		31.0-36.0 g/dL

For adults, a slight decrease in the calculated MCHC value (in the range of 30 to 32 g/dL) is most likely not clinically significant; however, it should be interpreted with caution in correlation with other red cell parameters and the patient's clinical condition.

RDW	12.2		11.0-15.0 %
PLATELET COUNT	214		140-400 Thousand/uL
MPV	10.6		7.5-12.5 fL
ABSOLUTE NEUTROPHILS	5429		1800-8000 cells/uL
ABSOLUTE LYMPHOCYTES	2777		1200-5200 cells/uL
ABSOLUTE MONOCYTES	401		200-900 cells/uL
ABSOLUTE EOSINOPHILS	240		15-500 cells/uL
ABSOLUTE BASOPHILS	53		0-200 cells/uL
NEUTROPHILS	61		%
LYMPHOCYTES	31.2		%
MONOCYTES	4.5		%
EOSINOPHILS	2.7		%
BASOPHILS	0.6		%

URINALYSIS MACROSCOPIC				
COLOR	YELLOW		YELLOW	
APPEARANCE		**CLOUDY**	CLEAR	
SPECIFIC GRAVITY	1.020		1.001-1.035	
PH	6.0		5.0-8.0	
GLUCOSE	NEGATIVE		NEGATIVE	
BILIRUBIN	NEGATIVE		NEGATIVE	
KETONES	NEGATIVE		NEGATIVE	
OCCULT BLOOD		**TRACE**	NEGATIVE	
PROTEIN	NEGATIVE		NEGATIVE	

Test Name	In Range	Out Of Range	Reference Range	Lab
NITRITE		**POSITIVE**	NEGATIVE	
LEUKOCYTE ESTERASE		**3+**	NEGATIVE	
IRON AND TOTAL IRON BINDING CAPACITY				CB
IRON, TOTAL	111		27-164 mcg/dL	
IRON BINDING CAPACITY	389		271-448 mcg/dL (calc)	
% SATURATION	29		15-45 % (calc)	
FERRITIN	32		6-67 ng/mL	CB
HEPATITIS B SURFACE ANTIBODY QL	NON-REACTIVE		NON-REACTIVE	CB
HEPATITIS B CORE AB TOTAL	NON-REACTIVE		NON-REACTIVE	CB

For additional information, please refer to
http://education.questdiagnostics.com/faq/FAQ202
(This link is being provided for informational/
educational purposes only.)

C-PEPTIDE	1.63		0.80-3.85 ng/mL	CB
INSULIN	11.4		uIU/mL	CB

Reference Range < or = 18.4

Risk:

Optimal	< or = 18.4
Moderate	NA
High	>18.4

Adult cardiovascular event risk category
cut points (optimal, moderate, high)
are based on Insulin Reference Interval
studies performed at Quest Diagnostics
in 2022.

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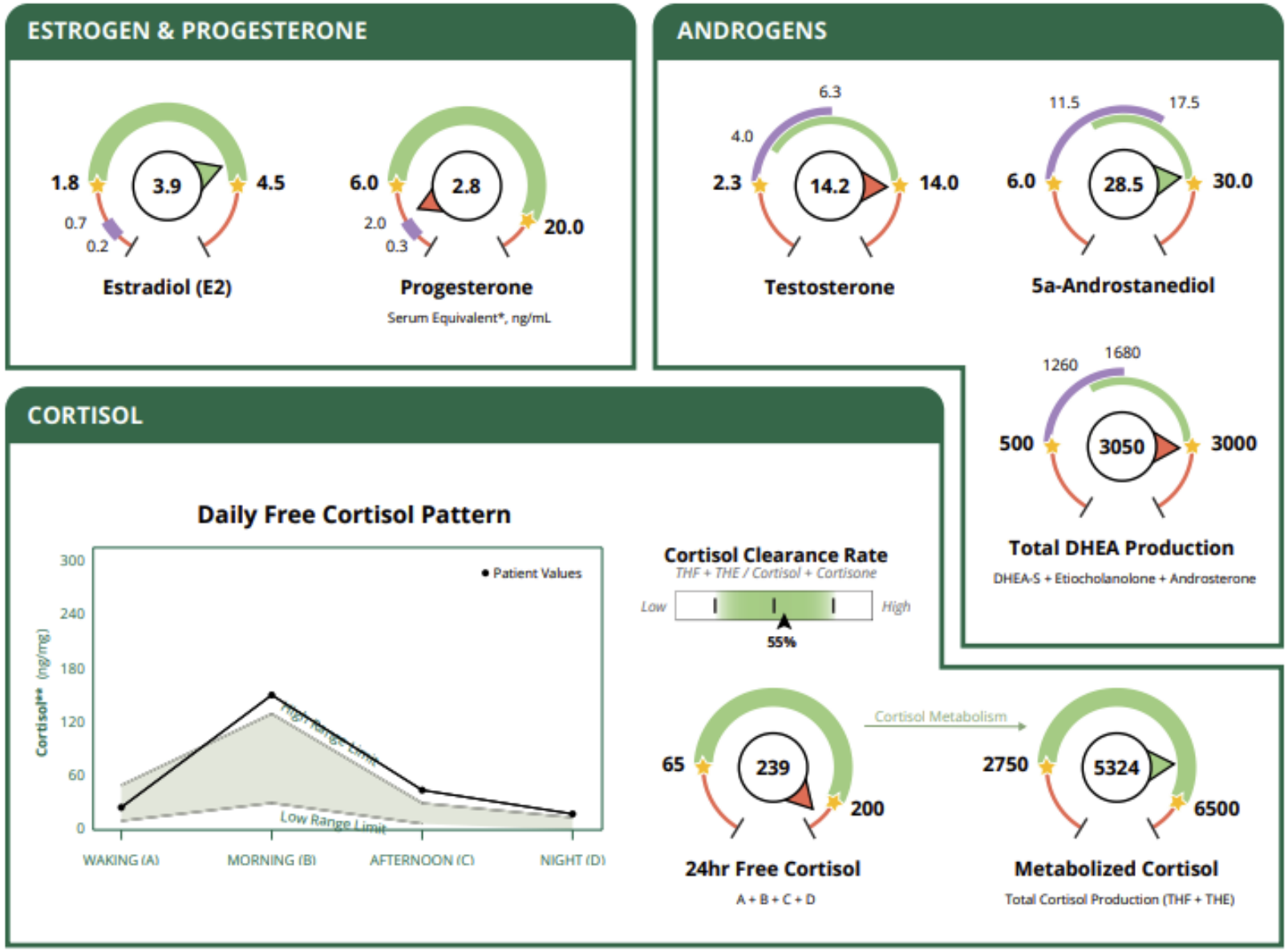
BLOOD:

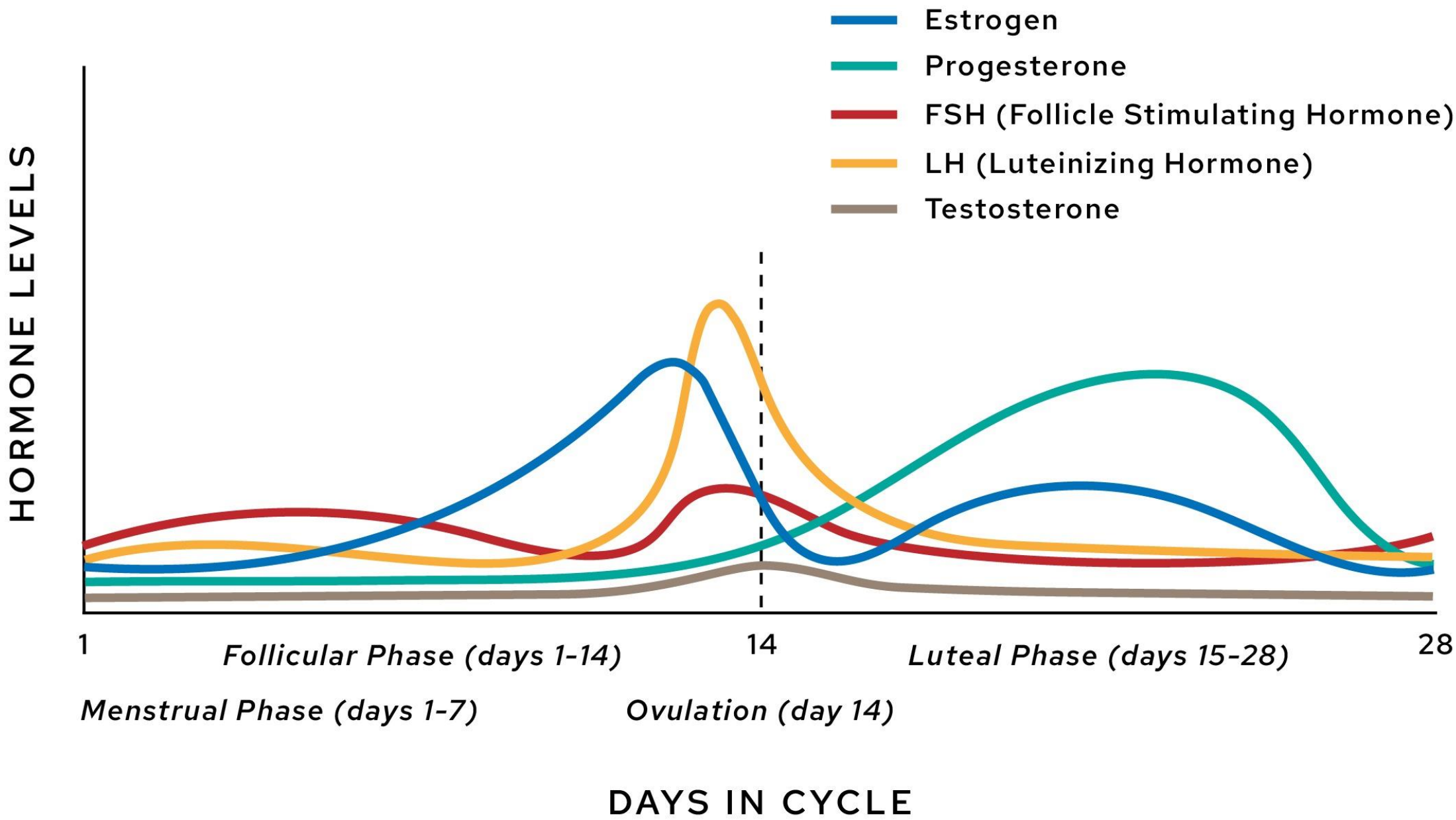
ANA positive, nuclear and speckled.
CRP elevated
LDH elevated
Total protein elevated.
Glucose low, A1c top of range.
Insulin resistance.
WBC elevated, perfect differential.
B12 need.
UTI.

DUTCH:

Last Menstrual Cycle:
6-23

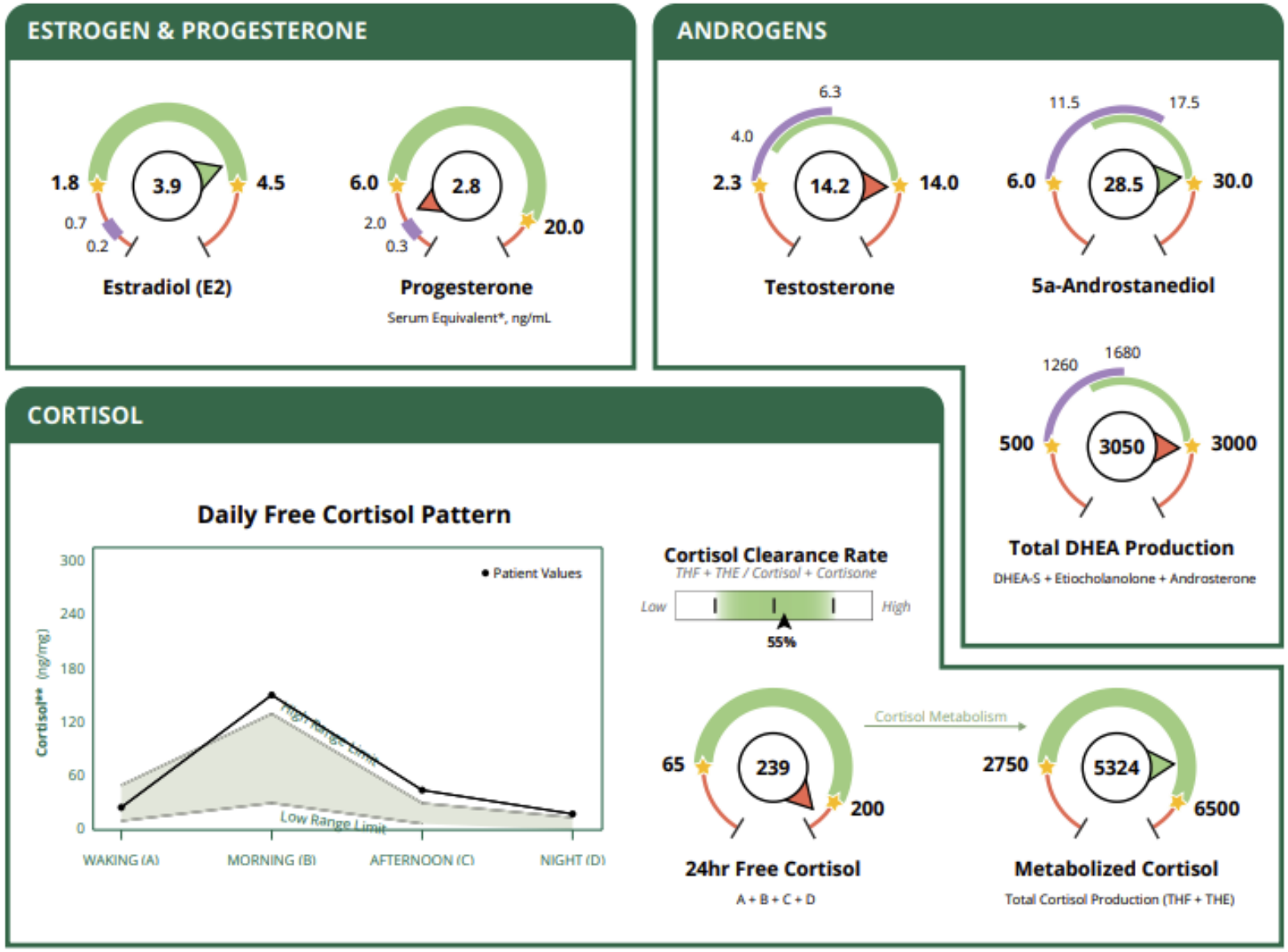
Test filled:
7-7

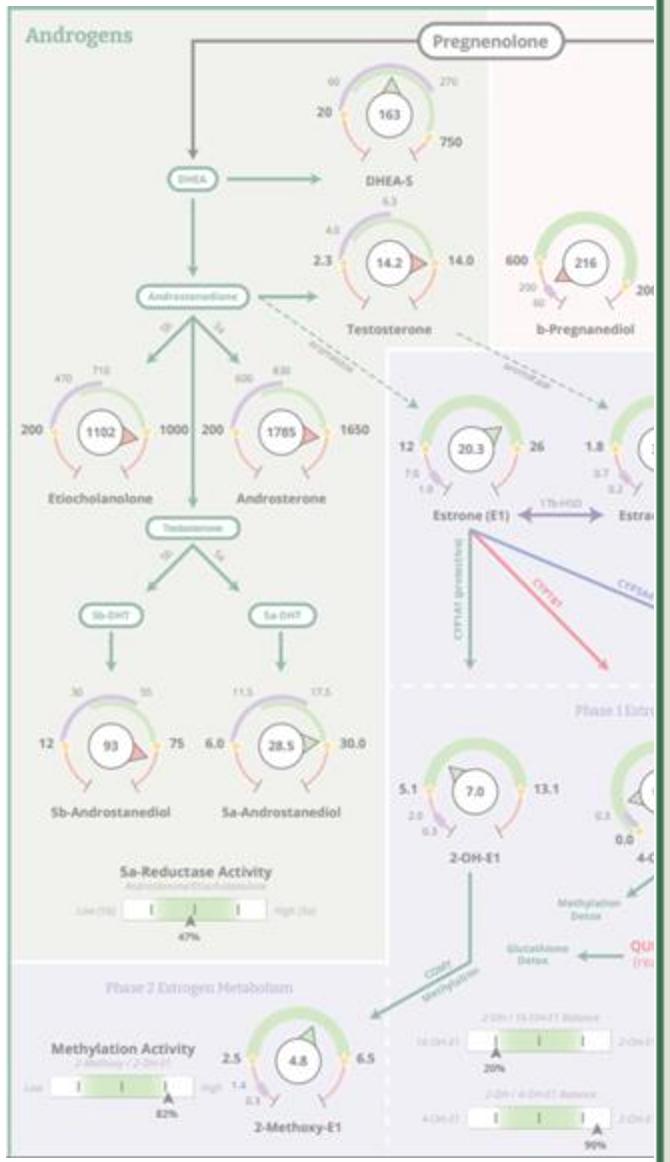


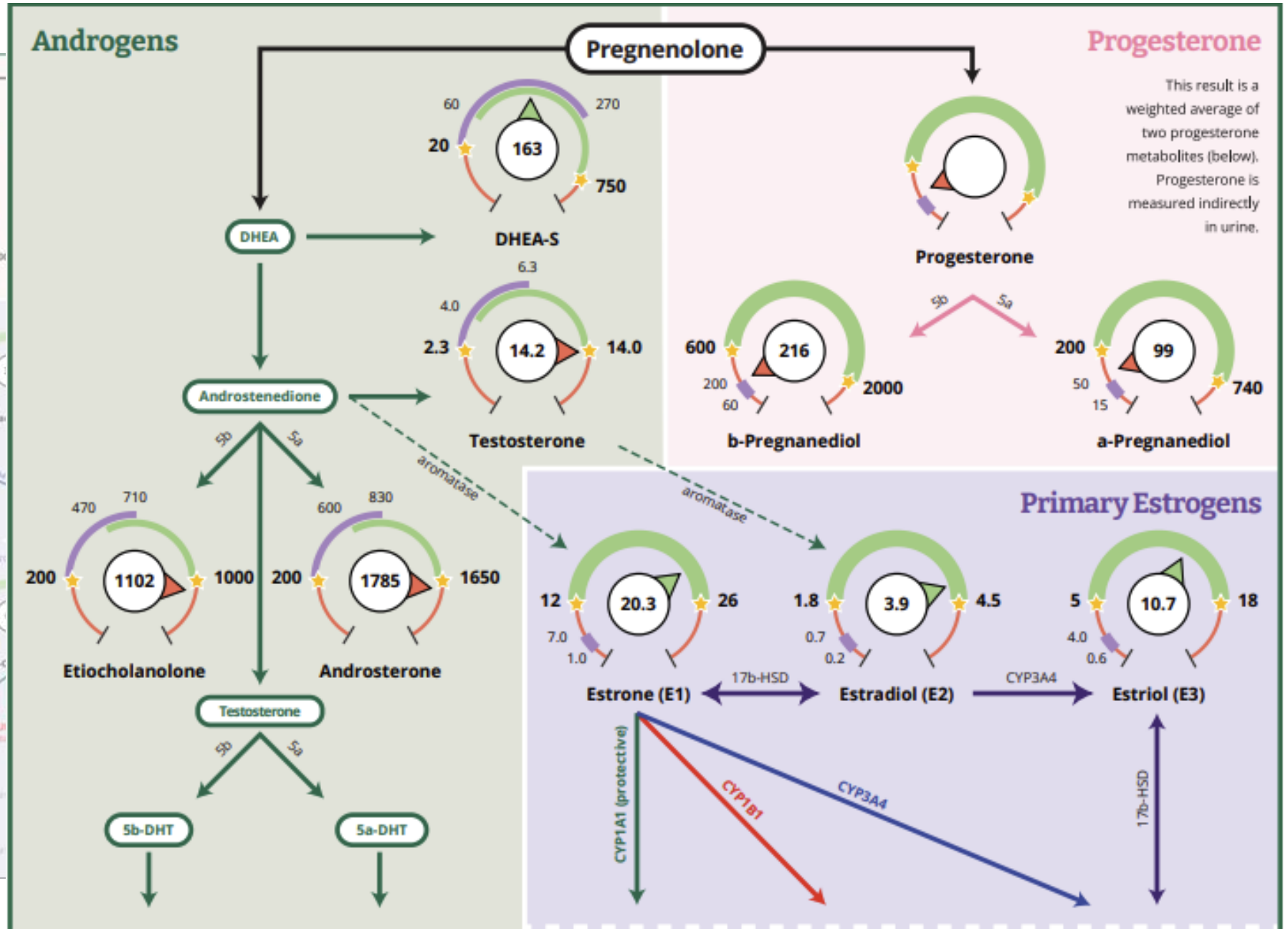

Estrogen
Progesterone
FSH (Follicle Stimulating Hormone)
LH (Luteinizing Hormone)
Testosterone
HORMONE LEVELS
1
14
28
Follicular Phase (days 1-14)
Luteal Phase (days 15-28)
Menstrual Phase (days 1-7)
Ovulation (day 14)
DAYS IN CYCLE

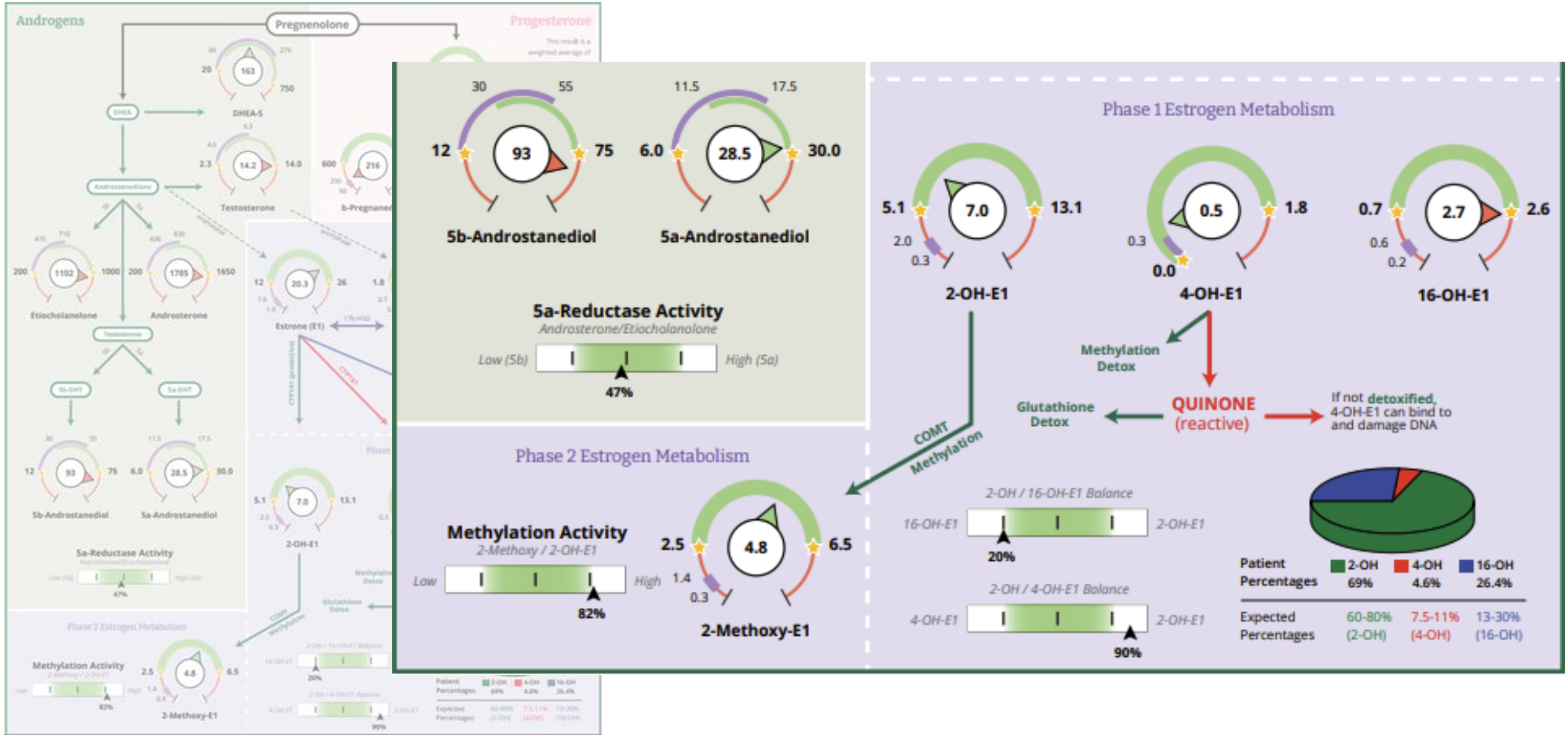
Last Menstrual Cycle:
6-23

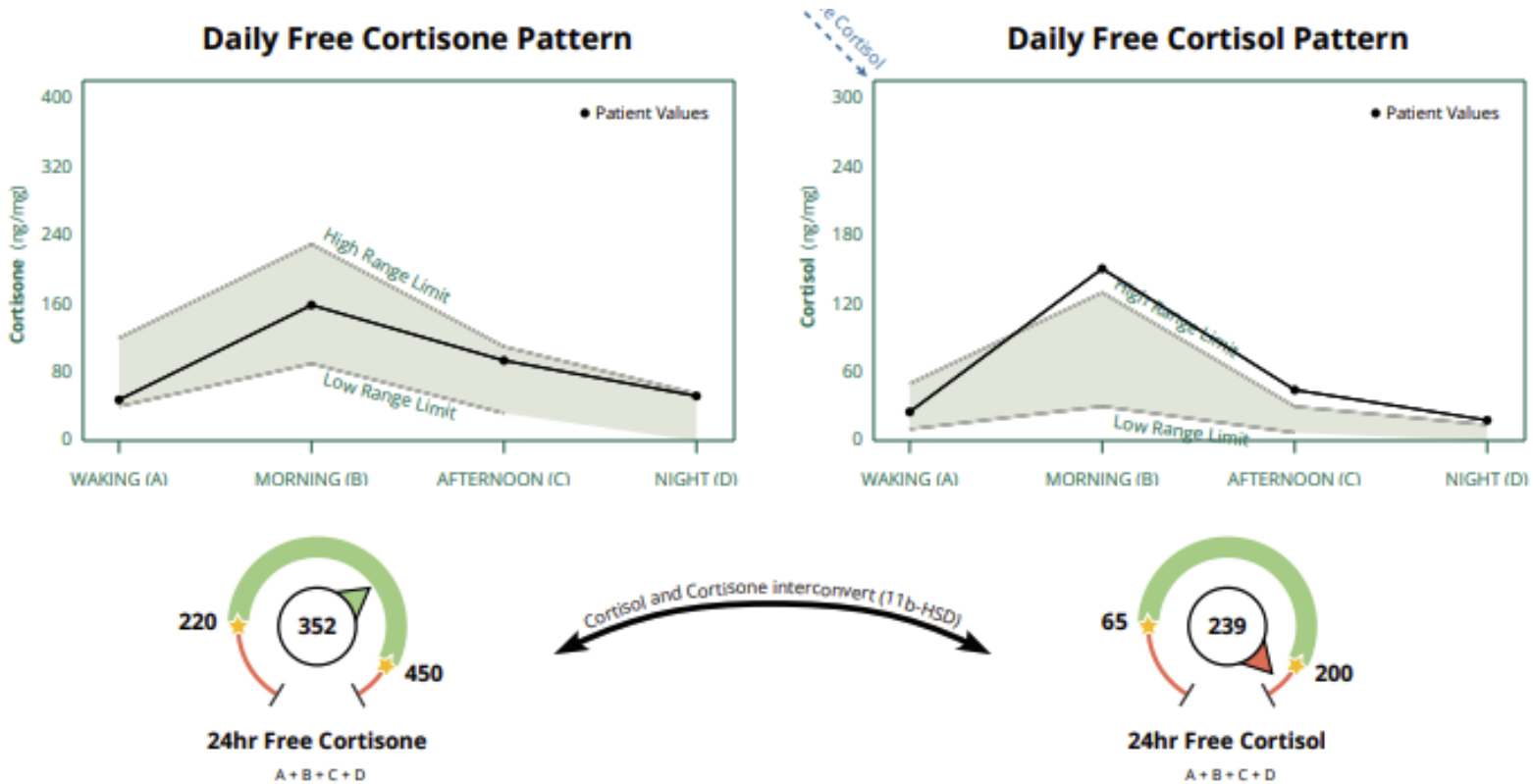
Test filled:
7-7




Androgens
Pregnenolone
DHEA
DHEA-S
Androstenedione
Testosterone
b-Pregnanediol
Etiocholanolone
Androsterone
Estrone (E1)
5b-DHT
5a-DHT
5b-Androstanediol
5a-Androstanediol
5a-Reductase Activity
2-OH-E1
Methylation Activity
2-Methoxy-E1
Phase 2 Estrogen Metabolism


Androgens
Pregnenolone
DHEA
DHEA-S
Androstenedione
Testosterone
5b-DHT
5a-DHT
Etiocholanolone
Androsterone
5b
5a
aromatase
Progesterone
Progesterone
This result is a weighted average of two progesterone metabolites (below). Progesterone is measured indirectly in urine.
b-Pregnanediol
a-Pregnanediol
Primary Estrogens
Estrone (E1)
Estradiol (E2)
Estriol (E3)
17b-HSD
CYP3A4
CYP1A1 (protective)
CYP1B1
CYP3A4
17b-HSD


Androgens
Pregnenolone
Progesterone
DHEA-S
Testosterone
Etiocholanolone
Androsterone
Sb-Androstanediol
Sa-Androstanediol
Sa-Reductase Activity
Androsterone/Etiocholanolone
Low (5b)
High (5a)
47%
Estrone (E1)
2-OH-E1
Phase 2 Estrogen Metabolism
Methylation Activity
2-Methoxy / 2-OH-E1
Low
High
82%
2-Methoxy-E1
Phase 1 Estrogen Metabolism
4-OH-E1
16-OH-E1
Methylation
Detox
QUINONE
(reactive)
Glutathione
Detox
If not detoxified,
4-OH-E1 can bind to
and damage DNA
COMT
Methylation
2-OH / 16-OH-E1 Balance
20%
2-OH / 4-OH-E1 Balance
90%
Patient
Percentages
2-OH
69%
4-OH
4.6%
16-OH
26.4%
Expected
Percentages
60-80%
(2-OH)
7.5-11%
(4-OH)
13-30%
(16-OH)


Daily Free Cortisone Pattern
Cortisone (ng/mg)
400
320
240
160
80
0
Patient Values
High Range Limit
Low Range Limit
WAKING (A)
MORNING (B)
AFTERNOON (C)
NIGHT (D)
Daily Free Cortisol Pattern
Cortisol (ng/mg)
300
240
180
120
60
0
Patient Values
High Range Limit
Low Range Limit
WAKING (A)
MORNING (B)
AFTERNOON (C)
NIGHT (D)
220
352
450
24hr Free Cortisone
A + B + C + D
Cortisol and Cortisone interconvert (11b-HSD)
65
239
200
24hr Free Cortisol
A + B + C + D

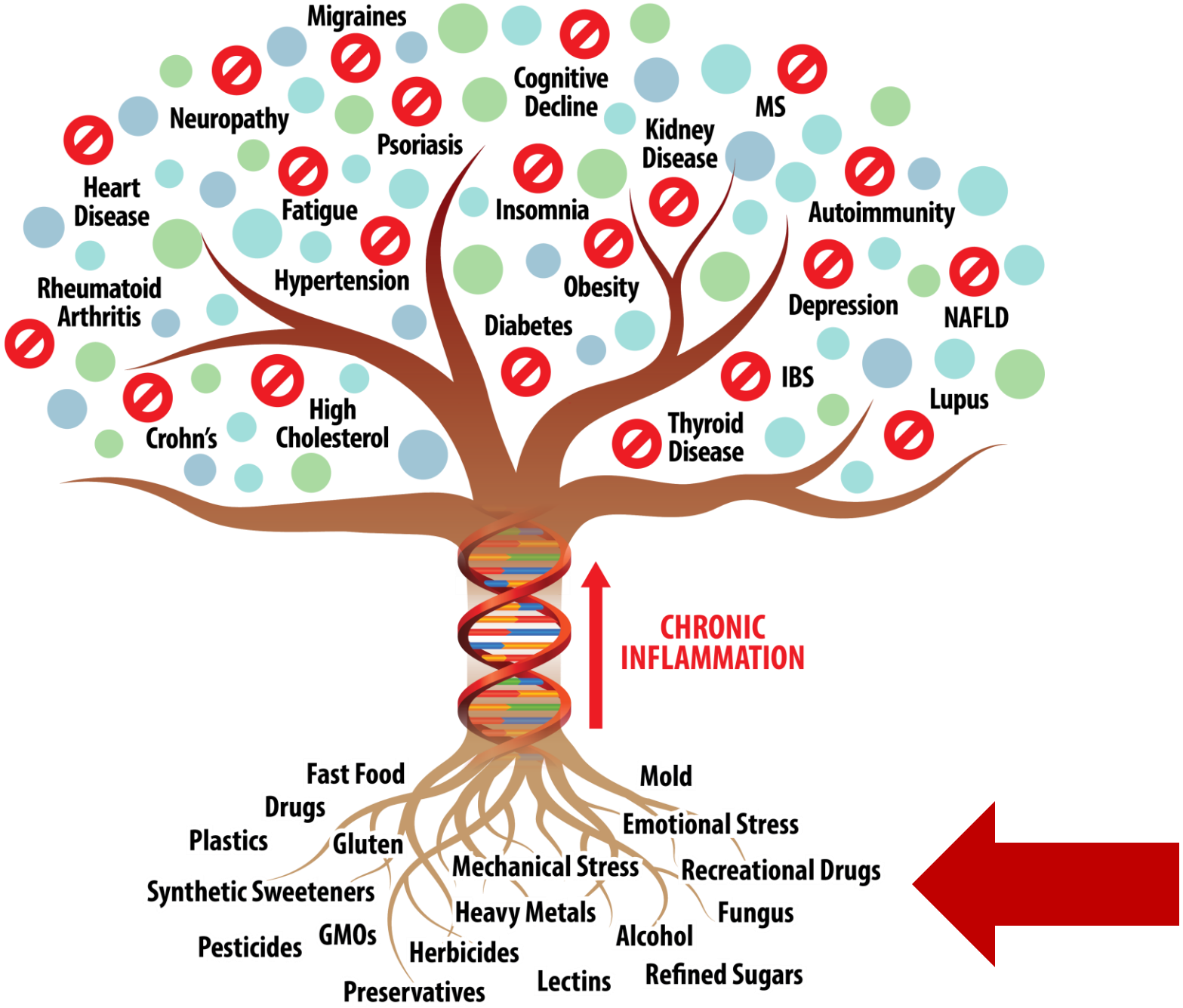
BLOOD:

ANA positive, nuclear and speckled.
CRP elevated
LDH elevated
Total protein elevated.
Glucose low, A1c top of range.
Insulin resistance.
WBC elevated, perfect differential.
B12 need.
UTI.

DUTCH:

Sluggish progesterone.
Elevated androgens.
High Cortisol, sparing mechanism.
5b dominant, high side bilaterally.
Strong methylation

→ Sympathetic tone


Migraines
Neuropathy
Psoriasis
Cognitive Decline
MS
Kidney Disease
Heart Disease
Fatigue
Insomnia
Autoimmunity
Rheumatoid Arthritis
Hypertension
Obesity
Depression
NAFLD
Diabetes
IBS
Lupus
Crohn's
High Cholesterol
Thyroid Disease
CHRONIC INFLAMMATION
Fast Food
Drugs
Plastics
Gluten
Synthetic Sweeteners
Pesticides
GMOs
Herbicides
Preservatives
Lectins
Refined Sugars
Heavy Metals
Mechanical Stress
Alcohol
Mold
Emotional Stress
Recreational Drugs
Fungus

Biogenetix