FM Dermatological Applications: Rosacea

A Biogenetix Clinical Presentation

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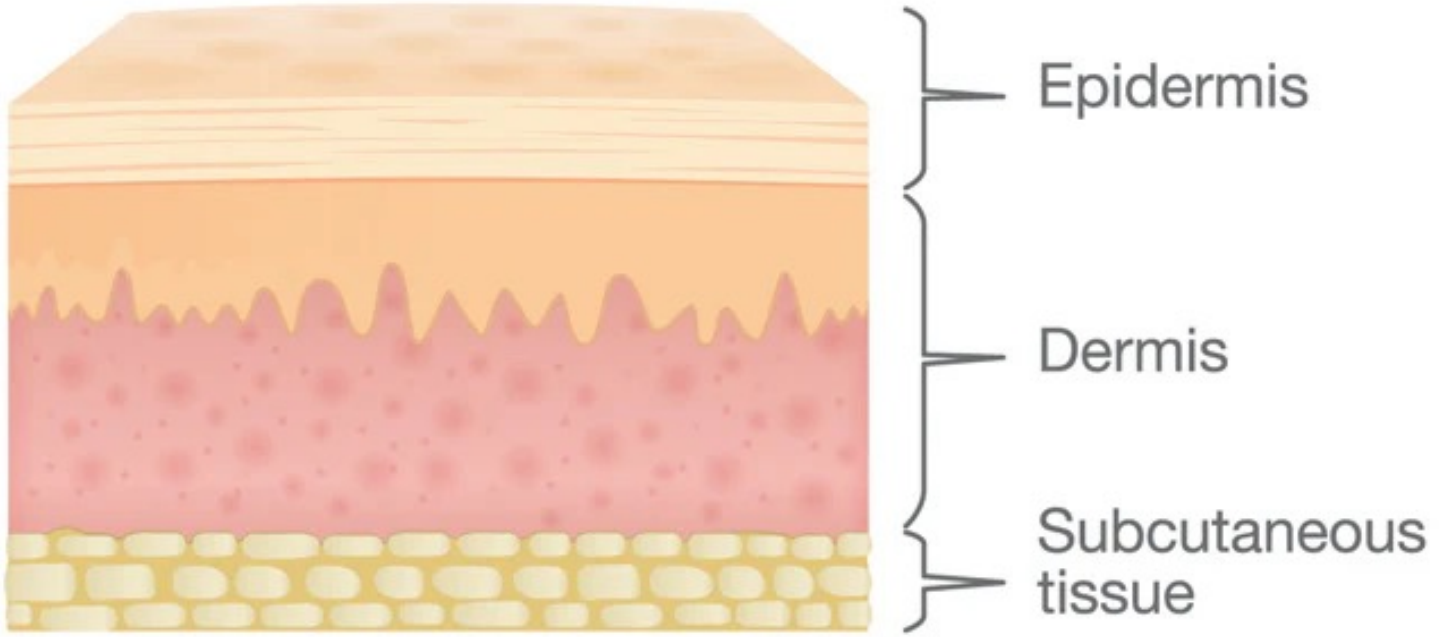
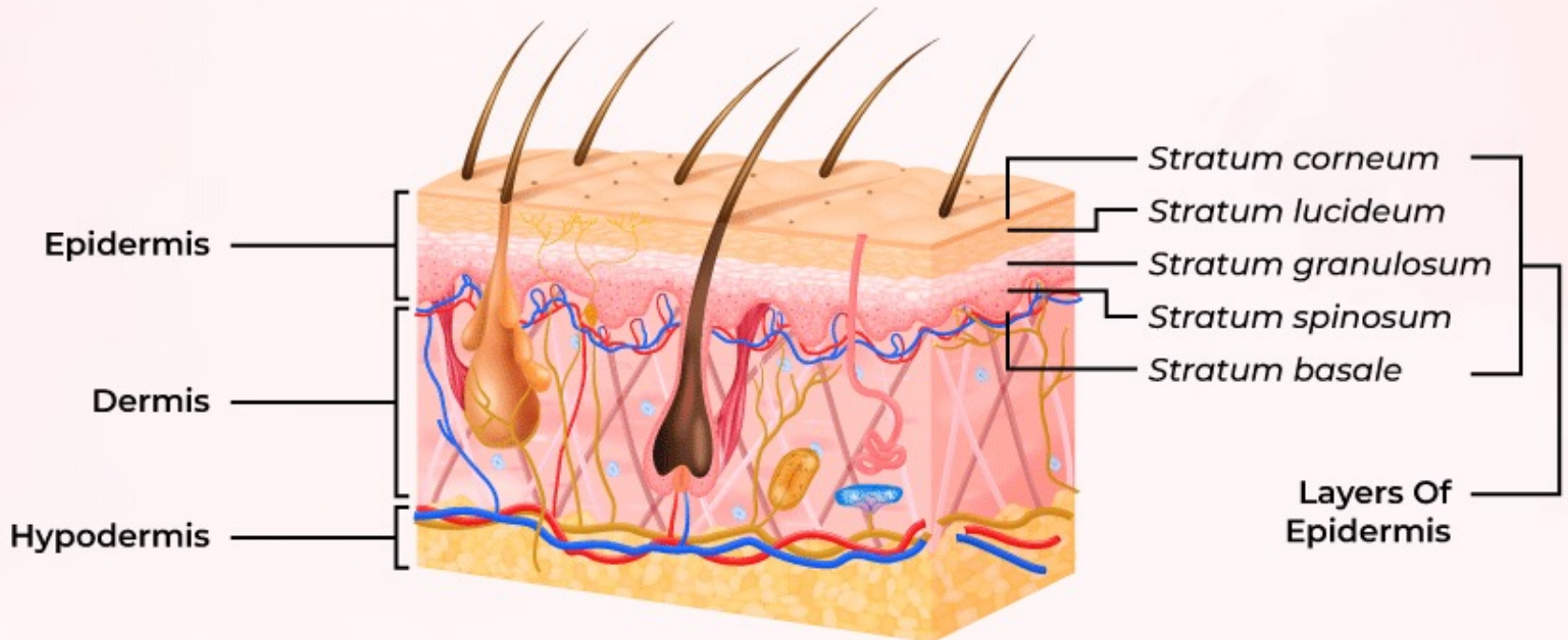
- *The information provided in this presentation is for your consideration only as a practicing health care provider. Ultimately you are responsible for exercising professional judgment in the care of your own patients.*

The Layers of Skin



https://skinkraft.com/cdn/shop/articles/Layers-Of-Skin_1024x1024.jpg?v=1582612390

Layers of the Skin



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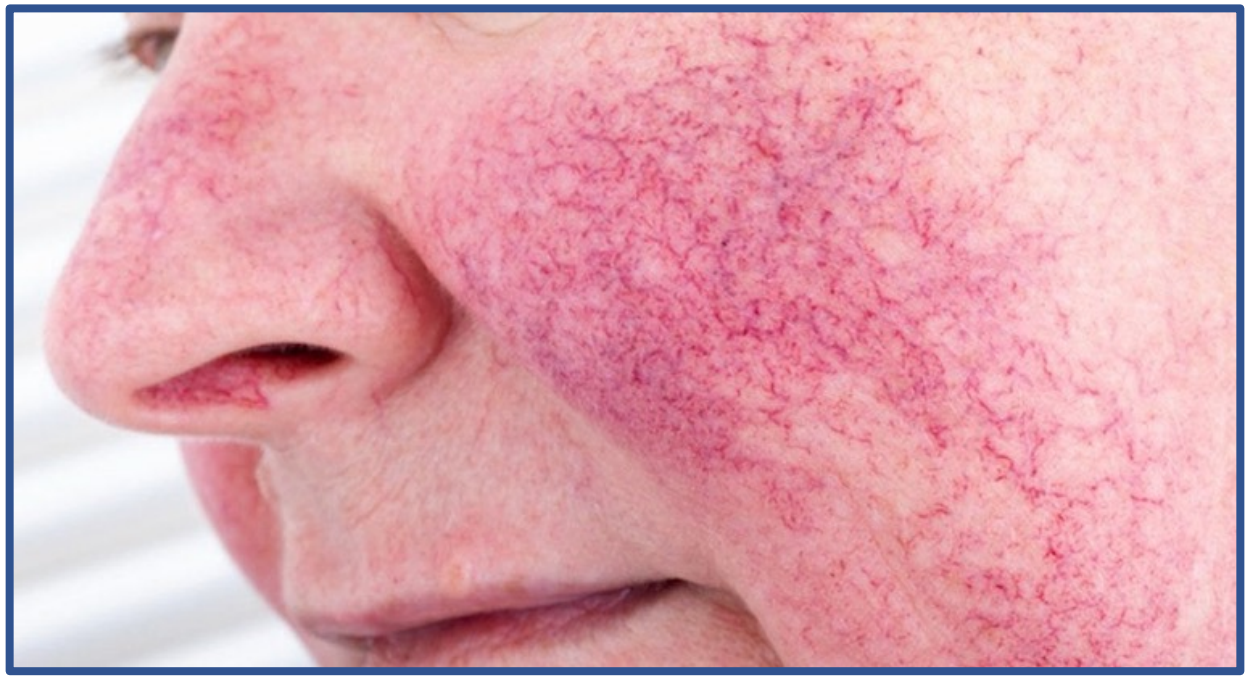
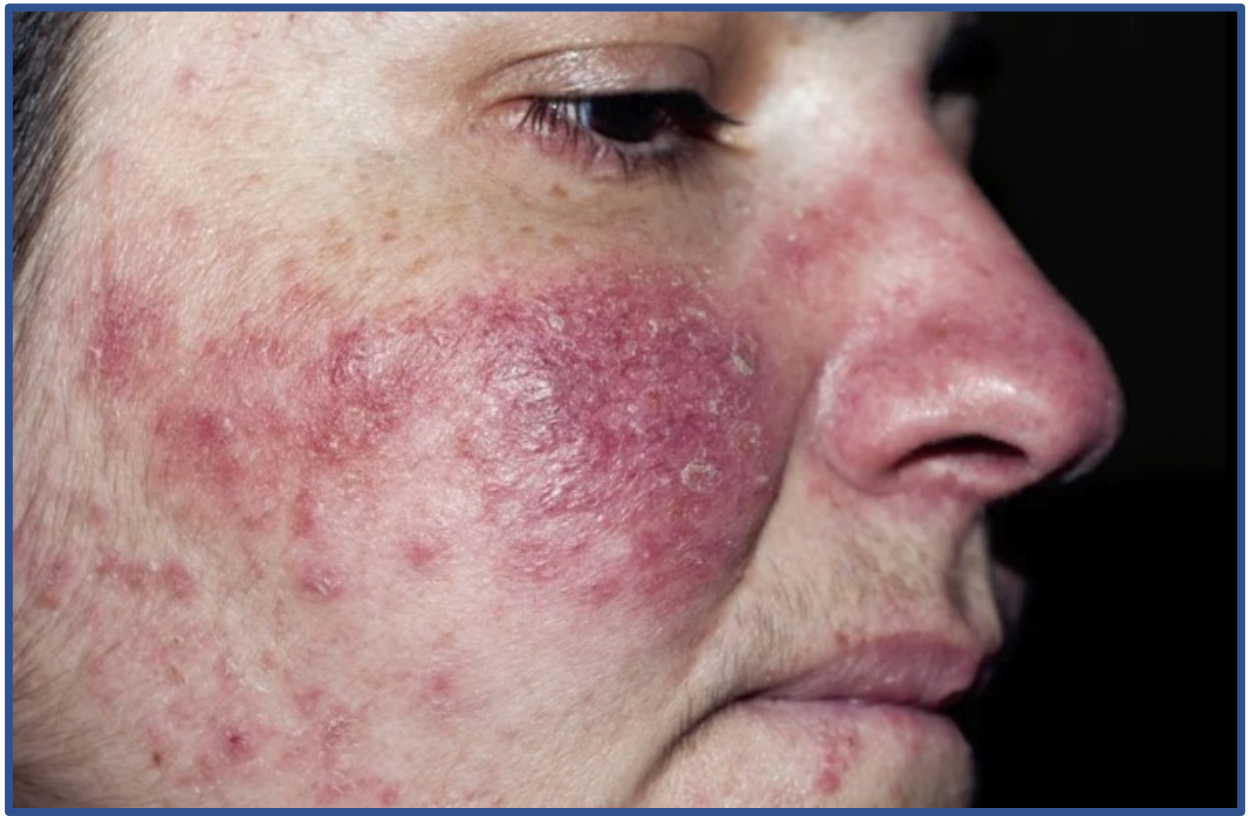
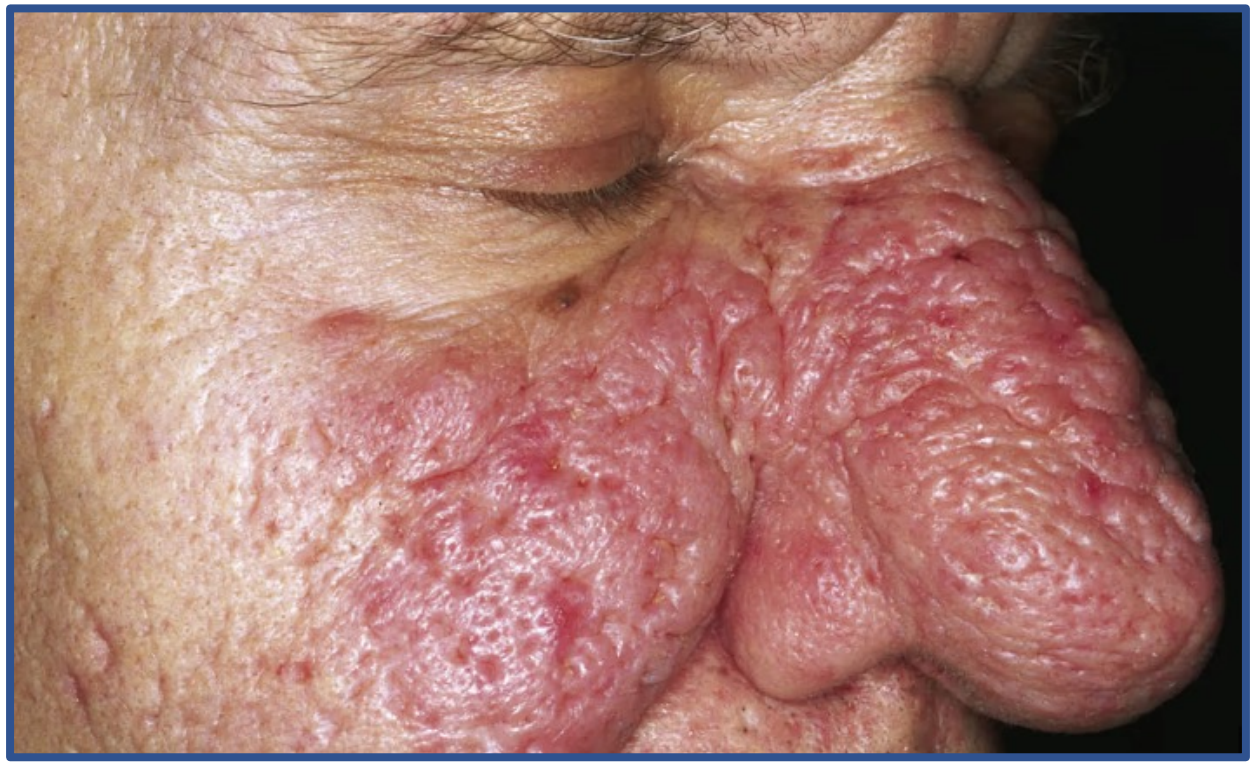
Rosacea is a common chronic inflammatory disease that presents with recurrent flushing, erythema, telangiectasia, papules, or pustules on nose, chin, cheeks, and forehead. There are four clinical subtypes of rosacea based on the predominant signs and symptoms: erythematotelangiectatic, papulopustular, phymatous, and ocular. The subtypes are not mutually exclusive. Patients can present with features of multiple subtypes, and the predominant features and areas of involvement can change over time. Fifty to seventy-five percent of patients with rosacea have eye involvement with symptoms including dryness, redness, tearing, tingling/burning sensation, foreign-body sensation, light sensitivity, and blurred vision. In addition to the skin and eye symptoms, rosacea can cause anxiety, embarrassment, and depression and can have a significant impact on the quality of life. Although usually limited to the skin, an association of rosacea with systemic comorbidities such as neurologic diseases, inflammatory bowel disease, and cardiovascular diseases has been reported.[1][2][3][4]



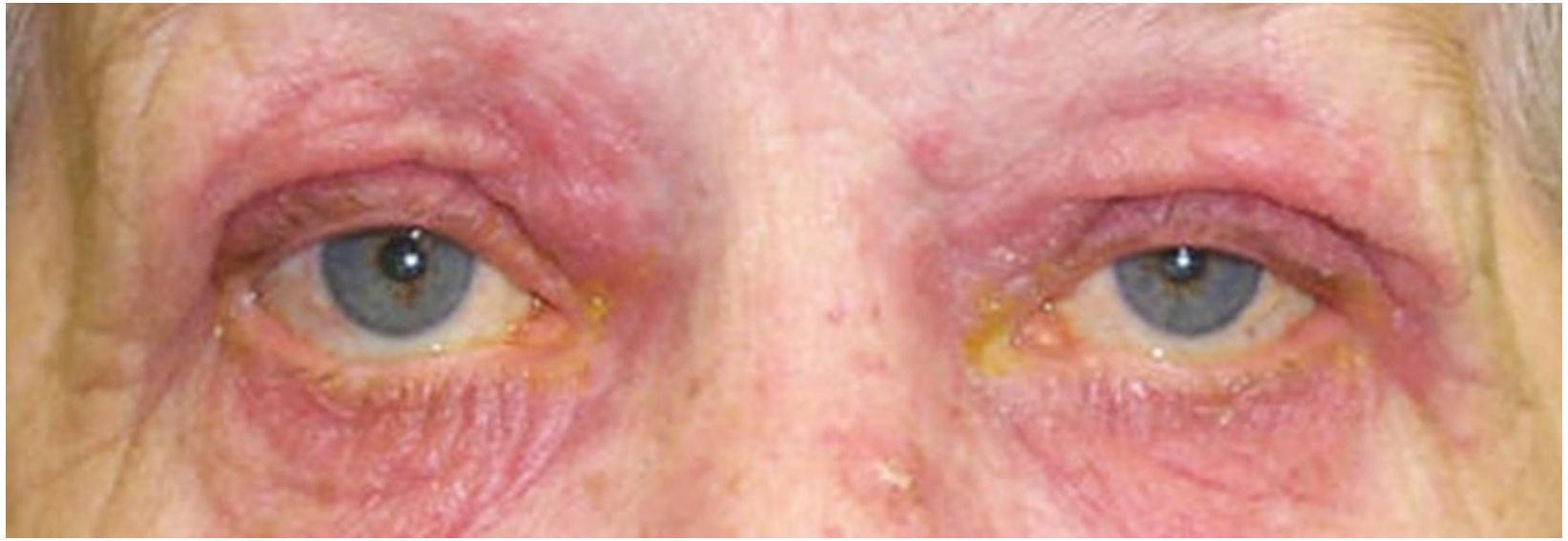
Subtype 1: Erythematotelangiectatic, aka spider vein distribution.



Subtype 2: Papulopustular.



Subtype 3: Phymatous, skin thickening.



Subtype4: Ocular.

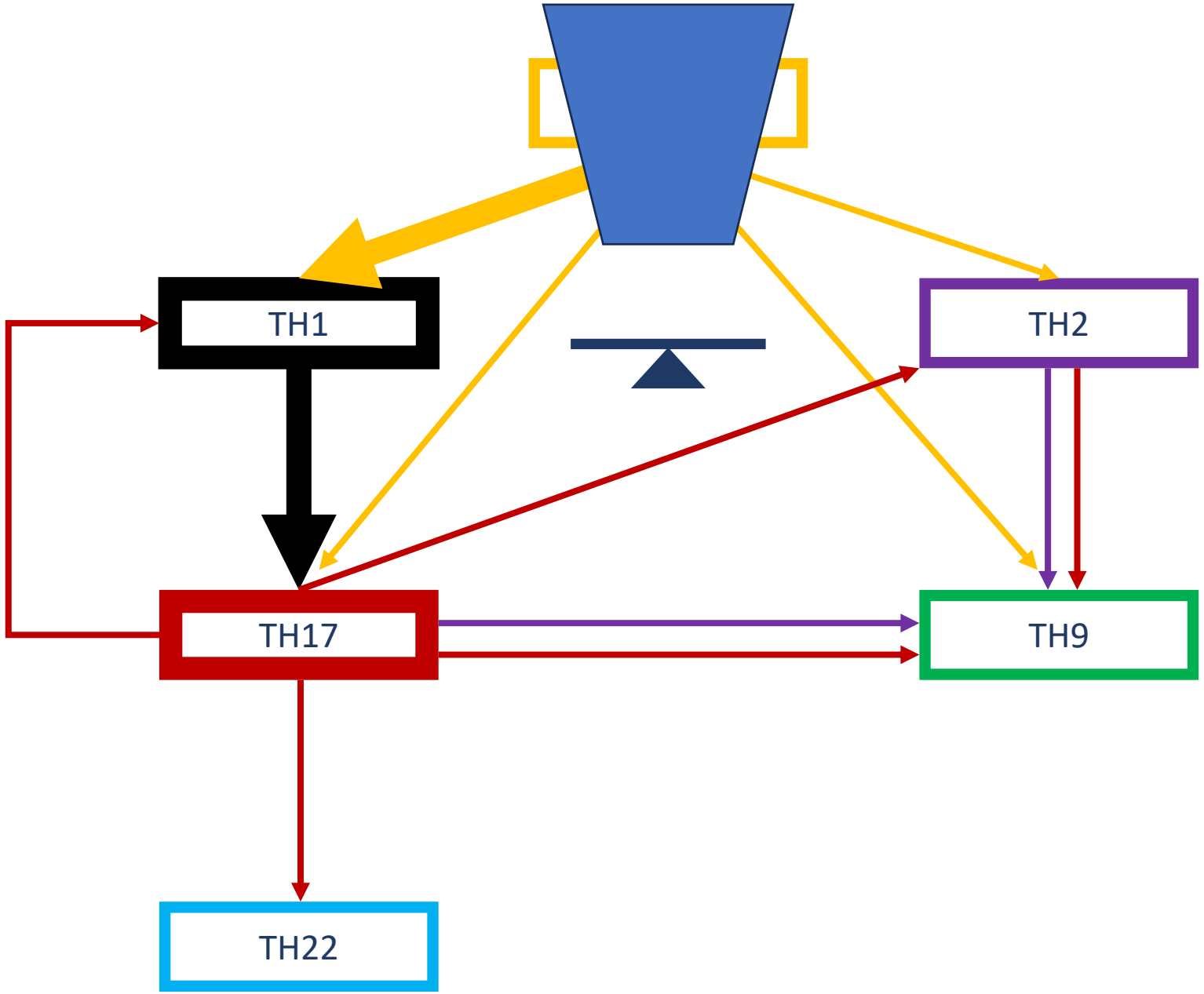
The exact etiology of rosacea is not fully understood. Genetics, immune reaction, microorganisms, environmental factors, and neurovascular dysregulation are among the known etiological factors for the development of rosacea. In addition, besides the known effect of ultraviolet (UV) exposure as a trigger for rosacea, it may also play a role in the etiology of the disease.[5] A genetic predisposition is supported by a higher incidence of disease in patients with a family history of rosacea. Furthermore, specific human leucocyte antigen (HLA) loci have been identified in patients with rosacea.[6]

Among microorganisms, Demodex mites appear to play a role in rosacea as they are seen in higher numbers on rosacea-affected skin, though it is not clear if this is a cause or consequence of rosacea.[4] Helicobacter pylori is another organism with reported association with rosacea.[7]

Neurovascular dysregulation, activation of the immune system, and infestation with Demodex mites are among the pathophysiological mechanisms postulated for rosacea.

Dilation of lymphatic and blood vessels with exposure to extreme temperatures, spices, and alcohol has been observed in rosacea. Elevated expression of nonspecific cation channels such as transient receptor protentional vanilloid 1 (TRPV-1) and ankyrin 1 on sensory neurons and keratinocytes and release of vasoactive peptides following exposure to triggers is the proposed mechanism for the erythema and flushing.[2]

Activation of the adaptive and innate immune system response by overexpression of Th1/Th17 and toll-like receptor 2 (TLR-2), respectively, are other known pathomechanisms for rosacea. TLR-2 activation results in increased activity of mast cells via an increase in LL-37 production. In addition, expression of matrix metalloproteinases and vascular endothelial growth factor is increased in rosacea.[2][4] In rosacea, microbes may trigger activation of the immune response. This hypothesis is supported by an increased number of organisms, such as Demodex folliculorum on the skin and helicobacter pylori infection in the gut of patients with rosacea.[2][6][8]


TH1
TH2
TH17
TH9
TH22
(Dermatologic)

Topical Treatment

Erythema

- Brimonidine tartrate (alpha-2 agonist) 0.33% gel (Daily application on the face)
- Oxymetazoline hydrochloride (alpha-1 agonist) 1% cream (Daily application on face)
- Inflammatory papules and pustules
- Ivermectin 1% cream (daily application)
- Azelaic acid 15% gel, foam or 20% cream (daily 1 to 2 times application)
- Metronidazole 0.75% and 1% gel or cream (daily 1 to 2 times application)

Ocular Involvement

Artificial tears

- Fusidic acid gel (daily 1 to 2 times application on eyelids) limited data available for efficacy
- Metronidazole 0.75% gel (daily 1 to 2 times application on eyelids) limited data available for efficacy
- Cyclosporine 0.05% eyedrops, (one drop every 12 hours) limited data available for efficacy

Inflammatory papules and pustules

- Subantimicrobial-dose doxycycline, modified-release (40 mg daily, 30 mg immediate-release and 10 mg delayed-release beads, for 8 to 12 weeks)
- Minocycline (50 to 100 mg twice daily for 8 to 12 weeks)
- Tetracycline (250 to 500 mg twice daily for 8 to 12 weeks)
- Azithromycin (250-500 mg 3 times weekly for 4 to 8 weeks)
- Isotretinoin (0.25 to 0.3 mg/kg/day for 12 to 16 weeks)

Phyma (inflamed)

- Doxycycline (100 mg 1 to 2 times daily for 8 to 12 weeks)
- Tetracycline (250 to 500 mg twice daily for 8 to 12 weeks)
- Isotretinoin (0.25-0.3 mg/kg/day for 3 to 4 months)

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Rosacea, microbiome and probiotics: the gut-skin axis

Pedro Sánchez-Pellicer, [1] Cristina Eguren-Michelena, [2] Juan García-Gavín, [3] Mar Llamas-Velasco, [4] Laura Navarro-Moratalla, [1] Eva Núñez-Delegido, [1] Juan Agüera-Santos, [1] and Vicente Navarro-López [1,5,*]

Therefore, an exacerbated innate immune response is established in the skin of rosacea patients due to TLR-2 stimulation involving the production of the active form of the cathelicidin LL-37. In a healthy skin, activation of an innate immune response via TLRs would induce a controlled secretion of cytokines, chemokines, and AMPs, with recruitment and activation of leukocytes to eradicate the threat but without tissue damage. Rosacea patients do not experience the same balanced inflammatory response, so that there is a sustained anomalous innate immune response. In this regard, the role of mast cells in the pathogenesis of rosacea is remarkable (Wang et al., 2019). Mast cells are one of the major sources of cathelicidins and KLK-5 in the skin and are highly active in rosacea patients. In turn, released LL-37 exerts a powerful stimulus on the activity of mast cells inducing their chemotaxis, degranulation, and release of proinflammatory cytokines, generating a positive feedback mechanism. LL-37 has been injected intradermally into mast cell-deficient mice and no inflammation has been observed unlike in wild-type mice. However, when these mast cell-deficient mice have been supplied with mast cells and then injected with LL-37, they have exhibited inflammation (Muto et al., 2014). Moreover, inflammatory mediators secreted by LL-37-activated mast cells such as interleukin 6 (IL-6) lead to an infiltration of neutrophils that continue to amplify the feedback process releasing matrix metalloproteinases (MMPs) (Marson and Baldwin, 2020). KLK-5 can also be stimulated by MMP-9 in the skin of rosacea patients (Jang et al., 2011).

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Adaptive immunity is also dysregulated in rosacea patients. The involvement of the adaptive immune system in the pathogenesis of rosacea is less well understood than relevance of the innate immune system. The T-cell response in rosacea is dominated by Th1/Th17 cells as evidenced by significantly increased interferon γ (IFN-γ) or IL-17. Macrophages and mast cells are increased in all subtypes of rosacea, whereas neutrophils reach a maximum in PPR (Buhl et al., 2015). Regarding B-cell-mediated response, Mylonas et al. have recently published that an overexpression of type I IFN in rosacea flare-ups correlates with the accumulation of plasmacytoid dendritic cells (pDCs) in the dermal infiltrate of skin lesions. In addition, this study showed that commensal skin bacteria are necessary for pDCs activation and type I IFN production, but in rosacea patients dysbiotic bacteria and AMPs increase this capacity. Moreover, cleaved fragments of LL-37 cause infiltration of pDCs into the skin, which are activated to produce high quantities of type I IFN inducing a strong immune response with increased expression of Th17/Th22 cytokines (Mylonas et al., 2023).

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The coexistence of rosacea and gastrointestinal disorders has been documented. This supports the relationship between the gut and the skin in the pathophysiology of this disease. Egeberg et al. in 2016 published a Danish nationwide cohort study with 49,475 rosacea patients and 4,312,213 general population controls, investigating the association between rosacea and celiac disease, Crohn's disease, ulcerative colitis, *Helicobacter pylori* infection, small intestinal bacterial overgrowth (SIBO), and irritable bowel syndrome (Egeberg et al., 2016). The baseline prevalence of all these gastrointestinal diseases was significantly higher in patients with rosacea compared to control subjects. However, through a 5-year follow-up survival analysis, adjusted hazard ratios did not reveal significant associations between rosacea and *H. pylori* infection and SIBO. Therefore, this large cohort study reported an increased prevalence of *H. pylori* infection and SIBO in patients with rosacea, whereas the risk of new onset of *H. pylori* infection and SIBO was not increased in rosacea patients. A singular question would be whether patients treated with antibiotics for SIBO or *H. pylori* infection will improve the symptomatology of rosacea. In this regard, a 3-year follow-up study evaluating the role of SIBO in the pathophysiology of rosacea revealed that SIBO treatment with rifaximin also led to clinical remission of rosacea in all patients, and then it persisted in the majority throughout follow-up period (Drago et al., 2016). Furthermore, this study revealed that the risk of SIBO is significantly higher in PPR than in ETR. Remission of rosacea concomitant to SIBO treatment has been evidenced in other studies (Wang and Chi, 2021). The subjacent mechanism relating SIBO to rosacea has not been clarified. Nevertheless, bacterial invasion in the small intestine leads several pathological consequences such as direct mucosal injury, toxins, malabsorption, decreased brush border enzyme

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et al., 2020; Thompson et al., 2020). Moreover, rosacea severity is related to changes in skin microbiota (Zaidi et al., 2018; Woo et al., 2020). On the other hand, studies characterizing the gut microbiota of rosacea patients based on NGS are also scarce. In this regard, significant differences have been consistently identified at genera level between rosacea patients and rosacea-free individuals (Nam et al., 2018; Chen et al., 2021; Moreno-Arrones et al., 2021). All these findings at skin and gut microbiota level reinforce the role of the skin-gut axis in the pathophysiology of rosacea. At this point and at this moment, oral probiotics, or even topical probiotics (mainly postbiotics) would come into play. However, we identify a deficiency of preclinical and human clinical trial evidence on the efficacy of these products in rosacea patients. In this narrative review we have established the basics and compiled the main directions of current knowledge to understand the mechanisms by which the microbiome influences the pathogenesis of rosacea, and how modulation of the skin and gut microbiota could benefit these patients.

TOTAL TOX BURDEN, VIBRANT WELLNESS

High (>95th percentile) — Mycotoxins | Heavy Metals | Environmental Toxins

TEST NAME	CURRENT RESULT	PREVIOUS RESULT	CURRENT RESULT / PREVIOUS RESULT	REFERENCE
Citrinin (CTN)	38.38		0 — 7.05 — 12.5	≤12.53 ng/g
Dihydrocitrinone	38.21		0 — 9.3 — 16.5	≤16.53 ng/g
Fumonisins B1	17.68		0 — 3.45 — 6.13	≤6.13 ng/g
Gliotoxin	575.86		0 — 116 — 207	≤207.87 ng/g
Patulin	29.2		0 — 6.53 — 11.6	≤11.6 ng/g
Arsenic*	98.65		0 — 11.9 — 52	≤52 ug/g
Thallium*	0.44		0 — 0.24 — 0.43	≤0.43 ug/g
Thorium	0.09		0 — 0.02 — 0.07	≤0.07 ug/g
Tungsten*	0.71		0 — 0.12 — 0.33	≤0.33 ug/g
Bisphenol A (BPA)*	10.83		0 — 2.12 — 5.09	≤5.09 ug/g
Diethyldithiophosphate (DEDTP)*	0.7		0 — 0.17 — 0.3	≤0.3 ug/g

* Indicates NHANES population data reference ranges.

TOTAL TOX BURDEN, VIBRANT WELLNESS

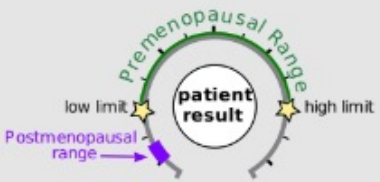
Moderate (75th-95th percentile) — Heavy Metals — Environmental Toxins

TEST NAME	CURRENT RESULT	PREVIOUS RESULT	CURRENT RESULT / PREVIOUS RESULT	REFERENCE
Barium*	5.45		0 2.33 5.59	≤5.59 ug/g
Beryllium*	0.26		0 0.2 0.76	≤0.76 ug/g
Cesium*	8.96		0 6.37 10.3	≤10.3 ug/g
Gadolinium	0.21		0 0.17 0.45	≤0.45 ug/g
Mercury*	1.49		0 0.57 1.61	≤1.61 ug/g
Tellurium	0.69		0 0.42 0.89	≤0.89 ug/g
Uranium*	0.04		0 0.02 0.04	≤0.04 ug/g
Dimethyl phosphate (DMP)*	22.63		0 9.1 33.6	≤33.6 ug/g
Dimethylthiophosphate (DMTP)*	11.1		0 5.91 33.7	≤33.7 ug/g
Methylparaben*	193.8		0 180 653	≤653 ug/g
Propylparaben*	67.4		0 36.7 222	≤222 ug/g
Tiglylglycine (TG)	0.3		0 0.09 3.24	≤3.24 ug/g
Triclosan (TCS)*	219.05		0 29.9 358	≤358 ug/g

* Indicates NHANES population data reference ranges.

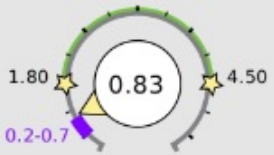
DUTCH TEST, dutchtest.com

Key (how to read the results):

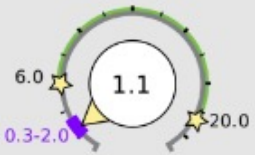


Sex Hormones

See Pages 2 and 3 for a thorough breakdown of sex hormone metabolites



Estradiol(E2)



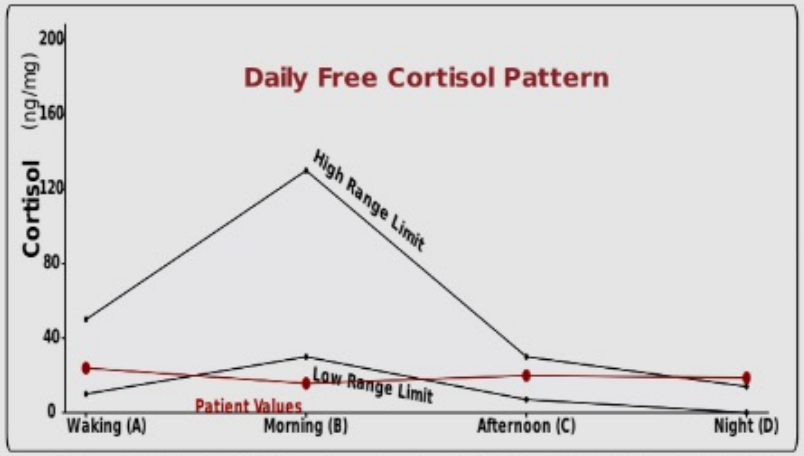
Progesterone
(Serum Equivalent, ng/mL)

Progesterone Serum Equivalent is a calculated value based on urine pregnanediol.

Testosterone

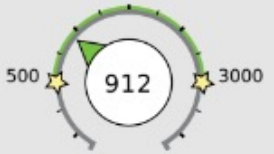
Adrenal Hormones

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



Total DHEA Production

Age	Range
20-39	1300-3000
40-60	750-2000
>60	500-1200



Total DHEA Production
(DHEAS + Etiocholanolone + Androsterone)

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

cortisol metabolism

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

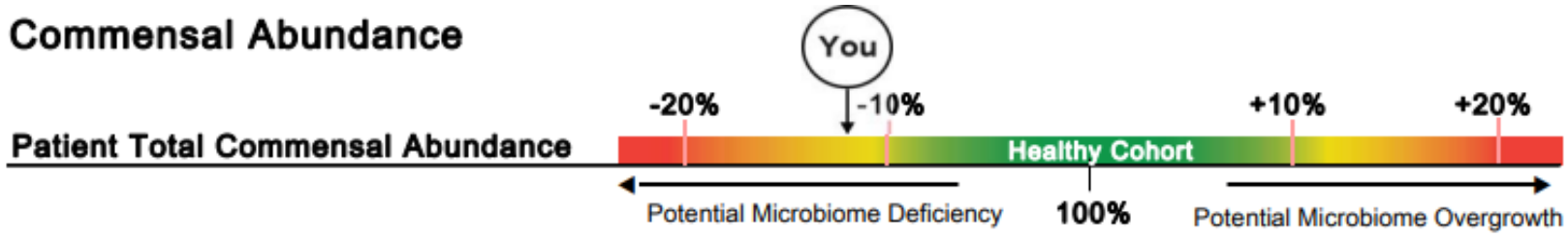
Free cortisol best reflects tissue levels. Metabolized cortisol best reflects total cortisol production.

GI Effects, Genova Diagnostics

Functional Imbalance Scores

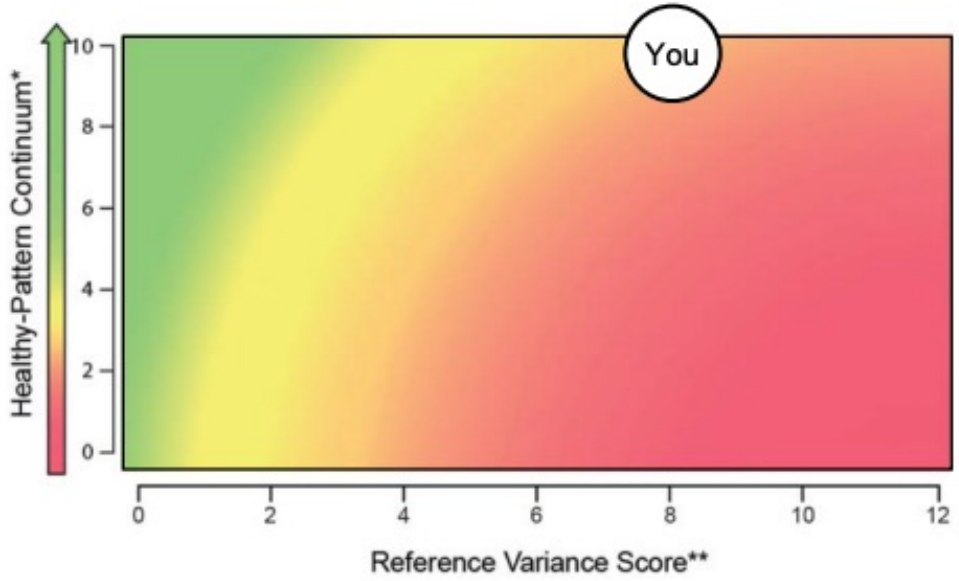
Key (< 2): Low Need for Support (2-3): Optional Need for Support (4-6): Moderate Need for Support (7-10): High Need for Support

Need for Digestive Support	Need for Inflammation Modulation	Need for Microbiome Support	Need for Prebiotic Support	Need for Antimicrobial Support
MALDIGESTION	INFLAMMATION	DYSBIOSIS	METABOLIC IMBALANCE	INFECTION
6	0	10	1	2
Products of Protein Breakdown ▲	Calprotectin ●	PP Bacteria/Yeast ▲	Total SCFA's ▽	PP Bacteria/Yeast ▲
Pancreatic Elastase ▽	Eosinophil Protein X ●	Reference Variance ▲	n-Butyrate Conc. ▽	Total Abundance ▽
Fecal Fats ●	Secretory IgA ●	IAD/Methane Score ▲	SCFA (%) ●	Parasitic Infection ●
	Occult Blood ●	Total Abundance ▽	Beta-glucuronidase ●	Pathogenic Bacteria ●
• Digestive Enzymes • Betaine HCl • Bile Salts • Apple Cider Vinegar • Mindful Eating Habits • Digestive Bitters	• Elimination Diet/ Food Sensitivity Testing • Mucosa Support: Slippery Elm, Althea, Aloe, DGL, etc. • Zinc Carnosine • L-Glutamine • Quercetin • Turmeric • Omega-3's • GI Referral (If Calpro is Elevated)	• Pre-/Probiotics • Increase Dietary Fiber Intake • Consider SIBO Testing • Increase Resistant Starches • Increase Fermented Foods • Meal Timing	• Pre-/Probiotics • Increased Dietary Fiber Intake • Increase Resistant Starches • Increase Fermented Foods • Calcium D-Glucarate (for high beta-glucuronidase)	• Antibiotics (if warranted) • Antimicrobial Herbal Therapy • Antiparasitic Herbal Therapy (if warranted) • *Saccharomyces boulardii*



GI Effects, Genova Diagnostics

Commensal Balance

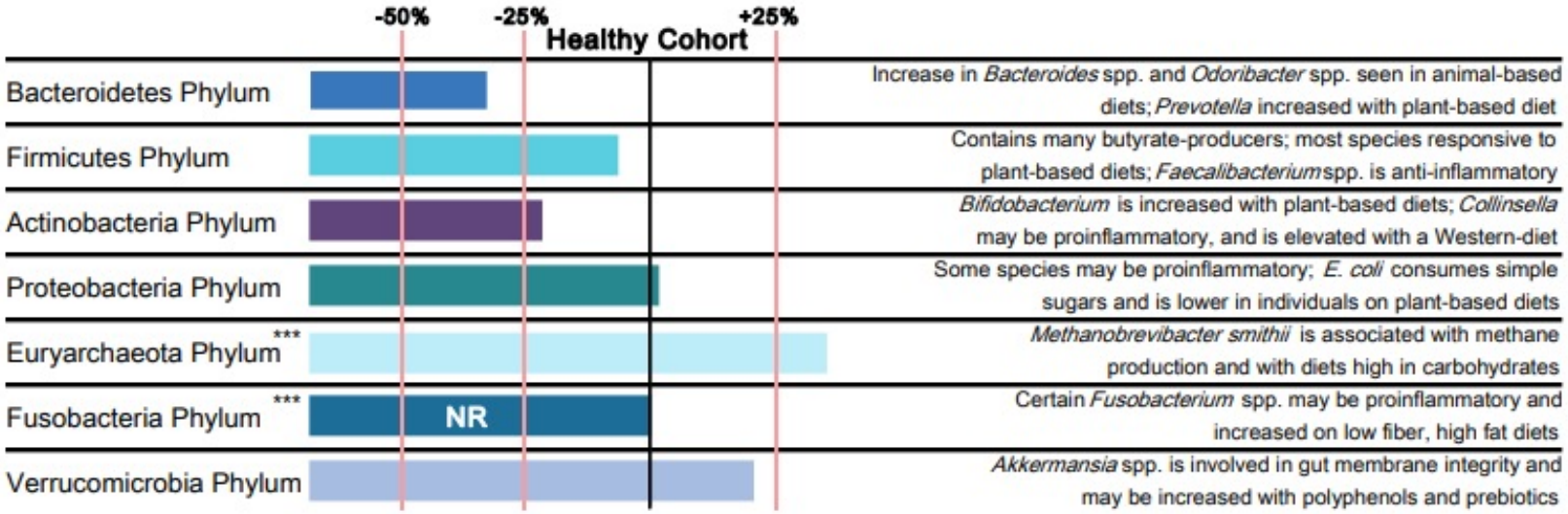


Balanced	Represents 95% of healthy individuals
Borderline	Represents 5% of healthy individuals
Imbalanced	Represents 60% of unhealthy individuals

*A progressive ranking scale based on a Genova proprietary algorithm that differentiates healthy and unhealthy commensal patterns.

**The total number of commensal bacteria (qPCR) that are out of balance for this individual on a scale of 0 to >12.

Relative Commensal Abundance



Increase in *Bacteroides* spp. and *Odoribacter* spp. seen in animal-based diets; *Prevotella* increased with plant-based diet

Contains many butyrate-producers; most species responsive to plant-based diets; *Faecalibacterium* spp. is anti-inflammatory

Bifidobacterium is increased with plant-based diets; *Collinsella* may be proinflammatory, and is elevated with a Western-diet

Some species may be proinflammatory; *E. coli* consumes simple sugars and is lower in individuals on plant-based diets

Methanobrevibacter smithii is associated with methane production and with diets high in carbohydrates

Certain *Fusobacterium* spp. may be proinflammatory and increased on low fiber, high fat diets

Akkermansia spp. is involved in gut membrane integrity and may be increased with polyphenols and prebiotics

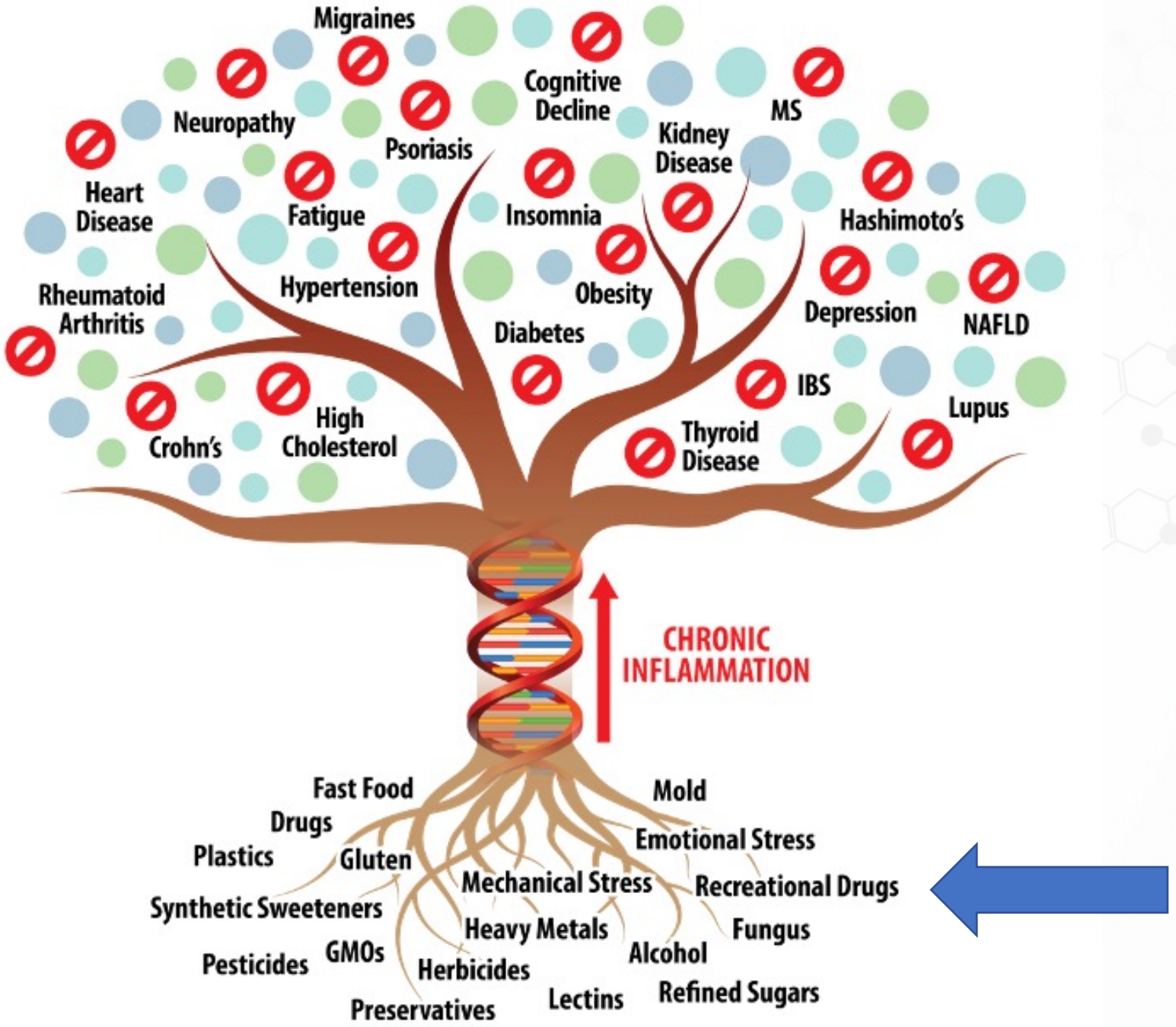
GI Effects, Genova Diagnostics

Additional Bacteria

Salmonella spp.		NG
Shigella spp.		NG
alpha haemolytic Streptococcus	4+	NP
Citrobacter freundii	4+	PP
Klebsiella pneumoniae	3+	NP
Bacillus species	3+	NP
gamma haemolytic Streptococcus	3+	NP
Enterobacter cloacae	4+	PP

Mycology (Culture)

Candida albicans/dubliniensis	1+	NP


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