VibrantWellness

Oxidative Stress Profile

Interpretive Guide

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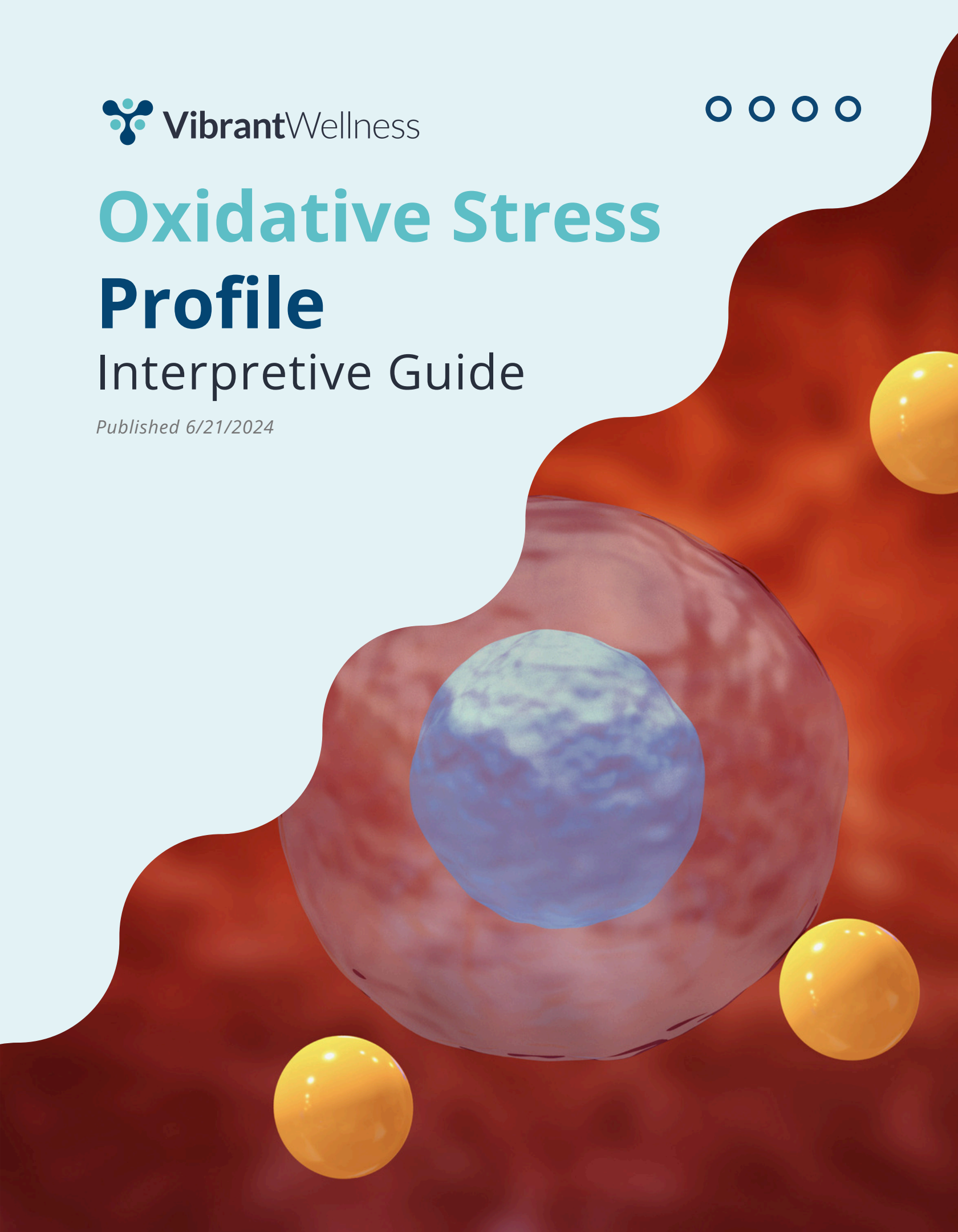

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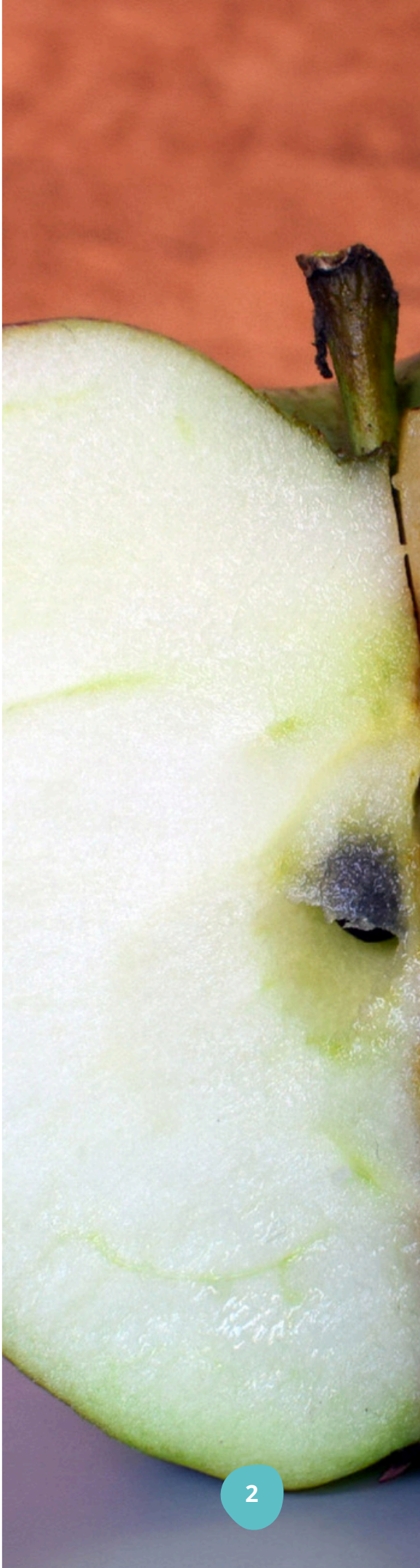

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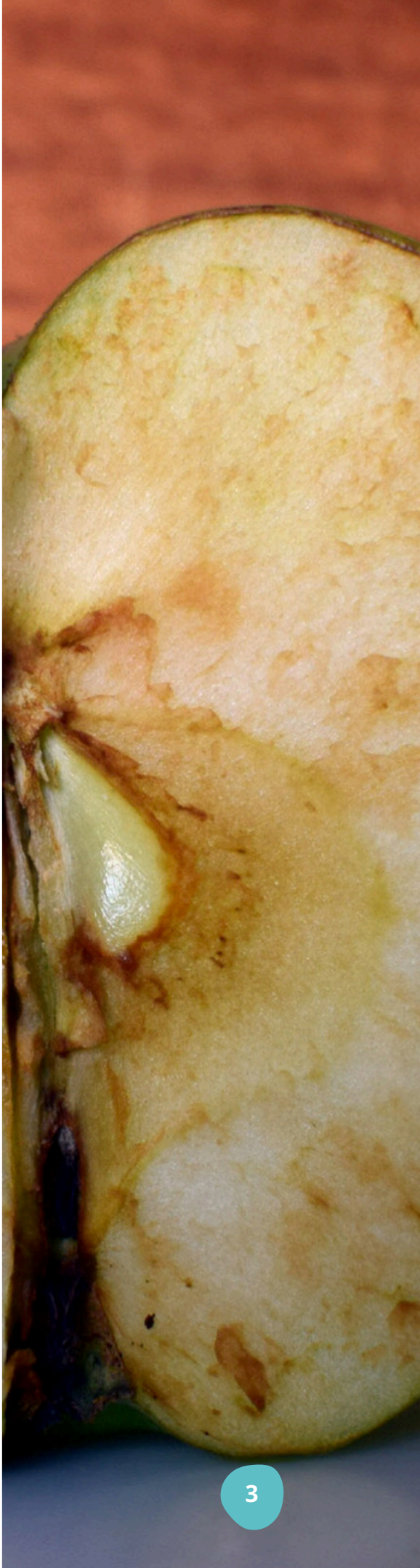


Oxidative Genetics Panel Markers

Gene	SNP ID
PRKAA2	rs2796498
PRKAA2	rs10789038
CAT	rs1001179
CAT	rs7943316
CAT	rs4756146
COX-2	rs20417
CYB5R3	rs916321
CYP1A1	rs1048943
GLUL	rs10911021
GPX1	rs1050450
GPX1	rs1987628
GPX2	rs4902346
GPX2	rs2071566
GPX4	rs713041
GSTM1	rs366631
GSTM5	rs3754446
GSTP1	rs1695
GSS	rs121909307
GSR	rs8190955
HMOX1	rs2071746
CYBA	rs4673
CYBA	rs9932581
SELENOP	rs3877899
SOD1	rs2234694
SOD2	rs4880
SOD3	rs1799895
SOD3	rs8192287
TXNRD1	rs7310505
TXNRD2	rs1548357
TRXR2	rs4485648
XDH	rs206812
XDH	rs2073316

Oxidative Stress Profile Markers

The **Vibrant Wellness Oxidative Stress Profile** offers a detailed analysis of oxidative stress by identifying 32 single nucleotide polymorphisms (SNPs) involved in the degradation of reactive oxygen species (ROS), as well as 16 markers of oxidative damage.

Oxidative Damage Products Panel Markers

Lipid Peroxidation	
Malondialdehyde	Glutathione 4-hydroxynonenal (GS-HNE)
8-iso-prostaglandin F2α (8-iso-PGF2α)	11-β-Prostaglandin F2α
15(R)-Prostaglandin F2α	
DNA Damage	
8-Hydroxy-2-deoxyguanosine (8-OHdG)	
8-Hydroxyguanine	8-Hydroxyguanosine
Protein Oxidation	
Dityrosine	3-Bromotyrosine
3-Chlorotyrosine	
Nitrative Stress Biomarkers	
8-Nitroguanosine	8-Nitroguanine
Nitrotyrosine	
Advanced Glycation Products	
Nε-(carboxymethyl) lysine (CML)	Nε-carboxyethyllysine (CEL)

Oxidative Stress Profile Methodology

Genetic single nucleotide polymorphisms (SNPs) are measured using the real time-polymerase chain reaction (RT-PCR) technology platform. With 100% accuracy and 100% precision, RT-PCR provides highly accurate and reproducible results. Damage products are measured using liquid chromatography-tandem mass spectrometry (LC-MS/MS), a highly sensitive and selective technique in which the mass spectrum of the sample determines the concentration of each analyte measured. The analyte results are expressed by normalizing to the quantity of creatinine measured to account for urine dilution variations.

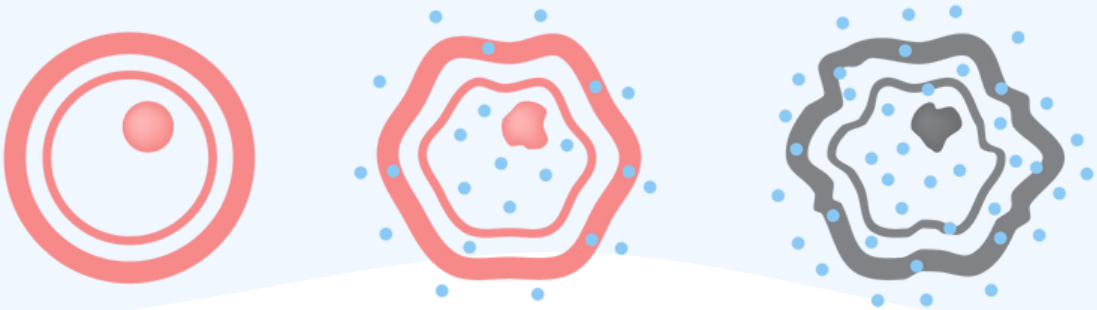
Oxidative Stress Profile Clinical Utility

This comprehensive profile is instrumental in understanding an individual's genetic susceptibility to oxidative stress and specific antioxidant needs, enabling personalized wellness plans. Central to this profile is assessing genetic variations in the enzymes responsible for regulating ROS. These variations can either impair ROS degradation or lead to increased production. Impaired degradation or heightened ROS production can significantly damage lipids, proteins, and nucleic acids (DNA and RNA). This damage is especially pronounced in individuals with genetic variations, affecting both ROS degradation and production and placing them at a higher risk.

Oxidative stress can be an antecedent, trigger, or mediator of chronic disease. Targeting oxidative stress may modify disease initiation, promotion, or progression.

What is Oxidative Stress?

Oxidative stress is an imbalance between the production of ***reactive oxygen species (ROS)*** and reactive ***nitrogen species (RNS)*** and the body's antioxidant defenses, which cannot effectively neutralize these reactive compounds. ROS and RNS are collectively called ***free radicals.*** Free radicals are volatile molecules with unpaired electrons readily available to react with various organic substrates such as lipids, proteins, carbohydrates, DNA, and RNA. Excessive oxidation can harm these critical cellular components, which are the building blocks of the human body. The body generates ROS and RNS continuously through essential processes like cellular metabolism, aerobic respiration, and inflammatory and immune responses.



Cell | Free Radicals Attacking Cell | Oxidative Stress

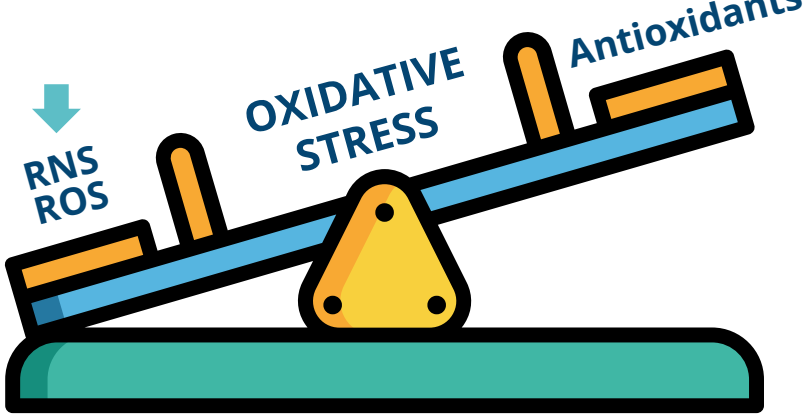
Several external factors exacerbate oxidative stress, including ***lifestyle factors*** like tobacco and alcohol use, inactivity or excessive exercise, poor diet quality (e.g., Western diet pattern), and inadequate dietary antioxidants, which activate inflammatory pathways that produce ROS and RNS. This surge in reactive molecules can cause cellular damage and contribute to oxidative stress. ***Environmental exposure to toxins,*** heavy metals like lead and mercury, pollutants, and industrial chemicals can induce oxidative stress. Metals like lead and mercury can catalyze ROS production.

At the same time, pollutants and industrial chemicals trigger oxidative stress by promoting free radical production, damaging DNA, depleting antioxidants, and inhibiting their protective functions. ***Certain medications, ultraviolet, and ionizing radiation*** contribute to oxidative stress by disrupting cellular balance and producing excessive ROS. These oxidative processes damage DNA, proteins, and lipids, overwhelm the body's antioxidant defenses, and generate oxidative ***damage products.*** Managing and maintaining oxidative stress at optimal ***(balanced)*** levels is crucial for overall health. Oxidative damage, if left unmitigated and untreated, contributes to the deterioration of physiological functions and disease and aging processes.

Lifestyle
Smoking, alcohol, poor diet, lack of exercise

Environment
Phthalates, pesticides, heavy metals, drugs, infections

- Catalase
- Gluthathione
- Superoxide dismutase
- Peroxidase
- Vitamins A, C, E



Oxidative stress is beneficial at low levels and harmful at high levels.
Balance is crucial.

Damage To:

Mitochondrial DNA
Nuclear DNA

Lipid Peroxidation
Apoptosis

Reactive Oxygen Species and Reactive Nitrogen Species

Examples of ROS in Oxidative Stress

Singlet oxygen ($^1O_2$) forms when O_2 is electronically excited by the activation of neutrophils and eosinophils or by enzymatic reactions of lipoxygenases, dioxygenases, and lactoperoxidase. $^1O_2$ is a potent oxidizing agent capable of causing DNA damage.

Superoxide anion radical ($O_2\bullet^-$) is formed enzymatically via the action of xanthine oxidase, lipoxygenase, cyclooxygenase, and NADPH-dependent oxidase, or non-enzymatically by the transfer of an electron to O_2.

$O_2\bullet^-$ can induce lipid peroxidation, oxidize proteins, and react with NO to form peroxynitrite, leading to protein nitration and accelerated development of ***advanced glycation end products (AGEs).***

Hydroxyl radical (*OH) is produced during a Fenton reaction in which H_2O_2 reacts with the metal ions Fe^{+2} or Cu^+, which are often bound to ferritin, ceruloplasmin, or other molecules. During acute physiological stress, excess $O_2\bullet^-$ releases free iron from ferritin. *OH can react with DNA, proteins, lipids, and carbohydrates.

Peroxyl radical (ROO*) is derived from O_2 and can induce lipid peroxidation.

Hydrogen peroxide (H_2O_2) forms via the dismutation reaction catalyzed by the enzyme superoxide dismutase (SOD). H_2O_2 can damage DNA by producing *OH in the presence of transition metal ions.

Examples of RNS in Nitrative Stress

Nitrite (NO_2^-) is relatively non-reactive with DNA under normal physiological conditions; however, under certain conditions or in the presence of other ROS, nitrite can contribute to the formation of nitrosating agents (like N_2O_3) or react to form nitrogen dioxide (NO_2), which can damage DNA. Nitrite can participate in lipid nitration, especially in the presence of other ROS. Nitrite indirectly contributes to protein modification, forming nitric oxide or other RNS that can modify amino acids like tyrosine (forming nitrotyrosine) or cysteine.

Nitric oxide (*NO) is synthesized from the oxidation of L-arginine to L-citrulline by nitric oxide synthase (NOS), with the reaction requiring O_2, NADPH, and tetrahydrobiopterin. There are three forms of NOS:

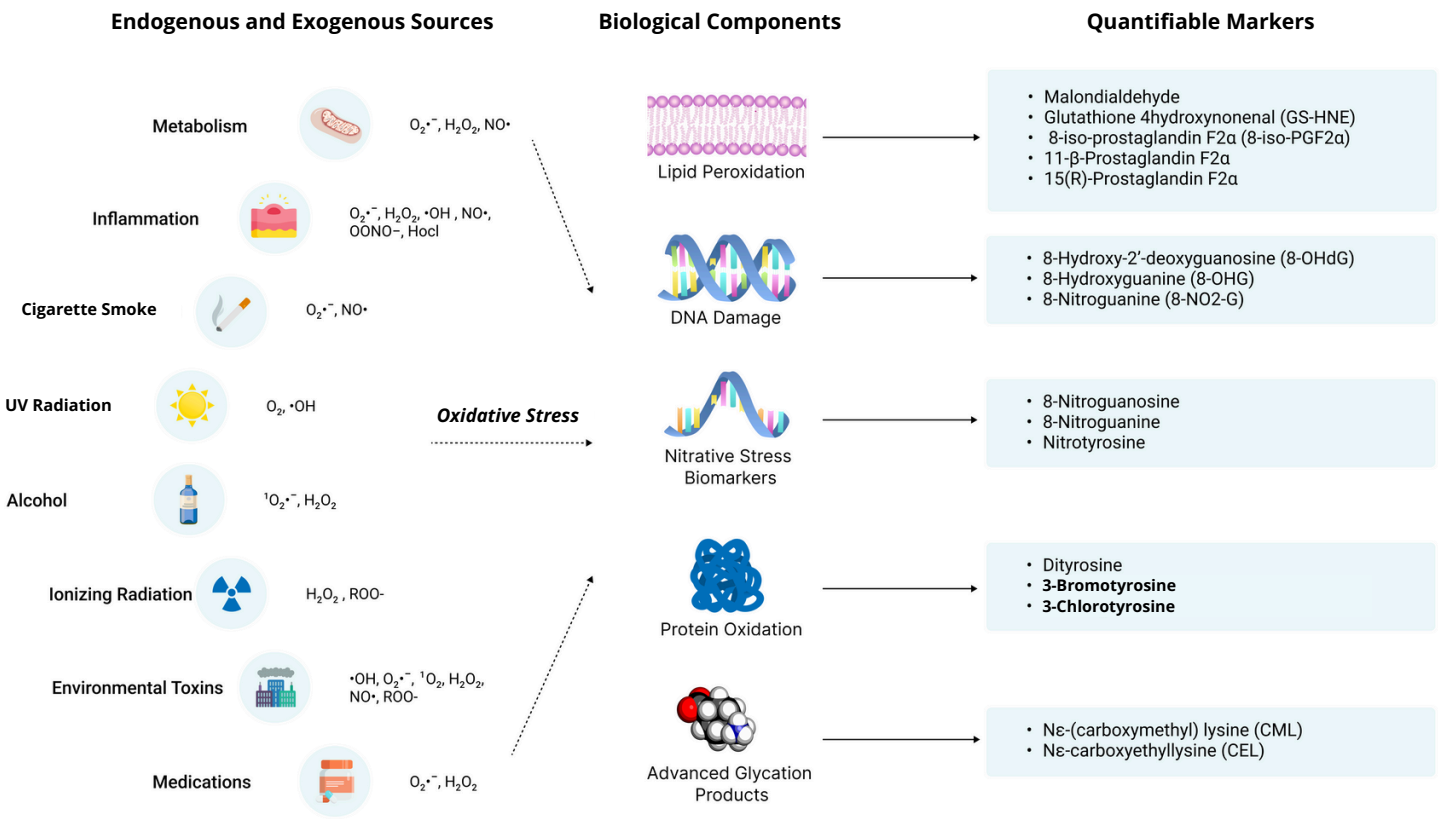
- Endothelial NOS (eNOS), which is crucial for vasodilation, endothelial function, and vascular health
- Neuronal NOS (nNOS), which is essential to neurotransmission
- Inducible NOS (iNOS), which is induced in response to inflammatory stimuli

*NO has pro-oxidant and antioxidant effects, dependent upon the underlying oxidative status of a tissue. NO can also be produced via non-enzymatic pathways under stress, disease, and hypoxia conditions.

Peroxynitrite ($ONOO^-$) is generated from the reaction between $O_2\bullet^-$ and *NO. $ONOO^-$ oxidizes lipids, methionine, and tyrosine residues in proteins, and oxidizes DNA to form 8-nitroguanine.

Nitrogen dioxide ($*NO_2$) is not produced endogenously—it's an atmospheric pollutant produced by combustion processes, tobacco smoke, and bacterial action. It can be produced in water systems from the decomposition of nitrite, as well as by the exposure of nitrite or nitrate to ionizing radiation.

Because direct quantification of ROS and RNS is not feasible due to their high reactivity and short half-live, the Vibrant Oxidative Stress Profile measures antioxidant genetics *and* oxidative damage products.



Antioxidant Defense System

Endogenous Antioxidants

Enzymatic Antioxidants

The ***antioxidant defense system (ADS)*** is a crucial network within the body that helps to combat oxidative stress. The ADS comprises enzymatic and non-enzymatic components. The enzymatic components include primary enzymes like ***superoxide dismutase (SOD)***, which catalyzes the dismutation of superoxide radicals into hydrogen peroxide; ***catalase (CAT)***, which converts hydrogen peroxide into water and oxygen; ***glutathione peroxidase (GPX)***, which reduces hydrogen peroxide; and ***glutathione S-transferases (GST)***, which catalyze the conjugation of the glutathione to a wide range of endogenous and xenobiotic electrophilic compounds.

Aside from the primary antioxidant enzymes such as SOD, CAT, GPX, and GST, the ADS includes a host of other enzymatic components that are essential in combating oxidative stress. ***Glutathione reductase (GR)*** plays a crucial role in maintaining the reduced form of glutathione in the cell, which is essential for the activity of glutathione peroxidase by converting glutathione disulfide back to its reduced state using NADPH. Another vital enzyme is ***thioredoxin reductase (TXNRD),*** which is part of the thioredoxin system that includes thioredoxin, thioredoxin reductase, and NADPH, reducing protein disulfides and maintaining proteins in their reduced state, crucial for cell growth and survival. ***Heme Oxygenase-1 (HMOX1)*** is an inducible enzyme that catalyzes heme degradation to biliverdin, carbon monoxide (CO), and free iron. The biliverdin is then further reduced to bilirubin by biliverdin reductase. Bilirubin, in turn, is a potent antioxidant that can neutralize free radicals. The induction of HMOX1 is often considered a protective response against oxidative stress due to its role in heme catabolism and the resultant generation of antioxidants.

Non-Enzymatic Antioxidants

Non-enzymatic antioxidants include ***glutathione, coenzyme Q10, uric acid, albumin, bilirubin, melatonin,*** and ***alpha lipoic acid,*** and trace elements like selenium and zinc, which act as antioxidants or cofactors for the enzymatic antioxidants. These antioxidants can scavenge free radicals, chelate metal ions that can catalyze free radical production, and act in signal transduction pathways that upregulate the expression of other antioxidant enzymes. In concert, the ADS regulates the levels of ROS, ensuring cellular homeostasis. Under oxidative stress conditions, the ADS is upregulated, which may involve the transcription factor Nrf2, which enters the nucleus and binds to the antioxidant response element in the DNA, initiating the transcription of antioxidant proteins.

Endogenous antioxidants are found in different cellular compartments, providing a wide-ranging cellular defense mechanism.

Oxidative Stress in Health (The “Good”)

Oxidative stress plays a critical role in the pathogenesis of chronic diseases and aging, as ROS cause cellular damage when their levels exceed the body's detoxifying and antioxidant defense capabilities. This ***oxidative damage,*** which includes modifications to DNA, proteins, and lipids, plays a critical role in the pathogenesis of cancer, cardiovascular diseases, diabetes, Alzheimer’s and Parkinson’s diseases, Down syndrome, depression, schizophrenia, bipolar disorder, renal disease, chronic pulmonary obstruction, lung cancer, and aging, and can be a predictor of all-cause mortality.

In aging, oxidative stress is implicated in the gradual decline of physiological functions. It influences the aging process by affecting cell signaling pathways, telomere shortening, and mitochondrial dysfunction. The accumulation of oxidative damage over time contributes to the degeneration of tissues and organs, leading to age-related conditions. Furthermore, the oxidative stress theory of aging suggests that the accumulation of ROS-induced damage is a significant determinant of lifespan and healthspan. Additionally, oxidative stress modulates inflammatory processes integral to many chronic diseases. Chronic inflammation itself can induce oxidative stress, creating a feedback loop that exacerbates disease progression.

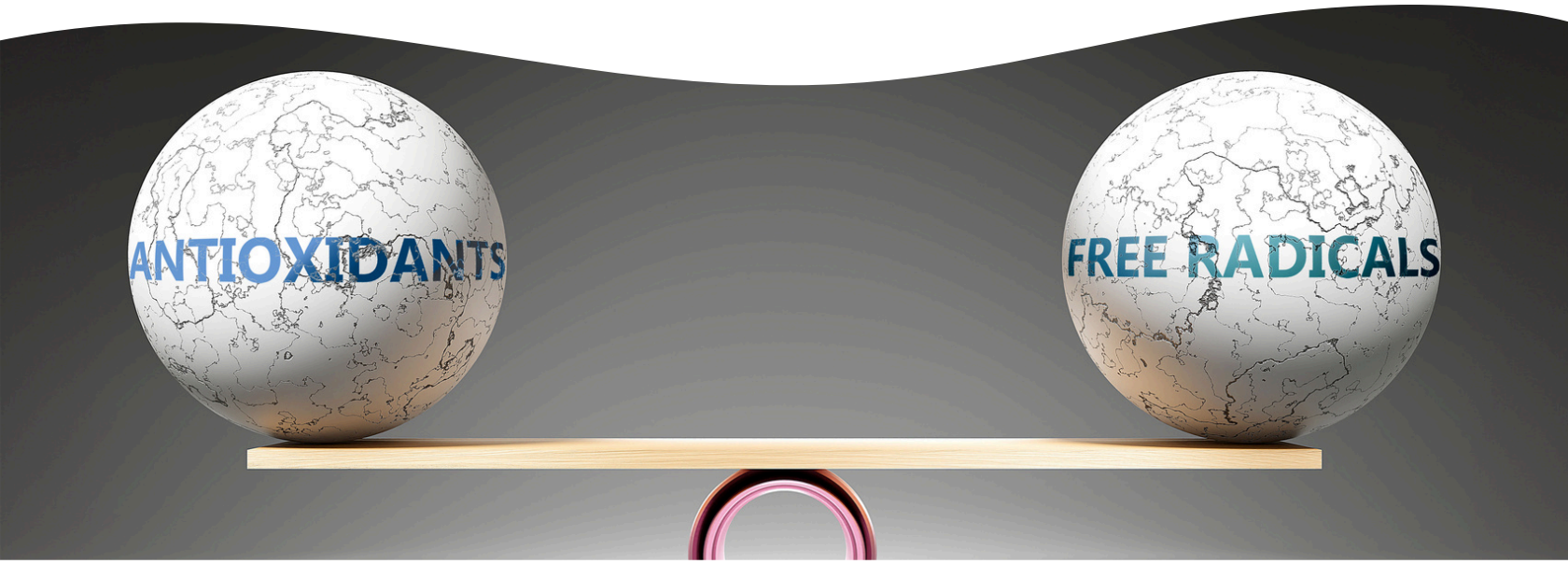
The interplay between oxidative stress, inflammation, and immune response underscores its multifaceted role in disease mechanisms. Recent research emphasizes the need to understand the nuanced role of ROS critical functions in cellular signaling and homeostasis. Therefore, targeting oxidative stress in chronic diseases and aging is not about completely eradicating ROS but achieving a balance to minimize pathological effects while preserving their physiological roles. This perspective is crucial for developing effective strategies to combat chronic diseases and promote healthy aging.

Oxidative damage involves modifications to DNA, RNA, proteins, and lipids.

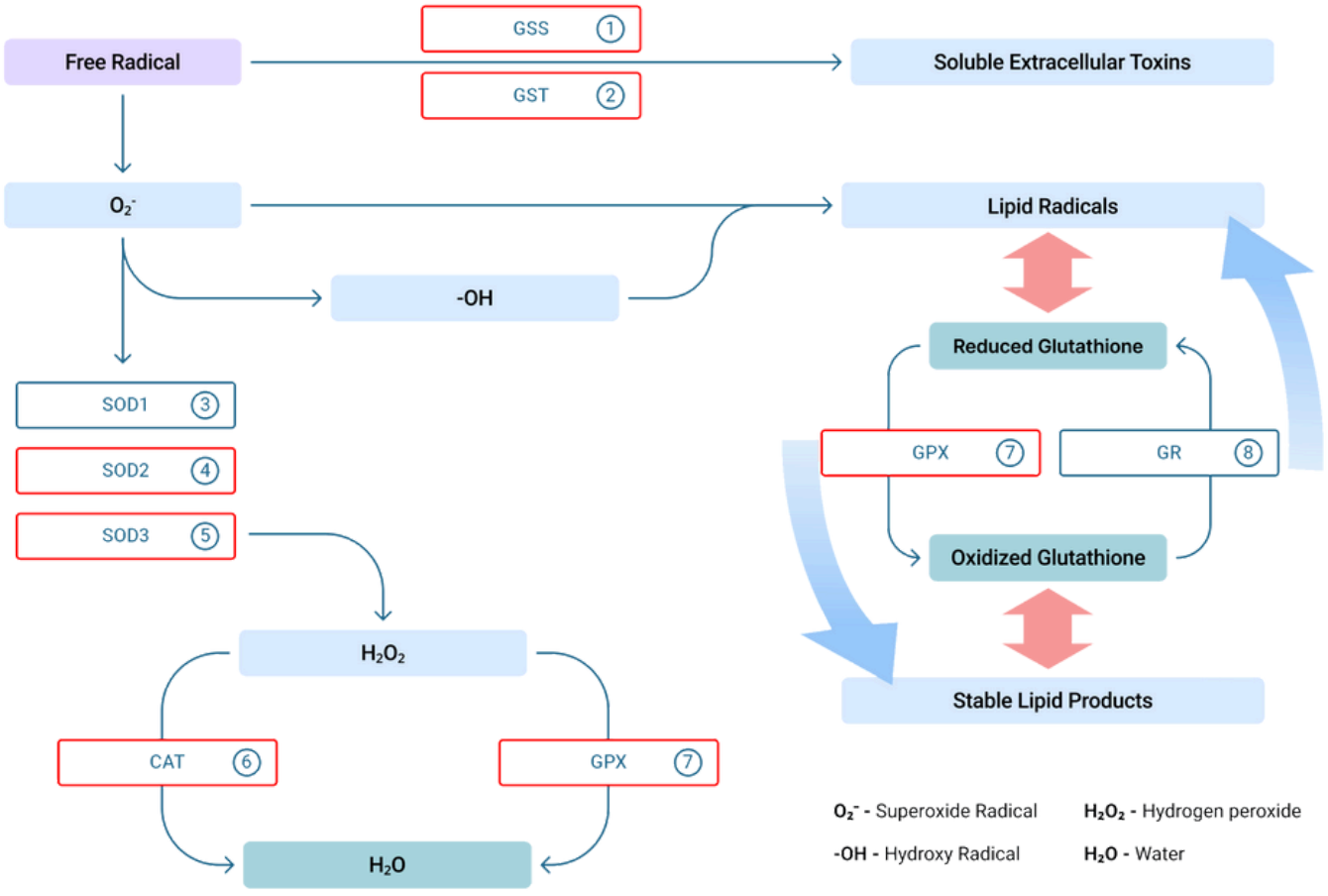
Oxidative Stress in Health (The "Good")

Redox Reactions

Oxidation-reduction ***(redox)*** reactions are fundamental biochemical processes. At their core, redox reactions involve the transfer of electrons between molecules, leading to changes in their oxidation states. This electron transfer is vital for numerous metabolic pathways, most notably those involved in energy production, such as the electron transport chain in mitochondria. The efficiency and balance of redox reactions are critical for maintaining cellular homeostasis and function and the generation and detoxification of ROS and RNS.



Interpreting Results



The Oxidative Stress Profile Summary Flowchart displays a pathway for the detoxification of ROS and lipid peroxides via redox reactions and processes shown:

GSS—Glutathione synthetase catalyzes the final step in synthesizing glutathione (GSH), linking glycine to the dipeptide gamma-glutamylcysteine. This reaction completes the formation of glutathione, a tripeptide composed of glutamate, cysteine, and glycine.

GST— Glutathione S-transferase catalyzes the conjugation of glutathione (GSH) to soluble extracellular toxins, aiding in their detoxification.

SOD1, SOD2, SOD3— Superoxide dismutases isoforms 1, 2, and 3 catalyze the dismutation of $O_2^{\cdot-}$ into hydrogen peroxide (H_2O_2) and oxygen (O_2).

CAT— Catalase catalyzes the conversion of H_2O_2 into water (H_2O), effectively neutralizing ("quenching") this potentially harmful byproduct of cellular metabolism.

GPX— Glutathione peroxidase aids in the reduction of H_2O_2 by glutathione by catalyzing the reduction of lipid hydroperoxides to their corresponding alcohols and reducing free hydrogen peroxide to water to help prevent the oxidative modification of lipids, which is critical for maintaining the integrity of cell membranes and preventing cellular damage.

*Boxes outlined in **red** indicate the antioxidant genetics markers with genetic variants, resulting in impaired antioxidant defenses and increased oxidative stress.*

The GSH redox cycle is sometimes referred to as "glutathione recycling."

Antioxidant Genetics Panel

Interpreting Results

Single Nucleotide Polymorphism Classification (Genetic Sequence)

A nucleotide is the basic building block of the nucleic acids DNA and RNA. A nucleotide is made up of a nitrogen-containing base, a phosphate group, and a sugar molecule (deoxyribose in DNA and ribose in RNA). A nucleotide is a fundamental building block of DNA and RNA, which carries genetic instructions in living organisms. The sugar and phosphate form the backbone of DNA and RNA strands, while the bases carry the genetic information. There are four different nitrogen-containing bases in DNA:

1. **Adenine (A)**
2. **Thymine (T)**
3. **Cytosine (C)**
4. **Guanine (G)**

The bases pair up between two DNA strands to form the double helix structure of DNA. In RNA, the base Thymine (T) is replaced by Uracil (U). Genetic testing for single nucleotide polymorphisms (SNPs) typically focuses on DNA because DNA provides a reliable template since it is more stable and less susceptible to rapid changes than RNA.

A **SNP** (pronounced "snip") is a variation in a single nucleotide (A, T, C, or G) that occurs at a specific position (rsID) in the DNA sequence. SNPs can occur in coding regions (exons), non-coding regions (introns), or regulatory regions of genes. By studying SNPs, researchers can gain insights into genetic associations with various health conditions and traits, potentially leading to personalized medicine and targeted treatments. SNPs can have multiple possible variants at a specific location, including the reference (wild type) allele and other alternative alleles (variant alleles). SNPs are categorized based on their relationship to a reference sequence.

- **Wild Type:** This term refers to the **most common** allele, also known as the reference allele. The wild type is typically considered the "normal" type and often, **but not always**, carries the least risk.

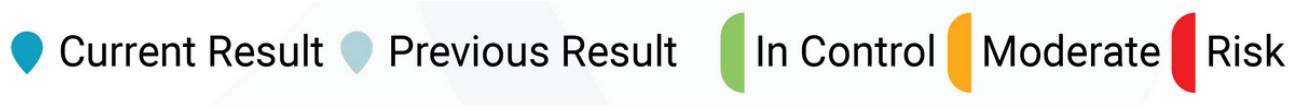
- **Variant:** This term refers to any other allele that differs from the wild type or reference allele. Variant alleles typically occur **less frequently,** meaning fewer people have this variation.

The **rsID**, also known as the reference SNP ID, is a unique identifier assigned to a specific single nucleotide polymorphism (SNP) in a genetic database, such as the dbSNP database maintained by the National Center for Biotechnology Information (NCBI). The identifier starts with "rs" followed by a series of numbers (e.g., rs123456). This ID helps researchers easily reference a particular SNP across different studies and datasets. It provides a standardized way to identify and share information about a specific SNP, including its location on the genome, the type of genetic variation, and any known associations with diseases or traits.

Interpreting Risk

Depending on the gene and rs location, a wild type or variant allele may or may not result in elevated risk. Therefore, risk is communicated via the following colors.

- **Green:** Normal risk (in control)
- **Yellow:** Partially elevated risk
- **Red:** Elevated risk



Since humans have two copies of each gene, each gene has three possible combinations:

- **Homozygous Wild:** Two copies of the normal "wild type" allele. This combination occurs most often, is typically considered the “normal” type, and often—but doesn’t always—carry normal risk. In some instances, however, homozygous wild may confer increased risk.
- **Heterozygous Variant:** One copy of the normal "wild type" allele and one copy of the variant allele. Depending on the gene and rs location, a heterozygous variant may or may not result in elevated risk.
- **Homozygous Variant:** Two copies of a variant allele. This combination occurs least often and is often, but not always, associated with increased risk. In some instances, however, a homozygous variant may confer protection.

Homozygous wild often—but don’t always—*carry normal risk.* In some instances, homozygous wild may confer *increased risk.*

Homozygous variants are often—but not always—associated with increased risk. In some instances, homozygous variants may confer *protection.*

As research evolves and more populations are tested, "wild type" may evolve if new genetic variations are identified, redefining the standard genetic sequence.

Antioxidant Genetics Markers

CAT— Catalase

Risk Association–Mitochondrial Dysfunction

The CAT gene encodes for the catalase enzyme, localized in mitochondria. Mitochondrial catalase is shown to protect cells from oxidative injury induced by hydrogen peroxide by degrading hydrogen peroxide generated by peroxisomal oxidases to water and oxygen, thereby protecting cells from the toxic effects of hydrogen peroxide. Thus, the enzyme participates in antioxidant functions in the body. Variations in the gene lead to decreased catalase production, producing excess ROS. This induces mitochondrial dysfunction and elevated oxidative stress.

Catalase Reference SNP ID Reference Allele	Homozygous Wild	Heterozygous Variant	Homozygous Variant	Nutrient Support For Enzyme Activity
rs7943316 Reference: AA, AT	AA	AT	TT	Alpha Lipoic Acid[1], Vitamin D3[2], Vitamin E[3], Coenzyme Q10[4], Vitamin C[5], Vitamin A[6], Selenium[7], Manganese[8]
rs4756146 Reference: CC	CC	CT	TT	
rs1001179 Reference: CC	CC	CT	TT	

**Note: For rs7943316, both AA and AT genotypes are considered normal with regard to risk. Only the TT genotype confers elevated risk.*

COX-2— Cyclooxygenase-2

Risk Association– Elevated ROS Production

The COX-2 gene encodes the cyclooxygenase-2 enzyme, which is central to the body's inflammatory responses and oxidative stress processes. Under normal conditions, COX-2 expression is inducible, triggered by various stimuli, including ultraviolet radiation. In the context of oxidative stress, the enzyme contributes to the production of inflammatory molecules, prostaglandins, notably prostaglandin E2, with diverse roles, such as impacting melanocyte proliferation and immunomodulation. These prostaglandins play a crucial role in the cellular response to oxidative stress. Studies propose that individuals with the CG genotype possess a variant creating a binding element for the E2F transcription factor, potentially enhancing the body's capacity to manage oxidative stress. Conversely, individuals with the GG genotype may experience oxidative stress due to reduced prostaglandin levels.

COX-2 Reference SNP ID	Homozygous Wild	Heterozygous Variant	Homozygous Variant	Nutrient Support For Enzyme Activity
rs20417 Reference: CC, CG	CC	CG	GG	Vitamin D[9], Pycnogenol[10], Beta-Carotene[11], Quercetin[12]

CYB5R3— Cytochrome B5 Reductase 3

Risk Association– Elevated ROS Production

The CYB5R3 gene encodes for an enzyme called cytochrome b5 reductase 3, which is involved in the electron transport chain (ETC) in mitochondria. This enzyme plays a vital role in regenerating the antioxidant coenzyme Q10 (CoQ10), an essential component of the ETC and a potent antioxidant. Cytochrome b5 reductase 3 exists in both membrane-bound and soluble forms. The soluble form in erythrocytes reduces methemoglobin (MetHb) back into functional hemoglobin, allowing for the efficient transport of oxygen throughout the body. Accumulation of MetHb can lead to ROS production, causing oxidative damage. Enzymes like cytochrome b5 reductase 3 and methemoglobin reductase help reduce MetHb and prevent ROS production. Variants in the CYB5R3 gene can result in reduced enzymatic activity of cytochrome b5 reductase 3, leading to decreased CoQ10 regeneration and impaired reduction of MetHb back into functional hemoglobin. This results in an elevated production of ROS, which consequently heightens susceptibility to oxidative stress.

CYB5R3 Reference SNP ID	Homozygous Wild	Heterozygous Variant	Homozygous Variant	Nutrient Support For Enzyme Activity
rs916321 Reference: GG	GG	AG	AA	Vitamin C[13], Glutathione[14]

CYBA— Cytochrome B-245 Alpha Chain

Risk Association– Elevated ROS Production

The CYBA gene encodes the p22phox subunit of NADPH oxidase, an essential enzyme in the immune system. Upon the detection of foreign invaders, phagocytes are stimulated, and NADPH oxidase is assembled. This enzyme catalyzes the conversion of oxygen to superoxide, a toxic molecule that generates several highly reactive and toxic substances collectively known as ROS. Phagocytes use these ROS to kill foreign invaders, preventing them from reproducing in the body and causing illness. Variants in the CYBA gene are associated with higher p22phox expression and increased levels of ROS. The accumulation of ROS can thus result in oxidative stress.

CYB5R3 Reference SNP ID	Homozygous Wild	Heterozygous Variant	Homozygous Variant	Nutrient Support For Enzyme Activity
rs4673 Reference: TT	TT	CT	CC	Alpha Lipoic Acid[15], Quercetin[16], Epicatechin[16], Catechin[16], Myricetin[16], Red Grape Juice[16], Dealcoholised Red Wine[16]
rs9932581 Reference: GG	GG	AG	AA	

CYP1A1— Cytochrome P450 Family 1 Subfamily A Member 1

Risk Association– Elevated ROS Production

The CYP1A1 gene encodes a member of the cytochrome P450 superfamily of enzymes. Cytochrome c (Cyt c) is located in the mitochondrial intermembrane spaces, where it functions as an electron shuttle in the respiratory chain. They participate in electron transport, inhibit ROS formation, and prevent oxidative stress.

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CYP1A1 metabolism is significant in detoxifying foreign chemicals and activates metabolic enzymes, which leads to oxidative damage. Variants in the gene decrease enzyme activity, impairing the detoxification of toxic compounds. This leads to decreased antioxidant activity and increased ROS production, thus contributing to oxidative stress.

CYP1A1 Reference SNP ID	Homozygous Wild	Heterozygous Variant	Homozygous Variant	Nutrient Support For Enzyme Activity
rs1048943 Reference: GG	GG	GA	AA	Indole-3-Carbinol[17], Soy Bean[18], Green Tea[19], Curcumin[20], Garlic[21], Fish Oil[21], Rosemary[22], Astaxanthin[23]

GLUL— Glutamate Ammonia Ligase

Risk Association– Decreased Glutamine Synthetase and Glutathione Levels

The GLUL gene encodes for glutamate ammonia ligase (glutamine synthetase) enzyme. Glutamine synthetase plays a role in maintaining cellular levels of glutamine, an amino acid with multiple functions, including antioxidant properties. Glutamine serves as a precursor for synthesizing glutathione, a key antioxidant molecule. Glutathione protects the cell from oxidative stress—its availability in reduced form is mandatory to control the cell's redox status. Variants lead to the downregulation of the gene, leading to enzyme inefficiency that may cause a deficiency of glutamine required for synthesizing glutathione, thus increasing the risk of oxidative stress.

GLUL Reference SNP ID	Homozygous Wild	Heterozygous Variant	Homozygous Variant	Nutrient Support For Enzyme Activity
rs10911021 Reference: CC	CC	CT	TT	Selenium[24], Vitamin D[25], Vitamin C[26], Lutein[27], Aged Garlic Extract[28]

GPX1— Glutathione Peroxidase 1

Risk Association – Aberrant Redox Signaling (rs1050450)

Risk Association – Reduced Enzyme Activity Leads to Selenium Deficiency (rs1987628)

GPx1 is an endogenous selenium-dependent antioxidant enzyme encoding for the major antioxidant enzyme called glutathione peroxidase 1. This enzyme detoxifies hydrogen peroxide to water and lipid peroxide to alcohol by utilizing glutathione. Selenium (Se) is an essential micronutrient for antioxidant defense and is an integral part of selenoproteins. The most well-known selenoprotein is GPx, which protects cells from damage caused by ROS. Variants affect the enzyme activity's synthesis, resulting in selenium deficiency. This leads to weakening an individual's capacity to respond to oxidative damage involved in the aging process and in most chronic diseases, including cancer, cardiovascular disease, diabetes, and dementia.

GPX1 Reference SNP ID	Homozygous Wild	Heterozygous Variant	Homozygous Variant	Nutrient Support For Enzyme Activity
rs1050450 Reference: CC	CC	CT	TT	Selenium[24], Vitamin D[25], Vitamin C[26], Lutein[27]
rs1987628 Reference: CC	CC	CT	TT	

GPX2— Glutathione Peroxidase 2

Risk Association – Higher Selenoprotein Concentrations

GPx2 is an endogenous selenium-dependent antioxidant encoding for the major antioxidant enzyme glutathione peroxidase 2. The GPX2 enzyme catalyzes the reduction of hydrogen peroxide to water and oxygen and the reduction of peroxide radicals to alcohols and oxygen, thus participating in the antioxidant defense system by protecting cells against reactive oxygen species. GPX2 modulates redox-dependent mitochondrial function where mitochondria generate ROS and respond to ROS-mediated changes in the cellular redox state. Variants in the gene lead to higher selenoprotein enzyme levels and reduced oxidative damage.

GPX2 Reference SNP ID	Homozygous Wild	Heterozygous Variant	Homozygous Variant	Nutrient Support For Enzyme Activity
rs1050450 Reference: CC	TT	CT	CC	Selenium[24], Vitamin D[25], Vitamin C[26], Lutein[27]
rs1987628 Reference: CC	GG	AG	AA	

**For both rs4902356 and rs2071566, variants in the gene lead to higher selenoprotein enzyme levels and reduced oxidative stress. Homozygous wild individuals have a reduced enzyme level and GPX activity, leading to increased oxidative stress.*

GPX4— Glutathione Peroxidase 4

Risk Associations– Elevated ROS Production

The GPX4 gene encodes glutathione peroxidase 4, which is an antioxidant selenoprotein. GPx4 is the only enzyme that reduces phospholipid hydroperoxides. It protects cells against membrane lipid peroxidation. GPX4 modulates redox-dependent mitochondrial function where mitochondria generate ROS and respond to ROS-mediated changes in the cellular redox state. Variants in the gene lead to higher selenoprotein enzyme levels and reduced oxidative damage.

GPX4 Reference SNP ID	Homozygous Wild	Heterozygous Variant	Homozygous Variant	Nutrient Support For Enzyme Activity
rs713041 Reference: CT, TT	CC	CT	TT	Selenium[24], Glutathione[29]

**For rs713041, variants in the gene lead to higher selenoprotein enzyme levels and reduced oxidative damage. Homozygous wild individuals experience increased oxidative stress.*

GSR— Glutathione-Disulfide Reductase

Risk Association– Increased Oxidative Stress in Red Blood Cells

The GSR gene encodes the glutathione-disulfide reductase (GSR) protein. The GSR protein plays a central role in the antioxidant defense system within cells by maintaining the reduced form of glutathione (GSH), a vital cellular antioxidant. GSH helps neutralize ROS and participates in detoxification processes. Variants in the gene lead to hereditary glutathione reductase deficiency, which generally impairs cellular energy balance and increases oxidative stress levels in red blood cells. This deficiency has been associated with hereditary hemolytic anemia.

GSR Reference SNP ID	Homozygous Wild	Heterozygous Variant	Homozygous Variant	Nutrient Support For Enzyme Activity
rs8190955 Reference: CC	CC	CT	TT	Curcumin[30], Ellagic Acid[31], Garlic[32], Glutathione[29], Selenium[33], Vitamin C[34], Vitamin E[3], Alpha Lipoic Acid[1]

GSS— Glutathione Synthetase

Risk Association– Lower Glutathione Levels

The GSS gene encodes for the glutathione synthetase enzyme, crucial in glutathione synthesis. Glutathione is a tripeptide composed of three amino acids: glutamate, cysteine, and glycine. It is a powerful antioxidant within cells, helping protect them from oxidative stress. The function of glutathione synthetase is to catalyze the final step in the biosynthesis of glutathione. This enzyme combines the three precursor amino acids mentioned above to form glutathione. The synthesized glutathione is then involved in various cellular processes, including detoxifying harmful substances, neutralizing ROS, and maintaining the cellular redox balance. Variants in the GSS gene can lead to a decrease in the activity of the glutathione synthetase enzyme. This reduced enzymatic activity results in a diminished ability to produce glutathione, which, in turn, contributes to increased oxidative stress within cells.

GSS Reference SNP ID	Homozygous Wild	Heterozygous Variant	Homozygous Variant	Nutrient Support For Enzyme Activity
rs121909307 Reference: TT	TT	TC	CC	Astaxanthin[23]

GSTM1— Glutathione S-Transferase Mu-1

Risk Association– Decreased Antioxidant Capacity

The GSTM1 gene encodes for an enzyme, glutathione S-transferase Mu 1. In addition to the cytoplasm, it is found in the mitochondria, lysosomes, and nuclear regions. By inhibiting cardiolipin (a lipid found in mitochondria), peroxidation, and cytochrome c release, mitochondrial GST protects organelles from oxidative stress. The enzyme plays an essential regulatory role in detoxification by catalyzing the modification of toxic compounds to glutathione, an antioxidant that helps combat ROS. Variants in the gene lead to significant damage in cells and mitochondrial function, causing a build-up of ROS and thereby increasing the risk of oxidative stress.

GSTM1 Reference SNP ID	Homozygous Wild	Heterozygous Variant	Homozygous Variant	Nutrient Support For Enzyme Activity
rs366631 Reference: TT	TT	CC	CC	Broccoli Extract[35], S-Adenosylmethionine (SAMe)[36], Pomegranate-Black Carrot Juice[37], Grape Pomace Extract[38]

GSTM5— Glutathione S-Transferase Mu-5

Risk Association– Decreased Antioxidant Capacity

The glutathione S transferase Mu 5 (GSTM5) gene belongs to the GST gene family. In addition to the cytoplasm, it is found in the mitochondria, lysosomes, and nuclear regions. By inhibiting cardiolipin (a lipid found in mitochondria), peroxidation, and cytochrome c release, mitochondrial GSTM5 helps protect organelles from oxidative stress. The enzyme plays an important regulatory role in detoxification by catalyzing the modification of toxic compounds to glutathione, an antioxidant that helps combat ROS. Variants in the gene lead to significant damage in cells and mitochondrial function, causing a build-up of ROS and thereby increasing the risk of oxidative stress.

GSTM5 Reference SNP ID	Homozygous Wild	Heterozygous Variant	Homozygous Variant	Nutrient Support For Enzyme Activity
rs3754446 Reference: TT	TT	GT	GG	Broccoli Extract[35], S-Adenosylmethionine[36], Pomegranate-Black Carrot Juice[37], Grape Pomace Extract[38]

GSTP1— Glutathione S-Transferase Pi-1

Risk Association– Decreased Antioxidant Activity

The GSTP1 gene encodes glutathione S-transferase pi-1. In addition to the cytoplasm, it is found in the mitochondria, lysosomes, and nuclear regions. By inhibiting cardiolipin (a lipid found in mitochondria), peroxidation, and cytochrome c release, mitochondrial GSTP helps protect organelles from oxidative stress. The enzyme plays an important regulatory role in detoxification by catalyzing the modification of toxic compounds to glutathione, an antioxidant that helps combat ROS. Variants in the gene decrease enzyme activity and directly elicit mitochondrial dysfunction, resulting in the rapid generation of ROS and thus leading to oxidative stress.

GSTP1 Reference SNP ID	Homozygous Wild	Heterozygous Variant	Homozygous Variant	Nutrient Support For Enzyme Activity
rs1695 Reference: AA	AA	AG	GG	Broccoli Extract[35], S-Adenosylmethionine (SAMe)[36], Pomegranate-Black Carrot Juice[37], Grape Pomace Extract[38]

HMOX1— Heme Oxygenase 1

Risk Association– Decreased Heme Oxygenase 1 Activity
HMOX1 gene encodes for the enzyme heme oxygenase 1. HMOX1 is anchored to the inner mitochondrial membrane in the mitochondria, where it may detoxify mitochondrial heme. HMOX1 can reduce oxidative stress because of the consumption of molecular oxygen in the heme oxygenase reaction pathway, where it catalyzes the degradation of heme b to carbon monoxide, ferrous iron, and biliverdin. Polymorphisms in the HMOX1 gene can reduce enzyme activity, which impairs the detoxification of mitochondrial heme and antioxidant activity and increases oxidative stress.

HMOX1 Reference SNP ID	Homozygous Wild	Heterozygous Variant	Homozygous Variant	Nutrient Support For Enzyme Activity
rs2071746 Reference: AA	AA	AT	TT	Resveratrol[39], Aged Garlic Extract[28], Extra Virgin Olive Oil[40]

SOD1— Superoxide Dismutase 1

Risk Association– Increased Superoxide Radical Levels
The SOD1 gene encodes superoxide dismutase-1, a major cytoplasmic antioxidant enzyme that metabolizes superoxide radicals to molecular oxygen and hydrogen peroxide, thus providing a defense against oxygen toxicity. SOD1 regulates the superoxide levels arising from mitochondrial intermembrane space, cytosol, and peroxisome. By neutralizing superoxide radicals, SOD1 helps prevent oxidative damage to cells and maintains their overall health. Variants in the gene lead to the deficiency in SOD1, resulting in increased levels of superoxide radicals and thereby increasing oxidative stress.

SOD1 Reference SNP ID	Homozygous Wild	Heterozygous Variant	Homozygous Variant	Nutrient Support For Enzyme Activity
rs2234694 Reference: AA	AA	AC	CC	Copper[41], Vitamin E[3], Vitamin D3[42], Vitamin C[43], Selenium[33], Manganese[44], Green Tea Extract[45], Coenzyme Q10[46], Curcumin[47], N-Acetyl-Cysteine[48]

SOD2— Superoxide Dismutase 2

Risk Association– Impaired Antioxidant Activity
The SOD2 encodes a mitochondrial protein, superoxide dismutase 2, that protects cells against mitochondrial superoxide. This protein binds to the superoxide byproducts of oxidative phosphorylation and converts them to hydrogen peroxide and diatomic oxygen. This function allows SOD2 to clear mitochondrial ROS and, as a result, confer protection against oxidative stress. It was shown that the SOD2 T allele putatively reduces gene expression, mRNA stability, and enzymatic activity of the SOD, as well as impairs the import of this enzyme into the mitochondrion, reducing antioxidant activity and leading to oxidative stress.

SOD2 Reference SNP ID	Homozygous Wild	Heterozygous Variant	Homozygous Variant	Nutrient Support For Enzyme Activity
rs4880 Reference: CC	CC	CT	TT	Copper[41], Vitamin E[3], Vitamin D3[42], Vitamin C[43], Selenium[33], Manganese[44], Green Tea Extract[45], Coenzyme Q10[46], Curcumin[47], N-Acetyl-Cysteine[48]

SOD3— Superoxide Dismutase 3

Risk Association– Elevated ROS Production

The SOD3 gene, also known as the superoxide dismutase 3 gene, produces the extracellular superoxide dismutase (EC-SOD) enzyme. EC-SOD is an antioxidant enzyme that plays a critical role in protecting tissues and cells from the harmful effects of ROS. EC-SOD is primarily found in the extracellular space, where it acts as a defense mechanism against oxidative stress by converting superoxide radicals into hydrogen peroxide and oxygen, which are less damaging to cells. Variants in the SOD3 gene can disrupt the normal function of EC-SOD and impair its ability to protect against oxidative stress.

SOD3 Reference SNP ID	Homozygous Wild	Heterozygous Variant	Homozygous Variant	Nutrient Support For Enzyme Activity
rs1799895 Reference: CC	CC	CG	GG	Copper[41], Vitamin E[3], Vitamin D3[42], Vitamin C[43], Selenium[33], Manganese[44], Green Tea Extract[45], Coenzyme Q10[46], Curcumin[47], N-Acetyl-Cysteine[48]
rs8192287 Reference: GG	GG	GT	TT	

PRKAA2— Protein Kinase AMP-Activated Alpha 2

Risk Association– Impaired Antioxidant Activity

The PRKAA2 gene encodes for an enzyme AMP-activated protein kinase (AMPK). AMPK is an important energy-sensing enzyme that monitors cellular energy status. AMPK plays a role in cellular energy homeostasis, largely to activate glucose and fatty acid uptake and oxidation when cellular energy is low. AMPK is part of the antioxidant defense system and is needed to protect the cells from oxidative stress. AMPK promotes mitochondrial biogenesis, a process that occurs in response to increased energy expenditure to produce more ATP. Variants in the gene reduce the expression of the PRKAA2 gene, causing impaired AMPK synthesis and impaired antioxidant activity, leading to oxidative stress.

PRKAA2 Reference SNP ID	Homozygous Wild	Heterozygous Variant	Homozygous Variant	Nutrient Support For Enzyme Activity
rs2796498 Reference: AA	AA	AG	GG	Folate, Alpha-Lipoic Acid[49], Magnesium[50], Vitamin C[34]
rs10789038 Reference: AA	AA	AG	GG	

SELENOP— Selenoprotein P

Risk Association– Impaired Selenium Production and Risk of Selenium Deficiency
SELENOP encodes a protein selenoprotein P that affects blood selenium or selenoprotein levels in response to supplementation. This selenoprotein accounts for most of the selenium in plasma. It has been implicated as an extracellular antioxidant and in the transport of selenium to extra-hepatic tissues via apolipoprotein E receptor-2 (apoER2). Variants in the gene reduce the gene activity and impair plasma selenium production, which leads to increased selenium deficiency, which has the potential of weakening an individual's capacity to respond to oxidative damage involved in the aging process and in most chronic diseases, including cancer, cardiovascular disease, diabetes, and dementia.

SELENOP Reference SNP ID	Homozygous Wild	Heterozygous Variant	Homozygous Variant	Nutrient Support For Enzyme Activity
rs3877899 Reference: CC	CC	CT	TT	Selenomethionine[51]

TrxR2— Thioredoxin 2

Risk Association– Impaired Mitochondrial Redox Balance
The TrxR2 gene encodes for the enzyme thioredoxin reductase 2. Thioredoxin reductases are a family of enzymes that maintain cellular redox balance and regulate various cellular processes. TrxR2 is primarily located in the mitochondria and is crucial in maintaining the redox state of proteins and other molecules within the mitochondria. TrxR2 is responsible for reducing oxidized thioredoxin, an antioxidant protein, which allows thioredoxin to carry out its antioxidant and regulatory functions. Variants in the TrxR2 gene can disrupt the normal functioning of the enzyme and impair mitochondrial redox balance, resulting in increased oxidative stress.

TrxR2 Reference SNP ID	Homozygous Wild	Heterozygous Variant	Homozygous Variant	Nutrient Support For Enzyme Activity
rs4485648 Reference: TT	TT	CT	CC	Quercetin, Selenomethionine[51]

TXNRD1— Thioredoxin Reductase 1

Risk Association– Impaired Antioxidant Activity
The TXNRD1 gene encodes a member of the thioredoxin (Trx) system, a selenocysteine-containing enzyme essential for mitochondrial oxygen radical scavenging. This protein plays a role in antioxidant defenses by reducing thioredoxin 1 (TXN), which in turn reduces oxidized cysteine in cellular proteins and scavenges peroxides by peroxiredoxins (PRDX), thus protecting cells against oxidative stress. Variants in the gene decrease enzyme activity, which can affect mitochondrial oxygen radical scavenging and antioxidant functions, increasing oxidative stress.

TXNRD1 Reference SNP ID	Homozygous Wild	Heterozygous Variant	Homozygous Variant	Nutrient Support For Enzyme Activity
rs7310505 Reference: CC, CA	CC	AC	AA	Quercetin[52], Selenomethionine[51]

**Note: For rs7310505, both CC and CA genotypes are considered normal with regard to risk. Only the AA genotype confers elevated risk.*

TXNRD2— Thioredoxin Reductase 2

Risk Association– Impaired Mitochondrial Oxygen Radical Scavenging Activity
The TXNRD2 gene encodes a member of the thioredoxin (Trx) system, a selenocysteine-containing enzyme essential for mitochondrial oxygen radical scavenging. This protein plays a role in antioxidant defenses by reducing thioredoxin 2 (TXN2), which in turn reduces oxidized cysteine in cellular proteins and scavenges peroxides by peroxiredoxins (PRDX), thus protecting cells against oxidative stress. Variants in the gene decrease enzyme activity, which can affect mitochondrial oxygen radical scavenging and antioxidant functions, increasing oxidative stress.

TXNRD2 Reference SNP ID	Homozygous Wild	Heterozygous Variant	Homozygous Variant	Nutrient Support For Enzyme Activity
rs1548357 Reference: TT	TT	CT	CC	Quercetin[52], Selenomethionine[51]

XDH— Xanthine Dehydrogenase

Risk Association– Elevated ROS Production
The XDH gene encodes the enzyme xanthine dehydrogenase, which is primarily involved in the metabolism of purine compounds. Xanthine dehydrogenase converts hypoxanthine to xanthine and xanthine to uric acid, an antioxidant. However, under certain conditions, xanthine dehydrogenase can undergo conversion to its other form, called xanthine oxidase (XO). XO, the oxidized form of xanthine dehydrogenase, can produce superoxide radicals as a byproduct of its enzymatic activity. Variants in the XDH gene can disrupt the normal regulation of xanthine dehydrogenase and more readily promote the conversion to XO. This increases the XO activity for higher production of ROS, including superoxide radicals. The accumulation of ROS can thus result in oxidative stress.

XDH Reference SNP ID	Homozygous Wild	Heterozygous Variant	Homozygous Variant	Nutrient Support For Enzyme Activity
rs206812 Reference: GG	GG	AG	AA	Quercetin[52], Papaya[53]
rs2073316 Reference: TT, TC	TT	CT	CC	

**Note: For rs2073316, both TT and TC genotypes are considered normal with regard to risk. Only the CC genotype confers elevated risk.*

Oxidative Damage Products Panel

Interpreting Results

- **Green**: Corresponds to 0 - 75th percentile
- **Yellow**: Corresponds to 75th – 95th percentile
- **Red**: Corresponds to >95th percentile

Lipid Peroxidation Biomarkers

Lipid peroxidation is a degenerative process wherein free radicals attack and break down lipids under oxidative stress. The process affects cell membranes, lipoproteins, and other lipid-containing structures.

Malondialdehyde

Malondialdehyde (MDA) is generated from the lipid peroxidation process (free radicals attack and breakdown lipids) by the peroxidation of membrane polyunsaturated fatty acids, including omega-3 (n-3) and omega-6 (n-6) fatty acids. ROS can cause the peroxidative breakdown of phospholipids that lead to the accumulation of MDA, thus making MDA a biomarker of oxidative stress. MDA is also produced in the process of prostaglandin synthesis. Elevated MDA levels are seen to be associated with conditions like diabetes, sepsis, and coronary heart disease. MDA is also involved in the pathogenesis of conditions such as Alzheimer's, Parkinson's disease, cancer, diabetes, cardiovascular and liver diseases.

MDA Nutrient Support	Magnesium[54], Vitamin E[55], Olive Oil[56], Melatonin[57], Vitamin C[58], Beta Carotene[59], Selenium[60], Glutathione[61], Grape Seed[62], Green Tea Extract[63], Neem[64], Curcumin[65], Holy Basil[66], Ashwagandha[67]

Glutathione 4-Hydroxynonenal

Glutathione 4-Hydroxynonenal (GSH-4-HNE) represents a crucial detoxification product formed during the cellular response to oxidative stress. 4-Hydroxynonenal (4-HNE) is a highly reactive aldehyde and a major end product of lipid peroxidation of polyunsaturated fatty acids, known for its role in mediating oxidative stress-induced cellular damage. Glutathione conjugates with 4-HNE to form GSH-4-HNE. This conjugation not only facilitates the eventual excretion of 4-HNE, thereby mitigating its cytotoxic and genotoxic effects, but also serves as a biomarker for oxidative stress and lipid peroxidation, with significant implications in the pathogenesis of various diseases, including cardiovascular, neurodegenerative, and inflammatory disorders.

GSH-4-HNE Nutrient Support	Vitamin C[68], Carnosine[69], Quercetin[70], Tea Catechins[71], Anthocyanins[72], Vitamin E[73], Beta-Carotene[74], Lutein[75], Selenium[76], Manganese[77], Glutathione[78], Grape Seed[79], Green Tea Extract[71], Scutellaria baicalensis[80], Korean Red Ginseng[81], Curcumin[65], Ashwagandha[82]

8-Iso-Prostaglandin F2α

8-iso-prostaglandin F2α (8-iso-PGF2α) is an isoprostane generated through the non-enzymatic peroxidation of arachidonic acid in membrane phospholipids. It is found in human plasma and excreted in urine. This biomarker serves as an indicator of oxidative stress and can reliably reflect lipid peroxidation in chronic diseases. Elevated levels of 8-iso PGF2α can lead to DNA oxidation and subsequent structural DNA damage. 8-iso PGF2α is valuable in assessing DNA oxidative damage and understanding its implications for cellular health and disease development. Studies have shown that increased levels of 8-iso PGF2α contribute to heightened oxidative stress associated with aging, hypertension, diabetes mellitus, hypercholesterolemia, smoking, and coronary artery disease.

8-iso-PGF2α Nutrient Support	Vitamin E[83], Lycopene[84], Beta-Carotene[74], Selenium[85], Vitamin C[86], Omega-3 Fatty Acids[87]

11-β-Prostaglandin F2α

11-β-prostaglandin F2α (11-PGF2α) is produced from the non-enzymatic oxidation of arachidonic acid. It is irreversibly produced from prostaglandin D2 via the enzyme prostaglandin-F synthase. Thus, elevated levels of 11-PGF2α indicate the increased oxidation of arachidonic acid by free radicals. Its increased levels can lead to inflammation. It may contribute to cardiac diseases owing to their involvement in vasoconstriction and cardiomyocyte hypertrophy (thickening of heart muscles). 11-PGF2α is also regarded as a marker of oxidative stress linked to inflammation.

11-PGF2α Nutrient Support	Omega-3 Fatty Acids[88]

15(R)-Prostaglandin F2α

15(R)-Prostaglandin F2α (15-F2t-IsoP) is an isoprostane generated through the non-enzymatic peroxidation of arachidonic acid in membrane phospholipids. This biomarker serves as an indicator of oxidative stress and can reliably reflect lipid peroxidation in chronic diseases. Elevated levels of 15-F2t-IsoP can lead to DNA oxidation and subsequent structural DNA damage. 15-F2t-IsoP is valuable in assessing oxidative damage to DNA and understanding its implications for cellular health and disease development. Studies have shown that increased levels of 15-F2t-IsoP contribute to heightened oxidative stress associated with aging, hypertension, diabetes mellitus, hypercholesterolemia, smoking, and coronary artery disease.

15-F2t-IsoP Nutrient Support	Omega-3 Fatty Acids[88]

DNA Damage Biomarkers

Damage to DNA by oxidative stress occurs via several mechanisms:

1) **Base modifications:** ROS, particularly hydroxyl radicals (• OH), are highly reactive and can directly modify nitrogenous bases.

2) **Sugar-phosphate backbone damage:** ROS can also attack the deoxyribose sugar in the DNA backbone, leading to single- or double-strand breaks that can lead to chromosomal fragmentation and translocations if not properly repaired.

3) **Formation of DNA cross-links:** ROS-mediated reactions can lead to the formation of DNA-protein cross-links and DNA-DNA inter-strand cross-links that can interfere with DNA replication and transcription, contributing to genomic instability.

4) **DNA adduct formation:** ROS can induce the formation of DNA adducts, a critical event in the chemical process of mutagenesis, carcinogenesis, and other forms of toxicity that can lead to disease.

8-Hydroxy-2-Deoxyguanosine

The guanine molecule, which is one of the four main nucleobases found in the nucleic acids in DNA, gets oxidized to produce the modified 8-hydroxy-2'-deoxyguanosine (8-OHdG), which acts as one of the predominant forms of free radical-induced lesions of DNA. Thus, 8-OHdG can indicate the effect of oxidative damage in DNA. The marker also estimates the risk for atherosclerosis, diabetes, and various cancers. Additionally, 8-OHdG helps assess the damage in the DNA after exposure to cancer-causing agents, such as tobacco smoke, asbestos fibers, heavy metals, and polycyclic aromatic hydrocarbons.

8-OHdG Nutrient Support	Alpha Tocopherol[89], Garlic Extract[90], Coenzyme Q10[91], Red Yeast Rice-Olive Extract[56], Resveratrol[92], Curcumin[93], Vitamin C[94], Creatine[95]

8-Hydroxyguanine

Guanine is the most easily oxidizable nucleic acid in the DNA. 8-Hydroxyguanine (8-OHG) is the oxidation product of guanine. It is an abundant lesion in genomic, mitochondrial, and telomeric DNA. It is considered to be a marker of oxidative damage in DNA. It is also seen to have mutagenic (capable of inducing genetic variation) potential. The accumulation of 8-OHG is believed to gradually increase with age. As a result, 8-OHG has been associated with various age-associated pathological conditions, including tissue and organ dysfunctions, neurodegenerative and cardiovascular diseases, and aging processes.

8-OHG Nutrient Support	Selenium[96]

8-Hydroxyguanosine

Reactions of ROS and RNS with RNA yield 8-hydroxyguanosine (8-HdG). Among the known oxidative lesions in nucleic acids, 8-HdG is abundant and appears to be most deleterious due to its high mutagenic potential. This implies that 8-HdG is capable of inducing genetic variation. RNA dysfunction caused by oxidative damage may contribute to the development of various degenerative diseases. Elevated urinary level of 8-HdG is an indicator of oxidative damage of RNA by ROS.

8-HdG Nutrient Support	Tart Cherry Juice[97]

Protein Oxidation Biomarkers

Post-translational modification (PTM) is a normal protein modification process in cells. Many PTMs are dependent on environmental factors. Changes in the structure of proteins can occur when a cell is exposed to oxidative/nitrative stress.

Dityrosine

Dityrosine is formed from protein-protein cross-linkage between two tyrosine molecules. This can be mediated by the oxidative species, hydroxyl radical and nitrative species, peroxynitrite, and nitrosoperoxycarbonate, leading to increased hydroxylation and nitration of tyrosine. Thus, dityrosine is produced due to oxidative/nitrative stress under various biological conditions and may also participate in lipid peroxidation. Elevated dityrosine levels have been linked with pathologies such as eye cataracts, atherosclerosis, acute inflammation, and Alzheimer's disease. Thus, dityrosine has risen as an important biomarker for oxidative stress, especially for oxidatively modified proteins during UV and gamma-irradiation, aging, and exposure to oxygen free radicals, nitrogen dioxide, peroxynitrite, and lipid hydroperoxides.

Dityrosine Nutrient Support	N-Acetyl-Cysteine[98]

3-Bromotyrosine

3-Bromotyrosine (Br-Tyr) is a compound generated by halogenating tyrosine residues in plasma or tissue proteins. Br-Tyr synthesis is primarily catalyzed by the enzyme eosinophil peroxidase (EPO). Eosinophils, specialized white blood cells, are central to immune responses. When eosinophils become activated in response to various immune challenges, they release enzymes like EPO. EPO is an enzyme that can generate ROS as part of its normal enzymatic activities; during this process, the subsequent production of Br-Tyr as a stable byproduct occurs. Elevated levels of Br-Tyr in biological samples serve as a crucial marker of oxidative stress, particularly associated with eosinophil-driven oxidative processes. This unique characteristic positions Br-Tyr as a valuable indicator, shedding light on the extent of oxidative stress induced by eosinophil activation and its potential implications in various physiological and pathological conditions.

3-Bromotyrosine Nutrient Support	Ascorbic Acid[99]

3-Chlorotyrosine

3-Chlorotyrosine is a significant marker of oxidative stress, particularly related to myeloperoxidase (MPO) activity—an enzyme found in white blood cells that plays a central role in immune response and inflammation. Elevated 3-chlorotyrosine levels indicate increased MPO-mediated oxidative stress, with potential implications for conditions like atherosclerosis and various other inflammatory disorders. 3-Chlorotyrosine's uniqueness lies in its heat stability and resistance to artificial formation. These distinctive properties make it an excellent marker specifically for MPO-induced oxidation, providing a clear indicator of MPO activity and associated oxidative stress. A high concentration of 3-chlorotyrosine occurs in human atherosclerotic tissue, in dialysis patients due to oxidative stress, and in cystic fibrosis patients with high levels of myeloperoxidase.

3-Chlorotyrosine Nutrient Support	Ascorbic Acid[99]

Nitrative Stress Biomarkers

Post-translational modification (PTM) is a normal protein modification process in cells. Many PTMs are dependent on environmental factors. Changes in the structure of proteins can occur when a cell is exposed to oxidative and nitrative stress. Elevated levels of nitric oxide (NO) can lead to nitrative stress. It is a phenomenon of cellular stress due to increased production and accumulation of damaging RNS.

8-Nitroguanosine

Oxidation of guanosine on the RNA by a nitro (NO2) group yields 8-nitroguanosine (8-NdG). Thus, 8-NdG is an RNA oxidation marker. Its production is enhanced under inflammatory conditions. It is believed to be a mutagenic RNA lesion, which means it can induce genetic variation. Urinary levels of 8-NdG are indicative of RNA oxidation of RNS.

8-NdG Nutrient Support	L-Glutathione[100]

8-Nitroguanine

NO reacts with superoxide to form the highly reactive peroxynitrite. Peroxynitrite can then react with guanine (on the DNA) to produce nitrative the DNA lesion, 8-nitroguanine (8-NO2-G). 8-NO2-G is indicative of RNS-induced nitrative DNA damage. Chronic infection and inflammatory conditions can lead to elevated levels of 8-NO2-G. 8-NO2-G is believed to be a mutagenic DNA lesion capable of inducing genetic variation. It is associated with various pathophysiological conditions, such as inflammation and neurodegenerative and cardiovascular diseases. Thus, urinary 8-NO2-G has become a marker of RNS-induced nitrative DNA damage.

8-NO2-G Nutrient Support	Curcumin[101], Dihydrolipoic Acid[102], N-Acetyl-Cysteine[102], Folic Acid[102]

Nitrotyrosine

Nitrotyrosine is generated by the PTM of proteins due to the effect of elevated concentrations of RNS. The formation of nitrotyrosine is associated with peroxynitrite-mediated protein modification of tyrosine. Peroxynitrite is a powerful oxidant exhibiting a wide array of tissue-damaging effects, including lipid peroxidation, inhibition of mitochondrial respiration, and inactivation of enzymes and ion channels via protein oxidation and nitration. As a result, nitrotyrosine is a biomarker for endogenous peroxynitrite activity and, thereby, oxidative stress. Elevated levels of nitrotyrosine are associated with aging, rheumatism, atherosclerosis, systemic lupus, diabetes, and neurodegeneration. Thus, nitrotyrosine is a crucial marker of protein oxidation by RNS.

Nitrotyrosine Nutrient Support	Resveratrol[103], Vitamin C[104], Vitamin E[105], Tetrahydrobiopterin[104], L-Arginine[104]

Advanced Glycation Products Biomarkers

Glycation is a spontaneous non-enzymatic reaction wherein free reducing sugars bind to free amino groups of proteins, DNA, and lipids. This results in the formation of AGEs. Glycation and oxidative stress are closely linked, and they are together referred to as "**glycoxidation** ."All steps of glycoxidation generate free radicals, some of them being common with the lipid peroxidation pathway. Therefore, AGE has been considered a urinary biomarker of oxidative stress.

Nε-(Carboxymethyl)-Lysine

The AGE product, Nε-(carboxymethyl)lysine (CML), is formed when glyoxal (formed from the oxidation of lipids and sugars) reacts with lysine. CML is believed to act as a chelator of redox-active copper, resulting in increased oxidation of ascorbate, thereby the body's reducing antioxidant potential. Elevated levels of CML may exert stronger oxidizing potential, which may lead to oxidative stress. Thus, urinary levels of CML can be used to monitor the degree of oxidative stress in the body system.

CML Nutrient Support	Epigallocatechin Gallate[106], Quercetin[107], Alpha Lipoic Acid[108], Vitamin D[109]

Nε-(Carboxyethyl)-Lysine

The AGE product, Nε -carboxyethyllysine (CEL), is formed when methylglyoxal (formed from the oxidation of lipids and sugars) reacts with lysine. CEL interacts with AGE receptors (RAGEs), which may give rise to oxidative stress and induce cellular dysfunction. Urinary levels of CEL can be used to monitor the degree of oxidative stress in the body system.

CEL Nutrient Support	Taurine[110]

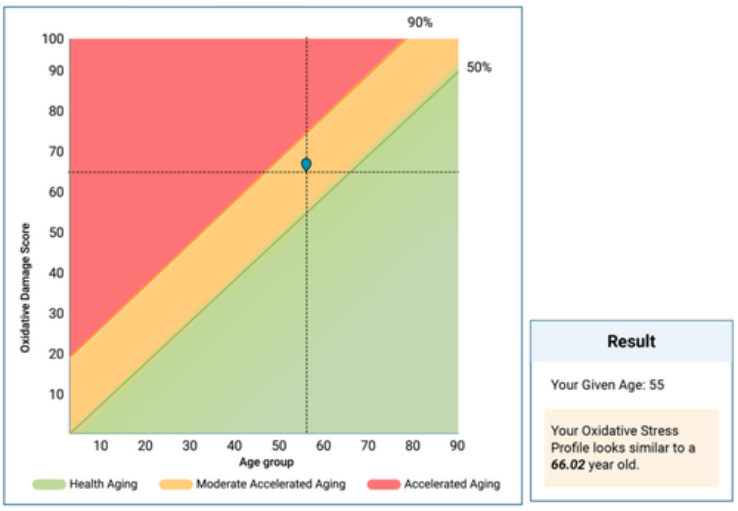
Oxidative Damage Score

Interpreting Results

The Oxidative Damage Score illustrates the overall level of oxidative damage based on a comprehensive analysis of various urine damage markers. The score is calculated using a linear regression model and is graphically presented relative to the patient's age group. The scores are color-coded for clarity in the graph.

The Oxidative Damage Score indicates the speed of aging based on oxidative stress damage to DNA, lipids, and proteins:

- The x-axis represents the patient's age
- The y-axis represents the total oxidative damage score



The score indicates percentile compared to an apparently healthy reference population.

- **Green**: Normal level of oxidative damage based on the 50th percentile of the reference population; suggestive of Healthy Aging
- **Yellow**: Moderate score based on the 90th percentile of reference population; suggestive of Moderately Accelerated Aging
- **Red**: High score based on the reference population; suggestive of Accelerated Aging

Nutrient Recommendations

The Oxidative Stress Profile report includes evidence-based nutrient recommendations based on a proprietary algorithm. This summary includes the suggested nutrient, dosage, and purpose. These suggestions are not intended to diagnose, treat, cure, or prevent any disease and are for educational purposes only. Healthcare providers should utilize clinical correlation in their assessment, differential diagnoses, and intervention decision-making.

Lifestyle Modifications to Ameliorate Oxidative Stress

Diet and Nutrition

A Western dietary pattern, along with diets high in calories, carbohydrates, fats, ultra-processed foods, or diets with a high Dietary Inflammation Index (DII) or Dietary Oxidative Balance Score (DOBS), can induce oxidative stress. However, there are several dietary approaches and patterns that can alleviate oxidative stress, including the **Mediterranean diet, DASH diet, vegetarian and plant-based diets, the USDA Healthy Eating Index-based diet,** and the **Paleolithic diet**.[111] [112] [113] [114] Of note, oxidative stress that occurs during the immediate postprandial state may be a significant contributing factor to chronic diseases and may be mitigated by ensuring that adequate dietary antioxidant intake is consumed at all meals.

Oxygen Radical Absorbance Capacity (ORAC) units are a method of quantifying the antioxidant capacity of foods and supplements. Developed by the National Institute on Aging, the ORAC score measures a substance's effectiveness and capacity to scavenge free radicals. The range for ORAC scores can vary widely depending on the food or substance being measured due to differences in growing conditions, harvest time, processing, cooking, and storage methods. The ORAC score is expressed in micromoles of Trolox equivalents per 100 grams of food (µmol TE/100 g). Studies of dietary intake at or above 10,000 ORAC units daily are associated with reduced risk of hypertension, myocardial infarction, stroke, endometrial cancer, and all-cause mortality, with some studies finding ORAC intakes as high as 19,000 units per day are possible from foods if selected properly[115,116]. However, determining the average dietary intake of ORAC units in the US or any population is challenging because comprehensive data on this specific measurement is not routinely collected as part of national dietary surveys.

Additionally, there is some scientific disagreement about whether ORAC values measured in vitro reflect the actual antioxidant capacity of these foods within the human body, leading the USDA to withdraw the publicly accessible ORAC Database. Other measures of dietary antioxidant intake used for research purposes include the **Dietary Antioxidant Quality Score (DAQS)** and the **Dietary Antioxidant Index (DAI)**. However, these measures are less practical for individual use. Dietary tracking apps (e.g., MyFitnessPal and Cronometer) may be used to track the adequacy of dietary intake of several vitamin and mineral antioxidants (e.g., vitamins A, C, and E, selenium, zinc, beta-carotene). However, these apps underestimate total dietary antioxidant intake from unmeasured phytonutrients (e.g., resveratrol, curcumin, lycopene, glucosinolates).

Despite these limitations in quantifying dietary antioxidant intake, there is broad scientific agreement that a "**dietary antioxidant gap**" exists in the US. That gap can be reduced by meeting dietary guidelines for the intake of vegetables and fruits, particularly red, orange, yellow, green, blue, violet, and white colors, hence the popular recommendation to "**eat the rainbow**" daily.

Reduce the dietary antioxidant gap by eating the rainbow daily.

Target exogenous antioxidant goals for a precision medicine approach by measuring blood and cellular levels of antioxidant micronutrients and micronutrient SNPs.

Movement and Exercise

Exercise-induced oxidative stress can vary depending on several factors, including the intensity and duration of the exercise, the individual's fitness level, age, and overall health. Vigorous intensity exercise generates oxidative stress. This is evidenced by an increase in the production of ROS and other free radicals during and following high-intensity exercise. A systematic review investigating the effects of high-intensity exercise on oxidative stress and antioxidant status in humans found strong evidence of acute oxidative stress occurring at the cessation of high-intensity exercise compared to resting states. The induced oxidative stress from high-intensity exercise is transient and is typically restored to normal levels due to the stimulated endogenous antioxidant system. This recovery phase is crucial, allowing the body to return to its normal oxidative balance[117]. Generally, oxidative stress markers can increase following exercise but are often restored to baseline levels within a short period, typically within hours to a day after exercise[118]. Notably, creatine supplementation decreases oxidative DNA damage and lipid peroxidation induced by a single session of resistance exercise[95].

The time course of oxidative stress responses to different training intensities has been studied in various groups, including middle-aged and elderly individuals. These studies emphasize the adaptability of the body's antioxidant defenses in response to regular exercise, suggesting that a physically active lifestyle can enhance antioxidant capacity and improve resilience against exercise-induced oxidative stress[119]. Exercise stimulates the production of antioxidants, such as SOD, CAT, and GPX- an example of hormesis. Hormesis is an adaptive two-phased dose-response relationship in which exposure to a stressor, in this scenario, exercise-related oxidative stress, is beneficial and adaptive at low doses and harmful at high doses. Exercise also stimulates mitochondrial biogenesis and mitochondrial adaptation, enhancing cellular functioning and activating cellular mitophagy in which cells selectively wrap and degrade damaged mitochondria through an autophagy mechanism, acting as additional hormetic and resilience mechanisms.

In summary, while oxidative stress is a natural response to vigorous exercise, regular physical activity can improve the body's antioxidant defense system and reduce the negative impacts of oxidative stress over time. This suggests a beneficial adaptation process associated with regular exercise. Healthcare providers may wish to target nutrient support according to exercise intensity, duration, and training and recovery times.

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*Exercise exhibits an oxidative stress **biphasic response**, often referred to as **hormesis**. This concept suggests that while exercise increases oxidative stress by generating ROS during the activity, it simultaneously triggers the body's antioxidant defense systems, enhancing protection against oxidative stress over time.*

Sleep Support

The relationship between oxidative stress and impaired sleep quality or duration is a complex interplay of various physiological mechanisms involving circadian rhythm disruption, inflammatory pathways, endocrine changes, and mitochondrial dysfunction, leading to increased oxidative damage and reduced antioxidant defense capabilities.

Sleep duration is inversely correlated with oxidative stress[120] [121]. Evidence suggests that individuals with less than 6 hours of sleep per night exhibit significantly higher oxidative stress biomarkers levels than those with adequate sleep (7-8 hours). Research has demonstrated that both acute and chronic sleep deprivation can lead to increased oxidative stress, indicated by elevated levels of MDA, 8-OHdG, and 15(R)-Prostaglandin F2α, and altered SOD, CAT, and GPX, and antioxidant enzyme[120]. Additional inflammatory and oxidative stress markers elevated in acute and chronic sleep deprivation include oxLDL and myeloperoxidase (MPO)[122]. Studies examining "recovery sleep" after acute and chronic sleep deprivation suggest that recovery sleep of one night or one week can only partially ease the oxidative damage caused by sleep deprivation, with sustained sleep recovery needed to resolve alterations in MDA, CAT, GSH levels, SOD activity, and redox metabolites[123].

Interventions that may help alleviate impaired sleep-induced oxidative stress include melatonin, cognitive behavioral therapy for insomnia (CBT-I), and sleep hygiene practices. A meta-analysis of 16 studies demonstrated that melatonin supplementation significantly attenuated oxidative stress by reducing MDA and enhancing total antioxidant capacity (TAC)[124]. CBT-I addresses the underlying causes of insomnia to improve sleep quality and duration, and this improvement has been correlated with reductions in biomarkers of oxidative stress[125]. Interventions focusing on sleep hygiene education have been effective in improving sleep quality and duration, which in turn can mitigate oxidative stress (Chen et al., 2011).

Stress Management and Relaxation

Emerging evidence supports the efficacy of various stress management and relaxation interventions in modulating oxidative stress, including Cognitive Behavioral Therapy (CBT), Mindfulness-Based Stress Reduction (MBSR), meditation, yoga, Tai Chi, breathing exercises, and biofeedback.

- **CBT** has been shown to contribute to the reduction of psychological stress, which in turn may lower the biochemical markers of oxidative stress. Although specific pathways of CBT's impact on oxidative biomarkers are not well-delineated, the down-regulation of HPA activation and reduction in stress-related hormones like cortisol, which can induce oxidative stress when chronically elevated, is a likely putative mechanism[126] [127].

- **MBSR**, similar to CBT, alleviates stress and its physiological consequences, potentially reducing oxidative stress markers. MBSR may enhance the expression of genes involved in oxidative stress defense, thus bolstering the body's natural antioxidant defenses. This includes the upregulation of antioxidant enzymes such as SOD and GPX, offering a buffer against the cellular damage typically associated with oxidative stress[128].

- **Meditation**, often incorporated into both MBSR and yoga, has been found to reduce psychological stress and enhance metabolic and neuroendocrine functions that contribute to oxidative stress. Regular meditation practice is associated with the downregulation of pro-inflammatory genes and pathways[129], which can mitigate the oxidative damage inflicted by chronic inflammation, reduce markers of lipid peroxidation, and increase the level and activity of GSH, CAT, SOD, GPX, and GR[130].

- **Yoga** studies indicate that regular yoga practice can modulate several oxidative stress markers, including reducing levels of MDA, 8-OH2dg, protein oxidation markers, and ROS, and increasing glutathione, vitamin C, SOD activity, and total antioxidant capacity[131] [132] [133]. The physical postures and breathing exercises inherent in yoga improve the balance between sympathetic and parasympathetic nervous systems, reducing overall stress and indirectly supporting antioxidant defenses.

- **Tai Chi**, a form of gentle exercise known for its slow and flowing movements, has been found to enhance the antioxidant defense system by increasing SOD and catalase activity and reducing MDA and lipoperoxide levels[134] [135].

- **Breathing exercises** have long been used in pulmonary rehabilitation and clinical settings. These exercises work by extending the duration of breaths, reducing the breathing rate, and decreasing the oxygen difference between the alveoli and arteries. This enhances the strength and stamina of the respiratory muscles, improving pulmonary ventilation and gas exchange efficiency. As a result, these exercises help alleviate hypoxia and boost endurance. A systematic review and meta-analysis of breathing exercises on oxidative stress found that breathing exercises increased SOD and GSH activities and decreased MDA content[136].

- **Biofeedback** teaches individuals to control physiological processes that are typically considered involuntary. Using sensors that provide real-time feedback on body functions such as heart rate, muscle tension, and skin temperature, biofeedback helps individuals learn how to enact physiological changes that reduce stress levels. This reduction in physiological stress can mitigate the effects of oxidative stress by lowering the production of ROS, increasing SOD, and decreasing lipid peroxides, enhancing the body's capacity to handle oxidative challenges[137].

Integrating CBT, MBSR, meditation, yoga, Tai Chi, breathing exercises, and biofeedback into health routines can be a strategic approach to managing oxidative stress. These interventions foster an enhanced antioxidant defense system and mitigate oxidative damage, crucial in maintaining cellular health and preventing disease onset.

Psychosocial Support & Relationships

Social isolation, loneliness, lack of social support, and adverse social determinants of health can all contribute to an increased physiological stress response, which, in turn, can elevate oxidative stress biomarkers. The physiological link between these social factors and oxidative stress is rooted in the body's stress response. Chronic psychological stress can lead to an overproduction of stress hormones and free radicals and decreased antioxidant defenses.

Social isolation refers to the objective lack of social contacts and interactions, while loneliness is the subjective feeling of isolation. Both can trigger chronic stress responses in the body. Chronic stress is known to activate the sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis, leading to increased production of stress hormones like cortisol. Loneliness and social isolation are linked to an increased risk of cardiovascular disease, and one mediating molecular mechanism identified is oxidative stress, which induces HPA axis activation and subsequent increased vascular tone and atherogenicity[138].

Social determinants of health, such as socioeconomic status, education, neighborhood, physical environment, and employment, have been linked to oxidative stress. Lower socioeconomic status can lead to increased exposure to environmental toxins, poor nutrition, higher levels of stress, and reduced access to healthcare, all of which can contribute to higher levels of oxidative stress. Additionally, educational and employment opportunities influence lifestyle choices and access to resources that can either mitigate or exacerbate oxidative stress.

Adequate social support and healthy relationships can act as a buffer against the harmful effects of oxidative stress. Social support can mitigate the impact of stress by providing psychological and material resources that help individuals cope with life's challenges, boost their resilience, and decrease oxidative stress. Healthcare providers and patients may wish to target psychosocial and relationship support in their oxidative stress reduction care plans.

Other Therapies

Cold Water Immersion

Cold water immersion (CWI) influences systemic oxidative stress and related biomarkers, particularly in physical exercise and athletic recovery. The biphasic response of oxidative stress to CWI refers to a dual-phase reaction where the body exhibits varying levels of oxidative stress at different stages, intensities, or duration of exposure to cold water. Initially, CWI may lead to an acute increase in oxidative stress. This is due to the body's immediate response to cold exposure, which can include increased metabolic rate, heightened sympathetic nervous system activity, and elevated production of ROS. However, with repeated or prolonged exposure to cold water, the body may exhibit a second phase characterized by an adaptive response. This adaptation can lead to a decrease in oxidative stress markers. It is thought to be due to the upregulation of antioxidant defense mechanisms and improved cellular tolerance to ROS. Essentially, the body becomes more efficient at neutralizing and managing oxidative stress with regular cold exposure. This concept is vital in understanding the physiological implications of CWI, especially in therapeutic and athletic settings.

A study of cold water-adapted winter swimmers was examined to determine the effects of CWI on cardiovascular risk factors. The “cold-adapted” group had significantly lower GPX1 activity and oxidative stress markers and significantly increased zinc concentrations. Another study of cold water swimmers found that repeated cold exposure of 3-5 minute sessions once weekly upregulated most antioxidant defenses and attenuated most oxidative stress indicators. A study of CWI's effect on oxidative and inflammatory response after resistance exercises found CWI reduced lipid peroxidation and increased antioxidant capacity against peroxyl radical, with the authors concluding that CWI at an upper limit of 59 °F and a lower time limit of 10 minutes favors redox balance.

Overall, CWI may have beneficial effects on oxidative health. However, potential harms of CWI may include cardiac arrhythmias and risk of hypothermia, and risks may be influenced by biological sex, age, general health condition, body size and composition, CWI experience, water temperature, active vs passive CWI, and immersion duration. For CWI risk reduction, start at higher temperatures (e.g., 68 °F) to help acclimation and habituation and shorter durations (e.g., 2 minutes), and gradually adjust temperature and time as tolerated.[141]

Cold water immersion exhibits a biphasic, or hormetic, response.

Photobiomodulation– Near-Infrared and Infrared Light Therapy

Photobiomodulation therapy (PBMT), using red or near-infrared light, has garnered attention for its potential therapeutic effects on tissue regeneration, wound healing, pain reduction, edema, inflammation, and oxidative stress alleviation. PBMT applications have been studied across different contexts and settings.

In animal muscle injury models, PBMT effectively reduces oxidative stress markers like thiobarbituric acid-reactive substances (TBARS) and enhances antioxidant defenses, including CAT, GPX, and SOD[142]. In humans, PBMT administered before or after exercise, can improve performance metrics, reduce muscle soreness, and aid muscle recovery by reducing inflammatory and oxidative stress markers[143].

In an aging rat model of Alzheimer's disease, PBMT reduced oxidative stress and induced brain-derived neurotrophic factor (BDNF) expression in the hippocampus, suggesting potential neuroprotective effects[144]. Additionally, studies demonstrate that transcranial PBMT (tPBMT) is an emerging therapeutic modality for targeting brain metabolism, inflammation, oxidative stress, and neurogenesis in Alzheimer's disease, major depressive disorder, comorbid anxiety disorders, and traumatic brain injury. However, large mechanistic, placebo-controlled, randomized clinical trials are necessary to determine safety, efficacy, and therapeutic potential[145] [146].

While the results of PBMT for oxidative stress are promising, the variation in equipment and protocols used vary widely, from single laser probes to mixed clusters of lasers and LEDs, and coupled with a lack of uniform terminology, calls for more standardized research protocols. Overall, the broad applicability and positive outcomes associated with PBMT point to its significant potential in medical and athletic settings, warranting further exploration and standardization.

Photobiomodulation exhibits a biphasic, or hermetic, response.

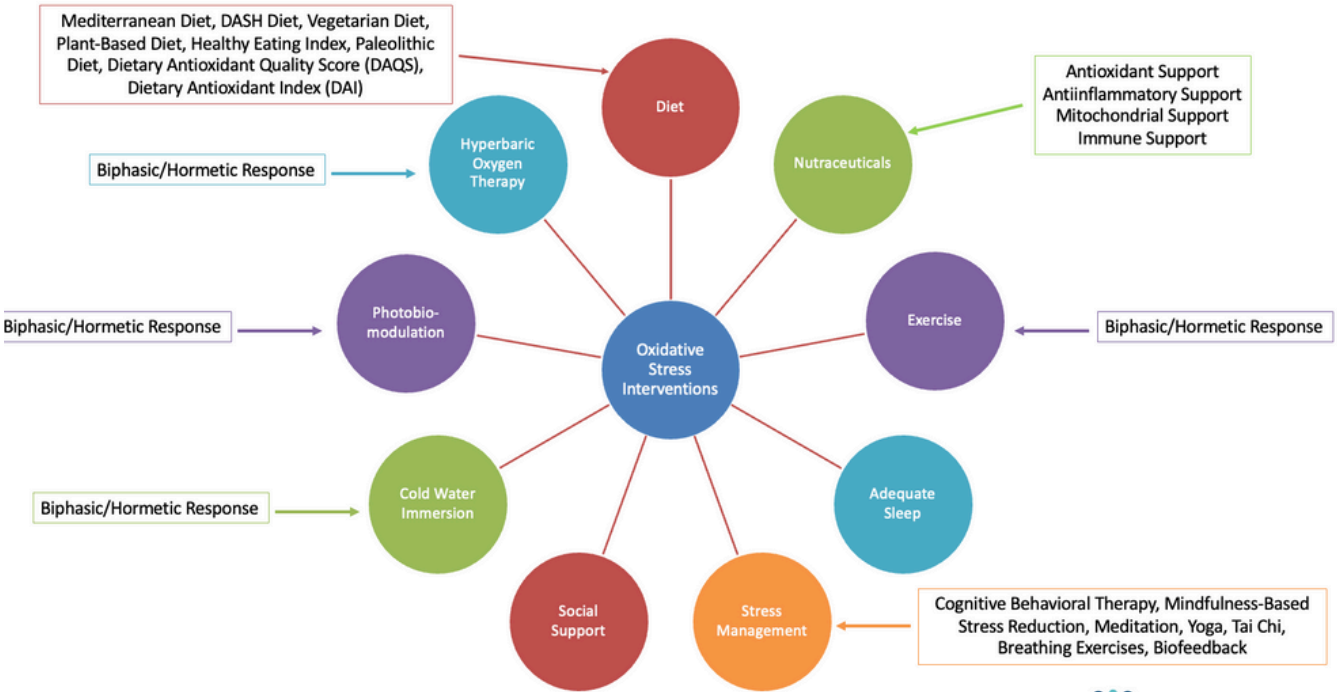
Hyperbaric Oxygen Therapy

Hyperbaric Oxygen Therapy (HBOT) involves breathing 100% pure oxygen in a pressurized environment, increasing oxygen concentration in the blood and tissues. The heightened oxygen levels can improve tissue oxygenation and enhance mitochondrial function and respiration, leading to efficient energy production and reduced leakage of electrons that form ROS. HBOT also has been shown to upregulate antioxidant enzymes like SOD and CAT to mitigate oxidative damage and can reduce inflammatory processes, thereby indirectly reducing the oxidative stress associated with inflammation[147].

The effectiveness and impact of HBOT can vary based on its application specifics, such as duration, pressure, and the number of sessions. Short-term treatments of HBOT may adversely affect mitochondrial function and increase ROS production. Conversely, longer-term therapies enhance mitochondrial activity and reduce ROS production.

HBOT is a potentially promising treatment option for oxidative stress, but it carries potential risks, especially for certain groups. Common complications include barotrauma due to the increased pressure in the hyperbaric chamber, which can cause ear pain or damage to the sinuses and, in severe cases, lung damage. There is also a risk of central nervous system oxygen toxicity, which can lead to seizures. Temporary vision changes, particularly myopia, may occur due to the effect of oxygen on the eye's lens. The enclosed space of the chamber can also induce anxiety or claustrophobia in some individuals. Populations at greater risk include those with pre-existing respiratory conditions such as COPD or asthma, individuals with ear and sinus issues that make pressure equalization difficult, patients with unstable cardiac conditions, those with a history of seizures, and individuals prone to severe anxiety or claustrophobia.

Hyperbaric oxygen therapy exhibits a biphasic or hermetic response.



Complementary Testing

Tests that complement the Oxidative Stress Profile for further workup of antecedents, triggers, and mediators of oxidative stress include:

- **Total Tox Burden (Environmental Toxin, Mycotoxin, and Heavy Metals tests):** To assess an individual's specific level of toxins in the body. Heavy metals, mycotoxins, and environmental toxins induce oxidative stress by increasing the production of ROS, overwhelming antioxidant defenses, and disrupting cellular function, leading to increased oxidative damage to DNA, proteins, and lipids, and contributing to various diseases and aging.

- **PFAS Chemicals Test:** To assess an individual's specific level of per- and polyfluoroalkyl substances in the body. Experimental research and preliminary epidemiologic studies suggest a relationship between PFAS exposure and oxidative stress based on systemic responses and cellular reactions[148].

- **Micronutrient Panel and NutriPro:** Provides insights into intra- and extracellular micronutrient and antioxidant levels (Micronutrients) and nutrition-related genetic SNPs (NutriPro) that impact oxidative stress.

- **Cardiac Health Panel:** Oxidative stress can cause increased inflammation, a known driver of cardiovascular disease risk, pathogenesis, and progression. Additionally, higher ROS levels reduce nitric oxide, causing vasoconstriction and hypertension, impair myocardial calcium regulation, leading to arrhythmia, promote cardiac remodeling and apoptosis, and contribute to atherosclerotic plaque formation[149].

- **Diabetes Panel:** Oxidative stress can increase inflammation, which drives diabetes risk, pathogenesis, and progression, with a systematic review finding significant differences in levels of MDA, nitric oxide, glutathione, and total antioxidants in people with diabetes compared to healthy controls[150].

Disclaimer and Regulatory Statement

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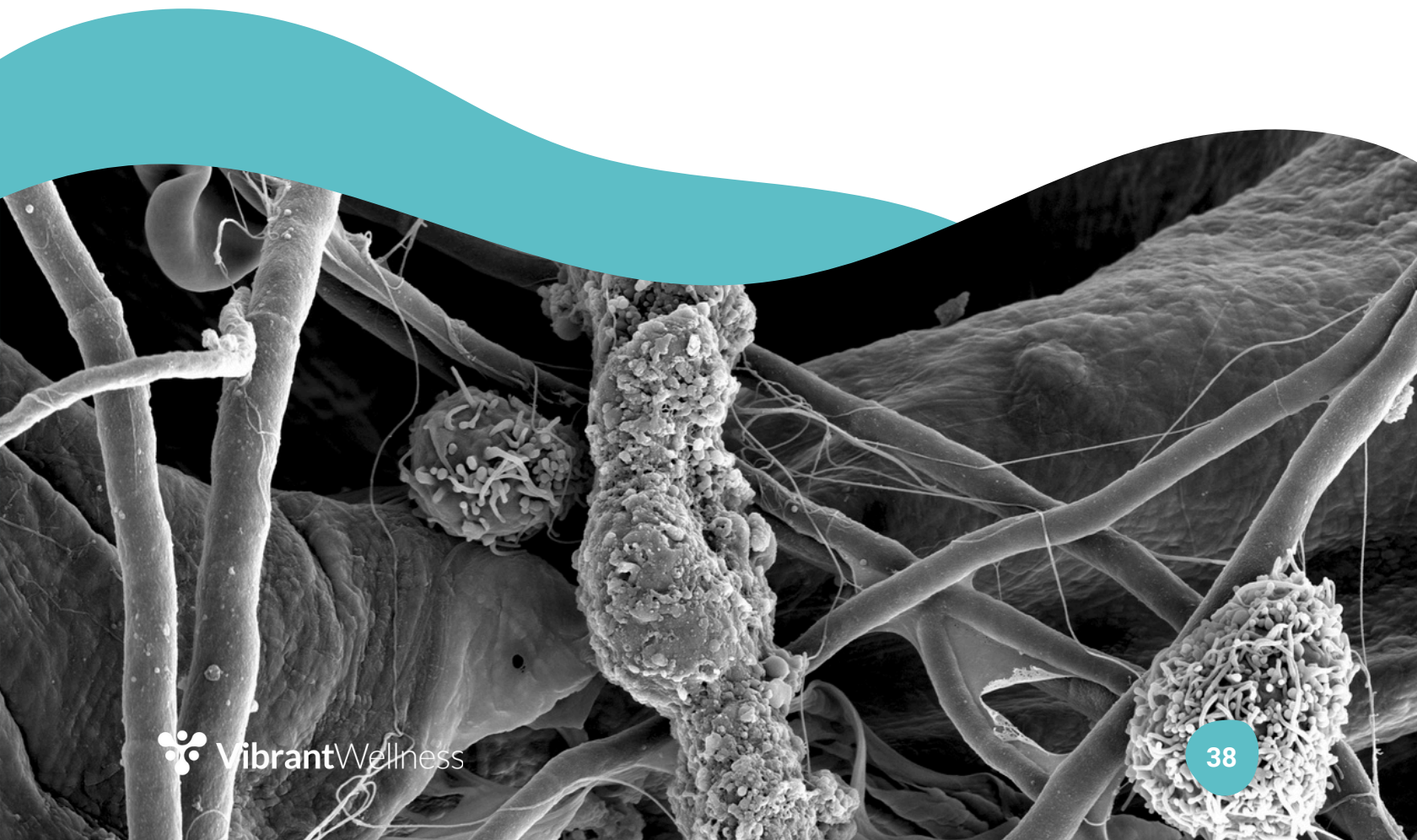

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