Optimizing Patient Care
Identifying and Bypassing Genetic Polymorphisms

Presenter:
Benjamin Lynch, ND

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"*Clinicians will be central to helping consumer-patients use genomic information to make health decisions*." – NEJM

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  I am President and CEO of SeekingHealth.com, SeekingHealth.org and founder of MTHFR.Net

How are these linked?

- Orange skin and beta carotene
- Low RBC folate yet high serum folate
- Anger from cheese
- Symptoms improve during pregnancy
- Methylfolate and Itchiness/Rash
- Depression and Chronic Disease
- Elevated serotonin in autism
- Preeclampsia and nitric oxide

Genetic and Epigenetic Contributions to Human Nutrition and Health: Managing Genome–Diet Interactions

PATRICK J. STOVER, PhD; MARIE A. CAUDILL, PhD, RD

ABSTRACT

The Institute of Medicine recently convened a workshop to review the state of the various domains of nutritional genomics research and policy and to provide guidance for further development and translation of this knowledge into nutrition practice and policy. Nutritional genomics holds the promise to revolutionize both clinical and public health nutrition practice and facilitate the establishment of (a) genome-informed nutrient and food-based dietary guidelines for disease prevention and healthful aging, (b) individualized medical nutrition therapy for disease management, and (c) better targeted public health nutrition interventions (including micronutrient fortification and supplementation) that maximize benefit and minimize adverse outcomes within genetically diverse human populations. As the field of nutritional genomics matures, which will include filling fundamental gaps in knowledge of nutrient–genome interactions in health and disease and demonstrating the potential benefits of customizing nutrition prescriptions based on genetics, registered dietitians will be faced with the opportunity of making genetically driven dietary recommendations aimed at improving human health.

J Am Diet Assoc. 2008;108:1480-1487.

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Public health nutrition continues to be challenged by increasing expectations from the food supply on one hand, and fundamental gaps in nutrition knowledge on the other, which can constrain the development and implementation of nutrition and food policy (1). Current demands on the food supply are no longer limited to ensuring general safety and preventing micronutrient deficiencies. Increasingly, there is interest in engineering medicinal qualities into the food supply to enable diets that promote health and "nurture" a sense of well-being that transcends the mere absence of disease by improving biological functions and even increasing lifespans.

Unquestionably, nutrition is one of the primary environmental exposures that determines health. Common human chronic diseases, including type 2 diabetes, metabolic syndrome, cardiovascular and neurological disease, and many cancers are initiated and/or accelerated by nutrient/food exposures. However, it is also recognized that chronic diseases are complex in their etiology and include a substantial genetic component; individuals respond differently to foods and even individual nutrients. Investigation in this new field of nutrition research, often referred to as *nutritional genomics*, focuses on deciphering the biological mechanisms that underlie both the acute and persistent genome-nutrient interactions that influence health.

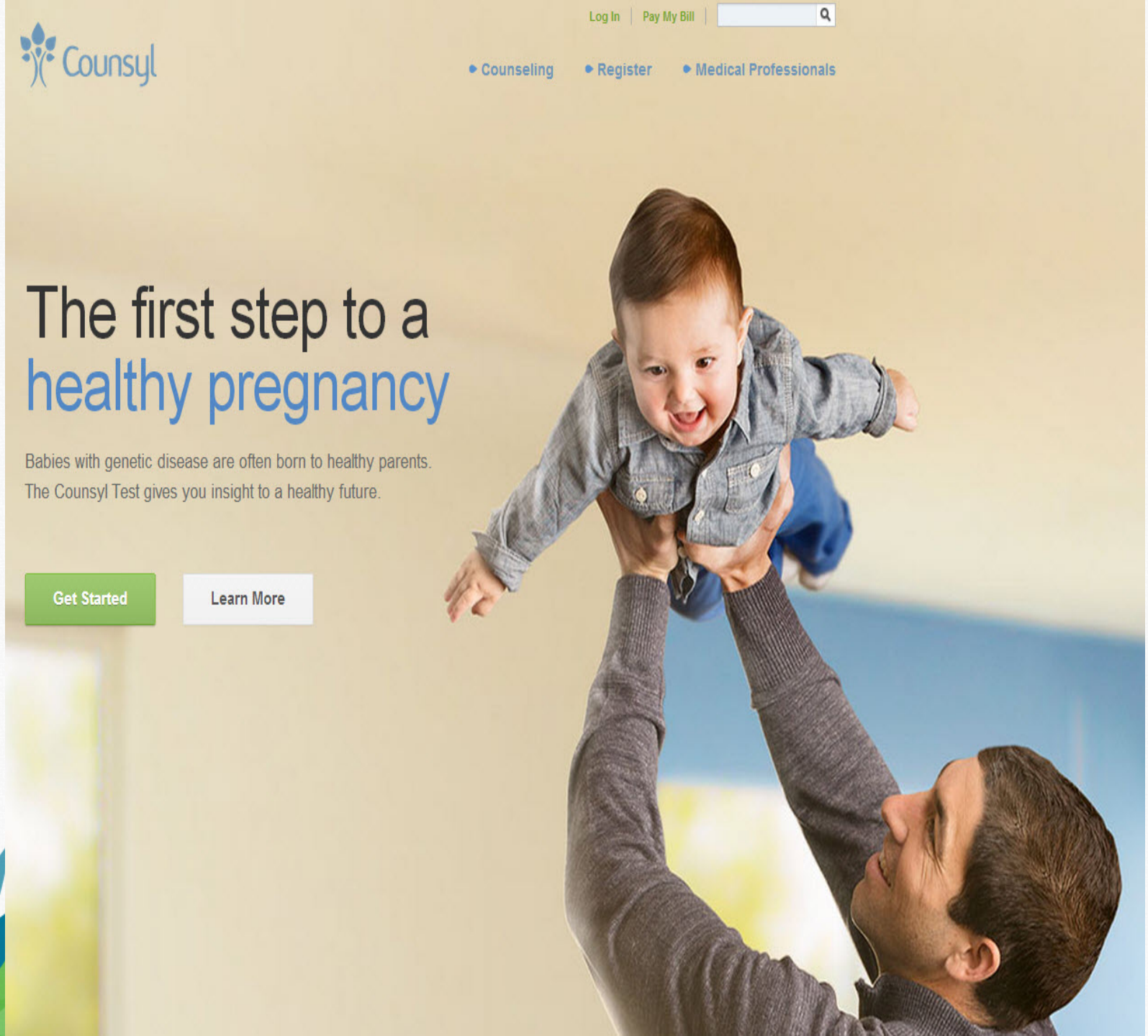
Nutritional genomics, while centered on the biology of individuals, distinguishes itself from other "omics" fields by its unique focus on disease prevention and healthy aging through the manipulation of gene–diet interactions. Nutritional genomics promises to revolutionize both clinical and public health nutrition practice and facilitate the establishment of (a) genome-informed nutrient and food-based dietary guidelines for disease prevention and healthful aging, (b) individualized medical nutrition therapy for disease management, and (c) better

Why?

Treat the Patient. Not the SNPs

Key Points about SNPs and Clinical Use

- Most SNPs not clinically relevant
- Optimizing pregnancy
- Increases compliance
- Fantastic for disease prevention
- Ability to optimize patient's wellness
- Identify possible nutrient deficiencies
- Identify predispositions and risks
- Contributing cause towards patient signs/symptoms
- Ability to create a long-term plan
- Forces a need to understand the normal function and interactions.
- Identify reasons why patient responds poorly/favorably to treatment.


Log In
Pay My Bill
Counsyl
Counseling
Register
Medical Professionals
The first step to a
healthy pregnancy
Babies with genetic disease are often born to healthy parents.
The Counsyl Test gives you insight to a healthy future.
Get Started
Learn More

RESULTS			
Gene Name / Variation	Mutation Not Present	Mutation(s) Present	Call
SHMT / C1420T		+/-	Hetero
AHCY / 1	-/-		A
AHCY / 2	-/-		T
AHCY / 19	-/-		A
MTHFR / C677T	-/-		C
MTHFR / A1298C	-/-		A
MTHFR / 3	-/-		C
MTR / A2756G		+/-	Hetero
MTRR / A66G		+/-	Hetero
MTRR / H595Y	-/-		C
MTRR / K350A	-/-		A
MTRR / R415T	-/-		C
MTRR / S257T	-/-		T
MTRR / 11		+/-	Hetero
BHMT / 1	-/-		A
BHMT / 2		+/-	Hetero
BHMT / 4		+/+	C
BHMT / 8		+/+	T
CBS / C699T	-/-		C
CBS / A360A	-/-		C
CBS / N212N	-/-		C
COMT / V158M		+/+	A
COMT / H62H		+/+	T
COMT / 61	-/-		G
SUOX / S370S	-/-		CG
VDR / Taq1	-/-		C
VDR / Fok1	-/-		C
MAO A / R297R	-/-		G
NOS / D298E	-/-		G
ACAT / 1-02		+/-	Hetero

Minus "-" represents no mutation

Plus "+" represents a mutation

"-/-" indicates there is no mutation

"+/-" indicates there is one mutation

"+/+" indicates there is a double mutation

Do you recommend this product?

I Have homozygous mutation in COMT V158M, COMT H62H, VDR Taq, MAO-A R297R and CBS C699T.

I have heterozygous mutations MTRR A66G, MTRR K350A, BHMT-02, and BHMT-08.

Please help I want to buy the right supplements. I am 29 year old mom with 3 babies, I need al the energy and mood and every thing and beyond help.

Methylation Profile; plasma

PRIMARY & INTERMEDIATE METABOLITES				
	RESULT/UNIT		REFERENCE INTERVAL	PERCENTILE (2.5th, 16th, 50th, 84th, 97.5th)
Methionine	**2.0**	µmol/dL	1.6 - 3.6	
Cysteine	**50**	µmol/dL	20 - 38	
S-adnosylmethionine (SAM)	**205**	nmol/L	86 - 145	
S-adenosylhomocysteine (SAH)	**46.1**	nmol/L	10 - 22	
				68th, 95th
Homocysteine	**20.6**	µmol/L	< 11	
Cystathionine	**0.30**	µmol/dL	< 0.05	

METHYLATION INDEX				
	RESULT		REFERENCE INTERVAL	PERCENTILE (68th, 95th)
SAM : SAH	**4.5**		> 4	

Testing Levels of Various Folate Forms

AMINOACIDS IN PLASMA			
Glutathione (oxidised)	**0.51**	µmol/L	0.16 - 0.50
Glutathione (reduced)	**3.2**	µmol/L	3.8 - 5.5
DERIVATES			
S-Adenosylmethionine (RBC)	**213**	µmol/dl	221 - 256
S-Adenosylhomocysteine (RBC)	**52.0**	µmol/dl	38.0 - 49.0
FOLIC ACID DERIVATES			
5-CH3-THF	**8.8**	nmol/l	8.4 - 72.6
10-Formyl-THF	**3.7**	nmol/l	1.5 - 8.2
5-Formyl-THF	**1.60**	nmol/l	1.20 - 11.70
THF	**0.52**	nmol/l	0.60 - 6.80
Folic Acid	**9.2**	nmol/l	8.9 - 24.6
Folinic Acid (WB)	**7.1**	nmol/l	9.0 - 35.5
Active folate (RBC)	**359**	nmol/l	400 - 1500
NUCLEOSIDE			
Adenosine	**23.6**	10^-8 M	16.8 - 21.4

http://www.hdri-usa.com/tests/methylation/

AMINOACIDS IN PLASMA			
Nitrotyrosine	28.7	µg/l	1.1 - 6.8
Glutathione (oxidised)	0.51	µmol/L	0.16 - 0.50
Glutathione (reduced)	3.0	µmol/L	3.8 - 5.5
MISCELLANEOUS			
Ammonia (plasma)	50	µmol/L	8 - 40
NO (Nitric oxide)	82.5	ng/mL	18.0 - 35.0
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Folic Acid, active (RBC) *mislabeled*	326	nmol/l	400 - 1500
BIOLOGICALI AMINES			
CATACHOLAMINES IN PLATELETS			
Histamine (whole blood)	29.4	µg/l	10.0 - 65.0
NUCLEOSIDE			
Adenosine	24.8	10^-8 M	16.8 - 21.4

Genetics: Nuclear DNA

Nuclear DNA (nDNA)
- Paternal and Maternal Sets
- Histones = Protection
- Repair mechanisms

Folate
- DHFR
- MTHFD
- MTHFR
- SHMT
- FOLR
- TYMS
- SLC19A1

B12
- TCN2 and TCN3
- MMAB (aka cblB)

Methionine Cycle
- MTR/MTRR
- MAT1
- AHCY
- CBS

Methyltransferases
- COMT
- PEMT
- BHMT
- GAMT
- HNMT
- GNMT
- PNMT

Glutathione
- GSTM1
- GCS
- GPX1
- GR

Detoxification
- Cyt P450's
- SULT
- NAT

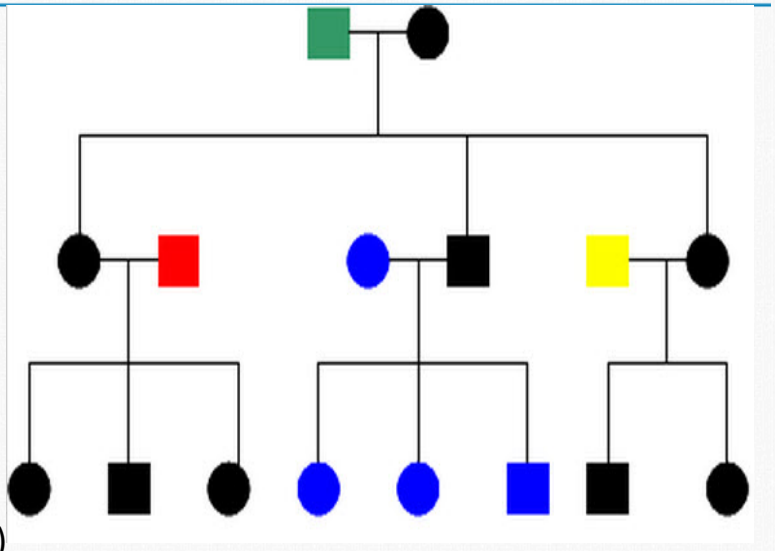
Additional:
- APOE
- BCMO1
- FUT2
- GAD
- MAOA
- PON1
- SOD2
- DAO
- G6PD
- NOS1, 2 and 3

http://www.ornl.gov/sci/techresources/Human_Genome/project/info.shtml

Genetics: Mitochondria

Mitochondrial DNA (mtDNA)

- Inherited only from Maternal side (family hx Important)
- Majority of ATP produced in mitochondria
- Require importing nDNA gene products to function
- SNPS/mutations in mtDNA may be pathological
  - Cancer
  - Diabetes
  - Cardiovascular Diseases
  - Neurodegenerative Diseases
  - Aging
  - Degenerative Diseases
- Lack of Histones = high rate of mtDNA mutagenesis (10x nDNA)
- Mitochondrial Transcription Factor A (TFAM) = Protective coating and regulation
- mtDNA copy number ↑ cell survival and function



Mitochondrial

- SOD
- CAT
- NDUF
- ATP
- COX

http://cshperspectives.cshlp.org/content/5/5/a012641.full.pdf and
http://www.nature.com/scitable/topicpage/mtdna-and-mitochondrial-diseases-903 and
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3753274/pdf/pone.0074513.pdf

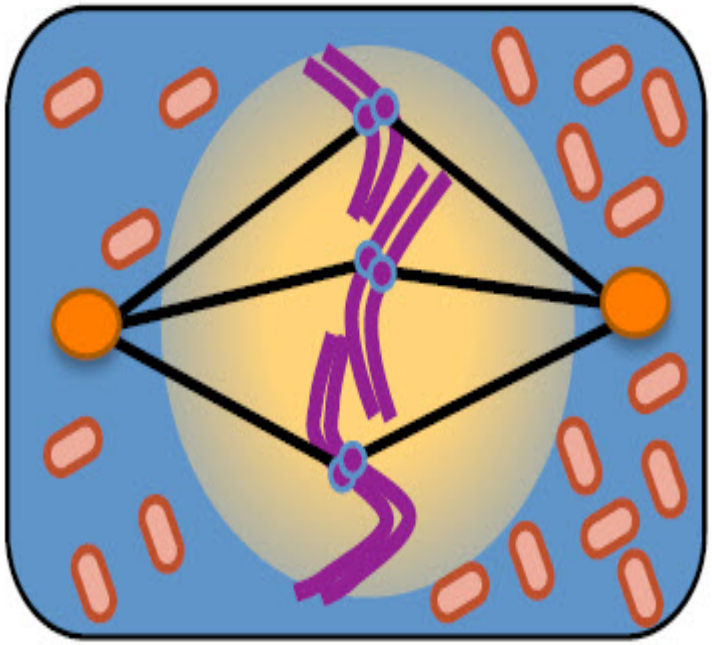
Genetics: Mitochondria

Mitochondrial DNA (mtDNA)

- Sperm – 700 molecules of mitochondria
- Oocytes – 200,000 molecules of mitochondria

Cell Division and Mitochondria:

- Mitochondria 'float' in cytoplasm
- Lack of Spindles
- Randomized



Acton B et al. Mol. Hum. Reprod. 2004;10:23---32 European Society of Human Reproduction and Embryology

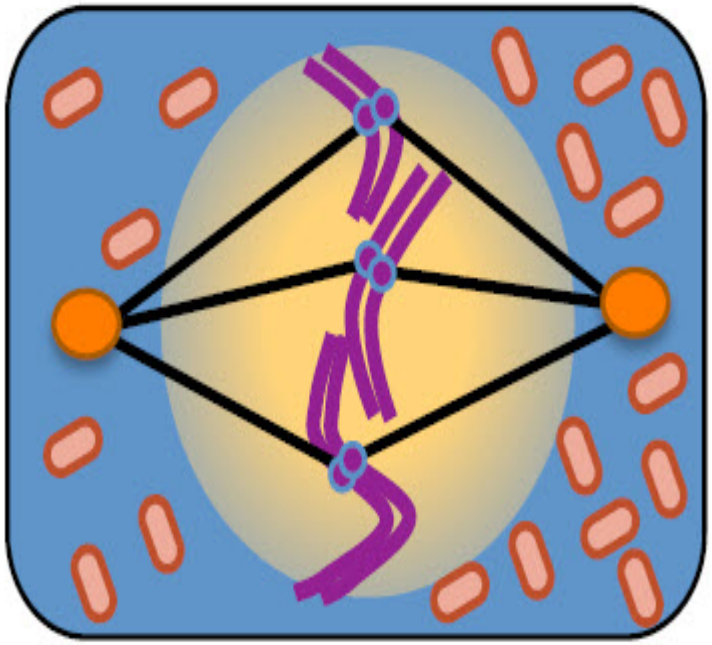
Cell Division and Replication of 'Sick' Cells?

Stimulate DNA Bases and ↑ Cell Proliferation

- "New" cells created:
  - ↓ Glutathione
  - Oxidized cell membrane
  - ↓ Potassium
  - ↑ ROS
  - ↑ Cell death

Flare of Patient Symptoms with addition of Folate / B12.

Necessitates Treatment Flow



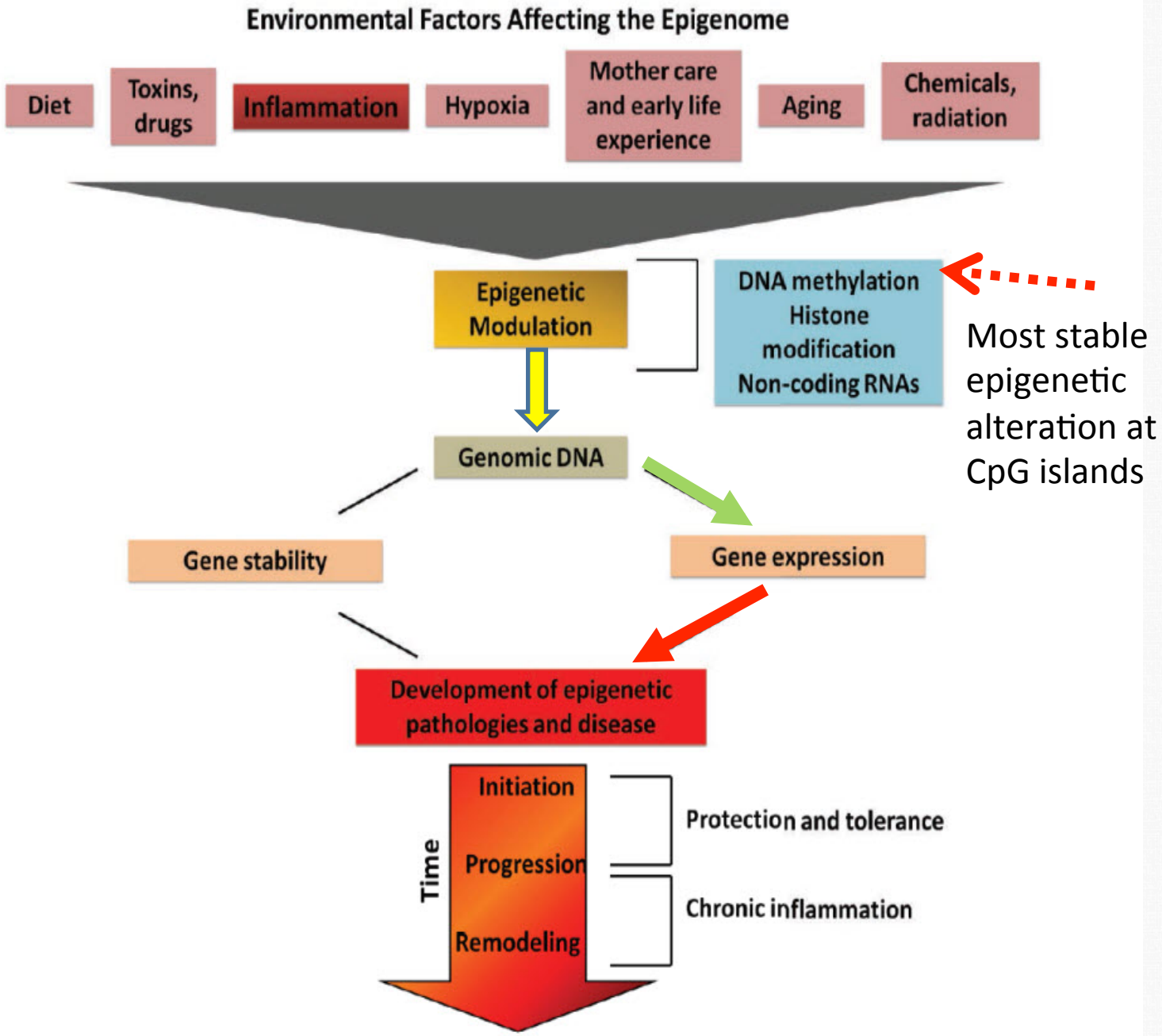
Epigenetics

- "As an organism grows and develops, carefully orchestrated chemical reactions activate and deactivate parts of the genome at strategic times and in specific locations.

  Epigenetics is the study of these chemical reactions and the factors that influence them."

- "Epigenetic changes are environmentally responsive mechanisms that can modify gene expression independently of the genetic code."

http://learn.genetics.utah.edu/content/epigenetics/ and Epigenetics and the developmental origins of inflammatory bowel diseases.



DNA Methylation in the Inflammatory Response and Relevance to Chronic Kidney Disease Wafa M. Elbjeirami *Department of Pathology and Laboratory Medicine King Hussein Cancer Center, Amman, Jordan*

Epigenetic Example: Inflammatory Bowel Disorders

- High monozygotic twin discordant rates in Crohn disease and UC.
  70+ loci associated with CD. 40+ for UC = epigenetic control.

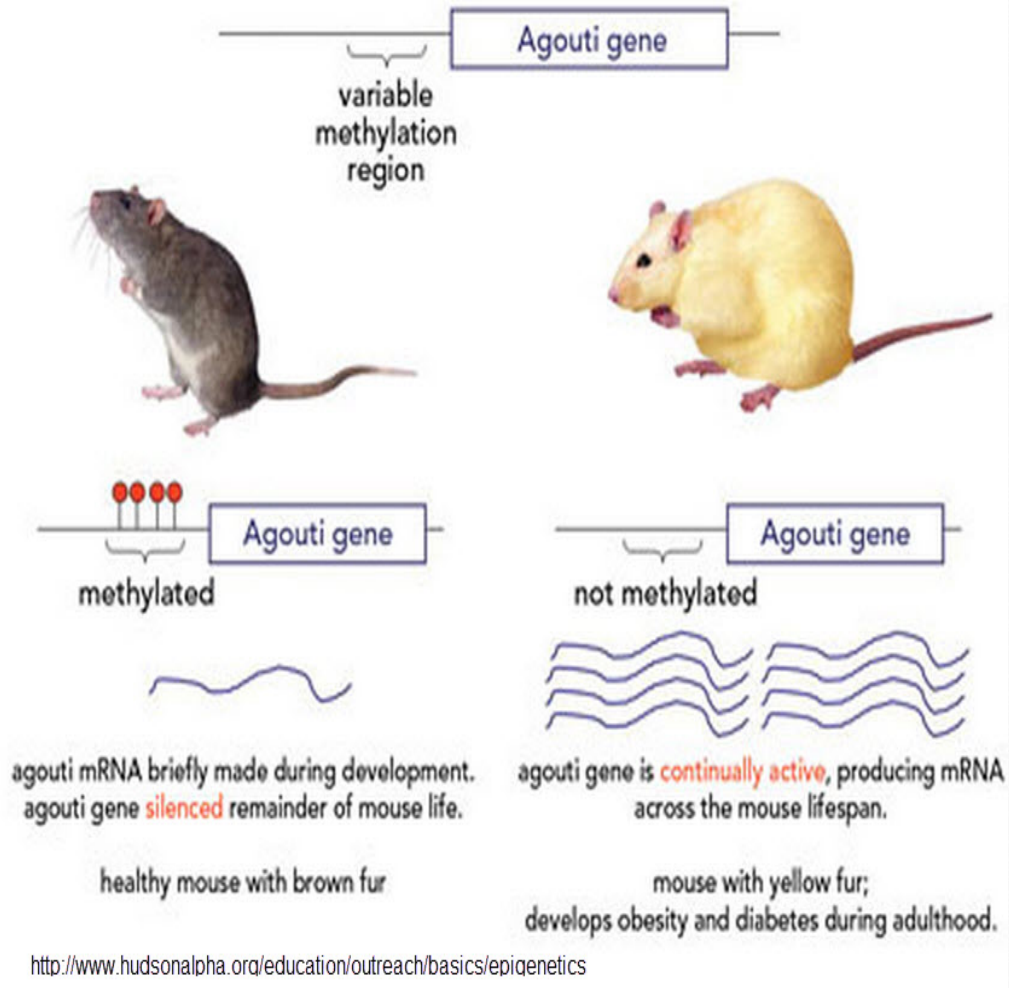
- High monozygotic twin concordant rates in Celiac disease.
  Single HLA locus linked to 40% of heritability = genetic control

Epigenetic Control in Crohn's Disease and UC

Source: Epigenetics and the developmental origins of inflammatory bowel diseases.

Epigenetics in Action

a) Lab Setting



b) Environment

Epigenetics 1st

Key ‘Big Picture’ Disturbances

- Environment
- Lifestyle
- Diet
- Pathogens
- Heavy Metals
- Xenobiotics
- Oxidative Stress
- Nutrient Deficiencies
- Nutrient Excess
- SNPs

System-Wide Dysfunction

MTHFR: Why now?

Folic Acid → GMH

- MTHFR increasing in the population.
  - Folic acid fortification
    - ↑ Full-Term Pregnancies
    - ↑ Folate SNPs
    - ↑ Methylation SNPs
    - ↑ Inferior SNPs
    - ↑ Metabolic Issues

↑ Susceptibility to Environmental Exposures

Natural *De*Selection:
Survival of the 'Unfittest'

Folic Acid Fortification, Increase in MTHFR and Rise in Autism?

by Dr Lynch on May 11, 2012 in MTHFR and Pregnancy

If we sit back and evaluate the dates when folic acid fortification began and the fast rise of autism – do they correlate?

> "In Spain, the prevalence of the MTHFR 677TT genotype has reportedly approximately doubled in the population since the introduction in 1982 of folic acid supplements for women in early pregnancy"...
>
> "Folic acid fortification and supplement use might be "a genetic time bomb." The first premise of this dramatic claim, that folic acid use increases the proportion of children born with the T allele of MTHFR, is as yet poorly documented and is clearly in urgent need of further study.
>
> Studies of the MTHFR genotype frequencies in children before and after fortification should be carried out in countries planning fortification of food with folic acid. Thus, saving fetuses that have a genetic constitution that favors abortion or nonsurvival could lead to children being born with genotypes that favor increased disease during life""[1]

Folic acid fortification started heavily in 1992.[2]

Autism began to quickly rise in 1993.

> In the early 1990s, autism diagnoses began to soar. In the 10 years between 1993 and 2003, the number of American schoolchildren with autism diagnoses increased by over 800%. In 2006, the CDC noted a slight decrease in the number of new cases diagnosed.[3]

Autism began to rise at the same time folic acid fortification began.

Is the rise of autism due to an increased survival rate of babies with MTHFR defects?

Methylation

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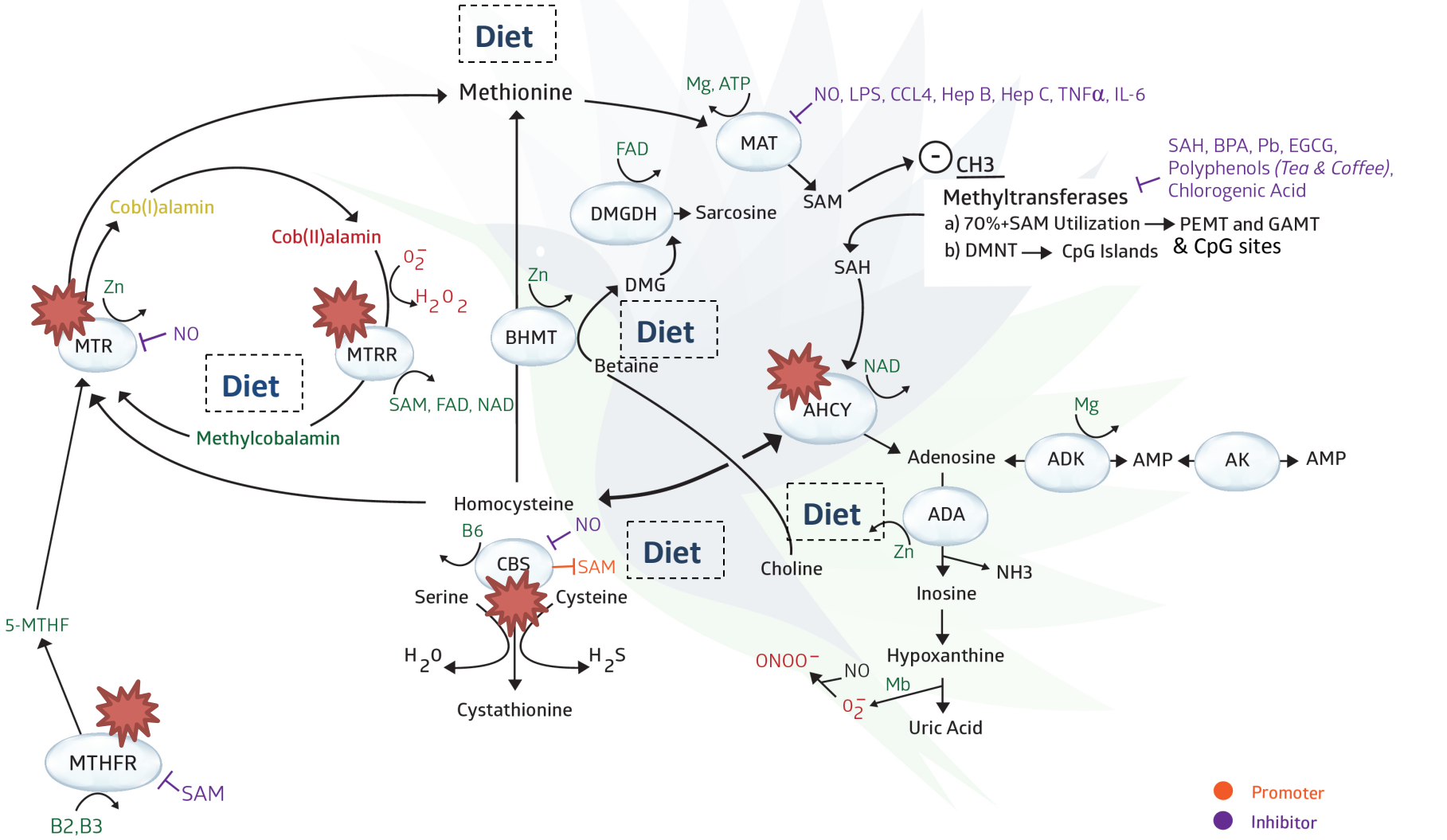
Pathway Planner

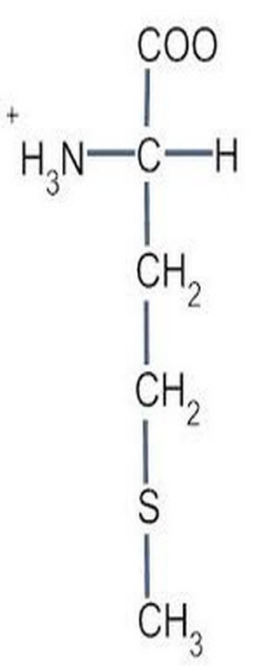
Methionine



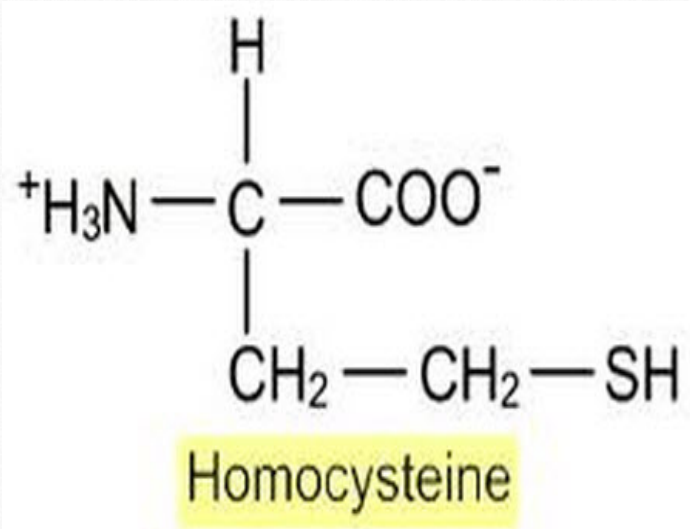
Homocysteine

Homocysteine

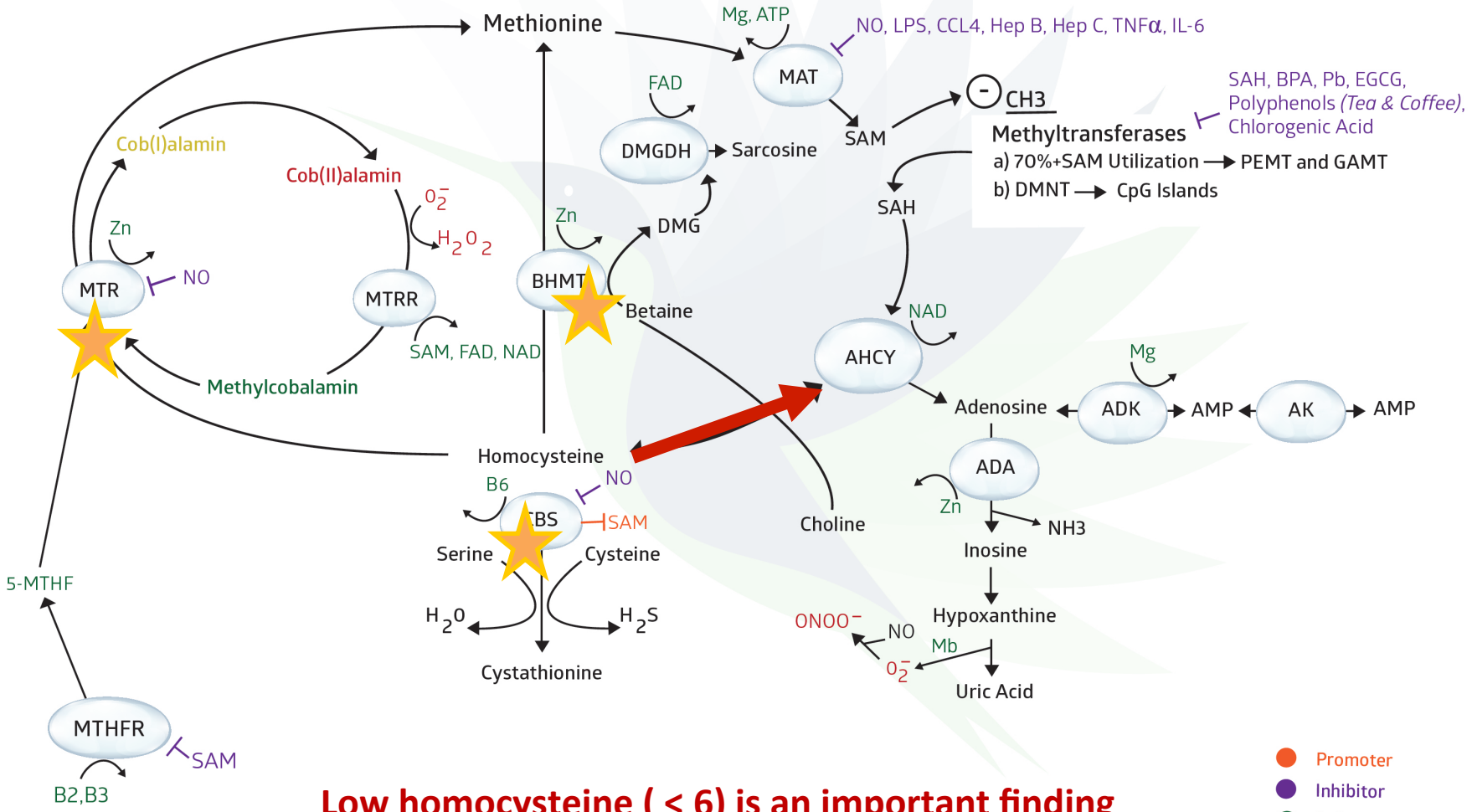
- Methionine = Methyl-Homocysteine
- Breakdown product of SAM → SAH via AHCY



Methionine



Homocysteine Metabolism (Routes)



Low homocysteine (< 6) is an important finding

- Promoter
- Inhibitor
- Cofactor
- Reactive Oxygen Species
- Genes

What did the doctor do? What happened here?

Methylation Profile; plasma

PRIMARY & INTERMEDIATE METABOLITES	RESULT/UNIT	REFERENCE INTERVAL	PERCENTILE 2.5th 16th 50th 84th 97.5th
Methionine	3.2 µmol/dL	1.6- 3.6	
Cysteine	34 µmol/dL	20- 38	
S-adenosylmethionine (SAM)	409 nmol/L	86- 145	
S-adenosylhomocysteine (SAH)	20.1 nmol/L	10- 22	
			68th 95th
Homocysteine	8.2 µmol/L	< 11	
Cystathionine	0.01 µmol/dL	< 0.05	

METHYLATION INDEX	RESULT	REFERENCE INTERVAL	PERCENTILE 68th 95th
SAM : SAH	20.3	> 4	

Here is the consequence. What happened? How to restore?

Methylation Profile; plasma

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METHYLATION INDEX			
	RESULT	REFERENCE INTERVAL	PERCENTILE (68th, 95th)
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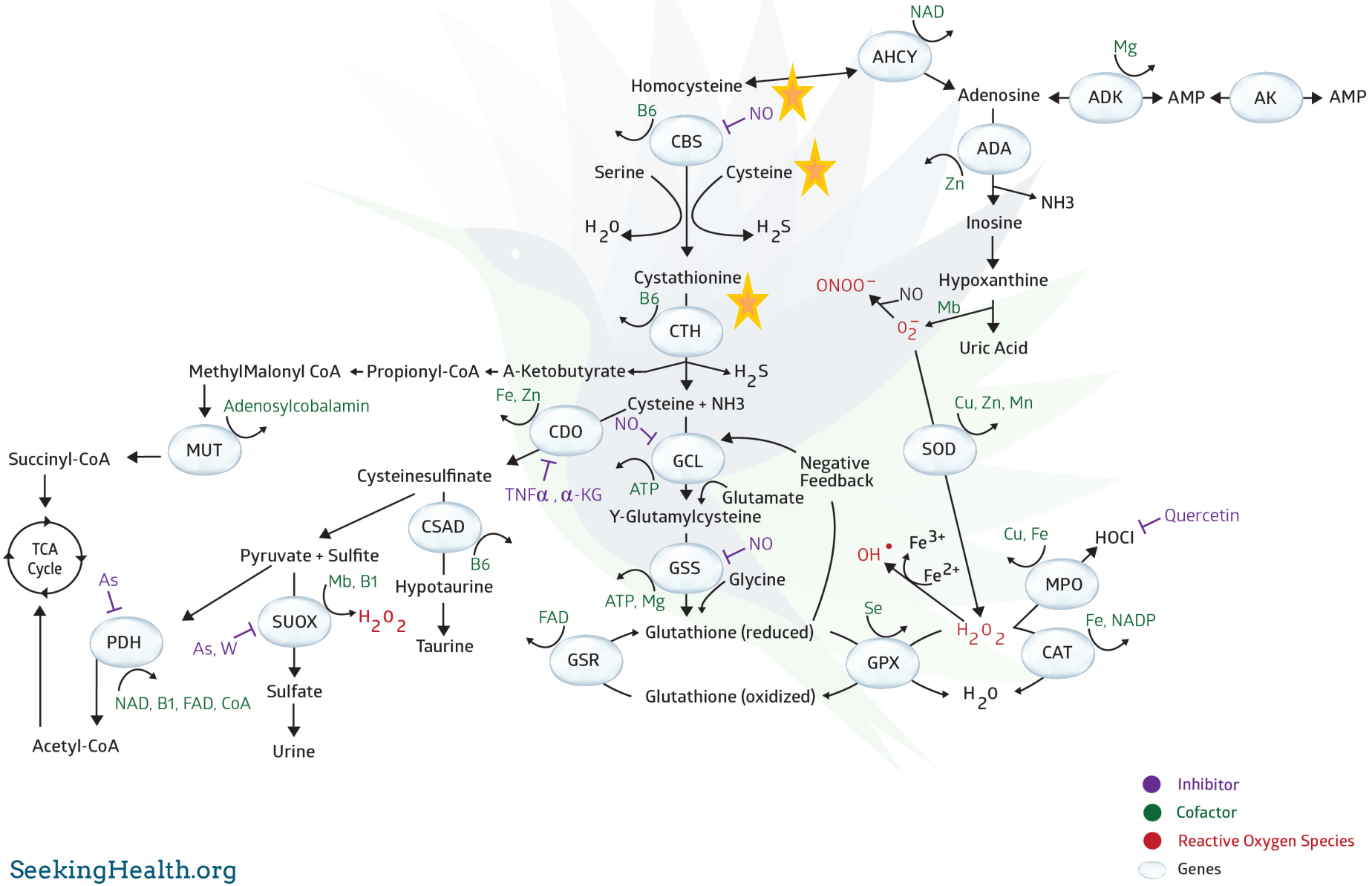
Pathway Planner

Transsulfuration



Folate Cycle

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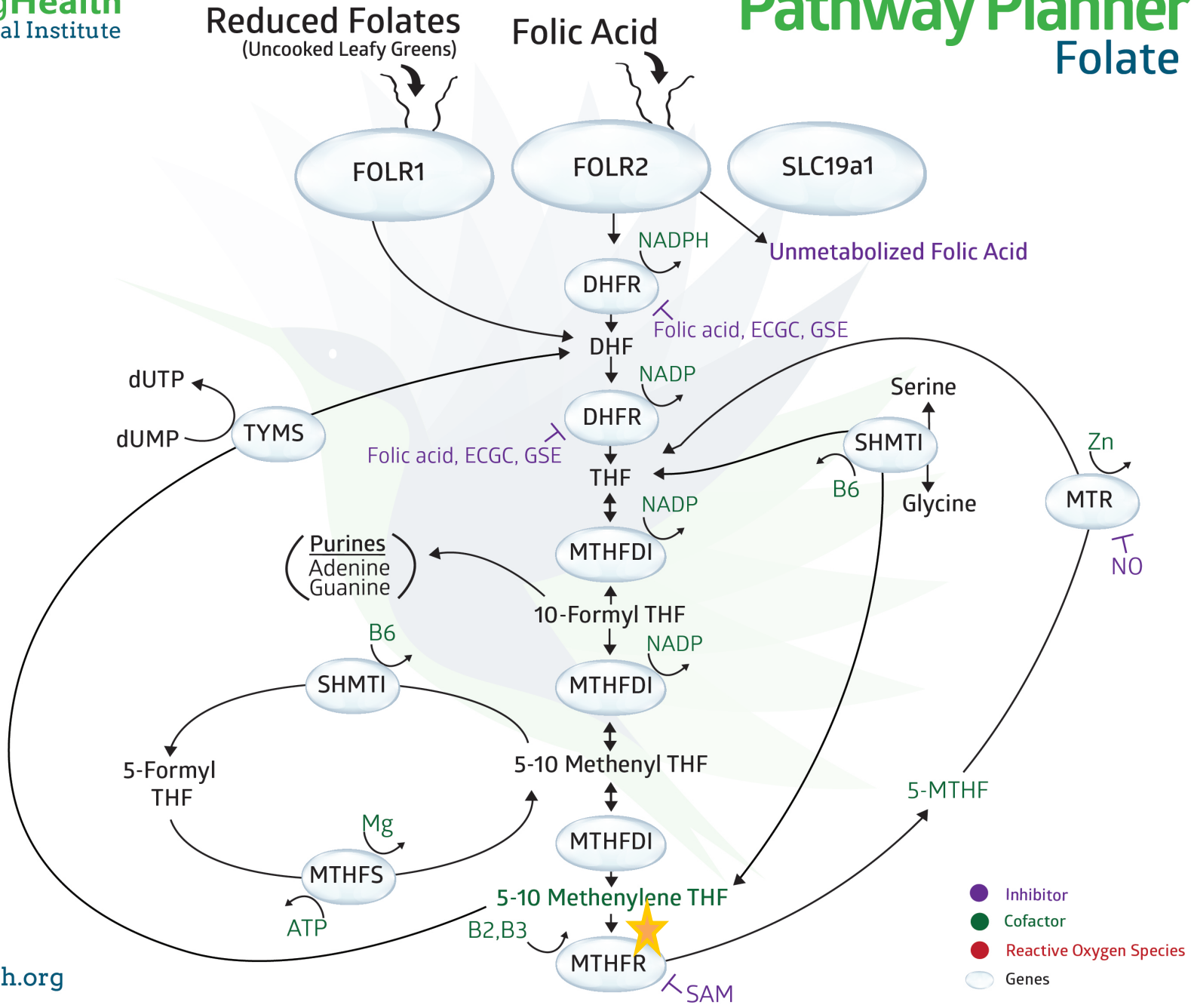
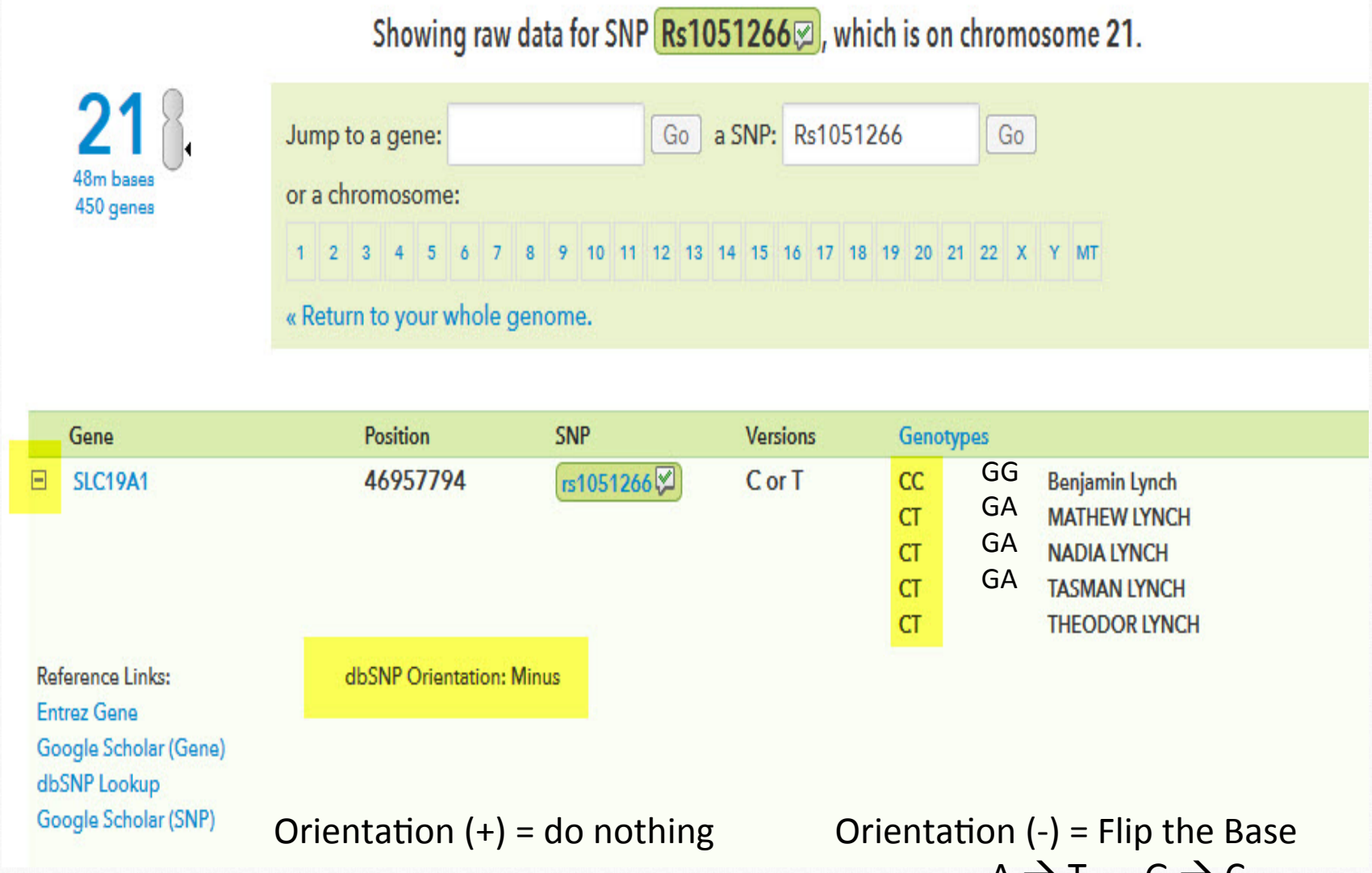
Pathway Planner
Folate



Gene	Variant	rsID & (orientation)	Risk Allele	Issue
SLC19A1	80A>G	Rs1051266 (-)	G	↑ Serum folate levels (↓ RBC Folate)
MTHFD1	1958G>A	Rs2236225 (-)	C	↓ Stability and Activity
MTHFR	C677T	Rs1801133 (-)	T	↓ One carbon metabolism
MTHFR	A1298C	Rs1801131 (-)	C	↓ One carbon metabolism (with 677)



Orientation (+) = do nothing

Orientation (-) = Flip the Base

A → T G → C

T → A C → G

AMINOACIDS IN PLASMA			
Nitrotyrosine	28.7	µg/l	1.1 - 6.8
Glutathione (oxidised)	0.51	µmol/L	0.16 - 0.50
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NUCLEOSIDE			
Adenosine	24.8	10^-8 M	16.8 - 21.4

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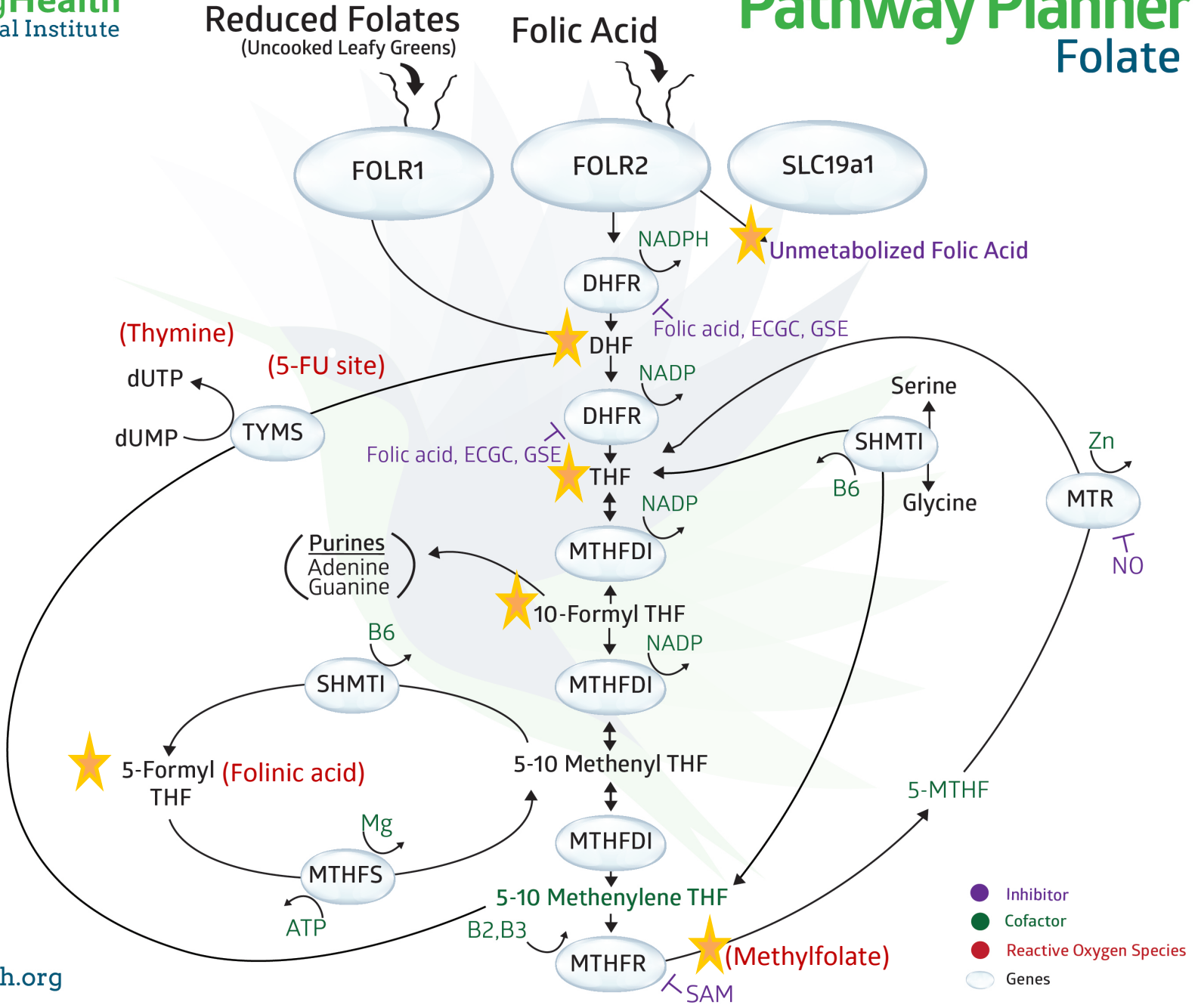
Pathway Planner
Folate



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Methionine Cycle

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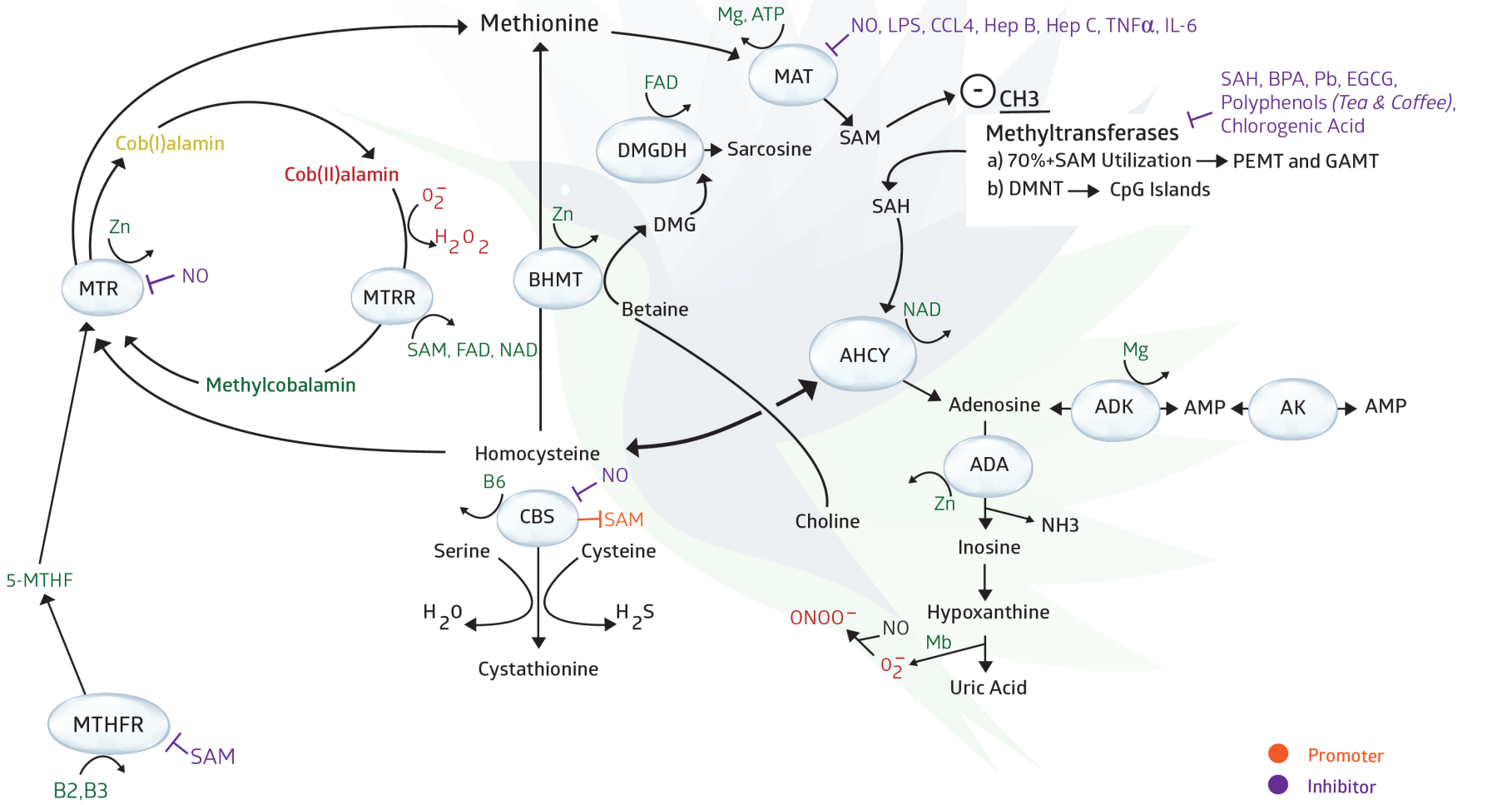
Pathway Planner

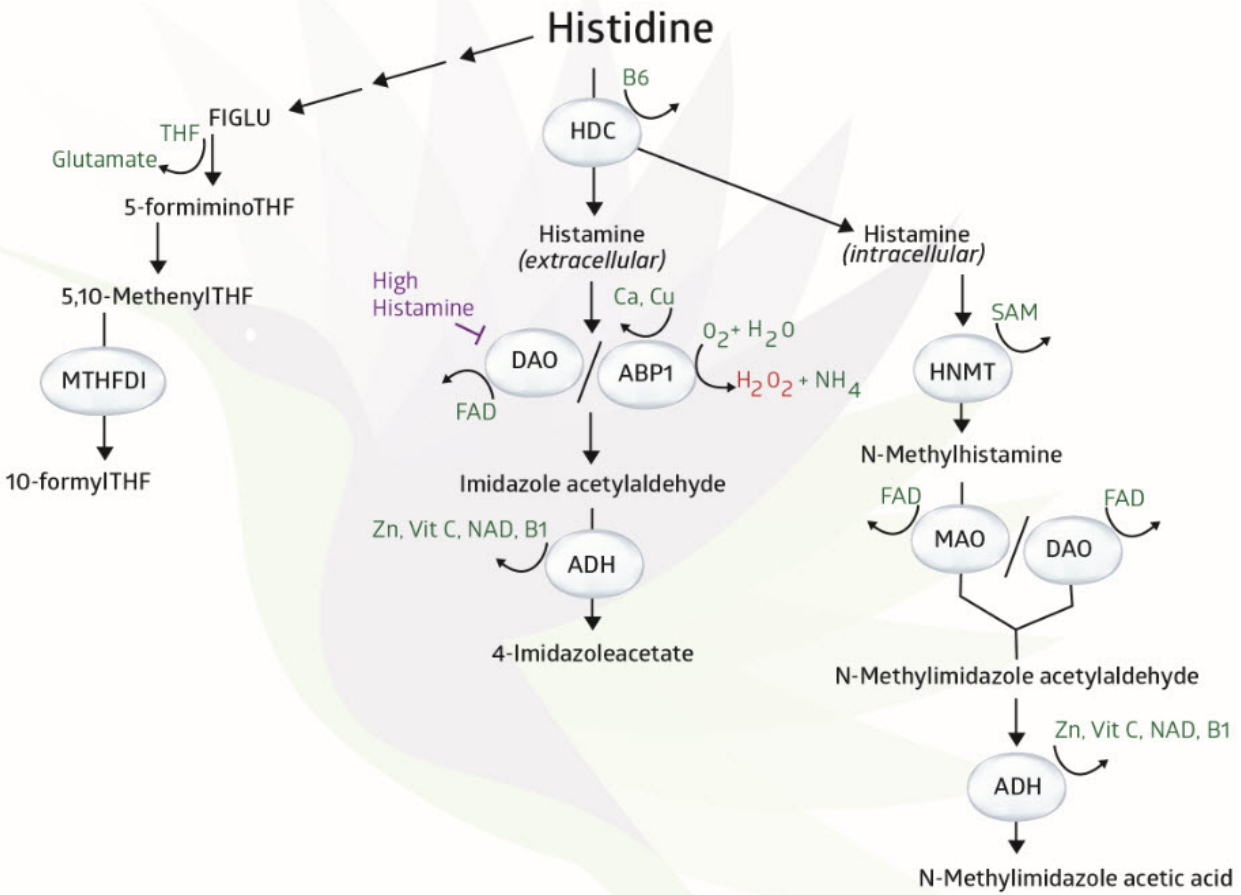
Methionine



Histamine

Pathway Planner

Histamine



Inhibitor
Cofactor
Reactive Oxygen Species
Genes

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www.SeekingHealth.org

Gene	Support	Function	Issue
MTHFR	B2	Provides substrate for MTR/MTRR	↓ MTHF = ↓ MTR/ MTRR
MTR (methionine synthase)	B12 / Zinc	Transfers CH3- from MethylB12 → to Hcy = cob(I)alamin + methionine. Then, remethylates the cob(III) alamin with MTHF.	↓ THF, ↑ Hcy, ↓ SAM, ↑ ROS
MTRR (methionine synthase reductase)	B2 (FAD)	Remethylates the cob(I)alamin with MTHF. 2 [methionine synthase]-cob(II)alamin + NADPH + 2 SAM = 2 [methionine synthase]-methylcob(III)alamin + 2 SAH + NADP(+)	↑ reduced Cb(I), ↓ MTR, ↑ Hcy, ↓ SAM, ↑ ROS
MAT1A	Magnesium, Cobalt, K	Catalyzes the formation of SAM from methionine and ATP	↓ SAM, ↑ Hcy
AHCY	NAD	catalyzes reversible hydrolysis of SAH (AdoHcy) to adenosine (Ado)	↑ SAH, ↑ Adenosine → ↑ uric acid. ↑

Gene	Variant	rsID & (orientation)	Risk Allele	Issue
MTR	A2756 G	Rs1805087 (+)	G	↑ MTR function
MTRR	A66G	Rs1801394 (+)	G	↑ Oxidation of B12
CBS	833T>C	Rs5742905 (-)	C	↓ Homocysteine

http://www.genecards.org

Effects of methionine synthase and methylenetetrahydrofolate reductase gene polymorphisms on markers of one-carbon metabolism

SAM Deficiency via MATI/III Inhibitors

- Oxidative Stress
  - NO
  - TNFα
  - IL-6

Causes vicious cycle
↓ SAM → ↓ CBS activity → ↓ Glutathione

Methionine intake may NOT ↑ SAM

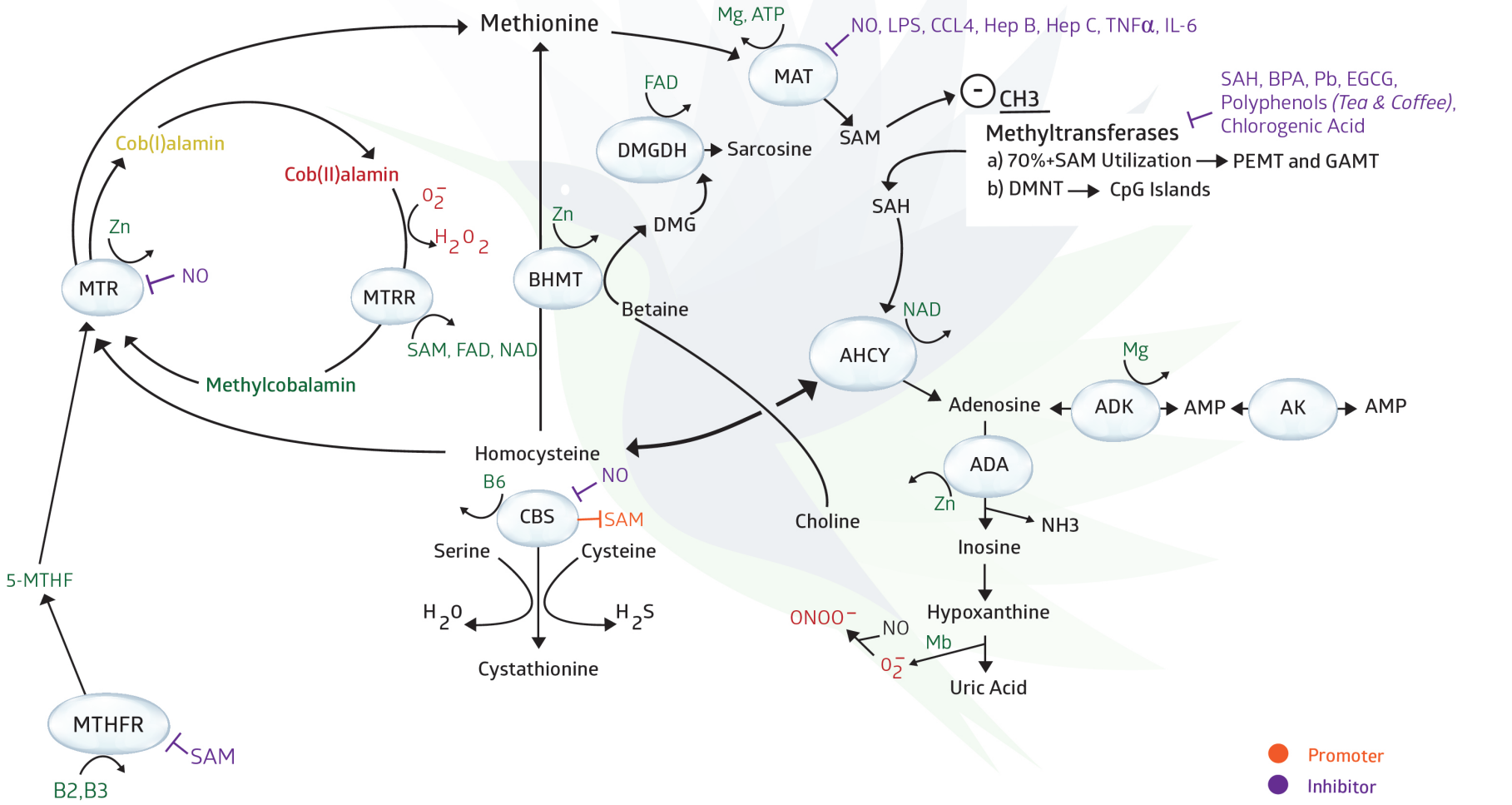
http://emergency.doctorsonly.co.il/wp-content/uploads/2011/03/SAMe-therapy-in-liver-disease-J-HEP-11.12.pdf

Choline Cycle

SeekingHealth® Educational Institute

Pathway Planner

Methionine



Transsulfuration Cycle

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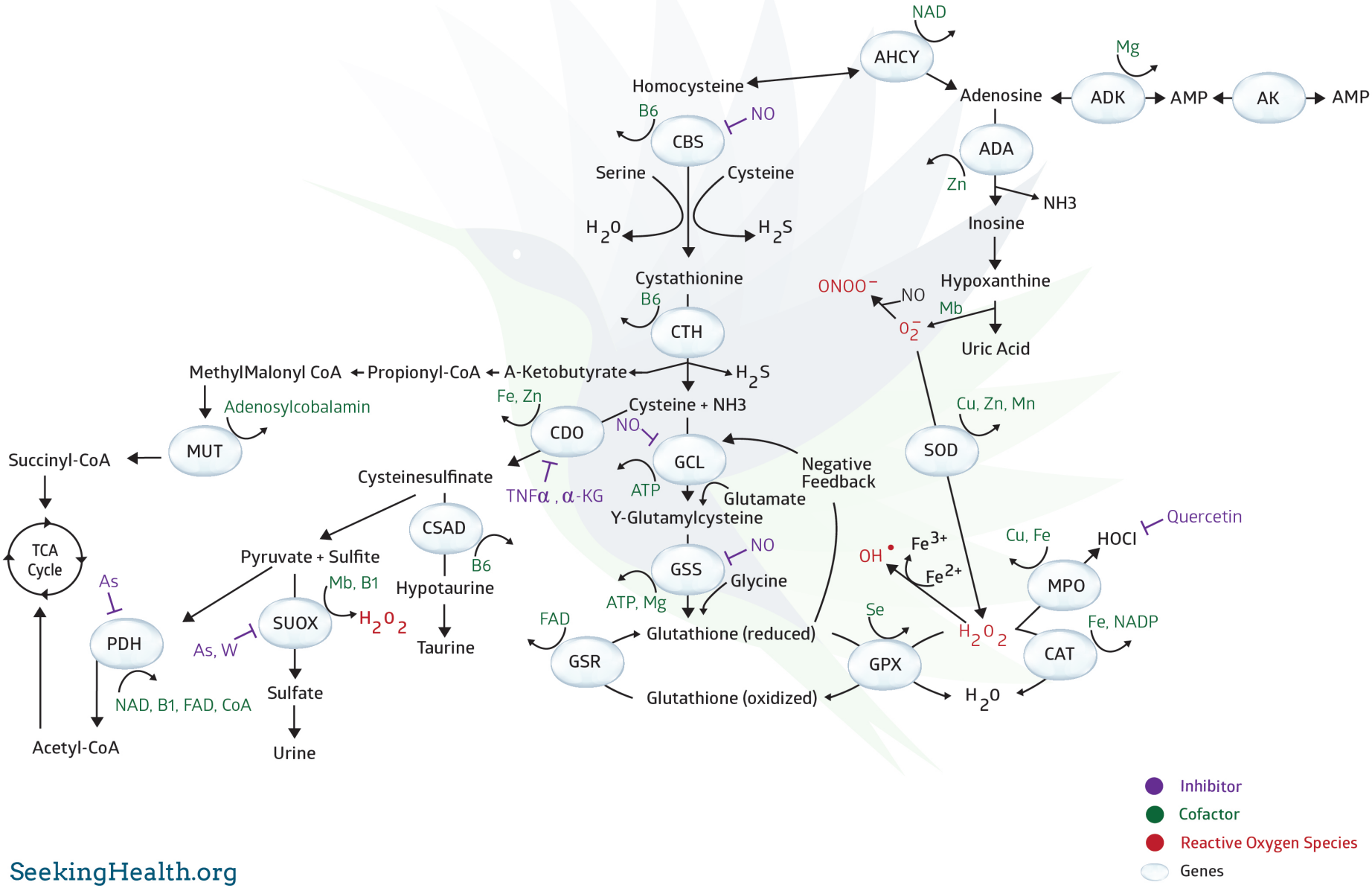
Pathway Planner

Transsulfuration



Neurotransmission

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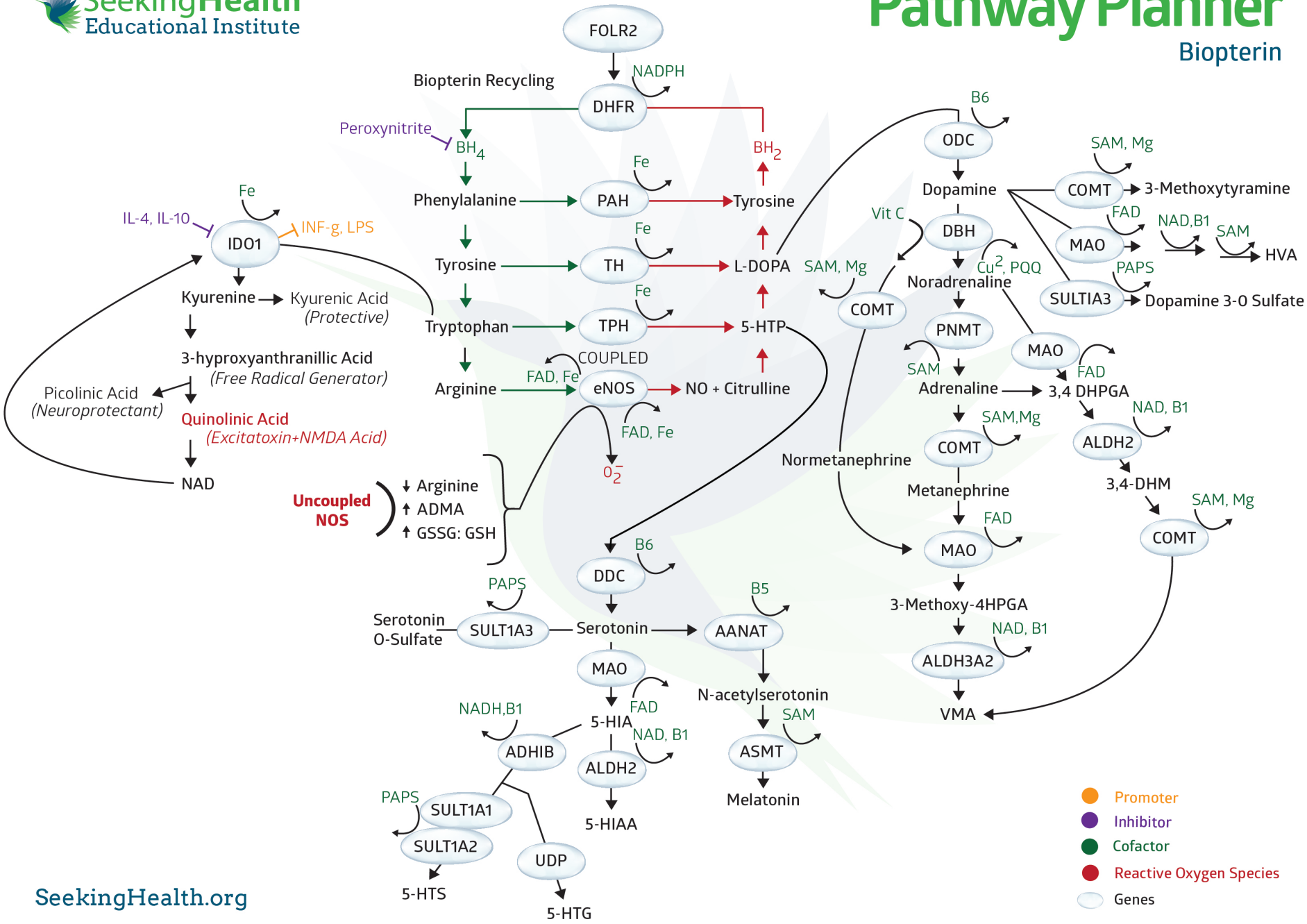
Pathway Planner

Biopterin



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Neurotransmission: More than SNPs

- Diet
- Lifestyle
- PAPS (Sulfonation)
- IDO (Kyurenine – Tryptophan)
- Th1/Th2 (Cytokines)
- Methylation (SAM)
- Cofactors
- Substrate
- Infections
- Heavy Metals

SNPs

- COMT
- MAOA
- GAD1
- GAD2
- HNMT
- PNMT
- MAOB

Gene	Cofactor	Function	Variant	Issue
COMT	SAM, Mg	Catalyzes catecholamine and catechol hormones	rs4680, rs769224, rs4633	Downregulation ↑ Catechols/ Catecholamines
MAOA	B2 (FAD)	Catalyzes deamination of amines (dopa, serotonin, epi/norepi)	rs6323 and rs10548 363	Downregulation ↑ amines
GAD1 and 2	Mg, B6	Glutamate → GABA	many	Downregulation ↓ GABA, ↑ Glutamate

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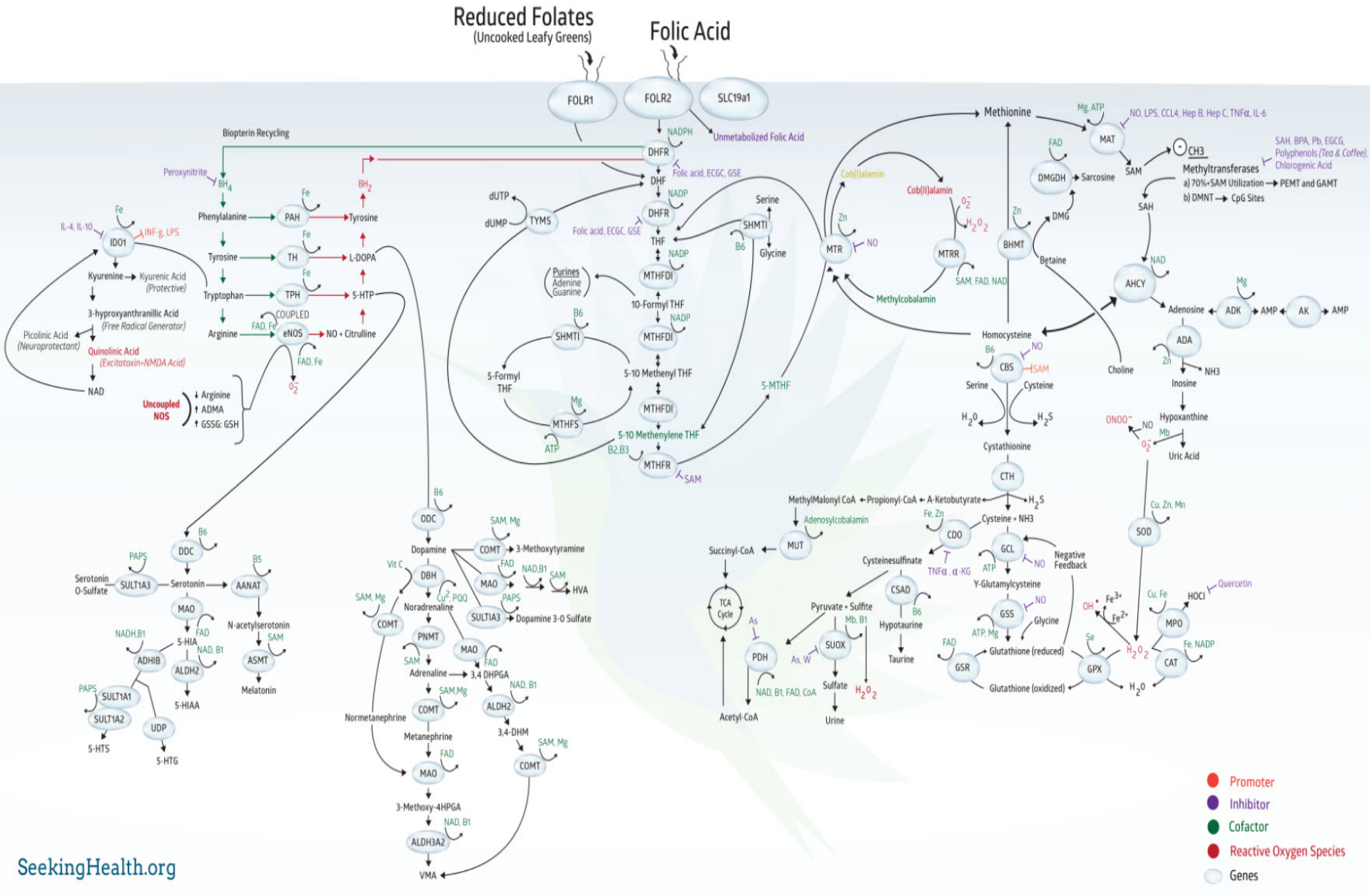
Pathway Planner



Promoter
Inhibitor
Cofactor
Reactive Oxygen Species
Genes

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Thank You