



An Educational Review:

MTHFR & Other
Methylation Gene
Polymorphisms in
Psychiatric Disease

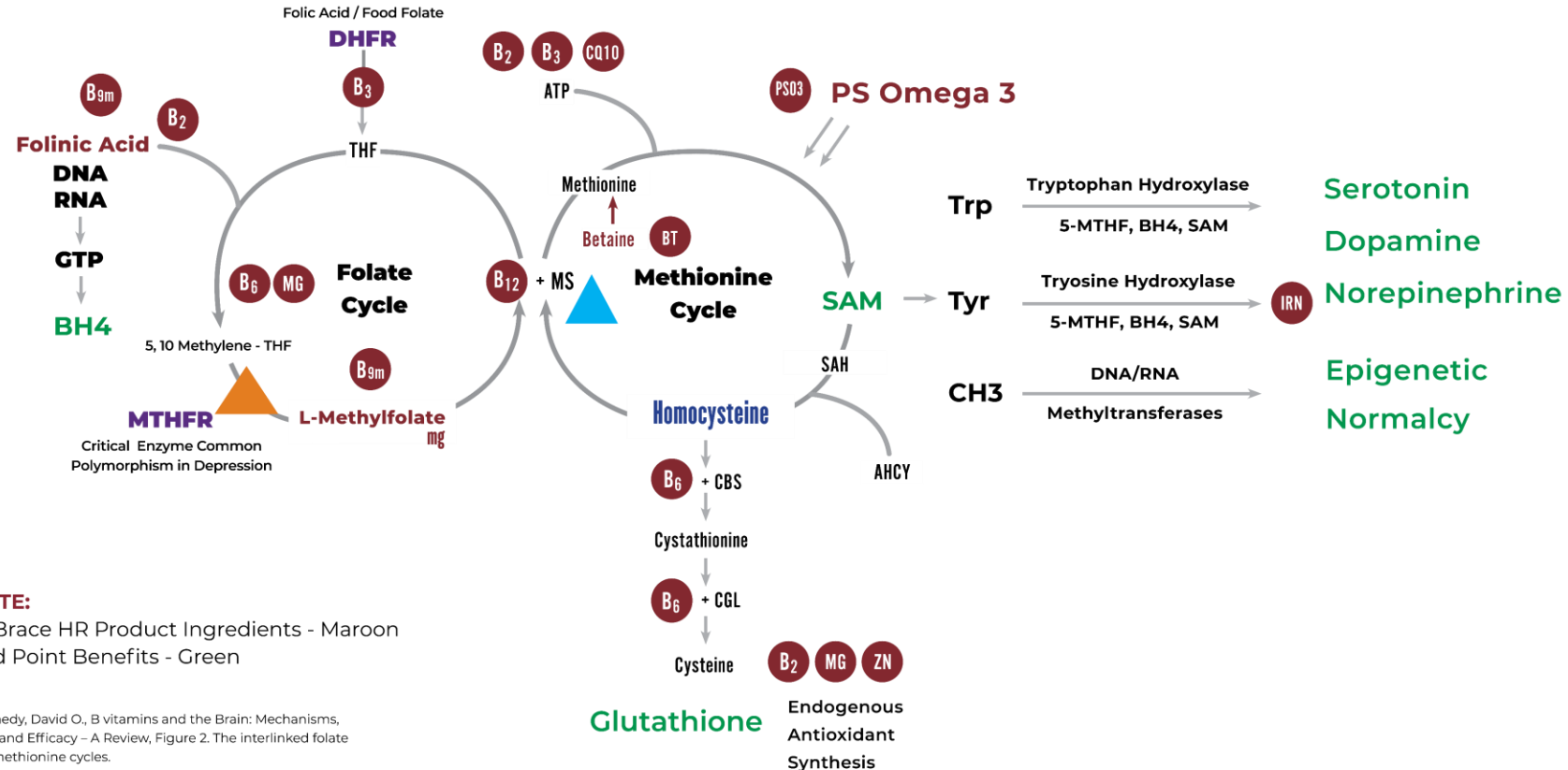
An Evidence-Based
Treatment Option

What is MTHFR?

▲ MTHFR is Methylene tetrahydrofolate reductase, a folate cycle **ENZYME** that catalyzes/converts the folate metabolite 5,10 methylenetetrahydrofolate to 5-methyltetrahydrofolate (L-Methylfolate).

▲ B9/Methylfolate, B12/Methylcobalamin and MS/Methionine Synthase combine to methylate **HOMOCYSTEINE** to produce SAM-E, Serotonin, Dopamine and Norepinephrine, which keeps homocysteine in check.

Brain homeostasis and mood stability requires optimal production and balance of **brain chemicals**.



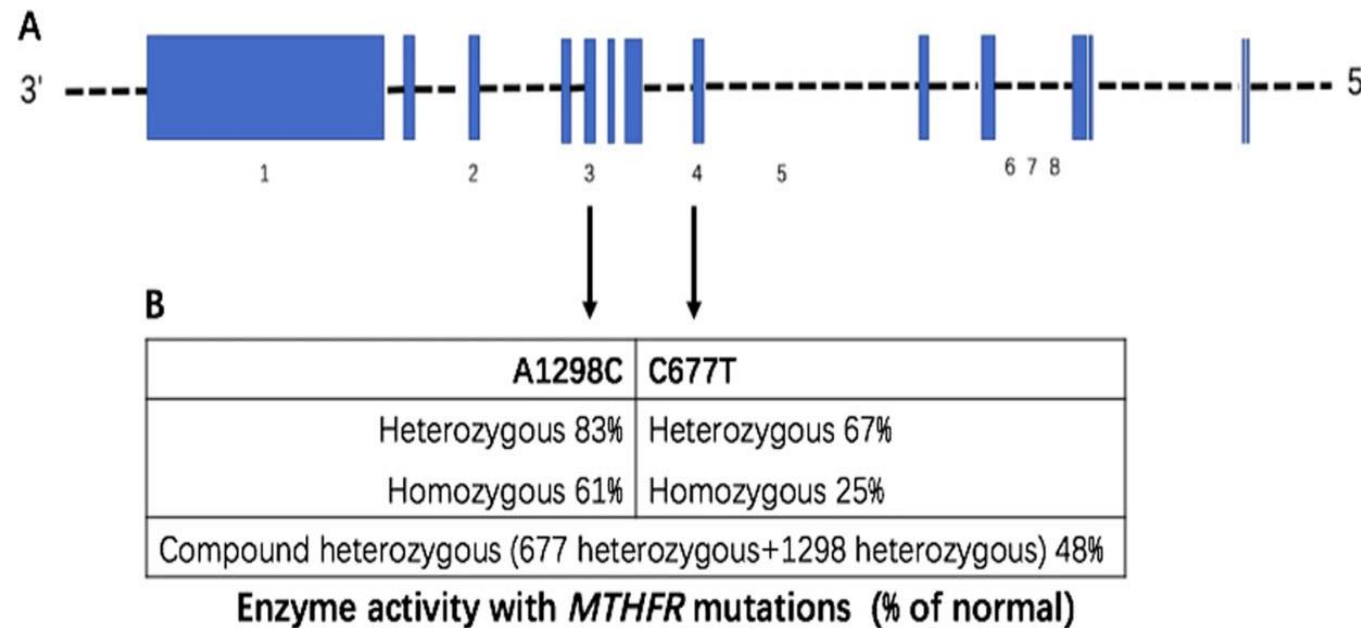
The MTHFR Gene

Fig.1 Wan et al. Methylenetetrahydrofolate reductase and psychiatric disease, Translational Psychiatry, 2018

The MTHFR gene resides on chromosome 1 and has been identified to possess 14 common or rare single nucleotide polymorphisms (SNPs) that are associated with enzymatic deficiency.

Among them, **C677T** and **A1298C** SNPs are the most reported that may reduce the MTHFR activity in various degrees.

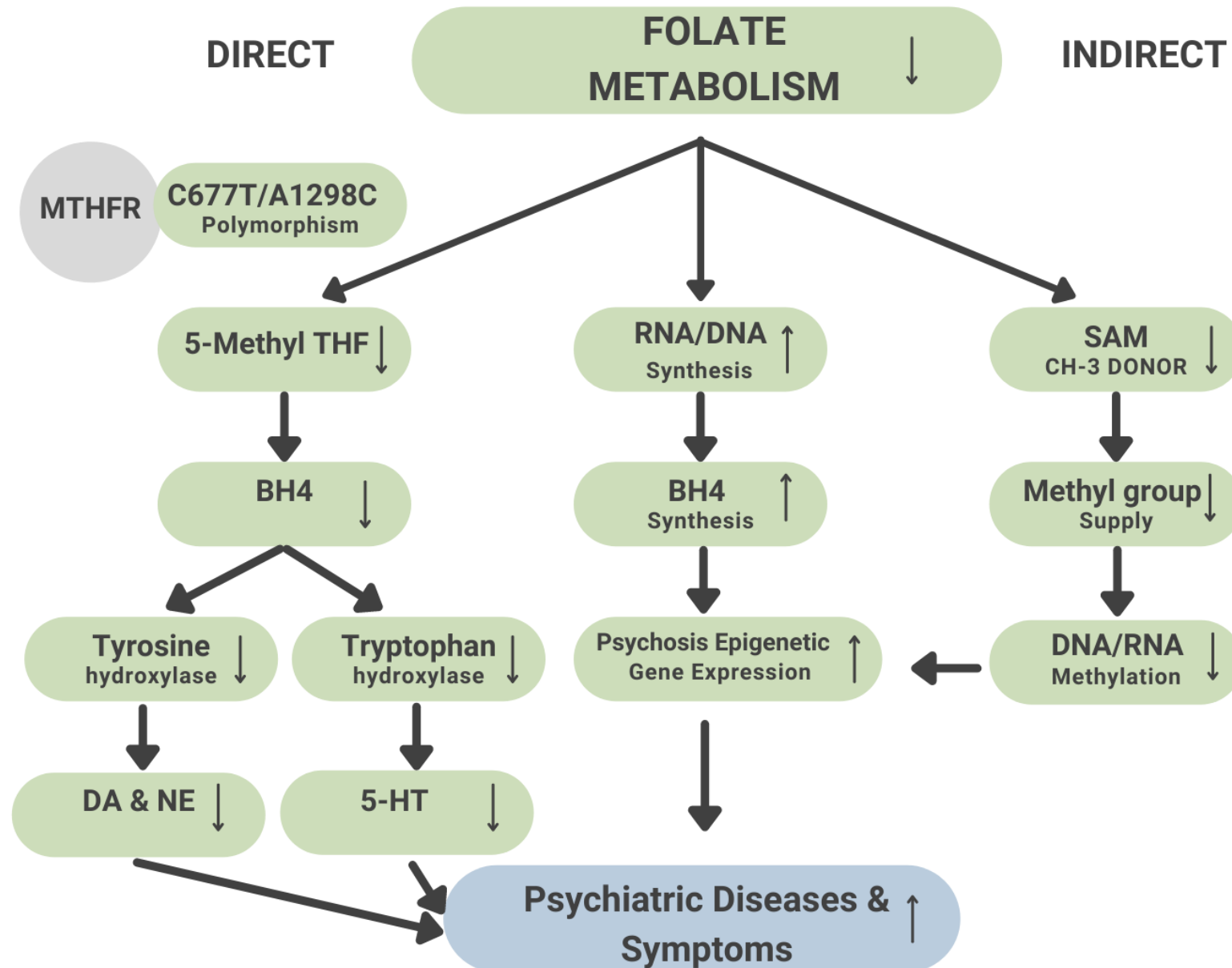
MTHFR Enzymatic Activity with MTHFR Mutations



As DNA methylation and folate are important in mental health, reduction of MTHFR activity or folate deficiency have been associated with an onset of several psychiatric diseases: depression, schizophrenia, bipolar disorder, autism and ADHD.

Biochemical Mechanisms of MTHFR in Psychiatric Disease

Fig 3. Wan et al. Methylenetetrahydrofolate reductase and psychiatric disease, Translational Psychiatry, 2018



Direct Effects

Frontiers in Psychiatry, A Systemic Review

Association between variants of MTHFR genes and psychiatric disorders: A meta-analysis

Yu-Zin Zhang et al August 18, 2022
81 screened studies out of 893 found

49,755 subjects

20,981 patients

28,794 controls

Meta-analysis Findings

The findings of our meta-analysis imply the MTHFR C677T and A1298C both heterozygous and homozygous play a significant role in the common pathogenesis of Major Depressive Disorder, Schizophrenia and Bipolar Disease.

These mental disorders are more likely to occur in families suggesting that they are related to genetic factors.

Indirect Effects

Fooling Mother Nature: Epigenetics and Novel Treatments for Psychiatric Disorders

Stephen M. Stahl, MD, PhD, CNS Spectrum, June 2010

- Epigenetic disease actions can activate risk genes to make an altered gene product or to make normal gene products but at the wrong time; increasing the chances of developing symptoms of a psychiatric disorder.
- To silence risk genes and normalize epigenetics, DNA, RNA, DNA gene promoters, and histones must be methylated properly by CH₃ molecules provided by SAM-E.
- Production of SAM-E can dramatically be reduced in patients with MTHFR polymorphism; thus, risk genes can be hypomethylated causing aberrant expression leading to psychiatric disorders.
- One simple approach is already in hand to treat methyl donor deficiency states: namely, to boost the availability of methyl donors (SAM-E) by administering folate or L-methylfolate and B12.
- Administering Pharmacologic SAM-E however can cause build up of the unwanted metabolite homocysteine that can interfere with epigenetic mechanisms, and eventually deplete METHYL PRECURSORS for SAM-E itself.

COMMON YET MOSTLY UNTESTED GENETIC METHYLATION POLYMORPHISMS AFFECTING YOUR PATIENTS

- **FOLH1**- Catalyzes early folate conversion
- **MTR**- Provides for Methionine Synthase
- **FUT2**- B12 Absorption
- **DHFR**- Provides Dihydrofolate Reductase
- **MTHFD1**- Catalyzes late folate conversion
- **CBS**- With B6(P-5-P) converts Hcy to Cystathionine
- **MTTR**- Converts SAH into SAM with B12(MC)
- **TCN1/2**- B12 absorption and transport
- **FOLR1**- Folate Receptor 1, signaling cascade
- **COMT**- Dopamine maintenance in the PFC
- **TPH1**- Tryptophan serotonin conversion

Mitchell et al. B vitamin polymorphisms and behavior: Evidence of associations with neurodevelopment, depression, schizophrenia, bipolar disorder and cognitive decline, Neuroscience and Behavioral Reviews, 2014

“ The homocysteine theory of psychiatric disorders argues that, for each patient, a unique cluster of genetic vulnerabilities will result in not only low neurotransmitters, but a baseline of elevated CNS homocysteine, impaired methylation of DNA, RNA and histones, suboptimal antioxidant production and impaired hormonal signaling. ”

“ A unique set of polymorphisms may not be clinically significant at baseline, yet disease may manifest in times of psychosocial or environmental stress prompting major psychiatric disorders. ”

Andrew Farah, MD DFAPA
Adjunct Professor for Psychiatric Research High Point Univ.
Attending Psychiatrist at Novant Health
Medical Director at Strategic Interventions

EnLyte/EnBrace HR/ENL contains all the natural coenzymes and mineral cofactors to circumvent/nullify the negative effects of methylation polymorphisms to normalize methylation biochemical end points that correlate to clinical wellness.

EnLyte/EnBrace HR Small Gel Cap

INGREDIENTS

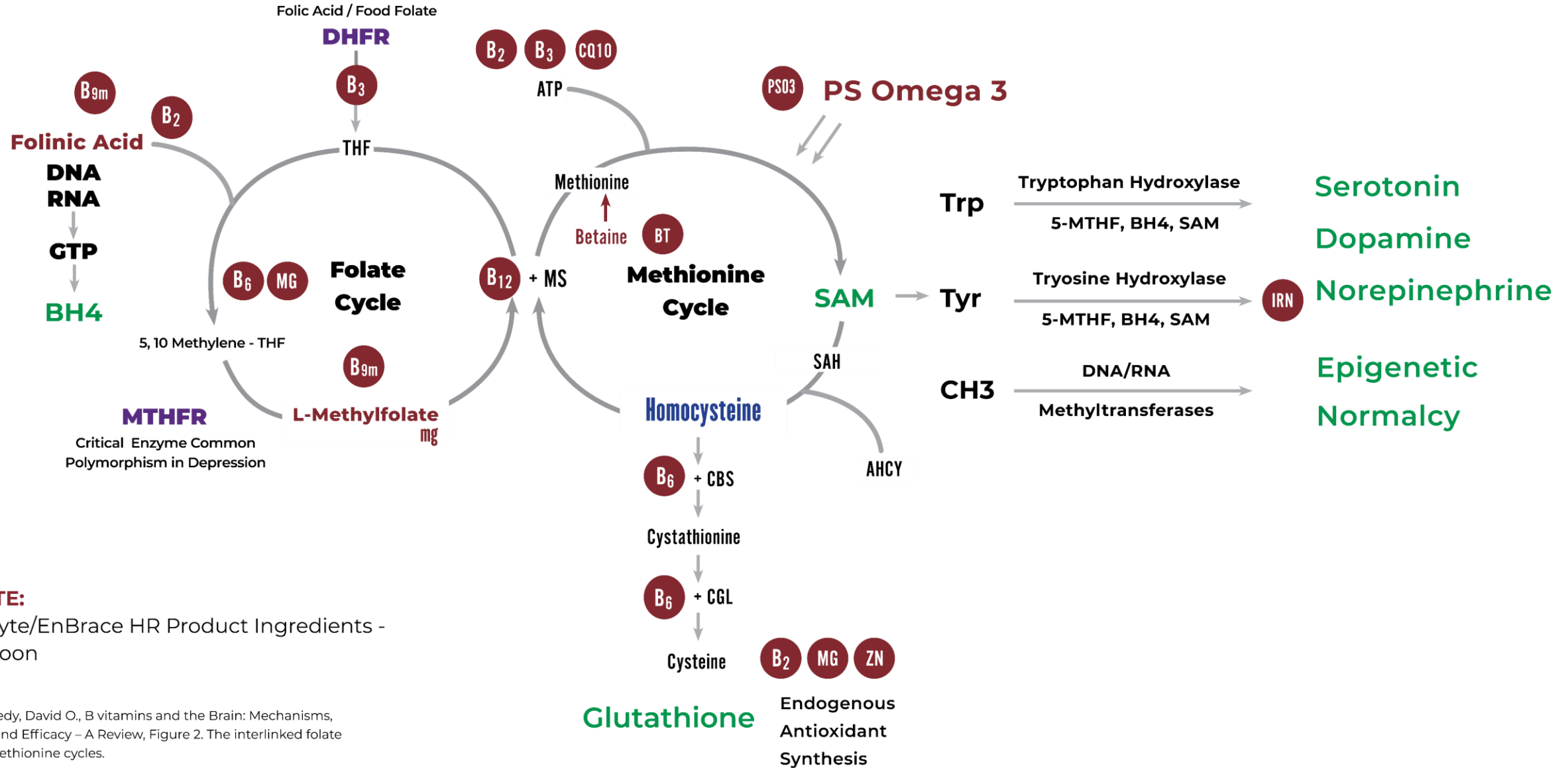
Rx | All Natural | Unique | Bioactive Coenzyme Vitamin Gel Cap

“EnLyte/EnBrace HR contains 7mg. of L-Methylfolate Magnesium and small quantities of other folate derivatives (1mg. DHF and 2.5mg of folinic acid) optimal for a depressed population with high rates of MTHFR polymorphism that affect folic acid metabolism and high risk of neural tube defects and other birth defects.”

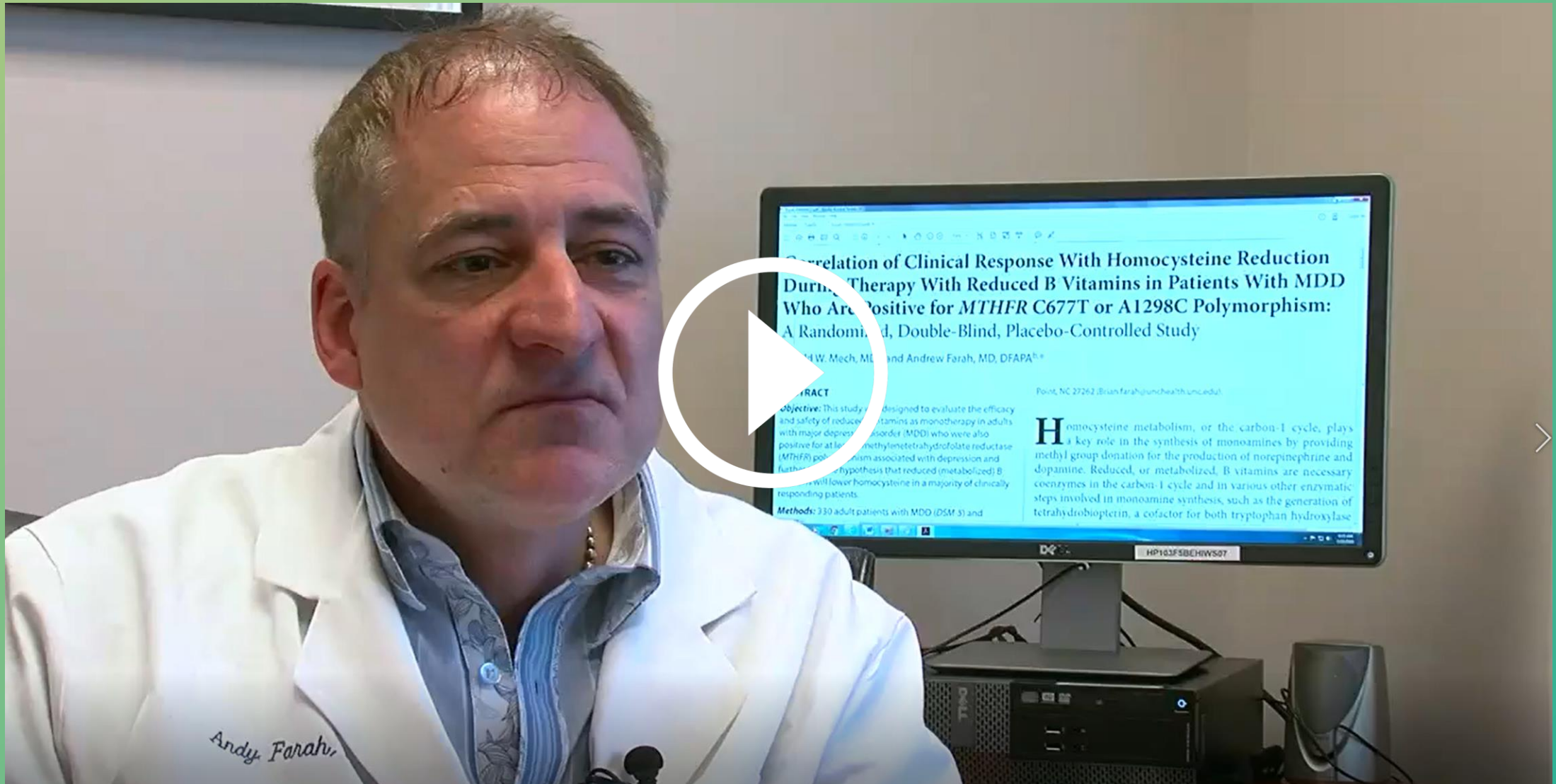
Freeman M. et al: A prenatal Supplement with Methylfolate for the Treatment and Prevention of Depression in Women Trying to Conceive and During Pregnancy, Annals of Clinical Psychiatry, February 2019.

L-Methylfolate Magnesium	7mg
Folinic Acid	2.5mg
DHF	1mg
B12 (Adenosylcobalamin)	50mcg
B6 (Pyridoxal-5-Phosphate)	25mcg
B1 (Thiamine Pyrophosphate)	25mcg
B2 (Flavin Adenine Dinucleotide)	25mcg
B3 (Nicotinamide Adenine Dinucleotide)	25mcg
PS-Omega-3 (Phosphatidylserine, EPA, DHA)	20mg
Magnesium Ascorbate	24mg
Magnesium L-Threonate	1mg
Iron	1.5mg
Zinc Ascorbate	1mg
Betaine	500mcg
Citric Acid Monohydrate	1.83mg
Sodium Citrate	3.67mg
CoQ10	500mcg
Piperine (B Vitamin Bioenhancer)	500mcg

METHYLATION CHART



CLINICAL STUDY OVERVIEW



THE JOURNAL OF CLINICAL PSYCHIATRY

330 ADULT PATIENT RANDOMIZED DOUBLE BLIND PLACEBO CONTROLLED STUDY

OBJECTIVE:

This 8-week study was designed to evaluate the efficacy and safety of EnLyte/EnBrace HR as monotherapy in adults with major depressive disorder (MDD) who were also positive for at least 1 methylenetetrahydrofolate reductase (MTHFR) polymorphism associated with depression and further test the hypothesis that EnLyte/EnBrace HR will lower homocysteine in a majority of clinical responding patients.

MAY 2016

Correlation of Clinical Response With Homocysteine Reduction During Therapy With EnLyte/EnBrace HR in Patients With MDD Who Are Positive for MTHFR C677T or A 1298C Polymorphism - Andrew Farah, MD

1) Mean MADRS Symptom Score of EnLyte/EnBrace HR Versus Placebo



2) 30% Reduction in Homocysteine Levels (Compared to Placebo)

**NO SIDE EFFECT WAS REPORTED AT GREATER RATE
THAN PLACEBO**

ONSET OF ACTION: 2 WEEKS

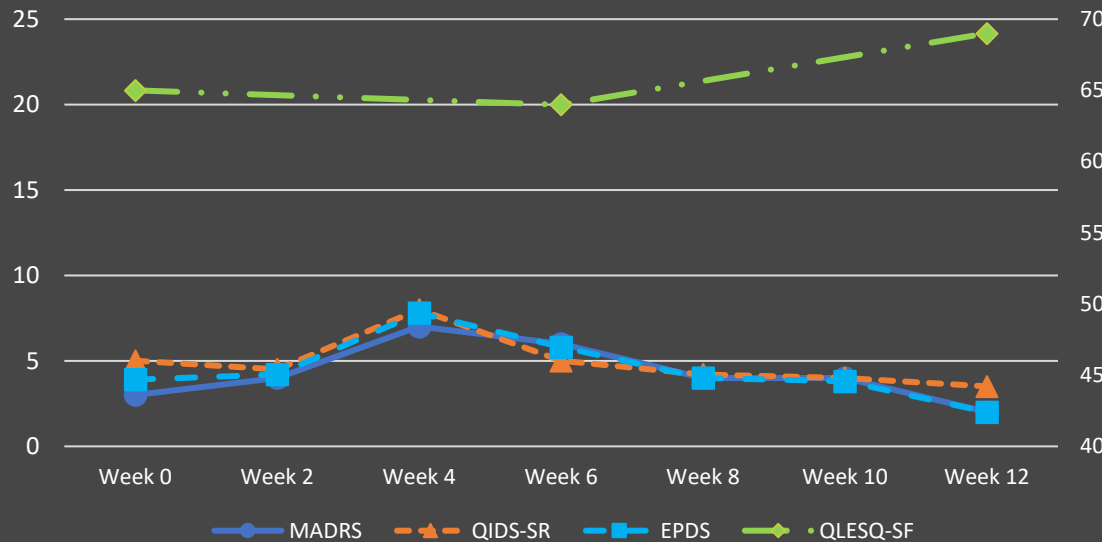
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EnBrace HR For The Treatment and Prevention of Depression in Women

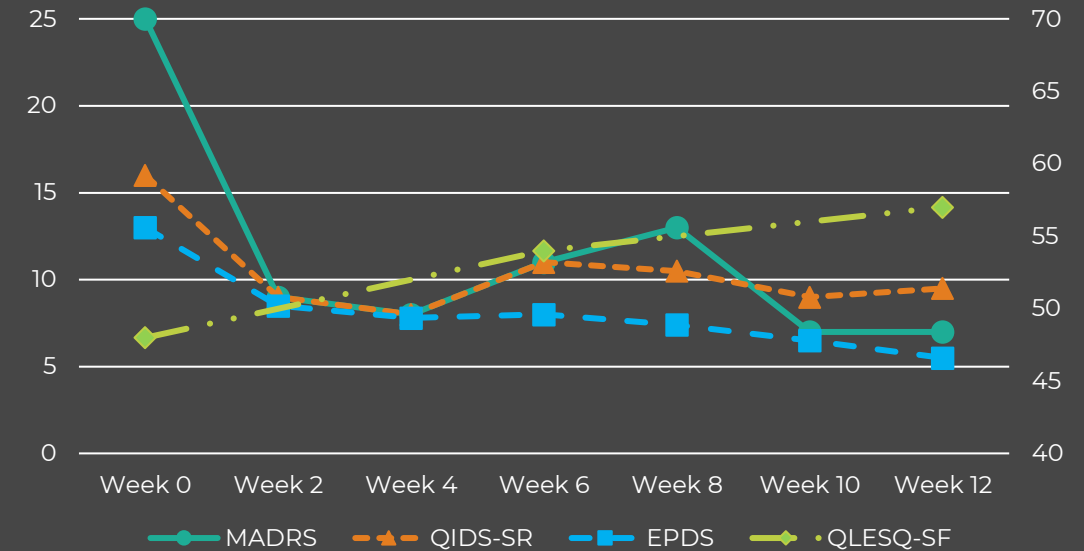
Trying to Conceive and During Pregnancy

Marlene P. Freeman, MD et al, Annals of Clinical Psychiatry February 2019

Group 1 - Relapse Prevention Group;
Well at Baseline



Group 2 - Acute Treatment Group;
Depressed at Baseline

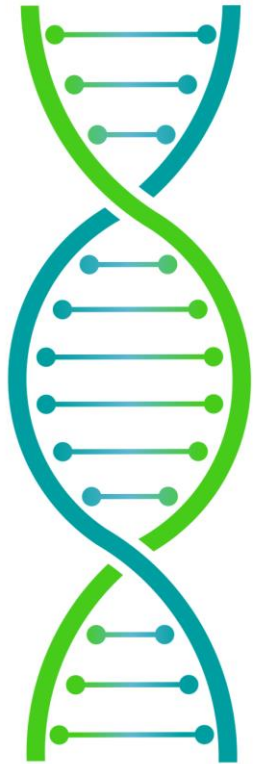


CONCLUSION

Study results suggest EnBrace HR is a novel and well tolerated intervention with efficacy for the prevention and treatment of depression among women planning pregnancy and who are pregnant.

Figure 1. The aim for Group 1 was to prevent depression relapse, and the aim for Group 2 was to improve depression symptoms, measured through several mood and quality of life questionnaires. Trends shown by group for the primary mood outcome measure, the MADRS (Montgomery-Asberg Depression Rating Scale) in dark blue; for secondary mood measures, the QIDS-SR (Quick Inventory of Depressive Symptomatology-Self Report) in orange and the EPDS (Edinburgh Postnatal Depression Scale) in light blue; and for a quality of life outcome, the QLESQ-SF (Quality of Life Enjoyment and Satisfaction Questionnaire -Short Form) in green. Group 1 experienced no significant changes in any of the four measures, and Group 2 experienced significant improvements in the mood questionnaires but not the quality of life questionnaire. All ANOVAs indicating significance are reported in Table 3.

Genetic Test Kits



Genetic
Test
MTHFR
\$99

CLICK HERE

Process:

1. Order Test - Genetic tests are mailed directly to the patient
2. Swab your mouth
3. Mail to the Certified Lab in a prepaid envelope

Results:

Once a patient's buccal swabs have been received by our accredited 3rd party lab, results are normally available in 1 week. Results will be emailed or faxed to the medical provider and/or patient.

HOW TO PRESCRIBE

STEP 1

USE OUR ONLINE PRESCRIBER FORM

Fill in prescriber and
patient information and
then hit “submit”

CLICK HERE

STEP 2

WE WILL OFFER YOUR PATIENT THEIR FIRST BOTTLE AT A DISCOUNTED PRICE OF \$29.95

We will also provide them with the
insurance steps and help
determine the most cost-effective
option moving forward

STEP 3

IF IT'S COVERED ON INSURANCE, WE WILL CONTACT YOUR OFFICE WITH PRESCRIBING INFO

If your patient does not have
coverage or has a high co-pay, we
will offer our discounted cash-pay
option for EnLyte/EnBrace HR. No
further action is needed for your
office.