Case Report ISSN: 2689-1077

Genetics & Molecular Medicine

# Therapeutics for Health Maintenance: A New Paradigm

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**Received:** 03 Jan 2025; **Accepted:** 02 Feb 2025; **Published:** 11 Feb 2025

**Citation:** Isabela Machado Barbosa Stoop. Therapeutics for Health Maintenance: A New Paradigm. Genet Mol Med. 2025; 6(1): 1-6.

For decades, laboratories worldwide have focused their efforts on driving discoveries and developing innovative treatments for various diseases. At first glance, discussing therapeutics for health maintenance might seem unconventional, misconceived, or even unreasonable. However, this article aims to highlight the vast potential of proactive health maintenance strategies, that is, steps we can take before diseases manifest. While I personally reject the notion of isolated chronic diseases, believing they are merely labels that oversimplify the approach to complex conditions, this broader debate lies beyond the scope of the current discussion.

Exploring genetic polymorphisms enables us to identify clear correlations between these variations and some associated conditions. For instance, Apolipoprotein E **(APOE)** [1] ε4 allele is a known genetic factor that increases the risk of Alzheimer's Disease, contributing to more severe brain atrophy and exacerbated symptoms [2]. The Fat Mass and Obesity-Associated **(FTO)** [3] gene has been widely studied for its connection to obesity [4]. Variants within the FTO gene, particularly the rs9939609 polymorphism, have been strongly associated with an increased risk of obesity in numerous populations worldwide [5]. The FTO protein functions as an RNA demethylase, regulating N6-methyladenosine (m6A) levels in RNA [6]. Its activity influences multiple biological and metabolic processes, including appetite regulation, adipogenesis, and energy balance [6-8]. On its turn, Methylenetetrahydrofolate Reductase **(MTHFR)** [9] C677T and A1298C variants have been linked to a wide range of conditions, among them Neural Tube Defects (NTDs) [10], cardiovascular diseases [11], reproductive issues (miscarriages and infertility) [12] and psychiatric disorders [13], such as depression, anxiety, schizophrenia, and bipolar disorder. Similarly, countless correlations can be drawn between specific genes and well-established medical conditions. Nonetheless, I have emphasized the concept of *The Symphony of Genes* in my article of the same title [14], reflecting my belief that genes function collectively, like instruments in a unified orchestra. Within this framework, disease manifestations are not isolated events but, rather, can be compared to a spotlight on a specific set of signs and symptoms associated with a condition, while the rest of the body — a complex and interconnected system—remains under dim light, subtly influencing and being influenced by the broader physiological context.

The purpose of this article is to explore the potential benefits of nurturing individual members of this genetic "orchestra" through tailored nutrition with food and, mainly, supplements, even before the manifestation of clinical conditions. This supports the idea of health optimization as a means to achieve health maintenance. Would it be considered a reasonable proposition to suggest that, by optimizing the performance of individual genes, the entire genetic orchestra could produce a more harmonious melody, ultimately symbolizing sustained health and well-being?

Key considerations include the interconnection between genes, methylation and other epigenetic mechanisms, and the correlation between gene expression and laboratory test results. This is where technology comes into play, enabling the development of effective strategies to streamline the selection of supplements. It would also facilitate their formulation based on pharmacokinetics, prioritize interventions, determine optimal dosages, and support the identification of the most suitable administration routes.

Let us explore two simple examples to illustrate my points. These are not actual case reports but are meant to inspire and encourage further research into potential "therapeutics" for health maintenance. It is important to emphasize that any prescribed treatment is initially based on a comprehensive evaluation of nutritional, metabolic, and hormonal parameters. This thorough analysis ensures the optimization of key biochemical markers, forming the foundation upon which the health maintenance approach is built.

## Case 1

A female patient in her forties presented with advanced lipedema, a pathology of adipose tissue with a pronounced female predominance. Clinically diagnosed, this condition is characterized by an unclear etiopathogenesis [15]. However, it is known to involve an estrogen-related component, a pro-inflammatory state, and edema in most cases, together with other features [15]. Polyphenol-rich dietary supplements, such as resveratrol derived from grapes [15], and plant-based superoxide dismutase extracted from *Cucumis melo* [16], are frequently (though not "*officially*") recommended for managing lipedema. Interestingly, genetic panels focusing on oxidative stress, aging, and longevity often highlight two key genes: Sirtuin 6 **(SIRT6)** [17-20] and Superoxide Dismutase 2 **(SOD2)** [21-23]. The SIRT6 protein is known for its involvement in genomic stabilization, aging, cellular metabolism, and the regulation of adipose tissue inflammation [17-19]. Meanwhile, SOD enzymes are critical components of the antioxidant defense system, neutralizing superoxide anions ($O_2^{\bullet-}$) and modulating oxidative stress [21]. Beyond the specific context of lipedema, altered polymorphisms in the **SIRT6** and **SOD2** genes often lead to recommendations for using resveratrol and *Cucumis melo* supplements to optimize their expression. Our patient's genetic findings further reinforced the rationale for prescribing resveratrol and *Cucumis melo* extract to support these pathways.

This patient also presented genetic alterations in the Interleukin 6 **(IL-6)** [24-26] and Tumor Necrosis Factor-Alpha **(TNF-alpha)** [27-31] genes, both of which are critical mediators of inflammation. Additionally, genetic variants associated with adipogenesis and fat metabolism were identified, including those in the Leptin **(LEP)** [32,33], Peroxisome Proliferator-Activated Receptor Gamma **(PPARγ)** [32,34,35] and **FTO** [3,36] genes. These genes influence crucial processes such as appetite regulation, energy expenditure, and fat storage and distribution [32-36]. Variants in the Estrogen Receptor 1 **(ESR1)** [37,38] gene, related to estrogen metabolism and hormonal balance, were also detected.

At the time it was not possible to investigate genetic polymorphisms associated with lymphatic function and vascular integrity such as Forkhead Box C2 **(FOXC2)** [39,40], Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha **(PIK3CA)** [41,42], and FmsRelated Tyrosine Kinase 4 (**FLT4)** [43,44], known as Vascular Endothelial Growth Factor Receptor 3 **(VEGF3)**, which may also contribute to the development and progression of lipedema. Nevertheless, her condition significantly improved over the following months after using the prescribed supplements, together with vitamins, minerals, and polyunsaturated fatty acids to optimize her nutritional status. This intervention resulted in a considerable positive impact on her overall health. This case demonstrates that lipedema is not an isolated condition but a complex interplay of oxidative stress, inflammation, and adipose tissue metabolism. These observations raise critical questions: Could early identification of genetic polymorphisms, combined with targeted supplementation and timely interventions, have changed the patient's clinical trajectory? Might the condition have been prevented entirely, or its severity significantly mitigated, by addressing the interconnected pathways of oxidative stress and inflammation at an earlier stage?

While further research is needed to establish standardized guidelines, these observations underscore the potential of precision supplementation in addressing genetic predispositions – a promising adjunct for managing lipedema.

## Case 2

A young teenager was struggling with learning difficulties at school. Upon examining his genetic profile, we identified heterozygous and homozygous mutations in key genes associated with brain health: **APOE** [1], Brain-Derived Neurotrophic Factor **(BDNF)** [45], ELOVL Fatty Acid Elongase 2 **(ELOVL2)** [46], Myelin Regulatory Factor **(MYRF)** [47], and Phosphatidylethanolamine NMethyltransferase **(PEMT)** [48]. Among the growing number of genetic risk factors for Alzheimer's Disease, **APOE** remains the strongest and most prevalent, implicated in more than half of all cases [49-52]. The ε4 allele, in particular, significantly increases the risk [49-52]. Moreover, the combination of the **APOE** ε4 allele and the **BDNF** Val66Met polymorphism has been linked to poorer memory performance and an elevated risk of cognitive decline in older adults [53]. **ELOVL2** enzyme, the protein encoded by **ELOVL2** gene, plays a crucial role in elongating polyunsaturated fatty acids, converting Eicosapentaenoic Acid (EPA, C20) to Docosahexaenoic Acid (DHA, C22). DHA, the most abundant fat in the brain, is essential for maintaining neuronal membrane fluidity and function [54]. The protein encoded by **MYRF** gene functions as a transcription factor essential for the development and maintenance of myelin sheaths, which insulate nerve fibers and facilitate efficient neural signaling [55]. Similarly, **PEMT** enzyme contributes to the synthesis of phosphatidylcholine, a key component of cell membranes crucial for neuronal membrane integrity and cognitive processes, including memory and learning [56,57]. However, within the framework of *The Symphony of Genes,* these polymorphisms cannot be considered in isolation. Their impact must be evaluated alongside the expression of other genes, such as **MTHFR**, Cystathione Beta-Syntase **(CBS)** [58], Fucosyltransferase 2 **(FUT2)** [59], Solute Carrier Family 44 Member 1 **(SLC44A1)** [60], and Peroxisome Proliferator-Activated Receptor Delta **(PPARδ)** [61], all of which exhibited altered variants in this case.

The **MTHFR** enzyme, encoded by the **MTHFR** gene, plays a crucial role in converting 5,10methylenetetrahydrofolate to 5-methyltetrahydrofolate, an active form of folate (vitamin B9) required for the remethylation of homocysteine to methionine a precursor essential for protein synthesis, DNA repair, and other biological processes [62]. A 2020 study highlighted that individuals carrying both **BDNF** Val66Met and **MTHFR** C677T polymorphisms may experience reduced hippocampal volume, potentially leading to cognitive impairments [63]. Additionally, a 2021 study linked the **MTHFR** C677T variant to decreased gray matter volume in patients with amnestic mild cognitive impairment (aMCI) [64].

The **CBS** gene encodes an enzyme vital for the transsulfuration pathway, which converts homocysteine to cystathionine and, subsequently, to cysteine [65,66]. This pathway is critical for maintaining homocysteine balance and supporting brain processes [66,67]. Mutations in the CBS gene can result in homocystinuria, characterized by elevated homocysteine levels, contributing to cardiovascular, skeletal, and neurological issues [67].

The **FUT2** gene produces fucosyltransferase 2, an enzyme involved in adding fucose to glycoproteins and glycolipids, influencing secretor antigen production in bodily fluids like saliva and mucus [68,69]. It impacts gut microbiome composition and vitamin B12 absorption, both essential for cognitive health [68,69].

The **SLC44A1** gene encodes a transporter protein critical for choline metabolism. Choline supports cell membrane integrity and acetylcholine synthesis, vital for brain function [70,73]. Although not directly involved in folate metabolism, choline interacts with folate in the methylation cycle, influencing DNA methylation and gene regulation [70-76].

The **PPARδ** gene is key for mitochondrial biogenesis and oxidative metabolism. Variants in PPARδ can affect energy production and cellular function, both crucial for brain health [77-79].

The patient also exhibited a predisposition to excessive glycation, confirmed by genetic findings involving **MTHFR** [80-82], Melatonin Receptor 1B **(MTNR1B)** [83,84] and Peroxisome Proliferator Activated Receptor Gamma **(PPARγ)** [85,86] genes. Although further investigation of genes associated with hyperglycatiion such as Glyoxalase 1 **(GLO1)** [87,88], Advanced Glycation EndProduct Receptor **(AGER)** [89,90], and Fructosamine-3-Kinase **(FN3K)** [91,92] was not available at the time and could provide deeper insights. Preventive guidance on managing sugar metabolism was provided.

The patient was treated with a targeted supplementation regimen. This included R-alpha-lipoic acid, Bacopa monnieri, DHA, EPA, choline, phosphatidylserine, phosphatidylcholine, methylfolate, methylcobalamin, pyridoxal-5-phosphate, riboflavin-5-phosphate, acetyl-L-carnitine, ubiquinol, magnesium, and other nutrients. Over three months, his mental health significantly improved, with noticeable enhancements in focus, alertness, and academic performance.

This case also raises critical questions: Could sustained and personalized support significantly reduce this individual's lifetime risk of dementia, including Alzheimer's disease? Would it substantially improve his quality of life?

These findings highlight the transformative potential of a genetics-informed, proactive approach to health optimization and maintenance, which offers a positive and sustainable alternative to the traditional focus on disease prevention and treatment [SEP].

## New Technologies for Health Maintenance

From a broad perspective, laboratories focused on advanced technologies typically prioritize fundamental research, product development, or industrial applications over direct clinical interventions [93-97]. Translating cutting-edge research into clinical practice is a complex process involving multiple stages, such as preclinical studies, regulatory approval, and clinical trials. This transition is usually managed by pharmaceutical companies or specialized research organizations, rather than by the research labs themselves. In other words, technology researchers specialize in materials science, engineering, and innovation, while clinicians focus primarily on patient care and treatment. These distinct areas of expertise often result in limited direct collaboration between the two. Translational medicine, which bridges scientific research and clinical practice, is receiving growing attention.

When developing technologies that orchestrate ***The Symphony of Genes***, clinical experience becomes crucial for bridging the gap between these two domains. Advanced resources, such as CRISPR technology, have the potential to revolutionize the landscape. However, to make a meaningful impact on the "ordinary patient" particularly in underdeveloped and developing countries, supplements present a more affordable and practical solution. I have already implemented this approach in my clinical practice with promising results, relying solely on genetic tests obtained through Next-Generation Sequencing (NGS) techniques, without the help of additional complex technological resources. The quality of life of these patients has improved over the years, instead of experiencing the expected decline and associated health conditions that often occur with old age.

In terms of supplements, this article focuses on developing innovative, targeted formulations tailored to genetic predispositions. These formulations use nutrients and active ingredients that are already available, enhanced by the support of advanced technologies. Nanotechnology, for instance including nanoencapsulation, nanoemulsions, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs), has significantly improved the bioavailability and efficacy of natural compounds like curcumin and resveratrol, both renowned for their potent antioxidant and anti-inflammatory properties. Synergistic blends such as vitamin C, N-acetylglucosamine, hyaluronic acid, bioavailable marine collagen peptides, and Japanese green apple extract are designed to optimize skin health, hydration, and regeneration while providing powerful antioxidant protection. Organic spirulina, rich in protein, iron, chlorophyll, phycocyanin, and carotenoids, is combined with other beneficial nutrients from apple, freeze-dried acerola, and spices such as clove, cinnamon, and cardamom to boost energy, vitality, immune function, and digestion, while offering numerous other benefits. These are just a few examples of the many remarkable products available for use.

The pharmaceutical industry should play a critical role in this transition, shifting its focus from traditional disease treatment to proactive health maintenance. This new paradigm has the potential to benefit a much larger population, as most individuals could

experience the long-term advantages of using supplements. I envision a future where technology seamlessly integrates artificial intelligence, imaging techniques, nanotechnology, genetics, advanced data analytics, and the clinical use of supplements to precisely regulate the expression of specific genes, paving the way for personalized, precision healthcare. Adopting a multidisciplinary approach has the potential to usher in a new era of personalized medicine. This approach would enable the development of targeted interventions aimed at optimizing gene expression and prioritizing health maintenance in a more scientific, evidence-based, and well-documented manner.

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