Case Report

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Precision Medicine Treatment of Alzheimer's Disease: Successful Randomized Controlled Trial

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Abstract

Background: There is a critical need for effective therapeutics for Alzheimer's disease. However, the majority of previous clinical trials have pre-determined a single treatment modality, such as a drug candidate or therapeutic procedure, which may be unrelated to the primary drivers of the neurodegenerative process. Therefore, a personalized, precision medicine approach, with increased data set size to include the potential contributors to cognitive decline for each patient, and treatment of the identified potential contributors, has emerged as a potentially more effective strategy. Recent proof-of-concept trials have provided clinical data that support this approach. **Objective:** To determine whether a precision medicine approach to Alzheimer's disease at the mild cognitive impairment or early dementia stage is effective in a randomized controlled clinical trial. **Methods:** Seventy-three patients with mild cognitive impairment or early dementia, with Montreal Cognitive Assessment (MoCA) scores of 18 or higher, were evaluated for markers of inflammation, chronic infection, dysbiosis, immune dysfunction, insulin resistance, protein glycation, vascular disease, nocturnal hypoxemia, hormone insufficiency or dysregulation, nutrient deficiency, toxin or toxicant exposure, and other biochemical parameters associated with cognitive decline. Genetic and epigenetic evaluations were included, as well as Alzheimer's-associated biomarkers. Brain magnetic resonance imaging with volumetrics was performed at baseline and study conclusion. Participants were randomly assigned to either a personalized, precision medicine protocol or standard of care

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treatment. Cognition and clinical symptoms were assessed at 0, 3, 6, and 9 months. **Results:** Relative to the standard of care protocol, statistically significant incremental effects of the precision medicine protocol were observed for broad neurocognitive functioning, composite memory (verbal plus visual), executive function, processing speed, cognitive symptom severity, and Alzheimer's disease symptom severity. Furthermore, overall health was enhanced, with improvements in blood pressure, body mass index, glycemic index, lipid profiles, and methylation status. The treatment effect size for overall cognitive function was calculated to be greater than previously published clinical trials, seven times the effect size of the lecanemab trial and four times the effect size of the donanemab trial. **Conclusion:** A personalized, precision medicine approach represents an effective treatment for patients with mild cognitive impairment or early-stage dementia due to Alzheimer's disease. In most cases, this treatment leads to cognitive improvement rather than simply retarding decline, and it does so without significant negative side effects such as brain edema, microhemorrhage, or atrophy.

Keywords: mild cognitive impairment; randomized controlled clinical trial; systems medicine; MRI volumetrics; neurodegeneration

1. Introduction

Neurodegenerative diseases such as Alzheimer's disease (AD), frontotemporal dementia, and amyotrophic lateral sclerosis are without therapeutics that effect sustained improvement. There are approximately seven million people with Alzheimer's disease in the United States, and one study estimated that it has become the third leading cause of death [1]. Unfortunately, the best results from AD monotherapeutic clinical trials have been to slow cognitive decline rather than improve cognition or halt decline [2].

In the field of oncology a personalized, precision medicine approach—in which the presumptive molecular drivers of the disease process are targeted therapeutically—has improved outcomes in at least some studies [3]. In the field of neurology, there is increasing interest in an analogous approach, and recent proof-of-concept clinical trials have reported cognitive improvement in patients with mild cognitive impairment (MCI) or early dementia [4,5], providing support for precision medicine in the treatment of neurodegenerative disease, as well. However, one complicating feature is that the etiology of Alzheimer's disease remains controversial, with many competing theories, such as the theory that Alzheimer's disease is "type 3 diabetes"[6], or is due to chronic *Herpes simplex* infection [7], or due to amyloid-β [8], or to misfolded proteins such as tau [9], or prions [10], among numerous other theories. None of these theories, when addressed in isolation, has led to effective treatment. Meanwhile, epidemiological, pathological, toxicological, genetic, and biochemical studies have provided candidate mechanisms for the neurodegeneration associated with Alzheimer's disease, such as neuroinflammation [11], insulin resistance [12], and reduction in trophic support [13].

Addressing these candidate mechanisms with a personalized, precision medicine-based protocol has led to anecdotal reports of cognitive improvement in patients with Alzheimer-related dementia and its forerunner, MCI [14–16], in addition to the proof-of-concept trials noted above. These reports have provided support for the conduction of a randomized controlled clinical trial, the results of which are presented herein.

2. Methods

Trial design: The trial was designed as a randomized, controlled clinical trial, comparing treatment of patients with MCI or early dementia treated with a personalized, precision medicine protocol [17] to a control group that received standard-of-care treatment [18]. Treatment was carried out for nine months, with 50 patients receiving the precision medicine protocol and 23 receiving the standard of care treatment. The number of subjects chosen was based on the treatment effect observed

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in an earlier, proof-of-concept trial [4], which indicated that a total number of subjects between 50 and 60 would provide a 90% likelihood that the trial would document a statistically significant effect.

Participants: Seventy-three patients with MCI or early dementia, ages 45-76, were recruited to six clinical sites: Walnut Creek, California; San Rafael, California; Folsom, California; Hollywood, Florida; Rocky River, Ohio; and Nashville, Tennessee. Patients were recruited to the nine-month trial, 50 in Group A (the precision medicine protocol arm) and 23 in Group B (the standard of care treatment arm). Six were homozygous for ApoE4, 29 were heterozygous for ApoE4, 33 were homozygous for ApoE3, and 4 were heterozygous for ApoE2 and ApoE3. Demographics are listed in Table 1.

Table 1. Demographic characteristics for each treatment condition.

		Group		Comparison	
Variable	**Total sample (N=73)**	**A (N=50)**	**B (N=23)**	***p***	**ES**
Age, M (SD)	65.0 (7.6)	65.1 (7.3)	64.7 (8.2)	.868	*d*=0.04
Education, M (SD)	16.2 (2.9)	15.9 (2.9)	16.8 (2.7)	.211	*d*=-0.32
Education, n (%)	--	--	--	.629	*V*=.154
High school or less	6 (8.2)	5 (10.0)	1 (4.3)	--	--
Some college	17 (23.3)	11 (22.0)	6 (26.1)	--	--
College graduate	27 (37.0)	20 (40.0)	7 (30.4)	--	--
Post-graduate	23 (31.5)	14 (28.0)	9 (39.1)	--	--
Sex, n (%)	--	--	--	.191	φ=-.153
Female	46 (63.0)	29 (58.0)	17 (73.9)	--	--
Male	27 (37.0)	21 (42.0)	6 (26.1)	--	--
Race, n (%)	--	--	--	.213	*V*=.248
White	68 (93.2)	48 (96.0)	20 (87.0)	--	--
Black	1 (1.4)	0 (0.0)	1 (4.5)	--	--
Asian	3 (4.1)	2 (4.0)	1 (4.5)	--	--

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Not reported	1 (1.4)	0 (0.0)	1 (4.5)		
Ethnicity, n (%)	--	--	--	.824	*V*=.073
Not Hispanic	63 (86.3)	44 (88.0)	19 (82.6)	--	--
Hispanic	5 (6.8)	3 (6.0)	2 (8.7)	--	--
Not reported	5 (6.8)	3 (6.0)	2 (8.7)	--	--
ApoE alleles, n (%)	--	--	--	.485	V=.219
ε2/ε3	4 (5.5)	3 (6.0)	1 (4.3)	--	--
ε2/ε4	1 (1.4)	0 (0.0)	1 (4.3)	--	--
ε3/ε3	33 (45.2)	24 (48.0)	9 (39.1)	--	--
ε3/ε4	28 (38.4)	19 (38.0)	9 (39.1)	--	--
ε4/ε4	6 (8.2)	3 (6.0)	3 (13.0)	--	--

ES: effect size. Group A was treated with a precision medicine protocol. Group B was treated with standard of care. M: mean. SD: standard deviation.

Inclusion criteria were the following: age 45-76 years; cognitive impairment, as demonstrated by complaints of cognitive decline plus a combination of AQ-21 >4 and either MoCA of 18-26 or two or more scores on CNS Vital Signs <50th percentile (neurocognitive index, executive function, verbal memory, visual memory, or composite memory). Thus all patients had symptomatic cognitive decline as well as multiple areas of impairment, as judged by their significant others or study partners, as well as cognitive testing indicative of MCI or early-stage dementia.

Exclusion criteria were the following: MoCA score <18 at baseline; uncontrolled major medical illness such as seizures, unstable cardiovascular disease, or cancer (a diagnosis of cancer within the past five years (excluding non-melanoma skin cancers), or any history of breast cancer (excluding ductal carcinoma in situ) or prostate cancer); a positive blood test for human immunodeficiency virus, hepatitis C, or syphilis; a major psychiatric diagnosis that affected activities of daily living; ongoing psychoactive medications known to impact cognition; ongoing anticoagulant therapy or history of recurrent deep vein thrombosis; MRI findings of hydrocephalus, cerebral infarct, extensive white matter disease consistent with multiple sclerosis, or intracranial neoplasm; symptomatic traumatic brain injury; lack of study partner (family member or care partner); inability to exercise; lack of computer access; positive pregnancy test; diagnosis of a neurodegenerative disease other than Alzheimer's (e.g., frontotemporal dementia); previous or ongoing treatment for MCI or dementia with the precision medicine protocol used here or a very similar approach. Menopausal and perimenopausal women who were unwilling or unable to use bioidentical hormone replacement therapy, or men who were unwilling or unable to use testosterone replacement therapy; any contraindication to enclosed MRI; off-label use of donepezil; unwillingness to remediate or move away from identified sources of toxicity such as mycotoxins; or unwillingness to forgo alcohol (other than up to two small servings weekly of dry red wine).

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Evaluation: Standard physical and neurological examinations were performed on each patient. Trained external raters (i.e., unaffiliated with the treatment teams) performed and assessed the Montreal Cognitive Assessment (MoCA) remotely. Computerized neuropsychological assessment batteries were performed at the study sites using CNS Vital Signs, which samples multiple domains (verbal memory, visual memory, simple attention, complex attention, cognitive flexibility, executive function, processing speed, psychomotor speed, motor speed, and reaction time) as well as providing an overall Neurocognitive Index (NCI) and composite memory score. The AQ-21 (Alzheimer's Questionnaire) is an informant-based subjective assessment with sensitivity and specificity for amnestic MCI and AD of over 90% [19], answered by the significant other or study partner, with scores ranging from 0 (no problems noted) to 27 (all positive responses to questions regarding impairment). A score of 5-14 is compatible with mild cognitive impairment, and 15-27 is compatible with dementia. In this study, 67 subjects had AQ-21 scores of 5-14, and six had scores of 15-17.

Brain training baselines: Guidelines for clinical trial design from the National Institutes of Health suggest that trials should include measures of target engagement in order to facilitate the interpretation of both positive and negative results. BrainHQ brain health assessments, designed on neuroscientific principles, were used to assess target engagement and training-related gains [20–22].

The battery included two assessments, Double Decision and Syllable Stacks, and took approximately 6 minutes to complete [20]. Double Decision evaluates visual speed of processing and cholinergic network health [21]. In this dual-task paradigm, participants discriminate and identify which one of two perceptually similar cars appeared in the center of gaze while simultaneously locating a traffic sign in the peripheral visual field. The adaptive dimension is display exposure duration and scores are recorded in milliseconds, with lower scores indicating better performance (range: 32ms - 3162ms). Syllable Stacks measures verbal memory. Using an auditory span paradigm, participants recall a list of nonsense syllables. The adaptive dimension is set size, and scores are recorded as the number of syllables recalled, with higher scores indicating better performance (range: 1 - 12). To calculate the BrainHQ composite percentile score, raw threshold scores for each subtest were first converted to z-scores to standardize performance across measures, with higher scores indicating better performance. These z-scores were transformed into percentiles and averaged to produce the overall composite. Composite construction was aligned with prior published studies using BrainHQ measures [20].

Genetic testing was carried out using the IntellxxDNA clinical decision support tool. This allowed us to evaluate a few hundred genomic variants that can contribute to cognitive decline, including ApoE genotype, markers for hypercoagulation (e.g., Factor V Leiden), detoxification (e.g., null alleles affecting glutathione-related enzymes and other detoxification pathways), and methylation (e.g., MTHFR and MTRR), as well as a variety of other markers associated with cognitive decline such as gene variants contributing to brain hormone levels, inflammation, and nutrient transport.

Epigenetic testing was carried out by TruDiagnostic (Lexington, KY). Whole blood was collected at baseline and at the conclusion of treatment (nine months). DNA methylation analyses included participants with complete paired samples and high-quality array data at both timepoints (Group A: n = 25; Group B: n = 13), yielding 76 total methylomes. The imbalance in paired sample counts reflects the 2:1 randomization and sample availability at the methylation profiling stage. All participants and study partners provided written informed consent, and study procedures were performed in accordance with the Declaration of Helsinki and were approved by the relevant institutional review board.

Genomic DNA was extracted from whole blood using standard column-based procedures, and DNA quantity, purity, and integrity were confirmed prior to bisulfite conversion. Bisulfite-converted DNA was whole-genome amplified, enzymatically fragmented, and hybridized to the Illumina Infinium MethylationEPIC v2.0 Custom BeadChip (Illumina, San Diego, CA), which assays >935,000 CpG sites. Arrays were scanned on an Illumina iScan system and raw intensity data were exported as IDAT files (methylated and unmethylated channels).

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DNA methylation age and aging-related biomarkers were computed using published algorithms for established clocks, including the Horvath pan-tissue clock, the Hannum blood clock, PhenoAge, and GrimAge (v1 and v2) [23–26]. Clock calculations were implemented using methylclock (R) [27] and the Python aging-clock framework pyaging [28], with additional support via BioLearn where applicable [29]. We additionally computed next-generation measures including DunedinPACE [30] and principal-component (PC) clocks (PCHorvath, PCHannum, PCPhenoAge, PCGrimAge) to improve reliability of clock readouts in longitudinal settings [31]. Brain-relevant aging estimates included the cortical clock (DNAmClockCortical) [32].

Epigenetic age acceleration (EAA) was defined as the residual from regressing DNAm age on chronological age such that positive values indicate accelerated epigenetic aging relative to chronological age.

DNA methylation–based epigenetic biomarker proxies (EBPs) representing circulating proteins and clinical traits were computed using published regression models (EpiScore/EBP-style predictors) derived from large methylation–omic association studies, including multi-omic proxy resources used in the OMICmAge ecosystem and related proxy catalogs [33–35].Proxy outputs were analyzed as standardized scores relative to their reference model scale.

Given the pilot nature of the trial and unequal paired sample sizes, analyses are considered to be exploratory and hypothesis-generating. Longitudinal within-arm changes were tested using paired Wilcoxon signed-rank tests or paired *t* tests depending on distributional diagnostics. Treatment-associated differential trajectories were evaluated using linear mixed-effects models implemented in lme4, with fixed effects for Treatment, Time, their interaction, and Site, and a random intercept for participant ID.

The interaction term (Treatment × Time) tested whether temporal change differed between arms. Cross-sectional between-group comparisons at each timepoint used Wilcoxon rank-sum tests or independent *t* tests as appropriate. To address multiple testing across clock families and proxy panels, false discovery rates were computed using the Benjamini–Hochberg procedure [36].

Epigenome-wide association testing was performed on logit-transformed methylation values (M-values) using limma with empirical Bayes moderation [37–39]. Differentially methylated positions (DMPs) were prioritized at an uncorrected discovery threshold of $p < 1\times10^{-4}$, while Benjamini–Hochberg FDR-adjusted q-values were additionally reported for transparency.

Differentially methylated regions (DMRs) were identified using DMRcate, which detects spatially correlated methylation signals by fitting probe-wise statistics across the genome and applying Gaussian kernel smoothing to aggregate evidence across neighboring CpGs [40]. In the functional annotation pipeline, DMRcate was run via cpg.annotate followed by dmrcate using a kernel bandwidth of $\lambda = 1000$ and minimum consecutive CpGs $C = 2$. This DMR approach is distinct from comb-p; comb-p/SLK correction was not assumed unless separately executed.

DMPs and DMRs were annotated to genomic features using GRCh38/hg38 annotations (https://github.com/jokergoo/IlluminaHumanMethylationEPICv2anno.20a1.hg38), including CpG island context and proximity to transcription start sites, and genomic feature mapping/visualization for DMR coordinates was supported by ChIPseeker [41]. Functional enrichment was performed using complementary bias-aware strategies tailored to methylation arrays. In addition, region-based functional enrichment of DMR genomic coordinates was performed using rGREAT, which implements the GREAT algorithm locally for functional interpretation of regulatory-region–like inputs [42].

Tracking cognitive symptoms utilized the Cognitive Symptom Tracker, a structured, patient-reported outcome tool that quantifies both the severity and frequency of common cognitive and functional symptoms across memory, language, executive function, navigation, and social engagement domains. In clinical practice, longitudinal changes in Tracker scores have shown strong concordance with changes in objective cognitive testing, allowing early detection of improvement or stagnation that often precedes measurable shifts on standardized neuropsychological measures. This

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tool was applied in the trial to quantify subjective cognitive performance and complement objective outcomes.

In addition, the Patient-Reported Outcomes Measurement Information System-10 (PROMIS-10) developed by the NIH (https://www.healthmeasures.net/explore-measurement-systems/promis/obtain-administer-measures) was used to determine subject estimates of physical health (PROMIS-P) and mental health (PROMIS-M).

Biochemical tests and biomarkers were performed to identify markers of insulin resistance (HOMA-IR), protein glycation (hemoglobin A1c), vascular disease (advanced lipid panel), systemic inflammation (C-reactive protein, fibrinogen, homocysteine), iron markers, chronic infection associated with cognitive decline (titers for *Herpes* family viruses (*Herpes simplex type 1*, *Herpes simplex type 2*, *Cytomegalovirus*, *Epstein-Barr virus*, and *Human herpesvirus 6*), *Borrelia* (including tick-borne relapsing fever) by IFA, immunoblot, and immunoblot speciation, *Babesia (in situ hybridization)*, *Bartonella (in situ hybridization)*, spotted fever group, *Anaplasma*, *Ehrlichia*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Toxoplasma gondii*, *Treponema pallidum*, *Human immunodeficiency virus,* and *Hepatitis C virus*), gastrointestinal health (stool analysis of gut pathogens, digestion, absorption, gut immune markers, and microbiome analysis), hormone dysregulation (serum estradiol, progesterone, pregnenolone, DHEA sulfate, testosterone (free and total), sex-hormone binding globulin, prostate-specific antigen (in males), free T3, free T4, reverse T3, and TSH), nutrient status (B vitamins, vitamin D, vitamin E, iron markers, magnesium, zinc, copper, CoQ10, lipoic acid, omega-6:omega-3 ratio, omega-3 index), toxin or toxicant exposure (metals, organic toxicants, and biotoxins (urinary mycotoxins)), autoimmune markers (e.g., anti-thyroid peroxidase antibodies, anti-thyroglobulin antibodies, anti-nuclear antigen), immunoglobulins, CD57, nocturnal hypoxemia (oximetry for three nights to identify sleep apnea and upper airway resistance syndrome), and other biochemical parameters associated with cognitive decline.

Neuroimaging: Magnetic resonance imaging of the brain with volumetrics (Neuroreader) was performed for each patient, during initial evaluation and again at the completion of the 9-month treatment protocol. All scans at baseline and follow-up were performed on clinical 3-Tesla MRI scanners with either MPRAGE or SPGR sequences. Segmentation and quantification of the hippocampus and total gray matter were carried out computationally, as described previously [43]. Volumetric change over the 9-month trial period was calculated on a percent annualized rate of change. Additionally, each of these volume change rates was adjusted for each participant's total head size, computed as the sum of gray matter, white matter, and cerebrospinal fluid. Rates of change in brain volumes of the hippocampus, total gray matter, white matter, frontal lobes, temporal lobes, parietal lobes, occipital lobes, cerebella, and ventricles were then compared between the two treatment groups.

Statistical analysis: Baseline continuous and categorical demographic data were compared between groups using t-tests and chi-squared tests of independence, respectively. Skew, kurtosis, and outliers were also screened for primary outcomes prior to proceeding to main analyses. Due to non-normality, AD biomarkers (42/40 ratio, p-tau217) were rank-transformed. To assess the incremental effect of the precision medicine intervention on the primary clinical (AQ, CST, PROMIS) and cognitive (CNS-VS, MoCA, brainHQ) outcomes, repeated measures general linear models (GLM) were constructed. This allowed for testing treatment x time interaction effects between group assignment (precision medicine vs. standard of care) and change in outcomes over time (Month 0 (screening], Month 3, Month 6, Month 9). Only Month 3, Month 6, and Month 9 timepoints were entered into the AQ GLM model as screening used a different scale (whereas the other three timepoints captured AQ change scores). A significant interaction effect in the GLM indicates the groups changed (on the respective outcome) at a different rate over the study period. Descriptive statistics and line plots were used to interpret interaction trends. We also computed delta (Δ) variables for each outcome as the difference between the final and screening visits (i.e., month 9 - month 0), then compared change (Δ's) between groups using t-tests to estimate incremental effect sizes via Cohen's *d* values. Due to non-normality, biochemical and AD biomarker variables were

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analyzed using non-parametric analyses (Wilcoxon signed-rank tests for looking at within-group changes and Mann-Whitney U tests for comparing change from baseline between groups). Ferguson's (2009) criteria were applied across analyses to operationalize the minimum effects necessary to denote a *practically meaningful* effect: $d \geq 0.41$ (for t-tests and non-parametric analogs), ϕ or $V \geq .20$ (for chi-squared tests), and $\eta_p^2 \geq .04$ (for GLMs). Level of significance (α) was set to .05 (two-tailed).

Treatment: Patients were treated for nine months with either a standard-of-care protocol [18] (Group B) or a personalized, precision medicine protocol that addressed each patient's identified potentially contributory factors [17] (Group A), and cognition was assessed at 0, 3, 6, and 9 months. Physicians met monthly with subjects from each group. Note that, at the time of the planning, and then IRB approval, of this trial in 2022-2023, anti-amyloid antibodies were not included in the standard of care for patients with Alzheimer's disease.

The goal was to identify and address the factors associated theoretically and epidemiologically (though in some cases yet to be proven causally) with Alzheimer's-related cognitive decline: restore insulin sensitivity, improve hyperlipidemia, resolve inflammation if present (and remove the cause(s) of the inflammation), treat pathogens, optimize energetic support (oxygenation, cerebral blood flow, ketone availability, and mitochondrial function), optimize trophic support (hormones, nutrients, and trophic factors), treat autoimmunity if identified, and detoxify if toxins were identified.

The treatment team included a physician, health coach, nutritionist, and physical trainer, and was overseen by a study coordinator.

Diet was a plant-rich, high-fiber (soluble and insoluble), mildly/moderately ketogenic diet, high in leafy greens and other non-starchy vegetables (raw and cooked), high in unsaturated fats, low in glycemic load, with a fasting period of 12-16 hours each night. Organic produce, wild-caught low-mercury fish (salmon, mackerel, anchovies, sardines, and herring), and modest consumption of pastured eggs and meats were encouraged, as well as avoidance of processed food, simple carbohydrates, gluten-containing foods, and dairy. Subjects were asked to avoid alcohol, alcohol sugars, and artificial sweeteners. Blood ketone levels were monitored with fingerstick ketone meters, with a goal of 1.0-4.0 mM beta-hydroxybutyrate at least once during each day. The importance of including ketosis as a goal has been supported by the work of Cunnane et al. [44].

Exercise, both aerobic and strength training, as well as balance training and stretching, was included as part of the protocol, for at least 45 minutes per day, at least six days per week (for aerobic exercise) and at least twice per week (for strength training), and facilitated by the personal trainers. High-intensity interval training (HIIT) was recommended a minimum of twice per week.

Sleep hygiene was supported to ensure 7-8 hours of quality sleep per night, and sleep was tracked by Oura ring. All patients without known sleep apnea were tested over several nights using home sleep study devices. In those diagnosed with sleep apnea or upper airway resistance syndrome (UARS), referral for treatment with a continuous positive airway pressure apparatus (CPAP) or a dental splint device (for those identified with UARS) was provided.

Stress management included biofeedback and heart-rate variability training with a HeartMath Inner Balance for IOS device, for a minimum of 10 minutes per day [45], chosen because of the ease of patient use and thus high compliance.

Brain training was carried out using BrainHQ (Posit Science, San Francisco, CA), an evidence-based [46] online cognitive training program that is compliant with HIPAA and SOC-2 security standards. The training includes 29 adaptive exercises designed to improve the speed and accuracy of information processing across vision and audition, with demonstrated effects on brain health [47], cognitive performance [48], and everyday functioning [49]. Participants were instructed to train for a minimum of 15 minutes per day, corresponding to completion of approximately six exercise levels, with a goal of 36 levels per week. The platform automatically adjusted task difficulty on a trial-by-trial basis to maintain engagement and ensure training at each participant's performance threshold.

Hormones and nutrients: For those patients with suboptimal hormonal status, bioidentical hormone replacement and appropriate supplements were provided to optimize sex hormone levels

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[50], neurosteroids (dehydroepiandrosterone, pregnenolone, and vitamin D), and thyroid medications as indicated were utilized for suboptimal thyroid function. For those with suboptimal nutrients (e.g., vitamin D, omega-3, B vitamins, CoQ10, or minerals), the appropriate nutrients were provided.

Gastrointestinal health: The following gut markers were tested and optimized for digestive support (pancreatic elastase, fecal fats, protein breakdown products), Inflammation (secretory IgA, calprotectin, eosinophilic protein X, occult blood), dysbiosis, metabolic imbalance (short-chain fatty acids, butyrate, beta-glucuronidase), and infection. For those with gastrointestinal hyperpermeability, infections, inflammation, or impaired absorption and digestion, gut healing with dietary restriction, gut-healing nutrients, and digestive enzyme support if indicated, along with treatment of any identified dysbiosis, was undertaken.

Inflammation: For those with evidence of systemic inflammation, specialized pro-resolving mediators and anti-inflammatory herbal supplements (such as liposomal glutathione, fish oil, turmeric, resveratrol, vitamins C and D, boswellia, and quercetin) were provided, low-dose naltrexone was prescribed (if there was evidence of autoimmunity), and omega-3 fats included via diet and supplements. Note that low-dose naltrexone was chosen for those with autoimmunity because of its ability to increase endorphins, which in turn bind to the opioid receptors on the T-regulatory cells to regulate immune function, reducing autoimmune responses [51].

Infectious agents associated with cognitive decline or systemic inflammation were identified and treated. For those with evidence of *Herpes simplex* infection or a history of outbreaks, valacyclovir was prescribed for 2-9 months. Active *Epstein-Barr Virus* (EBV) was treated with herbal protocols (such as Monolaurin, Olive Leaf, and Lysine or Gemmotherapy with Juniperus, Acer, and Tamarix). For those with evidence of tick-borne infections [52] such as *Borrelia*, *Babesia*, or *Bartonella*, organism-sensitive treatment was prescribed with herbal antimicrobials, such as Cryptolepis and Japanese knotweed [53] and immune support or antibiotics, such as dapsone, doxycycline, azithromycin and rifampin.

Toxins and toxicants: For those with toxicity associated with metals (e.g., mercury or lead), organic pollutants (e.g., benzene, xylenes, toluenes, styrenes, parabens, methyl tert–butyl ether, phthalates, or organophosphate insecticides), or biotoxins (e.g., trichothecenes, ochratoxin A, zearalenone, or gliotoxin), targeted detoxification was undertaken with binding agents (e.g., cholestyramine, charcoal, chlorella, or bentonite clay), sauna, herbs, sulforaphane, and dietary restriction of seafood if indicated.

Photobiomodulation: Based on the extensive literature on photobiomodulation and its cognitive benefits [54], most of the sites included photobiomodulation in the overall protocol, either gamma frequency from Auragen, Vielight, Neuronic Neuradiant 1070, or, at one site, Aspen Apex Laser (triple wavelength with pulsing from 20-40 Hz).

Adjunctive therapeutics: Three of the six sites also used adjunctive therapeutic approaches, including hyperbaric oxygen at 1.3 atmospheres (one site), hyperbaric oxygen at 2.0 atmospheres (one site), exercise with oxygen therapy (one site), cranio-electrical stimulation (one site) and neurofeedback (two sites).

3. Results

Metabolic effects: Table 2 lists metabolic parameters prior to, and at the conclusion of, the 9 months of treatment. Relative to the standard of care group, the precision medicine group displayed a statistically significant reduction in body mass index, systolic blood pressure, diastolic blood pressure, glycation (as a reduction in hemoglobin A1c), and insulin resistance (as HOMA-IR, homeostasis model assessment-estimated insulin resistance). Significant improvements were observed in lipid profile (as reduction in triglyceride-to-high-density-lipoprotein ratio) and methylation (as reduction in homocysteine), as well as a significant increase in serum vitamin D (as serum 25-hydroxycholecalciferol).

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Table 2. Serum biochemical tests, BMI, and blood pressure prior to, and following, treatment for 9 months in Group A (precision medicine protocol) vs. Group B (standard of care).

				Δ within group		Δ between groups	
Group	Variable, Med (IQR)	Month 0	Month 9	Med (IQR)	d[a]	Med dif	d[b]
Precision medicine	Vitamin D (25-OH)	43.3 (18.3)	62.6 (19.9)	20.5 (33.7)	1.60‡	22.8	0.86†
	hs-CRP	0.6 (1.0)	0.6 (1.4)	-0.02 (0.6)	-0.44	0.0	-0.42
	Fasting glucose	96.0 (11.0)	91.0 (9.0)	-6.0 (11.0)	-1.18†	-4.5	-0.38
	HDL cholesterol	65.0 (26.0)	72.0 (27.0)	3.0 (10.0)	0.54	3.0	-0.26
	Hgb A1c	5.5 (0.3)	5.3 (0.3)	-0.2 (0.3)	-1.93‡	-0.3	-1.14‡
	Homocysteine	9.8 (3.5)	7.8 (3.8)	-2.1 (3.0)	-2.04‡	-1.3	-0.86†
	Fasting insulin	5.9 (6.3)	5.0 (4.9)	-1.1 (3.2)	-0.83†	-1.8	-0.51
	Total cholesterol	212.5 (55.0)	204.0 (68.0)	-3.0 (65.0)	-0.54	0.5	-0.17

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		77.0 (45.0)	61.0 (29.0)	-13 (37.0)		-19.5	-0.59†
	Triglycerides				-1.08†		
		647.0 (428.0)	1452.0 (846.0)	659.5 (768.3)		685.5	1.18‡
	Vitamin B12				2.58‡		
		1.4 (1.3)	1.1 (1.1)	-0.4 (0.8)		-0.4	-0.61†
	HOMA-IR				-1.46‡		
		1.2 (1.1)	0.9 (0.7)	-0.3 (0.6)		-0.4	-0.55†
	TG:HDL ratio				-1.07†		
	BMI	24.0 (6.8)	22.4 (5.4)	-1.2 (3.1)	-1.52‡	-1.7	-1.27‡
	Systolic BP	123.0 (25.5)	118.0 (18.0)	-9.0 (23.5)	-0.99†	-10.0	-0.49‖
	Diastolic BP	73.0 (11.3)	70.0 (9.3)	-5.0 (14.3)	-0.84†	-5.0	-0.36
Standard of care	Vitamin D (25-OH)	43.2 (23.3)	51.5 (30.3)	-2.3 (17.9)	-0.02	--	--
	hs-CRP	0.5 (1.2)	0.8 (2.0)	0.2 (1.0)	0.62	--	--
	Fasting glucose	92.5 (14.0)	93.0 (10.0)	-1.5 (10.3)	-0.50	--	--
	HDL cholesterol	62.0 (38.0)	62.0 (28.0)	0.0 (14.8)	-0.08	--	--
	Hgb A1c	5.7 (0.3)	5.7 (0.5)	0.1 (0.3)	0.42	--	--
	Homocysteine	9.6 (3.0)	9.6 (3.4)	-0.8 (3.7)	-0.24	--	--
	Fasting insulin	6.3 (6.3)	7.4 (5.9)	0.7 (5.1)	0.33	--	--

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Total cholesterol	230.0 (73.0)	220.5 (45.0)	-3.5 (42.5)	-0.23	--	--
Triglycerides	82.0 (39.0)	89.0 (68.0)	6.5 (59.0)	0.29	--	--
Vitamin B12	819.5 (686.0)	960.0 (965.0)	-26.0 (223.0)	-0.31	--	--
HOMA-IR	1.4 (1.3)	1.6 (1.5)	0.02 (1.2)	0.22	--	--
TG:HDL ratio	1.5 (1.5)	1.6 (1.3)	0.1 (1.0)	0.30	–	–
BMI	24.0 (6.4)	25.0 (6.5)	0.5 (0.8)	1.76*	--	--
Systolic BP	121.0 (22.5)	124.0 (23.5)	-1.0 (18.5)	0.19	--	--
Diastolic BP	74.0 (11.5)	74.0 (10.5)	0.0 (14.0)	-0.27	--	--

Note. ‡$p \leq .001$, †$p < .05$, ‖$p = .056$ *BMI significantly *increased* for the standard of care group (p=.002). a Cohen's d and p-values estimated from Wilcoxon signed-rank tests to compare medians (month 9 vs. month 0) within each group. BP, blood pressure. b d and p-values estimated from Mann-Whitney U tests comparing median change (i.e., from month 0 to month 9) between groups. Month 0 values were subtracted from month 9 to compute delta scores, where positive values indicate increase and negative indicate decrease in lab value. Hgb, hemoglobin. Hs-CRP, high-sensitivity C-reactive protein. HOMA-IR, homeostasis model assessment-estimated insulin resistance, calculated based on fasting insulin and fasting glucose (fasting insulin in mIU/L times fasting glucose in mg/dL, divided by 405.45). TG:HDL ratio, serum triglyceride-to-high-density-lipoprotein ratio. Vitamin D was measured as 25-hydroxycholecalciferol. Post-treatment tests were taken at the conclusion of the 9-month protocol for each patient, as described in the text.

Cognition: Cognitive results are summarized in Table 3.

Table 3. Primary neurocognitive and clinical outcomes over the study period, stratified by treatment condition.

Variable, *M* (*SD*)		**Timepoint (month)**				**Δ from baseline, *M* (*d*)[a]**	**Δ between groups, *M* (*d*)[b]**	**Group x timepoint interaction**		
Group		**0**	**3**	**6**	**9**			***F***	***p***	η_p^2
Precision Medicine	NCI	92.04 (12.3)	98.89 (11.1)	103.76 (8.9)	106.19 (8.1)	14.02 (1.23)‡	18.39 (1.12)‡	21.08	<.001	.260
	CM	89.45	95.29 (17.3)	100.38 (15.9)	101.56 (17.0)	13.12 (0.73)‡	18.51 (0.94)‡	17.92	<.001	.224

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	(16.4)								
EF	90.63 (16.0)	99.13 (15.6)	103.16 (13.2)	108.02 (10.8)	16.86 (1.19)‡	15.04 (0.89)‡	11.25	.001	.154
PS	103.5 (13.0)	107.6 (16.0)	111.0 (13.3)	116.1 (15.7)	12.26 (0.85)‡	9.74 (0.67)†	6.98	.010	.103
BrainHQ	33.1 (10.9)	--	--	58.2 (20.5)	25.15 (1.27)‡	14.8 (0.75)‡	6.98	.011	.111
AQ*	10.46 (3.3)	2.70 (5.1)	5.93 (7.3)	8.74 (10.4)	8.74 (10.4)**	11.11 (1.26)‡	16.34	<.001	.211
CST	47.57 (28.4)	36.79 (26.4)	24.84 (22.6)	16.35 (21.4)	-33.27 (-1.19)‡	-28.27 (-1.05)‡	15.94	<.001	.231
PROMIS-P	49.1 (8.5)	51.7 (6.5)	52.8 (6.0)	55.1 (6.1)	5.36 (0.77)‡	5.25 (0.77)‡	11.02	.002	.193
PROMIS-M	46.5 (8.1)	49.4 (8.5)	50.2 (6.4)	54.1 (6.3)	6.70 (0.93)‡	6.35 (0.97)‡	12.41	<.001	.212
MoCA	24.0	25.1 (3.2)	25.8 (3.1)	27.6 (2.5)	3.79 (1.52)‡	1.23 (0.41)	2.08	.154	.032

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		(2.4)								
Standard of care	NCI	96.91 (6.7)	95.74 (13.6)	96.09 (11.9)	92.35 (24.2)	-4.36 (-0.19)	--	--	--	--
	CM	92.87 (14.1)	91.43 (17.8)	88.78 (14.1)	87.48 (22.0)	-5.39 (-0.24)	--	--	--	--
	EF	96.41 (10.1)	93.04 (21.5)	97.83 (13.7)	97.74 (20.7)	1.82 (0.09)	--	--	--	--
	PS	103.9 (11.9)	103.0 (13.0)	103.9 (13.6)	106.4 (16.1)	2.52 (0.17)	--	--	--	--
	BrainHQ	33.1 (10.4)	--	--	42.4 (18.9)	10.36 (0.54)†	--	--	--	--
	AQ*	9.52 (3.2)	-1.30 (2.4)	-0.87 (5.7)	-2.36 (4.4)	-2.36 (4.4)**	--	--	--	--
	CST	51.55 (26.9)	48.10 (25.4)	46.18 (21.2)	46.95 (25.8)	-5.00 (-0.20)	--	--	--	--
	PROMIS-P	52.0	50.4 (6.8)	51.4 (9.4)	52.3 (7.5)	0.11 (0.02)	--	--	--	--

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	(8.2)								
PROMIS-M	46.3 (5.8)	47.5 (6.5)	46.8 (6.5)	46.4 (6.5)	0.35 (0.07)	--	--	--	--
MoCA	22.91 (3.0)	23.74 (3.5)	24.09 (4.0)	25.48 (4.0)	2.57 (0.67)†	--	--	--	--

Note. ‡$p \leq .001$, †$p < .05$, *The AQ for month 0 (screening) is the AQ-21 (higher=more symptomatic) whereas subsequent months are AQ-20 (AQ change, higher=improvement; see methods), **Δ from baseline score reflects M (SD) AQ-20 change at month 9. AQ: Alzheimer's Questionnaire; CM: Composite Memory CNS-VS Composite; CST: Cognitive Symptom Tracker; EF: Executive Function CNS-VS Composite; MoCA: Montreal Cognitive Assessment; NCI: Neurocognitive Index CNS-VS Composite; PROMIS-P: Patient-Reported Outcomes Measurement Information System-Physical Health subscale; PROMIS-M: Patient-Reported Outcomes Measurement Information System-Mental Health subscale. PS: processing speed; [a]within-group delta capturing score change between months 9 and 0 (screening), with Cohen's d and p-value reflecting within-group paired-samples t-test. [b]between-group comparison of deltas, with Cohen's d and p-value reflecting independent-samples t-test.

The AQ-C is a subjective change scale that is derived from the AQ-21. It is informant-based (significant other or study partner) and has a range from -40 (marked decline in all functions) to +40 (marked improvement in all functions). A Likert-type scale was used, such that the scoring for each of the 20 questions was -2 (much worse), -1 (slightly worse), 0 (no change), +1 (slightly better), or +2 (much better).

In the precision medicine protocol group, the AQ-C improved by 8.74 ± 10.35 points, whereas in the standard of care group, the AQ-C declined by 2.36 ± 4.41 points, indicating that the partners of the PMP group noted improvement, whereas those of the SOC group noted decline ($p < 0.001$). Results are graphed in Figure 1.

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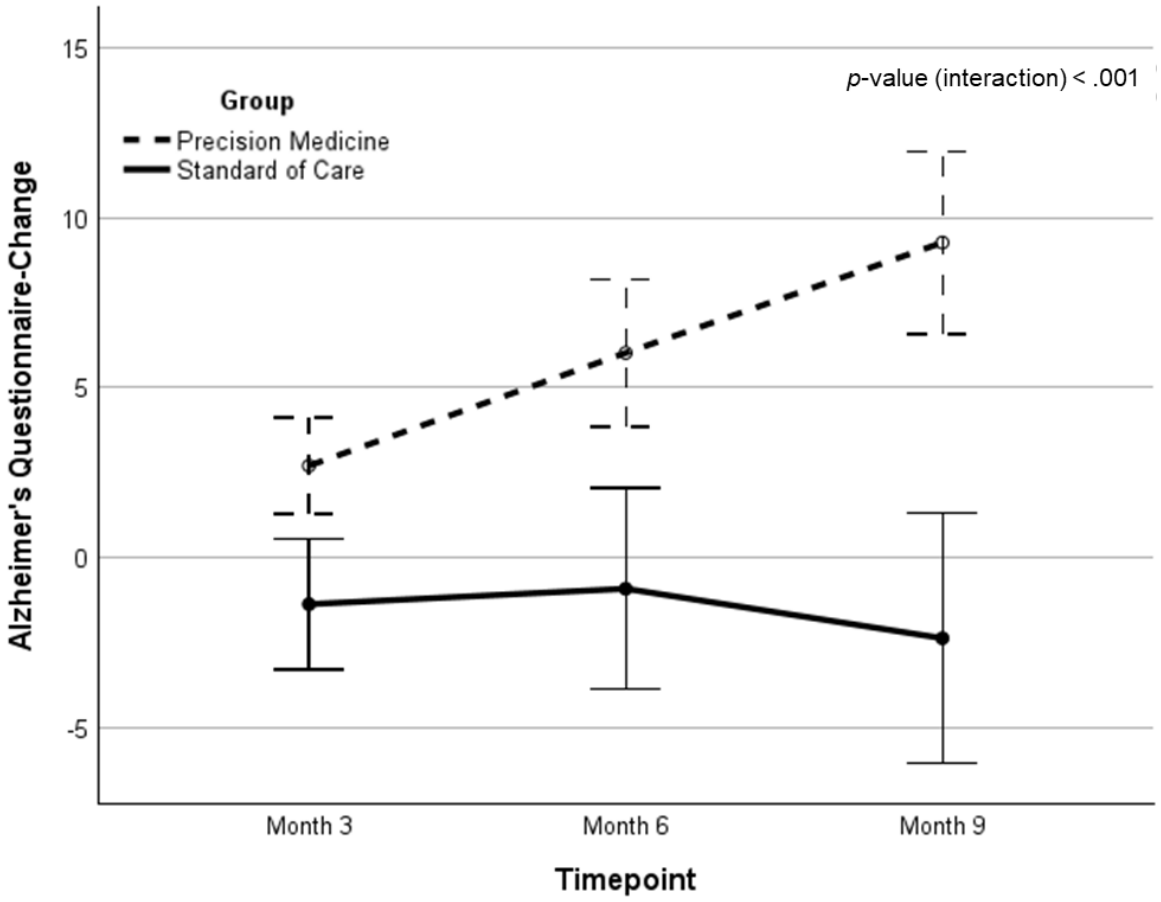

Figure 1. Line graph of AQ-Change scores (higher values = improved symptoms; time zero = zero by definition, since it is a change score) over time with lines separated by group. Error bars depict 95% CI.

Similarly, the cognitive symptom tracker (CST) differed between the two groups, reflecting improvement in the PMP group but only minimal improvement in the SOC group, with a p value < 0.001 and an effect size of 0.231 (Figure 2).

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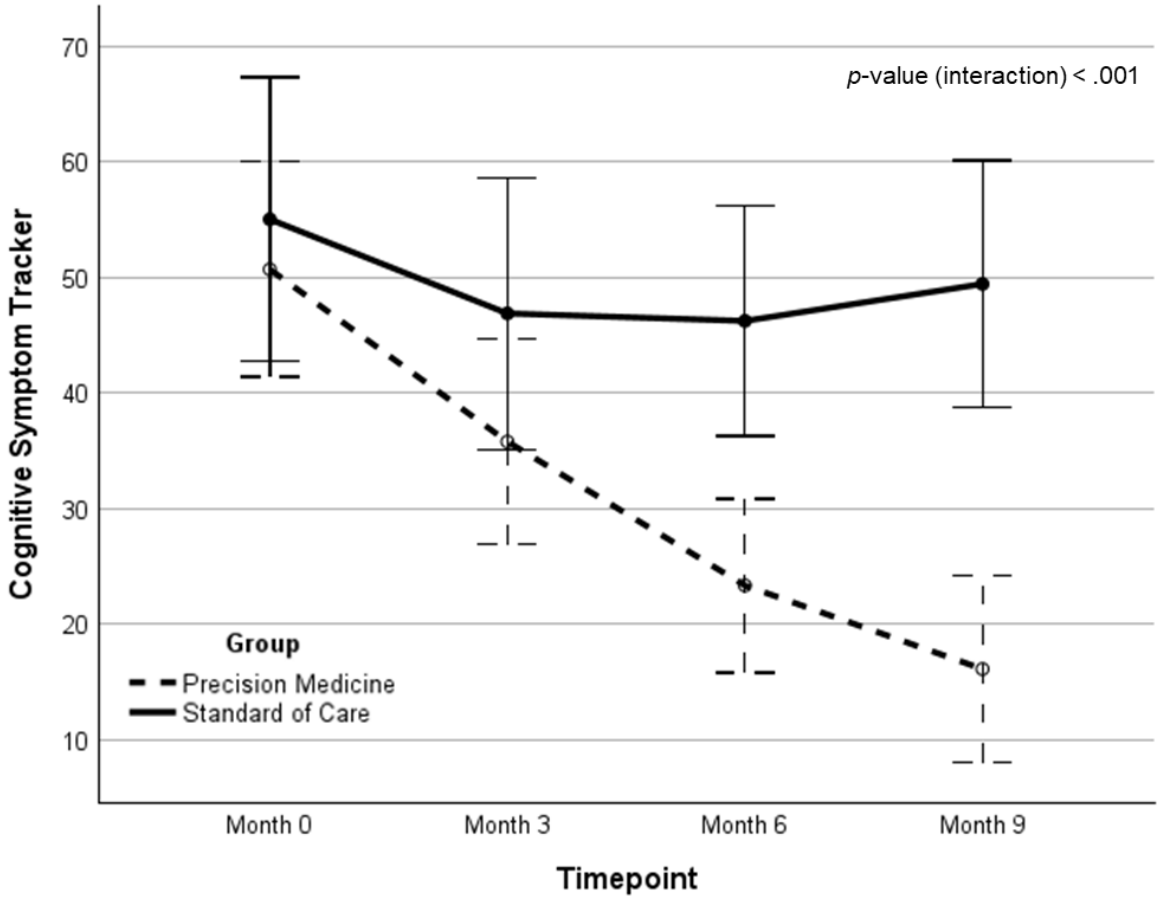

Figure 2. Line graph of cognitive symptom tracker (CST) scores (higher = worse symptoms) over time with lines separated by group. Error bars depict 95% CI.

PROMIS-10-Physical Health (Figure 3) and PROMIS-10-Mental Health (Figure 4) also showed significant improvements, with $p = 0.002$ and $p < 0.001$, respectively.

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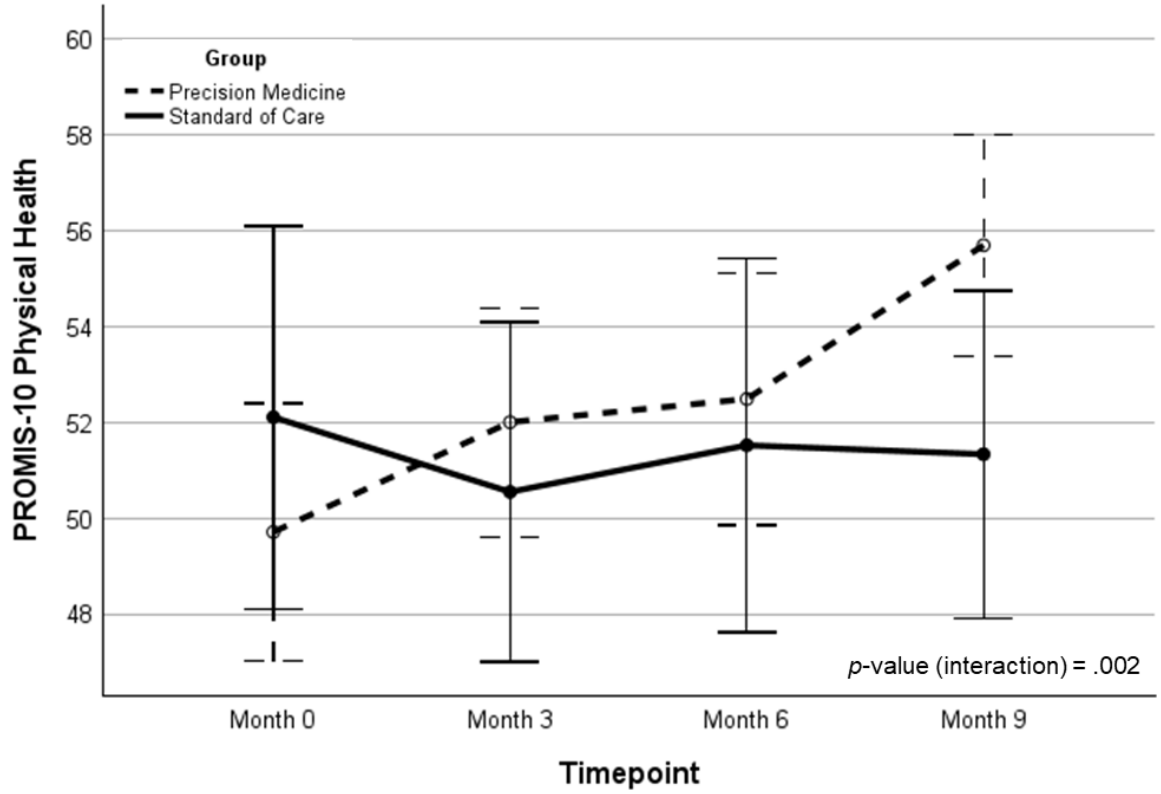

Figure 3. PROMIS-10 Physical Health results in Group A (broken line) and Group B (solid line). Higher numbers indicate better symptoms.

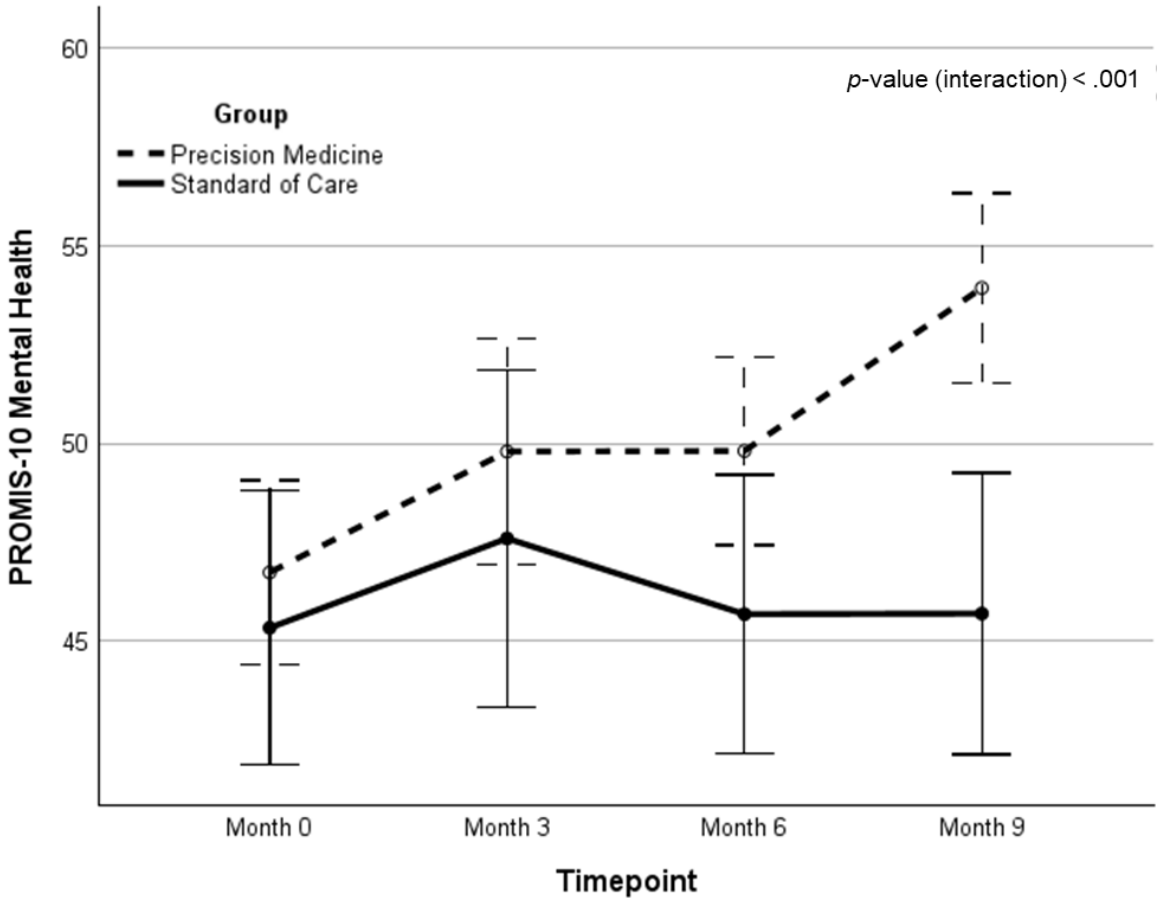

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Figure 4. PROMIS-10 Mental Health results in Group A (broken line) and Group B (solid line). Higher numbers indicate better symptoms. .

CNS Vital Signs is a computerized neuropsychological assessment used to evaluate cognitive performance and change. The reliability and validity of this battery have been described in previous publications [55], and this assessment tool is more sensitive than the MoCA in the identification of mild cognitive impairment [56]. The test battery administered for this study included assessments of verbal memory, visual memory (both immediate and delayed), symbol digit coding, Stroop performance, shifting attention, continuous performance, and finger-tapping. Age-matched domain standard scores and percentile ranks were calculated for visual memory, verbal memory, composite memory, motor speed, psychomotor speed, processing speed, reaction time, cognitive flexibility, simple attention, complex attention, and executive function, as well as an omnibus domain score, Neurocognitive Index (NCI). Scores are set such that a score of 100 indicates the 50th percentile, with a standard deviation of 15.

Table 3 (above) lists CNS Vital Signs results of the NCI, composite memory, executive function, and processing speed from all patients who completed the study at baseline, 3 months, 6 months, and 9 months of treatment. Figure 5 (below) displays the NCI means and 95% confidence intervals for each group. Comparing the results at outset to those at completion revealed an improvement in the Neurocognitive Index from 92.0 ± 12.3 to 106.2 ± 8.1 in Group A, whereas there was a decline in Group B from 96.9 ± 6.7 to 92.4 ± 24.2 ($p < 0.001$).

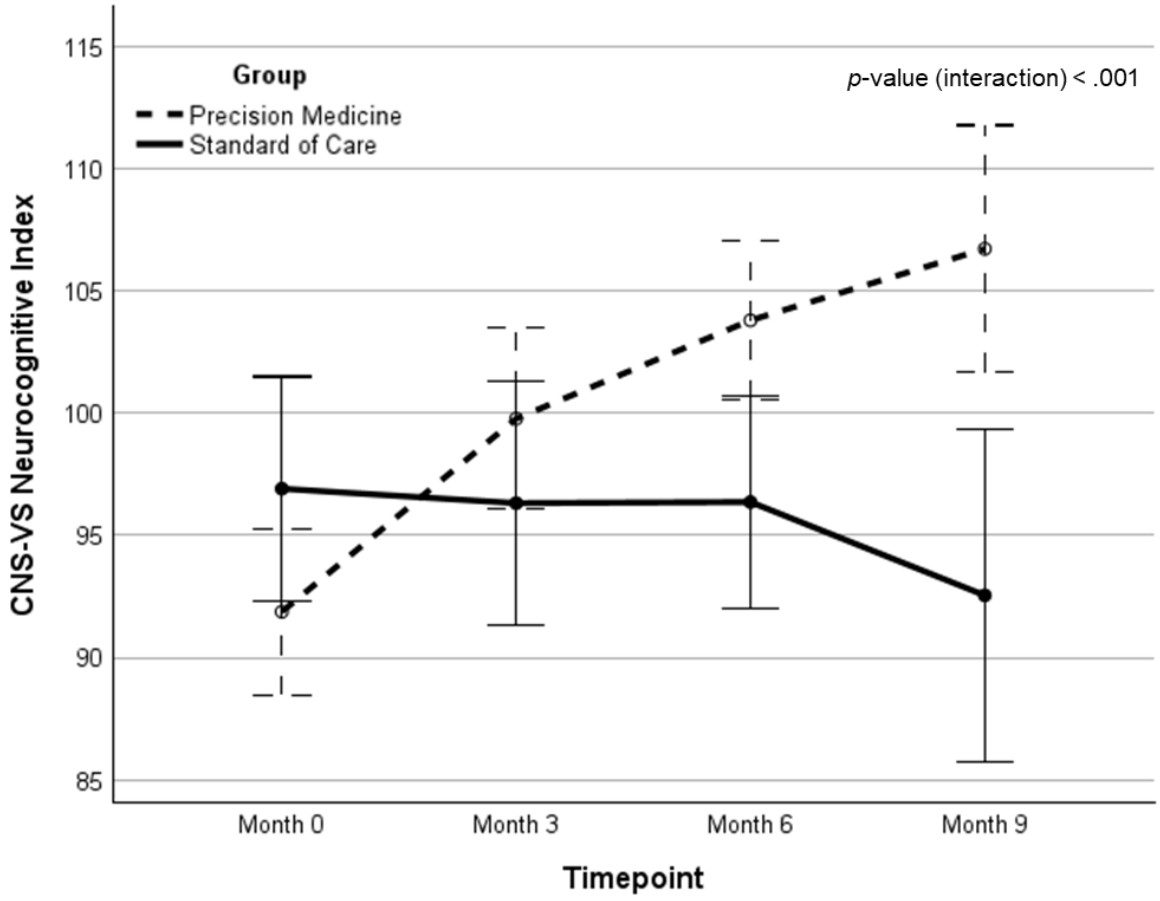

Figure 5. Line graph of CNS-VS NCI composite scores over time with lines separated by group. Error bars depict 95% CI.

Composite memory scores are shown in Figure 6. Group A improved by approximately one standard deviation (14.0 ± 11.4), whereas Group B declined by 5.4 ± 22.7 ($p < 0.001$ with effect size of 0.224).

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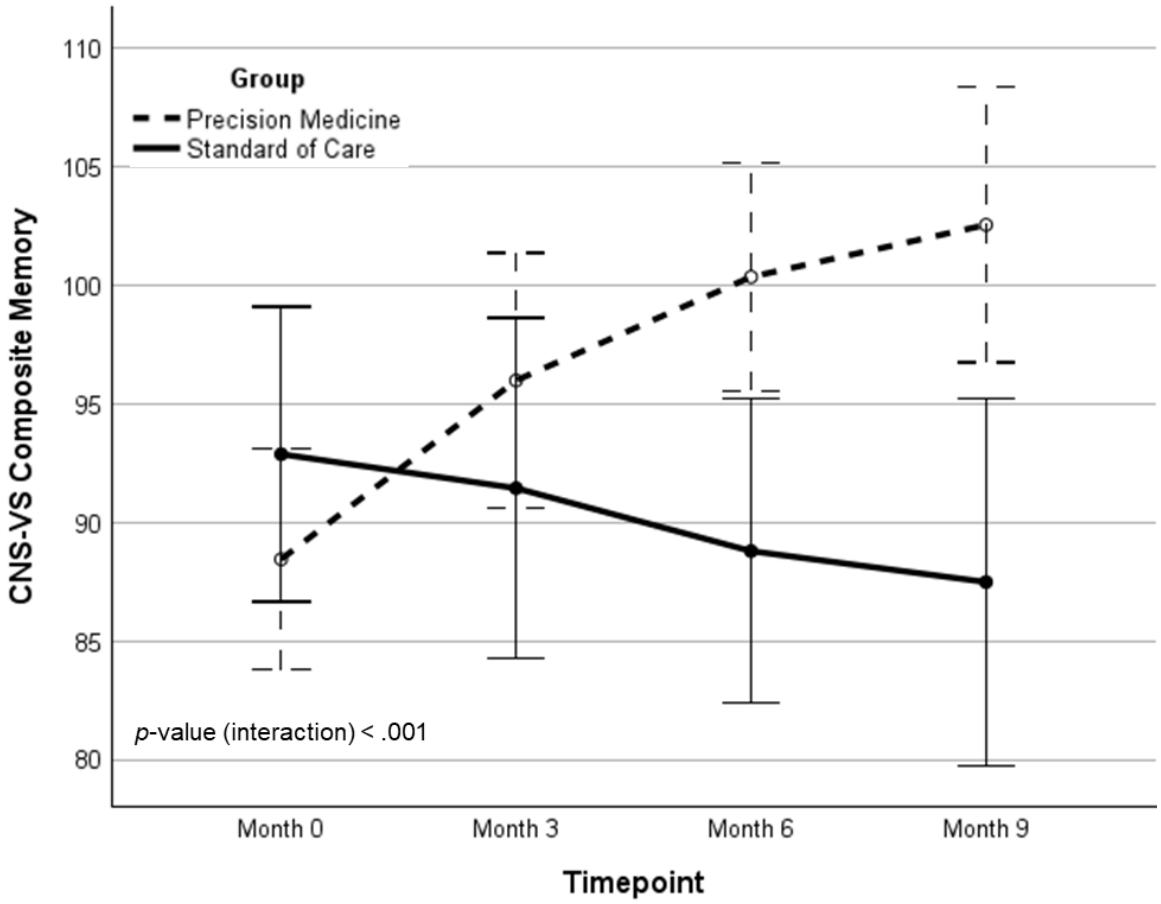

Figure 6. Line graph of CNS-VS composite memory scores (verbal memory + visual memory) over time with lines separated by group. Error bars depict 95% CI.

Executive function scores (Figure 7) also showed an approximately one standard deviation improvement in Group A subjects (16.9 ± 14.2), whereas there was little change in Group B subjects (1.8 ± 21.3). This difference was significant (p = 0.001, with an effect size of 0.154).

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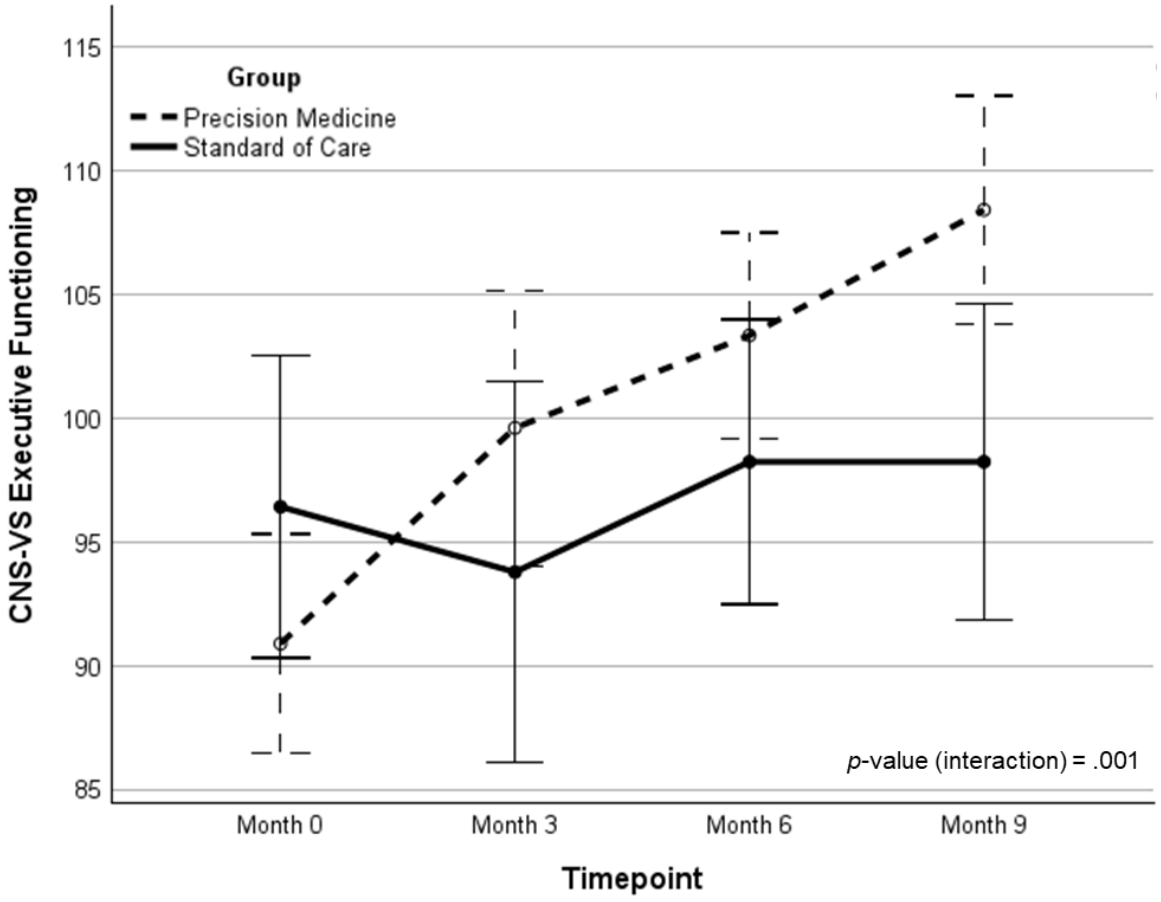

Figure 7. Line graph of CNS-VS executive function scores over time with lines separated by group. Error bars depict 95% CI.

Processing speed also displayed a significant difference between groups (Figure 8), with Group A improving from 103.5 ± 13.0 to 116.1 ± 15.7, whereas Group B improved more modestly, from 103.9 ± 11.9 to 106.4 ± 16.1 ($p = 0.01$).

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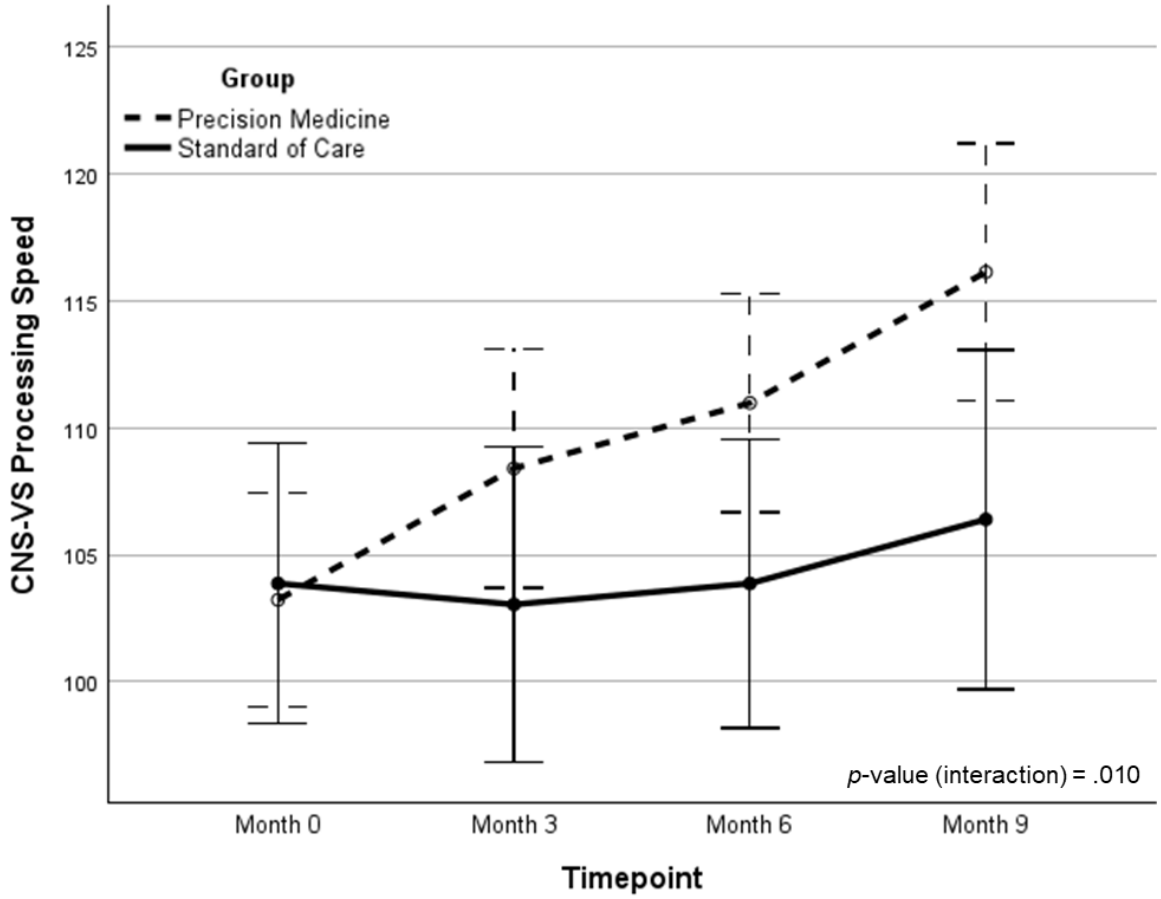

Figure 8. Line graph of CNS-VS processing speed over time with lines separated by group. Error bars depict 95% CI.

Montreal Cognitive Assessment (MoCA) was also used to evaluate the patients (version 8.1 at baseline, 8.2 at 3 months, 8.3 at 6 months, and 8.1 at 9 months). Group A improved the MoCA scores by 3.8 ± 2.5 (Figure 9), whereas Group B improved MoCA scores by 2.6 ± 3.8. Thus the difference between the two groups showed a trend that did not reach statistical significance (p = 0.154, effect size 0.033).

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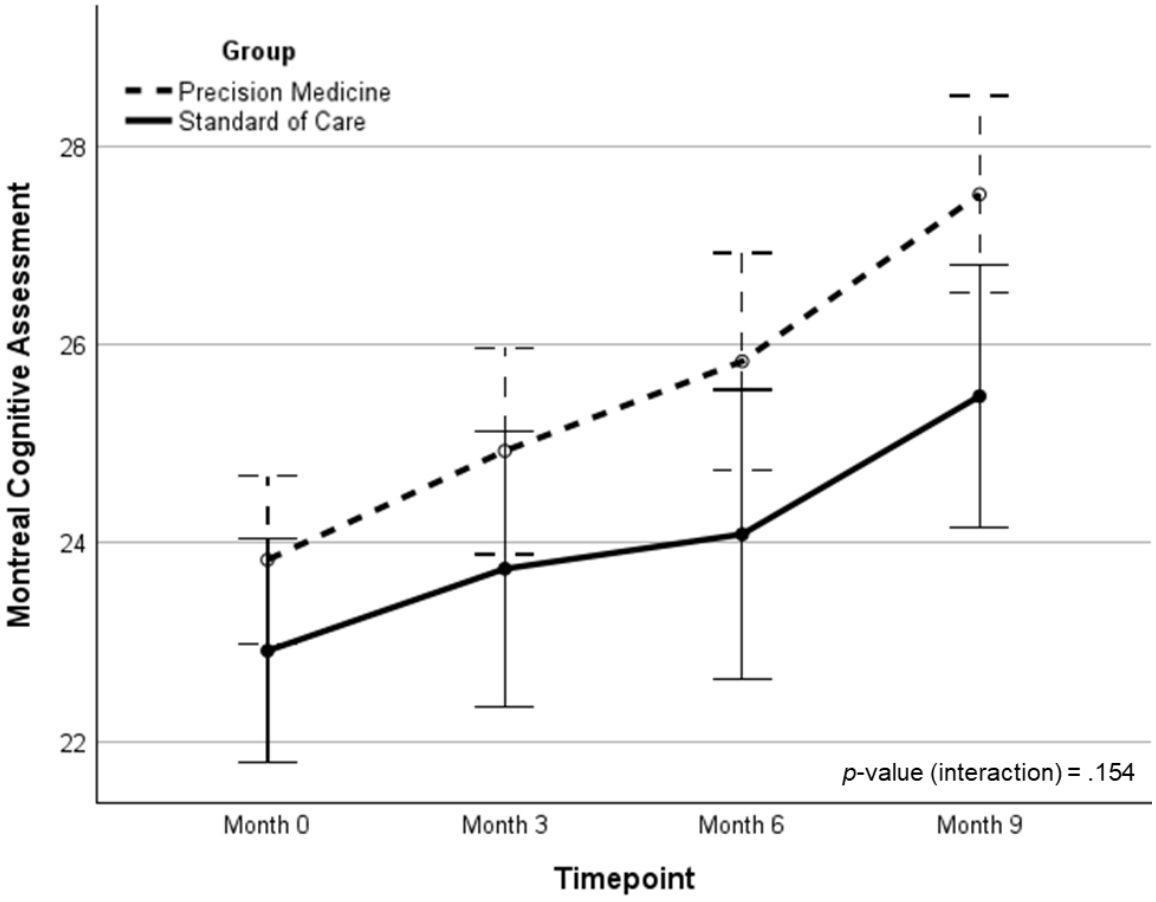

Figure 9. Line graph of MoCA scores over time with lines separated by group. Error bars depict 95% CI.

Brain training: Participants in the precision medicine (Group A) and standard of care (Group B) groups demonstrated similar BrainHQ assessment composite percentile scores at baseline (Group A mean = 33.1 ± 10.9 percentile, Group B mean = 33.1 ± 10.4 percentile). At the conclusion of the trial, Group A demonstrated a 25.1 percentile point improvement on assessment performance (mean = 58.2 ± 20.5 percentile), while Group B demonstrated a 9.3 percentile point improvement in scores (mean = 42.4 ± 18.9 percentile). Change scores ranged from declines (Group A: -14 percentile, Group B: -21.5 percentile) to substantial improvement (Group A: +66 percentile, Group B: +45 percentile). These results suggest successful target engagement and demonstrate that the study cohort was responsive to cognitive training.

Although BrainHQ was implemented as an intervention (for Group A only), participants' performance trajectories within the platform provide preliminary indicators of cognitive change over the course of the trial. All participants demonstrated improvement in their BrainHQ composite percentiles during the intervention period, with a mean increase of 19 percentile points (range: 3 - 29). Participants engaged with the training for an average of 52 hours across the study (range: 15 minutes - 164 hours). These performance metrics offer supplemental evidence of individual engagement with the intervention and the degree of cognitive improvement achieved during the study period.

Brain MRI with volumetric quantification: Table 4 shows the comparison between Group A and Group B with respect to how many subjects increased vs. decreased the volumes of the brain regions analyzed. These changes favored Group A (i.e., a greater percentage of the Group A subjects increased their regional volumes than did the Group B subjects) for gray matter, frontal lobes, temporal lobes, parietal lobes, occipital lobes, hippocampi, and cerebella; whereas they favored Group B for white matter and ventricles.

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Table 4. Number of subjects in each group showing increases vs. decreases in brain region volumes.

Brain Region	Group A Increase	Group A Decrease	Group B Increase	Group B Decrease	p-value	Odds Ratio
Gray Matter	20	20	7	15	0.167	**2.12**
White Matter	23	17	13	9	0.903	**0.94**
Lateral Ventricles	32	8	15	7	0.298	**1.85**
Frontal Lobes	19	21	5	17	0.055	**3.02**
Temporal Lobes	21	19	10	12	0.596	**1.32**
Hippocampi	23	17	12	10	0.822	**1.13**
Parietal Lobes	22	18	6	16	0.036	**3.20**
Occipital Lobes	25	15	11	11	0.340	**1.65**
Cerebella	27	13	10	12	0.090	**2.45**

Odds ratio > 1 means that Group A underwent more volume increases vs decreases than did Group B.

However, mean group changes in annualized rate of volume change showed no significant differences between groups (Table 5).

Table 5. Comparison of changes in brain volumes in various neuroanatomical regions in Group A vs. Group B.

Variable	Mean A (%)	SD A (%)	Mean B (%)	SD B (%)	p-value (Wilcoxon)
Gray Matter Vol / mTIV (rate)	−2.59	9.83	−1.30	7.52	NS
White Matter Vol / mTIV (rate)	0.026	19.9	0.868	6.47	NS
Lateral Ventricle Vol / mTIV (rate)	5.85	14.9	4.59	7.82	NS
Frontal Lobe Vol / mTIV (rate)	−2.08	8.65	−1.44	4.43	NS
Temporal Lobe Vol /mTIV (rate)	−1.50	8.92	−0.829	5.59	NS
Hippocampus Vol / mTIV (rate)	−0.578	9.68	1.32	9.48	NS

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Parietal Lobe Vol / mTIV (rate)	−1.60	7.59	0.311	6.33	NS
Occipital Lobe Vol / mTIV (rate)	−0.237	12.3	0.499	7.56	NS
Cerebellum Vol / mTIV (rate)	1.46	4.24	0.215	3.36	NS

mTIV: measured total intracranial volume. NS: not significant. SD: standard deviation. Vol: volume.

Epigenetics: Epigenetic studies were carried out on blood samples from both groups of subjects at t = 0 and t = 9 months, i.e., prior to treatment and at the end of the trial, as described above. Comparisons of the two groups (Group A, precision medicine protocol, and Group B, standard of care), and comparison of the before-treatment samples of each group to the completion-of-treatment samples from each group, revealed multiple differences, summarized below:

•Epigenetic indicators of aging revealed that the mortality clock, OMICmAge, was reduced in Group A by approximately 1.3 years ($p = 0.016$), but not in Group B, suggesting slower mortality-linked epigenetic aging in Group A.

•Synaptic plasticity increase was implied by an epigenome-wide association study (EWAS), which identified 14 protocadherin genes that were differentially methylated ($p < 10^{-17}$), arguing for modulation of synaptic specificity and neural circuit organization in Group A.

•Reduced systemic inflammation and neuroinflammation in Group A were indicated by reduction in multiple inflammatory markers, including TNFRSF17, EN-RAGE, OSM, VCAM1, and multiple cytokines.

•Convergent changes in glutathione-related metabolites, PON1, sphingomyelin species, and ornithine suggest enhanced antioxidant and detoxification capacity, vascular and nitric oxide signaling, and white matter integrity in Group A.

•Tryptophan-serotonin pathway markers, such as tryptophan betaine and indole butyrate, were consistent with shifts toward serotonergic signaling.

As noted above, given the small number of samples and unequal paired sample sizes (Group A: $n = 25$; Group B: $n = 13$), these analyses are considered to be exploratory and hypothesis-generating.

Biomarkers: Blood-based biomarkers p-tau 217, GFAP, NfL, and Aβ42/40 ratio were evaluated by Neurocode prior to treatment and again at the completion of the trial. Sixty-eight of the 73 subjects had an abnormal Aβ42/40 ratio (<0.170), two had a normal ratio, and three were early terminations that had no reported Aβ42/40 ratio. Analysis of p-tau revealed that 29 subjects had normal p-tau 217 (<0.34ng/L), whereas 41 did not: 21 were at a level that is strongly associated with amyloid accumulation (>0.63ng/L), 8 were at a level that is greater than 95% of amyloid-negative patients (0.48-0.63ng/L), and 12 were in the indeterminate range (0.34-0.47ng/L).

In Group A, p-tau 217 declined modestly, whereas in Group B it did not. Non-parametric within-group analyses revealed the precision medicine group had a significant reduction in p-tau-217 from baseline (p=.028, d=-0.71) whereas the standard of care within-group reduction did not reach significance (p=.234, d=-0.51). However, the magnitude of reduction in p-tau-217 between groups was not significant. That is, non-parametric comparison of the p-tau-217 change from baseline (Δ) between groups was statistically negligible (p=.609, d=-0.13).

However, this small difference may be amplified when weight changes are taken into account: it has been noted previously that obesity is associated with reduced blood-based biomarkers, including p-tau 217 and NfL [57]. In the current trial, several of the subjects in Group A lost weight of 10-30 pounds when they adopted a plant-rich, mildly ketogenic diet and began regular exercise; these same individuals demonstrated marked improvement in cognitive scores and symptoms, yet showed increased p-tau 217. In contrast, Group B subjects did not undergo weight loss similar to

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what occurred in Group A. Therefore, if the p-tau scores are normalized for any weight changes that occurred, the significance of the difference would likely be increased.

Overall, however, brain biomarker concentrations underwent little change during the study, and this may have been in part due to the offsetting associated with weight loss that occurred in Group A subjects, which could have compromised any biomarker improvements. None of the changes in Aβ42/40 ratio, GFAP, or NfL reached statistical significance. There was a slight increase in Aβ42 in Group A (136.4 ± 161.3→139.7 ± 138.4), with a slight reduction in Group B (169.3 ± 148.3→164.2 ± 143.3), but this was not significantly different. There was also a minimal decrease in GFAP in Group A (64.0 ± 29.8→57.5 ± 34.4), and minimal increase in Group B (50.7 ± 23.9→51.5 ± 20.1), but these differences were not statistically significant.

4. Discussion

The randomized controlled trial reported here compared the effects of a precision medicine approach to the standard of care in patients with mild cognitive impairment or early dementia (initial MoCA scores of 18 or higher). The magnitudes of effects, proportion of patients improved, and combinations of improvements observed here—in metabolic parameters, memory scores, executive function scores, overall cognitive indices, processing speed, cognitive symptoms, partner-judged cognitive status (AQ change), brain training scores (BrainHQ), and epigenetic profiles—have not been reported with any other treatment approach. Thus the overall results support the notion that a precision medicine approach to the cognitive decline of Alzheimer's disease at the mild cognitive impairment and early dementia stages is the most effective strategy reported to date. This is supported by a Forest Plot comparing the overall cognitive outcomes of randomized controlled trials of anti-amyloid antibodies or lifestyle interventions vs. the personalized precision medicine approach in the trial reported here (Figure 10). Furthermore, the approach used here did not lead to side effects such as brain edema, microhemorrhage, or atrophy, and instead improved overall health including blood pressure, body mass index, insulin sensitivity, fasting glucose, homocysteine, and lipid profiles.

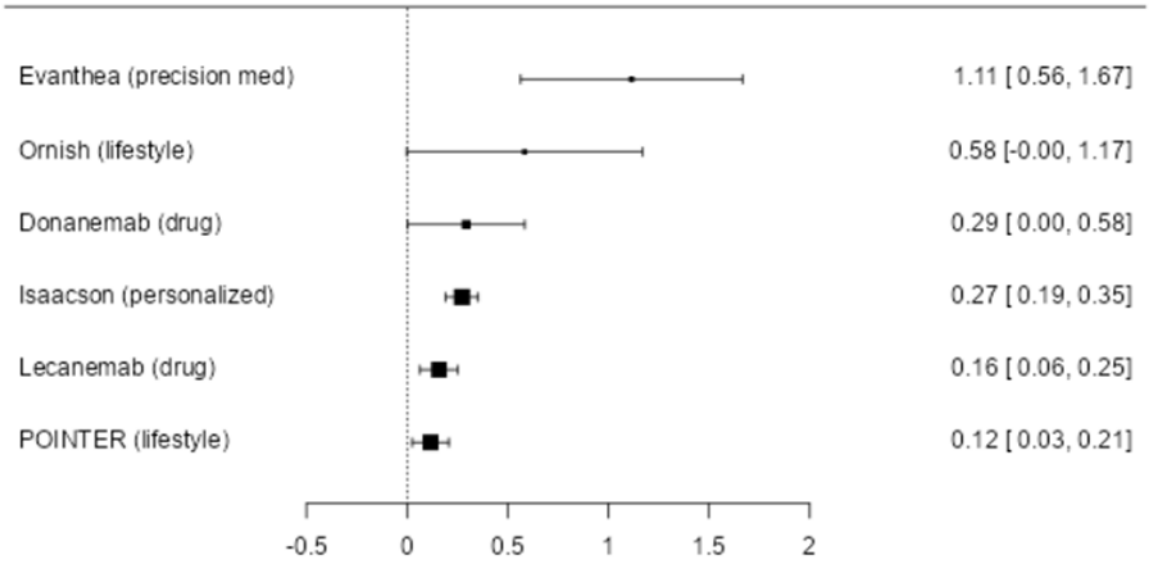

Figure 10. Forest plot comparing effect sizes on overall cognition outcomes in randomized controlled trials of anti-amyloid antibodies, lifestyle, or precision medicine. Standardized M difference [95% CI] displayed where values <0 favor the "placebo" condition and >0 favor the target intervention in each trial.

Because of the contribution of numerous systemic factors, a personalized, multimodal precision medicine approach to cognitive decline is necessarily a systems medicine approach. This therapeutic

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approach is distinct from traditional treatment strategies for MCI and Alzheimer's-related dementia, which have largely been monotherapeutic, monophasic, non-personalized, and blind, i.e., cause-independent, thus not targeted to the underlying drivers of the disease in each person, but rather to common downstream consequences and/or secondary drivers, such as amyloidosis. This is at least in part because Alzheimer's disease remains a disease of controversial etiology, with many competing theories, none of which has led to effective treatment when addressed in isolation. The dominant theory over the past three decades has been the amyloid cascade hypothesis [58], but numerous antibodies targeting the associated amyloid have failed to improve cognition (although a trial that failed to improve cognition or halt decline nevertheless slowed decline by 32% [2]).

The strategy utilized in this study also differs from preventive management of Alzheimer's disease risk factors [59], a strategy whose interventions are derived from statistical associations rather than individual network diagnostics, and whose main purpose is to delay rather than to halt and reverse cognitive decline, although the two strategies are compatible in ideology and complementary in practice.

The positive results from the randomized controlled trial reported here, along with similar results from the two proof-of-concept trials referenced above, are compatible with the notion that Alzheimer's disease represents a complex network insufficiency. Therefore, multifactorial optimization of network function and support offers a rational therapeutic strategy. It might be argued that the strategy utilized for this trial targets associated biochemical pathways but not necessarily causal ones. However, both the utilization of genomics to help identify underlying causal factors and the cognitive, epigenetic, and overall health improvements documented in this study argue that at least some of the biochemical targets addressed are indeed causal. Moreover, due to the small-world nature of biochemical and signaling networks, targeting a sufficient number of associated pathways is likely to impact the causal ones, even if indirectly. Nonetheless, it will be important for future studies to continue to dissect and prioritize the targeted interventions in order to develop an optimal protocol for each individual.

5. Limitations of the Study

There are several limitations inherent to the trial reported here, as well as obvious concerns. One limitation is that the trial was not double-blind, due to the difficulty in blinding subjects to significant lifestyle changes. The neuropsychology and neuroimaging assessments were blinded, but the subjects and physicians' treating teams were not.

A second limitation is that it did not address patients with intermediate stage or advanced Alzheimer's disease: potential trial patients with MoCA scores of 17 and lower were excluded from this study, and therefore, although there are anecdotal reports of patients with such scores showing improvement with a similar precision medicine approach [14], the current study offers no insight into the treatment of patients in that group. In treating patients who had mild cognitive impairment or early-stage dementia, this trial focused on a similar group to those treated in recent pharmaceutical trials [2,60].

One potential concern regarding the positive results is whether they may simply be due to practice effects, and indeed the MoCA scores suggested a learning effect, since they did not correlate with reported symptoms, brain training analyses, epigenetic results, or the more sensitive computer-based testing.

However, the marked improvements in CNS Vital Signs scores make practice effects an unlikely explanation for the overall results: (i) the CNS Vital Signs testing has been designed to minimize such effects, and this has been demonstrated experimentally [18]; (ii) the 3-month interval in CNS Vital Signs testing renders practice effects less likely than shorter duration intervals; (iii) the magnitude of the effects is incompatible with practice effects, which are typically much more modest; (iv) the AQ-C score improvements provided confirmation of the increased cognitive scores; (v) the cognitive symptom tracker scores and the PROMIS-10 results provided further confirmation of the increased cognitive scores.

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A previously reported precision medicine approach to cognitive decline [61] showed no significant improvement in those with MCI or dementia, arguing at least superficially against the results reported here. However, that study was more modest in both the evaluation and treatment protocols employed—for example, many of the pathogens and toxins evaluated and treated in the current study were not addressed in that study—and therefore, it is possible that success with such an approach requires identifying and targeting the many potential contributors to cognitive decline, as opposed to restricting the therapy to a more limited subset.

A third limitation is that none of the subjects had spinal fluid analysis or amyloid PET scans, raising the question of how many had Alzheimer's-associated pathology. However, the blood-based biomarkers were compatible with early-stage Alzheimer's pathophysiology: 68 of the 70 tested had abnormal plasma Aβ42:40 ratios (<0.170), and 41 of the 70 tested had plasma p-tau 217 levels higher than normal. This does not exclude the possibility that some of the patients in the study could have had non-Alzheimer pathology, but it supports the conclusion that the protocol used is effective for patients with Alzheimer's pathophysiology, at least those with MoCA scores of 18 and higher.

A fourth limitation is that, although both biochemical parameters (as shown in Table 2)—such as those reflecting insulin sensitivity, glycation, vascular risk, and methylation—and cognitive tests improved, this study provides no proof that the cognitive amelioration was caused by the metabolic enhancements. However, the application of artificial intelligence methods to similar data sets from larger studies may be capable of identifying candidate causal relationships.

Fifth, the patients who responded to the trial announcement and became trial participants were only a modestly diverse group racially and ethnically. Therefore, the trial results reported here may or may not prove to be applicable to non-Caucasian patients.

Sixth, although cognitive scores improved markedly, MRI volumetrics did not show any significant difference between the two treatment groups. Furthermore, although p-tau showed a significant decline in the treatment group, other Alzheimer-related biomarkers–Aβ42/40 ratio, GFAP, and NfL–showed no significant differences between groups.

There was a single severe adverse event (SAE) during the nine months of the study, which was deemed to be unrelated to treatment: a subject in the precision medicine protocol treatment group developed chest pain and hypotension during exercise, and underwent cardiac catheterization, which revealed 60% narrowing of the left anterior descending coronary artery. However, his cardiologist did not recommend intervention, and he had no further problems. A second SAE occurred after a patient in the standard-of-care group had completed his nine months in the trial. All standard-of-care patients were offered six months of treatment with the precision medicine protocol that had been followed by Group A during the trial, and one patient who elected to follow this post-study treatment died in his sleep. Autopsy results revealed significant coronary artery disease and the death was declared a cardiac death, unrelated to the treatment protocol (although he did exercise as part of the treatment protocol, he had been an avid exerciser for many years, so this did not represent a change for him).

Most patients improved their overall health (Table 2, Table 3, Figs. 3-4), and unpublished observations show that some patients will no longer require antihypertensives, antidiabetes drugs, or lipid-lowering agents, as they address the contributors to cognitive decline. This is compatible with the approach of identifying and targeting the root cause contributors to cognitive decline, improving resilience and overall health.

Finally, this study confirms and extends anecdotal reports and previous proof-of-concept trials by showing once again that it is possible to reverse cognitive decline in MCI and early dementia with a personalized, precision medicine (/systems medicine/functional medicine) protocol, but it does not show that it is practical to do so. The analysis involved is more comprehensive than is currently in use in memory centers, the data sets collected more extensive, the behavioral alterations required of the patients more demanding, the time required by the team of practitioners greater, and the cost significant (although far less than an assisted living facility or anti-amyloid antibodies, which are both much more costly and less effective). Further refinement and simplification of the protocol may

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render it more feasible, accessible, affordable, and ultimately, reimbursable. Furthermore, given the recognized biochemical targets of the interventions, novel pharmaceutical agents may become a critical part of an optimal protocol, and, in a complementary fashion, future trials of new drug candidates may enjoy more successful outcomes when conducted in the context of precision medicine protocols.

The results of this randomized controlled trial support the performance of a larger, randomized, double-blind, placebo-controlled clinical trial, which will require the utilization (and in some cases, development) of various therapeutic entities, including lifestyle factors, that mimic those shown to be effective but exert only a placebo effect.

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