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. Personalized, precision medicine approaches represent a potentially effective strategy, and proof-of-concept trials have provided supportive data. **Objective:** To determine whether a precision medicine approach to Alzheimer's 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 were evaluated for biochemical, microbiological, genetic, epigenetic, and imaging parameters associated with cognitive decline, then assigned randomly to a precision medicine approach or standard of care treatment. **Results:** Statistically significant effects of the precision medicine approach were observed for overall neurocognitive functioning (d=1.12; 95% CI, 0.56-1.66; p<0.001), memory (d=0.94; 95% CI, 0.40-1.46; p<0.001), executive function (d=0.89; 95% CI, 0.35-1.43; p=0.001), processing speed (d=0.67; 95% CI, 0.14-1.19; p=0.012), self-reported cognitive symptom severity (d=-1.05; 95% CI, -1.60, -0.49, p<0.001), and partner-reported cognitive symptom severity (d=1.26; 95% CI, 0.70-1.81; p<0.001), with MoCA scores showing a trend to improvement (p=0.154). Furthermore, overall health was enhanced, with improvements in blood pressure, body mass index, glycemic index, lipid profiles, and methylation status. Treatment effect size on overall cognitive function exceeded previous trials, being 2-3 times larger than effects of lifestyle interventions and 4-7-times larger than those of anti-amyloid therapies. **Conclusion:** A personalized, precision medicine

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approach represents an effective treatment for patients with mild cognitive impairment or early-stage dementia. This treatment improves cognition and overall health rather than simply retarding decline, without significant negative side effects such as brain edema, microhemorrhage, or atrophy.

Trial registration: Clinicaltrials.gov Identifier: NCT05894954 (https://clinicaltrials.gov/study/NCT05894954)

Keywords: Alzheimer's disease; mild cognitive impairment; cognition; randomized controlled clinical trial; systems medicine; precision medicine; neurodegeneration

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 AD in the United States, and one study estimated that it has become the third leading cause of death. [1] Unfortunately, therapeutic approaches to date have not led to sustainable improvements, and the best results from 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 AD remains controversial, with many competing theories, such as the theory that AD is "type 3 diabetes". [6] Other theories implicate chronic *Herpes simplex* infection, [7] amyloid-β, [8] misfolded proteins such as tau, [9] or prions. [10] 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 AD, 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.

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 (PM) approach [17] to a control group that received standard-of-care (SOC) treatment. [18] Treatment was carried out for nine months, with 50 patients randomized to the PM approach and 23 to the SOC treatment. The number of subjects chosen was based on the treatment effect observed 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

Of 139 patients screened for trial participation eligibility, 66 (47%) failed the screening, over half of which was due to clinical and/or cognitive scores outside of the criteria presented below (see Figure 1 for flowchart summarizing patient selection and Supplemental Table S1 for detailed screening

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failure reasons). 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, and randomized to either the PM approach or SOC treatment arm. The random codes as well as the replacement random codes for this study were generated from Proc Plan based on the 2:1 randomization (PM:SOC) with specific seed numbers using SAS version 9.4 software. This resulted in treatment arm *n*'s of PM=50 and SOC=23.

Seven patients from the PM treatment arm prematurely dropped out of the study (three of which were due to issues or concerns with compliance with the intervention, two related to study partner health issues, and two related to participant voluntary decision to discontinue). Demographics and primary cognitive endpoints at baseline were comparable between precision medicine patients who dropped out and completed the study (Supplemental Table S2). Six participants were homozygous for ApoE4, 26 were heterozygous for ApoE4, 30 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*=66)**	**Precision medicine (*n*=43)**	**Standard of care (*n*=23)**	***p***	**Effect size**
Age, *M* (*SD*)	65.2 (7.7)	65.4 (7.5)	64.7 (8.2)	.736	*d*=0.09
Education, *M* (*SD*)	16.3 (2.9)	16.0 (3.0)	16.8 (2.7)	.252	*d*=-0.30
Education, *n* (%)	--	--	--	.498	*V*=.190
High school or less	6 (9.1)	5 (11.6)	1 (4.3)	--	--
Some college	14 (21.2)	8 (18.6)	6 (26.1)	--	--
College graduate	25 (37.9)	18 (41.9)	7 (30.4)	--	--
Post-graduate	21 (31.8)	12 (27.9)	9 (39.1)	--	--
Sex, *n* (%)	--	--	--	.305	φ=-.156
Female	42 (63.6)	25 (58.1)	17 (73.9)	--	--
Male	24 (36.4)	18 (41.9)	6 (26.1)	--	--
Race, *n* (%)	--	--	--	.277	*V*=.242
White	61 (92.4)	41 (95.3)	20 (87.0)	--	--
Black	1 (1.5)	0 (0.0)	1 (4.3)	--	--
Asian	3 (4.5)	2 (4.7)	1 (4.3)	--	--
Not reported	1 (1.5)	0 (0.0)	1 (4.3)	--	--
Ethnicity, *n* (%)	--	--	--	.933	*V*=.046
Not Hispanic	56 (84.8)	37 (86.0)	19 (82.6)	--	--
Hispanic	5 (7.6)	3 (7.0)	2 (8.7)	--	--
Not reported	5 (7.6)	3 (7.0)	2 (8.7)	--	--
ApoE alleles, *n* (%)	--	--	--	.562	V=.212
ε2/ε3	4 (6.1)	3 (7.0)	1 (4.3)	--	--
ε2/ε4	1 (1.5)	0 (0.0)	1 (4.3)	--	--
ε3/ε3	30 (45.5)	21 (48.8)	9 (39.1)	--	--
ε3/ε4	25 (37.9)	16 (37.2)	9 (39.1)	--	--
ε4/ε4	6 (9.1)	3 (7.0)	3 (13.0)	--	--

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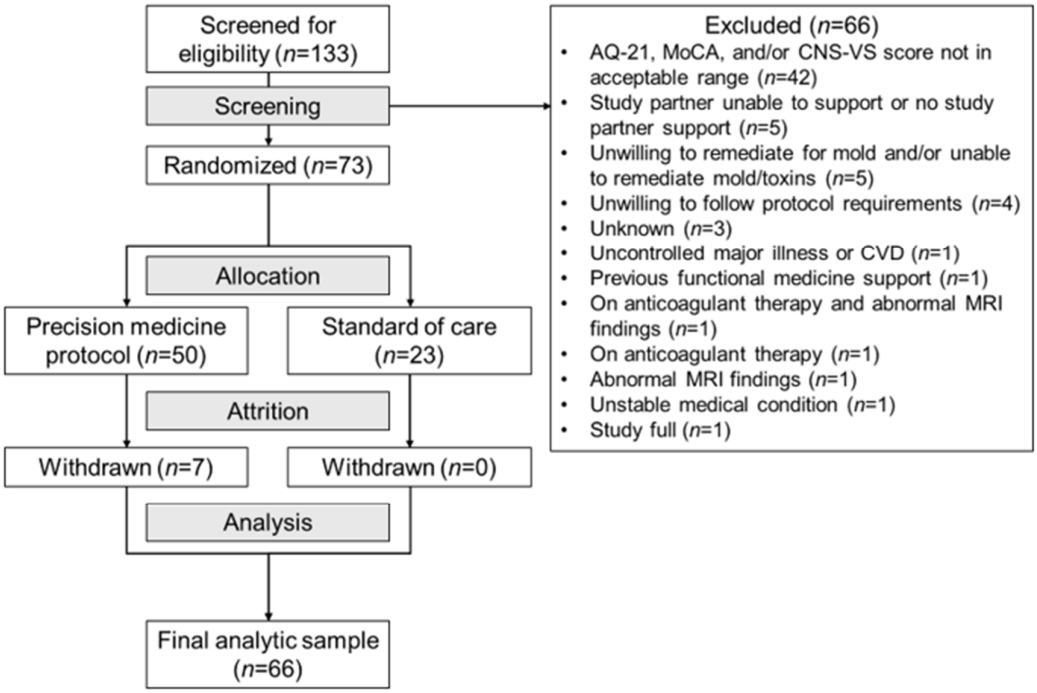

Figure 1. Flowchart of participant screening and allocation.

Inclusion criteria. Age 45-76 years; cognitive impairment, as demonstrated by complaints of cognitive decline plus a combination of Alzheimer's Questionnaire (AQ-21) >4 and either Montreal Cognitive Assessment (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. MoCA score <18 at baseline; uncontrolled major medical illness such as seizures, cardiovascular disease, cancer diagnosis 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 use of psychoactive medications known to impact cognition; ongoing anticoagulant therapy or history of 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; pregnancy; diagnosis of a neurodegenerative disease other than Alzheimer's (e.g., frontotemporal dementia); previous or ongoing treatment for MCI or dementia with the PM approach 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 environmental toxicity (e.g., mycotoxins); or unwillingness to forgo alcohol (other than up to two small servings weekly of dry red wine).

Measures

Cognitive functioning. Standard physical and neurological examinations were performed on each patient. Trained external raters (i.e., unaffiliated with the treatment teams) performed and

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assessed the MoCA remotely. The MoCA is a brief cognitive screener that covers domains of executive functioning, visuoconstruction, attention, language, memory, and orientation. [19] It is scored out of 30 points with higher scores indicating better global mental status. Version 8.1 was administered at baseline, 8.2 at three months, 8.3 at six months, and 8.1 at nine months.

Next, neuropsychological assessment batteries were performed at the study sites using CNS Vital Signs (CNS VS), a computerized neuropsychological assessment. The reliability and validity of this battery have been described in previous publications, [20] and this assessment tool has been demonstrated to be more sensitive than the MoCA in the identification of MCI. [21] 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 (i.e., NCI, neurocognitive index). CNS VS scores are reported as Standard Scores such that a score of 100 indicates the 50th percentile, with a standard deviation of 15.

The MoCA and CNS VS NCI were the primary independent outcome measures for this trial. Secondary endpoints included CNS VS Executive Functioning, CNS VS Composite Memory, discontinuation rate, safety, and symptom assessments described below.

Symptom assessment. The AQ-21 is an informant-based subjective assessment with sensitivity and specificity for amnestic MCI and AD of over 90%, [22] answered by the study partner (usually the significant other), 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 MCI, 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. The Alzheimer's Questionnaire change scale (AQ-C) is a subjective change scale that is derived from the AQ-21. It is informant-based (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).

We also utilized the Cognitive Symptom Tracker (CST), a structured, patient-reported clinical 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 (see Appendix A for CST items). In clinical practice, longitudinal changes in CST 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 exploratory tool was applied in the trial to quantify subjective cognitive performance and complement objective outcomes in this precision-medicine intervention vs. standard of care.

In addition, the Patient-Reported Outcomes Measurement Information System-10 (PROMIS-10) [23] developed by the NIH was used to determine subjective estimates of physical health (PROMIS-P) and mental health (PROMIS-M).

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. [24–26]

The BrainHQ test battery included two assessments, Double Decision and Syllable Stacks, and took approximately six minutes to complete [1]. Double Decision evaluates visual speed of processing and cholinergic network health. [26] 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

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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. [24]

Genetics. 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.

Epigenetics. Epigenetic testing was carried out by TruDiagnostic (Lexington, KY). Please see Appendix B in the Supplementary Materials for a detailed description of epigenetics procedures.

Biochemical and microbiological testing. Biochemical and biomarker tests were performed to identify indicators of insulin resistance (HOMA-IR), protein glycation (hemoglobin A1c), vascular disease (advanced lipid panel), systemic inflammation (C-reactive protein, fibrinogen, homocysteine), iron status, 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)*, *Rickettsia rickettsii*, *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, and nocturnal hypoxemia (oximetry for three nights to identify sleep apnea and upper airway resistance syndrome). AD biomarkers p-tau 217, Ab42/40 ratio, glial fibrillary acidic protein (GFAP), and neurofilament light chain (NfL) were evaluated by Neurocode using single molecule assay (SIMOA) technology and, for p-tau 217, the ALZpath antibody.

Neuroimaging. Magnetic resonance imaging (MRI) of the brain with volumetrics (Neuroquant or 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 (at four sites) or 1.5-Tesla (at two sites) with either MPRAGE or SPGR sequences. Segmentation and quantification of the hippocampus and total gray matter were carried out computationally, as described previously. [27] Volumetric change over the 9-month time 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.

Treatment Procedures

Patients were treated for nine months with either a standard-of-care protocol [18] or a personalized, precision medicine protocol that addressed each patient's identified potentially

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contributory factors, [17] 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 AD.

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. The precision medicine protocol used 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. [28]

Exercise. Both aerobic and strength training exercise, as well as balance training and stretching, were 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. 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. 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, [29] chosen because of the ease of patient use and thus high compliance.

Brain training. Brain training was carried out using BrainHQ (Posit Science, San Francisco, CA), an evidence-based online cognitive training program that is compliant with HIPAA and SOC-2 security standards. [30] 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, [31] cognitive performance, [32] and everyday functioning. [33] 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, [34] 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,

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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 participants 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 T-regulatory cells to regulate immune function, reducing autoimmune responses. [35]

Infectious agents. Those 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 [36] such as *Borrelia*, *Babesia*, or *Bartonella*, organism-sensitive treatment was prescribed with herbal antimicrobials, such as Cryptolepis and Japanese knotweed [37] 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, [38] 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), neurofeedback (two sites), and frequent QEEGs to guide adjunctive therapies (one site).

Statistical Analysis for Neurocognitive, Clinical, and Biomarker Outcomes

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. To assess the incremental effect of the precision medicine intervention on the primary (MoCA, CNS VS NCI) and secondary (AQ, PROMIS) outcomes, repeated measures general linear models (GLM) were constructed. We also repeated this process for other clinical/cognitive outcomes: BrainHQ, CST, and CNS VS subdomains. This allowed for testing treatment x time interaction effects between intervention assignment (PM vs. SOC treatment) 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,

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biochemical and AD biomarker variables were analyzed using non-parametric analyses (Wilcoxon signed-rank tests for evaluating 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). [39] We also interpreted the size of effects using Cohen's guidelines for d (small=0.20, medium=0.50, large=0.80) and η_p^2 (small=.01, medium=.06, large=.14). [40] Level of significance (α) was set to .05 (two-tailed).

Trial Safety

Adverse events (AE) and serious adverse events (SAE) were categorized using the Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. [41] The CTCAE is a standardized, comprehensive medical terminology rating system derived from the Medical Dictionary for Regulatory Activities for coding AE and SAE. These events were reported by site investigators and compiled by the project manager.

Results

There were no between-group baseline differences in demographic characteristics, including APOE genotyping (Table 1).

Metabolic Effects

Table 2 lists metabolic parameters prior to, and at the conclusion of, the 9 months of treatment. Relative to the SOC group, the PM group evidenced a statistically superior reduction in glycation (as a reduction in hemoglobin A1c) and insulin resistance (as HOMA-IR, homeostasis model assessment-estimated insulin resistance). Significant incremental improvements in lipid profile (as reduction in triglyceride-to-high-density-lipoprotein ratio), body mass index (BMI), systolic blood pressure, and methylation (as reduction in homocysteine) were also observed. Lastly, a significant increase in serum vitamin D was observed (as serum 25-hydroxycholecalciferol) in the precision medicine group. Whereas the PM group evidenced significant positive change from baseline in most biochemical markers, the only change observed for the SOC group was an increase in BMI over the study period.

Cognitive Function and Clinical Symptom Outcomes

Table 3 presents descriptive statistical information for cognitive and clinical outcomes over the study period (months 0 [baseline], 3, 6, and 9), as well as GLM findings. Table 4 provides detailed statistics for within-group change from baseline and between-group comparison of such. The AQ-C is a subjective change scale that is derived from the AQ-21. In the PM group, the AQ-C improved by 8.74 ± 10.35 points, whereas in the SOC group, the AQ-C declined by 2.36 ± 4.41 points, indicating that the partners of the PM group noted improvement, whereas those of the SOC group noted decline. The AQ-C GLM model interaction term was statistically significant and yielded a practically meaningful large effect ($p<0.001$, $\eta_p^2=.211$). AQ-C results are graphed in Figure 2. Similarly, the CST change differed between the two groups, reflecting improvement in the PM group but only minimal improvement in the SOC group, with a p-value<0.001 and an incremental effect size of $d=0.231$ (Figure 3 and Table 4). The GLM model interaction was statistically significant and yielded a clinically meaningful large effect ($p<0.001$, $\eta_p^2=.231$). PROMIS-10-Physical Health (Figure 4) and PROMIS-10-Mental Health (Figure 5) also showed significant improvements, with significant and large magnitude GLM model interaction effects $p=0.002$ ($\eta_p^2=.193$) and $p<0.001$ ($\eta_p^2=.212$), respectively.

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Table 2. Serum biochemical tests, BMI, and blood pressure prior to, and following, treatment for 9 months in the precision medicine protocol group vs. the standard of care group.

			Δ within group		Δ between groups	
Variable, Med (IQR)	**Month 0**	**Month 9**	**Median (IQR)**	***d*[a]**	**Med dif**	***d*[b]**
Precision medicine						
Vitamin D (25-OH)	43.2 (23.3)	62.9 (20.8)	22.6 (30.5)	**1.74‡**	24.7	**0.87‡**
hsCRP	1.0 (1.8)	0.6 (1.3)	-0.1 (3.8)	-0.34	0.0	-0.02
Fasting glucose	95.0 (12.0)	91.0 (8.0)	-5.0 (10.0)	**-0.91†**	-4.0	-0.30
HDL cholesterol	65.0 (27.0)	72.0 (26.0)	3.0 (10.5)	0.60‖	3.0	0.27
HbA1c	5.5 (0.3)	5.3 (0.3)	-0.2 (0.3)	**-2.01‡**	-0.3	**-1.18‡**
Homocysteine	11.0 (4.2)	7.7 (3.8)	-2.0 (3.1)	**-2.01‡**	-2.6	**-0.85†**
Fasting insulin	5.9 (5.3)	5.0 (4.9)	-1.1 (3.3)	**-0.82†**	-1.4	-0.47‖
Total cholesterol	213.5 (53.0)	204.0 (74.0)	-2.5 (63.5)	-0.23	1.5	0.12
Triglycerides	75.0 (44.0)	61.0 (29.0)	-14.5 (36.8)	**-1.07†**	-18.5	**-0.61†**
Vitamin B12	650.0 (418.0)	1421.0 (891.0)	654.0 (851.0)	**2.28‡**	680.0	**1.02‡**
HOMA-IR	1.4 (1.3)	1.1 (1.1)	-0.3 (0.8)	**-1.04†**	-0.32	-0.42‖
TG:HDL ratio	1.2 (1.1)	0.9 (0.7)	-0.3 (0.5)	**-1.09†**	-0.34	**-0.57†**
BMI	24.0 (6.4)	22.4 (5.5)	-1.2 (3.1)	**-1.60‡**	-1.7	**-1.30‡**
Systolic BP	122.0 (25.0)	118.0 (17.0)	-9.0 (22.0)	**-1.00†**	-7.0	-0.45‖
Diastolic BP	73.0 (11.0)	70.0 (9.0)	-5.0 (15.0)	**-0.84†**	-1.0	-0.22
Standard of care						
Vit. D (25-OH)	44.6 (25.3)	51.7 (35.7)	-2.1 (18.2)	0.10	--	--
hs-CRP	0.9 (2.4)	0.7 (1.9)	-0.1 (1.4)	-0.29	--	--
Fasting glucose	94.0 (14.0)	93.0 (12.0)	-1.0 (11.0)	-0.36	--	--
HDL cholesterol	62.0 (37.0)	61.0 (28.0)	0.0 (12.5)	0.04	--	--
Hgb A1c	5.7 (0.3)	5.7 (0.4)	0.1 (0.3)	0.50	--	--
Homocysteine	9.3 (3.2)	9.7 (3.3)	-0.4 (3.5)	-0.22	--	--
Fasting insulin	6.3 (6.7)	7.3 (6.3)	0.3 (5.0)	0.29	--	--
Total cholesterol	222.0 (61.0)	218.0 (51.0)	-4.0 (38.0)	-0.17	--	--
Triglycerides	82.0 (37.0)	89.0 (65.0)	4.0 (55.0)	0.35	--	--
Vit. B12	873.5 (760.0)	913.5 (968.0)	-26.0 (223.0)	-0.30	--	--
HOMA-IR	1.5 (1.9)	1.6 (1.6)	0.02 (1.2)	0.13	--	--
TG:HDL ratio	1.5 (1.3)	1.7 (1.2)	0.04 (0.9)	0.28	–	–
BMI	24.0 (7.0)	24.8 (6.5)	0.5 (0.8)	1.83*	--	--
Systolic BP	122.0 (22.5)	126.0 (23.5)	-2.0 (18.5)	0.20	--	--
Diastolic BP	74.0 (11.5)	73.0 (12.0)	-4.0 (14.5)	-0.43	--	--

‡$p \leq .001$, †$p < .05$, ‖$p \leq .10$ *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. Statistically significant effect sizes (*d*) appear **bold**. HbA1c: hemoglobin A1c; 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); HsCRP, high-sensitivity C-reactive protein. IQR: interquartile range; TG:HDL ratio: serum triglyceride-to-HDL (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.

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

Variable, *M* (*SD*)	Timepoint (month)				Group x timepoint interaction[c]		
	0	3	6	9	*F*	*p*	η_p^2
Precision medicine							
NCI	92.1 (12.2)	99.6 (10.5)	103.8 (8.9)	106.2 (8.1)	21.08	**<.001**	**.260**
CM	88.4 (15.1)	95.4 (17.2)	100.4 (15.9)	101.6 (17.0)	17.92	**<.001**	**.224**
EF	91.2 (16.0)	99.6 (15.9)	103.2 (13.2)	108.0 (10.8)	11.25	**.001**	**.154**
PS	103.5 (13.0)	107.6 (16.0)	111.0 (13.3)	116.1 (15.7)	6.98	**.010**	**.103**
BrainHQ	32.8 (11.7)	--	--	58.2 (20.5)	6.98	**.011**	**.111**
AQ*	10.5 (3.3)	2.7 (5.1)	5.93 (7.3)	8.7 (10.4)	16.34	**<.001**	**.211**
CST	49.7 (28.1)	35.4 (25.5)	24.8 (22.6)	16.4 (21.4)	15.94	**<.001**	**.231**
PROMIS-P	49.9 (6.5)	51.7 (6.6)	52.8 (6.0)	55.1 (6.1)	11.02	**.002**	**.193**
PROMIS-M	47.3 (6.5)	49.6 (8.5)	50.2 (6.4)	54.1 (6.3)	12.41	**<.001**	**.212**
MoCA	23.8 (2.4)	24.9 (3.3)	25.8 (3.1)	27.6 (2.5)	2.08	.154	.032
Standard of care							
NCI	96.9 (6.7)	95.7 (13.5)	96.1 (11.9)	92.4 (24.2)	--	--	--
CM	92.9 (14.1)	91.4 (17.8)	88.8 (14.1)	87.5 (21.9)	--	--	--
EF	96.4 (10.1)	93.0 (21.5)	97.8 (13.7)	97.7 (20.7)	--	--	--
PS	103.9 (11.9)	103.0 (13.0)	103.9 (13.6)	106.4 (16.1)	--	--	--
BrainHQ	33.1 (10.4)	--	--	42.4 (18.9)	--	--	--
AQ*	9.5 (3.2)	-1.3 (2.4)	-0.9 (5.7)	-2.4 (4.4)	--	--	--
CST	51.6 (27.5)	48.1 (25.3)	46.2 (21.2)	47.0 (25.8)	--	--	--
PROMIS-P	52.0 (8.2)	50.4 (6.8)	51.4 (9.4)	52.3 (7.5)	--	--	--
PROMIS-M	46.3 (5.8)	47.5 (6.5)	46.8 (6.5)	46.4 (6.5)	--	--	--
MoCA	22.9 (3.0)	23.7 (3.5)	24.1 (4.0)	25.5 (4.0)	--	--	--

*AQ for month 0 (screening) is AQ-21 (higher=more symptomatic) whereas subsequent months are AQ-20 (AQ change, higher=improvement; see methods), 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. The group x timepoint interaction findings were obtained from general linear models. Significant *p*-values and effect sizes appear **bold**.

Table 4. Within-group change from baseline and comparison of change between groups for primary neurocognitive and clinical outcomes.

	Within-group Δ from baseline						Between-group difference in Δ from baseline		
	Precision medicine			Standard of care					
Variable	***M* Δ**	***d* (95% CI)**	***p***	***M* Δ**	***d* (95% CI)**	***p***	***M* diff**	***d* (95% CI)**	***p***
NCI	14.0	1.23 (0.82, 1.63)	**<.001**	-4.4	-0.19 (-0.61, 0.24)	.392	18.4	1.12 (0.56, 1.66)[b]	**<.001**
CM	13.1	0.73 (0.39, 1.06)	**<.001**	-5.4	-0.24 (-0.65, 0.18)	.266	18.5	0.94 (0.40, 1.46)	**<.001**
EF	16.9	1.19 (0.79, 1.58)	**<.001**	1.8	0.09 (-0.33, 0.50)	.692	15.0	0.89 (0.35, 1.43)	**.001**
PS	12.3	0.85 (0.50, 1.20)	**<.001**	2.5	0.17 (-0.25, 0.58)	.427	9.7	0.67 (0.14, 1.19)	**.012**
BrainHQ	25.2	1.27 (0.84, 1.68)	**<.001**	10	0.54 (0.03, 1.02)	**.036**	14.8	0.75 (0.17, 1.32)	**.011**
AQ[a]	8.7	--	--	-2.4	--	--	11.1	1.26 (0.70, 1.81)	**<.001**
CST	-33.3	-1.19 (-1.59, -0.79)	**<.001**	-5	-0.20 -0.63, 0.23)	.369	-28.3	-1.05 (-1.60, -0.49)	**<.001**
PROMIS-P	5.4	0.77 (0.43, 1.12)	**<.001**	0.1	0.02 (-0.40, 0.43)	.939	5.3	0.77 (0.23, 1.30)	**.005**
PROMIS-M	6.7	0.93 (0.57, 1.29)	**<.001**	0.4	0.07 (-0.35, 0.49)	.750	6.3	0.97 (0.42, 1.51)	**<.001**
MoCA	3.8	1.52 (1.07, 1.95)	**<.001**	2.6	0.67 (0.21, 1.12)	**.004**	1.2	0.41 (-0.11, 0.92)	.121

AQ: Alzheimer's Questionnaire; BrainHQ: Brain Health Test Battery; CM: Composite Memory (CNS VS); CST: Cognitive Symptom Tracker; EF: Executive Function (CNS VS); MoCA: Montreal Cognitive Assessment; NCI: Neurocognitive Index (CNS VS); 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 from CNS VS. Significant p-values appear **bold**. [a]Δ from baseline score reflects *M* (*SD*) AQ-20 change (AQ-C) at month 9. [b]Levene's test indicated non-equality of group variances for NCI Δ. The incremental effect remained significant and robust after adjusting for these group differences in variance (Glass's delta=0.79). Significant *p*-values appear **bold**.

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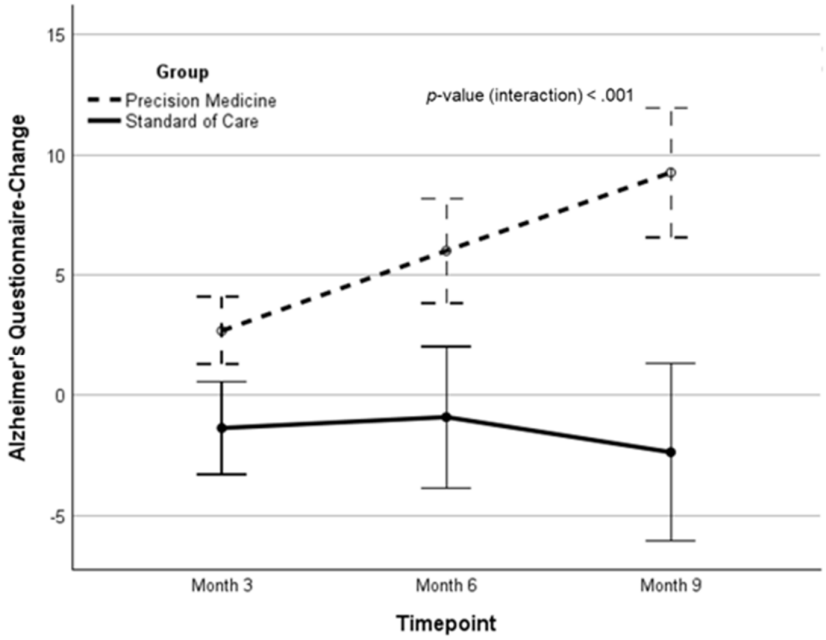

Figure 2. Line graph of AQ-Change scores (higher values = improved symptoms; time zero = zero by definition, since it is a change score) over time with lines separated by group. Error bars depict 95% CI.

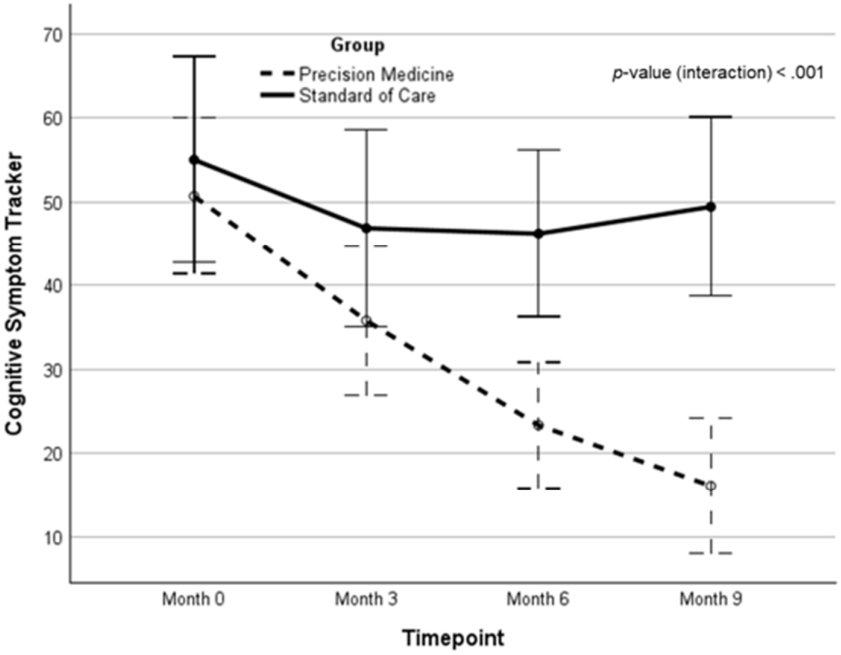

Figure 3. Line graph of cognitive symptom tracker (CST) scores (higher = worse symptoms) over time with lines separated by group. Error bars depict 95% CI.

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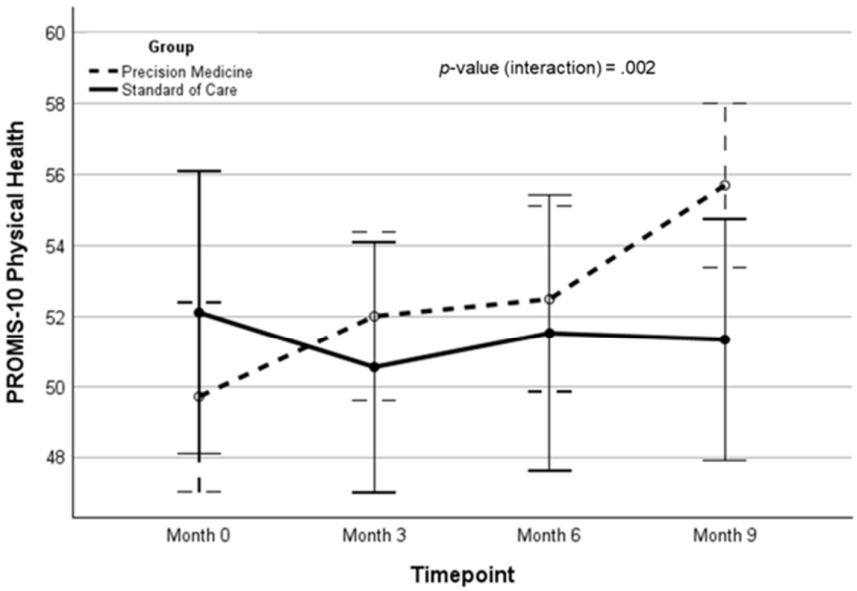

Figure 4. PROMIS-10 Physical Health results in precision medicine (broken line) and standard of care (solid line) groups. Higher numbers indicate better symptoms.

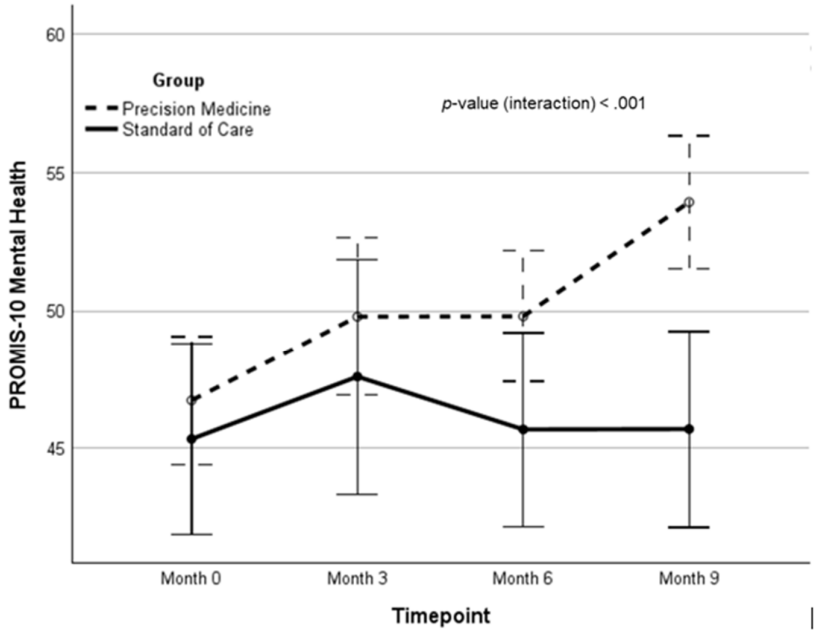

Figure 5. PROMIS-10 Mental Health scores over time with lines separated by group. Higher numbers indicate better symptoms. Error bars depict 95% CI.

In summary, for clinical symptom outcomes, the SOC group showed no significant change from baseline. In contrast, the PM group demonstrated statistically *and* clinically meaningful improvement across self- and other-reported symptom outcome measures (*d* ranging from 0.77 to 1.19) that exceeded changes in the SOC group (incremental *d* values ranging from 0.77 to 1.26; Table 4).

Figure 6 displays the NCI means over the study period and 95% confidence intervals for each group. Comparing the results at outset to those at completion revealed an improvement in the NCI from 92.0 ± 12.3 to 106.2 ± 8.1 in the PM group, whereas there was a decline in the SOC group from 96.9 ± 6.7 to 92.4 ± 24.2 (p<0.001). In turn, the GLM interaction term yielded a large and clinically important effect (η_p^2=.260).

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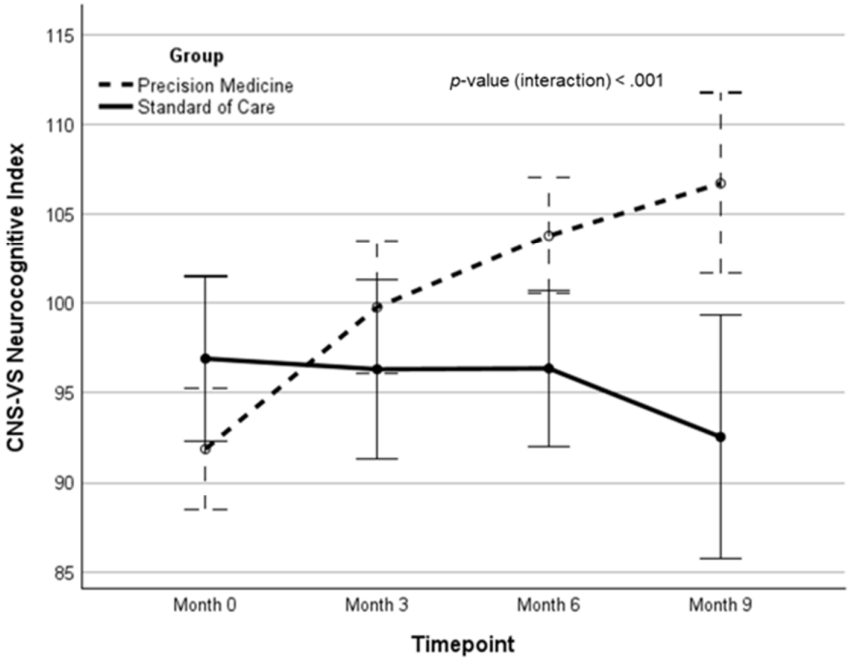

Figure 6. Line graph of CNS-VS NCI composite scores over time with lines separated by group. Error bars depict 95% CI.

Composite memory scores over the study period are shown in Figure 7. The PM group improved by approximately one standard deviation (14.0 ± 11.4), whereas the SOC group declined by 5.4 ± 22.7 (p<0.001 with large and clinically meaningful effect size of η_p^2=.224).

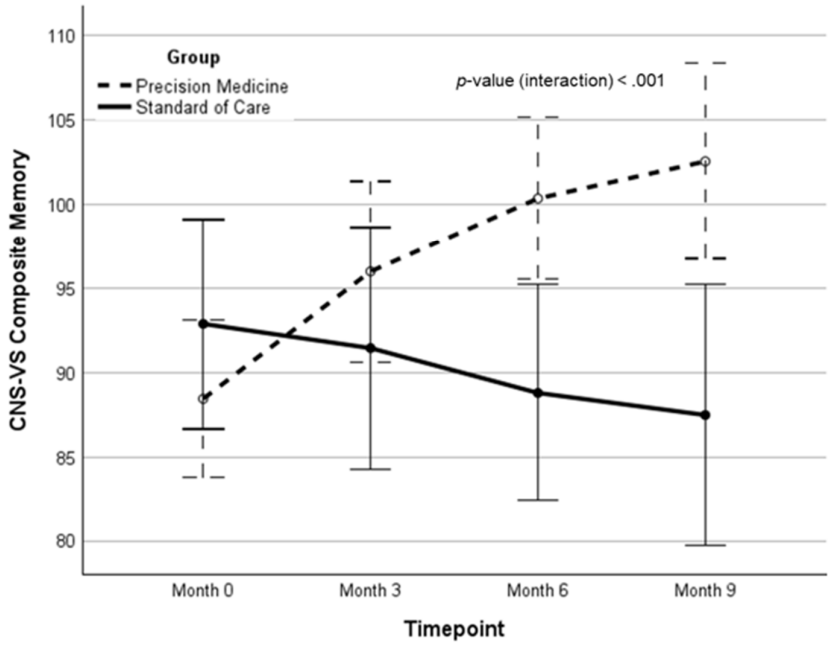

Figure 7. Line graph of CNS-VS composite memory scores (verbal memory + visual memory) over time with lines separated by group. Error bars depict 95% CI.

Executive function scores (Figure 8) also showed an approximately one standard deviation improvement in the PM patients (16.9 ± 14.2), whereas there was little change in the SOC patients (1.8

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± 21.3). The GLM interaction term was significant (p=0.001) and yielded a large and clinically significant effect size (η_p^2=.154).

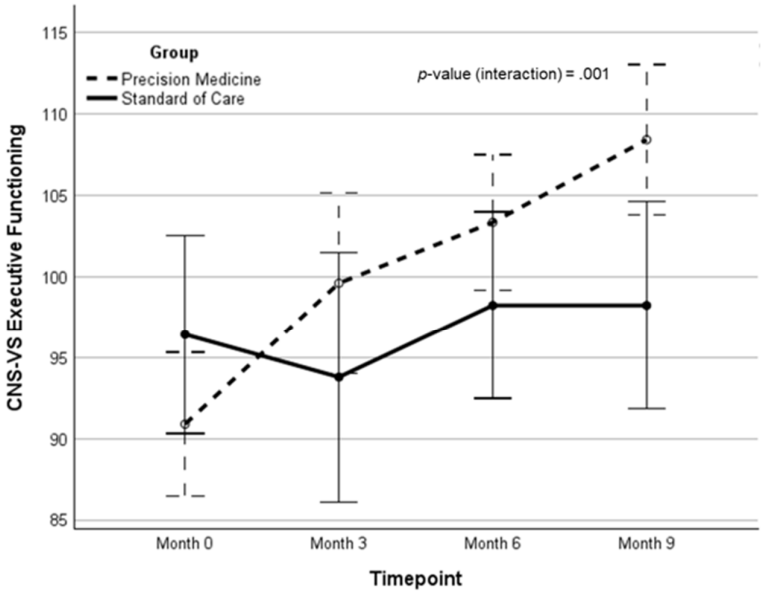

Figure 8. Line graph of CNS-VS executive function scores over time with lines separated by group. Error bars depict 95% CI.

The GLM model for processing speed indicated a significant group x time interaction (Figure 9), with the PM group improving from 103.5 ± 13.0 to 116.1 ± 15.7 points, whereas the SOC group improved more modestly, from 103.9 ± 11.9 to 106.4 ± 16.1 (p=0.010, η_p^2=.103). The CNS VS NCI and composite (memory and executive function) effects were both clinically meaningful and large in magnitude. Processing speed effect was also practically significant and medium-to-large in magnitude.

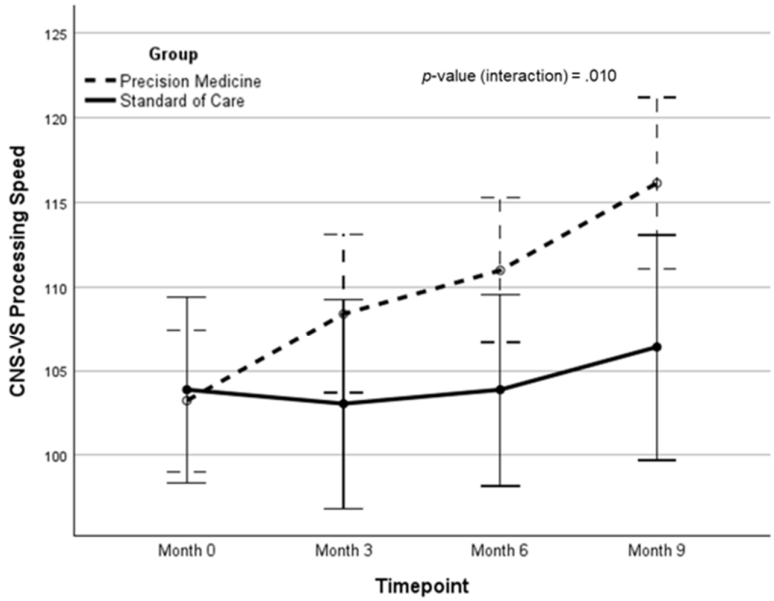

Figure 9. Line graph of CNS-VS processing speed over time with lines separated by group. Error bars depict 95% CI.

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Supplemental Table S3 presents GLM models and change-from-baseline statistics for other CNS VS subtasks (beyond processing speed). GLM model interaction terms were significant for all subtests including verbal memory (p=0.020, η_p^2=.087), visual memory (p<0.001, η_p^2=.201), psychomotor speed (p=0.002, η_p^2=.145), reaction time (p=0.001, η_p^2=.155), complex attention (p=0.003, η_p^2=.139), cognitive flexibility (p<0.001, η_p^2 =.171), simple attention (p=0.043, η_p^2 =.066), and motor speed (p=0.018, η_p^2=.090), all of which showed significantly greater improvement in the PM group. These effects were both clinically significant and medium to large in magnitude. Supplemental Table S4 shows change-from-baseline statistics for each group on the CNS VS subtests. The PM group significantly improved from baseline on all subtests except for visual memory (p=0.061) and simple attention (p=0.115). The only significant change from baseline in the SOC group was visual memory, which declined by about 12 standard score points (p=0.024). Between-group comparison of change-from-baseline statistics indicated the PM group had significantly greater improvements on all subtests than the SOC group. These incremental effects were all clinically meaningful and ranged from medium to large magnitude (incremental d values ranging from 0.57 to 0.93).

The GLM interaction for the MoCA revealed only a trend that did not reach statistical significance (p=0.154, η_p^2=.032). While both groups' MoCA performances significantly increased over the study period, there was a non-significant trend of greater improvement in the PM (3.8 ± 2.5 points) than SOC (2.6 ± 3.8 points) group by 0.41 *SD* units (95% CI, -0.11 to 0.92; Figure 10).

To summarize, the CNS VS primary outcome measures all significantly (p-values<0.001) and clinically meaningfully improved over the study period for the PM group (d ranging from 0.73 to 1.23) whereas there were no significant changes in the SOC group. Conversely, broad neurocognitive and composite memory performances declined from baseline in the SOC group. In turn, the PM improvements far exceeded SOC group changes (incremental d values ranging from 0.67 to 1.12; Table 4). Importantly, these CNS VS effects were virtually all large in magnitude. MoCA scores showed a weak trend favoring the PM group but the incremental effect of PM beyond SOC did not reach statistical significance.

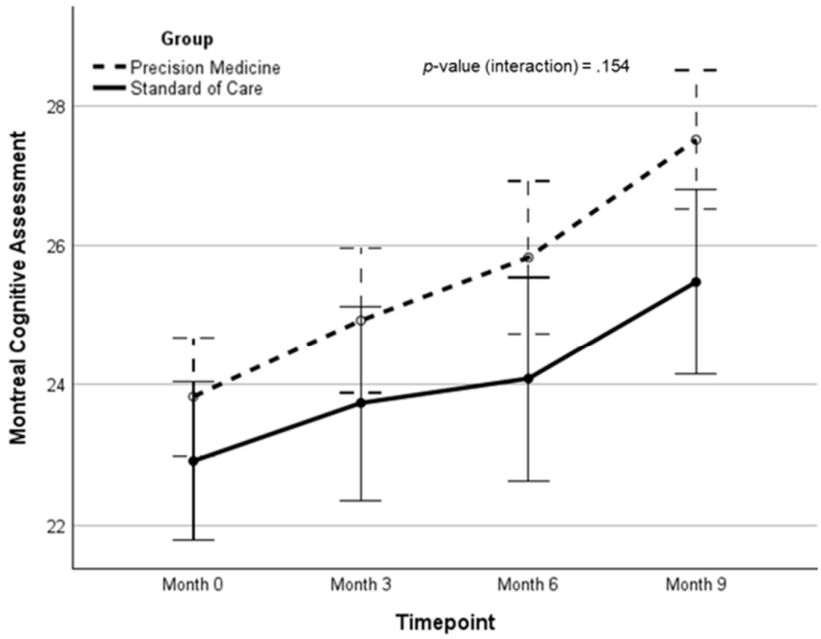

Figure 10. Line graph of MoCA scores over time with lines separated by group. Error bars depict 95% CI.

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Brain Training

Although BrainHQ was implemented as an intervention (for the PM group only), participants' performance trajectories within the platform provided 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 period (range: 15 minutes-164 hours).

The results also revealed a statistically and clinically significant group x timepoint interaction that approached large magnitude (p=0.011, η_p^2=.111). The PM group had greater improvement on the BrainHQ assessment composite by 0.75 *SD* units than the SOC group (95% CI, 0.17 to 1.32; Table 4 and Figure 11).

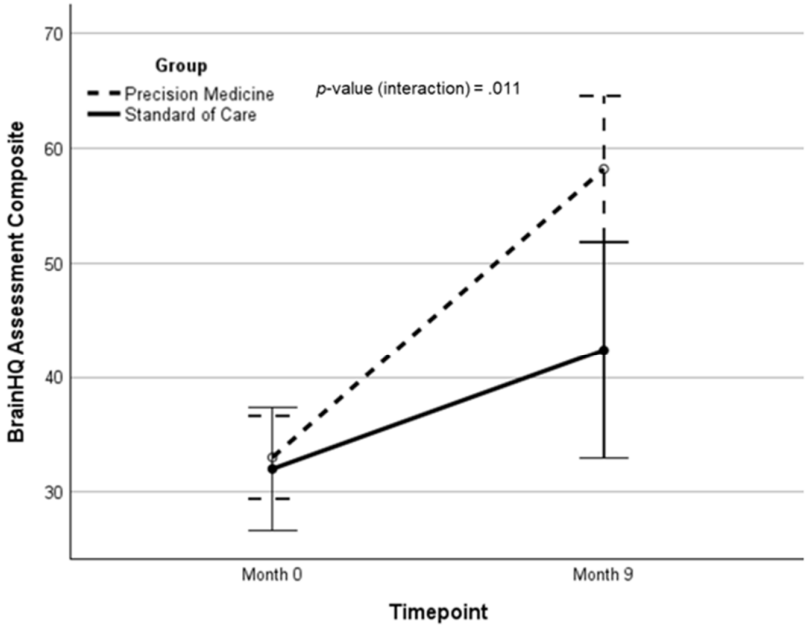

Figure 11. Line graph of BrainHQ scores over time with lines separated by group. Error bars depict 95% CI.

Brain MRI with Volumetric Quantification

Supplemental Table S5 shows the comparison between PM and SOC groups with respect to how many subjects increased vs. decreased the volumes of the brain regions analyzed. These changes favored the PM group (i.e., a greater percentage of the PM subjects increased their regional volumes than did the SOC subjects) for gray matter, frontal lobes, temporal lobes, parietal lobes, occipital lobes, hippocampi, and cerebella; whereas they favored SOC for white matter and ventricles. However, mean group changes in annualized rate of volume change showed no significant differences between groups (Supplemental Table S6).

Epigenetics

Epigenetic studies were carried out on blood samples from both groups of subjects at timepoint = 0 and timepoint = 9 months, as described above. Comparisons of the two groups, and comparison of the before-treatment samples of each group to the completion-of-treatment samples from each group, revealed multiple differences. First, epigenetic indicators of aging revealed that the mortality clock, OMICmAge, was reduced in the PM group by approximately 1.3 years (p=0.016), but not in the SOC group, suggesting slower mortality-linked epigenetic aging in the PM group. Second, synaptic

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plasticity increase was implied by an epigenome-wide association study (EWAS), which identified 14 protocadherin genes ($p<10^{-}$ [17]) that were differentially methylated, arguing for modulation of synaptic specificity and neural circuit organization in the PM group. Third, reduced systemic inflammation and neuroinflammation in the PM group were indicated by reductions in multiple inflammatory markers, including TNFRSF17, EN-RAGE, OSM, VCAM1, and multiple cytokines. Fourth, 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 the PM group. Fifth, tryptophan-serotonin pathway markers, such as tryptophan betaine and indole butyrate, were consistent with shifts toward serotonergic signaling. Given the small number of samples and unequal paired sample sizes (PM: n=25; SOC: n=13), these analyses are considered to be exploratory and hypothesis-generating.

Biomarkers of AD

Blood-based biomarkers p-tau 217, GFAP, NfL, and Aβ42/40 ratio were evaluated prior to treatment and again at the completion of the trial (Table 5). Sixty-four of the 66 subjects had an abnormal Aβ42/40 ratio (<0.170) at baseline, and two had a normal ratio. Analysis of p-tau revealed that 25 subjects had normal p-tau 217 (<0.34ng/L) at baseline, 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).

Table 5. Neuropathologic biomarker data at baseline and final visits, change statistics within group, and comparison of change between groups.

	Month		Δ within group[a]			Δ between groups[b]		
Variable, Med (IQR)	0	9	Median Δ	*d*	*p*	Median diff	*d*	*p*
Precision medicine	--	--	--	--	--	--	--	--
Aβ42/40	0.09 (0.02)	0.09 (0.02)	0.00	-0.13	.673	0.002	0.08	.741
p-tau 217	0.42 (0.68)	0.41 (0.71)	0.00	**-0.71**	**.028**	0.00	-0.13	.609
NfL	16.67 (11.20)	18.09 (12.80)	-0.29	-0.01	.986	-0.11	-0.04	.882
GFAP	51.35 (36.15)	45.30 (32.25)	-5.45	-0.63	.051	-8.55	-0.44	.084
Standard of care	--	--	--	--	--	--	--	--
Aβ42/40	0.09 (0.03)	0.09 (0.02)	-0.002	-0.28	.512	--	--	--
p-tau 217	0.46 (0.64)	0.41 (0.43)	0.00	-0.51	.234	--	--	--
NfL	18.98 (11.87)	18.06 (9.67)	-0.18	-0.03	.903	--	--	--
GFAP	42.00 (43.70)	52.30 (25.80)	3.10	-0.23	.584	--	--	--

Aβ42/40: Amyloid Beta 42/40 ratio; GFAP: glial fibrillary acidic protein; IQR: interquartile range; NfL: neurofilament light chain; p-tau217: phosphorylated tau 217. [a]Cohen's *d* and *p*-values estimated from Wilcoxon signed-rank tests to compare median Δ's (computed as month 9 – month 0 with negative and positive values indicating decline and increase in lab values, respectively) within each group. [b]Cohen's *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. Significant effect size and *p*-values appear **bold**.

In the PM group, p-tau 217 declined modestly, whereas in the SOC group it increased slightly. Non-parametric within-group analyses revealed the PM group had a significant reduction in p-tau-217 from baseline (p=0.028, d=-0.71) whereas the SOC within-group reduction did not reach significance (p=0.234, 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=0.609, d=-0.13).

None of the changes in Aβ42/40 ratio, GFAP, or NfL reached statistical significance. There was a slight increase in Aβ42 in the PM group (baseline: 136.4 ± 161.3, follow-up: 139.7 ± 138.4), with a slight reduction in the SOC group (baseline: 169.3 ± 148.3, follow-up: 164.2 ± 143.3), but this was not significantly different. There was also a minimal decrease in GFAP in the PM group (baseline: 64.0 ± 29.8, follow-up: 57.5 ± 34.4), and minimal increase in the SOC group (baseline: 50.7 ± 23.9, follow-up: 51.5 ± 20.1), but these differences were not statistically significant.

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Safety

Supplemental Table S7 presents AE information. There were 146 reported AEs of which 76 (52%) were assessed by the respective site principal investigator as likely, probably, or possibly related to the PM approach. The most common AE system organ class was "gastrointestinal disorders" (33%), defined as mild to moderate diarrhea (most common symptom), nausea, vomiting, stomach/abdominal pain, dyspepsia and colitis. The second most common AE class was "general disorders and administration site conditions" (16%) most of which were mild or moderate in nature and were defined as detoxification or keto flu symptoms, fatigue, brain freeze sensation, and non-cardiac chest pain. The tied third most common AE class was "investigations" (9%), characterized as mild and moderate lab changes (anemia; creatinine, lab function test, and white blood cell increases), and "reproductive system and breast disorders" (9%), characterized by mild to moderate severity events mostly related to irregular menstruation. There was one SAE reported, which was deemed not related to the intervention.

Discussion

The randomized controlled trial reported here compared the effects of a PM approach to the SOC in patients with MCI or early dementia (initial MoCA scores of 18 or higher). The magnitudes of cognitive 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-C), 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 PM approach to the cognitive decline of AD at the MCI 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 [2,42] or lifestyle interventions [43] vs. the personalized PM approach used in the trial reported here (Figure 12) and in one prior study [44] (see Appendix C in the Supplementary Material for methods on how the forest plot was generated; note: the forest plot comparison is illustrative and cross-compares trials using different instruments for cognitive assessment, albeit evaluating patients with similar degrees of impairment). 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, and lipid profiles.

The strength of this effect was similar if not stronger to what was seen in the proof-of-concept study. Two of the practice sites participated in the proof-of-concept study and there were four new sites that participated in this study, all of whom have been delivering this type of care in the real world.

We generally did not observe significant effects across brain biomarker assays in this nine-month trial. However, the trends noted above (i.e., that p-tau-217 was slightly reduced in the PM group but brain biomarker concentrations generally underwent little change over the study) may be underestimated when weight changes are considered. It has been noted previously that obesity is associated with reduced blood-based biomarkers, including p-tau 217 and NfL. [45] In the current trial, several of the subjects in the PM approach group lost weight of 10-30 pounds when they adopted a plant-rich, mildly ketogenic diet and began regular exercise, as well as the rest of the PM approach; these same individuals demonstrated marked improvement in cognitive scores and symptoms, yet showed increased p-tau 217. In contrast, SOC subjects did not undergo weight loss similar to what occurred in the PM group. Therefore, if the p-tau scores are normalized for any weight changes that occurred, the significance of the difference would likely be increased. Future lines of research will be important to clarify the utility of adjusting p-tau for weight metrics. Because of the contribution of numerous systemic factors, a personalized, multimodal PM approach to cognitive decline is necessarily a systems medicine approach. This therapeutic approach is distinct from traditional treatment strategies for MCI and Alzheimer's-related dementia, which have largely been

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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 AD 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, [46] 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]

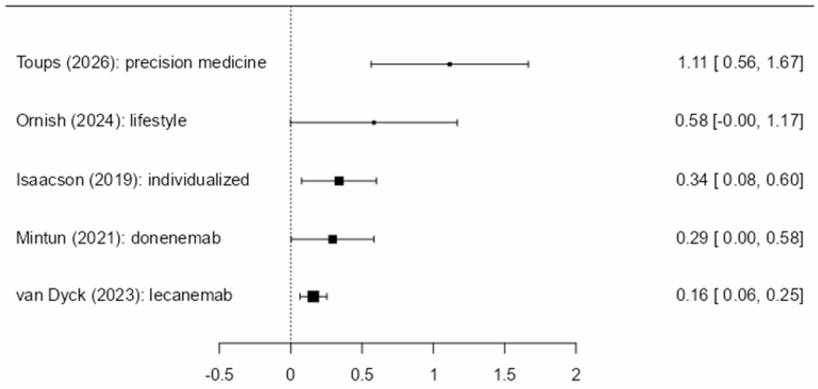

Figure 12. Forest plot comparing effect sizes on overall cognition outcomes in published randomized controlled trials of anti-amyloid antibodies, lifestyle, or precision medicine (Toups 2026 being the current trial). Standardized mean difference (i.e., Cohen's *d*) [95% CI] is displayed where values <0 favor the "placebo" condition and >0 favor the target intervention in each trial. See Appendix C in the supplementary materials for detailed description of methods, data, and outcomes used to generate this forest plot.

The strategy utilized in this study also differs from preventive management of AD risk factors, [47] 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 AD 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.

The current trial is compatible with previous trials in revealing a discordance between amyloid reduction and cognitive impact: anti-amyloid antibody therapy has documented marked reduction in amyloid burden without cognitive improvement (although a modest slowing of decline has been observed), whereas the current study documented significant improvement in multiple cognitive parameters, while the minimal effect on p-tau 217 suggests little if any change in amyloid burden. This raises the possibility of combining the two approaches, with the goal of improving cognition and reducing amyloid burden.

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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. Furthermore, by nature of the PM approach, patients in this trial received substantially more attention from treating clinicians thereby introducing an attention bias that could not be controlled

A second limitation is that it did not address patients with intermediate stage or advanced AD: 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 PM approach, [16] the current study offers no insight into the treatment of patients in that group. In treating patients who had MCI or early-stage dementia, this trial focused on a similar group to those treated in recent pharmaceutical trials. [2,42]

One potential concern regarding the positive results on cognitive testing is whether they may simply be due to practice effects. The CNS VS test was constructed to minimize practice effects, and the most robust effects were seen on these outcomes. [20] However, the MoCA scores suggested a learning effect which has been reported in recent literature. [48] Since the MOCA scores did not correlate with reported symptoms, brain training analyses, epigenetic results, and the more sensitive computer-based testing. If practice effects were present, both groups received the same number of serial assessments which may mitigate this factor. Even if all cognitive test gains were due to mere practice effects, this does not explain the PM group's consistently revealing greater gains ("a stronger practice effect") across these endpoints. Indeed, mounting literature conceptualizes practice effects as a potentially useful marker of neurocognitive health. [49]

However, the marked improvements in CNS VS scores make practice effects an unlikely explanation for the overall results: (i) the CNS VS testing has been designed to minimize such effects, and this has been demonstrated experimentally; [21] (ii) the 3-month interval in CNS VS 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.

A previously reported PM approach to cognitive decline [44] 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: 64 of the 66 patients had abnormal Aβ42/40 ratios (<0.170), and 41 of the patients had 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. In a separate vein, epigenetic analyses were statistically underpowered given the attenuated subsamples with available data.

A fourth limitation is that, although both biochemical parameters (as shown in Table 2)—such as those reflecting vascular risk, glycation, and methylation—and cognitive tests improved, this study provides no proof that the cognitive amelioration was caused by the metabolic enhancements.

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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. 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, AD biomarkers showed trends to improvement that did not reach statistical significance.

Seventh, we acknowledge selection bias introduced by baseline data from some outcomes (MoCA and CNS VS) having been used to include or exclude participants. In turn, participant selection was not fully independent of the outcome measures. That being said, this approach has been used in prior trials and was used to remove asymptomatic or severely impaired participants (at baseline) to mitigate floor/ceiling effects and optimize the ability to capture change over the study period. As a consequence, our findings may best generalize to those with mild to moderate AD clinical severity. As participants were randomized into treatment arms after this selection step, the internal validity of our findings is upheld. Nevertheless, we recognize that future trials should be careful to use screening tools that are independent of key study outcomes. Another bias that pervades interventional research, including in wellness studies, is participation bias. [50] That is, the participants were willing to do a significant amount of work to improve their health. Such participants may relate closer to others in wellness interventions rather than the general population. While this bias may reduce applicability to the general population, it is also likely that this bias created a SOC group susceptible to less decline than historical controls.

Eighth, adaptive functioning (e.g., activities of daily living) was not formally assessed, which is an important variable for differential diagnosis of MCI and dementia. That being said, baseline MoCA and AQ-21 scores in our RCT participants were all compatible with the degree of impairment being within the MCI to early-stage dementia phase.

We also acknowledge that the current study design precluded sensitivity analysis to test comparative efficacy of the various components of the PM approach. This remains a critical area for future PM research.

With respect to safety, there were no severe adverse events (SAE) during the nine months of the study. However, after the completion of the treatment period for both groups, a SAE occurred after a patient in the standard-of-care group had completed treatment. All SOC patients were offered six months of treatment with the PM approach after completing the trial's nine months of the SOC, 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).

Despite these limitations, most patients improved their overall health (Tables 2 and 3, Figures 4 and 5), and unpublished observations show that some patients will no longer require antihypertensives, antidiabetes drugs, or lipid-lowering agents, once 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, PM (/systems medicine/functional medicine) approach, 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 render it more feasible, accessible, affordable, and ultimately, reimbursable. Furthermore, given the

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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 PM approaches.

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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Declaration of conflicting interests: S. Hausman-Cohen is a founder of IntellxxDNA. K. Burke is a founder of TruNeura. D. Bredesen consults for Apollo Heath and Life Seasons. None of these for-profit entities had any role in study design, data collection, data analysis, data interpretation, writing the report, or providing any funding for the study. Life Seasons produces a brain health product, which was used at a single site in this study. None of the clinical trial data were shared with any corporation or for-profit entity prior to public availability.

Supplementary Materials: The following supporting information can be downloaded at: Preprints.org.

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