A Clinical Precision Medicine Approach Reduces Alzheimer's, Dementia and Vascular Risk and Improves Cognition:

A Prospective Cohort Study from the Alzheimer's Prevention Clinic at Weill Cornell Medicine and NewYork-Presbyterian

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Background

The Alzheimer's Prevention Clinic provides direct clinical care to patients who receive evidence-based, individualized early interventions applying principles of pharmacogenomics, nutrigenomics and clinical precision medicine.

Objectives

Our primary outcome measure was change in six AD, dementia, and vascular risk scales in response to multi-modal interventions. Secondary outcome measures include overall and differential effectiveness of interventions on blood biomarkers and cognition (based on genotype and physician & patient-reported adherence).

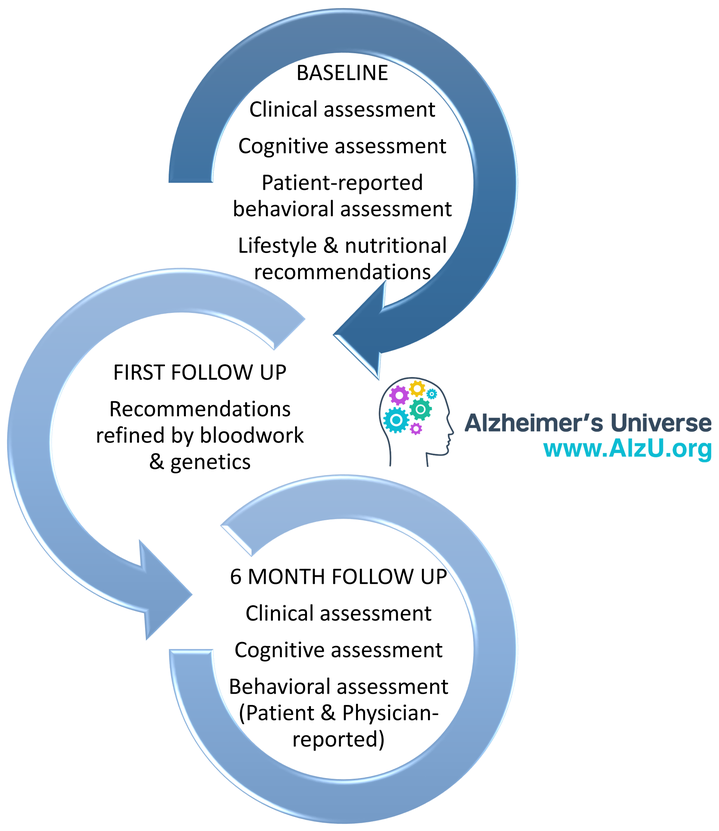
Study Design & Participants

This prospective cohort study includes patients with family history of AD and no or minimal cognitive complaints, and preclinical AD or MCI. 168 participants met inclusion criteria (mean age 63 ±14.6, 50.6% female). Using SPSS, paired sample t-tests were computed to compare changes in risk scales in subjects with blood biomarker data at baseline and six-months. Changes in blood biomarkers were compared using ANOVA within and across different genotype and adherence groups. Multiple repeated-measured general linear models were computed to compare changes in cognition per genotype and adherence. NIH Toolbox cognitive scores were corrected for age, gender, ethnicity, and education to account for multiple comparisons across groups.

Measures

Clinical assessment	• Visit with neurologist & neurological exam • Anthropometrics: vital signs/biometric assessment • Laboratory measures: blood biomarkers and genetics
Cognitive assessment	• *Traditional tests:* MMSE; FAS; ANT; Trails B; Boston Naming • *NIHTB-CB tests:* RAVLT Auditory Verbal Learning (Trials 1-3); RAVLT Delayed Recall & Recognition; Dimensional Change Card Sort (DDCS); Flanker Inhibitory Control and Attention; Pattern Comparison Process Speed; Odor Identification; Oral Symbol Digit (OSD); Picture Vocabulary; Oral Reading Recognition
Lifestyle & nutritional recommendations	• Preliminary evidence-based multi-modal lifestyle recommendations in accordance with clinical history: nutritional, exercise, cognitive training, social stimulation (Isaacson 2016, Ngandu 2015), stress reduction (Katz, 2016), sleep maintenance (Yaffe, 2014), hyperinsulinemia reduction (Luchsinger, 2014) • Recommendations refined based on clinical measures (see Biomarker-Intervention Paradigm below)
Behavioral assessment	• Adapted MIND-DIET questionnaire (Patient-reported) • Rapid Assessment of Physical Activity (RAPA) (Patient-reported) • Adherence to recommendations (Physician-reported & Patient-reported)
Education via AlzU.org	• Evidence-based course on AD prevention • Interactive lessons and activities throughout

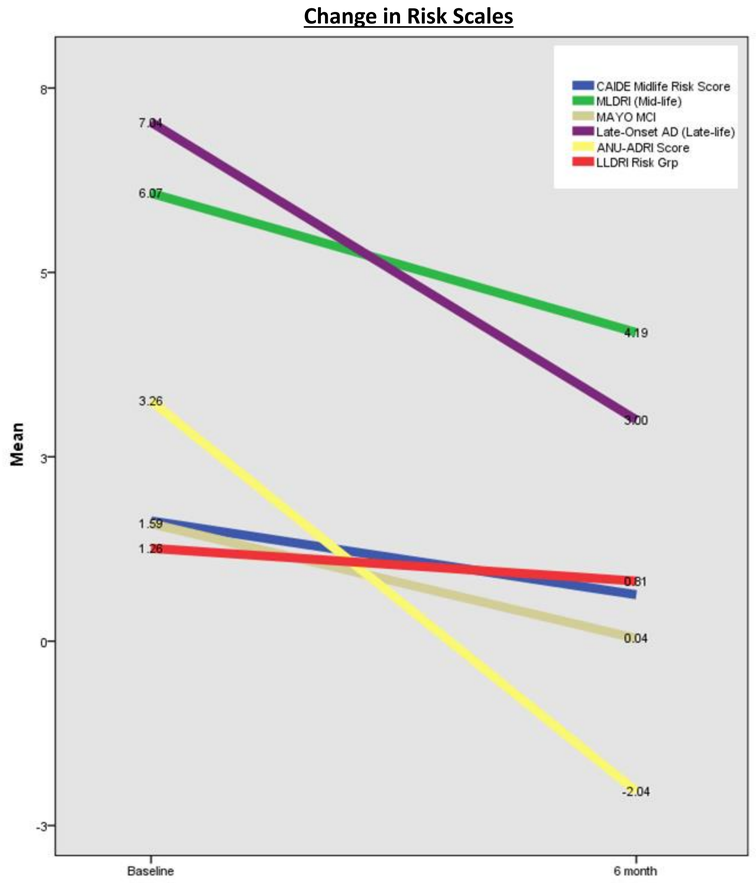
Study Design Continued



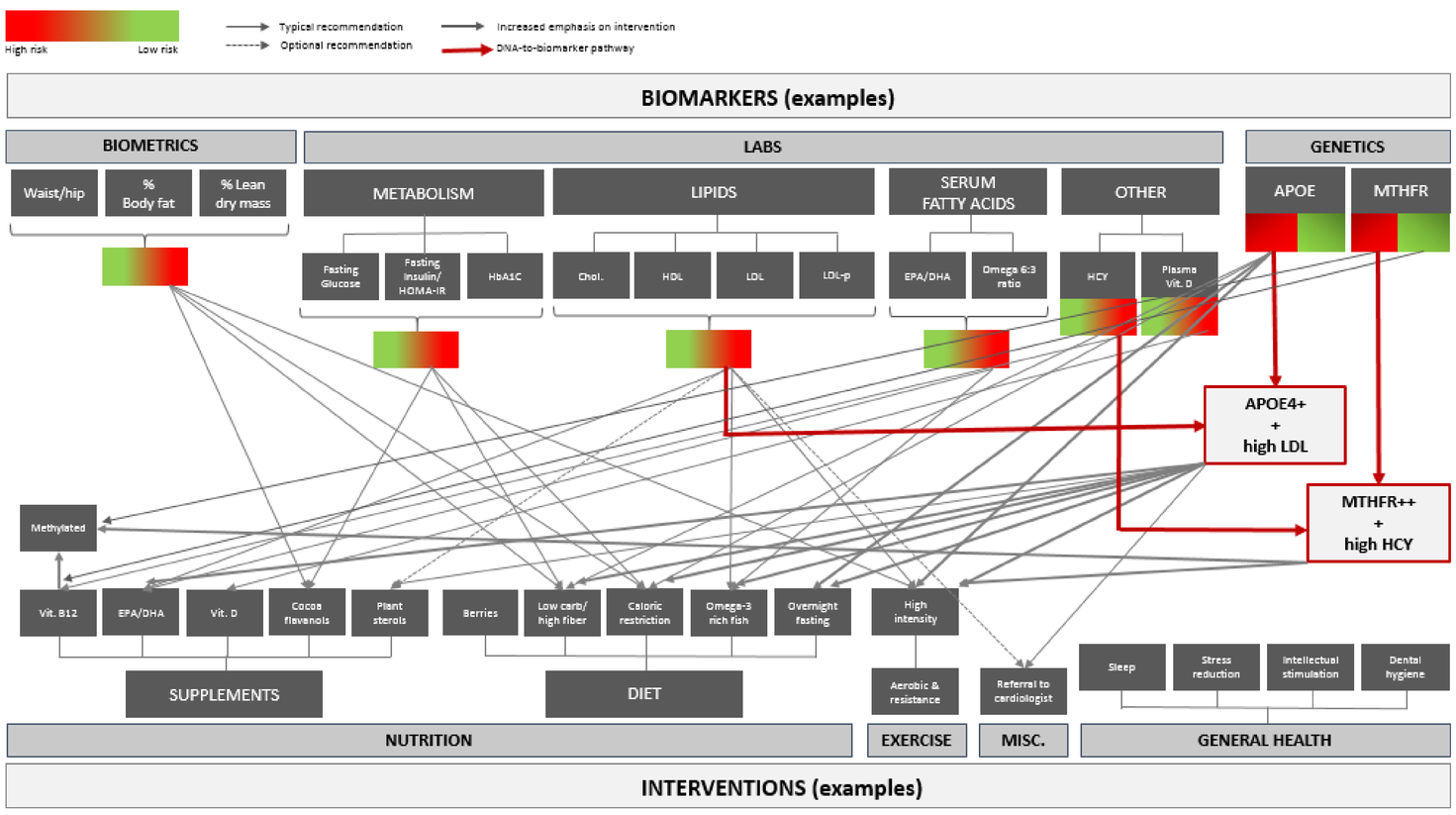
Overall Results

Risk Scales: After 6 months, improvements were observed in all risk scales (CAIDE Midlife, p=.046; MLDRI, p=.006; LLDRI, p<.001; MAYO MCI, p<.001; Late-onset AD, p=.001; ANU-ADRI, p<.001).

Change in Risk Scales



Biomarker-Intervention Paradigm



Overall Results Continued

Cognition: Tests of learning, memory, executive function and language improved in participants who completed cognitive assessments at baseline and 6 months (n=120).

Change in Cognitive Measures

Blood biomarkers: A host of blood biomarkers significantly improved in participants who completed labs at baseline and 6 months (n= 142) *see those with * in table below*

Adherence: Higher patient-reported adherence resulted in significant changes in 9 additional blood biomarkers (20) than lower adherence (11), however there was no difference in physician-reported higher vs. lower adherence groups.

Results by Genotype

Mediation by genotype: Stratification by APOE and MTHFR genotypes resulted in variations in response for a host of blood biomarkers and cognitive tests.

Change in Blood Biomarkers & Cognition Mediated by ApoE and MTHFR Status

Genotype	ApoE						MTHRF C677 1298c							
	E2/E2	E2/E3	E2/E4	E3/E3	E3/E4	E4/E4	C/C A/A	C/C A/C	C/T A/A	C/C C/C	C/T A/C	T/T A/A	T/T A/C	T/T C/C
n	*1*	*9*	*3*	*53*	*48*	*12*	*14*	*27*	*19*	*13*	*25*	*22*	*0*	*0*
Total Cholest.			■				■							
Direct LDL-C														
HDL-C*				■								■		
Non HDL-C							■							
Sd LDL-C*														
HDL-P										■				
HbA1C*											■			
Triglycerides*		■						■	■					
LDL P*				■				■				■		
Fibrinogen*				■	■						■	■		
Lp PLA*				■		■	■					■		
Adiponectin*				■	■		■		■			■		
ApoA-I*		■	■	■	■		■	■	■			■		
ApoB							■							
Homocysteine*				■	■			■	■	■		■		
Vitamin D			■	■	■			■	■		■			
Vitamin b12*									■					
Cystatin C*				■					■		■	■		
Saturated Fat*		■		■	■	■	■	■	■	■	■	■		
Transtotal*		■		■	■	■	■	■	■		■	■		
Cismonounsat*		■		■	■	■	■		■	■	■	■		
Omega3*		■		■	■		■	■	■		■	■		
Omega EPA*		■		■	■		■	■	■		■	■		
Omega ALA*		■		■	■	■	■	■	■		■	■		
Omega DHA*		■		■	■	■	■	■	■	■	■	■		
Omega 6*		■		■	■		■	■	■		■	■		
Arachidonic*				■	■			■	■		■	■		
Linoleic*				■	■			■	■		■	■		
RBC Folate*										■				
Myeloperoxidas					■									
Demest. ratio														
n	*1*	*9*	*3*	*47*	*38*	*6*	*13*	*23*	*15*	*8*	*23*	*18*	*0*	*0*
Flanker				■	■			■						
Boston Naming										■				
ANT				■					■					
FAS				■							■			
DDCS				■	■			■		■	■	■		
Pattern Comp.		■		■	■			■			■			
OSD				■	■			■	■		■			
Oral Reading										■				
Picture Vocab.				■										
RAVLT Trial 1		■					■							
RAVLT Trial 2				■					■		■			
RAVLT Trial 3		■							■		■			
RAVLT Delayed				■							■			

Blood Biomarkers

Cognition

■ = significant improvement over 6 months, p<.05

Conclusion

These data suggest a clinical precision medicine approach toward AD prevention reduces AD, dementia and vascular risk and improves cognition. Differential effects were observed based on genotype and adherence. These results are encouraging and warrant further evaluation via randomized trial utilizing AD-specific biomarkers pre vs. post-intervention. In addition to neuroimaging, we also plan to include an expanded genetics panel (including mitochondrial DNA) and microbiome assessments.