

# Changing the Paradigm for Patients with Cognitive Decline

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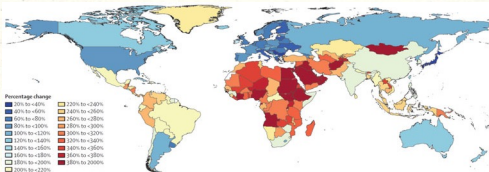
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*We always overestimate the change that will occur in the next two years and underestimate the change that will occur in the next ten.*

*Don't let yourself be lulled into inaction*



# Cognitive Decline is a Global Public Health Issue



Number of patients with dementia predicted to nearly triple from 57M in 2019 to 153M in 2050

2020 global societal costs of \$1.3 trillion which will also triple

10% of 65-year-olds ; 25% of 75-year-olds ; 50% of 85-year-olds



# 2012

- **PATIENTS** often do not seek medical care because they have been told there is nothing that can be done. They have significant fears with a diagnosis and often present very late in the process.
- **RESEARCH** is stuck on the Amyloid hypothesis with no new therapy being approved since 2000. Academic researchers who want to explore prevention or lifestyle treatments are told to explore other areas
- **PRIMARY-CARE CLINICIANS** typically simply start donepezil (Aricept), often without a firm diagnosis. They are told to not refer since there is no effective therapy.
- **SPECIALISTS** often put the patients through hours of neuropsychological testing, expensive imaging, lumbar punctures, and then have little or nothing to offer therapeutically.





- **PATIENTS** actively seek prevention and early treatment both in low- and high-income countries.
- **MULTI-MODAL PRECISION MEDICINE INTERVENTIONS** are the standard of care similar to HIV and Long Covid. There are multiple randomized clinical trials supporting care. Research into molecular networks that create and destroy synapses in neurodegenerative conditions have conclusively made the links between fatiguing illnesses and neurodegenerative. The toolkit used in multi-modal interventions is rapidly expanding with the ability to intervene in later cases.
- **PRECISION MEDICINE SPECIALISTS** are actively collaborating with Primary Care Physicians in initiating and managing multimodal treatment. There is a move to payment through global fixed rate of \$20k+ for the first year with decrease global rates for maintenance.
- **RETIREMENT COMMUNITIES**, especially CCRCs (continuing care retirement communities) are actively implementing multi-modal interventions in their residents with a significant reduction of nursing home use at the end of life as a result.



# So where are we in 2022?

- **PATIENTS** only seek prevention and early treatment if they are actively empowered with prior exposure or connections to functional / integrative medicine.
- **RESEARCH** community is beginning to realize that the amyloid hypothesis is a dead end. Several respected institutions such as Lancet Commissions and WHO have put their weight behind preventive strategies especially around vascular dementia. Significant new research money is flowing into Long Covid with concomitant exploration of neuroinflammatory pathways.
- **PRECISION MEDICINE SPECIALISTS** are developing practical insights into implementing Dr. Bredesen's ReCODE protocol and other similar approaches. There is active skepticism by the conventional medicine and neurology communities about these protocols especially when it comes to toxins and chronic infections.



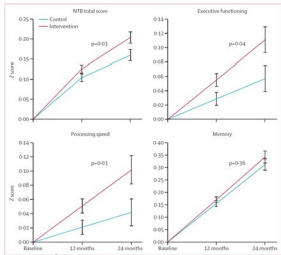
# FINGER Study

Four intensive lifestyle interventions of diet, exercise, cognitive training and vascular management in 1260 high-risk adults > 60. Published in Lancet in 2015

Intervention constitute 200 meetings (300 hours) with health professionals and trainers over 2 years

Control and intervention Z scores improved significantly compared to historical data

Statistically significant impact on executive function and processing speed, but **not** memory



# Lancet Commissions on Preventive Strategies in Dementia

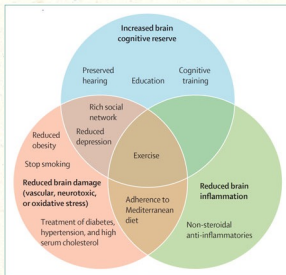


Figure 5: Potential brain mechanisms for preventive strategies in dementia

Their model showed 35% of incidence of cognitive decline is potentially modifiable with strategies listed on left

Dementia prevalence would be halved if onset of symptoms could be pushed out by 5 years





# Lessons from Aducanumab 2021-22

## No health benefit

- Insufficient to show a net health benefit for patients with MCI or mild AD
- One study showed a response, the other did not. In the pooled studies, both groups declined, the manufacturer claimed that that intervention declined less than placebo
- 35% of patients experienced amyloid-relating imaging abnormalities (ARIA); 6.2% of participants receiving high dose needed to discontinue the drug

## Spotlight on FDA decision making

- FDA approved; 3 committee members resigned as a result
- This decision was remarkable because the only evidence that amyloid removal (a surrogate) slows cognitive decline (clinical benefit) comes from their retrospective analysis of the single trial and ignores abundant evidence of no benefit, including the negative, identically designed trial.
- Harvard professor of medicine Aaron Kesselheim describing it as "probably the worst drug approval decision in recent US history"



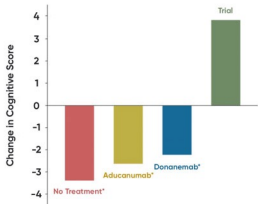
# Cost-benefit of Aducanumab

- If we assume, best case scenario of health benefit claimed by manufacturer, the price for medication to reach health – benefit price benchmark of \$50k to \$100k per QALY should be \$3k to 8.4k
- Instead, manufacturer started with a bid of \$56k / year which would have had a cost per QALY of over >\$1M
- Medicare issues a preliminary National Coverage Determination for Coverage with Evidence Development (CED); final decision due in April 2022
- What would be better alternative?
  - Lower cost intervention
  - Lower cost in subsequent years
  - Improvement in cognitive function rather than slowing decline



Is there  
a better option?

## Change in Cognitive Performance



\* <https://www.dzforum.org/therapeutics/aducanumab>

\*\* <https://www.nejm.org/doi/full/10.1056/NEJMoa2100708>

From Dr. Braden

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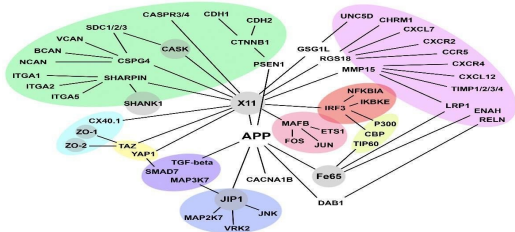


*There cannot be two kinds of medicine—  
conventional and alternative. There is only  
medicine that has been adequately tested  
and medicine that has not, medicine that  
works and medicine that may or may not work.*

*—Marcia Angell,  
Editor, New England Journal of Medicine*



# Precision Medicine: The APP Interactome



- Recognition and coupling of extracellular environment to the cytoskeleton and intracellular signaling - slow remodeling/recycling
- Proliferation-and-migration: pathfinding, ECM remodeling, autocrine/paracrine signaling - fast remodeling/recycling
- The Hippo pathway: adhesions-to-nucleus signaling and EMT control
- Specialized cell junctions/synapses
- Stress-activated signaling
- TGF-beta signaling
- Scaffolds
- Histone acetylation and regulation of transcription
- Proto-oncogene signaling
- Inflammation and immune response; NF-kB signaling



# Finding the tipping point for the master switch

$$p(AD) \propto f \frac{\sum \text{synaptoclastic signaling}}{\sum(\text{synaptoblastic signaling})} \approx f \frac{\sum[\text{inflammatory mediators+toxins}]}{\sum[\text{energetics+trophic support}]}$$

Trophic/Anti-Alzheimer's

Anti-Trophic/Pro-Alzheimer's



APP

From Dr. Brodson

# Goals of Precision Medicine Treatment



1

**Improve energetics** – ketosis (1-4.0 mM BHB) , cerebral blood flow & oxygenation, mitochondrial function

**Increase insulin sensitivity** - target HOMA-IR of 1.0 or lower

**Trophic support** – growth factors (e.g., BDNF), hormones, nutrients, cell regeneration

2

**Remove sources of inflammation & dysregulation** – remove mold / WDB toxins/ chemicals / metals, treat pathogens, optimize microbiome

**Reduce inflammation** – improve inflammatory, cardiometabolic and innate immune system biomarkers, reduction in amyloid beta

3

**Increase brain network function** – improved synaptogenesis, cognitive improvement, improved connectome function & regulation



# Four Winds Proof of Concept Trial 2020

**ELIGIBLE**



- 25 patients with mild cognitive impairment
- MOCA > 18 , CNSVS impairments (2 subsets < 50<sup>th</sup> percentile)
- Denied by IRB in 2011 & 18 ; finally approved in 2019 & completed in 2020

- Multiple lifestyle interventions over 9 months
- Precision medicine / root cause interventions guided by testing
- Team – patient, study partner, physician, nutritionist, health coach, exercise coach

- MOCA, CNSVS Cognitive Testing – 0, 3, 6, 9 months
- AQ-21
- MRI volumetrics with NeuroQuant and NeuroReader

From Dr. Raj Gupta

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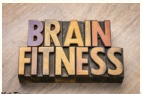
# Four Winds Lifestyle Interventions



- Grain-free, dairy-free, whole foods organic Paleo-type diet
- Healthy fats with at least mild ketosis (1.0 -4.0 mM BHB target)
- Time Restricted Eating to 8 – 12 hours / day; avoid eating 2-3 hours before sleep



- Strength and balance training
- Aerobics, and HIIT (High Intensity Interval Training)
- Heart Math
- Sleep hygiene, assessment for sleep apnea and intervention if necessary
- Fix indoor air pollution if an issue (e.g., mold / WDB)



- Brain HQ 5 x week



# Testing to Guide Precision Medicine Interventions



- **Genomics** (IntellXX DNA)
- **Micronutrients** and Omega Fatty acids (NutrEval)
- **Hormones** – stress, sex, thyroid
- **Inflammatory**, cardiometabolic, and immune markers
- **Gut** – intestinal permeability, digestion, metabolic (GI effects)
- **Microbiome** – stool, dental, nasal (PerioPath)
- **Toxins** – mycotoxins, chemicals, metals, organic acids, home mold testing (Environbiomics, GPL, Quicksilver)
- **Infections** – Viral, Tick-Borne Illness (IgenX, Armin)

From Dr. Kat Toups

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# Treatment to Support Energetics & Trophics

	Goals of Treatment	Interventions
Energetics	Improved mitochondrial function Insulin sensitivity (HOMA IR < 1.0) Ketosis (1-4.0mM BHB), metabolic flexibility Optimal cerebral blood flow & oxygenation	Mitochondrial support – nutraceuticals, NAD / NR Keto brain healthy diet (CGM guidance) Vascular interventions Hypercoagulability interventions Low (& high) intensity light therapy (Hyperbaric oxygen)
Trophic	Optimize hormones – stress, sex, thyroid Optimize micronutrients & trophic factors (e.g., BDNF) Optimize sleep & recovery Cell regeneration	Hormone support Exercise Micronutrient support Sleep hygiene, stress management Senolytics (Oura ring) (Stem cells)

Interventions in parentheses were not part of the proof of concept trial



# Addressing Inflammation & network function

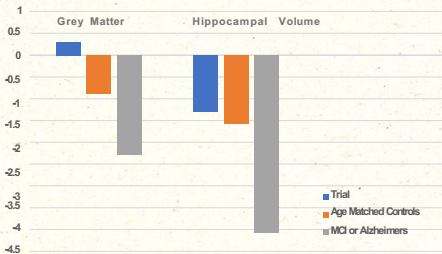
	Goals of Treatment	Interventions
Inflammatory markers	Improve inflammatory markers Improve innate immune system markers Reduce amyloid	Polyphenols, curcumin, resveratrol, Pharmaceuticals & nutraceuticals targeted at markers Anti-amyloid nutraceuticals, (monoclonal antibodies)
Toxins & pathogens	Remove toxins Treat pathogens Optimize microbiome	Address environmental exposures – clean indoor air, WDB, chemicals, dental health Detoxification protocols sequenced appropriately Antiviral & tick-borne disease protocols Dental health & gut support
Brain network function	Improve neurotransmitter function Reduced brainwave network dysregulation Improved cognitive function	Neurotransmitter support - choline, nootropics, Huperzine Brain training (QEEG guided neurofeedback) (Brain stimulation)

Interventions in parentheses were not part of the proof of concept trial



# Four Winds: Changes in MRI Volumetrics

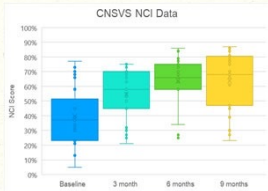
Percent



# Four Winds: Improvement in Cognition



76 % improved, 12% declined, 12% no change (P=.001)  
Ceiling of improvement in MOCAs of 29-30



84 % improved, 12% declined, 4% no change (P<.001)  
CNSVS removed ceiling of improvement



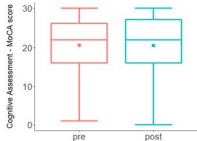
# Where Can Advanced Diagnostics & Therapies Help Beyond the Core Protocol?

- **QEEG** – a sensitive, inexpensive way to track brain network function to see at an early stage if treatment is making a difference
- **GENIE** – measuring hypometabolism & mitochondrial function through transcriptomics
- **Hyperbarics** – treatment of traumatic brain injury and jumpstarting energetics and trophic support
- **High intensity light therapy** – jumpstarting energetics & trophic support & mitochondrial function

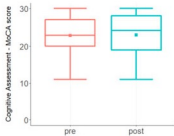


# ReCODE Apollo Health Experience 2019-21

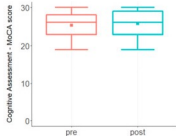
## Effectiveness versus Efficacy



Entire participant pool  
(N = 251) , P = 0.484



MoCA > 10  
(N = 212) , P < 0.05



MoCA > 18  
(N = 151) , P < 0.005





# Evanthea Randomized Controlled Clinical Trial to Start in 2022

## Design

- 6 sites – California (3), Florida, Ohio , Oregon
- 72 patients – 58 patients, 24 controls
- Controls will cross-over into intervention after 9 months

## Incorporating lessons learned

- Additional markers of biological changes, e.g., phosphorylated tau
- Willingness to address environmental issues as entry criteria



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# Accelerating Change When the RCT is Positive

- **Changing the narrative**
  - MCI is treatable if addressed at an early stage
  - Precision medicine addressing signaling pathways & networks
  - Highly cost-effective compared to pharmaceuticals
- **Addressing paradigm issues underlying inflammation, pathogens & toxins**
  - Research in Long Covid and ME / CFS will likely provide a path
- **Additional research** on patients with cognitive scores less than MCI, with more aggressive interventions ; comparing interventions with / without infection / toxin interventions ; RCTs and Registries
- **Addressing costs up front**
  - Package “metabolic” low-cost protocol for Medicare Advantage plans with a global fee arrangement based on outcomes
  - Protocolize and reduce costs



# Understanding Cost-Effectiveness Issues

## Results (CEA) - Over 20-year/Lifetime horizon

	No treatment	Treatment	Incremental
<b>Undiscounted</b>			
Costs	\$258,430	\$285,010	\$26,579
QALYs	6.62	7.65	1.033
Life Years	9.98	11.14	1.160
Cost per QALY gained			\$25,741
<b>Discounted</b>			
Costs	\$206,997	\$231,737	\$24,740
QALYs	5.52	6.27	0.749
Life Years	8.27	9.07	0.805
Cost per QALY gained			\$33,022

## Results (CEA) - Over 20-year/Lifetime horizon

	No treatment	Treatment	Incremental
<b>Undiscounted</b>			
Costs	\$258,430	\$257,631	-\$799
QALYs	6.62	8.14	1.522
Life Years	9.98	11.69	1.714
Cost per QALY gained			Dominant
<b>Discounted</b>			
Costs	\$206,997	\$206,221	-\$775
QALYs	5.52	6.60	1.078
Life Years	8.27	9.43	1.164
Cost per QALY gained			Dominant

## Scenario A Assumptions

- 5 years of treatment
- 70% reduction in progression / year
- \$15k average cost / year

## Scenario B Assumptions

- 10 years of treatment
- 80% reduction in progression / year
- \$6k average cost / year

THE IPECAD MODEL - International PharmacoEconomic Collaboration on Alzheimer's Disease ([www.ipecad.org](http://www.ipecad.org))

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# What can you do to help get to 2032?



- **PATIENTS** actively seek prevention and early treatment both in low- and high-income countries.
- **MULTI-MODAL PRECISION MEDICINE INTERVENTIONS** are the standard of care similar to HIV and Long Covid. There are multiple randomized clinical trials supporting care. Research into molecular networks that create and destroy synapses in neurodegenerative conditions have conclusively made the links between fatiguing illnesses and neurodegenerative. The toolkit used in multi-modal interventions is rapidly expanding with the ability to intervene in later cases.
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