

LEARNING ABOUT ALZHEIMER'S

THROUGH CLINICAL TRIALS



ABOUT ME

- **General counsel and director of program development at Fox Hill Village, a CCRC**
- **Master's in health policy**
- **Fellow at the Green House® Project**
- **Advisor, Hastings Center, a bioethics research center**
 - **Aging, Chronic Conditions and Care Near End of Life Sector**
- **My father and father in law both lived with dementia**

WHITE OAK COTTAGES



WHITE OAK COTTAGES

- **Assisted living dementia residence on Fox Hill campus**
- **www.whiteoakcottages.com/blog-2/blog/**
 - **Green House adopter – attempting to radically change the way long term care is provided**
 - **Focused on quality of life and autonomy of residents**
 - **2 cottages, 12 private bedrooms in each**

FAMILIES SEEKING ANSWERS

- **Is there a cure in sight?**
- **What can I do to prevent or delay the onset of this disease?**
- **How can I better understand scientific findings in the news?**

WHAT CAUSES ALZHEIMER'S?

- **Still trying to understand what triggers the disease process**
- **Rift within research world as to which protein accumulation should be the focus of research**
- **Study of lifestyle giving some information about possible protections**
- **Epidemiology critical to developing and confirming hypotheses**

WHAT IS EPIDEMIOLOGY?

- **Medical detectives trying to discover what causes disease and effective treatments**
- **Study of disease patterns among populations**
 - Who gets sick?
 - Where?
 - When?



HOW IT WORKS

- **Data driven science**
- **Requires statistical analysis**
- **Iterative in nature**
- **Different tools depending on focus of study**

OBSERVATION OF POPULATIONS

- **Observational studies of past exposures to identify source of disease**
 - May not understand how exposure causes the disease, but can lead to preventative measures
 - Develop a theory based on one case, or several cases
 - Review data to determine if they support hypothesis
 - John Snow 1854 cholera outbreak
 - AIDS 1980s
 - Zika

PROSPECTIVE TRACKING

- **Cohort study usually focused on understanding influences on specific diseases**
 - Population without disease
 - Track going forward
 - Questionnaires
 - Physical exams and/or specimens
 - Can include study of specific exposures/activities

EXAMPLES OF COHORT STUDIES

Framingham Heart Study: risk factors for heart disease

www.framinghamheartstudy.org

- 1948: 5200 subjects
- 1971 5124 subjects
- 2002
- Omni studies 1994 and 2003

• **Nurses Health Studies: oral contraceptive study**

www.channing.harvard.edu

- 1976: 238,000 subjects
- 1989: second generation 116,000 subjects

CLINICAL TRIALS

- **Clinical trials test the efficacy of potential treatments**
- **Epidemiology is essential component**

- **Phase I**
 - **Safety, small group of healthy volunteers**

- **Phase II**
 - **Dosage**
 - **Some measure of efficacy**
 - **Larger group with disease in question**

- **Phase III**
 - **Clinical trials with controls**
 - **Large groups, replications**

CLINICAL TRIALS

- **What is “gold standard”**
 - Double blind
 - Placebo
 - Randomized
- **Statistically significant outcomes**
 - P value : probability that the effect observed could have happened by chance $>.01$ goal
- **Peer Reviewed Publication**
- **Replication**

APPLICATION TO ALZHEIMER'S

- **Challenge of chronic disease investigation**
 - Develops over many years
 - Likely to be result of multiple exposures
- **Challenge of studying the brain**
- **Diagnosis not determinative without autopsy**

SEARCHING FOR BIOMARKERS

- **What are biomarkers?**
 - Something that can be accurately and reliably measured to indicate presence of disease
 - Not yet
- **“Hallmarks”?**
 - Amyloid and tau build up
 - Shrinkage of hippocampus
- **2012: FDA approves Amyvid radioactive dye**

VALIDATION ELUSIVE

- **What FDA test suggested**
- **Led to realization that not everyone with Abeta had dementia;**
- **Some with dementia did not have Abeta**
- **Unresolved question of the role of Abeta and tau**
- **No scan test for Tau approved as of yet**

CURRENT DRUG TRIALS

- **Eli Lilly/ NIH Solanezumab A4 Study**
- **Eli Lilly/NIH LEARN Study**
- **Biogen Aducanumab Phase 1 → Phase III**

SOLANEZUMAB

Solanezumab: The A4Study: Can early treatment prevent or delay onset of cognitive decline?

- **Joint study by NIH and Eli Lilly**
- **Screening 10,000 people, 60 different sites**
- **Ages 65 to 85**
- **All have Abeta build up, but no cognitive issues yet**
- **Results must show improvement in cognition and function**

LEARN TRIAL

What are the non-amyloid drivers of cognitive decline?

- **Offshoot of the A4 Study**
 - 500 subjects rejected from A4 due to no amyloid
- **Testing efficacy of new testing protocols for A4**
- **Tau sub-study with tau imaging agent TBD**
 - 150 subjects (50 from LEARN; 100 from A4)
- **Results in 2020**

ADUCANUMAB

- **Biogen trial**
- **Phase I results in July 166 subjects**
- **Showed dose dependent response at high doses**
- **High levels of side effects**
- **Phase III results expected 2018**

WHAT CAN WE DO TO PREVENT OR DELAY ONSET?

- **Diet**
- **Sleep**
- **Exercise**
- **Mental stimulation**
- **Social engagement**
- **Stress management**
- **Avoidance of some medications**

- **What do the epidemiologists have to say?**

BEYOND CURE: WHAT WILL PROTECT?

FOODS

- **Chocolate**
- **Red wine**
- **Ginko balboa**
- **Cocoanut oil**
- **Mediterranean diet**



HOW TO LOOK AT FOOD

- **Who conducted trial?**
- **How many subjects?**
- **How was it structured?**
 - **Randomized, double blind, placebo**
- **How long did trial last?**
- **Published in a peer reviewed journal?**
- **Replicated?**
- **Real food equivalents?**
 - **Dosage calculation: how much food would you have to eat to get benefits described?**

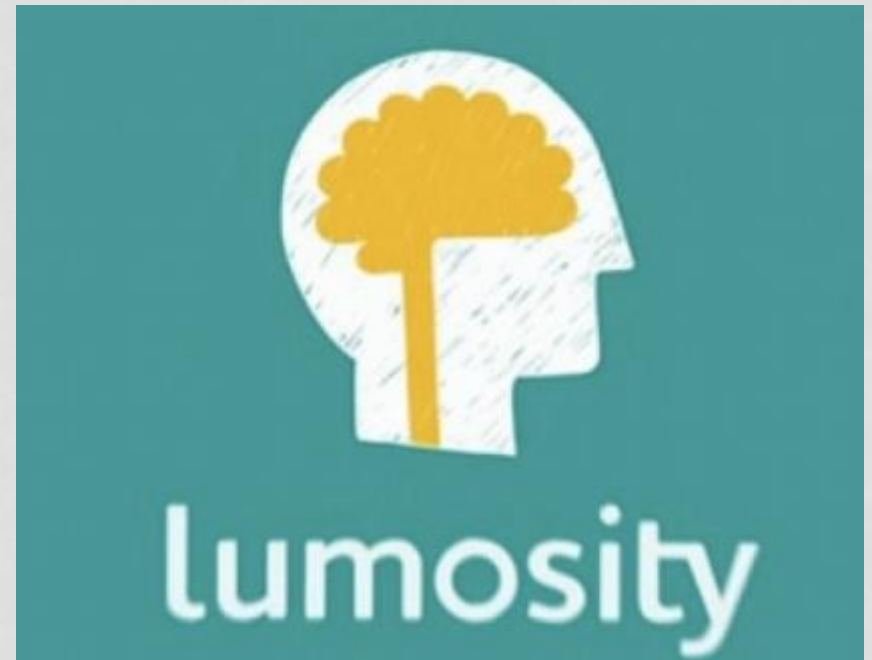
SUPPLEMENTS/LIFE STYLE

- **Prevagen**
 - Supplement not subject to FDA approval
 - Cease and desist due to no clinical trial
 - 56 subjects
 - Self-reported results
 - Class action suit



MENTAL STIMULATION

- **Lumosity**
 - Settlement with FTC for deceptive advertising
 - No credible trial showing improved general cognition



EXERCISE!

- **Multiple studies suggesting exercise improves cognition**
- **Both in humans and animals**
- **Measured by either size of hippocampus or brain activity during mental exercise**



DRILLING DOWN

- **APOE4 positive subjects**
 - Those who exercised regularly showed greater brain activity when performing mental exercise.
 - Dose dependent
 - 68 people aged 65 to 85
 - Exercise self reported
 - Brain activity measured by MRI
 - P values < 0.033 and 0.014
- **Walking study of 120 cognitively intact people**
 - Aerobic exercise 4x/week vs. stretching exercises
 - Measured size of hippocampus by MRI
 - 2% increase in size in aerobic group, 1.4% decreased volume in stretching group
 - P values <0.001

POTENTIALLY DANGEROUS DRUGS

- **Several well designed studies show an association between long term use and an increased risk of dementia**
- **Not known why the drugs are linked with risk; could be circumstantial**
- **Provides tools for further study**

POTENTIALLY DANGEROUS DRUGS

- **Sedating and anti-nausea meds (Benadryl, Sominex, Dramamine)**
- **Followed 3500 people in Seattle health plan for 7 years**
 - Had access to pharmacy records
 - Use of anti-cholinergics associated with development of dementia
 - P value < 0.001
 - Published in JAMA, March 2015
- **Acid reflux medications (Prilosec, Nexium, Prevacid)**
 - German study of 73,000 subjects over 7 years
 - 44% increase in development of dementia for those taking drugs for more than 18 months

ARE FEWER PEOPLE DEVELOPING DEMENTIA ?

- **Framingham Heart Study**
 - 44% decline in rate since 1970s
 - Limited to those with a high school education
 - Better diet?
 - Meds for stroke and heart?
- **Stay tuned!**



INFORMATION ON CLINICAL TRIALS

- clinicaltrials.gov
- nia.nih.gov/alzheimers/clinical-trials
- http://www.alz.org/research/clinical_trials/clinical_trials_alzheimers.asp

SUMMING IT UP

- **No drugs to cure, slow or delay in near future**
- **Pro-active steps may provide protection**
 - **Healthy diet**
 - **Exercise**
 - **Sleep**
 - **Cognitive reserve?**
- **Cautious use of other drugs**
- **What is good for the heart is good for the brain; data is suggesting that prevalence is dropping**