“Alzheimer’s Disease and Cognitive Impairment of Aging”
Café Scientifique * 29 September 2016 * 49 West Annapolis

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Alois Alzheimer, M.D.
1864-1915

German Psychiatrist
Neuropathologist

University of Wurzburg
Stadtische Anstalt fur Irre und Epileptische, Frankfurt am Main
CLINICAL HISTORY 1901

51 year old woman from Kassel Germany, with 2 year history of progressive memory loss and delusions, wandering the house at night screaming. Her husband brought to the City Asylum for Insane and Epileptics in Frankfurt where Alzheimer first examined her in November 1901. He followed her course intently until her death 5 years later. Stadische neurologist Franz Nissl had developed a method of silver staining of histological sections. Alzheimer applied this technique to Auguste’s brain and published his finding of amyloid plaques and neurofibrillary tangles in 1907.
Amyloid Plaque and Tau Neurofibrillary Tangles
Cognitive Impairment and Dementia

Summary of Tonight’s Presentation

I. Differential Diagnosis
   A. Pseudodementia
      1. Normal Aging
      2. Psychiatric
   B. Organic Dementias
      1. Other Treatable Causes
      2. Neurodegenerative

II. Symptoms (Subjective)
   A. Cognitive Impairment
   B. Neurologic Complaints

III. Signs (Objective)
   A. Mental Status Exam
   B. Neurologic Exam

IV. Pathophysiology and Testing
   A. Laboratory Studies
   B. Imaging Studies
      1. CT
      2. MRI
      3. SPECT
      4. PET
   C. Genetic Studies
      1. APOE-4
      2. APP
      3. Tau
      4. Harvard PGP

V. Treatment
   A. Treatable Dementias
   B. Alzheimer’s Disease
      1. Pharmaceutical
      2. Physical, Social, Mental

VI. Future Trends and Studies GLEAMS
Mild Cognitive Impairment

Normal Aging
1. Sometimes forgetting appointments or names, but later remembering.
2. Occasionally forgetting why you came into a room or were going to say
3. Sometimes having trouble finding words, later coming to you.
4. Not always knowing the precise date, day of week; able to figure it out.
5. Having occasional difficulties balancing a checkbook.
6. Misplacing keys or wallet temporarily but retracing steps to find
7. Occasionally feeling moody or sad.
8. Sometimes weary of social obligation
9. Worried that mild memory problems mean that you have Alzheimer’s.

Alzheimer’s Disease
1. Forgetting recently learned information and not remembering.
2. Losing track of steps to prepare a meal, place a phone call, play a game
3. Often forgetting simple words, making speech hard to understand.
4. Not knowing age; becoming lost and not able to get back home.
5. Difficulty performing complex tasks; forget what numbers are for.
6. Putting things in unusual places; wallet in freezer, keys in sugar bowl.
7. May have mood swings. No reason.
9. Not concerned about memory; in denial; many excuses for problems.
Other Treatable Causes of Dementia

I. Medical Metabolic
   A. Endocrine
      1. Diabetes
      2. Thyroid
   B. Kidney Disease
      Uremia
   C. Liver
      Hepatic Encephalopathy
   D. Pulmonary Disease
      Hypoxia

II. ASCVD Vascular Disease
   A. Cardiac Disease
   B. Stroke CVA
      1. Thrombotic
      2. Embolic
      2. Small Vessel Cerebrovascular

III. Rheumatologic
   A. Systemic Lupus Erythematosus
   B. Giant Cell (Temporal) Arteritis
   C. Rheumatoid Arthritis
   D. Cerebral Vasculitis

IV. Deficiency
   A. Vitamin B12
   B. Vitamin D

V. Toxic
   A. Prescription Drug Effect
   B. Substance Abuse
   C. Heavy Metals

VI. Neoplastic
   A. Brain Tumor
      1. Primary
      2. Embolic
   B. Paraneoplastic
   C. Limbic Encephalopathy

VII. Infectious
   A. Bacterial Meningitis
   B. Chronic Meningitis
      1. Fungal
      2. AFB
   C. Viral Encephalitis
   D. Neurosyphilis
   E. HIV

VIII. Psychiatric
   A. Depression
   B. Anxiety Disorder
   C. Schizophrenia
## Dementias – Neurodegenerative and Vascular

<table>
<thead>
<tr>
<th>Disease</th>
<th>First Symptom</th>
<th>Mental Status</th>
<th>Psychiatry</th>
<th>Neurology</th>
<th>Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD - Alzheimer’s Disease</td>
<td>Memory loss</td>
<td>Episodic memory loss</td>
<td>Initially normal</td>
<td>Initially normal</td>
<td>Entorhinal. Hippocampal atrophy.</td>
</tr>
</tbody>
</table>

*Source: Alzheimer’s Disease & Other Dementias Harrison’s Neurology in Clinical Medicine, 3rd ed McGraw-Hill Company*
Mental Status Examination
Mini-Mental State Exam I.

I. Orientation (10) (+5)
   1. What is the month?
   2. What is today’s date?
   3. What is the year? (+Age?)
   4. What is the day of the week? (+Birthday?)
   5. What is the season? (+Year of Birth?)
   6. What is your street address?
   7. What city do you live in?
   8. What county do you live in?
   9. What state do you live in? (+Family Phone?)
  10. What is your telephone number? (+Cell Phone?)

II. Registration (3)
   11. Monday: banana, 1, sit
   12. Tuesday: lemon, 2, stand
   13. Wednesday: plum, 4, walk (-Number of Tries)

Mini-Mental State Exam II.

**III. Attention and Calculation (5)**
- 14. Begin with 100, subtract 7 = 93 or Spell WORLD or HOUSE in reverse
- 15. 93-7 = 86
- 16. 86-7 = 79
- 17. 79-7 = 72
- 18. 72-7 = 65 (+Down to 30)

**I. Three-Minute Recall (3)**
- 19. Thursday: orange, 5, run
- 20. Friday: apple, 6, climb
- 21. Saturday: pear, 9, jump (-Reinforcement = fruit, number, verb)

**II. Language (9)**
- 22. Naming: pen (+Order in the alphabet of the last letter of this state)
- 23. Watch: (+People who live in glass houses should not throw stones)
- 24. Repetition: “No, ifs, ands or buts”
- 25. Three Step Command: “Take your left thumb,
- 26. ...put it on your right ear,
- 27. ...and stick out your tongue” (+Don’t look a gift horse in the mouth)
- 28. Read the sign and do what it says: CLOSE YOUR EYES
- 29. Write a sentence (+VP Biden, Cheney, Gore, Quayle, Bush, Mondale)
- 30. Copy intersecting pentagons (+Clock at 11:10pm)

Mini-Mental State Exam III.

Intersecting Pentagons

Clock Drawing 11:10
Neurologic Examination
Neurologic Examination

Mental Status: The patient is oriented x3. Gives a good history. Has good fund of knowledge and insight. Recalls 3/3 objects in 3 minutes time. Performs serial 7s to 65 and/or spells house in reverse. Good abstractions. Good language function. MMSE.

Cranial nerves I-XII: Taste, smell and vision are intact. Funduscopic exam is normal. Peripheral fields are intact to confrontation. Extraocular movements are full in all directions. No nystagmus or vertigo. Normal facial sensory and motor function. Hearing is intact. Sternocleidomastoid is normal. Palate and tongue are unremarkable.

Motor testing: Deep tendon reflexes are 2+ and symmetric. Muscle bulk and tone are normal. There is no focal motor weakness or fasciculations. Motor strength is full 5/5 and symmetric. There is no pronator drift on arm abduction. Performs deep knee bend. Able to walk on toes and heels, forward and reverse, eyes closed.

Sensory: Sensation to sharp, light touch, temperature, vibration, and proprioception is intact. Graphesthesia is intact in the hands.

Coordination: The patient has excellent finger to nose and heel to shin testing. Station and gait are normal. Tandem gait is good. Romberg's is negative.
Diagnostic Evaluation of Dementia

I. MEDICAL
   A. Comprehensive Metabolic Panel
   B. Complete Blood Count
   C. TSH and Thyroid Panel
   D. Arterial Blood Gases
   E. Urinalysis

II. ASCVD VASCULAR
    A. EKG
    B. Echocardiogram
    C. 24-Hr Holter Monitor
    D. Carotid Doppler
    E. MRA of Brain

III. RHEUMATOLOGIC
     A. Antinuclear Antibody
     B. Erythrocyte Sedimentation Rate
     C. Rheumatoid Factor
     D. C-Reactive Protein

IV. DEFICIENCY
    A. Vitamin B12 Level
    B. Vitamin D Level

V. TOXIC
    A. Therapeutic Blood Levels
    B. Urinary Toxicology Screen
    C. 24-Hr Urine for Hg, Pb, As

VI. NEOPLASTIC
    A. Brain Computed Tomography
    B. Brain Magnetic Resonance Imaging
    C. Chest, Abdomen and Pelvic CT
    D. Radionuclide Bone Scan
    E. Serum and Urine Electrophoresis

VII. INFECTIOUS
     A. Lumbar Puncture for
     B. Protein, Glucose, Cell Count
     C. Bacterial, Fungal, AFB Culture
     D. Viral Antigens, HIV, VDRL

VIII. SPECIAL ALZHEIMER’S TESTS
      A. Amyloid PET Scan of Brain
      B. CSF tau/p-tau; A beta 42
      C. SPECT Scan of Brain
      D. Genetic Testing APOe-4
Alzheimer’s Pathophysiology I
Tau Proteins & Neurofibrillary Tangles
Amyloid Plaque and Tau Neurofibrillary Tangles
Neuropathology Brain Atrophy in Alzheimer Disease
Magnetic Resonance Imaging
MRI in Alzheimer’s Disease
Pittsburgh Compound PET Scan
Alzheimer’s Beta Amyloid Plaque
N-methyl-D-aspartate receptor is a glutamate receptor and ion channel protein found on nerve cells that when activated allows positive ions Na Ca K to flow across the membrane.
Prescription Drugs in Alzheimer’s

1. Memantine
2. Donepezil
Drug Therapy in Alzheimer’s Disease

Acetylcholinesterase Inhibitors

Levels of acetylcholine (ACh), the chemical messenger important for learning and memory, are low in the brains of people with Alzheimer’s disease. Cholinesterase inhibitors (AChE inhibitors) partially correct the deficit by blocking the action of acetylcholinesterase (AChE) and thereby increasing the amount of acetylcholine that remains in the synaptic cleft.
Prescription Drugs in Alzheimer’s

3. Galantamine

4. Rivastigmine
There is Currently Little Understanding of the Role of Environmental Factors in AD

Which is the most important?
The Bottom Line. While all four are important: 1. Good Diet 2. Keeping Active Mentally 3. Keeping Active Socially 4. The Most Important: Keep Active Physically (WALK!)
Background: The etiology of Alzheimer's disease (AD) is believed to involve environmental exposure and genetic susceptibility. The aim of our present systematic review and meta-analysis was to roundly evaluate the association between AD and its modifiable risk factors.

Methods: We systematically searched PubMed and the Cochrane Database of Systematic Reviews from inception to July 2014, and the references of retrieved relevant articles. We included prospective cohort studies and retrospective case-control studies.

Conclusions: Effective interventions in diet, medications, biochemical exposures, psychological condition, pre-existing disease and lifestyle may decrease new incidence of AD.

Authors: Xu W\textsuperscript{1}, Tan L\textsuperscript{2}, Wang HF\textsuperscript{3}, Jiang T\textsuperscript{3}, Tan MS\textsuperscript{1}, Tan L\textsuperscript{4}, Zhao QF\textsuperscript{1}, Li JQ\textsuperscript{1}, Wang J\textsuperscript{1}, Yu JT\textsuperscript{5}, \textsuperscript{1}Departments of Neurology, School of Medicine Qingdao University, \textsuperscript{2}Nanjing Medical University, \textsuperscript{3}China College of Medicine and Pharmaceutics, \textsuperscript{4}Ocean University of China, \textsuperscript{5}Memory and Aging Center University of California San Francisco California USA.
Meta-Analysis Of Modifiable Risk Factors For Alzheimer's Disease. 

**Results:**

17. **PROTECTIVE FACTORS**

10. **INCREASED RISK FACTORS**

16,906 articles were identified of which 323 with 93 factors met the inclusion criteria for meta-analysis. Among factors with relatively strong evidence (pooled population >5000) in our meta-analysis, we found grade I evidence for 4 medical exposures (1. estrogen, 2. statin, 3. antihypertensive medications and 4. non-steroidal anti-inflammatory drugs therapy) as well as 4 dietary exposures (5. folate, 6. vitamin E and 7. vitamin C and 8. coffee) as **PROTECTIVE FACTORS** of AD. We found grade I evidence that one biochemical exposure (1. hyper homocysteine) and one psychological condition (2. depression) significantly **INCREASE RISK** of developing AD. We also found grade I evidence indicative of complex roles of pre-existing disease (3. frailty, 4. carotid atherosclerosis, 5. hypertension, 6. low diastolic blood pressure, 7. type II diabetes mellitus (Asian population) **INCREASING RISK** whereas 9. history of arthritis, 10. heart disease, 11. metabolic syndrome and 12. cancer **DECREASING THE RISK** and lifestyle (8. low education, 9. high body mass index (BMI) in mid-life and 10. low BMI **INCREASING THE RISK** whereas 13. cognitive activity, 14. current smoking (Western population), 15. light-to-moderate drinking, 16. stress, 17. high BMI in late-life **DECREASING THE RISK**) in influencing AD risk. We identified no evidence suggestive of significant association with occupational exposures.

**Authors:**

Xu W¹, Tan L², Wang HF³, Jiang T³, Tan MS¹, Tan I⁴, Zhao QF¹, Li JQ¹, Wang J¹, Yu JT⁵
International groups join forces to find elusive gene variants in largest-ever sample set

November 1, 2013
Peggy Vaughn | (301) 496-1752 | nianews3@mail.nih.gov

An international group of researchers has identified 11 new genes that offer important new insights into the disease pathways involved in Alzheimer’s disease. The highly collaborative effort involved scanning the DNA of over 74,000 volunteers—the largest genetic analysis yet conducted in Alzheimer’s research—to discover new genetic risk factors linked to late-onset Alzheimer’s disease, the most common form of the disorder.

Until 2009, only one gene variant, Apolipoprotein E-e4 (APOE-e4), had been identified as a known risk factor. Since then, prior to today’s discovery, the list of known gene risk factors had grown to include other players—PICALM, CLU, CR1, BIN1, MS4A, CD2AP, EPHA1, ABCA7, SORL1 and TREM2.

The researchers identified the new genes by analyzing previously studied and newly collected DNA data from 74,076 older volunteers with Alzheimer’s and those free of the disorder from 15 countries. The new genes (HLA-DRB5/HLA0DRB1, PTK2B, SLC24A4-0RING3, DSG2, INPP5D, MEF2C, NME8, ZCWPW1, CELF1, FERMT2 and CASS4) add to a growing list of gene variants associated with onset and progression of late-onset Alzheimer’s. Researchers will continue to explore the roles played by these genes, to include:

- How SORL1 and CASS4 influence amyloid, and how CASS4 and FERMT2 affect tau, another protein hallmark of Alzheimer’s disease
- How inflammation is influenced by HLA-DRB5/DRB1, INPP5D, MEF2C, CR1 and TREM2
- How SORL1 affects lipid transport and endocytosis (or protein sorting within cells)
- How MEF2C and PTK2B influence synaptic function in the hippocampus, a brain region important to learning and memory
- How CASS4, CELF1, NME8 and INPP5 affect brain cell function
Multiple Genes (23) Identified for Alzheimer’s

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<tr>
<th>Alzheimer’s</th>
<th>Bipolar</th>
<th>Schizophrenia</th>
<th>Autism</th>
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<tbody>
<tr>
<td>ABCA7</td>
<td>CACNA1C</td>
<td>CACNA1C</td>
<td>ADNP</td>
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<tr>
<td>APOE</td>
<td>CACNB2</td>
<td>CACNB2</td>
<td>CHD2</td>
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<tr>
<td>APP</td>
<td>DHH</td>
<td>DPYD</td>
<td>CHD8</td>
</tr>
<tr>
<td>BIN1</td>
<td>ITIH3</td>
<td>LAMA2</td>
<td>GRIN2B</td>
</tr>
<tr>
<td>CASS4</td>
<td>ITIH4</td>
<td>LRRIQ3</td>
<td>KATNAL2</td>
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<tr>
<td>CD2AP</td>
<td>MAPK3</td>
<td>MAD1L1</td>
<td>PAX5</td>
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<tr>
<td>CELF1</td>
<td>NCAN</td>
<td>NOTCH4</td>
<td>POGZ</td>
</tr>
<tr>
<td>CLU</td>
<td>ODZ4</td>
<td>NRGN</td>
<td>PTEN</td>
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<tr>
<td>CRJ</td>
<td>PBRM1</td>
<td>SNX19</td>
<td>SCN2A</td>
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<tr>
<td>EPHA1</td>
<td>RHEBL1</td>
<td>TCF4</td>
<td>SYNGAP1</td>
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<tr>
<td>FERMT2</td>
<td>SYNE1</td>
<td>TRRAP</td>
<td>TBR1</td>
</tr>
<tr>
<td>HLA-DRB5</td>
<td>TRPC4AP</td>
<td>TSNARE1</td>
<td>TRIP12</td>
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<tr>
<td>INPP5D</td>
<td>ZNF804A</td>
<td>VPS39</td>
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<tr>
<td>MEF2C</td>
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<td>ZNF804A</td>
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<td>MS4A</td>
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<td>ZSWIM6</td>
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<td>NME8</td>
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<td>PICALM</td>
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<td>PSEN1</td>
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<td>PSEN2</td>
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<tr>
<td>PTK2B</td>
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<tr>
<td>SIC24A4</td>
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<tr>
<td>SORL1</td>
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<tr>
<td>ZCWPW1</td>
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Alipoprotein E (ApoE-4)

- Involved in the catabolism of triglyceride-rich lipoprotein constituents. Produced by astrocytes in the brain and involved in the transport of cholesterol to neurons via ApoE receptors.

- Of the various genetic factors underlying Alzheimer’s disease, ApoE, the gene for Apolipoprotein E has been most studied. Of the three alleles (E2, E3 and E4), the ApoE-4 variant doubles the risk of late-onset Alzheimer’s, while E2 protects against this disorder.

- Dr. Steven Pinker, Harvard psychologist, and member of the original PGP-10, in his 2009 essay for The New York Times entitled My Genome My Self stated that while he was interested in fully participating in the Personal Genome Project, he “figured that his current burden of existential dread was just about right” and that he therefore planned to follow the lead of James Watson and request that he NOT be told about his ApoE gene information when it became available.

- 24.6% of the first Personal Genome Projects’ participants PGP1-224 are heterozygous for ApoE-4; and 1.3% are homozygous.
So what do we know about genetics of August Deter, the original “Alzheimer’s” patient from Kassel Germany who died in 1906, and whose brain showed that beta amyloid plaques and neurofibrillary tangles that have been the neuropathologic hallmarks of this disease? Genetic studies on her tissues in 2008 revealed that Auguste was double negative ApoE-3, but carried a different mutation for PSEN1.
Original article

Histopathology and APOE genotype of the first Alzheimer disease patient, Auguste D.

M.B. Graeber · S. Kisel · E. Grasbon-Frodl · H.J. Muller · P. Mehrain

Received: 29 December 1997 / Accepted: 15 January 1998

ABSTRACT

Alois Alzheimer published two papers on the disease which was named after him by Emil Kraepelin in 1910. Each of these papers contains clinical and pathological data on a patient Alzheimer had seen at the hospital. We have previously reported on the rediscovery of tissue sections from Alzheimer’s second published case of Alzheimer disease, Johann F., which probably gave the disease its name (Neurogenetics 1995; 1:73–80). Here, we describe the histopathology and APOE genotype of Alois Alzheimer’s first patient, Auguste D. As in the case of Johann F., a large number of tissue sections belonging to Alzheimer’s laboratory, which was later headed by Spielmeyer, were found among material kept at the Institute of Neuropathology of the University of Munich. As described by Alzheimer in his original report (Allg. Zeitschr. Psychiatr. 1907; 64:146–148), there were numerous neurofibrillary tangles and many amyloid plaques, especially in the upper cortical layers of this patient. Yet, there was no microscopic evidence for vascular, i.e., arteriosclerotic, lesions. Interestingly, Alzheimer’s histological preparations did not include the hippocampus or entorhinal region. The APOE genotype of this patient was shown to be ε4/3 by PCR-based restriction enzyme analysis, indicating that mutational screening of the tissue is feasible. The historical importance of the case of Auguste D. lies in the fact that it marks the beginning of research into Alzheimer disease. In addition, neurofibrillary tangles were first described in this brain.

Key words Alzheimer disease · Amyloid plaques · APOE gene · Dementia · Neurofibrillary tangles

INTRODUCTION

Following our report on the rediscovery of tissue sections from Alois Alzheimer’s case Johann F. [1, 2], efforts were intensified to find material belonging to the first Alzheimer disease patient, Auguste D. [3]. The clinical notes of this case were found in Frankfurt and have been widely publicized [4, 5]. The great interest in the case of Auguste D. appears to be at least in part due to speculations that Alzheimer’s original patient might be classified as having a different, i.e., vascular, dementia [4]. In addition, the hypothesis has been put forth that Auguste D. may have been suffering from metachromatic leukodystrophy (MLD; [6, 7]). However, these speculations seem ill-founded. In his 1907 publication summarizing the talk he gave at the 37th Meeting of the Southwest German Psychiatrists in Tübingen, Alzheimer, in fact, notes “arteriosclerosis of the larger blood vessels” of Auguste D.’s brain [5] but Perusini, according to Simchowicz [8] reporting on the same case, states that these changes were “not considerable” (case I; [9]).
Physicians’ Health Study II

2. Environmental Factors & 3. Traits:

• 1. Harvard Medical School
• 2. 15,000 Male Physicians >50 years old
• 3. 15 years (1997-2012)
• 4. Vitamin E, C, Beta-Carotene, Multivitamin vs Placebo
• 5. Conclusion: Multivitamin Lowers Cancer Incidence by 12%
Multivitamins in the Prevention of Cancer in Men
The Physicians' Health Study II Randomized Controlled Trial

J. Michael Gaziano, MD, MPH; Howard D. Sesso, ScD, MPH; William G. Christen, ScD; Vadim Bubes, PhD; Joanne P. Smith, BA; Jean MacFadyen, BA; Miriam Schwartz, MD; JoAnn E. Manson, MD, DrPH; Robert J. Glynn, ScD; Julie E. Buring, ScD

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**Context** Multivitamin preparations are the most common dietary supplement, taken by at least one-third of all US adults. Observational studies have not provided evidence regarding associations of multivitamin use with total and site-specific cancer incidence or mortality.

**Objective** To determine whether long-term multivitamin supplementation decreases the risk of total and site-specific cancer events among men.

**Design, Setting, and Participants** A large-scale, randomized, double-blind, placebo-controlled trial (Physicians' Health Study II) of 14,641 male US physicians initially aged 50 years or older (mean [SD] age, 64.3 [9.2] years), including 1312 men with a history of cancer at randomization, enrolled in a common multivitamin study that began in 1997 with treatment and follow-up through June 1, 2011.

**Intervention** Daily multivitamin or placebo.

**Main Outcome Measures** Total cancer (excluding nonmelanoma skin cancer), with prostate, colorectal, and other site-specific cancers among the secondary end points.

**Results** During a median follow-up of 11.2 (10.7-13.3) years, there were 2669 men with confirmed cancer, including 1373 cases of prostate cancer and 210 cases of colorectal cancer. Compared with placebo, men taking a daily multivitamin had a statistically significant reduction in the incidence of total cancer (multivitamin and placebo groups, 17.0 and 18.3 events, respectively, per 1000 person-years. Daily multivitamin use was associated with a reduction in total cancer among 1312 men with a baseline history of cancer. This did not differ significantly from that among 13,329 men initially without cancer.

**Conclusion** In this large prevention trial of male physicians, daily multivitamin supplementation modestly but significantly reduced the risk of total cancer.
## Inside the Personal Genome Project

The project will turn information from 100,000 subjects into a huge database that can reveal the connections between our genes and our physical selves. Here’s how. — Thomas Dootz

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<table>
<thead>
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<tbody>
<tr>
<td><strong>1. Entrance Exam</strong></td>
<td><strong>2. Data Collection</strong></td>
</tr>
<tr>
<td>Volunteers take a quiz to show genetic literacy. One question: How many chromosomes do unfertilized human egg cells contain? a) 11, b) 22, c) 23, d) 46, or e) 92? (Answer: c.) Only those with a perfect score proceed, but retests are allowed.</td>
<td>Volunteers sign an &quot;open consent&quot; form acknowledging that their information, though anonymized, will be accessible by others. They fill out their phenotype traits, listing everything from waist size to diet habits. Suitable respondents go on to the next step.</td>
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<tr>
<td><strong>3. Sample Collection</strong></td>
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<td>Volunteers hit the medical center, where they are interviewed by an MD. Then a technician draws some blood, gathers a saliva sample, and takes a punch of skin. Don’t worry: It hurts about as much as a bee sting.</td>
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<td><strong>4. Lab Work</strong></td>
<td><strong>5. Research</strong></td>
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<td>The tissues are sent to a biobank, where DNA is extracted from the blood. One percent of it — the exome — is sequenced. Meanwhile, bacteria DNA is extracted from the saliva and sequenced to reveal the volunteer’s microbiome.</td>
<td>Now the fun part: Crunching the numbers. PGP scientists and other researchers start working with the data assembled from 100,000 individuals to investigate potential links between phenotypes and genotypes. The team will look for patterns and statistically significant anomalies.</td>
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<td><strong>6. Sharing</strong></td>
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<td>The volunteers get access to not only the raw data from their genome, but anything the research team gleaned from their information. Insights — a newly discovered cancer risk, for example — are posted in a volunteer’s file, which they’ll be free to share with other PGP participants.</td>
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Harvard Personal Genome Project
GET Conference 25-26 April 2016
Genomes Environments & Traits
### Variant report for

- **This report:** [evidence.pgp-hms.org/genomes?display_genome_id=5ddfd4b0b0f1e7c14ea1a0021d19aa0b8fa13eh5f&access_token=9a72a8cd558ac64c41d530192e255410](evidence.pgp-hms.org/genomes?display_genome_id=5ddfd4b0b0f1e7c14ea1a0021d19aa0b8fa13eh5f&access_token=9a72a8cd558ac64c41d530192e255410)
- **Download:** source data, dbSNP and nsSNP report (116 MB)
- **Processing status:** processing
- **Show debugging info**

<table>
<thead>
<tr>
<th>Variant</th>
<th>Clinical Importance</th>
<th>Impact</th>
<th>Allele freq</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>APOE-C130R</td>
<td>High</td>
<td>Well-established pathogenic</td>
<td>14%</td>
<td>This is generally known as the ApoE4 allele of ApoE and is associated with increased risk of Alzheimer's. 20-25% of individuals are heterozygous for this variant, and 1-2% are homozygous. Data from Khachaturian et al. suggests an average 7% of all individuals developed Alzheimer's by the age of 86; when this is split by ApoE4 status: 10% of ApoE4 heterozygotes (3% increased attributable risk), 40% of ApoE4 homozygotes (33% increased attributable risk), and 5% of non-carriers (2% decreased attributable risk). Notably, their model suggests 70-75% of people would eventually develop Alzheimer's by the age of 100 regardless of ApoE4 genotype (and 25-30% are resistant, regardless of genotype), but that ApoE4 variants shift the disease onset to occur significantly earlier (4 years earlier for heterozygous carriers, 13 years for homozygotes).</td>
</tr>
<tr>
<td>NOD2-R702W</td>
<td>Low</td>
<td>Likely pathogenic</td>
<td>3.3%</td>
<td>NOD2 encodes a protein involved in bacterial recognition. This variant is associated with Crohn's disease in European populations, but not in Korean or Japanese groups.</td>
</tr>
</tbody>
</table>
The Harvard Personal Genome Project

II. Trait & Disease Survey

There are 16 open surveys.

- PGP Participant Survey
- PGP Trait & Disease Survey 2012: Cancers
- PGP Trait & Disease Survey 2012: Endocrine, Metabolic, Nutritional, and Immunity
- PGP Trait & Disease Survey 2012: Blood
- PGP Trait & Disease Survey 2012: Nervous System
- PGP Trait & Disease Survey 2012: Vision and hearing
- PGP Trait & Disease Survey 2012: Circulatory System
- PGP Trait & Disease Survey 2012: Respiratory System
- PGP Trait & Disease Survey 2012: Digestive System
- PGP Trait & Disease Survey 2012: Genitourinary Systems
- PGP Trait & Disease Survey 2012: Skin and Subcutaneous Tissue
- PGP Trait & Disease Survey 2012: Musculoskeletal System and Connective Tissue
- PGP Trait & Disease Survey 2012: Congenital Traits and Anomalies
- PGP Basic Phenotypes Survey 2015
- Absolute Pitch Survey
- Geographic Information
Genomic Longitudinal Environmental Aging Memory Study

III. Environmental Factor Survey

- PGP Environmental Factor Survey 2015 A: Demographics, Family History
- PGP Environmental Factor Survey 2015 B: Perinatal, Childhood, Adolescence
- PGP Environmental Factor Survey 2015 C: Birthplace, Residence, Travel
- PGP Environmental Factor Survey 2015 D: Education, Career, Avocation
- PGP Environmental Factor Survey 2015 E: Sexual, Reproductive
- PGP Environmental Factor Survey 2015 F: Alcohol, Tobacco, Psychoactive
- PGP Environmental Factor Survey 2015 G: Trauma, Poisoning
- PGP Environmental Factor Survey 2015 H: Diet, Nutrition, Weight
- PGP Environmental Factor Survey 2015 I: Exercise, Physical Fitness
- PGP Environmental Factor Survey 2015 J: Infection, Immunity
- PGP Environmental Factor Survey 2015 K: Medications, Supplements
- PGP Environmental Factor Survey 2015 L: Mental, Cognition Disorders
2015 PGP ALZHEIMER’S LONGITUDINAL STUDY     SMMSEP   SCORE SHEET
PARTICIPANT: _____________________  PGP ID: _______  PGP NO: ____  DATE: ______

I. Orientation (10)
☐ 1. What is the month?
☐ 2. What is today’s date?
☐ 3. What is the year?
☐ 4. What is the day of the week?
☐ 5. What is the season?
☐ 6. What is your street address?
☐ 7. What city do you live in?
☐ 8. What county do you live in?
☐ 9. What state do you live in?
☐ 10. What is your telephone number?

II. Registration (3)

VI. Drawing Plus (3)
☐ 31. Draw: clock ten minutes after eleven
☐ 32. Connect 10 dots A1B sequence 4 total
☐ 33. All correct 3+8 total = 10-point star

VII. Orientation Plus (6)
☐ 34. How old are you now?
☐ 35. What is your birthday?
☐ 36. What year were you born?
☐ 37. What time is it now? w/i 16 minutes
☐ 38. What is the ZIP code where you live?
☐ 39. Another phone (cell, work, family)?
What Is The Problem?

• Alzheimer’s Disease and other forms of progressive cognitive impairment are world-wide and growing phenomena of epidemic proportion as our populations age.

• The underlying causes are poorly understood but are thought to represent a complex interaction between various gene sets and environmental factors.

• GLEAMS aspires to develop on-line methods to survey and record metrics of cognitive function along with demographic, behavioral and health history with goal of discovering how these factors relate to cognitive impairment during the aging process.

www.GLEAMS.org
GLEAMS

What Is The Study?

• GLEAMS is a study of volunteers from the Harvard Personal Genome Project who are expected to eventually have their complete genomes sequenced.
• It is Longitudinal following volunteers over 20-30 years.
• Analyzing data and looking for correlates between genes, environments and cognition
• The pilot may last 1-5 years as we work out procedural details, developing secure and reliable on-line methods.

Participants will undergo quarterly on-line or in-person at annual Genes Environments and Traits GET Conference:

• Cognitive testing
• Designated family contact interview
• Environmental factors survey
• Health and safety questionnaire.

Clifford G Andrew MD PhD, Assistant Professor Neurology, Johns Hopkins University
www.Neurol.org  GLEAMS PO Box 285 Severna Park MD 21146  www.GLEAMS.org