Title Page

"Will new funding improve Alzheimer's Dementia outcomes?"

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"Will new funding improve Alzheimer's Dementia outcomes?"

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Alzheimer dementia mortality is increasing in the United States, while heart disease and cancer death rates have decreased at least 25% recently.[1] New cardiac and cancer treatments frequently make headlines. However, the assessment of Alzheimer's therapy is stark: "*…there are currently no treatments that change the course of this progressive brain disorder,*" [original italics] so stated in the 2014-2015 Alzheimer Disease Progress Report by the National Institute of Aging (NIA).[2]

President Obama signed the National Alzheimer's Project Act in 2011, with a goal of having effective therapy by 2025. Now five years later, clinicaltrials.gov lists fewer than 120 Alzheimer drug trials in the US recruiting subjects, with nearly 500,000 new patients each year. Heart disease has almost 800 drug trials, while adult cancer has almost 4000 drug trials listed.

Clinical research efforts in a disease are reflected by the number of pertinent clinical trial publications. We examined Pub Med data along with US mortality statistics to show the juxtaposition of those measures for Alzheimer's disease, heart disease, cancer and six other leading causes of death, (Figure 1).[3,4]

Reductions in US disease mortality have been proportional to the number of trials conducted in each disease except Alzheimer's, during the years 2000-2013. Alzheimer's disease is a significant outlier, since mortality is increasing while the number of peer-reviewed publications lags behind other conditions.

One could argue that research efforts and subsequent publications are dependent on funding. Dementia research funding has usually been a fraction of cancer funding, as an example, by four to ten fold less at the National Institutes of Health. The 2015 US Congress will be improving this situation, specifically increasing funds for dementia research by $350M.

Nevertheless, in NIA projected budgets, dementia clinical trials are allocated less than a third of the funds. Last summer's Con-

gressional Bypass Budget for Alzheimer's and related dementias lists the "Translational Research and Clinical Interventions" portion at only 29%. The budget otherwise lists 71% for research in genetics, imaging, biomarkers, epidemiology and other areas not directly therapeutic.[5]

The assumption is that laboratory science will discover the right target, and a designer drug will modify the progression of dementia. But in cancer, even with proven molecular targets, we still need multiple chemotherapy agents to effect a cure.

Over $300M has been spent yearly in dementia research through the NIA since 2011. In contrast, the national Children's Oncology Group (COG), granted about $25M yearly, provides comprehensive leadership, strategic coordination and multi-institutional collaboration in over 200 pediatric cancer centers for nearly 100 clinical trials. COG trials have a substantial record of improving survival and quality of life in childhood cancer.

Investigators examined a decade of dementia drug discovery efforts, and found a 99% failure rate.[6] Undaunted, researchers have proposed creative ideas for comprehensive trials of existing drugs, supplements and combinations of therapy, but to our knowledge few have come to fruition.

So how will the new money be spent? To find effective therapy, the NIA has presented rational recommendations, emphasizing basic science. Recently, commercially developed monoclonal immunotherapy and certain chemotherapy agents have shown some promise, but an overall strategy for discovering new agents and sustaining clinical development seems lacking in NIA documents.

Unconventional approaches may be necessary. Budgets may need to be re-proportioned to emphasize clinical trials. With a deadline of 2025, perhaps the lengthy grant process should be bypassed to commission trials at clinical research organizations. Pragmatic, strategic, directive, creative, ambitious and accountable clinical leadership will be necessary.

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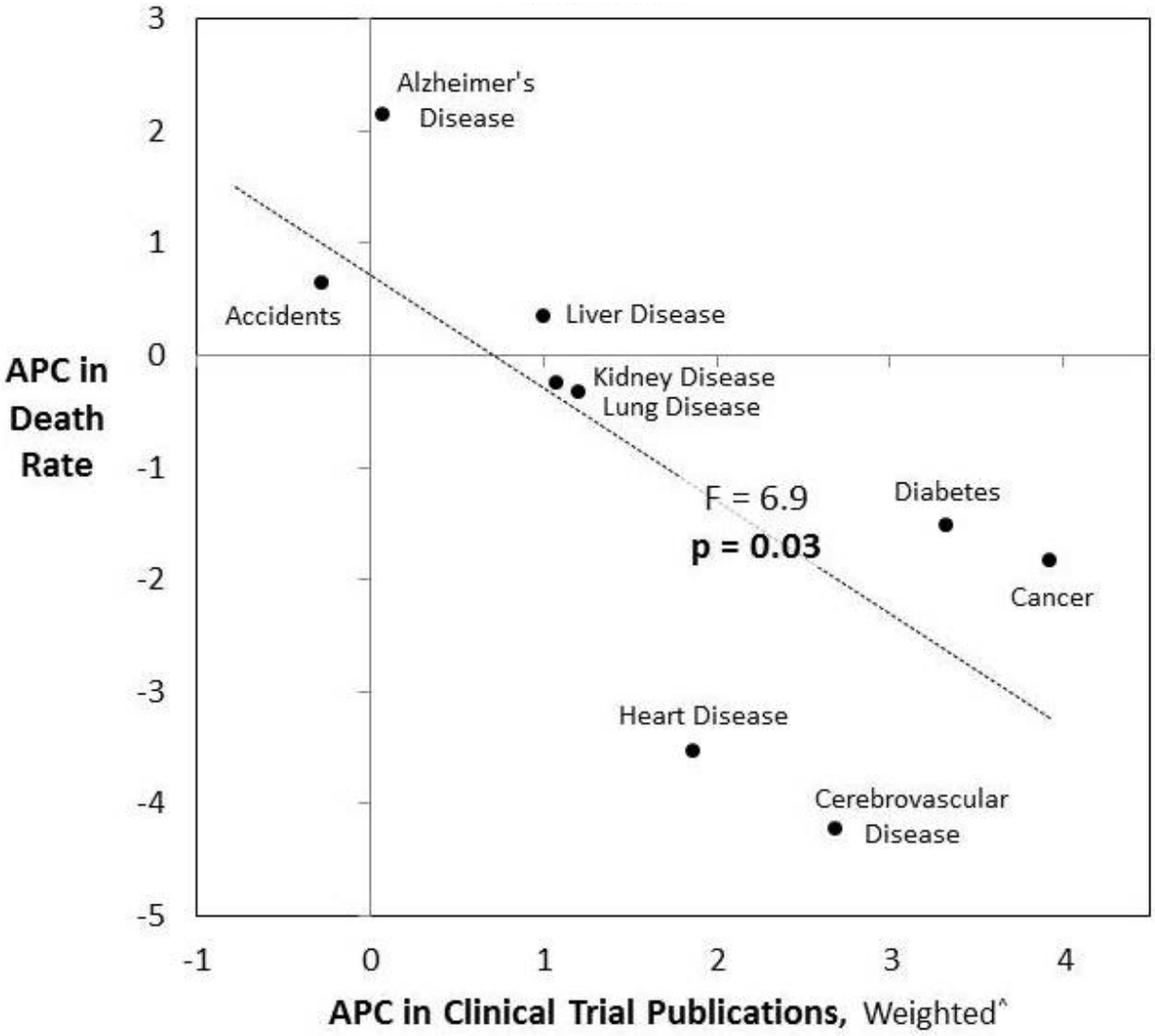

Figure Title

Figure 1: Average percent change (APC) in the death rate and number of peer-reviewed publications compared for the top ten causes of death in the US, excluding suicide, 2000 to 2013.

Figure Legend

Death rates from the National Cancer Institute Surveillance, Epidemiology and End Results database.[3] Publication numbers from PubMed.[4] ^Square root of average number of publications during 2000-2013