Title:

**Occult, cryptic chronic infection as a substantial contributor to chronic diseases.**

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**Abstract:**

According to Peterson-Kaiser Health System Tracker the highest cost disease category between 2000 and 2013 was "ill-defined" conditions. Well-defined conditions including cancer, autoimmune diseases, diabetes, and neurodegenerative diseases continue to increase despite improved early detection and highly sophisticated targeted treatment. Cardiovascular diseases, which exhibited a downward trend starting in about 1975, which coincided closely with smoking trends, started increasing again in 2012 despite a broad approach of prevention and treatment using statin and other pharmaceutical drugs. Even with some limited triumphs, it's clear that a fundamental root-cause understanding of chronic disease processes and related treatment is lacking. Historically, when the true cause of a disease was discovered and appropriate treatments for the cause was affected, morbidity and mortality rates fell precipitously and rapidly.

We illustrate here, that chronic infection, particularly those classified as obligate intracellular, and medically referred to as occult and cryptic, are often causal agents in many of the most common, and possibly uncommon, chronic diseases continually facing our populations.

Methods: Two distinct and separate cohorts were part of this study. Cohort 1 was composed of clinical patients observed, evaluated and treated by an ophthalmologist on staff at Harvard Medical School over a 30-year period. Patients generally presented with a degenerative eye complaint such as cataract, macular degeneration, or glaucoma. Subsequent evaluation often revealed comorbidities, complement activation, inflammation, intracellular infection, vascular disease, and neurodegeneration. An advanced blood panel was obtained on each patient at initial consult, during, and at the end of treatment regiments. This testing included usual care tests along with acute phase reactants associated with chronic inflammation. Pathogen titers were also drawn on those presenting with a chronic indication. In addition, detailed eye pathology measurements were conducted at appropriate intervals on all subjects. Cohort 2 included a group of 100 volunteers, all workers or family members at a manufacturing facility in Indiana. Each person presented with unresolved chronic health complaints ranging from chronic migraines to Parkinson's disease despite having access to an on-site medical clinic, affiliated hospitals and specialty care covered by comprehensive medical insurance. In this study, advanced blood panels similar to cohort 1 were drawn on all participants throughout the study. Eye pathology investigation was recorded selected members of the cohort based on complaints or reported neurodegeneration.

Results: A statistically significant number of subjects with persistent, unresolved chronic conditions tested positive for obligate intracellular infection compare to those without such complaints. In cohort 1, approximately 75% of those presenting with a chronic eye pathology had at least 1 positive titer for infection. Treatments targeting the specific intracellular infection consistently resulted in 1. Reduced titers for the infection(s), 2. Improvement in blood labs, specifically those for chronic inflammation and infection, 3. Frequent improvement in eye pathologies such as cataract, glaucoma, macular disease, and dry eye, and 4. Improvement in chronic conditions as indicated by

reduction in medication use and change in diagnosis status by an independent physician. In cohort 2, of 85 of 100 initial participants who remained active after the first 3 months of an intensive disease reversal protocol were then evaluated periodically with blood tests. Of the 85 participants, 42 where classified as severely chronically ill based on multiple chronic conditions determined by a team of independent physicians. In the group of 42, 41 tested positive for 1 or more intracellular pathogens while only 5 of the other 43 tested positive. In the group of 41, after 3 months of targeted pathogen treatment all showed subjective improvement in symptoms, in some cases with complete resolution of previous diseases. Approximately 50% showed improvement in lab values associated with infectious agents and 97% showed improvement in their non-infectious blood profile.

Conclusion: Occult obligate intracellular infection is a substantial contributor to systemic inflammation and chronic disease pathologies both identified by common chronic disease classification and ill-defined. Therapy targeting these organisms reduces infectious burden, blood biomarkers for inflammation and leads to positive clinical outcomes in diseases as varied and RA, migraines, eye diseases and Alzheimer's disease suggesting a common underlying mechanism in all these sequelae.

**Introduction:**

Developed nations, and particularly the United States, continue to confront a chronic disease crisis. [1] The WHO reported that in 2010, non-communicable chronic diseases including: cardiovascular diseases, diabetes, cancers, and chronic respiratory diseases, accounted for 2/3rds of deaths worldwide. [2] The Institute of Medicine reported that America is less healthy compared to high-income nations in obesity, diabetes, heart disease, chronic lung disease, and disability. [3] The Organization of Economic Cooperation and Development tracks the health of 36 developed nations.[4] The U.S. scores in the lower half compared to 36 nations on all major indicators of health, and longevity. When considering that the per person per year cost of healthcare in the U.S. is more than two and a half times higher compared to the OECD nation average, a health paradox exists in America. This American Paradox is the worst cost-to-value benefit for chronic disease outcomes compared to the 35 other nations, by far. The chronic disease management system is failing in both disease prevention and disease management (disease reversal or stopping progression of the underlying condition). Health and prevention recommendations currently supported by the major medical societies thus are proven ineffective, laboratory tests are of limited scope and don't address the root-causes of chronic diseases. Pharmaceuticals indicated based on test results have limited statistical success at preventing or reversing disease as eighty-six percent of the nation's nearly 4 trillion annual health care expenditures is for people with chronic conditions. [5] In America, if treatments were solving, rather than managing chronic conditions, our healthcare spending would be more in line with the OECD average, and based on spending our outcomes should be superior.

On average, Americans with five or more chronic conditions spend 14 times more on health services than people with no chronic conditions. [6] As of 2014, 60 percent of American adults had at least one chronic condition, and 42 percent had more than one chronic condition. [6] Five percent of the population accounts for an estimated 49-53% of total health care expenses. [7] The 15 most expensive health conditions account for 44 percent of total health care expenses. [8] The financial and productivity costs impact our corporations, who fund over half of national healthcare at a price of roughly 4% of gross corporate revenues. And much of this cost is segmented in high cost beneficiaries where, for example, the top 1% of claimants cost $150,000/y compared to the population mean of $4800/y. [9] In a report compiled by the Health Care Cost Institute, there is a surprising large turnover from year to year among the highest cost healthcare spenders. Three out of five top spenders in any given year were not top spenders in the prior year. In 2015, only 39% of the top 5% spenders were in the top 5% of spenders in 2014. Moreover, this trend was consistent

in each year from 2009 to 2015. These new top spenders came from all portions of the spending distribution. For example, in each year studied, almost 15% of top spenders were in the bottom 50% of spenders or had no spending in the previous year. [10] Thus, there is a need for better predictive analytics and patient workup to determine causal factors of chronic disease to better identify and manage risk to finally reverse the escalating chronic disease and cost trend facing America, and to a lesser degree, nations globally.

Obligate intracellular bacterial pathogens and other infectious species including virus, fungi, and parasites are an understudied but significant group of human disease agents. [11] Despite dramatically reduced genomes relative to most free-living bacterial pathogens, obligate intracellular bacterial pathogens retain potent pathogenetic potential that can manifest in infections ranging from asymptomatic to fulminating and deadly [12, 13] It is now widely recognized that microscopic species including bacteria play a key role, both beneficial and adversarial, in human physiology. For example, complete sequences of numerous mitochondrial, many prokaryotic, and several nuclear genomes confirm that the mitochondrial genome originated from a eubacterial ancestor. [14] Pathogenic bacteria are slowly regaining notoriety as important in human disease as indicated by the Nobel Prize and Medicine or Physiology in 2005 for the evidence that H-pylori infection is a causal agent in stomach ulcers. [15] Now it is widely understood that this pathogen causes a broad spectrum of chronic gut issues including cancer.

According to Ewald, "Over the past two centuries, diseases have been separated into three categories: infectious diseases, genetic diseases, and diseases caused by too much or too little of some noninfectious environmental constituent. At the end of the 19th century, the most rapid development was in the first of these categories; within three decades after the first cause-effect linkage of a bacterium to a disease, most of the bacterial causes of common acute infectious diseases had been identified. This rapid progress can be attributed in large part to Koch's postulates, a rigorous systematic approach to identification of microbes as causes of disease. Koch's postulates were useful because they could generate conclusive evidence of infectious causation, particularly when (1) the causative organisms could be isolated and experimentally transmitted, and (2) symptoms occurred soon after the onset of infection in a high proportion of infected individuals. While guiding researchers down one path, however, the postulates directed them away from alternative paths: researchers attempting to document infectious causation were guided away from diseases that had little chance of fulfilling the postulates, even though they might have been infectious. Fulfillment of Koch's postulates confirms infectious causation, but doing so has become less feasible over the past century [16]; it is likely to become even less feasible in the future because many of the characteristics that make infectious causation cryptic also hinder fulfillment of the postulates. [17]

Fields, et. al., state, "Obligate intracellular bacteria represent consummate parasites, often covertly co-opting host resources to enable development and ultimately transmission to a new host. The overall success of this survival strategy is doubtless derived from co-evolution with respective eukaryotic hosts over hundreds of millions of years. Indeed, many species of obligate intracellular bacteria represent pathogens capable of significant negative impact on world-wide human health. This link to human disease and the fascinating infection biology exhibited by these parasites render them exquisite subjects for investigation. Despite the overarching absolute requirement for growth within eukaryotic cells, this class of bacteria has evolved distinct strategies that enable colonization of diverse tissues, cell types, and even subcellular niches." [18] While Ewald's work substantially rationalizes the infection-chronic disease connection for known and common chronic conditions such as cancer and cardiovascular diseases that of Fields helps us understand that pathogens are a logical place to look in ill-defined and refractory chronic conditions.

Chlamydophila pneumoniae (Chlamydia pneumonia, CP) is an obligate intracellular pathogen that is known to infect a large percentage of the human population. According to Crother and Porritt, "The majority of individuals are exposed to C. pneumoniae throughout their lifetimes with an antibody prevalence of 50% by age 20 and 80% by 60–70 years old. [19] Although C. pneumoniae infection is predominantly asymptomatic or mild, it can result in the development of acute upper and lower respiratory illness including bronchitis, pharyngitis, sinusitis, and pneumonia. [20] C. pneumoniae infection and its relationship to chronic inflammatory diseases remains a controversial topic. A mounting body of evidence shows that not only is C. pneumoniae involved in respiratory infection, it also contributes to the pathogenesis of a range of inflammatory diseases including, but not limited to, atherosclerosis, arthritis, asthma, lung cancer, and chronic obstructory pulmonary disease as well as neurological disorders, namely, Alzheimer's disease, multiple sclerosis, and schizophrenia." [21]

Epithelial cells infected with C. pneumoniae are resistant to apoptosis induced by treatment with drugs or by death receptor ligation. [22] "The induction of protection from apoptosis depended on the infection conditions since only cells containing large inclusions were protected. The underlying mechanism of infection-induced apoptosis resistance probably involves mitochondria, the major integrators of apoptotic signaling. In the infected cells, mitochondria did not respond to apoptotic stimuli by the release of apoptogenic factors required for the activation of caspases." This data suggest a direct modulation of apoptotic pathways in epithelial cells by the organism, the purpose of which is organism survival and proliferation.

Infectious agents are known to reprogram host cell gene expression to the benefit of their life cycle and these changes can be long lasting and global or transient and of limited breadth. [23] A landmark review of 32 studies involving 77 different host-pathogen interactions demonstrated that pathogens impact the host cell genetic program. And a large percentage of the studies reported examples of pathogens that down regulate innate immunity. Interesting the 2018 Nobel Prize for Physiology or Medicine was awarded for "cancer therapy by inhibition of negative immune regulation." Cancer impacts innate immunity, or more probably infectious species like h-pylori, HPV, chlamydia pneumonia and other organisms that are part of the complex cancer cascade and are likely the basis for this effect. [24]

Kellam et. al., were the first to publish the concept of "infectogenomics." [25] Some key teachings manifest from this original paper. They explain how "the dose of infection and the fitness of the host and pathogen will determine sickness" as demonstrated by van Opijnen, [26] and state "After all, unfit pathogens can make excellent live attenuated vaccines." They go on to conclude: "The functional genomics of the host is of crucial importance in analyzing host-pathogen interactions. Host genetic variation plays a key role in determining the outcome of many potentially pathogenic infections, and the prevalent pathogens have influenced the genetic make-up of human populations. Infectogenomics can be harnessed to identify infectious states, to understand the host response, to predict disease outcomes, to monitor responses to antimicrobial therapies, and to indicate promising new types of treatment."

Stratton et. al explain that intracellular organisms can exist in lifecycle phases cleverly crafted to avoid detection by the host immune system. [27] "Chlamydiae organisms growth cycle alternates between 1) intracellular life forms, of which two are currently recognized, a metabolically-active, replicating organism known as the reticulate body (RB) and a persistent, non-replicating organism known as the cryptic phase; and 2) an extracellular life form that is an infectious, metabolically-inactive form known as the elementary body (EB)." Stratton indicates that patients infected with C. Pneumoniae have high IgM and IgG titers as indicated by elevation above reference ranges. Upon specific antibiotic therapy, over time the IgM titers fall and IgG titers rise, as expected based on

organism life cycles. However, with detoxification, the IgG titers fall indicating the partial or complete elimination from the perspective of clinical significance.

There continues to be controversy and confusion over IgG positive antibody tests and the presence of an organism. The usual view is that IgG must be positive in order to indicate a potential infection. [28] IgM antibodies are the first antibodies to be produced in the body in response to an infection. IgM antibodies are larger than IgG antibodies and when present in high numbers, may indicate a recent or new active infection. The IgG antibodies are produced once an infection has been going on for a while, and may even be present after the infection has apparently been resolved. The presence of IgG antibodies to an organism when accompanied by a negative IgM test for the same organism classically means that the person was exposed to that organism at one time and developed antibodies to it, but does not have a current active infection of that organism. However, it does not indicate the eradication of the organism and often implies that the organism is dormant or hiding in a life cycle phase that is purposefully invisible to the immune system. [29]

Toxoplasma gondii is an intracellular parasite known to cause brain-altering manifestations in humans and animals. It is classified as one of five "neglected parasitic infections of the United States" by the Centers for Disease Control. [30 One of the characteristic manifestations of toxoplasmosis is retinal eye scarring. It is presumed this is a sign of past infection and people with these scars often test positive for toxoplasma gondii serologically with igG antibodies. However a recent study showed that tissue cysts are not dormant but rather quite active. [31] Sinai et al. state, "Despite over a third of the world's population being chronically infected with Toxoplasma gondii, little is known about this largely asymptomatic phase of infection. This stage is mediated in vivo by bradyzoites within tissue cysts. The absence of overt symptoms has been attributed to the dormancy of bradyzoites. In this review, we reexamine the conventional view of chronic toxoplasmosis in light of emerging evidence challenging both the nature of dormancy and the consequences of infection in the CNS. New and emerging data reveal a previously unrecognized level of physiological and replicative capacity of bradyzoites within tissue cysts. These findings have emerged in the context of a reexamination of the chronic infection in the brain that correlates with changes in neuronal architecture, neurochemistry, and behavior that suggest that the chronic infection is not without consequence." Thus the immune system never clears the parasite. Immunity causes it to morph into the "dormant" tissue cyst form, leading to a life-long chronic infection that can reactivate in a compromised host, similar to chicken pox. [32]

Fagerberg et al., showed that any positive titers including just elevated levels of IgG for C. pneumoniae were associated with an increased risk for future stroke, with a relative risk of 8.58 and for any cardiovascular event with a relative risk of 2.69. [33] They concluded that seropositivity for C. pneumoniae including when only IgG was elevated, was associated with an increased risk for CVD, independent of all other usual risk factors. In the Northern Manhattan Stroke Study, [34] "titers for IgG, IgA, and IgM antibodies specific for C. pneumonia were measured and ≥1:16 were considered positive." "Elevated C pneumoniae IgA titers were significantly associated with risk of ischemic stroke after adjusting for other stroke risk factors (adjusted OR 4.51, 95% CI 1.44 to 14.06). IgG titers were less strongly associated with stroke risk (adjusted OR 2.59, 95% CI 0.87 to 7.75). The association of IgA with stroke risk was detected in both younger and older groups, in men and women, and in whites, blacks, and Hispanics. There was also a significant continuous increase in risk associated with the log-transformation of the titer for IgA (adjusted OR 1.32, 95% CI 1.05 to 1.66)."

Amyloid formations in humans are referred to as the disease state "amyloidosis." Most authorities consider these formations a serious health problem that can lead to life-threatening organ failure. Beta-amyloid, a type of amyloid formation is considered the hallmark of Alzheimer's disease and an important treatment target. After dozens of clinical trials that successfully reduced the level of beta-

amyloid, and nearly $1 trillion dollars spent, not one study participant with Alzheimer's showed any improvement. [35] These Alzheimer's amyloid plaques may actually be part of the immune system, a Harvard study has revealed. The research indicates that amyloid-beta may be the 'first line of defense' against infection in the brain and other tissues. [36,37] The Harvard team reports, "Members of this evolutionarily ancient family of proteins, collectively known as antimicrobial peptides (AMPs), share many of the amyloid's purportedly abnormal activities." [38] This connection should not have been met with surprise in the medical community as many researchers and clinicians have reported infection as a contributor to Alzheimer's since the 1990s. Judith Miklossy, in particular, has published over 20 papers explaining the evidentiary link between spirochetes and Alzheimer's beginning with a landmark paper published in 1993 titled, "Alzheimer's – A Spirochetosis?"[39]

Many examples of infection causing chronic disease are focal in nature. Frank Billings was the first to promote the profound impact on health by infection residing in localized tissue. [40] Charles Mayo presented the concept of dental focal infection in 1913 and subsequently was involved in over 50 publications addressing the cripticity of disease cased by focal dental infections. [41 Gorzó reviewed the history of focal infection in 2003. [42] A scant 3 papers have cited this work indicating that focal infection theory of disease is considered an archaic concept among members of the medical community. Tissue tropism is noted as a cause of inflammation and secondary diseases beyond the foci. Párkányi et. al. demonstrate how odontogenic focus, in particular periodontitis and periapical periodontitis, causes disease in distant areas of the body in general leading to the development of particular conditions, such as cardiovascular diseases, pneumonia, diabetes mellitus, metabolic syndrome, rheumatoid arthritis and adverse pregnancy outcomes. [43]

Focal infection raises white blood cell counts concomitant with the extent a severity of the infection. However, the elevated leukocyte levels seldom elevate beyond normal reference ranges. Al-Rasheed demonstrated that periodontitis patients have significantly higher WBC count than that of control patients, 7.22 +- 1.42x109 cells/L as opposed to 5.64 +- x 109 cells per liter. At 7.22 x 109 cells per liter few medical practitioners indicate future health risk is inferred. The Women's Health Initiative clearly demonstrates that WBC counts consistent with those in the periodontal cohort warn of a significant increase in fatal heart attacks. Harvard University, by way of The Harvard Gazette, in a 2005 article titled, "*Simple test predicts heart attack. White blood cells sound a new alarm*" [44] explain: "As part of the federally supported Women's Health Initiative, investigators at medical centers all over the United States collected information on 72,242 postmenopausal women 50 to 79 years old. All were free of heart and blood vessel disease at the start of the study. During six years of follow-up, 1,626 heart disease deaths, heart attacks, and strokes occurred. Women with more than 6.7 billion white cells per liter of blood had more than double the risk of fatal heart disease than women with 4.7 billion cells per liter or lower. A count of 6.7 billion white cells per liter of blood is considered to be normal, so what is "normal" may have to be redefined."

In their original investigation, Margolis et. al., conclude: "The WBC count, a stable, well-standardized, widely available and inexpensive measure of systemic inflammation, is an independent predictor of CVD events and all-cause mortality in postmenopausal women. A WBC count greater than 6.7 billion white cells per liter of blood may identify high-risk individuals who are not currently identified by traditional CVD risk factors. [45] Neither infection nor the concept of focal infection was considered in that article but inflammation as causal was.

Focal infection caused by periodontal disease results in elevation of other markers of inflammation and tissue repair. Fibrinogen and CRP serve as important biomarkers for determining the presence and extent of focal infection. [46] Fibrinogen has been used as a biomarker for detecting periprosthetic joint infection. [47] Iqbal, et. al., show that an increase in WBC, neutrophil,

lymphocyte, and platelet count and a decrease in total protein, albumin, and globulin in aggressive periodontitis patients when compared to healthy individuals. [48]

The eye is a profound marker of inflammation and infection. Ebola survivors describe major limitations in vision due to cataract formation even at ages as young as 5. [49] Elevation in WBC is frequently noted in people with Age-related Macular Degeneration. According to the Blue Mountain Study, individuals with a WBC >6.7 billion cells/liter are twice as likely to have ARMD compared to people with counts of 5.5 × billion cells/liter). The Age Related Eye Disease Study (AREDS) demonstrates well the connection between major eye diseases and early mortality. [50] For cataract, the increase in mortality is particularly significant at 11% in 6.5 years compared to <1% in the general age-matched population. Cataracts and macular degeneration reflect systemic rather than only local processes. Viral infections are known to contribute to cataract. Hepatits virus infections are associated with cataract formation and age-related macular degeneration. [51,52] Glaucoma, a neurodegenerative eye condition similar to Alzheimer's disease [53] is potentially caused or exacerbated by infection. C. pneumonia, long ago implicated in Alzheimer's disease, [54] is also shown to be a potential cause of optic nerve head ischemia. [55] The eye, then, may find important use as a screening tool for focal and general low-grade chronic infection and inflammation.

Cholesterol-lowering drugs, led by statins, have been the dominant approach to cardiovascular disease primary and secondary prevention. However leading authorities indicate that even the most efficacious of these agents do not improve mortality. According to an article in "Proto" from the Massachusetts General Hospital, "What statins might do for you: Lower cholesterol // Reduce risk of cardiovascular disease //Cause muscle paint and fatigue // Fail to significantly prolong your life." [56] Objective data seriously question the effectiveness of statins in prevention. In an observational study of 136,905 people hospitalized for a heart attack, 72.1 percent had admission LDL levels less than 130 mg/dL. [57] Diabetics are much more susceptible to dying from heart disease with published rates around 250% higher mortality compared to non-diabetics. Statin therapy increases the risk of diabetes by 9%-12% in two meta-analyses of statin trials and by 18%-99% in five population-based studies. [58] Feingold et. al. note, "The changes in lipids and lipoproteins that occur during inflammation and infection are part of the innate immune response and therefore are likely to play an important role in protecting the host." [59].

Obligate intracellular bacteria manipulate the cholesterol levels of the host. [60] The outcomes are increased host levels of total cholesterol, LDL and oxidized low-density lipoprotein. Infection may well explain the source of elevated cholesterol in many chronic diseases while also explaining why statin and other cholesterol-lowering approaches have failed to provide morbidity and mortality benefits projected based on LDL and the cholesterol molecule being disease-causal agents.

In "Infectious Causes of Chronic Inflammatory Diseases and Cancer," [61] Dr Gail Cassell leads with, "Powerful diagnostic technology, plus the realization that organisms of otherwise unimpressive virulence can produce slowly progressive chronic disease with a wide spectrum of clinical manifestations and disease outcomes, has resulted in the discovery of new infectious agents and new concepts of infectious diseases. The demonstration that final outcomes of infection is as much determined by the genetic background of the patient as by the genetic makeup of the infecting agent is indicating that a number of chronic diseases of unknown etiology are caused by one or more infectious agents."

Immune system vitality may be the most important risk factor in any chronic disease included those with contributions from infection. The World Health Organization in "Risk Factors of Communicable Diseases" states, "Apart from symbiotic coexistence of human with micro-organisms, disease causing organisms breed in man made unhygienic conditions of air water and

soil. People with low immunity, weak, and living in unhygienic conditions are at greater risk for contracting the infections from surroundings." [62] Chronic inflammation is an accepted cause of chronic disease. [63, 64] As defined by Opie, "Inflammation may be defined as the process by which cells and serum accumulate about an injurious agent and tend to remove or destroy it." [65] Chronic inflammation continues to be blamed for tissue damage but this complex cascade, stimulated by internal and external mediators, results in the release of danger signals that promote immune responses to antigens. [66] Chronic, occult infection is a significant stimulator of chronic inflammation that often is overlooked as a cause of the chronic inflammation due to its enigmatic nature. Associations between IgG titers for intracellular pathogens, when elevated, normally considered a sign of past infection, and disease has yielded mixed results. Yet sufficient evidence for a causal relationship between bug and illness exists, based on the preponderance of existing evidence, magnitude of ill-defined conditions, and continued unacceptably high morbidity and mortality in common chronic diseases. [67-82]

The occult nature of certain pathogens, especially those thriving intracellularly necessitates more robust and comprehensive assessments for risk and disease causation. For example, heart disease continues to be the #1 cause of morbidity and mortality in the U.S. and globally, in developed nations, despite broad use of cardiovascular disease medications for both prevention and intervention. [83] The LDL study in 136,905 patients hospitalized referenced above imply there is room for more robust testing to augment evaluation of cardiovascular risk and cause. Infection with species like Helicobacter pylori, Lyme disease, and C. pneumoniae may contribute to an explanation for a lack of association to disease and lipid lowering approaches. [84, 85, 86] In older populations, "concentrations of homocysteine alone can accurately identify those at high risk of cardiovascular mortality, whereas classic risk factors included in the Framingham risk score do not," [87] potentially reflecting the ability of homocysteine to measure infectious antigen load. [88] In healthy men, adding C-reactive protein levels to traditional risk factors, the Reynolds Risk Score, improved cardiovascular risk prediction. [89] The Intermountain Risk Score uses common blood measures and assesses risk from the group of markers to develop a risk score. Although limited in application, this scoring system has been reported to be more predictive of increased mortality risk compared to that used in the standard-of-care. [90] C-reactive protein, used in both these scoring systems provides incite into infectious burden. [91, 92, 93]

Approaches designed to augment usual care diagnostics are emerging including the "Allostatic Load" and "InflammAging" measurements. Each or these concepts consider a broader molecular view, rather than an organ system view, of disease. According to McEwen, "When these (our body's) adaptive systems are turned on and turned off again efficiently and not too frequently, the body is able to cope effectively with challenges that it might not otherwise survive. However, there are a number of circumstances in which allostatic systems may either be over-stimulated or not perform normally, and this condition has been termed "allostatic load" or the price of adaptation." [94] Claudio Franceschi coined the term "inflammaging" in 2000 to describe the concept of low-grade chronic inflammation and its impact on health. [95] Inflammaging was described as an extension of the "network theory of aging." [96] Similar to the allostatic load, a global reduction in the capacity to cope with a variety of stressors, including stealth infection, and a concomitant progressive increase in proinflammatory status are considered the major characteristics of the inflammation aging process and susceptibility to premature disease and mortality.

According to Salinas et al., the allostatic load leads to dysregulation of the neuroendocrine system and subsequent elevation in inflammatory markers, leading to metabolic syndrome and chronic diseases such as cardiovascular disease. [97] Thus the allostatic load and inflammaging are both measured, at least in part, through inflammatory markers like C-reactive Protein, cortisol levels, glycosylated hemoglobin, white blood cell counts, and fibrinogen as examples. Inflammaging is

associated with a cumulative lifetime exposure to antigenic load caused by both clinical and subclinical infections. [98, 99] Non-infective antigens are also implicated in this process and may well be the first step to proliferating or activating existing infection or otherwise lowering resistance to future exposures.

Measuring inflammatory biomarkers offers the potential to provide a better assessment of both infective and non-infective antigen burden. Multiple biomarkers, in general, improve the predictive power of a panel. In a study of 3209 people assessed with 10 biomarkers, persons with multi-marker scores in the highest quintile as compared with those with scores in the lowest two quintiles had elevated risks of death and major cardiovascular events of 4.08 and 1.84 (adjusted hazard ratios) respectively. [100] This far exceeds the predictive hazard ratio for cholesterol alone, as an example, which varies from 0.89 to 1.25 depending upon the study. [101, 102, 103] Numerous studies and reviews consistently show the value of multiple markers in real world prediction of disease events and premature mortality. [104, 105, 106, 107, 108, 109] Thus expansion of the depth and breadth of diagnostics and risk assessment beyond lipids, A1C, blood pressure, and basic chemistry testing is required to better access risk, future outcomes, and get to the root causes of diseases and offer solution beyond disease management.

The Chronic Disease Temperature™ (CDT) risk scale used in these studies combines emerging concepts for improving the evaluation of disease risk and measurement of active disease. The significant attributes of the CDT scale are: 1. Consideration of multiple biomarkers, 2. Selection of markers based on traditional and new predictive markers based on inflammaging and the allostatic load, 3. Harmonizing each marker to a standard endpoint – statistically significant increase in early all-cause mortality risk, 4. Consideration of risk contribution based on log-linear scales appropriate to each biomarker fitted to individual marker hazard ratios for mortality, and 5. Mathematical modeling of the risk values from each marker to generate a single, highly predictive value for current or future risk of chronic illness. The aggregate CDT score is an indicator of early mortality and, it is well established that those who die early statistically suffer from longer periods and more frequent morbidity. [110] The values for each marker reflect both mortality risk and disease risk based on the association of a given marker to disease indication. This single number may be an important bridge to better appreciation of antigen burden and health literacy, as most patients do not understand the meaning of their current lab values. [111] The CDT does not constitute a medical diagnosis of disease any more than does any individual marker, like homocysteine, but does afford better statistical predictive capability and measurement of disease progression or regression compared to single biomarkers.

Accurately measuring disease burden is important in establishing objective health risks and evaluating interventions. Lifestyle, however, is the fundamental root cause of many common chronic diseases. Lifestyle diseases, including the major recognized chronic diseases, account for up to 86% of total disease burden in developed nations. [112, 113, 114, 115, 116] Meng et. al [117] developed and evaluated a semi-quantitative composite chronic risk index (CDRI) and investigated its relation with chronic disease. In a group of over 30,000 individuals over 5 years, they showed that positive health behavior they measured was associated with a lower risk of cancer and greater longevity. In this study, as a companion to the CDT, we implemented an expanded version of a CDRI that assesses risks beyond smoking, alcohol use, body mass index, fat intake, and fruit and vegetable consumption. The risk evaluation tool used in this study, the Chronic Disease Assessment™ (CDA), is an on-line, health risk assessment and mitigation tool and involves answering 120 ± questions that probe deeply into lifestyle and environmental sources of risks, along with behaviors, health attitudes, readiness to change, current and past complaints, problems and diagnoses. The output of the CDA is a raw subjective, but comparable risk score based on numerical risk scores assigned to question and answer combinations. A letter “grade” associated

with risk score ranges reflects the extent of the risk and health "portfolio" of an individual. The letter grade is provided to participants as an easily understood value for their risks to overcome generally poor health literacy that especially impacts high-risk populations. [118] In addition, the Chronic Disease Assessment output generates a series of actions including personalized education and actionable solutions specific to each risk in a participant's risk portfolio. Finally, a Health Revival Care Plan™ is generated from the risk portfolio, and adjusted by a health providers and the participant, to create a comprehensive yet manageable personalized roadmap to overcome risks and improve health.

Expansion of the depth and breadth of risk assessment and linked prevention and mitigation programs is important because the limited set of measures of usual care of today is providing marginal results. A well-studied disease prevention arena is a corporate wellness program. Most of these programs rely on "usual care" that includes: basic dietary recommendations, weight loss, smoking, alcohol consumption and metabolic and lipid index targets. [119] A broad-based team of wellness professionals and academics evaluated workplace wellness programs.[120] They unanimously concluded that few wellness programs meet expectations and most are abysmal failures. What separates bad, good, and great programs are "a combination of good design built on behavior change theory, effective implementation using evidence-based practices, and credible measurement and evaluation." To further support the need for more thorough risk assessment, in a global study of 84 risks, the authors concluded "Increasingly detailed understanding of the trends in risk exposure and the relative risks for each risk-outcome pair provide insights into both the magnitude of health loss attributable to risks and how modification of risk exposure has contributed to health trends. [121] These types of data clearly illustrate a path to improved health outcomes and the urgent need for more robust root-cause assessments of disease risks.

Within the present study, in cohort 2, health coaches, interacted face-to-face and electronically with participants and implemented health professional-developed (including by medical doctors) care plans based upon the finding from the CDA and CDT. Coaching activates patients to change through collaborative learning and social support. [122] Patient engagement and P4 medicine is an increasingly important component of strategies to prevent and reverse chronic disease. [123] In addition, doctors evaluated patients, their records, ordered and interpreted labs, removed participants from pharmaceutical, and prescribed treatments based on new findings, when necessary. In cohort 1, the presiding doctor expanded his role to include health coaching that included frequent office visits and phone encounters with a frequency of well beyond usual care. In some cases daily calls were made to specific high-risk patients with many patients receiving phone call follow-ups at least weekly.

The purpose of this study was to assemble and report the work of Dr. Clement Trempe who successfully treated numerous patients with neurodegenerative conditions using methods he developed over a 30-year clinical career. Also, we sought to illustrate, through a cohort of individuals with ill-defined and usual chronic conditions that the processes developed by Trempe for neurodegenerative diseases applies to a broad array of common chronic ailments. In addition the scalability, effectiveness, and safety of this novel diagnostic and care model for the prevention and reversal of a broad spectrum of chronic diseases and complaints was evaluated in the context of population health management. Primary endpoints to assess effectiveness of the program were measurement of unexpected potential sources of causation, specifically infectious antigens, and interventions that targeted lowering antigen burden along with concomitant evaluation of subjective and objective health status. We demonstrate the infectious antigen predictive power of labs from a novel biomarker panel, particularly when the lab values were assessed with consideration of low-grade, chronic inflammation being part of the disease cascade as a departure from an acute "indication" interpretation of normal and abnormal labs. Our goal was to illustrate

that, in a population of mid-western Americans with a broad range of usual, not extraordinary, but largely unexplained chronic health complaints and diagnoses, that infectious antigen burden may be an important contributor to morbidity and mortality. Further, that improved lifestyle risk factors, known to be associated with adverse health conditions, can improve them independent of direct treatment of the detected infection. Finally, we demonstrated that a program of anti-inflammatory and anti-infective pharmaceuticals, used as an adjuvant to lifestyle modification further improves antigen burden and health status.

**Methods:**

In cohort 1, archival data were reviewed from 151 patients seen by Dr. Clemente Trempe between 1995 and 2014. Each patient initially presented for an ophthalmic examination and an eye indication including cataract, macular disease, or glaucoma. Those with severe conditions and comorbidities were eligible for blood testing that included usual care biomarkers and additional markers including homocysteine, hs-CRP, fibrinogen, and uric acid. The participants described in this study included 151 people who elected to undergo systemic treatment under the direction of Dr. Trempe. In addition, many of these patients obtained additional diagnostics, including neurological evaluations, blood tests, MRIs and other radiology-based examination from their appropriate physicians. These data were not obtained consistently and were subject to the judgment of the participant's physician. Those treated suffered from a chronic eye condition and had some indication of non eye-related neurodegenerative conditions including Alzheimer's, Parkinson's, or MCI. The lab panel used for all participants in this cohort was the panel we now refer to the chronic disease temperature biomarker panel, Table 1. Every member of this cohort had subsequent labs obtained for intracellular bacterial and parasitic infection and viruses, Table 2. A standard course of treatment was applied at 1 to 3 month intervals consisting of 100 mg minocin bid and 500 mg clarithromycin bid. In addition, each participant was instructed to take supplemental cod liver oil at a dose of 15g/day. Dr. Trempe and staff followed patients closely over a minimum of 6 months, sometimes extending care for >10 years. Labs and eye tests were obtained at a minimum of 6-month intervals. Total treatment time with the antibiotic combination was approximately 6 months. Most individuals were given the antibiotics without any break in treatment unless they suffered from an intolerable Jarisch-Herxheimer's reaction. The longest time without treatment for any reason was 2 weeks.

In cohort 2, a very similar method was applied with the following exceptions. Individuals were offered free participation in a disease prevention and reversal program. One hundred individuals was the recruitment goal. An initial group of 100 was obtained upon which risk and health assessments by way of the chronic disease assessment and chronic disease temperature were obtained. Each participant then met with a physician and a health coach to discuss their indications, problems, assessment information and labs. A personalized care plan was created for each individual and bi-weekly 45-minute health coaching sessions commenced within 1 month of joining the program. Within 2 months the participation level dropped to 85 people who were deemed fully engaged with health improvement and committed to a 1-year intensive interventional program. There were no specific criteria for joining the program other than poor chronic health. The group varied in age from 18 – 71. Everyone had at least 1 chronic condition diagnosed by an independent physician that was still active. These conditions were as varied as clinical depression, insulin-dependent T2D, chronic constipation, chronic migraines, heart disease, and Parkinson's disease. Of the 85 participants, 42 agreed to infectious testing and possible treatment. In general, this group reflected people with more severe chronic conditions who were encouraged to engage in deeper and broader causal testing. Testing for chronic infection was conducted on cohort members who agreed to this testing and also agreed to participate in at least 3 months of treatment, outlined in cohort 1 or similar, if they tested positive. There was a "phase-in" period for antibiotics as

follows: 100 mg minocin qd; 100 mg minocin bid; 100 mg minocin bid and 500 mg clarithromycin qd; and 100 mg minocin bid and 500 mg clarithromycin bid. The phase-in period varied from 2 weeks to 6 weeks depending upon the severity of any Jarish-Herxheimer's reaction. Forty one of the 41 were found to harbor clinical relevant levels of chronic bacterial infection and many also tested positive for virus based on reference ranges provide by the testing lab. Two participants, on reconsideration, elected treatment that was not pharmaceutical. These participants we provided medicinal mushroom instead of minocycline and clarithromycin. Specifically, these individuals received Cordyceps sinensis, Agaricus Blazei, Lentinula edodes, Grifola frondosa, Ganoderma lucidum, and Coriolus versicolor per label instructions. The 43 participants not tested or positive for infection constituted the control group.

Although not a formal clinical study, all procedures performed in the program involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Ethical oversight was provided by the existing primary care clinic management organization, but not under any formal written agreement other than to monitor for patient safety. Informed consent, medical releases, and participation contracts were obtained from all participants included in the program. These documents were completed after each participant was provided detailed information on the program. Medical personnel acquired all data in strict conformance with health data privacy laws and all stored data were contained on a HIPPA compliant encrypted server and EMR system.

The lifestyle interventions affected by the HCP through the HCCP were individualized to each participant and included a consideration of the participant's readiness to change and the likely sustainability of any given change as determined by their responses to chronic disease assessment health risk assessment questions and discussions with their health coach. The intensity of coaching was pre-determined, but not fixed, by the health risk grade generated by an algorithm for risk included in the risk assessment. Physician time allocation was approximately $1/10^{th}$ coaching time. The main risk strategies were reduction in inflammation through: more movement, increased nutrient density of foods, improvement in digestion/absorption by improving stomach acid, increasing probiotic and prebiotics foods, elimination of high glycemic foods, better oral health maintenance, increased intake of healthy fats and omega-3 fatty acids, increased micronutrients, stress reduction, brain health through reducing whole-body inflammation, and consumption of greater amounts of fat soluble vitamins, as examples. No specific nutrition program was recommended to the participants as a whole. Instead a simple process of substitution of one food for another was made as recommended by the health coach, on an individualized basis, to affect a gradual and sustainable change from the Standard American Diet (SAD) that was prolific throughout the cohort, to a new food consumption pattern with increased micronutrient density, fiber, and healthy fats with less carbohydrate and sugar consumption. Short-term (2-3 months) nutritional ketosis was offered as a method to improve insulin sensitivity..

Supplements were provided as part of the program and compliance with supplementation was near 100% based on self-reporting, resupply requests, and measurement of markers including blood 25-hydroxy vitamin D levels. At onset of the program, after evaluation of CDT labs and chronic disease assessment dietary information, participants were provided any of the following, based on individually assessed deficiencies: multivitamin/mineral; 2000-10,000IU vitamin D3, up to 15g cod liver oil, 100-400 mg magnesium glycinate; 50-100 mcg vitamin K2, and a probiotic (20-70 billion organisms daily). Supplements, when deemed appropriate by the physician, were phased in then phased out over the 6-month period as food nutrient density consumption improved.

In-clinic vital signs, weight change, health risk assessment risk grade, a 55 biomarker panel, the participant chronic disease temperature, 55 biomarker panel was obtained on every participant.

Those involved in the infectious evaluation and treated were tested for antibody levels of infectious species at baseline and one month after the end of the treatment program. Diagnoses, problems, complaints and medications were reconciled at each health coaching and physician encounter.

Cognitive function before and after measurements were recorded on 26 cohort 1 participants. The participant's neurologist or other healthcare professional not involved in this treatment study performed mostly these measurements. The cognitive function test most commonly recorded was the mini-mental state exam (MMSE). Of the 26 obtaining this assessment, all had evaluation for complete eye exams before and after treatment and 11 had complete labs drawn.

**Results:**

Table 2 presents demographics of cohort 1 and cohort 2 participants. Ninety five percent of participants were Caucasians and 5% were Hispanic. At baseline, 98% of cohort 1 participants were actively taking pharmaceuticals for a medical problem and 100% were diagnosed with at least 1 chronic condition. In cohort 2, 92% were actively on pharmaceuticals and 100% of those with measured infection were actively taking pharmaceuticals. This reflects a substantially higher percentage of chronically ill individuals compared to the U.S. national average of ~50% of U.S. adults having at least one chronic condition. [6] On average, the aggregate group was taking 3 prescriptions per person. The major class of medications included: diabetes medications, injectable insulin, statins, blood pressure lowering, pain, mood (SSRIs), bisphosphonates, steroids, thyroid hormone, and proton pump inhibitors.

| Participant Information | C1 Male | C1 Female | C2 Male | C2 Female |
|---|---|---|---|---|
| # Participants (%) | 21 (52%) | 19 (48%) | 30 (34%) | 55 (66%) |
| Average Age | 62 | 67 | 53 | 52 |
| 20-29 | 0 | 1 | 0 | 2 |
| 30-39 | 1 | 1 | 4 | 2 |
| 40-49 | 1 | 2 | 2 | 22 |
| 50-59 | 2 | 1 | 13 | 20 |
| 60 -69 | 6 | 5 | 11 | 7 |
| 70-79 | 11 | 9 | 0 | 2 |
| College Degree | 8 | 11 | 8 | 23 |
| Some College | 6 | 9 | 6 | 11 |
| High School Only | 16 | 21 | 16 | 21 |

Table 2: Demographics Initial Participant Cohorts. C1 and C2 signifies cohort 1 and 2 respectively.

Health risk assessment: The health risk assessment includes 120 health-related questions in a multiple-choice format. Each question and answer pair is assigned a numeric risk value between 0 and 10 based on a subjective scaling of risk within that question concept. This provides a subjective score of the depth and breadth of an individual's risk portfolio. It does afford population risk stratification as every participant is answering the same questions. This assessment was used for cohort 2 participants only. Initial raw scores varied from 62 to 175. On average, the 40 participants with infection lowered their CDA score by 38 points from a raw average value of 127 to a new value of 99 over 6 months. The participants not tested for or not found positive for infection had an initial CDA raw value of 108 which lowered to 86 over 6 months of health coaching. Ninety four percent of the group experienced an improvement in their lifestyle risks while six percent of the cohort experienced a worsening.

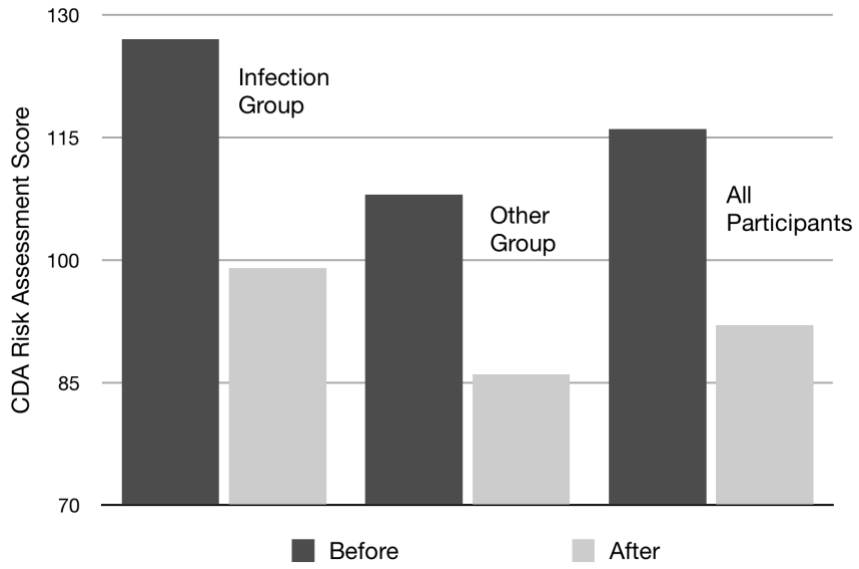



Figure 3. Change in CDA (Risk Assessment) score before and after program, cohort 2.

Biomarker Panel: Biomarkers blood labs were obtained on all participants before and after treatment. Labs were obtained for cohort 1 according to each individual's diagnoses. White blood cell counts with differential, hs-CRP, and homocysteine were most commonly obtained. The Chronic Disease Temperature™ (CDT) blood panel was obtained on every participant in cohort 2. The full panel is provided in Appendix A and encompasses 55 markers, 16 of which are used to calculate a participant's CDT score. The CDT uses a base value of 98.6 and is a 7-point scale. On average, cohort 1 saw a reduction from 102.9 (4.3 out of 7) to 101.1 (2.5 out of 7) over a 1-year treatment period or a reduction of 42%. This calculation was based on a sub-set of 33 cohort 1 individuals as these were the only ones with sufficient lab biomarkers drawn to allow calculation of the CDT value. The Cohort 2 infectious group experienced a reduction from 101.9 (3.3 out of 7) to 100.4 (1.8 out of 7) or a reduction of 55%. The non-infectious group from cohort 2 saw a reduction from an average of 101.3 (2.7 out of 7) to 100.6 (0.7 out of 7) or a reduction of 26%.

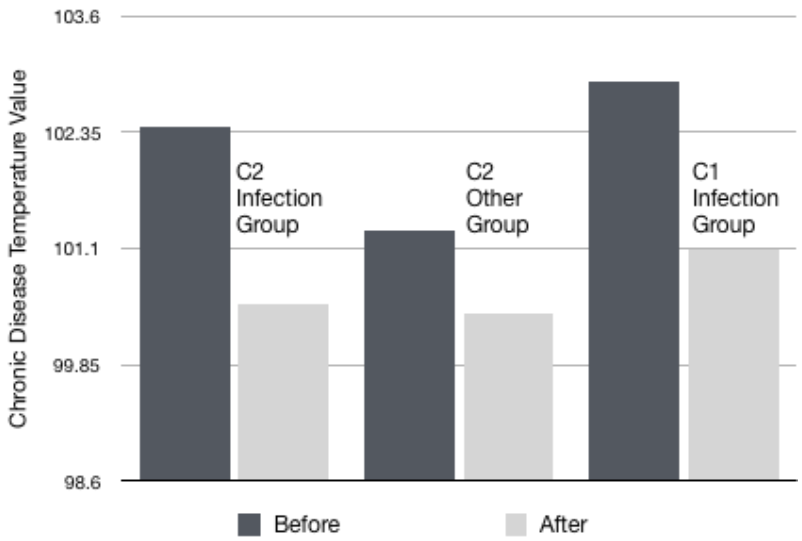



Figure 4. Change in the CDT (Biomarker) score, cohorts 1 & 2.

Relationship between health risks and biomarkers

There are numerous studies on the relationship between lifestyle behaviors and chronic disease risk.[124] In large prospective studies, like the Nurses' Health Study, [125] vague conclusions are made about the association of smoking, regular physical activity, maintaining normal body mass index, eating a healthy diet and chronic disease proliferation. The individualized risk values measured in this study potentially increase the precision of risk-to-disease relationship. Figure 5 the risk-to-lab value relationship at the beginning and end of the program for all participants in cohort 2.

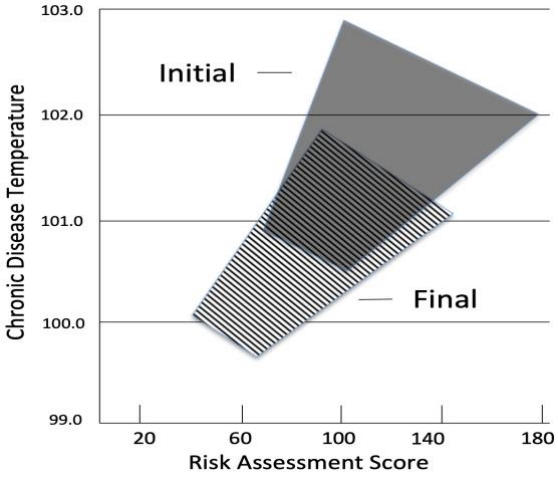



Figure 5. Correspondence between Lifestyle Risks and Blood-Based Biomarkers Before and After in cohort 2.

In Figure 5, the shape of the funnels reflects a degree of scatter in the data for the relationship between the risk algorithm and the blood marker algorithm. Increasing the "n" in our database and making appropriate adjustments to assigned risk values within the algorithm offers the potential to improve the correlation between risk and physiological status. Figure 5 does demonstrate a relationship between improvement in multiple lifestyle risks and improvement in physiological biomarkers.

Data for individual biomarkers and the CDT aggregate score are provided in Table 3-5.

| | initial mean | final mean | mean diff | initial stdv | final stdv | p value |
|---|---|---|---|---|---|---|
| CDT | 101.9 | 100.4 | 1.4 | 0.92 | 0.65 | 0.0731 |
| WBC | 6624 | 5933 | 690 | 1877 | 1597 | <0.0001 |
| hs-CRP | 2.9 | 1.7 | 1.1 | 3.7 | 2.1 | 0.0866 |
| Insulin | 11.3 | 6.9 | 4.4 | 6.2 | 3.4 | 0.0001 |
| A1C | 5.8 | 5.3 | 0.5 | 0.6 | 0.3 | <0.0001 |
| Glucose | 100 | 95 | 5 | 18 | 10 | 0.1111 |
| Triglycerides | 124 | 106 | 19 | 70 | 57 | 0.1867 |
| Total Cholesterol | 197 | 216 | -19 | 46 | 40 | 0.0459 |
| HDL | 56 | 61 | -5 | 16 | 17 | 0.1669 |
| LDL | 113 | 134 | -21 | 27 | 33 | 0.1970 |
| Vitamin D | 38 | 56 | -18 | 13 | 10 | <0.0001 |
| Uric Acid | 5.2 | 5.1 | 0.0 | 1.0 | 1.4 | 0.9545 |
| RBC | 4.7 | 4.6 | 0.1 | 0.4 | 0.4 | 0.4288 |
| RDW | 13.9 | 13.0 | 0.9 | 1.0 | 0.6 | <0.0001 |
| Abs Neutrophils | 4114 | 3392 | 721 | 1565 | 1117 | 0.0172 |
| Abs Lymphocytes | 1940 | 1909 | 31 | 619 | 565 | 0.8103 |
| % Neutrophils | 61.1 | 56.8 | 4.3 | 8.3 | 7.4 | 0.0134 |
| NLR | 2.3 | 1.9 | 0.4 | 1.1 | 0.7 | 0.0365 |
| ESR | 8.6 | 6.4 | 2.3 | 9.3 | 5.6 | 0.1762 |
| Fibrinogen | 306 | 290 | 16 | 69 | 51 | 0.2241 |
| Homocysteine | 9.0 | 9.9 | -0.9 | 2.7 | 3.1 | 0.1665 |

Table 3: Cohort 2, 41 individual infectious group lab values before and after treatment for intracellular infection and lifestyle modifications.

| | initial mean | final mean | mean diff | initial stdv | final stdv | p value |
|---|---|---|---|---|---|---|
| CDT | 101.3 | 100.6 | 0.7 | 0.8 | 7.9 | <0.0001 |
| WBC | 6330 | 5900 | 425 | 1525 | 2 | 0.0113 |
| hs-CRP | 2.2 | 1.8 | 0.4 | 2.0 | 1.9 | 0.0338 |
| Insulin | 8.6 | 7.3 | 1.3 | 6.4 | 4.4 | 0.2900 |
| A1C | 5.7 | 5.2 | 0.5 | 0.5 | 9.3 | <0.0001 |
| Glucose | 98 | 95 | 3 | 16 | 2 | 0.0480 |
| Triglycerides | 114 | 101 | 13 | 71 | 2 | 0.0578 |
| Total Cholesterol | 194 | 210 | -16 | 38 | 24 | 0.0198 |
| HDL | 58 | 62 | 4 | 13 | 3 | 0.0047 |
| LDL | 123 | 127 | -4 | 30 | 34 | 0.0019 |
| Vitamin D | 38 | 60 | 22 | 17 | 11 | <0.0001 |
| Uric Acid | 5.2 | 5.2 | -0.1 | 1.0 | 0.0 | ------ |
| RBC | 4.8 | 4.7 | 0.1 | 0.3 | 0.4 | 0.3576 |
| RDW | 13.8 | 13.0 | 0.8 | 1.0 | 6.8 | <0.0001 |
| Abs Neutrophils | 3830 | 3380 | 452 | 1565 | 1117 | 0.0020 |
| Abs Lymphocytes | 1909 | 1880 | 29 | 611 | 559 | 0.8079 |
| % Neutrophils | 59.2 | 55.7 | 3.5 | 7.0 | 11.0 | 0.0805 |
| NLR | 2.2 | 1.9 | 0.3 | 0.9 | 2.5 | 0.0083 |
| ESR | 8.5 | 7.1 | 1.4 | 7.6 | 1.6 | 0.0598 |
| Fibrinogen | 301 | 295 | 5.61 | 61.05 | 0.77 | 0.2221 |
| Homocysteine | 8.9 | 9.3 | -0.4 | 2.4 | -1.4 | ------ |

Table 4: Cohort 2, 44 individual non-infectious group lab values before and after treatment for lifestyle modifications only.

| | initial mean | final mean | mean diff | initial stdv | final stdv | p value |
|---|---|---|---|---|---|---|
| CDT | 102.9 | 101.3 | 1.6 | 1.4 | 1.6 | 0.0005 |
| WBC | 7070 | 6224 | 846 | 1817 | 1666 | 0.0632 |
| hs-CRP | 2.8 | 1.7 | 1.1 | 3.8 | 2.2 | 0.1786 |
| RDW | 14.1 | 13.0 | 1.1 | 1.1 | 0.6 | <0.0001 |
| Abs Neutrophils | 4422 | 3563 | 859 | 1572 | 1179 | 0.0146 |
| % Neutrophils | 62.6 | 55.6 | 7 | 7.9 | 11.7 | 0.0057 |
| NLR | 2.4 | 1.8 | 0.6 | 1.2 | 0.7 | 0.0374 |

Table 5: Cohort 1, 33 individuals from Trempe group lab values before and after treatment for intracellular infection only.

## Infectious Studies

Stealth and apparent infection is a contributor to chronic diseases. Patients with chronic periodontitis, for example have elevation of white blood cells and platelet counts. [126] A diagnosis of a severe chronic eye disease along with white blood cell counts, hs-CRP, absolute neutrophils, neutrophil %, insulin levels, A1C, glucose, and homocysteine values were used to determine who would be a candidate for infectious testing in cohort 1. In cohort 2, the same labs were used to

determine whom to test for stealth infection along with our CDT aggregate score. In cohort 2, 41 of 42 tested had positive antibody titers for one of more of the bacterial species in the panel (Table 1). All participants in cohort 2 agreed to a treatment program designed for intracellular bacteria infection. Two participants elected to engage in a non-pharmaceutical treatment using cordyceps and a mixture of medicinal mushrooms. Treatment i

Cohort 2

| Data / Organism | C Pneumoniae | M. Pneumoniae | Toxoplasmosis | Lyme | CMV | R. Typhii | Q Fever | C. Trachomatis |
|---|---|---|---|---|---|---|---|---|
| Positive | 28 | 28 | 12 | 18 | 7 | 1 | 1 | 1 |
| Same | 12 | 10 | 12 | 4 | 3 | 0 | 0 | 0 |
| Lowered | 4 | 17 | 0 | 1 | 3 | 0 | 0 | 0 |
| Halfed | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Quartered | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Resolved | 6 | 1 | 0 | 13 | 1 | 0 | 1 | 1 |
| % Improved | 57 | 64 | 0 | 78 | 57 | 0 | 100 | 100 |

Cohort 1

sheet ROI-V-inf

| Data / Organism | C Pneumoniae | R. Conorii | Toxoplasmosis | Lyme | R. Typhii | Q Fever | C. Psittaci |
|---|---|---|---|---|---|---|---|
| # Tested | 151 | 151 | 151 | 45 | 45 | 45 | 151 |
| Positive | 52 | 12 | 54 | 10 | 10 | 1 | 4 |
| Same | 6 | 4 | 45 | 3 | 4 | 1 | 1 |
| Lowered | 9 | 3 | 9 | 1 | 1 | 0 | 1 |
| Halfed | 18 | 1 | 0 | 2 | 1 | 0 | 0 |
| Quartered | 9 | 1 | 0 | 1 | 1 | 0 | 0 |
| Resolved | 10 | 3 | 0 | 3 | 3 | 0 | 1 |
| % Improved | 88 | 67 | 17 | 70 | 60 | 0 | 50 |

Finally, the cohort experienced a reduction in chronic disease burden. Chronic disease reduction was determined by changes in any of the following: actual change to a medical diagnosis; elimination of a medication associated with an existing diagnosis; changes in a vital sign that indicated a migration out of a diagnosis that was effected without the use of a medication; or change in a biomarker value or values that were initially used to make the diagnosis into a “normal” range without the use of medications, Table 12.

Cognitive results were mixed but encouraging. Of the 26 with MMSE scoring before and after, 5 showed substantial improvement, 11 showed improvement, 6 showed no change and 4 worsened, Figure X. Those that showed the most improvement had the following before and after MMSE values: 14:25; 12:23; 11:25; 17:24, a 10 point improvement, on average.. Note none of these participants achieve a normal score of 26 or above. Those that worsened showed a 3-point loss on the MMSE, on average. The before and after lab values for these participants were similar to cohort 1 data presented in Table X.

| | initial mean | final mean | mean diff | initial stdv | final stdv | p value |
|---|---|---|---|---|---|---|
| MMSE | 17.8 | 20.0 | 2.2 | 4.68 | 4.93 | 0.0504 |

All 151 patients in cohort 1 presented with at least 1 eye indication. The same ophthalmologist determined before and after eye disease ratings. Glaucoma ratings were based on a combination of eye pressure measurements, retinal nerve fiber layer thickness and volume, measurements with OCT, and visual fields. Cataract ratings were determined based on standard measures of cataract burden. Macular disease ratings were based on optic disc evaluation, retinal blood vessel health,

and drusen assessment. Tables X and Y show before and after eye ratings. The indication of a lens being replaced indicated that the participant had severe cataracts. Interesting, in one instance, a mild cataract dissolved as confirmed by before and after digit imaging of the lens. Reduction or elimination of bleeding (wet macular disease) was a common endpoint with 36 patients having bleeding in the initial group while only 11 were so classified after treatment. No anti-VEGF treatments were applied to the eye during this study.

| | Total | Mild | Moderate | Severe | Lens Replaced |
|---|---|---|---|---|---|
| Glaucoma | 136 | 31 | 31 | 74 | |
| Macular disease | 99 | 45 | 18 | 36 | |
| Nuclear cataract | 68 | 47 | 12 | 9 | 38 |
| Cortical cataract | 37 | 15 | 17 | 5 | 38 |
| 2 or more | 111 | | | | |

Table: Eye disease diagnoses in cohort 1 prior to treatment

| | Total | Mild | Moderate | Severe | Resolved |
|---|---|---|---|---|---|
| Glaucoma | 107 | 45 | 29 | 33 | 29 |
| Macular disease | 55 | 35 | 9 | 11 | 44 |
| Nuclear cataract | 67 | 46 | 12 | 9 | 1 |
| Cortical cataract | 37 | 15 | 17 | 5 | 0 |
| 2 or more | 89 | | | | |

Table: Eye disease diagnoses in cohort 1 post treatment

| | Total | Mild | Moderate | Severe | Lens Replaced |
|---|---|---|---|---|---|
| Glaucoma | 21 | 5 | 5 | 11 | |
| Macular disease | 15 | 3 | 8 | 4 | |
| Nuclear cataract | 13 | 7 | 3 | 3 | 7 |
| Cortical cataract | 11 | 2 | 6 | 3 | 7 |
| 2 or more | 11 | | | | |

Table: Eye disease diagnoses of cohort 1 with recorded before and after MMSE evaluation – before treatment.

| | Total | Mild | Moderate | Severe | Lens Replaced |
|---|---|---|---|---|---|
| Glaucoma | 16 | 4 | 7 | 5 | |
| Macular disease | 8 | 3 | 3 | 2 | |
| Nuclear cataract | 12 | 8 | 2 | 2 | 7 |
| Cortical cataract | 11 | 2 | 6 | 3 | 7 |
| 2 or more | 7 | | | | |

Table: Eye disease diagnoses of cohort 1 with recoded before and after MMSE evaluation – post treatment.

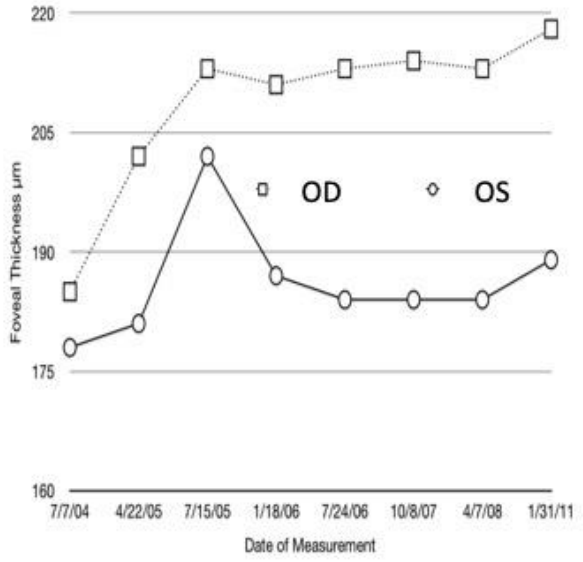
Several patients in this study received continuing care for eye indications including glaucoma. We report here positive changes in retinal nerve fiber layer thickness and volume in four patients who were evaluated over a minimum of a 3-year period.

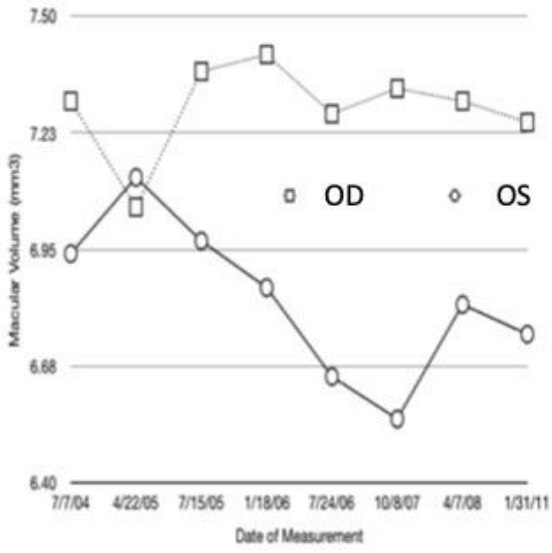
Condense these with focus on eye and MMSE

Case 96134:

Eye Case Study 96134: **A** 76 yo female presented with early indications of a neurodegeneration. The patient's husband reported memory problems including repeating the same comment or question "several times within the same conversation." She also displayed a slight hand tremor although recent neurology reports did not indicate Parkinson's disease or essential tremor. Subsequent eye evaluation revealed comorbid pathologies including: early cortical (supranuclear) cataract, nuclear cataract not sufficient to perturb vision, elevated retinal pressure indicative of glaucoma, and decline in foveal thickness and macular volume based on OCT evaluation when compared to the mean of individuals of her age and sex. She scored a 22 on the mini mental state exam upon first visit and subjective memory assessment based on questions referring to her past and present confirmed some indication of short-term memory loss. Slight tremor was observed when the patient was asked to extend her arms and try to be as steady as possible.

| Measurement | Initial | Follow-up 1 | Follow-up 2 | Follow-up 3 |
|---|---|---|---|---|
| Year | 2004 | 2005 | 2007 | 2011 |
| Cortical Cataract | Grade 2 (OS), NONE (OD) | Grade 2 (OS), NONE (OD) | Grade 2 (OS), NONE (OD) | Grade 1 (OS), NONE (OD) |
| Glaucoma | Moderate | Borderline | No Glaucoma | No Glaucoma |
| Ocular pressure | 24 (OS) 25 (OD) | 18 (OS) 22 (OD) | 12 (OS) 15 (OD) | 12 (OS) 14 (OD) |
| Visual field | Constricted | Constricted | Improved | Near normal |
| Nuclear cataract | Grade 1 (OS), None (OD) | Grade 1 (OS), None (OD) | Grade 1 (OS), None (OD) | Grade 1 (OS), None (OD) |
| MMSE | 22 | 24 | 24 | 27 |
| Foveal Thickness (OD) | 185 | 211 | 213 | 218 |
| Foveal Thickness (OS) | 178 | 187 | 179 | 189 |
| Macular Volume (OS) | 7.05 | 7.37 | 7.30 | 7.25 |
| Macular Volume (OD) | 6.94 | 6.97 | 6.82 | 6.75 |
| WBC | 8800 | 5800 | 6200 | 5900 |
| Homocysteine | 15.9 | 13 | 9.9 | 10.6 |
| CRP | 6.1 | 3.1 | 3.6 | 1.5 |
| C Pneumoniae (IgG) | 1:512 | 1:64 | <1:64 | <1:64 |
| M Pneumonie (IgG) | 724 | 550 | 254 | 265 |
| Abs. CD8-CD57 | 25 | 45 | 75 | 112 |




110401

Eye Case Study 110401: A 64 yo male presented with significant cognitive impairment. He was an MD who was forced to leave his practice due to memory-related issues. He was a former college basketball star and one of the first doctors employed by the Mayo Clinic in Tuscon, AZ. He was 6' 4" and 225 pounds at the time of first encounter. He indicated use of tobacco (cigars) and had a drinking problem that developed recently, maybe tied to reported depression. He did not present with any type of cataract or macular degeneration. OCT revealed retinal nerve fiber layer thinning and was assigned a diagnosis of low-tension glaucoma. Neurologists assigned a diagnosis of Alzheimer's based on clinical observations and MMSE score. Patient recalled being exposed to TB and having poor oral hygiene over the past several years.

| Measurement | Initial | Follow-up 1 | Follow-up 2 | Follow-up 3 | Follow-up 4 |
|---|---|---|---|---|---|
| Year | 2009 | 2009 | 2010 | 2010 | 2011 |
| Cortical Cataract | ND | | | | |
| Glaucoma | Moderate | Moderate | Low tension | Low tension | Low tension |
| Ocular pressure | 30 (OS) 25 (OD) | 28 (OS) 31 (OD) | 21 (OS) 21 (OD) | 21 (OS) 18 (OD) | 19 (OS) 20 (OD) |
| Visual field | Constricted | Improved | Improved | Near normal | Near normal |
| Nuclear cataract | Neg | | | | |
| Macular degeneration | Neg | | | | |
| Foveal Thickness (OD) | 398 | 259 | 241 | 294 | 323 |
| Foveal Thickness (OS) | 416 | 379 | 325 | 352 | 383 |
| Macular Volume (OS) | 8.45 | 7.78 | 7.80 | 8.00 | 8.05 |
| Macular Volume (OD) | 7.71 | 6.97 | 7.42 | 7.22 | 7.45 |
| MMSE | 18 | 19 | 25 | 26 | 24 |
| WBC | 7700 | 6800 | ND | 6400 | 5800 |
| Homocysteine | 13.9 | 15.1 | ND | 12.5 | ND |
| CRP | 2 | 2 | ND | 1 | 0.9 |
| C Pneumoniae (IgG) | 1:256 | 1:128 | 1:64 | <1:64 | <1:64 |
| TB | Positive | Positive | Negative | Negative | Negative |
| Periodontal disease | Suspect | Suspect | Suspect | Suspect | Suspect |
| M Pneumoniae (IgG) | 452 | 411 | 201 | 211 | 108 |
| R Conorri | Neg | | | | |
| Toxoplasma gondii (IgG) | Neg | | | | |
| Lyme Western Blot (IgG) | 4 bands | 2 bands | Non-Reactive | Non-Reactive | Non-Reactive |

- Minocycline: 100mg one daily, at night, with water for 10 days
- Biaxin: 500mg one daily, at night, with water for 10 days

Increase the dose to two daily (morning and night) for each if the side-effects are minimal. You can refer to the Mass General report as this treatment and potential side effects are the same as for the Lyme disease treatment of a couple of years ago. They used doxycycline alone. Minocycline and Biaxin cross the blood/brain barrier more efficiently.

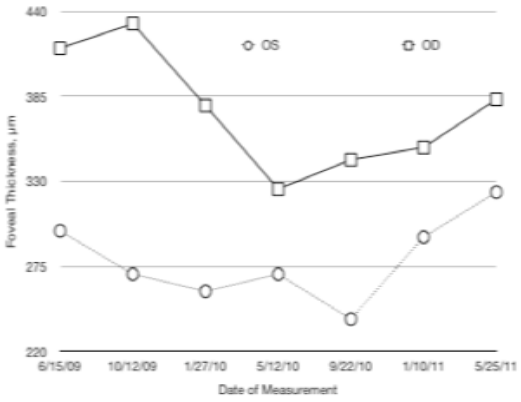
Based on the suspect TB, we will also be prescribing amox/clav – which is a combination antibiotic with a substance know to inhibit antibiotic resistivity. This is required because TB is difficult to treat and is much more susceptible to the combinations.

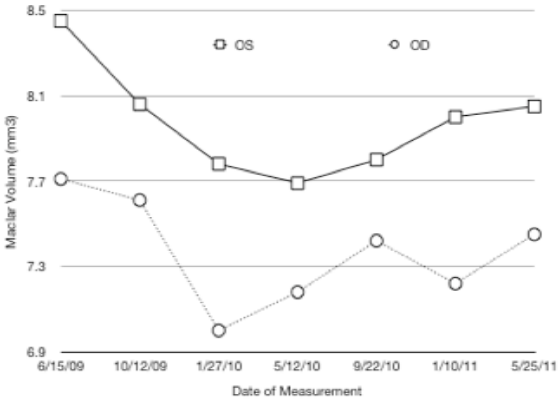
Dosing: Take one of each (3 medications) twice daily. If Dr. Leeland experience dizziness and flu-like symptoms, reduce the dosage to once/day and contact Dr. Trempe for advice. This reaction is mostly likely NOT due to an adverse reaction to the medication, but rather in response to effective treatment – per the Herxheimer's reaction.

Also, continue to follow the brain maintenance program described below. In addition, add 2000 units of vitamin d3 for 3 month or until blood tests reveal vitamin d3 levels above 50. Finally, follow the homocysteine vitamin regiment. See. http://www.empromedical.com/Homocysteine.html

Herx very strong in brain and generally.

Treatment for 6 months. Showed significant cognitive improvement. Felt he could go back to work. Did not change habits.




102034

76 yo female

Clinical Findings and recommendations, Jeanne Bette

May 2011

Ms. Betette was evaluated for possible neurodegenerative and cardiovascular diseases in the eye based.

**Summary**: It is our opinion that Ms. Betette, based on eye markers, has minor indications of neurodegenerative processes that should be treated. The classic biomarker for this disease, cortical cataracts, was not observed but one lens was replaced due to cataract surgery. Optic disk, retina, and retinal nerve fiber layer not in optimal condition inferring that degenerative processes may be occurring in the brain. Blood testing shows clear inflammatory markers and titers reveal potential and treatable root-causes.

**Comment:** Ms. Betette is on a variety of medications. We are suggesting certain treatments and must confer carefully to consider interactions(refer Dr. Glick report).

**Test Results:**

- Elevated c-Reactive Protein in one of the two labs presented., a marker of general inflammation usually tied to systemic infection and statistically predictive of future cardiovascular disease.
- Nuclear cataracts: statistically tied to cardiovascular disease.
- High while blood count and other high blood parameters consistent with infection and inflammation. Some labs give a range of 85 for neutrophil count. We consider 68 to be out of range with a healthy range of 54-62.
- Elevated mycoplasma pneumonie – infection that can be found in the brain. Needs to be treated.
- Elevated chlamydia pneumonie – infection that can be found in the brain. Needs to be treated
- Good cholesterol and ldl/hdl ratio. Recommend that patient not take any medication to lower cholesterol.
- Borderline/high uric acid.

**Approach:**

Treat for mycoplasma and chlamydia using a combination of Biaxin and Minocycline. These drugs work together to both control the intracellular infectious species such as and manage the inflammatory response. These compounds are to be taken as follows:

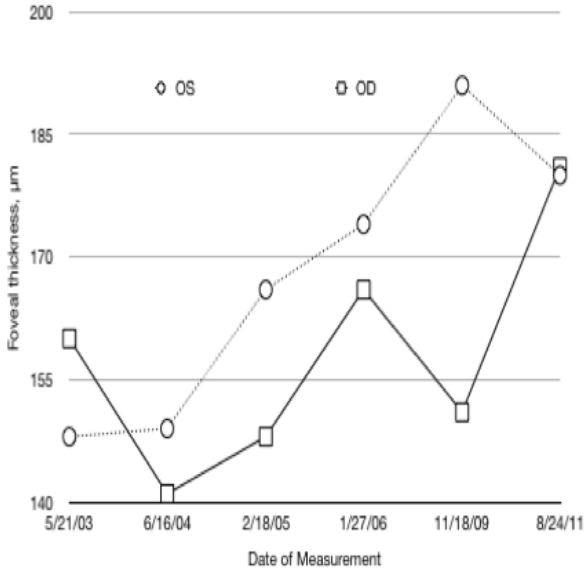
- Minocycline: 100mg one every other day, in the am, prior to breakfast, with water for 10 days.
- Biaxin: 500mg one every other day, in the am, prior to breakfast, with water for 10 days.

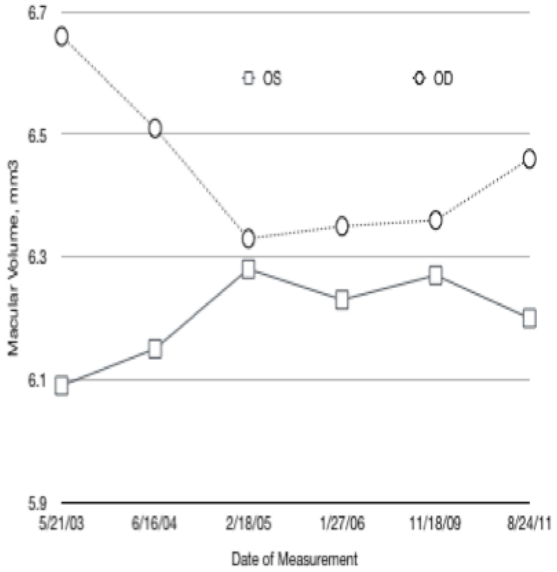
After 10 days, increase the dose to one of each, daily and finally, after another 10 days, Increase the dose to two daily (morning and night) for each if the side-effects are minimal.

Monitor very very carefully for Herxheimer's reaction considering the high wbc.

Ms. Betette's vitamin d level is adequate but maintain current levels and begin the brain maintenance program that adds vitamin d through the cod liver oil.

| Measurement | Initial | Follow-up 1 | Follow-up 2 | Follow-up 3 | Follow-up 3 | |
|---|---|---|---|---|---|---|
| Year | 2003 | 2004 | 2005 | 2006 | 2009 | 2011 |
| Cortical Cataract | | | | | | |
| Glaucoma | | | | | | |
| Ocular pressure | | | | | | |
| Visual field | Constricted | Improved | Improved | Near normal | Near normal | |
| Nuclear cataract | | | | | | |
| MMSE | ND | ND | 24 | 27 | 27 | |
| Macular Volume | 6.94 | 6.97 | 6.82 | 6.75 | 6.75 | |
| WBC | 12600 | 10000 | 10700 | 9400 | 8400 | |
| Homocysteine | 18.3 | 12.1 | 10.7 | 9.9 | 10.6 | |
| CRP | 12.6 | 3.3 | 1.7 | 1.7 | 1.5 | |
| C Pneumoniae (IgG) | 1:1024 | 1:64 | 1:64 | ND | ND | |
| Toxoplasma Gondii | value | | | | | |
| Lyme | | | | | | |




81808

56 yo female

Clinical Findings and recommendations, Susan Garrity, May 2011

Mrs. Garrity was evaluated for possible neurodegenerative and cardiovascular diseases in the eye based on a complaint of osteoarthritis and insulin resistance.

**Summary**: It is our opinion that Mrs. Garrity does not have an indication of ocular manifestation of AD. None of the classic biomarkers for this disease including cortical cataracts of the lens or drusen in the retina (both amyloid beta protein) were noted. Optic disk, retinal and retinal nerve fiber layer are all healthy. Early nuclear cataract is indicative of inflammation and potential chronic systemic disease that was corroborated with blood testing.

**Clinical History:** Mrs. Garrity has a history of stomach problems with heartburn and potentially TB positive among other indications (refer Dr. Glick report).

**Test Results:**

- Highly elevated c-Reactive Protein, a marker of general inflammation usually tied to systemic infection and statistically predictive of future cardiovascular disease.
- Nuclear cataracts: statistically tied to cardiovascular disease.
- Elevated homocysteine (11.8 – 9 or less is preferred). This marker is an indicator of cardiovascular disease and is often elevated in "vascular" or "inflammatory" dementia patients.
- High while blood count and other high blood parameters consistent with infection and inflammation. Some labs give a range of 85 for neutrophil count. We consider 68 to be out of range with a healthy range of 54-62.
- Elevated mycoplasma pneumonie – infection that can be found in the brain. Needs to be treated
- Elevated helicobacter pylori (h-pylori). This is a bacterium found in the stomach but can migrate to the brain. Subject of the 2005 Nobel Prize in medicine.
- Low vitamin d3 (29 – we consider >45 appropriate)

Spot-on description of Herxheimer's reactionhttp://www.lauricidin.com/herxheimer_reaction.asp

http://www.rain-tree.com/myco.htm - mycoplasma

http://hpylorisymptoms.org/ (note the treatment they recommend is exactly what we prescribe..)

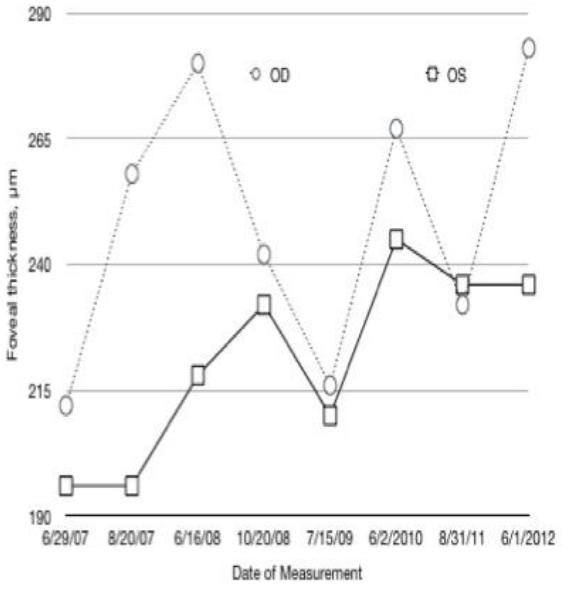
**Reference from** Cognitive & Behavioral Neurology:
September 2010 - Volume 23 - Issue 3 - pp 199-204

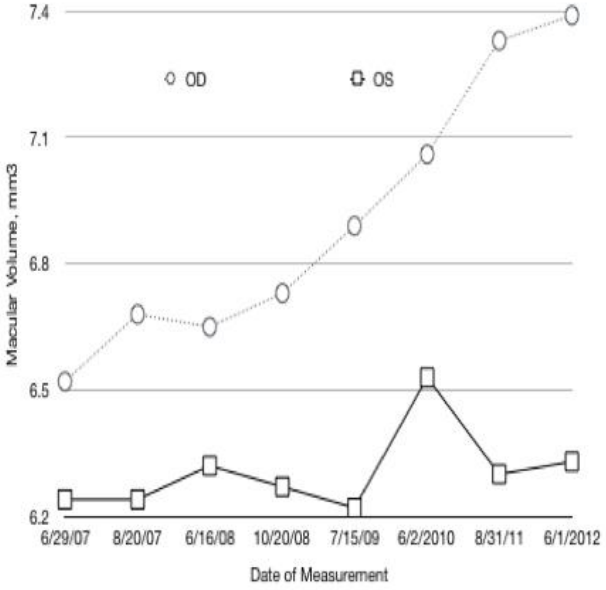
**Five-year Survival After Helicobacter pylori Eradication in Alzheimer Disease Patien ts**
**Abstract**

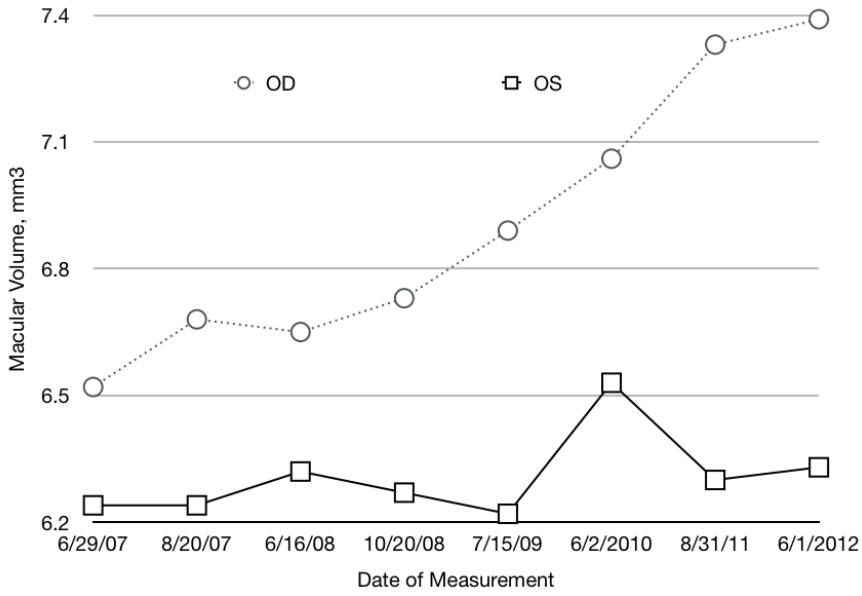
Results: During the 5-year follow-up [47.19±15.11 mo (range 12 to 60)], overall 21 patients died and 25 patients remained alive. Patients who died were older and exhibited lower mean MMSE score compared with the patients still alive. Successful eradication of *Hp*-I was associated with a significantly lower mortality risk [HR (95% CI)=0.287 (0.114-0.725), *P*=0.008]. The results were similar in adjusted and unadjusted models, for age and MMSE at baseline.

Conclusion: *Hp* eradication regimen in AD patients is associated with a higher 5-year survival rate.

| Measurement | Initial | Follow-up 1 | Follow-up 2 | Follow-up 3 | Follow-up 3 |
|---|---|---|---|---|---|
| Year | 2007 | 2008 | 2009 | 2010 | 2011 |
| Cortical Cataract | | | | | |
| Glaucoma | | | | | |
| Ocular pressure | | | | | |
| Visual field | Constricted | Improved | Improved | Near normal | Near normal |
| Nuclear cataract | | | | | |
| MMSE | ND | ND | 24 | 27 | 27 |
| Macular Volume | 6.94 | 6.97 | 6.82 | 6.75 | 6.75 |
| WBC | 12600 | 10000 | 10700 | 9400 | 8400 |
| Homocysteine | 18.3 | 12.1 | 10.7 | 9.9 | 10.6 |
| CRP | 12.6 | 3.3 | 1.7 | 1.7 | 1.5 |
| C Pneumoniae (IgG) | 1:1024 | 1:64 | 1:64 | ND | ND |
| Toxoplasma Gondii | value | | | | |
| Lyme | | | | | |






Trempe Case 5 – Zena Fax male: dob 7/8/38 **9/19/2016**

Decreased vision right eye worse than left – considering cataract surgery OD always weaker, Hx of macular pucker, Cataracts OU, grandmother had glaucoma, warfarin, prone to ear infections, arrhythmia with detected calcification on aorta, constipation, osteoporosis (warfarin for many years), visual field ok, +2 nclear sclerosis and mild pscc OD, +1 nuclear sclerosis OS, optic nerve 0.6 – thinning noted, No drusen, retinal scarring – minor thinning on both sides – OCT. Found high titer for Lyme and CP. Eloiquis, clarithromycin, minocycline – 60 days

3 vit D, CP 1:256, aspirin and CLO

crp 16

low serum magnesium

wbc 8900

chol 202 HDL 91, ldl 91

Notes: bilateral early cataract with overlying fibrosis in the macular region. Plan for cataract surgery but suggested no due to fibrosis and edema contributing to visual loss

**3/28/17** – patient – vision improved in right eye

20/30-2 OD NOW 20/20

20/100-2 NOW 20/20

IOP OD 16 OS 17 – down from 18 / 22

Improvement in the overlying edema & fibrosis

Continue treatment for 2 more months

**7/12/2017**

atrial fibrillation improvement

Trempe Case – Len Peterson

Early macular drusen, dementia, hemorrhagic stroke mid April 2010 – R temporal with microbleed – vascular dementia, vague eye history, cortical type of cataract with feather-like (cortical change inferiorly) fibrils early drusens both eyes, mother MS, slight anemia,

Aricept prior to stroke

CP 1:128 **4/3/2015**, 1:512 2014, incontinence, dyslipidemia (80 mg Lipitor pre stroke)

OD OS SC 20/60 +2

Severe blepharospasm

IOP OD 15, OS 15 time 1:07

A comprehensive meta-analysis on the relationship between C pneumonia infection and cerebrovascular disease shows a strong relationship between C. pneumoniae infection and stroke due to large artery atherosclerosis. [127] This conclusion was based on 52 published studies that met selection criteria. There are many reported vascular responses to C pneumonia infection including cytokine expression, impact on toll-like receptors, and vessel calcification. [128] Several reports demonstrate the C. Pneumoniae – large vessel calcification connection and microbleeds. [129, 130, 131, 132, 133] Vascular dementia is another potential manifestation of chronic C. Pneumoniae infection. In a case controlled study, vascular dementia with highly prevalent when C. Pneumoniae seropositivity indicated by IgG and IgA C. antibodies and hs-CRP were elevated. [134] Drusen are documented to contain proteins related to inflammation, [135] and elevated levels of CRP show associated elevations in age-related macular degeneration. [136]

Patient shows many manifestations of persistent chronic CP infection.

Case 1: Debilitating Psoriasis – 62 year old female seamstress with high school education, Table 13.

| Marker | Before | After |
|---|---|---|
| **LP** | **D** | **C** |
| **CDT** | **101.4** | **99.9** |

Table 13. Case 1: Participant LP Grade and CDT Before and After 5 Months in the HCP.

This participant presented with major risk factors and complaints including: lack or exercise; fast food diet; high carbohydrate diet; high fructose corn syrup containing beverages; use of omega-6 containing oils in cooking; statin drug for primary cardiac event prevention; severe arthritis; psoriasis; and cataract. The severity of the psoriasis and her job function put her at risk of imminently going on disability. She had seen multiple specialists, was placed on antihistamines and topic steroids but her condition continued to worsen. The next treatment option for her was to be Enterecept which she declined pending the outcome from the HCP. She indicated that she had not washed her hands without pain in two years. The HCP included 50 minute bi-monthly health creation coaching following the participant/care team agreed upon care plan and elimination of statin therapy as directed by our medical doctor. Health coaching mainly focused on food substitutions, more exercise, value and use of supplements, and additional care to her oral hygiene.

After 5 months of intensive health creation coaching, many risk factor and complaints were either removed or reduced including nagging chronic pain. Her main complaint, debilitating psoriasis completed resolved, Figure 6.

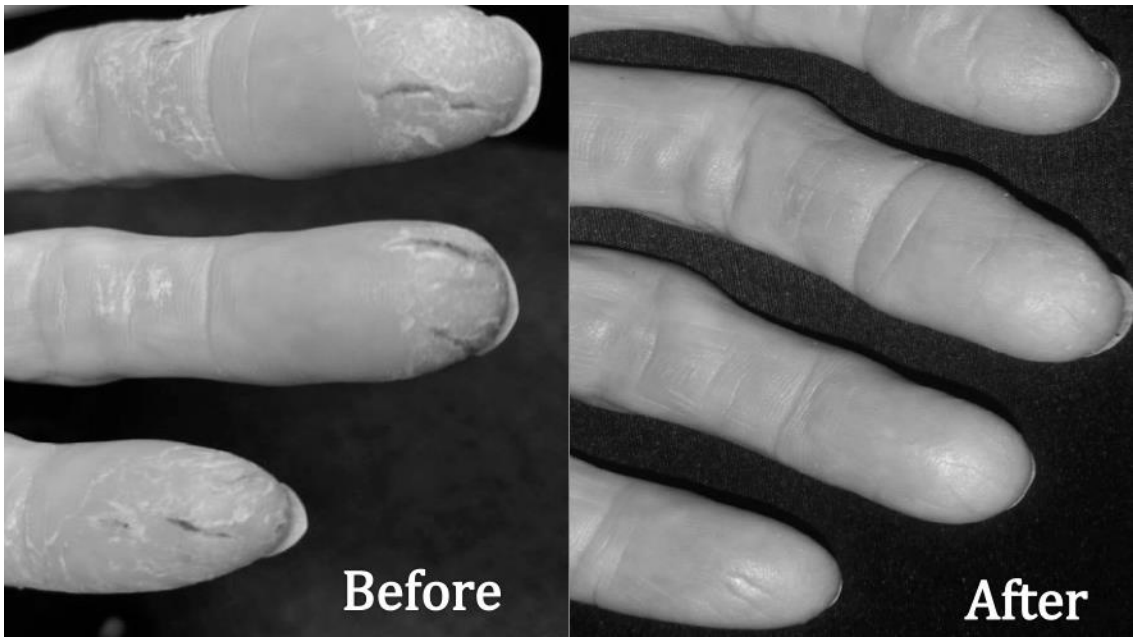



Figure 6. Visual Change in Severe Psoriasis after 5 Months in HCP.

Normally, in the case of autoimmune diseases like psoriasis, food sensitivities or allergies must be addressed. This participant was unwilling to eliminate some of the common allergens like gluten and dairy. She was placed on a modest supplement regiment based on nutritional deficiencies including: cod liver oil (5g/day); vitamin D3 (5000IU/day) and a multivitamin/mineral supplement (taken per label instruction), and the other general supplements included in the "Methods" section, identified from her LP information and CDT. Positive changes in lab values included: 25-Hydroxy vitamin D status (24 to 55ng/ml); white blood cell counts (6200 to 5500); RDW (14.6% to 13.0%); and Fibrinogen (339 to 292mg/dL).

Case 2: Rheumatoid Arthritis and Type 2 Diabetes – 62 year old male factory worker with a high school education, Table 14.

| Marker | Before | After |
|---|---|---|
| **LP** | **$D_+$** | **$C_+$** |
| **CDT** | **101.5** | **100.8** |

Table 14. Case 2: LP Grade and CDT Before and After 5 Months in HCP.

This participant presented with major complaints including: history of cancer; poor oral hygiene; high carbohydrate, high sugar and low healthy fat diet; previous history of tick bites; low vitamin D status; rheumatoid arthritis (RA), chronic back and joint pain, and type 2 diabetes. He refused pharmaceutical drugs per his choice. In addition he almost never participated in traditional healthcare visits. He decided to participate in the HCP. However, he was considering Adalimumab pending the outcome of the HCP. The health creation process included supplements to match identified deficiencies and bi-monthly 50 minute coaching sessions.

This participant lost 25 pounds through a reduction in carbohydrate consumption. The participant embarked on a substitution diet where, over 5 months, gluten containing foods were removed from his diet and replaced with vegetables and healthy fats. He was also put on a modest supplementation program including cod liver oil (10g/day); vitamin D3 (5000IU/day); magnesium glycinate (400mg/day); vitamin K2 (50 mcg/day) and a multivitamin/mineral (per label

instruction). His type 2 diabetes was reversed with his A1C dropping from 8.8% to 5.4% and his fasting glucose dropping from 180 to <90 mg/dL. His pain was eliminated from a daily score of 8/10 to 0/10 and his RA improved to enable him to be able to bend his fingers into a full fist for the first time in over 5 years, Figure 7.

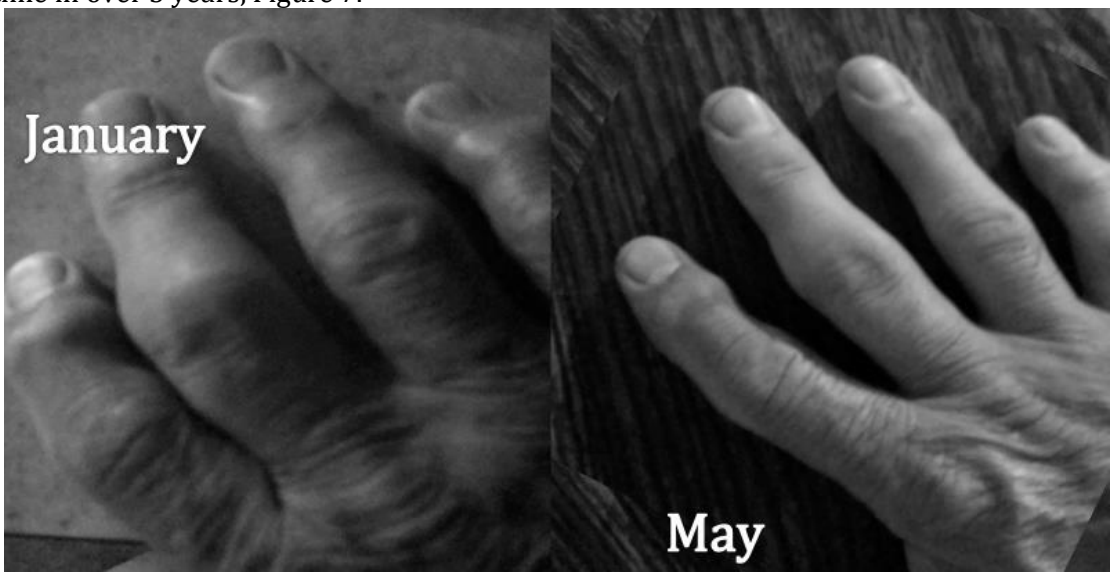



Figure 7. Visual Change in severe Rheumatoid Arthritis after 5 Months HCP.

Case 3. Polychondritis, breast cancer, cataracts – 42 year old female factory worker with high school education, Table 15.

| Marker | Before | After |
|---|---|---|
| **LP** | **C-** | **C+** |
| **CDT** | **104.1** | **101.5** |

Table 15. Case 3: LP Grade and CDT Before and After 5 Months in HCP.

This participant reported with a severe autoimmune disease, polychondritis, that produced monthly painful flares in cartilage above her shoulders including her ears and eyes. Long-term use of steroidal anti-inflammatories were implicated in the cataracts and a breast lump that was removed surgically. The cataracts had progressed sufficiently to cause her to be on disability and be unable to drive a car. Cataract surgery was not an option due to the severity and unpredictability of eye flares that could cause extremely adverse outcomes if they coincided with surgery. She had seen several specialists including local rheumatologists, natural doctors, and doctors from Cleveland Clinic with no relief to her condition. She had researched polychondritis on her own, prior to joining this program and eliminated gluten and dairy from her diet but this change did not alter the disease severity or frequency.

This participant had made significant changes in her lifestyle prior to this program as reflected in her LP grade, but these changes were insufficient to improve her blood biomarkers with a CDT of 104.1, indicative of serious health risk and poor prognosis. Our health creation process guided her to continued better choices and involved bi-monthly 50 minute lifestyle coaching. The main changes made over a 6 month period included: increasing healthy fats, reducing carbohydrate intake, increasing micronutrient density, stopping nicotine dependence, improving digestive health with optimizing food choices including: increasing stomach acid status, and repopulating gut microflora. At month 6 in the program, her eye and ear flares had subsided sufficiently to allow for a meaningful reduction in eye and oral steroids, (50 mg/day to 5mg/day prednisone). In addition,

she was able to have successful cataract surgery, begin driving again, and return to work. The polychondritis may never be cured, however, with appropriate lifestyle management of this condition, it is no longer impacting her quality of life.

**Discussion:**

Prevention and control of non-communicable diseases continues to be a topic of discussion with insufficient resources applied or action taken to curb this global scourge. [137] One impediment is the often vagueness of the risk, poor diet as an example, or the presentation of the same risk to the same individual who has historically been unable to overcome it, with smoking or alcohol consumption as examples. According to Khullar in, "We're Bad at Evaluating Risk. How Doctors Can Help." [138] "A broader approach involves helping patients systematically identify what's important to them, and based on these goals and preferences, suggesting to them how to think about their options." This logic is best applied across the entire continuum in the development of chronic disease, from lifestyle decisions early in life, to changes in chronic disease biomarkers in asymptomatic people, to pathology changes identified in advanced diagnostics, and least optimally, when a person is diagnosed with a chronic disease. Each individual has their own motivations. Thus, providing patients with an array of choices and recommendations along this continuum has a higher probability of inciting action and improving outcomes or prevention.

This study evaluated a new population risk and health assessment and mitigation system where measurements of risk and disease were made across the disease continuum. The output was a broad-reaching care plan assembled through integration of current health survey results, biomarkers, problems, complaints, medications, vital signs, verbal input from the participant to the health coach, and contributions from the care team. The output was a path to improved health through a consensus of agreed upon steps and actions, that were malleable as the process moved forward. According to Khullar, "Patients need to understand their values but also their possible futures…The idea is not to reduce uncertainty, but to help patients clearly envision what life would look like in one outcome versus another, and to better prepare them for the various futures that might unfold." This program was designed to give participants options beyond management of disease once it has struck. And it included regular monitoring and concomitant course adjustments to help participants attain their goals.

This study prospectively observed adults with chronic conditions and unresolved health complaints that remained unresolved under usual care treatment. Following 6 months of HCP, participants achieved subjective and objective improvement in health status with 90% seeing a reduction to multiple blood-based biomarkers and 94% achieving a reduction is a broad measure of lifestyle risk factors. Concurrently participants reported weight loss (34% total and 80% of those with a reported weight loss goal), reduction in reported pain, sleeplessness, memory issues, heartburn, skin rashes, migraines, and daily fatigue. Although no formal control was conducted, the diabetics in the program had all progressively worsen over the previous 2 years, as measured by fasting glucose, HbA1C, and medication usage and all improved under the HCP program.

The HCP meaningfully improved HbA1c, fasting insulin, neutrophil-to-lymphocyte ratio, hs-CRP, vitamin D, white blood cell counts, red blood cell distribution width, absolute neutrophils – all part of the CDT panel. In addition, HDL, fasting glucose, triglycerides, GFR, Atherogenic Index of Plasma (AIP) [**Error! Bookmark not defined.**] liver enzymes, and blood pressure improved is most participants with initial abnormal values. AIP is emerging as a valuable representation of increased mortality risk based on lipid levels. Improvement in similar lab value panels were consistent with previous studies using carbohydrate-restricted interventions. [139, 140] However, although the HCP included some level of carbohydrate restriction, this was not a mandate of the HCP and carbohydrate consumption goals were not set. Instead, participants were afforded broader options that met each

at their level of readiness to change and did not overwhelm anyone with unachievable objectives. In general, small swap-out suggestions were agreed upon at each encounter.

The “PURE” study reports are a set of studies that describe well the nutritional approach used in the HCP. [141, 142, 143] In "Fruit, vegetable, and legume intake, and cardiovascular disease and deaths in 18 countries (PURE): a prospective cohort study,” fruit, vegetable and legume consumption recommendations were 375-500 g/day to achieve maximum benefit at reducing non-cardiovascular and total mortality. The HCP coaches encouraged consumption of three to four servings of these foods per day, focusing on lowest glycemic index choices. In “Associations of fats and carbohydrate intake with cardiovascular disease and mortality in 18 countries from five continents (PURE): a prospective cohort study,” healthy fats were found to be indicated for a reduction of total mortality risk and saturated fats were shown to be inversely associated to stroke risk. The HCP coaches guided participants to swap out carbs, sugars, and some protein in favor of healthy fats in foods and cooking oils with emphasis on increasing saturated, monosaturated, and marine fats. Obtaining nutritional ketosis for a 2-3 month window was suggested for all the diagnosed type 2 diabetics, however none achieved sustained ketosis while their metabolic markers indicated resolution of their diabetic conditions during the 6-month HCP. This suggested that the broader risk reduction approach of this HCP, compared to strict carbohydrate restriction, affords metabolic profile results without the potential risks associated with carbohydrate starvation.

Reducing whole body inflammation was the primary objective of each encounter, not just reducing the glycemic value of food. Examples included switching out proinflammatory for anti-inflammatory cooking oils, lowering glycemic value and load of substituted foods, reducing frequency of fast food consumption, improving oral hygiene, managing stress, establishing better sleep and rest patterns, enhancing hydration, improving micronutrient density of food, establishing more frequent movement routines, and consuming more gut-supporting foods.

The regular health coach encounters and monitoring of risk factor, vitals, and medication changes may have provided behavior reinforcement. Further, it is plausible that this multi-risk amelioration care model allowed from both broader and greater adoption and improvements compared to interventions focused on fewer factors. [120, 144] In this HCP we effectively leveraged credible measurement and evaluation, linked these findings to participant’s unresolved and nagging health complaints and facilitated behavioral change leading to health improvement in most participants. The program did not rely only on usual care measures of health. Participants were not confronted with high hurdles to health improvement that often discourage engagement. Instead, the program centered around meeting a person at their level of readiness and capitalizing on small triumphs that eventually, measureable health improvements recognized by the individual that led to further compliance with recommendations.

No episodes of adverse events were attributable to the HCP. One insulin dependent type 2 diabetic participant showed a sudden increase in fasting insulin, from 1.8 to 53 μU/ml, which was reported to his PCP for medication adjustment. Several participants reported dizziness and either the HCP or PCP lowered their blood pressure medication dose that resolved the complaint.

Prior studies have demonstrated favorable cost reductions in a broad-based wellness and disease management programs. [145, 146] Most of the cost saving and health maintenance were attributed to the management of existing disease rather than prevention and required a strong evidence-based approach. A strength of this HCP was an emphasis on root-causes of and reversal of disease rather than just case management. Additionally, this study reflected a real world workplace environment with a distribution of both white and blue collar workers participating and with a range of diseases and aliments. Weaknesses included a lack of a representative control group, single

location and participants were mostly Caucasian. The study was not of sufficient size and duration to measure hard endpoints including mortality and adverse health events. Future trials could include multisite randomized controlled trials with greater racial and ethnic diversity and longer duration.

**Conclusion:**

This highly personalized and scalable health creation study demonstrated that a broad array of health complaints and problems can be controlled and reversed by methodically eliminating seemingly small lifestyle-induced health risks. It also demonstrated that the lifestyle risk tool, the Living Profile™, and the biomarker panel, the Chronic Disease Temperature™, that were used to develop care plans, changed in correspondence with noted health improvements. Therefore these tools may be valuable for the measurement and mitigation of risk and disease generally. More studies using this overall HCP approach are required to validate the measurement methods, processes, and outcomes. This approach offers an important health delivery modality for the future.

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