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Review Article

Proposing the Diagnostic Age Print [DAP]™ Map for Prevention and Mental Healthcare Management for the Aging Complex Patient

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Abstract

Each year, tobacco related use accounts for approximately 430,000 deaths, while heart disease claims around 630,000 lives in United States. Cancer contributes to another 600,000 deaths annually. Together with cerebrovascular disease, chronic lower respiratory diseases, unintentional injuries, diabetes, and Alzheimer's disease these conditions constitute the seven leading causes of mortality in the United States, with prevalence rates increasing significantly with age. For example, over 83% of individuals who die from coronary artery disease are 65 years or older. Age is a major determinant of life-threatening diseases and illnesses, emphasizing the need for early detection and comprehensive management. Overcoming silent and hidden diseases by unifying whole body (holistic) diagnostic approach (head to toe) utilizing electrophysiological, endocrine, genetic, neurochemical and molecular evaluation seems prudent in light of these statistics concerning. To combat this pressing health challenges dilemma, we hereby propose a new paradigm shift involving the development and implementation of a novel "Diagnostic Age Print (DAP™) map. This innovative tool aims to prevent premature fatalities and optimize the management of complex aging patients. By enabling a systematic, comprehensive evaluation within a single primary care physician's office, the DAP™ map has the potential to reduce the need for multiple specialists' visits, streamlining care and improving patients' outcomes.

Keywords: *Diagnostic Age Print [DAP]™ Map; Mental Healthcare Management; Aging Complex Patient*

Introduction

In general, at least 120 million people die each year according to the United Nations' World Population Prospects (2024) (OurWorldinData.org/population-growth). The Centers for Disease Control and Prevention (CDC) have utilized the Smoking Attributable Mortality, Morbidity, and Economic Costs (SAMMEC) model to estimate average annual smoking-attributable mortality in the U.S [1]. Based on data from 2005-2009, CDC estimated that cigarette smoking claimed an average of about 480,000 American lives annually, including deaths among current and former smokers and individuals exposed to second-hand smoke (439,000 and 41,000, respectively) [1]. Over the past 15 years, smoking prevalence in the U.S. has dropped substantially, from 20.9% in 2005 to 11.2% in 2022 [2,3]. While this substantial decline might be expected to correspond to a decrease in smoking-related mortality, several counterbalancing factors complicate this expectation. First, the total U.S. population has grown substantially, from 296 million in 2005 to 332 million in 2021 [4,5]. Second, the population of current smokers has aged. In fact, between 2005-2009 only 7% of this group were aged ≥65 years, but by 2020, individuals aged 65 and above comprised 16% of all current smokers. Additionally, the proportion of former smokers within the 65+ age group increased from 30% in 2005-2009 to 36% in 2020. Smoking-related mortality is concentrated among older individuals who currently smoke or formerly smoked as smoking-related risks diminish gradually [6]. For instance, age-adjusted lung cancer mortality-80%-90% attributable to smoking-reached its peak in 1993, almost 3 decades after the 1964 peak in adult smoking prevalence [7-9]. Although the CDC has not issued an updated estimate of the smoking-related mortality, this figure is commonly treated as if it reflects the current burden.

Cardiovascular disease is projected to cause approximately 20.5 million deaths worldwide in 2025 [10]. Moreover, demographic-based predictions indicate that the number of new cases of cancer will reach 35 million by 2050. Investments in prevention strategies, particularly those targeting key risk factors such as smoking, obesity, and infections have the potential to avert millions of future cancer diagnoses and save many lives worldwide, bringing huge economic as well as societal dividends to countries over the forthcoming decades [11].

It is important for scientists and primary care physicians to understand several key aspects of the aging process. These include but are not limited to the following: (1) aging is a slow deterioration of the body, and some parts deteriorate faster than others; (2) Chronological age, represented by the number of birthdays is an inaccurate assessment of the biological age of individuals organs or systems; (3) Most diseases develop progressively, with each stage representing an older version of the particular organ or system it is affecting [12]. To exemplify these facts, a 50-year-old man may have a heart with the biological age of an 80- years old due to risk factors such as smoking, hypertension, or other lifestyle or genetic influences. Such a man's cardiovascular health would be equivalent to that of an 80-year-old man with a heart of similar biological age. This simple understanding of the aging process provides the impetus of systematically evaluating the "true" biological age of an individual's organ systems and functional pathways, whether peripheral or central. In this regard we are reminded of the old adage "a patient is only as young as their oldest part".

A recent PubMed search (accessed 12-20-24) has revealed only 1,797 published studies attempting to determine the age of human organs and functions. For example, radioiodinated metaiodobenzylguanidine (MIBG) imaging has been used to evaluate adrenergic nerve activity in different organs. Cardiac and pulmonary MIBG uptake has proven valuable in predicting the prognosis of certain cardiopulmonary diseases. It has been reported that cardiac MIBG uptake decreases with age and is significantly lower in the elderly [13].

Understanding the need for a unified methodology to diagnose the age of a particular organ in not only the elderly but in the younger patient presenting with complications, we call Diagnostic Age Print [DAP]™. The "Age Print" represents a quantitative profile that determines the biological age of each organ. It is used as a diagnostic map to direct medical attention to the part of the body that has aged the most with particular attention on the kidneys and the immune system. An individual's "Age Print" is influenced by a variety of factors, including behavioral, environmental, and genetic determinants [14]. These factors impact the function of peripheral organs regulated by neurological activity of the central nervous system (CNS) [15].

Diagnostic Age Print [DAP]™

Determination of organ age has advanced in-renal failure and other organ systems [16-30]. Wang., *et al.* [31] concluded that Acute Physiology and Chronic Health Evaluation (APACHE II) score and the number of organ system failure (OSF) measured prior to initiation of dialysis are reliable predictors of outcomes in acute renal failure (ARF) patients requiring dialysis. The mortality rates increase as the APACHE II score or OSF number rises. For predicting mortality, the APACHE II score ≥ 24 was found to have 63% sensitivity and 96% specificity, while an OSF number ≥ 2 showed 81.6% sensitivity and 60.9% specificity.

What if there were a rapid, inexpensive, and accurate blood diagnostic tool capable of determining which patients were infected, identifying the responsible organism(s), and identifying those patients who were not responding to therapy? Polpitiya., *et al*. [32] hypothesized that systems analysis of the transcriptional activity of circulating immune effector cells could be used to identify conserved elements in the host response to systemic inflammation, and furthermore, to discriminate between sterile and infectious etiologies.

They [32] validated, a systems biology approach demonstrating that 1) abdominal and pulmonary sepsis diagnoses can be made in mouse models using microarray (RNA) data from circulating blood, 2) blood microarray data can be used to differentiate between the host response to Gram-negative and Gram-positive pneumonia, 3) the endotoxin response in normal human volunteers can be mapped at the level of gene expression, and 4) a similar strategy can be used in the critically ill to follow septic patients and quantitatively determine immune recovery. These findings provide a foundation for immune cartography and demonstrate the potential of this approach for rapidly diagnosing sepsis and identifying pathogens. Further their data suggests a new approach to determine how specific pathogens perturb the physiology of circulating leukocytes in a cell-specific manner. Large, prospective clinical trials are needed to validate the clinical

utility of leukocyte RNA diagnostics (e.g. the riboleukogram). The concept here is that appropriate accurate diagnostics involving system functioning are critical for patient success, especially in the elderly populations, but equally important for the management of complex medical cases independent of age.

Diagnosing brain dysfunction: Can we determine its AGE?

The brain controls all bodily functions, with dopaminergic integrity playing a critical role [33]. It regulates memory, attention, intelligence, and various aspects of behavior through interaction of many neurotransmitters with specific receptor sites. The pathways involved include serotonergic, enkephalinergic, GABAergic, dopaminergic, cholinergic and adrenergic systems, along with involvement of multiple second messengers. Alzheimer's disease and dementia are associated with imbalanced cholinergic neurotransmission [34].

Acetylcholine levels can drop by as much as 90 percent in Alzheimer's patients. Additionally, dopamine plays a central role in regulating metabolism, reward, memory, stress responses, and energy levels [35-37].

A dopamine imbalance has been implicated in obesity and is linked to three of the top seven leading causes of death in America including heart disease, diabetes, and cerebrovascular disease [38]. Additionally, serotonin plays a critical role in regulating mood and sleep patterns, while GABA is involved in regulation of anxiety. There are many review articles that explore the relationship between behavior, neurological disease states and cognition focusing on the genetic underpinnings of neurochemical pathways [39]. Advancements in non-invasive genotype techniques now enable the evaluation of brain activity via polymorphisms and brain deficits. Along these lines our laboratory has embarked on utilizing large datasets and performed GWAS combined with in deep pharmacogenomic analyses to uncover a map to the fountain of youth discovering 16 potential genes involved in aging, longevity and telomer length [40].

An additional diagnostic tool includes Brain Electrical Activity Mapping (BEAM), which measures brain function regarding the above cited neurotransmitter pathways and can be used to identify health risks and potential diseases including substance use disorders [41].

Head-to-toe ultrasounds are also necessary to further understand an individual's overall health, particularly the state of the brain and body. Diagnostic imaging, such as transcranial, carotid, breast and abdominal ultrasounds can detect silent diseases and cancers in aged organs [42]. For example, a thyroid ultrasound may reveal goitrous changes, calcification, or nodules indicative of thyroid cancer, which, in a normal physical exam, would have gone unnoticed. A renal ultrasound reveals kidney stones, cysts, or tumors, often as an accidental finding in patients without complaints. In these early stages of detection, a disease can be cured or a cancer removed. Early utilization of ultrasound could potentially be earmarked or identify a silent disease or cancer. Preventing their progression to a stage where treatment becomes more challenging.

Specifically, cancer is the second leading cause of death in America and as such is the major subject of research exploration by the National Institute of Health. While we have not made overwhelming progress in curing this dreaded disease, we are least cognizant that in order to succeed early diagnosis is key. Recent research emphasizes the importance of understanding the interplay between genetic predispositions and environmental factors. It is the interaction of multiple factors coupled with appropriate imaging diagnostic tools that will pave the path to remission or prevention. With this stated there are methods to stop cancer before it kills like a colonoscopy to remove polyps so they can be studied to determine whether or not they are precancerous. A Papanicolaou test determines if cells are malignant in order to prevent the development of cervical cancer.

Alzheimer's disease (AD), a debilitating neurodegenerative disorder, is expected to quadruple the incidence over the next decade. Extensive research efforts are focused upon identifying new treatments, and early diagnosis is considered key to successful intervention. Although advanced imaging and cerebrospinal fluid biomarkers show promise in detecting early-stage AD, more noninvasive cost-

effective tools have remained elusive. Recent studies have reported plasma-based screening approaches. One study using an 18-analyte multiplexed plasma panel demonstrated the potential to distinguish AD patients from controls. Further evaluation of a subset of this panel using bead-based multiplex technology yielded a diagnostic accuracy of 61%. Expanding to an 89-analyte multivariate panel improved diagnostic accuracy to 70%, suggesting that a plasma-based AD signature could serve as a valuable, accessible screening tool [43].

Positron emission tomography (PET) scans: A "valuable diagnostic modality"

Positron Emission Tomography (PET) scans are among the most accurate methods of cancer detection. Cancer cells exhibit a high metabolic rate due to their rapid division and as a result metabolize a radioactive form of glucose, FDG, unlike normal cells. When FDG is injected into a patient, a PET scan creates an image of glucose metabolism, highlighting areas with cancerous activity. PET scans are sensitive enough to detect cancer in its earliest stages [43,44].

Beyond cancer, PET scans are invaluable in detecting early-stage AD. For example, a 79- year-old man with a history of cognitive decline underwent a PET scan at PATH Medical Clinic in New York City. The scan revealed decreased glucose metabolism within the biparietal region of the brain as well as within the bitemporal lobes, findings are compatible with Alzheimer's dementia. Follow-up studies with other patients are underway in our clinic. This finding is in agreement with over 1068 published PubMed papers showing the important utility of PET as diagnostic tool for AD [45].

A typical scenario in conventional medicine, a patient visits a doctor or specialist when he/she is already experiencing symptoms due to the presence of a disease. He/she did not know that they were at risk for such a disease. In this case, the illness has progressed enough for the physical or behavioral signs to develop to induce the patient to visit a physician. In this case, many patients disregard the family history of disease, a very important link to inheritable diseases.

However, with the advancement of science and technology, waiting for symptoms to manifest is no longer necessary. Importantly, for certain diseases, such as cerebrovascular disorders or AD, symptoms often indicate advanced pathology. In preventative medicine, early detection is crucial to mitigate disease progression. Through appropriate brain scans as early predictors of cognitive decline [14] the primary care physician is armed with DAP and at least a delay of onset of such devastating neurological diseases could be accomplished.

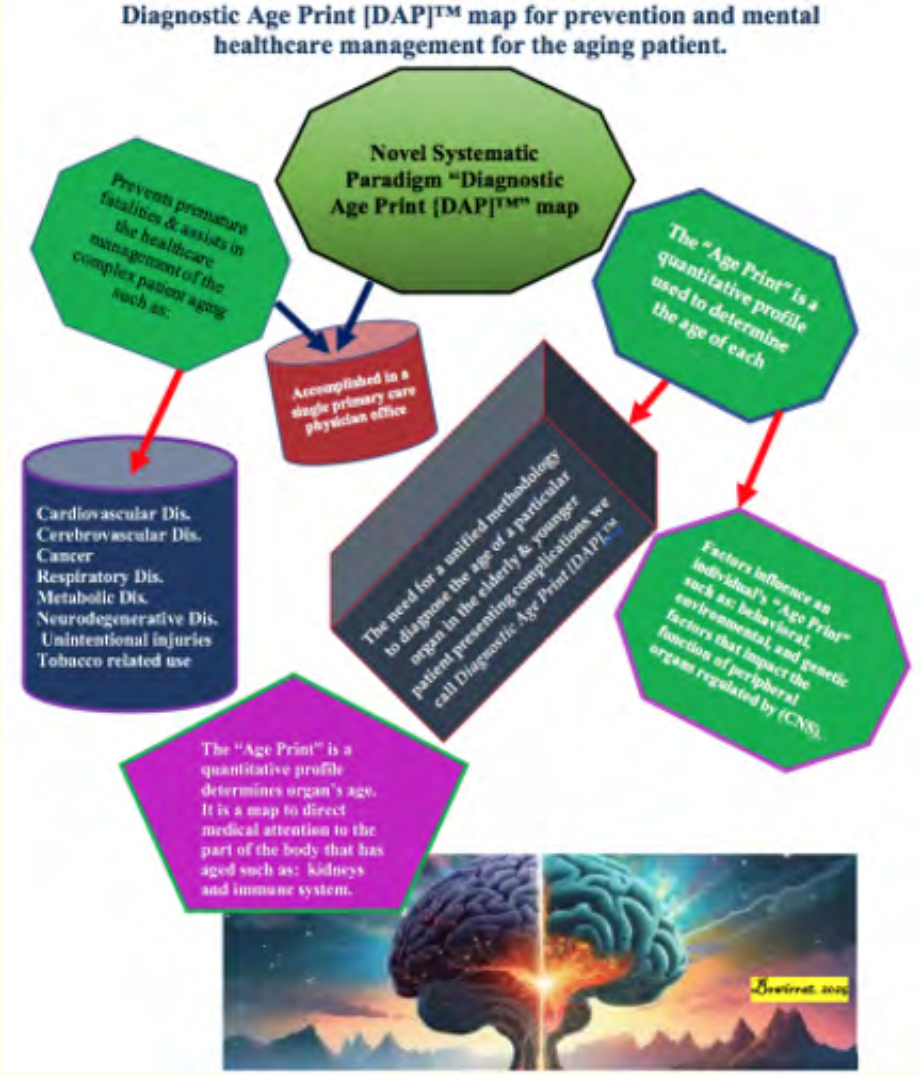
It is noteworthy that as practicing physicians, three important stages must be considered in terms of the progression of any disease. Stage 1: Early biochemical and intracellular changes can be identified through blood tests; Stage 2: Radiological scans discover structural changes within the body; Stage 3: Physiological changes allowing physicians to detect and address the disease directly.

Summary

Americans are aging today in a way unlike any preceding generation. The demographic swell of the post-war baby boom combined with medical achievements in the 20th century that reduced mortality from infectious diseases, has shifted the primary causes of death in the United States to chronic diseases. This transition is resulting in an unprecedented number of older people with chronic illnesses. More importantly, the American health care system is largely unprepared to address the challenges posed by this growing population of patients with complex combinations of chronic diseases, some of which are even silent or hidden. Managing these conditions is complicated by intricate medical regimes, the interplay of multiple diseases, especially those with psychiatric illnesses, reliance on specialists, significant healthcare costs, and the cumulative impact of these factors on morbidity, mortality and quality of life. While significant evidence exists to support the diagnosis and management of cardiovascular diseases and associated risk [46] there remains a notable lack of standard guidelines for assessing and mitigating brain health risks, as previously proposed by our group [47].

An important aspect of addressing this gap involves the development of national guidelines for preventive healthcare services. Current guidelines often target healthy patients and fail to provide sufficient guidance on the timing and appropriateness of preventive measures

for patients with chronic diseases. Furthermore, patients with multiple comorbidities frequently face excessively complex medical regimens due to inadequate identification of underlying core elements. Specialists may continue to add or intensify therapies without robust evidence, often resulting in interventions that neither improve the quality nor extend the duration of life. In fact, for some patients with comorbid conditions, preventive or therapeutic interventions may pose increased risks, particularly when the functional status of the central nervous system is not adequately considered.



Figure

Conclusion

Certainly, early diagnosis is the key, and we are hereby proposing that specialists focus on a particular area of the body most relevant to the disorder, while recognizing that many conditions ultimately originate in the brain. It is important that physicians consider a patient's biochemical profile Age Print when making a diagnosis to address the root of the patient's problem and to ensure that such ailments do not recur. Comprehensive diagnostic approaches, such as head-to-toe ultrasounds, PET scans, and Pap tests play a critical role in identifying potential disorders or cancers before they have the opportunity to manifest. The seven leading causes of death in America, especially smoking is largely preventable with timely interventions. However, achieving this requires a holistic approach to healthcare that considers the body as an interconnected system, rather than focusing solely on individual organs. Emphasizing the integration of brain health and musculoskeletal integrity within this framework is particularly important for advancing preventive medicine and improving patient outcomes.

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Author Contribution

The initial manuscript was developed by KB, MSG, ND, RDB, SK and commented by all co-authors. AB developed the graph.

Conflict of Interest

The authors have nothing to disclose.

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Informed Consent

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