EDIFICE
HEALTH

The critical role of understanding chronic inflammation - the root cause of all age-related diseases, and the importance of novel inflammatory biomarkers immune profiling in prediction of coronavirus disease severity

Immune Health and Resilience Against Disease

3 E 3rd Ave #200, San Mateo, CA 94401
P: 628.222.4006 F: 404.829.2897
www.edificehealth.com

Executive Summary

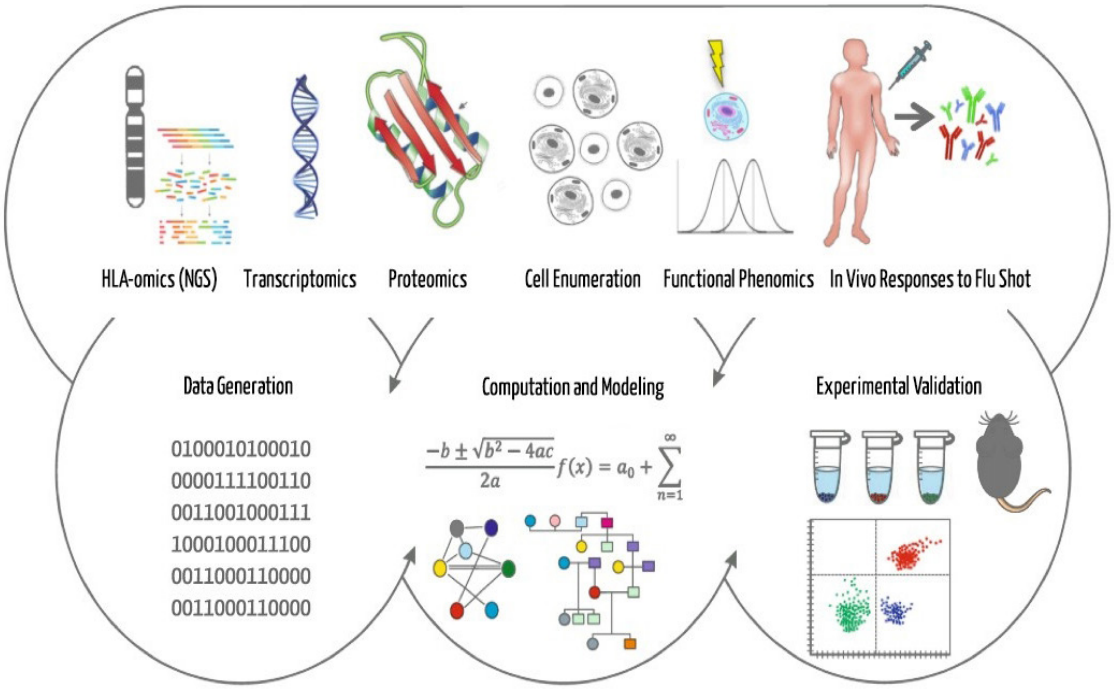
Non-communicable diseases of aging are the #1 killer worldwide. It is now a consensus in the scientific community that **Systemic Chronic Inflammation (SCI), arising as an immune response to environmental and social insults, is the root cause of these diseases**, which include cardiovascular disease, cancer, neurodegenerative disorders, musculoskeletal conditions, and many others. Despite the major role of SCI on the pathophysiology of these diseases, at present there are no standard biomarkers of this condition and studies aimed at defining 'metrics' for SCI have yielded conflicting results.

The Stanford 1,000 Immunomes Project was established in the year 2008 with the aim of finding immunological biomarkers of human health and disease. By measuring thousands of blood parameters from 1,000 humans over 10 years, a group of eight scientists lead by Professor David Furman at the Stanford School of Medicine and the Department of Biomedical Data Science used state-of-the-art artificial intelligence to derive the first score for SCI – or Inflammatory Age® (iAge®) – which predicts cumulative chronic diseases and cardiovascular aging even in those apparently healthy individuals, and has applications for many other disease conditions including autoimmunity.

The Stanford 1,000 Immunomes Project was funded by the National Institute of Health (NIH) with approximately $30M. The goal was to answer one important question for medicine and healthcare economics:

What are the immunological determinants of human health and disease?

The Stanford Project studied 1,000 individuals ages 9 - 96 whose blood samples were comprehensively profiled by measurement of circulating protein levels, cell types, cellular function assays, and whole-genome blood gene expression. From circulating protein levels, it identified a novel set of 5 serum proteins including cytokines, chemokines and hormones that are the first known biomarkers specific for systemic chronic inflammation. These proteins, measured using a multiplex Luminex assay, are highly predictive of immune function and multimorbidity, and can be used for many applications including disease risk stratification of individuals, early detection of disease or guided therapeutics and lifestyle interventions[1,2].



Summary of the Stanford 1,000 Immunomes Project:
The project measured a wealth of biomarkers of about 1,000 people in up to 10 years and applied state-of-the-art analytics to create the first biomarker composite scoring system (or Inflammatory Age®, iAge®), which predicts multi-morbidity and cardiovascular aging [2,3].

The resulting inflammatory clock of aging (iAge®) tracked with multiple morbidities and immunosenescence; analysis of a separate cohort of centenarians, showed that iAge averaged 40 years lower than their corresponding chronological age. The strongest contributor to this metric was the chemokine CXCL9, which is involved in cardiac aging, adverse cardiac remodeling, and decreased vascular function. Furthermore, aging endothelial cells derived from human induced pluripotent stem cells show indicators of early cellular senescence and hallmark phenotypes of arterial stiffness, which are reversed by silencing CXCL9. Thus, the research identified blood biomarkers of age-related chronic inflammation and derived a 'metric' for age-related multi-morbidity which can also be used for early detection of cardiovascular aging[4].

In 2018, Professor Furman and colleagues formed IUVE, Inc., which later changed its name to EDIFICE Health, Inc. to bring the iAge® scoring system to the medical community to be used as a new tool for health risk assessment.

EDIFICE Health Products

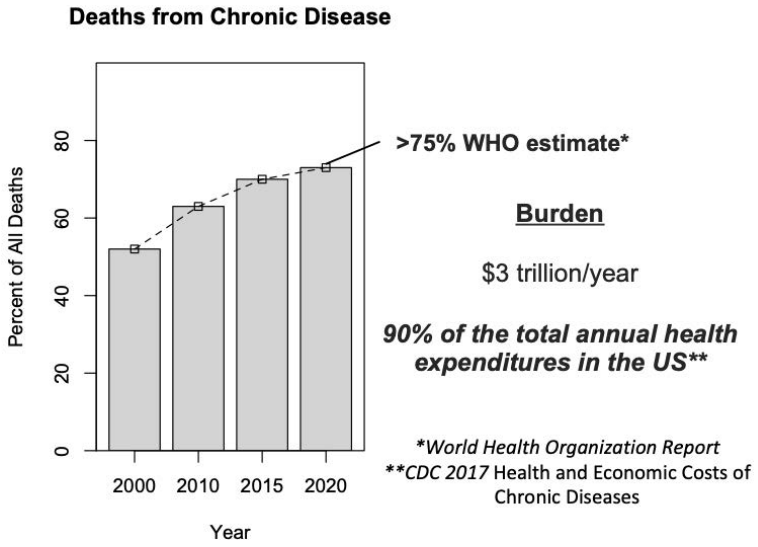
The company has two product lines:

Inflammatory Age® - iAge®	COVID-19 Infection Risk Index - CIRI™
Developed - A marker for biological age with interventions that predicts multi-morbidity and immune decline.	**In Development** - A marker for immune resilience against viral infections (Example SAR-CoV-19)

Inflammatory Age® - iAge®

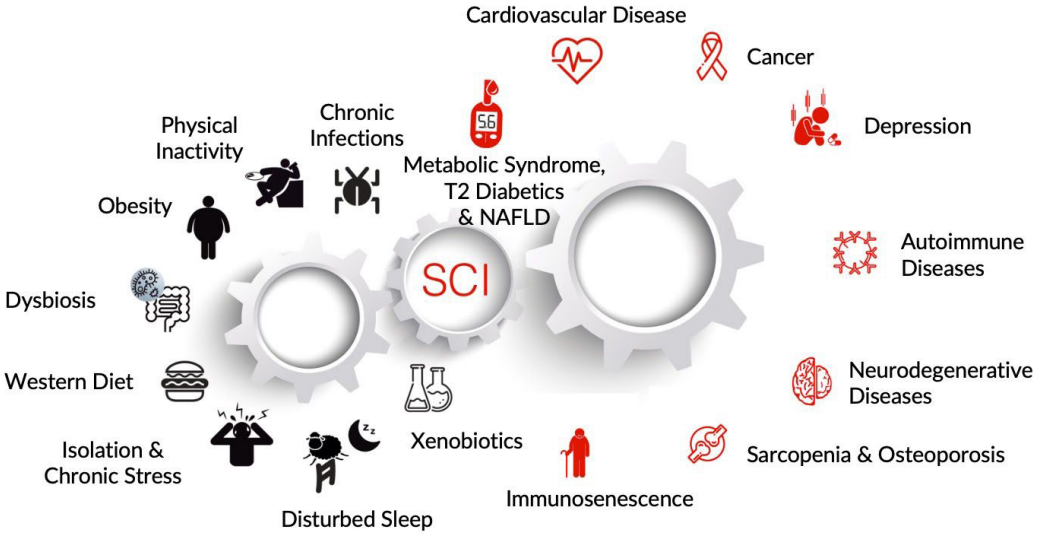
Problem

Despite the major role of SCI on the pathophysiology of these diseases, at present there are no standard biomarkers of this condition and studies aimed at defining 'metrics' for SCI have yielded conflicting results. A total of 71% of humans die from non-communicable chronic diseases of aging worldwide[3]. The economic burden of these diseases is estimated to be $3 trillion/year, 90% of the total annual health expenditures only in the US[5,6].



The proportion of deaths from chronic diseases is rising.
Estimates from WHO have reported that about half of the population died from chronic illnesses in 2000, increasing an alarming 70% in 2015.

Contrary to "acute inflammation" which is an immune response triggered by infections or trauma that can be measured by standard blood tests (for example Interleukin-1β, interleukin-6, Tumor Necrosis Factor-α, and C-reactive protein); given the complexity of age-related SCI, at present, there are no standard biomarkers for this type of inflammation and studies of aging have generally yielded conflicting results[7,8].



Environmental and social triggers of chronic inflammation and its consequences on human health: Data from many thousands of scientific peer-reviewed articles have repeatedly demonstrated that a state of Systemic Chronic Inflammation (SCI) is induced by environment lifestyle insults, known as the "Exposome" (black, left) causing collateral damage in multiple tissues and organs increasing the risk for the most feared diseases of aging (magenta, right)[1].

It is now well accepted in the scientific and medical communities that a major contributor in the development of these diseases is a state of low-grade systemic and chronic inflammation (SCI) that increases with age as an immune response to environmental and social insults, known as the "Exposome"[9]. This type of age-related inflammation impinges collateral damage on tissues and organs causing cellular dysfunction and increasing the risks for cardiovascular disease, cancer, neurodegenerative disorders, musculoskeletal conditions and many other illnesses[1].

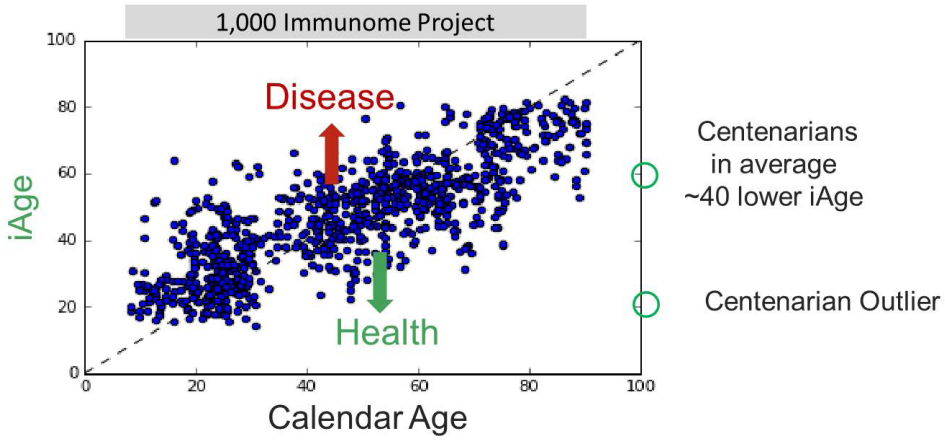
Autoimmune diseases affect an estimated 50 million Americans with annual treatment costs exceeding $100 billion, forming a substantial burden of disease[7]. In autoimmune diseases, mis-regulation of the immune system leads to development of an immune attack against the body's own tissues, leading to inflammation and tissue damage. Factors contributing to autoimmune disease include a combination of environmental triggers (infection, microbiome, traumatic insults), genetic predispositions, and defective regulation that result in activation and proliferation of self-reactive immune cells which cause tissue injury[8].

Solution

iAge® - The world's first test to measure systemic chronic Inflammation and it aligns with our vision to become the world leader in detecting and measuring systemic chronic inflammation.

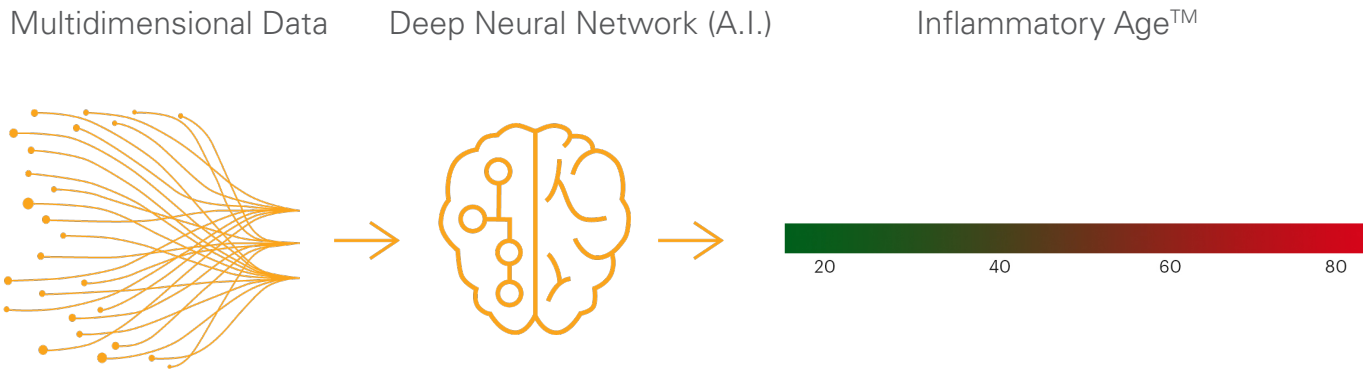
From the thousands of biomarkers tested in the Stanford Project, a subset of novel blood protein markers was screened and identified to give an exact inflammatory age of a person. Proteins that make up the iAge® score can be measured using standard lab equipment. The assay for these proteins is proprietary and customized for the iAge® score and will be the world's first commercially available test to measure SCI. iAge® will be positioned in the healthcare space as the first knowledge-based AI-fueled diagnostic test to detect and combat SCI, aligning with our vision to become the world leader in the field of SCI, the root cause of all age-related diseases.

The long-term mission is to contribute substantially to a decrease in the incidence and prevalence of chronic diseases with the aim to extent the health span and lifespan globally.



iAge® score of the Stanford 1000 Immunomes Project.
People with an iAge® score above the diagonal are prone for disease and early onset of age-related diseases. People below the diagonal are healthy.

The inflammatory age of a person determines how much older or younger someone appears with respect to the chronological age.



Artificial Intelligence applied to immunological data from blood samples identifies 'Inflammatory Age'. Using the Stanford 1000 Immunomes Project database, the Stanford researchers applied state-of-the-art analytics to create the first biomarker composite scoring system (or Inflammatory Age, iAge®), which predicts multi-morbidity and cardiovascular aging[2].

This new metric for SCI predicts cumulative damage, as measured by the accumulation of up to 10 diseases of aging (cancer, cardiovascular, respiratory, gastrointestinal, urologic, neurologic, endocrinemetabolic, musculoskeletal, genital-reproductive and psychiatric). Strikingly, in a validation study of cardiovascular function, iAge® identified individuals with increased stiffness of their vasculature and a subclinical cardiac hypertrophy, who were apparently healthy based on standard clinical assessment and laboratory testing procedures[2].

The iAge® inflammatory score is calculated from a standard serum blood draw and can be measured once to give a snapshot profile, or tracked over time to give a measurement of longitudinal changes of the effect of interventions.

The iAge® is an actionable score. Importantly, based on the iAge® test results, EDIFICE Health identified over 150 actionable interventions which may be suggested to a patient to improve their iAge® score. These include specific combinations (or protocols) of nutritional supplements, nutraceuticals, medical foods, prescription drugs, and life-style modification.

Benefits

Chronic disease is preventable. We can help reduce the $3 trillion/year cost burden impacting insurers, healthcare stakeholders and patient lives.

Inflammatory Age® Applications

Life Insurance

Data helps qualify insurance applicants, provide metrics for incentive insurance pricing models and aids in understanding population depending aging processes to improve the predictability of disease outcomes.

Preventative Medicine

Easy to understand report motivates patients towards improved health with actionable and trackable results while providing insight into the onset of age-related diseases (neurodegenerative diseases, cancer, cardiovascular, etc.). The information promotes healthy decision-making by providing guidance on environmental factors that may have an impact on their health, thus empowering patients to take control of their inflammatory aging.

Pharma
(Companion diagnostics developers)

Data can be utilized to evaluate the potential role of pharmacological or nutraceutical preparations in lowering chronic inflammation and decreasing the risk of multiple chronic diseases.

Wellness Healthcare Providers

Inflammatory Age® can inform health providers about the risks of early aging in nominally healthy populations, which can prompt additional testing procedures and early interventions.

COVID-19 Infection Risk Index, CIRI™

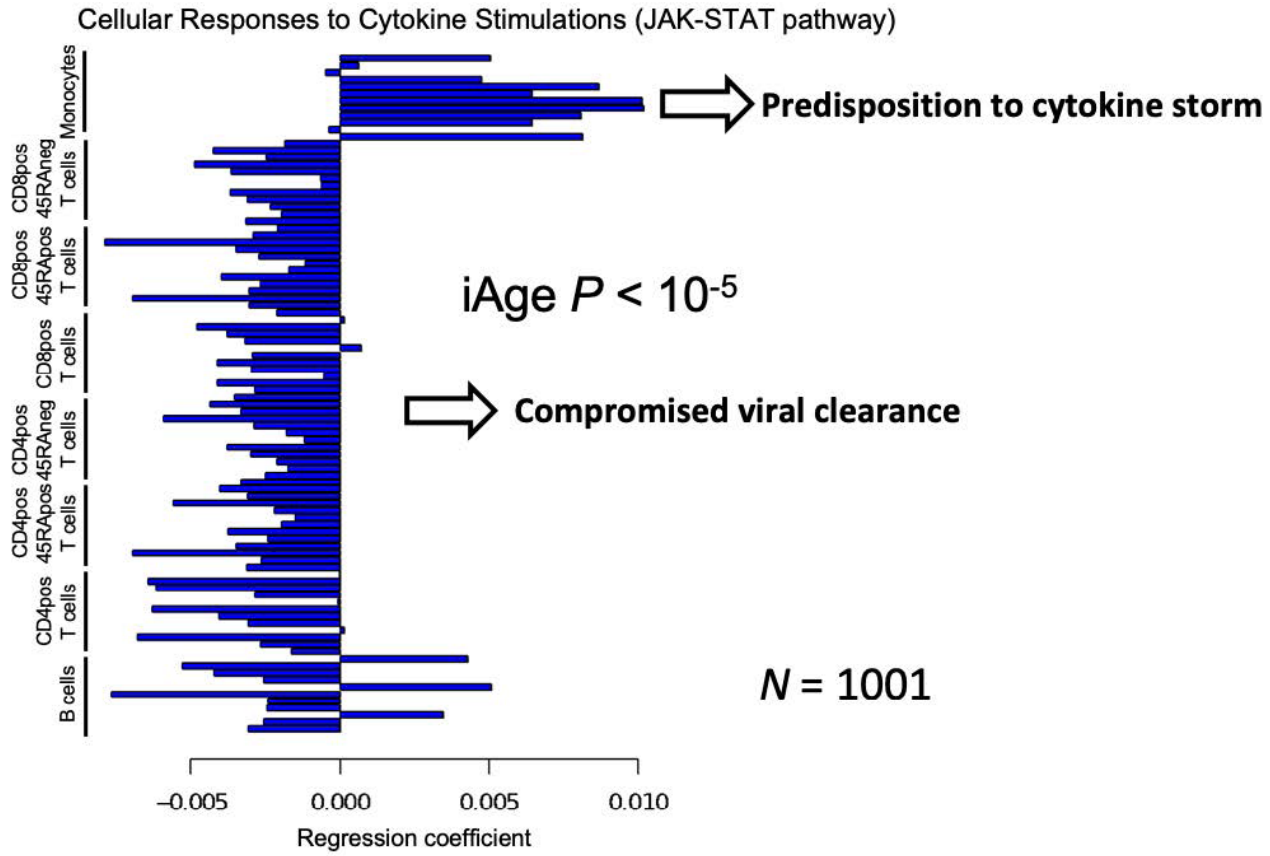
Problem

During the first SARS outbreak in 2002, gene expression profiles of peripheral blood mononuclear cells (PBMCs) derived from SARS patients were analyzed and compared to healthy controls. The patients' response to SARS was shown to be mainly an innate inflammatory response[10]. Preliminary data from the current SARS-CoV-2 infected patients showed that 14 cytokines are significantly elevated upon development of Coronavirus disease (COVID-19) and that a continuous high level of certain cytokines, known as a cytokine storm, are associated with Acute Respiratory Distress Syndrome (ARDS) and is frequently fatal[11]. This suggests that an appropriate cytokine profile can provide valuable prognostic nformation about a patient's disease state.

COVID-19 is caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and has reached pandemic status with over 2,222,000 cases worldwide resulting in 154,000 deaths, (as of 18th April 2020)[12].

Diagnostic testing is critical in helping to identify and control the emergence of this rapidly spreading and serious illness. While SARs-Cov-2 diagnostic testing capacity using PCR[13] and antibody-based[14] tests are increasing, no current test can predict the severity of a patient's disease. The determinants of COVID-19 disease severity are still largely unknown. Comorbidity and age are factors, but there are also severe cases in young patients with no clear explanation[2]. These tests could be highly valuable both clinically and in terms of managing the massive load on the healthcare system.

Infected patients who succumb to the disease exhibit a dysregulated immune response to the virus, and it is this immune reaction – so called cytokine storm[16]– that induces pulmonary edema and lung failure. The cells that are responsible for this disproportionate immune reaction are part of the innate immune system (e.g. monocytes, macrophages) and those involved in viral clearance are part of the adaptive arm of the immune system (e.g. T cells, B cells). Strikingly, EDIFICE Health's inflammatory age score tracks a dampened antiviral response and hyperreactive monocytes, likely correlating with lowered viral clearance and predisposition to a cytokine storm and ARDS.



Elevated inflammatory score: Path to severe COVID-19 outcome

Immune response of the 1000 individuals recruited in the Stanford 1,000 Immunomes Project study measured in isolated cells shows that high levels of inflammatory age leads to a poor response in B cells, CD4(+) T cells (and the CD45RA(+) and CD45RA(-) subsets), CD8(+) T cells (and the CD45RA(+) and CD45RA(-) subsets) ($P < 10^{-5}$ by self-contained test of modified Fisher's combined probability) and hyperreactive monocytes ($P < 0.005$), indicated by the direction of the regression coefficient.

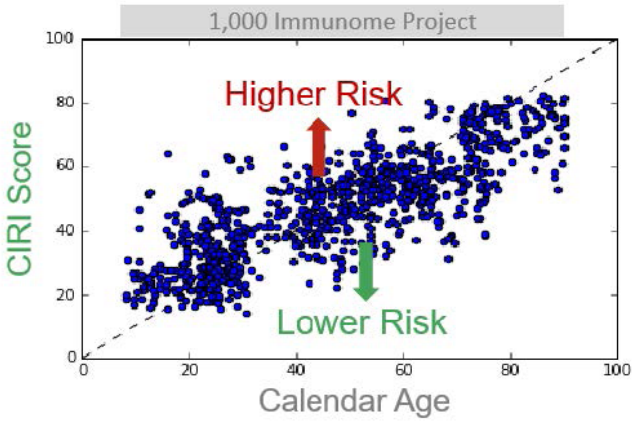
Without insights into the patient's underlying comorbidities or biomarkers for COVID-19 disease severity, doctors currently have to make difficult decisions on how to allocate scarce therapeutic resources with very limited information. At a local and national level, allocation of resources like ICU beds and ventilators is even more important[17,18]. An AI-driven point-based system is being explored in the management of potential COVID-19 patients' surge[19], but has only been trained with historical non-COVID-19 data.

Being able to accurately determine the number of severe cases in a given time window could be immensely valuable to help manage the load on the healthcare system. Examples from cases worldwide show that there are significant differences between disease severity in different populations. Predicting population-level severity to guide resource allocation by local and federal governments could save many lives.

Solution

The CIRI™ Score - EDIFICE Health will carry out a study where serum samples will be collected and analyzed from COVID-19 diagnosed patients at an early stage of the disease. Detailed cytokine profiles of the SARS-CoV-2 infected patients will be compared to baseline data from the Stanford 1,000 Immunomes project. Machine learning will be applied to derive a predictive cytokine profile.

A patient's medical treatment information coupled with a molecular and serological test results and disease outcome combined with the precise COVID-19 immunological signature corresponding to either severe, moderate, or mild COVID-19 case will be used to derive a 'COVID-19 Infection Risk Index' (CIRI™).



CIRI™ score - SARS-CoV-2 infected patients with a CIRI™ score above the diagonal are at a higher risk prone for disease severity, providing valuable information and quicker triage decision for COVID-19 cases. Patients below the diagonal are at a lower risk indicating a possible milder severity reaction to the COVID-19 disease.

Benefits

Immediate Benefits

- Triage test for COVID-19 cases
- Tool to predict which patient will need an ICU bed and ventilator
- Actionable information for officials to drive resource allocation and deployment
- Baseline and COVID-19 immune profiling of different ethnic groups
- Technology transfer to developing countries

Long Term Benefits

- Point-of-care test to assess disease severity and predict outcomes
- Aid the development of novel therapies
- Develop a template for future viral outbreaks

About EDIFICE Health, Inc.

EDIFICE Health, Inc. (www.edificehealth.com) is a digital health / AI (Artificial Intelligence) spin-out company from the 10-year research initiative from Stanford University, the Stanford 1,000 Immunomes Project, which demonstrated that Systemic Chronic Inflammation is one of the leading underlying causes of age-related diseases. Using AI and machine learning approaches, the technology comprises of two products, iAge® (developed) and CIRI™ (developing), a scoring system used as a new tool for health risk and triage assessment, together with the therapeutic interventions for use by physicians, care-providers and patients.

References

1) Chronic inflammation in the etiology of disease across the life span. Furman D, et al. Nature Medicine. 2019 Dec;25(12):1822-1832. doi: 10.1038/s41591-019-0675-0.
2) Chronic Inflammation Predicts Multi-morbidity, Immunosenescence and Cardiovascular Aging in Humans. Sayed, et al. Science Translational Medicine (under review), pre-print BioRxiv doi: https://doi.org/10.1101/840363.
3) Noncommunicable diseases country profiles 2018. Geneva: World Health Organization; 2018. License: CC BY-NC-SA 3.0 IGO.
4) Interdepartmental Centre L. Galvani (CIG), Alma Mater Studiorum, University of Bologna, Bologna, 40126, Italy.
5) Multiple Chronic Conditions in the United States. Buttorff C, Ruder T, Bauman M. Santa Monica, CA: Rand Corp.; 2017.
6) Center for Medicare & Medicaid Services. National Health Expenditure Data for 2016—Highlights.
7) Inflamm-aging does not simply reflect increases in pro-inflammatory markers. Morrisette-Thomas V., et al. Mech Ageing Dev. 2014 Jul;139:49-57.
8) Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. Ferrucci L, Fabbri E. Nat Rev Cardiol. 2018 Sep;15(9):505-522.
9) Epidemiology. Environment and disease risks. Rappaport SM, Smith MT. Science. 2010 Oct 22;330(6003):460-1
10) Expression profile of immune response genes in patients with Severe Acute Respiratory Syndrome. Reghunathan R, Jayapal M, Hsu LY, Chng HH, Tai D, Leung BP, Melendez AJ. BMC Immunol. 2005 Jan 18;6:2. doi: 10.1186/1471-2172-6-2. PMID: 15655079; PMCID: PMC546205.
11) Exuberant elevation of IP-10, MCP-3 and IL-1ra during SARS-CoV-2 infection is associated with disease severity and fatal outcome. Yang Y, Shen C, Li J, Yuan J, Yang M, Wang F, Li G, Li Y, Xing L, Peng L, Wei J, Cao M, Zheng H, Wu W, Zou R, Li D, Xu Z, Wang H, Zhang M, Zhang Z, Liu L, Liu Y. 2020 medRxiv preprint doi: https://doi.org/10.1101/2020.03.02.20029975.
12) https://www.statnews.com/2020/03/26/covid-19-tracker/
13) Covid-19 diagnosis: clinical recommendations and performance of nasopharyngeal swab-PCR. Kokkinakis I, Selby K, Favrat B, Genton B, Cornuz J. Rev Med Suisse. 2020 Apr 8;16(689):699-701.
14) Development and Clinical Application of A Rapid IgM-IgG Combined Antibody Test for SARS-CoV-2 Infection Diagnosis. Li Z, Yi Y, Luo X, Xiong N, Liu Y, Li S, Sun R, Wang Y, Hu B, Chen W, Zhang Y, Wang J, Huang B, Lin Y, Yang J, Cai W, Wang X, Cheng J, Chen Z, Sun K, Pan W, Zhan Z, Chen L, Ye F. J Med Virol. 2020 Feb 27. doi: 10.1002/jmv.25727.
15) Johns Hopkins Medicine, Coronavirus and COVID-19; Younger Adults are at Risk, Too.
16) COVID-19 in the heart and the lungs: could we "Notch" the inflammatory storm? Rizzo P, Vieceli Dalla Sega F, Fortini F, Marracino L, Rapezzi C, Ferrari R. Basic Res Cardiol. 2020 Apr 9;115(3):31. doi: 10.1007/s00395-020-0791-5. PMID: 32274570; PMCID: PMC7144545.
17) https://covid19.healthdata.org/united-states-of-america
18) Intensive care management of coronavirus disease 2019 (COVID-19): challenges and recommendations. Phua J, Weng L, Ling L, Egi M, Lim CM, Divatia JV, Shrestha BR, Arabi YM, Ng J, Gomersall CD, Nishimura M, Koh Y, Du B; Asian Critical Care Clinical Trials Group. Lancet Respir Med. 2020 Apr 6. pii: S2213-2600(20)30161-2. doi: 10.1016/S2213-2600(20)30161-2.
19) Human experts will make the call': Stanford launches an accelerated test of AI to help care for Covid-19 patients. Stat, Health Tech, By Rebecca Robbins, April 1, 2020

Contact Information

Wolfgang Daum, CEO and Chairman of the Board
978-273-8266
wolfgang@edificehealth.com

Please contact company EDIFICE Health, Inc. at info@edificehealth.com to get more information about collaboration opportunities and/or to set up an account.