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Healthcare Evolves From Reactive to Proactive

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Decoding health and disease pathways drives healthcare evolution. Historically, therapeutic paradigms have relied on interventions that mitigate symptoms of established diseases. Increasingly, molecular insights into pathophysiology now provide unprecedented opportunities to offer curative solutions or even prevent disease and thereby secure longitudinal wellness. These opportunities extend past individual patients to entire populations and geographies. Moreover, they optimize prospective healthspan across lifespan. Linking discovery science and its translatable innovations beyond reactive disease intervention to proactive prevention will maximize society's returns creating the greatest benefit for the greatest number of people globally.

Innovation distinguishes between a leader and a follower.

Steve Jobs

Biological discovery, associated with advances in enabling technologies, have transformed healthcare management paradigms for patients and populations.¹ This transformation reflects logarithmic expansion of our molecular, technological and engineering enterprises, driven by investments from the public and private sectors.² Evolution in discovery and technology impels the emergence of precision healthcare solutions, extending insights in biological systems to the pathophysiology underlying disease, yielding mechanism-based targets for curative therapies.³ In that context, the growing toolkit of enabling omic and informatics platforms has yielded extraordinary opportunities to customize curative therapies that can be deployed to individuals, communities, and global populations.⁴ Indeed, molecular and technological innovations have been translated by a burgeoning biopharmaceutical industry into new paradigms that interrupt the lifecycle of disease, whose reach and impact are amplified by international regulatory agencies that ensure safe access to global populations.⁵ Moreover, clinical paradigms emerging from these molecularly-directed therapies shifts the “average patient” model of healthcare management to individualized solutions for disease interventions.⁶ These advancements are positioned to transform our concepts of health, revealed in developing fields like regenerative medicine, impelling the control of degenerative diseases by mobilizing inherent reserves that support rebuilding (tissue) health.^{7, 8}

An ounce of prevention is worth a pound of cure.

Benjamin Franklin

This revolution in molecular insights into the pathophysiological underpinnings of disease has created an unprecedented opportunity to go beyond our reactionary approach to healthcare.⁹ In that context, much of medicine today is based on the practice of intervening to interrupt the progression of established disease.¹⁰ Traditionally, therapeutic intervention is designed to treat the patient to correct the cause of the pathophysiology and alleviate the symptoms of, or even cure, disease.¹¹ We are all familiar with the paradigms of treating infections with antimicrobials; intervening with chemotherapy in patients with cancer to improve disease-free and overall survival; and placing stents in blood vessels occluded with plaque to relieve the risks of coronary artery disease.^{11, 12} Over the past decades, the advantages of preventing disease, rather than intervening with therapy in established disease, have become manifest. In that context, it is more effective to prevent infections through vaccination; cancer by mitigating environmental exposures like smoking; and heart disease through diet, exercise, and metabolic management.¹³ Indeed, preventing disease, rather than interventions that interrupt the progression of established disease, is more effective from the perspective of providing the greatest health benefits to the greatest number of people.¹³ Moreover, prevention has proven to be one of the most cost-effective ways to achieve improved population health.¹³ To place that economic argument into context, three fourths of US health spending is directed at treating chronic disease, and two-thirds of the growth in health spending is attributable to worsening health habits of the American population.^{8, 12-14} This, in part, reflects a healthcare delivery system that places a priority on reimbursing for the treatment of chronic illness, rather

than preventing disease in the first place.¹³ In that context, advancing molecular and regenerative approaches, in conjunction with enabling informatics and omic technologies, offer unique opportunities to evolve preventive strategies that promote healthy aging and longitudinal wellness across the continuum from inception to senescence.^{1, 3, 5}

Beauty is only skin deep

Sir Thomas Overbury

These considerations of primary prevention are exemplified by considering skin and aging. Skin is equipped with an intricate network of antioxidants and antioxidant enzymes that oppose damage, induced by ultraviolet radiation and airborne pollutants which lead to accelerated photoaging, preneoplasias, and cancers. In that context, topical antioxidants, including vitamins C and E and selenium, create a reservoir that prevents, and reverses, environmental oxidative stress.¹⁵ Vitamin C is the body's major aquaphase antioxidant, but must be provided exogenously because primates lack the appropriate synthetic enzymes. As an antioxidant, vitamin C deactivates UV- and pollution-induced free radicals, reactivates tumor suppressor genes to protect against UV-induced apoptosis, and directly opposes inflammation by deactivating nuclear factor $\kappa\beta$. Vitamin E is the most important lipid-soluble, membrane-bound antioxidant, brought to the stratum corneum by sebum. Vitamin E significantly reduces acute damaging effects to skin, including erythema, edema, sunburn cells, lipid peroxidation, DNA-adduct formation, and inflammation. Selenium is an essential trace element required by selenoproteins which regulate antioxidant defenses, inflammation, thyroid and lipid metabolism, DNA synthesis, and immunity. Topical antioxidants not only photoprotect but also reverse environmental damage. Topical application of these agents reactivates senescent skin

fibroblasts, and inactivates UV-induced matrix metalloproteinases, to restore collagen and elastin production and accumulation opposing and reversing photo- and environmental-aging underlying wrinkles, preneoplasias, and skin cancers. Regular protection using these topical approaches has the potential to prevent injury, and maintain the youthfulness, of the largest surface area of the body.¹⁵

Body building is the closest we have to the fountain of youth

Lee Labrada

Increases in average life expectancy, in part, reflecting reductions in childhood mortality, the development of antibiotics, and, more recently, advances in the treatment of chronic diseases have produced greater numbers of individuals living to adulthood.¹⁶ In turn, increases in longevity result in more older adults experiencing age-related senescence across multiple physiological systems. Geriatric syndromes, including sarcopenia, or muscle loss, and frailty, reflect declines in physiological function that occur over decades. These conditions have become more clinically relevant, reflecting a greater percentage of our total healthcare expenditure, as the population ages. The goal of preventative efforts in this domain is to improve mobility, strength, functional independence and quality of life to promote healthy aging and the maintenance of longitudinal wellness in older adults. Indeed, for these individuals, the focus is directed at increasing the number of years of life without disability. While, historically, geriatric medicine has typically been delivered through maintenance approaches, including clinical care, physical rehabilitation, and nutritional support, recent advances in the biology of aging and senescence have revealed opportunities for new preventive interventions.¹⁶ These recent innovations raise the possibility of not only

attenuating the negative effects of aging, but in many cases reversing those effects.^{16, 17} Indeed, these insights have led to the development of molecular interventions opposing the frailty and the loss of functional muscle mass associated with growing old that promise to extend healthy aging and create a virtual fountain of youth.¹⁶

At the other extreme of the developmental continuum, novel approaches in regenerative medicine are being applied in utero to address severe congenital conditions at the prenatal stage, offering a unique opportunity for the earliest forms of disease prevention and prophylaxis.¹⁸ In that context, prenatal regenerative prophylaxis' harnesses the plasticity of developing fetal organs to deliver postnatal pediatric health. Here, fetal surgery, implemented to reconstitute early normal organ growth and restore function in select congenital conditions, is increasingly considered to improve postnatal outcomes. Thus, congenital diaphragmatic hernia (CDH) is characterized by a diaphragmatic defect during fetal development that allows abdominal cavity contents to herniate through, and ultimately interfere with, lung development. CDH affects 1 in 3,836 births, and is associated with a high morbidity and mortality due to severe pulmonary hypoplasia and pulmonary arterial hypertension. IN that regard, fetal endoscopic tracheal occlusion has been performed for isolated severe CDH to promote fetal lung re-growth and restitution of organ development.¹⁸ Further, spina bifida is a congenital defect of the neural tube defined by the exposure of meninges and spinal cord due to incomplete closure of the spinal canal. Exposure of the neural tube to amniotic fluid and trauma in utero increase the risk of paralysis, abnormal mental development, and bladder and/or bowel dysfunction. Advances in ultrasound technology allow diagnosis of this condition as early as the first trimester. Accordingly, in utero surgical repair approaches have been

developed and children who underwent this procedure had improved brain and motor function, and reduced risk of postnatal hydrocephalus, resulting in higher psychomotor development scores.¹⁸ These observations highlight the transformative potential of regenerative therapeutic care in utero to preventive postnatal disease and disability.¹⁹

These considerations underscore the importance of maintaining a focus on preventive approaches that complement therapeutic interventions, as our mechanistic armamentarium evolves from discoveries of the biological bases of health and disease.^{2, 11, 20-22} While molecular innovation has been impressive, the translation of those discovery-based insights into preventive therapies for individual patients which are scalable to populations must remain a priority.^{1, 3, 5} Emerging clinical paradigms should maximize the impact of discovery innovations by facilitating their translation into novel preventive algorithms to maintain longitudinal health and wellness, at all points along the developmental continuum. Indeed, advances in the emerging science of disease prevention offer the greatest opportunities to favorably impact the largest number of people across global communities and populations.¹³

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