AI as a Principal Driver of Mortality Improvement

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INTRODUCTION

Mortality improvements can be generated by positive changes in population lifestyle, the health environment, advances in drug discovery, progress in regenerative medicine, and the biology of aging. To complement traditional actuarial models, a prospective longevity risk model framework was formulated sixteen years ago[1] explicitly recognizing these five classes of mortality improvement. The 20th century history of mortality improvement was punctuated by significant drivers, e.g. sanitation, public health services, vaccination, antibiotics, etc. But so far this century, there has yet to appear a major systemic driver of future mortality improvement. However, with the award of the 2024 Nobel Chemistry prize to Google DeepMind pioneers, AI promises to be this long-awaited 21st century driver, with notable advances anticipated across the spectrum of medical discovery, as well as in the health environment, and potentially also in the other classes.

NOBEL PRIZE IN CHEMISTRY 2024

In October 2024, Demis Hassabis, CEO of Google DeepMind, was awarded a half-share of the chemistry Nobel Prize with his colleague, John Jumper, for solving the 50 year-old grand challenge of the folding geometry of proteins, the complexity of which is determined by the sequence of their amino acids. Demis Hassabis turned to this challenge after Google DeepMind's AlphaGO program defeated a top GO champion in 2016; an AI feat that Elon Musk, co-founder of OpenAI, had reckoned was still a decade away. AlphaFold was launched by Google DeepMind in 2018. In an international test of protein modeling in 2020, AlphaFold2 attained a score nearly equivalent to the experimentally determined structure. By May 2022, AlphaFold2 had helped determine the structure of a key malaria parasite protein and worked out where antibodies that could block transmission of the parasite were likely to bind.

AlphaFold3, published online in May 2024, has the additional ability to model molecule interactions, supporting the scientific consensus that deep learning establishes a revolutionary road map for rational drug discovery. It was named by *Time* magazine as one of the best inventions of 2024, under the AI category. AlphaFold3's enhanced capabilities should enable drug developers to quickly identify promising targets and so have a major impact on drug R&D. A drug is essentially just a small molecule that ultimately attaches to a protein inside the body in some configuration to target a very specific pathology. Isomorphic Labs, spun out of Google DeepMind by Hassabis in 2021, has the goal of using machine learning to transform drug discovery. Hassabis expects AI to halve the time to discover new medicines, a process that can last more than a decade.

<u>In addition to expediting drug discovery, AI can accelerate the lengthy drug trial process and make it more efficient and successful. AI can assist with the recruitment of patients for trials, and with the use of wearables to gather</u>

[1] Woo G. et al. (2009), "Prospective longevity risk analysis." *British Actuarial Journal*, 15, S1, pp.239-247.

patient data, streamlining the trial process. Notably, for Pfizer's COVID vaccine trials, AI assisted with data cleaning, which saved several months of precious time. Altogether, clinical trial deployment timelines might be halved through the adoption of intelligent automation capabilities.

HOW OZEMPIC MIGHT HAVE BEEN DISCOVERED EARLIER WITH AI

To show how AI could transform the discovery of drugs, even blockbusters, insight is provided by the best-selling drug Ozempic, the Novo Nordisk brand name for semaglutide. As with many drug discoveries, it starts with serendipity. In 1990, endocrinologist, John Eng, became intrigued by research showing that venom from a southwestern U.S. lizard, known as the Gila monster, enlarged the pancreas where insulin is synthesized. The Gila monster, after long periods without food, can slow down its metabolism and maintain constant blood sugar levels. Dr. Eng assayed the venom and discovered a peptide, exendin, that triggers synthesis and release of insulin.

Exendin was similar in both structure and function to a hormone found in the human pancreas that stimulates insulin production. This led to the discovery of drugs that mimic the action of this hormone: Glucagon-Like Peptide-1 (GLP-1). The problem with GLP-1 is that enzymes in the blood cause it to degrade quickly. The development of the long-acting GLP-1 analogs liraglutide and semaglutide, has represented a significant advance in GLP-1-based therapies. Liraglutide was approved by the FDA for chronic weight management in adults in 2014; semaglutide was approved for medical use in the U.S. in 2017.

The development history of liraglutide and semaglutide has been documented by Novo Nordisk[2]. Crucially, the drug discovery process involved a systematic scan of the entire amino acid GLP-1 sequence to understand the role of each of the thirty amino acids. This scan showed that specific amino acids were vital for GLP-1. This type of detailed scan is so much quicker using the deep learning of AlphaFold3. Counterfactually, had AlphaFold3 existed back in the 1990s, when GLP-1 was discovered serendipitously, liraglutide and semaglutide might well have been discovered in half the time.

In 2024, the FDA gave approval of semaglutide as the first treatment to reduce the risk of serious heart problems in overweight adults. Remarkably, people taking GLP-1s have seen their blood pressure and cholesterol levels improve. Improving health in this multi-disease manner may actually be a characteristic of slowing down the aging process. Such is the surprising health horizon of drug discovery to be boosted by AI in coming decades.

IMPROVED DISEASE DIAGNOSIS WITH AI

AI has already demonstrated significant promise for the present and future diagnosis of diseases. According to the Harvard School of Public Health, when using AI for diagnosis, there is 40% projected improvement in health outcomes. The application of AI in multiple medical models suggests that the integration of AI in the realms of diagnostic algorithms, programs of risk reduction and prevention, and improvements in scheduling could effectively reduce healthcare spending in the U.S. alone by as much as 5% to 10%. This might be especially beneficial for less affluent vulnerable communities, which have notably higher mortality rates.

AI-powered diagnostic technologies can help physicians decipher medical pictures like X-rays, magnetic resonance imaging, and computed tomography scans, resulting in quicker and more precise diagnoses. AI helps analyze digital pathology slides, finding potential cancerous cells. In genomics, AI can analyze complex genetic data, identifying mutations and risk factors for various diseases, allowing for personalized medicine and preventive interventions. In the future, AI may find obscure patterns in medical data, aiding in disease prediction and prevention before

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[2] Knudsen L.B. et al. (2019), "The Discovery and Development of Liraglutide and Semaglutide." *Front*. Endocrinology/doi:10.3389/fendo.1019.00155.

symptoms appear. Additionally, by combining genetic data, lifestyle data, and environmental variables, AI may help in the diagnosis of complicated diseases.

Malignancies, surgical complications, and neurological, cardiac, and urological issues are the five conditions that are most often misdiagnosed. Diagnostic errors are primarily cognitive and may be avoidable through assistance from AI. Already in 2025, AI examination of brain-imaging scans can enable faster and more accurate stroke detection, identifying when a blood vessel is blocked. To illustrate the importance of such AI-enhanced diagnostic technology, consider U.S. stroke misdiagnosis. Over 9% of stroke victims are initially misdiagnosed, but this percentage may be much higher for patients with non-specific or transient symptoms. Each year, about 800,000 people in the U.S. have strokes, and about 140,000 people die. AI has the potential of saving the lives of many thousands of American stroke victims annually.

FUTURE MORTALITY IMPROVEMENT WITH AI

AI is a systemic driver of improved health span, contributing to all the five classes of mortality improvement, as summarized below, telescoping the waiting period for future healthcare advances. For the middle-aged in 2025, this foreshortening of the medical progress horizon should be a source of hope and optimism about extending their golden years. Even baby boomers in 2025 can expect to benefit to a lesser extent from an AI health dividend; if not from an effective treatment for Alzheimer's within their lifetime, then from earlier, more accurate disease diagnoses.

[A] Lifestyle

Apart from AI applications to nudge healthier population consumption and exercise, additional effective weight-loss drugs might well be discovered through AI. These could have lifestyle benefits other than for obesity. Ozempic has been shown to decrease the abrupt surge of dopamine which is linked to nicotine addiction.[3] Overdose deaths from opioids have been a growing U.S. mortality factor this century. AI is being used to search for non-addictive, non-opioid options to treat chronic pain.

[B] Health Environment

Throughout the health environment, AI is enhancing the quality of healthcare, especially in early disease diagnosis, where the benefit of AI may be 40% improvement in projected U.S. health outcomes. AI supports the diagnosis, characterization, and monitoring of patients using real-time data. The diagnosis of unfamiliar or complex symptoms is prone to cognitive errors. AI-assisted diagnostics are seen as the greatest hope in suppressing misdiagnoses and other medical errors. Issues that cause medical errors and erode the quality of care include low staffing levels, fatigue, and burnout. AI adoption can play a significant supportive role in addressing these capacity issues as well as promoting health equity for communities lacking adequate healthcare resources.

[C] Drug Discovery

Rather than rely on serendipitous drug discovery, rational drug design requires the enhanced resolution of molecular structure achievable with AI. Nobel laureate, Demis Hassabis, expects that drug discovery time might be halved with AI. With a similar anticipated AI benefit for the length of drugs trials, the whole development time for new drugs might be halved with AI. In projecting the future time for the delivery of new long-awaited drugs, AI

[3] Wang W. et al. (2024), "Association of semaglutide with tobacco use disorder in patients with type 2 diabetes." *Annals of Internal Medicine*, 177, 8.

allows the time scale to be compressed accordingly, even if the delivery time for specific drug development remains intrinsically uncertain.

[D] Regenerative Medicine

Regenerative medicine has enormous potential for transforming healthcare with the development of 3D mini-organs (organoids), and the construction of artificial tissues using nanomedicine and 3D bio-printers. In the next few decades, revolutionary approaches in regenerative medicine are likely to emerge based on AI.[4] The integration of AI and stem cell research not only expedites drug discovery processes but also paves the way for personalized medicine and targeted treatment strategies.

[E] Biology of Aging

Aging is an ongoing process of damage that is occurring within the body. One of the most promising routes to treat age-related diseases is to identify therapeutic interventions that selectively remove senescent cells from the body. Clinical research into senolytics is still at an early stage in 2025. But there are grounds for optimism. AI can expedite the search for new senolytic drugs that might slow the aging process, whilst avoiding potentially serious side effects. This is a very challenging and arduous search process. But already, neural networks have been trained to predict the senolytic activities of more than 800,000 molecules to reveal three drug candidates.[5] Besides senolytics, AI can expedite the discovery of drugs, like Ozempic, that can lower mortality from multiple causes and so extend life expectancy.

LONGEVITY RISK MANAGEMENT FOR MILLENNIALS

The contributions of public health, pharmaceuticals, and other medical care to U.S. life expectancy changes for the quarter century period 1990 to 2015, prior to COVID, has been evaluated by health economists.[6] Life expectancy in the U.S. increased 3.3 years between 1990 and 2015. Around 44% of improved life expectancy was attributable to public health; 35% was attributable to pharmaceuticals; 13% was attributable to other medical care, and the residual 8% was attributable to other factors—but not including AI. This quarter century increase in life expectancy of 3.3 years is much less than the three years per decade during the twentieth century, meriting categorization as radical life extension.[7]

The remarkable publication of AlphaFold3 in May 2024 marks a watershed in the use of AI for drug discovery, and more generally for healthcare innovation. According to 2024 Chemistry Nobel Laureate, Demis Hassabis, *"Just as mathematics turned out to be the right description language for physics, AI may turn out to play a similar role for biology."* He anticipates revolutionary advances in drug discovery over the next five years.[8] In November 2024, the prestigious *New England Journal of Medicine* issued a compendium of papers on the AI revolution in medicine. Allowing the period until the end of this decade for a rapid accelerated phase of AI development and upskilling throughout the healthcare industry, the subsequent quarter century period from 2030 to 2055 should be an exceptionally exciting and prolific time for public health advancements and pharmaceutical discoveries, yielding a greater increase in life expectancy in the U.S. than observed in the quarter century from 1990 to 2015.

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[4] Altyar A.E. et al. (2023), "Future regenerative medicine developments and their therapeutic applications." *Biomedicine and Pharmacology*, 158, 114131.
[5] Wong F. et al. (2023), "Discovering small molecule senolytics with deep neural networks." *Nature Aging*, 3, 734-750.
[6] Buxbaum J.D. et al. (2020), "Contributions of public health, pharmaceuticals, and other medical care to US life expectancy changes, 1990 to 2015." *Health Affairs*, 39, 1546-1556.
[7] Olshansky S.J. (2024), "Implausibility of radical life extension in humans in the twenty-first century." *Nature* aging/doi.org/10.1038/s43587-024-00702-3.
[8] Economist interview, November 18, 2024.

Given the anticipated halving of time for the development of new drug treatments, facilitated by AI, as well as AI-enabled advances in public health, the increase in U.S. life expectancy in this quarter century might reach five years, or an average of twoyears per decade. This is below the increase of three years per decade associated with radical life extension but is substantial nevertheless in the context of recent U.S. mortality experience.

In this 25 year time window extending into the second half of the 21st century, public healthcare should benefit from important advances that might not have been achievable until much later in the century, if at all, without AI. The impact of AI is to foreshorten the future horizon, bringing game-changing medical discoveries within the health span of more adult Americans.

Not just for Gen Z, but also for millennials in 2025, their retirement years should be enhanced by significantly increasing health spans, far less burdened by neurological disease, and reaping the health and longevity benefits of AI-accelerated progress in regenerative medicine and the biology of aging. According to an Urban Institute study,[9] half of early millennials born in the 1980s will have inadequate retirement income at age 70, if there are Social Security shortfalls. Born in the latter part of the 20th century, between 1981 and 1996, before Google was founded in 1998, millennials need prudent longevity risk management informed by prospective AI progress by the middle of the 21st century. Prospective longevity risk analysis will help actuaries guide millennials in making key decisions about their future retirement. In particular, despite beginning to save for retirement at age 25, the early retirement aspirations of one-third of millennials may be unrealistic for those wishing to enjoy the extended health span provided to their generation by AI.

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[9] Johnson R.W. et al. (2022), "How might millennials fare in retirement?" Urban Institute, Washington DC.