AI in Longevity Medicine

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Abstract

Since 2013, deep learning systems, a form of artificial intelligence (AI), outperformed humans in image, voice, and text recognition, video games, and many other tasks. In medicine, AI has outperformed humans in dermatology, ophthalmology, and several areas of diagnostic medicine. Since the first publication of aging clocks based on methylation data in 2013 by Horvath and Hannum, AI techniques were used to predict human age, mortality, and health status using blood biochemistry in 2016 and later using transcriptomics, proteomics, imaging, microbiome, methylation, activity, and even psychological survey data. Today, these deep aging clocks (DACs) are being used by the research physicians to evaluate the effectiveness of longevity interventions, clinical trial enrollment and monitoring, risk profiling, biological target identification, and personalized medicine. The advent of data type-specific and multi-omics DACs allowed for the nascent field of aging clock-driven preventive and regenerative medicine, referred to as longevity medicine, to emerge.

1 Introduction

Over the past decade, we witnessed unprecedented advances in the field of biogerontology and the massive convergence of biotechnology, information technology, AI, and medicine. The birth of longevity medicine, which integrates the latest advances in many of these fields of science and technology, is not surprising but rather embraced by progressive clinicians, scientists, and patients. Longevity medicine is advanced personalized preventative medicine powered by deep biomarkers of aging. This domain is extremely novel – aging clocks were first published in 2013 by Steven Horvath et al. [1] and deep aging clocks first published in 2016 by Alex Zhavoronkov et al. [2]. Nevertheless, it became one of the most important areas of precision medicine. What started with a symbiotic effort of mathematics and biochemistry evolved to an artificial neural network approach – deep learning. The method is used to develop deep age predictors with the potential to accelerate research and clinical translation of causal relationships in nonlinear systems. Applying the clocks in the clinic may allow clinicians to determine the efficacy and efficiency of interventions and prognostic and preventative measures. A tailored longevity medicine education is incumbent in order to train clinical experts in longevity medicine, who will play a crucial role, since the universal process of aging renders every human a patient of longevity medicine, therefore preventing the multimorbidity characterized by old age, including physical and/or mental limitations. Drug therapy poses a further problem of multimorbidity. This is because older people often take many different medicines, and this can also increase the number of undesirable side effects (Fig. 1).

Longevity medicine is suited for advances in machine learning for numerous reasons. Longevity is affected by a large number of intrinsic factors such as genetics and epigenetics [3] and by extrinsic factors such as medical history, diet, exercise, socioeconomic determinants of health, and geolocation [4, 5]. Additionally, the effects of these exposures summate over the course of a lifetime affecting, among other factors, development or progression of age-related disease. Collating this data on biomarkers and drug candidates using a trial-by-trial basis conducted on sufficiently large patient or participant cohorts over long-term follow-up is resource-intensive and unpragmatic. For such heterogeneous and complex data, machine learning is a well-suited candidate both to identify suitable biomarkers in advance of physical trials and to do so with higher accuracy than traditional statistical analysis.

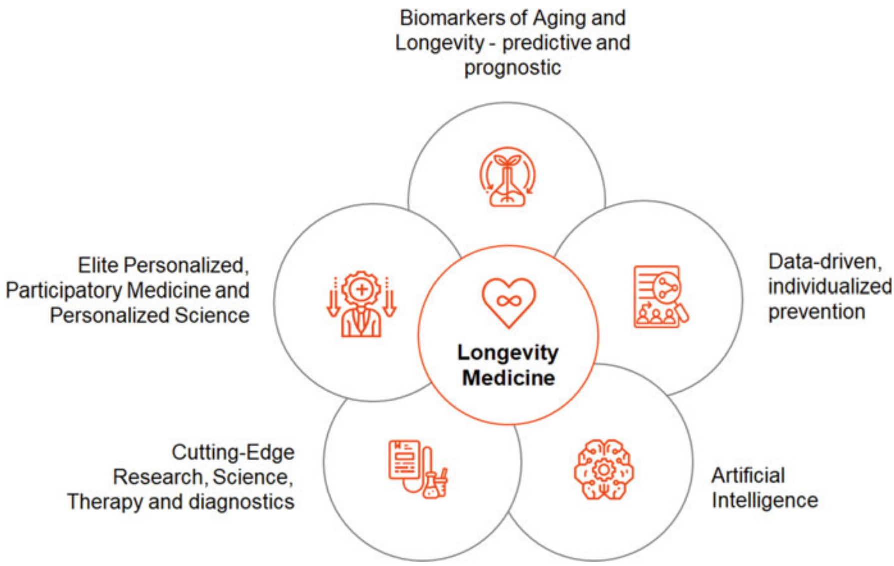

Fig. 1 The technologies enabling the field of longevity medicine

A quintessential tense of a machine learning algorithm is endpoint selection. Actual age and clinical outcomes such as the development or progression of age-related disease provide a limited view of one's age status. Biological age, which more closely explains age status in the context of one's physiology, is a measure that focuses on progression through aging instead of actual age. Surrogate biomarkers of biological age, termed deep aging clocks, have been shown to estimate disease mortality [6], discern the age of developmental tissue [7], and estimate time remaining before onset of age-related pathologies [8]. The utility of these tools is often based on multi-omics or panomics databases with extensive measures generated on trillions of data points. The interpretation and analysis of these datasets requires advanced techniques for which machine learning may be better suited over traditional methods.

It is often difficult to train an accurate model based on a single dataset as this makes the model prone to bias and it may not have the desired complexity given the project aims. Additionally, databases are generated interinstitutionally with different protocols and specifications across potentially diverse biological features, which makes some of them prone to having gaps in data provision, necessitating the imputation of missing or unknown values. Access to multiple datasets will negate these effects, but this is practically near impossible due to inherent issues of confidentiality and governance surrounding sensitive medical data. Therefore, techniques like federated learning [9] that train unified models across multiple databases without sharing the data sources would overcome some of the strong barriers around patient confidentiality. This may also bridge together wisdom gained from the academic and medical fields with wisdom generated from data collected in the private sector, which is traditionally difficult due to large conflicts of interest.

1.1 The Advent of Deep Aging Clocks

Many biological characters have demonstrated broad correlations with chronological age, including telomere attrition and racemization of amino acids in proteins [10]. The primary progenitor, however, in the advent of aging clocks is what would become known as the "epigenetic clock." In 2013, Steve Horvath et al. established significant correlations between CpG methyl groups and chronological age, suggesting that this deep aging clock demonstrated the cumulative effect of an epigenetic maintenance system [1]. This has led to significantly increased attention in the fields of longevity, biogerontology, biomarkers of aging, and the role of machine learning in consolidating these data into precise and coherent models.

What was not well established were geroprotective interventions that could reduce the rate of aging in the novel epigenetic clock and whether these could translate to the actual lengthening of both healthspan and lifespans. Hence, research proliferated utilizing hematological biomarkers indicative of morbidity and mortality putatively involved with aging. This would include a hematological, biochemical clock developed by Putin et al. [2]. Through the use of deep neural networks (DNN), the group were able to train AI to produce a robust model utilizing 41 factors that could predict one's chronological age with impressive accuracy ($R^2 = 0.82$, MAE = 5.5). The benefit of employing DNN architecture in model generation in this instance was that it was able to recursively remodel and account for nonlinear associations among features. Importantly, they established for their model the five most important markers for predicting human chronological age: albumin, glucose, alkaline phosphatase, urea, and erythrocytes. What was particularly useful for this deep aging clock was that interventions that could ameliorate the biomarkers used in the model were already well established, and hence, some of the first truly geroprotective interventions were identified.

Indeed, the advent of deep biomarkers of aging has led researchers to target different loci in human and animal biology. For example, researchers as early as 2015 were investigating the role of gene expression through relative quantitative changes in mRNA presence for particular genes and correspondent proteins [11]. Using a cohort of 14,983 individuals, they identified 1497 genes that are differentially expressed with chronological age and used this to develop a clock with a 7.8-year MAE. Importantly, they established that individuals for whom transcriptional differentiations departed above the model's slope exhibited biological features associated with aging, notably, blood pressure, cholesterol levels, fasting glucose, and body mass index. They also established that their gene panel was enriched for the presence of potentially functional CpG-methylation sites in enhancer and insulator regions that associate with both chronological age and gene expression levels, therefore discovering a mechanism by which the epigenetic clock (DNAm age) could behave as an actor in the development of morbidities with age.

Another transcriptome aging clock was produced in 2018 by Mamoshina et al. [12]. In this instance, they employed the use of DNNs to predict chronological age from 545 gene expression profiles in skeletal muscle of healthy individuals. Among currently published transcriptomic clocks, this clock is the most accurate, demonstrating an MAE of 6.24 years, which may indicate that transcriptomic age prediction requires more complex machine learning techniques than those commonly used in DNAm clocks [13].

1.2 Federated Learning for Biomarker Discovery and Development

One's longevity is dependent on a large number of covariates such as dietary habits, exercise levels, and socioeconomic determinants of health. As a result, unbiased long-term trials are used to identify or repurpose new or existing agents that contribute toward greater longevity. For example, the Targeting Aging with Metformin (TAME) trial [14] investigates the use of metformin to delay development or progression of age-related chronic disease in 3000 participants aged between 65 and 79 for 6 years. Aging is chronic and develops in conjunction with long-term environmental exposures. Thus, it may be a further 10 or more years posttrial for the clinical endpoints to appear in participants before the impact toward longevity can be fully evaluated.

The long time-to-event in trials may come at high cost for longevity drug discovery. Machine learning (ML) algorithms may be employed to generate advanced accurate predictions into the efficacy of interventions, particularly for repurposing existing medicines. Data on existing medicines is collected in electronic health records and the generation of research repositories. This applies especially for commonly prescribed medicines such as metformin.

ML is well suited to the complex variability of human studies and is already being applied for fields such as drug target discovery and protein folding, but a limitation into their application is often a shortage of usable data [15]. Large panomics databases are generated to provide ample numbers of data points for medical research, such as the UK BioBank [16] comprising 500,000 participants. Despite the large number of participants, when variables of interest are selected such as a given disease and when covariates such as ethnicity are stratified, the usable numbers of participants may be insufficient to train an accurate machine learning algorithm. Furthermore, curated datasets may also have biases stemmed from processes such as participant acquisition. To address these limitations, it may be tempting to consolidate different datasets in order to have a sufficiently sized dataset including all variables of interest generated from a variety of sources to counter bias that would be present in a single dataset.

Medical data is highly sensitive and there are many regulations over how it is used [17]. Anonymization by removing personally identifiable information is generally insufficient to surpass this barrier making it practically difficult to combine medical datasets. Another reason why medical data is unstandardized is that generating shared datasets is time intensive and may be costly.

Federated learning [9] is a ML algorithmic methodology which was created for collaborative model generation where the learned wisdom is shared but the data is not shared between repositories. This means that a single model can be generated without breaking data governance over a large number of datasets. Federated learning by design consists of using a central server to distribute nodes for each database source behind the owner institution's firewall. The local nodes train the model and return it to the central server for aggregation and redistribution to the local nodes. Split learning, a type of federated learning, uses a peer to peer design, where there is no central server and the individual nodes share their trained models, aggregate them locally, and redistribute them with each other. These protocols for both designs are repeated until the training is completed [18]. Federated learning performs faster than split learning as the clients generate models in parallel, but split learning has improved privacy as the architecture is split between the clients and the server but is more computationally intensive on each local node [19].

In addition to federated learning, other methods can be employed either as alternatives when federated learning is unavailable or to help validate a federated learning model. The bias and variability of single nonfederated models trained on small datasets can be compensated against using traditional statistical methods. ML models on small data can have a tendency to overfit training data and may not interpret unknown data accurately, but using models such as logistic regression on expert selected features and selectively removing outliers may improve the efficacy of the model. This methodology may be further optimized by running multiple models and generating a weighted average [20].

2 Longevity Physicians: Emerging Specialists and the Need of a Tailored Education

With the progress in geroscience and biogerontology, as well as in AI-based diagnostic and therapeutic tools, longevity medicine as a field has been increasingly in demand by educated patients. For longevity medicine to become an organic expertise area or, preferably, a specialty, just as oncology or cardiology, it needs to be practiced. This in turn implies a solid education of physicians, allowing them to not only acquire the necessary fundamentals, such as hallmarks of aging, but also to rapidly internalize and apply related research outcomes and tools.

Furthermore, as to develop and adequately practice longevity medicine, an ongoing continuous learning is required, encompassing the likewise rapidly evolving areas of precision, prevention, and functional medicine. Ultimately, educating physicians in longevity medicine is one of the most challenging endeavors, requiring a structured, meticulous approach of interdisciplinary educators. Overall, physicians' continued education is still inadequate to meet the challenges and opportunities of longevity medicine.

Current medical training does not include AI, not to mention machine or deep learning [21]. The AI-enforced tools for early diagnostics and prevention of communicable and noncommunicable (NCD) diseases are thus unpopular among the majority of physicians [2, 22, 23]. The so-called millennials are increasingly exposed to innovative solutions in medicine and to active patients' inquiries. Facing a lack of structured, physician-oriented, conceptualized curricula, this new generation, with a tremendous potential for global healthy longevity, is deserting and often diffusing away from the field. At the same time, a growing interest in longevity medicine is observed among related fields including biotechnologists, biologists, geroscientists, as well as among the general public, pharmacologic companies, and target industry groups. Interestingly, the latter two demonstrate an extremely high interest in growing a longevity physician community, while specific approaches to incentivize specific educational approaches (building of certified courses, curricula, accreditations) require significant resources. As long as academia will not sufficiently support such endeavors, the educational initiatives remain grandly scattered, in a form of individual or lecture series given by mostly nonclinical experts. In addition, despite the benefits longevity-focused medicine has to offer, currently, only its fragmentary aspects are available within the certification system: lifestyle, holistic, integrative medicine, or geriatrics. Extremely time-limited clinicians rarely can accommodate extracurricular educational activities in their schedules. Currently, we mostly face reactive medicine, managing diseases rather than mitigating risks toward pathogenesis. Since most healthcare systems are fragmented, specialists are often dispersed and comprehensive patient care is suboptimal. Most importantly, there is extremely limited access to the practitioners who have self-initiated their education into longevity sciences, follow the rapid development of various diagnostic and monitoring solutions, and implement these from the longevity standpoint.

The paradigm of longevity and healthy aging as the top priority will greatly impact the primary, secondary, and tertiary prevention rates; it is essential that doctors have the access to well-structured and practitioner-friendly course contents. Development of such courses is only possible through interdisciplinary efforts that would generate contents and contexts teaching both the fundamentals and ways of how they can be implemented in the clinical practice.

Education is the foundation for longevity health findings to be implemented in the daily practice for patients and in preventative settings. It decimates the knowledge gap between physicians and nonclinical longevity experts (bio-/gerontologists, AI and computer scientists, etc.) and reduces stigmatization of longevity medicine being falsely dismissed as a highly anecdotal movement toward life prolongation. In contrast, longevity medicine is a highly scientific approach toward the extension of a healthy and productive lifespan, with an AI-based precision approach using measurable markers of aging.

An accurate physicians' education in longevity medicine must aim to clearly demonstrate current medical practice, which evaluates and optimizes the parameters of patients within the reference range for their corresponding age groups from truly personalized medicine based on large data. Even if an age group is selected based on a variety of further variables, such an approach is at most a personalized one, but not a precise or individual one. Longevity medicine brings together the best practices from various biomedical disciplines and AI to evaluate the patient's biological age throughout his/her course of life in order to reduce the gap between the current and the parameters of maximum physical performance (based on a calculated ideal biological age). A longevity

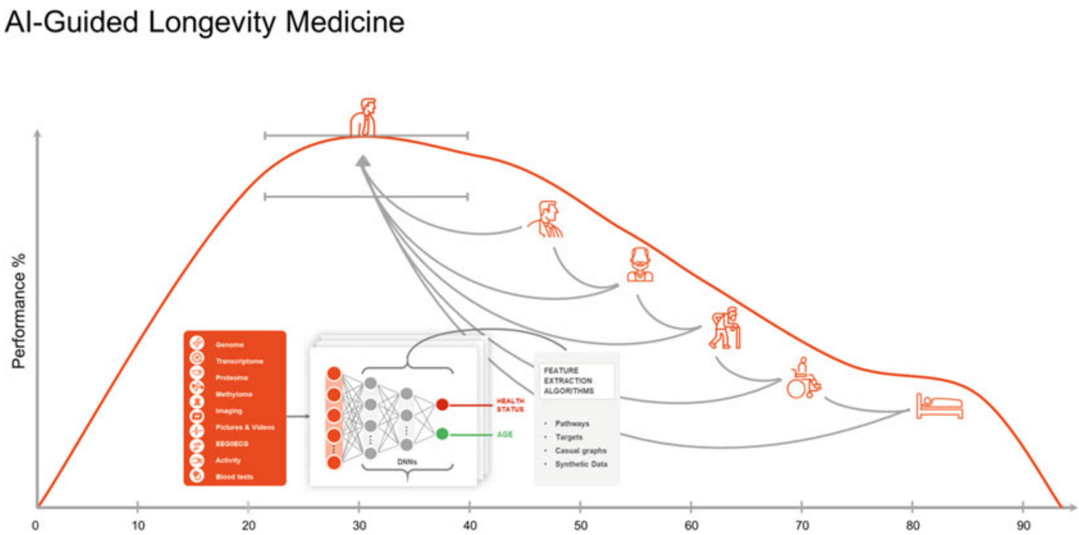

Fig. 2 How human performance changes with age. Panomics technologies integrated with deep neural networks can interpret this and identify geroprotective pathways

physician is thus required to be able to not only apply measurements of aging clocks but also to then (with AI assistance) identify ways to reduce the gap between the current and the optimal biological age. These ways include, at the moment, noninvasive lifestyle modifications (e.g., physical activity, intermittent fasting, circadian rhythm readjustment) or geroprotective supplements and anecdotal invasive methods. It is apparent that these approaches will require ongoing data collection in order to customize and improve protocols, as well as individual AI-supported recommendations (Fig. 2).

Only in the year 2020, a global interdisciplinary team developed the first official Longevity Medicine for Physicians course, covering topics of biogerontology, machine learning, biostatistics, differential diagnosis, programming, molecular biology, immunology, geroprotective interventions, drug design, healthcare organization, and others, as well as providing an overview of clinical applications of recent advances in aging research, skills to evaluate the validity of biomarkers of aging and other biological age testing systems, and knowledge of the available longevity therapies to tackle diseases that are mostly based on senescence-related processes in the organisms. It additionally bridges discrepancies in awareness and information on advances in research while bringing practicable examples of implementation into clinical practice. The unprecedented increase in the percentage of people over 65 years of age and corresponding increase in the illness, social, and economic burden associated with aging require us to advance our understanding of the aging process and how to tackle those processes and provide the care needed. This and similar initiatives will ultimately lead to major beneficiations in healthcare systems as paramount, effective management of diseases, since progress in longevity and biogerontology research will likely increase the healthy productive lifespan and the number of years of government support in old age. It is therefore incumbent to educate physicians about the most recent parameters that can be applied to established models of prevention of diseases by tackling and applying biogerontology advancements. As such, they will be linked to economic growth via biomedical progress rate, the rate of clinical adoption, and the rate of change in retirement age.

Aging is a complex multifactorial process leading to loss of function, causing multiple NCDs, rendering prone toward CDs and premature mortality [24, 25]. There are many theories explaining the origin of the overall process [26, 27] and cause

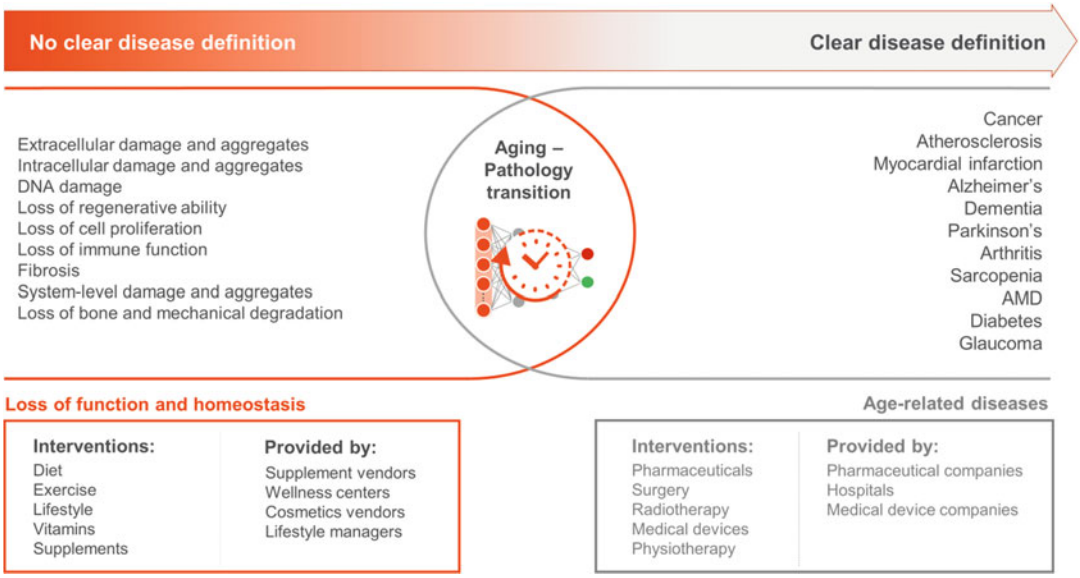

Fig. 3 Cellular processes with no clear disease definition contribute to aging and pathology over time and are affected by environmental factors such as diet. These can then lead to age-related disease

and effect relationships between different processes and systems, including aging of the immune system [28], inflammation [29–32], fibrosis [33, 34], mineralization of connective tissue [35], cellular senescence [36], wear and tear, and many others. In addition, many genetic and epigenetic changes implicated in aging and longevity are associated with aging in model organisms [37, 38]. Even though their role and action in human aging are uncertain, many of these changes are also associated with noncommunicable diseases [37–43]. Recent discoveries showing that mechanisms involved in cancer are strongly associated with the aging process have led to multiple proposals to prevent cancer and other age-related diseases using drugs that increase lifespan in model organisms [44, 45]. AI and machine learning in the course are an inseparable aspect of modern medicine, especially tackling the prevention of global burden diseases. AI is expected to have a major impact in healthcare, where it can be used for the development of effective personalized medicine based on the interpretation of large medical databases gathered over the years by companies and healthcare providers [22, 46–49] (Fig. 3).

3 Healthy Versus Wealthy Longevity: Longevity Medicine and Public Health

The debate around longevity medicine allowed a valid but easily refutable argument that it might lead to an increase in health inequity. There are abundant reasons to counter-resonate. Firstly, novel technologies and interventions are developing rapidly in a competitive ecosystem. We have seen a decline in, e.g., genetic testing pricing or CT/MRI imaging. With this trend, the longevity medicine might actually be one of the most affordable domains in terms of diagnostics and follow-up, as well as regarding geroprotectve supplements or even specific invasive interventions, such as plasmapheresis. Secondly, most of the hallmarks of aging can be co-influenced by lifestyle modifications (exercise, nutrition, supplements, caloric restriction, intermittent fasting, cognitive activities, etc.), led by inexpensive app-based solutions, such as DACs and CGM [2, 22]. Such management toward risk prevention and short-term improvement of performance does not require strong financial inputs and is accessible to the majority of digitalized populations. An accompanying longevity physician navigating the measurements and interventions is an optimal way too fully extrapolate and exploit these tools, since they are able to customize the interventions and interpret the measurements for an individual, minding the biovariability, comorbidities, chronological age, and – importantly – personal goals and preferences (which determine the compliance). As mentioned previously, these experts are still underrepresented and imply a speedy advent of appropriate education. Thirdly, healthcare institutions across virtually all countries globally face overcrowding and limited resources due to high healthcare costs, which in return aggravate the health inequality and inequity [50]. Most cost burden derives from age-related and chronic diseases [51, 52]. Mitigating those is now a priority in the medical and scientific field, as to circumvent a clash of health systems challenged with the spiraling chronic multimorbidities. Another example is the simple illustration of cost and time efficacy of AI-based drug discovery and repurposing, which allows to save millions of USD and several years on identification and testing of new compounds. At the moment, the sobering facts are as follows: 90% of all drug trials fail, very few that do succeed take an average of 10 years to reach the market, and cost ranges from $2.5 to $12 billion. In addition, in computero clinical trial simulations are promising to bring more equity: algorithms can be trained and retrained to include features that are largely ignored, such as the aspect of biological sex and gender, elderly, multimorbid patients, ethnical minorities, and importantly the age [53, 54].

Surely, as for any emerging field, also precision medicine will face barriers related to socioeconomic inequities and demand solutions toward financial viability, especially in systems based on solidarity. Targeting and empowering coordinated discussions of multidisciplinary stakeholder by continuous updates on the current state of science by KOLs in a transparent manner is a crucial approach toward a successful democratization of longevity medicine for all [55].

Since healthy longevity medicine is precision medicine driven by aging biomarkers and is not seeking a bare extension of life, but an extension of a healthy, productive lifespan, the field can notably contribute to improve the economy of healthcare and as a whole.

4 AI Applications in Medicine: The Fundament of Precision Medicine

Tangible AI applications in medicine are rapidly increasing in number, complexity, and accuracy, even though overall, they are still in very preliminary stages [56]. The vast variety of areas and problems that securely designed AI systems in medicine can tackle in practice bear major opportunities toward improvement of the healthcare as entity. At the entrance of the new decade (2020), most AI appliances are targeted at assisting physicians in their diagnoses and treatment decisions [57]. The ultimate goal for the reactive medicine is to achieve an individualized prediction which treatment will work for which patient and how well in order to avoid chronification, physical and emotional burden, and costs. There are several overarching AI appliances that trespass current healthcare. Firstly, the basic prerequisite for AI applications – the data – is now mostly collected in a planned electronic manner. Secondly, AI allowed telemedicine to be established and flourish speedily. Public health impacts are indisputable alone through the provision of medical care in rural regions with a low density of specialists (thus, faster diagnosis, better prognosis, less morbidity and mortality, less costs, less burden on the patients and caregivers, etc.).

AI-based diagnostic systems are able to detect features quickly, quantitatively, objectively, and reproducibly and thus classify conspicuous skin lesions with high accuracy. Machine learning supports diagnostics in numerous specialties, e.g., oncology (lung cancer detection [58, 59]), neurology (CT-assisted stroke detection), ophthalmology (early detection of maculo- and retinopathies [60]), cardiology (risk assessment of myocardial events, sudden cardiac death based on ECG and cardiac MRI), dermatology (detection and classification of dermal lesions based on a body scan or even images [61]), etc. The latter exemplifies the abundant potential of AI applications in patient care, e.g., remote care, patient engagement, and auto-monitoring. Even though the dermatologic smartphone apps for self-examination by patients are still under a strict scrutiny and depend on compliance, pre-identification of suspicious skin lesions by the AI algorithm and a following analysis by specialists improve the early detection of, e.g., melanoma [62]. “AppDoc-Online Dermatologist” and the “Derma-App” are prominent examples in Germany. More studies are needed to confirm the outperformance of AI over dermatologists, based on verified benchmarks [63–65]. A close follow-up of conspicuous lesions in high-risk patients is further enabled with digital dermoscopy, a 3D whole-body photography [66, 67].

AI can further facilitate and optimize medical processes, such as division and delivery of blood products – a problem that is virtually universal and leads to massive losses in resources (both time and costs). “AutoPiLoT” AI system and app, for example, approaches this issue by evaluating past data and thus is be able to make predictions of amount and timing of blood units needed in a specific hospital, as well as to recognize patterns that can further be readjusted individually. The app has now also implemented blood donation, capturing the donor data and thus simplifying the matches [68].

AI can also simplify the diagnostics of complex diseases, through complex diagnostic tools, such as MRI in multiple sclerosis (MS). AI algorithms, encapsulated in a user-friendly app, will allow nonexperts (such as GP) to accompany the patient, interpret complex images over time, and gain experience [69].

Tailoring an optimal treatment for a patient involving all aspects of the clinical picture is considered but optimally also other information about the patient’s biological features (e.g., genetic data), health data, and examination results. Data from a large number of patients must be analyzed and intelligently linked to predict the course of the disease and the optimal therapy for a specific group of patients sharing similar features. AI is incumbent in order to conduct these steps and thus enable what is defined as precision medicine.

5 Conclusion and Future Perspectives

Longevity medicine is a groundbreaking dynamic field, emerging as one of the most essential medical disciplines combining the most advanced and complex diagnostic and interventional approaches. As an AI-driven precision medicine, longevity medicine harnesses innovative and state-of-the art technologies and science to exploit the potential of the human genome, deep quantitative phenotyping, -omics (e.g., epigenomics, metabolomics, proteomics, etc.), microbiome, radiogenomic precision imaging, etc. With the help of continued data collection, the development of new features, improvements in ways of interpretation, and further optimizations in the implementation of an individual patient protocol, longevity medicine will be self-perpetuating. The longitudinal approach enables a trifold dynamic, interrelated longevity practice: data mining, patient compliance, and physicians’ lead. This shifts reactive medicine with limited human data analysis capacity toward longevity doctors that can collect and apply gigabytes of patients’ data toward identification, mitigation, and elimination of actionable diseases, preferably years and decades ahead.

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