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Review

From geroscience to precision geromedicine: Understanding and managing aging

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SUMMARY

Major progress has been made in elucidating the molecular, cellular, and supracellular mechanisms underlying aging. This has spurred the birth of geroscience, which aims to identify actionable hallmarks of aging. Aging can be viewed as a process that is promoted by overactivation of gerogenes, i.e., genes and molecular pathways that favor biological aging, and alternatively slowed down by gerosuppressors, much as cancers are caused by the activation of oncogenes and prevented by tumor suppressors. Such gerogenes and gerosuppressors are often associated with age-related diseases in human population studies but also offer targets for modeling age-related diseases in animal models and treating or preventing such diseases in humans. Gerogenes and gerosuppressors interact with environmental, behavioral, and psychological risk factors to determine the heterogeneous trajectory of biological aging and disease manifestation. New molecular profiling technologies enable the characterization of gerogenic and gerosuppressive pathways, which serve as biomarkers of aging, hence inaugurating the era of precision geromedicine. It is anticipated that, pending results from randomized clinical trials and regulatory approval, gerotherapeutics will be tailored to each person based on their genetic profile, high-dimensional omics-based biomarkers of aging, clinical and digital biomarkers of aging, psychosocial profile, and past or present exposures.

INTRODUCTION

The last decade has witnessed a dramatic change in aging research. Geroscience is an emerging field that seeks to understand the biological mechanisms of aging and how they contribute to age-related diseases.[1] It operates on the principle that aging is the primary risk factor for many age-related diseases, such as diabetes, cardiovascular disease, cancer, and neurodegenerative disorders. By studying the biological processes that drive aging, mostly in rodents and occasionally in

non-human primates, geroscientists aim to develop interventions that can extend the quality of life and healthspan, i.e., the period of life spent in good health. In addition, geroscientists analyze specimens from healthy and diseased individuals of various ages to identify diagnostically relevant biomarkers of biological aging and to deconvolute age-associated pathways that can be targeted by gerotherapeutics for prevention or treatment of specific diseases.[1] The acceleration of geroscientific discoveries has been fueled by the growing societal interest in aging, the creation of specific research centers, the expansion of public and private funding programs, and the increasing number of venture funds and biotech companies developing potential anti-aging remedies.[2] The field holds promise for transforming the way we approach age-related diseases, shifting the focus from treating manifest conditions to targeting aging itself as a root cause.[1]

The emergence of geroscience is paralleled by that of geromedicine, which we define as a new specialty of medicine concerned with optimizing health and preventing diseases by targeting their underlying aging process.[3] Since aging is not (yet) considered a disease and hence cannot be treated as such in human clinical trials authorized by the Federal Drug Administration (FDA) or the European Medical Agency (EMA), therapeutic research and development focus on the treatment and, less frequently, the prevention of multimorbidity or specific diseases.[4] Nonetheless, within its International Classification of Diseases 11th Revision (ICD-11), the World Health Organization (WHO) nosologically defines an "aging-associated decline in intrinsic capacity" as a disease category. WHO considers intrinsic capacity as "the composite of all the physical and mental capacities that an individual can draw on at any point in time." Its underlying physiological principle, which is vitality capacity, is considered to be "a state resulting from the interaction between multiple physiological systems, reflected in energy and metabolism, neuromuscular function, and immune and stress response functions of the body."[5] Accordingly, the maintenance, optimization, or recovery of intrinsic capacity is one of the major goals of geromedicine.

Here, we will discuss recent developments in geroscience that fuel new concepts, approaches, and opportunities applicable to geromedicine with respect to diagnostics and therapeutics to optimize health and prevent or treat age-related diseases across the lifespan.

HALLMARKS OF AGING

An important conceptualization of the field of geroscience arose in 2013 with the publication of the first version of "The hallmarks of aging,"[6] followed by the enumeration of the "Pillars of aging" in 2014.[1] In this initial work[6] and its update,[7] a biological phenomenon was only considered as an aging hallmark if it fulfilled three stringent criteria, namely, (1) the association of aging with its manifestation over time, (2) an acceleration of the aging process due to its experimental accentuation, and (3) a deceleration of biological aging resulting from its experimental attenuation. Based on these criteria, in early 2023 we listed 12 hallmarks of aging: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, disabled autophagy, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communication, chronic inflammation, and dysbiosis. These 12 hallmarks of aging were subdivided into "primary" hallmarks driving the aging process, "antagonist" hallmarks that constitute responses to the primary alterations, and "integrative" hallmarks that explain the aging phenotype (Figure 1).[7]

The description of the hallmarks of aging sparked a major expansion of public awareness and shaped the area of aging research to the point that many venture funds and biotech companies exhibit the iconic 12-sector circle representing the hallmarks as they claim to target one, several, or all of them at once. Although we do not contest the heuristic utility of this concept, it does have intrinsic limitations.

For instance, the molecular pathways involved in each hallmark are closely interlinked with those from other hallmarks, likely explaining why interventions on each of the 12 hallmarks can mediate anti-aging effects that often slow down the manifestation of other hallmarks.[7] For example, insulin/insulin-like growth factor-1 (IGF1) signaling not only contributes to the hallmark "deregulated nutrient sensing" but is also one of the major autophagy-inhibitory signaling routes. Moreover, reversal of the hallmark "disabled autophagy" by genetic or pharmacological activation of autophagic flux can improve the phenotypic manifestations of several other hallmarks, including "genomic instability" (by improving the bioenergetic state of cells), "mitochondrial dysfunction" (due to the preferential removal of dysfunctional mitochondria by autophagy), "chronic inflammation" (due to the elimination of dysfunctional organelles and components of inflammasomes that together trigger all major inflammatory pathways), and "intestinal dysbiosis" (due to improvement of intestinal barrier functions).[8,9] Similarly, the elimination of senescent cells (senolysis) suppresses chronic inflammation (due to the abrogation of the senescence-associated secretory phenotype, SASP) and improves altered intercellular communication (for instance, by preventing immune paralysis).[10] SASP-associated cytokines induce the expression of CD38, a nicotinamide adenine dinucleotide (NAD) hydrolyzing enzyme, leading to lower NAD levels at higher chronological age. Suboptimal NAD concentrations then favor epigenetic alterations, genome instability, deregulated nutrient sensing, and stem cell exhaustion.[11] Thus, more than separate pathways, the hallmarks of aging reflect distinct entry points to facilitate experimental manipulation of biological aging.

Another reasonable critique of the hallmarks of aging relates to the difficulties with quantifying them or using them as biomarkers of biological aging. For instance, telomere length of peripheral blood mononuclear cells (PBMCs) is highly variable within groups of individuals of similar age,[12] and the reduction of telomere length over time in older individuals does not predict the loss of functional capacity.[13] Cellular senescence is highly heterogeneous in its phenotypes and presence in tissues,[14] depending on the upstream stimuli and cell types, hence requiring omics technologies for its detection.[15] Inflammation and dysbiosis also must be measured by the bioinformatic integration of multiple parameters.[16,17] Moreover, there is no standardized assay to measure autophagic flux *ex vivo*. Beyond the methodological difficulties of measuring individual hallmarks of aging, optimization of assays to ensure

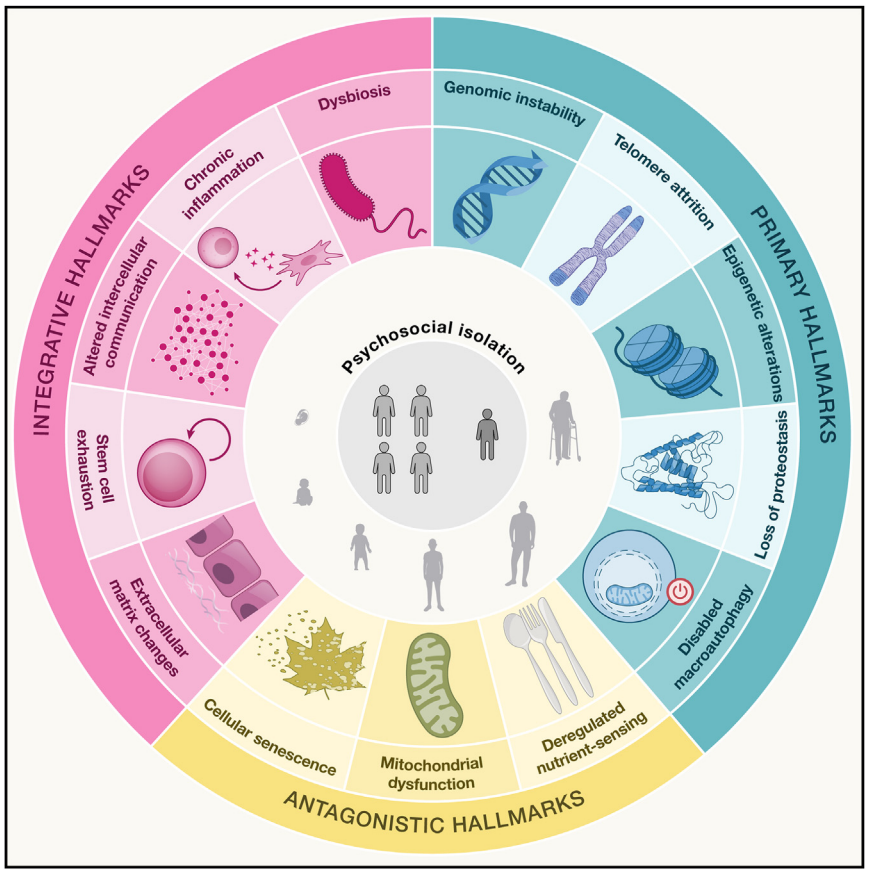

Figure 1. Schematic overview of the 14 hallmarks of aging and their roles in the aging process at the primary, antagonist, and integrative levels

Note that 2 new hallmarks have been added to the older description of the 12 aging hallmarks published in *Cell* in 2023. These 2 hallmarks are "extracellular matrix changes" and "psychosocial isolation."

the highest validity and reliability, including cross-laboratory replication to establish generalizability of the preclinical and clinical findings, is lacking.

Finally, the 12 hallmarks reflect the actual state of knowledge in an expanding area of research on a systemic process,[18] meaning that they are inherently outdated. Since early 2023, the literature has evolved to allow for the addition of a 13th hallmark that we dub "extracellular matrix (ECM) changes" (Figure 1). Indeed, a progressive reduction of ECM viscoelasticity accompanies the aging process throughout the organism.[19] The transfer of a gene encoding hyaluronic acid synthase 2 (Has2) from naked mole rats, a rodent species that is famously long-lived, into the genome of mice was sufficient to extend the healthspan and lifespan of the latter species.[20] Naked mole rat Has2 (nmrHas2) produces high-molecular-mass hyaluronic acid, a non-proteinaceous ECM component that exerts unique cytoprotective effects on mouse and human cells *in vitro*.[21] Aging mice expressing transgenic *nmrHas2* exhibit a reduced incidence of spontaneous cancers, improved musculoskeletal functions, a younger transcriptomic age of internal organs, reduced inflammation, and preserved gut barrier function.[20] Moreover, ECM has a strong impact on mitochondrial homeostasis,[22] cellular senescence,[19] and stem cell exhaustion.[23] ECM modifications contribute to tissue fibrosis either as a cause or a consequence of aging.[24] Altogether, ECM changes may be considered as a new integrative hallmark of aging.

Another hallmark that has been neglected due to excessive focus on molecular and cellular pathways can be dubbed as "psychosocial isolation" (Figure 1). Indeed, there is strong evidence from animal experiments and human clinical trials that psychosocial adaptation is an essential feature of organismal health[25] and that psychosocial isolation fulfills all the criteria of a hallmark of aging.[6] Thus, old age is often coupled to the progressive (self-)exclusion from societal activities commensurate with compromised fitness, motor incoordination, memory loss, and reduced responsiveness. The resulting enfeeblement of social and affective bonds, as well as their psychological or psychiatric consequences (such as anxiety, depression, loneliness, and disrupted sleeping patterns), is intrinsically pathogenic, likely due to chronic activation of neuroendocrine stress responses.[25–27] Indeed, social support is one of the variables that is quantified in clinical assessment, and lack of social support is considered a prognostic marker for poor health.[28] Accordingly, a randomized clinical trial demonstrated that psychosocial group rehabilitation not only improves subjective health but also reduces mortality in older adults.[29] In mice, social interaction between adult and old individuals increases the healthy longevity of the latter,[30] echoing reports suggesting that communities or families in which several generations live together provide optimal support for older adults, improving their health.[31]

In sum, it can be argued that the hallmarks of aging are useful for geroscientific explorations but that their application to geromedicine is limited (1) by difficulties in neatly separating them from each other, (2) by methodological issues regarding their quantification, and (3) by their intrinsic incompleteness. In the next section, we propose a complementary, gene-centric view of aging that may be more suitable for medical applications.

GEROGENES AND GEROSUPPRESSOR GENES

In the same way that cancers are provoked by the activation of oncogenes and the loss of oncosuppressor genes, biological aging can be viewed as a process that is not only modulated by the environment but also accelerated by the activation of gerogenes and the inactivation of gerosuppressive genes.[3] Contrasting with

Table 1. Examples of gerogenes and gerosuppressor genes

Category	Gene	Detection method	Phenotypic consequences	Refs.
Gerogenes	*APOB*	genomic (allelic variants), proteomics	increased risk for cardiometabolic disease, type 2 diabetes, and Alzheimer's disease	Richardson et al.[40] and Martin et al.[41]
	APOE ε4	genomic (allelic variant)	increased risk of arteriosclerosis and Alzheimer's disease	Neel[35]
	CDKN2A/B	genomic (allelic variants)	increased risk for cardiovascular alterations, diabetes, glaucoma, and cancer	Melzer et al.[42] and Bae et al.[43]
	DBI	immunoassay (plasma)	augments with age; increased risk of future cardiovascular events, cancer diagnosis, frailty and mortality if protein is overabundant	Montégut et al.,[44] Montégut et al.,[45] Liu et al.,[46] and Gadd et al.[47]
	ERVs	transcriptomics	increases with age; elevated risk of autoimmune disease and neurodegenerative disease	Gorbunova et al.[48] and Liu et al.[49]
	GHR	genomic	Laron syndrome (short stature with reduced cardiovascular and malignant disease)	Werner and Laron[50]
	IGF1	genomic, immunoassay (plasma)	increased cardiovascular and cancer risk if protein is overabundant	Teumer et al.[37]
	IL11	immunoassay (plasma)	increases with age; neutralization inhibits fibrosis and extends lifespan in mice	Pinti et al.[51] and Widjaja et al.[52]
	LMNA	genomic, progerin immunoblot	Hutchinson-Gilford progeria syndrome (HGPS), familial partial lipodystrophy, LMNA-related dilated cardiomyopathy	Misteli[53]
	LINE-1 and related transposons	transcriptomic	increases with age; elevated risk of autoimmune disease and neurodegenerative disease	De Cecco et al.[54]
	miR-29	transcriptomic	correlation with normal and progeroid aging phenotypes	Swahari et al.[55]
	PCSK9	genomic (allelic variants)	elevated risk of cardiovascular and cerebrovascular events; specific variants cause familial hypercholesterolemia (HCHOLA3)	Csiszar et al.[38] and Liu et al.[56]
Gerosuppressors	*APOE* ε2	genomic (allelic variant)	association with healthy longevity (counteracts *APOE* ε4 variant)	Jackson et al.[57]
	ATM	genomic (loss-of-function mutation)	ataxia telangiectasia	Aguado et al.[58]
	BNP	proteomics (detection of N-terminal pro-BNP)	longevity associated with N-terminal pro-BNP	Liu et al.[59]
	BRCA1 and *BRCA2*	genomic (germline or somatic loss-of-function mutation)	breast, ovarian, and prostate cancer; reduced longevity	*Nature Aging*[60]
	DNMT3A	CHIP (loss-of-function mutation)	chronic inflammation, cardiopulmonary diseases	Emon et al.[61]
	ERCC6	genomic (loss-of-function mutation)	Cockayne syndrome type B	Karikkineth et al.[62]
	ERCC8	genomic (loss-of-function mutation)	Cockayne syndrome type A	Karikkineth et al.[62]

(*Continued on next page*)

Table 1. *Continued*

Category	Gene	Detection method	Phenotypic consequences	Refs.
	FOXO3A	genomic (variant rs2802292 G-allele)	longevity, especially in men	Revelas et al.[63]
	KL	α-klotho ELISA	longevity (if high in plasma)	Abraham and Li [64]
	SH2B3	genomic (allelic variants)	increased risk of autoimmune and cardiovascular diseases; cancer	Melzer et al.[42] and Kuo et al.[65]
	SIRT6	genomic (allelic gain-of-function variant centSIRT6)	longevity, especially in Ashkenazi Jewish populations	Simon et al.[66]
	TET2	genomic (truncation mutation) or CHIP (loss-of-function mutation)	chronic inflammation	*Nature Aging*[60]
	TERT	genomic (loss-of-function mutation)	aplastic anemia, dyskeratosis congenita, idiopathic pulmonary fibrosis, predisposition to clonal hematopoiesis	Chakravarti et al.[67] and Kubota and Viny [68]
	WRN	genomic (loss-of-function mutation)	Werner syndrome	Tsuge and Shimamoto [69]
	ZMPSTE24	genomic (loss-of-function mutation)	mandibuloacral dysplasia-type B, restrictive dermopathy	Worman and Michaelis[70]

the hallmarks concept, this gene-centric view of aging bears three advantages: (1) to be pathway-agnostic; (2) to rely on simple and scalable genomic, epigenomic, or postgenomic methodologies; and (3) to be definable by objective genotype-phenotype associations and precise thresholds. Emulating the precedent of "precision oncology," in which treatments are personalized based on the genomic characteristics of cancers (and hence the action of oncogenes and oncosuppressor genes),[32,33] a future, yet-to-be-developed "precision geromedicine" might treat individuals based on their molecular characteristics.

Gerogenes and gerosupressors have not purposely evolved as a part of the aging process. Instead, they support diverse molecular functions, the consequences of which contribute to aging. Gerogenes hasten the aging process if they are overactivated. This can occur as a consequence of gain-of-function mutations, as exemplified for *LMNA* giving rise to the age-accelerating protein progerin,[34] the presence of allelic variants, as illustrated by the lipid storage-favoring *APOE* ε4 variant,[35] or enhanced gene expression. Age-accelerating overexpression of gerogene-encoded mRNAs is exemplified by *DBI*[36] and *IGF1*,[37] which both code for autophagy-inhibitory and anabolism-stimulatory tissue hormones, as well as by *PCSK9*, which binds to and degrades the low-density lipoprotein (LDL) receptor on hepatocytes.[38,39] Conversely, loss-of-function mutation, reduced expression, or deficient function of gerosuppressor genes/proteins increases the pace of aging (Table 1). According to our tentative definition,[3] gerogenes or gerosuppressor genes should fulfill two stringent criteria. First, their (epi-)genetic or post-genetic alterations should associate with normal or pathological human aging in observational studies. Second, experimental interventions on such genes should modulate the aging process in non-human model organisms. In the future, definitions of gerogenes and gerosuppressor genes will be based on the successful conclusion of human clinical trials targeting them, their products, or their downstream mediators, showing improvements of biomarkers of aging.

Loss-of-function or gain-of-function mutations of gerogenes and gerosuppressor genes are easily detected by genomic sequencing or polymerase chain reactions (PCRs) if they occur at the germline level (Table 1). If mutations occur at the somatic level, as exemplified by the so-called "clonal hematopoiesis with indeterminate potential" (CHIP), deep sequencing methods or single-cell genomic sequencing can detect the emergence of mutant clones by examining PBMCs.[71] Of note, CHIP is clearly associated with an elevated risk of neoplastic disease, such as acute myeloid leukemia arising from mutated progenitors.[72] In addition, CHIP is associated with chronic inflammation and its downstream consequences that include (but are likely not limited to) periodontitis,[73] cardiovascular disease,[71] renal failure,[74] and non-small cell lung cancer.[75] Of course, somatic mutation does not only concern the hematopoietic lineage but also affects other cell types, including epithelia[76] and neurons.[77] Hence, an ongoing challenge for the study of human aging will be to develop routine technologies allowing the characterization of somatic mutations in biopsies from various organs.

Changes in the expression of gerogenes and gerosuppressor genes can be indirectly determined at the level of the epigenome through methods that are pathway agnostic and may capture variations in the expression of multiple genes, each of which, if taken alone, has a rather minor phenotypic impact.[78] Currently, most studies concentrate on DNA methylation patterns, usually of PBMCs, whole blood, or saliva. The bioinformatic integration of such data yields so-called "methylation clocks" or "epigenetic clocks" that can be trained based on chronological age, specific diseases, and future mortality.[79,80] Such clocks are even purported to detect deviations of the trajectory of individuals of the same chronological age, as well as modulable

aging-relevant lifestyle factors such as obesity and smoking.[80] Attempts are underway to refine this approach so that other epigenetically relevant chromatin modifications or non-coding RNAs can be measured[81] and methylation is determined at the single cell rather than at the bulk level.[82] One challenge with current methylation clocks is linked to the fact that blood-derived DNA arises from many different leukocyte subtypes (each of which exhibits a different methylation pattern) and that alterations in the ratio of such subtypes occur as individuals age and develop age-related diseases.[83,84] For example, an elevation of the neutrophil-lymphocyte ratio is a universal biomarker of poor prognosis in several diseases, including cancer, cardiovascular, and infectious disease.[85,86] Moreover, changes in the neutrophil-lymphocyte ratio can occur acutely, for instance, in the context of surgery,[87] which is known to severely and transiently accelerate the "methylation age."[88] Epigenetic clocks have also been shown to vary dependent on daytime, perhaps reflecting intracellular epigenomic oscillations or shifts in the blood counts.[89] Hence, it will be necessary to refine methylation clocks by integrating information on fluctuating proportions of circulating leukocytes.[90] One step in this direction is a bioinformatic approach to render epigenetic clocks insensitive to changes in the relative abundance of immune cells.[91] Alternatively, this may involve "immunomics," i.e., high-dimensional immunocytometric profiling or single-cell transcriptomics of these leukocytes, including that of B and T lymphocytes, to deconvolute their antigen specificities. Moreover, additional methods for generating aging clocks based on clinical analytes,[92] plasma proteomics,[93] metabolomics,[94] lipidomics,[95] or fecal and oral microbial metagenomics[96] might be combined with epigenetic data to create artificial intelligence (AI)-supported integrated biological aging clocks.[97] Hence, AI algorithms might canalize the "data tsunami"[98] into clinically useful metrics.[93] While there is reasonable hope that AI will provide useful phenotypic classifiers,[93] it remains to be seen whether AI will succeed in identifying clinically useful molecular targets in such omics datasets. Most likely, in the foreseeable future, target discovery will rely on insights from basic science, mechanistic approaches, and preclinical model systems.

At the post(epi)genomic stage, the expression of gerogenes and gerosuppressor genes can be measured at the mRNA level (e.g., by transcriptomic analyses or by RT-qPCR) or, more conveniently, at the protein level (by unbiased proteomics or targeted analyses including immunoassays). For practical reasons, most studies concentrate on circulating proteins present in plasma. Unfortunately, commercially available proteomics kits are not yet fully accurate, meaning that only a (however increasing) fraction of analytes is correctly measured,[99] calling for further technological developments, especially at the level of the detection of splice variants and post-translational modifications. Nonetheless, some plasma proteins (e.g., α-klotho) emerge as being positively associated with healthy aging and longevity, while others (e.g., ACBP/DBI and IGF1) correlate with the early manifestation of age-related diseases (Table 1). Interestingly, plasma proteomic signatures have been shown to outperform clinical parameters in their ability to predict common and rare diseases,[100] as well as the loss of cardiorespiratory fitness associated with age-related diseases and mortality.[101]

Some gerogene products can be directly targeted by FDA and EMA-approved drugs (Table 2), as in the case of proprotein convertase subtilisin/kexin type 9 (PCSK9) for which two neutralizing monoclonal antibodies (alirocumab and evolocumab) are available for the treatment of familial hypercholesterinemia.[102] Lamivudine, a nucleoside reverse transcriptase inhibitor approved for treatment and prophylaxis of HIV, is being tested in Alzheimer disease patients based on the rationale that this compound inhibits LINE-1 transposition as well.[54] Other gerogenes may be targeted indirectly by FDA/EMA-approved drugs such as resmetirom, which blocks transcription of the *DBI* gene[103]; pasireotide, which suppresses growth hormone secretion and hence activation of GHR[104]; or lonafarnib, which inhibits the generation of progerin from mutated *LMNA*.[105] IGF1 may be targeted indirectly by fasting regimens that increase its antagonistic IGF1 binding proteins IGFBP-1 and IGFBP-2, as does the treatment with glucagon-like peptide-1 (GLP1) receptor agonists (GLP1-RAs) such as semaglutide and tirzetapide.[106,107] Importantly, GLP1-RAs are being clinically evaluated for their possible effects against multiple age-related cardiovascular and neurodegenerative diseases.[4] It will be important to determine to which extent such effects are mediated by reduced IGF1 signaling, improved body composition, or other effects. In addition, IGF1 receptors can be neutralized by monoclonal antibodies or by small-molecule tyrosine kinase inhibitors. The sole gerosuppressor gene product that is currently explored in the clinics is human recombinant brain natriuretic peptide (rhBNP), also known as nesiritide, which has been FDA approved for acute decompensated congestive heart failure. The senolytic combination of two drugs (dasatinib and quercetin) increases the levels of α-Klotho in patients with idiopathic pulmonary fibrosis and has a substantial positive effect on symptoms and clinical progression[108] (Table 2). Additional clinical trials are needed to examine the therapeutic relevance of the activation of other gerosuppressor genes and their products.

In sum, several gerogene and gerosuppressor gene products are being evaluated in human clinical trials with respect to their utility for targeting a range of distinct age-related diseases. Theoretically, molecular diagnoses regarding the (in)activation of such age-relevant genes (Table 1) might trigger specific therapeutic interventions (Table 2) and hence inaugurate the era of precision geromedicine. To be broadly applicable, however, such gene-centric, omics-based diagnostic approaches must involve yet-to-be-developed AI-driven polygenic risk scores integrating the vast number of alleles/mutations, epimutations, and variations of gene expression that are rare and have small effects, but which in aggregate drive individual phenotypes.[78] Moreover, given the crucial importance of gene-environment interactions,[113] the integration of past and present exposures and health trajectories will be crucial for optimizing the diagnostic accuracy of such omics-based AI-based algorithms.

AGING VERSUS AGE-ASSOCIATED DISEASES

Most human diseases manifest and progress with higher chronological age (Figure 2). In a desirable scenario, prophylactic or therapeutic interventions that decelerate the manifestation

Table 2. Therapeutic targeting of gerogenes and gerosuppressor genes in past and ongoing clinical trials

Gene	Drugs	Reference or clinical trial no.	Disease and primary endpoint
APOE ε4	ALZ-801 (prodrug of homotaurine preventing ß-amyloid aggregation)	NCT04693520, NCT06304883	signs of Alzheimer's disease: plasma tau181, hippocampal volume change from baseline in Alzheimer's disease assessment scale
DBI	resmetirom (thyroid hormone receptor-β agonist reducing *DBI* mRNA)	Harrison et al.[109]	efficient against non-alcoholic liver disease
		NCT05500222	non-alcoholic liver cirrhosis: complications and biomarkers of cirrhosis
GHR	pasireotide (somatostatin receptor ligand reducing growth hormone secretion)	Bolanowski et al.[104]	efficacious against acromegaly (due to inhibition of GH secretion) and Cushing syndrome (due to inhibition of ACTH secretion)
IGF1	linsitinib (inhibitor of IGF1 receptor tyrosine kinase)	NCT05276063	thyroid eye disease: clinical amelioration
	teprotumumab (antibody against IGF1 receptor)	NCT06275373, NCT06248619	thyroid eye disease: clinical amelioration, reduction of proptosis
	veligrotug (antibody against IGF1 receptor)	NCT06021054, NCT05176639	thyroid eye disease: reduction of proptosis
	indirect targeting by GLP-1 receptor antagonists that potentially induce upregulation of the IGF1 antagonistic proteins IGFBP1 or IGFBP2	Guarente et al.,[4] Xie et al.[110]	reduced incidence of atrial fibrillation, Alzheimer's disease, chronic kidney disease, coagulation disorders, coronary artery disease, infectious illnesses, ischemic stroke, Parkinson's disease, respiratory conditions
		NCT02673931	organ protection by exenatide after heart surgery: avoidance of death, renal failure, stroke, or heart failure
		NCT02829502	stroke treated with exenatide: mean flow velocity in the middle cerebral arteries
		NCT03856632	atrial fibrillation treated with liraglutide: change in size of left atrial epicardial adipose tissue
		NCT04232969	Parkinson's disease treated with exenatide: Movement Disorder Society Unified Parkinson's Disease Rating Scale
		NCT04777396, NCT04777409	early Alzheimer's disease treated with semaglutide: clinical dementia rating
		NCT05371496	heart failure with preserved ejection fraction treated with semaglutide: pulmonary capillary wedge pressure during exercise
		NCT05822609	nephropathy in T1D treated with semaglutide: Renal oxygenation
		NCT06184633, NCT06499857	atrial fibrillation treated with semaglutide: signs of fibrillation, sinus rhythm
		NCT06324461	reduction of myocardial injury by dulaglutide after non-cardiac surgery: inhibition of troponin T elevation
		NCT06555146	nephropathy in T2D treated with semaglutide: total and local blood flow
LMNA	lonafarnib (farnesyltransferase inhibitor reducing the generation of progerin from mutated LMNA)	Gordon et al.[105]	reduced progression of Hutchinson-Gilford progeria syndrome

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Table 2. *Continued*

Gene	Drugs	Reference or clinical trial no.	Disease and primary endpoint
PCSK9	alirocumab (neutralizing antibody)	NCT04731155, NCT05292404	acute myocardium infarction: myocardial salvage index
		NCT04781322	alcoholic liver disease: safety (and reduction of liver disease)
		NCT05469347	sepsis: endotoxinemia
		NCT05553834	non-small cell lung cancer: synergy with PD-1 blockade at the level of response rates
		NCT06385262	non-small cell lung cancer: pathological complete response rate in synergy with neoadjuvant PD-1 blockade and chemotherapy
	evolocumab (neutralizing antibody)	NCT05144529	non-small cell lung cancer: safety of combination with PD-1 and CTLA-4 blockade and T cell infiltration of tumors
		NCT06284564	metastatic renal carcinoma: safety of combination with PD-1 blockade
	tafolecimab (neutralizing antibody)	NCT06304987	rectal cancer: synergy of combination with neoadjuvant chemoradiotherapy and PD-1 blockade at the level of response rates
		NCT06421298	advanced non-small cell lung cancer: progression-free survival in synergy with adjuvant PD-1 blockade and chemotherapy
BNP	nesiritide (recombinant human brain natriuretic peptide, rhBNP)	NCT02608996	hypertension: reduced blood pressure
		NCT05714618	cardiac inflammation post-stroke; reduced MRI signs of inflammation and fibrosis in the heart
		NCT05723315, NCT06463808	myocardial infarction: microvascular obstruction assessed by MRI, ultrasonographic exam, decline of blood markers of heart failure
		NCT06745206	recovery from septic shock: pressure gradient of venous return
KL	dasatinib plus quercetin (which restore α-klotho in aged mice and patients with idiopathic pulmonary fibrosis)	Zhu et al., Gonzales et al., and Farr et al.[108,111,112]	Alzheimer's disease and idiopathic pulmonary fibrosis: safety and feasibility; postmenopausal osteoporosis: potential effects on women with high T cell *CDKN2A* mRNA levels
LINE-1	emtricitabine (reverse transcriptase inhibitor)	NCT04500847	Alzheimer's disease: inhibition of LINE1 reverse transcriptase, cognition, biomarkers of neurodegeneration + neuroinflammation
	lamivudine (reverse transcriptase inhibitor)	NCT04552795, NCT06519357	Alzheimer's disease: inhibition of LINE1, cognition, biomarkers of neurodegeneration + neuroinflammation; mild cognitive impairment: biomarkers of neurocognitive impairment and type-1 interferon stimulated genes in plasma

ACTH, adrenocorticotropic hormone; GH, growth hormone; MRI, magnetic resonance imaging; PD-1, programmed cell death protein 1; T1D, type 1 diabetes; T2D, type 2 diabetes.

or halt the progression of one specific condition mediate positive effects on other age-related diseases. For example, the oral anti-diabetic metformin slows down systemic and brain aging in monkeys.[114] Metformin has broad effects on various age-related diseases in clinical studies, including in non-diabetic participants, in which cardiovascular events are reduced, although the exact molecular mechanisms of these favorable effects remain elusive.[115] The (regrettably still unfinanced) Targeting Aging with Metformin (TAME) phase 3 trial proposes to administer metformin or placebo to patients who experienced one recent

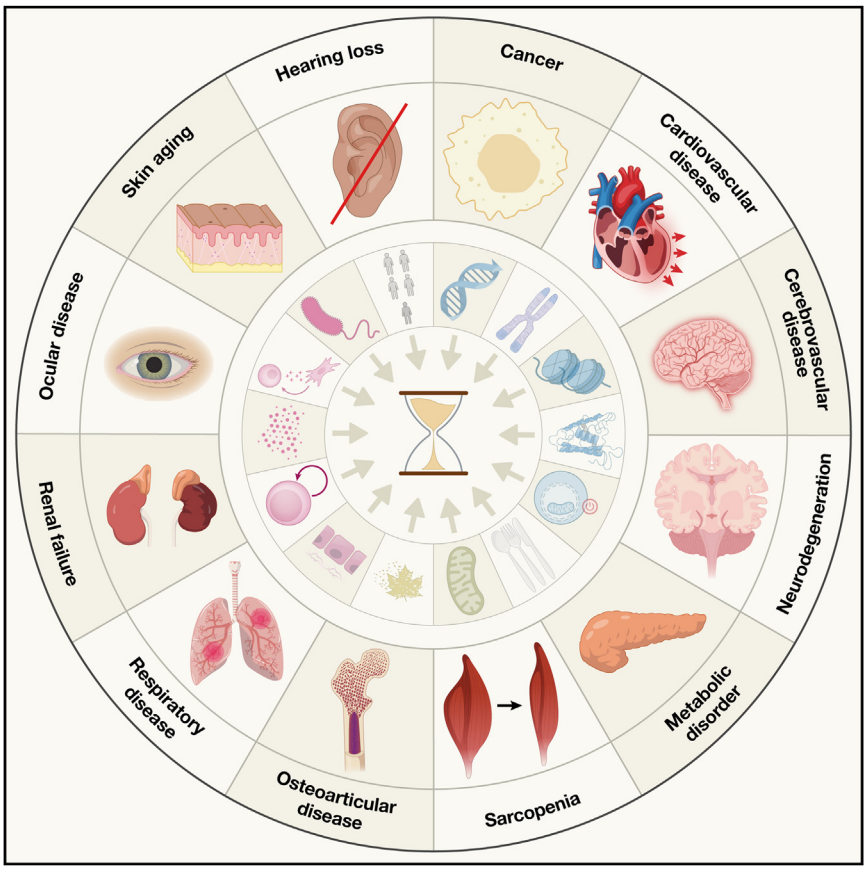

Figure 2. Examples of age-related diseases
Such diseases are causally linked to a variable degree with the 14 hallmarks of aging indicated by the same icons as in Figure 1. Note that this graph is not intended to suggest that specific age-related diseases are connected to specific hallmarks of aging.

cardiovascular event to investigate the possibility of postponing the manifestation of a second event.[115] Modern antidiabetics such as inhibitors of sodium/glucose cotransporter 2 (SGLT-2, which is required for glucose reabsorption in the kidney) also have effects on other diseases, including heart failure[116] and dementia.[117] GLP1-RAs, which are clinically approved for the treatment of type 2 diabetes and obesity, are as efficient as SGLT2 inhibitors in improving cardiac function in patients with heart failure with preserved ejection fraction.[118] GLP1-RAs reduce the incidence of all major cardiovascular events, including myocardial infarction, stroke, and hospitalization for heart failure, and these effects are similar in diabetic and non-diabetic patients.[119] Pending confirmation in dedicated trials, GLP1-RAs may reduce the progression of neurodegenerative diseases such as Alzheimer's and Parkinson's[4] and reduce the risk of major adverse kidney events, hepatic failure, infectious illnesses, and several respiratory conditions.[110] Drugs designed to prevent or halt atherosclerosis, such as statins (which inhibit 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase, the rate-limiting enzyme in cholesterol biosynthesis) or PCSK9 inhibitors (which reduce LDL particle concentrations), may have anticancer effects that most likely involve improved immunosurveillance.[39,120] The combination of evolocumab (an anti-PCSK9 antibody) and atorvastatin (a statin) improves the neurological deterioration in non-cardiogenic acute ischemic stroke, as observed in a phase 3 trial.[121] Retrospective analyses indicate that denosumab, an antibody against RANK ligand used for the treatment of postmenopausal osteoporosis, reduces the incidence of type 2 diabetes and all-cause mortality.[122] Thus, several FDA-approved drugs might be reclassified as gerotherapeutics due to their broad effects on several age-related diseases. However, for this to occur, the FDA would have to requalify healthy aging (or the optimization of intrinsic capacity) as a pharmacological objective.

Theoretically, to obtain broad drug effects on multiple age-related diseases, at least one of two conditions should be fulfilled. Either the drug should target the root causes of several diseases, ideally the entire aging process, or, alternatively, the disease-specific process that is targeted (e.g., hyperglycemia or dyslipidemia) should be involved in disease-aggravating feedforward loops that involve several organ systems (e.g., the metabolic, cardiovascular, and immune/inflammatory systems), thus compromising general health.[123]

In this context, it can be debated on a case-per-case basis whether the manifestation of an age-related disease (e.g., cancer, myocardial infarction, heart failure, hearing loss, or osteoarthritis) reflects general organismal aging, defined as systemic changes that affect the entire organism, or, on the contrary, depicts segmental aging, which refers to the age-related deterioration of specific organs or organ systems as defined by the American Physiology Society (https://www.physiology.org/career/teaching-learning-resources/student-resources/what-is-physiology?SSO=Y). The idea that age-related diseases reflect the pace of general aging is supported by associations between biological and clinical biomarkers of aging (such as epigenetic clocks, signs of metabolic syndrome, or high ACBP/DBI and IGF1 levels) and multiple distinct diseases,[37,44,45,80,124,125] as well as by the fact that the clinical manifestation of a first disease often constitutes a risk factor for developing others. For example, smokers that developed a cardiovascular event are at a significantly higher risk of lung cancer than age-matched smokers without clinical manifestations of atherosclerosis.[126] Similarly, acute ischemic stroke precipitates early vascular aging with exacerbated arterial stiffness indicated by increased pulse wave velocity.[127] Moreover, there are numerous examples of genetic variations affecting gerogenes and gerosuppressor genes that simultaneously predispose to several apparently

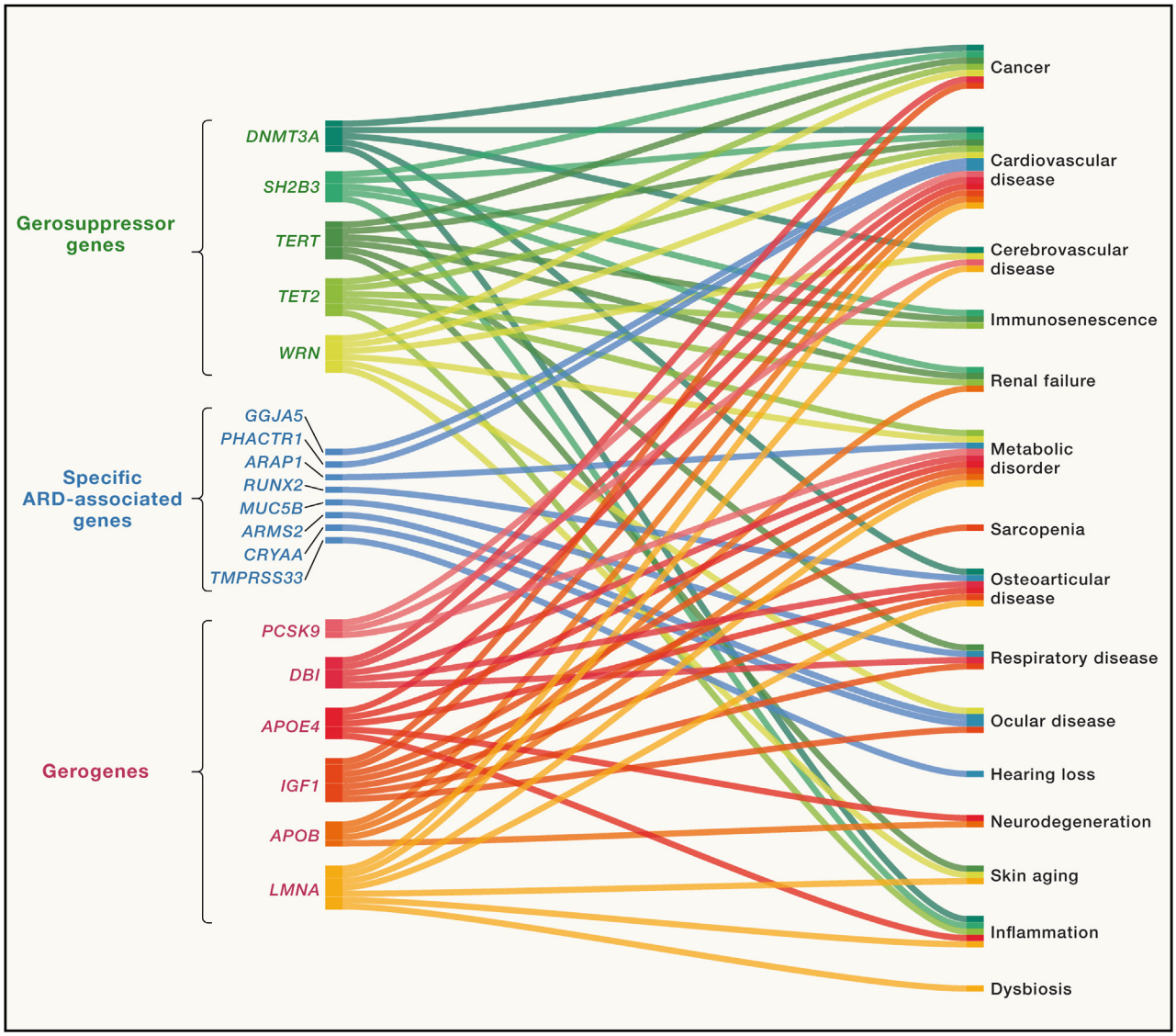

Figure 3. General versus disease-specific genotype-phenotype correlations

Gerogenes and gerosuppressor genes tend to affect multiple age-related diseases (ARDs), contrasting with specific ARD-associated genes that have a more reduced phenotypic impact. See Table 1 for a more exhaustive list of gerogenes and gerosuppressor genes. Note that this scheme provides examples of genotype-phenotype correlations and does not pretend to be comprehensive.

unrelated pathologies such as Alzheimer's disease, cardiovascular disorders, and cancer (Figure 3).

That said, none of the known gerogenes or gerosuppressor genes affects all age-related diseases at once (Figure 3). Moreover, specific genetic variants predispose to single diseases but not general aging, as exemplified by polymorphisms associating *ARAP1* with type 2 diabetes,[128] *ARMS2* with age-related macular degeneration,[129] *CRYAA* with cataracts,[130] *GJA5* with atrial fibrillation,[131] *MUC5B* with idiopathic pulmonary fibrosis,[132] *PHACTR1* with atherosclerosis,[133] *RUNX2* with osteoporosis and osteoarthritis,[134,135] *TMPRSS3* with hearing loss,[136] as well as by polygenic scores predicting the development of breast cancer[137,138] or other cancers[139] (Figure 3). It is tempting to speculate, yet remains to be demonstrated, that genetic variations in loci predisposing to specific diseases (rather than general aging) may contribute to the variegated phenotypic representation of old age in humans. Together with environmental, behavioral, and psychosocial factors, they might contribute to the "ageotypes" marked by specific longitudinal shifts in omics that accompany four distinct (metabolic, immune, hepatic, or renal) aging trajectories.[140] However, it can be suspected that such a categorization into ageotypes is not definitive. For example, magnetic resonance imaging (MRI) interpreted by AI has led to the classification of brain aging into five patterns of atrophy, each of which is associated to a variable degree with genetic, environmental, and neuropsychiatric features.[141] Although this has not been investigated in a systematic fashion, it can be speculated that whole-body MRI would reveal

specific patterns of the anatomical distribution of malignant lesions or atherosclerotic plaques (and their precursors) or other alterations in large populations. Thus, each age-related disease might develop following different stereotyped trajectories. Irrespective of these uncertainties, pending further in-depth validation,[142] ageotyping might guide personalized approaches in precision geromedicine.

Organ- and cell-type-specific omics approaches can unravel localized rather than organism-wide aging trajectories elicited by specific genetic and environmental perturbations. Single-cell (and spatially resolved) transcriptomics can be used to explore such localized trajectories in model organisms[143] but not in humans in which peripheral blood is generally the sole easily accessible organ for biological analyses. The plasma proteome, which contains proteins derived from all tissues composing the human body, can be bioinformatically deconvoluted to analyze aging in 11 major organs.[144] When applied to a cohort of nearly 500 individuals, this approach (which, however, excluded all proteins expressed in several organs and hence might inform on general aging) revealed that only 1.7% of the population are multi-organ agers, while 20% exhibit accelerated aging of one organ associated with an organ-specific risk of morbidity, as well as with all-cause mortality.[144] Similarly, clinical organ-specific clocks based on parameters such as lung function, cardiac health, and musculoskeletal measures predict mortality and the incidence of diseases in healthy middle-aged individuals. These clocks also reveal the sequence of deterioration in multi-organ aging networks.[145] Attempts are underway to purify exosomes that are shed from specific organs into the circulation and to characterize them by omics technologies to gain additional insights into the risk and evolution of age-related diseases.[146,147] Technological progress in this area of plasma analytics, which requires improvements in both hardware and software, might facilitate early disease detection in the future.

In summary, while an ideal scenario would involve evaluating the pace of aging across individuals using a single biomarker, this approach is complicated by the significantly varying rates of aging among different cell types[148] and organ systems within individuals,[149] as well as by potentially heterogeneous organ-specific aging processes contributing to age-related diseases. This complexity pleads in favor of the development of composite biomarkers of aging for gerodiagnostics, as recommended by the Biomarker of Aging Consortium (https://www.agingconsortium.org).

THE FUTURE OF PRECISION GEROMEDICINE

Family medicine, internal medicine, and geriatrics are traditionally focused on the diagnosis and treatment of aging adults and older individuals who are at elevated risk of manifesting age-related pathologies or who have already developed these conditions, which are often associated with debilitating health outcomes and frequently culminate in frailty.[150] In contrast to these essential and well-established medical specialties, the emerging field of geromedicine seeks to optimize health and extend healthspan by targeting fundamental aging processes across the entire adult lifespan, encompassing individuals regardless of their current health status, except in cases of palliative care or severe cognitive impairment that precludes adherence to safety protocols. Thus, geromedicine does not concentrate solely on older adults or diseased populations but emphasizes the inclusion of younger individuals prior to the clinical manifestation of age-related diseases. In this context, the prefix "gero" does not define the target population but rather refers to the overarching objective of promoting healthy aging trajectories.

In our vision, geromedicine should pursue three general objectives that distinguish this discipline from other medical specialties that usually target manifest diseases (Figure 4A). First and foremost, in (apparently) healthy individuals, geromedicine should apply a systems biology approach analyzing interactions of biological, clinical, psychological, social, and environmental measures to model and predict health trajectories, incidence of disease, and utilization of gerotherapeutics, hence proposing "proactive measures" to decelerate, halt, or reverse such effects. Second, geromedicine should spot "precocious derangements"—the potential precursors of disease—in still-healthy individuals to prevent the development of specific pathologies. Third, geromedicine should seek the biomarker-informed detection of "subclinical lesions" (such as asymptomatic cancers or arterial stenoses) to intercept them by early therapeutic intervention and hence to avoid their transition to clinically manifest diseases and the consequent health deterioration that would affect the entire organisms.

Admittedly, some of the prerogatives of geromedicine are already a part of routine practice under the label of preventive medicine. Examples include the early detection of "risk factors" such as *BRCA1* and *BRCA2* mutations, usually based on a family history of female cancers,[151] as well as public campaigns in favor of smoking cessation, healthy eating, and physical exercise.[152] Similarly, general practitioners perform annual health screenings that, beyond clinical physical examinations, may include measurements of body composition, blood pressure, pulmonary function, exercise capacity, blood cell counts, levels of serum lipids, glucose, and liver enzymes, renal clearance, and antibodies against sexually transmitted diseases.[153] General practitioners also prescribe medications to correct dyslipidemia or hypertension, which are "precocious derangements" predisposing to cardiovascular disease. Cardiologists diagnose "subclinical lesions" by electrocardiography with or without exercise stress, echocardiography, computer tomography (CT) for cardiac calcium scoring, coronary angiography, and echo doppler exams of the supra-aortic arterial trunk.[154] Oncologists detect early neoplastic lesions by mammography for breast cancer, human papilloma virus (HPV) and Pap testing for cervical cancer, stool-based tests and colonoscopy for colorectal cancer, and low-dose CT scanning for lung cancer.[155] Ophthalmologists screen for early signs of cataract, glaucoma, and macular degeneration.[156] However, these examinations are conducted within the confines of traditional medical specialties, rather than through an integrated, systems-based approach, and often do not lead to truly personalized interventions. Moreover, they do not specifically address the aging process itself but are primarily aimed at early disease detection. If integrated with modern biological multi-omics data, as well as with clinical and digital

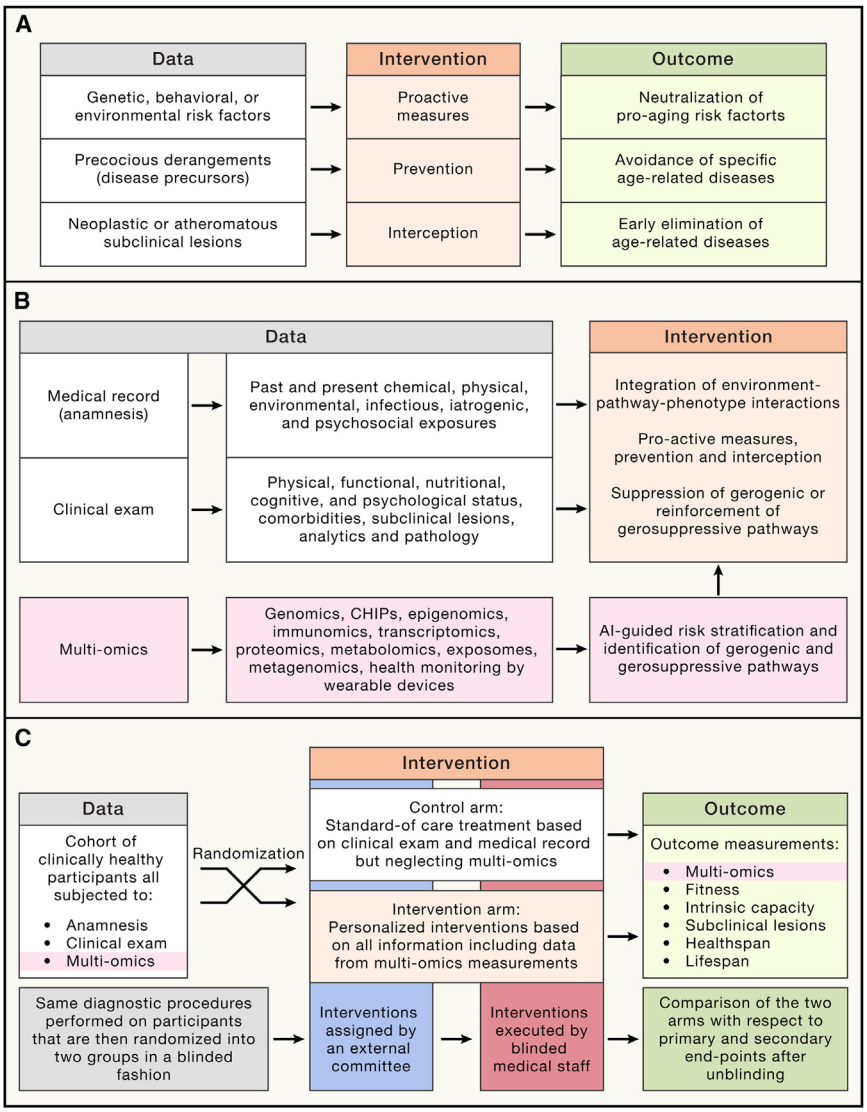

Figure 4. Principles of precision geromedicine

(A) Geromedicine involves proactive, preventive, and interceptive interventions to reduce risks of precocious aging, avoid the manifestation of age-related diseases, and eliminate them at an early stage, respectively.

(B) Precision geromedicine is based on accurate medical records, exhaustive clinical exams, and multi-omics measurements, the results of which must be integrated for optimal intervention strategies.

(C) Blueprint of a double-blinded randomized clinical trial potentially leading to regulatory approval of precision geromedical strategies. In this platform trial, a maximum of information is obtained from healthy individuals, leading to interventions that are either based on established sources of information, i.e., the medical record and clinical exam (control arm), or on these established sources plus the outcome of multi-omics analyses (intervention arm). The precise nature of these interventions (which can target lifestyle and environmental factors or involve drugs and supplements) must be designed in the future but should involve measures to reinforce gerosuppressive or to inhibit gerogenic pathways identified by multi-omics technology in the intervention arm. In addition, the identification of risk factors may trigger exams designed for the early identification and interception of subclinical lesions.

AI, artificial intelligence; CHIP, clonal hematopoiesis of indeterminate prognosis.

biomarkers of aging, they could yield precious information on organ-specific aging trajectories.

From our perspective, the nascent discipline of precision geromedicine should provide a systematic framework for evidence-based proactive measures, prevention, and interception (Figures 4A and 4B). This goes well beyond the current context of "longevity clinics"[157] that often operate to propose a compendium of health checks, cosmetic interventions, physiotherapy, supervised physical and cognitive exercises, dietary schedules, food supplements, hormone therapies, and over-the-counter drugs. Some clinics also propose treatments such as hyperbaric oxygen chambers, red light therapy, and cryotherapy, as well as injections of autologous platelet or extracellular vesicle-rich plasma, micro-fragmented adipose tissue, and even stem cell therapies that have not been validated for effects on aging and longevity in randomized, double-blinded phase 3 clinical trials. Often such treatments are catered to wealthy individuals on demand and hence are not truly personalized based on medical need. Some of the treatments offered by these clinics appear to be proven based on observational analyses, which is often misleading. In this context, it appears mandatory to create longevity clinics that scrupulously respect the credo of evidence-based medicine and that ideally should be part of publicly funded hospitals, embedding this new specialty into existing educational and healthcare services and making longevity-focused healthcare more accessible to the general population.[158] Although longevity clinics represent a pioneering clinical service model, evidence regarding their feasibility and effectiveness in public practice remains to be established. Fundamental data on participant acceptability to the service, recruitment, retention, and adherence is needed to comprehensively evaluate the components of the clinical service. This foundational data will lay the groundwork for subsequent large-scale, multicenter studies of clinical utility, economical effectiveness, and feasibility of implementation.

From a geroscientific perspective, it is desirable to obtain a maximum of information from each individual (Figure 4B). Beyond a detailed anamnesis encompassing a complete medical history—including past and current diseases and surgeries, family history of disease and lifespan, past and present medications, supplement and drug use, occupation, infections, allergies, and exposure to air pollution, chemicals, and radiation, as well as past and present lifestyle and psychosocial stress—the clinical

assessment should include a comprehensive characterization of all physiological systems, incorporating often overlooked aspects such as cognitive, oral, gut, sensory, and reproductive health.[158] This is the basis for future geromedical exploration (which is spearheaded by some longevity clinics) using multi-omics diagnoses, some of which are already used in cancer diagnosis. This will involve the detection of germ line and somatic mutations (CHIPs), DNA methylation patterns (and other epigenomic alterations), and transcriptomics (ideally at the single-cell level) in circulating leukocytes; metabolomics of the plasma (and perhaps exhaled breath, saliva, and urine); proteomics of the fluid-phase of the plasma and specific organ-derived exosomes; metagenomics of the fecal microbiota; the characterization of the chemical exposome; and the monitoring of digital biomarkers of aging by wearable devices.[80,82,94,96,97,146,147,159,160] Pending collection of data from several large and diverse cohorts, such multi-dimensional data will be interrogated to identify risk factors for physical and functional decline, early morbidity, and mortality. Such risk factors may be ascribed to the reinforcement of general or organ-specific gerogenic pathways or the debilitation of gerosuppressive mechanisms.

The combined information outlined above may then be used to personalize interventions on each individual by blocking gerogenic pathways or reinforcing gerosuppressive mechanisms with either pharmacological agents (Table 2) or supplements, specific lifestyle interventions at the levels of diet, exercise, and sleep, psychosocial support, as well as eliminating persistent environmental risk factors and optimizing the environment based on the individual's needs and goals (Figure 4B). The impact of such interventions will be assessed by longitudinal profiling of biomarkers of aging to identify surrogate markers that predict the success or failure of such personalized interventions in the context of precision geromedicine.

As the field of geromedicine continues to advance, medications and supplements designed as gerotherapeutics are rapidly evolving. The principle of "first, do no harm" remains essential, requiring rigorous evaluation in randomized clinical trials in humans before the introduction of such gerotherapeutics into longevity clinics. For individuals with existing medical conditions and medication use, gerotherapeutics need to be evaluated with respect to drug interactions. It is also critical to ensure that supplements meet the quality and safety requirements of the country in which the clinician practices, given the variability in regulatory standards across local legislations.

The formal establishment of precision geromedicine as a distinct medical specialty necessitates the creation of robust clinical scope of practice, detailed practice guidelines, standardized licensing frameworks, and comprehensive educational structures. Specialized training programs are crucial for equipping healthcare professionals with the requisite knowledge and skills to effectively deliver care in this emerging field, as recommended by the Healthy Longevity Medicine Society (HLMS) (https://hlms.co).

THE PATH FORWARD TOWARD REGULATORY APPROVAL

We surmise that the development of multi-omics-based biomarkers, their AI-aided interpretation, and their medical widespread application will occur in several steps. At this point, none of the biomarkers of aging detected by multi-omics methods abide by the rules of the FDA concerning laboratory-developed tests and *in vitro* diagnostic products (https://www.fda.gov/medical-devices/in-vitro-diagnostics/laboratory-developed-tests) that ensure their safety and effectiveness. Hence, rigorous and standardized manufacturing and use of such multi-omics tests ensuring their accuracy and reproducibility will be necessary for their diagnostic use.[93] Similarly, AI and machine learning software used for the interpretation of multi-omics data must be subjected to regulatory approval (https://www.fda.gov/medical-devices/software-medical-device-samd/artificial-intelligence-and-machine-learning-software-medical-device). Only compliance with these regulations will allow the transition from the current exploratory, purely geroscientific use of multi-omics technologies to their use as diagnostic tools to either observationally monitor aging trajectories or select therapies and evaluate their effect.

In the same way that diagnostic methods require refinement and regulatory clearance, potential therapeutic strategies must undergo regulatory approval with respect to safety (in phase 1 studies) and signals of efficacy (in phase 2 studies). Then they must be evaluated in randomized double-blinded clinical phase 3 trials tested in relevant populations.[161] Ongoing trials follow a traditional design in which each single therapeutic intervention is tested for safety and efficacy regarding one single age-related disease.[4] Although this approach is laudable and necessary, the future development of precision geromedicine requires a leap into a new (multi-)dimension in which diagnostics are coupled to therapies in a new way.

To enhance efficiency and flexibility, the best study design is likely a multicenter platform trial in which multiple treatments of (future) diseases are evaluated within the same protocol (transcending the scope of basket trials, in which one therapy is tested on more than one disease, or umbrella trials, in which multiple therapies are tested for a single disease) in the context of a master protocol.[162] Given the overarching goal of geromedicine, which is optimizing health and prevention rather than cure, such a trial should involve clinically healthy individuals, preferably with a higher biological age.[163] In a plausible scenario (Figure 4C), the compounded participant information obtained by anamnesis, clinical and digital assessment, and multi-omics technologies will be obtained from all participants enrolled in the platform trial, who then are randomized into two groups: (1) a control group that receives standard of care and (2) the intervention group that receives personalized medical treatments based on all the information, including the multi-omics methods. Interventions would involve non-medical treatments (lifestyle modifications such as diet and exercise, cognitive stimulation, psychological, social interventions, etc.), additional investigations based on the identification and interception of subclinical lesions, prescription drugs (e.g., for the control of diabetes, hypercholesterinemia, and hypertension), over-the-counter drugs, as well as supplements that fall into the category of 370 food substances that are generally recognized as safe (GRAS) by the FDA and that might have therapeutic effects. The randomization process and the assignment of such personalized interventions to each participant in the control and intervention arms would be overseen by an off-site committee, and such treatments then would

be administered on-site by the medical personnel with evaluations performed by blinded assessors.

The primary endpoint of a registration trial must be clinical efficacy (Figure 4C). Obviously, it would be too long to measure efficacy as lifespan/mortality. Therefore, responsive clinical biomarkers of aging, serving as surrogate markers for (subclinical) age-related diseases, should be assessed. These outcomes should be FDA-accepted clinical endpoints such as HbA1c, blood pressure, cognition, and muscle strength, or at least surrogate endpoints (such as cholesterol levels). Additionally, relevant clinical biomarkers of aging that are not yet recognized as FDA-accepted outcomes—such as specific measures of intrinsic capacity (i.e., by assessing five domains ranging from cognition, psychology, locomotion, vitality, and sensory function),[5,164,165] maximal oxygen consumption (VO_2 max), body composition (determined by, e.g., dual-energy X-ray absorptiometry or CT), muscle mass (e.g., by means of the D_3-creatine dilution method), neuromuscular and respiratory function (e.g., by dynamometers and respirometers), and anatomy/morphology (e.g., by whole-body MRI), along with digital and laboratory biomarkers[5,164]—should be proposed for regulatory clearance.

In the event of successful outcomes meeting the primary endpoints, regulatory approval might be bestowed on the entire strategy evaluated in the trial, i.e., the combination of multi-omics diagnosis and all personalized treatments, or on segments of the procedure, i.e., the combination of specific interventions with their companion diagnoses. Conceivably, approval might occur as the platform trial is ongoing. In this case, the approved procedures would be incorporated into the control arm, while new preventive or therapeutic agents and innovative procedures such as interventions on the microbiota[166,167] or epigenetic reprogramming,[168] which would have to undergo prior phases 1 and 2 trials, would be incorporated into the intervention arm.

Obviously, clinical trials leading to the practical implementation of precision geromedicine will require considerable financial resources, as well as the implication of rather large and diverse cohorts for more than a decade. Thus, multicentric trials involving multiple countries across continents should be supported by large and potent organizations such as the National Institute of Aging Translational Geroscience Network,[169] the European Union, or the Hevolution Foundation. We anticipate that such efforts will ultimately pay off because they will push the frontiers of modern medicine toward an extension of healthspan applicable to large segments of the population. Nevertheless, we acknowledge that the diversity of public health systems operating in distinct countries may limit the equitable access to geromedicine, posing an ethical dilemma that must be resolved in the future.

CONCLUSIONS

Geroscience is providing ever more insights into aging phenotypes and age-related diseases by a combination of hypothesis-driven preclinical research and deep digital, clinical, and pathological phenotyping coupled with the omics-based characterization of DNA, RNA, protein, and metabolites, mostly from participants' blood, saliva, and stool, thus generating genomic, epigenomic, transcriptomic, proteomic, lipidomic, metabolomic, and metagenomic datasets that yield profound insights into aging phenotypes. This combination of methods has led to the discovery of gerogenic and gerosuppressive pathways that, in interaction with environmental, behavioral, and psychosocial factors, have broad aging-accelerating or aging-decelerating effects, respectively, offering targets for medical interventions. Moreover, organ-specific aging processes leading to peculiar diseases may be precipitated by additional genes and pathways that contribute to the manifestation of ageotypes.

We have discussed opportunities to pharmacologically target specific gerogenic and gerosuppressive pathways, as well as to develop drugs effective against specific age-related pathologies for the prevention of other diseases. In addition, we have proposed a blueprint for future randomized clinical trials that would be age-related disease agnostic, gather a maximum amount of information on each participant, including digital, clinical, and laboratory biomarkers of aging, and then adapt preventive or therapeutic interventions in a highly personalized fashion. Pending regulatory approval of multi-omics diagnostic procedures and surrogate markers of clinical efficacy, such a strategy might inaugurate the era of precision geromedicine. With the support of large international consortia and adequate governmental, philanthropic, and private funding, along with a careful blend of ambition and realism, this endeavor should lead to the successful clinical implementation of precision geromedicine with the supreme goal of optimizing health and maximizing healthspan. Scalable and hence cost-effective approaches, accompanied by suitable policies, should provide broad, equitable access to precision geromedicine. Humanity and humankind cannot prosper without audacious goals.

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DECLARATION OF INTERESTS

G.K. holds research contracts with Daiichi Sankyo, Kaleido, Lytix Pharma, PharmaMar, Osasuna Therapeutics, Samsara Therapeutics, Sanofi, Sutro, Tollys, and Vascage; is on the Board of Directors of the Bristol Myers Squibb Foundation France; is a scientific co-founder of everImmune, Osasuna Therapeutics, Samsara Therapeutics, and Therafast Bio; is on the scientific advisory boards of Centenara Labs (formerly Rejuveron Life Sciences), Hevolution, and Institut Servier; and is the inventor of patents covering therapeutic targeting of ACBP/DBI, aging, cancer, cystic fibrosis, and metabolic disorders. G.K.'s wife, Laurence Zitvogel, has held research contracts with Glaxo Smyth Kline, Incyte, Lytix, Kaleido, Innovate Pharma, Daiichi Sankyo, Pilege, Merus, transgene, 9 m, Tusk, and Roche; was on the Board of Directors of Transgene; is a co-founder of everImmune; and holds patents covering the treatment of cancer and the therapeutic manipulation of the microbiota. G.K.'s brother, Romano Kroemer, was an employee of Sanofi and now consults for Boehringer Ingelheim. A.B.M. is co-founder of Chi Longevity, Chief Medical Officer of NU, and holds research or advisory contracts with Abbott, Danone, Haleon, Borealis Pharma, Rejuveron, Institute for Healthier Living Abu Dhabi, Atria Institute, Hevolution, and PwC. A.M.C. is co-founder of Selphagy (a program under LifeBioscience). V.G. is a consultant to Genflow Bio, DoNotAge, Elysium, WndrHLTH, and BellSant and is a co-founder of Matrix Bio and Faunsome Bio. V.N.G. is an inventor of patent applications dealing with aging biomarkers. B.K.K. reports a relationship with Ponce de Leon Health that includes consulting or advisory and equity or stocks. E.V. is a member of the SAB of BioAge, Deciduous, Rejuvenate Biomed, GenFlow, Amazentis, Longevity Clinic Europe, and Institute of Healthy Living Abu Dhabi. F.S. is the founder of Geroscience Consulting LLC. The funders had no role in the design of the study, in the writing of the manuscript, or in the decision to publish the results.

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