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Research Article

Clinical Pathways in Longevity and Rejuvenation Medicine: An Evidence-Based Synthesis of Diagnostic, Therapeutic, and Monitoring Protocols (Patient Workup)

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ABSTRACT

Background: Longevity and rejuvenation medicine combines established preventive care with emerging diagnostic and therapeutic approaches, but clinical practice varies and claims often exceed the available evidence.

Objective: This review synthesizes a patient pathway covering assessment, diagnostic evaluation, lifestyle and pharmacological management, reproductive and regenerative interventions, and longitudinal monitoring.

Approach: This is a narrative clinical review based on the literature cited in the manuscript; it is not a systematic review and does not claim exhaustive database searching or formal risk-of-bias assessment.

Main findings: Established preventive care and treatment of diagnosed conditions have a stronger clinical basis than interventions marketed to reverse aging. Biological-age biomarkers and many regenerative approaches have not demonstrated sufficient clinical utility for routine use across general longevity populations.

Conclusion: Clinical pathways should be indication-driven, transparent about uncertainty, attentive to safety, and anchored to meaningful patient outcomes rather than surrogate biomarkers alone.

KEYWORDS

Longevity medicine, Rejuvenation medicine, Clinical assessment, Preventive medicine, Biological aging, Regenerative medicine, Monitoring.

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Review Scope and Approach

This article is a narrative clinical review intended to organize established practice and emerging approaches into a patient-care pathway. The cited literature is discussed according to its relevance to the clinical claims made in the text. Because a reproducible database search, prespecified eligibility criteria, and formal risk-of-bias assessment were not documented in the source manuscript, this article should not be represented as a systematic review. Before submission, the authors should either document and perform a reproducible search appropriate to the intended review type or retain the narrative-review designation and state this limitation explicitly.

Introduction

Population aging has shifted the clinical focus from survival alone toward preservation of physiological function, independence, and quality of life. Age-related decline is characterized by progressive dysregulation across interconnected systems, including metabolic homeostasis, endocrine signaling, musculoskeletal integrity, and reproductive capacity. In response, a rapidly expanding sector of clinical practice—often described as rejuvenation or longevity medicine—has emerged, offering integrated interventions targeting these domains. However, the field is marked by substantial heterogeneity in practice standards and frequent extrapolation from preclinical or early-phase data. A critical, evidence-based synthesis of contemporary clinical protocols is therefore required.

This review delineates the full clinical pathway employed in such settings, from initial consultation through intervention and longitudinal monitoring, integrating validated medical practice with emerging and investigational approaches. Particular emphasis is placed on mechanistic plausibility, strength of evidence, and clinical applicability.

Clinical Assessment and Risk Stratification

Initial consultation is structured to identify both established disease and early functional decline. Comprehensive history includes cardiometabolic risk factors, endocrine disorders, reproductive health, medication exposure, sleep patterns, physical activity, dietary habits and emotional state. Symptoms such as fatigue, reduced exercise tolerance, loss of muscle mass, central adiposity, decreased libido, and menstrual or erectile dysfunction are evaluated as potential manifestations of underlying endocrine or metabolic dysregulation.

Risk stratification prioritizes cardiovascular and metabolic disease because these conditions contribute substantially to morbidity and mortality. Use a cardiovascular risk equation validated for the patient's population and jurisdiction; in the United States, contemporary tools such as the PREVENT equations may be appropriate for eligible adults. Coronary artery calcium scoring may refine risk in selected patients when the result is expected to change management. Chronological age should be considered alongside established clinical risk factors and functional status; no single measure currently provides a universally validated estimate of an individual's biological age.

Contraindications to intervention—particularly hormone therapy—are systematically assessed, including history of hormone-sensitive malignancy, thrombophilia, uncontrolled hypertension, or advanced cardiovascular disease. This stage establishes the clinical boundaries within which subsequent interventions are considered.

Diagnostic and Phenotypic Evaluation

Core Clinical Diagnostics

Physical examination includes anthropometric measurements (BMI, waist circumference), blood pressure, and evaluation for signs of endocrine dysfunction (e.g., gynecomastia, hirsutism, sarcopenia).

Laboratory evaluation should be individualized to the patient's history, symptoms, examination, risk profile, medications, and clinical question. Potential tests include:

- Metabolic markers: HbA1c or plasma glucose as indicated, lipid profile; fasting insulin is not a routine screening test for every patient and should be ordered only when a defined clinical question justifies it
- Inflammatory markers: high-sensitivity C-reactive protein only when clinically appropriate; it is not a universal longevity screening test
- Endocrine testing: testosterone, estradiol, LH, FSH, and SHBG only when indicated by symptoms, examination, or a specific diagnostic question; interpretation depends on sex, age, reproductive status, timing, medications, and assay
- **Thyroid function**: TSH ± free T4
- **Cancer markers such as CA 15-3, CA-19-9, CEA to identify patient eligibility for certain interventions.**
- Additional markers (context-dependent): IGF-1 or DHEA-S only for a defined clinical indication; neither should be used as a general-purpose biological-age or longevity screen

Test selection and interpretation should follow current disease-specific guidelines and the relevant clinical indication. The tests listed above are not intended as a universal panel for all patients.

Functional and Structural Assessment

- DXA: assessment of bone mineral density when osteoporosis evaluation is indicated; body-composition measurements may be useful in selected settings but should not be presented as a stand-alone diagnostic test for sarcopenia
- Cardiopulmonary exercise testing (CPET): assessment of exercise capacity when clinically indicated or when the result will inform a defined performance or rehabilitation plan. Cardiorespiratory fitness is associated with health outcomes, but CPET is not required for every longevity-clinic patient.
- Ultrasound imaging: targeted assessment of ovarian, testicular, or vascular pathology when indicated; routine imaging of asymptomatic patients is not recommended solely to measure

aging
- Reproductive diagnostics: semen analysis for an appropriate male-infertility evaluation; anti-Müllerian hormone and antral follicle count may inform selected fertility assessments but should not be presented as definitive measures of natural fertility or general biological age

Emerging Biomarkers and Technologies: Investigational Uses
- Epigenetic clocks (DNA methylation-based aging indices)
- Metabolomic and proteomic profiling
- Microbiome composition
- ZBG genetic testing and ownership
- Freudenspanne testing using the 3 laws of longevity as a foundation
- Brain scans

Epigenetic clocks, multi-omics, and microbiome profiles remain research-oriented for most general longevity decisions. Analytical validity, clinical validity, and clinical utility must be assessed separately. An association with age or disease does not establish that testing improves outcomes, and these results should not direct treatment outside an appropriate evidence-based or research context [1]. See Figure 1.

The blending of these varied disciplines into a coherent diagnosis is still at very early stages partly due to academic inertia and in part due to lack of cross-disciplinary cooperation, between Clinicians, scientists and social scientists.

Lifestyle and Nutritional Interventions

Lifestyle modification remains the most evidence-supported intervention in longevity medicine. Mediterranean dietary patterns have demonstrated reductions in cardiovascular events and all-cause mortality in randomized trials [2]. Mechanistically, these diets improve lipid profiles, reduce inflammation, and enhance endothelial function.

Adequate protein intake is essential for preservation of lean mass, particularly in older adults, where anabolic resistance necessitates higher intake (1.0–1.6 g/kg/day) [3]. Micronutrient adequacy is addressed selectively, with correction of deficiencies such as vitamin D shown to improve bone health and potentially muscle function [4].

Energy restriction and fasting-related interventions have demonstrated improvements in metabolic parameters and cardiometabolic risk markers in clinical studies [5]. Proposed mechanisms include improved insulin sensitivity, modulation of nutrient-sensing pathways (e.g., mTOR, AMPK), and reduction of oxidative stress. However, evidence for sustained effects on lifespan or global aging processes in humans remains limited.

Whilst there has been some research that shows emotions are integral to longevity there is still no quantified broad-based research to validate this.

Exercise and Physical Function Optimization

Exercise is a central therapeutic modality with robust evidence across multiple domains. Resistance training increases muscle mass and strength, counteracting sarcopenia and improving insulin sensitivity [6]. Aerobic exercise enhances mitochondrial function, cardiovascular efficiency, and metabolic flexibility.

VO_2max, measured via CPET, is among the strongest predictors of mortality, underscoring the importance of cardiorespiratory fitness [7]. Grip strength is the other major predictor of mortality

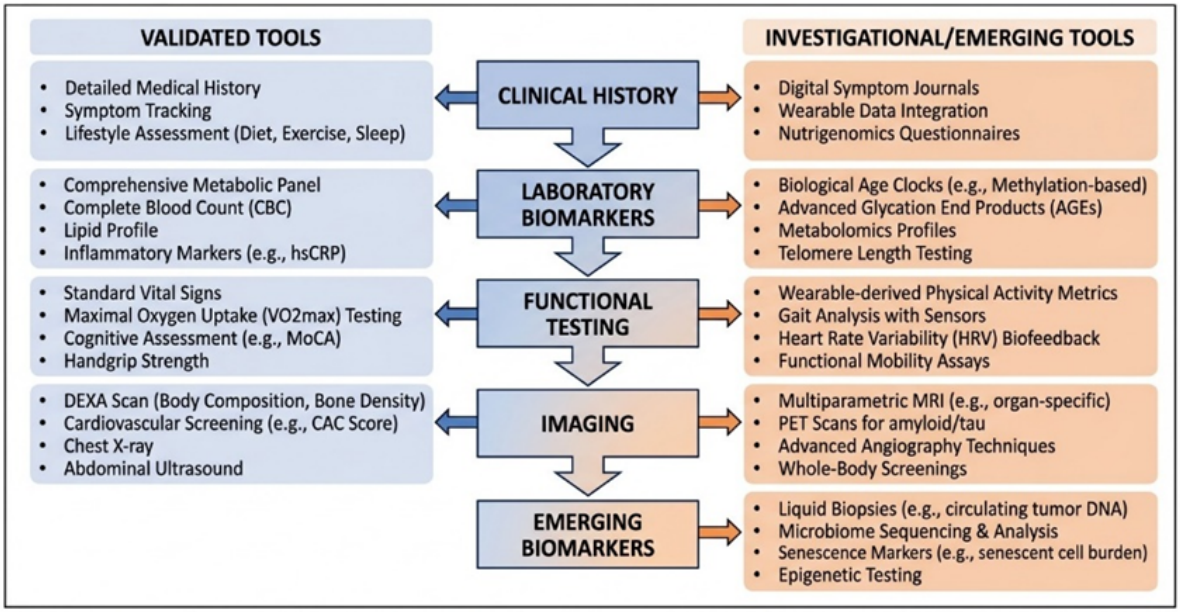


Figure 1: Integrated Diagnostic Framework in Longevity Medicine.

emphasizing the importance of muscular skeletal strength [8] Multimodal exercise programs incorporating balance and neuromuscular training reduce fall risk and preserve functional independence.

At the molecular level, exercise influences myokine signaling, mitochondrial biogenesis, and insulin signaling pathways. These adaptations contribute to systemic improvements in metabolic and endocrine function, although the magnitude of hormonal effects varies. For more see Figure 2.

Sleep, Circadian, and Behavioral Interventions

Sleep disruption is associated with metabolic dysfunction, including insulin resistance and obesity [9]. Clinical management includes screening for sleep apnea, optimizing sleep hygiene, and promoting circadian regularity.

Chronic stress contributes to dysregulation of the hypothalamic–pituitary–adrenal axis, with downstream effects on metabolic and immune function. Behavioral interventions may improve quality of life and reduce stress-related physiological burden, although direct effects on aging remain incompletely defined.

Endocrine and Pharmacological Management

Endocrine therapy is indicated for diagnosed deficiency states rather than generalized anti-aging use. Testosterone replacement in men with confirmed hypogonadism improves sexual function, bone density, and body composition [10]. However, risks include erythrocytosis, suppression of spermatogenesis, and potential cardiovascular effects, necessitating careful monitoring.

Menopausal hormone therapy is effective for symptom control and prevention of bone loss when used in appropriate populations [11]. Thyroid hormone replacement is indicated in overt hypothyroidism.

Pharmacological management of cardiometabolic disease—including statins, antihypertensives, and antidiabetic agents—remains foundational to risk reduction [12].

Investigational Longevity Pharmacology

- **Metformin**: observational and trial data suggest reduced incidence of age-related disease, but lifespan extension in non-diabetic populations remains unproven [13]
- **Rapamycin (mTOR inhibition)**: extends lifespan in animal models; human data limited to immune and metabolic endpoints [14]
- **Nicotinamide Mononucleotide (NMN)**: A cellular precursor that directly boosts **NAD+** levels, a coenzyme critical for DNA repair, sirtuin activation, and mitochondrial energy production that depletes with age.
- **Nicotinamide Riboside (NR)**: Another prominent NAD+ precursor widely evaluated alongside NMN in head-to-head clinical trials for systemic bioavailability and tissue distribution.
- **Coenzyme Q10 (Ubiquinol)**: A critical electron transport chain component in the mitochondria. The active ubiquinol form is utilized to combat age-related mitochondrial drop-off.
- **Quercetin**: A flavonoid compound typically paired with Dasatinib (D+Q) or taken standalone to reduce systemic inflammatory cytokines (SASP) secreted by senescent tissues.
- **Alpha-Ketoglutarate (Ca-AKG)**: An intermediate in the Krebs cycle that acts as a cofactor for epigenetic enzymes, demonstrating a capacity to reverse epigenetic age metrics in human cohorts.
- **Berberine**: A botanical compound utilized as a natural **AMPK**

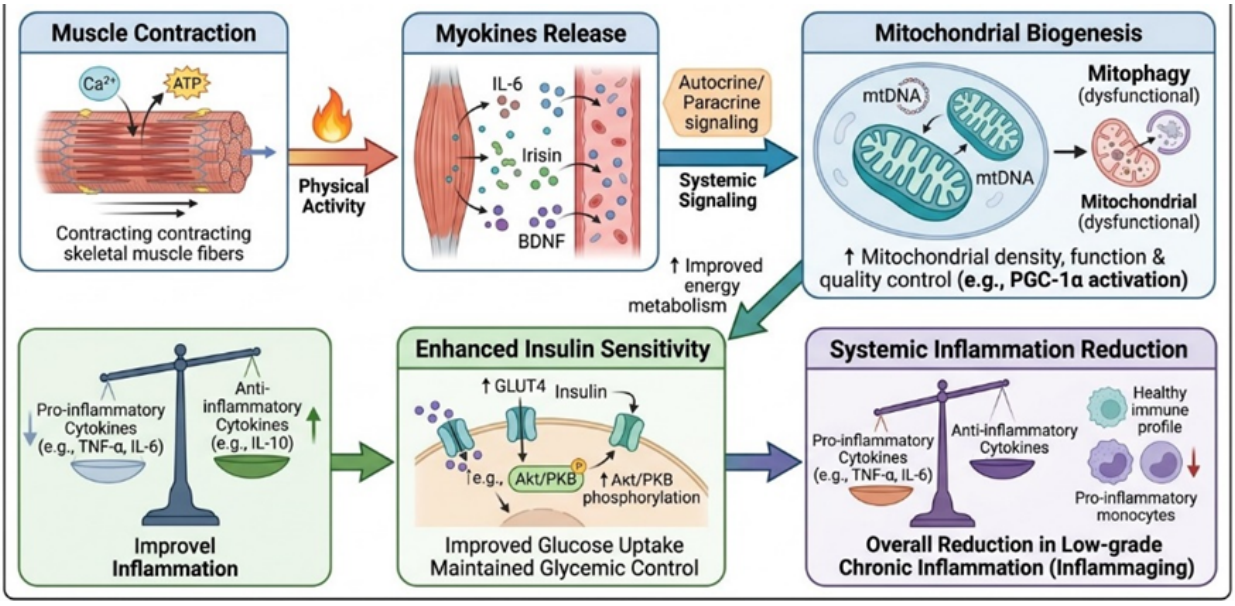


Figure 2: Mechanistic Effects of Exercise on Aging Physiology.

activator and glucose modulator, acting as a mild over-the-counter proxy for metformin's metabolic pathways.

These compounds stated above should not be presented as established treatments for aging in otherwise healthy people. Any use for longevity outside an approved indication should be described as investigational, with uncertainty about long-term benefits and harm made explicit. See Table 1.

Gonadal Function and Reproductive Interventions: Evidence and Clinical Boundaries

Established Clinical Practice

- Hormonal therapy for hypogonadism and menopause
- Fertility-preserving therapies (e.g., hCG, SERMs) [15]

Supported but Limited Evidence

- Platelet-rich plasma (PRP) for ovarian insufficiency: evidence is limited and heterogeneous; changes in hormonal markers do not establish improved pregnancy or live-birth outcomes [16]
- Exosome therapies for increasing estradiol and reducing FSH have shown promising results but are supported by only preliminary studies [17,18].
- In vivo activation of ovarian follicles using Autologous Mesenchymal stem cells [19,20]

Investigational / Experimental

- Stem cell–based ovarian or testicular therapies [19,21]

Evidence for these approaches is limited, often based on animal or small or uncontrolled studies, and does not establish reliable long-term restoration of fertility in advanced gonadal aging. They should be described as investigational unless high-quality evidence and applicable regulatory authorization support a specific use.

Erectile Dysfunction Regenerative Therapies

Intracavernosal stem-cell approaches for erectile dysfunction remain investigational. Small early-phase studies do not establish efficacy, durability, or safety sufficient for routine care, and surrogate or preliminary changes should not be interpreted as definitive clinical benefit [22]. See Figure 3.

Table 1: Pharmacological Interventions in Longevity Medicine.

Intervention	Indication	Evidence Level	Clinical Status	Key Risks
Metformin	Age-related disease risk reduction / cardiometabolic health	Observational, clinical trials	Investigational (in non-diabetic populations for aging)	Gastrointestinal upset, vitamin B12 deficiency, rare risk of lactic acidosis
Rapamycin	Lifespan extension and immune/metabolic function modulation	Preclinical (animal models), limited human trial data	Investigational	Immunosuppression, lipid dysregulation, oral mucositis, impaired wound healing
Testosterone Replacement	Confirmed hypogonadism	RCTs, clinical practice guidelines	Established (for hypogonadism)	Erythrocytosis, spermatogenesis suppression, potential cardiovascular risk
Menopausal Hormone Therapy (MHT)	Vasomotor symptom control, prevention of bone loss	RCTs	Established (in appropriate populations)	Venous thromboembolism, stroke, hormone-sensitive malignancy risk
Statins & Antihypertensives	Cardiovascular and metabolic disease risk reduction	RCTs	Established	Myopathy/myalgia, elevated liver enzymes, electrolyte disturbances

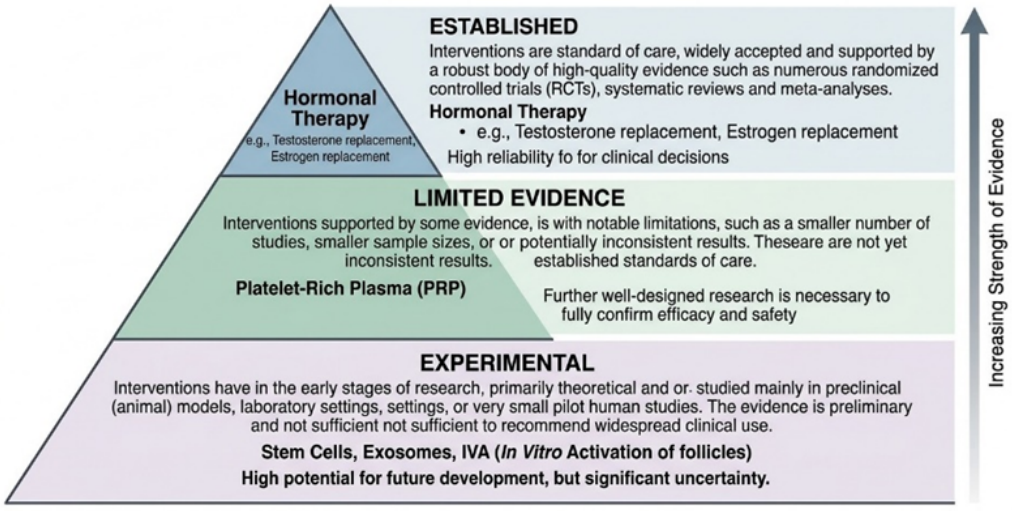


Figure 3: Evidence Hierarchy for Gonadal Rejuvenation Interventions.

Regenerative and Cellular Medicine

Regenerative therapies aim to restore tissue function through mechanisms including paracrine signaling, angiogenesis, and immunomodulation. PRP and autologous cell therapies have established roles in certain musculoskeletal conditions [23].

However, claims of systemic anti-aging effects remain unsupported by high-quality evidence. Most studies are limited by small sample sizes, lack of controls, and reliance on surrogate endpoints. Distinguishing mechanistic plausibility from clinical efficacy is essential.

Body Composition, Physique, and External Phenotype

Reducing excess visceral adiposity and preserving muscle function are associated with better metabolic and functional outcomes. Nutrition, physical activity, behavioral support, and—when clinically indicated—evidence-based obesity treatment should be selected according to the patient's health status and goals.

Aesthetic interventions—including laser resurfacing, radiofrequency-based skin tightening, and minimally invasive body contouring—can improve external appearance but do not modify underlying biological aging. These should be considered adjunctive rather than therapeutic.

Surgical Interventions

Surgical approaches are reserved for clear clinical indications. Bariatric surgery provides substantial and sustained weight loss and reduces mortality in severe obesity [24]. Reproductive and endocrine surgeries are performed when indicated for structural or pathological conditions.

Procedures marketed as anti-aging interventions without medical indication lack evidence and should not be considered part of standard care

Technology, Monitoring, and Data Governance

Longitudinal monitoring should be individualized and linked to a clinical question, treatment decision, or patient-centered outcome. Possible components include:

- Laboratory biomarkers
- DNA testing for foundational response metrics
- DEXA for body composition
- CPET for functional capacity
- Imaging (ultrasound, MRI) when clinically indicated
- Continuous glucose monitoring only for appropriate clinical indications or clearly described investigational use; it should not be presented as a validated screening or diagnostic tool for all asymptomatic patients
- Freudenspanne and emotional health testing and consultations
- Wearable devices for activity and sleep tracking

While digital health technologies provide valuable data, their clinical utility varies, and interpretation should be grounded in validated metrics. (See Figure 4). Also, there is no factoring in for certain candidates that are averse to tracking and monitoring



Figure 4: Longitudinal Monitoring Loop in Longevity Clinics.

Follow-up and Iterative Management

Management is dynamic and individualized. Follow-up includes reassessment of symptoms, laboratory markers, body composition, and functional performance. Adjustments to therapy are guided by objective data rather than subjective claims.

Follow-up intervals should be determined by the condition being treated, the intervention, baseline risk, treatment stability, and relevant clinical guidance. Laboratory testing may be needed soon after treatment initiation or dose changes and less often once stable. Imaging and functional testing should be repeated only when clinically indicated or when results are expected to change management. Adverse-event surveillance is integral, particularly for hormonal and pharmacological therapies.

Clinical Decision-Making, Safety, and Governance

Clinical decisions should be based on the patient's symptoms, history, examination, risk profile, preferences, and applicable clinical guidance. A test or intervention should be ordered only when there is a defined clinical question and a reasonable prospect that the result will affect management. Abnormal screening results should be confirmed using appropriate diagnostic criteria before labeling a patient or initiating treatment, unless urgent clinical circumstances require otherwise.

Before any pharmacological, hormonal, procedural, or regenerative intervention, clinicians should document the indication, expected benefit, material risks, alternatives (including no intervention), contraindications, relevant fertility goals, and the patient's informed preferences. Investigational interventions should be clearly identified as such; consent should explain uncertainty about efficacy, durability, and long-term safety. The regulatory status of a product or procedure must be checked in the jurisdiction where it will be provided. A clinic pathway should also define referral thresholds, adverse-event reporting, emergency escalation, and

criteria for withholding, modifying, or discontinuing treatment.

Monitoring should prioritize outcomes meaningful to the patient and relevant to the intervention, such as symptom improvement, functional capacity, disease-specific measures, quality of life, and adverse events. Changes in a surrogate biomarker should not be treated as proof of disease prevention, rejuvenation, or lifespan extension unless that relationship has been demonstrated for the specific context. Data governance should address confidentiality, access, retention, and the limitations of consumer wearables and digital platforms.

Limitations of This Review

This narrative review is limited by the scope and date of the cited literature, the absence of a documented systematic search and formal risk-of-bias assessment, and variation in the populations, interventions, outcomes, and follow-up periods represented in the underlying studies. Findings from selected patient groups may not generalize to healthy adults seeking longevity services. Several emerging interventions are supported by early-phase or observational evidence, and long-term clinical outcomes remain uncertain. Recommendations should therefore be interpreted as a framework for evidence-informed assessment rather than a validated, universally applicable clinical guideline.

Evidence Limitations

The field is constrained by several limitations. Many interventions lack randomized controlled trial evidence demonstrating improvements in clinically meaningful outcomes such as mortality or disease incidence. Regenerative therapies are particularly limited by small, uncontrolled studies and short follow-up.

There is also no account for variable in real life situations which cannot be accounted for, as no system acts in isolation (3rd Law of Longevity).

Biological age metrics remain insufficiently validated for clinical use. Furthermore, Cultural skew, publication bias and commercial influences may overstate efficacy of emerging therapies.

Conclusions

A clinically responsible approach to longevity and rejuvenation medicine integrates prevention, evidence-based management of established disease, lifestyle interventions, and selective use of diagnostic technologies. The strongest support is for interventions with demonstrated benefits for defined health outcomes, including appropriate nutrition, physical activity and emotional well-being, Tobacco and other narcotic avoidance, vaccination and preventive care where indicated, and management of cardiometabolic and endocrine disease.

Hormonal therapies can be beneficial for specific, appropriately diagnosed conditions, but should not be used indiscriminately as anti-aging treatments. Many regenerative interventions and pharmacological approaches proposed for longevity remain investigational for this purpose and should not be offered as established care without adequate evidence of clinical benefit, acceptable safety, and applicable regulatory authorization.

Progress will require well-designed human studies, transparent reporting, standardized patient-centered outcomes, adequate follow-up, and independent evaluation of benefits, harms, and cost-effectiveness. Until stronger evidence is available, clinical pathways should prioritize established preventive and therapeutic care, shared decision-making, and explicit communication of uncertainty.

Longevity therapies by their very nature are a long-term study.

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