Chapter 21
What Do We Need to Know to Treat Degenerative Aging as a Medical Condition to Extend Healthy Lifespan?

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21.1 The Urgent Need to Ameliorate Degenerative Aging and Extend Healthy Lifespan

It can be confidently stated that, at the present time, the extension of healthy lifespan (or "healthspan") for the global population is one of the most urgent and vital societal goals, if not the most urgent and vital. In its scope and potential significance for the well-being of the global human community, this goal dwarfs virtually any other development goal, even though the current support for the achievement of this goal is rather miniscule, compared to other types of expenditures. Yet, the importance of this goal for the society and every single individual cannot be overestimated. Throughout the world, due to the increasing aging population, the prevalence of chronic non-communicable diseases and disabilities – such as cancer, ischemic heart disease, stroke, type 2 diabetes, Alzheimer's disease, Chronic Obstructive Pulmonary Disease, etc. – rises steeply [1]. For the "developed countries" the problem is becoming acute. Thus, while 66% of deaths in the world occur from chronic age-related diseases, in the developed countries, this proportion reaches 90%, dramatically elevating the costs for healthcare and human suffering [2]. For the so called "developing countries" (or "low income countries") the problem of population aging may seem less visible, but is in fact not less, perhaps even more grave. Currently, while the highest life expectancies (and correspondingly the incidence of aging-related diseases) are still found in the "developed" countries, the rise in life expectancy is now the largest and most rapid in the developing countries, and the trend is likely to continue [3]. The faster and larger rise in life expectancy for the developing countries also means the stronger and faster population aging, and the larger and faster increase in the incidence of chronic age-related non-communicable diseases. At the same time, the geriatric and non-communicable disease care and

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research in these countries may be under par and unprepared, potentially threatening the lives of millions of the world's poorest and most disadvantaged older people. Also, in absolute terms, the number of people suffering from aging-related conditions in the "developing countries" exceeds the absolute numbers in the "developed" countries. Hence, also for the "developing world," the problem of population aging is strategically pressing, and the task of improving healthy lifespan for the population is urgent. Thus, it can be confidently stated that healthy lifespan extension is one of the most important healthcare, economic and humanitarian tasks for the entire global community. If transhumanism is understood as an aspiration for human development and for a solution of global problems, thanks to ethical use of new technological means, then the extension of healthy lifespan is undoubtedly one of the most central and urgent tasks of transhumanism, perhaps even the most central and urgent.

How can this task be accomplished? There is a wide range of the currently available lifestyle approaches for healthy longevity (such as moderate exercise, moderate and balanced nutrition, and sufficient rest and sleep), of which great many people are aware, even though the adherence and compliance with such approaches are often limited. At the same time, there is an ongoing massive search for additional novel biomedical means and technologies to ameliorate the degenerative aging process and in this way improve the healthy lifespan. The connection between amelioration of aging and extension of healthy lifespan should be obvious to everybody: Insofar as the deteriorative aging process either precipitates or lies at the root of chronic age-related diseases, the search for novel means and technologies for healthy lifespan extension necessitates the maximal possible amelioration of the degenerative aging process. Such amelioration of the aging process should lead to better health and quality of life for the elderly [4]. The possibility of therapeutic intervention into degenerative aging and the consequent significant healthy lifespan extension has been proven on both theoretical-biological grounds and experimental grounds in a variety of animal models. In particular, the ability of cell-based regenerative medicine, gene therapy, pharmacological therapy and nanomedicine to affect basic aging processes and extend healthy lifespan in animal models has been demonstrated, and even some encouraging preliminary results have been achieved in human experiments [5]. This possibility has also been conclusively proven by the existence of a large and continuously growing long-lived population, including centenarians and super-centenarians, that exhibit not only a high longevity potential, but also a reduced rate of age-related diseases compared to the general population [6].

Yet the pathway toward human healthy lifespan extension remains unclear and requires thorough elaboration, concerning many scientific problems that need to be clarified and technologies that need to be developed. There is a tremendous variety of studies and approaches toward healthy lifespan extension, and roadmaps indicating priority directions [7]. Perhaps the most critical drawback in this variety is the lack of integration of the different approaches. The existing approaches often present lists of potential research directions, rather than coherent and coordinated entities. Hence the integration of the various approaches, shortening the pathways

between the various disciplines, could be highly valuable for the fundamental and comprehensive understanding of aging and longevity, as well as for the further translation of this knowledge to practical integrative medical applications.

21.2   The Need for an Integrated Approach to Healthy Lifespan Extension: Bridging the Gaps Between Knowledge Domains

Several important "gaps" may yet need to be "bridged" in the current variety of approaches to healthy lifespan extension to achieve integrated, practicable knowledge. One critical gap is between what may be termed *"environmentalist" and "internalist" approaches* to healthspan extension. On the one hand, it is often assumed that environmental and lifestyle factors alone are sufficient to affect healthy lifespan, disregarding genetic composition, the inner structure and function of the body. On the other, there is a "genetic" or "biological deterministic" approach that assumes the strict genetic or biological determination of the lifespan from birth that virtually cannot be influenced by environmental factors, and that can only be affected by internal invasive manipulations. There is a clear need to bridge this gap through the study of physiological, in particular metabolic, neuro-hormonal and epigenetic influences on the lifespan and healthspan, which recognizes the vital regulatory role of the environment on gene expression and internal physiological function [8].

Another gap that may need to be bridged is between *different types of analysis* that are often practically incompatible, for example between "omics" analysis, chiefly involving diverse biological markers at various levels of biological organization (e.g. genomics, proteomics, metabolomics, etc.) aiming to predict and personalize therapy vs. functional and clinical old-age "frailty" analysis and intervention, or between *molecular-biological, energy-metabolic and functional-behavioral evaluations and interventions*. A stronger alliance between these fields may be desirable. There may accrue a great therapeutic benefit from introducing "omics" type of analysis, its predictive and personalized philosophy for old-age frailty evaluation and treatment. And conversely, the researchers and developers of omics biomarkers may need to be more strongly involved in the problems of aging, to realize the critical need to address fundamental degenerative aging processes in order to alleviate virtually all health conditions, including those they are currently working on.

There is also a need for a stronger connection between *diagnosis and therapy* aimed at healthspan extension, or between *longevity factors analysis and therapeutic interventions*. There is often a deficit of interrelation between these areas. The research of "biomarkers of aging" and "longevity factors" is often descriptive, with uncertain implications for clinical practice. On the other hand, anti-aging (geroprotective) and healthspan-extending medicine approaches are often strongly empirical

and "prescriptive," testing for a variety of potential interventions, without a former comprehensive factor analysis, with the aim to empirically establish potentially effective treatments. There is a need for stronger interoperability between these areas. By providing an input for therapeutic interventions from population-based aging and longevity factor analysis, it may be possible to provide a broad evidential database for further experimentation in regenerative and geroprotective medicine, as well as shorten the pathway between longevity factor analysis and experimentation. The results of experiments may in turn immediately feed back to refine data collection and analysis, accelerating the process of discovery.

For testing potential anti-aging and healthspan-extending interventions, it appears to be critical to better relate among *different research models*, that may include population, individual, human, animal, culture, cell or molecular models. Often, studies are conducted at different levels of biological organization, with a disregard of other levels. There is an apparent need for an integrative approach, spanning across the relevant scales, using a wide array of physiological, environmental, genetic and epigenetic parameters. For actual human treatment, the human being as a whole should be the focus, with a special attention given to personalized factors characteristic of individual subjects, and selecting the most informative factors. Other models and levels could be studied as supplementary. Diverse integrated data from various levels of organization could enable the creation of truly holistic models for predictive diagnostic evaluation and preventive therapeutic intervention for human subjects. There may be a need to have a "common language" (e.g. non-dimensional measures) to describe the different model systems in common terms, that may be applicable for any system [9].

Of course, it must also be noted that the costs for such a comprehensive data collection and experimentation will likely be high, and funding will always be an issue. It may also be suspected that collecting and analyzing too much and too various data may become unwieldy (whatever the available computational power), and some simplification, abstraction and synthesis may be required. Yet, in any case, the more data can be available – the easier it will be to filter and simplify it.

Yet, the gaps that need to be bridged to achieve practicable knowledge of anti-aging and healthspan-extension do not only concern different types of biological analysis, but extend wider. The research of aging and lifespan and healthspan extension is not just a theoretical scientific or purely biological subject, but in many ways a technological subject, where the capabilities of biological research and manipulation are largely determined by technological capabilities. Virtually all technological fields can be ultimately enlisted for solving the problem of degenerative aging and for extending healthy lifespan. These would include such technological areas as novel measurement modalities (including comprehensive physiological vitality measurements, and a vast array of cell-based and molecular measurements), synthetic biology, nanotechnology and micro-fabrication, as well as advanced computational, modeling and visualization capabilities. *"Technological convergence" and "cross-fertilization"* may be key concepts for tackling the problem of aging.

But the solutions should not remain at the stage of fundamental research in the lab. Another key concept may be *"clinical translation"* understood as the process of

translating fundamental scientific research to its application in clinical practice, including all the stages of research and development: from studies on cells and tissues, through animal studies and human trials, up to marketing, production and distribution. The future translation into clinical practice should always be kept in mind as a primary objective. The studies of aging are not just academically intriguing (and they are), but also have a clear purpose – to improve health for the elderly, eventually for all of us. The translation from fundamental research to clinical practice is often difficult, and not only due to scientific and technological hurdles, but often also because of societal constraints, such as lack of social interest and investment or inefficient regulation and distribution. Careful thought should always be given for the facilitation and optimization of the translation process to make aging-ameliorating, life and health-extending therapies available to all of us.

Indeed, biomedical aging amelioration and life and healthspan extension are often considered just and only as scientific or technological problems. Yet, in fact, the development, translation, application and access to treatments designed to ameliorate degenerative aging processes and extend healthy lifespan will involve a vast host of *social issues and implications*, including both hindering and facilitating impact factors that will require comprehensive analysis and debate. Hence, it will be necessary to give due consideration to *social factors*, such as legislative, administrative, communal, economic, demographic, educational and even ethical factors that largely determine the *development* of lifespan and healthspan extension research and *translation* of this research into practice. Some of the issues include: regulatory requirements for the short and long-term testing and approval of potential geroprotective treatments; criteria for their efficacy and safety; administrative and organizational requirements needed for the active promotion of healthspan extension research and practice; incentives for the rapid development and translation of the results of this research into medical and clinical practice; provisions for the universal distribution of healthspan-extending technologies to the public, and much more. All these issues will yet need to become the subject of a broad and intense academic and public debate, including political debate [10].

Within the general need for stronger social involvement, there is an urgent need to educate more specialists who will be able to contribute to the various areas of aging and healthspan extension research. There is an even prior need to educate the broader student body and wider public on the importance of such research to prepare the ground for further involvement. Thanks to such *broad education*, many more new promising studies may emerge. The increased knowledge of the field may increase the demand for therapies, which may in turn increase the offer. Even when the therapies are available, it should be the general public who should use them, hence their willingness to embark on and adhere to a preventive anti-aging and healthspan-improving regimen, their ability to intelligently choose and apply effective and safe therapy, will be vital for its successful application. Therefore comprehensive and wide-ranging "patient and consumer education," and moreover "citizen scientist" and "do-it-yourself maker" education in the field of aging and healthspan extension will be necessary. Such education is currently very limited. In practical terms, globally there are very few centers or dedicated structures to coordinate

knowledge exchange and dissemination on biology of aging and healthy lifespan extension. There are even few courses in this field in university curricula around the world. There is a need for more courses and training materials on the subject, in order to make the narrative on biology of aging and healthy lifespan extension an integral part of academic curriculum and public discourse.

21.3   The Problem of Clinical Definition of Degenerative Aging: Bridging the Gaps in Scientific Understanding and Communication

One of the major factors hindering the discussion of aging amelioration, lifespan extension and healthspan extension research, development and application, may be the basic *deficit of definitions*. What is it exactly that we wish to ameliorate, and what is it exactly that we wish to extend? Such agreed definitions appear to be among the necessary conditions for the communication, dissemination and advancement of the field. But such agreed definitions are currently lacking.

There is a growing realization that in order to combat the rising aging-related ill health and improve the healthy lifespan – the research, development and distribution of anti-aging and healthspan-improving therapies need to be accelerated [11]. It was suggested that one of the accelerating factors could be the general recognition of the degenerative aging process itself as a medical problem to be addressed [12]. It has been assumed that such a recognition may accelerate research, development and distribution in several aspects: (1) The general public would be encouraged to actively demand and intelligently apply aging-ameliorating, preventive therapies; (2) The pharmaceutical and medical technology industry would be encouraged to develop and bring effective aging-ameliorating therapies and technologies to the market; (3) Health insurance, life insurance and healthcare systems would obtain a new area for reimbursement practices, which would encourage them and their subjects to promote healthy longevity; (4) Regulators and policy makers would be encouraged to prioritize and increase investments of public funds into aging-related research and development; (5) Scientists and students would be encouraged to tackle a scientifically exciting and practically vital problem of aging. Here we would leave aside the question whether this medical condition should be termed a "disease," a "syndrome," a "risk factor," an "underlying cause" or some other designation. Here "the aging process as a medical condition" just means a processes that can be materially intervened into, improved (treated) and even eliminated (cured) by medical means.

Yet, in order for degenerative aging process to be recognized as such a diagnosable and treatable medical condition and therefore an indication for research, development and treatment, a necessary condition appears to be the development of evidence-based diagnostic criteria and definitions for degenerative aging. So far, there are still no such commonly accepted or formal criteria and definitions. Yet

without such scientifically grounded and clinically applicable criteria, the discussions about "ameliorating" or even "curing" degenerative aging processes will be mere slogans. Indeed, how can we "treat" or "cure" something that we cannot even diagnose? It may even be found that such criteria are explicitly or implicitly required by several major international and national regulatory and policy frameworks, such as the International Classification of Diseases (ICD), the WHO Global Strategy and Action Plan on Ageing and Health (GSAP), the European Medicines Agency (EMA), the US Food and Drug Administration (FDA), and others [13]. Such frameworks are thirsting for evidence-based criteria for the effectiveness of interventions for "healthy aging." Nonetheless, nobody has yet done the necessary work of devising such comprehensive evidential criteria. It may seem that the problem has not been solved just for the lack of enough trying. But it must be admitted that the problem is not at all easy even to dare to take on. Many formidable methodological challenges may arise in attempting to develop commonly acceptable diagnostic definitions and criteria for degenerative aging. But try we must!

A major challenge is related even to the *semantic understanding* of the term "degenerative aging." The term "degenerative" may imply both the present *state of degeneration and the process leading to the state of degeneration*. This distinction may have major implications for intervention, respectively implying a curative approach to the already manifest state of degeneration (a late stage intervention) as opposed to a preventive approach to block a process leading to degeneration (an early stage intervention). It may be particularly helpful to explore "degenerative aging" in the latter sense, as a process leading to degeneration that can be prevented. Yet, many questions remain with such a definition. Obviously, not every time-related change leads to degeneration and disease, and some aging-related changes may be beneficial for the person (e.g. the proverbial "wisdom of age" [14]). Obviously also, many changes leading to age-related degeneration begin at conception, and may be necessary concomitants of the processes of growth and development. Then for which processes and at which stages is intervention warranted? In other words, *which aging processes can be considered truly "degenerative"* (leading to degeneration) that would require preventive intervention? Several sets of such candidate processes have been proposed [7], yet there is still little empirical evidence that intervention into them will have clinical benefits. The potential interrelation and regulation of these various processes are also uncertain. In this regard, a practical worry is that under the title of "prevention" and "early intervention" – drugs and other treatments will be sold to young and relatively healthy individuals without a real need and without proven benefits in actually preventing degenerative states and/or extending healthy lifespan. A more thorough, *quantitative and formal understanding of old-age degeneration (frailty) as a physiological state* is required as well. Should it be measured as a lack of function and adaptation to the environment? Should it be evaluated as an impairment of homeostatic or homeodynamic stability? [15] Should it be presented as an index or as physiological age?

Each of these options would raise a host of questions of its own, whose mere mentioning would go far beyond the scope of this work. To provide evidence-based answers to those questions, *vast empirical and theoretical research* yet appears to

be needed to establish diverse age-related changes as predictors of adverse age-related outcomes (such as multi-morbidity and mortality) as well as evaluate the effects of various preventive and curative treatments on those outcomes. Based on such data, better formal, clinically applicable models and criteria of degenerative aging as a process and as a state can be developed.

It may be stated that the development of *clinical definitions and criteria for degenerative aging*, and the corresponding definitions and *criteria for the effectiveness of anti-aging and healthspan-extending therapies* would be the penultimate "gap" in the common scientific understanding of the problem that needs to be "bridged" before proceeding toward its practical solution. This would in fact mean bridging multiple "gaps" between multiple conceptions and approaches to the problem of aging amelioration and healthspan improvement, to achieve a good level of mutual understanding and agreement. With the current diversity of theories, approaches, models and prospective remedies, it may be yet a long road ahead before such a level of *common understanding and agreement* is reached. It may not be necessary that every researcher should accept a standard universal metrics and agree on most of the fundamental concepts and processes (as it has been accomplished in mathematics and physics), but at least some degree of commensurability for the field may be desirable. Such commensurability would not mean dictating the same approach to all, or even worse, prescribing the same measures and treatments for all, but rather providing a common language that would enrich general discourse and creativity in the field. The continuous active consultation and debate on these issues may be key to progress.

21.4   Some Particular Methodological Issues for Anti-Aging and Healthspan-Improving Diagnostic and Therapeutic Criteria

The present work could not presume to even begin to provide any definitive answers for the above methodological problems. It does not provide any specific building blocks for the bridges between the various areas that may need to come into closer, more impactful synergistic contact. This work is only intended to attempt to emphasize some of those potential problems and stimulate their discussion (in addition to any discussions of these issues that may take place anywhere else). If it succeeds to enhance this discussion and improve this knowledge even slightly, then it has fulfilled its purpose.

As a way of a conclusion, which is not really a conclusion, but just an attempt to raise further discussion, a few particular challenges may be listed, including some of the earlier points, problems and gaps. This list includes some of the major concerns for the development of diagnostic and treatment criteria against degenerative aging and for healthy lifespan extension, the knowledge of which yet needs to be improved. These can be tentatively classified as follows: (1) establishing definitions,

(2) minimizing confounding factors, (3) improving informative value, and finally (4) improving the practical utility of the criteria. This could also be the putative priority order at which the problems can be tackled. (It must be reemphasized that these propositions are only intended to stimulate academic and public discussion.) Within the larger categories, several sub-categories may be suggested.

For the first category – "**establishing definitions**" – it is important both to establish basic terms and definitions, as well as to define specific clinical benefits and end points of anti-aging and healthspan-improving treatments. As often exemplified in medical history, e.g. for sarcopenia, clear basic definitions and clinical endpoints are indispensable for the development of a new medical field [16]. *Establishing basic terms and definitions* may include some of the questions raised above. For example, should "degenerative aging" be understood as a process or as a state? Or is "healthy aging" a helpful term for developing clinical measurements of aging, considering that most aging processes increase morbidity? Should we instead speak in terms of *"healthy longevity" as opposed to "degenerative aging"*? Such definitions are needed for the basic communication and mutual understanding.

In turn, clearly and consensually *defining* c*linical benefits* from anti-aging and healthspan-improving treatments appears to be absolutely indispensable for the development of evidence-based diagnosis and therapy of degenerative aging as a treatable medical condition. Just and only biomarkers of aging may not be sufficient to provide clinically applicable diagnostic criteria for "degenerative aging" or for interventions against it. For example, as many studies of Alzheimer's disease have shown, treatments can modify "biomarkers" of the disease very well (in some types of models), but do little or nothing clinically beneficial for actual human patients [17]. Hopefully, this problem can be avoided when addressing general aging as a medical condition. There is a need to precisely define measurable *clinical* end points, demonstrating evidential clinical benefits, especially for the *reduction of age-related multimorbidity*. The combination of structural biological and functional behavioral parameters may increase diagnostic capabilities. In practical terms, the establishment of clinical benefits would also mean more direct and fast transitions between descriptive measurements and experiments (in both directions), "bridging the gap between longevity factors analysis and therapeutic interventions."

Secondly, insofar as aging is an extremely complex process, involving both internal physiological and external environmental factors, "**minimizing confounding factors**" in diagnosis and therapy of aging appears to be a daunting, yet crucial task. In this regard, a primary question may concern the very *relevance of particular studies to human patients*, both actual and potential. How are particular research models relevant or close to apply to humans generally or to individual humans particularly? How likely are those models to lead to human applications? It may be desirable to develop some formal and quantifiable measures for the closeness of relevance range for research models, according to biological levels of organization, types of experimental models, or predictive values of computational models.

Moreover, the applied longevity research may need to be eventually relevant not just for humans generally, but for older persons particularly. Hence the *focus on older persons* appears to be essential for developing evidence-based effective

"anti-aging" therapy. The clinical benefits need to be evaluated, or at least confidently predicted, for the primary target population – the older frail persons, rather than the younger and healthier ones who may exhibit entirely different biological responses [18]. In practice, often the results of clinical trials done in young and healthy subjects are then uncritically projected to old and frail subjects. Further strong confounding effects may be introduced when attempting to apply treatments tested in young patients with a single disease, on old patients with multiple diseases. Aging biomarkers and treatments need to be examined in the actual aged, multi-morbid and frail patients as reflecting the most common clinical settings, rather than relying on potentially misleading hypothetical projections from the young and healthy to the old and frail people. The specific examination of older persons is in fact an explicit requirement of "The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)" and of the World Health Organization [19], but it is too seldom accomplished in practice. In case direct applicability cannot be shown, at least some relevance should be considered for the aging process and aging subjects.

Another critical concern appears to be the *long term consideration* of treatment effects. The clinical criteria and biomarkers, as well as resources available to the organism, need to be considered for the long term. Thanks to long-term evaluation it may be possible to control for effects of over-stimulation, as well as rule out transient compensatory and psychosomatic effects and seeming short-term benefits that may arrive at the expense of long-term deterioration. In particular, seeming short-term "rejuvenation effects" may increase mortality and shorten the actual lifespan [20]. Such long-term follow up and analysis are quite rare in the field of "anti-aging medicine" as it is commonly practiced and, truth be told, also for other medical fields.

These are some of the potential confounding factors that may obscure or even negate the effects of truly effective anti-aging and healthspan-improving therapies. This list is far from being exhaustive and may be expanded and more specifically elaborated. Yet, with any classification, confounding factors should be controlled for as much as feasible. Of course, some confounding effects are virtually unavoidable, but this should not discourage or abolish the pursuit of longevity research, attempting to ameliorate the harms that could be ameliorated, yet always keeping in mind the *possibility of confounding influences and thus misleading recommendations*.

Thirdly, in order to control for confounding factors vs. truly beneficial therapeutic effects, specific informative value measures are needed to quantify those effects, as opposed to confounding noise, with the aim of "**improving the informative value**" of diagnostic and treatment parameters. Such informative value measures are first of all needed for the *selection* of diagnostic parameters and therapies. As almost any age-related biological parameter may be considered a "biomarker of aging," and almost any physiological intervention can in some way affect the aging process, there is a need to select the most predictive and economic biomarkers and intervention effects, for the population as well as for individuals, with reference to the aging process and aging-related diseases [21].

The informative value measures are also needed for the *integration* of diagnostic parameters and therapies. Criteria for degenerative aging may not be only molecular and cellular, but at every level of biological organization – from the molecular to cellular to tissues and organs, to the entire organism and to the organism's interrelation with the environment – that need to be integrated [22]. Moreover, these criteria may not necessarily be chemical and biological, but can also be physical, in particular as relates to various resuscitation technologies as applied to the elderly, such as hypothermia and suspended animation [23], oxygenation and energy metabolism [24], electromagnetic stimulation [25]. Social (engagement) and psychological (motivation) criteria also need to be added. Among other implications, this drive for integration would also mean "bridging the gaps" between "environmental" and "internal" evaluations and interventions, between "multi-omics" and "functional frailty" analysis, and between different, currently often incomparable "research models." Quantifiable integrated models of such factors may be desirable, as difficult as their creation may be.

Insofar as the organism reacts as a whole, in an integrated and interrelated manner, individual biomarkers may not be indicative of the process or state of degeneration, and individual "magic bullet" therapies may not be effective for the amelioration of this process, but need to be considered in combinations, or ideally in a systemic balanced or "homeostatic" way – otherwise interventions on particular biomarkers and pathways may exacerbate other biomarkers and pathways, and disrupt the system as a whole. The general methodology for the evaluation of the effects of multiple integrated therapeutic agents and risk factors (including biomarkers of aging) on multiple integrated adverse effects and age-related diseases (multimorbidity) needs to be improved, to allow the evaluation of non-linear, cumulative or synergistic effects [26].

Quantifiable informative values may also be desirable to establish the balance of the therapies' *safety vs. efficacy* (actual or potential). For any potential intervention, including anti-aging and healthspan-improving interventions, there is an essential need to weigh potential benefits against potential safety risks. These values are often antagonistic, as therapies may be safe but ineffectual, or potentially effective against particular conditions but carrying risks for severe side effects. Quantifiable balance relations between efficacy and safety may be hoped for to create novel anti-aging therapies that could practically benefit human beings.

Finally, the ultimate measure of the anti-aging and healthspan-improving diagnostics and therapies would be their "**practical utility**" for as many people as possible. In this regard, *standardization* of anti-aging diagnostics and therapies appears to be a major requirement. Particular batteries of assays and interventions are usually related (and potentially biased) to particular theories, research agendas, academic schools and commercial interests. There is an apparent need to allow pluralism of investigation, discovery and application, while maintaining rigorous standards, based on the scientific method, that would facilitate interoperability and common discourse and utility. Consensus standards often emerge as a result of data-sharing [27], which may become a practical challenge of its own. Beyond developing agreeable standards, extensive thought should also be given to ways to improve

adherence and compliance with those standards, once again keeping in mind the need both for *pluralism and rigor*. Very often, highly beneficial recommendations are not rigorously followed, and conversely harmful requirements are imposed against pluralistic choice. Hopefully, the field of anti-aging and healthspan extension could avoid both extremes.

And perhaps one of the most critical and complex sets of evaluation criteria may concern the a*ffordability and cost-effectiveness* of new anti-aging and healthspan-improving diagnostics and therapies. Such considerations may be decisive for the investment in and development of new anti-aging and healthspan-extending therapies. As the experience of many years of fund-raising for life-extension research and development often teaches, even for the most humanitarian causes, investments and donations are largely decided by considerations of actual costs vs. potential profit returns. On the positive side, an expectation of profit may encourage entrepreneurs to develop and distribute new therapies. Still, as the goal of healthspan care is not just to produce profit for the providers, but to improve actual healthspan for as many people as possible, the considerations of cost-effectiveness should involve not only profitability, but also affordability for the population and the non-monetary improvement of well-being, while still providing a return on investment. In terms of the general practical utility, the costs of diagnostic biomarkers assays and therapeutic interventions may become prohibitive or even impractical for use by most people in the world. Hence, there may be a need to focus on such therapies, biomarkers and functional assays that may be most affordable, especially those that are already routinely used in clinical practice, while still encouraging the development of more sophisticated assays and therapies, that may become more accessible in time, and specifically devising means to increase their accessibility [28]. The subject of cost-effectiveness analysis for the anti-aging and healthspan-improving medicine is only nascent [29], and must be developed.

The issue of "affordability" actually involves most of the problems and "gaps" between "science and technology" (the problem of translating fundamental research to practical affordable therapies), between "science, technology and society" (making the therapies widely available, and not only "for the rich and powerful"), as well as between "research and education" (making the knowledge of the field more accessible and wider spread, to catalyze even more knowledge generation). The main overarching question to ask in this regard is: "How can we make the best, most effective therapies available (affordable) as fast as possible to as many as possible?" The details are to be established in a broad academic, public and political discussion [30].

21.5   Motivation for Further Discussion

These are some of the issues that we may need to know how to solve in order to treat degenerative aging as a medical condition and improve healthy lifespan in a scientifically grounded way. These are rather complex issues, yet in order to successfully

achieve healthy lifespan extension for the general population, they need to be collectively tackled, "not because they are easy, but because they are hard." All these issues must become a subject of massive and pluralistic consultation, involving scientists, policy makers and other stakeholders. Thanks to such a consultation it may be possible to develop agreeable scientific clinical criteria for degenerative aging that could improve diagnostic capabilities and allow better informed clinical decisions. Such criteria can stimulate further research and development of effective, evidence-based anti-aging and healthspan-extending therapies, treating the underlying processes of aging-related diseases rather than their particular symptoms. In such a broad consultation, various diagnostic and therapeutic approaches to aging amelioration and healthy lifespan extension may be brought together, their relative merits and drawbacks may be compared, points of their convergence may be clarified. Such a discussion may facilitate the creation of a comprehensive and actionable roadmap toward healthy lifespan extension. It is hoped that the present work will contribute to raising the demand for more of such discussion, research and knowledge.

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