The Fountain of Youth Revisited: Regulatory Challenges and Pathways for Healthspan Promoting Interventions

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ABSTRACT

For centuries, humankind has tried to evade the inevitability of aging and death by searching for the elusive fountain of youth, but the search has yielded only disappointment, false hopes, and charlatans. In the last decade or so, however, real progress has been made in the scientific understanding and modulation of the aging process. This progress has come about from a new paradigm called the "geroscience" hypothesis, which recognizes that aging is the number one risk factor for all chronic diseases. Therefore, there may be some intrinsic aging factors that can be targeted with interventions, rather than the futile attempt to extend healthy life by treating one chronic disease at a time. Utilizing genetic and other data showing that the aging process is malleable and can be slowed, scientists have recently identified key aging processes that underlie most chronic diseases and the symptoms of aging, such as frailty and cognitive decline. The next step has been to identify potential interventions that can affect or slow those aging processes, and a number of such candidate "geroprotectors" have now been identified, mostly in animal studies but in some cases in humans. The scientific progress that has been achieved in the past decade has advanced a number of promising interventions to the point where they are now ready for human clinical trials, regulatory approval and commercialization. Yet, just as the scientific advances have made significant healthspan extension a realistic possibility for the first time in human history, regulatory and legal impediments have arisen to impede the further advancement of such interventions. Specifically, because the FDA drug approval process is based on prevention and treatment of diseases, and aging is not recognized as a "disease," there is no obvious regulatory approval pathway for therapeutics that may slow aging and extend healthspans. This paper describes this dilemma, identifies a number of alternative regulatory and commercialization pathways for healthspan extending interventions, and argues that the Food and Drug Administration (FDA) should take a more proactive role in expediting the clinical trials and regulatory approval of healthspan extension agents.

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> "As we live our precarious lives on the brink of the void, constantly coming closer to a state of nonbeing, we are all too often aware of our fragility."
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> - Iris Murdoch, Nuns and Soldiers
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> "What you shall seek, you shall never find. For the Gods made man, they kept immortality for themselves."
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> -The Epic of Gilgamesh (2100 B.C.)

I. INTRODUCTION

The realization and acceptance of individual mortality is one of the most difficult and common challenges human beings face. For centuries, humans have resisted their own mortality by searching for the elusive Fountain of Youth.[1] After centuries of futility, that search may finally be bearing fruit, not in providing immortality, but in significantly extending both the quality and length of human life. Consider some relatively recent headlines. On February 21, 2011, *Time* magazine's cover proclaimed, "2045: The Year Man Becomes Immortal."[2] Four years later, the cover story claimed, "This Baby Could Live to be 142 Years Old."[3] Not to be outdone, Newsweek's cover on July 24, 2013 stated, "You *Can* Live Forever,"[4] followed by a cover two years later that proclaimed "Never Say Die: Billionaires, Science and Immortality."[5] Moreover, various news sources have recently reported that, "[t]he first person to live for 500 years has already been born."[6]

What is going on here? Are humans finally on the cusp of immortality? Has the legendary Fountain of Youth been found? Or is this just more hype and quackery that has given anti-aging such a bad reputation for decades, if not centuries? The answer is somewhere in the middle. Over the past decade or so, there has been real scientific progress in understanding the aging process, how it relates to chronic disease, and how we might intervene to extend both the duration and quality of human life, the

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[1] JIM MELLON & AL CHALABI, JUVENESCENCE: INVESTING IN THE AGE OF LONGEVITY 18 (1st ed. 2017) ("Throughout history, a wide variety of people, ranging from Taoist sages, medieval alchemists, and Spanish conquistadors, have searched for a literal or figurative *fountain of youth*, an elixir which would restore youth to the aged.") (emphasis in original).

[2] *2045: The Year Man Becomes Immortal*, TIME MAGAZINE, Cover (Feb. 21, 2011), http://content.time.com/time/covers/0,16641,20110221,00.html [https://perma.cc/DRK9-R5DV].

[3] *This Baby Could Live to be 142 Years Old*, TIME MAGAZINE, Cover (Feb. 23, 2015), http://time.com/magazine/us/3706680/february-23rd-2015-vol-185-no-6-u-s/ [https://perma.cc/NEQ9-H6TV].

[4] *You Can Live Forever*, NEWSWEEK, Cover (July 24, 2013), https://www.newsweek.com/2013/07/24/issue.html [https://perma.cc/2UAK-7LLJ].

[5] *Silicon Valley Is Trying to Make Humans Immortal—and Finding Some Success*, NEWSWEEK, Cover (Mar. 13, 2015), https://www.newsweek.com/2015/03/13/issue.html [https://perma.cc/X8EH-NHHV].

[6] *See, e.g.,* Simon Shepherd, *The First Person to Live for 500 Years Has Already Been Born*, MSN NEWS (Feb. 20, 2018), https://www.msn.com/en-in/news/techandscience/the-first-person-to-live-for-500-years-has-already-been-born/ar-BBJlou7 [https://perma.cc/JWE8-YHW7].

combination of which is known as "healthspan."[7] None of these potential interventions will provide immortality or even extend human life to 500 years, at least in the foreseeable future, but they do have the potential to significantly improve human healthspans.

As Dr. James Kirkland of the Mayo Clinic recently wrote, "[a] new era in the basic biology of aging may be beginning, a time in which we can begin to translate findings from the basic biology of aging into a range of clinical applications."[8] Moreover, a recent edition of the *Journal of the American Medical Association (JAMA)* dedicated three articles on the issue of aging and increasing healthspan, seeking to educate physicians and regulators on the impressive progress and pending availability of interventions that extend human healthspans.[9] However, just as the science of aging has finally made real progress, a new obstacle has emerged through the lack of a proven regulatory pathway for getting such interventions to market.[10]

The current regulatory environment, overseen by the United States Food and Drug Administration (FDA), is primarily designed for the approval of drugs, biologics and medical devices that treat "diseases." However, FDA does not currently define aging as a disease,[11] and therefore an intervention that is intended to delay aging may lack an obvious regulatory approval pathway. As some leading scientists in this field recently wrote:

> One major challenge for improving human health by treating aging processes is that from a regulatory perspective (eg, the US Food and Drug Administration) there is no indication that is similar to targeting aging. Even if safe and effective drugs are available, health care payers will be reluctant to pay for such treatment without regulatory approval. Consequently, for now, drug companies are reluctant in invest in treatments targeting aging. Regulatory changes . . . . will be needed to start making major strides in improving human health.[12]

An aging-related regulatory endpoint is not the only challenge to regulatory approval of agents that extend healthspan. Medical interventions often undergo clinical testing for specific disease indications using biomarkers to monitor safety and efficacy.[13] This system works well when applied to acute diseases in which symptoms appear rapidly and the effect of the medication is similarly relatively rapid. It is less

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[7] *See* Neil Savage, *Growing Up*, 552 NATURE S57, S57 (2017) ("Most anti-ageing researchers are . . . hoping to extend the 'healthspan,' the period in which people remain disease-free and vigorous, shortening old age and perhaps adding a decade or two to life.").

[8] James L. Kirkland, *Translating the Science of Aging into Therapeutic Interventions*, 6 COLD SPRING HARBOR PERSP. MED. 1, 9 (2016).

[9] *See* Nir Barzilai et al., *Aging as a Biological Target for Prevention and Therapy*, 320 JAMA 1321, 1321 (2018) [hereinafter "Barzilai 2018"]; S. Jay Olshansky, *From Lifespan to Healthspan*, 320 JAMA 1323, 1324 (2018); Tamara Tchkonia & James L. Kirkland, *Aging, Cell Senescence, and Chronic Disease*: *Emerging Therapeutic Strategies*, 320 JAMA 1319, 1319 (2018).

[10] Ilaria Bellantuono et al., *Find Drugs that Delay Many Diseases of Old Age,* 554 NATURE 293, 293 (2018).

[11] Celine E. Riera & Andrew Dillin, *Can Aging Be 'Drugged?'*, 21 NATURE MED. 1400, 1404 (2015).

[12] Barzilai 2018, *supra* note 9, at 1322.

[13] U.S. FOOD & DRUG ADMIN., *FDA Facts: Biomarkers and Surrogate Endpoints*, https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm606684.htm (last visited July 5, 2018).

ideal when studying diseases with multiple indications and a lengthy time progression, and which lack validated biomarkers.[14]

The current FDA regulatory paradigm therefore stands as an obstacle to the commercialization of promising interventions that directly extend the quality and duration of human life. Of course, most drugs and other products approved by FDA indirectly improve lifespan and healthspan by treating individual diseases that cause premature morbidity and mortality. But the new generation of emerging treatments that directly extend healthspan, known as geroprotectors,[15] do not fit the current FDA drug approval paradigm. It is ironic that, after searching for treatments for aging unsuccessfully for centuries, now that science has finally identified some real candidates for slowing aging, law and regulation, a human-made invention, stands as the principal barrier to extending the quality and length of our lives. New approaches and innovations are needed in the existing regulatory system to allow these promising interventions to get to market in a timely and cost-effective manner. That is the challenge that this article seeks to address.

This article begins with a brief history of humankind's quest for immortality and anti-aging elixirs in Part II, demonstrating why the image of anti-aging research has been so tainted. Part III then summarizes the exciting recent scientific research in extending human healthspan, while providing realistic limitations and caveats for the promising research that has been reported to date. Part IV describes the regulatory pathways and challenges to moving such interventions to the market. Part V offers several different alternative regulatory and commercialization pathways, along with their limits and qualifications.

II. THE PERPETUAL HUMAN QUEST FOR IMMORTALITY

The desire to extend human life, and more significantly, the quality of human life has been around as long as humans have understood their own mortality.[16] The self-aware human has a hard time grappling with the reality of the finality of death,that the conscious self will someday cease to exist. For centuries, people have strived for eternal life through the promises of religion and a heavenly eternity after life on earth comes to an end. More recently, some people have turned their hopes to future scientific breakthroughs, such as cryonics, head transplants, or uploading human minds to nourish their hopes for immortality. Over the decades, others have placed their faith in promised cures that would slow or halt the aging process.

The study of anti-aging and subsequent strategies for dealing with aging are not new. Unfortunately, virtually every historical attempt to understand and control aging until very recently has failed. Many of the schemes have been, at least in retrospect,

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[14] *See e.g.,* U.S. FOOD & DRUG ADMIN, STATEMENT FROM FDA COMMISSIONER SCOTT GOTTLIEB, M.D., ON ADVANCING THE DEVELOPMENT OF NOVEL TREATMENTS FOR NEUROLOGICAL CONDITIONS; PART OF BROADER EFFORT ON MODERNIZING FDA'S NEW DRUG REVIEW PROGRAMS (2018), https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm596897.htm [https://perma.cc/MKZ6-66X2]. Here, the FDA acknowledged that the single endpoint requirement did not work with Alzheimer's disease, and modernized it to allow trials to be more dynamic.

[15] Bellantuono et al., *supra* note 10, at 293.

[16] *See generally* BILL GIFFORD, SPRING CHICKEN: STAY YOUNG FOREVER (OR DIE TRYING) (1st ed. 2015).

laughable, usually promoted by quacks, charlatans, or self-deluded believers, and consequently have done much to cement the reputation of this area of research as fringe medicine.[17] For example, a businessman named John Brinkley became one of the richest men in America in the early 20th century by marketing a rejuvenation treatment that involved implanting fresh goat test testicles into the scrota of middle-aged men.[18] Dozens of patients died during this procedure, and many hundreds more were maimed, but that did not stop thousands of men (and a few women) from paying for such a dangerous and ultimately ineffective treatment for aging.[19]

The long history of faux anti-aging treatments has continued into the present day. One needs to just walk down a pharmacy aisle and look at the labels on various facial creams and other cosmetics claiming "anti-aging" benefits to see how common such claims have become. Various celebrities such as Suzanne Somers hawk a variety of hormone and supplement treatments that purport to slow or stop aging in magazines, at alternative health conferences, and on late night TV infomercials.[20] The scientific support for these treatments is limited or non-existent. Although FDA has taken enforcement action against some of these misleading claims for lacking substantiation, regulators cannot keep up with the blizzard of unproven anti-aging claims.

The bogus claims of anti-aging interventions pair with various failed attempts of legitimate scientists to validate anti-aging benefits of once promising interventions to give the whole field of anti-aging a bad reputation. For example, a highly publicized study published in 2006 found that resveratrol, a chemical found in red wine, had important longevity benefits when tested in mice.[21] While additional research continues to show tantalizing anti-aging potential for resveratrol and similar compounds,[22] and resveratrol remains one of the best-selling "anti-aging" supplements on the market, attempts to develop a proven effective anti-aging treatment in humans based on this compound have been frustrated to date due primarily to metabolic differences between humans and rodents.[23] Many other promising interventions, from human growth hormone (HGH) and testosterone therapy, to interventions involving diet, fasting, caloric reduction and exercise, have produced some suggestive results but have yet to provide a silver bullet to slow, stop or reverse aging.[24]

Notwithstanding the lack of any proven success with anti-aging treatments to date, these myriad historical attempts to control the aging process have served two important functions. They highlight the universal desire to better and even extend life, and they have produced valuable information for gerontologists to put the puzzle together for future generations. We are now in a position in which top researchers have strategies

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[17] *Id.* at xiv–xvi.

[18] *Id.* at xvi.

[19] *Id.*.

[20] *Id.* at 41–52.

[21] J.A. Baur et al., *Resveratrol Improves Health and Survival of Mice on a High-Calorie Diet*, 444 NATURE 337, 337 (2006).

[22] *See*, *e.g.*, Nathan L. Price et al., *SIRT1 Is Required for AMPK Activation and the Beneficial Effects of Resveratrol on Mitochondrial Function*, 15 CELL METABOLISM 675, 676–77 (2012).

[23] *See* GIFFORD, *supra* note 16, at 216–219, 307–08.

[24] *See generally id.*

to combat aging but are being met with strict regulatory hurdles, perhaps a residue of the failures of the past.[25]

III. SCIENTIFIC PROGRESS IN STUDYING AND EXTENDING HEALTHSPAN

To emphasize the importance of quality in addition to quantity of additional years of life, but likely also to set apart recent scientific progress from the bluster and puffery of past anti-aging claims, scientists refer to the recent efforts to slow aging as enhancing *healthspan*.[26] Healthspan research seeks primarily to add life to years rather than years to life, although the secondary effect may also be to extend lifespan. The recent progress in healthspan research falls into two broad categories. The first is progress in understanding the factors that limit the quality and quantity of life as we grow older (see subsection A below). The second category of progress is in applying this improved understanding of the aging process to identify promising specific interventions that recent evidence suggests may limit aging and extend healthspan (see subsection B below).

A. Recent Progress in Understanding Aging and Healthspan

Several threads of scientific progress have propelled a better understanding of aging and opened the door to new interventions for extending healthspan. These developments are: (i) the geroscience paradigm; (ii) the revelation that the pace of aging is malleable rather than fixed; and (iii) the identification of key pathways and mechanisms mediating aging.

1. The Geroscience Paradigm

Much of the progress in understanding aging and healthspan interventions can be attributed to the "geroscience" hypothesis or paradigm.[27] The geroscience paradigm is in one sense a simple and obvious idea. Yet, it turned the effort to control aging on its head and is largely responsible for the progress and excitement that has transformed the field of aging studies in the past few years.

Previously, the problem of aging was dealt with on a disease-by-disease basis. We know that most elderly people die of one or a combination of chronic diseases such as cancer, heart disease, stroke or Alzheimer's disease, among others. The strategy until recently was to try to cure or prevent each of these diseases individually, thereby having the effect of increasing lifespan.[28] Indeed, the National Institutes of Health (NIH), the primary government funder of biomedical research in the United States, is organized into a series of Institutes that focus on a specific disease group or organ – examples include the National Cancer Institute, the National Institute of Allergy and

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[25] Sarah Karlin-Smith, *Why a Drug for Aging Would Challenge Washington*, POLITICO (Dec. 13, 2017), https://www.politico.com/agenda/story/2017/12/13/anti-aging-research-drugs-000595 [https://perma.cc/F3HS-EA8T].

[26] *See* Savage, *supra* note 7, at S57.

[27] Brian K. Kennedy et al., *Geroscience: Linking Aging to Chronic Disease*, 159 CELL 709, 709 (2014); Kirkland, *supra* note 8, at 1; Felipe Sierra, *The Emergence of Geroscience as an Interdisciplinary Approach to the Enhancement of Health Span and Life Span*, 6(4) COLD SPRING HARBOR PERSP. MED. 1, 2–3 (2016).

[28] Sierra, *supra* note 27, at 4.

Infectious Diseases, and the National Institute of Diabetes and Digestive and Kidney Diseases.[29] The problem with this siloed approach to health is that these chronic diseases are stacked one upon another in older people – many people have multiple chronic diseases, and even if an older person had only one chronic disease, they would run the gauntlet of chronic diseases and soon develop and succumb to another chronic disease even if their first disease was successfully treated.[30] Thus, this disease-by-disease strategy was swimming upstream, playing a whack-a-mole game against one chronic disease after another, and making at most minimal progress in enhancing the duration and quality of older age.

The geroscience paradigm, developed through the National Institute of Aging (NIA) and its internal and external scientists, starts with a simple observation.[31] The number one risk factor for most chronic diseases is age[32] – the risk of every chronic disease goes up dramatically with age.[33] Why is that? It doesn't necessarily have to be that way, it could be that the risk of these diseases is constant over one's life, just as is the chance of being struck by lightning. The significance of the observation that the risk of all chronic diseases goes up exponentially with age means that there is something intrinsic to the aging process that increases the risk of every chronic disease, and thereby the risk of death. If those intrinsic aging factors can be identified and attacked as a primary strategy, it may be possible to reduce the risks of all chronic disease simultaneously, thereby extending both the length and quality of life.[34] The geroscience paradigm can therefore be stated as follows: "because aging is malleable . . . and aging is also the main risk factor for those [chronic] diseases and [elderly] conditions, then addressing the basic biology of aging is likely to provide a better payoff than addressing diseases one at a time, as is often done currently."[35]

2. The Rate of Aging is Modifiable

Another key finding is that the rate of aging is not fixed but may be modified by genetic and environmental factors. In other words, the intrinsic aging process at the center of the geroscience paradigm is not constant and inevitable, but rather can be sped up or slowed. The rate of these aging processes is different for each person and can potentially be altered by gene therapy, pharmaceuticals, and future technology.[36] Of course, it has been long known that healthy diets and exercise can extend

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[29] NAT'L INST. OF HEALTH, *List of NIH Institutes, Centers, and Offices*, https://www.nih.gov/institutes-nih/list-nih-institutes-centers-offices [https://perma.cc/273V-XXNV] (last visited Nov. 5, 2018). A few of the Institutes, such as the National Institute of Aging (NIA), are more cross-cutting, but unfortunately has one of the smallest budgets in the NIH. *See* GIFFORD, *supra* note 16, at 37.

[30] *See* GIFFORD, *supra* note 16, at 36–37.

[31] Sierra, *supra* note 27, at 2–3.

[32] Luigi Ferrucci et al., *Frailty as a Nexus Between the Biology of Aging, Environmental Conditions and Clinical Geriatrics*, 32 PUB. HEALTH REV. 475, 475 (2010); Riera & Dillin, *supra* note 11, at 1400.

[33] Kirkland, *supra* note 8, at 1; WORLD HEALTH ORG., *Ageing and Health,* http://www.who.int/news-room/fact-sheets/detail/ageing-and-health [https://perma.cc/68ER-Z2CM].

[34] Riera & Dillin, *supra* note 11, at 1400.

[35] Sierra, *supra* note 27, at 3.

[36] *See* Daniel W. Belsky et al., *Quantification of Biological Aging in Young Adults*, 30 PROC. NAT'L ACAD. SCI. E4104, E4104 (2015).

healthspan, but there is now a growing body of additional evidence that aging can be sped up or slowed by a variety of factors.[37]

Some of the evidence that the basic aging process is malleable comes from animals. Certain animal species that appear to be very similar in size and appearance can have dramatically different lifespans, suggesting that some relatively small genetic difference significantly affects the aging process.[38] A prime example is the naked mole rat, which lives for approximately 29 years, even though it is quite similar in size and appearance to related rat species that only live two to three years.[39] Thus, some relatively small genetic difference between these two similar species increases the lifespan of the naked mole rat by an order of magnitude over its rodent relatives.

Additional evidence that the rate of aging can be modified comes from genetic modification studies in animals.[40] A key discovery was that inducing mutations in one gene in the nematode worm *C. elegans*, a frequently used animal research model, doubled the life expectancy of that species.[41] The lifespan of such worms has now been extended 10-fold through genetic changes.[42] Similar studies in other species, such as fruit flies (*Drosophila)*, demonstrate that mutations in a single gene can significantly extend lifespan. These genes that alter aging so dramatically are also present in humans, suggesting that similar effects may be possible in humans.[43]

There is also evidence from humans that the rate of aging is variable and potentially subject to modification. There are a set of tragic human genetic conditions where young children age very rapidly and become "old" and die in their teens. In these conditions, the most well-known of which is progeria, the aging process appears to have been sped up by a genetic change.[44] These unfortunate individuals could be the greatest beneficiaries of new interventions to slow aging, assuming that their rapid premature aging is similar in mechanism to the more natural aging that occurs in the rest of us as we grow older. Indeed, some anti-aging interventions are being tested in such children, although the relatively small number of children affected with these very rare conditions limits the ability to research potential cures for these diseases.

There is also growing evidence that the rate of aging varies in otherwise healthy people. It is well known that some people just seem to age better than others. There are probably biological reasons for the differential rate of aging that may be discoverable, especially as we move into the era of health big data. One of the most

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[37] Sierra, *supra* note 27, at 2.

[38] S.N. Austad, *Methusaleh's Zoo: How Nature Provides Us with Clues for Extending Human Health Span*, 142 J. COMP. PATHOLOGY S10, S11 (2010).

[39] Kaitlyn N. Lewis, Nimrod D. Rubinstein & Rochelle Buffenstein, *A Window into Extreme Longevity; The Circulating Metabolomic Signature of the Naked Mole-Rat, a Mammal That Shows Negligible Senescence,* 40, 40 GEROSCIENCE 105 (2018).

[40] Sierra, *supra* note 27, at 2.

[41] Cynthia Kenyon et al., *A* C. elegans *Mutant That Lives Twice as Long Wild Type*, 366 NATURE 461, 461 (2011).

[42] MELLON & CHALABI, *supra* note 1, at 45.

[43] *See Over* 300 genes that affect the aging process in humans have been identified. *GenAge: The Ageing Gene Database*, HUMAN AGEING GENOMIC RESOURCES, http://genomics.senescence.info/genes/stats.php [https://perma.cc/U42E-P7L4] (last visited Nov. 4, 2018).

[44] MELLON & CHALABI, *supra* note 1, at 40. Progeria is technically known as Hutchison-Gilford progeria. Other examples of premature aging diseases are Werner syndrome and Syskeratosis congenital. *Id.*

intriguing research efforts has been the study of centenarians – people who are selected for study because they have already survived past the age of 100.[45] Studies of such centenarians show how the aging process can vary across humans. Most of these centenarians had very little chronic disease, and when they eventually died, they did so quickly and without the need for much medical care or significant cost. In fact, centenarians consumed less medical expenses in their final year of life than an average person who dies in their seventies or eighties.[46] These centenarians who had such a healthy life and death did not have healthier lifestyles or environmental factors than other people – their diet, smoking habits, and exercise frequency were not significantly different than younger decedents in their same community.[47] Children of centenarians also generally live longer, healthier lives than other people.

This research suggests that longer human healthspans that extend past the century mark are possible, that genetics play a key role in the extended healthspan of centenarians,[48] and that the goal of human aging research should be to find interventions that can replicate these genetic effects to provide for longer, healthier human healthspans for a greater share of the population. The bottom line of recent understanding of the aging process is a paradigm shift to one in which "aging will be regarded as a single disease complex rather than as an inevitable process or condition."[49]

3. Aging Pathways

One of the key insights from research into aging and longevity is that there are a few key metabolic pathways and related physiological processes that appear to be central to mediating the aging process, and that experimental perturbation of these pathways and processes has been shown to extend longevity and slow aging related symptoms in a number of species.[50] Some of these pathways were initially identified in studies on the genetics of aging, which, as discussed above, identified gene variants

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[45] *See* GIFFORD, *supra* note 16, at 87–96.

[46] Nisha C. Hazra, Caroline Rudisill & Martin C. Gulliford, *Determinants of Health Care Costs in the Senior Elderly: Age, Comorbidity, Impairment, or Proximity to Death?,* 19 EUR. J. HEALTH ECON. 831, 835 (2018).

[47] Swapnil N. Rajpathak et al., *Lifestyle Factors of People with Exceptional Longevity*, 59 J. AM. GERIATRICS SOC'Y 1509, 1510–12 (2011).

[48] Because extended lifespan is post-reproduction for most people, natural selection for longer lives would be expected to be weak or non-existent. Not surprising, then, the role of genetics in variation in human lifespan is relatively modest, with most studies finding a heritability of 20-30 percent for human variation in lifespan. *See e.g.,* Peter K. Joshi et al., *Genome-Wide Meta-Analysis Associates* HLA-DQA1/DRB1 *and* LPA *and Lifestyle Factors with Human Longevity*, 8 NATURE COMM. 1, 2, 9 (2017). One recent study reported an even lower heritability below 10 percent, suggesting that previous lifespan heritability had been generally over-estimated due to the effect of assortative mating. *See* J. Graham Ruby et al., *Estimates of the Heritability of Human Longevity Are Substantially Inflated Due to Assortative Mating*, 210 GENETICS 1109, 1109 (2018). However, the contribution of genetics to lifespan in centenarians appears to be much greater than in the general population. *See* Alejandro Santos-Lozano et al., *The Genetics of Exceptional Longevity: Insights from Centenarians,* 90 MATURITAS 49, 50–52 (2016); Rajpathak et al., *supra* note 47, at 1512.

[49] MELLON & CHALABI, *supra* note 1, at 39.

[50] Simon C. Johnson et al., *Preserving Youth: Does Rapamycin Deliver?*, 5 SCI. TRANSLATIONAL. MED. 1, 1 (2013); Carlos López-Otín et al., *Metabolic Control of Longevity*, 166 CELL 802, 802–03 (2016); J.B. Mannick et al., *mTOR Inhibition Improves Immune Function in the Elderly*, 6 SCI. TRANSLATIONAL MED. 1, 1 (2014).

that are conserved between species that would alter the rate of aging. Understanding the protein products of these genes and the metabolic pathways that may be enzymatically involved helped to identify key pathways affecting the aging process. Finally, other observations of anti-aging effects, such as the impact of caloric restriction, were also helpful in identifying or confirming the central importance of certain metabolic pathways.[51]

The key metabolic pathways affecting aging seem to be concentrated in the energy metabolism pathways of the cell, and in particular related to the mitochondria, which are the energy power plants of eukaryotic cells. One such key pathway is the mTOR pathway, which is the abbreviation for mechanistic target of rapamycin.[52] The mTOR protein detects the nutritional supply to the cells, and when nutrients are abundant signals the cell to actively grow, but when scarce it shuts down the cell's reproduction and makes the cell stress-resistant, which extends the cell's longevity.[53] This mTOR pathway was identified from the observation that severe caloric restriction in small mammals significantly extended the lifespan of those animals, and did so by inhibiting the mTOR pathway.[54] While caloric restriction may also be effective in humans in terms of extended lifespan, the extreme reduction in caloric intake would have all types of unpleasant effects in the human subject, including uncontrollable shivering and emotional problems.[55] However, several drugs have been identified that simulate the effects of caloric restriction in inhibiting the mTOR pathway and extending lifespan and healthspan, such as metformin and rapamycin and its derivatives (discussed further below), and these have become promising targets for healthspan interventions.[56]

In addition to research on specific metabolic pathways associated with the aging process, scientists have also identified a series of inter-linked physiological processes that are associated with aging and linked to the metabolic pathways discussed above. These physiological processes include low-grade chronic inflammation, macromolecule and organelle dysfunction, stem cell dysfunction, and cell senescence.[57] The increasing realization that these various metabolic pathways and physiological mechanisms that are associated with aging are often linked, and that an intervention that affects one such pathway or mechanism has a similar benefit on other pathways and mechanisms, has helped to focus the search for anti-aging interventions.

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[51] Leanne M. Redman et al., *Metabolic Slowing and Reduced Oxidative Damage with Sustained Caloric Restriction Support the Rate of Living and Oxidative Damage Theories of Aging*, 27 CELL METABOLISM 805, 805, 812 (2018).

[52] Simon C. Johnson, Peter S. Rabinovitch & Matt Kaeberlein, *mTOR is a Key Modulator of Ageing and Age-Related Disease*, 493 NATURE 338, 338 (2013).

[53] Savage, *supra* note 7, at S58.

[54] Johnson, Rabinovitch & Kaeberlein, *supra* note 52, at 338–39.

[55] Sierra, *supra* note 27, at 2; Amie J. Dirks & Christiaan Leeuwenburgh, *Caloric Restriction in Humans: Potential Pitfalls and Health Concerns*, 127 MECH. AGEING & DEVELOP. 1, 4-5 (2006).

[56] Johnson, Rabinovitch & Kaeberlein, *supra* note 52, at 343.

[57] James P. Kirkland et al., *The Clinical Potential of Senolytic Drugs*, 65 J. AM. GERIATRIC SOC'Y 2297, 2298 (2017) [hereinafter "Kirkland 2017"].

B. Recent Scientific Progress in Therapeutics Targeting Biologic Aging

The recent progress in understanding the nature of aging and its malleability has both resulted from and spurred a resurgence in research on interventions to potentially extend healthspans by mainstream scientists. This includes research by medical experts at prestigious academic medical centers, such as the Mayo Clinic, Harvard Medical School and the Albert Einstein College of Medicine; the creation and growth of dedicated academic research centers focused on aging, such as the Buck Institute for Research on Aging; the creation of private research companies devoted solely to longevity research by major entities, such as Google (Calico) and the Craig Venter Institute (Human Longevity); and an explosion of new start-up anti-aging companies in Silicon Valley and elsewhere.[58]

Due primarily to the efforts of these researchers, a number of promising candidate interventions have been identified that appear to attack and delay the intrinsic aging process, and thereby extend healthspan; among other things, the interventions delay several chronic conditions, such as cancer, diabetes, arthritis, and dementia.[59] Most (but not all) of this progress has come in animal studies to date, so additional research and clinical trials are needed to determine whether and to what extent these interventions work in humans. To date, over 200 compounds have now been classified as geroprotectors, or agents that have been found to slow the generic aging process.[60] These initial results have spurred a sense of optimism in the scientific community and have squarely raised the issue of what will be the regulatory and commercialization pathways for such agents. Some of the progress has been made with non-regulated interventions such as diet and lifestyle, or even procedures such as young-blood infusions.[61] But much of the progress has come from investigating existing or new pharmaceutical and other therapeutic products that would require FDA approval before they could be marketed. Some of the key evidence and candidates are summarized below.

1. Metformin

Metformin is a generic diabetes drug, originally discovered in 1922, that has been used for the treatment of type 2 diabetes since 1957.[62] It was not approved by the FDA until 1994, but it had been used as a diabetes treatment in Europe for several decades

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[58] João Pedro de Magalhães, Michael Stevens & Daniel Thornton, *The Business of Anti-Aging Science,* 35 TRENDS BIOTECHNOLOGY 1062, 1063–67 (2017). A recent industry landscape identified over 100 companies working on life extension interventions in the United States. *See* LONGEVITY INTERNATIONAL ET AL., LONGEVITY INDUSTRY LANDSCAPE OVERVIEW 2017 (2017), http://longevity.international/longevity-industry-landscape-overview-2017 [https://perma.cc/UZ3P-W3KU].

[59] *See* John C. Newman et al., *Strategies and Challenges in Clinical Trials Targeting Human Aging*, 71 J. GERONTOLOGY SERIES A: BIOLOGICAL SCI. & MED. SCI. 1424, 1425–27 (2016).

[60] Bellantuono et al., *supra* note 10, at 293.

[61] Gavin Haynes, *Ambrosia: The Startup Harvesting the Blood of the Young*, THE GUARDIAN (UK) (Aug. 21, 2017), https://www.theguardian.com/society/shortcuts/2017/aug/21/ambrosia-the-startup-harvesting-the-blood-of-the-young [https://perma.cc/7TDH-7F5Y].

[62] Rosina Pryor & Filipe Cabreiro, *Repurposing Metformin: An Old Drug with New Tricks in its Binding Pockets,* 471 BIOCHEMICAL J. 307, 307 (2015).

previously.[63] Although there is still uncertainty about its precise mechanism of action, it treats diabetes by suppressing glucose production in the liver (gluconeogenesis) and increasing insulin sensitivity in tissues of the body.[64] Metformin is inexpensive (having been off-patent for decades), has few side effects, and is included on the World Health Organization Model List of Essential Medicines, meaning that it is an essential part of the basic drug formulary for sustaining health and life.[65] Recently, metformin has been identified as a drug that appears to have anti-aging properties, and it is known to affect a number of molecular and cellular pathways associated with energy metabolism and aging.[66]

Retrospective human studies have shown, quite surprisingly, that type 2 diabetics taking metformin live longer than individuals without diabetes, even though the condition typically takes an average of eight years off a person's life.[67] One study, for example, found that diabetics on metformin are more obese and sicker than people without diabetes when they start taking metformin, yet they ultimately outlive people without diabetes."[68] Moreover, researchers have recently observed that the drug appears to have anti-cancer properties, inhibiting the growth and proliferation of some types of cancer in animal studies and both improving outcomes in patients with several different types of cancer and preventing cancer in numerous human observational studies.[69] However, because of limitations in the data, randomized clinical trials are needed to evaluate both the potential cancer treatment and prevention benefits of metformin.[70] Many such clinical trials are now underway examining the potential benefits of metformin in cancer treatment and prevention.[71] Recent data also suggests that metformin may limit or be used to treat cognitive decline and neurodegenerative disease.[72]

Metformin is one of the few potential healthspan interventions for which human data have shown an anti-aging protective effect. The human data is also backed up by

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63 Elizabeth Sanchez-Rangel & Silvio E. Inzucchi, *Metformin: Clinical Use in Type 2 Diabetes*, 60 DIABETOLOGIA 1586, 1586 (2017).

64 *Id.* at 1586–87.

65 Pryor & Cabreiro, *supra* note 62, at 307.

66 Nir Barzilai et al., *Metformin as a Tool to Target Aging*, 23 CELL METABOLISM 1060, 1060–61 (2018) [hereinafter "Barzilai 2016"].

67 *See* Stephen S. Hall, *A Trial for the Ages*, 349 SCIENCE 1274, 1276 (2015).

68 *Id*. at 1277.

69 Barzilai 2016, *supra* note 66, at 1062; Jacek Kasznicki, Agnieszka Sliwinska & Józef Drzewoski, *Metformin in Cancer Prevention and Therapy*, 2 ANNALS TRANSLATIONAL MED. 1, 5 (2014); Daniel R. Morales & Andrew D. Morris, *Metformin in Cancer Treatment and Prevention*, 66 ANN. REV. MED. 17, 21–25 (2015).

70 Morales & Morris, *supra* note 69, at 24–26; Newman et al., *supra* note 59, at 1426.

71 Clinicaltrials.gov currently lists 323 clinical studies on metformin and cancer, most of which are currently ongoing. *See* NAT'L INST. OF HEALTH: U.S. NAT'L LIBRARY OF MED., https://clinicaltrials.gov/ct2/results?cond=cancer&term=metformin&cntry=&state=&city=&dist [https://perma.cc/PE3U-N24C] (visited Aug. 2, 2018).

72 *See, e.g.,* Barzilai 2016, *supra* note 66, at 1062; P. Katse et al., *Parahippocampal Gyrus Expression of Endothelial and Insulin Receptor Signaling Pathway Genes Is Modulated by Alzheimer's Disease and Normalized by Treatment with Anti-Diabetic Agents,* 13 PLOS ONE 1, 10–11 (2018); Magdalena Markowicz-Piasecka et al., *Metformin – A Future Therapy for Neurodegenerative Diseases,* 34 PHARMACEUTICAL RES. 2614, 2614 (2017).

animal studies.[73] For example, after testing the drug in the roundworm *C. elegans*, researchers in Belgium found that the worms not only aged slower, but they stayed healthier for a longer period of time.[74] Additionally, mice treated with the drug had their lifespan increased by almost 40 percent, with signs that they stayed healthier and more youthful.[75] Another reason why metformin is likely to be the first major anti-aging treatment is that it has a demonstrated safety record, with over sixty years of clinical use with very few side effects.[76] A clinical trial to directly evaluate the anti-aging effect of metformin is currently in the planning stages and is known as the "Targeting Aging with Metformin" (TAME) study.[77]

2. Senescent Cell Removal

One hallmark of aging that has been identified is cellular senescence.[78] Stem cells divide through a lifetime, renewing muscles, blood vessels, and especially skin and blood cells that turn over rapidly.[79] However, in the process, chromosomes in stem cells exhibit continual shortening of the telomeres, the caps at their ends which protect the chromosomes from damage to their DNA. When chromosomes have telomeres that are too short, a cell becomes dormant or "senescent." Although it has been postulated that this mechanism of senescence exists to prevent instability of the body's genome and prevent aging cells from proliferating abnormally and causing cancers, recent literature has indicated that senescent cells with shortened telomeres may actually cause damaging inflammation which itself may promote aging-related conditions and diseases such as cancer formation.[80] Recent animal studies suggest that senescence is not only a marker of aging but is also involved in an increase of age related diseases.[81] As such, cellular senescence is an "imperfect" process which perhaps has not evolved quickly enough to compete with humans' increased lifespan.

There have been significant advances in the past few years suggesting that it may be possible to delay aging by selectively removing senescent cells.[82] Researchers at the Mayo Clinic genetically modified mice in such a way that senescent cells had a "trigger" attached to them. Mice were fed a molecule that matched this trigger, which then caused the senescent cells to self-destruct, while leaving normal cells intact.[83] A subsequent experiment compared the same genetically-modified mice, with and

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[73] For a review of the animal data, *see* Barzilai 2016, *supra* note 66, at 1060–61.

[74] Wouter De Haes et al., *Metformin Promotes Lifespan Through Mitohormesis via the Peroxiredoxin PRDX-2,* 111 PROC. NAT'L ACAD. SCI. E2501, E2506 (2014).

[75] Marta G. Novelle et al., *Metformin: A Hopeful Promise in Aging Research*, 6 COLD SPRING HARBOR PERSP. MED. 1, 5 (2016).

[76] Barzilai 2016, *supra* note 66, at 1063.

[77] *Id.; see also infra* notes 152–154 and accompanying text.

[78] Kirkland 2017, *supra* note 57, at 2298.

[79] Manuel Collado et al., *Cellular Senescence in Cancer and Aging*, 2 CELL 223, 223 (2007).

[80] Jan M. van Deursen, *The Role of Senescent Cells in Ageing*, 509 NATURE 439, 439 (2014).

[81] Virginia Boccardi & Utz Herbig, *Telomerase Gene Therapy: A Novel Approach to Combat Aging*, 8 EMBO MOLECULAR MED. 685, 685 (2012).

[82] Darren J. Baker et al., *Clearance of $p16^{Ink4a}$-Positive Senescent Cells Delays Ageing-Associated Disorders*, 479 NATURE 232, 232 (2011).

[83] *Id*. at 233–34.

without pulling the trigger.[84] The "triggered" mice lived 20-25% longer with a single treatment.[85] Mayo and other researchers have developed therapeutics that remove senescent cells and extend lifespans in animals; such treatments are now ready for clinical trials in humans.[86]

3. Rapamycin

Rapamycin is a drug with immunosuppressant functions that is currently approved by FDA and used to coat coronary stents to help prevent clotting in oral form for prevention of organ transplant rejection and to treat the rare lung disease lymphangioleiomyomatosis.[87] Rapamycin inhibits mTOR (mechanistic target of rapamycin), which pushes cells into a life-extending survival mode, which may increase longevity.[88] Rapamycin has been shown to extend longevity in mice by about 10 percent or more, even when administered late in life,[89] and also mitigates many aging-related symptoms in older mice, including decreased mobility, cognitive decline and tendon stiffening.[90] Other studies have demonstrated that rapamycin has a similar effect in extending lifespan and healthspan in other animal model systems, including yeast, nematodes, and fruit flies.[91]

A problem with rapamycin is that it is known to have significant side effects, including suppressing immune function and negatively affecting metabolic health, and because of this much of the latest anti-aging research on rapamycin is focusing on closely related analogs of rapamycin.[92]

4. NAD^+/Sirtuins

Nicotinamide adenine dinucleotide (NAD+) is a coenzyme found in all living cells.[93] It serves to aid enzymes by fueling reduction-oxidation reactions and carrying electrons from one reaction to another.[94] Essentially, it is fundamental to biological function and unfortunately, it decreases with age. Recent studies have demonstrated

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[84] *Id.* at 234.

[85] *Id*. at 234.

[86] Kirkland, *supra* note 8, at 2300.

[87] U.S. FOOD & DRUG ADMIN., HIGHLIGHTS OF PRESCRIBING INFORMATION: RAPAMUNE, https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/021083s058,021110s075lbl.pdf [https://perma.cc/PX5V-A5LY] (last visited Nov. 7, 2018).

[88] Dan Ehninger et al., *Longevity, Aging and Rapamycin*, 71 CELLULAR MOLECULAR LIFE SCI. 4325, 4325 (2014).

[89] David E. Harrison et al., *Rapamycin Fed Late in Life Extends Lifespan in Genetically Heterogeneous Mice*, 460 NATURE 392, 393–95 (2009); Richard. A. Miller et al., *Rapamycin, but Not Resveratrol or Simvastatin, Extends Life Span of Genetically Heterogeneous Mice*, 66 J. GERONTOLOGY SERIES A: BIOLOGICAL SCI. & MED. SCI. 191, 191 (2011).

[90] Johnson, *supra* note 50, at 1–2; John E. Wilkinson et al., *Rapamycin Slows Aging in Mice,* 11 AGING CELL 675, 675–76 (2012).

[91] Johnson, Rabinovitch & Kaeberlein, *supra* note 52, at 338–340.

[92] Riera & Dillin, *supra* note 11, at 1401.

[93] *What Is NAD+ and Why Is It Important for Aging and Health?,* ELYSIUM, https://www.elysiumhealth.com/en-us/knowledge/science-101/everything-you-need-to-know-about-nicotinamide-adenine-dinucleotide-nad [https://perma.cc/383B-4ZB2] (last visited Nov. 9, 2018).

[94] *Id.*

that cellular NAD+ concentrations change during aging and manipulation of NAD+ production can prolong both healthspan and lifespan.[95]

A category of drugs that interact with the NAD^+ enzymatic system are known as sirtuin activators, and such agents increase longevity in mice and protects mice against the deleterious metabolic effects of high-fat diets.[96] The most well-known sirtuin activator is the red wine ingredient resveratrol, which has been shown to have some modest effects in improving health in animal models, but so far has only produced inconclusive benefits in human trials.[97] Nonetheless, there remains significant promise that this category of drugs may have anti-aging benefits in humans.[98]

5. Targeting Inflammation

There is also growing evidence that chronic inflammation may play in important role in accelerating aging, and the aging process may be slowed by interventions that control inflammation.[99] To this end, the NIA has identified inflammation as a key target for slowing the aging process.[100] Similar to senescence, inflammation is a natural, controlled response. It offers protection and healing when the body is met with infection or injury.[101] However, if left unregulated for extended periods, this process can cause additional tissue injury and impairment.[102]

While it is unclear how chronic inflammation influences the pace of aging, these processes have been associated in a number of chronic diseases and conditions of aging.[103] The term "inflammaging" has been coined to describe the chronic, low-grade inflammation that is characteristic of the aging process.[104] The NIA is currently researching this topic in order to better expose the biological connection between inflammation and aging.[105] Specifically, they are hoping to address: (i) how inflammatory mediators (the molecules that direct cellular inflammatory response) change with age and if that contribute to disease; (ii) how natural age-related cellular changes may generate an inflammatory response; and (iii) how chronic inflammation

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[95] Eric Verdin, *NAD^+ in Aging, Metabolism, and Neurodegeneration*, 350 SCIENCE 1208, 1208 (2015).

[96] Newman et al., *supra* note 59, at 1427.

[97] *Id.*; Khushwant S. Bhullar & Basil P. Hubbard, *Lifespan and Healthspan Extension by Resveratrol*, 1852 BIOCHIMICA BIOPHYSICA ACTA 1209, 1209 (2015); *see also supra* notes 21–23 and accompanying text.

[98] Bhullar & Hubbard, *supra* note 97, at 1209; Newman et al., *supra* note 59, at 1427.

[99] *See, e.g.,* W.K. Eddie Ip et al., *Anti-Inflammatory Effect of IL-10 Mediated by Metabolic Reprograming of Macrophages*, 356 SCIENCE 513, 514 (2017); Yun-Hee Youm et al., *Canonical Nlrp3 Inflammasome Links Systemic Low Grade Inflammation to Functional Decline in Aging,* 4 CELL METABOLISM, 519, 519 (2013).

[100] U.S. DEP'T HEALTH & HUM. SERV., *Inflammation Plays an Important Role in the Aging Process*, NAT'L INST. ON AGING, https://www.nia.nih.gov/about/living-long-well-21st-century-strategic-directions-research-aging/inflammation-plays [https://perma.cc/K5KB-2HVN] (last visited Nov. 10, 2018).

[101] *Id.*

[102] *Id.*

[103] *Id.*

[104] Claudio Franceschi et al., *Inflammaging: A New Immune-Metabolic Viewpoint for Age-Related Diseases*, 14 NATURE REV. ENDOCRINOLOGY 576, 576 (2018).

[105] U.S. DEP'T HEALTH & HUM. SERV., supra note 100.

resulting from disease relates to further cellular dysfunction.[106] This research suggests there may be therapeutic avenues for treating inflammation in order to lessen the diseases of aging.

6. Regenerative Medicine

Many people believe regenerative medicine, with processes such as stem cell treatments, represent the long-term hope for anti-aging interventions. Regenerative medicine is intended to replenish and restore aged and damaged tissue, and therefore is inherently an anti-aging approach. However, the era of regenerative medicine is still in its earliest stages, and few regenerative medicine therapies have been proven to be safe and effective.

A recent study successfully converted differentiated cells into pluripotent stem cells[107] by genetically inducing the four "Yamanaka Factors."[108] This process has the potential to erase differentiation and aging at a cellular level.[109] The study induced the Yamanaka Factors in the cells of a genetically altered mouse, using a compound of doxycycline (an antibiotic) and drinking water.[110] The mouse was engineered to model Hutchinson-Gilford progeria, which causes premature aging.[111] They reported that short pulses of induction can reverse aging in older mice, while longer induction can cause too much de-differentiation, which can lead to loss of tissue identity and cancer.[112] There are concerns with this approach, however. Inducing the Yamanaka factors in humans is not easily translated from mice. Additionally, it is worrisome that over-induction leads to organ failure and cancer in mice, as this could translate to humans. Nevertheless, the concept is intriguing and offers new potential for mitigating aging in the future.

IV. REGULATORY PATHWAYS AND CHALLENGES

Although scientists have made enormous progress in understanding the science of aging and identifying potential interventions to extend human healthspan, this progress has generally not advanced to the point where the general public can or should try to benefit from these interventions – at least yet. Most of the progress to date has been accomplished in animal studies, and there are an almost unlimited number of past disappointments of putative health advances in animal studies that subsequently failed

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[106] *Id.*

[107] Alejandro Ocampo et al., *In Vivo Amelioration of Age-Associated Hallmarks by Partial Reprogramming*, 167 CELL 1719, 1719 (2016). An induced pluripotent stem cell is a cell taken from any tissue (usually skin or blood) from a child or adult and is genetically modified to behave like an embryonic stem cell. As the name implies, these cells are pluripotent, which means that they have the ability to form all adult cell types.

[108] Yamanaka factors (Oct3/4, Sox2, Klf4, c-Myc) are highly expressed in embryonic stem (ES) cells, and their over-expression can induce pluripotency in both mouse and human somatic cells, indicating that these factors regulate the developmental signaling network necessary for ES cell pluripotency. *See* Kazutoshi Takahashi & Shinya Yamanaka, *Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors*, 126 CELL 663, 671 (2006).

[109] Ocampo, *supra* note 107, at 1721.

[110] *Id*. at 1726.

[111] *Id*. at 1719.

[112] *Id*. at 1730.

in human clinical trials. So, a modicum of caution is warranted. Moreover, even when an intervention may have anti-aging benefits in specific treatment modalities, it is not clear that it will not have negative effectives if delivered widely to healthy, heterogeneous populations.[113] Therefore, prospective randomized control trials are needed to provide the best assurance of the effectiveness and safety of potential healthspan promoting interventions. But what the progress to date has achieved is to advance the science to where human clinical trials are now appropriate for many of the interventions that have been identified.[114] However, such clinical trials are very expensive, and companies will not invest the necessary funds into such trials if there is no obvious pathway to regulatory approval and commercialization.

While the new science surrounding drugs targeted at increasing healthspan is promising, the current FDA regulatory framework is not particularly welcoming to their potential approval. The problem is three-fold. First, the current drug regulatory environment is disease-focused, and "aging" is not currently defined as a disease. Second, FDA has traditionally approved drugs primarily on an indication-by-indication basis and not the multi-indication simultaneous approval that would be needed for anti-aging drugs. Lastly, there are no currently validated biomarkers of aging. This leaves compounds targeted at increasing healthspan in limbo, with a great deal of promise but no simple way to move forward to allow regulatory approval and commercialization with full realization of these drugs' potential benefits. This section explains these regulatory hurdles in more detail.

A. Current Regulatory Framework

After a new drug has been developed and tested in pre-clinical studies in the laboratory, the drug sponsor then seeks to have it approved by FDA for human clinical testing.[115] The required pre-clinical studies include testing of the drug in cellular assays and then animal studies, with multiple species being used to gather basic information on the safety and efficacy of the compound being investigated.[116] The sponsor then submits an Investigational New Drug (IND) application to FDA based on the results from the initial animal testing.[117] The IND includes information on the drug's composition, how it is manufactured, the results of various cellular and animal studies, and the proposed plan for testing the drug on humans.[118] FDA reviews the IND to ensure that the proposed clinical trials do not place human subjects at unreasonable

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[113]Riera & Dillin, *supra* note 11, at 1401. Different people may be affected differently by healthspan extension agents, just like they are by most pharmaceuticals, which can only be evaluated with carefully conducted human studies. *Id.* at 1403.

[114]An interesting interim step being tried by some scientists is to test some of these anti-aging interventions in dogs before going on to humans. *See* Savage, *supra* note 7, at S57–S58.

[115]U.S. FOOD & DRUG ADMIN., *Development & Approval Process (Drugs)* (Jun. 13, 2018), https://www.fda.gov/drugs/developmentapprovalprocess/default.htm [https://perma.cc/4L45-PXJM].

[116]*Id*.

[117]U.S. FOOD & DRUG ADMIN., *Investigational New Drug (IND) Application* (Oct. 10, 2017), https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/investigationalnewdrugindapplication/default.htm [https://perma.cc/2C3K-XEXE].

[118]*Id*.

risk of harm.[119] FDA also verifies that there is adequate informed consent and human subject protection.[120]

The clinical trials that follow traditionally include three phases. Phase 1 typically has 20-80 healthy participants.[121] The goal of this phase is to determine safety, specifically elucidating the most frequent side effects and how the drug is metabolized and excreted.[122] If the drug passes this phase, it moves to Phase 2. Here the drug is tested on hundreds of patients, emphasizing effectiveness.[123] The goal of this phase is to gather preliminary data on whether the drug works in people who have the targeted disease or condition.[124] If this is a controlled trial, patients receiving the drug are compared with similar patients ("controls") receiving either a placebo or a different drug that is already approved for the condition being studied.[125] Safety continues to be evaluated and short term side effects are studied. After successful completion of the Phase 2 trial, FDA and sponsors will discuss how the larger Phase 3 trials will be implemented.[126] The Phase 3 trials involve testing the drug on thousands of participants, usually from several hundred to about 3,000.[127] The trials usually run for two to five years. While these studies gather more information about safety and effectiveness, they also study different populations, dosages, and the uses of this drug in combination with other drugs.[128] Once Phase 3 trials are completed, FDA meets with the drug sponsor for a review meeting, the drug sponsor submits a New Drug Application (NDA) application, and a drug label is produced. If the trials are successful and the NDA is approved, the facilities being used for production will be inspected before the new drug is allowed to be produced.[129]

According to the Tufts Center for the Study of Drug Development, the total time for this entire process is approximately eight to twelve years, with an average cost of $2.6 billion (approximately half in out of pocket expenses and half in loss of returns that investors forego while drug is in development).[130] After approval, there is sometimes a Phase 4 trial, which involves collecting data on drug effects after it is on the market. [131]

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[119] *Id*.

[120] *Id*.

[121] U.S. FOOD & DRUG ADMIN., *The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective* (Nov. 24, 2017), https://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143534.htm [https://perma.cc/L28K-SR7D].

[122] *Id*.

[123] *Id*.

[124] *Id*.

[125] *Id*.

[126] *Id*.

[127] *Id*.

[128] *Id*.

[129] *Id*.

[130] PR Tufts CSDD, *Cost to Develop and Win Marketing Approval for a New Drug Is $2.6 Billion*, Tufts Center for the Study of Drug Development (Mar. 9, 2018), https://csdd.tufts.edu/csddnews/2018/3/9/march-2016-tufts-csdd-rd-cost-study.

[131] U.S. FOOD & DRUG ADMIN., *Drug Approval Process* (2015), https://www.fda.gov/downloads/drugs/resourcesforyou/consumers/ucm284393.pdf [https://perma.cc/CY4H-KRNU].

The rigorous testing employed by FDA has become the "gold standard" for the approval of therapeutics.[132] Prior to the FDA regulatory approval system, consumers could potentially take useless products, believing they were medicinal, or more drastically could be taking actively harmful medications, such as Elixir Sulfanilamide, which in 1937 poisoned and killed more than 100 people (mostly children).[133] The FDA approach has evolved over the years into an intricate system of testing and approvals that have kept the population predominantly safe, as they are using drugs that have been thoroughly tested and are well understood.

FDA's regulatory system is optimized to approve drugs with a single indication and a clear biomarker to track results. A biomarker is a biological characteristic that can be objectively measured and evaluated as an indicator of normal biological processes, pathogenic perturbations, or biological responses to a therapeutic intervention.[134] An example is cardiovascular disease, in which high cholesterol would be a biomarker. This system works well for drugs approved for treating large populations for common diseases, such as cardiovascular disease and diabetes. Unfortunately, this system is not particularly well-suited for evaluating drugs intended to modify healthspan, as "aging" lacks defined biomarkers or quantifiable symptoms, and is not considered a disease by FDA, as elaborated in the following section.

B. Problems for Healthspan Extending Interventions

FDA has been relatively silent on how it plans to regulate drugs that are shown to have a significant anti-aging or healthspan extending benefit. However, the well-established FDA clinical trial system for approving new therapeutics does not appear to be a good fit for healthspan extending agents. First, drugs are defined under FDA's governing statute as a substance "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease" or "intended to affect the structure or any function of the body of man . . . ."[135] If a substance is shown to cure, mitigate, treat or prevent aging, it would likely not be approvable for that indication unless aging is defined as a "disease." While again FDA has not publicly and definitely addressed whether or not it considers aging to be a disease, its actions to date and some limited informal communications suggest that the agency does not consider aging to be a disease.[136] If that is the case, an anti-aging or healthspan extending agent could not be approved by FDA as a drug for that indication. FDA drug approval is generally needed, however,

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[132]James E. Valentine, *Room for Flexibility in FDA's "Gold Standard "of Drug Approval*, THE NETWORK FOR PUBLIC HEALTH LAW (July 16, 2015),

https://www.networkforphl.org/the_network_blog/2015/07/16/663/room_for_flexibility_in_fdas_gold_standard_of_drug_approval [https://perma.cc/6JYZ-EYN3].

[133]Carol Ballentine, *Taste of Raspberries, Taste of Death: The 1937 Elixir Sulfanilamide Incident*, FDA CONSUMER MAGAZINE (June 1981), https://www.fda.gov/downloads/AboutFDA/WhatWeDo/History/ProductRegulation/UCM593517.pdf [https://perma.cc/9QM4-287R].

[134]Shashi Amur, *From Our Perspective: Clinical Biomarker Qualification*, U.S. FOOD & DRUG ADMIN. (Jan. 5, 2015), http://www.fda.gov/Drugs/NewsEvents/ucm424545.htm [https://perma.cc/V7XJ-2J5F].

[135]21 U.S.C. § 321(g)(1) (2012).

[136]Companies that have taken products to the FDA that may have a general healthspan effect have been forced to seek approval on a piecemeal basis for one condition at a time without a general aging indication. *See* Savage, *supra* note 7, at S58.

for a substance to be prescribed by physicians, reimbursed by health insurers, and integrated into the health care system.

Even if aging was considered by FDA to be a disease for purposes of regulatory approval, there would be other more practical hurdles to clinically demonstrating that a putative drug had anti-aging effects. The most straightforward way to show such an effect would be to give the drug to one set of research subjects and compare their outcomes to an appropriately matched control group. Clinical outcomes endpoints would be needed that "have been validated clinically, are reproducible, can be measured in a short time frame, are as noninvasive as possible, are accepted by regulatory agencies, and for which there are acceptable animal models."[137] However, unlike traditional clinical trials where the patients have an existing condition, the patients here will generally be healthy. To get a statistically robust measure of anti-aging effect, a study would likely need tens of thousands of patients tracked for decades. This would be an order of magnitude more expensive than existing clinical trials, which are already very expensive and time-consuming.[138]

The most feasible way to address this problem is with surrogate biomarkers – which are biological changes that are early indicators that a therapy is working before the ultimate outcome (in this case extended healthspan) is achieved.[139] FDA allows a drug sponsor to rely on surrogate endpoints in some clinical trials, and requires the sponsor to follow-up with a Phase 4 trial after approval to verify that the surrogate endpoint indeed is a valid predictor of the actual endpoint for which the therapy has been approved. Unfortunately, despite many years and millions of dollars of effort, robust biomarkers of aging have not yet been validated.[140]

However, in recent years there has been some progress in identifying biomarkers of aging. Given the complexity of the aging process across all body systems, it is unlikely there will be a single biomarker that accurately measures aging.[141] A number of biomarker "signatures" that integrate several different indications of aging have been developed and are being tested.[142] For example, a recently reported study purported to identify a set of nine clinical biomarkers that collectively can be used to measure something the researchers call "phenotypic age," a measure of the biological aging in an individual that better characterizes age than chronological age.[143] In a study of a nationally-representative sample of approximately 10,000 Americans, the Phenotypic Age measure was highly predictive of remaining life expectancy in the study

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[137]Kirkland, *supra* note 8, at 4.

[138]*See* Tufts Ctr. for the Study of Drug Dev., *supra* note 130 and accompany text (clinical approval of traditional drugs generally takes 8-12 years and costs approximately $2.6 billion on average).

[139]C.D. Lathia et al., *The Value, Qualification, and Regulatory Use of Surrogate End Points in Drug Development*, 86 CLINICAL PHARMACOLOGY & THERAPEUTICS 32, 32 (2009).

[140]Riera & Dillin, *supra* note 11, at 1403.

[141]Paola Sebastiani et al., *Biomarker Signatures of Aging*, 16 AGING CELL 329, 329 (2017).

[142]*Id.* at 335–36.

[143]Zuyun Liu et al., *Phenotypic Age: A Novel Signature of Mortality and Morbidity Risk* (2018), bioRxiv: THE PREPRINT SERVER FOR BIOLOGY 1, 4–5 (2018), https://www.biorxiv.org/content/early/2018/07/05/363291.figures-only [https://perma.cc/4N45-522Z]. The nine cross-validated biomarkers used in this test are albumin, creatinine, glucose, (log)C-reactive protein, lymphocyte percent, mean cell volume, red blood cell distribution width, alkaline phosphatase, and white blood cell count. *Id.* at 6.

subjects.[144] The study authors suggest that this measure of phenotypic age has the potential to serve "as an outcome variable in basic research, with the goal of identifying molecular mechanisms that regulate the rate of aging."[145]

Moreover, there have been identified a number of other physiological parameters that are indicators of frailty and aging, including metabolic health, cardiac function, muscle strength, cardiac performance, immune response, and improvements in mobility, among others.[146] These types of measurements may also function as biomarkers of aging.[147]

Progress is also being made in identifying molecular biomarkers of aging.[148] Molecular biomarkers have been identified that correlate with lifespan, healthspan, chronological age, frailty, and senescent cells, for example.[149] An epigenetic biomarker tool consisting of measuring methylation at over 500 specific sites in the human genome has also been developed that is highly predictive of morbidity and mortality outcomes in initial studies.[150] Although impressive and important progress has been made in identifying and studying these molecular biomarkers of aging, additional work is needed to validate the biomarkers as well as the other types of biomarkers discussed above before they can be relied on in clinical trials or clinical care.

Another challenge is that a drug intended to slow aging would likely be given to many people who are otherwise healthy. There is no paradigm for "treating" healthy people, which is likely to also become an issue as more enhancement interventions that do not treat disease but rather enhance human capabilities or performance are used. For FDA to approve a healthspan drug for healthy people, it would likely need to be almost completely safe, a challenging requirement.[151] However, many clinical trials involve healthy subjects, especially in Phase 1 trials, so a clinical test of a potential anti-aging intervention in healthy subjects would not present any unique ethical issues. The key issue would be whether FDA would approve such a drug for general use as a healthspan extension agent in the general population, and this would require clinical trials showing a significant benefit in terms of improving the health of patients (both quality and perhaps quantity of healthy years) with minimal or at least smaller risks.

V. REGULATORY OPPORTUNITIES AND PATHWAYS

Given the obstacles discussed above to traditional regulatory approval of healthspan agents, there are a number of possible options for obtaining or bypassing regulatory

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[144] *Id.* at 2, 11.

[145] *Id.* at 14.

[146] Bellantuono et al., *supra* note 10, at 295; Riera & Dillin, *supra* note 11, at 1403.

[147] *See* Bellantuono et al., *supra* note 10 at 295; Kirkland, *supra* note 8, at 2; Riera & Dillin, *supra* note 11, at 1403.

[148] L.J. Niedernhofer, J.L. Kirkland & W. Ladiges, *Molecular Pathology Endpoints Useful for Ageing Studies*, 35 AGEING RES. REV. 241, 242 (2017).

[149] *Id.* at 243–46.

[150] Morgan E. Levine et al., *An Epigenetic Biomarker of Aging for Lifespan and Healthspan*, 10 AGING 573, 583–85 (2018).

[151] *See* GIFFORD, *supra* note 16, at 269; Kirkland, *supra* note 8, at 4.

approval on the pathway to commercialization. These alternatives are summarized below.

A. TAME Study

The most promising and innovative development in regulatory approval of healthspan agents is a recent informal agreement with FDA to approve a single prospective trial studying metformin and aging.[152] The Targeting Aging with Metformin or TAME study will be a double-blind randomized trial which will test metformin against a placebo in approximately 3,000 elderly people who suffer from or have a high risk of developing conditions such as cancer, heart disease, and Alzheimer's Disease.[153] Over six years, researchers will track how many patients in each group develop the targeted age-related conditions, and will also hope to assess whether the drug appears to impact longevity. FDA has informally indicated it may permit a general healthspan promoting indication if this trial is successful.[154] Such a result could create a pathway for bringing other medications targeted at increasing healthspan to market.

B. Multi-Indication Approval Process

The TAME trial could set a precedent for a multi-indication approval process for healthspan promoting agents. As discussed above, an intervention that promotes healthspan will be expected to have a beneficial effect on the prevention and treatment of a variety of chronic diseases, as has been reported for various candidate healthspan drugs such as metformin, rapamycin and senolytic agents.[155] The FDA dug approval process generally focuses on a single indication at a time, and a drug that has benefits for more than one health endpoint usually requires sequential approvals, which can be very expensive. To accommodate the unique beneficial properties of healthspan extension agents, FDA could also allow for a more streamlined multi-indication approval process. Although the healthspan products approved via this pathway would not be expressly approved for an anti-aging or healthspan extending indication, their approval for multiple chronic health diseases would send a strong signal to patients and prescribing physicians that these are indeed validated healthspan extending agents. In addition, if the clinical trials show that any such drug not only treats but also prevents multiple chronic diseases, the potential exists to move the existing paradigm of treating diagnosed disease toward providing preventive therapies in healthy individuals before they develop age-related diseases.

C. Aging as a Disease

Perhaps the most direct but dramatic step that FDA could take would be to define aging itself as a disease. If aging itself were considered a disease, then the potential to define new biomarkers of aging such as telomere length and senescent cell counts would exist, opening the path toward studying pharmaceutical effects on these

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[152]Barzilai 2016, *supra* note 66, at 1063; Hall, *supra* note 67, at 1275–76. Notes 62–77 and accompanying notes provide a summary of the anti-aging evidence for metformin and why metformin was selected for this study.

[153]Erika Brutsaert, Metformin in Longevity Study, NAT'L INST. OF HEALTH: U.S. NAT'L LIBRARY OF MED (May 31, 2018), https://clinicaltrials.gov/ct2/show/NCT02432287 [https://perma.cc/HUK9-J4LH].

[154]Hall, *supra* note 67, at 1278.

[155]*See* Kirkland, *supra* note 8, at 3.

markers. It can be difficult to conceptualize aging as a disease as it is fundamentally believed to be a "normal" and "natural" process.[156] However, what is considered normal versus a disease is strongly influenced by social norms of the time. There are many examples of occurrences that were thought of as diseases but are not considered pathological anymore. For example, "drapetomania," the flight of slaves to flee captivity, was once seen as a legitimate mental illness.[157] Additionally, homosexuality was until recently also considered a disease.[158] Conversely, there are also events that were deemed natural that are now viewed as disease. Osteoporosis, isolated systolic hypertension, sarcopenia, and Alzheimer's disease were once labeled normal components to aging but now are considered pathologic processes in their own right.[159] Moreover, there are conditions such as pregnancy, balding or menopause that are also "natural,"[160] and yet FDA approves drugs to treat such conditions.

Furthermore, there are diseases associated with accelerated aging that are considered a disease. For example, photoaging, which is the accelerated deterioration of skin as a result of UV exposure, is seen as a mechanism for skin cancer. That said, skin aging associated with age is viewed as normal.[161] To further illustrate, there are "accelerated aging diseases" (e.g. Hutchingson-Gilford progeria syndrome and Werner syndrome) that are considered diseases, despite the fact that when the same symptoms manifest in an elderly person it is considered normal and not treatable.[162]

The benefits of labeling aging as a disease are significant. This recognition would allow medical efforts to work towards minimizing undesirable conditions associated with aging or eliminating it.[163] It would also allow for an increase for funding and research in aging research, the further commitment to medical intervention, and potential treatments to be covered by health insurance providers.[164]

D. Approvals for Symptoms of Aging

Even if aging itself is not a disease, there may be symptoms of aging that can be targeted and used for regulatory approval of a healthspan extending drug. Examples of such potential symptoms include frailty, sarcopenia (muscle wasting), loss of resilience or wrinkles.[165] Even if these symptoms are not themselves a disease, an agent may be approved by FDA as a drug under its statutory authority if it is "intended

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[156]Sven Bulterijs et al., *It Is Time to Classify Biological Aging as a Disease,* 6 FRONTIERS.IN GENETICS 1, 2 (2015).

[157]Daniel Callahan & Eva Topinkova, *Is Aging a Preventable or Curable Disease?,* 13 DRUGS & AGING 93, 94 (1998).

[158]Jack Drescher, *Out of DSM: Depathologizing Homosexuality*, 5 BEHAV. SCI. 565, 565-66 (2015).

[159]Gerbrand J. Izaks & Rudy GJ Westendorp, *Ill or Just Old? Towards a Conceptual Framework of the Relation between Ageing and Disease,* 3 BMC GERIATRICS 1, 2 (2003).

[160]MELLON & CHALABI, *supra* note 1, at 40.

[161]Jessica H. Rabe et al., *Photoaging: Mechanisms and Repair,* 55 J. AM. ACAD. DERMATOLOGY 1, 2-3 (2006).

[162]MELLON & CHALABI, *supra* note 1, at 40; Arthur L. Caplan, *Death as an Unnatural Process: Why Is It Wrong to Seek a Cure for Ageing?*, 6 EMBO REP. S72, S73 (2005).

[163]Callahan & Topinkova, *supra* note 158, at 94–95.

[164]Bulterijs et al., *supra* note 156, at

[165]*See, e.g.,* Ferrucci*, supra* note 32, at 479–83; Riera & Dillin, *supra* note 11, at 1403.

to affect the structure or any function of the body of man . . . "[166] Of course, a drug sponsor would still be left with the challenge of how to demonstrate such effects on the structure or function of humans to FDA's satisfaction.[167]

Moreover, sarcopenia has recently been recognized as a disease by the World Health Organization, and various national and international health organizations are currently working on a definition and diagnostic criteria for sarcopenia.[168] Clinically validated scales have been developed to diagnose frailty in humans,[169] and a number of international medical societies are working on finding a consensus definition of frailty.[170] Researchers have begun discussing and even moving forward with clinical trials to discuss such effects. For example, one recently published study demonstrated that a rapamycin derivative helped senior citizens response better to the flu vaccine, perhaps showing an increase in resiliency.[171] It has also been suggested that easily measured and meaningful phenotypic responses such as "improvement in mobility" could be used as a phenotypic biomarker of an anti-aging effect.[172]

A drug approved to treat or prevent frailty, muscle wasting or even wrinkles would likely be perceived by both doctors and patients as an anti-aging treatment. Thus, if aging is itself is not defined as a disease, targeting these symptoms of aging for a drug approval indication could be a second-best way to obtain approval of a drug that slows or prevents aging.

E. Off-Label Prescribing

There are also pathways that could circumvent the standard FDA process. First, for drugs such as metformin, which is already approved for diabetes, physicians could choose to prescribe "off-label", or purposely prescribe the medication for an indication other than its FDA-approved use. There are anecdotal reports that this is already starting to occur.[173] The off-label use of previously approved drugs will likely accelerate if feasible drug approval pathways are not developed for healthspan extending agents.

In a case between Amarin Pharmaceuticals and FDA, the court protected off-label prescribing of medications by physicians as free speech.[174] This was seen as a blow to the regulatory authority of FDA and could potentially leave a large window open for pharmaceuticals to be re-marketed for new indications without going through full FDA approval.[175] This presents an opportunity for healthspan extension treatments that may have beneficial impacts on numerous disease endpoints linked by their common etiological connection to the general aging process. A sponsor of such an agent could

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[166]21 U.S.C. § 321(g)(1) (2012).

[167]Kirkland, *supra* note 8, at 5.

[168]Liam Drew, *Lifting the Burden of Old Age,* 555 NATURE S15, S15–S16 (2018).

[169]Kirkland, *supra* note 8, at 2.

[170]Bellantuono et al., *supra* note 10, at 294.

[171]Mannick et al., *supra* note 50, at 1, 3.

[172]Bellantuono et al., *supra* note 10, at 295.

[173]Through their activities in aging-related meetings, the authors have met a number of individuals, including some physicians, who have been prescribed metformin off-label for an anti-aging purpose.

[174]Amarin Pharms. Ir. Ltd. v. U.S. Food & Drug Admin., 106 F. Supp. 3d 196 (D.D.C. 2015).

[175]*See generally* Jeffrey Chasnow & Geoffrey Levitt, *Off-Label Communications: The Prodigal Returns*, 73 FOOD & DRUG L.J. 257 (2018).

obtain regulatory approval for one indication, but then market the drug for the full range of aging-related endpoints that the drug improves, provided it had reliable effectiveness data for each endpoint it promotes. This path to market, however, is only a solution for pre-approved drugs such as metformin and would not be a route to bring new pharmaceuticals targeting healthspan to market. Moreover, off-label prescribing also lacks the backing of proper clinical trials and regulatory review for the off-label indication, which is not optimal for ensuring efficacy and safety.

F. Over the Counter (OTC)

For a prescription drug like metformin, which has a proven safety record, allowing patients to purchase it over the counter could be an option. Unfortunately, there are a number of barriers to this option. First, FDA requires that an OTC drug be both safe and effective.[176] Here, there is no proven efficacy for a healthspan indication. As metformin is primarily a drug for diabetes, FDA is unlikely to move it to OTC for a new indication that has not been studied in prospective clinical trials. Moreover, OTC status would prevent patients taking the drug for a new indication from being monitored closely by their physicians. There is the additional policy concern that if metformin were made OTC the effective price to the consumer would increase, as insurance copays for older generic medications are often lower than what one would pay for a similar drug without a prescription. According to the Centers for Disease Control and Prevention (CDC), 30.3 million people in the United States have diabetes, many of whom benefit from metformin's generic status.[177]

G. Dynamic Biomarkers

FDA could also work with dynamic biomarkers to meet the goals of increasing healthspan. Instead of looking at one endpoint to treat, dynamic biomarkers would incorporate an evaluation of multiple endpoints leading to a system change, such as aging. This concept has been discussed in the context of certain neurological diseases, in which traditional biomarkers are not an ideal fit. In a 2010 *Lancet Neurology* article, Jack Clifford et al. from the Mayo Clinic presented a hypothetical model for dynamic biomarkers for Alzheimer's disease.[178] According to these authors, Alzheimer's disease (AD) was originally viewed as a static diagnosis, a patient either had AD pathological changes, and therefore had dementia, or he or she was cognitively normal. That view however, has evolved, to one in which the AD pathological process and clinical decline develop gradually, and dementia is often the end stage of many years of increasing pathology.[179] Clifford et al., propose looking at five specific biomarkers for AD, and evaluating them over time in order to diagnose and treat earlier. In early 2018, FDA looked to modify this process, so as to not deny development of drugs for

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[176]U.S. FOOD & DRUG ADMIN., *How Drugs Are Developed and Approved: OTC (Nonprescription) Drugs* (Nov. 3, 2016), https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ucm209647.htm [https://perma.cc/CY93-S6RN].

[177]Centers for Disease Control*, National Diabetes Statistics Report, 2017* (2017), https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf.

[178]Clifford R. Jack Jr. et al., *Hypothetical Model of Dynamic Biomarkers of the Alzheimer's Pathological Cascade*, 9 THE LANCET NEUROLOGY 119, 119 (2010).

[179]*Id*. at 119–20.

early stage Alzheimer's, in which patients often lack the functional decline needed to test a drug.[180]

As there is obviously great incentive to treat patients as early as possible, FDA moved to create a dynamic system of approvals.[181] In this new organization, FDA is allowing patients with stage 1 Alzheimer's, who lack clinical symptoms of the disease but nonetheless have a biomarker of Alzheimer's, often a positive PET scan of the brain or positive tests for beta-amyloid or tau (proteins that serve as trademarks of Alzheimer's disease), to have improvements in those biomarkers alone, without cognitive or function improvements, as a basis for drug approval[182] Patients with stage 2 Alzheimer's have biomarker evidence and some cognitive impairment but lack functional decline.[183] For drugs in these trials, FDA will consider only cognition as an endpoint if it is strongly justified.[184] Lastly, for patients with biomarker evidence as well as cognitive and functional decline, drug trials should include measures of cognition and function, but FDA also encourages novel approaches here as well.[185] This innovative pathway for drug approval allows patients to be treated earlier and offers a prototype for future therapeutics targeting healthspan.

This has been similarly proposed for Parkinson's disease.[186] Likewise, the use of dynamic markers could be potentially beneficial to studying healthspan drugs. Healthspan studies could look at lipid panels, a cardiac stress test, bone density for fragility, and blood sugar regulation in conjunction with one another to access aging in a more complex and dynamic manner. This also could allow clinical trials for this drug category to be conducted in a few years, instead of waiting for end of life to measure results.

H. Dietary Supplements

Although FDA has tight control over approval of pharmaceuticals, dietary supplements are not required to obtain approval from FDA before they are marketed. FDA defines a dietary ingredient as a "vitamin; mineral; herb or other botanical; amino acid; dietary substance for use by man to supplement the diet by increasing the total dietary intake; or a concentrate, metabolite, constituent, extract, or combination of the preceding substances. Unlike drugs, supplements are not intended to treat, diagnose, prevent, or cure diseases."[187] Before a firm can market a dietary supplement, it is responsible for ensuring that: the product it manufactures or distributes is safe, any claims made about the products are not false or misleading, and the product complies

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[180]U.S. FOOD & DRUG ADMIN., DRAFT GUIDANCE: EARLY ALZHEIMER'S DISEASE: DEVELOPING DRUGS FOR TREATMENT, GUIDANCE FOR INDUSTRY (Feb. 2018), https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM596728.pdf.

[181]*Id.* at 1, 3-4.

[182]*Id*. at 3–4.

[183]*Id*. at 4.

[184]*Id*. at 5.

[185]*Id.* at 4–5.

[186]Jose A. Santiago & Judith A. Potashkin, *Network-Based Metaanalysis Identifies HNF4A and PTBP1 as Longitudinally Dynamic Biomarkers for Parkinson's Disease*, 112 PROC. NAT'L ACAD. SCI. 2257, 2259 (2015).

[187]U.S. FOOD & DRUG ADMIN., *Products & Ingredients: Dietary Supplement Products & Ingredients*, (Nov. 20, 2018), https://www.fda.gov/Food/DietarySupplements/ProductsIngredients/default.htm [https://perma.cc/7QTV-WDRS].

with the Federal Food, Drug, and Cosmetic Act.[188] There are many dietary supplements on the market that are making anti-aging or age-defying claims, and because these claims have not been approved by FDA, their validity has not been independently verified.[189]

Elysium Health (Boston, MA) avoided the need for pre-market clinical trials and FDA approval by marketing its product as a dietary supplement, even though it believed its supplement called Basis could be a powerful compound for promoting longevity. [190] Elysium has seen promising results when testing its product on mice, but it recognizes that it would take a decade or longer to prove a similar benefit in humans, if it can even get a trial approved.[191] Therefore, Basis is sold as a "nutraceutical," which does not require clinical trials or FDA approval.[192] Elysium has committed to studying and reporting the effects of its Basis product and recently published an initial randomized, double-blind, placebo-controlled study showing that its Basis product increased NAD^+ levels in human subjects in a sustainable ongoing effect without any detectable safety issues.[193]

Elysium claims to target mitochondrial dysfunction through optimizing NAD+ levels and sirtuin function in cells to support the metabolic process.[194] The ability to bring powerful biologically-active compounds to market as a dietary supplement rather than as a therapeutic creates a potential "loophole" that may be exploited by companies looking to bring healthspan drugs to market. However, if a drug is already FDA-approved for an indication (such as metformin), or biologically similar to an FDA-approved drug, it may not be remarketed as a nutraceutical.[195] The potential exists for FDA to lose control of the healthspan treatment industry entirely with this loophole. The "supplement loophole" could potentially allow for sham healthspan supplements to flood the market, leaving consumers vulnerable. Although the FDA has limited authority in the pre-market approval of dietary supplements, it does have authority to recall supplements that are mislabeled or adulterated in ways that harm patients.[196] More significantly, if another company was to seek and obtain drug

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[188] *Id*.

[189] Alexander Vaiserman & Oleh Lushchak, *Implementation of Longevity-Promoting Supplements and Medications in Public Health Practice: Achievements, Challenges and Future Perspectives,* 15 J. TRANSLATIONAL MED. 160 (2017).

[190] Karen Weintraub, The Anti-Aging Pill, MIT Technology Review (February 3, 2015), https://www.technologyreview.com/s/534636/the-anti-aging-pill/ ("it's nearly impossible to prove, in any reasonable time frame, that drugs that extend the lifespan of animals can do the same in people; such an experiment could take decades. That's why [Elysium] decided to take the unconventional route of packaging cutting-edge lab research as so-called nutraceuticals, which don't require clinical trials or approval by the FDA.").

[191] Abhirup Das, *Impairment of an Endothelial NAD+-H 2 S Signaling Network Is a Reversible Cause of Vascular Aging*, 731 CELL 74, 74 (2018).

[192] Weintraub, supra note 190.

[193] Ryan W. Dellinger et al., *Repeat Dose NRPT (Nicotinamide Riboside and Pterostilbene) Increases NAD^+ Levels in Humans Safely and Sustainably: A Randomized, Double-Blind Placebo-Controlled Study*, 4 NPJ AGING MECHANISMS DISEASE 1, 2–7 (2017).

[194] Elysium, *About Basis: How Does Basis Work*?, https://www.elysiumhealth.com/basis [https://perma.cc/8KSM-EYMH].

[195] Pharmanex v. Shalala, 221 F.3d 1151, 1159 (10th Cir. 2000).

[196] Ziv Harel et al., *The Frequency and Characteristics of Dietary Supplement Recalls in the United States*, 173 JAMA INT. MED. 926, 927 (2013).

approval for a NAD+ therapeutic, the sale of supplements with the same ingredient would be prohibited, as it is well-settled that a company may not sell a supplement that contains an FDA-approved drug.[197] If that were to happen, Elysium may end up having to halt sales of its existing supplement.

VII. CONCLUSION

Changes in the regulatory system will be paramount for the new category of healthspan extension drugs rapidly approaching readiness for clinical testing and regulatory approval. We are at a point in which the science is no longer "snake oil," but rather is beginning to piece together the complex puzzle that is aging. This puzzle cannot be completed within the current framework of FDA. FDA should alter the drug approval process for therapeutics targeting aging. From a pragmatic standpoint, this would allow for the elderly population to age healthier, thus being productive longer, as well as not burdening individuals with the unmanageable healthcare costs associated with the diseases of aging. This would overall lessen the societal costs of caring for an aging population, which will be especially important as population rates continue to decrease and the ratio of workers to consumers gets stressed.

Interest in healthspan prolongation has crossed a tipping-point and will only continue to grow and develop, outside the purview of FDA if necessary. Hence, FDA would be wise to adapt its system of review to create a pathway forward to keep control over this class of drugs. Rather than sitting on the sidelines and just watching, FDA should proactively encourage and promote the study and commercialization of safe and effective healthspan extension drugs by taking actions such as convening workshops and publishing guidance documents intended to give clarification, guidance and support to the growing number of scientists and companies working in the healthspan field.

If FDA fails to take proactive action, the inevitable development and use of healthspan interventions will continue largely outside FDA's purview, through pathways such as off-label prescribing and dietary supplements. Indeed, these trends have already begun. It would be far more preferable for FDA to oversee the safety and effectiveness of healthspan drugs, providing the assurance that patients, doctors, health insurers, and drug manufacturers seek. Successful clinical trials of healthspan extension agents "would be groundbreaking, with enormous implications not only for medical practice and policy but also for society in general."[198] FDA should be leading, not impeding, this progression to a healthier future for all.

[197] Pharmanex v. Shalala, 221 F.3d at 1159.

[198] Newman et al., *supra* note 59, at 1425.