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4 **Classifying Aging as a Disease in the context of ICD-11**

5
6 Alex Zhavoronkov^{1,2*}, Bhupinder Bhullar³
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8 ¹ The Biogerontology Research Foundation, Oxford, United Kingdom

9 ² Insilico Medicine, Johns Hopkins University, Emerging Technology Centers, Baltimore, MD,
10 21218, USA

11 ³ Novartis Pharma AG, Department of Developmental and Molecular Pathways, Novartis
12 Institute for Biomedical Research, Fabrikstrasse 22, 4056 Basel, Switzerland
13

14 *Alex Zhavoronkov, PhD, +1 626 593 7957, alex@biogerontology.org
15

16 **Abstract**

17
18 Aging is a complex continuous multifactorial process leading to loss of function and crystalizing
19 into the many age-related diseases. Here, we explore the arguments for classifying aging as a
20 disease in the context of the upcoming World Health Organization's 11th International Statistical
21 Classification of Diseases and Related Health Problems (ICD-11), expected to be finalized in
22 2018. We hypothesize that classifying aging as a disease will result in new approaches and
23 business models for addressing aging as a treatable condition, which will lead to both economic
24 and healthcare benefits for all stakeholders. Classification of aging as a disease may lead to more
25 efficient allocation of resources by enabling funding bodies and other stakeholders to use
26 quality-adjusted life years (QALYs) and healthy-years equivalent (HYE) as metrics when
27 evaluating both research and clinical programs. We propose forming a Task Force to interface
28 the WHO in order to develop a multidisciplinary framework for classifying aging as a disease.
29

30 **Introduction**

31
32 The recognition of a condition or a chronic process as a disease is an important milestone for the
33 pharmaceutical industry, academic community, healthcare and insurance companies, policy
34 makers, and individual, as the presence of a condition in disease nomenclature and classification
35 greatly impacts the way it is treated, researched and reimbursed. However, achieving a
36 satisfactory definition of disease is challenging, primarily due to the vague definitions of the
37 state of health and disease. Here, we explore the potential benefits of recognizing aging as a
38 disease in the context of current socioeconomic challenges and recent biomedical advances.
39

40 **Brief History of Disease Classification**

41
42 The concept of disease classification has existed for centuries, with professional classification
43 dating back to 15th century Italy, but international classification systems were not established
44 until relatively recently. One of the first major strides was made by William Cullen, who
45 provided a classified list of diseases in his *Nosologiae Methodicae* synopsis in 1769. The first
46 authoritative sources of disease terminology were then developed in 19th century England

47 (Robb-smith 1969; Moriyama et al., 2011), followed by the nomenclature of diseases by the
48 American Medical Association (National Conference on Nomenclature of Disease, 1933;
49 American Medical Association, 1961). Real progress toward the modern classification system,
50 however, began when efforts were internationalized. The first international nomenclature and
51 disease classification was created and maintained by the International Statistical Institute (ISI)
52 and is generally referred to as ICD-1, as it was developed at the first international conference to
53 revise the International Classification of Causes of Death in 1900. Since 1948, the World Health
54 Organization (WHO) has assumed the responsibility of maintaining, preparing and publishing
55 the revisions of the ICD. The 10th revision of the ICD, referred as ICD-10, was first published in
56 1992 (World Health Organization, 1992), and the 11th revision (ICD-11) is expected to be
57 released in 2018 (<http://www.who.int/classifications/icd/revision/timeline/en/>). Thus, as this date
58 approaches there is a sense of urgency among all stakeholders to codify classification proposals
59 before the window of opportunity closes for another decade or longer (World Health
60 Organization, 2006).

61
62 In its current definition, published in 1948, WHO describes health as a “state of complete
63 physical, mental and social well-being, not merely the absence of infirmity” (World Health
64 Organization, 1948). This definition is restrictive and there have been an increasing number of
65 calls to change it (Saracci, 1997; Bircher, 2005; Huber et al., 2011). The criteria for disease, on
66 the other hand, have historically changed over time. This is partly due to increasing health
67 expectations or changes in diagnostic abilities, but mostly due to a combination of social and
68 economic reasons (Scully, 2004). It was not until the 6th revision of ICD (ICD-6) in 1949 that
69 mental disorders were first classified as diseases (Katschnig, 2010). On the other extreme,
70 homosexuality was classified as a disease until 1974 by the American Psychiatric Association
71 (APA) (Reznek, 1987), an organization which frequently disagrees with the ICD on disease
72 classification. Since the completion of ICD-10, debates in biomedical literature have been
73 primarily focused on psychiatric disorders (First et al., 2015). A recent PubMed search using
74 “ICD-11” since 1992 produced 333 results, while “‘ICD-11’ NOT mental NOT psychiatric”
75 produced only 61 results.

76
77 While mental health issues continue to stay at the forefront, another major socioeconomic
78 problem has surfaced and is here to stay. Over the past decade, there has been an enormous shift
79 in the percentage of the world population that is elderly, and age demographics are projected to
80 continue to change dramatically in this direction in the next few decades. The socioeconomic
81 burden of this shift cannot be understated. Without advances in the ability to slow the aging
82 process, extend the healthy life span, and prevent the associated diseases, it will be difficult to
83 support the large numbers of those no longer enrolled in the workforce and instead enrolled in
84 costly long term health care.

85
86 Fortunately, the ability to track multiple underlying causes of death has provided a more granular
87 view on the causes of death in old age and in turn has facilitated better disease association and
88 classification (Moriyama et al., 2011). Our understanding of aging mechanisms is constantly
89 evolving. Similarly, disease classification is an evolving process and advances in our
90 understanding of aging may enable the classification of aging as a disease in the upcoming
91 revision of the ICD. To do so would have multiple benefits, garner more attention on the topic,
92 and ultimately boost progress in this active area of biomedical research.

93

94 **Biology of aging as a disease**

95

96 Aging is a complex multifactorial process leading to loss of function, multiple diseases, and
97 ultimately death. There are many theories explaining the origin of the overall process (Lopez-
98 Otin et al., 2013;Deleidi et al., 2015), cause and effect relationships between different processes
99 and systems, including aging of the immune system (Montecino-Rodriguez et al., 2013),
100 inflammation (Bruunsgaard et al., 2001;Sarkar and Fisher, 2006;Franceschi et al., 2007;Michaud
101 et al., 2013), fibrosis (Cieslik et al., 2011;Kapetanaki et al., 2013), mineralization of connective
102 tissue (Shindyapina et al., 2014), cellular senescence (van Deursen, 2014), wear and tear, and
103 many others. In addition, many genetic and epigenetic changes implicated in aging and longevity
104 are associated with aging in model organisms (Lombard et al., 2005;Moskalev et al., 2014). Even
105 though their role and action in human aging are uncertain, many of these changes are also
106 associated with human diseases (Kennedy et al., 2015; Aguilar-Olivos et al., 2015;De Rosa et al.,
107 2015;Helling and Yang, 2015;Lardenoije et al., 2015;Renauer et al., 2015). Recent discoveries
108 showing that mechanisms involved in cancer are also associated with the aging process have led
109 to multiple proposals to prevent cancer and other age-related diseases using drugs that increase
110 lifespan in model organisms (Blagosklonny, 2013;Zhavoronkov et al., 2014).

111

112 Surprisingly, aging shares many characteristics with Human Immunodeficiency Virus (HIV), as
113 while having a specific ICD-10 code, HIV is the cause of many fatal diseases associated with a
114 broad range of ICD-10 codes. However, unlike HIV, classifying aging as a disease is difficult
115 because of the absence of a clear set of aging biomarkers and the uncertainty of the time of
116 transition from loss of function to disease. There is some progress in this area; recent population
117 statistics and studies clearly demonstrate the relationship of aging and increased risk of multiple
118 diseases (Marengoni et al., 2011;Federal Interagency Forum on Aging-Related Statistics,
119 2012;Salive, 2013), and there are several frailty indexes that measure the rate of physical decline
120 and sets of aging biomarkers (Moreno-Villanueva et al.;Horvath, 2013). However, the transition
121 from aging to disease remains unclear both at the individual and population levels (Figure 1).

122

123 **Public opinion and stakeholders' views on aging as a disease**

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125 At the start of the twentieth century, most causes of death in advanced age were attributed to “old
126 age” and “natural causes” (Moriyama et al., 2011). However, over the course of the twentieth
127 century, the understanding of aging and disease changed (Shock et al., 1984;Bulterijs et al.,
128 2015;Faragher, 2015), with many age-related diseases and causes of death being clearly defined
129 (Vellas et al., 1992). Over time, many chronic diseases of old age previously considered to be a
130 part of normal aging including hypertension, rheumatoid arthritis, cardiomyopathy, and
131 osteoporosis received classification codes (Bennett et al., 1956;force, 1980;WHO, 1994).
132 Historically, “old age” was among the acceptable causes of death and was used on death
133 certificates (Moriyama et al., 2011). Most countries now provide guidelines limiting the use of
134 the term on medical certificates by age and issuing recommendations to avoid using only “old
135 age” as a cause of death (Office for National Statistics, 2010), since “terms such as senescence,
136 infirmity, old age, and advanced age have little value for public health or medical research”
137 (Centers for Disease Control, 2004). The same arguments are commonly used in debates against

138 classifying aging as a disease, as many stakeholders would prefer to have a more granular view
139 into causes of death.

140
141 To illustrate these differences in opinion about aging, a recent survey in Finland assessed
142 stakeholders' perspectives on what constitutes a disease. The study surveyed 3,000 laypeople,
143 1,500 doctors, 1,500 nurses and 200 parliament members and asked them to rate 60 "states of
144 being" by their perception of disease. And while most cancers like breast cancer (#1) and
145 prostate cancer (#2) were clearly classified as diseases, wrinkles (#60), smoking (#59) and
146 ageing (#58) were not classified as diseases (Tikkinen et al., 2012). Most of the doctors and
147 nurses did not consider sarcopenia, age-related muscle loss (#31) as a disease. Surprisingly,
148 obesity (#50), was not considered to be a disease by any of the stakeholder groups even though it
149 is now classified as a disease with multiple disease codes (E65-E68) in endocrine, nutritional and
150 metabolic diseases (E00-E90), representing a considerable part of chapter IV in ICD-10 (World
151 Health Organization, 2011). The case of obesity provides clues that the opinion of multiple
152 stakeholders including medical, general public, doctors and nurses may deviate from the WHO
153 consensus for the purposes of disease classification, and other stakeholders may play a larger
154 role in forming ICD revisions.

155
156 In another survey of pension funds, insurance companies, and employee benefits industries; only
157 11% of respondents felt that aging is a disease and less than 22% used simulations involving
158 biomedical advances in forecasting life expectancy (Zhavoronkov, 2015). Considering the
159 relatively conservative responses, these stakeholder groups may not be in favor of classifying
160 aging as a disease in the ICD-11 revision.

161
162 The debate on whether aging should be classified as a disease is taking place primarily in
163 academic circles (Ries, 1976;Glasser, 1986;Williams, 1987;Blumenthal, 1993;Callahan and
164 Topinkova, 1998;Blumenthal, 2003;Faragher, 2015;Gems, 2015b) with no consensus opinion
165 (Garber, 2008;Donmez and Guarente, 2010) and even some opposing views from
166 biogerontologists (Ardeljan and Chan, 2013;Rattan, 2014). Even though some of these views aim
167 at higher citation rating or other objectives, these opposing views do not propose concrete plans
168 for addressing the aging problem at the level of WHO.

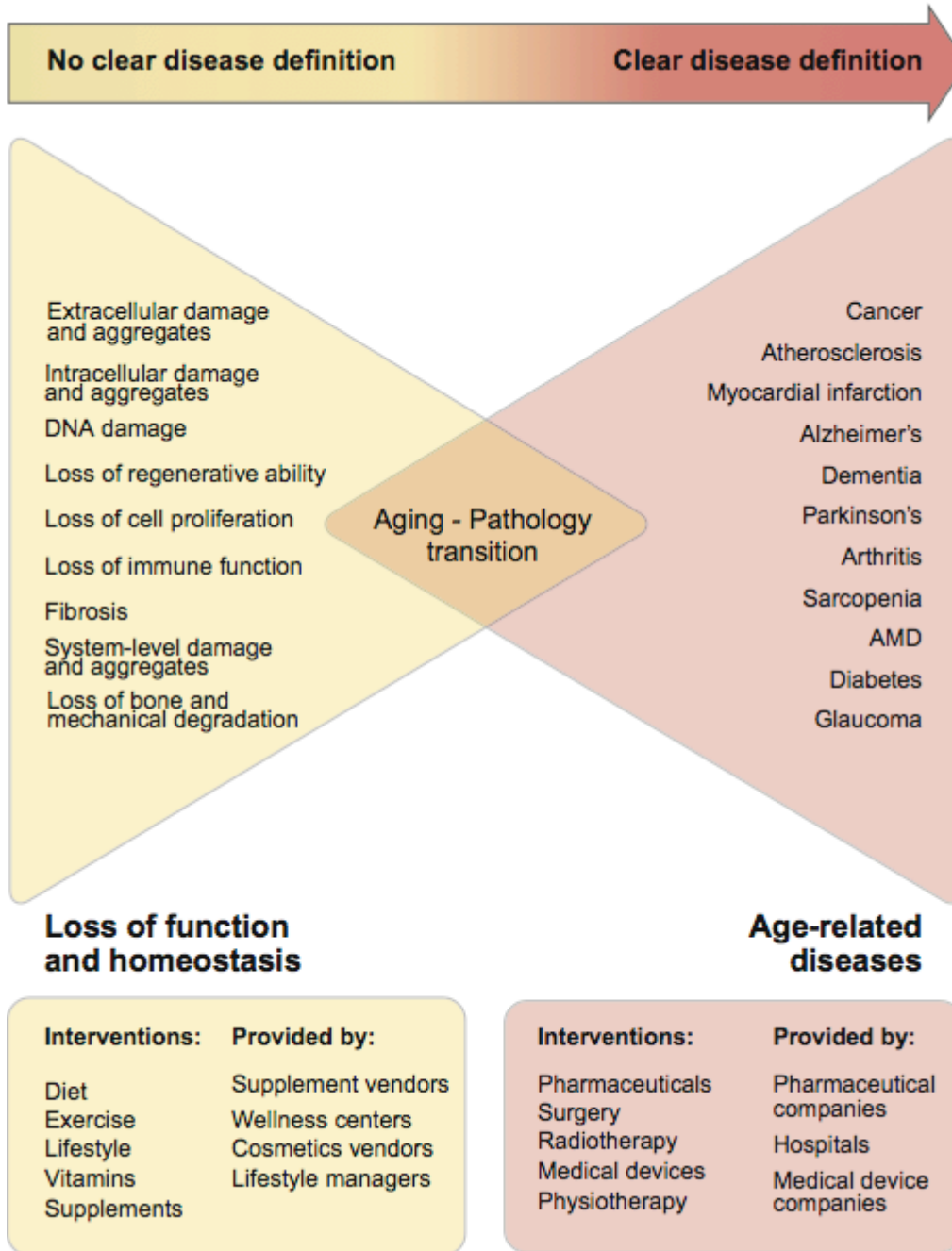
169
170 Prior history with many mental disorders, including autism (Lord and Jones, 2012), demonstrates
171 that classifying a state of being as a disease leads to an increased attention to the subject, the
172 development of more accurate diagnostic methods, and increased involvement of the
173 pharmaceutical industry and policy makers. It also provides the basis for clinical trials.

174 175 **Strategies in moving forward**

176
177 *Large scale studies in humans.* There are many strategies that can be pursued to test the efficacy
178 of geroprotectors in humans, including large scale publicly-funded supplement studies and
179 studies designed to address a specific set of biomarkers of aging (Hefti and Bales, 2006;Le
180 Couteur et al., 2012;Scott and DeFrancesco, 2015). The results from the Novartis RAD001 study
181 in healthy elderly patients as a vaccine-potentiating agent (Mannick et al., 2014) elucidated the
182 possibility of ameliorating immunosenescence in the elderly and raises the prospect of delaying
183 the onset of age-related diseases.

184
185 *Aging biomarkers.* Even though major advances have been made since the final ICD-10 meeting
186 in tracking aging at all levels of organization (Sprott, 2010;Le Couteur et al., 2012;Hatse et al.,
187 2014;Wu et al., 2015), there is no universal set of biomarkers and guidelines for measuring aging
188 as a system. However, in order to successfully evaluate the effect of any drug that influences
189 aging, it is essential have a measureable endpoint, such as biomarkers. Gerontologists have
190 previously struggled to extrapolate biomarkers from animal models to humans (Butler et al.,
191 2004). But with the advent of Big Data, it is now possible to track aging on the epigenetic level
192 and measure accelerated aging in many diseases (Horvath et al., 2014;Horvath and Levine,
193 2015). There are also promising studies of transcriptomic (Nakamura et al., 2012;Dhahbi, 2014),
194 telomere-length (Zhang et al., 2014;Shamir, 2015) and multi-variate (Sanders et al., 2014) blood-
195 based biomarkers that may lead to minimally invasive diagnostic tests. It is also possible to track
196 signalome-level biomarkers . Recent studies have shown that signaling pathways found in aging
197 are comparable to and share many characteristics with Hutchinson-Gilford Progeria Syndrome
198 (HGPS) (Aliper et al., 2015) and Age-related Macular Degeneration (AMD) (Makarev et al.,
199 2014). It is also possible to use system-wide biomarkers like heart rate variability (HRV) as
200 biomarkers of aging (Corino et al., 2007). There is a rapidly growing body of evidence that
201 biomarkers of aging contributes and is very similar to the many age-related diseases on all levels
202 of organization and it is possible to multiplex epigenetic, transcriptomic, proteomic, signalomic,
203 metabolomic, metagenomic and phenotypic biomarkers to track the progression of aging as a
204 disease.

205
206 Since the transition from age-associated processes to disease is unclear (Figure 1), in the absence
207 of readily available and highly personalized biomarkers, one of the approaches to set the gold
208 standard for health, is to select the age when peak performance is observed in the majority of the
209 population. There are conflicting theories without convincing empirical evidence that the human
210 skeleton stops growing at approximately the age of 20 (Nilsson et al., 2005). Peak age for
211 athletic performance depends upon sports disciplines and is usually in the range of 20-30 years
212 with younger age of peak performance in short distance races and gradually increasing age of
213 peak performance in longer racing distances (Elmenshawy et al., 2015). In prenatal diagnostics,
214 statistics for Down's and other chromosomal abnormalities led to recommendations for invasive
215 prenatal screening after 35, which is generally referred to as advanced maternal age, procedures
216 that have gradually been replaced by non-invasive prenatal procedures. (Chiu et al., 2009;Nakata
217 et al., 2010;Benn et al., 2013;Lo, 2013;Nepomnyashchaya et al., 2013;Twiss et al.,
218 2014;Neufeld-Kaiser et al., 2015).



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220

221 **Figure 1:** Gradual transition from the loss of function and homeostasis due to aging into age-
222 related pathologies. It is clear that with time the combination of many age-related processes
223 becomes more granular and crystallizes into specific diseases. However, it is unclear when aging
224 starts and when the transition between aging and pathology occurs.

225

226 Discussion

227

228 Many scientists throughout the world have argued that aging should be classified as a disease
229 (Bulterijs et al., 2015; Gems, 2015a). The recent decision of the Food and Drug Administration

230 (FDA) to test the potential of metformin in reducing risk of developing age-related conditions
231 including cancer, heart disease and cognitive impairment resonated in the community, increased
232 attention to the field, and suggested that aging may be an indication appropriate for clinical trials
233 (Check Hayden, 2015). However, there are no visible global or national efforts to include aging
234 in the ICD-11 classification as a disease. This is primarily due to the structure and clear
235 separation of the supplement and wellness markets and disease treatment markets. Stakeholders
236 in the wellness market are selling billions of dollars worth of goods and services and are not
237 interested in increased regulation. Also, the structure of the supplement market, where large
238 ingredient vendors supply product to compounders that in turn supply brand holders that sell
239 through distribution networks, does not provide incentives or ability at any level to engage in
240 discussions with policy makers.

241
242 As demonstrated in Figure 1, individual consumers of healthcare cannot formulate the demand
243 for evidence-based medicine (pharmaceuticals) to combat aging and rely on the less-regulated
244 wellness and alternative medicine industry. The fact that the supplement industry is prosperous,
245 with a total estimated sale of \$36.7 billion in the US in 2014, implies that there is consumer
246 demand for anti-aging treatments (Nutrition Business Journal, 2015). Increasing regulation of the
247 supplements and wellness industry may lead to more demand and a supply of evidence-based
248 approaches to interventions in aging.

249
250 Increasing productive longevity in the developed countries is likely to reduce healthcare costs,
251 boost employee productivity and lead to substantial economic growth (Zhavoronkov and
252 Litovchenko, 2013), while the inability to increase productive longevity quickly may result in
253 economic collapse (Zhavoronkov et al., 2012). Yet when it comes to aging, policy makers, the
254 general public, and even pension funds lack the sense of urgency to address it as a curable
255 disease (Zhavoronkov, 2015) even though there is a growing realization of the likely economic
256 problems (Zhavoronkov, 2013). Even some of the most reputable demographers, gerontologists
257 and biogerontologists express conflicting opinions on the subject, providing arguments against
258 classifying aging as a disease. While these papers promote debate and increase their citation
259 ratings, they are certainly not helpful for making the case for formal classification of aging as a
260 disease or family of diseases. Formal classification of aging as a disease is likely to unite both
261 scientists and medical practitioners in this effort.

262
263 There are also ethical considerations associated with classifying aging as a disease (Caplan,
264 2005). A large portion of the population may feel uncomfortable with the idea and resist being
265 classified as disease carriers either at birth or after a specific age certain age while lacking clear
266 representation of a disease. However, the recent inclusion of obesity in ICD-10 has shown that it
267 not only helped to attract resources to research, but it also resulted in more frequent diagnosis of
268 the condition. Since obesity has been classified as a disease, it is now easier for medical
269 practitioners to convince patients to pursue healthier lifestyles and prescribe medication, even in
270 cases where patients are comfortable with the condition.

271 272 **Recommendations for Implementation**

273
274 *Form a task force.* As part of the upcoming ICD-11, the International Association for the Study
275 of Pain (IASP) Task Force was created to classify chronic pain as a disease (Treede et al., 2015),

276 with a clear organizational structure to interact with the WHO to create a classification system of
277 all manifestations of chronic pain, resulting in 7 categories: musculoskeletal pain, visceral pain,
278 headache, neuropathic pain, post surgical and posttraumatic pain, cancer pain and primary pain.
279 A similar task force should be created to interact with the WHO on the classification of aging.

280
281 *Develop an “ideal norm.”* Despite the growing abundance of biomarkers of aging, classifying
282 aging as a disease will be challenging due to the absence of the “ideal norm.” Despite significant
283 effort from the academic and industry communities, sarcopenia is still not classified as a disease
284 despite clear clinical and molecular representation and similarity with premature musculoskeletal
285 aging and myotonic disorders (Cruz-Jentoft et al., 2010; Muscaritoli et al., 2010; Fielding et al.,
286 2011; Morley et al., 2011; Mateos-Aierdi et al., 2015). One approach to address this challenge is
287 to assume an “ideal” disease-free physiological state at a certain age, for example, 25 years of
288 age, and develop a set of interventions to keep the patients as close to that state as possible.
289 Considering the WHO definition of health, it may be possible to agree on the optimal set of
290 biomarkers that would be characteristic to the “state of complete physical, mental and social
291 well-being, not merely the absence of infirmity” and agree on the physiological threshold after
292 which the net totality of deviation of these biomarkers from norm can be considered a disease.

293
294 *Set effective metrics.* When performing cost-effectiveness analysis (CBA), economists often
295 evaluate the outcomes of various programs in terms of the quality-adjusted life years (QALYs)
296 and healthy-years equivalent (HYE) (Mehrez and Gafni, 1989). The most effective altruistic
297 causes are now also evaluated using these metrics (Macaskill, 2015). Studies also demonstrate
298 that each QALY can be valued at \$24,777 to \$428,286 depending on the method (Hirth et al.,
299 2000). Many projects in aging research do not result in QALY and are currently not prioritized to
300 maximize healthy lifespan (Zhavoronkov, 2013). Classifying aging as a disease would facilitate
301 the development of programs and prioritize projects in aging research that maximize QALY and
302 HYE today and in the future.

303 304 **Conclusion**

305
306 There are definite benefits for many stakeholders in having aging classified as a disease, and the
307 research community should consider uniting and working as a single voice to increase the chance
308 of having aging classified as a disease by the WHO.

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No clear disease definition

Clear disease definition

Extracellular damage
and aggregates

Intracellular damage
and aggregates

DNA damage

Loss of regenerative ability

Loss of self-cleaning

Loss of immune function

Fibrosis

Systemic toxic damage
of all aggregates

Loss of homeostatic
regulation

Ageing - Pathology
transition

Cancer

Alzheimer's

Myocardial infarction

Alzheimer's

Dementia

Parkinson's

Atrial fibrillation

Senescence

Diabetes

Obesity

Disability

Loss of function
and homeostasis

Age-related
diseases

Interventions:

Provided by:

Gen

Supplemental vitamins

Exercise

Wellness centers

Lifestyle

Diagnosed patients

Vitamins

Lifestyle management

Supplements

Interventions:

Provided by:

Pharmaceuticals

Pharmaceutical companies

Surgery

Hospitals

Radiotherapy

Medical devices

Medical device companies

Physiotherapy