To: MK Tali Ploskov. Chair Knesset Committee on the National Masterplan on Aging

Re: Research, development and education for the promotion of healthy longevity and prevention of aging-related diseases

Executive summary

Today, there are about 980,000 people in Israel over the age 65 (about 11% of the country's population), and it is expected that the number of the elderly will increase to 1.6 million by 2035. This reality demands the preparedness of the healthcare and welfare system to provide worthy and sufficient services for the elderly, adequate solutions for the prevention of systemic economic collapse, as well as for the equitable social inclusion of the elderly, and as a result the improvement of their quality of life and the county's economic growth. To achieve those goals, the advancement of medical research and development is a necessary condition. The aging-related health decline is the major cause of mortality, morbidity and disability. It is thus the root cause of all healthcare and economic challenges related to the population aging and should be addressed according to the severity of the problem. Therefore, considerable resources must be dedicated to the advancement of research, development and education aimed at the amelioration of degenerative aging process and debilitating aging-related diseases in order to extend healthy longevity as much as possible for the entire population.

This program recommends:

1. **Increasing the R&D budget for the field** – A significant increase in the level of governmental and non-governmental funding must be ensured for basic, applied, translational and clinical research and technological development for the prevention of degenerative aging processes, aging-related chronic non-communicable diseases and disabilities, in order to extend the healthy and productive life expectancy for the entire population throughout the entire life course. Specifically, a defined significant percentage of the research and development budgets of the relevant ministries must be dedicated to the field, including bi-national and international research programs in which Israel is a partner.

2. **Increasing education in the field** – Academic and public education frameworks and programs must be created and expanded considering the basic and applied research on aging processes and aging-related diseases, promoting healthy longevity, preventing aging-related diseases and improving the quality of life for the elderly, including biological, medical, technological, environmental and social aspects.

3. Establishing and improving public health systems for the early detection and prevention of aging-related diseases – Evidence-based measures and indicators must be developed and applied to estimate the effects of aging, predict and detect at an early stage multiple aging-related diseases, and examine the effectiveness of therapeutic and preventive interventions against them. Concomitantly, measures and indicators must be advanced for the functional and employment capacity of the elderly and for the improvement of their functional capacity.

Background

Population aging – the critical health challenge

Over the past decades, the average life expectancy has increased globally, reaching a world-wide average of about 72 years in 2017 and around 80 in the developed countries, including Israel, where the life expectancy reached 82.5 years. This development has been achieved especially due to improvements in sanitation, medical advances, rising living standards and a decline in child mortality. Although the increasing life expectancy generally reflects positive human development, new challenges are arising due to the fact that the aging process is strongly associated with biological and cognitive degeneration, whose severity can vary between individuals. Today, there are about 980,000 people in Israel over the age 65 (about 11% of the country's population), and it is expected that the number of the elderly will increase to 1.6 million by 2035. This reality demands the preparedness of the healthcare and welfare system to provide worthy and sufficient services for the elderly, adequate solutions for the prevention of systemic economic collapse, as well as for the equitable social inclusion of the elderly, and as a result the improvement of their quality of life and the county's economic growth. Presently, the level of preparedness for the population aging is still inadequate. The national expenditures, both private and public, for the long-term nursing care of the elderly in Israel are about NIS 14.5 billion (~$ 4 billion) yearly, which comprises 1.2% of the entire Gross Domestic Product, and are expected to grow by over 300% by 2059.[1] Nonetheless, the State of Israel expends only about 0.5% of its general research budget for the research of aging and aging-related diseases.

Generally, degenerative aging processes are the major underlying cause for non-communicable diseases (NCDs), including cancer, ischemic heart disease, type 2 diabetes, COPD, neurodegenerative diseases, such as Alzheimer's disease, and others. Mental health deterioration due to chronic neurodegenerative diseases represents the largest cause of disability in the world. Aging also increases the risk of morbidity and mortality from infectious diseases like pneumonia and influenza, as a result of aging-related immunodeficiency. Moreover, the susceptibility to injury and trauma (such as falls and concussions), due to the impairment of balance and mental state, are strongly increased by the aging process. Also, the processes of aging exacerbate and reinforce the effects of other risk factors of non-communicable diseases (tobacco use, unhealthy diet, physical inactivity, and harmful use of alcohol). In sum, aging-related health decline is the major cause of mortality and morbidity and should be addressed according to the severity of the problem.

The social and economic challenge as a result of aging-related ill health

Aging is presently regarded as one of the greatest economic and societal challenges that most countries will face in the coming decades. The aging process is the main contributing factor for the rise of morbidity and frailty in old age, and as a result the suffering, loss of function and mortality of the elderly. This is in fact the biological root for all the problems and challenges that

[1] Bank of Israel. Annual Report 2012. Public service system for the long-term care for the elderly in Israel https://www.boi.org.il/he/NewsAndPublications/PressReleases/Pages/120318t.aspx
Bank of Israel. Annual Report 2017. National program for the long-term care for the elderly (the data are of 2015) http://www.boi.org.il/he/NewsAndPublications/RegularPublications/DocLib3/BankIsraelAnnualReport/%D7%93%D7%95%D7%97%20%D7%91%D7%A0%D7%A7%20%D7%99%D7%A9%D7%A8%D7%90%D7%9C%202017/page1.pdf

are defined as “problems and challenges of population aging” including the burden on the healthcare system, the impairment of working capacity, the deficit of work force, the dependence on the younger generations, the impairment of the quality of life and the decline in the status of the senior citizens.

Therefore, considerable resources must be dedicated to the amelioration of degenerative aging process and debilitating aging-related diseases in order to extend healthy longevity as much as possible for the entire population. Due to the importance of the problem, the WHO Thirteenth General Programme of Work for 2019−2023 (GPW13) posits that “Ensuring healthy ageing is an urgent challenge in all countries”. The program suggests the use of healthy life expectancy as the main measure of health care success, and sets clear goals to increase healthy life expectancy and "reduce the number of older adults 65+ yrs who are care dependent".[2] To achieve those goals, the advancement of medical research and development is a necessary condition. Accordingly, the WHO Global Strategy and Action Plan on Ageing and Health (GSAP) - 2016-2020, and the preparations for the “Decade of Healthy Aging – 2020-2030” include the strategic objective of enhancing research of aging, “improving measurement, monitoring and understanding of healthy ageing”.[3]

The need to enhance research and development for healthy longevity and prevention of aging-related diseases

A necessary condition for the promotion of healthy longevity and for finding therapeutic and preventive solutions for aging-related diseases is the advancement of medical research and development in the field. Presently, the level of scientific knowledge and technological capabilities are not sufficient to provide comprehensive solutions for severe chronic aging-related diseases. Therefore, the research and development must be intensified and accelerated in order to improve those capabilities. The research and development are needed in order to create novel therapeutic means based on a deeper fundamental understanding of aging processes, as well as to optimize and implement the means that are already ostensibly known, such as existing therapeutic means and healthy life style (nutrition, physical activity, etc.).

There is robust scientific evidence, from basic science, experimental and theoretical research, that demonstrates the real capability to intervene into the aging process, prevent aging-related diseases and extend healthy life. [4] The main objective of enhancing the research and development in the field is to obtain more profound basic scientific knowledge, and to accelerate the transition from basic research to applied, translational and clinical research, in order to create new, safe and effective therapeutic means for the aged population, and to implement them in the clinic. The means that have already proven their effectiveness in the clinic, need to be beneficially applied in a wider population. This is the principal reason for the vital need to increase support for the field, in order to facilitate and accelerate the research, development and

[2] World Health Organization (2018). Thirteenth general programme of work 2019−2023 (GPW13). http://www.who.int/about/what-we-do/gpw-thirteen-consultation/en/

[3] World Health Organization (2015). Global Strategy and Action Plan on Ageing and Health (GSAP) - 2016-2020. http://who.int/ageing/global-strategy/en/

[4] Jin K, Simpkins JW, Ji X, Leis M, Stambler I (2015). The critical need to promote research of aging and aging-related diseases to improve health and longevity of the elderly population. Aging and Disease, 6(1), 1-5. http://www.aginganddisease.org/EN/10.14336/AD.2014.1210

application of effective and safe new therapies and medical technologies for the improvement of health of older persons. These means will be able to reduce the burden of the aging process on the economy and to alleviate the suffering of the aged and the grief of their loved ones. On the positive side, if granted sufficient support, these means can increase the healthy life expectancy for the elderly, increase their period of productivity and their contribution to society, and enhance their sense of enjoyment, purpose and valuation of life

There are specific reasons to advance the medical research and development (R&D) on aging in order to prevent chronic aging-related diseases, as a means to improve the health, longevity and quality of life for the elderly population:

1. This R&D is already supported by scientific proofs of concept, involving the evidential increase in healthy lifespan in animal models and the emerging technological capabilities to intervene into fundamental aging processes. There are also experimental proofs of the possibility to prevent multiple aging-related diseases by intervening into the aging process as the main risk factor common to all these diseases, including positive experimental results in humans.[5] Any reinforcement of such R&D will lead to additional cumulative reinforcements, speed up the translation of basic research to clinical practice and facilitate the faster and wider distribution of the R&D results for the public.

2. This R&D can provide real solutions to a number of non-communicable, age-related diseases and conditions, such as heart disease, cancer, neurodegenerative diseases, type 2 diabetes, chronic obstructive pulmonary disease, and general frailty. These diseases and conditions are strongly determined by degenerative aging processes (such as chronic inflammation, cross-linkage of macromolecules, somatic mutations, loss of stem cell populations, impairment of systemic regulation and homeostasis, and others).[6] Moreover, such R&D solutions are likely to decrease susceptibility of the elderly also to communicable diseases (such as influenza) due to improvements in immunity. Such means will enable a significant increase in the expectation of healthy, productive and creative life for the aged population.

3. The innovative, applied results of such research and development will lead to sustainable solutions for a large array of age-related medical and social challenges, that may be globally applicable. [7] The most important of them are the savings in healthcare for chronic age-related diseases and increase in the period of active and productive employment for the elderly population. This will result in their diminished dependence on external entities and the corresponding release of resources for further social and economic development in Israel. As it is known, the vast majority of health expenditures and loss of productivity occur in the late development stages of chronic aging-related diseases. Therefore, any postponement of this period by early detection and prevention will create vast humanitarian and economic benefits,

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[5] Newman JC, Milman S, Hashmi SK, Austad SN, Kirkland JL, Halter JB, Barzilai N (2016). Strategies and challenges in clinical trials targeting human aging. The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 71, 1424–1434. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5055653/

[6] Kennedy BK, Berger SL, Brunet A, Campisi J, Cuervo AM, Epel ES, et al. (2014). Geroscience: linking aging to chronic disease. Cell, 59, 709-713. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4852871/

[7] Goldman DP, Cutler D, Rowe JW, Michaud PC, Sullivan J, Peneva D, Olshansky SJ (2013). Substantial health and economic returns from delayed aging may warrant a new focus for medical research. Health Affairs, 32 (10), 1698-1705. http://www.ncbi.nlm.nih.gov/pubmed/24101058

both for the individual and the society as a whole. Excellence in this field will ensure competitive advantage and positive image of the State of Israel, insofar as the subject is globally relevant.

4. Due to the points 2 and 3 above, the investments into the biomedical research and development on aging and aging-related diseases, can be the most beneficial and profitable for the Israeli economy compared to any kind of fundamental or applied research generally and biomedical research in particular. Despite this, the actual investments in the field in Israel are miniscule, both in absolute terms and relatively to the entire budgeted R&D expenses. The lack of investments into the field can contribute to a future crisis that may be due to the lack of preparedness of the healthcare and welfare system to provide worthy and sufficient services for the elderly, the lack of adequate solutions for the prevention of systemic economic collapse, as well as for the equitable social and economic inclusion of the elderly.

5. Such research and development should be supported by the government on ethical grounds, to provide equal health care chances for the elderly as for the young. This would correspond with the Jewish principle “Do not reject a soul for another soul” and with the UN Sustainable Development Goal “Ensure healthy lives and promote well-being for all at all ages”.

Recommendations

1. **Increasing the R&D budget for the field** – A significant increase in the level of governmental and non-governmental funding must be ensured for basic, applied, translational and clinical research and technological development for the prevention of degenerative aging processes, aging-related chronic non-communicable diseases and disabilities, in order to extend the healthy and productive life expectancy for the entire population throughout the entire life course. Specifically, a defined significant percentage of the research and development budgets of the relevant ministries must be dedicated to the field. These include the Ministry of Health; the Ministry of Science, Technology and Space; the Planning and Budgeting Committee of the Council for Higher Education; the Israel Innovation Authority; the Israel Science Foundation; the Israel Academy of Sciences and Humanities including the National Infrastructure Forum for Research and Development; the Ministry for Social Equality; the National Insurance Institute; the bi-national and international research programs in which Israel is a partner, particularly in the divisions concerning the research and treatment of non-communicable chronic diseases.

Explanation – Except for the budget framework for science, technology and innovation for the older persons within the Ministry of Science, Technology and Space, there are no other defined budget frameworks in Israel for research and development in the field of aging, healthy longevity and prevention of aging-related diseases. There are limited support frameworks that can be adapted to the subject, such as research budgets for specific diseases, such as Alzheimer's disease, diabetes, cancer, etc., which by their nature are aging-related diseases. But in fact, there are no dedicated support frameworks specifically addressing aging-related ill health as a whole (old-age multimorbidity), neither addressing aging as the primary risk factor for age-related diseases, and there is almost no reference to the special medical needs and characteristics of the aging individuals and the older population. Their characteristics and medical needs are often dramatically different in terms of diagnosis and treatment from the younger population, and the

difference may have a decisive impact on the effectiveness of treatment. There is also a lack of centralized R&D support frameworks for the field of aging in Israel, such as the NIH's National Institute on Aging that exists in the US. Therefore, budget frameworks must be established for medical research and development that will specifically address the issue of aging, and promote healthy longevity and prevention of aging-related diseases. These frameworks will provide calls for research proposals, grants, scholarships, services and action plans designed to alleviate the degenerative aging process and improve the longevity and quality of life of the older population, on behalf and in cooperation of the relevant ministries.

2. **Increasing education in the field** – Academic and public education frameworks and programs must be created and expanded considering the basic and applied research on aging processes and aging-related diseases, promoting healthy longevity, preventing aging-related diseases and improving the quality of life for the elderly, including biological, medical, technological, environmental and social aspects.

Explanation – Due to the severe deficit of educational material in the field in Israel, educational teaching and training material should be developed and disseminated for people at all education levels, both for the academia and the general public, for all age groups, for different sectors and in different languages, in accordance with their specific abilities and characteristics. Teaching programs that increase motivation and stimulate scientific thinking in the field should be developed for children, university students at different study stages (undergraduate and graduate), for interns and specialists, and as a part of adult enrichment studies. In particular, it is necessary to develop study materials, such as courses and professional specialization programs in the biology of aging (biogerontology), especially for physicians and biologists in the fields adjacent to aging research, as well as educational materials for the general public. The materials for the general public should include lectures, reviews of the latest scientific developments in the field and practical recommendations for the promotion of healthy longevity and for the preparation of the younger generation to the challenges that expect them. There must be prepared and disseminated authoritative, evidence-based information about lifestyle regimens (such as nutrition and physical activity) that promote healthy longevity and prevent aging-related ill health. A variety of educational teaching and training means should be developed, including conferences, printed materials, interactive web platforms and other accessible technological means. Relevant ministries and institutions should be involved in the development of and providing access to these educational programs, from the Ministry of Education and the Council for Higher Education to local authorities, third sector organizations, and community centers. In order to facilitate the progress, there is a need to encourage the establishment of educational pilots and the examination of good practices in relevant ministries and other frameworks.

3. Establishing and improving public health systems for the early detection and prevention of aging-related diseases – Evidence-based measures and indicators must be developed and applied to estimate the effects of aging, predict and detect at an early stage multiple aging-related diseases, and examine the effectiveness of therapeutic and preventive interventions against them. Concomitantly, measures and indicators must be advanced for the functional and employment capacity of the elderly and for the improvement of their functional capacity.

Explanation – In order to develop and implement improved measures for assessing the aging process, for the early diagnosis and prediction of multiple aging-related diseases, for examining the effectiveness of treatments for their prevention and for estimating and improving the older persons' functional and employment abilities, it is necessary to increase and improve the collection and processing of various types of data on aging, including biological and medical data in combination with behavioral and social, economic and environmental data.[8] In this process, it is necessary to establish and/or expand relevant databases (registries) and analytical platforms and tools (knowledge centers) in order to facilitate the collection, design, accessibility, analysis, integration and sharing of data on aging, promotion of healthy longevity and prevention of aging-related diseases. These databases and analytical tools should be used predictively to model large amounts of data for more effective diagnosis and treatment and to allow personalized medicine for the older subjects, with reference to their aging process.[9] In order to establish and expand these measurement and analysis systems, it is necessary to involve the relevant ministries and institutions, in particular the Ministry of Health, with the maximum possible cooperation of other entities who have access to data on aging, such as research institutions, hospitals, health management organizations, local authorities and public and commercial research communities. The goals of evaluating the aging processes, early detection and prevention of aging-related ill health as a whole (preventing old-age multimorbidity) and extension of healthy lifespan, should be specifically defined in relevant frameworks and programs, such as the National Program for Personalized Medicine and the National Program for Digital Health as well as relevant international health promotion programs where Israel takes part. Initiatives and pilots of different extents on the subject should be encouraged in all sectors, while supporting their cooperation.

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December 24, 2018

[8] Lara J, Cooper R, Nissan J, Ginty AT, Khaw KT, Deary IJ, Lord JM, Kuh D, Mathers JC (2015). A proposed panel of biomarkers of healthy ageing. BMC Medicine, 13, 222. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4572626/

[9] Blokh D, Stambler I (2017). The application of information theory for the research of aging and aging-related diseases. Progress in Neurobiology, 157, 158-173. http://dx.doi.org/10.1016/j.pneurobio.2016.03.005