Israel can and should become an important contributor to the international geroscience research, development, application and education

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Summary

Due to the aging of the global population and the derivative increase in major aging-related non-communicable diseases and their economic burden, there is an urgent international need to promote the research, development and application of and education on effective and safe therapeutic geroscience interventions. These interventions are designed to mitigate degenerative aging processes, thus preventing and eliminating the main underlying contributors for major chronic aging-related diseases and thus improving the healthy and productive longevity for the elderly population. Insofar as aging is the main contributing factor of major chronic age-related diseases, the research and development efforts in the fields of geroscience and of major chronic diseases are integrally related. Israel can be an important contributor to these international R&D efforts, for which it can offer its proven record of scientific and technological achievements and innovation, its strong supportive infrastructure for research and development, its highly skilled scientific and technological work force, including leadership in diverse branches of biomedical research on aging and aging-related diseases. Yet a stronger effort will be needed to build on those strengths and realize the country's potential in the field for the benefit of the Israeli and global population. Israel can help further promote the field, not only locally, but internationally, by creating and sharing policy suggestions for the advancement of the field.

1. Israel has made significant progress in the fields related to geroscience and combat of major aging-related diseases.

Israel can and should be an important contributor to the global geroscience endeavors, building on its scientific, technological and societal achievements in the field of aging and related fields[1]:

- In recent years, Israel has seen a substantial rise in the maturity of its academic landscape relevant to the research of aging and longevity. At least one aging research center or cluster is either present or planned for every Israeli university. Moreover, there is an extensive network of geriatric hospitals and geriatric departments in all of Israel's major hospitals where cutting edge clinical aging research takes place.

- Dozens of labs and R&D departments in Israel excel in all areas related to geroscience and healthy longevity, including developing geroscience-based drugs and other therapies, regenerative medicine and bioengineering, genetic and epigenetic interventions, personalized medicine, data mining and digital health, nanomedicine, diagnostics and biomarkers of aging, nutrition and ergonomics, assistive technologies (see the report "Longevity Industry in Israel" 2019[1]).
- The Israeli government has made promising first steps toward addressing Healthy Longevity as a core national priority. Several state-supported programs emerged for the advancement of aging-related biomedical R&D, such as the "Scientific and Technological Infrastructure for the Elderly" and the "Healthy Aging" programs of the Ministry of Science and Technology[2], and the bi-national Britain-Israel Research and Academic Exchange Partnership on Ageing (BIRAX Ageing) supported by the Israeli and UK governments[3]. Such support programs can and need to be reinforced and analogous programs in additional ministries can and need to be established. Yet the existing programs set a precedent and a proof of impact.
- Israel is among the top 10 countries in the world in general life expectancy (~82.5 years)[4] and in the 5th place in healthy life expectancy (~73 years)[5], with an intermediate gap between healthy and general life expectancies (~9.5 years). These achievements give encouragement and confidence in the ability to further improve the healthy longevity metrics.
- Israel excels in scientific and technological innovation. In 2019, Israel was in the 5th place in the Bloomberg Innovation Index[6]. In 2015, Israel was in the first place in the world for research intensity, investing in research about 4.3% of its GDP[7]. For the past several years, Israel has been among the top ten countries in terms of scientific publications and patents per capita, as well as percent of scientists and technicians per 10,000 employees[8]. In 2018 Israel was ranked the world's third most educated country[9].
- Israel is in the 6th place in healthcare efficiency, showing a high general and healthy life expectancy with relatively low health care expenditures[10]. The Israeli government spends 7.5% of GDP on public healthcare, compared to 8.8% average in OECD. Israel is home to an advanced socialized healthcare system, with all of its citizens guaranteed high quality medical care.
- Strong advances have been made in implementing preventive medicine and new medical technologies, which has led to significant improvements in people's health. Thus, the frequency of heart attacks dropped in Israel by 50% in the last decade due to improving health technologies and prevention[11]. Since 2000, the general mortality rates decreased by close to 30%[12].
- Israel has the lowest rate of diet-related deaths worldwide[13] and is among the top ten countries in the Bloomberg Healthiest Country Index[14].
- Israel is strongly involved in international cooperation in biomedical science and technology. International R&D cooperation departments exist in several ministries, including Ministry of Health, Ministry of Science and Technology, the Israel Innovation authority of the Ministry of Economy and Industry, Ministry of Foreign Affairs, with science and technology collaboration agreements with dozens of countries.
- Israel provides platforms for international networking in the field of aging. It has been host to several large national and international summits on aging, such as "The 8th European Congress of Biogerontology: Healthy Aging and Regenerative Medicine" in

2013 in Beer Sheba University; the series of National Conferences "Pathways to Healthy Longevity" in Bar Ilan University in 2014 and 2017; the conference "International Perspectives on Geroscience – Israel" in Weizmann Institute of Science in 2019 co-sponsored by the US National Institute on Aging via the Nathan Shock Centers of Excellence in the Basic Biology of Aging, and others.

- Israel has a strong and diverse healthcare market. The nation's reputation as a global technology R&D hub allows for interdisciplinary approaches to healthcare that take advantage of the latest advances in IT and digital health technologies. Israel's healthcare technologies market is estimated to be worth $5.8 billion ($2 billion devices market and $3.8 billion pharmaceuticals market). The Israeli digital health market has grown considerably in recent years, with the number of digital health startups increasing from 65 in 2005 to 400 in 2016, and with investments in digital health increasing by 27% in 2016[1]. About 1500 life science companies operate in Israel, and are supported by the government.
- Israel is a global leader in digitization of health records. Electronic medical records have existed in the Israeli Health Maintenance Organizations (HMO) since the early 1980, and presently the entire health system in Israel is digitized. This provides unique opportunities for longitudinal data-mining to find determinants, risk factors and successful interventions against aging-related diseases and for healthy longevity. Based on this infrastructure, the Israeli government has approved large investments into the national digital personalized health project aiming to utilize digitized personal health records of all of Israel's 9 million citizens, with the aim to assist in developing new drugs through big data analysis.
- Israel's population is uniquely diverse, including residents stemming from over 100 countries, Jewish and non-Jewish, from all races, with uniquely diverse genetic and other biological backgrounds. This diversity will allow wide possibilities for cross-fertilization and cross-referencing of findings and the widest possible applicability of the research results.
- Due to Israel's strengths in aging-related scientific, technological, healthcare and policy infrastructure, it was ranked 3rd in the world in "longevity progressiveness index"[15].
- Aging is increasingly recognized in Israel as an important national challenge, including the recognition of the need to develop specific policies to prepare for and address the aging challenge. Following the significant electoral gains of the Israel Pensioners Party "Gil" in the election of 2006 under the leadership of Mr. Rafi Eitan, in 2007 there was established the Ministry for Senior Citizens specifically to address the problems and needs of the aging population. Yet, in 2015 the ministry became the Ministry for Social Equality, and the relative proportion of involvement with the aging challenge has diminished. In recent years, several policy initiatives have aimed to address particular areas of the aging challenge, such the "National Program for Long-term Nursing Care for the Elderly" of 2017. Yet, perhaps the first truly comprehensive and far-reaching policy program to improve the preparedness of the Israeli society for the population aging, including all of its aspects, is the "National Masterplan on Aging" initiated in 2018, and developed by a topical Knesset committee, as a joint effort of the Knesset committees on Health, Labor and Welfare. The Masterplan generally considers the improvement of well-being of the elderly in Israel, addressing such problems of their life as: poverty, employment and retirement, nursing in community and institutions, family caregivers,

loneliness, inter-departmental coordination, abuse and neglect, independency, healthcare services, welfare services, pensions and allocations, public housing, and technologies. During the program preparation, there was the recognition of the critical need to support biomedical research and development for the amelioration of degenerative aging processes and aging-related diseases and extension of healthy longevity. On the initiative of the associations "Vetek (Seniority) – the Movement for Longevity and Quality of Life" and "Israeli Longevity Alliance" (partners of the "International Society on Aging and Disease") and "Disabled, Not Half a Person," two special hearings were held in Knesset by the masterplan preparation committee on "Enhancing research, development and education for the promotion of healthy longevity and prevention of aging-related diseases" and recommendations were submitted to the committee. Following this initiative, the subject of "Enhancing research, development and education for the promotion of healthy longevity and prevention of aging-related diseases" was included in the published report of the Israel National Masterplan on Aging as a strategic subject for future discussion[16]. This subject and the recommendations will be further promoted in the next Knesset term.

Building on the past achievements, there is still a vital need to develop the geroscience and healthy longevity field in Israel, and there exists a large space for the growth of the field.

2. Building on the past achievements, there is still a vital need to enhance geroscience and healthy longevity R&D in Israel to address the urgent problems and future demands of the aging society.

There are several specific pressing needs and demands for the development of the geroscience and healthy longevity field in Israel. The needs and the corresponding recommendations listed below closely follow the points made by the Vetek and allied associations in their recommendations for "Enhancing research, development and education for the promotion of healthy longevity and prevention of aging-related diseases" in the Israel National Masterplan on Aging. Yet, here they are given a wider international perspective, insofar as these needs and recommendations are quite common and applicable for virtually any country. Moreover, these needs and recommendations can be advocated and promoted via international frameworks and organizations, both globally and for specific countries on a case-by-case basis.

- *The need to increase resources and investments for the geroscience and healthy longevity field.*

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 systems to provide worthy and sufficient services for the elderly, adequate solutions for the prevention of systemic economic and healthcare 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 processes and debilitating aging-related diseases in order to extend healthy longevity as much as possible for the entire population.

Yet, the investment of human and material resources in the field is still insufficient in Israel. Presently, the State of Israel expends only about 0.5% of its general research budget for the research of aging and aging-related diseases (just about $5M dedicated annual state budget). Except for the budget framework for science, technology and innovation for the older persons within the Ministry of Science and Technology, 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 contributing 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, defined 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. Specifically, a defined significant percentage of the research and development budgets of the relevant ministries must be dedicated to the field. These should include the Ministry of Health; the Ministry of Science and Technology; 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.

These frameworks must provide funding for 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 and institutions.

- *The need to increase education in the field of geroscience and healthy longevity, on all levels and for all segments of society***.**

There is a now a severe deficit of relevant educational materials of any kind in Israel, in the field of aging generally, and particular areas of geroscience and healthy longevity promotion in particular. Currently, aging research is severely under-represented in all academic and other educational frameworks. Good education may be considered a primary condition for progress. There is a need to address the large deficit of knowledge and training on the subject of biological aging, its biomedical improvement and healthy longevity, in most existing institutions of learning. The need should be obvious. It should be clear that prior to any research, development and application on biological aging, there is a need to educate specialists who will be able to contribute to the various aspects of the field. There is an even prior need to educate the broader public on the importance of such research to prepare the ground for further involvement.

Such education is currently very limited. In practical terms, there are presently rather few dedicated structures in Israel to promote and coordinate knowledge exchange and dissemination on biological aging and healthy longevity promotion. There is an urgent necessity for such educational structures to make the narrative on biology of aging and healthy longevity prevalent in the public and academic discourse. To improve the communication and integration, it appears to be crucially important to commonly include the subjects of biogerontology, geroscience and healthy longevity promotion as central parts of learning curricula, and not only in universities, but in every learning and teaching framework, especially those related to biology, medicine or natural sciences generally. Yet, unfortunately, and strangely enough, the study of the biology of aging and longevity is rarely a part of university curriculum and virtually never a part of high school or community education curriculum. Thus, there is a vast range of opportunities to develop educational and training materials and courses, including materials and courses of professional interest, from undergraduate to postgraduate levels, as well as of general interest, presenting recent advances in aging and longevity science. Educational teaching and training materials on the subject 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, text books, problem solvers, guidelines and professional specialization programs in the biology of aging, 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, physical activity and rest) 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, knowledge competitions, interactive web platforms, games 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, public associations, 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 institutional frameworks.

- *The need to establish and improve evaluation measures for degenerative aging, early detection and prevention of aging-related diseases and to implement these evaluation measures in preventive health programs for the aging population.*

One of the primary specific needs to develop the geroscience field, in Israel and elsewhere, appears to be the establishment of agreeable, scientific evidence-based evaluation criteria for the efficacy and safety of geroprotective (geroscience or healthspan-enhancing) therapies. Such commonly agreed evaluation criteria are presently lacking, in Israel and elsewhere. Yet, they appear to be absolutely necessary in order to set up the end points for the development of geroscience-based therapies and diagnostics and provide value-based incentives for academic, public and commercial R&D entities involved in the field. The field of geroscience is predicated on the recognition of aging as a major contributing and modifiable factor of pathogenesis, including such recognition in regulatory and budgeting frameworks. Yet, it appears that the primary necessary requirement for the degenerative aging process to be recognized as such a modifiable factor and therefore an indication for research, development and intervention, is to develop evidence-based diagnostic evaluation criteria and definitions for degenerative aging and for the efficacy and safety of potential means against it[17]. Without such scientifically grounded and clinically applicable diagnostic evaluation criteria and definitions, the discussions about "treating," "postponing," "intervening into" or even "curing" degenerative aging processes will be mere slogans. It appears to be impossible to "treat," "postpone," "intervene into" or "cure" a condition that it is impossible to diagnostically evaluate and measure the effectiveness and safety of treatment. Such evaluation criteria and measurements would need to become the basis for public geroscience-oriented health programs designed for the prevention of aging-related diseases, while measuring the effectiveness and safety of the interventions.

Therefore, it is necessary to develop and implement improved evaluation measures and criteria for assessing the aging process, for the early diagnosis and prediction of multiple aging-related diseases (old-age multimorbidity), for examining the effectiveness of treatments for their prevention and for estimating and improving the older persons' functional and employment abilities. Commonly agreed, science-based and authoritative guidelines should be provided for such measures by authoritative and representative national and international organizations. To develop such measures, 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. 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.

In Israel, 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 maintenance 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.

3. Suggestions on how to promote innovation and development of the geroscience and healthy longevity field through international organizations in terms of science and education, in Israel and internationally.

The above needs and demands for the development of the geroscience and healthy longevity field, directly yield policy recommendations for the field's advancement. Currently, official policy recommendations for the promotion of the geroscience and healthy longevity field are lacking in most major international as well as national frameworks. Such recommendations, for both international and national policy frameworks, must be developed and advocated by authoritative and representative international organizations promoting geroscience research and education.

An exemplary effort to develop and advocate such policy recommendations is the position paper of the International Society on Aging and Disease (ISOAD), entitled "The Critical Need to Promote Research of Aging and Aging-related Diseases to Improve Health and Longevity of the Elderly Population" (2015)[18]. This position paper makes the general appeal that "*Governments should ensure the creation and implementation of the policies to promote research into the biology of aging and aging-related diseases, for improving the health of the global elderly population."* It further provides specific policy suggestions with reference to enhancing funding, institutional support and incentives for biomedical aging research. This position paper has been translated to 12 languages and submitted for consideration to several governments. It has stimulated further discussion, encouraging the academic community, the general public and decision makers to elaborate on the policies to support the aging R&D field[19].

Such position papers and consultations can have tangible effects on public health policy and research policy, as evidenced by another position paper, jointly advanced by the International Society on Aging and Disease, American Federation for Aging Research, International Federation on Aging, International Association of Gerontology and Geriatrics and other leading organizations on aging, entitled "Aging health and R&D for healthy longevity must be included into the WHO Work Program" (2018)[20]. Largely thanks to this position paper and the associated advocacy campaign, the subject of healthy aging that had been originally absent, was eventually included into WHO's 13th General Programme of Work for 2019-2023, including specific end points for the reduction of elderly disability and increasing their healthy life expectancy. The contribution of this advocacy campaign was acknowledged by the director of the WHO Ageing and Life Course Division[21]. Another position paper followed the recent establishment of the UNESCO-affiliated Executive Committee on Anti-Aging and Disease Prevention, entitled "The urgent need for international action for anti-aging and disease prevention"[22].

These are preliminary examples, and more of such position papers, guidelines and advocacy efforts are needed to advance the geroscience and healthy longevity field, both at the national and international levels. Authoritative and representative international organizations should take on this work, preparing and advocating policy suggestions and guidelines, creating educational materials and providing platforms for scientific cooperation in the geroscience and healthy longevity field.

Specifically, building on the experience of the Israeli program for "Enhancing research, development and education for the promotion of healthy longevity and prevention of aging-related diseases" within the Israel National Masterplan on Aging (see the previous section), such international organizations may consider advancing the following activities and policies, within specific countries and globally:

- *Advocate to increase the R&D budget for the geroscience and healthy longevity field.*

International organizations should advocate for a significant increase in the level of governmental and non-governmental funding for basic, applied, translational and clinical research and technological development for the mitigation 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, the international organizations should advocate for the allocation of defined significant percentages of the research and development budgets of the relevant budgeting frameworks to be dedicated explicitly for the geroscience and healthy longevity field, including bi-national and international research and development programs.

- *Increase education in the geroscience and healthy longevity field.*

International organizations should create and expand academic and public education frameworks, programs and educational materials, 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.

- *Develop and implement measures for the evaluation and prevention of degenerative aging and aging-related diseases.*

International organizations should develop and implement and/or advocate for the development and implementation of evidence-based evaluation criteria, measures and indicators to estimate the effects of aging, predict and detect at an early stage multiple aging-related diseases, and examine the effectiveness and safety of therapeutic and preventive interventions against them. Concomitantly, evaluation criteria, measures and indicators must be developed and advanced for the functional and employment capacity of the elderly and for the improvement of their functional capacity. Such evaluation criteria, measures and indicators should be used for establishing and/or improving public health systems for the early detection and prevention of degenerative aging processes and aging-related diseases.

Combined, these measures and policies should advance the geroscience and healthy longevity field, nationally and internationally, for the benefit of the elderly and the entire population.

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