CHAPTER 8

The national longevity ecosystem in Israel: An international frame of reference and collaboration

Ilia Stambler

International Society on Aging and Disease (ISOAD), US
Global Healthspan Policy Institute (GHPI), US
International Longevity Alliance (ILA), France
Vetek (Seniority) – The Movement for Longevity and Quality of Life, Israel
Department of Science, Technology and Society, Bar Ilan Unviersity, Israel

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Significant progress in the fields related to geroscience, longevity and combat of major aging-related diseases

Israel can and should be an important contributor to the global geroscience and longevity medicine endeavors, building on its scientific, technological and societal achievements in the field of aging and related fields [1, 2]:

- 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 reports "Longevity Industry in Israel" 2019, 2023 [1, 2]).

- 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, and the bi-national Britain-Israel Research and Academic Exchange Partnership on Ageing (BIRAX Ageing) supported by the Israeli and UK governments. 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 (~82.6 years) [3, 4] according to the WHO data, and in about the 6th place in healthy life expectancy (~73 years) [3] with an intermediate gap between healthy and general life expectancies of ~9.5 years. The high healthy life expectancy contributed to Israel being ranked the world's 4th in the UN World Happiness Index in 2023 [5]. These achievements give encouragement and confidence for the ability to further improve the healthy longevity metrics.
- Israel excels in scientific and technological innovation. In 2021, Israel was in the 7th place (a decline from the 5th place in 2019) in the Bloomberg Innovation Index [6, 7]. Israel has been in the first place in the OECD and in the world in research intensity, in terms of R&D expenditure as a percentage of GDP, reaching as high as 5.56% GDP in 2021 [8] and 5.44% GDP in 2022 [9]. Israel has kept the leading position in this rating of research intensity at least since 2000, when its research spending reached 3.8% GDP which was also the world's first [8]. 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 [10]. In 2022, Israel was ranked the world's 5th most educated country, with over 50% citizens with higher education [11, 12]. These capacities indicate a strong potential for developing R&D-intensive industries generally, including longevity industry.
- Between 2018 and 2023, Israel oscillated between the 5th to the 7th place in healthcare efficiency, showing a high general and high healthy life expectancy with relatively low health care expenditures [13, 14]. The Israeli government spends ~7.5% of GDP on public healthcare, compared to 8.8% average in OECD, with over 18% GDP spent on healthcare in the US. Israel is home to an advanced socialized healthcare system, via its Health Maintenance Organizations (HMO), 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 [15]. Since 2000, the general mortality rates decreased by close to 30% [16].
- Israel has had the lowest rate of diet-related deaths worldwide [17] and has been among the top ten countries in the Bloomberg Healthiest Country Index [18].
- 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, including the Israel Innovation Authority, 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; the "Longevity Nation" conference organized in Bar-Ilan University in cooperation with over 30 international longevity R&D and Education related organizations, 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. As of 2019, Israel's healthcare technologies market was 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]. In 2020, the investment in Israeli life sciences industry reached the highest level, with health tech firms raising a record $2.5 billion, up 55% from the previous year [19].
- As of the end of 2020, about 1,750 life science companies operated in Israel (including about 500 digital health and about 500 biotechnology companies) and were supported by the government [19]. Most (perhaps the majority) of those companies are potentially able to address the challenges of aging, using their technologies and capabilities, and thus represent an integral part of the longevity ecosystem in Israel and/or a strong potential

basis for its further development. Building on Israel's culture of technological incubators, accelerators, consortia and other technology support programs, that have given a boost to such industries as AI and bioinformatics, cyber-security and general biotech, specific accelerators, incubators, consortia and other support programs for longevity medicine R&D, application and education may be envisioned.

- 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 1980s, 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 projects 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 [20].
- In March 2023, the nation-wide Mosaic Project was launched that aims to utilize the genetic and clinical information of donors across the Israeli healthcare, to accelerate innovation in personalized medicine, including aging-related health, led by the Clalit Healthcare Insurance Fund, together with the Sheba, Ichilov, Sha'arei Tzedek and Hadassah Medical Centers and the Galilee Medical Center, in partnership with the Ministry of Health, the Israel Innovation Authority, the Planning and Budgeting Committee, the Planning Division at the Ministry of Finance and the Directorate for the Development of Weapons and Infrastructure, as well as Healthcare Insurance Funds, other hospitals and academia [21].
- Israel's population is uniquely diverse, including residents stemming from all over the world, 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 the 3rd in the world in "Longevity Progressiveness Index" in 2019 [22]. In 2023, Israel was ranked as the world's 5th in the Longevity Governance Index that "reflects its top performance in addressing aging-related challenges and highlights the huge opportunities for the country to further advance in this field" [2].
- 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. 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 "Vetek (Seniority) Association – the Movement for Longevity and Quality of Life", 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 [23]. This subject and the recommendations were planned to be further promoted in the next Knesset terms. With the encouragement of this program, there were issued in Israel calls for research proposals on healthy aging by the Ministry of Science and Technology, and additional calls for proposals and programs were initiated in several ministries.

The COVID-19 period of around 2020-2022 put several such initiatives to address the aging challenge on hold, such as the National Masterplan on Aging whose implementation was not initiated. At the times of COVID, it should have been clear that aging represents the main risk factor also for COVID-19, yet no strong effort at the state level was made to address aging health challenge generally, despite advocacy initiatives [24, 25] and some calls for proposals [26] that emphasized the connection between aging health and the COVID-19 health crisis, and called to address the aging health challenge. Now, with the subsiding of the COVID crisis, several initiatives have been resumed and the advocacy for research, development and education for healthy longevity has been intensified [27].

A vital need to enhance geroscience and healthy longevity R&D and Education 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 of 2019. 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. And furthermore, a successful implementation of these elements in a specific country, such as Israel, can help promote those elements in other countries, for example in the European Union where Israel is an associated state, for all intents and purposes of collaborative research, development and education programs [28].

The international promotion can be achieved by providing examples, frames of references and standards, and helping create new collaborative frameworks with a stimulus and basis from a particular country where the element is strongly developed.

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 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 of and in cooperation with the relevant ministries and institutions.

Notably, the problems with funding for healthy longevity research, development and education are present not only for Israel, but are commonly shared in the developed world, including the EU. Thus, it appears there were few programs within the EU "Health, demographic change and wellbeing" challenge of the EU "Horizon 2020" research and innovation funding programme (2014-2020) that would be related, even indirectly, to biomedical therapeutic research of aging [29, 30]. Neither are such research topics prominent in the plans for the "Horizon Europe" R&D funding program for 2025-2027 [31].

More advocacy efforts are needed to persuade decision makers about the importance of funding for biomedical longevity research and development. As Israel is an associated state of the EU for all EU research and development programs, an improvement of funding and policy for the longevity field in Israel can instigate analogous changes at the European level and globally.

Education in the field of geroscience and healthy longevity, on all levels and for all segments of society

There is 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. Such a deficit of educational programs in relation to aging and healthy longevity is similarly apparent in most developed countries, including the EU. 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 (and elsewhere in the developed and developing countries) 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 developing 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.

If such educational programs (or pilots) on healthy longevity are developed in Israel, they can be easily transferred, translated on emulated in other countries. Moreover, educational programs on healthy longevity can be developed from the start as international collaborations. This is one of the crucial, yet not sufficiently emphasized policy requirements in relation to the aging challenge.

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 and longevity medicine 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-based 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 longevity 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 [32]. 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 [33]. 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.

From the outset, this is a task for international cooperation, including the EU where evidence-based standardized metrics for aging-related frailty and for the effectiveness of aged-specific medicines have been demanded by the regulators, such as the European Medicines Agency (EMA) and "the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)" (applicable in the EU, US and Japan) for over a decade [32], but have not yet been developed or implemented on a consensual basis. The development and implementation of such actionable metrics of aging in a particular country, such as Israel, can provide a tremendous boost for the development and application of the longevity medicine field also in Europe and globally.

Conclusion

We need to actively promote policies for the advancement of research, development, education and medical application for healthy longevity.

The above needs and demands for the development of the geroscience and healthy longevity field directly suggest policy recommendations for the field's advancement, such as enhancing funding, education and metrics for the longevity field. 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 healthy longevity and geroscience research, medical application and education, such as the European Society of Preventive, Regenerative and Anti-Aging Medicine (ESAAM), International Society on Aging and Disease (ISOAD) and International Longevity Alliance (ILA). 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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