Ageing and the Grey Society:
An Opportunity to Change Our Views in Medicine?

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Abstract

Population ageing will increase spending on health care and long-term care. According to the projections in the 2018 Ageing Report, spending on health care and long-term care as a percentage of gross domestic product (GDP) is projected to rise by an average of 0.7 and 1.3 percentage points respectively over the period 2013-60. As life expectancy increases, the individual, social and financial burden of assisting these disabled patients will particularly grow in developed countries. Therefore, we must rethink the approach to ageing and neurodegenerative diseases according to current needs and new challenges. We need a personalized approach to the single subject: as shown in other fields, such as oncology, this approach may lead to an improved efficacy in treatments and also in significant economic outcome. To this aim Information and Communication Technology (ICT) and Artificial Intelligence (AI) are two major innovative tools which may support healthy ageing and precision medicine in the elderly, reducing the economic costs of care.

World population growth has been accompanied by a progressive increase in the number of older people. Medical research and scientific discoveries as well as improved education and living conditions have greatly reduced the chances of pandemics caused by infectious pathogens. In developed countries, life expectancy is now rising well above 80 years. Although in older people the prevailing causes of death are still cardiovascular diseases and cancer, Alzheimer's and Parkinson's diseases, Amyotrophic Lateral Sclerosis and other neurodegenerative disorders that are known to be strongly age-related are among the top ten illnesses ending with death that cannot yet be cured or slowed significantly. In fact, neurological disorders are a leading cause of disability (10%) and major cause of death (17%). The increase in the frequency of disabling, currently almost incurable neurodegenerative disorders is likely to have a devastating impact on individuals, families and societies, unless effective means to reduce the incidence and progression of these diseases are discovered. Alzheimer's disease alone will affect between one-third and one-half of people above 85 years of age; thus, the number of people affected, estimated at 40 million worldwide in 2015, is anticipated to increase to 135 million by 2050. In fact, researchers estimate there are 46.8 million people worldwide living with dementia, with Alzheimer's the cause in up to 80 percent of cases. The number is expected to almost double every 20 years in the absence of medical breakthroughs on preventions or cures.

Population ageing will also increase spending on health care and long-term care. According to the projections in the 2018 Ageing Report, spending on health care and long-term care as a percentage of gross domestic product (GDP) is projected to rise by an average of 0.7 and 1.3 percentage points respectively over the period 2013-60. As life expectancy increases, the individual, social and financial burden of assisting these disabled patients will particularly grow in developed countries.

Indeed, older people are more likely to make use of healthcare services, which in Europe are predominantly provided by the public sector. A recent report by the European Commission says that, "overall in the EU, the total cost of ageing (public spending on pensions, health care, long-term care, education and unemployment benefits), is expected to increase by 1.7 percentage points to 26.7% of GDP between 2016 and 2070". Long-term care and health care costs are expected to contribute the most to the rise in age-related spending, increasing by 2.1 percentage points. In 2050 the economic toll is expected to rise to about one trillion US$ per year in the United States of America alone. Moreover, in low- and middle-income countries the number of afflicted per- sons will increase in parallel with life expectancy, with serious negative impacts on their economies unless affordable healthcare and treatments become available.

Overall, population ageing is expected to place a burden on fiscal sustainability. In fact, the increases in the life expectancy, combined with the low natality countries will soon pose the pension and the health care systems under stress, notwithstanding the strong immigration of young workers that may arrive other continents providing low-cost caregivers and contribute to the sustainability of pensions. In absence of major changes in healthy ageing and in health care systems the economic burden will soon become unbearable. In fact, population ageing will place further upward pressure on the already elevated levels of age-related public spending. The European Commission's 2018 Ageing Report anticipates public expenditure on pensions, health care and long-term care rising from 21% of GDP in 2013 to 23% of GDP in 2060. Pension schemes will be particularly affected. As populations age, the number of beneficiaries of public pension schemes will increase, while the number of contributors is expected to decline, resulting in deficits unless parameters are adjusted. In fact, demographic effects alone are projected to raise pension expenditure by an average of 7.6% of GDP in the euro area over the period 2013-60. In particular, the cost of dementia care, estimated at about 818 billion USD in 2015, represents 1.09 percent of global GDP.

Ageing consists not only in a process of progressive changes in the biological conditions of the individual, which may lead to deterioration of the overall performance. The occurrence of several comorbidities may accelerate the progression of the regressive processes due to ageing. The first signs of this progressive deterioration of the performance of the individual consist in the different manifestations of frailty: a physical frailty which impairs physical activity and predisposes to loss of balance and falls, and, due to bone demineralization, to fractures; cognitive frailty, which causes a progressive deterioration in the independence of the individual and his/her capability of living at home; psychological frailty, which leads to depression and prevents social interaction; as a result of all the above, social frailty leads to isolation of the individual, which in turn impacts negatively on the other frailties. All these events, from pre-frailty to frailty, and, re cognitive frailty, the conversion from frailty to Mild Cognitive Impairment, and then eventually to dementia occur with different time courses in the individuals and is at some extent not ineluctable and eventually preventable. The endpoint, dementia, has become a major problem for the society, since it renders people not autonomous and quite often requires the admission in care homes where the elderly requires continuous assistance.

On the other hand, Alzheimer's disease, the brain-shrinking progressive illness has emerged as one of the planet's biggest public health challenges. More than a century after the tell-tale signs of Alzheimer's were first seen under a microscope, a few drugs treat the disease's symptoms, but there are still none that slow, let alone reverse, its progression. In fact, despite enormous research efforts, disease-modifying treatments revealed elusive as yet. Most clinical trials to test compounds which were expected to prevent dementia showed poor results, thus indicating that the way for a healthy ageing is a long road.

For example, in mid-2018 Eli Lilly & Co. and AstraZeneca ended two late-stage trials of an experimental drug for Alzheimer's disease after the treatment failed to show any signs of working. An independent data-monitoring committee found that the medicine, lanabecestat, was unlikely to meet the goals of the studies, one for early Alzheimer's and the other for mild dementia related to the disease. Like several others that failed, such as Merck & Co.'s verubecestat, the drug targeted a protein called amyloid, thought to be a cause of the disease. The class of medicines known as BACE inhibitors operate before the amyloid has formed into deposits, called plaques. Many researchers now believe that administering drugs after amyloid has built up in the brain may come too late to affect Alzheimer's progress.

So far, more than 190 Alzheimer drugs have failed in trials. Drug companies working to combat the underlying disease have long targeted the protein amyloid, which clumps in the brain of Alzheimer's patients. Researchers do not know whether amyloid triggers Alzheimer's or is a minor contributor. Multiple trials of drugs targeting the protein have proved disappointing. That prompted companies to try testing them on patients with very mild forms of Alzheimer's, but Merck & Co. stopped such a trial that was in its final stages in February 2018, saying it was unlikely to show positive results. Meanwhile, interest has grown in new approaches, especially in those focused on an aberrant protein called tau. As Alzheimer's progresses, tau spreads through the brain, accumulating in tangles that strangle brain cells. Among the companies testing tau strategies are Eli Lilly, Johnson & Johnson, Biogen, AbbVie and TauRx Pharmaceuticals.

The first to connect dementia to abnormal protein deposits in brain tissue was the German psychiatrist Alois Alzheimer, back in 1906. Research into the symptoms, causes, risk factors and treatment of the disease later named for him has taken place mostly in the last 30 years, yet the precise chemistry remains largely unknown. Until recently, the only way doctors could be certain patients had Alzheimer's disease was to check their brain tissue under a microscope for amyloid deposits. The exam was not especially helpful because the patient was already dead. A breakthrough came in 2012, when the U.S. Food and Drug Administration approved a dye used

in scans to detect the plaques. For the first time, live people could be reliably diagnosed. The scans also enabled doctors to track plaque growth with the progression of dementia, and to observe that the plaques emerge decades before symptoms. More important, the scans enabled people with other forms of dementia to be excluded from drug trials, producing more reliable results, and plaques could be used to measure the efficacy of drugs.

If on the diagnostic side progress were made, on the therapeutic side not enough have been achieved to ease patients' sufferance and care givers' burden. Lacking a cure, more than 20 national governments have set forth a jumble of formal dementia-fighting plans that include commitments to pay more for research, build residential care centers, increase awareness of palliative measures and draw up ethical guidelines for caregivers. France was the first in Europe, in 2001. The U.S. released its version in 2012. Alzheimer's advocates are in a contest for resources against groups representing heart disease, cancer and other maladies that kill many more people. Financial challenges overlap with cultural ones. China mandates that children take care of the aged to protect Confucian values. In Japan, there is fear that the strain on the welfare system will conflict with an obligation to care for the elderly. A rape prosecution in Iowa against the husband of a woman with Alzheimer's raised disquieting questions about sexual consent. Studies reporting behavioral improvement from treatment with turmeric and green tea vex skeptics of dietary nostrums. Stigma is a concern. The country-music singer Glen Campbell cited it as a reason for making his own struggle with Alzheimer's disease public. Julianne Moore portrayed an attractive, comparatively young Alzheimer's patient in the movie "Still Alice." She won an Oscar.

These efforts clearly show that we must rethink the approach to ageing and neurodegenerative diseases. First, we need a personalized approach to the single subject: lessons in oncology showed that targeting specific molecular pathways represent a winning approach. Therefore, also neurological diseases could strongly benefit from genome-wide association studies, thus allowing to design drugs that target narrow groups of patients. On the other hand, these data from the genetic profile of the single subject should be matched with the electronic medical record (EMR) and with data which may be collected from medical devices. Therefore, precision medicine, together with prevention medicine might change completely the approach to neurodegenerative diseases and ageing. Re ageing, it is mandatory to provide intervention before frailties occur, i.e. to prevent their occurrence. Dietary suggestions (Voelker et al. 2018), sleep health by resetting the circadian clock (Ruehn 2018), control of blood pressure and increased physical activity (Yaffe 2018) may change significantly the curve of disease onset and progression. Of course, prevention and intervention have their economic burden, and should be at low cost and high gain, i.e. aimed to target populations. Information and Communication Technology (ICT) and Artificial Intelligence (AI) are two major innovative tools which may support healthy ageing and precision medicine in the elderly, reducing the economic costs of care.

The special issue "ICT and Neurodegenerative Diseases" aimed to discuss some of these aspects in the modern society.

ICT can provide a fundamental support to the characterization and prevention of neurodegenerative diseases. In the two papers by Ikeda et al. and Aumayr et al. it is shown how medical devices can be used to monitor individuals and to detect early risks of disease. In the paper by Ghibaudi et al. it is shown as new technologies in detection of biomarkers can be used for precision and personalized medicine. The big amount of data which are collected by the medical devices must be analysed with artificial intelligence, i.e. machine and deep learning to identify early signs and symptoms as shown in the paper of Summers et al. In this task, AI might either be instructed by the professionals involved in medical care to identify in the individual the appearance of specific signs already know as associated to disease, or investigate to find new signs to be validated by the professionals in a second time.

In the paper by Vercelli et al., assistive robots in elderly care are described. They can represent both collectors of data (through cameras, microphones and direct interaction with the subject) and as support for care. They are not supposed to substitute caregivers, but may be useful in assistance and also in administrating learning therapy, promote physical activity and implementing social interactions.

The underlying idea of this new approach consists in the concept that there are potentially modifiable risk factors, which may be identified early in each individual with precision medicine and early detection and may be modified with early intervention. To this aim, cognitive training, increased physical activity, depression treatment and sleep quality interventions might modify the progression from ageing to frailty to mild cognitive impairment. ICT can support multimodal approach communication with the public, and biomarkers can be used both in early detection and as intermediate outcomes.

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