HEcoPerMed

Health Economic Models for Personalised Medicine

Deliverable 4.1: Scenario Development - Overview of major findings from workshops and interviews

version 1.1

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1 INTRODUCTION

A strong underlying assumption enforcing the call for Personalised Medicine (PM) is its implicit promise that it will make health care more cost-efficient through better targeting of treatments. However, while the development of PM treatments is an academic endeavour, its commercialization is often in commercial hands, reducing the efficiency potential of technologies through high pricing. Commercially marketed products such as biomarkers are often priced at the margin, following an analysis of companies of 'what the market can bear', rather than based on the size of the health increase of patients. As a consequence, PM adds to the debate on public control of health costs.

While the assessment of quantified models is one essential part of the project, another is to anticipate various societal challenges and future developments which our European health care systems will have to encounter. This report gives an overview on the current and future trends and drivers PM is facing in the context of European health care systems. In the second part we present four distinctive scenarios to address questions as to how PM is integrated into future societies and their institutional contexts, including innovation and payment models.

Presently and in the future European health systems will be confronted with trends and drivers demanding a response from the relevant actors with the likelihood to significantly change what we have known as our health systems so far as indicated in graph 1. Not only since the COVID19 crisis has health as a topic become a policy issue with a high impact. But the COVID19 crisis has made clear that health is interlinked with a lot of other policy areas and it is even possible to shut down the economy for a while in order to better cope with pressing health issues. Even before the CCVID19 crisis has the EU president Ursula von der Leyen declared that the battle against cancer is a top priority of Horizon Europe[1].

Among the technological trends we witness in the health sector are the advances in collecting, connecting and analysing data in a dimension that we have never witnessed before and more is yet to be expected. Data is very likely to be an essential source, if not THE essential source, for the future of health and health care system. It is connected with the creation of new jobs and profession and with better health care in general. A lot of privacy issues such as the right to one's own data, the right not to know, etc. are also important issues for the public debate.

At the same time, the increase in medical knowledge and innovation that is exceeding the knowledge levels we have had ever before and our capacity to keep an overview already seems to be exhausted. As the consequence, the health system gets more and more differentiated and specialised.

Health is also increasingly becoming a commodity, attractive for investors outside the traditional health sector. Multi-national diversified companies show interest in investing in R&D, in hospitals, production facilities, insurance companies, services, etc. In the near future we might see a new era of mergers and acquisitions, not limited to pharma companies but affecting the health sector significantly.

[1] https://ec.europa.eu/commission/presscorner/detail/en/speech_20_190

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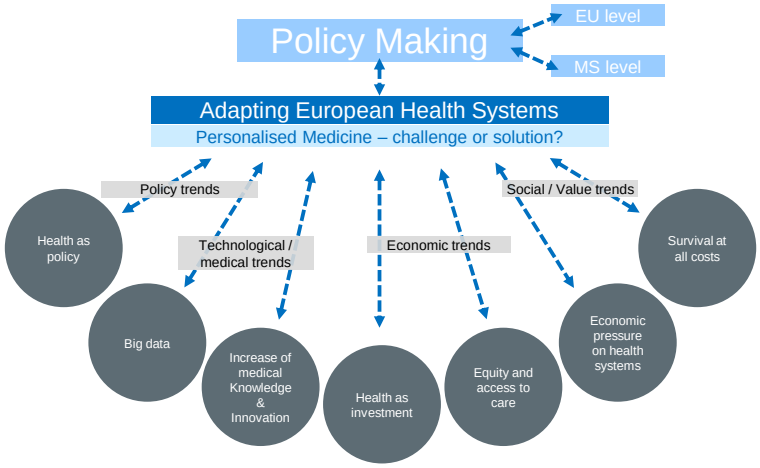
Most importantly, decent health care and access is increasingly a matter of equity. The majority of non-communicable diseases, for example, hit the part of our society that is economically disadvantaged, has less education and less health literacy, is geographically further away from high-quality health care institutions. Personlised Medicine has often been associated as being primarily for the rich. So, technological advances can have diverse social effects. Who determines which patients will receive expensive treatment and which don't if the resources are scarce? Debates like this hit the core of our value systems.

The social and economic divide contribute to the debate of public health vs. private health and the question to what extend should public authorities regulate the pharmaceutical market and the costs of health care, e.g. medication.

We can read about the economic stress of our health system every day in the paper. Already before the COVID19 crisis, the burden on health systems increased because the percentage of people in jobs and paying social benefits is continuing to decrease whereas the percentage of elderly and very old people not paying into the systems and demanding a large share of care is on the rise.

Finally, we are also confronted with ethical debates: Should we prolong live at all costs, invest in very expansive medication even if they can prolong a patient's life only by a few months? And what about a patient's right to terminate her/his life if the pain gets unbearable?

Graph 1: Pressures on the European Health Systems



2 METHODOLOGICAL APPROACH OF HORIZON SCANNING

Personalised medicine has many aspects: next to financial implications, the future of PM depends also on megatrends such as demographic change, economic growth, innovations in

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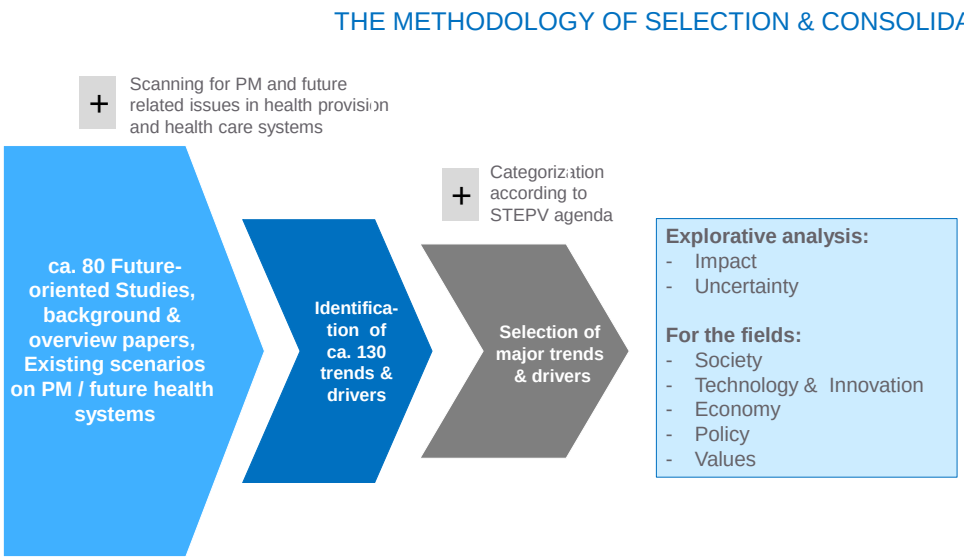
medicine and (health) technologies, health literacy among citizens, but also cuts in health care costs to name just a few. The analysis of published and grey literature, forecast and foresight studies, existing scenarios and visions, policy papers etc. in combination with interviews of experts and stakeholders is the basis for this report. It sketches the main future trends and drivers of PM and provide inputs for scenarios for European models of health care. This analysis serves as the basis for identifying the critical uncertainties for the future of PM and its relation to the European health care systems in terms of access, reimbursement and affordability. Further, it helps define critical uncertainties having the highest impact and creating the highest uncertainties.

We started with a corpus of some 80 future-oriented studies, background and overview and policy papers, including some scenarios on the future of health in general and PM in particular as well as future outlooks of health systems. From these sources, we identified some 130 trend and drivers on very different levels of granularity and scope. For a better overview we condensed and categorised these trends and drivers according to a STEPV scheme: differentiating between the fields Society, Technology, Economy, Policy/regulations and Values. After assessing the greatest impact and uncertainty from these trends and drivers: Those with the highest scores were selecting, and they were the most promising for the scenario work (graph 2).

Graph 2: The Methodology of Selection and Consolidation



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3 TRENDS AND DRIVERS

3.1 A Definition

For our work we relied on a common definition of trends and drivers. Megatrends are the great forces in societal development that will very likely affect the future in (almost) all areas over the next 10-15 years. Once in place, megatrends influence a wide range of activities, processes and perceptions, both in government and in society, possibly for decades. They are the underlying forces that drive trends. (i.e. digitalization, aging). A trend - in contrast - is an emerging pattern of change likely to impact large social groups or even state government and require a response. Trends are experienced by everyone and often in more or less the same contexts (e.g. personalized medicine to diagnose/fight cancer). Drivers are defined as developments causing change, affecting or shaping the future. A driver is the cause of one or more effects, e.g. debate in vaccination, tax, incentives, etc. In practice, it is often easy to identify a megatrend, but it is difficult to distinguish a trend from a driver, especially since at times they may influence each other.[2]

There are of course many trends and drivers which might have direct or indirect effects on the European health systems and the performance of PM. We selected the ones with the highest criticality, but the list is not exhaustive. The table below lists the trends and drivers discussed here as having significant impact on the future development PM and European health systems.

Table 1: Trends & Drivers under discussion

Society-related trends & drivers
demographic change
multimorbidity and chronic diseases
change in family structures
increase in patient empowerment
contribution of personal data
access to more information and data
PM to include information beyond the molecular dimension
Technology-related trends & drivers
linkage with big data and artificial intelligence:
technologies that are expected to have indirect impacts on the future of health systems and PM
eHealth and mHealth
Economy-related trends & drivers
burden for R&D funding for public sector
Health care expenditure increase
private health insurance is on the rise
Asia as a rising market for PM
Policy-related trends & drivers

[2] Council of State Governments (USA) http://ssl.csg.org/Trends/Megatrends%20Definitions%20and%20Categories.pdf

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unsustainability of European health systems
secrecy around costs for research and development
asymmetries of bargaining power
effective pricing system to ensure accessibility
increasing financialisation of the pharmaceutical sector
offshoring of production
upstream use of intellectual property rights
extension of certain patents
compulsory licensing
coordinated Health Technology Assessment
mission-oriented approach to medical research

4 SOCIETY-RELATED TRENDS & DRIVERS

One megatrend for the future of European health systems is **demographic change.** Life expectancy in all OECD countries has risen by more than 10 years in recent decades compared to 1970.[3] Consequently, the world population is growing continuously and expected to reach 8.5 billion people by 2030 and 10 billion by 2050.[4] While the number of people is increasing, especially in the less developed countries, the population numbers are stagnating or even falling in developed countries, resulting in a demographic aging of the population. About 10% of the world's population will be aged over 80 by the middle of the 21st century.[5] The main reasons for increased life expectancy include better health care and hygiene, sufficient and adequate food, lower infant mortality and improved medical care.

The ageing of the population is also reflected in lower lifetime incomes, which may lead to lower tax revenues and thus to less resources to finance pensions and public investment in public health services. As the working-age population providing social and economic support is simultaneously decreasing, the proportion of people (children and elderly people) depending on the working-age population will consequently increase. The OECD (2016) expects the working population to decline by up to 77 million (11%) by 2050 if not compensated by immigration.[6]

Due to the ageing of the population, the prevalence of age-related diseases (e.g. chronic diseases, physical disabilities, mental illnesses), **multimorbidity and chronic diseases** will increase. It is expected that the ageing population will have a significant impact on public health and health care in developed countries.[7] In addition, changes in lifestyle (e.g. tobacco consumption, harmful use of alcohol, unhealthy diet, and lack of physical activity) may lead to

[3] OECD (2019) Health at a Glance 2019: OECD Indicators, OECD Publishing, Paris, https://doi.org/10.1787/4dd50c09-en.

[4] OECD (2016) An OECD horizon scan of megatrends and technology. Trends in the context of future research policy.

[5] Ibid.

[6] OECD (2016) An OECD horizon scan of megatrends and technology. Trends in the context of future research policy.

[7] National Institute for Public Health and the Environment (2018) The Public Health Foresight Study 2018. A healthy prospect. Synthesis. https://www.vtv2018.nl/en

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an increase of non-communicable diseases, such as cardiovascular diseases (e.g. heart attacks and stroke), cancers, chronic respiratory diseases (e.g. chronic obstructive pulmonary disease and asthma) and diabetes, unless countermeasures are taken. Non-communicable diseases are currently responsible for 71% of all deaths worldwide each year, with low- and middle-income countries particularly affected.[8] Increasing numbers of oncological, cardiovascular and infectious diseases, and brain pathologies which will shift the heath needs of populations towards more coordinated care as the health burden shifts toward chronic diseases.[9] For example, the incidence of most cancers is expected to increase until 2030, with prostate, breast and lung cancer becoming the most frequent malignancy by 2030; lung cancer will remain the major cause of cancer-related deaths; and the number of deaths will steadily increase until 2030.[10] The number of people who will need more complex and long-term health care and assistance will increase, especially among the elderly, even is no acute chronic disease is diagnosed.

Another important trend is the ongoing **change in family structures**. The increasing need for health care also puts pressure on informal care provided by family members and friends. However, as nuclear families (a couple and their children) are on the decline and are increasingly replaced by single-person households, the feminization of the work force, and work force mobility make more difficult to care for the chronically ill and elderly. As family structures will change, informal care responsibilities will either have to be shifted to people who have not traditionally been considered as family, such as unmarried partners and neighbours, or welfare states will have to provide care.[11] It is expected that with increasing age, a growing number of people will also experience feelings of loneliness due to a lack of social networks and social isolation.[12]

These challenges require new methods for specific and accurate diagnosis and treatment, made possible by advanced medical technologies, especially the use of genomic-based data screening and analysis and sensor-based technologies and tools for monitoring at home, which is driving the personalisation of health care. Improvements in the treatment of some diseases and technological innovations will have an impact on overall requirements for health care for patients and health professionals and increase the desire to improve the quality of life of patients and well-being throughout life. In return, patients will be less tolerant of the fact that a disease cannot be cured. Structural trends also include the positive correlation

[8] https://www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases

[9] The Public Health Foresight Study 2018. Thematic report - Future health care demand National Institute for Public Health and Environment (RIVM). Bilthoven. 2018 [Available from: https://www.vtv2018.nl/en/thematic-foresight-studies]

AXA (2019) Powering Fast Forward Thinking. The AXA 2019 Foresight Trendbook.

[10] Quante A.S., Ming C., Rottmann M., Engel J., Boeck S., Heinemann V., Westphalen C.B., Strauch K. (2016) Projections of cancer incidence and cancer-related deaths in Germany by 2020 and 2030. Cancer Med. 2016 Sep; 5(9): 2649–2656. doi: 10.1002/cam4.767

[11] OECD (2012) The Future of Families to 2030, OECD Publishing. http://dx.doi.org/10.1787/9789264168367-en

[12] Kemperman A., van den Berg P., Weijs-Perrée M, and Uijtdewillegen K. (2019) Loneliness of Older Adults: Social Network and the Living Environment. Int J Environ Res Public Health. 2019 Feb; 16(3): 406. doi: 10.3390/ijerph16030406

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between income and education on the one hand, and the health care consumption and health status on the other.[13], [14]

Over recent years we can witness an **increase in patient empowerment** and this trend is expected to continue in the future as we see it also in other areas. Data-driven health care (using genomic and other molecular data, biophysical data, and also behavioural data that characterise people's "lifestyle") will become the new standard in health systems, as the amount and complexity of medical knowledge is continuously growing.[15] The increasing number of personal monitoring and analytical devices accessible to both healthy and sick people via m-health tools such as apps, portable, wearable and implantable and biometric sensors will contribute to an ever-growing amount of health data generated by the patients themselves. The wealth of data can promote the development of applications and tools for the prevention, diagnosis and treatment of diseases. As a result, citizens will become more involved in the health system and experience increased empowerment in relation to their health and behaviour, e.g. though self-monitoring and self-treatment and as providers of data. By taking more control over their health, preventive measures are also likely to increase. When patients generate large amounts of digital data through self-monitoring devices, social media applications, and other online activities, they are not always aware that the data can be related to health. Nevertheless, people in both Europe and the US are willing to share a considerable amount of health-related digital data for health research.[16],[17] A recent survey in the US revealed that more than 67% of respondents in academic hospitals are willing to share all data with researchers at their own health institute, but to a lesser extent with other non-profit or for-profit health institutes; about 25% are willing to share their data with all interested researchers.[18] This finding is in line with the trend that data exchange between various actors in the health system will continue to develop, as, on the one hand, more opportunities for responsive health services will arise and, on the one hand, the availability of data may also increases the pressure to use them. However, a recent survey in the UK on public attitudes towards health data sharing before and during COVID19 crises has shown that public opinion can easily turn into public scepticism about the willingness to share data when 'big tech' companies are the recipients of the data.[19] The survey found that about two-thirds (60% of about 2,000 respondents) of the public are willing to provide data to the National Health Service, only about 40% are comfortable to share their data with the government, and between one-third and one-quarter with start-ups and 'big tech' companies, respectively. The collaboration between the UK government and large data companies such as

[13] Woolf S.H., Aron L., Dubay L., Simon S.M., Zommerman E., Luk K.X. (2015) How Are Income and Wealth Linked to Health and Longevity? Income and Health Initiative: Brief One. https://www.urban.org/sites/default/files/publication/49116/2000178-How-are-Income-and-Wealth-Linked-to-Health-and-Longevity.pdf

[14] Yamada T., Chen C.-C., Naddeo J.J., Harris J.R. (2015) Changing Healthcare Policies: Implications for Income, Education, and Health Disparity. Front Public Health. 2015; 3: 195. doi: 10.3389/fpubh.2015.00195

[15] Ambacher, N., Carl, M., Knapp, D. (2015): Personalisierte Medizin der Zukunft. Trendstudie des 2b AHEAD ThinkTanks. Leipzig. http://www.2bahead.com/studien/trendstudie/detail/trendstudie-personalisierte-medizin

[16] Karampela M., Ouhbi S., Isomursu M. (2019) Connected Health User Willingness to Share Personal Health Data: Questionnaire Study. J Med Internet Res. 2019 Nov; 21(11): e14537. doi: 10.2196/14537

[17] Seltzer E., Goldshear J., Guntuku S.C., Grande D., Asch D., Klinger E., Merchant R. (2019) Patients' willingness to share digital health and non-health data for research: a cross-sectional study. BMC Medical Informatics and Decision Making 19/157 doi:10.1186/s12911-019-0886-9

[18] Kim J., Kim H., Bell E, Bath T., Paul P., Pham A., Jiang X., Zheng K., Ohno-Machado L. (2019) Patient Perspectives About Decisions to Share Medical Data and Biospecimens for Research. JAMA Network Open, 2019; 2 (8): e199550 DOI: 10.1001/jamanetworkopen.2019.9550

[19] https://www.healthtechdigital.com/survey-reveals-public-scepticism-around-sharing-health-data-with-big-tech-and-government-since-covid-19-pandemic/

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Apple and Google, for its new Test and Trace application during the COVID19 pandemic, has contributed to a reduced trust in the government concerning data sharing issues.

Patient empowerment does not stop here. Patients will not only donate data, but also demand **access to more information and data**. The European General Data Protection Regulation will give patients access to their own personal data generated by health professionals such as medical records, containing information such as diagnoses, examination results, assessments by treating physicians and any treatment or interventions provided.[20] At the same time, the need for cybersecurity measures will increase. However, as patients do not necessarily have more knowledge for interpretation of the data, they still need to consult health care professionals to interpret data and risks.[21] At the same time, health is evolving from an individual concern to a community-driven concern, as health risks due to specific genetic predisposition may also be shared with "DNA cousins".[22] To understand their diseases and their treatments, patient engagement is becoming increasingly important. People who share the same health conditions and risks will join online communities to gather and share their experiences and create learning health communities. Such platforms could be supported by patient networks[23] connecting people with similar biological characteristics for information exchange.[24] In addition, governments establish national health data hubs to promote data-sharing communities for promoting prevention.[25]

This approach to intensify exchange of information between people with the same genetic make-up concerning their genetic disposition to diseases can also be seen as a response by patients to the professional specialisation of health staff and reductionism to biological data, where health professionals "deal with diseases rather than treating human beings".[26]

The future of European health system does not rely on data generation only. PM will include information **beyond the molecular dimension**. Increasingly, PM expands the notion of 'omics' (e.g. genomics, proteomics, metabolomics) to areas that go beyond molecular information, such as socioeconomic, cultural, environmental and behavioural factors.[27] For example, behavioromics focuses on the impacts on health created by changes in behaviour, and exposomics investigates health effects that may be explained by environmental factors (e.g. pesticides, plasticizers and industrial emissions).[28]

[20] Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the fre https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32016R0679

[21] Ambacher, N., Carl, M., Knapp, D. (2015): Personalisierte Medizin der Zukunft. Trendstudie des 2b AHEAD ThinkTanks. Leipzig. http://www.2bahead.com/studien/trendstudie/detail/trendstudie-personalisierte-medizin

[22] AXA (2019) Powering Fast Forward Thinking. The AXA 2019 Foresight Trendbook.

[23] For example, Patientslikeme is a for-profit patient network and research platform, which connects who suffer from the same disease or condition to share their experiences aiming at improving outcomes. https://www.patientslikeme.com/

[24] AXA (2019) Powering Fast Forward Thinking. The AXA 2019 Foresight Trendbook.

[25] Ibid.

[26] Codagnone C. (2009) Reconstructing the Whole: Present and Future of Personal Health Systems. Deliverable of the PHS2020 project.

[27] Prainsack B. (2019) Precision Medicine: Creating value for everyone. Newsweek Vantage.

[28] https://www.radboudumc.nl/en/research/radboud-technology-centers/mass-spectrometry/exposomics/what-is-exposomics

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5 TECHNOLOGY-RELATED TRENDS & DRIVERS

Societal trends in the health area such as the ones pointed out in the section above are directly or indirectly linked to technological advances and trends. Systems biology, for example, is increasingly linked with **big data and artificial intelligence**: In recent decades, there have been fundamental advances in technological developments of profiling techniques related to "omics" sequencing and the screening of epigenetic patterns (e.g. via next-generation sequencing technologies using DNA, RNA, or methylation sequencing), which have had a significant impact on life sciences and PM.[29] Improvements in the use of big data techniques and analytical methods using quantum computing and artificial intelligence (AI) algorithms for biological functional levels such as genomics, proteomics, and metabolomics will also help to advance the translation of PM into clinical practice. This trend has also been boosted by the implementation of large national sequencing projects in and outside Europe (e.g. 100,000 Genomes Project in the UK and Japan) [30],[31] and rapidly decreasing sequencing costs. While sequencing a human genome (using Sanger-based technologies) was estimated to cost $20–25 million in 2006, the cost in 2020 was calculated at £6,841 per cancer case and £7,050 per rare disease case.[32]

As a tangible result of these technological advances and massive experience with parallel sequencing, the understanding of the genetic evolution and heterogeneity of cancers has improved considerably, allowing the researchers to place the identified catalogues of mutations in a meaningful context and address new targets and therapies in cancer research and treatment.[33] The concept of PM is well established in oncology, as indicated by the number of treatments approved for cancer therapies, by both the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA).[34] In 2018, cancer accounted for the majority of approved personalized treatments.[35] In that year, the FDA approved 25 personalized medicine drugs, representing 42% of all new drug approvals of that year.[36] In cancer drug development, biomarkers have become an integral part.

Biomarkers (i.e. components of a diagnostic method or product) discovered using omics, proteomics, or metabolomics technologies, are developed to identify genetic variations in diseases and to help diagnose target pathways for therapeutic interventions. Biomarkers can also be used in risk assessment, molecular diagnostic, disease diagnosis, DNA fingerprinting

[29] Kulski J.K. (2016). Next-Generation Sequencing — An Overview of the History, Tools, and "Omic" Applications, Next Generation Sequencing - Advances, Applications and Challenges, Jerzy K Kulski, IntechOpen, DOI: 10.5772/61964. Available from: https://www.intechopen.com/books/next-generation-sequencing-advances-applications-and-challenges/next-generation-sequencing-an-overview-of-the-history-tools-and-omic-applications

[30] https://www.esmo.org/oncology-news/Large-National-Sequencing-Projects-in-Europe

[31] https://www.clinicalomics.com/topics/translational-research/biomarkers-topic/biobanking/10-countries-in-100k-genome-club/

[32] Schwarze K. *et al* (2020) The complete costs of genome sequencing: a microcosting study in cancer and rare diseases from a single center in the United Kingdom. Genetics in Medicine volume 22, pages85–94(2020)

[33] Fittall M.W., Van Loo P. (2019) Translating insights into tumor evolution to clinical practice: promises and challenges. Genome Med. 2019; 11: 20. doi: 10.1186/s13073-019-0632-z

[34] Ritzhaupt A., Hayes I., Ehmann F. (2020) Implementing the EU in vitro diagnostic regulation – a European regulatory perspective on companion diagnostics, Expert Review of Molecular Diagnostics, 20:6, 565-567, DOI: 10.1080/14737159.2020.1720653

[35] https://www.pharmaceutical-technology.com/features/precision-medicine-2020/

[36] Personalized Medicine Coalition (2018) Personalized Medicine at FDA. A Progress & Outlook Report. http://www.personalizedmedicinecoalition.org/Userfiles/PMC-Corporate/file/PM_at_FDA_A_Progress_and_Outlook_Report.pdf

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and other molecular applications. Research into biomarkers is necessary for the development of diagnostic tests. These tests indicate whether a patient will benefit from a specific personalized treatment and are therefore crucial in determining whether or not a patient will be treated with a specific drug. Although the concept of a biomarker (including measurements such as fever or blood pressure) has been applied for many years, the demand for biomarkers in the diagnostic market is growing as they constitute a key component of a diagnostic test and, more often, even of early diagnosis. Biomarkers may include imaging technologies that enable them to produce images of, for example, tumors.

Due to the widespread use of digital devices and health-related mobile applications by citizens, biomarker development has turned towards "digital biomarkers", which are objective, quantifiable, physiological, and behavioural measurements obtained through sensor-based portable, wearable, implantable or digestible devices.[37] This development has also been driven by the COVID19 pandemic, as the devices can be used by infected patients.

There are also a couple of advances in **technologies that are expected to have indirect impacts on the future of health systems and PM**. Advances concerning medical imaging in areas such as cinematic rendering for photorealistic visualization of medical images and three-dimensional visualization are an important component for patient-specific computational models and minimally invasive procedures and thus for the implementation of PM in clinical practice.[38] In addition, it is estimated that technologies that are not primarily related to medicine, such as robotics (e.g. to support medical personnel during surgery, people treated at home, or to address social needs such as loneliness) and automation as well as 3D printing (e.g. for personalised organ implants), have a major impacts on PM and overall health care and society.[39] Technologies such as nanotechnology will enable early diagnosis and treatment of cancer. Advances in computer sciences and ultra-fast computing speeds, including the use of quantum computers, will benefit the processing of big data including the deciphering of genomics and allow for more appropriate models and predictions.

eHealth and mHealth have the potential to make health systems more efficients and could also promote PM**.** eHealth (i.e. tools and services for the use of information and communication technologies (ICT) for health) and mHealth (medical and public health practices supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants (PDAs)), and other wireless tools and devices that help citizens to collect non-genetic determinants of diseases in large amounts. [40] Such physiological and behavioural data usually originate from personal health systems and are collected remotely while personal health data are routinely monitored. Wearable and (implanted) body sensors for recording multiple parameters related to people's health have already entered daily life, as a variety of applications for individualized eHealth and mHealth technologies are available, not least because of their easy access via smartphones.[41] Self-measured data on people's behaviour and health recorded by sensors can easily be made accessible to family members

[37] https://www.pharmaceutical-technology.com/comment/digital-biomarkers-healthcare-trends/

[38] Comaniciu D., Engel K., Georgescu B., Mansi T. (2016) Shaping the Future through Innovations: From Medical Imaging to Precision Medicine. Medical Image Analysis. 33. 10.1016/j.media.2016.06.016.

[39] van der Maaden et al. (2018) Horizon scan of medical technologies. Technologies with an expected impact on the organisation and expenditure of healthcare. RIVM Letter report 2018-0064.

[40] van der Maaden et al. (2018) Horizon scan of medical technologies. Technologies with an expected impact on the organisation and expenditure of healthcare. RIVM Letter report 2018-0064.

[41] Firouzi F., Rahmani A.M., Mankodiya K., Badaroglu M., Merrett G.V.,. Wongg P., Farahani B. (2018) Internet-of-Things and big data for smarter healthcare: From device to architecture, applications and analytics. Future Generation Computer Systems 78 (2018) 583–586

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and health professionals via Internet of Things (IoT) systems. IoT systems can automatically learn from sensor measurements and the patient's medical history using artificial intelligence (AI) algorithms and machine learning techniques, make intelligent decisions to assist healthcare professionals, provide feedback on current health status and predict the future health of the patient[42]. In addition, cognitive programs are used to read and analyse the available scientific literature and consolidate electronic medical records of previous years. In this way, AI impacts medical practice by influencing the course of chronic diseases of patients, suggesting precision therapies for complex illnesses, and improving subject enrolment in clinical trials.

To be able to take fully advantage of the promising new technologies, it will be important that all major stakeholder groups involved in PM, such as health care professionals, patients, health insurers, industry and the public authorities, join forces as early as possible.[43] Due to digitalization, integrated digital platforms will manage to connect patients with doctors and other care providers and allow for data sharing. To be able to take advantage of the vast amounts of data that will be created, multiple data integration at all levels of the health care system (including social support and primary care) is a prerequisite for the use of simulation and modelling tools from primary care to policy-making and high-level monitoring.

6 ECONOMY-RELATED TRENDS & DRIVERS

Taking a macro-level perspective, the **burden for R&D funding within the health sectors lies heavily on the public sector.** R&D funding in the health sector comes from both public and private institutions.[44] European public funders are the nation states and the European Commission. Total annual health expenditure in the EU-27 increased by 7.7%, between 2010 (€5,610.113 million) and 2018 (€6,040.183 million), although it varies between years. The differences in national public funding of health-related research projects between 2010 and 2018 varied between an increase of 2,461% (Malta) and a decrease of 80% (Rumania). As only sporadic data on private budget spent on health R&D are available, these data are not presented here.

The European Commission's public R&D funding for health-related projects increased from €5,571 million[45] in the 7th Framework Programme (FP7; 2007-2013) to about €8,033 million (including €254 million for EIT) in Horizon 2020 (H2020, 2014-2020)[46]. The European Commission has built on "omics" and biotechnology research within the EU funding programmes, and has supported PM research from the 7th Framework Programme for Research and Technological Development towards the Horizon 2020 research funding programme.[47] EC funding

[42] Miller D.D., Brown E.W., (2018) Artificial Intelligence in Medical Practice: The Question to the Answer? The American Journal of Medicine (2018) 131, 129–133

[43] van der Maaden et al. (2018) Horizon scan of medical technologies. Technologies with an expected impact on the organisation and expenditure of healthcare. RIVM Letter report 2018-0064.

[44] Source: All data from the paragraph come from EUROSTAT and own calculations. https://ec.europa.eu/eurostat/data/database

[4545] https://wayback.archive-it.org/12090/20191127202808/http://ec.europa.eu/research/fp7/index_en.cfm?pg=budget

[46] EC Breakdown of the Horizon 2020 budget https://ec.europa.eu/research/horizon2020/pdf/press/horizon_2020_budget_constant_2011.pdf

[47] Nimmesgern E., Benediktsson I., Norstedt I. (2017) Personalized Medicine in Europe. Clin Transl Sci (2017) 10, 61–63; doi:10.1111/cts.12446

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for health-related R&D will continue in the forthcoming funding programme Horizon Europe. The EC provides only about 10% of the total investment in biomedical research in Europe. [48]

The main source for covering health care costs will continue to be public funding. At present, public sources cover more than 70% of health expenditure across OECD countries.[49] Public sources mainly include government revenues generated from tax income and social insurance contributions. In 2017, 15% of total government expenditure across OECD countries (via government transfers and social insurance contributions) was used to cover health costs. Countries with higher shares of public funding of health include Japan and the United States (23% each), Ireland and Germany (20% each). Public spending of around 10% is found in countries such as Greece, Hungary and Latvia. On average across OECD countries, the share of public funding has remained stable at around 71% between 2005 and 2017. As exceptions, the share of public funding of health has increased in countries such as Mexico (by 9%) and the United States (by 5%) due to the introduction of new policies, or has decreased for example in Spain (by 5%) and in Portugal (by 4%) as a consequence of policy measures to cope with an economic downturn caused by the economic crisis.

Health care expenditure as a percentage of Gross Domestic Product (GDP) increased substantially in all OECD countries in the 1990s and early 2000s, indicating a higher growth rate in heath spending than in the rest of the economy.[50] After a slump in growth between 2009 and 2011 and period of volatility during the economic crises, the growth rates of health care expenditure across OECD countries and in the rest of the economy developed similarly. Thus, health care expenditure across OECD countries stabilised at around 8.8% of the GDP for health in 2018, without any significant changes since 2013. High-income countries spent considerably more than the average on health care in 2018: For example, the United States spent about 16.9% of its GDP, Germany, France, Sweden and Japan just under 11%. While a large group of OECD countries (including European countries, Australia, New Zealand and Korea) are in the range of 8-10% of GDP, many Central and Eastern European countries such as Greece, Lithuania and Poland spend between 6-8% of their GDP to health care.

Health care expenditure in Europe, expressed in absolute numbers in Euro, increased in the 21 EU Member States that provided data to EUROSTAT between 2012 and 2017, with the exception of Greece (see Table). Largest increases in health expenditures between 2012 and 2017 were observed for Romania (+54%) as well as Estonia, Bulgaria, Lithuania and Germany (each over 20% increase).

[48] Nimmesgern E., Benediktsson I., Norstedt I. (2017) Personalized Medicine in Europe. Clin Transl Sci (2017) 10, 61–63; doi:10.1111/cts.12446

[49] OECD (2020) Focus on public funding of health care. Brief February 2020. https://www.oecd.org/health/Public-funding-of-health-care-Brief-2020.pdf

[50] OECD (2019), *Health at a Glance 2019: OECD Indicators*, OECD Publishing, Paris, *https://doi.org/10.1787/4dd50c09-en*.

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Table 2: Current health care expenditure, 2012-2017

	2012	2013	2014	2015	2016	2017	Overall change 2012-2017 (%)
	(EUR million)						
EU-27 (1)	:	:	1 178 491	1 214 255	1 247 897	1 286 220	:
Belgium	39 780	40 684	41 667	42 262	43 753	45 405	14.1
Bulgaria	3 186	3 293	3 640	3 715	3 961	4 183	31.3
Czechia	:	12 314	11 989	12 202	12 610	13 864	:
Denmark	26 072	26 313	27 033	27 922	28 720	29 598	13.5
Germany	297 255	308 962	322 083	338 058	351 701	368 597	24.0
Estonia	1 045	1 138	1 227	1 319	1 410	1 518	45.3
Ireland	18 715	18 506	18 850	19 254	20 172	21 130	12.9
Greece	16 985	15 201	14 203	14 340	14 616	14 492	-14.7
Spain	94 327	92 519	93 649	98 486	100 367	103 489	9.7
France	236 358	242 116	248 752	251 920	256 455	259 638	9.8
Croatia	:	2 855	2 908	3 028	3 184	3 326	:
Italy	144 485	143 648	146 150	148 490	150 067	152 705	5.7
Cyprus	1 303	1 252	1 193	1 208	1 255	1 313	0.8
Latvia	:	1 233	1 291	1 389	1 556	1 610	:
Lithuania	2 097	2 147	2 266	2 424	2 581	2 724	29.9
Luxembourg	2 899	2 638	2 768	2 826	2 915	3 031	4.6
Hungary	7 429	7 396	7 488	7 731	8 127	8 535	14.9
Malta	:	:	795	889	945	1 053	:
Netherlands	68 816	69 901	70 964	71 236	72 963	74 448	8.2
Austria	32 500	33 317	34 541	35 692	37 117	38 457	18.3
Poland	:	25 166	25 681	27 280	27 756	:	:
Portugal	15 742	15 477	15 616	16 132	16 854	17 456	10.9
Romania	6 282	7 467	7 568	7 923	8 509	9 672	54.0
Slovenia	:	:	3 200	3 309	3 429	3 520	:
Slovakia (2)	5 550	5 583	5 256	5 418	5 666	5 721	3.1
Finland (3)	18 584	19 328	19 506	20 374	20 372	20 614	10.9
Sweden	46 306	48 372	48 207	49 428	50 836	52 364	13.1
United Kingdom	:	202 540	223 220	253 013	233 105	225 187	:
Iceland	939	992	1 109	1 275	1 522	:	:
Liechtenstein	:	289	296	339	343	337	:
Norway	34 806	35 130	35 132	35 220	35 319	37 010	6.3
Switzerland	57 469	58 648	61 486	72 810	74 031	74 250	29.2

(1) 2017: including 2016 data for Poland.
(2) 2014: break in series.
(3) 2015: break in series.
Source: Eurostat (online data code: hlth_sha11_hf)

eurostat

At the same time, **private health insurance is on the rise** (at least in some EU countries): People are investing in voluntary health insurance (VHI) to cover gaps in publicly funded health insurance, to get faster access to treatment, and to increase choice of health care providers. Private spending on health through VHI is in general low in Europe. In 2014, only 5% of total health spending in only 11 out of 53 countries in the WHO European Region was done via VHI, with large markets in EU and EFTA countries.[51] Voluntary health insurance increased between 2000 and 2014 in many countries, however, the growth did not exceed half a percentage point.

Asia, and especially China is a rising market for PM. It is expected that the market for healthcare through personalized medicine in Asia will increase significantly in the years to come. The Asia-Pacific genomics market is expected to grow from USD 30.6 million in 2018 to USD 61.9 million in 2027, with an estimated annual market growth of 8.5% (CAGR) from 2018-2027.[52] This development is driven by factors such as the increasing number of people over 65 years of age (approximately 329 million people in China by 2050[53]), significant growth in the health care system and a general increase the population income.

[51] Sagan A., Thomson S. (2016) Voluntary health insurance in Europe: role and regulation. Observatory Studies Series 43.

[52] https://www.globenewswire.com/news-release/2019/05/13/1822656/0/en/Asia-Pacific-Metagenomics-Market-to-2027-Opportunities-in-Precision-Metagenomic-Analysis-In-Personalised-Medicine.html

[53] https://www.pacificbridgemedical.com/ameing-for-asia/china-fast-becoming-top-player-in-booming-asia-genomics-market/

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R&D investment in genetic research is increasing, and genomics-related activities are booming due to the growing demand for genetic sequencing. For example, in 2016 the Chinese Academy of Sciences launched a Precision Medicine Initiative aimed at the Chinese population, providing some US$ 9 billion for a sequencing project that will analyse more than 100 million human genomes by 2030.[54] In 2017, the Chinese Ministry of Science and Technology launched a human genome research project to document the genetic make-up of 100,000 people from different ethnic backgrounds and regions.[55] The Chinese company BGI Genomics is the world's leading provider of genomic sequencing services and proteomic services, working for customers in more than 66 countries.[56]

7 POLICY-RELATED TRENDS & DRIVERS

Innovation model – public vs. private

Public controversy has sparked off by recent focus of large pharmaceutical companies and the private, for profit and patent-driven model of innovation, reacting to an increase of treatment and **unsustainability of European health systems**. This model is criticised for not responding to the needs of patients and putting the insurer in a disadvantaged bargaining position. Some experts demand that pharmaceutical innovation be structured to meet health needs globally and deliver medications that are affordable and accessible to all and not just profitable for the manufacturers (BMJ2016; 354)[57]. [58],[59] As a recent study on prices for cancer drugs by the WHO pointed out, pharmaceutical companies tend to set prices according to their commercial goals, not based on actual R&D costs.[60]

One basic problem is that the pharmaceutical companies usually have the power to determine the price for medication while **costs for research and development remain opaque**. A few initiatives in Europe have undertaken concerted efforts to jointly negotiate prices with pharmaceutical companies, such as the Beneluxa Initiative[61] and the Valletta Declaration[62] which try to level information asymmetries and bargaining power.[63]

[54] https://www.pacificbridgemedical.com/ameing-for-asia/china-fast-becoming-top-player-in-booming-asia-genomics-market/

[55] https://www.geneticsandsociety.org/article/china-launches-worlds-largest-human-genome-research-project

[56] https://www.bgi.com/global/company/about-bgi/

[57] one example is the case of Gilead's price strategy for sofosbuvir and ledipasvir-sofobuvir in the UK where the price demanded could not be afforded by the National Health Service. Sofosbuvir and ledipasvir relied on early stage funding from the NIH and the Veterans Administration. Sales of the two drugs were around $12bn in 2014, far in excess of the $880.3m which Gilead reported for sofosbuvir related trials from 2012 to 2014 showing a complete disconnection between price and development costs.

[58] https://corporateeurope.org/sites/default/files/2019-05/High%20Prices%2C%20Poor%20Access_Full%20report.pdf

[59] https://www.contagionlive.com/news/doctors-without-borders-among-30-groups-to-challenge-hcv-drug-patent-in-europe

[60] https://www.healthpolicy-watch.org/who-member-states-call-for-transparency-access-to-innovation-on-cancer-drug-pricing/

[61] Beneluxa initiative is a concerted efforts of Austria, Belgium, the Netherlands and Luxemburg to bring more transparency and balance to the pricing and supply of medication in the EU. It wants to contribute to common bargaining power vis-à-vis the pharmaceutical sector. https://beneluxa.org/collaboration

[62] https://southeusummit.com/about/valletta-declaration/

[63] https://corporateeurope.org/sites/default/files/2019-05/High%20Prices%2C%20Poor%20Access_Full%20report.pdf

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Several studies could show that the price for expensive drugs is not justified by **R&D costs**.[64],[65] Further, the curative effects of many drugs, expansive or not, are also questionable. As critical scholars in study published in the Journal of Economic Perspectives showed, of 58 cancer drugs approved in the US between 1995 and 2013, two thirds did not represent any therapeutic benefit for patients. Many of these drugs were based on reframing old combinations or on additional uses for existing ones. We find a similar scheme in Europe: The independent drugs bulletin, Prescrire, assessed over 50 orphan drugs authorised by the European Medical Agency (EMA) and found little to no therapeutic advantages over existing drugs.[66]

The secrecy around R&D costs and also discounts for some insurers leads to **uneven price policies** where pharma companies charge some payers more for the same drug than others.[67] This policy makes it impossible for the insurers or governments to negotiate for the lowest price or to create more equity and fairness for the patients.[68], [69]

The increasing financialisation of the pharmaceutical sector is another noteworthy current and future trend. This financialisation where many companies spend an increasing amount of their net income to buyback shares in order to boost stock prices and stock options[70],[71] is a company policy which drives prices up and has inhibiting effect on innovation.[72]

Another trend of concern is the drive to cut costs of manufacturing by outsourcing or **offshoring production**, leading the shutdown of local capacities and increasing dependence on overseas relationships which can be precarious as we just saw in the COVID19 crisis.

The research and development of PM is affected by this debate because of the fear of many that it will make medication more expensive. It relies on the basic research conducted and in (often publicly funded) universities and is upscaled and marketed by larger pharmaceutical firms which then negotiate the price with the insurer or government.[73] A study by University College London estimates that between one and two-thirds of up-front **investment into new drugs come from public bodies**.[74] Thus, one of the questions arising is how does the innovation system need to change in order to pay a decent price that reflects R&D investments (both public and private) and how can all patients benefit from the treatment they need. More

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[64] https://corporateeurope.org/sites/default/files/2019-05/High%20Prices%2C%20Poor%20Access_Full%20report.pdf

[65] https://www.theatlantic.com/health/archive/2015/09/an-expensive-medications-human-cost/407299/

[66] prescrire.org/en/3D3B93E1C3DE20A599FBA073C5442463/Download.aspx89AIDES, Appendix I – Legal arguments, https://www.aides.org/sites/default/files/Aides/bloc_telechargement/Aides%20CJEU%

[67]BMJ 2020; 368 doi: https://doi.org/10.1136/bmj.l4627 (Published 13 January 2020) Cite this as: BMJ 2020;368:l4627

[68] *The cost of drug development: a systematic review. Health Policy2011;100:4-17. doi:10.1016/j.healthpol.2010.12.002 pmid:21256615*

[69] *The $2.6 billion pill—methodologic and policy considerations. N Engl J Med2015;372:1877-9. doi:10.1056/NEJMp1500848 pmid:25970049*

[70] https://corporateeurope.org/sites/default/files/2019-05/High%20Prices%2C%20Poor%20Access_Full%20report.pdf

[71] https://www.ineteconomics.org/uploads/papers/WP_60-Lazonick-et-al-US-Pharma-Business-Model.pdf

[72] *BMJ 2020; 368 doi: https://doi.org/10.1136/bmj.m769 (Published 04 March 2020) Cite this as: BMJ 2020;368:m769*

[73] *Contribution of NIH funding to new drug approvals 2010-2016. Proc Natl Acad Sci USA2018;115:2329-34. doi:10.1073/pnas.1715368115 pmid:21256615*

[74] https://www.ucl.ac.uk/bartlett/public-purpose/sites/public-purpose/files/peoples_prescription_report_final_online.pdf

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indirect public support reaches pharmaceutical companies through tax reductions and tax credits. These measures can significantly lower R&D investments by manufacturers, not only for orphan drugs.[75]

Another inhibitor to the innovation system is seen in the mere **upstream use of intellectual property rights** which does not encourage innovation, especially in SMEs. As Morgan et al. (2020) point out, "patents are not backward looking policy tools meant to compensate firms for their previous investments. Instead, patents are forward looking policy tools. They are meant to signal to firms that the potential return on innovation will be in proportion to the social value of the discovery, but never in excess of that value. This gives firms an incentive to choose research projects expected to generate a positive net social value after taking into account research costs, which they will also have an incentive to manage efficiently."[76] The **Supplementary Protection Certificate** (SPC) even allows the extension of certain patents and thus monopoly pricing.[77] The SPC is a European invention allowing national patent offices to grant extensions of up to five years to patents protecting pharmaceutical and agricultural inventions. The justification is the compulsory length of testing and clinical trials to obtain market approval.[78] Many societal stakeholder groups, such as the Médecines Sans Frontières regard this tool as inhibitor to innovation and fair competition because SPCs are often routinely given, keeping pharma prices high, delaying the entry of generic competitors and thus threatening the sustainability of national health care systems. This discussion is relevant for PM because pharma companies often argue, that the R&D cost of PM products are unusually high and they might want to claim longer protection than the usual 20 years patent protection. Any attempts to revise SPC for a more user/patient friendly modification that would also allow lower market entries for competitors were subject to long discussions between the Dutch Council (in 2016), the European Parliament and several social pressure groups pledging for better access and better regulations on the one side,[79] and the representatives of the big pharma industry on the other.[80] In the end, the European Council succumbed the pressure of the industry lobby groups and made only minor amendments for an export waiver.[81] However, the Dutch Council attempt to amend the SPC is interpreted by observers as the first significant sign of a European government to acknowledge the misbalance between governments and society on the one side and the pharma industry on the other side with regard to the current model of innovation.[82] The move from the part of the European Parliament can also be seen as an attempt to solve such issues in favour of the European citizens at a European level.

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[75] *Orphan medicinal products in Europe and United States to cover needs of patients with rare diseases: an increased common effort is to be foreseen. Orphanet J Rare Dis2017;12:64. doi:10.1186/s13023-017-0617-1 pmid:28372595*

[76] *BMJ 2020; 368 doi: https://doi.org/10.1136/bmj.l4627 (Published 13 January 2020) Cite this as: BMJ 2020;368:l4627*

[77] https://www.politico.eu/article/future-of-pharma-incentives-fine-line-between-incentives-and-favoritism-drug-research/

[78] https://ec.europa.eu/growth/industry/policy/intellectual-property/patents/supplementary-protection-certificates_en

[79] https://epha.org/the-top-5-issues-in-medicines-policy-for-2019/

[80] https://www.efpia.eu/news-events/the-efpia-view/blog-articles/policy-principles-on-cross-country-collaborations-on-medicines-pricing-and-access/

[81] https://www.internationallawoffice.com/Newsletters/Healthcare-Life-Sciences/European-Union/Eversheds-Sutherland-Germany-LLP/SPC-Regulation-amendment-and-export-manufacturing-waiver-in-depth-analysis

[82] https://epha.org/the-top-5-issues-in-medicines-policy-for-2019/

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For some extreme cases, **compulsory licensing** has recently been discussed.[83] Alternatively, some argue that patents could be limited on new medicines. Policy makers could establish a competitive prize system, rewarding well-targeted innovation, thus providing access to drugs at competitive prices through generics, while stimulating pharma companies to focus on innovations for urgent medical need.[84]

Another attempt to better govern the current model of pharma-related innovation at European level is the initiative of a **coordinated Health Technology Assessment** (HTA) institutionalised in the European Medicines Agency (EMA). HTA as a scientific analysis helps to classify new drugs. Its role is to judge whether a new drug is working better or worse than already existing alternatives. As such, HTA is a crucial gatekeeper for public spending on effective and efficient therapies and their affordability. Thus, in the debate about sustainability of the European (or any) health care system and equity, HTA delivers valuable indicators. It is essential for a sustainable publicly funded or tax-based health care system to get objective information from independent HTA, this means also independence from industry influence. So far, the HTA and price negotiations were done on member state level, but in 2018 the European Commission started an initiative for an EU wide legislative process at EU level. While this would have several advantages with regard to negotiating power vis-à-vis the pharma industry, some EU countries already have very high standards and are afraid that these would be diluted by a new European standard.[85] Earlier attempts for voluntary cooperation for a European wide HTA were not very successful and had difficulties staying independent from EMA.[86] The current initiative is still under discussion and there is no sight of a near solution[87] as the EU Parliament and insurance pressure groups such as the European Social Insurance Platform (ESIP) representing public payers, call for certain procedural rules ensuring the independence and transparency of HTA processes while pharma lobbies such as EFPIA try to defend their industry's interest. The status quo serves the interest of the pharma industry better because they are used to negotiate prices in a fragmented health system.[88] There are, however, good arguments for a European wide HTA by independent players based on transparent, accessible evidence to empower national authorities to negotiate sound pricing for necessary drugs and treatments, thus putting a hold on increased pricing and insecure health provision.

Mission-oriented approach to medical research

The trend for a more structured approach of research and development at EU level and in several EU Member States is getting stronger as policy makers and the public recognise that the future challenges lying ahead of us seem increasingly complex and structured policy

[83] UK *Labour Party's new policy document, Medicines for the Many, recommends this option, e.g. for Orkambi. The policy document says the UK should follow the examples of Argentina, Brazil and India, which already challenge patents and make affordable versions of some medicines in the public interest.*

[84] BMJ 2016; 354 doi: https://doi.org/10.1136/bmj.i4136 (Published 27 July 2016) Cite this as: BMJ 2016;354:i4136

[85] https://medicineslawandpolicy.org/2019/01/cancer-drug-pricing-on-the-world-health-organizations-executive-board-agenda/

[86] https://epha.org/proposed-ec-regulation-on-hta-golden-opportunity-for-patients-and-health-budgets/

[87] https://www.politico.eu/article/brussels-to-find-out-how-much-it-can-do-on-drug-pricing/

[88] https://epha.org/proposed-ec-regulation-on-hta-golden-opportunity-for-patients-and-health-budgets/

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making requires concerted strategy efforts.[89] Not the least by the 50th anniversary of the first moon landing has the so called mission-oriented approach experienced a renaissance, implying that the government through wise priority setting in R&D has the power to drive investment-led growth and achieve social goals as the fight against cancer.[90] Recently, the US has initiated a mission-oriented R&I policy initiative in the field of cancer, involving also PM, called Cancer Moonshot. [91]The mission-orientation of R&D policy is important for the discussion on the future of PM because PM has the potential if it is not becoming a mission itself, to be at least part of a mission-oriented approach. Because by its nature it is rooted in a collaborative approach and can have widespread societal and economic effects - for health but also for related areas (e.g. big data). As several mission-oriented undertakings so far have been realised through the collaboration of many different actors and partners to innovate together, stimulated by government instruments to fuel bottom-up experimentation on a vast scale, the new EU R&I tool of "**European Partnerships**" points towards this direction.[92]

To be of significant impact, mission-oriented approaches in R&I require co-creation, i.e. the **involvement of citizens**. For the context of PM this would mean, not only patients and their families but citizens at a more global scale because every citizen is somehow involved with PM sooner or later, e.g. as a tax payer, data provider, etc. "This greater public engagement, in every stage of the innovation chain, requires to be correctly balanced with an effective portfolio management of these missions with flexible governance structures that enable cross-sectoral and cross-institutional coordination."[93] Public engagement is definitely a deficit in the development of PM, its financing and funding and a large field yet to be explored by governments, the EU, companies, NGOs, the medical sector and other stakeholders affected.

In sum, we can say that several policy experts funnel the discussion, pledging for major changes of the medical innovation system and the health care system on the various fronts to meet future needs and contribute to a sustainable health system in Europe, to deliver therapies at affordable prices, accessible to the general public.[94]

One determining factor is an **effective pricing system** to **ensure accessibility** and at the same time reflect the public investments (e.g. university education, research), so tax payers do not pay twice. Costs of medication should thus be linked to innovation and production costs. One mechanism pointing towards future options could be to limit patents on new medicines and to establish a competitive price system rewarding well targeted pharmaceutical innovation. The idea behind this approach is to provide widespread access to drugs at competitive prices through generics, and nudging pharmaceutical companies and SMEs to focus on new innovations for urgent medical need that is not served otherwise. Complementary to this

[89] https://ec.europa.eu/info/sites/info/files/research_and_innovation/contact/documents/ec_rtd_mazzucato-report-issue2_072019.pdf

[90] https://ec.europa.eu/info/news/joint-meeting-h2020-programme-committee-configuration-sc1-health-and-steering-group-health-promotion-disease-prevention-and-management-non-communicable-diseases-2020-jan-24_en

[91] https://op.europa.eu/en/publication-detail/-/publication/84ce6df7-235a-11e8-ac73-01aa75ed71a1/language-en

[92] https://ec.europa.eu/info/horizon-europe-next-research-and-innovation-framework-programme/european-partnerships-horizon-europe/candidates-european-partnerships-health_en

[93] https://ec.europa.eu/info/sites/info/files/research_and_innovation/contact/documents/ec_rtd_mazzucato-report-issue2_072019.pdf

[94] BMJ 2016; 354 doi: https://doi.org/10.1136/bmj.i4136 (Published 27 July 2016) Cite this as: BMJ 2016;354:i4136

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strategy, patents should be less upstream and narrower in order not to exclude new or additional discoveries in certain disease areas.

In addition, a future direction for the health system is to **make the drug pricing system transparent** so that insurers/governments have more bargaining power for price negotiations and can make sure that all patients in need have access to the appropriate treatment. This could also imply that public funders retain a significant share of the patent rights in an innovation is made possible through public funds directly or indirectly. This approach would allow spillovers through licensing and a better management of diffusion, ensuring that the price of a new drugs reflects the burden of financial risk paid by the general public. A more sustainable health system for the future that provides incentives for valued innovations needs to ensure that pharmaceutical prices do not exceed comparative value for money, that returns for R&D investments are fair and that price competition occurs as early as possible.[95]

A law like the Bayh-Dole Act in the US (1980) could also be an option for European countries. The law grants the government power to license a generic competitor if a company is not making a taxpayer-funded drug available to the public on "reasonable" terms.[96] This was never implemented in the US, though. Still, the example points into a direction to give governments more power to shape the pharmaceutical eco system in a direction that is more friendly to competition and to the patient and tax payer. Change of some parameters are also necessary to increase incentives for new drugs. Large pharmaceutical companies usually like to rely on block busters and prefer new studies to apply approved drugs to other indications as well and conduct clinical studies towards these directions instead of innovating into new, unprecedented areas. They do not like to invest in risky areas. The change of IP rights might not only attract start-ups and SME but also incumbents.

To conclude, some political economy analysts argue that MS and the European Union should govern the drug innovation process more like a mission-oriented approach, steering innovation, achieving fair prices and access for treatment for the patients, ensuring that patents and competition stimulate innovation, and that profits are reinvested in innovation activities.[97]

From Trends and Driver Assessment to Scenario Development

Above we have presented some to the core trends and drivers in the context of Personalised Medicine, especially with regards to its affordability and access, payment strategies and innovation model. To do so we have contextualised the trends and drivers from policy, society, economy and technology in the more general discussion around the sustainability of the European health care systems and the rational of its current innovation model. The next step in this paper is to link the trends and drivers from this context to the future options of PM and the paths its development could chart.

[95] *BMJ 2020; 368 doi: https://doi.org/10.1136/bmj.l4627 (Published 13 January 2020) Cite this as: BMJ 2020;368:l4627*

[96] https://www.washingtonpost.com/business/economy/a-rare-deterrent-to-limitless-drug-price-increases-may-die-under-trump/2019/04/17/7578e5e0-5bcd-11e9-a00e-050dc7b82693_story.html

[97] *BMJ 2020; 368 doi: https://doi.org/10.1136/bmj.m769 (Published 04 March 2020) Cite this as: BMJ 2020;368:m769*

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8 SCENARIO DEVELOPMENT FOR THE FUTURE OF PERSONALISED MEDICINE IN THE EU

In this work package, we apply a forward-looking approach in form of scenario development. The scenario method is a policy analysis tool that helps describe a possible set of future conditions. At national, regional and local level scenarios can be used to improve planning capacity, to enrich strategic public policy decisions and to guide major capital investments. For example, the development of scenarios allows new insights into the opportunities and risks involved in making decisions about changes in the funding of health systems that would have major consequences for the significance of the financing of personalized medicine products in the next few decades. To be effective, scenarios must be plausible, consistent and offer insights into the future. Scenarios can help public sector executives to think in a disciplined way about the future when making public policy decisions. The method helps the decision-maker to consider the range of plausible futures, to articulate preferred visions of the future, to use what is learned during the scenario development process in the formal decision-making process to foster exceptional leadership. It also helps to stimulate creativity and to break from the conventional obsession with present and short-term problems.[98] Therefore, one of the purposes and uses of scenarios is to help decision-makers acquire knowledge and understanding to anticipate the context in which they have to act.

Based on the identification of trends and drivers from the literature and their significance to first: highest impact, and second: highest uncertainty, we developed four distinctive scenarios, with regard to innovation systems of Personalised Medicine. Following the practice of many foresight exercises in research and development, it is common practice to explore three to four scenarios. The number of three scenarios has the advantage that one best practice scenario can be developed, contrasted by one that depicts the “business as usual” (what happens if not much is changing), and one worst case. Where there are four scenarios, the forth one often depicts an unexpected and/or polarized direction. In the process of scenario development for the topic of financing of PM, we chose a different approach in order to avoid sheer optimism or pessimism. Instead, all of the scenario, though different in their cores, contain some optimistic as well as pessimistic features. They may not be understood as representing a realistic case for the future. Rather, each of them has elements that might sound more realistic than others and in the future we will see that a combination of them will prevail, though in different granularities. We do not know to which degree. It is not the attempt of this document to predict the future but rather to point toward possible future directions in order to become aware that we might have to take certain decisions today in order to be better prepared for the future.

All four scenarios are structured in a similar way to make them comparable on the basis of their key assumptions (see Table 3). Starting with a general overview on the situation of the country or society each scenario depicts the frame in with PM may unfold well or not so well. The scenarios differ in their description of actors and institutions, beneficiaries, financing mechanisms, and especially the integration of PM into the health system of each case.

[98] For more information see *http://www.foresight-platform.eu/community/forlearn/how-to-do-foresight/methods/scenario/*

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Table 3: Comparisons of basic assumptions of scenarios (STEPV categories: S: social; T: technology; E: economic; P: policy; V: value)

Indicators	STEPV category	Privatisation ***Boutique Medicine vs. Automated Medicine***	Technology-driven ***Personalised Medicine by Subscription***	Cooperation ***Personalised and Holistic Medicine***	Scepticism ***Personalised Medicine in a Niche***
Benefit (of financing system for PM) for whom? Driver for technology	E / S	Pharmaceutical companies, multi-national integrated companies, shareholders, start-ups; shareholder	Researchers, research organisations; data specialists; data recipients (e.g. biobanks)	Society / patients as a whole and as individuals	Society/patients as a whole but not individuals
Financing model	E	Public: for basic care, but inefficient Private: more efficient, for advanced, high quality care, incl. PM	Subscription model	Derivate of the "Singapore model" (high taxes and government subsidies); cost transparency	PM: Pay-for-performance, other: solidarity-based
Insurance system (public/private)	E	Private	Private (with basic public insurance)	Subsidised public insurance for nationals and private insurance for health tourists	Public
Demographic change, increase in elderly, decrease in net payer into social system	S	Decrease in birth rate, increase in aging	Rising (aging population)	Increased birth rate, immigrants from around the world; young population;	Rising aging population
Role of non-evidence-based approaches	V	Low	Low	Medium	High
Role of government in the health sector (insurance)	P	Low	Low (influence on insurance system)	High (influence on insurance system)	High
Role of government in health R&D	P	High in universities and research organisations	High	High	Low-medium

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Indicators	STEPV category	Privatisation ***Boutique Medicine vs. Automated Medicine***	Technology-driven ***Personalised Medicine by Subscription***	Cooperation ***Personalised and Holistic Medicine***	Scepticism ***Personalised Medicine in a Niche***
Patents (period)	P / T	Adjusted for more competition and fairness towards newly entering companies	Discussions to limit patent protection	Legislative issues between patent rights and the push for open data are recurring themes in the social discourse.	If necessary patent periods are ignored, generics produced by public-private national companies
Data (provision, collection, use, protection) – role of data; as resource;	T	High	High	High	Low
Pharma industry / SME	E	High (increasing competition, increase of players)	High (users of data: pharma industry and SME)	Medium (cooperation with health centres; financers of research; not valid for SMEs)	In part public-private national companies, some private companies, some multinational data companies on negotiation basis with national health system
Patients/relatives	V / S	Passive	Active (data); high (data providers) relevant actors in subscription model (payers)	Passive (data); medium (data providers)	PM: passive General health system: active
Insurers (companies, public insurers)	E	Horizontally and vertically integrated multinational companies	Merger of private insurers, pharma companies, research organisations and other technologically active actors)	Public insurers and private insurers (for health tourists)	Traditional, tax based
General Practitioners	S	Substituted by specialised professionals	Low	High	Social values
Trust	V		Trust in technology	Trust in general practitioners and other health care professionals	No trust in data, but in personal relationships

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Indicators	STEPV category	Privatisation *Boutique Medicine vs. Automated Medicine*	Technology-driven *Personalised Medicine by Subscription*	Cooperation *Personalised and Holistic Medicine*	Scepticism *Personalised Medicine in a Niche*
Inequity	S / E	High	High	Medium	Low
Medical innovations	T	High	High	High	Low (if innovation, it is foreign)
Burden of risk for R&D	E	Externalised to public	Public funding for R&D	Public funding for R&D	Private/foreign for PM
Public Perception of PM	V	High	high	medium	low
Who sets research priorities	V	Private enterprises	An independent commission decides on investments and prioritization of technologies for further investment; subscribers of insurances	Public R&D funding programmes	National health system
Focus of public health policy (prevention, diagnostics, therapy, survivorship, etc.)	P	Diagnostics, therapy	Technological advancement, diagnostics, therapy, survivorship	Prevention	Prevention
Degree of participation (Mitsprache im Gesundheitssystem)	S	Low	High	Medium	Medium

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To get expert feedback for the scenarios and further input on possible funding mechanisms we invited internal experts of the HEcoPerMed team to participant in a face-to-face workshop and further external experts to take part in online scenario workshops. There professional backgrounds next to health economics were clinicians, medical researchers at university level and from pharmaceutical companies, health experts from public research organisations, from public health institutes, experts in societal, legal and future issues of health.

Key questions that guided the discussion were:

- How can diagnostics and treatments based on PM be paid for in the future?
- Can these innovative health products be integrated into our current health insurance systems?
- Or do health insurance systems need to change fundamentally to provide high quality long-term care accessible to all?
- What can be incentives for pharmaceutical companies and start-ups to invest in future diagnostics and treatments based on PM?
- Have the framework conditions for health services and finance changed under the COVID19 crisis? Are these changes forward-looking of only temporary?

The subsequent chapters present the final scenarios as a result of this research and cooperative work:

1. Privatisation: Boutique Medicine vs. Automated Medicine
2. Technology-driven: Personalised Medicine by Subscription
3. Cooperation: Personalised and Holistic Medicine
4. Scepticism: Personalised Medicine in a Niche

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9 SCENARIO: PRIVATIZATION – *BOUTIQUE MEDICINE VS. AUTOMATED MEDICINE*

9.1 Social system under stress

In this society we find a social system under stress, mainly due to the fact that for the previous decades the population in the EU has aged and the younger generations had difficulties to bear the burden of the increased health care and pension costs. Even though pension reforms have prolonged retirement age, many people reach 90 years of age and even higher. Especially the very old agers are affected by mental diseases and cancer and are often in need of permanent care. For such a high rate of elderly and sick people, even basic health care on the basis of a public insurance system is impossible to provide. Thus, getting old and sick for many people means to be confronted with a low quality of life. Especially since the government has ruled that no costly treatments are provided for people 90 years and older. Only private insurance plans can compensate this care deficit. Health care is more and more becoming a private domain, affordable only for the well-to-do, which accounts for a few percent of the population. The emergence of a “boutique medicine” leads to increasing inequality of health outcomes between a small rich segment and the poor majority. There is also an uneven landscape of wealth and health distribution across the EU and within nation states.

Multi-national diversified companies are merging with insurance and pharmaceutical companies, offering pan-European insurance plan and world-wide provision of health care.

Medical innovation is cost-increasing rather than cost-saving and advanced medical technologies are not available in remote and poorer areas. Public, respective tax-funded insurance systems are still focusing on national clientele and are in competition with trans-European and multi-national approaches which offer also services to Asian, African and American patients; private hospitals offer services to wealthy elites from disadvantaged regions around the world. This causes substantial public debate on national and European value chains, following the argument that medical research and services financed by European tax payers should exclusively be supplied to Europeans.

In this society, public sentiments for state led social care are very low despite the two-tier class system. The social division is not only visible in the social system but even more so in the urban areas where massive gentrification takes place, offering well-resourced life style services and a high quality of life in the elegant and rich quarters with access to high quality health care, while poor living quarters are faced with pollution, noise, crime and overcrowded living spaces.

9.2 Economic divergence

Not only the social system is under stress, so are state budgets. In order to prevent fiscal bankruptcy due to overstrained social services, some nation states sell more and more public properties and goods.

In this polarised health system, many services of Personalised Medicine are affordable only by the wealthy people. They live longer and healthier, they get access to high quality hospitals and medication. A small number of wealthy people live technically longer. However, stratified medicine based on big data, labelled “automatic medicine”, makes diagnostics and treatment more efficient and cheaper than ever before and works for the benefit of the larger

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segment of the population that cannot afford boutique medicine. Patients have to see a doctor only in exceptional cases, instead their data is analysed and monitored by automated algorithms, with automated diagnosis and suggestions for treatment. This approach contributes to more saved lives e.g. from cancer.

Another way to save costs for individuals is through self-medication, including apps that collect and interpret data, compensating for the subsiding contact between doctors and patients. Because of the unhealthy lifestyles of the poorer classes, these people are more susceptible to disease, but they often cannot take care of prevention and have limited access to high-quality diagnosis and treatment. The extension of the working life was a policy measure to cope with the budget deficit for pensions and social care. But this measure was still not sufficient enough to pour sufficient money into the fiscal coffers. Instead, people at higher age with certain non-communicable diseases (NCDs) and other severe health issues were forced to keep on working in order not to lose part of their benefits. This trend is accompanied by reduced intergenerational solidarity: other than the COVID19 crisis, priority now is economic growth and increase in per capita income.

The increase in inequity between the small rich and large poor segment starts already at early age, as rich people can afford full genomic sequencing right after birth, their medical treatment is based on this analysis during their life course. Those who want to know more about their genetic dispositions can profit from more data collection and interpretation and live a healthier and longer life.

There are a number of PM therapies, but they are costly and only the wealthy can afford them. The small percentage of people ascribing to boutique medicine is willing to pay a high price for granular analysis of their health-related data, thus providing incentives for start-ups to develop rapid tests and reliable interpretations. This private sector moves more and more into the direction of value-based medicine outpacing the conventional model of standardized care and reimbursement independent of the outcome.

Due to only a small market with questionable evidence, small size studies and high costs of development, incentives for private companies for investment in PM are poor. For those therapies and diagnostics available on the PM market, privatization means supply is looking for demand.

In fields where automated health reaches its limits, health care has become increasingly complicated to understand (e.g. new diseases, interpretation of newly discovered genetic information, combination with new breakthroughs in artificial intelligence) causing only highly educated people to be able to understand and identify the right health care for them. This contributes to an increasing differentiation of the health sector where the general practitioner is disappearing.

9.3 Changes in values

Instead of solidarity, individuals are held more accountable for their own health while social and behavioural aspects that determine a person's health are ignored. In this society, the individual is the focus of social discourse and values. In this sense, privatization fits the increase in narcissism and focus on the use of "I", "me" and "my" in iPhone, iPad, iPod. Even though there is reduced solidarity and reduced willingness to pay for public insurance, there is also considerable ethical pressure to apply PM to all patients incl. prevention strategies.

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Among wealthy patients, acceptance of PM is high. Buying new organs from stem cells or 3D-printing is a matter of prize. Genetic test kits are also available for purchase just like any other commercial product.

9.4 Health becoming a commodity

Pharmaceutical companies are making most money with blockbusters for the less well-to-do. Progress in PM and any investments are usually not done in public organisations but by private industry. They expect high profits with focus on affluent patients and indications that are more common among affluent patients. People who do not want to pay the price will miss out on the drug.

Monopolies grow in certain disease areas, crowding out smaller competitors. Multi-national corporations invest in health insurance assets, not only in hardware. The role of private players in the production and delivery of health care services is also on the rise. We witness substantial increase of private financing and expenditure substituting public financing, also in the health sector. The interest of the pharma industry is to increase the evidence base from the patients. They might be willing to lower the price to get the data. Every patient/citizen can decide for her/himself if they want to make use of PM. Personalised Medicine is the hype of this epoch, not only for investors and researchers but also for society. Whenever affordable, people take the chance for screenings as often as possible to detect any potential health threats. This pours considerable money into the coffers of pharma industry even though there is hardly any evidence that screening has saved many lives.

Since it is a market and health has become a commodity it is very difficult for the individual to keep an overview on the services. This requires consultation with specialists. The private market offers tests directly to consumer (easy access, data is not shared with insurers/providers). This is merely a matter of affordability. This is also the case of mHealth services which are on the rise in an affluent segment. PM turns into personalised “lifeline” from rich.

Thanks to PM, there is longer survival (e.g. cancer survival) in chronic diseases, with satisfactory QoL. For common diseases (e.g. cancer) the pharmaceutical industry (not only in PM) is interested in keeping patients alive for a long time, so that these people can buy their products for longer. Cross-border care increases market competition of the health sector (shopping for the best cost effectiveness) and poses some reimbursement challenges. Some insurers, health economists and health policy makers propagate a “global health care system”.

Instead of relying on the advice of experts, therapies are increasingly chosen by consumers, who are not always well informed.

For the poorer patients, the market offers “sick” organs for replacement which are cheaper to obtain than the best quality ones. At the same time, the black market for health, misinformation in the social media and unapproved medication are on the rise.

9.5 Liberal laissez-faire state approach

In the recent past, a larger proportion of per capita income went to health care. But now, public expenditure is trying to cut down on health costs and to refocus on non-health public goods such as defence and education. The laissez-faire state approach leaves matters of

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healthy behaviours and compliance entirely to individuals' free choice. There is fear of a further increase of health cost and that unnecessary disease screening might waste limited health care resources instead of reducing the costs and benefitting the patient. Accordingly, public health insurance is retreating the service step by step, private insurance companies are cherry picking their clients as genetic test results affect not only customers but also family members. As a consequence, an increasing number of citizens is without any health insurance.

The role of the state is not very active and mostly limited to setting regulations and standards that help the private development of PM and safety for the patients. The public insurance system guarantees only minimum standards for sick people and has little to offer for prevention programs. Everyone is encouraged to insure health risks with private insurers. Medical tourism is increasing across borders and also the need for medical market regulation above statue (e.g. EU level).

There is no regulation by the state concerning pricing for specific treatments or tests. From the patient perspective: the free market makes shopping for the best testing and treatment internationally possible, offering a variety of solutions for those who can afford it.

Charity organisations try to fill the gap of sufficient health support for the marginalized.

9.6 PM progress and achievements

PM has made considerable advances in diagnostics and treatment of diseases that are lucrative for the big pharmaceutical companies treating major worries of wealthy people. A growing share of medicine is gene-mutation based. Medical and technological breakthroughs are provided not so much by the private sector, however, but by public research institutes and universities that provide the basic research for the understanding of the genome and the interpretation of its information. The largest share for medical research is provided by public finds, private companies are investing more in incremental research and in development. To enable wealth from discoveries, the principle of capitalism has been turned upside down: "private risk yields private loss or gain" became "public risk yields public loss or private gain"—a form of "heads I win, tails you lose." This was formerly known in the US and is now realized in Europe and beyond.

Testing and treatment is quite time consuming and costly, physically and psychologically exhausting for the patients. Some diseases can be detected quite early and treated accordingly, others can be detected but effective treatments are still missing. Over the last decades there have been a lot of innovations, but also much inefficiency due to monopolies. More drugs reach patients before phase III testing, leading to more waste in the health care system (drugs that may not work). In diabetes, improved care continuum is provided by a single integrated company.

Patients who cannot afford these extra services or who suffer from a rare disease hardly get customized solutions. PM is by definition not for the masses. Some observers argue that increased privatization requires increased price negotiation skills.

Medical and other experts take an interest in provider induced demand, thereby generating high additional costs for the health system

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9.7 Investment and financing strategies

Analogous to strategies of a soccer team recruiting young talents this model functions like a buddy system: In the first round (age groups) the pharma industry invests in the 'young boy'; the investment in the person and the training is analogous to the investment in the development of PM products. Then the player moves on and is sold to the next age group, and so on until he reaches the highest professional league. The investors take the money from the latter and reinvest it into the first round.

Pharma industry, however, is not willing to reduce the price of their product as long as patent protection lasts. For example, a competitor comes in with a new product and needs compensation for the work done and opening the market. This is stimulated by a change of patent law, reducing the patent time. The innovator who enters the market later, e.g. to improve the product, possibly with a smaller market share, needs some compensation to be stimulated to enter the market. There is potential to stimulate more competition. For stimulating more competition and innovation, patent protection is lowered.

In the past, there was a small group of patients who paid a very high price. In order to make the PM products more affordable to more people, the price needed to be reduced but at the same time guarantee return on investments. Another problem was also that if a company was already investing in R&D in a certain field and held a market share, other companies stopped investing in R&D in the same field because they did not expect to get a lucrative share of the market.

New strategies have to be found to keep the innovative power of pharma companies alive. For example:

1. If several companies (e.g. A, B and C) collaborate, R&D costs can be pooled to make bigger investigations. The three companies get an exclusivity time and share the risk for e.g. 15 years to pay off the risks. Once this period has finished, the companies A, B, and C can think about how to go into the market individually (i.e. first comes a blockbuster treatment and then a competitive approach).
2. Pharmaceutical manufacturers are collaborators in the same products in the beginning. After an exclusivity period (15 years), each of them tries to find a niche for further incremental innovation and product refinement, and this product diversification can be done in a competitive way. As a result, less money is wasted because there is only one original collaborative investment and not several competing ones.

In both examples the investment would be the same, but in the latter example the risk would be shared.

Whereas in the past, we were trading off competition for inefficiency, with the new models, we will have more efficiency thanks to competition.

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10 SCENARIO: TECHNOLOGY-DRIVEN - *PERSONALISED MEDICINE BY SUBSCRIPTION*

10.1 Aging society

The world population is continuously growing and expected to reach 8.5 billion people by 2030 and 10 billion people by 2050[99]. While the number of people is increasing predominantly in less developed countries, population numbers are stagnating or even falling in developed countries, resulting in a demographic aging of the population. Approximately 10% of the world's population will be aged over 80 by the middle of the 21st century[100]. Among the main reasons for increased life expectancy are better hygiene, sufficient food, reduced child mortality and improved medical care. Advancements in biotechnology and medical technology drive even more the extension of the lifespan.

10.2 Health care system aims at increasing the life expectancy even more

The number one priority of the health care system is to prolong life regardless of what it costs. Ongoing scientific and technological advances in medicine spur on the ambition of medical professionals to exploit all available medical knowledge, technical devices and pharmacological therapies to save lives and reduce overall mortality. Clinical advances enable the transformation of previously fatal diseases into chronic diseases. Death is no option, even though attempts to lower the mortality rate are often paralleled with extended periods of morbidity in patients, resulting in chronically ill and care-intensive people ("living dead").

Scientific and technological developments are driven forward with enormous expenditure and effort to conquer every disease. Health care professionals are dealing with genetic deficiencies, rather than treating human beings. More complex diseases or rare diseases get more attention from the health care system than common diseases, as they are considered more demanding scientific challenges. Since a wide range of technological instruments and apparatuses are available, the medical focus is primarily on dealing with the genetic deficiencies rather than on preventing illnesses. Prevention is the responsibility of the individual and encouraged by government initiatives, which promote for example personalised virtual health care. Evidence-based medicine is the overarching standard in the health care system and leaves no room for alternative medical approaches.

10.3 Technological advancement in health care

The last decades saw unprecedented technological advancements in areas such as artificial intelligence, quantum computing, analytical methods for biological functional levels (genomics, proteomics, metabolomics, etc.), cinematic rendering for photorealistic visualization of medical images and three-dimensional visualization of medical data. All of them have spurred the transformation from patient-centred health care to a technology-driven one and promoted the widespread translation of PM into daily routine.

'Omics" sequencing as well as the screening of epigenetic patterns are established procedures for diagnostics and routinely performed for every citizen. The processing costs are low

[99] OECD (2016) An OECD horizon scan of megatrends and technology. Trends in the context of future research policy.

[100] Ibid.

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and the results available within a few hours. ‘Omics’ sequencing is also expanding the application potential for the development of pharmaceuticals. An individual’s first genome sequencing is done on the day of his or her birth and places their full genomic information into this individual’s medical record. Based on the early discovery of potential gene mutations and advances in gene therapies, people can be cured of diseases (of which they may or may not ever experience symptoms) already during childhood. Genetic screenings are repeated in regular intervals as integrated part of health screening programmes or whenever an individual feels an urge to do so to gain more knowledge about one’s own state of health. The gathered information allows Biomedical Informaticians and medical staff to implement more effective health care approaches. The rapid decrease in genome sequencing costs makes it not only affordable for everyone but is even expected from everyone.

It has become easy to obtain enormous amounts of biological data. Advances in computer sciences and ultra-fast computing speeds, also relying on the use of quantum computers, benefit the processing of big data including deciphering genomics and allow for more appropriate models and predictions. However, there is the risk that data are sometimes only analysed because it is possible to do so without any real information gain for the patient. Health data are owned by the collecting institution, and these data companies have become the big players in the health system. Data sharing agreements between the various providers and users, which regulate the security of data and consequences of data breaches, are common practice as part of a information security framework.

Non-genetic determinants of diseases and drug response tend to be marginalized, unless these patient data are provided in structured ways and with sufficient quality and quantity to be incorporated smoothly into the pool of big data, originating from genetic information. Such physiological and behavioural data usually originate from personal health systems and are collected remotely while routinely monitoring personal health data. Wearable and (implanted) body sensors for recording multiple parameters related to people’s health have invaded daily life, as a vast range of applications for individualized eHealth and mHealth technologies are available, not least because of their easy access via smartphones. Providers of such tools are located around the world. Self-measured data on people’s behaviour and health recorded by sensors are easily made available to data companies as well as to family members, doctors and other health care professionals via Internet of Things (IoT) systems. IoT systems can learn automatically from sensor measurements and the patient’s medical history via artificial intelligence (AI) algorithms and machine learning techniques. AI assists health care professionals to make intelligent decisions, provide feedback about the current health state as well as predict the future health of the patient. In addition, cognitive programs are used to read and analyse the available scientific literature and consolidate electronic medical records of each patient of previous years. Thereby, AI impacts medical practice by influencing the course of chronic diseases of patients, suggesting precision therapies for complex illnesses, and improving subject enrolment into clinical trials. AI has proven to parallel or even outperform human experts at key health care tasks such as diagnosis, treatment recommendation, patient engagement and adherence, as well as administrative activities. Large-scale automation is common practice not only for routine tasks but also for broad medical process domains.

As a result, PM has become more and more an activity area for engineers and IT specialists rather than a field of medical expertise. Physicians specialised in PM become increasingly technological experts. Consequently, technology advancement, increased robotization and

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3D-printing of organs results in fewer health care staff being required in hospitals and patients in need of transplant organs are no longer dependent on human donors. However, as AI is not intuitive, humans are still essential to cognitive medical practice.

As the quality of health-related decisions in a system dominated by AI algorithms depends on the quality and availability of sufficient data, extensive donation of personal health data (be it genetic or non-genetic) by the patients has been triggered by making it a prerequisite for access to medical treatment. At the same time patients can sell their cells, tissues and data to the ever-increasing number of biobanks. As biobanks are profit-seeking companies, the remuneration is not very high.

10.4 The social value of health care technology in everyday life

Patients place great trust in technology-driven medicine and the achievements of PM. They are just as motivated and engaged by the idea of getting ICT solutions for tailored diagnosis and treatment under their own control (from world-wide providers) and readily provide their health data not only to the health care system but also to pharma companies and providers of medical devices. People are convinced that they can prevent diseases by doing so and cure everything in the long run, be it minor ailments or complex diseases such as cancer. They blindly believe in the output of the health apps of their cell phones. Should a disease occur, they usually turn to the internet for personalised help. Remote care has become the norm for everyone. In contrast, visiting a doctor is the exception rather than the rule, as the trust and reliance in algorithms and AI decisions is steadfast. It is only occasionally that some patients, especially the elderly, miss the “warm care” of physicians, as doctors and other health care staff are sometimes the only personal contact in their daily life. In contrast to the overall strong belief in technology of a majority of the population, these people with limited social contacts and without access to personal care lament the reduced social interactions and are prone to anxiety and depression.

There is also great concern among people that they may have a predisposition to a genetic disease or that there may not be adequate treatment options for an identified risk of disease. For them the power of PM lies not only in treatment, but in information about their current and potentially future health status as well as prevention. Consequently, people are willing to participate in many of the numerous screening programs available and are ready to undergo even unnecessary disease screenings. The screenings are sometimes justified by the mere fact that they are possible. However, knowing your genetic predisposition obligates to act. There is high social pressure for the individuals to take personal responsibility for their own health and be proactive rather than reactive. People are judged for not acting the way they are expected to do. Therefore, it is of utmost importance to everybody to prevent and reduce their risks for diseases, to detect diseases at an early stage or at least rule out any genetic predisposition or susceptibility to a disease. Everyone is responsible for their own health and the prevention of illnesses and to alleviate the potential consequences of genetic diseases. Many people use the service of genetic screenings as they are offered by many private companies at low cost. More screenings usually result in the detection of more potential diseases. In such cases, patients insist on receiving therapies, even if there are no suitable medical means available to treat the disease.

Screening for diseases that cannot be treated can create incentives for the developments of treatment, but it can also create a lot of disutility from knowing such as anxiety. Patients also

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experience increased fear of potentially adverse outcomes of the screenings, of their possible future health situation, and, as in a vicious circle, decide even more frequently in favour of follow-up care and treatment, even if this does not bring any real health benefit.

Due to the availability of comprehensive data sets and prognosis models for probabilities of therapeutic success, patients adhere more strictly to prescribed therapies. The prognosis promises to indicate precisely whether an intervention can be expected to be successful or unsuccessful. False positive results due to dependence on AI and algorithms and the lack of cross-checks by qualified medical personnel are widely accepted or even ignored in order not to undermine one's personal confidence in technology and the supposed feeling of safety.

10.5 The government takes a "whatever it costs" approach

The government aims to maximise welfare and the quality of health care. It has great confidence in the opportunities offered by technological advances in PM to counteract every disease, and financially supports screening programmes and research into data-intensive health care. Overall, preventive medicine has a low priority, as the prevention of disease is considered to be the responsibility of the individual.

The government regularly promotes promising technologies for medical application through its research funding programmes. In selecting specific technologies, it relies on advice from external experts, who are also expected to indicate where quality should be improved for the individual. An independent commission decides on the investments and prioritizes the technologies in which further investment should be made. As the funding does not come from the Ministry of Health, but from the Ministry of Finance, health experts do not always have the last word. The government tends to rush the investments into public-private cooperation.

10.6 Unclear economic situation in health care

Public and private funding is available for both technological research and research in Personalised-Medicine. The government is rationing its investment in public-private R&D by giving priority to technologies that maximize social welfare and minimize health inequalities. The government advocates that there should be no restrictions on patients' health care costs. It trusts that the widespread use of technology will reduce health care costs in the long term. However, unnecessary disease screening and false-positive results due to wrong conclusions drawn from AI-controlled decision-making systems waste limited health care resources instead of reducing the costs and benefitting patients. In addition, more health-related data require more administration, which in turn absorbs a large amount of resources. As a result, the overall costs of the health care system increase. These costs, especially screening costs, must now be increasingly borne by the patients themselves. As technologies are often privately owned, care is increasingly commercialized. It is usually the private companies that offer health care interventions. Ongoing innovations have led to a wealth of patents. Discussions are underway at political level to limit patent protection because it is increasingly considered an obstacle to technological progress.

Public authorities prioritize a technology reimbursement system that uses effectiveness of the technology rather than the cost-effectiveness of a technology. After all, cost effectiveness of certain technologies is difficult to assess and might not be provided by public agencies. Less evidence-based (and inefficient) health care interventions are the result.

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10.7 Rising inequity among population groups

Individuals are considered responsible for their (genetic) health. Consequently, they are expected to cover a large part of their health care costs as well as pay high premiums for their health insurances to gain extended access to PM. The population is divided into those who can afford such costs and others who cannot. Genetic testing goes beyond one's personal health and is also applied to the offspring (e.g. through prenatal screening). Inequity increases as rich people have better access than ever to medical tools to increase their personal advantage, e.g. by selecting optimal genetic predisposition for their off-spring using expensive technologies to enhance performance and/or appearance. Good genes can affect life beyond health care.

10.8 Investment and financing strategies: “Geneflix & pill”

The technology-driven and screening-intensive health care system is quite expensive. People no longer have “diseases” but “genetic deficiencies” or simply “health problems”. Every health problem is now considered to be a rare disease with certain deficiencies on genes or alleles. As a result, treatments must be developed on the basis of small sample sizes of patients. The development of the treatments carries a significant risk and leads to high prices, as research requires the sampling and processing of a large amount of data.

As public, tax funded schemes cover health insurance, no additional insurance is needed. However, private insurances are becoming common practice, as potential genetic diseases or adverse epigenetic patterns can never be ruled out, even if people do not suffer from the disease. Since insurance companies have access to genetic and behavioural data, they can refuse to cover high-risk patients, unless people with a genetic condition are willing to pay high premiums. If predispositions are hereditary, relatives and offspring must also pay high insurance premiums to cover the expected high costs of treatment. Insurers differ in the number of personalised medical treatments they include in the benefit package.

The health focus on the genetic causes of health problems has led to the creation of “genetic insurances” that deal with all problems arising from a person’s genetic pattern. The “geneflix model” is the new business model. People take out subscriptions (e.g. regular payments throughout life or only once shortly after birth), which make them direct payers of R&D. During the subscription period, people have the right to use the research results, i.e. the R&D services for treatment, free of charge. The system works in a similar way to the Netflix media service, which uses the subscription fees for online streaming services of films and television programmes to invest in new shows, and the subscriber receives these shows free of charge. Subscription fees can be reduced if personal data are provided; subscribers can sell their personal data to R&D organizations or pharmaceutical industry to generate revenue or at least reduce the subscription fee. There is a market for different subscription models for health services, which may have different relevance to one’s individual genetic predisposition. Therefore, people subscribe to a programme that best suits their own genetic predisposition and that does research on their health problems. By subscribing, people become research funders and thus owners of the research results. This allows them to influence the decision about which treatments they receive. Direct payers of R&D have more influence on the use of the results. However, the subscriber subscribes not only to the opportunity for free research findings, but also to the risk, because the funded research may not lead to a relevant cure for the subscriber’s health problem.

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The subscription business model brings with it a set of new rules of the game, which also requires a new set of regulations and incentives, as subscribers can easily switch from one company to a competing company. Because of competition, companies will make more effort to retain people as consumers/subscribers to the service, e.g. by outcome-oriented services rather than providing just medical interventions. The subscription model guarantees a regular income for scientists and developers, which sometimes means that developers no longer make a major innovative effort and slow down the drive for innovation. To prevent this, a regulation on basic R&D is needed. Since each person is free to choose which provider to subscribe to, it is likely that not much funding will go to providers who conduct research into minority diseases. Regulation is therefore needed to prevent market failure. Every subscription service provider is therefore obliged to invest money in the development of treatments for minority diseases. If the R&D organization behind the provider is free to select only promising research areas, massive inequalities can arise.

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11 SCENARIO: COOPERATION - *PERSONALISED AND HOLISTIC MEDICINE*

11.1 The community comes first

Since the enormous potential of key enabling technologies was recognised by policymakers at an early stage, long-term funding programmes and investments in research and development have promoted not only technological and industrial innovations in many economic sectors but also social innovations. All these innovations have led to economic growth and created many new jobs and positions, with far-reaching positive socio-economic effects on society. As a result of the high immigration rates and increased birth rates of recent years, there is no longer an over-aged population and a large proportion of the population is employed. As the economy flourishes, many people have created a considerable wealth for themselves.

Due to its many years of experience of social and financial security, the society is characterized by a strong sense of community. People are willing to make a financial (high taxes) and social commitment to society. Every citizen should benefit from the wealth of the country and be able to lead a good life until the end of his or her life. For older people, extending the number of years of life spent in good health becomes a priority. People prefer to have good years of life rather than just prolonging life at any rate. Previous crises, such as the COVID19 pandemic, have underlined the importance of the services provided by health professionals. The increased social prestige of the health professions has led to an increase in the number of people working in the health sector, which benefits not only the sick, but also the elderly people and those in need of care living at home. Although automation has not stopped at nursing care, the population greatly appreciates the personal care provided by the excellently trained health professionals.

Biotechnological and biomedical developments have also led to advances in medicine and in particular in PM. As the number of patients receiving a specific medical treatment based on their genetic predisposition is often low, transnational alliances for PM have been fostered in order to pool the available resources and reduce the costs for diagnostics in the large-scale settings. There is a network of health centres across an alliance of countries specialised in individual disease areas to make more effective use of the available resources for research and medical treatment and to maintain the necessary scale. Since a single country cannot afford to cover a large number of disease areas, each country publicly funds only a few regional specialised health centres. These centres benefit from the fact that nation states and, to some extent, pharmaceutical companies make health data available worldwide. Since the majority of the population uses the tax-based state health insurance system, each citizen is obliged to make their health data available to the public health insurers for R&D via an electronic health record system. Such regional health centres collaborate intensively with global pharmaceutical companies and have developed into centres of excellence that attract not only local patients but also foreign patients. Since the health care system is open to all patients, it is very costly. The high health care costs are to be alleviated by public-private cooperation between the medical centres and the medical industry (i.e. pharmaceutical, biotechnology, biomedical (for medical devices) companies, including health care IT companies).

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11.2 People value a good and healthy life

The population appreciates their prosperity and the social well-being that goes with it. Comprehensive health care and preventive health care are of great value, because they are not only a prerequisite for a healthy life in old age, but also for a functioning working world and economy. Disease prevention is not only high on the public health agenda, but it is also seen as a responsibility of the individual and the community.

People are not afraid to take advantage of every opportunity for health care, regardless of whether the methods are evidence-based or not. They are open to holistic medicine and like to rely on proven home remedies suggested by family, friends or general practitioners. Technological advances in PM are viewed sceptically because they are considered to benefit only a few patients rather than the entire population, thereby ignoring the fact that PM is not only a question of developing new treatments but of using existing treatments in a personalised way.

11.3 The social system is open and inclusive

The society is quite healthy due to the excellent prevailing health care system. As all people have access to all available medical treatments, including PM, the costs of the health care system have exploded despite efforts to promote cost-effective treatments and efforts to increase automation within the health care sector. The population is heavily taxed to provide the resources for the health care system. As a result, people are working longer and have an extended working life time to sustain high public expenditures and ensure a decent income. However, the high taxes have a disproportionate impact on the spending possibilities of low income groups.

Patients and patient organizations, doctors, researchers, insurers, medical technology companies, innovators/start-ups, public funding organisations for health research, health policy makers and related policies – all actors in the health system cooperate to achieve the best possible health outcomes. The cooperation and collaboration of all actors involved brings together a diversity of knowledge and perspectives, thereby increasing the translation of PM to patients. All actors are united in their firm believe in technological progress and its benefit for the health care system, although citizens like to put the benefit for the community above the benefit for the individual. However, believe in technology does not affect the strong trust patients place in general practitioners and other health professionals, who motivate them to take measures to improve public health, such as conducting regular health screenings, donating health data, and completing health-related questionnaires. Due to a lack of individualism, the people's focus is on the benefit to society rather than the individual. Overall, there is little interest in PM, even though people are willing to freely donate personal data. After all, if there is a "right" patient in "the right treatment for the right patient at the right time", there are also "wrong" patients, and this creates inequity. Preventing disease is not always a matter of personal choice. Knowing you have a predisposition for a disease may help you reacting to it, but you cannot always reverse your genetic predisposition. The basic idea of PM and stratified groups of patients raises fears that you might belong to the wrong groups and might not have access to treatment when needed.

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11.4 Technological advances due to openly available and shared data

Open data policies are implemented in the health systems of most countries in the world. Databases for health data are networked worldwide and data exchange has become common practice between most countries. Unrestricted access to shared health data and biobanks has led to an extensive and globalised research in the field of PM, increasing knowledge about many diseases and their treatments. As a result, a number of new genes and genetic mutations have been discovered and pharmaceutical treatments developed. Most of the new drugs are based on 'omics' data and linked to companion diagnostics. SMEs and start-ups that develop kits for companion diagnostics are flourishing. Furthermore, clinical tests are more efficient because of prior genetic sequencing of study participants.

Patients also have free access to anonymous health data and are often overwhelmed by the vast amount of available data. This requires a complete reorientation in the data governance. Society is moving away from the granular consent of individuals to the use of their data to collective responsibility. More and more representatives from civil society belong to Data Use Commissions, who are dedicated solely to the common good and not primarily to commercial use. Collective responsibility for the way data is used is delegated to experts from NGOs, patient organisations, etc., who have no commercial interests.

The pharmaceutical industry has agreed to provide access to data generated in clinical trials, if part of their investment is reimbursed by public funds. This means that scientists can now also learn from failures, i.e. "negative results" in drug development and do not have to waste money on previously proven unsuccessful research designs of clinical trials. Providers of improved information and communication technology and globalisation result in international care providers. However, not all developed dugs are available on the market, as some pharmaceutical companies (e.g. in China), which mainly serve large overseas markets, are still unwilling to comply with the data-sharing requirements established in other continents.

In general, there is confidence in the government and other national data owners regarding the security of medical data based on clear national and international legislation. However, as genetic data are openly accessible worldwide, there is ample room for possible misuse of the shared data. Strict regulations are necessary to handle and use sensitive medical data and to maintain people's trust. Legislative issues between patent rights and the push for open data are recurring themes in the social discourse. More attention is being paid to privacy issues and misuse of information e.g. by life insurance companies. Challenges relating to the ownership and management of genetic databases and biobanks have not yet been resolved, and regulations that satisfy all stakeholders are not yet in place.

11.5 "Health is programme" for policy makers

Prevention of diseases is an important driving force for all policies in PM and rigorously promoted by health policy makers. Regular health screenings are compulsory for citizens and monitored by the health authorities. Genetic screening is widely used to strengthen preventive measures in health care, as some diseases can be detected at a very early stage. Although PM is a living reality and its benefits available to all people, the acceptance of PM by the population varies.

As health care is offered to all members of society, the social welfare system also appeals to medical tourists, and the question arises whether such tourists should be restrained.

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11.6 Health expenditures reach their limits

The population expects that everyone can have access to hospitals, medication and even PM. After all, research in the field of PM is largely financed by public funds. Currently, the economy can still support the expensive health system. Taxes have been continuously raised in recent decades to cover the rising health care costs. However, the tax-based financing system is constantly under criticism regarding what therapy or early diagnostics to fund. Preventive screening programmes have not resulted in budget savings. Instead, as health care costs soar, there is a growing fear among the population that public funding will no longer be able to cover all the costs of health care in the future. In the long run, health insurance companies expect to save costs by offering cost-effective treatments and by limiting specific treatments to patients who are likely to benefit from the therapy. Not all treatments will be applied to everybody anymore. Regulation of care pathways is expected to make the health care system more efficient and reduce costs. Screenings and companion diagnostics as well as health expert organizations will support the decision makers, as treatment decisions will no longer be made solely between doctors and patients. There are tendencies that prices of drugs and medical devices will no longer be regulated by supply and demand, but by political intervention.

Since the health insurance system is tax-based and the tax burden is high, people are not willing to take out private insurances. Consequently, public-private funding is needed in the R&D phase to keep prices low. The population expects the government to reallocated budget funds from other sectors of the economy. Currently, a large part of the risk of drug development has been transferred to the public sector, resulting in higher profits for the pharmaceutical industry. Benefits in other parts of the economy should compensate for the risks and public funding should focus on health. Health policy makers still work on developing new business models and incentives for pharmaceutical companies to collaborate more extensively with public centres in a public private partnership to share risks. However, this will lead to situations where the state no longer has the sole right to decide on research priorities as cooperating pharmaceutical companies will also have a say in future research areas.

11.7 Investment and financing strategies

The entire health care system is rooted in the “Singapore model”, which offers every patient every type of medical treatment including PM, at a reasonable cost and with high-quality services. It comprises public and private health insurances, both of which cover the costs of high-quality medical care. However, the level of services offered, and the level of comfort differ. Health insurance and benefits depend on the national status and the employer. While Europeans are entitled to subsidized public health services through a mandatory national savings scheme, employed non-Europeans can only use private insurance to get health coverage for themselves and their dependents. In addition, employers must also provide health insurance benefits. Due to the high taxation for the national saving scheme, nationals hardly ever purchase a private insurance.

In public health care hospitals and other facilities, local patients receive subsidised health services. Although these facilities are fully owned by the government, the public-sector hospitals are operated as private limited companies and compete with the private sector in terms of service and quality. They provide excellent health services to masses of people and also set the benchmark for professional medical standards and fees for the private sector. Every

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patient has to pay a fee when he or she uses health services. In the public health care facilities, these fees are subsidised by the government, while in the private hospitals, patients pay the full amount charged by the hospitals and doctors on a fee-for-service basis. The amount of subsidy can range widely, as it depends on various factors. Additional aid in co-paying the balance of the medical bill is enabled through a compulsory savings scheme. Depending on factors such as age and income, a percentage of the monthly salary of an employee is transfered to this central fund. This fund is not redistributed at national level but is only used for one's own or dependents' medical needs. Part of the fund goes to other health insurance schemes, which together can pay a large proportion of a patient's co-payment amounts.

For decades most of the research funding for PM and early development of new and innovative therapies and PM in the academic setting has come from public funding (e.g. tax-paid funding). At a certain point of transition, the research findings are then bought by pharmaceutical companies which can have their headquarters around the world.

To be able to cover rising health care costs in the long term and to achieve maximum health care, the R&D costs for developments in PM and risks of development must be balanced between the public funder and the economic entity who commercializes the medical product or treatment. To ensure a return of funds from early investment to public funding bodies, shareholding is often chosen as an option as well as licensing. Shareholding has the additional advantage that if the company that has received public funding for developing a new medical product goes beyond the marketing of just this one product, the public body would also benefit.

Nevertheless, a new business model for strategic alliances between specialised health centres, hospitals, academic researchers and commercial companies to research and develop novel treatments for genetic disorders has been developed. For example, such an alliance can combine the pioneering research of leading scientists in the field of personalised treatments with the pharmaceutical expertise of a pharmaceutical company in manufacturing complex biological products. While the pharmaceutical partner benefits from the scientific partner's longstanding experience in developing new personalized treatments and acquires an exclusive license to develop and commercialize a personalized therapy, the scientific partner receives a substantial upfront payment and, depending on the successful achievement of predefined milestones, further payments to translate basic discoveries in the field of molecular medicine into potential medical treatments. Such alliances may also include insurers. In joint development with various partners, quality-adjusted life years (QALY) targets must be defined and agreed in advance to allow for fair reimbursement of personalised treatment costs by an insurer. Eventually, the health insurance system may become more diverse and competitive depending on the kind of QALY the insurers want to pay for, resulting in a group of regional health insurers. This opens the door for numerous opportunities for on and off public-private partnerships between developers/manufacturers and insurers to develop new medicines around novel endpoints of QALYs, which are agreed with insurers, and covering specific populations of patients. In these on and off partnerships, companies and insurers may have many different partners focusing on single issues, such as a single disease, medicine or treatment. Insurers might benefit most when they cooperate and enter negotiations with pharmaceutical companies as a group.

As PM approaches often focus on advanced diseases, insurers could alternatively invest more in early detection programmes to treat and possibly cure costly diseases at an early stage. Late-diagnosed and advanced diseases are associated with high mortality and high treatment costs. Companion diagnostics are used for personalised therapy with expensive

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drugs and should be prescribed when genetic tests or some diagnostic tests are available to support the use of that specific drug. There are good opportunities to reduce health care costs by using early diagnostic screening programmes instead of PM at the far end of companion diagnostics, when treatment success is often very low.

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12 SCENARIO: SCEPTICISM - *PERSONALISED MEDICINE IN A NICHE*

12.1 General scepticism

The society in this country is traditionally quite sceptic about innovations. This attitude, in part, stems from negative experiences with data collection and connection. People generally have a critical approach towards new technologies. There is the notion that “data belongs to me” and should not be shared at a level where the individual cannot control data use anymore. This does not concern health data only but personal data in general, even though people give their data with no concern at the private level, e.g. facebook, pay-back schemes and where they expect a small personal profit and have the feeling of being in control. The general scepticism is also expressed in the distrust in data-driven health-care systems and this society questions ever more evidence-based health care. People are hardly willing to donate their data for health research.

PM introduces a new form of threat, namely that you are the one that belongs to the non-responders and thus you are denied treatment. Some foreign observers have labelled the people in this country “post-truth society” because there is no trust in science-based evidence. Instead, there are more marketing-based consumer choices. PM however, is too technical for this society. There is some reluctance on receiving gene therapy as patients ‘don’t want to mess with DNA’.

As a consequence, there are reduced private investments in PM but possibly more public investments in long-term care and “warm care”, i.e., hand on the bed vs. high-tech. Many people share the attitude that loss of length of life is compensated for increased quality of life.

At international level, this country has experienced some isolation from other EU countries and beyond, since politicians have pursued rather protectionist strategies. For the health sector this meant less access of treatments developed abroad.

Companies that want to do research in this country have to pay for the data of patients. There is also a lack of trust in governments about safety of data and a higher need for legislation. In the social media and more conservative media channels often engage in hypes that peak and fade out, as an example the sceptical attitude of people in general makes it very easy to spark debates on the necessity and danger of vaccinations. Thus, anti-vaccination attitude increased fear and at the same time has caused major epidemics. More than in other countries, many citizens turn to religion as a result of decreased trust in science and the government. For those not prone to religious escapism, self-education becomes very important in the medical field, but people are confused due to the unlimited data available. Other patients turn to alternative medicine (such as Traditional Chinese Medicine).

Blockbuster in this country are more common than any Personalized Medicine. They are more lucrative for pharma companies and more trusted by patients. There are some private companies producing blockbuster drugs. And since the COVID19 crisis in 2019, also public-private enterprises, where the government holds a considerable number of shares, though less than 50%. This approach has helped to determine the R&D directions and financial resources in order to produce the medication required to contain epidemics and to copycat therapies of already approved medications that also helped against the COVID19 virus. Even

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after this exceptional crisis the strategy was kept on for being prepared for future epidemics by producing generics of even patent protected medications.

12.2 Health system based on personal relations

After the COVID19 crisis in the 2nd decade of this century, the society has acknowledged the importance of a well-functioning health system and is willing to dedicate a substantial amount of the state budget to health care. Social care and inclusion strategies are also very important in this health system and try to compensate for medical advances elsewhere. Instead of technological innovations, alternative medicine is on the rise as well as self-diagnosis, and this goes hand in hand with the potential for non-compliance. The emphasis is on prevention and healthy life styles, supported by government agencies and employers (e.g. focus on healthy nutrition, sufficient physical exercise, social interaction, health literacy, environmental protection). There is also a different perception of illness: it is regarded as belonging to life, and there is not always the need for treatment or diagnosis or understanding of the disease. This society appreciates the value of not-knowing (your gene sequence). The health insurance system is solidarity based but does not provide a lot of funds for advanced medical research, treatment or PM. Instead, the social networks are very tight, meaning that family and community provide support structure for those in need. For the most part, old people live with their children instead of nursing homes.

12.3 Low scale PM

Due to this scepticism toward PM, little public support is granted to explore its potential. Pharmaceutical companies and other investors in health are also reluctant because they do not envisage considerable profits. Against all odds, there are still research and development projects to explore the possibilities of PM in some niches, especially if there is international funding for it (EU framework programme, philanthropies, or private industry). Accordingly, in this country the PM scene lacks behind its international competitors. Due to the low scale of PM solutions and little experiences of the medical personnel in treatment, the quality of such therapies is rather low which results in even more scepticism. Actors in this field have not convinced society of the potential benefit of Personalised Medicine and instead have remained in a niche position. Compared to other European countries, patients in this society with certain indication are disadvantaged because they get no access to the latest technologies if they cannot afford it on their own to get treatment.

PM as a science cannot compete with international standards and this country is endangered to be marginalized, at least with regard to medical sciences. Due to the internationalization of the health sector however, patients in critical conditions go to countries for scanning and treatment where PM solutions are offered. These patients are usually wealthy and have international private health insurance or pay out of their own pocket.

Lagging behind on PM, however, is not necessarily bad, as there is still the chance of adopting evidence-based PM from other countries and gain from that experience. Once PM solutions have proven to be safe and affordable even the health policy makers in this country might integrate it into national health plans.

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12.4 Innovative social policies to cope with the increasing number very old and sick people

Despite this old-fashioned health care system, people in this society are getting older and the number of very old sick people, e.g. suffering from cancer or dementia, is rising. Unlike some other countries where PM was promoted more, the increase in this society cannot be stopped and the costs of care pose an extra burden to the health system and tax payer. The number of places at nursing homes and care centers is scarce and social policy is facing a major challenge. There are attempts to contain this development by giving the working population and the healthy retired people more incentives to be active in the care sector. More social innovations are developed and implemented through cooperation between the public and the grass-root sector to take care of the growing number of sick and very old people, such as dementia villages, senior sitters, senior gardens, inter-generational housing projects etc. Other policies pursue incentives for school graduates spending a social year caring for the elderly. And there is the possibility for filial leave from work not only for dependent family members but also for friends, neighbors, neighborhood care centers etc.

Measures by some private initiatives to encounter the scepticism include more health literacy on PM, e.g. involving international celebrities to show how PM has helped them. These initiatives also argue that good regulations on data ownership and privacy issues could counter balance the concerns of the citizens. They argue that now citizens have the illusion that they own their data. New suggestions to meet the scepticism include that patents are granted for mechanisms of actions instead of for genes, tests, drugs. Patents should be owned by universities, public bodies, governments, not by the industry.

12.5 PM available on international level

Even though PM solutions cannot be offered to an extended degree, there are a few information centers in the country where patients can turn to and ask for solutions in neighboring countries. If the private insurance pays for it and if it is feasible the technology is imported or the patient travels abroad. Besides, some philanthropic organisations support patients to raise money for PM solutions offered nationally and internationally. There is a small but growing crowd of people choosing to pay privately for genetic tests (but not to share data) to avoid discrimination (incl. discrimination in health insurances). The step out of scepticism is illustrated by the emergence of the first private umbilical cord banking for an infant's future use, an international network across Europe.

12.6 Pay per performance and incremental blockbuster strategies

PM development has become a very expensive undertaking worldwide, with only a few companies able to raise the necessary resources for such investments. Through mergers and acquisitions, the pharmaceutical market has become more and more consolidated and eventually some pharmaceutical companies have become part of "google health" and "amazon care": multinational companies, controlling not only the data sector, but also providing the means to develop diagnostics and treatments for Personalised Medicine. This move was possible because traditional pharma companies were not fit to integrate big data analysis into their strategies in order to combine personalized data sources with personalised treatment development. The data companies used the opportunity to move into the health market instead as data has become the essential resource for personalised health approaches.

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After a few PM medications have proven successful in neighbouring countries, the Health Ministry and the National Health Service of this sceptical country have started negotiations with the respective foreign pharmaceutical companies and agreed that such treatments should be offered to the national patients as well. However, the terms of financing are different within this system compared to the foreign examples. In the sceptical country, the health system will pay according to the performance of the medication. If a treatment has been successful, the company will get reimbursed. Thus, the relevant actors have developed a scale of indicators to define “success”. Whereas the survival of a patient for additional months is an objective criterium, others are more complicated as they concern the improvement of quality of life. This includes, for example, reduction of hospitalization, reduction of side effects, capability of the patient to take care of her/his own life, reduction of dependence from external care, etc. Depending on the results of regular monitoring, the success gets evaluated and the company gets reimbursed accordingly. Incentives for the pharma companies are thus different endpoints. The national structure of the health service and the close connection to the health ministry have given these actors a strong bargaining position vis-à-vis international health corporations because they do not only want to sell PM products but also blockbusters and other products and services of their vertically integrated company.

Several laws were passed to better protect privacy and keep the data exchange on personal information to the absolute minimum possible. A close coordination between the government, the National Health Service and the public-private pharma companies was a prerequisite for building more trust in the new data handling system.

Another strategy of the health system in this country is fostered by the worldwide advance of blockbuster medication, especially in the fields of cancer and Alzheimer. In a society, where the number of very old people is rising, these indications pose a high burden to the health system. Over recent years, the dominating multinational pharmaceutical companies have bought many Start-ups and other national pharmaceutical companies and were thus able to incrementally innovate medications, e.g. based on monoclonal antibodies, that were originally only approved for single cancer indications. Incremental refinement and expansive testing strategies have shown that these medications work also for other cancers. Similar advances were made in Alzheimer’s therapy. Thus, in this country, the National Health Systems buys the blockbuster drugs from the companies and ensures the provision for the patients. In a few cases, pharmaceutical companies were even nationalized in order to prevent that they are sold to a foreign corporation and to ensure the national production of essential medication.

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14 LIST OF ABBREVIATIONS

Abbreviation	*Terminology*
DNA	Deoxyribonucleic acid
EC	European Commission
eHealth	Electronic Health
EMA	European Medicines Agency
ESIP	European Social Insurance Platform
FDA	Federal Food and Drug Administration
GDP	Gross Domestic Product
HTA	Health Technology Assessment
IoT	Internet of Things
mHealth	Mobile health
MS	Member States
NCDs	Non-communicable diseases
NGO	Non-governmental organisation
OECD	Organisation for Economic Cooperation and Development
PDA	Personal Digital Assistant
PM	Personalised Medicine
QALY	quality-adjusted life year
R&D	Research and Development
RNA	Ribonucleic acid
SME	Small and medium sized enterprise
SPC	Supplementary Protection Certificate
VHI	Voluntary Health Insurance
WHO	World Health Organisation

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ABOUT HECOPERMED

With an increasing and persistent pressure on health care budgets across Europe, Personalised Medicine is the hope of many patients, health experts, policy makers and policy makers try to find and implement more efficient and effective ways to cure diseases in an era of demographic change, unbalanced age pyramid, increased demand of care and rising health care cost. Personalised Medicine aims to optimally match patient and treatment by assessing the characteristics of patients in which treatments yield (the most) results. Hence, Personalised Medicine reflects a paradigm change in health care by no longer focusing on effects on group means, but on individual differences between patients through deep phenotyping: the analysis of individual phenotypes using parameters such as biomarkers, (bio)imaging, functional parameters and others. A strong underlying assumption enforcing the call for personalized medicine is its implicit promise that it will make health care more cost-efficient through better targeting of treatments. However, while the development of Personalised Medicine treatments is often an academic endeavor, its commercialization is often in commercial hands, reducing the efficiency potential of technologies through high pricing. Commercially marketed products such as biomarkers are often priced at the margin, following an analysis of companies of 'what the market can bear', rather than based on the size of the health increase of patients. Therefore, there is a need for economic models that evaluate Personalised Medicine, as well as analysis of payment models that support innovations but link financial reward to health outcomes. Our project aims to identify the best modelling and payment strategies for Personalised Medicine in order to differentiate between promises and reality.

HEcoPerMed (Health care- and pharma economic models in support of the International Consortium for Personalised Medicine) responds to the demand for economic models that evaluate treatments made possible through innovations in personalised medicine and seeks to identify funding and reimbursement mechanisms that provide financial incentives for the rapid development and uptake of such innovations. HEcoPerMed goes beyond current assessment and payment models in order to serve the requirements of personalised medicine for more comprehensive cost-effectiveness estimates that incorporate patient and societal perspectives and enhance sustainable affordability of cutting-edge health innovations.

HEcoPerMed will provide a concise overview of and guidance on high-quality methodological approaches for model-based economic evaluations. In three case studies, HEcoPerMed will apply state-of-the art economic modelling to demonstrate practical and methodological issues in evaluating personalised medicine innovations. The project team will also study existing shortcomings in stimulating the adoption of personalised medicine and propose financial agreements that accelerate its diffusion in European health systems. To demonstrate the value of state-of-the art economic modelling and appropriate financial agreements, HEcoPerMed will construct future scenarios, considering the trends and drivers on the one hand, and challenges and benefits of personalised medicine for the European social model of care and its financial viability on the other hand. For a better financial integration of personalised medicine and new economic models, the project team will develop appropriate diffusion and communication strategies to be in direct contact with experts and a wide variety of stakeholders, taking their needs into account while offering new solutions for the players within the European health systems. These comprehensive and symbiotic measures of HEcoPerMed will thus fill a gap identified by the ICPerMed to support their efforts in the promotion of personalised medicine in Europe and beyond. Finally, the project will support health care decision makers to manage their budgets while providing the best possible and comprehensive care for patients in the field of personalised medicine.

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EcoPerMed
Health Economic Models for Personalised Medicine

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