

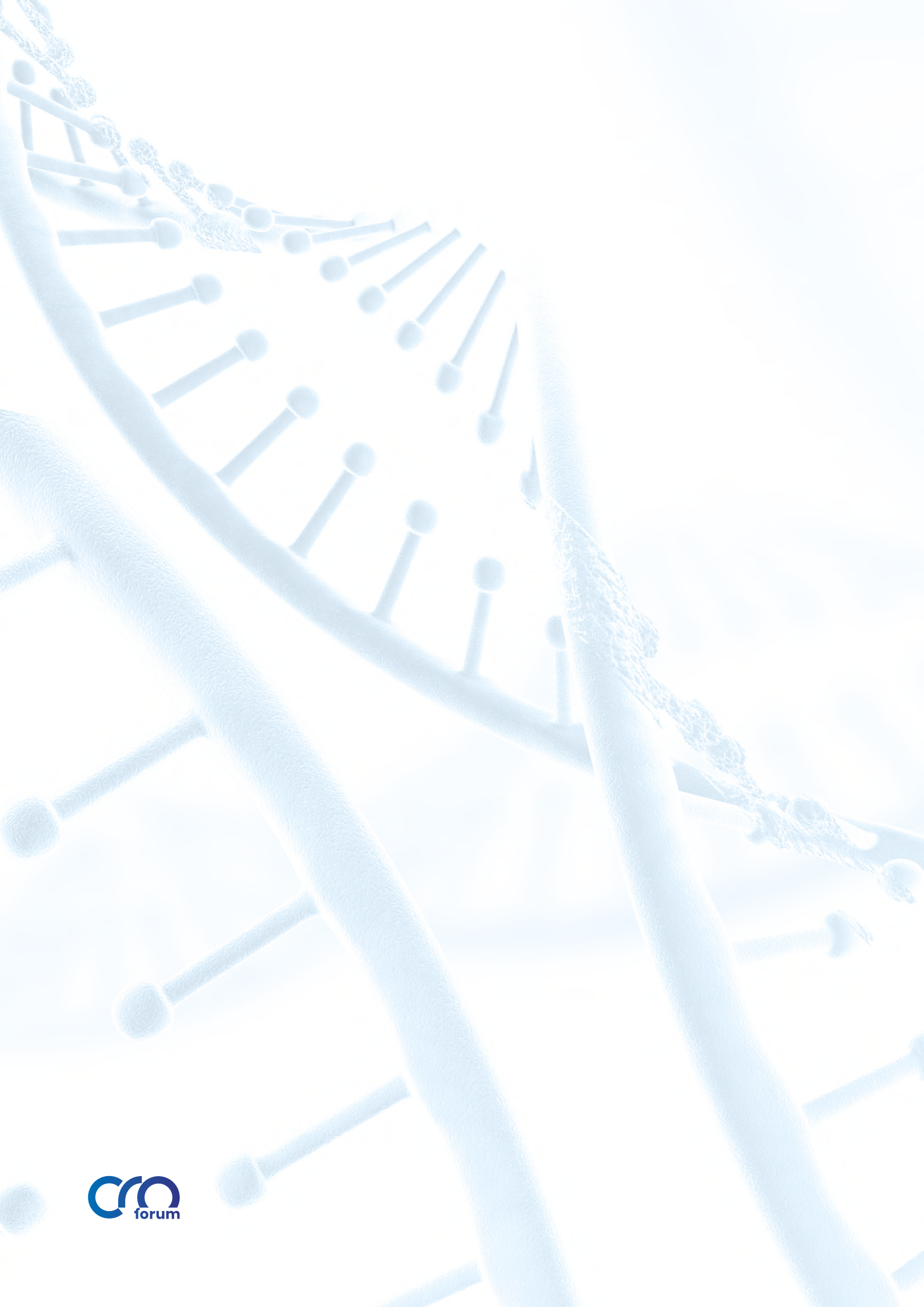


Medical Advances

Risks and opportunities for the
(re)insurance industry

Emerging Risk Initiative
– Position Paper

December 2019



Foreword

The 20th century and the first decades of the 21st century have brought a series of developments and medical advances which have hugely improved medical practice. Yet this is just the beginning. We expect to see many more innovations, such as liquid biopsy, genetic testing methods and telemedicine, which will have an impact on our daily lives and also on the health system in general.

These healthcare developments will bring not only benefits for clinicians and patients, but also challenges to insurers adapting their business models to the ongoing progress in medicine. This position paper aims at providing an overview of upcoming medical advances and the questions that insurers need to consider in order to be prepared.

Certainly, it is not possible to cover all medical advances in detail in only one paper. Therefore, we have decided to focus on those medical advances that prevent, diagnose or cure disease. Treatments that have the purpose to purely increase life expectancy or performance (such as 'smart drugs') are out of scope.

New technologies often come with new risks. It is vital for insurers to understand the impact of such medical advances, evaluate and price the risk in a reasonable way, and at the same time retain customers' trust. We must reflect on these upcoming major changes in healthcare, in order to assess their future impact on our industry.

Finally, we highlight that we could not have prepared this paper alone. I would like to express my gratitude and appreciation to my colleagues on this CRO Forum working group from Allianz, AXA, Generali, Hannover Re, Munich Re, NN Group, Prudential, RSA, Swiss Re, SCOR and Zurich Insurance Group, for their tireless work, inspiring dedication and ongoing participation in researching this important topic.

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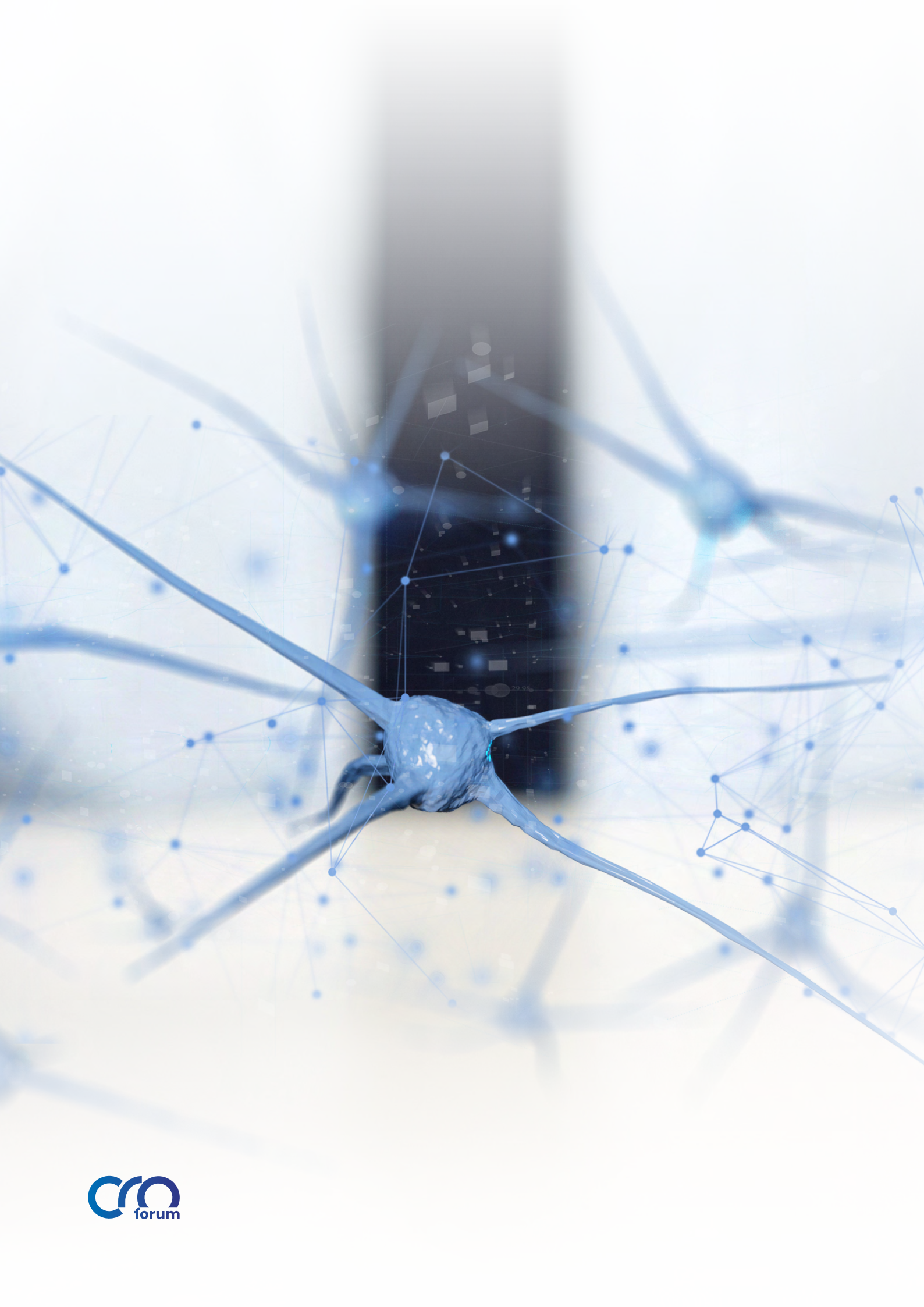


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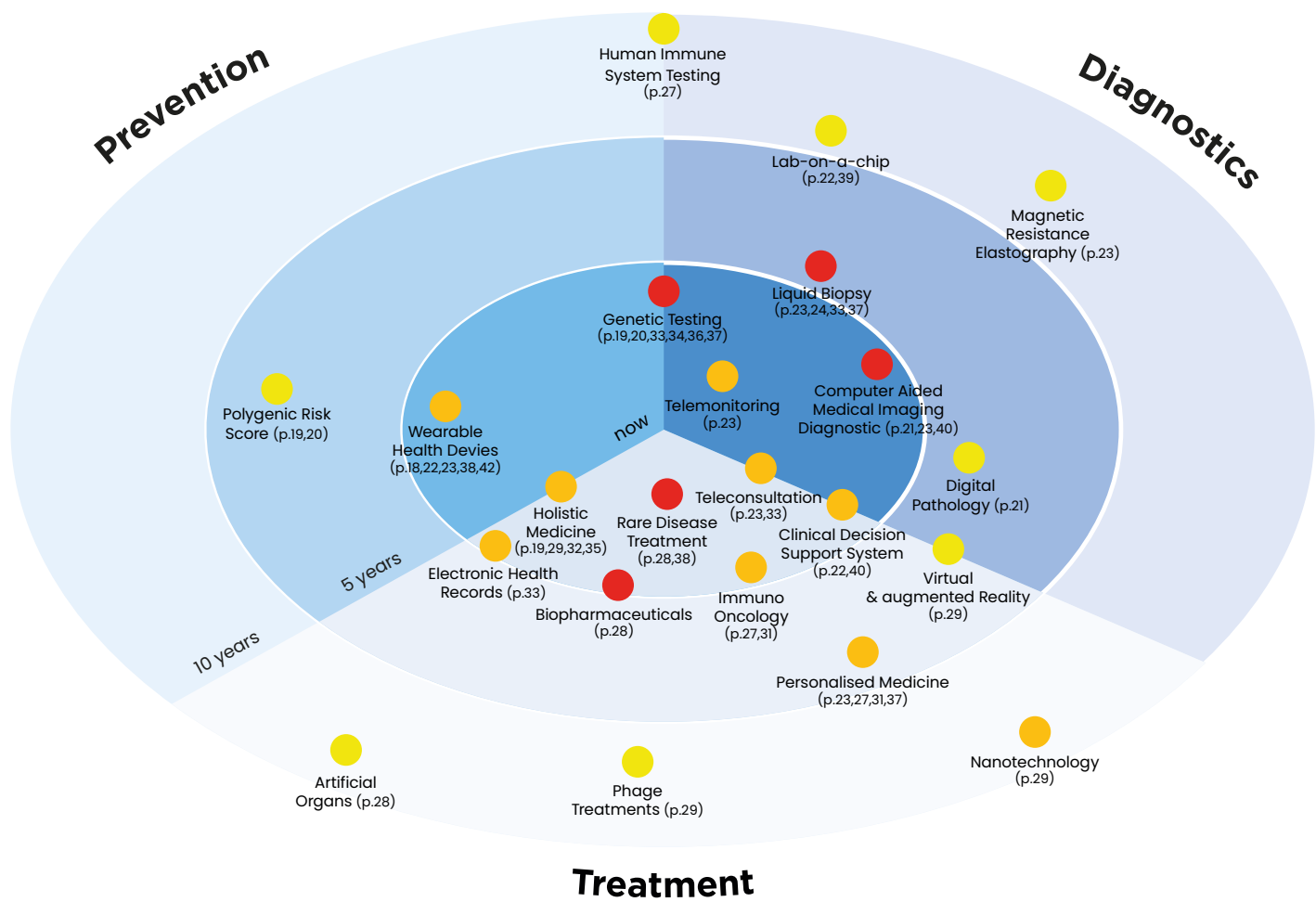
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**Healthcare
developments will
bring not only benefits
for clinicians and
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challenges to insurers
adapting their business
models.**

Medical advances & insurance industry

Possible impact & time horizon



Disclaimer: The diagram reflects the current expectation of the Emerging Risk Initiative Working Group on the possible impact and future time horizon for the medical advances described in this paper. The impact and time horizon is dependent on several factors which are extremely difficult to quantify and could therefore only be based on a high-level, qualitative assessment which is therefore likely to change rapidly and significantly over time.

- Low impact
- Moderate impact
- High impact



Executive Summary

One of the rewards of societal progress is medical advancement and its ability to save and improve lives. As science and technology advance, new frontiers are opening and new challenges are coming into sight.

Medical advances are not only relevant for individuals, but also for societies overall, as well as for the private sector, in particular for the insurance industry. Medical advances should be looked at in the context of existing healthcare systems. Depending on the country, healthcare systems are funded through a

mix of government subsidies, charging of patients, and voluntary health insurance schemes. The size of space for voluntary cover depends on the strength of social systems and the degree of regulation.

Improvements in prevention and diagnostics

Recent medical developments in the area of prevention, such as genetic sequencing, will lead to more effective treatments. For example, in genetic information can be used to screen populations for cancer risk. Meanwhile, developments in health 'wearables' can improve the early stage detection and management of diseases. In other words, biometric data provided in real time has the potential to offer a minimally intrusive and personalized telemedicine platform for individuals and healthcare providers. Significant advances in diagnostics in the field of artificial intelligence and data mining have led to new methods and tools for medical analysis. As an example, computer-aided medical imaging diagnosis, or systems which may support clinical decision making, such as Clinical Decision Support Systems, will help doctors in their daily work. Non-invasive diagnostic methods can use the benefits of improved computing power now available, such as Optical Coherence Tomography and Magnetic Resonance Elastography.

More effective treatments

As with advances in tools and methods for prevention and diagnosis, medical treatment is also progressing. A new technique in this area is personalized medicine. This provides new opportunities to understand the causes and progression of diseases and to identify new approaches for treatment. Already used in clinical practice and with high potential for future developments are advances in immune-oncology such as the CAR-T cell therapy, and the use of biologicals such as monoclonal antibodies.

Opportunities and threats for insurers

While improvements in the prevention, diagnosis and treatment of diseases should improve mortality and morbidity risk (under the assumption that other factors such as higher levels of air pollution will not counterbalance this effect), they may create or exacerbate other risks. One of the possible threats could be anti-selection, which occurs when there is an imbalance of information between the insurer and insured. In turn, this could lead to a shift in the composition of insurance pools, resulting in a higher proportion of high-risk clients. Individuals with genetic test results indicating a high probability of becoming seriously ill will seek insurance cover more often. At the same time, insurers are generally prevented from asking clients for genetic test results, so they will not be able to adjust individual insurance prices accordingly; instead, the costs will be distributed among all insureds.

Naturally, medical advances could also generate important new opportunities for insurers, such as more tailored offerings. For example, technological advances, such as data mining techniques, could help assess risks that are difficult to identify prior to accepting insurance coverage. The demand for health insurance could also increase due to higher survival rates for critical illnesses and the increasing costs associated with their treatment. Furthermore, new types of products may be required for patients suffering from diseases that were not curable in the past.

Impact on societies and political choices

Affordability is another relevant aspect of medical advances that should be discussed. Rolling out medical advances to the patient population will come at a significant cost at a time when health budgets are constrained everywhere. Rising costs will make it harder for public healthcare systems and voluntary insurance schemes to maintain current levels of coverage. In addition, it is likely that both the frequency and severity of claims will increase. To cope with increasing costs, the premiums charged for public and private healthcare products will most likely have to increase at a faster rate than general inflation. Another challenge for the healthcare sector will be the treatment of rare diseases, as the costs of such treatments are currently extremely high.

Applying big data and artificial intelligence could be one way to reduce cost in the system. These techniques may be used to identify at-risk patients earlier, to encourage them to adopt a healthier lifestyle and other changes to prevent/treat a disease at an earlier stage, when costs are likely to be lower. The quality of interaction between individuals and healthcare providers will determine whether such an approach will be successful.

It is important to note that new technologies could initially increase product liability risk, which must be recognized accordingly by insurers. Initially, it might be a challenge for casualty insurers to understand the new risks, evaluate and price them appropriately, especially if there is no claims history.

Higher healthcare expenditure and the corresponding premium increases in recent years have been frequent topics in public debate. This topic will become even more prominent in the future. Questions around the role and responsibility of state, individuals and private sector will need to be asked. In this regard, the insurer's societal role will become even more important.



Introduction

In recent years, we have observed a broad spectrum of medical advances. Some of them are likely to have a transformative effect on our life and society. Recognising that this progress in healthcare is a very broad topic, this paper is organised into two sections covering the key themes.

The first section provides an overview of medical advances, starting with the current state of morbidity and healthcare around the world (1.1). Next, we analyse the impact of medical advances on healthcare, grouping the analysis into three pillars: prevention (1.2), diagnostics (1.3) and treatment (1.4). Some of the major trends, such as genetics and big data, are addressed in all three sections.

The second section describes possible threats and opportunities that could arise for (re)insurers. The insurance industry will use its experience to provide solutions (services and products) in life and health insurance, allowing people to take part in the benefits of medical advances (2.1). The issue of costs and benefits follows naturally (2.2). Also, the impacts on healthcare providers and their liability should be taken into account and supported by insurance (2.3).

Medical advances and their integration into healthcare systems will have a significant impact on societies. Insurance companies will invest to understand these trends and support this transformation together with other actors in the health system to serve customers as trusted partners (2.4). The extent of the role of insurance will depend not only on the readiness of the industry to take part in this change, but also on the emerging risk landscape as well as the development of legislation and the direction in which public healthcare moves.

A note on the approach taken

The term 'Medical Advances' can relate either to advances in 'conventional' medical diagnostics, prevention and treatment, or to treatments designed to slow down aging and extend longevity. The line between these two concepts is blurred, but the working group has taken the decision to focus the paper on the former as much as possible. We have clearly observed that

next to medical advances, other aspects have major positive impacts on health, such as regular exercise and healthy diet, nevertheless we touch on them only briefly. Physical machines used in healthcare (e.g. nursing robots) are also not discussed in this document, as the CRO Forum Emerging Risk Initiative published a position paper on Autonomous Machines in 2017.

A look back:

Minimally invasive surgery

The introduction of minimally invasive surgery was responsible for one of the major changes in surgical medicine in recent decades. The term endoscopic surgery is often used synonymously with minimally invasive surgery, in which surgical instruments and a camera are guided through small skin incisions to the surgical area via small tubes. The surgeon looks at the operating area on a television monitor and can then operate the instruments either directly or via an operating robot.

Initially, minimally invasive procedures were introduced in the 1980s for abdominal surgery (e.g. gallbladder removal). The establishment of surgical procedures in the 1990s led to an expansion of areas of practice. Examples include interventions in the chest (e.g. cardiac surgery), orthopaedic surgery or cosmetic surgery.

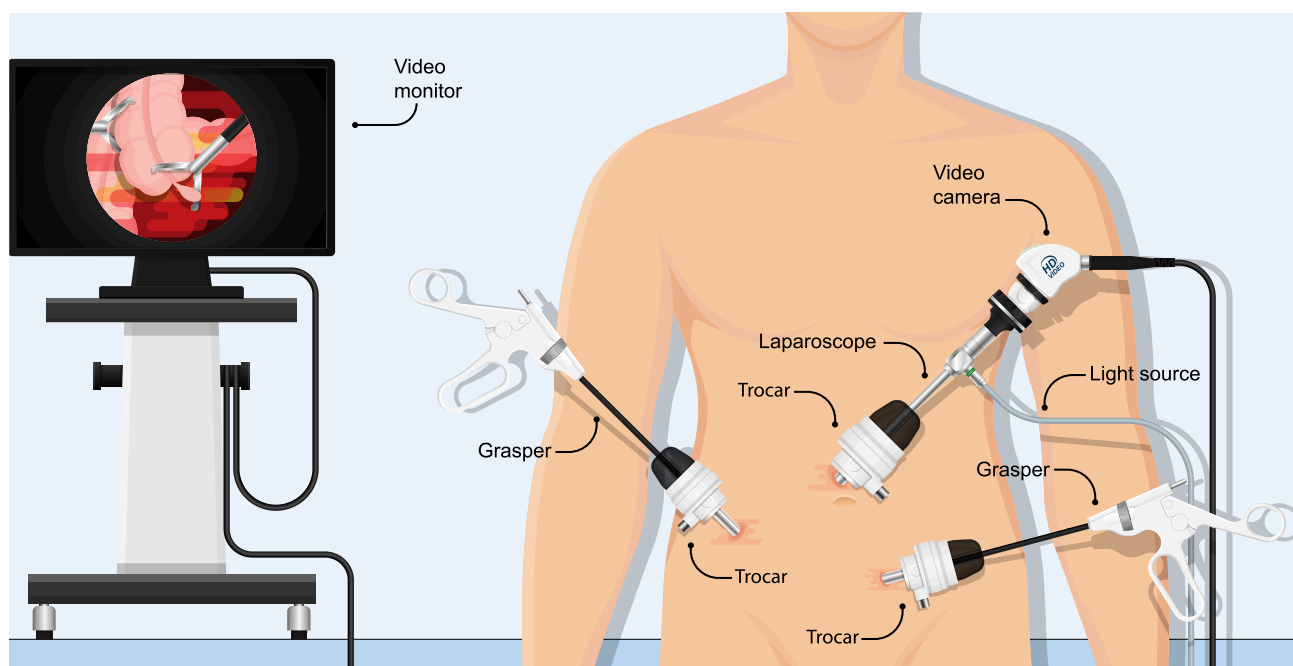
The main advantages of minimally invasive procedures are smaller incisions and lower impacts to the soft tissues during surgery. As a result, patients usually have less post-operative pain, can be mobilized sooner and can be discharged from hospital more quickly. Consequently, the patient's ability to return to work usually occurs more rapidly. These advantages have led to new 'Gold Standards'

in various surgical areas, where minimally invasive surgery has replaced the previously dominant open surgery procedures.

As always in medicine, new surgical procedures must show positive results for patient safety, not only in the short term but also in the long term. The use of minimally invasive procedures for certain tumour operations (e.g. ovarian carcinoma) is currently under discussion. Here, studies point to possible disadvantages in the long-term outcome compared to open surgery.



Patients usually have less post-operative pain, can be mobilized sooner and can be discharged from hospital more quickly.



1. Medical Advances and their impact

1.1. Current situation of healthcare

1.1.1 Causes of mortality

In the 19th and early 20th century, communicable diseases (CDS) have been the main cause for mortality worldwide. Due to better education, nutrition, antibiotics and living conditions the risk of death due to CDS has decreased significantly. Today, many non-communicable diseases (NCDs) tend to be of long duration and result from a combination of genetic, physiological, environmental and behavioural factors. Combined, they are by far the leading cause of death in the world. (WHO, 2018) In 2016, an estimated 40.5 million deaths occurred due to NCDs, accounting for 71.2% of the overall global total of 56.9 million deaths. The remaining share of deaths were caused by communicable

diseases, including infections, maternal and perinatal conditions, and nutritional deficiencies (20.2%) and injuries (8.6%). The majority of deaths were caused by four main NCDs, namely:

- Cardiovascular diseases, mostly represented by ischaemic heart disease and stroke;
- Cancer, with most deaths being caused by respiratory cancers (lung, trachea and bronchus);
- Chronic respiratory diseases, mostly represented by chronic obstructive pulmonary disease (COPD);
- Diabetes.

Also, deaths due to dementias

more than doubled between 2000 and 2016, making it the fifth leading cause of global deaths in 2016 compared to fourteenth in 2000 (WHO, 2018b).

According to Global Health official 2016-2060 projections by the World Health Organization (WHO), all main causes of global mortality mentioned above are expected to increase dramatically (see Table 1).

Table 1 Focused analysis of the main non-communicable diseases and their contribution to the global burden of mortality

	2016			2060 PROJECTION		
	Number of deaths	As % of NCD deaths	As % of all deaths	Number of deaths	As % of NCD deaths	As % of all deaths
Cardiovascular diseases	17 858 012	44.1%	31.4%	32 349 076	38.5%	31.8%
Ischaemic heart disease	9 433 224	23.3%	16.6%	16 560 299	19.7%	16.3%
Stroke	5 780 641	14.3%	10.2%	10 759 496	12.8%	10.6%
Malignant neoplasms	8 966 295	22.1%	15.8%	18 633 158	22.2%	18.3%
Trachea, bronchus, lung cancers	1 707 740	4.2%	3.0%	2 448 806	2.9%	2.4%
Respiratory diseases	3 807 942	9.4%	6.7%	8 765 670	10.4%	8.6%
Chronic obstructive pulmonary disease	3 041 446	7.5%	5.3%	7 053 057	8.4%	6.9%
Neurological conditions	2 538 460	6.3%	4.5%	8 348 100	9.9%	8.2%
Alzheimer's disease and other dementias	1 991 708	4.9%	3.5%	7 258 228	8.6%	7.1%
Diabetes mellitus	1 598 526	3.9%	2.8%	5 128 559	6.1%	5.0%
Non-communicable diseases	40 507 599	-	71.2%	84 094 252	-	82.6%
All Causes	56 873 404	-	-	84 094 252	-	-

source: World Health Organization. Projections of mortality and causes of death, 2016 to 2060.
Available at: https://www.who.int/healthinfo/global_burden_disease/projections/en/.

1.1.2 Healthcare expenditures

Medical advances and life expectancy

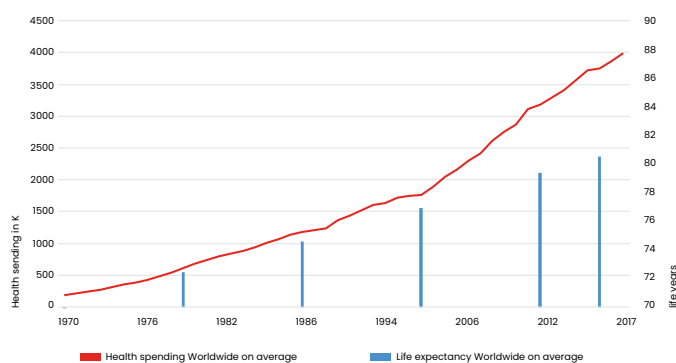
The life expectancy improvements in the early 20th century were the result not only of medical advances, but also from interlinkage of personal health and public administration, as well as through rising living standards (better nutrition and better housing) and better sanitation. New ideas about the germ theory of disease changed public health infrastructure and personal behaviour, as happened in the 20th century when people started to become more aware of the effects of smoking (Ritchie&Roser, 2019).

Globally, medical advances have contributed to an increased life expectancy. We all live more years in health but also more with a disability or chronic disease. In 1990 people lived on average 65.1 years and thereof 56.9 years in good health and 8.2 years with disability. In 2016 average life expectancy increased to 72.5 year and thereof 63.1 years in good health and 9.4 years with disability (Ritchie&Roser, 2019). As a consequence of population aging, the demand for long-term care has increased, with spending increasing more than any other type of healthcare. (OECD, 2017).

Healthcare and expenditure

Life expectancies and healthcare expenditures have not increased in proportion. As image 1 shows, medical costs have increased much more than the increase in life expectancy.

Image 1. Development of global life expectancies and healthcare expenditures



Source: own representation with reference to OECD, 2018a, 2018b, 2018c

In 2016, average health spending of the OECD countries was 9% of GDP (4.6% in 1970 and stable since 2009). In the WHO countries (including low income countries) we can see an increase from 8.6% in 2000 to 10% in 2016. However, the countries vary significantly in this respect. In 2017, the United States spent 17.1% of GDP on health whereas Turkey only spent 4.2% of its GDP. In 1970 the spread ranged from 2.3% (Portugal) up to 6.3% (Canada), which leads us to conclude that in many countries the expenses more than doubled (OECD, 2019).

Main cost drivers

The development and diffusion of medical technologies are the main drivers of rising health spending. Over the past twenty years, most OECD countries have seen a huge increase in the availability of diagnostic technologies such as computed tomography (CT) and magnetic resonance tomography (MRI). Spending on drugs has also risen sharply in many countries since 1990, as new and more expensive drugs have been launched regularly. Medicine cost doubled in Sweden and Australia between 1990 and 2001, while in Canada, Finland, Ireland and the US it increased by more than 70% (OECD, 2003).

Cost containment

Most OECD countries seek cost-savings in more frequent usage of generic drugs (copies of brand name drugs), although these still represent less than 25% of the volume of pharmaceuticals sold in Luxembourg, Italy, Switzerland and Greece (OECD, 2017).

An analysis of cost containment policies in OECD countries since 1970, showed that the evidence for many widely-used policies is very limited in terms of their effectiveness in containing healthcare costs. Moreover, many studies seem biased and these policies should be carefully evaluated after implementation. Nevertheless, the few high-quality studies suggest that a combination of cost sharing, managed care competition, reference pricing, generic substitution and tort reform could have the biggest impacts on cost containment. (Stathouders et al, 2019).

New developments; shift in healthcare cost accountability and value-based healthcare

Recently, many healthcare providers (hospitals and independent organizations) have been shifting towards a new healthcare supply system, known as the value-based health system, whose focus is to invest more in prevention and effectiveness. The mechanism relies on linking outcome of provided treatments with the provider's main source of income, with successful operations as a driver. In this scheme, it is the provider who bears the risk and responsibilities of late diagnoses and treating expensive complications.

Back pain could serve as a good example of the shift in managing illnesses from the current and expensive treatments (e.g. surgeries) to more efficient ones (e.g. physiotherapy). Diabetes type 2 is another example of a disease with a growing incidence rate that is currently curbed with expensive medicines, and yet it cannot be cured. However, its prevalence would be lower if healthier lifestyles were promoted and adopted.

In addition, an empowered patient becomes truly responsible for pursuing his/her well-being.

Patients and their families are enabled, supported and encouraged to become "CEOs" of their conditions, thereby shifting a lot of on-going care from professional providers to patients themselves. As such, caregiver empowerment on behalf of the patient may play an important role in fostering an effective patient-caregiver-provider model, which is becoming the optimal mode for healthcare delivery and is crucial for chronic diseases.

Obviously, this model will work only for some patients as their compliance (whether they follow their recommended treatment) is often not very high. Among patients with chronic illness, approximately 50% do not take medications as prescribed (De Geest&Sabaté, 2003).

1.1.3 Healthcare systems

Health spending measures the final consumption of healthcare goods and services (i.e. current health expenditure) including personal healthcare (curative care, rehabilitative care, long-term care, ancillary services and medical goods) and collective services (prevention and public health services as well as health administration). However, it excludes spending on investments. Healthcare is funded through a mix of financing arrangements, including government spending and compulsory health insurance ('government/compulsory') as well as voluntary health insurance and private funds such as households' out-of-pocket payments (OOP), NGOs and private corporations ('voluntary') (OECD, 2019). We see large variations in the reliance on voluntary insurance across healthcare systems depending on the different mix of public/private

sector and regulation. In countries with strong social systems and a high degree of regulation the space for voluntary cover might be smaller, whereas in countries with liberal systems and low regulation voluntary cover is much more important. The main source of funding tends to be 'OOP' (out of pocket), after the government schemes and compulsory health insurance. On average across the OECD, one-fifth of all health spending in 2015 was directly financed from private households (OOP). The share is above a third of health spending in Greece (35%), Korea (37%), Mexico (41%) and Latvia (42%) while in France it is less than 10% (OECD, 2017). The impact of development in healthcare spending on the life and health insurance market is further discussed in section 2.2.

DEEP DIVE:

Mental health

Mental health is defined as a state of well-being in which every individual realizes his or her own potential. The individual can deal with normal amount of stress, be productive at work and able to contribute to the community (WHO, 2014). Mental disorders, such as depression and anxiety disorders, are triggered by prevailing distress, functional impairment or premature death of someone close (Wittchen, 2011).

The cost of mental disorders

The cost of mood and anxiety disorders in the EU is estimated at € 170 billion per year (WHO, 2019a). It is claimed that the economy worldwide loses up to US\$ 1 trillion per year due to lost productivity caused by anxiety and depression (WHO, 2019a).

According to the WHO, about 13% of the global burden of disease is accounted for by untreated mental disorders. Depression alone accounts for over 4% of the burden of disease worldwide, making it one of the main variables (rank 3). It is predicted that depression will be the leading cause for disease burden by 2030 (WHO, 2011).



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Consequences of mental disorders

People with severe mental disorders (depression, bipolar disorder, schizophrenia and other psychotic disorders) generally have a 10-20 years shorter life-expectancy than the general population. They are often incapable of work and can no longer contribute to the community (WHO, 2019). Mental and substance use disorders are the leading cause of disability globally (Whiteford, Ferrari, & Degenhardt, 2016). About 1.4% of deaths worldwide are due to suicide. It is on the second rank for cause of death among 15 to 29 years old (WHO, 2018c). In high income countries, about 90% of suicides are due to mental disorders (Ritchie & Roser, 2018).

Prevention and Treatment

There are effective evidence-based treatments for mental disorders, such as psychological or pharmacological therapies (WHO, 2018a). However, about 80% of those affected in low- and middle-income countries, and 35-50% of those affected in high income countries do not receive treatment (WHO, 2018a). Only about one third of people with mental disorders seek help from a healthcare professional, often due to stigma and discrimination (WHO, 2001). The quality of treatment for those who receive it is often poor (WHO, 2018a).



1.2. Prevention

The importance of prevention in building effective health policies is increasingly acknowledged. At the global scale, political emphasis and engagement towards implementing measures to avoid preventable deaths is growing. For instance, the UN Sustainable Development Goal for 2030 aims at reducing premature mortality from non-communicable diseases by one third.

Preventive strategies

Preventive actions may range from sharing up-to-date knowledge to delivering innovative medical interventions. To simplify, they can be classified into three categories: primary, secondary and tertiary prevention.

Primary prevention seeks to prevent a disease before it occurs. It diminishes exposure to health risks (e.g. legislation against hazardous products or age restrictions on alcohol). It organizes immunisation of the population against infectious diseases (e.g. vaccination campaigns). Finally, it promotes healthy behaviours (e.g. awareness campaigns for better diets, for exercising or against smoking).

Secondary prevention aims at preventing and/or mitigating a potential impact of a disease before it affects a patient significantly. It promotes early detection of the disease and encourages timely treatment, as well as encourages strategies to prevent or inhibit relapses. The main policy applied is to offer screenings to large sections of asymptomatic, but potentially at-risk individuals. Screening tests are generally cheaper and simpler to perform than those used for diagnosis.

Tertiary prevention seeks to alleviate long-term diseases after they are diagnosed in order to maximise the remaining capacities and quality of life of a patient. It focuses on complex health problems such as chronic diseases and permanent disabilities. Examples of preventive action are rehabilitation programs, disease management plans and support groups for patients. The term quaternary prevention is sometimes used in the

European context to refer to strategies aiming at avoiding the over-medicalisation of patients.

To be effective, prevention is contingent on the volition of individuals to follow preventive advice. Proactive behaviour of individuals to expand their knowledge of health risks and adopt healthier behaviours remains indispensable. Over the past decade, public interest in the impact of lifestyle on health has widened. It is now accepted that a balanced diet, regular exercise and managing stress, enhance life expectancy in addition to helping to prevent and treat diseases such as cancer, diabetes, obesity and cardiovascular diseases. Awareness of the negative consequences on health of smoking, excessive alcohol consumption and of taking illegal substances is nowadays widespread.

Technological advances in prevention

Prevention is currently undergoing important changes due to recent medical and technological advances. Technological innovation enables access to certain treatments outside of hospital settings, thus improving overall patient comfort and decreasing saturation in hospitals. Examples include miniaturised ultrasound scanners and portable pulmonary functioning tests.

Individuals' use of wearable health devices (WHDs) to monitor their health during their day is increasing. Technology can thereby be a key factor for patient empowerment. Recorded variables include cardiorespiratory function, electrocardiogram, movement patterns, sweat analysis, tissue oxygenation, sleep, emotional state, and changes in cognitive functions. Personal awareness of one's physiological state may help patients to adopt

healthier behaviours.

Smart health – the use of intelligent networked technologies for improved health provision – is considered a promising solution for more effective and cheaper health practices, from prevention to cure. WHDs and connected sensors indeed improve the prevention and management of health risks. For



Personal awareness of one's physiological state may help patients to adopt healthier behaviours.

instance, sensors connected to apps can help people with asthma and chronic obstructive pulmonary diseases to identify symptoms, track uses of rescue medication and provide allergen forecasts.

Given that the physiological profiles generated by WHDs exceed standard episodic tests conducted in clinical settings, WHD data shared by patients could enhance clinical knowledge and enable more targeted and specific prevention campaigns. Surveys and samples could be replaced by real-world data gathered in large and interconnected databases regrouping information about patients and actors engaged in health prevention. The exponential surge in data sources raises the issue of interoperability and standardisation. Data regulation frameworks will be essential in ensuring safe, ethical and confidential use of the data (refer to section 2.1.).

Genetic testing increases an individual's awareness of potential personal health risks and encourages healthier behaviours and more frequent disease screenings. Nevertheless, clinicians recommend using home DNA tests with caution, since without an expert medical opinion, they tend to cause anxiety, while lacking a firm evidence basis in some of the

offered tests. Genetic knowledge will eventually become more precise with the improvement of polygenic risk scores (PRS), improving its potential for prevention (see deep-dive on genetic screening for more info on page 20).

Overall, the evolution of prevention methods will impact the relationship between insurance providers, healthcare professionals, policymakers and other civil society actors with respect to individual well-being and health. It is nonetheless unlikely that technological advances, such as WHDs, will lead all individuals to undertake drastic lifestyle changes in order to improve their health. Similarly, individual prevention via genetic testing will not capture the whole population. Public authorities will continue to play a key role in prevention. The latter will benefit from the explosion in health data that will enable more holistic and effective health prevention strategies, as well as better integration and effectiveness of prevention by health services. In addition, insurers can have a role in empowering individuals to actively care for their health (refer to section 2.4).



DEEP DIVE:

Genetic screening

The US National Human Genome Institute defines genetic testing as 'the use of a laboratory test to look for genetic variations associated with a disease'. (NGRI, 2019) Over the past few years, the once extremely expensive genetic tests reserved for exceptionally rare cases have gained in accuracy, scope and affordability, further improved by the developments in Artificial Intelligence (AI) and Machine Learning (ML).

Genetic diseases can be caused by a single gene mutation (monogenic disease) or mutations in several genes (polygenic disease). The completion of the Human Genome Project (HGP) in 2003, decoding the human genome, has laid the groundwork for thousands of scientific studies associating genes with human illnesses, such as food allergies but also Parkinson or Alzheimer's. (Fine, 2019; Ortiz, 2015) For instance, some mutations of the BRCA1 and BRCA2 genes are known to increase a woman's risks of breast and ovarian cancers (by as much as 69% and 50%, respectively). (NIH, 2018) Genetic variants finally play a role in determining somebody's weight. (Riveros&McKey, 2019)

Genetic knowledge will benefit from the qualitative improvement of polygenic risk scores (PRS). The latter is based upon data aggregates of millions of individual positions ('loci') across the human genome that are then weighted by the strength of their association to produce a single quantitative measure of genetic risk. While accuracy and reliability of current PRSs is limited, with low impact in medical practice, in the future, it could be expected to become an increasingly useful clinical tool; especially as improvements are made in attributing certain genes to the likelihood of developing certain conditions, thanks to the increased amounts of genetic data available and advances in algorithmic developments.

Genetic diseases can also be triggered by individual behaviour and/or the environment. Epigenetics is the branch of biology that studies variations in gene expression that do not involve changes in the DNA sequence. These variations are caused by methyl groups being attached to parts of a gene, affecting how cells read genes. Epigenetics seeks to explain

for instance the causation mechanisms between pollution and certain disorders. Researchers hope that epigenetic knowledge will lead to new therapies for chronic diseases, for instance by combining epigenetic reprogramming, chemoprevention and diet modification to fight cancer. (Zhang&Kutateladze, 2018) AI/ML progresses are expected to enable researchers to collect millions of data points on a single individual for improved results.

Although genetic testing was historically performed by healthcare providers and partly or fully covered by a health insurance company, direct-to-customer (DTC) tests marketed directly to customers via online and television advertisements are gaining in popularity. The latter are used to provide information about health (e.g. genetic risk of developing Parkinson's or Alzheimer's diseases), common traits (e.g. paternity testing) or to offer clues about an individual's ancestry (e.g. ethnicity, genetic connections between families). The global market for DTC genetic testing is estimated to surpass US\$1bn by 2020. (KPMG, 2018)

Growing availability of genetic tests, including DTC ones, increases individual awareness of health risk potential. This might improve early detection of diseases and timely treatment, helping reduce morbidity and mortality. Nevertheless, clinicians recommend proceeding cautiously with home DNA tests since without an expert medical advice, they tend to cause anxiety, whilst lacking firm evidence in some of the offered tests. (McCartney, 2015)

Genetic information is partly deterministic and is regarded as extremely sensitive, and therefore is mostly unavailable to insurers. Genetic tests, by increasing the asymmetry of information between the patient and the insurer, could lead to anti-selection biases, whereby individuals at risk would be more likely to subscribe an insurance. More on anti-selection effect on insurance in section 2.1.

1.3. Diagnostics

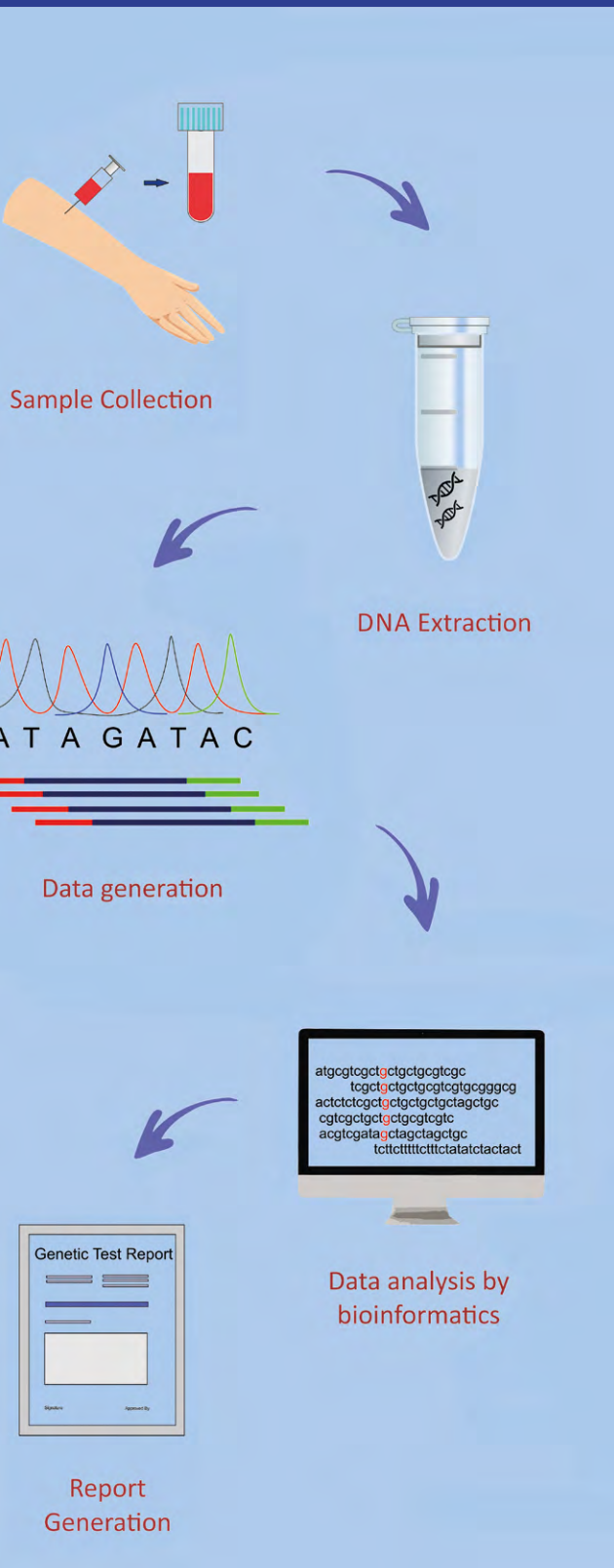
The past decade has seen the development of new methods and techniques for improving diagnostic precision, quality and speed of delivery. Compared to the traditional approaches, many of these innovations are also less invasive and more convenient for both physicians and patients. Although expectations are high, these new technologies and advances still face some challenges to be successfully integrated into clinical practice and existing clinical workflows in the foreseeable future.

Exploiting data

Digital pathology is a rapidly moving field in imaging technology. The first **Whole Slide Imaging (WSI)** system that allows for review and interpretation of digital surgical pathology slides prepared from biopsied tissue was approved in 2017 by the US Food and Drug Administration for primary diagnosis in surgical pathology. In pathology, biopsied tissues are mounted onto glass slides and stained to enable cell components to be visualised for medical evaluation under the microscope. WSI starts with the scanning (digitalization) of glass slides to produce digital slides, which are then processed by automatic imaging diagnosis algorithms based on machine learning image classification. Some algorithms focus on segmentation or classification of microanatomic objects such as cell nuclei, whereas others generate automated or semi-automated image classifications, disease grading, and diagnostic tests. The advantage of these digitised images is that they can be easily shared electronically and then be reviewed and interpreted by several pathologists in different locations, which is an advantage for complex or rare pathological diagnoses. Digital pathology can help determine a disease stage and its severity. Classification, validation and integration of imaging biomarkers into the clinical decision-making process will be key contributions of digital pathology to precision medicine. Furthermore, better computer-extracted images may be a useful addition to clinical appraisal, for example to aid decision-making regarding treatment escalation.

Computer-aided medical imaging diagnosis (CAD)

refers to the application of artificial intelligence to medical image analysis. Brought to the fore by IBM's "Watson for oncology" in 2014, the technique itself had already been used for quite some time prior to this. Current CAD systems can be divided into the following steps: image pre-processing, extracting "region of interest" (ROI), extracting ROI features, and classifying disease



according to those features. Recent advances in machine learning have boosted progress in the field. Systems may assist clinicians in interpreting medical images, allowing for data mining and automated interpretations, providing second opinions during the process of abnormality identification, predicting disease progression/aggravation and obtaining a differential diagnosis of the observed anomalies. Because CAD is fast and the system runs 24 hours a day, it can speed up the reporting of results. The next step for CAD will be to support the selection of suitable treatments, once the current barriers of software reliability and stability are overcome, interoperability between CAD and other systems is improved, links are established to clinical workflows, and regulatory approvals are achieved.

A **Clinical Decision Support System (CDSS)** is a health IT system using knowledge management aimed at providing advice for patient care based on clinical data. CDSS's aim is to support decision making, implementation of care algorithms and adherence to evidence-based clinical guidelines. CDSS are expected to bring improvements in quality, safety, efficiency, and effectiveness of healthcare. However, until now, the systems developed have had restricted field applications (i.e. only for fever assessment, emergency admission, antibiotic prescription). A liability issue emerges in the context of CDSS – more about it can be found in section 2.3. CDSS acceptance among healthcare workers remains currently low, due to various points such as: the perception that CDSSs are too rigid, the CDSS internal decision-making processes are opaque and not always evidence-based, legal implications in case of deviation from the recommended path.

Ideally, however, CDSSs bring the promise of reduced workload and improved workflow, for instance by routing a clinical consultation first via the CDSS and only as a second step via a trained medical professional.

App data with health-relevant content is another area that is being explored for use in prevention (refer to section 1.2) and diagnostics. There are many promising uses of wearable health devices in the clinic. Potential applications lead to a better understanding of lifestyle factors in the variability of the disease and response to treatments. Although the promises are clear, the challenges are not trivial and include scientific, regulatory, ethical, legal, data management, infrastructure, analysis and data security challenges (refer to section 2.1).

Making use of new technologies

A **lab-on-a-chip** is a device that integrates and automates multiple laboratory techniques into a small chip just a few square centimetres in size. Applications include tests for cancer, HIV, syphilis, and Lyme disease. Miniaturised analysis has various advantages such as short response times at low cost and low waste, ease of use, sensitivity even for very small sample sizes, and specificity, which are strengths in favour of increased use of lab-on-a-chip over the next years. The positive impact of lab-on-a-chip on costs is also described in section 2.2. One example is a device for counting red and white blood cells, developed in the California Institute of Technology in 2017. It uses micro-sized valves, pumps, and flow chambers and requires only a single drop of blood to give a reading. Particularly useful in less-developed countries and geographically isolated regions, the lab-on-a-chip technology brings the promise of early diagnostics and related earlier interventions to improve clinical outcomes. However, there are also technological disadvantages including physical and chemical effects that become apparent at small scale, such as capillary forces and low signal-to-noise ratio. Economies of scale have yet to become apparent.

Miniaturisation of technology employed in smartphones and wearable health devices can be re-purposed for diagnostic use. This already allows for indirect ophthalmoscopy to examine the eye's retina, for miniaturised ultrasound and melanoma screening via the smartphone camera. Even more sophisticated miniaturised technologies are in development. Many tests that previously required a laboratory for testing either can or will soon be accurately tested via wearable health devices. Sensortechnology enables the rapid analysis of blood samples, including electrolytes and blood gases, blood cells, coagulation, cardiac markers, glucose levels, and can also be used for drug screening. The opportunities related to miniaturisation lie in bringing tests faster to the patient and to provide quick and easy results that help speed up diagnosis and subsequent treatment at hospitals or doctors' surgeries.

Non-invasive diagnostics is possible due to the growth in computing power combined with artificial intelligence and sophisticated data treatment. Imaging techniques can now provide an almost complete rendering of cells, tissues, and organs as 2D or 3D images without the need for invasive procedures. **Optical Coherence Tomography**

(OCT) is a non-invasive imaging technology that produces cross sectional images of body tissues, which preserve the structural integrity of the sample taken, allowing for improvement in imaging quality for tissue examination. The method is based on infrared light and achieves penetration of several millimetres into the tissue with a resolution of a few micrometres. OCT is used in several medical specialties such as surgery, ophthalmology, otorhinolaryngology, dermatology, neurosurgery and cardiology. **Magnetic Resonance Elastography (MRE)** is an innovative imaging technique for the non-invasive quantification of soft-tissue elasticity through the visualisation of propagating shear waves. This allows the creation of tissue stiffness maps called elastograms. The main applications of this method are to assess liver fibrosis or breast density and to differentiate benign from malignant lesions in oncology.

Inventing new diagnostic tools

Personalised medicine is already commonly used in oncology, where different types of cancer are increasingly diagnosed based on their 'genetic fingerprint'. Other areas that could be important for developing novel approaches in precision medicine, include understanding the impact of the human microbiome on human health. Based on recent data, many believe that faecal microbiome profiling could become an important component of medical evaluation (see more on microbiome also in section 1.4).

Liquid biopsy (see also deep dive on page 24) refers to the molecular analysis of nucleic acids, subcellular structures, and – in the context of cancer – circulating tumour cells in biological fluids such as blood. Liquid biopsy is a non-invasive tool that detects and monitors tumour-related genomic alterations. Several studies have revealed the potential of liquid biopsy as an important cancer diagnostic and prognostic tool, including the monitoring of recurrences. As molecular technologies are rapidly progressing, many suggest that it may replace tissue biopsy in future as the standard tool for detecting and monitoring mutations in cancer.

Using telemedicine for medical diagnostics

Telemedicine refers to the use of digital technologies to deliver medical care, health education, and public health services. The aim is to improve care access and quality of life while at the same time to reduce

costs. There are several types of medical procedures made possible by telemedicine, with some success stories already coming from countries such as India.

Teleconsultation is a remote consultation offered to patients by a health professional. There are two types of teleconsultation programs. Synchronous programs take place in real time and allow interaction between the patient and healthcare provider. This includes virtual appointments that are conducted using the patient's smartphone, tablet, and computer with a camera, and connected medical devices that can transfer live data to consultants. Asynchronous programs, also known as 'store and forward' applications, are not live and involve the transfer of images, videos, or other information taken by wearable health devices, which healthcare providers can review before sending feedback. Teleconsultation allows patients living in both rural and urban areas to access healthcare when they need it. It also provides medical access to patients who cannot use transportation or may be too sick for long-distance travel. In addition, telemedicine helps to reduce healthcare costs, does not require the rental of any facilities, avoids unnecessary emergency visits and rationalizes hospital admissions.

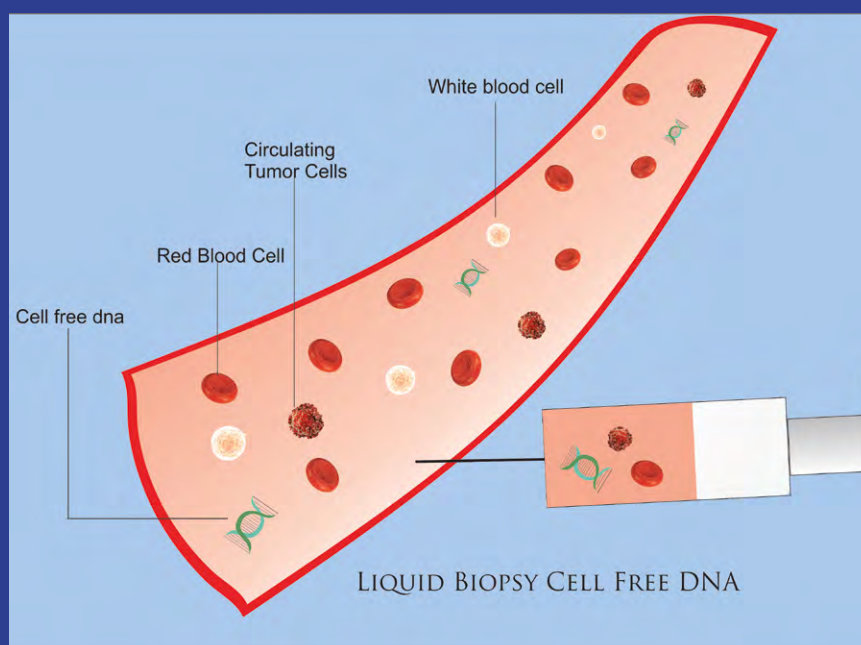
Tele expertise is a communication (video or mobile application) between two health professionals, wishing to exchange their medical views.

Telemonitoring is the use of devices for interpreting a patient's medical data remotely in order to make a diagnosis. Applications include monitoring of asthma and diabetes. The use of wearable health devices allows for tracking and monitoring clinical information, which is then transmitted to physicians. Telemonitoring may be a part of synchronous teleconsultations.

DEEP DIVE:

Liquid biopsy

Using just a tiny drop of blood, liquid biopsy testing is able to detect and monitor tumours in patients. It does so by analysing molecular biomarkers in blood and other body fluids. This new molecular technology is set to revolutionise the diagnosis, prognosis and treatment of disease. It is currently being explored for its benefits to treat and detect cancer, thus improving prevention, treatment and survival outcomes for patients. To the pharma industry, liquid biopsy presents an important step towards personalized medicine, as well as a significant field for product and service offerings.



How it is done

Liquid biopsy provides a minimally invasive alternative to surgical biopsies, while gathering a wide range of information from a simple blood sample. A physician takes a blood sample and sends it to the lab, where the sophisticated molecular testing and analysis is provided. The physician can deliver results to the patient within a day without performing surgery. More time can be spent on consultation and explanation. Thus, liquid biopsy holds the potential to positively transform clinical practice and doctor-patient relationships.





Behind the science

Liquid biopsy has been enabled by developments in DNA analysis. Historically, DNA analysis was neither sufficiently sensitive nor cost efficient enough to enable tumour DNA detection reliably and cost-effectively. With the advent of next generation sequencing techniques, liquid biopsy and epigenetic profiles are now able to detect specific changes in the genome of cancer cells. Tumours release a multitude of biomarkers into the bloodstream such as cell-free DNA or circulating tumour cells. With new DNA sequencing methods, DNA fragments and traces indicating a tumour and circulating in the blood can be picked up and analysed. By identifying clinically relevant biomarkers, clinicians gain insights about a tumour and the treatments most likely to work for the patient. The identification of mutations allows for treatment decisions as well for monitoring treatment responses.



Pros and cons of liquid biopsy use

Compared to the invasive procedures for tissue biopsy, the procedure of liquid biopsy itself carries less risk (of complications) for the patient. For both the patient and the physician, the procedure is simple and fast, and it is significantly less expensive than standard surgical biopsies, which are based on a time-intensive, invasive, sometimes painful and risky surgical procedure to obtain localized tissue sampling.

While cancer diagnosis today follows investigation of symptoms indicated by the patient and/or by the physician's routine examination, liquid biopsy holds the promise of much earlier detection and more efficient patient-tailored and successful treatment.

However, currently there is insufficient evidence to justify relying solely on liquid biopsy to screen for most cancers, and for the foreseeable future, histopathology will remain the standard procedure for cancer diagnosis and staging. Put bluntly: a 'negative' liquid biopsy test does not rule out the presence of cancer, and a 'positive' liquid biopsy test does not yet meet today's clinical standard for cancer diagnosis.

DEEP DIVE:

AI and machine learning in diagnostics

Artificial intelligence (AI), including machine learning, in medicine is receiving significant investment due to the potential of the approach to improve early diagnosis, to address resource challenges and to utilise the vast amounts of available data to aid medical judgements. Artificial intelligence can be based on 'machine learning', which works on structured data, or on 'deep learning' techniques, which have several layers of networks and do not require structured data. The aim is to make useful judgements based on large amounts of data without the need for continuous human involvement.

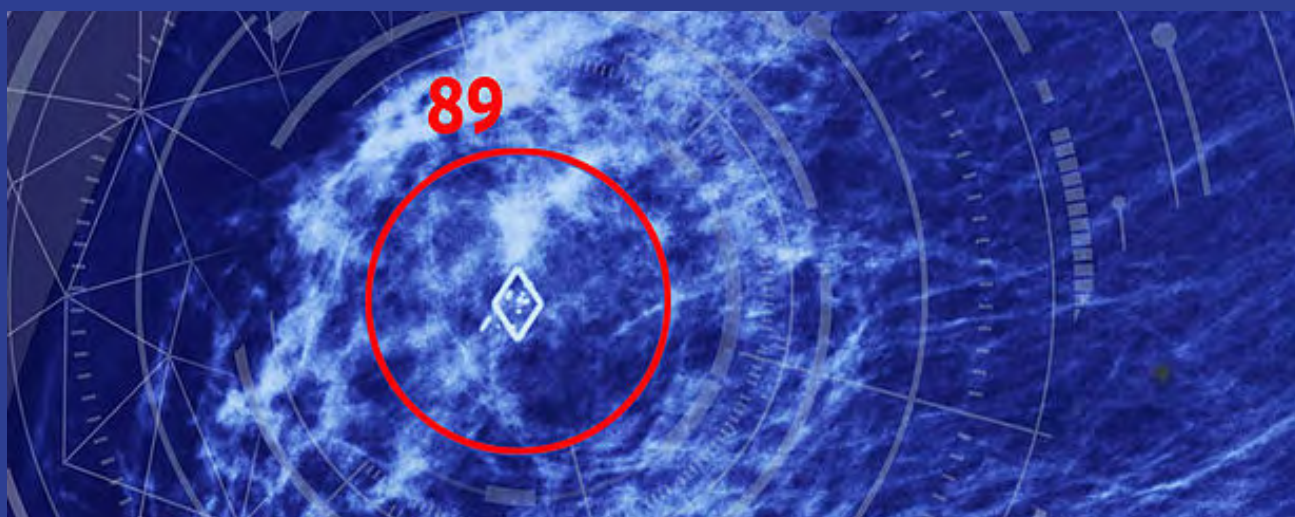
Breast cancer diagnosis has been an area of focus and is a good example to explore benefits and challenges of applying artificial intelligence. Due to commonality of breast cancer, AI facilitates early diagnosis, which is crucial for successful treatment. As the accuracy and speed of diagnosis improves, the more likely customised treatment offerings become, this in turn may reduce the need for invasive procedures. Breast scans have many features, and AI can support radiologists by highlighting suspicious areas for closer inspection, or by performing the diagnosis autonomously.

A number of organizations are working on specific AI-based software for breast scan interpretation and there are commercially available products on the market. A Massachusetts Institute of Technology

study from May 2019 included mammograms from 60,000 patients and used deep learning to accurately place 31 percent of all cancer patients in its highest-risk category, compared to only 18 percent for scans that were interpreted by traditional computer-aided diagnosis. (Simons&Gordon, 2019) One strength of software-based breast cancer diagnoses is that they are better at picking up cases with multiple foci compared to humans.

While the results of such studies are encouraging, other research has shown certain limitations. These include the use of imaging data that are non-representative of the screening setting, potential biases in model training and the lack of comparative data. (Houssami&Kirkpatrick-Jones, 2019) Current systems produce too many false positives that have to be manually removed, counterbalancing some of the efficiency gains. In addition, the adoption of AI in breast screening practice and healthcare in general still has barriers to overcome, including acceptance by both patients and clinicians, in addition to legal, ethical and social implications. However, in the end, AI as a tool could improve breast cancer mortality and patient experience. The current reality in clinical practice is a collaboration between trained experts and software, and it will be interesting to see how the roles shift with improving capabilities of AI.

Figure 2: *Autonomous detection of potentially cancerous cells within a mammogram*



Source: <https://www.screenpoint-medical.com>

1.4. Treatment

Advances in precision medicine provide the opportunity to deliver the most effective treatment for a given patient, thereby reducing the potential for side effects. In addition to improving morbidity and mortality, these advances can also provide improvements in quality of life. Several precision medicine treatments are expected to make their way into clinical practice over the next ten years, with the main challenge for clinical implementation often being cost-benefit effectiveness (see more on the cost topic in section 2.2). However, despite all the justified excitement around new treatment techniques, the importance of patient-human health professional relationships and their impact on treatment success should not be underestimated.

Personalised medicine and pharmacogenetics

Personalised medicine refers to medical care tailored to a genomic and molecular profile of an individual. The technique provides new ways to understand the origins and progression of diseases and can also reveal new approaches for the development of treatments. Personalised medicine is applied to a diagnosis of disease subtypes defined molecularly and is also used in drug development and therapeutic decision-making. In the context of treatment, the goal of personalised medicine is to decrease the number of adverse effects and enhance effectiveness.

Pharmacogenetics is aimed at identifying differences in inter-individual drug dispositions and effects, with the goal of selecting the optimal drug therapy and dosage for each patient. Most pharmacogenetic tools now have the capability to test multiple genes simultaneously. They measure genetic variations and single nucleotide polymorphisms (SNPs). Developing pharmacogenetic guidelines can provide guidance in routine treatment practices, enabling direct translation of genetic results into actionable prescribing decisions.

Pharmacokinetic genes affect absorption, distribution, metabolism, and elimination of medications. There is an enzyme 'family' in the human body that is the major mechanism for the biotransformation of medications; these enzymes can have several variations according to minor genetic changes that may affect the way medications are metabolised. Pharmacodynamic genes affect what the medication does to the body

and could alter the efficacy or the adverse-effect profile of the medication.

As of now, clinical evidence shows that pharmacogenetics is significant for drugs prescribed in the field of psychiatry, oncology, and cardiology. An increasing number of therapeutic agents are approved which are only effective in some groups of patients with specific molecular characteristics, especially in oncology. In future, all prescribed drugs could undergo pharmacogenomic analysis prior to being ordered for individual patients, according to their specific genetic background.

Immuno-Oncology

Immuno-oncology aims at using the body's innate human immune system to generate therapies that allow individuals a form of 'self-defence' against developing cancer, or to treat existing malignancies. For example, as the micro-environment may condition local anti-tumour effects, healthy cells in contact with cancer cells may be harvested and engineered to modify their functions, then reinjected to boost local immuno-reactions.

There are three different areas of immuno-oncology which are set to continue developing and could be combined to generate novel therapeutic strategies for cancer therapy.

The first area is the development of a preventative vaccine which primes the immune system for surveillance using defined repertoires of molecules called antigens that bind to target structures on the surface of cancer cells called antibodies. This ensures that defensive cells called T and B lymphocytes and macrophages can promptly react to the occurrence of early carcinogenic events.

Others are investigating the generation of so-called humanised recombinant antibodies: this type of antibody specifically kills cancer cells by inhibiting proteins essential for their survival. Recombinant antibodies also boost the immune response by acting on so-called immune checkpoints that regulate the immune response up or down. This 'checkpoint therapy' blocks inhibitory checkpoints and is based on discoveries that won the 2018 Nobel Prize in Physiology or Medicine. Another use of recombinant antibodies is delivering a payload consisting of cytotoxic drugs or radionucleotides to tumour cells.

Finally, T cells can be genetically engineered by gene insertion or deletion, such as Chimeric Antigen Receptor-T cells (CAR-T cells) – see also deep dive on personalised drugs on page 31.

Biopharmaceuticals

Insulin and growth hormone as well as a vaccine against hepatitis B are examples for biopharmaceuticals as a general category of treatments using agents that are derived from or based on living sources. Within this area, the term “biologics” is sometimes used to refer to a class of therapeutics based on artificial or “recombinant” DNA. This means that genetic sequences from various sources are combined to create a desired product. With the ongoing progress in the development of the underlying technologies, this field is expected to expand and grow. One example is fusion proteins, especially monoclonal antibodies. They are currently applied in chronic inflammatory conditions and specific cancers. Produced by identical immune cells, monoclonal antibodies are made to specifically bind to a cell surface and stimulate a patient’s immune system to attack those cells. Their application is expected to broaden in the future.

Rare disease treatment

The emergence of Next Generation Sequencing (NGS) technologies has been a turning point for understanding rare diseases. The number of newly identified genes associated with a disease has increased exponentially in all areas of medicine since the emergence of NGS technology. NGS has not only allowed molecular diagnosis, but also improved the search for treatments of diseases in several ways:

- in some cases, the detection of a molecular cause can identify an effective treatment. This is the case in many metabolic disorders for which the diet can be used to maintain a controlled metabolic state.
- When the origin of a rare disease lies in the presence of certain proteins in abnormal concentrations, an effective approach could be to influence mRNA or protein levels. The identification

of drugs that restore inadequate levels of mRNA or protein to a clinically significant level is a promising avenue of research. For example, dozens of artificial single-stranded molecules composed of nucleic acids (oligonucleotides), intended to treat a range of diseases such as difficulties with blood-clotting (haemophilia) or excess blood lipids, are in clinical trials.

- Genome editing technology can be used to correct genes responsible for endogenous diseases or specifically target the integration of a therapeutic gene into a defined genetic locus. These very sophisticated tools can be programmed to correct disease-causing mutations with high efficiency and represent a sophisticated tool for precision medicine. However, all gene editing tools will have to prove their effectiveness and safety before being used widely in clinical practice.

Viral vectors have been successfully used to carry the necessary tools for genome editing as they are capable of dissemination throughout the body, both intra- and extracellularly, and can penetrate the nucleus. Retroviruses, adenoviruses, and adeno-associated viruses are the three most commonly utilised classes of viruses because they are easy to manipulate in the laboratory, have a high speed of replication, and can integrate into human DNA.

Artificial organs

Regenerative medicine aims to repair or restore the function of altered tissues and organs. The field has recently seen advances from three-dimensional bio-printing, increasing the feasibility of living tissue synthesis. This technology involves the precise superimposition of cells, biological scaffolds and growth factors, in order to create a bio-identical tissue for a variety of

uses. A 3D-digital model of the tissue defect or organ is created by computer tomography, magnetic resonance tomography or ultrasound. Using computer aided design, the internal and external



The emergence of Next Generation Sequencing (NGS) technologies has been a turning point for understanding rare diseases.

architecture of the scaffold, such as porosity and pore size, can be integrated into the model. Materials such as cell types and bioactive molecules are used to create a 'bio ink' for printing depending on the type of defect, location and requirements. The cell-loaded structures are then made using bio-printing technology, placed in cell culture or directly implanted into the patient. Some promising 3D printed organs for transplant are at an advanced stage of development, namely skin, bone, cartilage, cornea, cardiac valves, and heart. As the liver and kidney have more complex structures there are some difficulties in their respective development. Despite all these complexities, advances in bio-printing are being made steadily and hopefully in the near future, 3D organs will be used in regenerative medicine and by the pharmaceutical industry for drug discovery, development, adverse effects studies and delivery systems, as well as in surgical training.

Nanotechnology

Nanorobotics is an emerging technology. It deals with creating machines or robots whose components are at, or close to, nanometre scale. Nanorobots can be programmed to perform specific biological tasks. For example, they can be injected into the blood, where they kill cancer cells without affecting healthy cells.

An example for a current DNA nanobot is one 200 times smaller than a red blood cell and only 35 nm in diameter. The outside of this nanobot carries short nucleotide strands with special sequences for recognizing molecules on target cells. Inside the bot active drugs are placed. Once a target cell is recognised based on its surface proteins, the nanobot delivers the drug to the target cells. DNA nanobots can now identify 12 types of cancer cells. With more trials and development, nanobots have the potential to bring about progress in various medical fields.

Virtual and augmented reality

In medicine, Virtual reality (VR) refers to the creation of a virtual environment for the assessment of various parts of the anatomy for diagnosis, surgical training and treatment. It allows the creation of an augmented reality (AR), using a technique that integrates data previously collected from medical images (e.g. from ultrasound) with live images of the patient. The superimposition of a 3D virtual picture specific to an individual patient onto the surgical

field using e.g. semi-transparent glasses to augment the scene, can improve surgical performance. For example, the position of blood vessels can be overlaid onto the screen of a microscope, to guide an eye surgeon during ophthalmic operations. (Peters et al, 2018)

Phage treatments

While already known for almost 100 years, phage therapy (PT) recently garnered new interest in the frame of antibiotic resistance. PT uses specific bacterial viruses that infect and destroy bacteria. This medical advance is currently highly specific to the patient and the infection, and in addition is very costly. In consequence, it is not likely to see widespread clinical application.

Holistic medicine

There is growing interest in using holistic approaches to understand the origins of disease, including the role of mental well-being and its impact on physical health (see also the deep dive on mental health). Such holistic approaches to human health tend to be the foundations of, for example, the medical traditions of China and India, where the emphasis is placed more on disease prevention rather than treatment, centred around a specific approach to diet, in addition to physical and mental exercises (e.g. practising yoga, breathing and meditation techniques). In the treatment of an individual, emphasis is placed on understanding the context of a person's life situation (including human relationships, occupation, living environment, in addition to lifestyle choices) in relation to the symptoms experienced. This is a relevant point for many medical advances that focus on a single element of treatment and that in doing so, fail to recognise the importance of the bigger picture. Also, the increase in the use of computers and robots at the expense of patient contact with a human medical professional, may have unexpected repercussions on patient well-being. There are qualitative elements in the practitioner-patient interaction that may be difficult to replicate by a machine or at distance. For example, empathy and trust are central elements of treatment success and patient outcome, for which a human touch – often in the literal sense – is essential.

Long-term horizon for innovation in medical treatment

When looking at research that might produce new medical advances over a longer time horizon compared to the other subjects discussed so far, two areas of novel treatment approaches are particularly promising: microbiome medicine and psychoneuroimmunology.

Microbial communities, including bacteria, archaea and fungi, are known as microbiota or microflora. Knowledge of the microbiome properties can contribute to identifying links between the microbiota and certain diseases. The human microbiota plays a key role in protecting the gut against pathogens, both through competing for space and nutrients and by activating the host immune system. The microbiota of healthy people is very diverse with a magnitude of beneficial microbes that help in maintaining balance during periods of physiological stress. Recent studies have also shown that the bidirectional 'gut microbiota-brain axis' regulates body weight by balancing the metabolism. Alterations of microbiota contribute to different pathogenic outcomes such as antibiotic-associated diarrhoea, inflammatory bowel disease, irritable

bowel syndrome, pseudomembranous colitis, obesity, cancer, depression and mood disorders. A better understanding of the mechanisms underlying these phenomena could lead to tailored treatment approaches, adjusted diets, and may also help in choosing therapies based on specific microbiota.

Psychoneuroimmunology is based on the ability of the psychological state of an individual to influence the immune system. The central nervous system and the immune system do not function independently: the central nervous system utilises cellular and molecular elements of immune communication.

Stress and depression have numerous inflammatory consequences (see also the deep dive on mental health). Immune symptoms include increased levels of proinflammatory cells (cytokines, monocytes, and neutrophils) in the peripheral circulation, alterations in morphology and activation of special cells in the central nervous system (microglia and cerebral endothelial cells), and dysregulation of bacterial populations in the gut. Future research will continue to bring advances in both understanding of inflammatory mediators of mood disorders and translation into clinical solutions and new therapies.



The term 'personalised medicine' is used in modern medicine following developments in molecular genetic medicine, meaning customised treatment that is not just based on clinical state but also reflects genetic factors.



DEEP DIVE:

Personalized drugs

'Personalised medicine' is a medical concept that aims to offer tailor made diagnosis and therapy to individual patients. While medicine has always aimed at addressing individual needs, the term 'personalised medicine' is used in modern medicine following developments in molecular genetic medicine, meaning customised treatment that is not just based on clinical state but also reflects genetic factors. The use of genetic information formed the scientific basis for the development of the whole concept. In the case of personalized drugs, an essential concept of individualized gene therapy is the focus of worldwide research and development activities, such as CAR-T cell therapy.

For many years, the standard treatment of leukaemia consisted of chemotherapy, radiation and stem cell transplants. With optimization and fine-tuning of these treatment methods, the survival rate could be significantly improved over time. Immunotherapy is a new therapeutic approach, where the immune system is stimulated in a specific way. The modified immune system then detects and kills cancer cells.

The idea is not new. First studies took place as early as in the 1990's; in 2017, the first drug for gene-altering treatment got FDA approval in the US. The procedure is referred to as CAR T cell therapy.

Chimeric antigen receptor (CAR) T cell therapy is a complex process used to produce the drug. In a first step, the patients' blood is collected. In a second step T cells, which are part of the white blood cells, are isolated out of the blood sample and then activated. The crucial point is then the T cell modification. A virus inserts a gene into the cell's genome, modifying the blood cells. The gene encodes a cancer specific antigen receptor that is formed on the T cell surface (CAR T cell). After CAR T cell expansion and product formulation the drug is then infused back to the patient. Within the patient's body, the CAR T

cells aim to identify specific antigens on cancer cells and kill them. Therefore, CAR T cells can be regarded as complex drugs that are created from the patients very own body cells.

CAR T cell therapy seems to work in malignant diseases like leukaemia and lymphomas, while they so far show no beneficial effects on patients with solid tumours (e.g. breast cancer, lung cancer, and liver cancer). Previously approved drugs have strong indication restrictions based on the potential serious side effects of the therapy. The most notable side effects are:

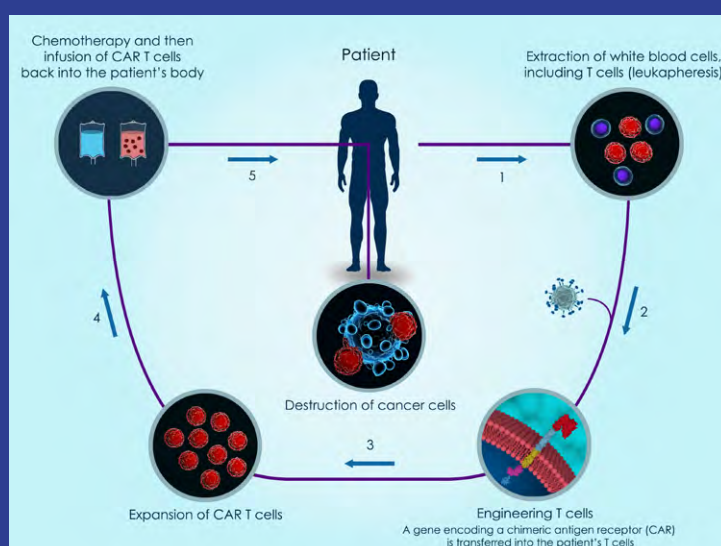
- killing healthy tissue,
- cross-reactivity with non-related surface proteins,
- neurotoxicity with cerebral impairment,
- cytokine storm, potentially leading to coma and death.

Many pharmaceutical companies are working on new CAR T cell drugs. Nevertheless, there are some

open questions such as the development of suitable animal models, optimal dosage or toxicity management.

Taking into consideration the above-mentioned issues it can be concluded that CAR T cell therapy may be a highly beneficial future option in cancer therapy. In the next phase of clinical use, it has to prove superiority over standard therapy. Currently, overall

survival data and long-term risk-benefit analyses are not available. The extremely high cost of this therapy is a critical point. In the future, new CAR T cell therapies may be available that could cost more than USD 1 million per patient, which is a real challenge for all healthcare systems driving complex ethical questions around allocation of funds and prioritisation of one need over another (further discussion in section 2.2 and 2.4).





Fast forward:

Hospitals in the future

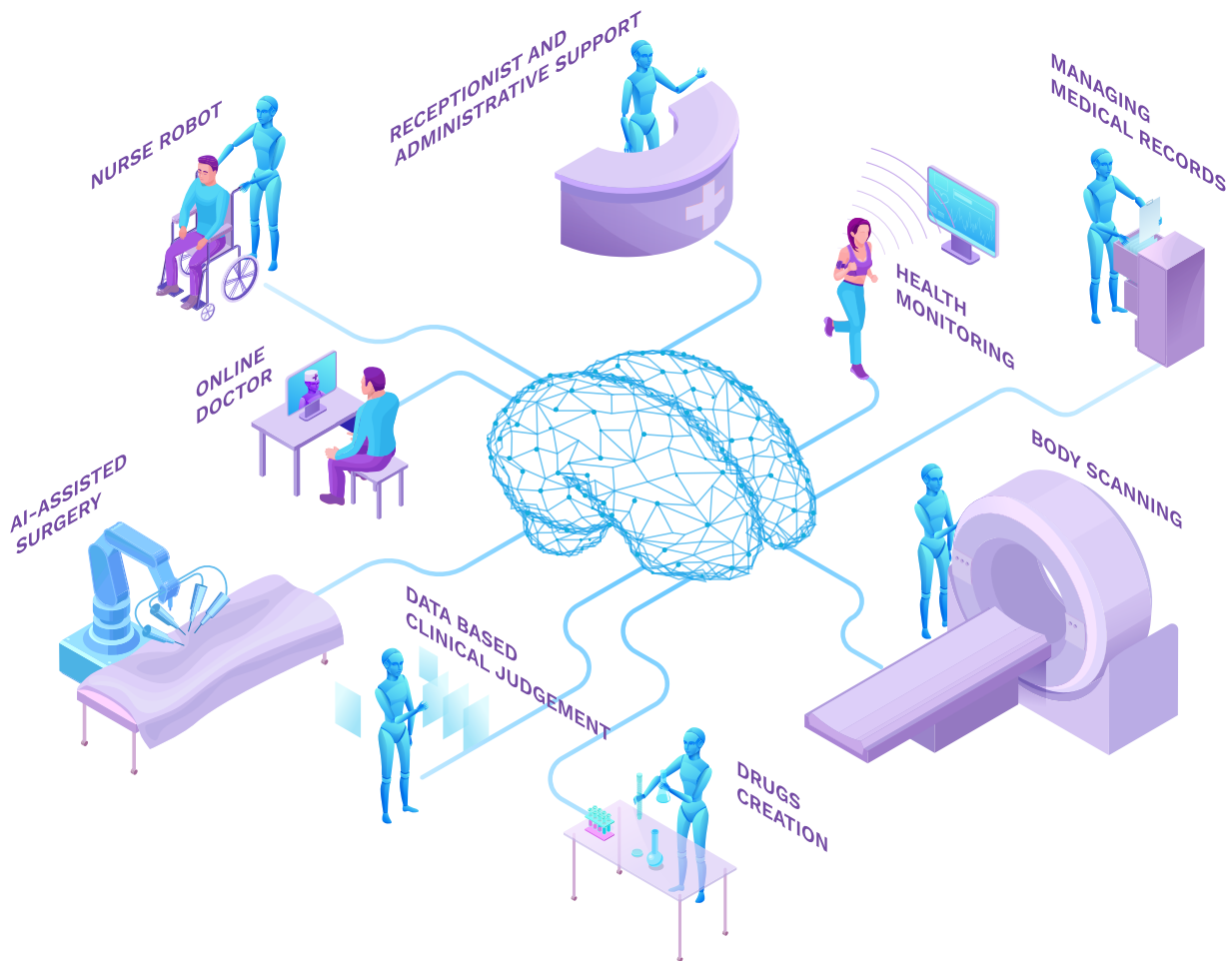
How will hospital organisation change by 2030?

Over the years the average length of a hospital stay has decreased continuously and this trend is expected to continue. Patients are increasingly treated on an outpatient basis or are only briefly admitted to hospital for treatment. Longer hospital stays will only be necessary in case of severe or complicated illnesses. In order to meet these changed requirements, there needs to be more capacity in the areas of intensive care medicine and intermediate care.

In addition to maximum care facilities, hospitals will continue to form focal points and specialist centres (e.g. for heart diseases). The trend towards specialisation that has already been initiated is likely to continue. Very small hospitals will be challenged to survive due to increasing economic pressure. For patients, this probably means that they will have to travel further to a hospital if no suitable treatment

options are available in the immediate vicinity.

The existing shortage of hospital staff will continue to be a major organisational problem in patient care in the coming years, which refers to both medical and nursing personnel. The lack of care in some specialist disciplines is already apparent today. It remains to be seen whether digitisation and the use of artificial intelligence in healthcare can help to overcome these resource pressures. Further specialisation and the increasing workloads of staff, without creating additional human resources, could mean that individual and holistic care could probably not be guaranteed to the desired extent in the future.



What will admission to hospital be like in 2030?

Due to advances in digitalisation, patients' records and history will be shared with the consulting team before a patient's admission. As a complete patient file will be stored on the digital health card, all involved primary practices and hospital departments will have access to relevant data. The record will include all consultation notes, digital images of x-rays and other advanced diagnostic results such as liquid biopsies or genetic tests.

When patients arrive to be admitted, hospital information systems will be able to reduce waiting times by scheduling the patient's appointment in advance. Rather than having to register with a receptionist, patients may simply tap their smartphone or their digital health card against a digital reader to confirm their identity and to 'log in' to the hospital patient management system. There will be no need to provide other details, as

all relevant information will be already stored in the patient record.

Operations such as the removal of the gall bladder would be performed on the same day. The endoscopic surgical technique means that the recovery time is much faster than in earlier times. As a rule, patients can be discharged two to three days after surgery. Unless there are serious complications, a patient would not need to go back to hospital for follow up visits and further care (e.g. control of wound conditions and removal of suture material) would be provided by the general practitioner instead. The seamless updating of patient files means that there is no information gap between the parties involved. For ongoing care following a patient's procedure, hospital specialists can be consulted via teleconsultation, which again would make many in-patient appointments redundant.

Fast forward:

Living with diabetes in the future

The technological advances of recent times have allowed for major improvements in the management and treatment of type 2 diabetes. Specifically, these improvements have helped with the testing and monitoring of blood sugar levels, as well as in reminding diabetics of the necessary routines to avoid insulin spikes. Before the 1920s, diabetes was fatal; however, the discovery of insulin and its therapeutic potential was a major breakthrough that allowed the disease to be managed. Even so diabetes remains a very serious disease and continues to impact life expectancy. The following is an attempt to provide a vision for the future, based on technology already in view and the possibility that management of the condition can continue to be improved and perhaps even cured.

Early diagnosis of diabetes

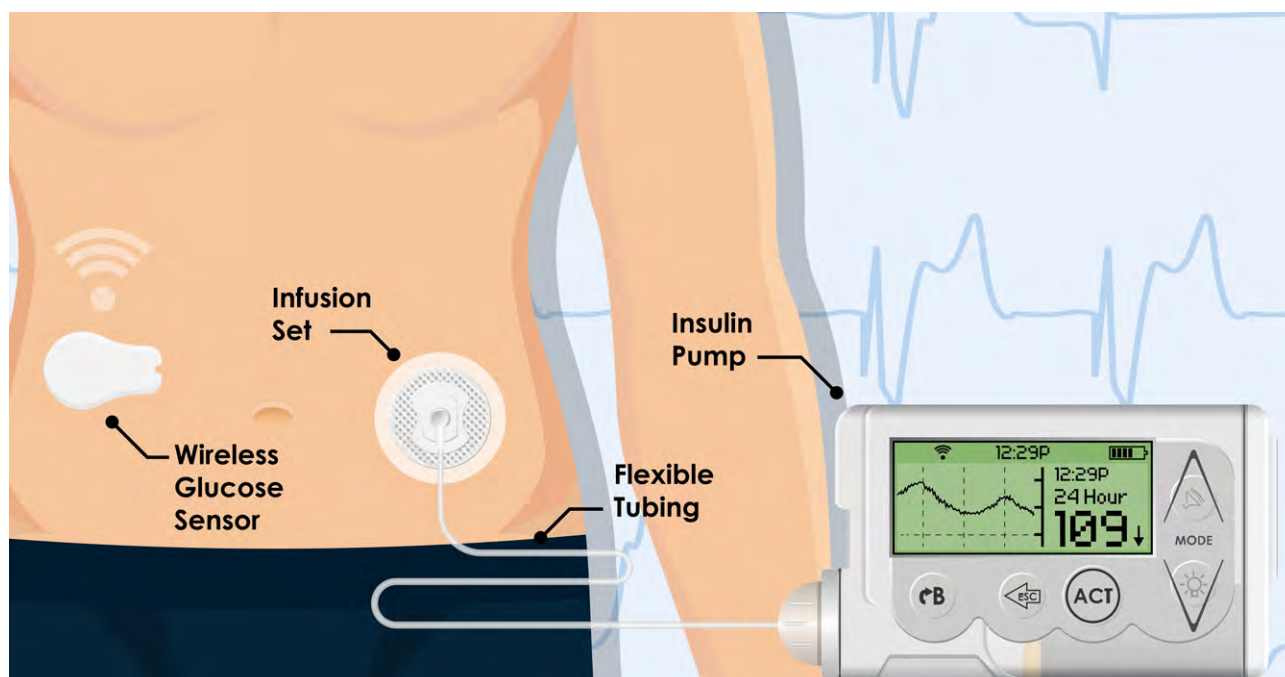
Diagnosis may occur well before symptoms become problematic, facilitating disease management and in some cases delaying or preventing development of symptoms altogether. Genetic testing will enable prediction of the potential for a person to develop

diabetes. Thus, regular tests will enable an individual to identify early warning signs. Genetics can also be used to clarify whether an individual is type 1 or type 2 diabetic.

Common use of sensors and AI supported monitoring

Sensors in the skin will monitor blood sugar levels and trigger an insulin pump to release insulin into the body, even around meal times (which is currently difficult). The sensors link up with a smart phone to inform the person when a dose is administered and the amount, enabling the device to be monitored. Any errors or spikes in blood sugar will be highlighted, triggering a self-diagnostic of the sensor and allowing manual overrides. If sugar levels reach abnormal values, then friends, families or colleagues will be alerted.

Sensors will not only monitor a person's blood sugar levels, but will also create an automatic log of a diabetic's diet, amount of exercise, number of hours of sleep and daylight exposure. This will help



the artificial intelligence in the monitoring device, or the user him/herself, to spot any potential trends, thus helping to manage the condition optimally. Using such devices to monitor and manage health and diet would enable a number of individuals to reverse or contain diabetes, depending on individual differences and diabetes type. Results of all tests will be documented and stored: not just routine blood sugar tests, but also other less routine tests, such as A1c or haemoglobin tests, and eye tests. Over many years users will be able to track changes and identify successes in managing their condition. The pooled data of many individuals will allow for big-data analysis, where gained insights would lead to better patient guidelines and care.

Incorporation of holistic medicine

Holistic medicine and better understanding of how our bodies function will be translated into increasingly effective treatments and care. Along with careful control of diet and lifestyle, it offers a promise to reverse or contain symptoms of type 2 diabetes, as many studies show.

Fewer hospital visits

Routine hospital check-ups may become a thing of the past. Doctors will monitor individual patient's data, review test results taken from remote devices, including actual insulin tests and call the patient to discuss their current condition and whether a hospital visit is needed. A combination of good compliance with technology advancements may prevent extreme interventions, like amputation. In cases where hospitalization is still required, future medical advances will make this stay much more efficient.



Sensors will not only monitor patient's blood sugar levels, but also create an automatic log of what diabetics eat and the exercise they get.

2. Impact on (re)insurance underwriting risks

2.1. Possible impact on life and health insurance

Medical advances imply for insurers risks, as well as opportunities. In response, pricing and underwriting

models amongst other aspects may need to be altered and contract wording revised.

2.1.1 Handling of sensitive data, mismatch between pricing and risks

At this stage two key risks emerge: linked to the impact of data protection rules (including those specifically aimed at preventing discrimination) on one hand, and the possibility that science may run ahead of changes in underwriting and pricing practices, leading to potentially costly mismatches of revenue and risk, on the other.

Anti-discrimination laws and data protection

Insurers' responsibility to manage risks generated by improvements in the accuracy and accessibility of information on an individual's susceptibility to a disease, could be impeded by regulations intended to prevent discrimination against individuals in the provision of life and health insurance. For example, the Association of British Insurers ('ABI') has published voluntary guidance on the use of genetic tests. It discourages insurers from asking insureds to undergo predictive diagnostic testing, except where the sum insured is above a high threshold (£500k) and only in respect to specific diseases (currently only Huntington's Disease). Precedents from regulations with similar impact, preventing insurers to use information also exist in other financial services areas, such as pensions, non-life and banking. (ABI, 2018)

Anti-selection and information asymmetry

Anti-selection (hazardous selection of risks that have a higher chance of loss than implied in the applicable insurance rate) is a well-known risk in life and health insurance. Anti-selection works differently for the two main forms of life insurance: mortality cover and longevity cover. For the former

(embedded in products such as critical illness cover and health insurance), the anti-selection occurs where the insured has more information on (expected) negative health than the insurer; while in the case of longevity risk (such as in annuity products), anti-selection occurs in case they have more information on (expected) positive health.

Generally, anti-selection occurs when there is asymmetric information between the parties involved in an insurance transaction. Historically, insurers were able to mitigate this risk through pooling of a large number of risks and through their ability to estimate mortality better than the individual, based on medical underwriting. However, improvements in both the accuracy, but also the accessibility of predictive genetic testing are threatening this advantage. One (of many) examples is the development of a new blood test to diagnose Alzheimer's disease. An individual testing positive for an increased risk of the disease could specifically look for that kind of product which would offer benefit payout in case of becoming ill with Alzheimer disease. Alternatively, an individual already aware that he/she is at an increased risk due to the occurrence of the disease in a close relative, might buy coverage before undergoing the Alzheimer's blood test. (GenRe, 2018)

With insurers generally prevented from demanding genetic test results from customers seeking cover, the information advantage could flip to the insured, and in consequence potentially increases anti-selection risk significantly. It might also increase insurers' losses and thus it would have other undesirable effects, including raised rates by the insurer to all insureds to balance costs. (Donnelly, 2011)

Early diagnosis: mismatch between pricing and risks

There is also the danger that science may 'run ahead' of changes in underwriting and pricing practices, in particular for life insurance as the ability to change the pricing is limited and the contract can run over several decades. Insurers may experience claims sooner than previously expected. As diagnostic advances continue, claims might be incurred that would never have arisen without them. These advances may ultimately make existing product features less valuable if diagnosis improves to the point of lowering treatment costs.

Another risk from earlier diagnosis is that if definitions used in policies are not specific enough, such as definitions of critical illness, contracts could become under pressure if they are out of touch with medical advances. For example, blood tests for cancer diagnosis are showing great promise in testing and could become the new gold standard for diagnosis. Patients who receive a diagnosis based on this but only have a minimum amount of cancer DNA present and not have yet developed a life-threatening disease, might still expect their CI cover to pay out. Current cancer claims definitions are based on traditional biopsy results and cancer staging, and might have to be adapted.

To keep up with medical progress, disease definitions will need to be updated in policy wording. However, the rapid progress in diagnostics and therapeutics make detailing the covered conditions definitions more challenging. Insurers risk being out of step with medicine if they are continually forced to repair gaps in policy wordings with subsidiary clauses. Furthermore, the ability to change definitions varies considerably across geographies. For example, in the UK, insurers have both the advantages and disadvantages of standardised definitions developed by the ABI, while in Canada, critical illness policies are typically non-cancellable – meaning the coverage can never be cancelled nor can terms or rates be adjusted. (GenRe, 2017).

In the case of liquid biopsy (see also deep-dive box on page 24) premature reliance on this method could lead to over-diagnosis, inadequate treatment and higher costs for health insurance. While liquid biopsy may positively impact on mortality improvement in the long run, direct-to-consumer liquid biopsy may first lead to information asymmetry and anti-selection. For CI policyholders, earlier detection could result in earlier claims if treatment is not effective.

2.1.2 Tailor-made offering and new types of products

Medical advances, of course, could also generate important new opportunities for insurers.

Impact on product development and distribution

Unless prevented by regulation on anti-discrimination, the market will push insurers to develop further tailor-made offerings. For insurers, this requires more specialised skills to understand diseases and identify their early indicators. Distribution may change, as the ability to generate relevant underwriting information is linked to specific channels, such as social media. Insurers will seek to develop the underwriting process to be simple and fast, without time-consuming and expensive medical testing, if enough other information is available.

More targeted, tailor-made offering

Technological advances could also help with risks, which are difficult to identify prior to accepting the risk. The classic example is mental health (see also in deep-dive box on page 16), for which no lab tests exist, and which can be difficult to detect at the

underwriting stage, but particularly impactful at the claims stage. However, by using other types of personal information, frequently already existing in social media, data analysis can provide indicators that can predict potential mental health issues. As an example, in a recent study, the Instagram feeds of study participants were analysed with machine learning and the researchers were able to identify markers for depression. Other emerging technologies – such as facial and voice recognition – will create new opportunities to mine data from social media. (GenRe, 2018). In the context of machine learning, the CRO Forum recently published a position paper on AI and Big Data Analytics governance (CRO Forum, 2019).

While anti-selection is, undoubtedly, a risk, as the predictive power of genetic testing improves, it might turn out to be beneficial. Both parties share a common interest: healthier and longer life. Consequently, insurers could encourage the development of personalised prevention, where an individual's DNA profile is used along with other

relevant information to more accurately predict risk and encourage preventative action to prevent or delay disease onset and severity.

Healthy lifestyle and good health condition can be constantly proven using wearable health devices. It would encourage insurers to decrease premiums for individuals who, for example exercise regularly. Another opportunity is to use regular health checks enabling effective treatment of illness at an early stage and thus significantly decrease costs from the insurer's perspective.

New type of products

As survival rates of critical illnesses continue to increase, the augmenting costs often associated with increased survival should lead to a greater appreciation of the value of critical illness insurance, potentially boosting a demand for the product. (GenRe, 2017)

Similarly, improved treatment, promising long-term



remission or cures, even for patients with advanced disease, could prompt a third generation of critical illness products, where insurers shift from providing broad compensation for all to delivering life enabling support, geared to individual health circumstances. (ABI, 2018)

2.2. Change of costs

As we have seen in the above sections, the pace of innovation in healthcare has escalated in recent years, bringing significantly improved chances of surviving diseases. While there are of course many

benefits from such innovation for society at large, this chapter reviews cost changes that the innovations challenge insurers with.

2.2.1 Healthcare costs likely to rise

It seems very unlikely that public systems will enlarge their scope substantially and consequently the role of private health insurance (PHI) will increase. In section 1.1 it was shown that in many countries public healthcare expenditures are rising constantly and that countries are under pressure simply to sustain their current level of protection.

Transition from mass pharmaceuticals to individual treatments (described in section 1.4) in combination with the aging population is a potential threat. The frequency and the severity of claims will increase i.a. due to aging of the population with chronic conditions. This development is likely to affect private health insurance, especially in countries where private health insurance duplicates or substitutes government schemes, like Ireland. (OECD/EU, 2018)

Another threat to the healthcare sector in general and private health insurance specifically, is the treatment

of diseases (refer to section 1.4). A sharp increase in individual treatment costs for rare diseases, driven by medical advances, is likely. By the middle of 2019, the costs of the world's most expensive drug, the gene therapy 'Glybera' was estimated to be around \$1.6m per patient. In May 2019, Novartis received the final approval for the US market for Zolgensma, a treatment for spinal muscular atrophy. In case of Zolgensma the costs per single treatment is likely to exceed \$2m. Still, Novartis stresses that the single treatment is supposed to replace a more expensive lifelong therapy. (APA, 2019) Even if pharmaceutical companies agree to accept payment by instalments, insurers will be severely challenged by costs of such treatments, even through the use of reinsurance. Furthermore, a risk-based premium calculation is almost impossible for treatment of rare diseases, leaving private and public health insurers in a difficult position. This threat particularly affects countries



where public healthcare is underdeveloped, and where private health insurance covers the full range of healthcare.

To absorb the mentioned above sources of increased costs premiums will have to rise at a faster pace than general inflation and likely, at a faster pace than the incomes of the ordinary insured. Alternatively, adjustment of benefits and adding exclusions to match the current premium level may be performed. Both options, premium increase or benefits limitation, will reduce either the attractiveness or affordability of private health insurance. Furthermore, existing clients will be dissatisfied and there will be a call for more consumer protection (as we have recently seen in Australia), resulting in price regulations and thus depriving the insurance industry of profit margins. (Parnell, 2019)

A further issue that affects private insurers is data. Driven by the steadily increasing amount of patient data available, insurers need to invest more in data capacity, data processing and data security, as insurers have a natural interest in getting as much data as possible to determine the most risk-based premiums. (Groves, 2013) Data protection issues, as described in section 2.1. may be slowing down this development.

In addition, this new data availability will lead to better informed customers who “will likely be pulling solutions rather than being pushed into services” and thus reversing the healthcare delivery model from a business-to-consumer (B2C) into a consumer-to-business (C2B) model. Innovative technologies, personalized treatments and even personalized drugs are a likely response to the changed customer behaviour. (Allen, 2019a)

2.2.2 Potential offsetting factors, opportunities

One possible solution to the problem of rising costs could be an increased cooperation with other players of the health system. In the United States for example, mergers between health insurance companies and pharmacy chains can be observed. If one of the two partners additionally also operates hospitals, the new company is able to provide the full range of healthcare to its customers and thereby achieve economies of scale and reduce administrative costs. One example is the US health insurer Cigna which acquired the pharmacy chain Express Scripts for \$52bn in December 2018. (Allen, 2019b)

Of course, not all medical advances mentioned in the first part of this paper, will lead to higher medical costs. Some, especially in the areas of prevention, screening and vaccination (e.g. ‘lab-on-a-chip’ and telemedicine) could lower costs through earlier detection and treatment of diseases. (EU HEALTH SUMMIT, 2018) Big data and artificial intelligence will play an important role in this development, since artificial intelligence can learn from the vast amounts of patient data and thereby help to make faster and more precise diagnoses. This could help to save costs and promises a more favourable disease course for patients. (DAS INVESTMENT, 2019)

In the latest industry analysis it is claimed that big data analysis has the potential to save in healthcare costs more than 300 billion USD per year just in the US. (Luo et al, 2016) Even if the potential should only be partially exploited, it represents a substantial cost reduction that insurers can ultimately pass on to their customers in the form of lower premiums or an expanded range of services.

Rising medical costs might lead to lower levels of government coverage, which in turn might generate an increased demand for private health insurance. The same applies if new medicines and treatments are covered by private health insurers earlier than by state systems. If customers rank private health as a more relevant spending priority in life, higher premiums could be perceived as acceptable.

2.3. Relevance of medical advances on casualty insurance

The societal shifts which are likely to accompany the considerable progress in medical research, robotic surgery systems and computer aided diagnostics, could impact the casualty insurance landscape in several ways. While the use of Artificial Intelligence decreases the dependence on medical experts, at the same time it raises the question of where liability for negligent decisions and deviations from the path recommended by a computer system is vested and is likely to increase patient expectations of treatment outcomes. System failures and new vulnerabilities due to cyber-attacks will be likely to lead to technology providers seeking insurance solutions covering the entire risk spectrum.

In medicine, considerable progress has been made in recent decades in most areas of research. Previous research has concentrated on the development of new forms of 'traditional' drugs and medical devices. This has changed considerably over time. Today, scientists are looking for 'smart' drugs, devices and computer systems that support diagnosis and therapy. Finally, decision making processes performed by humans may be replaced by automated diagnosis.

Robotic surgery systems and computer-aided diagnostic systems are examples of 'smart' products that are already available on the market. Robotic surgical systems are used to improve surgeons' skills and expand the use of 'keyhole' surgery (benefits including shorter hospital stays for patients and reduced risk of infection). Instead of moving instruments directly, the surgeon works by computer control, while robotic arms perform the movement of the surgical instruments ('joystick surgery').

In the past, radiology almost exclusively depended on the knowledge and analytical ability of the medical expert to read X-rays or computer tomography images. Nowadays Computer Aided Diagnostics (CADx) and Clinical Decision Support Systems (CDSS) support physicians in diagnosis and therapy. CADx systems are mainly used in radiology, while CCDS is available in all areas of clinical medicine. Both techniques use elements of artificial intelligence (AI) in medicine (refer to section 1.3).

Medical Malpractice

How will these developments affect professional

liability aspects? For the time being, liability remains with the doctor. With CADx systems, every radiologist is obliged to make his own findings for each image, even if he/she already has the results from the CADx system at hand. Even if these systems lead to fewer errors, according to current jurisdiction the physician is responsible for each error, not the system. A paradigm shift in liability distribution is still pending.

For physicians, the use of clinical decision support systems may be accompanied by legal consequences in the event of deviations from the path recommended by the computer system. Thus, physicians may increasingly avoid disagreeing with the inferences of a CDSS to avoid possible legal challenges at a later stage.

The consent procedure for patients must take into account all patient-relevant aspects of new technologies. In particular, if diagnosis and/or therapy have any experimental character, the specific provisions and issues must be discussed with the patient and documented in detail.

Medical Malpractice liability also becomes more complex, as a result of surgical robots documenting everything the surgeon does. It could be extremely helpful in case of questioning a physician's performance and filing charges, but could lead to further problems if all mistakes or deviations from standard practice are recorded by the technology.

Product liability

The use of new technologies in diagnosis and therapy has increased the demands upon education and training. This is particularly true in case of completely new and little researched therapeutic approaches. Technology providers may be affected if they do not deliver sufficient training and instructions for physicians working with the systems.

A failure of systems can also lead to product liability cases. Artificial intelligence system providers can be seen as having 'deep pockets' and therefore, may be at a greater risk of litigation. Additional premium will be needed to cover product liability and medical malpractice due to a higher degree of digitisation and accelerated technological developments.

Technology providers will seek insurance solutions that cover the entire risk spectrum, especially long-

term risks. New business areas for insurance will emerge, e.g. genetic medicine, telematics and robotics.

History has shown that technological progress does not necessarily improve patient safety and long-term benefits. (Sheets&Dimick, 2019) New technologies are likely to increase product liability risk initially, which must be recognised accordingly by insurers. Due to the long latency periods, cover concepts must also acknowledge it. Gene modification errors or biological reactions and resulting claims may only become apparent several years after treatment. Insurers will be challenged to understand the new risks, evaluate and price them appropriately, especially where there is no claims history. New causes of losses and new loss patterns will evolve over time. Underwriters, claims managers and technical experts in insurance who deal with the new technologies and risks will need to raise their profile.

If computer programs are used, e.g. for radiological diagnostics or radiotherapy, repeat errors could occur, which could magnify the extent of the loss. On the other hand, concepts such as personalized medicine can otherwise reduce the potential for

serial losses, as these are limited to individual patients or smaller patient groups.

Cyber liability

The issue of cyber liability touches all areas of technology and also affects clinical medicine as e-digitisation of medical devices and connection to apps, internet or other devices increases the possibility of various cyber security issues.

In recent years, hospitals have fallen victim to several cyber-attacks that have led to data breaches and disruption of medical services. A recent publication showed how external attackers used deep learning strategies to add or remove medical conditions (e.g. lung cancer) from computed tomography scans. (Mirsky, 2019) Both experienced radiologists and state-of-the-art deep learning Artificial intelligence are highly susceptible to this form of tampering. Such cyber-attacks represent a completely new dimension and potential for serial losses, as they challenge the whole concept of the electronic transmission of medical data.

2.4. Impact on society and the role of insurance

2.4.1 Healthcare affordability and efficiency

Can society continue to afford medical progress?

Medical progress is rightly celebrated as a significant beacon of hope in the fight against life-threatening diseases. But it is also a cost driver in the healthcare sector. Both factors lead to important questions: to what extent can society continue to afford the cost of new drugs and, ultimately, will hard decisions have to be made about who gets treated and what gets treated? Will the same innovations make it possible to reduce healthcare costs? Conversely, medical progress could increase the need for medical care – which would consequently elevate healthcare costs. Important choices need to be made by societies regarding how to integrate medical advances into standard healthcare, while at the same time providing for more cost-efficient healthcare system.

Insufficient accountability

Higher healthcare expenditure and the corresponding premium increases in recent years have been frequent topics in media and public debate (discussed also in section 1.1). A set of problems is obscured by various false incentives in the healthcare system – incentives that are themselves based on political conditions. One false incentive attracts particular attention: the insufficient cost accountability among healthcare providers and insured people, or insureds.

Some observers point to a lack of cost accountability on the part of insureds and healthcare providers. Defined in the literature as ‘moral hazard’, this phenomenon describes how insured parties behave differently when they know that their insurance

policy will cover their financial costs. In addition, insureds aim to maximise their personal benefit by using as many healthcare services as possible. The consequence of this behaviour is the charging of higher insurance premiums and is morally unfair towards public providers of health insurance. With respect to the healthcare system, insurance cover does not encourage policyholders to use available healthcare services sparingly. Insurance cover instead promotes more frequent high-risk behaviour and insufficient preventive medicine.

A lack of competition

In a market economy, competition has a disciplinary effect, helping to promote the most efficient supplier. However, the market mechanisms can only work to

a very limited extent, if at all, in a pay-as-you-go healthcare system that exhibits restricted freedom of contract and a non-transparent range of services.

Statutory regulations also restrict the choice of supplier and thus level of competition in the healthcare ecosystem. An alternative – freedom of contract at all levels – could possibly lead to health insurance providers becoming active purchasers of healthcare services and becoming more involved in pricing. More specifically, health insurance providers could potentially negotiate contracts more actively with provider associations, as well as individual service providers and medical device manufacturers. A health market exhibiting price-elastic demand would emerge.

2.4.2 Role of insurance

Medical progress strives to improve health and quality of life. This requires early detection of diseases, as well as delaying and alleviating symptoms and where possible, preventing or curing diseases altogether. As a result, medical advances increase life expectancy and quality of life (which was described in detail in section 1.1).

Furthermore it should be emphasized, that smoothening of the link between insured, physician and tech provider can strengthen effective medical advance tools and inventions. Both empowered patients and healthcare providers acting in a value-based health system can foster this positive development. Insurers should also be part of this change, stimulating patients and managing their co-operation with healthcare providers.

Insurance can help to encourage societal responsibility and generate public confidence. In this context, insurance can help to facilitate medical advances, for example through various uses of data from technologies, such as health sensors, wearables and trackers (more in section 1.2 and 1.3).

The insurance industry can foster medical progress by using medical advances in the context of insurance treaties, customer care and loss prevention strategies. It is advisable that insurance companies establish risk management strategies and conduct risk assessments of the health industry.

They should also acquire specialised underwriting knowledge in the fields of health, medical advances and new exposures – beyond the potential for business opportunities.

Insurers ought to be professional partners of their customers in evaluating liability-related health risks (compare with section 2.3) and developing appropriate health insurance policies.

As we have seen in the section 2.1, medical advances will likely lead to further tailoring of products and pricing. Importantly, such tailoring will include further differentiated pricing, based on better information on the expected future health of the insured. Insurance companies can enhance customer's knowledge and support them in mitigating risks, thereby improving individual's lives. Insurers can also actively promote awareness among their insureds of the importance of adopting a healthy lifestyle, by using awareness campaigns and reward healthy lifestyles with lower rates for insurance (e.g. by taking into account reports from wearable health devices).

2.4.3 Political choices

There are political risks associated with increased price differentiation. The premiums for higher risks are likely to increase and insurers could sometimes decide not to underwrite such risks at all. Therefore, insurance could become unavailable or unaffordable for parts of the population, potentially threatening solidarity among insureds. Legislators and regulators could consider this coverage gap problematic and decide to enforce availability for all through imposing mandatory insurance schemes based on solidarity.

Such schemes may include mandatory insurance and underwriting, as well as levelling of cost through premiums or taxes. In fact, such schemes, with varying degrees of enforced solidarity, already exist in several countries for health and pension insurance.

By contrast, individual mortality cover would be more difficult to include into a solidarity scheme because the need for such cover varies significantly across the population.

The extent to which legislators or regulators will intervene in the insurance market, may have a profound impact on the life and health insurance industry. But independently of the direction in which this legal and regulatory development may go, insurers will be accompanying and supporting society using the strengths of the insurance industry, such as its knowledge in assessing life and health risks, experience in management of these risks and resources to continue insuring individuals against significant life and health risks in the future.



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Insurers will be accompanying and supporting the society using strengths of the insurance industry.



Conclusion

The upcoming medical advances as discussed in this paper are likely to bring significant changes for individuals, insurance and society as a whole. The key drivers identified are the following three:

- Firstly, personalised medicine, allowing for a more tailored and effective medical journey. However, faster results and fewer side effects will come with higher costs per patient.
- Secondly, a general change in emphasis from diagnosis and treatment to prevention. The new possibilities for earlier action will help to avoid costs and patient burden later, although diagnosis and treatment are set to improve as well.
- Thirdly, the empowerment of patients such as via wearable devices will create new types of interactions between patients, medical professionals and insurers.

Still, these advances will not come without challenges. Costs in all areas – prevention, diagnosis and treatment – are likely to rise and trigger the question as to who should foot the bill. Health budgets are constrained everywhere leading potentially to some hard choices facing society. These issues will become more difficult to navigate as patient expectation around their right to access new treatments grows.

Medical advances are also likely to challenge the traditional model of insurers, as problems such as anti-selection risk become acute against a backdrop of improvements in genetic testing and the resulting information imbalance. Solving this with the interest of all insureds in mind will be complicated by regulations intent on preventing discrimination against individuals in the provision of life and health insurance.

The vast expansion in the quantity and specificity of medical and personal data will also increase the importance of data protection and privacy. Finally, the projected increasing reliance on AI raises separate and multiple issues, including the question of where liability might lie in the case of incorrect diagnosis by an algorithm.

How do these changes related to medical advances affect the insurance industry and its role? In general, insurers welcome and encourage medical progress. There is a fundamental and clear alignment of interest regarding people's well-being; and insurers support this through their products and services. Therefore, it can be expected that they will continue to develop products that are adapted to the needs of the evolving medical landscape. However, an appropriate sharing of the cost burden between the patient, the insurer and the state is needed to ensure that the system continues to be sustainable.

Improvements in technology will also create opportunities for insurers. For example, data mining techniques could help to assess risks that are difficult to identify prior to accepting insurance coverage. The demand for health insurance could also increase due to higher survival rates for certain conditions and the increasing costs associated with treatment of these illnesses. Furthermore, new types of products may be required for patients suffering from diseases that were not curable in the past. Given the complexities of medical advances, providing guidance to their customers/patients in relation to this subject will provide further opportunities for insurers to strengthen their positive relationship with clients.

In this rapidly changing and developing field that brings both risks and opportunities, insurers will have an important role to play.

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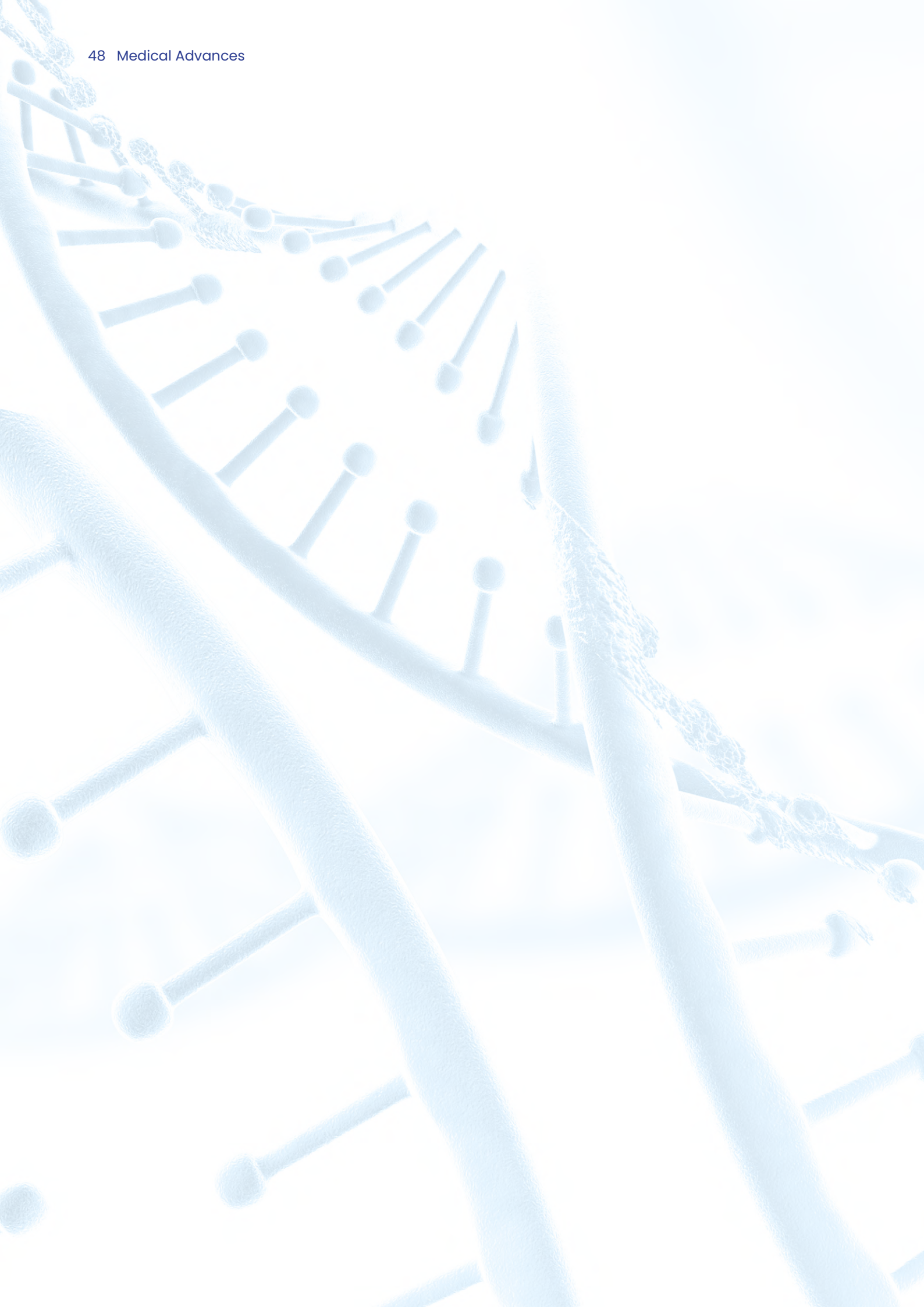
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Glossary

Term	Definition
Antibody	Antibodies (also called immunoglobins) are Y-shaped proteins found mainly on the surface of cells. They each binds to a specific antigen, similar to a lock and key mechanism.
Antigen	Antigens are molecules that can lead to an immune response if they are detected by a specific antibody.
Archaea	Archaea are single-celled microorganisms without a cell nucleus. They form one of the three domains of life, the other two being bacteria and eucarya.
B2C	Business to consumer means the communication and business relationships between entrepreneurs and private persons
Bacteroidetes	Bacteroidetes are gram-negative bacteria that in the human gut can ferment otherwise indigestible carbohydrates.
Biomarkers	This is a measurable indicator of some biological state or condition. Biomarkers are often measured and evaluated to examine normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention
Biopsy	A biopsy is an examination of tissue removed from a living body to discover the presence, cause, or extent of a disease.
Blood gases	Mainly oxygen and carbon dioxide.
C2B	The C2B, or consumer-to-business model, is when customers offer products or services to businesses
Capillary forces	Capillary forces denote the ability of a liquid to flow in narrow spaces without the assistance of, or even in opposition to, external forces like gravity.
Cardiac markers	Cardiac markers are substances used to evaluate heart function
Cardiac valves	The human heart has four valves, which control blood flow in and out of the chambers of the heart.
Cardiovascular events	refer to any incidents that may cause damage to the heart muscle.
CAR-T	Chimeric Antigen Receptor-T-cells are immune cells that have been genetically engineered to produce an artificial receptor. This receptor is engineered to give the T-cells the ability to target cancer-specific proteins.
CRISPR	Clusters of regularly interspaced palindromic repeats are specialized regions of DNA found in the genome of bacteria and archaea. These "CRISPR" sequences have been developed into a technique that allows for targeted gene editing; by using the CRISPR sequence as a guide together with a specific enzyme, "cas9", a specific section of the DNA helix can be targeted, cut out and replaced by a corrected sequence.
CDs, NCDs	Communicable diseases are e.g. HIV or hepatitis whereas non-communicable diseases include e.g. diabetes, Alzheimer's or cancer.
COPD	Chronic Obstructive Pulmonary Diseases is a lung disease characterized by chronic airway obstruction with limited airflow that interferes with normal breathing and is not completely reversible.
Coronary arteries	an artery supplying blood to the heart

Term	Definition
CRISPR	a family of DNA sequences found within the genomes of prokaryotic organisms such as bacteria and archaea. e.g. by defining the boundaries of a tumour, this would help in determining its size and treatment Clusters of regularly interspaced palindromic repeats are specialized regions of DNA found in the genome of bacteria and archaea. These "CRISPR" sequences have been developed into a technique that allows for targeted gene editing; by using the CRISPR sequence as a guide together with a specific enzyme, "cas9", a specific section of the DNA helix can be targeted, cut out and replaced by a corrected sequence.
Cytokine storm	Cytokine storm syndromes (CSS) are a group of disorders representing a variety of inflammatory causes. The primary symptoms of a cytokine storm are high fever, swelling and redness, extreme fatigue and nausea. In some cases the immune reaction may be fatal.
DNA	Deoxyribonucleic Acid is a molecule that contains the instructions an organism needs to develop, live and reproduce. These instructions are found inside every eukaryotic cell.
EHR	The Electronic Health Record is a digital version of a patient's paper chart, including information about medication, anamnesis, diagnoses and treatment.
Elastogram	medical imaging modality that maps the elastic properties and stiffness of soft tissue.
Enzymes	Enzymes are specialised proteins that enable or accelerate biochemical reactions in the body.
Epigenetic	This is the study of heritable phenotype changes that do not involve alterations in the DNA sequence
Firmicutes	Firmicutes are bacteria found in the human gut, most of which have gram-positive cell wall structure.
HGP	The Human Genome Project aims to identify both the genes and the entire sequence of DNA base pairs that make up the human genome.
HIV/AIDS	Human Immunodeficiency Virus infection and Acquired Immune Deficiency Syndrome
Immune checkpoints	Immune checkpoint is a kind of signal for regulating the antigen recognition of T cell receptor (TCR) in the process of immune response.
Inflammatory mediators	Inflammatory mediators are messengers that act e.g. on blood vessels or cells to promote an inflammatory response.
Invasive procedure	A procedure in which the body is penetrated or entered, e.g., by a tube, needle, or ionizing radiation.
Liver fibrosis	Liver fibrosis occurs when the healthy tissue of the liver becomes scarred and therefore cannot work as well. Fibrosis is the first stage of liver scarring
Lymphocytes	A type of immune cell that is made in the bone marrow and is found in the blood and in lymph tissue. The two main types of lymphocytes are B lymphocytes and T lymphocytes. B lymphocytes make antibodies, and T lymphocytes help kill tumour cells and help control immune responses.
Macrophages	A type of white blood cell that surrounds and kills microorganisms, removes dead cells, and stimulates the action of other immune system cells.
Malignancy	A malignancy is the tendency of a medical condition to become progressively worse, often used in reference to cancer.
Microbiota	Microbiota is the community of microorganisms found in and on all multicellular organisms. Microbiota includes bacteria, archaea, protists, fungi and viruses.
Microflora	Bacteria and other organisms that live inside the intestines. They help digest food. Vitamins such as biotin and vitamin K are made by microflora.
Minimum invasive surgery	Reduces postoperative pain, blood loss, speed recovery and lessen scarring by minimizing surgical incisions.
mRNA, micro RNA	MicroRNAs are small molecules involved in the regulation of gene expression.

Term	Definition
Nucleic acids	Nucleic acids are macromolecules that store genetic information and enable protein production. Nucleic acids include DNA and RNA.
OECD	Organization for Economic Co-operation and Development
Oligonucleotides	Oligonucleotides are short DNA or RNA molecules.
Ophthalmology	a branch of medicine and surgery which deals with the diagnosis and treatment of eye disorders.
Ophthalmoscopy	is a test that allows a health professional to see inside the fundus of the eye and other structures using an ophthalmoscope (or funduscope)
Otorhinolaryngology	a surgical subspecialty within medicine that deals with conditions of the ear, nose, and throat and related structures of the head and neck.
Pathogens	This is anything that can produce disease. A pathogen may also be referred to as an infectious agent, or simply a germ
Pharmacodynamic	Pharmacodynamics is the study of the biochemical and physiologic effects of drugs.
Pharmacogenetics	Pharmacogenetics is the study of inherited genetic differences in drug metabolic pathways or chemical reactions occurring within a cell.
Pharmacokinetic	Pharmacokinetic refers to the movement of drug into, through, and out of the body, its absorption, bioavailability, distribution, metabolism, and excretion.
PHI	Private health insurance refers to health insurance plans marketed by the private health insurance industry, as opposed to government-run insurance programs.
PRS	The polygenetic risk score is a number based on variations in multiple genetic locations and their associated weights to estimate the genetic component of a given disease or trait.
Prevalence	Prevalence is a term used in epidemiology. It denotes the proportion of a population with a particular condition at a specific point in time (point prevalence) or over a specified period of time (period prevalence).
Region of interest	e.g. by defining the boundaries of a tumour, this would help in determining its size and treatment
ROI	The region of interest references the part of a tissue or organ that needs to be analysed in order to give a diagnosis.
Signal-to-noise ratio	Is a measurement to compare the level of a desired signal to the level of background noise
SNP	Single nucleotide polymorphism are the most common type of genetic variation among people. Each SNP represents a difference in a single DNA building block, called a nucleotide.
Single nucleotide polymorphisms	the most common type of genetic variation among people. Each SNP represents a difference in a single DNA building block, called a nucleotide.
T-Cell	T-cells are specific cells of the immune system which develop in the thymus gland.
Type-2-diabetes	Type 2 diabetes (T2D), formerly known as adult-onset diabetes, is a form of diabetes that is characterized by high blood sugar, insulin resistance, and relative lack of insulin. In contrary, Type 1 diabetes (T1D), also known as juvenile diabetes, is a form of diabetes in which very little or no insulin is produced by the pancreas.
Viral vectors	Viral vectors are tools commonly used by molecular biologists to deliver genetic material into cells. This process can be performed inside a living organism (in vivo) or in cell culture (in vitro).
WHD	Wearable Health Devices
WSI	Whole Slide Imaging refers to scanning a complete microscope slide and creating a high-resolution digital file.

