n=1, a new paradigm

The value and challenges of precision medicine in the Netherlands

Gupta Strategists

Discussion document

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About this study

n=1, a new paradigm is a study on the value of precision medicine in the Netherlands, and the actions required to realize this potential. This paper is intended as a discussion document for a broad audience and serves to:

- spark discussion on how to accelerate precision medicine in the Netherlands;
- inspire the initiation of projects that help break down the barriers we experience.

The study was commissioned by the Personalized Healthcare Catalyst (PHC) Alliance and was conducted by Gupta Strategists.

The PHC Catalyst Alliance was founded in 2018 to bring together individuals driven to create a receptive system for precision medicine. By combining the knowledge of patient organizations, physicians, scientists, research organizations, health insurers, industry and data specialists, it is possible to think big and across disciplinary boundaries. The PHC Catalyst Alliance invites experts who are committed to accelerate personalized healthcare in the Netherlands to take part in the initiative.

Gupta Strategists is a strategy consulting firm focused entirely on healthcare. We provide independent, expert advice in all subsectors of the healthcare industry – from hospitals and insurance companies to pharmaceutical companies and governments. We transform complex issues into innovative ideas and practical solutions, using our expertise to drive impact. Next to our project work, we regularly publish independent research to provide socially relevant insights and highlight important trends. For more information on our work, visit our website: www.gupta-strategists.nl

Acknowledgements

We would like to thank the PHC Catalyst Alliance members and other experts we interviewed (see Appendix 4) for their thought-provoking input and discussions. The content and conclusions of this study have substantially matured because of their input.

This study was commissioned by the PHC Catalyst Alliance, with financial support of Roche Nederland BV.

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Foreword

On behalf of the Personalized Healthcare (PHC) Catalyst Alliance, I very much welcome this white paper. It carries the title n=1, but we need n=many to accelerate the transition to the new world of healthcare, driven by the possibilities offered by advances in medical and technological science. For this, we need many things in place: we need to build on mutual trust and understanding of the new, holistic value propositions. This report sparks the right discussions by offering us an excellent introduction on how value can be created and what enablers and barriers need to be addressed. I hope and expect that this work will stimulate the dialogue between all parties involved and that we as PHC Catalyst in this way can play a role in making Personalized Healthcare and its benefits a reality in daily clinical practice sooner rather than later.

Kind regards,
Paul Iske
Chairman PHC Catalyst

For more information on the PHC Catalyst Alliance, please visit www.phc-catalyst.org.

Executive summary

Personalization is in our nature. Addressing and treating people based on their personal characteristics is a deep human social need. Over the past century, personalization has given way to economy for the masses. One-size-fits-all strategies in food, apparel, transportation, tourism and services have flourished for decades.

But times are changing. Personalization is on its way back – and we live better lives because of it. It is happening not only in marketing: evidence of this movement can be found in almost all industries, from clothing manufacturing to banking services, tourism and recruitment. And customers like it. In fact, most consumers even expect it.[1] We buy products that better match our needs, we find better jobs (and employees), have better dates, vacations and banking services and discover new movies and music that we wouldn't want to miss.

Healthcare is no exception. Our health is one of our greatest assets in life. When we feel sick, in the most vulnerable moments of our lives, our needs are unique and deeply personal. We want healthcare to perfectly match our unique clinical and molecular situation. Mass medicine will not do that. It is therefore not surprising that a more personalized approach to health and care is a central theme in long-term policy goals.

Precision medicine, as the personalized approach to healthcare is called, is steadily bridging the gap between individual disease and treatment approach, leading to better outcomes and better patient experiences. Leading scientists and healthcare professionals are thrilled to see what precision medicine will bring to the treatment of individual patients and to society as a whole. In breast cancer, for example, the care has gradually become more and more tailored to the individual biology and needs of the patients. Where patients in the 1980s all received the same treatment regimens, we now have biomarkers and genetic tests to identify tumor subtypes. In addition, chemotherapy dosage schemes have become more personalized, surgery has become more precise and even the desired treatment outcome goals have become more personalized based on individual characteristics and needs. These advances in breast cancer care personalization have led to improved survival, fewer side effects of treatment and higher quality of life for patients living with breast cancer. Although experts acknowledge that personalization in medicine is unstoppable, many of them see barriers that slow down or limit its impact.

In this paper we aim to estimate the potential value of precision medicine in the Netherlands and lay out what we collectively need to do now in order to accelerate its advance.

We use the P4 framework to pin down the concept of precision medicine and to measure its advance

Precision medicine, as is often true for emerging paradigms, is a broad concept with different definitions being used by different experts. Therefore, before setting off to estimate the value of precision medicine, we needed to anchor the concept. To do so, we used the P4 framework.

The P4 framework was originally proposed by Leroy Hood to describe the way precision medicine makes it possible to provide care that is preventive, predictive, personalized and participatory. We developed a scoring system to evaluate the level of precision medicine using these four elements as a basis. With this method, we scored the level of precision medicine for a panel of 60 diseases that is routinely used by the Dutch government to evaluate the current and future state of the Dutch healthcare system. These diseases account for ~60% of the total disease burden in the Netherlands in 2017. Based on desk research, we scored each disease on each of the four Ps and validated the scores with medical doctors and experts in the field per disease area.

Within the current 'state of precision medicine', we see significant variations between diseases. Broadly speaking, we distinguish 3 groups of diseases:

1. **Leaders:** forming the frontline of precision medicine in the Netherlands and consisting mainly of oncologic diseases and several infectious diseases like HIV/AIDS.
2. **Followers:** representing the average level of precision medicine in the Netherlands and containing diseases such as stroke, coronary heart disease, diabetes and COPD.
3. **Laggards:** being behind on precision medicine and consisting of psychiatric disorders, neck and back pain, and osteoarthritis.

The ever-shifting technological frontier will stimulate the advance of precision medicine

The trend towards precision medicine is likely to accelerate further thanks to favorable socio-economic and technological movements. We identified what types of cutting-edge diagnostic and treatment possibilities are currently making the transition to clinical practice for the different diseases. We then rescored each of the diseases to see how these advances will shift them along the precision medicine continuum.

We found that by moving from current standard practices to the current cutting-edge level of diagnosis and care, there is significant potential to advance the level of precision medicine. It is interesting to observe that progress is expected in all disease groups. Public focus of precision medicine is often on the leaders, but it is not only the field of oncology that brings advances: we also expect significant progress in psychiatric, cardiovascular and musculoskeletal diseases.

A further advance in precision medicine can result in 3 to 7 additional healthy life years

If a clinician from 1990 was time warped forward, she would hardly recognize the treatment frontier today. Compared to three decades ago, more precise diagnostic, surgical, radio- and pharmacotherapeutic options have become available and are being routinely used. Such technological advances have consequently led to an advance in precision medicine. For several diseases, ranging from oncologic to respiratory and cardiovascular conditions, we have reconstructed their evolution in the last decades. We scored the level of precision in 1990 and compared it to the current level of precision and, using publicly available health data, we assessed the changes in burden per patient in the Netherlands during the same period. We found a clear correlation between increasing level of precision and a decreasing burden of disease, for each of the diseases.

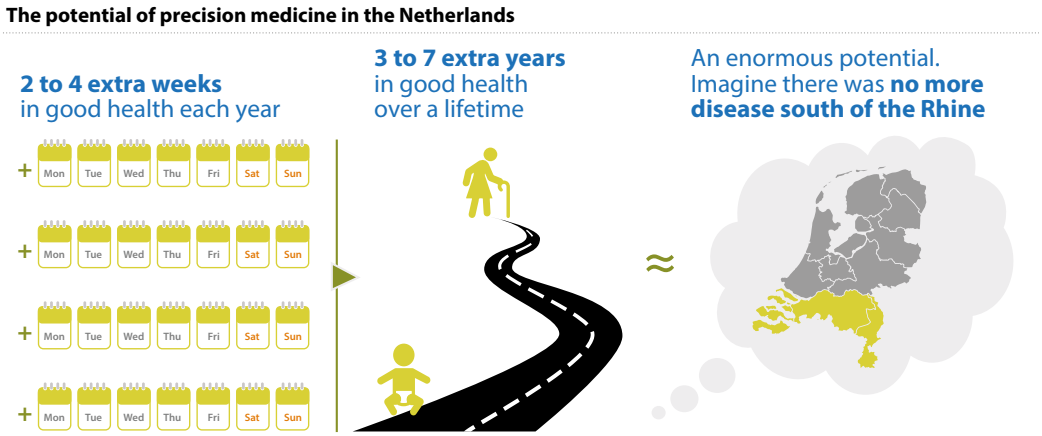


Figure 1: The potential of precision medicine in the Netherlands

Based on extrapolation of these insights, we estimate that it would be possible to add 2 to 4 weeks in good health each year for every Dutch citizen, decreasing the total burden of disease by 15-30% (Figure 1). Put differently, it would also mean that the average person could expect to live an additional 3 to 7 years in good health.

The potential is enormous. It has the same impact on a national level as if there would be no more disease burden at all south of the river Rhine. This potential is so big because precision medicine is likely to contribute to improvements in all disease classes, not only in oncologic diseases, the current leaders. The impact of advances in precision medicine in psychiatric disorders (current laggards) is at least as high.

To realize the full value potential of precision medicine, it's time to take action

Despite the prospect of further scientific breakthroughs and the growing momentum behind the precision medicine movement internationally and in the Netherlands, there remain substantial barriers to its broad implementation in medical practice. These barriers, and the actions required to overcome them, differ by stakeholder group – but we believe that concerted actions are needed to overcome them. If we wish to realize the value potential that precision medicine holds, it's time to take action collectively (Figure 2).

It's time to accelerate precision medicine


It's time to... generate evidence for the individual rather than the average


It's time to... adopt data collection into clinical practice


It's time to... combine and use the data we collect


It's time to... translate data into clinical decision support


It's time to... engage citizens in their health and care


It's time to... tweak the economics of precision medicine

Figure 2: It's time to accelerate precision medicine

It's time to generate evidence for the individual, rather than the average

In global evidence-based medicine, there is much attention for the average patient, but little attention for the individual. In this paper, we demonstrate a high-level assessment of the value potential of precision medicine. However, to convince clinicians a more robust evidence base is needed for the approach of precision medicine, i.e. using detailed characteristics to provide optimal and individualized treatment in various clinical settings.

We believe that improving evidence generation and evaluation to demonstrate the added value of precision medicine is a top priority. There is a need to build and support a strategic movement aimed at proving the value of the approach of precision medicine. The government should provide regulatory frameworks for what agile learning should look like to stimulate digital innovation. Funding agencies should develop a programmatic research agenda that is focused on proving the value of precision medicine and should ensure sufficient projects are funded that are in line with this agenda. Regulators should explore alternative approaches to evidence evaluation and regulation, including real-world evidence, early access and dynamic evaluation.

It's time to adopt data collection into clinical practice

For specific diseases, the shift towards precision medicine has already shown promise, resulting in more preventive, predictive, personalized and participatory treatments of individual patients. However, for a broader use of the approach, a continued pipeline of new biomarkers, diagnostics and treatment options is needed. This requires generating broader and deeper data in routine healthcare to be used for research. The use of genomic and other deep molecular data of individuals is still seen as exceptional rather than foundational. In many diseases, and in earlier phases of disease, data collection required to drive the precision medicine approach is still inadequate.

To overcome these challenges, the government should accept the temporarily high costs for deep data acquisition and its use in routine health and care. Researchers, funding agencies and policy makers should prioritize diseases that have a high burden. Payers and the government should work together to incentivize early diagnosis and a multi-omics approach to understanding an individual's disease.

It's time to combine and use the data we collect

The path to precision medicine requires access to large-scale, detailed, and highly integrated patient data to advance our understanding of the genomic, molecular, phenotypic, clinical, and digital signatures of disease. Precision medicine requires not only big data but data from different sources. Many obstacles remain that stand in the way of this requirement in the Netherlands. We don't always collect the right data, the data we do collect is often not structured appropriately for sharing, and there is a lack of interoperability between databases and electronic health record (EHR) systems. Additionally, data sharing and analytics is not a strategic priority for most providers, due to a lack of financial incentives. Finally, concerns about access, privacy and security prevail in the absence of clear direction and incentives to prioritize the safe collection of data.

To overcome these challenges, advocacy groups should encourage the government and payers to set guidelines for collecting health, care and outcome measures in a systematic fashion, and ensure they are adopted. Funding agencies and insurers should encourage the broad adoption by providers and scientists of the FAIR principles (while of course balancing labor intensity and costs with the intended use case). Providers should be financially incentivized to rethink the infrastructure of data analytics, turn data science into a strategic priority and ensure there is a legal basis for the use and reuse of patients' individual data for precision medicine purposes that is in line with privacy regulations.

It's time to translate data into clinical decision support

The key to achieve impact with precision medicine is to apply newly generated insights into health and disease by combining medicine with big data and artificial intelligence (AI). Insights should be incorporated into guidelines, tailored protocols and decision support systems. Digital decision support is feared more often than it is anticipated, due to a lack of understanding, value perception and fear of administrative burden amongst care providers, even though algorithms have the potential to make solid predictions based on many factors that are too complex for the human mind. Moreover, providers and IT firms lack strong incentives to make the necessary investments a strategic priority. A

fragmented and minimally regulated market of health applications and analytic scripts further limits trust building and adoption by the masses. Regulation of decision support algorithms similar to, for example, medical devices is needed to guarantee responsible and safe application.

To overcome these challenges, providers and medical specialist associations should train medical workers, motivate them and let them experience what value precision medicine can have. The government and healthcare institutions should prioritize and coordinate IT on their respective investment agendas. Together with regulators, the government should also translate the learnings of clinical application of decision support systems into a regulatory framework.

It's time to engage citizens in their health and care

For discovery in precision medicine to be accelerated and services based on it to be adopted, citizens – not just patients – must be involved.[2] While it is important for some aspects of the science to have data on individuals in the clinical context, it is also important to understand the continuum of health and disease on the basis of data of many people in diverse communities. Data from self-tracking devices, on the environment and other non-clinical aspects of people's lives will help to complete the picture essential for precision medicine. We consider the lack of trust between stakeholders a major barrier towards advancing this movement: citizens do not trust payers and providers with their data, and providers do not trust patients with data on quality and outcomes. Furthermore, individuals do not experience enough incentives to engage in their own health and care. Finally, professionals do not see a clear need to truly engage their patients: there is no substantive evidence base for participants' role in precision medicine.

To overcome these challenges, providers, insurers and suppliers should demonstrate trustworthiness and work with patient advocacy groups to systematically share and publish outcomes that matter. The government and insurers should not only stimulate healthy behavior (such as much more rigorous anti-smoking policies) but also incentivize data and knowledge sharing. The government and funding agencies should promote research that studies the role of participant engagement.

It's time to tweak the economics of precision medicine

The economics of precision medicine is one of the most important drivers of its success. A recent review on the cost-effectiveness of precision medicine showed that the majority of studies concluded that the precision medicine intervention was at least cost-effective compared to usual care.[3] Nevertheless, many obstacles stand in the way of full-blown implementation of the precision medicine approach. First, the importance of cost-effectiveness is growing, but a wide variety of outcome measures makes comparisons difficult. Second, there are many imbalances in (financial) risk versus reward. For example, the continuation of ineffective treatment is incentivized, while the adoption of new diagnostics and IT investments is disincentivized. Redistributing financial rewards may not be beneficial to all involved parties, but will be beneficial to the system as a whole. These efforts should therefore be led by those responsible for the health care system. Third, static reimbursement decisions based on averages instead of individual differences and pricing

hamper adoption of innovations, particularly when upfront costs are high. Finally, maintaining competitive market dynamics is increasingly difficult in a market where the indications for treatments become ever smaller.

To overcome these challenges, the government and funding agencies should encourage research on cost-effectiveness and unify outcome measures for policy purposes. Outcome measures should be simple and broadly adopted – not just in research, but also in daily practice. Payers, regulators and the government should not wait for broad policy frameworks, but rather tweak risk-reward imbalances on a case-by-case basis. The government should experiment with more dynamic pricing models when granting market access to new innovations. Regulators should revise IP regulations on very costly individualized treatments. Commercial and semi-commercial parties should rejuvenate their business model to make technology work for them and not against them.

Call to action

Although there are many challenges ahead, we also demonstrate in this paper that for each barrier there are hopeful initiatives that pave the way. Small countries may be well positioned to take the lead and the Netherlands with its knowledge-based economy could drive the acceleration of the precision medicine movement. We believe that we don't need to invent the wheel to move forward, we just need to fit the wheels we already have to the right vehicle and put them to good use for the entire system. Now is the right time for accelerating action and all parties should get involved: patients, payors, doctors, government, medical and data scientists, regulators, medtech, pharma and IT companies can all contribute.

Broadly speaking, we see two courses of actions that should be taken in parallel. The first is to engage individuals and organizations and put the acceleration of personalized healthcare on the national agenda. The second is to identify and prioritize specific projects that can help break down the barriers we experience in the system and strenghten the enablers. By collectively contributing to the success of these projects, we can lead the way to a receptive environment for precision medicine.

This paper serves to spark discussions on how to accelerate precision medicine in the Netherlands and to inspire the initiation of projects that actually break down the barriers we need to overcome for precision medicine to reach its potential.

1 The era of precision medicine is here

In this chapter, we show that across society, times are changing: whereas for many decades and across many industries there has been a trend towards one-size-fits-all strategies, the era of personalization has now arrived. This shift, driven by better data insights and better technology, has also arrived in healthcare in the form of 'precision medicine'. An analysis of major underlying trends tells us that precision medicine is here to stay. In this paper we aim to explore what the potential value of precision medicine could be and lay out what we collectively need to do now in order to accelerate precision medicine.

Personalization is the new normal in our society

Personalization is in our nature. Addressing and treating people based on their personal characteristics is a deep human social behavior. No matter how innate this behavior is to humans, personalization has been incompatible with the ever-growing economies of scale that characterize the globalization of our economies. Products and services have become available to the masses by depersonalization. One-size-fits-all strategies in food, apparel, transportation, tourism and services have flourished for decades.

But times are changing. Personalization is on its way back. And it's on steroids. Data-driven personalization is bringing back the experience that consumers desire. Large tech companies have pioneered personalized marketing, where customers receive personalized ads or offerings based on their personal profile. This has rapidly become the new standard. And customers like it. In fact, most consumers even expect it. Research shows that the majority welcomes companies accessing relevant data about them, anticipating their needs and providing specialized offers only to them.[1] This personalization, driven by data insights and technological advances, is happening not only in marketing, but is rapidly spreading to all parts of our lives. It can now be found in almost all industries, from clothing manufacturing to banking services, tourism and recruitment. We buy products that better match our needs, we find better jobs (and employees), have better vacations, find romance and discover new movies and music that we wouldn't want to miss. Data-driven personalization gives customers massive amounts of value. We have better lives because of it.

Personalization also characterizes the new era of healthcare innovation

Healthcare is no exception. Our health is one of our greatest assets. When we feel sick, in the most vulnerable moments of our lives, our needs are unique and deeply personal. We want healthcare to perfectly match our unique situation. Mass medicine will not do that. Data-driven healthcare is bridging the gap between individual disease and treatment approach, leading to better outcomes and better patient experiences. It is therefore not surprising that a more personalized approach to health and care is a central theme in long-term policy goals.[4] Such a personalized approach in medicine is called *precision medicine*.[5]

Precision medicine, sometimes also referred to as *personalized medicine*, tailors disease prevention and treatment to the characteristics of each individual.[6] Precision medicine is not merely the application of high-tech innovations like gene therapy. Rather, it is a different *approach* to medicine that uses environmental and behavioral data of an individual to develop tailored prevention and/or treatment plans. By doing so, over- and

undertreatment is prevented and the outcome and cost-effectiveness of care may improve. Therefore, personalization in healthcare is not contrary to solidarity; it may actually safeguard it. In short, the goal of precision medicine is to give each individual the right treatment at the right time.

Precision medicine is not new. In fact, the concept has been around since the 1960s.[7] Since then, scientific and technological advances have continuously pushed this field forward. In breast cancer, for example, the care has gradually become more and more tailored to the individual's characteristics and needs. Where patients in the 1980s all received the same treatment regimens, we have gradually learned that there are many variations in breast cancer that require different treatment strategies. We have implemented a national screening program for secondary breast cancer prevention, biomarkers and genetics have identified specific treatment targets, chemotherapy dosage schemes have become more personalized, surgery has become more precise and even the desired treatment outcome goals have become tailored to an individual's preferences. These advances in breast cancer care personalization have led to improved survival, fewer side effects of treatment and higher quality of life for patients living with breast cancer.

Similar to other areas of society, until recently advances in medicine were seen more in terms of *medicine-for-the-average* than in terms of precision medicine. However, we believe that the emergence and confluence of societal trends, advances in biomedical technology and the data science revolution all indicate that the era of precision medicine has now arrived (Figure 3).

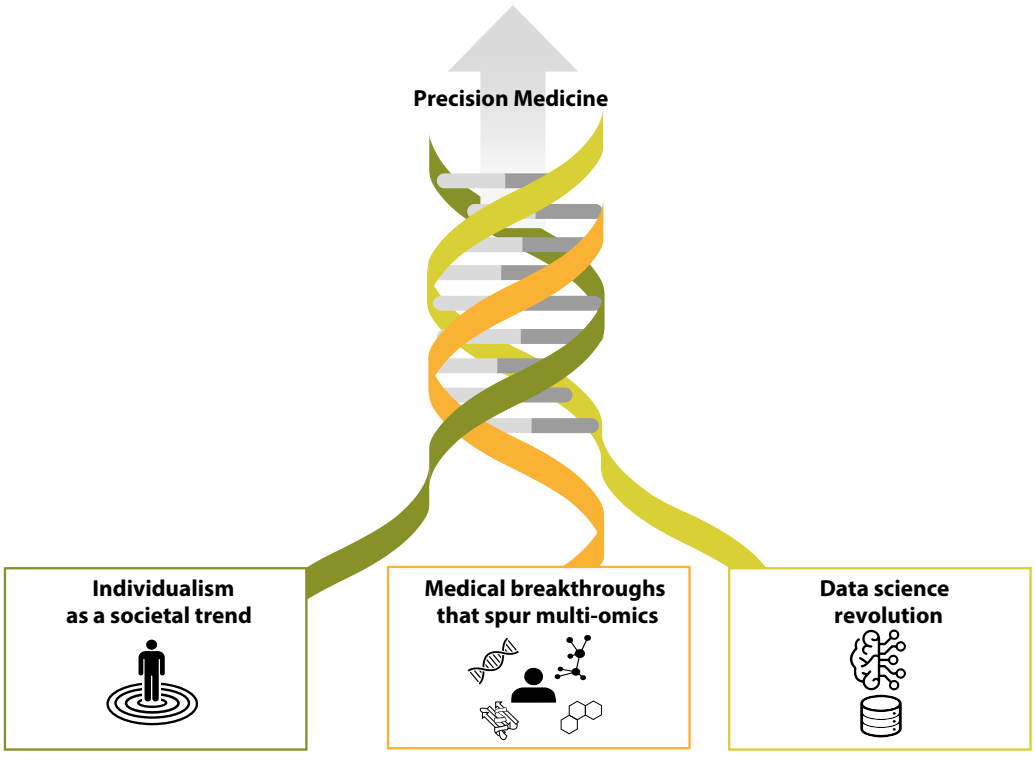


Figure 3: Emergence and confluence of trends that will help accelerate the field of precision medicine in the upcoming years

First, the overall trend in Dutch society is that we see ourselves more and more as individuals, pursuing individual goals and expecting to be treated as individuals. This individualization in people's attitude impacts the expectations they have of their health and care. In addition, the advances in data-driven personalization in other parts of society, as mentioned earlier, will create acceptance of personal data application in personalized medicine.

Secondly, scientific and technological advances now make deep characterization of individuals widely, rapidly and economically available. As an illustration, the sequencing of the first human genome took thirteen years and 2.4 billion euro, while it can now be done in a single day for less than a thousand euro, with prices expected to drop even further in the coming years.[8] Besides genomics, the fields of proteomics, metabolomics, transcriptomics and microbiomics are adding new layers to the characterization of individuals and costing increasingly less time and money.[9] In the relatively new field of digitomics, scientists are exploring the added value of an individual's digital signature. Wearables, sensor technologies and smart devices have opened possibilities to effortlessly measure health and behavior characteristics that were otherwise unmeasurable at low costs. These technologies allow us to have a much deeper profile of individuals that is required for better understanding and treatment.

The third trend is the rise of datascience and data-technology, fueling the understanding and application of the multi-*omics*. The large amounts of data generated on growing numbers of individuals can now be collected, stored and exchanged in larger quantities and in a secure and affordable manner. This opens many possibilities to build a knowledge base of individuals and the population at large. The computational revolution of deep learning and other types of artificial intelligence (AI) is extending beyond the computer world and allows us to better interpret personal data. These advances will spur the fields of systems biology and systems medicine that focus on better understanding the interconnected pathways that lead to specific health conditions,[10] with the goal of identifying new ways to diagnose, monitor, treat or - even better - prevent diseases.

Leading scientists and healthcare professionals are thrilled to see what precision medicine will bring to the treatment of individual patients and to society as a whole. Although experts acknowledge that the personalization in medicine is unstoppable, many of them see barriers that slow down or limit its impact.

In this paper we aim to explore what the potential value of precision medicine could be and lay out what we collectively need to do now in order to accelerate precision medicine.

2 Precision medicine may add 3 to 7 healthy life years

In this chapter, we estimate the value of the continuous advance of precision medicine in terms of a reduction in burden of disease. To do so, we measured the historic, current and 'cutting-edge' state of precision using a scoring system based on the four components of the P4-framework originally published by Leroy Hood: pprevention, prediction, personalization and participation. We find that by moving from current standard practices to the current cutting-edge level of care, precision medicine can advance significantly in the near future, and estimate that this advance can help regain ~3 to 7 years of life that we now lose to illness or premature death.

We use the P4 framework to pin down the concept of precision medicine and to measure its advance

Precision medicine, as is often true for emerging paradigms, is a broad concept with different definitions being used by different experts. Therefore, before setting off to assess the value of precision medicine, we needed to anchor the concept. To do so, we used the P4 framework.

The P4 framework was originally proposed by Leroy Hood to describe the way precision medicine makes it possible to provide care that is preventive, predictive, personalized and participatory.[11,12]A better understanding of disease mechanisms and technological advances transforms the traditional reactive discipline of medicine into a proactive discipline: instead of treating diseases the goal is to maintain health.

We adopted the P4 framework to assess the level of precision for different diseases. We developed a scoring system in which we assigned a score ranging from 1 (lowest) to 4 (highest) to each of the four Ps based on desk research, validated during conversations with experts in the field per disease area. A disease that scores 1 point on all four dimensions is considered to have a one-size-fits-all approach, while a disease that scores 4 points on all dimensions is considered to have achieved the highest level of precision medicine.

We used predefined scoring criteria to determine the appropriate score on each P. Frame 1 outlines the scoring methodology. In Appendix 1 we provide more detail on the scoring criteria as well as some examples of diseases and corresponding scores. In Appendix 2, we provide the scores that we assigned to each of the diseases.

We used the P4 metrics to approximate the level of precision for a panel of 62 diseases that are used for the monitoring of the Dutch state of health.[13] This panel of diseases is based on a selection of disease characteristics like burden of disease, costs and prevalence. Together, the diseases we assessed account for 62% of the total burden of disease in the Netherlands in 2017.

By quantifying the level of precision of different diseases, we are able to answer the following questions:

- What is the current level of precision medicine for different diseases?
- What level of precision medicine could different diseases reach if cutting-edge developments were to be broadly adopted?
- What is the potential impact of these increased levels of precision medicine on burden of disease?

This admittedly crude but simple and intuitive approach also allows us to compare across diseases and to highlight, within disease, which P(s) have the biggest potential to reduce burden of disease.

Frame 1:

How we scored the level of precision

To each disease we assigned a precision medicine score (PM score) reflecting the level of precision medicine of the treatment approach. The PM score is a composite score, based on the four Ps (preventive, predictive, personalized and participatory) that underpin the definition we use for precision medicine. Of course, advances in one of these apects may drive advances on other Ps, but in the end all four Ps are needed for true precision medicine.

We determined the PM score for a disease in two steps:

1. We assigned a score for each of the four Ps indicating the level of precision on that particular dimension. We used predefined scoring criteria to assign the score; ranging from 1 (lowest) to 4 (highest). We did not differentiate in the relative importance of the different Ps, because there is no basis to do so and the impact would be small. Table 1 shows a summary of the scoring criteria; a full description can be found in Appendix 1.
2. We calculated the average of the scores given on the four Ps to determine the PM score.

	Preventive	**Predictive**	**Personalized**	**Participatory**
	In which phase of the disease can we intervene?	*How well can we predict the individual response to treatment?*	*How well is the treatment tailored to individual patient?*	*How much is the patier involved in diagnosis and treatment?*
4	Prevention	High predictability	Unique medicine	Patient is co-leader
3	Non-symptomatic	Better predictability	Individualized medicine	Patient is involved
2	Symptomatic	Some predictability	Stratified medicine	Patient is consulted
1	Multimorbidic	Low predictability	Massmedicine	Patient undergoes

Table 1: Summary of the scoring criteria used to determine the level of precision medicine on each of the four Ps (preventive, predictive, personalized and participatory) of the P4 framework. The PM score is the average of the four individual scores.

Although scoring the diseases on the four Ps is by no means an exact science, we developed the following process of scoring and validating the scores:

- Medical master students and clinicians assigned the initial scores based on desk research (scientific literature, guidelines, published expert opinions);
- Medically trained Gupta Strategists team members reviewed the scores;
- Scientists, physicians and other experts were consulted to validate the overall findings.

We scored every disease twice:

1. **Current standard:** representing the level of precision reached considering current standard practice;
2. **Cutting-edge:** representing the level of precision that would be reached if cutting-edge technology/care, that is currently already available to at least some patients, would become standard practice.

The level of precision varies greatly: some diseases lead the way, while others lag behind

Figure 4 shows the current state of precision medicine in the Netherlands in relation to burden of disease. It reveals a mixed picture with significant variation in the level of precision medicine between diseases. We distinguish three main groups based on their position in the precision medicine continuum: leaders, followers and laggards.

Current level of precision medicine versus total burden of disease in the Netherlands
[PM score (x-axis), total DALY in the Netherlands in 2017 (y-axis) and prevalence (size)]

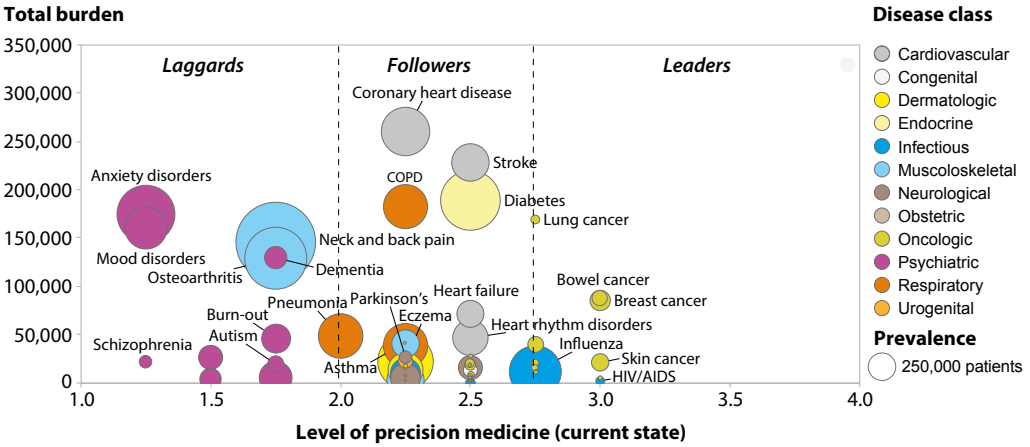


Figure 4: The current precision medicine landscape in the Netherlands. DALY = disability adjusted life years, a measure for burden of disease (see Appendix 3 for details).

Leaders form the frontline of precision medicine in the Netherlands and consists mainly of oncologic diseases, complemented with several infectious diseases like HIV/AIDS. Together, these diseases account for 17% of the burden of diseases we analyzed. With respect the four Ps, this group is characterized mainly by organized prevention programs and personalized treatment possibilities. Prevention and early detection are well organized and developed. For example, in the Netherlands all women between 50 and 75 years are biannually invited to participate in the mammography-based breast cancer screening, allowing pre-symptomatic tumor detection.[14] Also with bowel cancer, skin cancer, prostate cancer, cervical cancer and HIV/AIDS primary and secondary prevention are promoted through an organized program,[15, 16] awareness campaigns[17] or regular checks by the general practitioner.[18, 19, 20] Multiple factors classify patients into specific subgroups to guide clinical decisions. Again looking at breast cancer, individualized characteristics like hormone receptor and HER2 status determine whether endocrine therapy or HER2-targeted therapy are systemic treatment options.[21] For other cancer types, such as melanoma and lung cancer, treatment depends on the presence of mutations (BRAF, EGFR) or expression of proteins (PD-L1).[22] Patients with oncologic diseases are highly engaged, willing to share almost any data that could improve the often grim outlook on the course of the disease.

Followers represent the average level of precision medicine in the Netherlands and contain diseases such as stroke, coronary heart disease, and many chronic diseases like diabetes and COPD. Together, these diseases account for 51% of the burden of diseases we analyzed. Distinctive for this group is that our understanding of the pathogenesis has improved and treatment protocols exist for treatment. Increased disease understanding has helped us on the one hand to reduce risk factors and on the other hand to screen high-risk groups. Examples of this are promotion of healthy school canteens and regular measurement of blood glucose levels in elderly with high blood pressure in the prevention of cardiovascular diseases and diabetes.[23, 24] Treatment is clearly protocolized, but not yet targeted towards the characteristics of an individual patient. Only generic factors, such as comorbidity and age, are typically available to stratify patients into subgroups. For example, in case of atrial fibrillation the CHA_2DS_2-VASc score uses the variables medical history, high blood pressure and age to determine the risk of stroke and guide the choice between treatment with platelet aggregation inhibitors or oral anticoagulants.[25]

Laggards are characterized more by one-size-fits-all and trial-and-error approaches than by precision medicine approaches. This group, consisting of diseases like psychiatric disorders, neck and back pain, and osteoarthritis together accounts for 32% of the burden of diseases we analyzed. For most of the diseases belonging to this group, our understanding of the biology is still limited and treatments do not differentiate between patients, so called mass medicine. Laggards score relatively high on participation, since the patients' commitment is an essential part of treatment success. Psychiatric disorders are complex, multifactorial and often do not (yet) have an unraveled disease mechanism with tangible targets for pharmaceutical treatments or otherwise. This hinders efficient prevention. For example, currently some risk factors for depression are known – like family history of depression, previous depressive episodes or having a disease with physical impairment[26] - but still most cases are diagnosed when the person has a severe depression. Our lack of disease understanding also limits precise prediction of treatment response and the development of better drugs. Treatment options are uniform between patients with the same condition and it is hardly possible to stratify patients into different treatment groups. As we explored in a previous study,[27] this also makes phase III trials unpredictable and therefore a risky, costly undertaking. According to a study in the United Kingdom, 25 times less research money is spent on mental health research than cancer research per person affected.[28] It is then no surprise that the level of precision has lagged behind that of other diseases.

To conclude, the Dutch landscape of precision medicine is variable and clustered per disease class. Some diseases have already reached higher levels of medicine, while others still depend on a generalized approach. However, more personalization is coming for all diseases, as we discuss below.

The ever-shifting technological frontier will stimulate the advance of precision medicine

The trend towards precision medicine is likely to accelerate further thanks to favorable socio-economic and technological developments (see Chapter 1). We identified what types of cutting-edge treatment possibilities are making the transition to clinical practice for the different diseases. While this approach does not account for aspects like target population of individual interventions and precise effect-size estimations, we believe that the overall picture provides a decent basis for assessment of how the technology frontier will advance given cutting-edge developments.

We rescored the 62 diseases that make up the Dutch landscape to see how these advances will shift the diseases along the precision medicine continuum. A proven methodology to predict the potential impact of precision medicine does not exist nor do we pretend our scoring methodology is an exact science. However, with this approach we have been able to give an approximation of the progress in all diseases, which has provided a clear indication of the direction in which medicine as a whole is moving and what the near future has in store for the various disease areas.

We found that by moving from current standard practices to the current cutting-edge level of care, there is significant potential to advance the level of precision medicine for all diseases (Figure 5). It is interesting to observe that improvement is expected for all groups, although the underlying drivers of the increase in precision level vary.

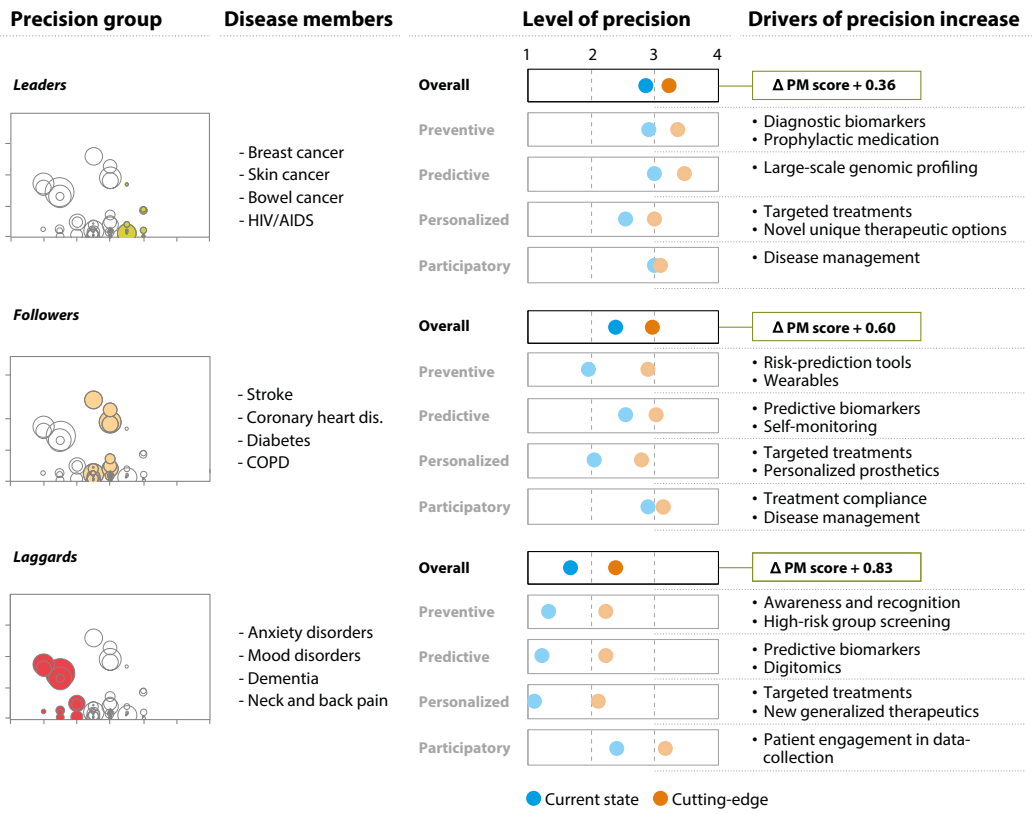


Figure 5: Diseases in the Netherlands are classified as leaders, followers and laggards, based on their current level of precision medicine. Per group, several diseases are mentioned as examples. The blue and orange points depict the current and cutting-edge level of precision medicine, respectively. For each of the four Ps the main factors driving the gain in precision are given.

Leaders, like oncologic and infectious diseases, will achieve higher levels of precision through the wide application of genomic profiling and highly targeted treatment. Genomic assays are increasingly used in clinical diagnostics as a way to identify the optimal treatment.[29] Molecular profiling of tumor samples is reaffirming that particular alterations in the genome are shared between tumors from different anatomical locations. For example, BRAF mutations historically associated with skin cancer, are now known to also occur in (amongst others) lung cancer and bowel cancer. The improved biological knowledge enables us to select the right targeted therapy more precisely irrespective of the tumor's location. In the future, a new disease taxonomy that reflects the shared pathways between diseases may even prove more appropriate.[30] The current nomenclature is simply based on the anatomical location of the primary tumor and subsequent cell type, but falls short in reflecting the underlying systems biology. In addition, combinations of targeted drugs with a synergistic effect are increasingly identified for the treatment of cancer.[31] Lastly, novel therapies are emerging that are truly custom-made. An example of this is tumor-infiltrating lymphocyte (TIL) therapy, in which the T cells that already recognize the tumor are taken from the patient, multiplied in the laboratory and then re-administered to the patient as a treatment.[32]

Followers will advance most in disease prevention and treatment personalization. With new technologies, self-monitoring of vital parameters will become accessible to many individuals. The use of wearables is expected to lead to better prevention of chronic diseases.[33] Cardiovascular conditions such as high blood pressure, but also diabetes often do not cause noticeable symptoms. However, leaving the diseases undiagnosed or unmanaged can eventually lead to complications like cardiac arrest or stroke. Constant and non-intrusive collection of data shall facilitate earlier disease detection, intervention and management. Modern technologies can also be used to improve treatment. For example, mobile applications are being developed that help rehabilitation after stroke, by instructing patients to perform specific physical exercises based on the severity of their condition and affected limbs.[34] Besides, better disease understanding is leading to the application of new drugs.[35, 36] As an example, it is now recognized that the formation of vascular plaques is not only lipid driven, but also inflammation driven. This has identified anti-inflammatory drugs as potent treatment for cardiovascular diseases.[36]

Laggards, such as psychiatric and musculoskeletal diseases are expected to improve on most dimensions of the P4 model. These diseases are taking advantage of new technologies to both unravel and treat diseases. It has been only twenty years since diseases such as depression, schizophrenia and autism were recognized as brain diseases.[37] This insight gave a boost to research. Over the last years, genetic research has identified genes that are involved in brain diseases. Brain scans allow to understand better what is going on inside the brain. This enables better subtyping of the traditionally diffuse diagnoses, e.g. for depression and anxiety disorders. In addition, we are starting to understand the impact of biological changes on the individual's phenotype, i.e. behavior. Digital phenotyping offers objective and real-time measurements using data from personal digital devices such as the smartphone.[38] As such, the unfolding of mental health problems can be identified and intercepted. All these developments shall lead to more timely and precise interventions. For musculoskeletal diseases, more biomarkers are being developed that can guide diagnosis and treatment.[39]

It is clear that science and technology of precision medicine is advancing remarkably. In our assessment we only took into account the developments we already know, the proverbial tip of the iceberg. Surely, disease understanding and treatment possibilities will advance far beyond this level, as science and technology builds on each advance like a snowball. But for estimating the potential value of precision medicine, we have been conservative in this perspective, focusing on the near future with a time horizon between 3 and 10 years.

The next question we pose is: how do these developments impact burden of disease in the Netherlands? History, that is past success, can help us quantify reduction of burden of disease through better precision medicine.

We estimate that precision medicine can help us gain 3 to 7 healthy life years

If a clinician from 1990 was time warped forward, she would hardly recognize the treatment frontier today. Compared to three decades ago, more precise diagnostic, surgical, radio- and pharmacotherapeutic options have become available and are being routinely used. For several diseases, ranging from oncologic to respiratory and cardiovascular conditions, we have reconstructed their evolution in the last decades. We scored the level of precision medicine in 1990 and compared it to the current level (Frame 2). Using publicly available health data we assessed the changes in disease burden per patient in the Netherlands during the same period (for more detail on how burden of disease is measured, see Appendix 3).[40] We found that level of precision medicine was inversely related to the changes in burden of disease over time: on average, every point gain in PM score was associated with a 30% (range 14 to 65%) decrease in burden of disease (Figure 6).

We find it of value to provide two thoughts on methodology here:

- In using burden of disease *per patient*, our methodology is conservative by design, as it does not account for effects of primary prevention (such as treatment of risk factors for stroke or programs to stop smoking, since these mainly drive down overall burden by decreasing the incidence, not by decreasing the burden of disease per patient). We believe it is a better approach than using overall burden of disease, as it accounts more narrowly for improvements due to diagnostic and treatment advances and thus more strictly focuses on the impact of precision medicine.
- One may argue that the methodology results in a correlation, not a proof of causality. In Frame 2, we provide a detailed analysis of the advances in diagnosis and treatment that have resulted in PM score improvements. For example, the reduction in burden of disease in rheumatoid arthritis (RA) is primarily due to disease modifying anti-rheumatic drugs (DMARDS) and biologic and to 'treat-to-target' approaches. As demonstrated in Frame 2, we performed such deep dives for a variety of diseases. Additionally, you would think that changes in treatment approaches over time are always intended to have a causal relation to better outcomes as pursued with precision medicine. Finally, the existing scientific evidence indicated that a majority of precision medicine initiatives are found to be cost-effective, implying that specific precision medicine initiatives result in improved value. Together, we believe these deep-dives and considerations provide ample material to make a causal relationship at least plausible, certainly enough for the level of certainty required for this study.

Relationship between level of precision medicine and burden of disease in the Netherlands
[level of precision medicine in PM score, burden of disease in DALY/patient, 1990 - 2017]

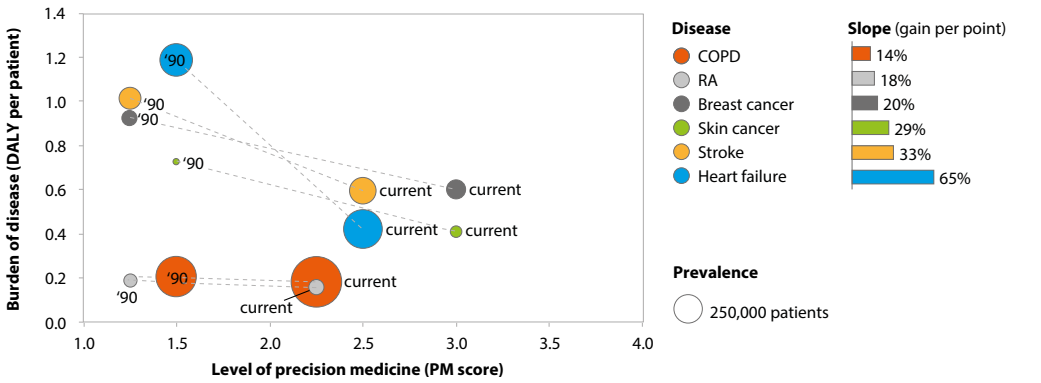


Figure 6: Circles on the left depict the level of precision in 1990 and circles on the right the current level for different diseases. The percentage decrease in DALY point gain in PM score in precision medicine point is shown on the right side. COPD =chronic obstructive pulmonary disease, RA = rheumatoid arthritis, DALY = disability adjusted life years, a measure of burden of disease (see Appendix 3 for more details).

Using the correlation between PM score gain and decrease in the disease burden per patient since 1990, we used a simple linear extrapolation to estimate for each disease the potential disease burden reduction if the cutting-edge level of precision would be reached. By adding up the reduced disease burden of all 62 diseases, we calculated the national disease burden and compared it with the current burden.

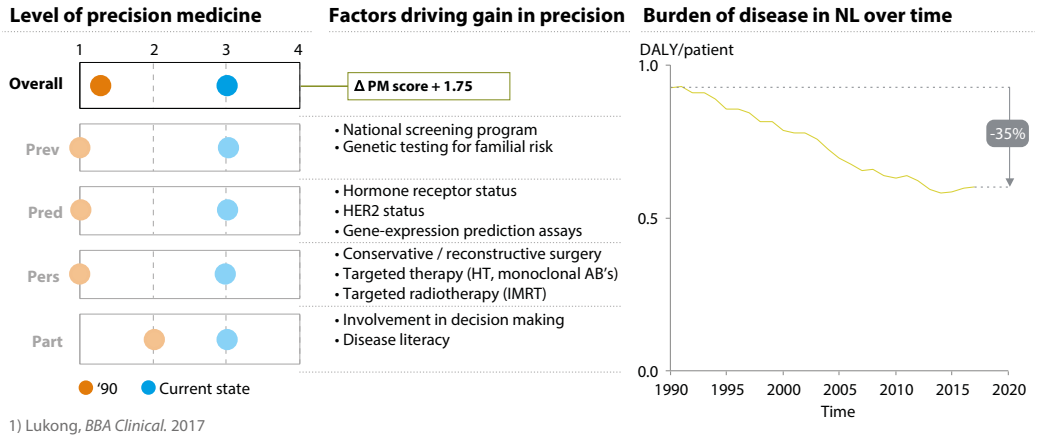
Clearly past successes in precision medicine are not a guarantee for success tomorrow. Also, by using the highly simplistic assumption based on average reduction in the past, we did not consider the variation between diseases observed in Figure 6, nor other developments that could have influenced disease burden, like less smoking, better housing and increased welfare (although, as explained above, our methodology, by accounting for disease burden *per patient*, reduces the impact of such effects on our results). Nevertheless, we believe that similar external influences will continue to impact health in the future. The fact that the six diseases that we studied all show a decline as PM scores increase, provides a good indication that we can use this method to roughly approximate what the future gains of precision medicine can be.

Frame 2:
Deep dive into the evolution of precision medicine

For breast cancer, rheumatoid arthritis (RA), chronic obstructive pulmonary disease (COPD) and stroke, the relationship between precision of treatment and burden of disease is displayed. The brown and blue points depict the level of precision medicine in 1990 and the current level of precision, respectively. For each of the four Ps the main factors driving the gain in precision are given. The graphs on the right show the reduction in burden of disease per patient that occurred during the period 1990 until now.

Breast cancer

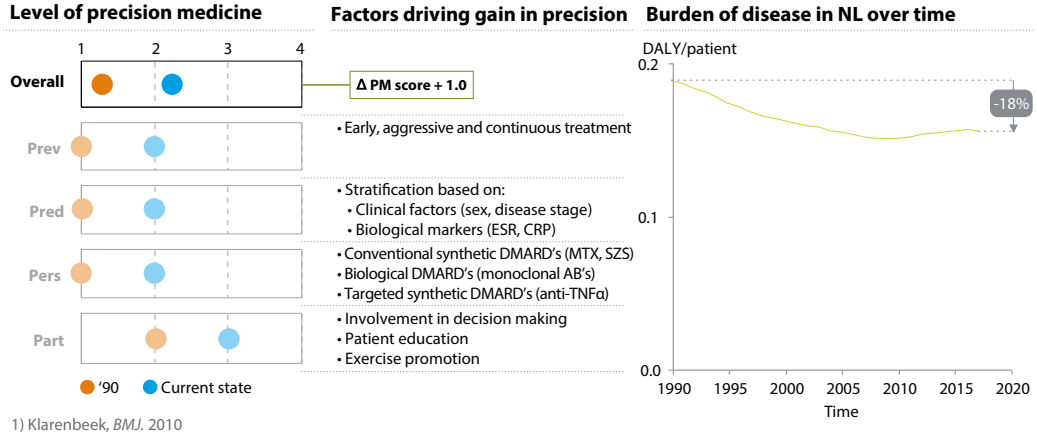
Since 1990, early detection of breast cancer has been promoted with the implementation of the national screening program. Identification of inherited mutations in BRCA1 and BRCA2 genes has initiated cancer prevention in high-risk families. Hormone receptor status, HER2 status and gene-expression arrays became predictors for treatment. Novel targeted drugs against estrogen (aromatase inhibitors) and HER2 (Herceptin) were approved as treatment.[1] Also more precise surgery and radiotherapy became available. Patients got a stronger voice in choosing the right treatment, resulting from improved counselling and increased disease literacy thanks to internet.



1) Lukong, *BBA Clinical.* 2017
HT = hormone therapy, AB = antibody, IMRT = intensity-modulated radiation therapy

Rheumatoid arthritis (RA)

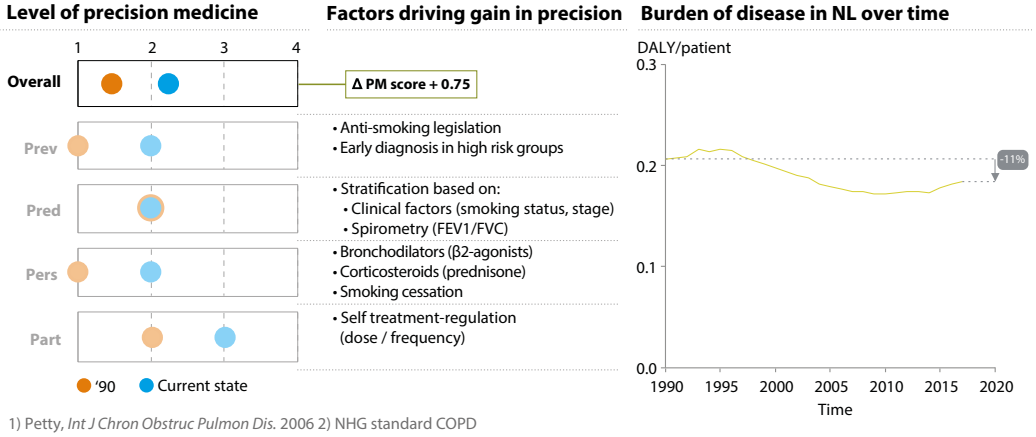
Until the 1990s patients with RA were initially treated with aspirin and other NSAIDs; DMARDS such as methotrexate were introduced only for patients with progressed or most severe disease. Better tools for monitoring treatment and tight control strategies, combined wit new drugs have improved the outlook of patients with RA.[1] Patients are now treated with DMARDs, corticosteroids, and biological agents early in the course to retard progression of disease and improve functional ability and health related quality of life. Patients have become more educated about their disease and take an active role in the treatment process.



1) Klarenbeek, *BMJ.* 2010
ESR = erythrocyte sedimentation rate, CRP = C-reactive protein, DMARD = disease modifying anti-rheumatic drugs, MTX = methotrexate, SZS = sulfasalazine

Chronic obstructive pulmonary disease (COPD)

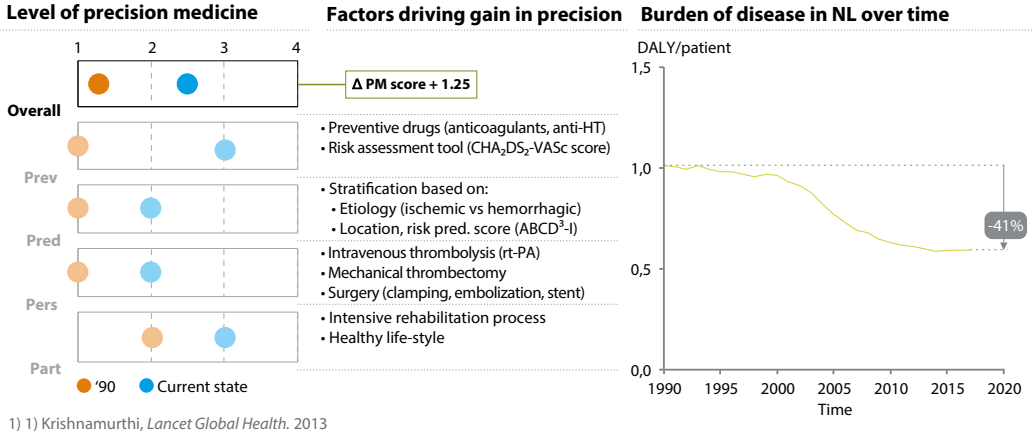
In the early 1990s research established that smoking cessation improved the outcomes of COPD in every stage of the disease.[1] The Tabacco law (Tabakswet) was adopted by the Dutch parliament that restricted smoking to protect public heath. Following the success of treatment guidelines for asthma, protocolized treatment recommendations were developed for the management of COPD. The use of systemic drugs (bronchodilators, corticosteroids) and smoking cessation gained recognition as part of treatment. Clinicians more actively involved patients in the treatment process to promote healthy lifestyle choices, disease coping and therapy compliance.[2]



1) Petty, *Int J Chron Obstruc Pulmon Dis.* 2006 2) NHG standard COPD
FEV = forced expiratory volume during the first second of the forced breath, FVC = forced vital capacity

Stroke

Since the 1990s, anti-smoking legislation, physical activity norms, blood pressure control and risk-assessment tools (e.g. for prophylactic oral anticoagulant therapy) have helped to delay and reduce stroke incidence.[1] More advanced imaging techniques, like diffuse weighted MRI, have enhanced the detection of small strokes and improved distinction between ischemic and hemorrhagic subtypes. In the mid-1990s and 2000s, intravenous thrombolysis, mechanical thrombectomy and several surgical techniques became available as treatment methods. Patients got an increasingly important role in the rehabilitation process after stroke.



1) 1) Krishnamurthi, *Lancet Global Health.* 2013
HT = hypertensive, rt-PA = recombinant tissue plasminogen activator

For calculation of the YLLs, a standard reference table for life expectancy is used based on the highest observed life expectancy at the time. In 2010, the table was updated, with life expectancy at birth increasing with more than four years. This alteration may have caused the flattening in DALY reduction observed after 2010.

Based on extrapolation of these insights, we estimate that it would be possible to claim back 2 to 4 weeks of the ~100 days per year the Dutch society loses per capita to disability or premature death from disease, a reduction of 15-30%. Put differently, it would mean that the average person could expect to live an additional 3 to 7 years in good health. This is an enormous potential that can be better appreciated when pictured differently: it would be equal to a situation in the Netherlands without disease south of the Rhine river. Figure 7 puts this substantial reduction in disease burden in perspective.

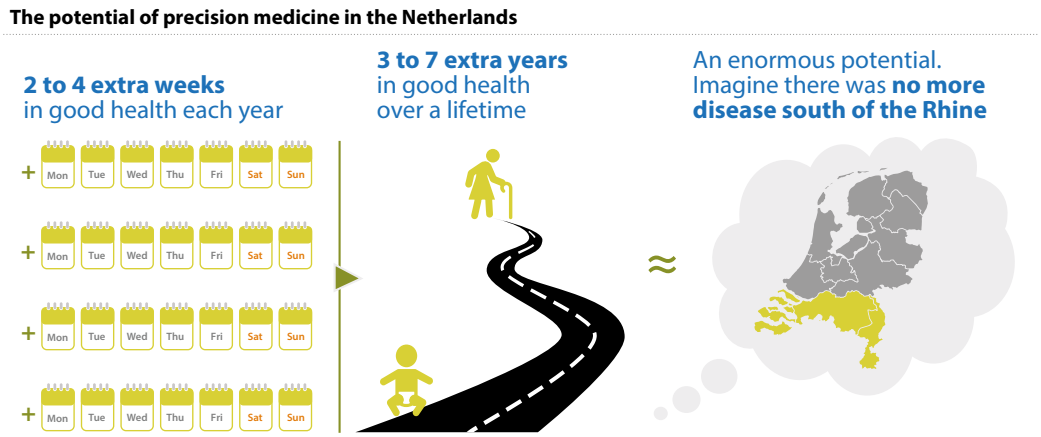


Figure 7: Potential reduction in overall burden of disease in the Netherlands that we can achieve if all diseases would reach the higher level of precision thanks to cutting-edge technology

This enormous reduction is achievable because all disease classes contribute their share. Oncologic diseases (current leaders in precision medicine) show a large contribution in the total reduction in disease burden, but the contribution of the psychiatric disorders (current laggards), is at least as high. Figure 8 illustrates the relative potential per disease class by the movement from current state to cutting-edge levels of precision.

Potential reduction in burden of disease in the Netherlands per disease class
[current burden in NL x10³ DALY (width), reduction in burden (%), remaining burden (%)]

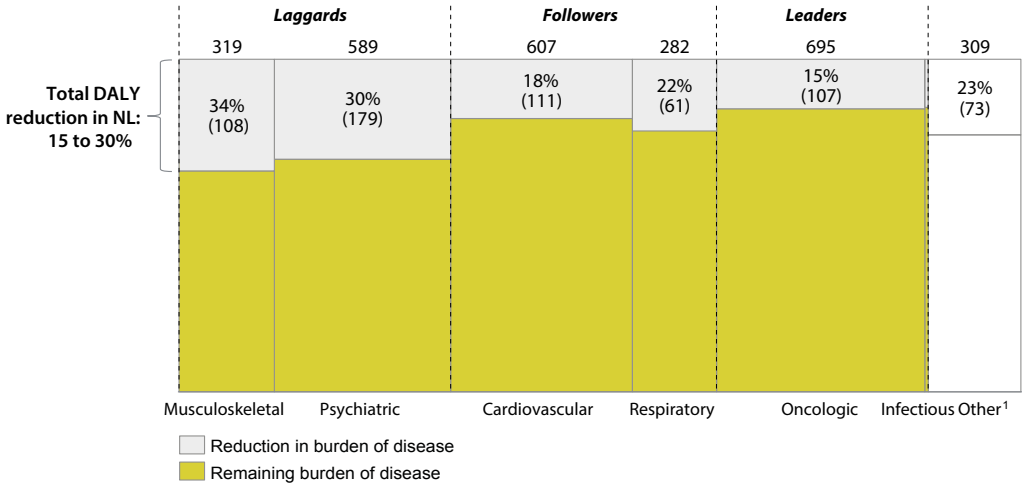


Figure 8: All disease classes would achieve a substantial reduction in burden of disease with cutting-edge technology/care. The percentages represent the DALY reduction with cutting-edge technology as share of the current disease burden. BoD = burden of disease. DALY = disability adjusted life years, a measure of burden of disease (see Appendix 3 for more details). Ad 1. 'Other' consist of congenital, urogenital, dermatologic, neurological and endocrine diseases.

Statistically the impact of precision medicine is the ultimate long tail: there is always potential to improve further. By using extrapolation our aim was to estimate what may be possible based on achieved results. We are however just beginning the precision medicine journey, it is therefore conceivable, even likely, that future gains will well exceed past results.

We conclude not the question whether precision medicine will deliver healthier and longer lives - it is already doing so - but rather how big and broad the impact will be and how we can improve. In order to leverage precision medicine in our quest to reduce the burden of disease, we need to identify the challenges that are holding us back and explore the routes to overcome them. This is what we explore next.

3 It’s time to accelerate the precision medicine movement

In this chapter, we explore the barriers that must be overcome for the precision medicine movement to accelerate, and what actions must be taken to do so. For each of the barriers, we provide an overview of who should do what, and provide ample examples of hopeful initiatives that are already being rolled out.

In the previous chapters, we analyzed the current state of precision medicine and that of cutting-edge developments in science and technology to explore how far precision medicine can progress in the near future. From there, we quantified the potential impact of precision medicine on national burden of disease. However, despite the prospect of further scientific breakthroughs and the growing momentum behind the precision medicine movement internationally and in the Netherlands, there remain substantial barriers to its broad implementation in medical practice.

In general, these barriers are not unique to any particular country. We have used an adaptation of a framework for the precision medicine challenges, as published in a report[41] by the United States National Academy of Medicine, to structure our discussion:


Evidence generation


Adoption of data collection into clinical practice


Combination and use of data


Translation of data into clinical decision support


Citizen engagement and trust


Economics

Building on the input of national leaders in precision medicine, we explore the importance of each of these barriers to the Dutch context and describe whose involvement is needed to break them down. In exploring how we can break the barriers we offer examples of many initiatives that are already doing so. Instead of focusing on what we lack, we show that we already have the answers to most issues. It's time we overcome barriers to make precision medicine happen.

In the next pages, we discuss for each of the six barriers, the challenges that we face and the actions that different stakeholders should take to overcome them.

It's time to generate evidence for the individual rather than the average

Why is it important?

- **Focus of evidence generation is largely on innovation for the average patient**
- **Regulatory approval for new treatments is largely based on a static, one-time evaluation**
- **There is no system to evaluate the validity of decision support algorithms**
- **There is limited evidence for the individual approach medicine, which makes it difficult to build a trust-base for the precision medicine movement**

In global evidence-based medicine, there is much attention for the average patient, but little attention for the individual.[50] In this paper, we demonstrate a high-level assessment of the potential value of precision medicine. However, to convince clinicians, a more robust evidence base is needed for the approach of using detailed individual data to provide an optimal, individualized treatment.

Focus of evidence generation is largely on innovation for the average patient. There is more focus on developing new (breakthrough) treatments than on optimization of the treatments that are already available. Choosing the right treatment plan with existing drugs, for example, is often done based on only a few factors like the patient's age, weight and size, resulting in over- and undertreatment of many patients.[42] The algorithms we use to build individual treatment plans with existing drugs can be greatly improved by incorporating many more factors that predict the drug's effects, like genotype, phenotype, and comorbidities. Multiple experts we interviewed indicate that improvement of diagnostics, biomarkers and outcome prediction of existing treatments receive less research focus, funding and prestige than finding new (breakthrough) cures. We need to seek a better balance between scientific glory and pragmatic heroism.

Regulatory approval for new treatments is largely based on a static, one-time evaluation. Evidence generation is based on static regulatory approval. The concept of precision medicine, however, would benefit from the use of real-world evidence and a more dynamic, regulatory approval process, including periodic or real-time evaluation when new biomarkers and outcome data become available to better predict the outcomes of existing treatments for individual patients.

There is no system to evaluate the validity of decision support algorithms. Several respondents argue for regulation of decision support algorithms similar to, for example, medical devices. This is consistent with the direction of the FDA, which recently published draft guidelines on AI software and clinical decision-support software.[43] In the Netherlands, regulatory frameworks for this purpose do not yet exist.[44] Such a framework is needed to rely on the quality of the decision support algorithms.

There is limited evidence for the individualized approach to medicine, which makes it difficult to build a trust base for the movement. In precision medicine the individual's profile is the starting point for developing a treatment plan. There are many treatments that demonstrate the value of tailored treatments to specific patient characteristics, but the evidence for the individualized approach for every patient, e.g. collecting broad and deep data and tailoring treatment plans based on the emerging individual profile is much shallower. Without broad acceptation of this approach, treatments for the current patients will not set off, but the generation of more knowledge and evidence on biomarkers and their value in precision treatment for future patients is also inhibited.[45]

Who should do what?

- **The government should prioritize and support evidence generation for the individual approach to medicine**
- **The government should provide guidance to agile learning through regulatory frameworks**
- **Funding agencies should stimulate research to the value of an individual approach**
- **Regulators should seek alternatives to market approval that fit precision medicine.**

The government should prioritize and support evidence generation for the individual approach to medicine. One approach is to participate and invest in pan-European evidence generation. For example, over 30 European research funders and policy-making organizations, together with the European Commission as observer, have established an initiative called the International Consortium for Personalized Medicine (ICPerMed). ICPerMed provides a platform to initiate and support communication and exchange on personalized medicine research, funding and implementation.[46] Such broad initiatives may help in setting standards and coordinating research efforts.

The government should provide guidance to agile learning through regulatory frameworks. The traditional approach to healthcare innovation is an ineffective approach for digital innovation due to long learning cycles associated with high costs. Agile learning (with short sprints focused on real-life value) is the preferred approach.[4] The NHS Topol review also highlights the importance of evaluating and learning in clinical practice by both practitioner and patient.

Funding agencies should stimulate research to the value of an individual approach. Fortunately, several of such initiatives are already under way. In one initiative, ZonMW, together with Zilveren Kruis and KWF, has funded five studies in the fields of oncology and rare diseases. Goal of the program is to study the cost-effectiveness of the implementation of whole genome sequencing in the Dutch healthcare system.[47] For example, the Drug Rediscovery Protocol (DRUP) is a unique and innovative pan-cancer clinical trial that seeks to expand the use of EMA- and/or FDA-approved targeted therapies beyond their approved indications.[48] However, the share of total research that such programs comprise is fairly small. For example, the entire, multiyear ZonMW precision medicine program has a budget of EUR 23 mln, which is ~1% of the annual EUR 1.6 bln Dutch public institutions spend on medical research.[49]
Therefore, a much larger, programmatic research effort is required. Such programs should study the value of the approach, not just individual diagnostics, algorithms and/or treatment options. Focus should shift to earlier-stage disease as soon as technically possible, and should include pharmacogenomics and other types of profiling that will help target medicines to maximize efficacy and minimize side effects. Research programs should fund the standardization and use of continuously collected 'real-world data' on diverse populations, and stimulate development of methodologies that enable real-world evaluating and learning by both practitioners and patients.

Regulators should seek alternatives to market approval that fit precision medicine. Regulators can search for ways to reduce time to market, for example by allowing pharmaceutical companies in certain instances to access the market already after phase 2. Phase 3 trials could transform from large and costly clinical trials into 'real-world evidence' gathering. This may improve the quality of evidence generated on efficacy for precision medicine. The benefits should be weighed against the potential downside of patients being exposed to medicines from which they may not benefit.

It's time to adopt data collection into clinical practice

Why is it important?

- **We don't collect what is needed: genomic and deep molecular data is still seen as exceptional rather than foundational, and is not routinely collected**
- **We don't collect where it's needed: focus of research is not always where disease burden is highest**
- **We don't collect when it's needed: lack of incentives for early diagnosis and predicting treatment effect**

For specific diseases, precision medicine has already shown promising results, resulting in more preventive, predictive, personalized and participatory treatments of individual patients. However, for a broader use of the approach, a continued pipeline of new biomarkers, diagnostics and treatment options is needed. This requires generating broader and deeper data in routine healthcare to be used for research. We see several issues that need to be addressed.

We don't collect what is needed: genomic and deep molecular data is still seen as exceptional rather than foundational and is not routinely collected. For precision medicine to succeed, our mindset on the genetic, molecular and other deep data should shift. Currently, an individual's genome is considered a source of information that is very different from other data, hampering the application of it as part of routine healthcare. We also conclude there is a lack of focus on real life clinical data, both with patients and practitioners, as a means of optimizing care and enabling self-management in real life practice

We don't collect where it's needed: focus of research is not always where disease burden is highest. Without a better disease understanding, hard evidence for biomarkers and actionable treatment options, precision medicine is not possible. While these exist for several smaller monogenetic diseases, and for certain forms of cancer, more complex diseases (such as diabetes and depression) require significantly more research effort before the concepts of precision medicine may be fully applicable. These diseases are also responsible for the largest share of total disease burden in the Netherlands. However, research focus is disproportionately on diseases where burden is lower, such as oncology, as we have published earlier.[51]

We don't collect when it's needed: lack of incentives for early diagnosis and predicting treatment effect. As pointed out by Dzau et al, 'beyond novel targeted therapies, some of precision medicine's greatest benefits may lie in identifying healthy people who are at high risk for disease and for whom efficacious therapies exist.[39] There is a need to improve diagnostic tests to better predict the treatment outcomes. This helps to prevent over- and undertreatment, and is especially important for costly treatments or treatments with potentially harmful side effects. Approval and fi nancing of innovations has also proven difficult in the Netherlands, for example in the case of MammaPrint, a gene expression test which returns a risk profile that can be used to determine treatment choices.[52]

Who should do what?

- **The government should accept the extra costs and incentivize payers and providers to collect and use deep data in the routine health and care pathways**
- **Funding agencies should target research funds towards diseases with the highest disease burden**
- **The government and payers should work together to rethink the economics of early diagnosis and a multi-omics approach to the individual's disease**

The government should accept the extra costs and incentivize payers and providers to collect and use deep data in the routine health and care pathways. With increasing understanding of the roles genes and molecular phenotypes play in pathogenesis and prediction of treatment effects, we should change the way we think about incorporating these data into routine care. As can be expected, the support for doing this is highest in diseases that are potentially lethal and burdensome, that have no treatment options available or that have treatment decisions based on this type of data. For diseases that are still less understood and have more complex causes, the privacy concerns weigh stronger and support gets weaker. It should be emphasized that a better understanding of the disease biology of individuals (patients and healthy individuals) through deep data drives progress towards precision medicine. The data of today is the knowledge of tomorrow that enables treatments of the future.

Funding agencies should target research funds towards diseases with the highest disease burden. Funding agencies, such as ZonMW, can encourage research that may ultimately help raise our understanding of high-burden complex diseases such as dementia, neck and back pain and depression. Similarly, university medical centers could be nudged to rebalance their research efforts. We of course do not argue for a radical shift, as the research done in these fields have greatly advanced our understanding and ability to treat cancer and continue to be of great importance - but a rebalancing now may better prepare us for the future in which other diseases will need to follow the example set in oncology. We should invest in research to deeper understand psychiatric disorders, a disease area with high burden of disease, but with promising developments. There is great potential in multimodal approaches that combine biological, behavioral and experiential deep data to lead to new insights that open doors to precision psychiatry. Dr. Christiaan Vinkers, psychiatrist and associate professor at Amsterdam UMC: "These different levels are often studied in isolation and not combined. Nevertheless, there is a large potential in multilevel profiling of stress resilience to improve depression risk assessment and outcomes."

The government and payers should work together to rethink the economics of early diagnosis and a multi-omics approach to the individual's disease. For example, the concept of pharmacogenomic profiling, useful for predicting adverse reactions and/or making dosage recommendation for the individual patient, is rarely applied in the Netherlands. The Dutch Institute for Pharmacogenomic Research (NIFGO) provides 'DNA passports' in which responses to many medicines are predicted based on the individual patient's genotype.[53] At present, however, insurance firm ONVZ is the only health insurer to cover such pharmacogenetic profiling. Separate add-on products within the hospital product structure, similar to those which exist for medicines, may provide a standalone avenue for innovative diagnostics to reach the market and prove their value.

It's time to combine and use the data that we collect

Why is it important?

- **We don't always collect the right data, the data we do collect is often not structured appropriately for sharing, and there is a lack of interoperability between databases**
- **Due to lack of financial incentives, data sharing and analytics is not a strategic priority for most providers**
- **In the absence of clear direction and incentives to prioritize the safe collection of data, concerns about access, privacy and security prevail**

The path to precision medicine requires access to large-scale, detailed, and highly integrated patient data to advance our understanding of the genomic, molecular, phenotypic, clinical, and digital signatures of disease. Precision medicine requires not only big data but diverse data.
Many obstacles remain that stand in the way of this requirement in the Netherlands. Based on expert interviews, we see several issues that need to be addressed.

We don't always collect the right data, the data we do collect is often not structured appropriately for sharing, and there is a lack of interoperability between databases. Several large centralized oncology databases, such as the Dutch Melanoma Treatment Registry[54], contain both detailed diagnostic and treatment information as well as outcome information. However, the collection of data in EHR systems is focused on registration of activities for claims processing – data on outcomes are typically not collected, certainly not in a structured way, unless for the purpose of clinical trials. Furthermore, clinical trials focus on testing a primary hypothesis and for reasons related to cost, time, and fear of the unknown-fail to incorporate exploratory genomic, digital, and other measures to help to create the learning necessary to drive precision medicine.[41]

Due to lack of financial incentives, data sharing and analytics is not a strategic priority for most providers. In daily clinical practice, hospitals and other providers are paid based on the care activities they perform and not for collecting or sharing data. This is a significant barrier to make it a strategic priority. Furthermore, many scientific institutions and businesses are built on the premise that owning patient data exclusively is a profitable business model. Examples are 1) diagnostic tests companies only sharing the 'result' with the doctor but not the raw data[55] 2) scientists unwilling to share research data with other scientists because of the competitive advantage and 3) pharma not sharing valuable clinical trial data publicly with the scientific community. Also the development and use of algorithms in daily clinical practice in hospitals (i.e. not in research) is limited. All in all, data and data science are not high on strategic agendas.

In the absence of clear direction and incentives to prioritize the safe collection of data, concerns about access, privacy and security prevail. Technology allows access and security management to be done safely, but the data leaks in tech companies and the high sensitivity of medical information has led to a low level of trust. This is demonstrated, for example, by the failure to get a national electronic medical record implemented.[56] Additionally, the fear of the consequences of violating the General Data Protection Regulation (GDPR)[57] has taken hold of healthcare organizations and professionals, leading to a spastic approach to data sharing. Concerns exist not only with patients, but also with those who steward the data, as it may enable benchmarking or reveal bad practices.

Who should do what?

- **Advocacy groups should encourage the government and payers to set guidelines for collecting health, care and outcome measures in a systematic fashion**
- **Funding agencies and insurers should encourage adoption by providers and scientists of the FAIR principles and stimulate investments that improve interoperability of databases**
- **Providers should be financially incentivized to turn data science into a strategic priority, and redesign informed consent**

Advocacy groups should encourage the government and payers to set guidelines for collecting health, care and outcome measures in a systematic fashion. For example, they could push insurers and care providers to agree on monitoring Disability Adjusted Life Years (DALYs) at the regional level, so that care pathways may be directly linked to macro-relevant outcome indicators. Parties should agree on durable ways to incentivize and finance such measurements, how to monitor them and and share insights. Insurees should also be encouraged to collect their own health data. Platform-based approaches, such as provided by Niped[58], may help in coordinating such efforts and provide economies of scale.

Funding agencies and insurers should encourage adoption by providers and scientists of the FAIR principles and stimulate investments that improve interoperability of databases. The GoFAIR inititiative, a bottom-up, stakeholder-driven initiative, promotes a useful set of principles to help realize that data are machine-actionable.[59] According to these principles, data should be made Findable, Accessible, Interoperable and Reusable (FAIR). Developing a data-marketplace could facilitate finding and combining data from different sources, as to get the most out of the available data. Funding agencies can enforce the use of these principles in research projects – e.g. ZonMW already does so.[60] University medical centers could be nudged by insurers to ensure that the data they produce is FAIR.

Providers should be financially incentivized to turn data science into a strategic priority, and redesign informed consent. Hospitals and other providers should ensure that the proper structuring of data is high on their strategic agenda and included in their capital budgets. We see a lot of infrastructure initiatives, but on a relatively small scale. For example, Personal Health Train (PHT) [61,62] is a joined initiative by LUMC, Maastricht UMC+ and the Dutch Techcentre for Life Sciences. It aims to connect distributed health data and to encourage the use of existing health data for citizens, healthcare, and scientific research. Other data sharing initiatives in the Netherlands are Data4lifesciences[63], Medmij[64] and Health-RI[65], but they are still early stage and require funding political will to succeed.

Data analysis can improve strongly from healthcare providers investing more in data science. Bringing data sciences high on the agenda of the doctors and the hospital board is needed for the investments in talent and uptake.

The GDPR regulations protect the data privacy of Dutch citizens. They leave room for collecting and sharing of health data. The Netherlands Cancer Institute (NKI) already implements consent forms 'at the gate'.[66] Additionally, digital tools are developed to facilitate enrolment in research and care programs and inform patients about the scope of their consent.[67] Privacy by design is an approach to systems engineering in which privacy is taken into account throughout the whole engineering process. It is a good starting point for the redesign of healthcare data systems to overcome the privacy challenges in precision medicine.[68]

It's time to translate data into clinical decision support

Why is it important?

- **Decision support is feared more often than it is anticipated, due to a lack of understanding, value perception and fear of administrative burden amongst care providers**
- **Providers and IT firms lack strong incentives to make the necessary investments a strategic priority**
- **Instead, there is a fragmented and minimally regulated market of health applications and analytic scripts – this fragmentation limits trustbuilding and adoption by the masses**

The key to achieve impact with precision medicine is to apply the knowledge generated from research into the clinical practice. Insights should be incorporated into guidelines, tailored protocols and decision support systems. This is not a trivial step. We see several challenges that must be overcome:

Decision support is feared more often than it is anticipated, due to a lack of understanding, value perception and fear of administrative burden amongst care providers. The conceptual understanding of precision medicine, big data analysis and deep medicine lag behind the rapid acceleration of these fields, as does the perception of its value for individual patients and medical professionals now and in the near future. Healthcare professionals are struggling for years with ever increasing demand for data registration, malfunctioning computer systems and user-unfriendly software, resulting in fear of new digital tools in their clinical practice.

Providers and IT firms lack strong incentives to make the necessary investments a strategic priority. Based on interviews and project experience, we know that long-term IT strategy is often not as high on the strategic agenda of hospitals as we believe it should be. Despite the declining importance of 'bricks and mortar' and the growing importance of information technology, IT departments are too often forced to focus on short-term fixes within outdated applications and systems.

Instead, there is a fragmented and minimally regulated market of health applications and analytic scripts – this fragmentation limits trust building and adoption by the masses. The lack of a regulated market forms a great challenge for procurement and integration of health applications and analytical scripts into the EHR. This often results in conservative investment decisions, temporary fixes, high implementation costs and negative business cases for healthcare organizations. Analytical scripts will become more important. With the growing knowledge of the patient profiles and tailored treatment plans, the practical and political process of writing a guideline is becoming increasingly cumbersome. Moreover, guidelines will grow outdated ever more rapidly when new insights are generated. This will drive the need for automated personalized treatment protocols based on algorithms that will eventually replace the traditional static guidelines written and updated only every couple of years.

Who should do what?

- **Advocacy groups should encourage the government and payers to set guidelines for collecting health, care and outcome measures in a systematic fashion, and ensure they are adopted**
- **Funding agencies and insurers should encourage the broad adoption by providers and scientists of the FAIR principles and stimulate investments that improve interoperability of databases**
- **Providers should be financially incentivized to rethink the infrastructure of data**

Advocacy groups should encourage the government and payers to set guidelines for collecting health, care and outcome measures in a systematic fashion, and ensure they are adopted. Medical workers should become aware of the potential of precision medicine, multi-omics and machine learning. By letting them experience what value it can have for them and for patients they can be motivated to shape their new role. Their job will not disappear, but it will most definitely change. As Wouter Kroese from health AI startup PacMed[69] stated: "There are giant steps being made to explain complex AI models to doctors and allow them to use and interpret them. This is the only way in which we can create synergy between the irreplaceable skills of a doctor and the increasing possibilities of computers".[70]

Funding agencies and insurers should encourage the broad adoption by providers and scientists of the FAIR principles and stimulate investments that improve interoperability of databases. A long-term strategic view should account for and prepare institutions for important trends like precision medicine. The government should facilitate and coordinate discussions to prevent unnecessary fragmentation and duplication of efforts. Institutions should also carefully consider asking versus buying decisions and possibilities for collaboration, for example at the regional level, and platform-based approaches to coordinate investments and avoid scale inefficiencies.

Providers should be financially incentivized to rethink the infrastructure of data. There are already many efforts to develop support tools that doctors can use, such as DEAR health[71], Alii[72]and PacMed[69]. The RIVM has reviewed the applications of precision medicine in various fields of medicine in the Netherlands.[73] The lessons we learn on the use of these applications should evolve into a set of criteria that these tools should meet. These criteria may concern validity aspects, interface design, interpretation and roles and responsibilities of the end user and the developer. These can form the basis of a regulatory framework. For personalized patient support applications, like tailored dietary, lifestyle, and medication protocols in chronic disease management, the validity of the algorithm is even more important since there is no intervention by medical professionals.

It's time to engage citizens in their health and care

Why is it important?

- There is lack of trust between stakeholders: citizens do not trust payers and providers with their data, and providers do not trust patients with data on quality and outcomes
- Individuals do not experience enough incentives to engage in their own health and care
- Professionals do not see a clear need to truly engage their patients: there is no substantive evidence base for participants' role in precision medicine

For discovery in precision medicine to be accelerated and services based on it to be adopted, people -not just citizens- must be involved.[78] That is because, although it is important for some aspects of the science to have data on individuals in the clinical context, it is also important to understand the continuum of health and disease on the basis of data of many people in diverse communities. Data from self-tracking devices, on the environment and other nonclinical aspects of people's lives will help to complete the picture essential for precision medicine.

There is lack of trust between stakeholders: citizens do not trust payers and providers with their data, and providers do not trust patients with data on quality and outcomes. In general, patient trust their doctor to make the right decision. So much so, that for most health problems travel time is still the most important determinant of which hospital a patient will visit. However, trust works both ways: are providers, insurers and other stakeholders transparent about service quality and outcomes? Do they trust patients and other stakeholders with this information? While there may be exceptions, based on interviews and project experience we conclude that the answer, overall, is no – or at least not yet. Besides this, while consumers readily share data with technology service providers like Facebook and Google, there is much greater reluctance towards sharing health data, as we witnessed in the failure to implement a national EHR system.

Individuals do not experience enough incentives to engage in their own health and care. The incentives for individuals to meaningfully engage in their health trajectory (besides the obvious aspect of wanting to maintain or improve their own health) are very limited. We observe that a large proportion of the population smokes even though diseases like lung cancer and COPD would barely exist if they did not. Obesity is on the rise, and healthy foods are typically more expensive than fast food. The cost of insurance is not based on behavior as it is in other forms of insurance, like car insurance. And there are no clear incentives (or even avenues) to pro-actively share health data, other than that this may benefit the good of many.

Professionals do not see a clear need to truly engage their patients: there is no substantive evidence base for participants' role in precision medicine. Researchers and clinicians have little experience in thinking of participants as partners in precision medicine endeavors.[39] Only when the effect of engagement has a solid evidence base will it be supported and even promoted by professionals.

Who should do what?

- **Providers, insurers and suppliers should demonstrate trustworthiness and work with patient advocacy groups to systematically share and publish outcomes that matter**
- **The government and insurers should stimulate healthy behavior (such as much more rigorous anti-smoking policies) and incentivize data and knowledge sharing**
- **The government and funding agencies should promote research that studies the role of participant engagement**

Providers, insurers and suppliers should demonstrate trustworthiness and work with patient advocacy groups to systematically share and publish outcomes that matter. We believe that true trust works both ways, and for patients to trust their providers, it is required that providers trust their patients. Much greater transparency on quality of care and outcomes would be a good start.

The government and insurers should stimulate healthy behavior (such as much more rigorous anti-smoking policies) and incentivize data and knowledge sharing. Obviously, more radical approaches towards smoking would be much more effective than any other precision-medicine based approach to COPD and lung cancer, and we support initiatives like the 'smoke-free generation'.[74] With respect to data sharing, at the minimum it should be made clear to consumers that if we put our data and knowledge to good use, our collective health could benefit greatly. Making it easy to share data would help – initiatives like the "personal health record (PHR, or in Dutch: Persoonlijke gezondheidsomgeving (PGO)) could eventually provide an avenue to do so, but we could certainly learn from initiatives like the Finnish Kanta,[75] a nationwide database of up-to-date social and healthcare records which makes information on health status, medical history and prescriptions available to all providers. In more extreme lines of thinking, financial incentives could be provided for the sharing of data (e.g. financial benefits or premium differentiation based on data sharing)[76] or data sharing could 'simply' be made a mandatory component of the health insurance legislation.

The government and funding agencies should promote research that studies the role of participant engagement. These may be stand-alone studies, but this aspect could also be incorporated in other studies. An initiative similar to the Patient-Centered Outcomes Research Institute (PCORI) in the US could jumpstart and coordinate such efforts. Patient-centered outcomes research involves questions and outcomes which are "meaningful and important to patients and caregivers" in order to help those individuals make informed decisions for their own care.[77]

It's time to tweak the economics of precision medicine

Why is it important?

- **The importance of cost-effectiveness is growing, but its definition is unclear**
- **There are imbalances in (financial) risk versus reward: continuation of ineffective treatment is incentivized, while adoption of diagnostics and IT is disincentivized**
- **Static reimbursement decisions and pricing hamper adoption of innovations**
- **In a market where the indications for treatments become ever smaller, maintaining competitive market dynamics is increasingly difficult**

The economics of precision medicine are one of the most important drivers for its success. In a recent review on the cost-effectiveness of precision medicine, it was shown that the majority of studies concluded that the precision medicine intervention was at least cost-effective compared to usual care.[3] Despite this observation, there remain many obstacles in the way of full-blown implementation of the precision medicine concept.[85]

The importance of cost-effectiveness is growing, but its definition is unclear. This leads to unclear decisions on reimbursement and value potential. The value may also differ based on the eye of the beholder. For example, insurers may in theory consider precision medicine effective if the quadruple aim of better outcomes, better patient experiences, appreciation by providers and affordability are met, while in practice they find many of these aspects difficult to measure and judge mainly on affordability. Patients may place much more value on outcomes and experience. In the context of uncertain definitions, health economic modelling is very difficult to perform fairly.

There are imbalances in (financial) risk versus reward: continuation of ineffective treatment is incentivized, while adoption of diagnostics and IT is disincentivized. Often, those who run the financial risk are not the ones who reap financial rewards. Likewise, innovation may lead to economic winners and losers. We have seen this in the case of diagnostics, where the value of early and/or precise diagnosis may be great, but clear marketing routes are yet to be developed. But it also occurs in data collection efforts, where much of the burden rests on hospitals and other providers while benefits go (partly) to other parties such as health insurers and pharma. Another example is the ex-post redistribution of costs for expensive medication,[79] which eliminates any competitive incentives between insurers to promote diagnostics to reduce overtreatment and costs. Such imbalances disincentive innovation.

Static reimbursement decisions and pricing hamper adoption of innovations. Once a treatment is approved for reimbursement in a certain indication, there is no incentive to improve the targeting of such treatment with new biomarkers and prevent over-treatment. On the other hand, it is also difficult to add indications for a treatment. The reimbursement price of the treatment is also set once, rather than dynamically in adaption to the real-world data.

In a market where the indications for treatments become ever smaller, maintaining competitive market dynamics is increasingly difficult. As therapeutics are being developed for ever more specific indications with smaller patient numbers, the potential health gains come with a downside. The market dynamics of these therapeutics move towards monopolies. Since an increase in the share of monopoly indications carries the risk of price increases, it is in the public interest to design a market structure that cultivates competition.[80]

Who should do what?

- **The government and funding agencies should encourage cost-effectiveness research and unify definitions**
- **Payers, regulators and the government should tweak risk-reward imbalances cas-by-case**
- **The government should experiment with dynamic pricing models for market access**
- **Regulators should revise IP regulations on very costly individualized treatments**

The government and funding agencies should encourage cost-effectiveness research and unify definitions. The HEcoPerMed initiative aims to provide guidance for model-based economic evaluations, using state-of-the art economic modelling in three personalized medicine innovations cases.[81] ISPOR is another initiative that aims to improve the economic evaluation of precision medicine.[82] In addition to stimulating such research, the government should take steps to form and unify definitions and methods for evaluating the value of precision medicine.

Payers, regulators and the government should tweak risk-reward imbalances case-by-case. Responsibility, coordination and funding for prospective data collection, especially in non-symptomatic insurees, could rest with health insurers, but - academic hospitals should also take a leading role in the regional collection of real-world evidence.[83] Providers should be financially incentivized to turn data collection and sharing into a strategic priority. This can be done in contracting discussions with health insurers, but also with dedicated funding programs. The marketing approval process for new diagnostics, devices and drugs should include more rigorous requirements for collecting real-world-data according to FAIR principles. Enabling separate reimbursement through add-ons may provide a standalone avenue for innovative diagnostics to reach the market and prove their value in precision medicine.

The government should experiment with dynamic pricing models for market access. The Ministry of Health could explore nonlinear pricing models in 'funnel' negotiations with pharmaceutical companies.[84] For example, the unit price could come down as more patients are treated, in return for easier and faster market access for line extensions. A more innovative approach is the use of value-based payment models. These models allowing for continuous value evaluation based on real-world outcomes and integral healthcare costs. This incentivizes the development of cost-effective precision medicine approaches in treatment protocols. The value-based healthcare partnership between Diabeter and insurer Zilveren Kruis on type 1 diabetes care is an excellent example of incentivizing precision medicine. Experimenting with different models will help to converge on a broadly usable model with limited administrative burden.

Regulators should revise IP regulations on very costly individualized treatments. The traditional business model of protected marketing time to recoup investments made over very long periods of time may not suit precision medicine innovations in the longer term. Stimulating innovation while also nurturing competition for the public interest of affordability and availability of these medication is key.[81] Alternatives should be sought, potentially in a European and global context – this is beyond the scope of this paper. Beyond this, a potential solution for high cost, one time administered drugs with potential curative effect is the mortgage model, in which the payor pays off the treatment costs over a longer time period.

4 Call to action

In this chapter, we provide some first thoughts on how to move forward on breaking the barriers and advance the precision medicine movement. Broadly speaking, we see two courses of actions that should be taken in parallel. The first is to engage individuals and organizations and put the acceleration of personalized healthcare on the national agenda. The second is to identify and prioritize specific projects and models for innovation that can help break down the barriers we experience in the system. By collectively contributing to the success of these projects, we can lead the way to a receptive environment for precision medicine.

In the previous chapters, we have shown the large value potential of precision medicine and have shown that there are many challenges ahead to accelerate precision medicine in the Netherlands. However, we have also seen that for each barrier there are hopeful initiatives that pave the way. Whether it is data collection, payment on outcomes, patient engagement initiatives, or any of the other issues, there are solutions that already exist. Thanks to the investments of many parties, precision medicine has already advanced to where it stands today. But it is equally clear that in order to accelerate the transition, a broad effort is necessary. Small countries may be well positioned to lead the way.[86] The Netherlands with its knowledge-based economy could drive the advance of the precision medicine movement.

We believe that we don't need to invent the wheel to move forward, we just need to fit the wheels we already have to the right vehicle and put them to good use for the entire system. This means it is time for action, and all parties should get involved: patients, payors, doctors, government, medical and data scientists, regulators, medtech, pharma and IT companies can all contribute.

Making the system more receptive for precision medicine will require a transformation in the way we innovate our healthcare system. We need a more agile and co-creative approach that engages all end users. Step one is to get everyone on board.
This document serves to spark discussions on how to accelerate precision medicine and to inspire the initiation of new, purposeful projects for short-term success. We see two routes ahead:

The first is to engage individuals and organizations and put the acceleration of personalized healthcare on the national agenda. The second is to identify specific projects that can help break down the barriers we experience in the system. By collectively contributing to the success of these projects, we can lead the way to a receptive environment for precision medicine.

Do you take personalized healthcare personally? Get involved…
Join the discussion. We are curious to hear your thoughts about precision medicine and the challenges ahead. Share your ideas and get involved in the transition towards precision medicine by going to the following link: www.gupta-strategists.nl/precisionmedicine .

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Appendices

Appendix 1

Scoring criteria to determine the precision medicine score per disease

For each disease, we used a set of predefined scoring criteria to determine the number of points earned on each of the four dimensions that underly precision medicine. The scoring criteria are specified in the figures below. The precision medicine score (PM score) was defined as the average of the four scores.

Preventive Predictive Personalized Participatory

In which phase of the disease can we intervene?

	Scoring criteria	Description	Examples
4	Prevention	• No symptoms, signs or abnormalities are present • Increased risk based on patient profile (e.g. genes, behavior) • Treatment goal is to reduce health risk	vaccination program
3	Non-symptomatic	• Disease treated when signs, but not symptoms are present • Abnormalities are present, e.g. a (small) tumor, elevated blood pressure or increased biomarker levels	breast cancer
2	Symptomatic	• Disease treated when symptoms are present • Patient has several symptoms, such as fatigue, pain	gastrointestinal infection
1	Multi-morbidic	• Disease treated when multimorbidity is present • Patient has many symptoms • Patient has multiple conditions	depression

Preventive **Predictive** Personalized Participatory

How well can we predict the individual response to treatment?

	Scoring criteria	Description	Examples
4	High predictability	• Good understanding of the disease has identified highly predictive factors for treatment outcome • Prediction of response to treatment based on deep profiling of the individual (e.g. multi-omics)	vaccination program
3	Better predictability	• Treatment outcome is better predictable • Multiple factors classify patients into specific subgroups, only limited unexplained variation in response remains • Response to treatment based on combination of several factors	breast cancer
2	Some predictability	• Treatment outcome may vary between subgroups • Factors classify patients into broad subgroups, but unexplained variation in response remains • Response to treatment is predicted based on a few factors	rheumatoid arthritis
1	Low predictability	• Treatment outcome is unpredictable, 'trial-and-error' • No factors are available to predict response • Response to treatment is predicted based on general disease course	burn-out

Preventive Predictive **Personalized** Participatory

How well is the treatment tailored to individual patient?

Scoring criteria	Description	Examples
Unique medicine	• Patient receives a unique treatment (n=1) • Treatment is based on personal profile • Treatment can be tailor-made or custom-designed drugs	CAR-T for melanoma
Individualized medicine	• Patient receives treatment that is highly specific for set of patient characteristics	breast cancer
Stratified medicine	• Different treatment protocols are in place for different patient cohorts	stroke
Mass medicine	• Treatment according to one single protocol for everyone • No treatment differentiation between patient characteristics	schizophrenia

Preventive Predictive Personalized **Participatory**

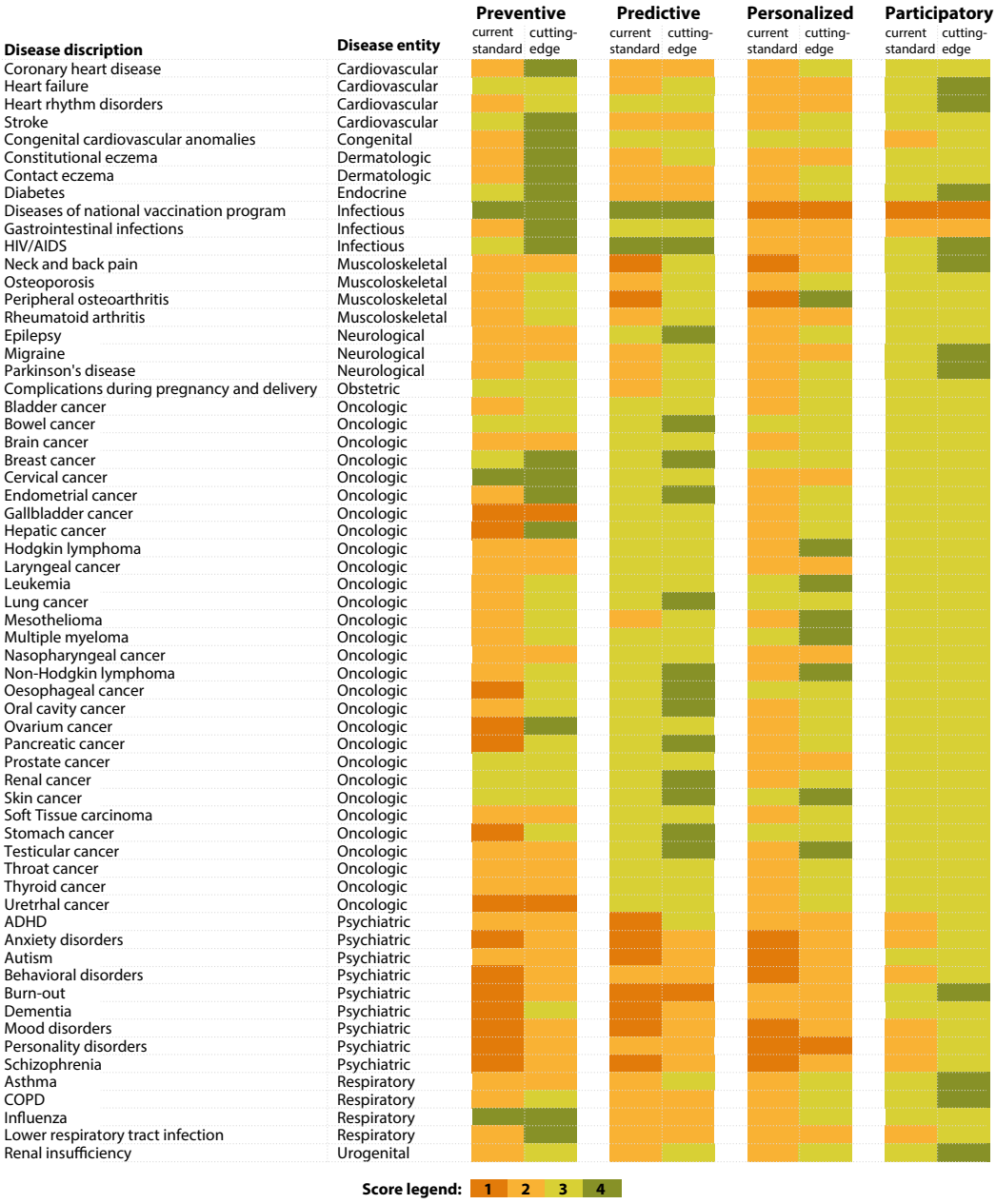
How much is the patient involved in diagnosis and treatment?

Scoring criteria	Description	Examples
Patient is co-leader	• Doctor and patient are equally involved in treatment decisions • Patient is co-leader in data collection and treatment adjustments • Patient is disease co-expert	type 1 diabetes
Patient is involved	• Patient is involved in choosing the right treatment • Pro's and cons of treatment options are explained • Patient has a role in treatment monitoring	breast cancer
Patient is consulted	• Patients opinion about treatment is considered • Doctor decides on treatment • Patient does not have an active role in treatment decisions and monitoring	gastrointestinal infection
Patient undergoes	• Patient has a passive role • Patient does not have choice but to undergo treatment • Patient is disease illiterate	vaccination program

Appendix 2

Scores assigned to each disease on the four Ps underlying precision medicine

The four Ps represent prevention, prediction, personalization and participation. For each P, the score for current standard and cutting-edge are given, 1 being the lowest score and 4 being the highest score.



Disease discription	Disease entity	Preventive current standard	Preventive cutting-edge	Predictive current standard	Predictive cutting-edge	Personalized current standard	Personalized cutting-edge	Participatory current standard	Participatory cutting-edge
Coronary heart disease	Cardiovascular	2	4	2	2	2	2	3	3
Heart failure	Cardiovascular	3	3	2	3	2	2	3	4
Heart rhythm disorders	Cardiovascular	2	3	3	3	2	2	3	4
Stroke	Cardiovascular	3	4	2	2	2	3	3	3
Congenital cardiovascular anomalies	Congenital	2	4	3	3	3	3	2	3
Constitutional eczema	Dermatologic	2	4	2	3	2	2	3	3
Contact eczema	Dermatologic	2	4	2	2	2	3	3	3
Diabetes	Endocrine	3	4	2	2	2	3	3	4
Diseases of national vaccination program	Infectious	4	4	4	4	1	1	1	1
Gastrointestinal infections	Infectious	2	4	3	3	2	2	2	2
HIV/AIDS	Infectious	3	4	4	4	2	2	3	4
Neck and back pain	Muscoloskeletal	2	2	1	3	1	2	3	3
Osteoporosis	Muscoloskeletal	2	2	2	3	2	2	3	3
Peripheral osteoarthritis	Muscoloskeletal	2	3	1	3	1	3	3	3
Rheumatoid arthritis	Muscoloskeletal	2	2	2	3	2	2	3	3
Epilepsy	Neurological	2	2	3	4	2	3	3	3
Migraine	Neurological	2	2	2	3	2	2	3	4
Parkinson's disease	Neurological	2	3	2	3	2	3	3	4
Complications during pregnancy and delivery	Obstetric	3	3	2	3	2	3	3	3
Bladder cancer	Oncologic	2	3	3	3	2	3	3	3
Bowel cancer	Oncologic	3	3	3	4	3	3	3	3
Brain cancer	Oncologic	2	2	3	3	2	3	3	3
Breast cancer	Oncologic	3	4	3	4	3	3	3	3
Cervical cancer	Oncologic	4	4	3	3	2	2	3	3
Endometrial cancer	Oncologic	2	4	3	4	2	3	3	3
Gallbladder cancer	Oncologic	1	1	3	3	2	3	3	3
Hepatic cancer	Oncologic	1	4	3	3	2	3	3	3
Hodgkin lymphoma	Oncologic	2	2	3	3	2	4	3	3
Laryngeal cancer	Oncologic	2	2	3	3	2	2	3	3
Leukemia	Oncologic	2	3	3	3	3	4	3	3
Lung cancer	Oncologic	2	3	3	4	3	3	3	3
Mesothelioma	Oncologic	2	3	2	3	2	4	3	3
Multiple myeloma	Oncologic	2	3	3	3	3	4	3	3
Nasopharyngeal cancer	Oncologic	2	2	3	3	2	2	3	3
Non-Hodgkin lymphoma	Oncologic	2	3	3	4	2	4	3	3
Oesophageal cancer	Oncologic	1	3	3	4	3	3	3	3
Oral cavity cancer	Oncologic	1	3	3	4	2	3	3	3
Ovarium cancer	Oncologic	1	4	3	3	2	3	3	3
Pancreatic cancer	Oncologic	1	3	3	4	2	3	3	3
Prostate cancer	Oncologic	3	3	3	3	2	2	3	3
Renal cancer	Oncologic	3	3	3	4	2	3	3	3
Skin cancer	Oncologic	3	3	3	4	3	4	3	3
Soft Tissue carcinoma	Oncologic	2	2	3	3	2	3	3	3
Stomach cancer	Oncologic	1	3	3	4	3	3	3	3
Testicular cancer	Oncologic	2	2	3	4	2	4	3	3
Throat cancer	Oncologic	2	2	3	3	2	3	3	3
Thyroid cancer	Oncologic	2	2	3	3	2	3	3	3
Uretrhal cancer	Oncologic	1	1	3	3	2	3	3	3
ADHD	Psychiatric	2	2	1	3	2	3	2	3
Anxiety disorders	Psychiatric	1	2	1	2	1	3	2	3
Autism	Psychiatric	2	2	1	3	1	3	3	3
Behavioral disorders	Psychiatric	1	2	2	3	1	3	2	3
Burn-out	Psychiatric	1	2	1	1	3	3	3	4
Dementia	Psychiatric	1	3	1	3	3	3	3	3
Mood disorders	Psychiatric	1	2	1	3	1	3	2	3
Personality disorders	Psychiatric	1	2	2	3	1	1	2	3
Schizophrenia	Psychiatric	1	2	1	3	1	2	2	3
Asthma	Respiratory	2	2	3	3	3	3	3	4
COPD	Respiratory	2	3	3	3	3	3	3	4
Influenza	Respiratory	4	4	3	3	3	3	3	3
Lower respiratory tract infection	Respiratory	2	4	3	3	3	3	2	3
Renal insufficiency	Urogenital	2	3	2	3	2	3	3	4

Appendix 3

Measuring burden of disease

Burden of disease is the impact of a health problem as measured by morbidity and mortality. Burden of disease is defined as loss of health and loss of life years due to diseases, injuries and risk factors. It is expressed in Disability Adjusted Life Years (DALY), which is the sum of the Years Lost due to Disability (YLD) from impairment of the disease and Years of Life Lost (YLL) due to premature mortality (Figure 9).[87] One DALY can be thought of as one lost year of "healthy" life.

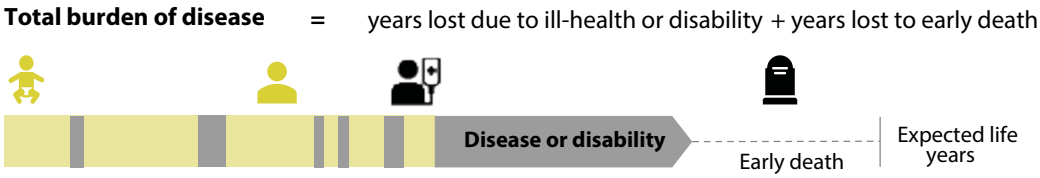


Figure 9: Disability Adjusted Life Year (DALY) is a measure of total disease burden, expressed as the number of years lost due to ill-health or disability (YLD) and due to early death (YLL)

The concept was introduced in a report by the World Bank and World Health Organization (WHO) to measure the Global Burden of Disease.[88] The measure was developed to 1) incorporate non-fatal conditions into assessments of health status, 2) produce objective, independent and demographically plausible assessments of burdens of particular conditions, and 3) measure disease and injury burden in a currency that can be used to assess cost-effectiveness of different interventions, such as the treatment of ischemic heart disease versus long-term care for schizophrenia.[85]
For calculation of the YLLs, a standard reference table for life expectancy is used based on the highest observed life expectancy at the time. In 2010, the table was updated, with life expectancy at birth increasing with more than 4 years. This alteration may have caused the flattening in DALY reduction seen after 2010 in Frame 2.

In this study, we used burden of disease to estimate the potential value of precision medicine. We calculated what the absolute reduction in burden of disease (in DALYs) would be with cutting-edge level of precision medicine. We calculated this both for the population as a whole and for the average Dutch citizen. Since one DALY can be thought of as one lost year of healthy life, we were able to calculate the reduction of lost days of healthy life per person thanks to cutting-edge care. By multiplying DALY reduction per citizen with the life-expectancy, we translated this into the reduction of healthy years achieved over a life time ■

Appendix 4

Overview of consulted experts (through interviews or through review of the manuscript)

André Dekker	Medical Physicist / Professor of Clinical Data Science, Maastro Clinic
Christiaan Vinkers	Psychiatrist, Associate Professor and Group Leaders Mood, Anxiety & Psychosis (Amsterdam Neuroscience) at Amsterdam UMC
Coen van Kalken	CEO, Qurin Diagnostics Founder, NIPED (Personal Heath check)
Edwin Bas	Health Market Research Lead NL at Ipsos Healthcare
Hein Moens	Rheumatologist, Ziekenhuisgroep Twente, Chair, Arthritis Research and Collaboration Hub
Ika van Doorn	Personalized Healthcare Partner at Roche
Jan Sonneveld	Field Access Manager at Roche
Jan-Willem Boiten	Program Manager, Lygature
Jeroen Kemperman	Senior Manager Strategy & Business Development of Zilveren Kruis
Jeske Timmermans	Chapter Lead Personalized Healthcare /FMI, Roche Nederland BV
Judith van Schaik	Business Development Lead, Personalized Healthcare, Roche
Marcel Joachimstahl	Vice President Healthcare Europe at Mobiquity
Maureen Rutten-van Molken	Professor of Economic Evaluation of Innovations for Health, Erasmus School of Health Policy & Management Scientific director of the Institute for Medical Technology Assessment
Paul Louis Iske	Chief Failure Officer, Institute of Brilliant Failures
Ron Herings	Director, PHARMO Institute for Drug Outcomes Research
Ron Mathijssen	Medical Oncologist and Clinical Pharmacologist / Professor in Individualized Oncological Pharmacotherapy, Erasmus MC Cancer Institute
Ruud Meijer	Scientific Healthcare Partner Foundation Medicine / PHC, Roche Nederland BV
Timothy Radstake	Group Leader Systems Medicine / Professor Rheumatology and Clinical Immunology, UMC Utrecht
Ton Schumacher	Group Leader Molecular Oncology and Immunology, Netherlands Cancer Institute

Gupta Strategists