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Precision medicine for cardiometabolic disease

White paper - abridged version

A framework & vision for the future of precision medicine in the diagnosis, prevention, & treatment of complex cardiometabolic disease

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Contents

1. Introduction	1	3. Vision & mission for precision medicine	14
2. Framework for precision medicine	2	3.1 Vision: treat the person & their susceptibilities, not the disease	14
2.1 The problem	3	3.2 Mission: develop high-functioning ecosystems for precision medicine	14
2.2 Terms & Definitions	4	3.2.1 Components of a high-functioning ecosystem for precision medicine for complex disease (Fig. 7):	15
2.2.1 Background on evidence-based medicine	4	References	12
2.2.2 What are precision medicine & personalised medicine?	4	Acknowledgements	12
2.2.3 The EPPI model of precision medicine	7	About the Foundation	12
2.2.4 Pillars of precision medicine	8		
2.3 What is complex cardiometabolic disease?	10		
2.4 Key initiatives: points of alignment & departure	11		

List of abbreviations

ADA	American Diabetes Association	EBM	Evidence-based medicine	FDA	Food and Drug Administration	UK	United Kingdom
BMI	Body mass index	eGFR	Estimated glomerular filtration rate	GWAS	Genome-wide association study	USA	United States of America
CGM	Continuous glucose monitor	EPPI	Evidence-based medicine, Precision medicine, Personalised medicine, Individualised medicine	HbA1c	Haemoglobin A1c	WHO	World Health Organization
CVD	Cardiovascular disease	FAIR	Findable, Accessible, Intraporal, Reproducible	NAFLD	Non-alcoholic fatty liver disease		
DNA	Deoxyribonucleic acid			NASH	Non-alcoholic steatohepatitis		
EASD	European Association for the Study of Diabetes			NHS	National Health Service		
				NNF	Novo Nordisk Foundation		

Executive Summary

Precision medicine has great potential to help reduce the burden of cardiometabolic disease worldwide. It is best viewed as an *evolution* rather than a *revolution* in medicine, as it is unlikely to replace contemporary medicine, yet may substantially enhance it. Under the banner of *cardiometabolic* disease lie several diagnoses including different types of diabetes, fatty liver disease, obesity, and coronary artery, cerebrovascular and peripheral arterial disease; these are accompanied by co-morbidities that damage the vasculature and heart and disrupt metabolism such as chronic kidney disease, neuropathies, and heart failure. There are six key “pillars” of precision medicine: *diagnostics*, *prediction* (of the primary disease), *prevention* (of the primary disease), *prognostics* (prediction of secondary disease), *treatment*, and *monitoring* (of behaviour, risk exposure, treatment response, and disease progression).

To encourage the successful translation of discovery science into clinical practice, we outline a model - the *EPPI* model - that builds on conventional *evidence-based medicine* and includes *precision medicine* (often through stratification of populations into subgroups of similar characteristics to improve disease-related predictions), *personalised medicine* (the use of a person’s data and/or samples to

gauge the efficacy, safety, and/or tolerability of therapeutics), and *individualised medicine* (the tailoring of medical decisions to the person’s needs, preferences, circumstances, and capabilities).

A key distinction between *personalised* and *individualised* medicine is that the latter is predominantly subjective, with the person’s perception and understanding of themselves, their circumstances, and their health ambitions being paramount. Thus, while *precision* and *personalised* medicine should aspire toward the quantification and standardisation of data and processes, *individualised* medicine will require a qualitative approach that is dynamic, with its success predicated on good bilateral communication between healthcare providers and recipients. For *precision* medicine to fulfil its potential, a well-functioning ecosystem will be necessary, comprised of multiple stakeholders such as patients, scientists, clinicians, health educators, health economists, funders, innovators of medicines and technologies, regulators, and policy makers. Large-scale, well-curated, and accessible health databases that contain high-quality, multidimensional, time-series data in people of diverse ethnicities are also required; so too are powerful computing infrastructures

to ensure data are appropriately and rapidly analysed. New prospective studies undertaken in people of diverse ethnicities, designed to generate high-value hypotheses, and clinical trials, designed to test these hypotheses, will also be needed.

In this document, each of these topics is carefully considered to derive a framework and vision for the future of precision medicine for diagnosing, preventing, and treating complex cardiometabolic disease.

1. Introduction



Many common diseases are diagnosed based on symptoms. Rarely is the underlying defect(s) causing the disease a feature of the diagnosis, inhibiting the timely and accurate characterisation of the disease, and predisposing subsequent medical decisions to error. It is exactly these challenges that have motivated the development of methods and processes intended to minimize error and improve accuracy in medical decision making – a concept broadly referred to as ‘precision medicine’.

The landscape of biomedicine is evolving quickly, driven by major advances in technologies and analytical methods, access to largescale health databases, and new insights into the molecular basis of disease manifestation and how it develops. In parallel, there is growing recognition that many blockbuster drugs are insufficiently effective¹ and that long-term healthy lifestyle interventions have little or no impact on mortality².

These observations are collectively fuelling interest in precision medicine, with the hope it will lead to safer and more efficacious, accessible, equitable, and economically viable approaches to tackling disease (Fig. 1).

There is also growing commercial interest in precision medicine³. Thus, building environments and infrastructures that facilitate synergies of population health, big data, and biotech is emerging as a strategic ambition of many nations.

Nevertheless, the health sector has been less effective in its utilisation of data in decision making than other sectors: take the airline industry for example, where automated processes for piloting and landing aircraft are now mainstream, or car navigation where mapping systems help minimise travel time and distance, or the music and advertising industries, where algorithms are used to personalise product pitches to the customer.

Thus, breakthroughs in precision medicine are not merely of academic interest, but, more importantly, necessary for humanity, if the burgeoning health demands of global populations are to be equitably addressed.

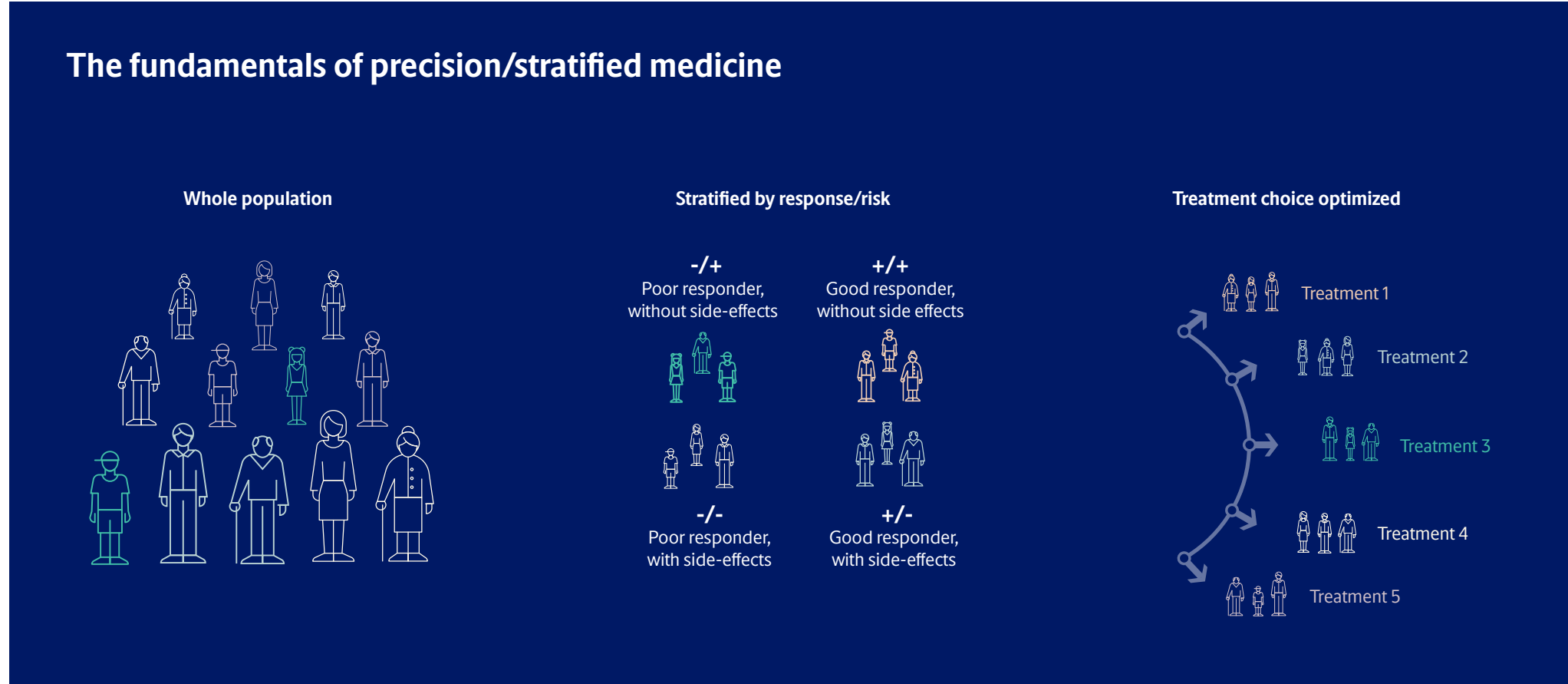
The Novo Nordisk Foundation has been an early supporter of research into precision medicine. Nevertheless, the Foundation has, to date, lacked a formal strategy to ensure synergies between precision medicine-aligned research and infrastructures.

To establish a strategic basis for cutting-edge, clinically impactful precision medicine, the Novo

Nordisk Foundation recently draft a White Paper. The White Paper includes a framework that clarifies terminologies, as well as a unifying model that emulates clinical decision making and links contemporary evidence-based medicine with precision and personalised medicine - the EPPI model.

The White Paper also provides a roadmap that highlights the work needed to bridge the gap between basic research in precision medicine and clinical practice. The current document is an abridged version of the White Paper.

Figure 1. Heterogeneity in treatment response or risk may justify a precision medicine approach. Data-driven stratification of a target population into relatively homogenous subgroups is often considered relevant to *precision medicine*.



2. Framework for precision medicine

There are numerous, often incompatible, definitions of precision medicine proposed by leading authorities. What is and what *is not* precision medicine remains unclear to many both within and outside of the area, particularly in the context of common diseases. At the same time, academia, governments, and industry are driving hard to advance the concept of precision medicine. A lack of clear consensus is likely to inhibit progress and detract from the ultimate goals of precision medicine: to improve the wellbeing of people and society.

Nevertheless, precision medicine has much to offer, providing the new technologies, services, and expertise it delivers are accessible and tailored to those in need. Specifically, precision medicine may help diminish the burden of complex disease on a major scale through early detection and targeted prevention, as well as by disrupting disease progression and providing new cures.

2.1 The problem

Cardiometabolic diseases are driven by features of industrialised lifestyles set against a backdrop of genetic susceptibility. According to the World Health Organization (WHO) [who.int/data/gho/data/themes/mortality-and-global-health-estimates](https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates), cardiovascular diseases (mainly ischemic heart disease and stroke) accounted for about one third of global mortality in 2019 (~20 million deaths), with diabetes directly causing a further ~1.5 million deaths worldwide. The WHO estimates that the lethality of heart disease and stroke is similar across socioeconomic groups, whereas diabetes has been more burdensome in mid- to high-income countries. However, with many developing countries shifting toward industrialised lifestyles, the burden is likely to fall more heavily on them in the coming years. Quality of life is substantially diminished in people living with these diseases, a problem that starts to peak in middle-age, with the impact being observed at younger ages in some ethnic groups.

Public health initiatives such as anti-smoking campaigns and bans on trans-fats in foods have helped substantially reduce the burden of cardiometabolic disease at a population scale. Nevertheless, doctors often rely on pharmacotherapies to prevent and treat these diseases, driven by the belief that sustained benefits from lifestyle interventions are rarely achieved owing to poor compliance, limited efficacy, and high resource burden⁴.

Drug development as currently deployed is risky and expensive, with the average prescription drug costing ~2.6b USD and taking 11-14 years to develop⁵, with only 1:10 000 compounds obtaining U.S. Food and Drug Administration (FDA) approval⁶. Moreover, blockbuster drugs are often ineffective in many to whom they are prescribed¹. Thus, improving the efficacy and safety of drugs is both morally and economically important.

As drugs go off-patent, the wider availability of low-cost generics will affect prescribing

decisions, with the risk of over-prescription. In this context, precision medicine may play an important role in minimising unnecessary risk amongst those prescribed therapeutics that deliver marginal benefits⁷.

Like pharmacotherapies, the efficacy of lifestyle therapy in the prevention and treatment of disease is also highly variable. Look AHEAD, a trial of intensive lifestyle intervention for the prevention of cardiovascular outcomes in people with type 2 diabetes (T2D), was stopped early owing to futility⁸. However, *post-hoc* analyses revealed subgroup effects, whereby the intensive lifestyle intervention was effective in people with younger onset diabetes compared with standard-of-care in this group. By contrast, cardiovascular event rates were highest in the subgroup of participants with poor glycaemic control who received the lifestyle intervention, with event rates exceeding those in the same subgroup receiving standard-of-care⁹, arguing against the idea of one-size-fits-all lifestyle recommendations.

2.2 Terms & Definitions

2.2.1 Background on evidence-based medicine

Best practice in the prevention and treatment of virtually all complex diseases relies on evidence-based medicine (EBM), typically informed by the combination of observational studies (particularly for disease prevention) and randomised controlled trials (particularly for pharmacotherapies); other types of experimental and/or real-world data complement medical decision making.

Guidelines typically rely on population-averaged estimates of risk (for prevention) and efficacy and/or safety (for treatment), under the assumption that such averages meaningfully predict a person's risk factor susceptibility or treatment response. Nevertheless, the accuracy of these predictions varies considerably within and between populations, failing many people in need. It is from this realization that the concepts of *precision* and *personalised* medicine emerged.

2.2.2 What are precision medicine & personalised medicine?

The terms *precision* and *personalised* medicine are often used interchangeably. Here, in the context of complex traits, the Foundation considers these concepts to be distinct yet complementary steps in a process that if managed correctly will help prevent disease and improve its treatment and management.

Although the word 'medicine' is often attributed solely to pharmacotherapies, it has throughout history described wide ranging processes focused on treatment and healing of the mind

and body. Here, we consider *medicine* to include not only drugs, but also lifestyle therapies such as health-promoting diets and exercise regimes, psychotherapy, as well as physically invasive treatments such as surgery.

Precision and *personalised* medicine seek to reduce error and improve accuracy in medical decision making, albeit in distinct ways. In medical parlance, 'precision' literally means a "relative lack of random error"¹⁰. Accordingly, precision medicine is very much focused on reducing error in medical decision making, for example by minimizing misdiagnosis or improving the specificity and/or timeliness of a diagnosis; it may also maximize the probability that a preventive intervention is needed and will work for a given individual, or that a prescribed drug is the best of those on offer for the patient.

Precision medicine typically involves the statistical interrogation of a reference population's high-dimensionality data to obtain precise and accurate estimates of risk and/or response. This process may involve stratifying the reference population into homogeneous subgroups sharing similar risk/response characteristics or deriving probabilistic scores that focus on predicting risk/response without the need to stratify. Thereafter, the most important (i.e. informative and accessible) biological, social, and behavioural markers are measured in patients outside the reference population to inform predictions of their specific diagnosis, risk factor susceptibility, and/or treatment response. The data obtained from this process can be conveyed to the clinician using decision support systems. While there are

considerable benefits to such systems there are also risks that require appropriate mitigation strategies (see¹¹ for overview).

The next step, *personalised medicine*, requires that the medical intervention is monitored and, where necessary, adjusted using biological and/or behavioural readouts obtained in the patient to monitor intervention dose, intensity, timing, and/or tolerability. Today, most feedback is not obtained in real-time, instead emanating from point-estimates of HbA1c, lipids, blood pressure, body weight, and other biomarkers of control (including pharmacodynamic biomarkers designed to give early indication of efficacy); the limited dynamic monitoring data currently obtainable comes predominantly from devices such as continuous glucose monitors (CGMs), heart rate monitors, blood pressure monitors, and movement sensors. Nevertheless, the arsenal of technologies available to the clinician will soon expand to include a comprehensive array of cutaneous (AKA 'wearables'), subcutaneous, and/or ingested sensors that can measure, in real-time, multiple circulating biomolecules and metabolites, psychophysical stress, blood flow, cardiac and vascular function, and health-related behaviours, etc.

In some settings, biological readouts that help refine a medical intervention can be obtained *ex vivo* using a patient's healthy or diseased cells to determine therapeutic response characteristics or to facilitate the delivery of a drug or enhanced cells. Such methods are already in use in the treatment of rare¹² and common¹³ cancers, and cutaneous and subcutaneous wounds¹⁴, including diabetic foot ulcers¹⁵. The extension

of these techniques using adult stem-cell-derived organoids¹² has expanded the range of accessible tissues, making way for personalised drug screening in many other diseases.

Although it has long been known that an individual's response to the effects of drugs and foods is determined in part by his or her biological characteristics¹⁶, only recently has the detailed assessment of a person's biological features (e.g. DNA variants, transcripts, epigenetic marks, proteins, metabolites, and microbial sequences) been possible at scale. Such data may help advance understanding of disease and therapeutic response variability.

The technological advances underpinning some aspects of precision medicine may imply that precision medicine is a *revolutionary* concept. However, over-selling the benefits of precision medicine before empirical evidence unequivocally demonstrates its strengths and weaknesses is likely to undermine public trust. Hence, at this stage, precision medicine is best viewed as the next step in the *evolution* of medicine, embracing and extending current medical knowledge and practice to enrich the overall ecosystem of healthcare.

For precision and personalised medicine to succeed, one must also *individualise* the process. Here, the Novo Nordisk Foundation adopts the definition of *individualised medicine outlined in the ADA's Standards of Medical Care in Diabetes*¹⁷, where the clinician is instructed to adapt guidelines to fit the patient's circumstances (e.g. food security, housing, and financial stability), characteristics (e.g. level of education and cultural practices), comorbidities (including

mental health), and preferences. Health and technological literacy will often be important for precision medicine to succeed, owing to the data-driven way medical decisions will be made.

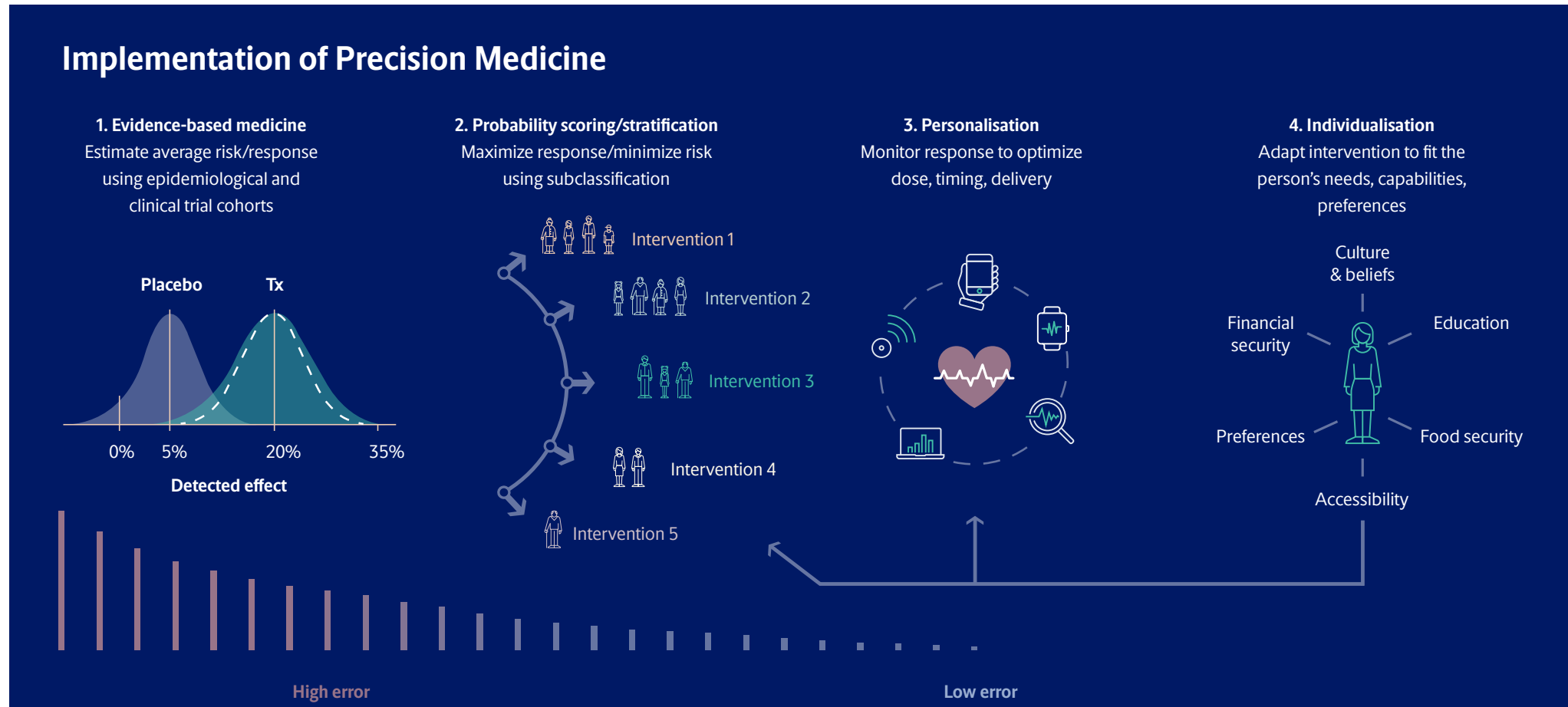
2.2.3 The EPPI model of precision medicine

The Novo Nordisk Foundation has proposed a model intended to help bridge a key gap in

precision medicine between basic research and clinical practice. This model (EPPI) begins by scrutinizing the best available data and EBM using the principles of precision medicine (probability scoring/stratification), after which personalisation and individualisation are undertaken to further refine medical decisions and to tailor the medical intervention to the person (see Fig. 2).

The EPPI model should not be considered a strictly linear process nor its output static. Instead, continuous monitoring and feedback from healthcare recipients to healthcare professionals, potentially through technologies that generate readily accessible time-series data, will be essential. Moreover, the individualisation of this process (see later) will require that healthcare recipients

Figure 2. The multi-step “EPPI” model for the implementation of precision medicine. EPPI: Evidence-based medicine; Precision medicine (probability scoring/stratification); Personalisation; Individualisation



(or their representatives) are able to contribute throughout, from the first steps where research is prioritised and evidence is generated, to the point where the medical intervention or advice is being tailored to the person for whom it is intended. This should be done by optimising disease diagnosis, prediction, prevention, and treatment by maximising benefit, safety, and equity in an economically viable way.

The EPPI model is intended to help unify perspectives and plans related to precision medicine at the Novo Nordisk Foundation, as well as to provide a paradigm that might prove useful to those applying for funding from the Foundation when designing research aligned with the principles of precision medicine.

2.2.4 Pillars of precision medicine

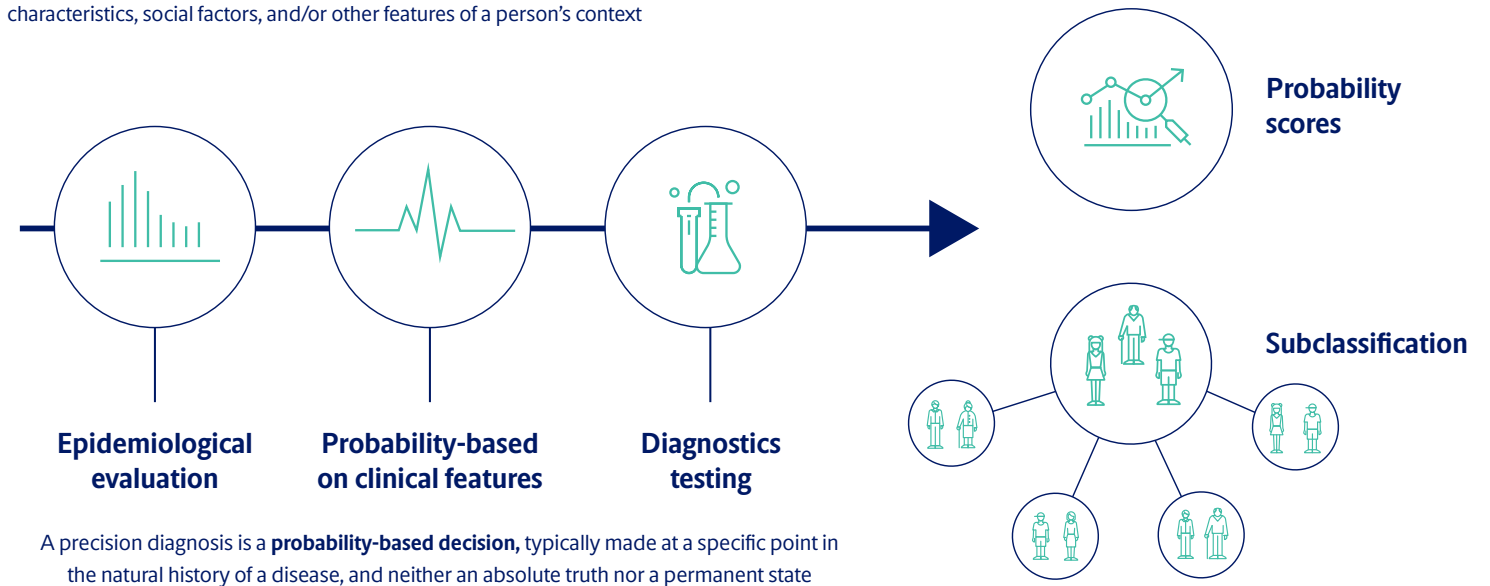
There are several key pillars that underpin precision medicine, representing the domains within which it will be applied to improve health. The following are adaptations of previously proposed definitions¹⁸. While each of these pillars helps provide a framework for precision medicine, one should consider that these domains will occasionally overlap or be entirely synonymous.

2.2.4.1 Precision diagnosis (Fig. 3):

is a refined characterisation of the disease diagnosis for therapeutic optimisation or to improve prognostic clarity using information about a person's biology, environment, clinical characteristics, social factors, and/or other features of their context. Precision diagnostics often involves subclassifying patients to optimise treatment and prognosis. Because

Precision Diagnostics

Refining the characterisation of cardiometabolic disease to optimize therapies and/or prognostication using information about a person's biology, environment, clinical characteristics, social factors, and/or other features of a person's context



A precision diagnosis is a **probability-based decision**, typically made at a specific point in the natural history of a disease, and neither an absolute truth nor a permanent state

cardiometabolic diseases tend to progress and treatment seeks to counter disease progression, an individual's assignment to a specific diagnostic stratum is not immutable; thus, monitoring of disease progression and treatment response will help the clinician determine if a patient's diagnosis should be revised. Importantly, precision diagnostics may begin with a relatively agnostic approach, using conventional and unconventional diagnostic information including classical blood-borne biomarkers, imaging data, or socioeconomic determinants, etc.

Precision diagnostics is likely to be especially impactful when optimizing diagnoses across ethnicities, where the manifestation of cardiometabolic diseases may vary greatly from one ethnic group to the next¹⁹.

Figure 3.

A precise diagnosis is necessary for almost all other features of precision medicine to reach their potential.

2.2.4.2 Precision prevention (Fig. 4):

includes using information about a person (e.g. biology, environment, clinical characteristics, social factors, and/or other features of a person's context) to determine their likely responses to health interventions and risk factors and/or to monitor progression toward disease or regression to a healthy state. Within the area of prevention falls the task of *prediction* (Fig. 5). This may involve the combination of biological markers and data about socioeconomy, gender, lifestyle behaviours, diet, sleep, and psychophysiological stress, etc., to minimize error in the prediction of disease incidence (time to event) and/or the severity with which a disease is likely to manifest in the future. Precision prediction should also focus on the probability with which an individual hovering just below the diagnostic threshold is likely to regress to a healthy state. Thus, precision prediction is not only a matter of probability and risk calculation, but also of directionality, acknowledging that the predictors of progression and regression may not reciprocate.

For the sake of distinguishing *precision prediction* from *precision prognostics*, we consider the former to relate only to prediction of the primary disease, whereas the latter would include the prediction of a disease that is viewed as secondary (i.e. a complication of another disease). In many instances, this distinction will not be absolute, but instead determined by the specific research question, study design, or clinical application.

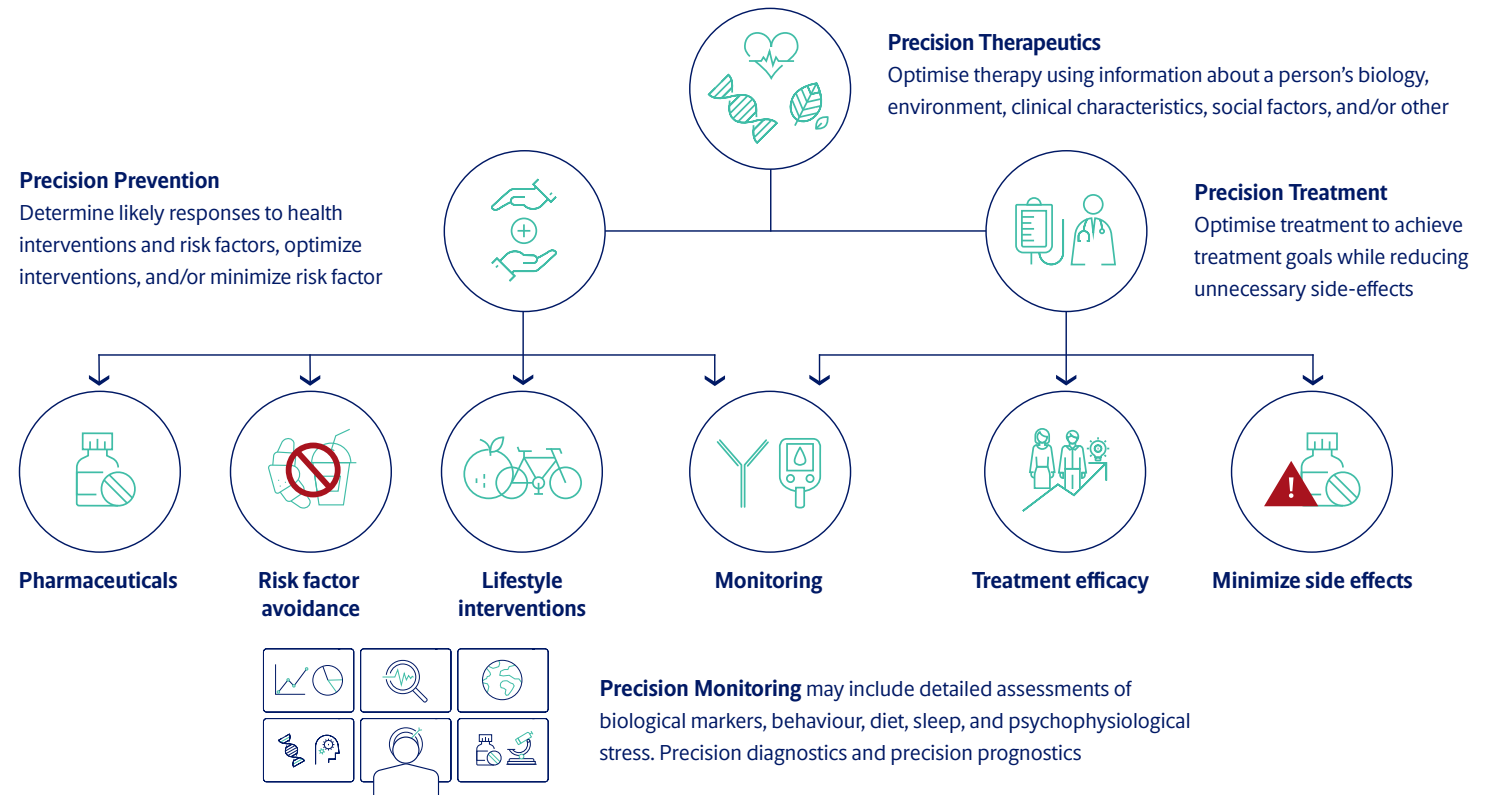


Figure 4.

Within precision therapeutics sit three components: i) *precision prevention*, which focuses on risk factor mitigation and health promoting actions; ii) *precision treatment*, which focuses on optimised decision making to help manage a patient's disease; iii) *precision monitoring*, which is necessary to ensure behavioural and environmental risk factors are accurately quantified (for precision prevention) and to monitor the progression and evaluate the success of precision treatments.

2.2.4.3 Precision monitoring (Fig. 4):

may include the detailed assessment of biological markers (e.g. continuous glucose or blood pressure monitoring), behaviours (e.g. physical activity), diet, sleep, and psychophysiological stress. Ultimately, the success of precision medicine is predicated on whether the recipient can and will adhere to the intervention. Accordingly, reliable predictors of adherence should be incorporated into precision medicine algorithms, and measures of adherence should be obtained during the personalisation step to gauge and adjust the intervention as needed.

Precision Prediction

Optimizing the prediction of incident disease by assigning precise estimates of a person's lifetime risk of disease & time to disease onset

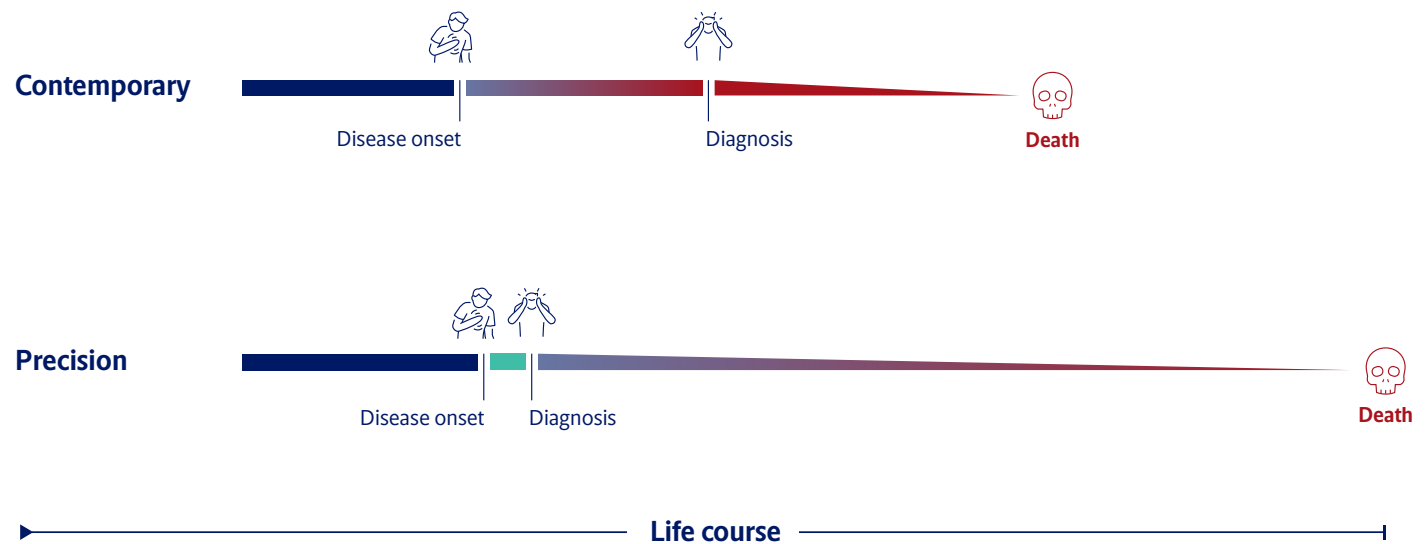


Figure 5.

Accurately predicting if a person is likely to develop a disease and when in the life-course disease will manifest will help channel resources for prevention to high-risk individuals, help optimise the timing of preventive interventions, and minimise the time from disease onset to diagnosis. Collectively, the optimisation of these processes may enhance the quality and duration of life

2.3 What is complex cardiometabolic disease?

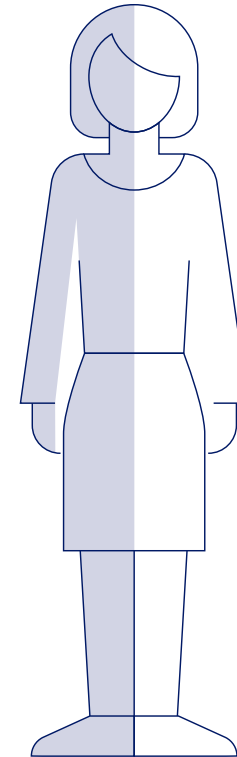
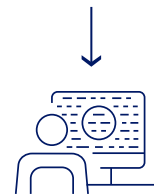
The aetiology, clinical manifestation, and path of most common diseases vary considerably from one person to the next. By contrast, some rare diseases have a relatively simple causal explanation, present in a similar way from one patient to the next, and follow a predictable path once manifest. To distinguish the former class of disease from the latter, our focus here, the term “complex disease” is used.

The term “cardiometabolic” was introduced in the late 1970s²⁰ and is now widely used. The American College of Cardiologists defines cardiometabolic disorders as “... a cluster of interrelated risk factors, primarily hypertension, elevated fasting blood sugar, dyslipidemia, abdominal obesity and elevated triglycerides”²¹.

Here, we consider cardiometabolic diseases to include different types of diabetes, coronary heart disease, cerebrovascular and peripheral arterial disease, NAFLD/NASH, and obesity. The common vascular and metabolic risk markers (e.g. impaired fasting and/or post-challenge blood glucoses, dyslipidaemia, hypertension, and elevated inflammatory markers) and complications of these diseases (e.g. nephropathy, neuropathy, and retinopathy) also fall within the realm of cardiometabolic disease, although not all are stand-alone markers of pathology (e.g. dyslipidaemia), or are of established clinical relevance (e.g. elevated inflammatory biomarkers).

Precision Prognostics

Improve the precision and accuracy with which a person's disease-related outcomes are predicted using information about their biology, environment, clinical characteristics, social factors, and/or other features of a person's context



Hypoglycaemia



Cerebrovascular disease



Retinopathy



Cardiovascular disease



Nephropathy



Neuropathy



Patient-centered outcomes



Death

Figure 6:

Accurately determining at or soon after diagnosis the rate at which the disease will progress and the complications that are likely to ensue could help optimise medical decision making and may reduce burden for the patient and the health system within which they are treated.

2.4 Key initiatives: points of alignment & departure

It is not only the pharmaceutical industry that is betting on genetics to help revolutionize healthcare. Many governments are also pursuing national strategies to help implement genomic medicine into healthcare. In the UK, the government has invested hundreds of millions of pounds in a genomics strategy designed to ensure that “... *patients in the UK will benefit from world-first advances in genomic healthcare through globally leading collaborations between the government, NHS and researchers, building on already successful programmes such as the 100,000 Genomes Project, delivered by NHS England and Genomics England, and UK Biobank.*” [Genome UK: the future of healthcare \(publishing.service.gov.uk\)](#).

The Danish Strategy for Personalised Medicine 2021-2022 [Personlig medicin til gavn for patienterne \(ngc.dk\)](#) is almost exclusively focused on genomic medicine; specifically, the use of genome sequencing to improve the diagnosis, prevention, and treatment of disease, under the assumption that “... *analysis of the genes might contribute to understanding why the patient has become ill and thus to finding the best treatment for the patient*”.

The UK Government's Life Sciences Vision [life-sciences-large-print.pdf \(publishing.service.gov.uk\)](#) makes it clear that a key additional aim is to profit economically from the huge and emerging market in genomic-driven biomedicine, with the ambition to make the UK a “Scientific

Superpower” that hosts environments and infrastructures to which outside investors in biomedicine will be attracted. The strategic partnerships required to realise this vision between public and private sectors are focused on three key areas: i) **diagnosis and personalised medicine**, with emphasis on cancer, rare/ inherited disease, pharmacogenomics, and infectious disease; ii) **prevention**, with emphasis on early-life and adult genomic screening; iii) **research**, with emphasis on “... *a seamless interface between research and health care delivery*” [Genome UK: the future of healthcare \(publishing.service.gov.uk\)](#).

Contrasting the UK's Life Science Strategy, the Danish equivalent [Aftale om strategi for life science \(002\).pdf \(sum.dk\)](#) makes no mention of genetics, touching only briefly on the need for synergies between Danish strategies for Life Sciences and Personalised Medicine [Personlig medicin til gavn for patienterne \(ngc.dk\)](#), without specifying how this might be achieved. Instead, the Danish Life Science Strategy focuses on improving opportunities for industry-initiated clinical trials, assimilation of large health databases, national data analysis infrastructures, and emphasises the importance of access to rich health data already available in Denmark. This is one area where the UK and Danish Life Science Strategies are aligned, both recognizing the value of large cohorts, biomedical datasets, and electronic health records.

The successful amalgamation of individual-level, highly sensitive health data for public health and commercial purposes, a core feature of many life science strategies, faces significant

regulatory, legal, organizational, societal, and logistical obstacles, for which adequate solutions remain outstanding in most countries.

A second significant concern is that the vast majority of genome-wide association studies (GWAS), from which evidence supporting clinical genetic tests for complex traits comes, were undertaken in European ancestry populations. This is problematic because the genetic architecture of almost any disease varies by ethnicity, which can in turn impact the validity of genetic tests designed using evidence from a different ethnic group²².

Hence, precision medicine and the methods to implement it will often need to be designed and/or adapted to the ethnicity and context of the recipient. To address this need, the datasets generated and developed for precision medicine research, genetic and otherwise, will need to accommodate these and other sources of human diversity, breaking from the tradition of prioritising data collection and analysis in European-ancestry populations located in the wealthiest regions of the world.

A third concern is that not all diseases are equally heritable, nor is the genetic basis to all heritable diseases understood to a comparable degree. Thus, applying a precision medicine strategy predicated heavily on genetics to all diseases is likely to promote inequity, with the quality of medical care dictated not by human need, but by the readiness of a single technology²³.

In highlighting these issues, the Novo Nordisk Foundation is not arguing that genetics

should be excluded from national strategies for precision medicine; quite the contrary, as genetics can be a powerful weapon in the arsenal when fighting disease. However, for precision medicine to be effective, it needs to exploit all accessible credible data.

For the diagnosis of rare disease, genetics can be supremely effective, yet for the diagnosis of complex diseases, non-genetic data are often more informative. Indeed, in the same sense that taking a one-size-fits-all approach to medical decision making is flawed (an argument often used to support precision medicine), so too is the view that a single method or data type to optimise medical decision making (e.g. genetics) is fit for all purposes. Thus, complex diseases are likely to vary in their data requirements, with some diseases needing multifaceted data, whilst others much less so.

There are many imaginable settings where the prediction and prevention of cardiometabolic disease will be enhanced using the principles of precision medicine applied using rudimentary, easily accessible, and inexpensive data. The TriMaster trial is illustrative of this point, where the use of simple markers of obesity and kidney function (BMI and eGFR respectively) to stratify choice of anti-diabetes medications was shown to substantially improve efficacy²⁴. Such simple treatment algorithms could easily be applied in the health care systems of developing countries, countering the view that precision medicine is only for rich nations.

3. Vision & mission for precision medicine

3.1 Vision: treat the person & their susceptibilities, not the disease

A standard approach to common complex disease diagnosis is to lump together symptoms that frequently co-occur, with the assumption they represent a common pathology. However, this 'diagnostic' approach risks leading scientists and clinicians astray in their attempts to prevent or cure disease, as not all co-occurring symptoms do in fact share the same pathology. An additional challenge is that many diagnostic procedures focus on symptoms, rather than pathology. Subsequently, many therapies for these diseases are designed to reduce symptoms rather than disrupt the disease process, the latter being necessary to cure disease. Moreover, the diagnostic approach focuses on the disease, rather than understanding the person with the disease.

This may hinder clinical care and biomedical discovery, because complex diseases like obesity, diabetes and cardiovascular disease are caused by many biological and non-biological factors acting in concert (e.g. through gene-environment interactions), and these combinations are often person-specific.

Understanding the person who has developed the disease may also facilitate treatment solutions and value chains that are most likely to succeed. Moreover, it may be the first step in understanding how to (re-)organise healthcare delivery systems that were originally designed at a time when people admitted to hospital with severe pathologies could expect one of two outcomes: cure or death. Since people now live for many years with chronic conditions, now may be the time to revisit healthcare delivery to stabilise disease, as part of a sustainable and more effective solution for the future.

3.2 Mission: develop high-functioning ecosystems for precision medicine

The successful implementation of a large-scale precision medicine strategy requires collaboration between many diverse stakeholders, consensus about definitions, protocols, and the format of clinical readouts, etc. No less important will be the seamless integration of relevant technical processes, robust data curation, intelligent data analyses, and adequate clinical infrastructures through which data can be communicated and translated. Denmark, like several other nations, already possess many of the components necessary to develop an ecosystem of this nature. These include many world-leading clinical and biomedical scientists, major health databases integrated with clinical record systems, an excellent social welfare system,

access to advanced medical technologies, a health- and technology-literate population, and the means to deliver precision medicine in practice through the Steno Diabetes Centers, particularly as it relates to cardiometabolic disease. What is absent in many countries, including the UK, US, and Scandinavia, is a national strategy to develop this ecosystem and the processes necessary for the clinical implementation of precision medicine (not merely genomic medicine) for complex diseases.

3.2.1 Components of a high-functioning ecosystem for precision medicine for complex disease (Fig. 7):

3.2.1.1 Capacity building:

focuses predominantly on data acquisition, harmonisation, management, and analysis. This will include: i) aligning and consolidating existing databases, ii) gap analyses, iii) generating new, high-value data to address significant data gaps, and iv) developing cutting-edge data management (e.g. federated databases) and analytical tools and processes. Addressing the legal, social, and ethical barriers to precision medicine research and practice will be required to ensure these elements of capacity building are successful. In most democratic societies, this will require both public and political will for change. To achieve this, a two-pronged approach is required: i) clear, appropriate communication with the public to address concerns regarding potential data misuse; and ii) ensuring politicians understand the benefits of data sharing for precision medicine purposes such as increased health equity at a reduced cost to society.

This ambition is closely aligned with the current UK and Danish life science strategies.

Importantly, access to powerful data means little unless there is adequate computational capacity and expertise in data management and analysis. Thus, some elements of a capacity-building strategy should include super-computers and education in data sciences; the rapid expansion in volume and dimensions of health databases, coupled with a shift toward

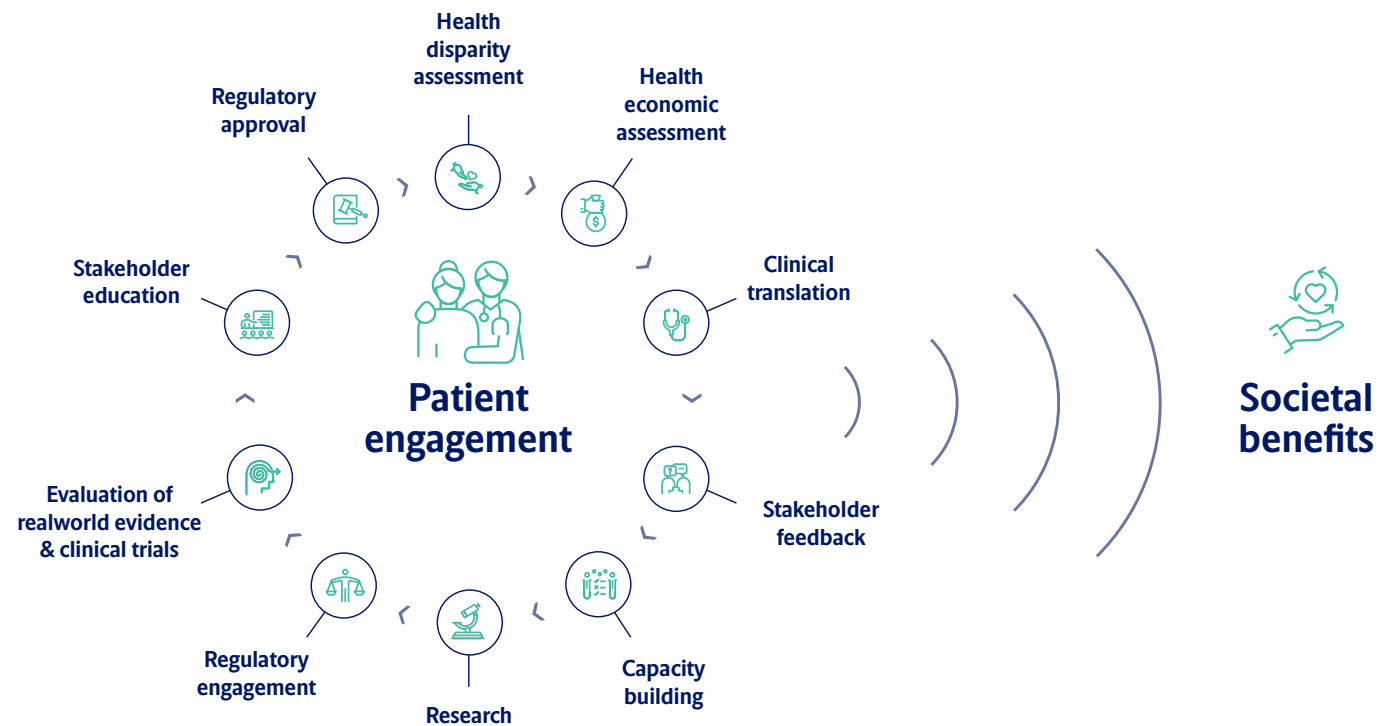


Figure 7:

The adequate translation of basic research in precision medicine to clinical practice requires a high functioning ecosystem

deep-learning data analysis methods, will place increasing demands on computational infrastructures. Quantum computing has already proven its ability to solve extremely complex problems in a fraction of the time a conventional super-computer would take²⁵. Hence, in precision medicine, a shift towards quantum computing is anticipated, requiring significant investments not only in physical infrastructures, but also in training in quantum programming.

3.2.1.2 Basic research:

Ensure adequate and appropriately targeted funding mechanisms that promote world-class epidemiology and data science research, which facilitates the strategy for precision and personalised medicine.

In the case of population genetics, classically trained epidemiologists have played a surprisingly marginal role. There are cases where the absence of sound epidemiological reasoning has led to misinterpretation of study findings driven by flaws in study design and data analysis methods: the impact of collider, spectrum, and other sources of bias, misunderstanding risk estimation and reclassification indices, and over-reliance on p-values, being examples. Nevertheless, genetic data is relatively robust to reverse causality, many common sources of confounding, and measurement error compared with many other types of data. Thus, as databases grow in volume and dimensionality, engagement of well-trained epidemiologists and statisticians will become increasingly important²⁶.

The Foundation seeks to support a portfolio of projects that i) minimises data and/or

knowledge silos, ii) actively promotes synergies between researchers, iii) is characterised by ground-breaking and internationally leading research, iv) promotes the FAIR data principles: Findability, Accessibility, Interoperability, and Reuse of digital assets (<https://www.go-fair.org/fair-principles/>), and v) has a demonstrable positive impact on the health and well-being of individuals and societies.

3.2.1.3 Regulatory engagement:

The clinical implementation of precision medicine that involves new therapies, technologies or companion diagnostics will often require regulatory approval from specific medicines agencies (in the EU the *European Medicines Agency* and in the USA the *US FDA*). The process of doing so should ideally begin early in the research process, through consultation between academic scientists and regulatory authorities. Furthermore, because academic researchers often lack regulatory knowledge, awareness of regulatory processes within the academic community needs to increase. Similarly, regulators expect those researching and developing drugs within precision medicine frameworks to provide feedback, so that any amendments to regulatory processes are pragmatic and beneficial for the approval of high-quality precision medicine products.

3.2.1.4 Evaluation of real-world evidence & clinical trials:

Clinical trials specifically designed to assess the efficacy and safety of precision medicine products are likely to be necessary for clinical translation. Trials that assess the repositioning of therapeutics using, for example, companion



diagnostics (an adjunct to a therapy to determine its suitability for a given patient), are likely to exceed the design complexity and costs of conventional phase III trials. By contrast, the development of new precision medicine therapeutics should accommodate such complexities into drug development pipelines in a way that delivers relatively parsimonious and cost-saving phase III trials. Specifically, after phase II, trials might focus on those who are predicted to respond, thereby reducing sample size and cost. Regardless of the specific approach, successful precision medicine trials are likely to be innovative in design and complimented by the re-analysis of existing clinical trial data and real-world evidence. There

is currently no consensus on how this should be done, highlighting standardisation of precision medicine trial design as a priority topic.

3.2.1.5 Stakeholder education & knowledge transfer:

The extent to which precision medicine will benefit society is predicated on two key social factors: i) widespread perception of benefit across multiple stakeholders, and ii) a sense of personal agency amongst health care providers and recipients about this process. Achieving these aims requires that the benefits are real and the processes through which these benefits will be realised are clearly understood. Even though the specific processes may vary between stakeholders, as will the

specific commodities that stakeholders are asked to invest and the derived benefits, there must be a collective sense that by investing in precision medicine, “all boats will rise on the same tide”. A challenge that we seek to address through this document is that there is currently little consensus about the concepts, terms, and definitions necessary for precision medicine to advance. Thus, alignment across key stakeholders is an early and necessary objective if those researching and practicing precision medicine are to operate efficiently and with a clear and appropriate mandate. Obtaining adequately informed support from the public and other partners requires clear communication, which can only be achieved with common, clear, and concise language.

Linguistic clarity is also important for the clinical implementation of precision medicine, so that health professionals can be trained, and health care recipients are able to understand and participate in medical decisions. However, training health care providers before consensus is reached may be counterproductive.

A keystone in the clinical translation of precision medicine will be the development and implementation of decision support systems, which will need to deliver potentially complex information in an easily understandable and actionable format.

3.2.1.6 Health disparity assessment

In an ideal world, precision medicine would improve health on the level of all individuals, helping neutralise health inequities across the board. However, the risk that precision

medicine will widen health disparities is significant, either because the technologies, products, and services are not ubiquitously accessible to, or are poorly designed for, those most in need. Take, for example, precision medicine that depends on advanced imaging technologies too costly for low-income settings, or on assays requiring cold-chains that are absent in many developing countries, or genome-screening technologies designed based on variation in European-ancestry genomes with uncertain validity elsewhere. In these settings, the introduction of precision medicine may widen disparities. Similarly, the types of data needed for precision medicine will vary by disease type and setting. In places like the UK, Denmark, and Sweden, where genomic medicine is being increasingly prioritised, the heritability of a patient’s disease will influence the efficacy of genomic medicines, emphasising the need for strategies that ensure data used in prediction models are optimised to the disease and population in question. Thus, health disparity assessments during the development and implementation of precision medicine will provide necessary benchmarks to success.

3.2.1.7 Health economic assessment

As with health equity, the success of precision medicine will be determined to a large degree by its cost-effectiveness compared to contemporary medicine. Because drugs developed using the framework of precision medicine are expected to be more efficacious than and as safe as conventional medicines, one might expect precision medicines to prove cost-effective²⁷. Diagnostic stratification to optimise medical decision making has already proven



cost-effective in coronary artery calcification, where a standard chest CT can help identify people at high risk as well as very low risk of a coronary event.

However, because regulatory approvals are likely to be restricted to specific patient subgroups, the cost of producing precision pharmaceuticals relative to the market size (and their market price) may be higher than conventional medicines. The counter argument is that regulator/payor requirements are so costly that there is limited space for the development of conventional medicines. The focus of industry may consequently shift to delivering precision pharmaceuticals as a minimal viable product to drive net benefit. These dynamics are further complicated by the possibility that with fewer companies working on the same product, and with a loss of critical mass, breakthroughs may be less likely. Thus, appropriate health economic assessments are essential, even though doing so is likely to be especially challenging, owing to the complicated market dynamics of precision pharmaceuticals²⁸.

3.2.1.8 Clinical translation

In the context of public health, translational medicine is the process of turning biomedical observations into interventions that improve health or prevent disease²⁹. This process requires knowledge of how the components of medical interventions (e.g. drugs, behavioural interventions, devices, and medical procedures) are developed, regulated, marketed, and dispensed³⁰. Thus, a well-functioning ecosystem for precision medicine will include

an expert process of clinical translation, which will require investments to train and equip those responsible for this process. Public-private partnerships will be essential to the process of translating precision medicine research into clinical practice, which will not automatically occur simply because all key components exist.

3.2.1.9 Stakeholder feedback & evaluation

Precision medicine in complex diseases is in its infancy, yet some of today's wild ideas will seed the clinical realities of the future. Inevitably, precision medicine will not evolve perfectly; there will be failures and the course will require correction from time to time. Knowing when and how to adapt this process will be guided by frequent structured feedback from key stakeholders. Stakeholder engagement will also help instil a sense of ownership, without which precision medicine is destined to fail.

Evaluating precision medicine in the context of monogenic disease is often relatively straightforward, owing to the clearly defined diagnostic and treatment process and success criteria. Precision medicine in complex diseases, such as cardiometabolic disorders, is likely to be more challenging to implement and assess. The first evaluation step will involve determining if precision medicine is indeed needed and the estimated cost-benefit ratio justifiable; where conventional EBM provides a framework for medical decisions that is already robust to error, there may be no need to pursue a precision medicine approach.

To gauge the performance and success of precision medicine (compared to traditional

EBM approaches) will require serial feedback from the health care recipient (see the EPPI model). Such feedback is likely to take the form of quantifiable, objective markers of disease progression, stasis, or regression, as well as the health care recipient's perceptions of life quality. It may also be valuable to ascertain how many of those receiving a treatment under conventional EBM guidelines would be spared this (and any side-effects and costs) through a precision medicine-guided approach. Any markers of performance chosen to quantify this will need to be precise and accurate, to minimize the obvious harm that inappropriately withholding treatment from someone in need is likely to cause.

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The Novo Nordisk Foundation is an independent Danish foundation with corporate interests. It has two objectives: 1) to provide a stable basis for the commercial and research activities of the companies in the Novo Group; and 2) to support scientific, humanitarian, and social causes.

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