Precision medicine – moving away from one-size-fits-all

Stefan Kohler discusses how precision health principles apply to various areas of healthcare, ranging from personalised drug treatment to precision population health interventions

More and more tools and technologies from genomics to big data can be used to help deliver the right health intervention, at the right time, to the right person or population. Step by step, better targeted care for individuals as well as populations may therefore be attainable in many areas of health.

FROM ONE-SIZE-FITS-ALL TO PRECISION MEDICINE

'Delivering the right treatments, at the right time, every time to the right person' [1] has been described as the promise of precision medicine (Figure 1). This promise has long been a goal of medicine, but the means available are changing. Hence, recent precision health approaches, including personalised medicine, represent no paradigm shift, but rather an evolution of healthcare. The Greek physician Hippocrates (460-370 BC) is frequently named as the father of Western medicine in recognition of his contributions to medicine and for founding the Hippocratic School of Medicine. Already Hippocrates, supposedly, advised 'give different ones [liquid medicines] to different patients, for the sweet ones do not benefit everyone, nor do the astringent ones, nor are all the patients able to drink the same things' [2]. At the time, Hippocrates suggested evaluating factors like a person's age, physical appearance and the time of the year when prescribing medicines [3] to better target drug prescription to individual patients.

'While Hippocrates used a person's physique and the seasons to personalise treatments, modern science and industry hope to use your DNA [3].'

The use of genetic and molecular diagnostics, in addition to other methods of differential diagnosis, for improved targeting of drug treatments is now often referred to as personalised medicine. There is no universal definition of personalised medicine. Personalised medicine in a broader sense strives to consider all differences between people that affect health outcomes to provide better targeted healthcare. However, in contrast, personalised medicine in a narrower sense, mostly refers to the use of genetic information about people and diseases for better targeted drug therapies. The terms personalised medicine, individualised medicine, stratified medicine and precision medicine overlap and are frequently used interchangeably. Sometimes the terms precision medicine and stratified medicine are preferred to the terms personalised medicine and individualised medicine to emphasise that so-called personalised approaches usually are neither designed for specific individuals nor take into account personal factors, such as individuals' preferences, health resources or experience of disease.

After the Human Genome Project demonstrated the feasibility of decoding human DNA, there were high hopes that precision medicine would rapidly evolve (see Box 1). Similar hopes currently carry over to other emerging sources of health-related data, ranging from health sensor data to routine health data, to socioeconomic, demographic and health surveillance data, to health proxy data from remote sensing, or to smartphone and smart home data (see Box 1).

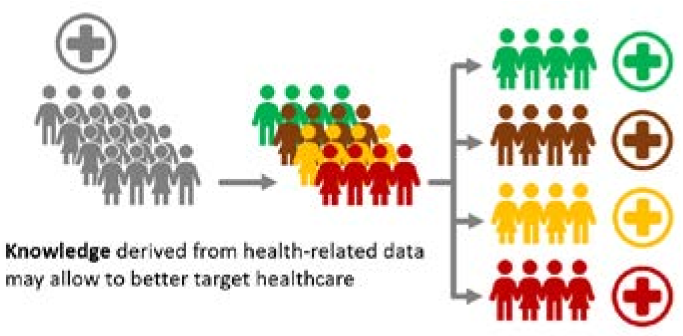

Figure 1(a). One-size-fits-all healthcare may not fit all.

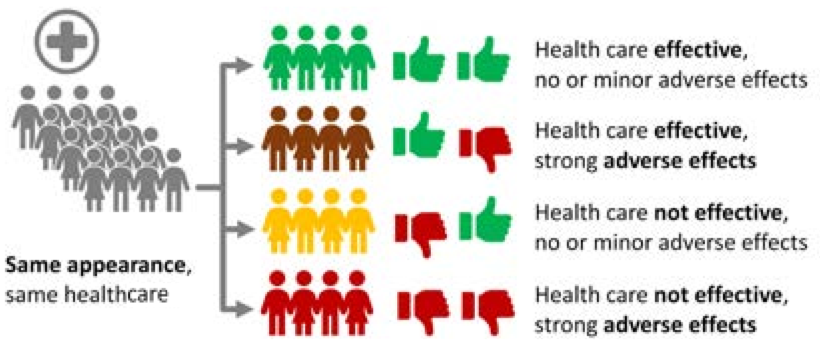

Figure 1(b). Precision health aims to use health-related data to better target healthcare. *Stefan Kohler*

A focus of current applications of precision medicine as well as most development of new precision medicine approaches have been, and continue to be in the field of cancer medicine (oncology). Few successful applications of personalised drug therapy have been discovered in areas other than the pharmacotherapy of cancers [4]. In Germany, for instance, 53 approved drugs were considered personalised medicine in 2017. Of those, 41 (77%) were for cancer treatment and only 12 (23%) in other areas of application (Figure 2). The fundamental idea of applying medicine more precisely, however, is neither restricted to drug therapy nor to cancer medicine (oncology). Precision medicine approaches can be pursued in all areas of health, from disease prevention to health promotion, including health interventions on the population and public health levels.

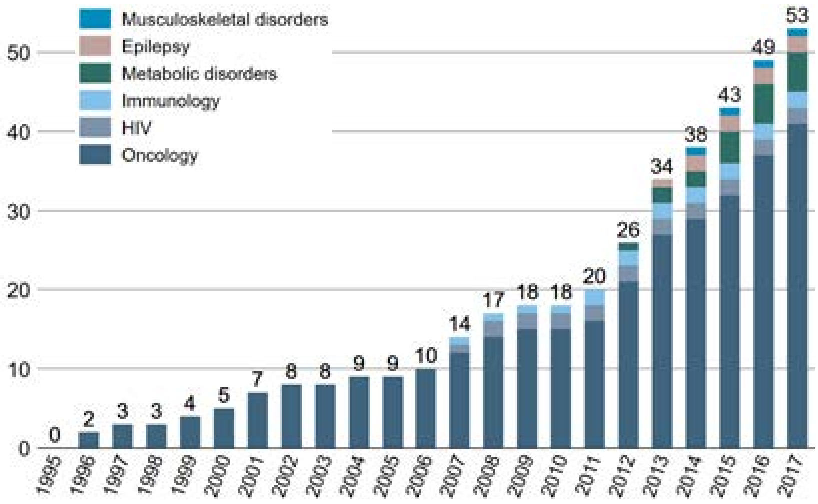

Figure 2. The number of personalised medicines in Germany has steadily increased. Drugs are classified as personalised medicines if a biomarker pre-test for efficacy or adverse drug effects is either required or recommended in the German prescribing information. *Stefan Kohler*

FROM PRECISION MEDICINE TO PRECISION HEALTH

'Precision health is a way of improving overall lifelong health, while precision medicine is generally not implemented until an individual becomes ill [5]. Precision medicine emphasises the targeted medical treatment of people who have fallen ill. However, the risk of disease is already influenced by biologic, social, environmental and economic processes, which affect different people in different ways. In other words, whether someone is healthy or remains healthy, is co-determined by the person's individual circumstances and environment. Figure 3 shows the main determinants of health. Knowledge and awareness about the determinants of health can be used to target preventive health interventions (Box 2).

Disease prevention and early detection of health changes by monitoring health and disease based on an individual's risk is the focus in the emerging field of precision health [6]. As new tools and technologies allow us to collect more data about the various determinants of health, e.g. genotyping at or before birth, health monitoring via health sensors or during clinic check-ups, or surveys about people's socioeconomic status and environmental risk exposure, such information, can be used to predict and prevent disease in health interventions that specifically target those with increased risk of specific diseases.

FROM PRECISION HEALTH TO PRECISION POPULATION HEALTH

Precision health principles can also be applied at the population level (Box 3) to deliver the right population health intervention, at the right time, to the right population.

Health programmes by the government or other organisations complement the work of nurses, doctors and other health workers, by aiming to improve population health. Population health is the health of whole groups or communities of individuals. The health of a population is

BOX 1

PERSONALISED MEDICINE: HOPE OR HYPE?

Examples of successes and setbacks in targeted drug treatment based on genetic markers are described in a *Nature Education* article by Leslie Pray [3]. Her examples continue to represent today's status and challenges of personalised pharmacotherapy.

The *Her2/neu* gene and response to breast cancer treatment – a success

The *Her2/neu* gene can be successfully used as a predictor of breast cancer patients' responses to a drug called trastuzumab (brand name Herceptin). In consequence, trastuzumab is only prescribed to women which have a type of breast tumour in which the cancer cells make too many Her2 receptors (caused by an overexpression of the *Her2/neu* gene). As trastuzumab increases the risk of heart dysfunction, drug regulatory authorities, like the European Medical Agency or the US Food and Drug Administration, typically recommend or require that only patients tested for an 'Her2-positive tumour' are treated with trastuzumab.

The *CYP450* gene and response to antidepressants – a setback

The information our body needs to produce a family of proteins known as the cytochrome P450 enzymes is encoded on the *CYP450* gene. Different forms of the *CYP450* gene have been associated with the function and strength of a commonly prescribed class of antidepressant drugs called selective serotonin reuptake inhibitors (SSRIs). Depending on their genetic makeup, individuals metabolise SSRIs differently - some quickly, others slowly. While, in theory, it should therefore be possible to predict what dose would be most beneficial, clinical studies could not show benefits from prescribing SSRIs based on *CYP450* gene variations.

Source: Adapted from Pray 2008 [3]

influenced by several of the factors that co-determine individuals' health (Figure 3). Increased knowledge and more data about the determinants of health on the population level can help to target population health interventions better.

For instance, we found in recent study in the Kingdom of eSwatini that younger people, people who do not know their partners' HIV status, or those with low self-perceived HIV risk are less likely than others to continue with oral HIV pre-exposure prophylaxis (PrEP) after one month of taking PrEP (Figure 4) [7]. PrEP is a combination of antiretroviral drugs that can be taken by HIV-negative people to reduce their risk of HIV infection. It is becoming an important additional tool for prevention of HIV infection (Figure 5). Since 2015, the World Health Organization has recommended that PrEP should be made available as an additional prevention choice for people at substantial risk of HIV infection.

Knowing which groups of people in a population may be more likely than others to not continue with a health programme, like PrEP, can help increase the programme's success by allowing programme coordinators to tailor care to the different needs of specific groups of people, like those more likely to drop out of a programme early. Furthermore, PrEP itself can be an example of precision health as well as precision population health.

On the one hand, PrEP offers a new, additional method of reducing the risk of HIV infection that complements other methods of HIV prevention. It can be particularly suitable for some people at a certain time in their lives. For instance, PrEP can be used by serodiscordant couples, that is, couples in which one partner is HIV infected while the other is not, who would like to pause the use of condoms to conceive a child. On the other hand, PrEP is not recommended for everyone, but a targeted recommendation for people who face a high risk of HIV infection (Figure 6). Assessing the individuals' risk for HIV infection, before offering PrEP as an additional HIV prevention option for people at substantial risk of HIV infection as part of a combination of HIV prevention approaches, makes PrEP a targeted population health intervention.

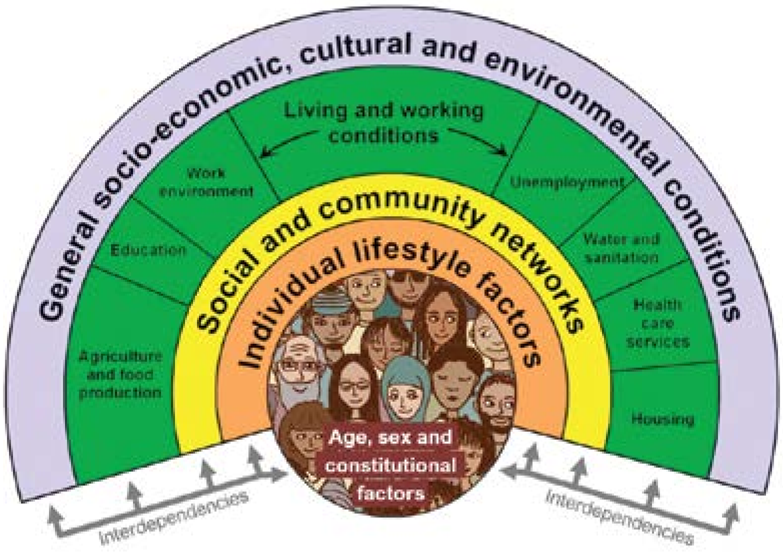

Figure 3. The main determinants of health. *Adapted from Dahlgren and Whitehead (1991)*

OUTLOOK AND CHALLENGES FOR PRECISION HEALTH

The amount and variety of data that may allow better targeting and so improve

BOX 2

WHAT IS THE DIFFERENCE BETWEEN PRECISION MEDICINE AND PRECISION HEALTH?

Precision health leverages the numerous assessments including [the fields of study ending in] omics, immune status, medical imaging, family history, physical condition and standard doctor visits to predict and prevent disease from occurring. Precision medicine uses similar tools, but is primarily focused on patient treatment after the onset of disease. Both health areas have overlap and are complementary in improving patient care. Precision health is a way of improving overall lifelong health, while precision medicine is generally not implemented until an individual becomes ill.

Reprinted from Precision Health and Integrated Diagnostics Center at Stanford [5]

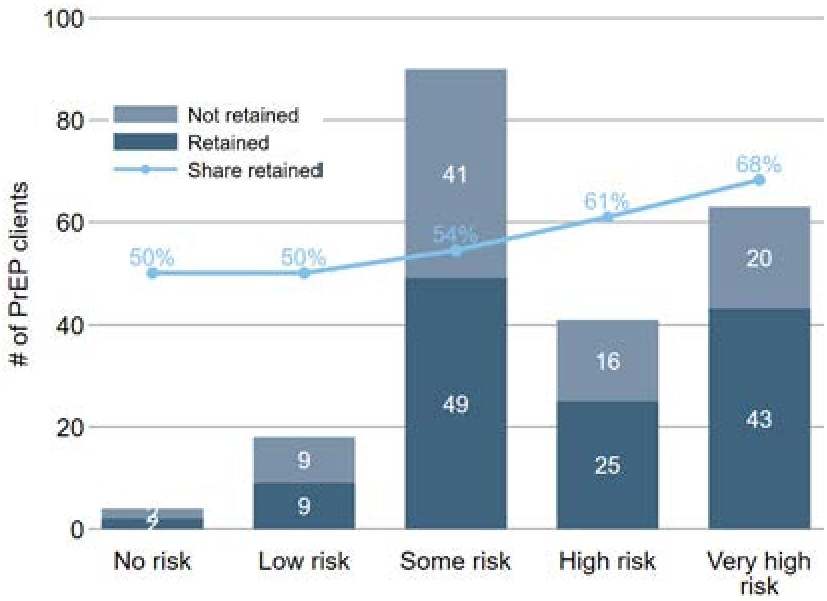

Figure 4: Share of clients retained on HIV pre-exposure prophylaxis (PrEP) after one month increases as self-perceived HIV risk increases. *Data from Hughey et al. 2018 [7]*

Figure 5. Pre-exposure prophylaxis as part of an HIV prevention package.
Hughey et. al. 2018 [7]

BOX 3

WHAT IS THE DIFFERENCE BETWEEN PRECISION HEALTH AND POPULATION HEALTH?

Population health refers to the health or health outcomes of a group of individuals and this information can be used to improve and learn about the health of a larger group or even the entire population. Precision health, on the other hand, is focused on the health of an individual. However, both precision and population health areas are complementary. The trends of individuals create the average trend of a group, and the trend of a group can be used in conjunction with individual health data to improve the overall predicative capabilities for individual disease prevention and, if needed, early intervention.

Reprinted from Precision Health and Integrated Diagnostics Center, Stanford [5]

healthcare is increasing in all parts of the world. The availability of genomic data has triggered a wave of hope for advances in precision health after the Human Genome Project. Precision health has, since then, experienced successes and setbacks, both of which show that there is still much more to be discovered. Successes achieved by personalised pharmacotherapy are concentrated in the field of cancer treatment, in which often expensive targeted treatments become available for patients with certain subtypes of some cancers. In other areas of health, few effective precision approaches have been found so far. Therefore, precision medicine in the form of genetic information to improve drug targeting is of minor importance for current population health.

To improve population health, at least in the short to medium term, prevention of unhealthy lifestyles and behaviours, as well as universal access to basic diagnostics and care, remain the most important global challenges. Individual- and population-level data on the prevalence of diseases, the determinants of health, access to and utilisation of care, as well as other health-related data, are becoming increasingly available to researchers and health decision makers (see references 6, 11-13). These data offer new opportunities to assess and potentially better predict how care can be provided with more impact through improved targeting in many areas of health, ranging from treatment of diseases and the strengthening of health in populations.

To conclude, precision health principles apply to all areas of health. Challenges are to mainstream precision health thinking in all areas of healthcare and to assess when and which precision health approaches can help to improve health outcomes. If these challenges are overcome, precision health can support health systems globally and allow them to fulfil their core functions, which include providing all people with access to the quality health services they need (see reference 8).

Figure 6. Targeting of HIV pre-exposure prophylaxis at the health facility level.
Stefan Kohler

References

1. Obama BH. Remarks by the President on Precision Medicine [Internet]. White House Off. Press Secr. 2015 [cited 21 August 2018]. Available from: https://obamawhitehouse.archives.gov/the-press-office/2015/01/30/remarks-president-precision-medicine

2. Potter P. Hippocrates. Diseases III. Hippocrates Vol VI. Cambridge, MA: Harvard University Press; 1988.

3. Pray L. Personalized Medicine: Hope or Hype? Nat Educ. 2008;1:72.

4. Kohler S. Entwicklung und Stand der personalisierten Medizin in Deutschland [Development and status of personalized medicine in Germany]. Dtsch Med Wochenschr; 2018; in press.

5. Precision Health and Integrated Diagnostics Center at Stanford. Frequently Asked Questions [Internet]. 2018 [cited 21 August 2018]. Available from: https://med.stanford.edu/phind/faq.html

6. Gambhir SS, Ge TJ, Vermesh O, Spitler R. Toward achieving precision health. Sci Transl Med. 2018;10:eaao3612.

7. Hughey A, Hettema A, Oldenburg C, Kohler S, McMahon S, Lejeune C, et al. Predictors of 1-month retention on PrEP for the general population in the public sector: A longitudinal study in routine care in Swaziland. Poster presented at the International AIDS Conference. Amsterdam; 2018.

8. WHO. World Health Report: Health Systems Financing: The Path to Universal Coverage. Geneva: World Health Organization; 2010.

9. Kohler S. Personalized medicine and global health. Public Health Forum. 2017;25:244–8.

10. Kohler S. Personalized Medicines and the Burden of Disease in Germany. Heidelberg: Institute of Public Health, Heidelberg University; 2017.

11. Flahault A, Geissbuhler A, Guessous I, Guérin P, Bolon I, Salathé M, et al. Precision global health in the digital age. Swiss Med Wkly. 2017;147:w14423.

12. Gakidou E, Afshin A, Abajobir AA, Abate KH, Abbafati C, Abbas KM, et al. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017;390:1345–422.

13. Dolley S. Big Data's Role in Precision Public Health. Front Public Heal. Frontiers; 2018;6:68.

14. Dahlgren G, Whitehead M. Policies and strategies to promote social equity in health: Background document to WHO-Strategy paper for Europe. Stockholm: Institute for Futures Studies; 1991.

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