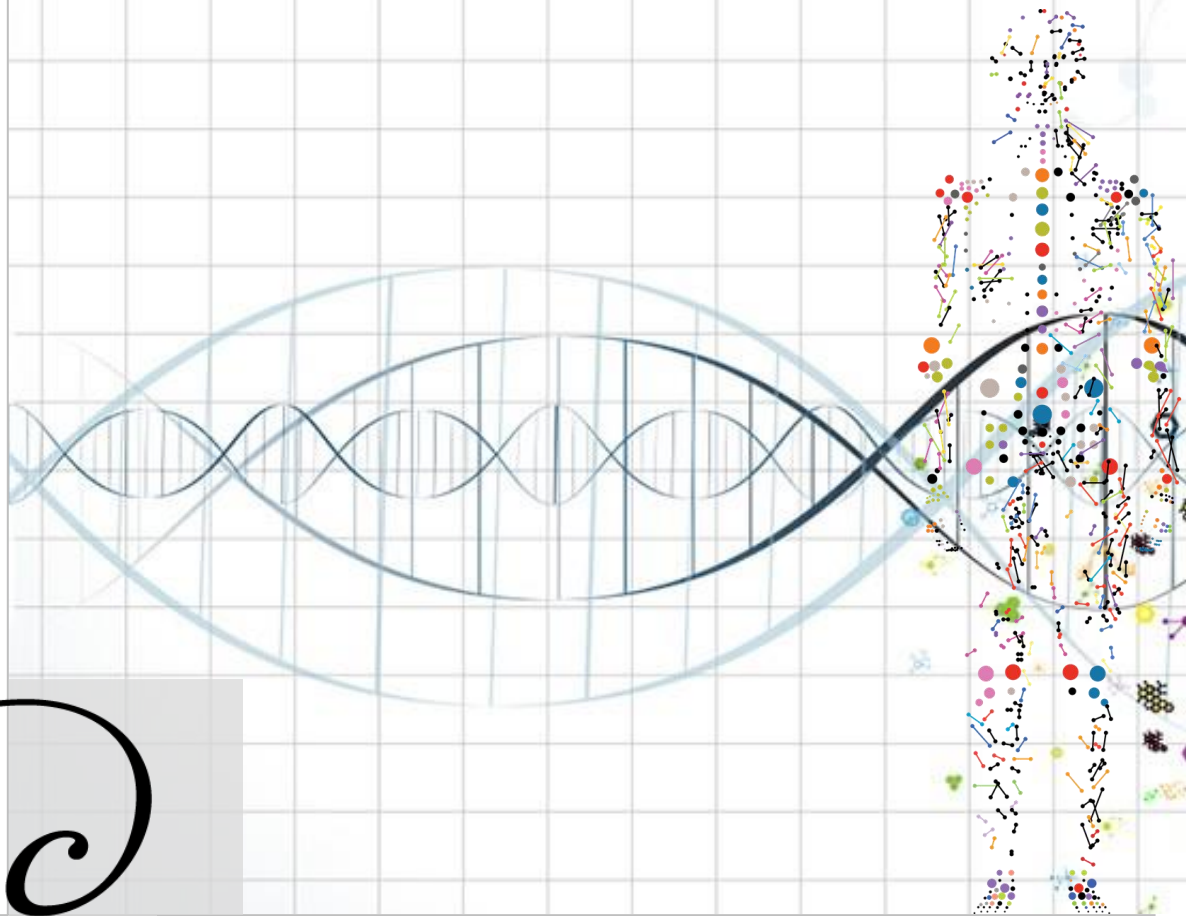




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WORKSHOP REPORT

The Economics of Precision Medicine

IRGC Expert Workshop

Campus Biotech, Geneva, 12-13 April 2018



This publication should be cited as: EPFL IRGC (2018). The Economics of Precision Medicine. A Risk Governance Perspective. Lausanne: EPFL International Risk Governance Center.

DOI: [10.5075/epfl-irgc-256776](https://doi.org/10.5075/epfl-irgc-256776)

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Acronyms

CDx	Companion Diagnostics
CEA	Cost-Effectiveness Analysis
DAA	Direct-Active Antiviral
EC	European Commission
EMA	European Medicines Agency
FDA	US Food and Drug Administration
GDP	Gross Domestic Product
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
IND	Investigational New Drug
MS	Multiple Sclerosis
NDA	New Drug Application
NICE	UK National Institute for Health and Care Excellence
PGx	Pharmacogenomics
QALY	Quality-Adjusted Life Years
RNA	Ribonucleic Acid
SDx	Standalone Diagnostics
SOC	Standard of Care
UK	United Kingdom
US	United States

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Preface

On 12-13 April 2018, IRGC gathered over 20 stakeholders representing insurance and pharmaceutical companies, academic research, regulators and patients to discuss issues of cost-effectiveness, affordability, value and innovative payment schemes in precision medicine. Workshop participants were mostly familiar with healthcare systems in countries such as the UK, Switzerland and the US.

Precision medicine is fundamentally patient-centric, facilitating better targeted and personalised medical care, but it must also make economic sense for society. At a time when healthcare systems around the world are pressed to make better use of scarce resources and maximise health benefits, precision medicine's salience augments in view of its potential to bring about improved health outcomes in ways that are affordable, economically viable and reflect social preferences.

Participants were invited to discuss the following questions:

Issues related to cost and cost-effectiveness

1. How to calculate cost-effectiveness for precision medicine?
2. How can precision medicine be cost-effective, maybe even more cost-effective than traditional approaches?
3. How to introduce flexibility in conventional payment systems to account for performance (outcome-based payments)

Towards innovative financing and payment systems

4. Cost and pricing: how to calculate the price of a unique life-time dose for an inherently individualised cure?
5. Payment: how to develop new payment systems such as those that are widely used in other fields affected by typically low-probability /high impact events (e.g. loans, mortgages, securitisation)? How to make these systems affordable and socially acceptable?
6. Performance: How to establish the performance of an individualised treatment and how to modulate the price in relation to its outcome or effectiveness and overall value? How to introduce planned flexibility?
7. Alignment of incentives: The cost of "curative" initial treatments may be at the expense of payers who are not those who will see the benefit in the long-term (e.g. Alzheimer's disease).

Concluding Discussion

8. Discussion of principles and guidelines for the development of affordable precision medicines

IRGC Highlights

It is worth highlighting that different types of precision medicine may involve different economic considerations and social judgments. More summarily stated, one can distinguish between ‘precision targeting’ (or precision medicine 1.0) and ‘breakthrough precision medicine’ (or precision medicine 2.0).

> ‘Precision targeting’ (PM 1.0) is about refining conventional medicines thanks to information about a patient’s ‘omics’ data¹, medical records and other lifestyle information. Pharmacogenomics is particularly relevant in this approach, because understanding the role of the genome in drug response helps target treatments better (e.g. distinguishing responders/non-responders, grouping patients according to characteristics, etc.). While there have been significant scientific developments to enable this type of precision medicine, also called ‘stratified medicine’ in some countries, it is not yet for granted. It is dependent on (a) the availability and analysis of large sets of data collected from patients and the population at large, (b) the development of effective and cheap genetic testing to help diagnose health conditions or predisposition, and (c) companion diagnostics or biomarkers that provide better prospective indications on the safety and efficacy of a certain therapeutic product.

Targeted genetic testing may become increasingly routine in some countries for a broad range of conditions, and key obstacles to making this type of precision medicine cost-effective may well be overcome in the years to come. Pharmacogenomics is increasingly used for cancer therapies, but perhaps also for neurodegenerative diseases, cardiovascular diseases, diabetes and other conditions, depending on scientific and medical advances.

The economics for precision targeting looks feasible if one takes a more long-term and dynamic view, that is considering important economies of scale (especially for large patient populations) and competitive dynamics that make the cost and price of treatments more affordable over time. Cost-effectiveness, as the measure of outcome on cost, should evolve and existing practices of measuring it should adapt to better account for efficiency² and other economic gains (including fiscal ones), as well as the amelioration of quality of life (perhaps as outcome reported by patients). Further, it will be important to generalise performance-based payments, calculated on the basis of effective outcome in use. While cost-effectiveness is often a key concept to evaluate the cost and quality of care in certain healthcare systems, it can only inform and support decisions and may not be the most appropriate decision-making criterion to account for value and sustainability.

Overall, concerns about affordability and access to ‘omics-based’ therapies remain important, but is not the only constraining factor. Improved transparency concerning payment systems and intellectual property (IP) rights, and better explication to patients and medical professionals of key benefits in practising targeted precision medicine will help to address resistance or reservations. Precision medicine has the potential to become more cost-effective than conventional medicine, and its affordability is not only a matter of accurate modelling but of appropriate dialogue between different stakeholders.

¹ E.g. genomics, proteomics, etc.

² E.g. cost-savings in overall health care due to better targeting, fewer unnecessary consultations, tests, or ineffective treatments, etc.

> The second type of precision medicine, 'breakthrough precision medicine' (PM 2.0), derives from the development of fully personalised curative drugs, especially regenerative cell and gene therapies that are tailored to each patient. Here, key economic considerations worth highlighting are: (a) the very large upfront costs³ and (b) the value that accrues with the curation of a patient for the rest of his/her life. These economic considerations must further be mediated with ethically and socially sensitive concerns around distributing pooled resources for expensive treatments of rare diseases as well as the patients' age. Thus the paradigm change needed to answer the question of affordability necessitates focusing on the broader economic and societal value of a cure, that is around framing health as an investment rather than a cost⁴ and at the same time finding new ways to sustain solidarity with the more vulnerable ones.

On a more pragmatic level, the challenge is how to pay for value. In addition to social and ethical considerations, there is a temporal misalignment that may dis-incentivise doing so. Not only must payers be able to align cash flow, annual budgets and amortize the price of a therapy over the life of the patient, but in multi-payer systems, payers may not see the benefits in the long term if patients change insurers and/or insurers do not agree on splitting the cost of treating such patients.

Thus developing the economic rationale to justify this type of precision medicine requires the development of new business models for pharmaceutical companies, payers (insurers, governments) and patients, and with appropriate incentives. Depending on the severability – the extent to which the cost of a drug is separable from the cost of overall treatment and management of the disease – and the value generation horizon – the time it takes to amortise the expense and realise the value –, various types of business models could and should be developed to overcome short-term budget constraints and strategic payer behaviour. These include (a) loans or debt financing (for insurers, not indebted patients), (b) inter-payer transfer payments, special 'cure funds' (pool solutions) or re-insurance, and (c) patent buyouts by government or tax coverage. Payment schemes for new curative drugs should be negotiated early in the development of the drug in a way that makes economic and social sense.

Generating evidence remains important to convince developers and payers that breakthrough precision medicines can be affordable and viable. A way forward could be to develop and share evaluations of **possible payment schemes, for specific therapies, under varied national regulatory contexts**⁵. This could serve to determine guidelines for (a) amortisation over time, (b) distribution across actors, (c) performance-based incentives and (d) indicators.

Differences in healthcare systems notwithstanding, an important consideration revolves not only around changes to business models and/or better analytics of where, how and to whom value accrues, but also around understanding and explaining why and when precision medicine enables better healthcare provision than what is currently practised.

³ E.g. treatments like Kymriah Car-T for leukaemia in children was priced 475'000 USD in the US. Note though that the cost of subsequent CAR-T treatments may be lower.

⁴ Or, re-orienting from transactions-driven to value-based health care provision

⁵ Candidates for such case studies could include Gilead's Sofosbuvir (Sovaldi) for chronic Hepatitis C patients, Nusinersen (Spinraza) for spinal muscular atrophy, Novartis's Car-T (Kymriah) for leukaemia, of RT-100 gene therapies for congestive heart failures.

1. Setting the Scene

1.1. Precision Medicine's Potential

Precision medicine allows the delivery of healthcare in a uniquely patient-centred way by combining an understanding of the influence of human genetics and environmental factors on health with highly specific clinical insights about the composition of diseases. Despite scientific advances and therapeutic breakthroughs, precision medicine's progress has been rather slow. It is often said that the key barrier may not be scientific but instead economic. Workshop participants were of the opinion that the costs of segmenting, targeting, or 'stratifying' (as in 'stratified medicine') do not, however, represent a key barrier.

To look deeper into the economics of precision medicine, it is important to distinguish between two broad types of precision medicine, within the precision medicine continuum.

- The first type, **Precision Medicine 'Targeting' (PM 1.0)** uses multidimensional 'omics' information (genomics, epigenomics, transcriptomics, proteomics, metabolomics) and other personal data for **more precise diagnostics and targeting of patients groups**, primarily improving safety and effectiveness of conventional (i.e., non-targeted) therapeutics. Efficacy, safety and cost-efficiency gains can be captured when drugs are properly rolled out, e.g., with the right diagnostics.
- The second type, **'Breakthrough' Precision Medicine (PM 2.0)** involves omics-based cell and gene therapies, such as CAR-T, with a focus on biologics rather than small molecules, for **truly custom-made treatments**. PM 2.0 usually consists of one-time administered treatments with expected definitive curative impact for the patient. The high research and development (R&D) and manufacturing costs translate into high upfront costs of PM 2.0 therapies, at least in the short run. Competition and scale economics can drive prices down in the medium to long-term.

In addition to these two broad categories of precision medicines, further segmentation relates to the different types of treatment: prevention or cures – e.g., curative vs. non-curative, single-dose treatment vs. multi-dose treatment, first-line vs. second-line treatments, disease types – e.g., progression speed (distinguishing also between germline vs. somatic mutations), disease prevalence (rare and ultra-orphan diseases), and mortality rate. Each category and sub-category is likely to require distinct pathways to access and affordability, which is one of the main building blocks of precision medicine going forward (Kohane 2015). The affordability challenge – in view of the high upfront cost – is perceived as particularly great today, since precision medicine is still in its infancy, and could remain a challenge depending on how payment systems are reformed. There is also much uncertainty on the real therapeutic potential, cost-effectiveness and speed of development, all of which are interlinked and potentially call for changes in the rules of the game of healthcare systems, which differ largely across jurisdictions.

1.2. A Vision for Precision Medicine

Views about precision medicines vary among the different actors within the healthcare system.

- **Patients.** For patients, accessing the right treatment at the right time is the promise that precision medicine affords. They look to PM for more targeted therapies that would be more efficacious, have less adverse effects, improve quality of life (with a positive impact on society and the economy), and lower treatment costs overall. Patients want to be able to access drugs when available, but this does not always happen, Hepatitis C Virus (HCV) treatment in Switzerland is a case in point (Box 1 below). Patient advocacy needs to be strengthened to ensure that some patient groups are not marginalised.
- **Pharmaceutical companies.** Pharmaceutical companies recognise their need for a different approach to drug discovery, specifically by getting better at applying a precision medicine approach in, e.g.,

cardiovascular disease and inflammatory disease, similar to oncology, where it has already demonstrated significant patient benefit. That means not only identifying the patients who are most likely to respond to therapies using proven targeting methods, such as genotyping or phenotyping, but also identifying, using and tracking biomarkers that help to identify diseases and specific pathological or physiological processes during the course of treatment so that patients' responses can be monitored in more real-time and so that treatment can be adjusted depending on the outcome. This requires that pharmaceutical companies (directly or via providers) have access to or are involved in patients' monitoring. Continuous testing and adaptive approaches are key for pharmaceutical companies to improve their research outcome.

- **Payers (public agency or private insurer).** In general private insurers are very excited about the potential of precision medicine to establish a health system that can deliver a more cost-efficient outcome and sustainable value to their patients, both in terms of high-quality medical treatment and pharmaceuticals. Sitting on a massive amount of data, payers aim to be a significant player in data-driven value determination – information that they can also use to help policymakers make better decisions and address, e.g., innovative pricing models. With the intent of promoting genetics and genomics as tools to improve healthcare, payers could wish that genomics eventually be part of private insurance contracts – not as a means of screening insured but for better risk pooling (by the law of large numbers).⁶ Last but not least payers realise the importance of understanding pharma through dialogue and joint workshops. The speed of innovation and the opportunities they afford – e.g., gene-based therapies, antigens RNA therapies and gene-based drug repurposing – are too great to continue working in silos.
- **Regulators (inter-governmental agencies and governments).** At a regulatory level, there are major differences across jurisdictions. In Europe, the European Commission (EC) is driving an initiative to sequence one million genomes, but it is not under its responsibility to see to its implementation at the national level. Unlike the UK or the US, the EC can at best try to generate the evidence that can be used to influence ministries, which as of today remain very hesitant. Against the backdrop of data paucity, ministries do not settle for model-based evidence and are often very critical about the underlying methodology. The views on precision medicine are very fragmented, as evidenced by the lack of Health Technology Assessment (HTA) harmonization across European countries. It appears that the groundwork for establishing the baseline that would enable reimbursement of precision medicine is still in process. It involves educating regulators on the technology, generating evidence on customized treatments – using a common methodology that is yet to be agreed upon, and harmonizing data to that end. In the US, the prospect of reducing the share of medical costs to GDP is one of the factors that have driven the Precision Medicine Initiative (PMI) launched by President Obama in 2015. Over US\$ 200 has been earmarked with a dual objective to making advances in tailoring medical care to the individual, and to improve the cost-effectiveness ratio, thus lowering cost to society.
- **Funding agencies.** From the perspective of a funding agency, costs specific to precision medicine will be mostly related to infrastructure and data harmonisation. These are areas where the EC is also likely to be most effective. No additional cost from the research and translational sides are expected. Countries within the EU are likely to move at different speeds. In Germany, for instance, there is a two-tiered approach to precision medicine, namely driving innovation for the economy, and addressing unmet needs with, currently, a focus on diseases with high prevalence such as depression. What is needed here are better diagnostic tests to streamline the treatment.

⁶ This is different from compulsory system where a pooled amount of money is distributed to form some solidarity.

Box 1 | Lessons from Innovative Drugs: Restricted Access to due to Limited System Awareness and Coordination

Insights from Hepatitis C Virus Worldwide

HCV DAAs is a major breakthrough for patients living with Hepatitis C, providing much shorter treatment cycles (12 weeks), much less toxicity, and more cost-effective than previous gold standard. But, despite the tremendous benefit of DAA and negotiations with regulators and industry since 2007, reimbursement remains bumpy and access is limited even in the UK and CH while patients continue to die. Cross-country differences in HTA assessment notwithstanding, it has been difficult to convince health authorities about the systemic impact condition and to commit to infectious diseases treatment strategies (e.g., in Switzerland).

Some of the barriers to HCV DAA updates include:

- Very slow disease progression
- Diverse patient population, particularly with respect to source of infection and type (mono- vs. co-infection)
- Weak epidemiological data, with WHO and CH early estimates (180M and 80M, respectively) almost halved
- Diverse treating physicians, e.g., gastroenterologists, hepatologists, whereas most patients are in GP care
- Diverse and generally weak patient groups, and low levels of collaborations between professionals & patients

Reasons for successful uptake vary widely across countries:

- Portugal and Scotland: high-level of system awareness, Portugal was also able to negotiate a volume deal
- Australia: HEP-C buyers club purchasing generics from India forces government to agree on treatment plan at a reasonably low cost (€3545 while cost price is €55 euros, DAA treatment in Germany cost €50425)
- US: screening strategy put in place

Insights from Multiple Sclerosis (MS) in Switzerland

Spiranza is a breakthrough therapy for spinal muscle atrophy that has been approved by the Swissmedic in September 2017, following FDA and EMA approval in December 2016 and June 2017 respectively. Despite the Swissmedic's approval for all disease types and ages, there was no reimbursement, due to:

- Unresolved issues among relevant authorities such as the Federal Social Insurance Office, the Federal Office of Health, the Disability Insurance and healthcare insurance companies
- Limited cooperation with patient organization, particularly no patient inclusion in decision making

The result is that today very few patients are treated in Switzerland (2 in an open label extension study, 5 in compassionate use programme funded by company, 2-3 children (one via health insurance), 2 adults). Treatment in delays lead to adverse consequences such as loss of motoric abilities.

These two examples highlight several generic systemic problems:

- The healthcare system is a complex system with many actors and where health expenses are considered as cost rather than as investment
- Narrow focus on costs, with price of new interventions taken once or over short-term and providing long-lasting effects compared with prices of medicines intended for daily intake
- Lack of HTA harmonization, despite successful medicines regulation harmonization in Europe
- People turning to generics as the system turns global with new players (India, China)
- Static medical labels and prices, changes to which are also tried to label changes

1.3. Basics of Healthcare Decision-Making Processes and Economics: Implications of Precision Medicine

The healthcare value chain is becoming increasingly complex and is intrinsically context dependent. The different actors have contrasting priorities that can lead to delays in decisions and therefore patient access to treatment, both existing and new. Starting with an Investigational New Drug (IND), pharmaceutical companies analyse the healthcare context to identify target patients and assess the market potential to determine a target profile. The drug development, particularly the clinical trials, is conducted taking into account the regulatory authorities' requirements in terms of safety, efficacy and comparative effectiveness.

Traditionally, it is only upon drug approval for an indication (New Drug Application, NDA) that reimbursement considerations come into the picture. Usually, payers (public or private) do not use the same comparators as the licensing body, resulting in a misalignment between approval and reimbursement. Other factors such as budgetary constraints also influence reimbursement decisions, leading to large variations in drug availability and prices across nations.

Even when a drug is reimbursed, providers may use different criteria altogether when prescribing drugs. The result is that pharmaceuticals companies often compete on prices, especially in the form of rebates to ensure market access. After introduction on the market, new indications are developed. The outcomes of these quasi-sequential processes are not necessarily optimal and suggest that payers, providers as well as patients ought to be involved earlier during the drug development process, and that decisions – such as pricing and payment mechanisms – ought to be adapted.

Health economics aims to support the decision-making process on how to best allocate scarce resources in the health system to maximize the health benefits. The way the allocation question is tackled depends very much on the scale – individual vs. societal vs. global level – of the system under consideration, and on the healthcare culture.

Precision medicine raises important concerns for health economics even in countries with high GDP, because of generally poor cost-benefit ratios of therapies. For example, treatments may cost between US\$ 80K to US\$ 100K for an overall survival improvement of barely two months. The cost-benefit ratio of precision treatment for diseases like cancer may be even higher unless the treatment is curative.

Public healthcare systems or private health insurance should a priori support access by paying for the treatments. For instance, private insurance pool risks and this mutualisation of risk should provide the solidarity mechanism to ensure access. There are concerns that precision medicine, by enabling risk stratification of the population, may lead to a breakdown of the solidarity mechanism whereby the population, which is not at risk, may be unwilling to pay for the those at risk. This could be the case where insurance schemes are flexible. Most importantly, curative precision medicine – due to the high cost of short-term treatments – poses financial liquidity challenges to both public and private healthcare systems under current annual accounting rules.

Moving beyond rich countries and considering the wider societal and global context, precision medicine should be balanced with a population-centred approach. Indeed, the highest attainable standard of health is highly resource-dependent. Today, countries with the lowest life expectancy are also the poorest countries, where the highest mortality rates are due to infectious diseases and non-communicable diseases.⁷ Alternative funding mechanisms are needed to address developing world's

⁷ Although the issue of global health is a very important topic and there are ways where precision medicine could be relevant, e.g., through the development of cheap biomarkers and diagnostics (e.g., mobile telephony-based skin lesions diagnosis), the

healthcare issues, while also harnessing the opportunities afforded by precision medicine to achieve sustainable health for all.

With precision medicine, risk-stratification of population ought to lead to new approaches for both prevention and treatment of acute and chronic diseases. Knowledge of who is most at risk of developing any disease coupled with the ability to detect the onset of diseases in its earliest stages enable early intervention to prevent or cure diseases. This will likely lead to a paradigmatic change to the way we diagnose, prevent and treat diseases, with costly treatment becoming a last-resort intervention.

workshop focused on the issues of access and affordability of precision medicine in developed countries, where need is backed by the ability and willingness to pay for expensive innovative treatments, considering also financial liquidity constraints.

2. Evaluating Precision Medicine

“There is too much focus on cost-effectiveness such as cost per QALY. A correct view of the value of medicine needs to account for the economic and fiscal benefits of avoiding ill health states. The cost of disease is the problem we face, and medicine can help avoid”

- Stefan Werner Weber, Director and Head of Health Policy, AMGEN

2.1. Cost-Effectiveness Approach

Among the prevailing methods for cost-effectiveness analysis, UK’s approach is the most transparent and traditional one, well accepted and a cornerstone of the UK healthcare system. It is based on a comparison of the costs and outcomes of UK healthcare system, which is designed to generate health as measured

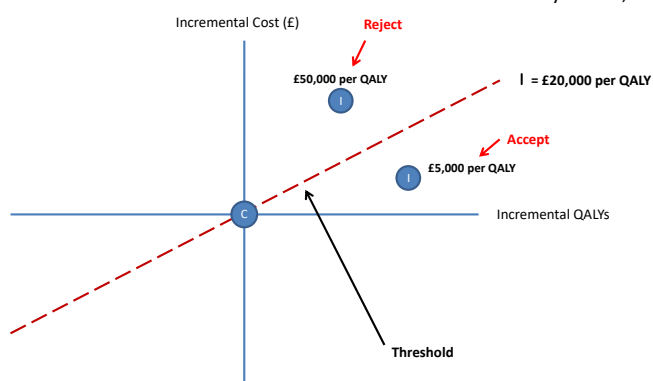


Figure 1: Making Decision with ICER – An Illustration.
Source: Gavan et al. (2018)

by Quality Adjusted Life Years (QALY) – a composite measure of health, and of quality and length of life, allowing to compare interventions across completely different disease areas. To evaluate the performance of the healthcare system over time – e.g., when a new technology/treatment is introduced, the ratio of the incremental cost of new technology to the incremental QALY (i.e., the Incremental Cost-Effectiveness Ratio, ICER) is computed and compared with a predefined threshold. A treatment is made available or reimbursed only if the ICER is

below the threshold (Figure 1), ensuring that a new treatment does not drive out treatments that have higher societal value.

In the UK, The National Institute for Health and Care Excellence (NICE) is tasked with technology appraisal,⁸ particularly with deciding whether or not to introduce a new medicine using an ICER-based decision-making framework. Properly implemented, the ICER framework allows generating more health with the same budget.⁹ The threshold is an upward-moving target: with time and innovation, more and more QALY is expected from each additional pound. The threshold is thus defined as an opportunity cost,

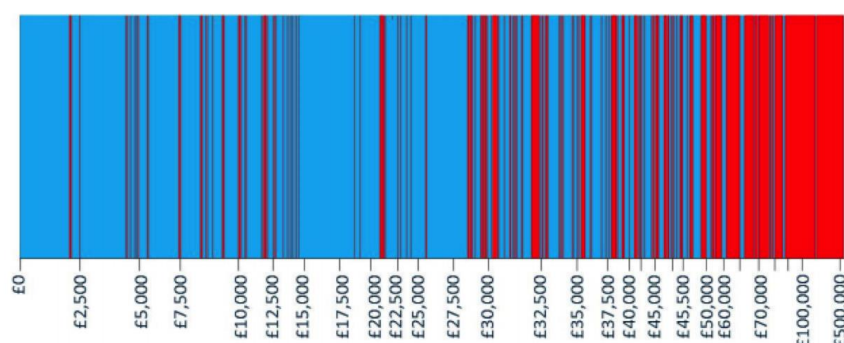


Figure 2: The Influence of Cost Effectiveness and Other Factors on NICE Technology Appraisals.
Source: Dakin et al. (2015)

Notes: Decisions are ranked by ICER, with NICE decisions to “recommend” shown in blue and to “reject” shown in red. For clarity, only the first five datasets of randomly-sampled ICERs are shown.

⁸ NICE also provides guidelines on pathways to care delivery, but these are not mandatory.

⁹ It forces disinvestment of treatments that are no longer cost-effective, whereas in many healthcare systems, such disinvestment does not usually happen.

i.e., the cost value of the benefit of the next best alternative, given a fixed healthcare budget. Whilst comparative cost-effectiveness is at the heart of the decision-making process, NICE also considers other factors such as the innovativeness of a new technology (Figure 2). The incentive structure is very clear: once NICE makes a positive recommendation for a technology or medicine, local commissioners are required to fund it within three months.

Some limitations of ICER

- ICER implementation is not as straightforward in the case of precision medicine. Diagnostics, in particular, poses numerous challenges to the traditional cost-effectiveness approach. And, to the extent that they are needed,¹⁰ standalone (SDx) and companion (CDx) diagnostics are two different beasts.

A CDx is often specific to a therapeutic product and provides information that is essential for the safe and effective use of the product. The CEA of CDx can be relatively straightforward to conduct – e.g., by bundling the CDx and medicine together as a package – provided the same CDx is used for critical trials and practice.

Conversely, an SDx is separate from any particular medicine/treatment and is quite likely to have been developed after medicines/treatments are on the market such that it is difficult to appraise the link between diagnostic and treatment decision. As a result, SDx does not lend itself to “conventional” CEA. Instead, economic modelling with data from a variety of sources may be needed to demonstrate the validity of SDx.¹¹

- ICER is a relative method, highly sensitive to the standard of care. This relativity means that small increments are favoured to fundamental breakthroughs. Consider cardiovascular diseases, where all the standard of care drugs, Statins and ACE inhibitors, are very cheap because they are off patent. New cardiovascular drugs, like Entresto, have unfavourable ICER ratios because of the low cost of generics that are the standard of care. ICER therefore pushes innovation towards indications where prices are high.
- ICERS do not have equity considerations. Patients with expensive to treat diseases are denied access to treatment if the outcome is not good enough from an ICER perspective. And, since QALYs are heavily driven by the gained life expectancy, treatments that show small increment in QALY – e.g., in patients with diseases with low mortality rates such as psoriasis and epilepsy – will also have poor ICER ratios, which limit access to innovative treatments.
- Finally, the assumptions underlying ICER are static, based on current state of knowledge, while in reality they are changing. The following example can illustrate this. Suppose there is a miracle drug that extends life by five years, but we assume that retirement ages are fixed and pension benefits are fixed, then obviously the effects on cash flows are very different from when some of those assumptions are changed. This suggests that when analyzing cost effectiveness, reimbursement and policy, it is important to decide with factors can be effectively assumed to be static and which ones are endogenous, and over what time period.

2.2. Cost-Effectiveness: Precision vs. Conventional Medicines

Additional Costs of Precision Medicine

Many precision treatments are more costly than conventional treatments. There are various costs associated with the setting of an end-to-end surveillance system, encompassing:

¹⁰ As one workshop participant pointed out, [complex] diagnostics are not always needed; one could look at phenotypes or conduct responder/non-responder tests, both of which are cheaper. But, in the UK, diagnostics – whether more accurate or less, complex or not – are conducted as long as they help reduce cost.

¹¹ It is anticipated that the cost of SDx is likely to be small at the expense of lower accuracy than CDx.

- People enrolment and screening
- Stratification (including genetic sequencing) and personalization, which involve collecting, recording, curating, storing and sharing information throughout the health system
- Intervention, treatments and drug development and tailoring, which include new approaches to treatment (dosage, formula, protocols), new targeted drugs for individuals with identified biomarkers, and new drugs for those who are not responsive to existing ones.
- Prescription – distribution of up-to-date medical information
- Patient adherence and treatment monitoring

Added Value of Precision Medicine

However, PM promises to increase the value of medicine by delivering a better outcome to more people for less money and this could be at different levels:¹²

- Tracking true costs of care/reducing waste: healthcare costs on the rise across most countries, yet according to the World Health Organization about 20-40% of spending is wasted in part due to providing treatment to non-responders.¹³ So PM can help eliminate some of the waste through targeted therapies, genetic testing and other precision approaches to health care.
- Value in outcomes: spending money upfront on precision diagnostic test can save money in the long run on treatment while at the same time increasing QoL for patients (not accounted for in NICE ICER) e.g. chemo avoidance in case less aggressive cancer detected. On the need for incentives for biomarkers, see Stern, 2017, 2018.
- Prescribing drugs that work based on drug-metabolizing protein gene testing. By reducing adverse effects to drugs, better quality of life. Particularly important in multi-drug treatment as in comorbidity as is generally the case among elderly.
- Genetic testing results can inform future health outcomes. An appropriate level recording of these results allowing doctors access: no test duplication and better treatment esp. in case of emergencies.
- Clinical Trials: There is also an important consideration from a cost perspective as to whether, today – in the big data era – placebo tests should be re-run. As one workshop participant suggested, it is important to look into the barriers to pooling of data from, e.g., failed Alzheimer trials, to generate additional insights that can help advance precision medicine faster.

Evidence: Cost-Effectiveness of PGx¹⁴

The cost of genetic testing is an important parameter of economic valuations of PGx, costing between US\$ 33 and US\$ 710 with a median value of US\$ 175 in 2014. There is wide variability in prices of tests both on average and for the same drug, with prices being higher in the United States and Canada than other regions of the world. A study by Verbelen et al. (2017) identified 44 economic evaluations, relating to 10 drugs, out of which 57% were in favour of PGx testing (30% were cost-effective and 27% where cost saving). Only one in four economic evaluations found the genetic testing option unequivocally not cost-effective. With an even higher project benefit under low-cost genetic typing, PGx has the potential to be a cost-effective or even cost-saving intervention. It therefore seems likely that PGx testing will become a core clinical service, particularly as projects such as the 100 000 Genomes Project pushes genomics to become part of healthcare infrastructure and as electronic health records become increasingly effective.

¹² <http://learn.genetics.utah.edu/content/precision/value/>

¹³ From an ethical perspective, treatment may have to be offered to non-responders unless there are serious side effects. So while precision medicine has the potential to reduce waste and inefficiencies in the system, the question is who will ensure that such waste is avoided. Payers/insurance companies? Informed patients?

¹⁴ Based on Verbelen et al. (2017)

2.3. Value-Based Approach

What is the right approach to valuing medicine? With a strong focus on the healthcare system and its cost-containment, the cost-effectiveness approach that is used by many HTA bodies provides only a partial view of the value of medicines. In the US, where no such HTA body exists, the Congress requires balanced information on the broad physical, biological, social and political effects of new technologies.

There are two broad ways by which to account for the full value of medicine. A first approach is to **account for the value of knowing and information externalities**, such as reduced response uncertainty thanks to CDx, insurance value due to protection against health and financial loss, the value of hope of a cure, real option value as life extension opens possibilities for individuals to benefit from future innovation, and scientific spillovers [Garrison et al. 2017, [Figure 3](#)]. Expanding CEA this way would improve the value of precision medicine.

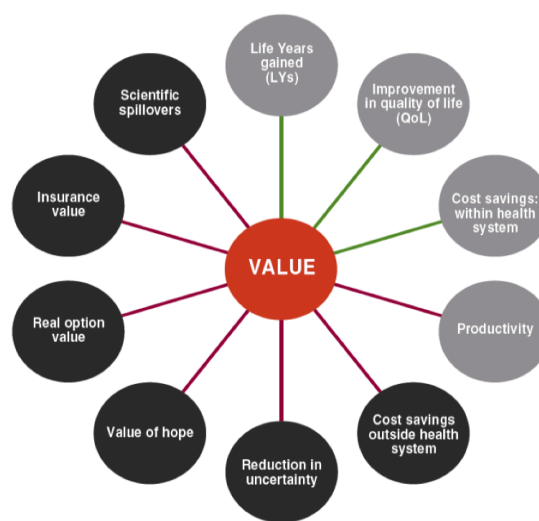


Figure 3: Value of a Medicine Beyond Drug Response.
Source: Garrison et al. 2017)

A second approach is to **account for the macroeconomic impacts of sick and healthy population**, such as the fiscal impacts and the full economic impacts. From a fiscal perspective, a healthy population contributes to taxes, representing positive cash flows, whereas sick and disabled people require some transfer payment from the government – a negative cash flow. Pensions are also affected, since poor health often results in early retirements. To the extent that new technologies such as precision medicine influence the cash flows, any valuation exercise should perhaps include these cash flows.

Accounting for the full economic impact a medicine entails incorporating the GDP and non-GDP related effects, and the trickle-down multiplier effects ([Figure 4](#)). A healthy population, for instance, makes positive economic contributions in terms of unpaid labour and consumption. Like any innovation, therefore, precision medicine should be considered is a growth driver, and associated value.

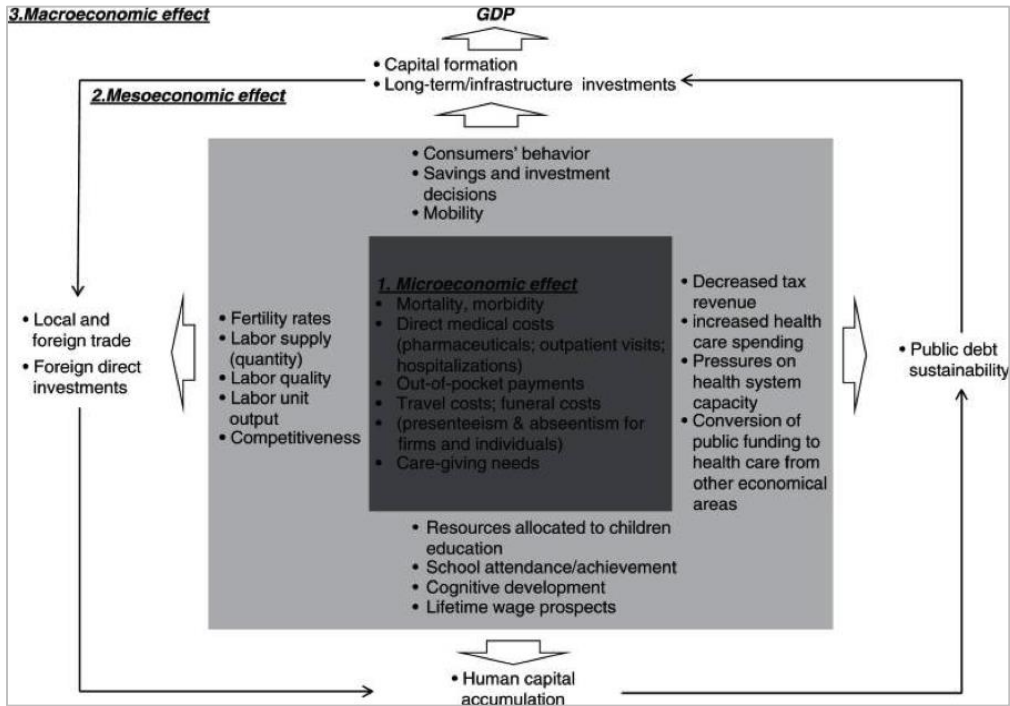


Figure 4: Broader Set of Values Associated with Precision Medicine. Micro, Meso, and Macro-economic Effects of Health. Source: Kotsopoulos and Connolly (2014)

Should the value of a medicine account for all the multiplier effects, there may be no need to assume a fixed healthcare budget. A limited and fixed budget can be a major pushback on innovation – through restricted access to innovative drugs – and is therefore detrimental to the equity and quality of any health system.

3. Innovating Pricing, Financing and Payment Systems

“[Emerging] solutions are very complex and you need to tailor them to the clinical properties and the trajectory of the product”

- Soeren Mattke, Director, Center for Improving Chronic Illness Care, University of Southern California

Pricing, financing and payments have to be aligned with the type of precision medicine, disease characteristics, and curative properties of treatments. **PM 2.0 in particular requires considering whether new forms of financing and payment are needed.** Financing and payment models have to be distinguished. Financing refers to the source of funding, e.g., who pays for a therapy (state, payer, patient) and how the funding is secured – e.g., debt financing and credit financing. Payment models refer to how the therapy is paid for, e.g., the structure of the transactional or cash flows.

This section discusses in particular specific needs for and ways of developing access and affordability to PM 2.0.

3.1. Pricing

Price of drugs are negotiated between pharmaceutical companies and payers at different stages of the value chain:

- During the drug development process, since payers can provide valuable information of the comparators that they are likely to use
- Post-licensing, to determine the market access price, which currently often involves rebates, for example for different patient tiers as in tiered-pricing schemes
- Post-marketing [new], when new evidence is generated through patient monitoring that may provide a rationale to increase or decrease price (outcome- or performance-based payment)

While the market access price is a negotiated price, the base price depends on fundamental economic such as development and manufacturing costs,¹⁵ firm size (proxied by the number of products in the pipeline and product portfolio¹⁶), potential market size and market structure, and drug effectiveness relative to alternatives. Although the FDA and EMA do not have a direct influence on prices,¹⁷ by setting the safety and effectiveness standards/thresholds, they influence the number of drugs in any market segment (i.e., the market structure). The negotiation processes and drug reimbursement decisions are different from country to country, which can result in large differences in prices.

There are also different types of feasible pricing schemes. The tendency is to a move away from cost-plus pricing towards outcome-based or value-based pricing, to which indication-based pricing is a precursor.

Cost-Plus Pricing

The general consensus at the workshop is that cost-plus pricing – i.e., a mark-up on production costs – is not appropriate. In fact there exists a WHO guideline to move away from cost-plus pricing (the main cost component here is R&D costs). Since R&D costs can be amortized over time, cost-plus pricing does not

¹⁵ The manufacturing costs (the marginal cost, more precisely) sets a price floor; development and fixed costs can be recouped over the several years

¹⁶ Firms with enough products on the market are more likely to be able to sustain business even by underpricing new products to gain market access

¹⁷ EMA and FDA focus on clinical safety and effectiveness for licensing decisions and are not involved in pricing/reimbursed decisions

optimize healthcare spending. Cost-plus pricing also entails the risk of upward spiralling drug prices as R&D effectiveness decline by Eroom's Law¹⁸ or that of rewarding companies that are not efficient at investing in R&D.

Departing from cost-plus pricing does not necessarily mean lower prices, because in precision medicine, advanced biological instead of small molecules are often used, and their production costs are far from trivial. Prices are also determined by firm size, in particular the pipeline portfolio. For instance, Luxturna – the Spark Therapeutics gene treatment for an ultra-rare eye disease – is priced at \$850,000. Since Spark Therapeutics only has a limited portfolio of drugs to develop, it can go bankrupt if one product fails. The high initial price ensures that the firm recoups the investment and financially survives. Larger companies can distribute the risk across their pipeline portfolio.

Indication-Based Pricing

Indication-based pricing is a new approach to reimbursement that involves contracting for drugs for specific uses, rather than across all indications. For instance, a medicine for acute glaucoma can be used for myeloma¹⁹ and other types of diseases. The value of one medicine is not the same for each of the different indications. Today, across most jurisdictions, it is not possible to tie the payment to the differential value in each of the clinical uses. In fact, drug companies have historically priced drugs equally across indications, regardless of the variation in value. But, both drug companies and payers are seeing value in indication-based pricing.

The non-value differentiability leads to perverse incentives both upstream and downstream. Downstream, pharmaceutical companies may restrict the sales of medicine to one or two indications in order to keep prices high, with the adverse impact that patients do not have access to that treatment. Consider, as an example, the case of a medicine for acute myeloid leukaemia as original indication. Should a company decide to expand that indication to, e.g., multiple myeloma, then the payer is likely to ask volume-related price cut of 20-30%. Since, the price cut will also influence the price of original indication, a company may decide to strategically not launch the second indication.

Upstream, the non-feasibility of indication-based value payment leads to the sequencing of development projects, whereby the downstream value anticipation takes precedence over the scientific "indication." Returning to the case of AML vs. multiple myeloma, science may first push development towards AML, while market considerations may require an R&D reorientation towards multiple myeloma, for which value-based pricing may be captured. More generally, in the absence of indication-based pricing, the highest-value indication is first launched, followed by lower value-indications, although it could have been possible to do develop and launch both indications in parallel, reducing the waiting time for patients/speeding access to patients.

¹⁸ Eroom's Law states that Pharma R&D becomes half as efficient every 9 years (inflation adjusted)

¹⁹ The examples of glaucoma and myeloma used in the section are for illustrative purposes; although not specific to precision medicine, they highlight issues that are likely pertinent to pricing precision medicines such as CAR-T and Concentyx, for which indication-based pricing is being explored in US and UK, respectively.

Box 2 | Potential and Challenges of Indication-Based Pricing

Leveling the playing field and helping to drive more competition. Using indication-specific pricing, payers see an opportunity to break the market-share dominance of several key therapeutics, boost their near-term rebate and distribution income, and re-shape traditional contracting. Consider for instance tiered-pricing. With indication-based pricing, a "blended" price at the drug level can be agreed upon regardless of indication. But there are additional discounts and enhanced competition at the indication level. This will allow smaller drugs that have only one or two indications to better compete with a drug that has all seven indications.

Indication-based pricing is part of a move toward value-based pricing. Multi-indication pricing presents an unprecedented opportunity to align the cost of the medicine to value in different diseases. Payment will be tied to value, with higher rebates for indications where drugs do not work as well. Such tiered-pricing policy, as negotiated by Novartis of psoriasis drug, Concentyx, in the UK has however been hard to replicate in other countries.

But the challenges to implementing multi-indication pricing are daunting, requiring changes across the entire health care spectrum, from systems used by patients and physicians to pharmacists and payers. For example multi-indication pricing would require pharmas to determine value for each indication and proving value in specific subpopulations in which they are uniquely advantaged against competition, since Indication-specific pricing will also allow pricing for subpopulations within a particular disease. One of the biggest challenges the pricing scheme poses is that in many other countries, including the US, prescriptions are not always monitored for how they are used. One possibility would be to develop the infrastructure that would allow to link information captured at point of sale to prescriptions/usage.

Source: Based on Pharma Intelligence (2016)

Outcome-Based Payment/Reimbursement

Going forward, indication-based pricing is a small pragmatic step towards performance-based or outcome-based payment / reimbursement, i.e., tying payment to the outcome of an individual patient. **The aim of outcomes-based reimbursement is to link the cost of a drug to a measurable outcome** in patients like reduction in hospital admissions or cholesterol reduction, or even complete cure. For instance, Novartis is collaborating with the US Centers for Medicare and Medicaid Services (CMS) to develop novel pricing approaches for CAR-T Kymriah that would support value-based arrangements, encompassing both indication-based pricing – as an important step for patients and the healthcare system as it could support different payments for a medicine based on the clinical outcomes achieved in each indication, and outcomes-based approach – that would allow for payment only if patients respond to Kymriah after one month. In other words, for patients treated at centres that have opted into the outcomes-based approach, there is no charge if the patient does not respond in this timeframe. However, linking to individual outcome may be problematic. Most of the interest currently lies in linking payment to outcomes in groups of patients (Garrison and Towse 2017, KPMG 2016, KPMG 2017, PMC 2017, Robinson and Megerlin 2017).

3.2. Harnessing New Financing Models

Against the backdrop of increasing healthcare costs, and the availability of PM 2.0 breakthrough, individualised and expensive therapies, new sources/models of funding are required. The alternative options depend on the existing country-specific systems. For instance, many European healthcare systems are increasingly provided by a combination of public and private healthcare providers, and paid by a combination of public and private insurance, including co-payment by patients. Going forward, new funding models need to be analysed within the context of emerging precision medicine, in particular,

with regards to gene and cell therapies that are likely to require large upfront expenditures, which the present and already ailing healthcare systems cannot support.

A low hanging fruit consists in reducing system waste, which amounts to about 20-40% of total care spending according to a conservative estimate of WHO, will likely release funds that can be used for curative treatments. To this end, implementation of indications and outcomes-based pricing can dynamically contribute to improving the efficiency of the healthcare value chain.

The debate about affordability of cures is as much about cash flows as about value, in particular the alignment between value generation and financing mechanisms. There is a dearth of such an alignment in today's system since (i) funds cannot be transferred between individual budgets and (ii) budgets are typically set on an annual basis. In theory, new financing models can mitigate the immediate impact. For instance, debt financing – which could be of bond type or mortgage type – can be used to overcome short-term budget constraints, or funds can be reallocated based on value generation, such as paying back debt from hospital budget, if “cure” avoids admissions (Mattke 2015)

In reality, things are a bit more complicated. In multi-payer systems such as the US or Swiss systems, patients may switch insurers. The result is that one insurer might pay for a high-cost cure, and another payer “inherits” a cured patient. This may lead to strategic behaviour that can impede access to high-cost cures. There are concerns in the US that insurers may discourage patients in need of treatment to enrol through its benefit design or marketing strategy or they may delay treatment until patient ages into Medicare. Such strategic behaviour can lead to so-called “death spirals” for generous payers with the potential to drive insurers with comprehensive coverage out of business and/or unravel the entire market for cures altogether. As some insurers restrict access to care, patients in need of treatment selectively migrate to others, so the cost of those more generous insurers goes up. They then have to either restrict access as well, or increase premiums. If they increase premiums, their healthier members leave, driving premiums up even further.

To mitigate the challenges of financing high-cost cures that are administered once or over the short term, several policy solutions could be developed, the suitability of each depending on two factors namely, severability – i.e., the extent to which cost of a drug is separable from the cost overall disease treatment – and the value generation horizon – i.e., the time until full value realisation or the time to break even (Figure 5).

These policy schemes are complex and target the relevant actors: the patient, the payer, and the government (Mattke et al. 2016). Patient-level solutions include multiyear insurance policies and

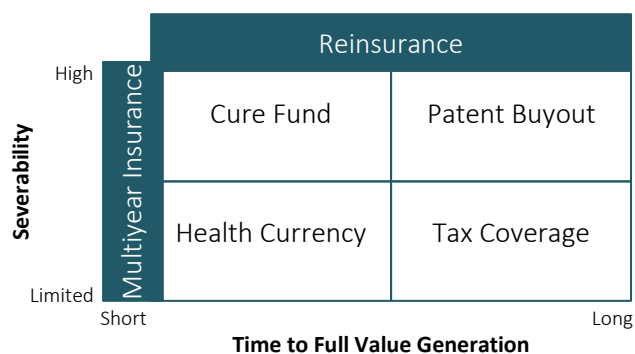


Figure 5: A Framework for Selecting Policy Option.
Source: Mattke et al. (2016)

and recourse to credit markets. Co-payment/out-of-pocket payment whether directly by the patient or by a dedicated private insurance coverage can also help finance expensive therapies. Higher shares of the out-of-pocket spending have the advantage of triggering a greater focus on outcomes and also enable patients to have access to new therapies if they are willing to pay. Some patient-assistance programme may need to be put in place, since patients can only pay up to their out-of-pocket limit.

Payers may purchase reinsurance against the unexpected high exposure to high-cost events or coordinate among themselves by institutionalizing either a **cure fund**, whereby all payers contribute to a pool from which a cure can be paid, or a **health currency**, allowing for inter-payer transfer payments. In

the long term, innovative securitized funds could be developed to ensure that all patients have access to high-cost curative cures at the right time (Montazerhodjat et al. 2016).

Precision medicine may call for specialised insurance that pool risk for a limited product or disease classes. For instance, private medical insurance is already used in many countries either a primary healthcare scheme (e.g., in Switzerland) or secondary/top-up scheme (e.g., in France), but they also have their limit as evidenced by Hepatitis C in Switzerland (Box 1).

Finally, the government can acquire the intellectual property (IP) at a fair price through a **patent buyout**²⁰ and the pharmaceutical company provides treatment at cost. For limited severability and long time to full value generation, the government can pay for selected high-cost treatment separately through **tax coverage** (Mattke et al. 2016).

These solutions are very complex and need to be tailored to the clinical properties and the trajectory of the product. To the extent that these complex schemes are needed to ensure access, it is imperative to start designing and planning early during clinical development, involving all relevant stakeholders. Crafting financing model that matches value trajectory will potentially also require regulatory changes.

3.3. Reforming Payment Systems

An *appropriate* payment system is one that “recognizes the potential of precision medicines, ensures patient access, and rewards continued innovation”²¹ while containing healthcare system costs. This is the particular challenge that must be addressed to pay for PM 2.0.

Paying for Curative Medicines

In PM 2.0, paying for curative medicines (single-dose treatment or treatment administered over short-period of time, typically 2-3 months), which can cost hundreds of dollars, is particularly challenging, since there is an **incentive mismatch arising from time inconsistency and distributional considerations within existing pay-per-treatment paradigm**.

Time inconsistency arises from the fact that speciality treatment generates a stream of benefits over the remaining lifetime of the patient while the treatment cost has to be incurred at a specific point in time (Yeung, 2017). This is analogous to purchasing a house, which is usually financed through mortgages, but unlike a house, a healthy state cannot be sold back and remaining mortgage paid, when the patient relocates. This leads to a distributional issue in multi-payer systems where the insurance bearer can switch insurance provider. For example if an insurer A pay for a patient’s treatment and the patient switches to insurer B, the latter inherits a healthy patient. This can lead to insurance-market shutdown as explained earlier.

Several payment solutions have been proposed to ensure equitable access to innovative, cost-effective yet unaffordable treatments. These include:

- **Upfront payment combined with innovative financing schemes**, such as Healthcare Loans (HCL) – so that costs are amortized over time – as well as appropriate burden sharing schemes in multi-payer systems or co-financing regimes;
- **Annuity/instalment as in lifetime leasing models**. Compared to upfront payment, annuity payments can be made portable with patients, but would require changes in payer accounting rules and regulations;

²⁰ To the extent that it does not involve society paying twice for the same innovation, e.g., when government funds part of the research

²¹ PMC 2015

- **Performance-based payment**, whereby payments are either only effected if patients are cured or adjusted depending on whether pre-specified health outcome is achieved. It is a form of risk sharing between manufacturers and payers/patients.

Value-Based Payments along the Care Pathway

Care delivery accounts for about 80% of the spending, where cost-effectiveness issues are often ignored and decisions left to physicians and the bedside decision-maker. Today cost effectiveness is, in effect, applied only to technologies – a drug, a new heart valve, a new pacemaker. It is not applied to everything else that physicians do when they deliver treatment, because that would be way too tedious to go through all the decision steps and all the treatments that doctors do. For instance, how do determine whether it is cost-effective to do another, say, electrocardiogram, in a patient, or whether to keep the patient another day in the hospital.

With the advent of precision medicine, particularly continuous monitoring of biomarkers, and the up trending of demand for chronic care related to co- and multi-morbidity, new payments have to be designed to incentivise appropriate care pathways.

3.4. Way Forward: Generating Evidence

Precision medicine is distinctly data-driven. Trust issues aside, the unresolved challenge is **how to collect, curate and share data to advance precision medicine from drug discovery to access**. Different actors are affected by the data revolution.

As one example, many pharmaceutical companies are interested in outcome-based payments. The effective functioning of a future outcome-based system (not in the conventional system) lies in developing efficient methods of data collection, of the ownership of data collection process and that of curating the data, and the financing thereof. Does the responsibility fall back on the payers (public body or private insurance company) or on the company that wants to launch a product? How to organise collaboration to generate the evidence needed? Do we need private consortia? Or do we need public-private partnerships? How to distribute value?

This points to a related question, namely **what is the case for changing the conventional system?** What are the incentives to change behaviour and move towards a long-term view? For the company, given current payment systems, such as the lack of indication-based payment, a pharmaceutical company has no incentive to change behaviour. So, the mandate needs to change, the momentum for which ought to come from political bodies. The government should change the rules of the game. Companies should do more to provide evidence of what is lost with the current system, not just evidence about what their medicines do but provide more policy-relevant talking points.

4. Concluding Discussion

“There is a need to shift away from a static view of the world and account for endogeneity, e.g., in market structure, number of indications”

- Kenneth Oye, Professor, MIT

The concluding discussion emphasized the importance to differentiate between PM 1.0 and PM 2.0, noting that **although PM 2.0 is most widely discussed because it draws policy and media attention, PM 1.0 provides cost-efficiency gains that could be easily justified**. With respect to PM 2.0, three broad sets of characteristics can be identified, related to the size of the population pool and market characteristics of competing drugs – both existing and potential. The combination of these characteristics has implications for pricing (Table 1) and reimbursement as well as competition and financing models.

In Precision Medicine 2.0, pricing and payment depend on 3 sets of characteristics:		
Size of Patient Pool (N)	Competition	Price Evolution
Large N, e.g., HCV	High	Decline over time (volume effect)
Small N, e.g., personalization	High (over time)	Decline over time * (competition effect)
Small N, e.g., rare diseases	Low	Unlikely price decline** (niche markets)

Table 1: Interdependence between Price and Market Characteristics

* For precision medicine driven by personalization methods and processes, there is significant competition, e.g., in oncology, that would eventually bring down prices.

** Rare diseases and orphan drugs are attracting interest, but it is unlikely that these niches markets will attract large numbers of firms. As a result, the incentives and market conditions for driving down prices are less likely to materialize.

The interaction between pricing and financing is non-negligible. For instance if measures (potentially complex, e.g., securitization) for upfront financing are developed, it may be possible to keep prices high. The issue of prices that will be supported and the financing available is a topic that needs to be further discussed, accounting for the time inconsistency problem – upfront cost and discounted stream of benefits over time – and the redistribution of benefits among actors – e.g., those who benefit over time may not be those who pay upfront. What matters here is the identification of funding mechanisms – for large upfront costs – that do not drive up prices.

Performance-based incentives/reimbursement is a promising avenue and could help address some of these trade-offs. Yet, its implementation could be hard. Performance-based payment systems may lead to perverse incentives, such as focusing on patient pools that improve overall performance. It requires stakeholders to agree on performance indicators that cannot be gamed. Table 2 highlights a framework that can potentially be used to design performance-based payments (PBP) and elaborate data-based indicators, for various types of precision medicines applications, depending on (1) amortization over time and (2) redistribution across actors.

Competition is also really fundamental. If there is only one actor, the bottom line is a monopoly situation or a situation of scarcity, then there is an incentive to increase price. This suggests that there is **public**

policy interest in cultivating competition – using, e.g., innovative licensing criteria to influence market structure. Promoting competition should not however come at the expense of providing the **incentives to develop**. Such incentives could call for the design of an intellectual property strategy that is adapted to the case of precision medicine.

It is critical to allow for flexibility and adaptation when developing new strategies – whether for pricing, financing and competition – since there is uncertainty in every assumption that are or will be made. So, the system should be approached in such a way as to mitigate the uncertainty and updating the assumptions as evidence emerge.

Table 2: A Possible Framework for Designing Payment Schemes for Precision Medicines; PBP: Performance-based Payments
 Payment schemes for various types of ‘2.0’ precision medicines, under conditions of uncertainty:

		(1) Amortisation over time	
		Short	Long
(2) Redistribution across actors	Patients	A Payment scheme, PBP, Indicators: ...	B Payment scheme, PBP, Indicators: ...
	Private (insurers & pharmas)	C Payment scheme, PBP, Indicators: ...	D Payment scheme, PBP, Indicators: ...
	Public	E Payment scheme, PBP, Indicators: ...	F Payment scheme, PBP, Indicators: ...

5. Suggested Elements for Principles and Guidelines for Delivering Affordable Precision Medicines

In revising or designing schemes for paying expensive precision medicine diagnostics, prevention and therapies, industry, health care providers and insurers/payers should strive to make them accessible and affordable to all. However, context – country healthcare systems and treatment categories – matters when it comes to precision medicine, making it difficult to come up with broad general guidelines on all topics related to precision medicine. The following elements for developing guidelines and principles and guidelines were discussed for delivering affordable precision medicines:

1. Acknowledging that affordability is important

As a guiding principle, precision medicine must not be developed only for just a few wealthy individuals. It is crucial to make it progressively available to all, to improve global health. So developing socially acceptable and economically viable financing and payment schemes is of utmost importance. **Availability of treatment, even if curative, does not guarantee its uptake if there is no effective demand, i.e., need for treatment backed by the ability to pay for the drug.** Public healthcare systems will not reimburse a treatment if it does not lead to Pareto improvement, i.e., improve the life of one person without making anyone else worse off. Existing private healthcare systems are also not designed to reimburse high upfront costs. Similarly, a person may be willing and able to pay if costs are amortized over a longer period of time. **Affordability is thus tightly linked with financial liquidity, and both are important for the mainstreaming of precision medicine.**

2. Acknowledging the need to adapt or revise ways to measure the value of health and medical care

As precision medicine advances within an already complex healthcare system, it is imperative to recognise the need to change the way value of medical care and health is created and accounted. On the one hand, **value is increasingly created by biomarkers, therapeutics, diagnostics and data jointly in a synergistic way.** On the other hand the **economic value of prevention and quality of life in good health must be reassessed and taken into consideration.** There is no one size fits all solution. Various solutions must be developed for various systems.

3. Designing payment systems that make sense in the long-term

Healthcare systems are potentially heading towards performance-based payment schemes. They require information about the performance of the product after treatment administration. However, although the conventional system has accumulated data for a product up to the product launch (e.g., safety and effectiveness), we are just entering the phase of acquiring data after product launch, and many questions remain open. An important step is to **start developing indicators for performance that are foolproof, i.e., that do not lead to perverse incentives, and to decide who is in charge of collecting data and how the evaluation of performance is made,** by which actors.

4. Need for real-world evidence

Real-world evidence (data) is set to play an increasing role in healthcare systems from drug development to new reimbursement schemes. Regulators, in particular, are looking for robust evidence , e.g., in order to adapt regulation in favour of precision medicine.

5. Adapting regulatory systems for incentivizing both IP and the common good

- IP as a strong pull factor: any drug approved is a stepping-stone to new discoveries; it is not just one drug, but there are about another 100 disorders that are awaiting for treatment.
- The legal and regulatory frameworks for PM need to be put in place in terms of **copyrights, patents** not only on therapeutics, but also regarding the patentability of medical devices and diagnostics which are weak.

6. Fostering competition

- Public policy should cultivate competition, since competition **is an important aspect related to pricing and affordability**.
- But competition **should not come at the expense of innovation**, which could include redefining roles and responsibilities (e.g. HTA mandate to account for broader economic impacts).

7. Ensuring access to breakthrough PM (2.0) through new financing mechanisms

Financing mechanisms, such as securitization could be developed to reconcile access to innovative treatment with considerations of justice, equity and solidarity.

8. Incentivizing research and development

To incentivise R&D, it is important to understand what makes PM an investible domain. Most therapies that are currently seeking approval from national regulators have some component of PM. **Clarifying the economic drivers of PM development** is important as they have repulsions, e.g., for the development of financial techniques such as securitization.

9. Incentivizing the development and use of biomarkers and diagnostics

- Improving access to biomarkers and diagnostics, particularly in continuous monitoring
- Acknowledging contextual shifts that are both disruptive and challenging: PM is shifting from single gene test, to multi-gene test and multi-diagnostic, raising new considerations about the role and value of biomarkers.
- Given synergies between biomarkers and diagnostics, new mechanisms are needed to distribute the value across the different players that may be involved in their development, use and payment. Otherwise, there may be underdevelopment of biomarkers and diagnostics.

10. Making patients responsible

Because PM is intrinsically patient-centric, responsible behaviour of the patient may be a key element of broad cost-effectiveness. **Patients could be held more responsible than now in case they do not adhere to their treatment or do not adopt behaviour that acts as prevention for predisposed conditions**. This necessitates that patients are also included in every step of the drug development and reimbursement decision chains. The patients should be able to participate in value assessments and decision processes made more transparent for them.

Moving towards a system where patients are required to be responsible also means that is important to incentivise responsible behaviour for instance by **reimbursing the cost of prevention** by responsible patients. Today's reimbursement systems are geared towards reimbursing therapies. In some countries such as Switzerland, some preventive activities that fitness and wellness are partially reimbursed. With the advent of monitoring devices (wearables), and without causing prejudice to privacy, it may be desirable that reimbursement systems reward responsible patients through some well-designed reimbursement schemes.

11. Enhancing data sharing schemes that respect privacy

It important is to **collect and improve access to data for differentiated uses across the value chain**, distinguishing between public use (research or use by public agency for the public good) and private use (pharmaceutical company or private research) in view of enabling, faster drug development, therapy optimization and innovative reimbursement schemes, and thereby contributing to improving affordability.

12. Harnessing the benefits of artificial intelligence (AI)

AI can lead to an overall reduction in healthcare system costs, e.g., when used for

- Analytics-based drug development by pharmas, payers → faster drug delivery at lower cost
- Adding precision to disinvestment decision by pharmas → reducing cost
- Better understanding of drug effectiveness by payers, pharmas, HTAs, governments → improving targeting access and reducing waste

- Better appraisal of drug performance by pharmas, payers → allowing innovative forms of payments, that better align incentives

13. Fostering multi-stakeholder collaboration and align incentives

Multi-stakeholder collaborations, including with academia, data scientists, pharmaceutical companies, policymakers, is key to unlocking the potential of precision medicine but issues of cost, pricing and reimbursement are difficult to discuss collaboratively. In particular, there is a need to:

- Better articulate **how payers should send signals to biopharmaceutical companies about what they value and what they are willing to pay for**
- Acknowledge the emergence of knowledge networks and markets that are independent of the product or service, e.g., analytics/data platforms.

14. Acknowledging and addressing uncertainty

There is uncertainty in every assumption, such as regarding how the market will evolve, or how performance-based payment could be designed in reality. For that reason, **flexibility and adaptation are important** and will allow approaching the system in such a way as to mitigate the uncertainty and update the assumptions as new evidence emerge.

Generating policy-oriented evidence when data is unavailable is difficult. It may be desirable to have recourse to modelling, in which case a more dynamic and long-term perspective (e.g. probabilistic models) should be taken.

From a governance perspective, when developing new payment and financing schemes, it is important to take an adaptive approach, starting with what is feasible within the boundary conditions of the regulatory and evidentiary environment, and then moving on to developing innovative schemes that would be truly game-changing.

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Discussion at the workshop was informed by a list of pre-readings among which a scoping literature review on ‘Cost-effectiveness of Precision Medicine’ and other papers including:

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Acknowledgements

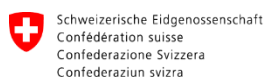
IRGC thanks the following individuals who provided specific contributions and insights during the discussions at the IRGC expert workshop on 12-13 April 2018: **Kujtesë Bejtullahu-Michalopoulos**, EPFL International Risk Governance Center (IRGC); **Isabella Beretta**, Swiss State Secretariat for Education, Research and Innovation (SERI); **Ulrike Busshoff**, German Aerospace Center (DLR); **Katrin Cramer**, Federal Office of Public Health (FOPH); **Thomas Cueni**, International Federation of Pharmaceutical Manufacture and Association (IFPMA); **Gérard Escher**, École polytechnique fédérale de Lausanne (EPFL); **Marc Friedli**, École polytechnique fédérale de Lausanne (EPFL); **Marie-Valentine Florin**, EPFL International Risk Governance Center (IRGC); **Cyrille-Claude Girardin**, Swiss State Secretariat for Education, Research and Innovation (SERI); **Fumie Griego**, International Federation of Pharmaceutical Manufacture and Association (IFPMA); **Thomas Hach**, Novartis International AG; **David H.-U. Haerry**, Positive Council Switzerland; **Richard Johnson**, Global Helix LLC; **Soeren Mattke**, University of Southern California (USC); **Anjali Nursimulu**, Independent; **Kenneth Oye**, Massachusetts Institute of Technology (MIT); **Séverine Rion-Logean**, Swiss Re; **Reto Schneider**, SWICA Gesundheitsorganisation; **Thomas Szucs**, University of Basel, Helsana Group; **Alexander Thompson**, University of Manchester; **Thomas Vogel**, University Hospitals of Geneva (HUG) and Healthcare consultant; **Sophie Voigt-Firon**, KPMG Global Strategy Group, Healthcare and Life Sciences; **Stefan Weber**, Amgen; **Daniel Widrig**, Bristol-Myers Squibb.

This workshop report was written by Anjali Nursimulu, with contributions and editing by Marie-Valentine Florin.

The views and recommendations in this report do not necessarily represent the views of workshop participants, individual members of the project team, other contributors, or their employers.

IRGC would like to thank Myriam Kasztura, Aude Richard, N. Bempong, D. Loncar and Antoine Flahault for their scoping review on *Cost-effectiveness of Precision Medicine*, which informed discussions at the workshop, and Gérard Escher, for his help in preparing the background reading list that supported the preparation of the workshop and provided additional material for analysing certain specific aspects.

IRGC also wishes to acknowledge and thank the Swiss State Secretariat for Education, Research and Innovation (SERI) that provided a financial contribution to the workshop, and Campus Biotech that hosted the workshop.



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