

# Value Creation in Precision Medicine

Acknowledging the need to devise new ways to  
measure the value of healthcare

Scoping review and annotated bibliography  
for the Health 2030 & IRGC@EPFL Workshop  
with and at the Brocher Foundation  
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## Acronyms

CEA	Cost-Effectiveness Analysis
Dx	Diagnostics
EAPM	European Alliance for Personalised Medicine
EMR	Electronic Medical Records
EHR	Electronic Health Records
IBP	Indication-Based Pricing
NICE	(UK) National Institute for Health and Care Excellence
NHS	National Health System
PM	Precision Medicine
PMC	(US) Personalised Medicine Coalition
PMI	(US) Precision Medicine Initiative
PPVF	Patient-Perspective Value Framework
OBPM	Outcome based payment models
QALY	Quality-Adjusted Life Years
RCTs	Randomised-Controlled Trials
Rx	Therapeutics
RWE	Real-World Evidence
VAFs	Value Assessment Frameworks
VBHC	Value-Based Health Care
WTP	Willingness-to-pay

### The 5 Recent US Value Assessment Frameworks

ACC/AHA	American College of Cardiology/American Heart Association
ASCO	American Society of Clinical Oncology
ICER	(US) Institute for Clinical and Economic Review,
MSKCC	Memorial Sloan-Kettering Cancer Center (DrugAbacus)
NCCN	National Comprehensive Cancer Network

### EU VAF - Oncology

ESMO	European Society for Medical Oncology (ESMO) Magnitude of Clinical Benefit Scale (MCBS)
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# Introduction

Precision medicine (PM) holds the promise of bringing the right treatment to the right patient at the right time with the upside of reduced undesirable effects. But the impact on healthcare costs are not clear. While targeting of conventional drugs through precision diagnostics may be relatively cost-effective [3] and provide better performance and reduced side effects, fully personalised PM treatments, such as cancer gene therapies, are generally high cost at least in the short term. PM may not be cost-saving unless the regulatory framework requires less burden of proof, lowering development costs. There also remains scientific, clinical and economic barriers to the creation and capture of PM's benefits.

Precision medicine, driven by genomic medicine, is only beginning to revolutionize healthcare delivery; clinical translation of multi-omics data will give further momentum to PM [5]. Uncertainty about the sustainability of high-cost treatments in our health systems may stunt however adoption and diffusion. Indeed, while the cost of individual treatments remains manageable for both private and public payers with only few approved high-cost treatments and a small addressable population, there are concerns about the sustainability of healthcare budgets as precision medicine comes to the fore. In line with [1], **ensuring access to high-cost diagnostics and treatments necessitates reappraisal of value creation by precision care, new means to incentivise value delivery and unlock value creation by precision medicine.** Because of varying degrees of de-/centralisation of health systems, no-one-size-fits-all solution is likely to emerge.

## Reassessing Value

- There are key gaps in health economics and outcomes research best practices, decision standards, and value assessment processes [40].
- Evidence for many interventions accrues over time and indications evolve. To avoid risk of underinvesting in innovation, the dynamic aspects of value creation should be integrated into emerging value frameworks [7].
- Value creation calls for a fine balance between personalisation and standardisation, since “the underlying science may support virtually unlimited differentiation, but economic forces may advance commoditization” [29].
- Value creation and assessment is an increasingly data-driven endeavour and advanced analytics a key enabler. Multistakeholder collaboration along the value chain is necessary to unlock and quantify the value potential of precision medicine.

## Incentivising Value Delivery

- With the foreseeable market entry of new high-cost treatments, payers' ability to absorb the impact of the aggregate cost of multiple gene therapies while delivering affordable access to healthcare is less certain.
- New approaches to financial management, leveraging novel financing and reimbursement strategies—involving risk-sharing mechanisms and annuitization, will be needed to ensure market access.
- Since pharmaceutical companies and diagnostics companies are mutually interdependent in the stratified medicine world [52], it is important to bring forth the jointly-created value since market access depends on co-reimbursement.

## International Differences

- There is broad awareness about precision medicine as well as public belief that treatment costs should be covered by public or private insurance schemes [55].
- Countries differ not only in the extent of public vs. private insurance, but also in the degree of overlap between drug approval and health technology assessment. Separate bodies may cause market access delays or high out-of-the-pocket expenses, both of which are undesirable.
- Contemporaneous value assessment differs between single-payer and multi-payer systems, while readiness to use innovative financing schemes do not seem to depend on healthcare systems beyond natural variations.

## Unlocking Value of Prevention

- From a utilitarian point of view, it may be useful to break down PM by its components across the **continuum of care**, to be met under specific time constraints [36]:
  - Disease prevention, or prediction of disease risk before the disease symptoms manifest,
  - Differential diagnosis, or timely/instantaneous identification of an illness, and
  - Disease treatment, i.e. strategies to cure or optimally treat once disease has been identified.
- To encourage the shift towards prevention, new evidence will have to be generated based on longitudinal data that is currently missing. Data must be collected on a broad population base, calling for international collaboration.
- Absence of robust cost-effectiveness evidence in favour of prevention should not disincentive preventive care, and science should aim at unravelling the root cause of diseases to enhance future preventive interventions.
- Even if prevention is not cost-effective, it may present adequate value for money and there may be value from a societal perspective.

# The Value Imperative

## 1 | What Is Value-Based Healthcare?

The term “value-based” was first introduced by Brown et al. [2] in 2005 to refer to the practice of medicine that integrates evidence-based data—from clinical trials—with patients’ perceived value of healthcare interventions at a given cost, thereby accounting for quality of life improvement. Pharmacoeconomic principles underpin value-based medicine.

The term “value-based” is also used to specify how health-service provision is remunerated. In a value-based healthcare delivery model, “providers, including hospitals and physicians, are paid based on patient health outcomes. Under value-based care agreements, providers are rewarded for helping patients improve their health, reduce the effects and incidence of chronic diseases, and live healthier lives in an evidence-based way. Value-based care differs from a fee-for-service or capitated approach, in which providers are paid based on the amount of healthcare services they deliver. The ‘value’ in value-based healthcare is derived from measuring health outcomes against the cost of delivering the outcomes.”<sup>1</sup>

Value in healthcare has gained traction since Michael Porter’s seminal article on value-based healthcare (VBHC; [4]). Porter’s starting point is the excessive growth in healthcare spending relative to GDP in most developed countries, and that a healthcare system that delivers high value to patients ought to be financially sustainable (Box 1).

### Box 1: Porter’s Value Premise

- Achieving high value for patients must be the overarching goal of healthcare delivery, with value defined as the health outcomes achieved per dollar spent.
- If value improves, patients, payers, providers, and suppliers can all benefit while the economic sustainability of healthcare system increases.
- Rigorous, discipline measure and improvement of value is the best way to drive system process, yet value in healthcare remains largely unmeasured and misunderstood.
- Value should always be defined about the customer, and in a well-functioning healthcare system, the creation of value for patients should determine the rewards for all other actors in the system.
- Value depends on results, not inputs: value in healthcare is measured by outcomes achieved, not the volume of services delivered, yet shifting focus from volume is a central challenge.
- Outcomes are inherently condition-specific and multidimensional; outcome measures can be classified in a hierarchical way (Fig. 1).
- Cost measurement and apportionment are key elements since shared resources must be attributed to individual patients on the basis of actual resource use for their care, not averages.
- Failure to prioritize value improvement in healthcare delivery and to measure value has slowed innovation, led to ill-advised cost containment, and encouraged micromanagement of physicians’ practices, which imposes substantial costs of its own.
- Measuring value will also permit reform of the reimbursement system so that it rewards value by providing bundled payments covering the full care cycle or, for chronic conditions, covering periods of a year or more. Aligning reimbursement with value in this way rewards providers for efficiency in achieving good outcomes while creating accountability for substandard care.

Source: Based on [4]

VBHC recognises that **patients are the ultimate stakeholders in healthcare**, and that **patient preferences** play a significant role. For example, some patients prefer efficacy of a powerful drug regardless of side effects, while others may choose reduced efficacy with fewer side effects. This efficacy-risk trade-off is determined by patient-specific circumstances.

## 2 | Value in Precision Medicine

Precision Medicine, as defined by the (US) National Research Council, is “the tailoring of medical treatment to the individual characteristics of each patient...to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment. Preventative or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not.”

<sup>1</sup> *NEJM Catalyst* January 1, 2017 <<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4398974/>>

PM entails a welcome shift from population-based ‘average’ benefits/value calculation to value calculation for disease subtypes informed by multi-omics as well as more commonly used demographic, lifestyle and patient factors (weight, age, race). Such value calculation allows providers to better gauge the value of treatment for patient subgroups.

Based on the “Outcome Measures Hierarchy” proposed by Porter [4] (Fig. 1), PM is, hypothetically, a natural candidate for VBHC. PM has the potential to be an enabler of VBHC by providing superior outcome (A) faster and with potentially single treatment event (B), reduced side effects (C), coupled with lasting outcomes (D) and no long-term adverse effects (E). There are a number of barriers that can prevent value creation in PM. Testing costs significantly influence the value of personalized treatment and may not always be cost-effective. Also, as a “young” discipline, PM lacks aggregated evidence for improved outcomes with genotype-guided therapy and has only limited data on long-term outcomes.

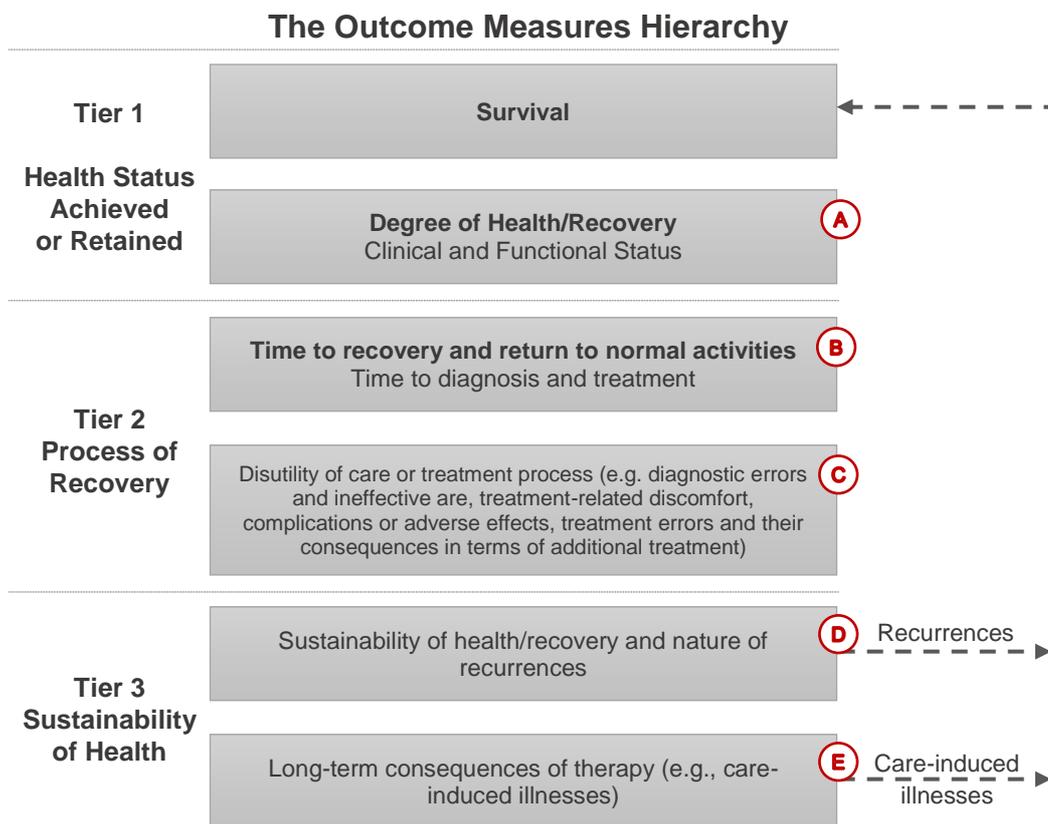


Fig. 1: The Outcome Measures Hierarchy. Source: Adapted from [4]

### Diversity of Value

Turning to value, VBHC looks at it from the perspective of the patient. But, more generally, value means different things to different groups, and, within those groups, different things to different subgroups and individuals [38], for example:

- Healthcare organisations and payers: value defined by resource utilization
- Healthcare providers: value can be found in workflow management and clinical outcomes improvements
- Patients: value is tied to the experience and outcome of care

As a result, there is a need for some kind of framework to communicate these value perspectives.

# Value Frameworks

“Value frameworks serve the necessity to introduce more rationality in health decision-making seen from the perspective of physicians, patients and financing bodies ... [and] help to avoid power struggles” [11]. Existing frameworks differ in their inclusion of costs and use of outcomes measures while also targeting different stakeholders and their decisional needs from coverage, access, and pricing to defining appropriate clinical pathways and supporting shared decision making [6].

## 1 | Value Frameworks in Oncology

New value frameworks have been developed to enable informed decisions about the benefit of novel cancer therapies [11], where precision medicine has made the biggest stride. The frameworks are intended to allow third-party payer or policymakers to decide on the societal benefit of funding those therapies. These tools—ESMO, ASCO, ICER and NCCN—have varying purposes (see Value Frameworks, page 22):

- The ESMO framework is designed to provide data on the relative clinical impact of anticancer drugs, but leave comparative effectiveness calculations to European health technology assessment committees (e.g. Swiss Network for HTA in Switzerland, Haute Autorité de Santé in France, NICE in the UK (coordinated in the European Network for Health Technology Assessment (eunetha.eu)).
- The ASCO tool has been developed to assess net health benefit and demonstrates the costs of the anticancer drugs as these are discussed between oncologists and patients.
- Cost-effectiveness analyses, which include costs and QALYs, are the approach used by the Institute for Clinical and Economic Review (ICER) Value Assessment Framework.
- The NCCN initiative is also designed as a tool to discuss the variety of regimens that can be offered to a patient, supplemented by an assessment of affordability.

Besides differing in decision contexts, these frameworks take different perspectives [6] and have their own merits and limitations ([9], Table 1). These frameworks share the shortcomings that they do not incorporate real-world evidence, patient reported outcomes or considerations of sub-population analysis. There is also no consideration of patients’ priorities and preferences, while the scoring methodologies are ad-hoc [8].

Level	Decision Context	Framework	Merits and Limitations
Plan level	<b>Inclusion in health plan benefit package</b> Coverage and pricing: computing incremental premium cost and health goals	(US) ICER	<ul style="list-style-type: none"> <li>• Not intended to inform patient-level choices and may overlook patient subgroups</li> <li>• May not capture value over the life cycle of the product (i.e., topics may only be evaluated once, with no explicit schedule for updating over time); although update to the clinical and economic evidence is not ruled out</li> </ul>
		MSKCC	<ul style="list-style-type: none"> <li>• The DrugAbacus tool has a primary focus on efficacy outcomes associated with the first approved indication</li> <li>• Thus, it may underestimate product value and potential benefits associated with personalized medicine drugs</li> <li>• Does not take into account companion diagnostics</li> <li>• Does not explicitly account for combination drug regimens (particularly with regard to pricing)</li> </ul>
Benefit management/ patient level	<b>Management of health benefits and utilization</b> Standard treatment guidelines and utilization management	NCCN	<ul style="list-style-type: none"> <li>• Already aligned with personalized medicine in that some oncology agents are only recommended for use in patients with known mutations (BRCA1/2, KRAS, EGFR)</li> <li>• Quick-view format enhances approachability and ease of use, but may lack the detail necessary for personalized medicine beyond what is contained in the NCCN guidelines</li> </ul>
Patient level	<b>Shared decision making</b> Patient and provider interact to select the best therapeutic option	ASCO	<ul style="list-style-type: none"> <li>• Clinical trial data averages may not represent the individual patient</li> <li>• Framework components may miss considerations important to patients or may have weights that do not represent patients’ values</li> <li>• Requires user to seek out and assess the literature for the most relevant data</li> <li>• Does not take into account companion diagnostics</li> </ul>

Table 1: Value Frameworks in Oncology: Decision Context, Merits and Limitations. Source: Adapted from [6] [9]

## 2 | Patient-Perspective Value Framework (PPVF)

The PPVF is an on-going joint initiative between FasterCures, a think tank, and Avalere, a consulting firm, with the objective of putting patients to the front and centre in value calculation. Unlike the existing frameworks in which input from patients or other stakeholders is limited, the PPVF process included multiple stakeholders from the start, including a significant number of patient groups. Furthermore, to ensure the development of a framework that is truly built on the

patient perspective, the PPVF started with a list of considerations—or criteria—that are important to patients when making healthcare decisions. The patient-centered issues that affect patient-level decision-making were identified through workshops and working groups. These considerations were then organized into five domains, making it significantly different from any of the other existing frameworks:

1. Patient preferences	Value is viewed through the lens of patient preferences
2. Patient-centered outcomes	The PPVF considers outcomes that matter to patients and incorporates real-world data necessary to measure those outcomes, instead of limiting the measures considered to those tracked in randomized clinical trials (RCT)
3. Patient and family costs	The PPVF measures the true cost to the patient and family instead of focusing on financial costs to the system alone; diagnostic costs can also be included
4. Usability and transparency	The PPVF acknowledges that different evidence applies to different patients using subgroup data where possible, allowing the integration of outcomes achieved in the precision medicine context
5. Quality and applicability of evidence	Usability and transparency are underlying principles that serve as a foundation on which the PPVF value assessment rests.

The PPVF has the advantage of being able to support provider-patient communication, integrate real-time measurement of priorities and preferences. Its scoring methodology is also consistent and can be further enhanced using multi-criteria decision analysis, which facilitates decision-making for complex choices [8].

### 3 | Components for Precision Medicine Value Frameworks

Precision medicine “**increases health impact by improving the matching process between patients and treatments and by improving a patient’s understanding of the risk of serious side effects**” [14], considering that responses to treatments are heterogeneous across individuals or population subgroups. As such, value should be measured on the basis of **outcomes and cost per patient**.

According to the (US) Personalized Medicine Coalition, the prerequisites for value assessments that guarantee patient access to new technologies and optimal care are multifaceted ([9]; see Fig. 2). Such Value Assessment Frameworks (VAFs)

- (1) Are intrinsically patient-centric, which is also a cornerstone of VBHC and PPVF
- (2) Incorporate patient’s genetic traits based on validated and clinically-relevant diagnostic tests
- (3) Account for possible outcome heterogeneity across patient subgroups, vitiating the limitations of RCTs and population-based “average” benefits
- (4) Capture both economic and clinical values, improving treatment efficiency
- (5) Recognize fundamental patient values and preferences with respect, e.g., to quality of life. These are not accounted for, e.g., in the ASCO and NCCN frameworks [8]
- (6) Acknowledge that value in healthcare is dynamic and include methods that allow to capture emerging or evolving value elements.

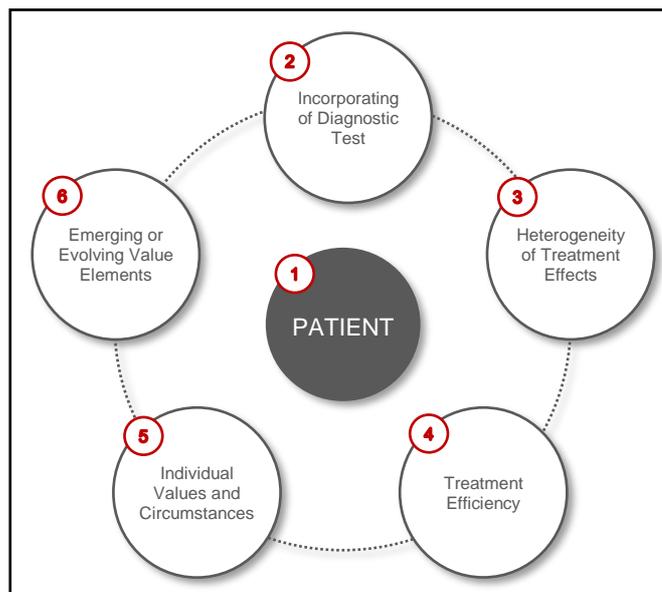


Fig. 2: Necessary considerations for precision medicine value framework. Source: Adapted from [9].

### 4 | Future perspectives

Decision-makers look to VAFs to rationalise decisions, but there are varying levels of awareness of, and use of each of the value frameworks in practice. Since the frameworks can steer the course of clinical and commercial development, it is important to understand the impact of these VAFs [10]. To that end, and in order also to foster internationally harmonised priorities, Walter [11] suggests that “meta-criteria” would have to be developed by international health organizations to elucidate the strengths and weaknesses of these value frameworks.

# Value Assessment for Precision Medicine

Delivering value in precision medicine is intrinsically linked to its adoption, leading to a circular problem. The scientific rationale for value creation by PM looks sound, but is hampered by deficiencies in both the clinical and economic evidence base.

## Improving the Evidence Base

Cost-effectiveness analysis (CEA) has been the cornerstone for value assessment, particularly in the UK, where the associated cost/QALY measure is used as a one-size-fits-all metric. In less centralized systems and in light of advances in science and medicine, CEA has important limitations. In particular, it fails to yield clinically relevant, patient-centred results [12], thus running counter to the premise of precision medicine.

### 1 | Putting the patient at the centre

- 1.1. Acknowledging heterogeneity of treatment effects.** Precision-medicine-specific value is partly driven by the variance of health impacts of a specific treatment across the whole population. By extension, when multiple precision therapies are considered, the lower the correlation of treatment effects across therapies, the higher the value [14]. One implication is that “economic case for precision medicine can improve the relative cost-effectiveness of care by **exploiting patient-level heterogeneity [in cost and] health outcomes**” [13].
- 1.2. Assessing value addition by biomarkers.** Biomarkers help reduce the uncertainty about treatment effects, where such uncertainty reduction is a key value component [13][16]. Thus, in order to better gauge the value of PM, it would be valuable to understand how much impact can be gained by integrating biomarkers more effectively into determining individual treatment effects [14] in terms of (1) the strength of evidence on the risk-reduction in severe adverse events associated with a pharmacogenomically-guided alternative therapy; (2) the additional social resources it takes to deliver a pharmacogenomic alternative; and (3) the likelihood that physicians procure and/or act upon genetic testing information [24].
- 1.3. Focusing on outcomes that matter to patients.** In line with Porter’s Outcome Measures Hierarchy [4] and the PPVF, outcomes that matter to patients, e.g., functional outcomes, should be included in value assessments [17]. By implication, providers should capture data on such outcomes over the relevant period of care. Such information also facilitates shared decision-making and enhances patient empowerment, both of which are fundamental features of value [35].
- 1.4. Accounting for dynamic efficiency.** Because precision medicine—and the diffusion of its enabling technologies: ‘omics’-based biomarkers; complex artificial intelligence-based algorithms; and digital health applications—will likely change the way some health services are delivered, adjustments to the way health services are evaluated will be required to take into account, e.g., emerging structural uncertainty and equity considerations [19]. For curative therapies, for example, the uncertainty around durability of clinical outcomes over time further compounds the assessment of benefit. Treatments are not received in a vacuum, and patient-specific care pathway should also be incorporated in the value analysis [12].
- 1.5. Developing single-index of value.** To the extent that value is determined by diverse components, it is important to assign weights to them and combine them into a single index that can be communicated in a meaningful way to different audiences [18], ideally against some benchmark.

### 2 | Accounting for broader societal impact

Broader social outcomes are multidimensional. They include, for example, the productivity impacts of both the patient who has received treatment and of caregivers. Ladkawalla et al. [16] also highlighted the importance of accounting for scientific spillovers in value assessment. Jena et al. [15] highlight yet another type of spillover that relates to the secondary effect of a cure. Specifically, curing Chronic Hep C has been shown to benefit those in need of organ transplants in the UK, corroborating similar evidence in the US.

### 3 | Developing better cost accounting

To get a better understanding of the value of precision medicine, it is imperative to account for the (extra) R&D costs associated with PM [14]. Additional cost elements that need to be assessed include:

1. Genetic testing costs
2. Development costs for companion diagnostics
3. Inclusion of biomarker-negative individuals in clinical tests

4. Collection of real-world data and non-clinical data, factoring in potential decrease in collection costs with the adoption and diffusion of innovative wearable devices

Of note, cost of collecting and curating data on outcomes that matter to patients can be initially high, considering that collection and sharing of such data have not been encouraged by the fee-for-service system and is hindered by the silos in the current organisational structure of medicine [17]. Where care services are bundled, the issue of **cost apportionment** also has to be resolved.

#### 4 | Encouraging biomarker development, qualification, and use

Diagnostics are a critical if not an integral part of the precision medicine equation [59][60], allowing to streamline the drug development process through better patient targeting, improving treatment efficacy within population subsets, and potentially reducing costs. Adoption is however hindered by the **dearth of clarity on their pricing and reimbursement**. Improvements here are anticipated and needed to encourage the discovery, development, and adoption of biomarkers. However, some initially promising innovations have failed to translate into clinical practice, as they have lacked **demonstration of real-world effectiveness and favourable economic endpoints** [26]. It is therefore imperative to understand and demonstrate the improvement of patient outcomes as well as the value that diagnostics create for diverse stakeholders [22].

Highlighting that over-reliance on RCTs limits the **types of value impact** that can effectively be investigated, the AdvaMedDx's Strategic Value Initiative (SVI, [22]) defines:

- a. A set of **core principles for effective diagnostic value assessment**: comprehensiveness, evidentiary, cost (incurred and avoided both within and outside health systems), specificity, flexibility, engagement (multiple stakeholder perspectives), transparency, relevancy;
- b. A **set of value drivers** (different ways a diagnostic test of technology can affect the quality and cost of care): clinical impact, non-clinical patient impact (e.g., patient experience and out-of-pocket costs), care delivery revenue cost and impact, public and population impact;
- c. **Key diagnostic stakeholder groups**: patients, clinical laboratories, payers, providers, government, employers, patient advocates, quality organizations, professional medical associations.

Focussing on the **stakeholder framework**, recommendations from Amur et al. [21] include:

- a. Coordinate existing partnerships and consortia so that they effectively direct their efforts toward development and qualification of the priority biomarkers identified by the US FDA and the scientific community;
- b. Develop and maintain the infrastructure for aggregation and curation of relevant biomarker data to expand qualification of priority biomarkers (e.g., develop data and/or sample repositories);
- c. Conduct substantive reviews and make recommendations to the FDA on the sufficiency of data packages developed by industry and public-private partnerships to support qualification of new biomarkers; and
- d. Support biomedical research that is necessary as the basis for the development of new biomarkers.

Based on several examples, St Jean et al.[60] emphasise the necessity to:

- a. Foster greater collaboration between/among relevant stakeholders—throughout R&D, regulatory, market access and reimbursement processes and for the duration of the product lifecycle—to ensure that the availability of precision medicines and diagnostics are aligned;
- b. Remove impediments to collaboration at the different stages of the value chain;
- c. Ensure early engagement between and among relevant stakeholders, e.g., between payers and diagnostic company, especially since clinical research trials assessing genomics-based precision medicine innovations often do not measure outcomes that would allow payers to properly assess their utility and value;
- d. Remove the compartmentalized approach to collaboration to fast-track the industry to the 'future of medicine'.

Finally, the overall value of genetic testing remains uncertain in part because the scientific evidence underlying pharmacogenomics is rapidly evolving. This uncertainty also arises because the cascading impact of existing research on the value of pharmacogenomics has focused primarily on the short-term cost-effectiveness of single gene tests—an approach that ignores the potential lifetime value of multiplexed genetic testing strategies.

It follows that there is a need for foresight and collaboration [27]. Companion diagnostics and the stratified medicines that they enable are a growing category of new and legacy therapies in oncology and other disease areas. Their ultimate success depends upon more than scientific discovery, but on a strategy that unites clinical benefits, ethical choices, and economic incentives in ways that significantly accelerate decision timing, decrease therapeutic outcome uncertainty, shift competition, and potentially increase ICER-justified product prices. Mechanisms to create, determine, and share value among all stakeholders from patients, providers, and payers to regulators, developers, and discovery scientists must also be advanced [47]. Likewise, providers should be encouraged to adopt new practices that incorporate diagnostics in care delivery [24].

# Paying for Value

## 1 | Treatments: Outcome-based pricing

“By linking drug prices with desired results, outcome-based pricing puts the focus on the patients while aligning all the players around the consequences for patients” [44]. Although outcome-based pricing strategies may take on a variety of forms for various drugs and devices, the drug company essentially establishes a risk-sharing model that allows for higher reimbursements for better outcomes and lower reimbursements for reduced outcomes. Outcome-based pricing is being tested in many countries [44], for example:

- Amgen – Repatha (cardiovascular product), wherein Amgen is to receive a higher rebate if patient outcome exceeds outcomes of clinical trials
- Merck and UnitedHealth developing and testing pay-for-performance models
- Eli Lilly and Anthem working together on policy dimensions, e.g., government regulations regarding pricing
- Medtronic – outcome-based agreement for Aetna, an insulin pump – for type 1 and type 2 diabetes

Because of the current applicability of outcome-based pricing to only a small subset of drugs, its impact on the quality of care or costs is still unclear [46].

## 2 | Diagnostics: Value-based differential pricing

Biomarker reimbursement is, today, by and large cost-based, in line with the traditional classification of diagnostic tests. Novel biomarkers enable not only patient stratification but also provide prognosis and predictive insights on treatment response, allowing individual-centric care delivery. Going forward, because biomarkers and biomarker-based predictive-tests have global public-goods characteristics, global **value-based differential pricing** is required to achieve dynamic efficiency in terms of the optimal rate of innovation and adoption [41]. One measure of value could be [20]:

$$\text{Value} = \text{Reference Price} + \text{Differential Value of a Targeted Therapy}$$

While the market for targeted medicine is rapidly expanding, it is important to quantify the interdependency between molecular testing and drug development in precision medicine. To realize the full value of PM for both molecular testing and therapeutics, thorough cost-benefit analysis is needed. There would be obvious challenges in performing these analyses, especially, given the complexity and intrinsic uncertainty in assessing tests with multiple biomarkers, along with heterogeneity across cancer types and stages in various subcohorts of the same disease [18]. And, although there is a trend toward a more general acceptance of such tests as having clinical utility and therefore in principle appropriate candidates for insurance coverage, not all biomarker assessment is linked to reimbursement [23]. Moreover, there is still a reluctance to cover tests deemed experimental and **relatively high bars for the evidence that can make coverage routine**—though in most cases the coverage usually follows rather than facilitates clinical practice [45]. The end result is a cycle in which three trends compete: evidence for and use of genetic testing increase over time; insurance coverage (though present) imposes higher cost-sharing by patients; test prices fall and coverage improves [45].

There are also discussions about the optimal level of test and treatments coverage. Varying threshold levels for diagnostic test results can lead to a demand curve to test and treatment that calls for partial cost-sharing [45]. This is because payers may recognise that the use of different companion diagnostic can create an inaccurate perception of differentiated products [29]. Partial coverage, however, runs counter to reducing patients' out-of-pocket expenses.

In light of these challenges, value-based, flexible reimbursement for innovative, patent-protected diagnostic and therapeutic products are critical to creating stronger economic incentives for the development of precision medicine [42]. Grosse [25] propose a prioritisation scheme for economic value assessment, wherein clinical utility (risk-benefit analysis) is emphasised, which aligns with the proposition that absence of evidence of economic value should not trump innovation in the short run [28].

## 3 | Providers: Value-based payment

A **shift from a volume-based to value-based or outcome-based payment** is necessary to incentivise providers to adopt new inventions and practices when they are available. Outcome based payment models (OBPM) can also solve the shortcomings of fee-for service [48], and can be of two types based on differences in design features: narrow OBPMs (financial incentives based on quality indicators) and broad OBPMs (combination of global budgets, risk sharing, and financial incentives based on quality indicators). Although strong empirical evidence on the effects of OBPMs on healthcare quality, utilization, and costs is limited, Vlaanderen et al. [48] find that broad OBPMs may be preferred over narrow OBPMs.

## 4 | Alternative Financing Models for Durable Therapies

Emerging classes of durable therapies with short (sometimes single dose) treatment regimens and lasting benefits create significant healthcare financial challenges. One key challenge is the heightened importance of uncertainty regarding the benefit level at the time of treatment [90]. Another is the behaviour of insurers, with the risk that strategic behavior by health insurers could unravel the market for curative therapies for chronic diseases. Because the cost of these cures is front-loaded but the benefits accrue over time, insurers might attempt to delay treatment or avoid patients who require it, in the hope that they might change insurers [88].

Alternative financing mechanisms are needed to ensure equitable market access to more durable therapies, and to facilitate access to expensive yet highly effective breakthrough medical treatments (see for example [89]). In effect, the traditional financing model, where both treatment costs and benefits are spread out over time, fits the yearly assessment of coverage, premiums, and member enrollment. Since the benefit of curative (gene) therapies—an emerging class of precision therapies—accrues over a patient's lifetime after (usually) a single high-cost administration event, this creates a budgetary imbalance in the traditional model, vitiating its viability for curative therapies.

Of the alternative financing and reimbursement mechanisms proposed, models address the payment-timing-induced financial challenge:

1. **Annuity:** Individual annuity that converts a one-time upfront high cost to multiperiod payments.
2. **Performance-based annuity:** An annuity payment that is contingent upon performance (e.g., efficacy, durability, safety), as proposed, for instance, by Spark Therapeutics (see [92] for details)
3. **Risk-pooling:** Pool risks for constant payments at plan or employer level using standard reinsurance or state-level bonding

Each of these models provides a buffer for different types of uncertainty associated with curative therapies [86][91][92], as highlighted below.

1. **Therapeutic performance risk.** The long-term real world outcomes associated with high-priced gene therapies are uncertain. This creates a preference for performance-based payments with or without annuity.
2. **Beneficiary turnover.** In multi-payer systems, patient churn in and out of plans will complicate if not avert performance-based payments for one-shot, high-cost treatment events.
3. **Actuarial risk.** The number of eligible patients in a payer's population may be uncertain and could vary significantly from period to period, favouring a risk-pooling mechanism.
4. **Adverse selection.** Differences in coverage by payers in competitive markets would lead to adverse selection for the plans covering durable/curative gene therapies, which would increase premiums.
5. **Payer diversity.** Because payers vary in their ability to absorb the cost of new durable gene therapies, the financing mechanisms need to be fine-tuned to specific challenges, potentially requiring that regulatory and operational barriers are addressed. Failing this, the insurance industry may become more concentrated.

### Towards a Precision Financing Model

Along with the increasing market penetration of durable therapies comes the need to develop a precision financing toolkit ([91], Fig. 3). Such a toolkit will, for instance, account for the benefits, e.g., improved functional status of both the patient and caregiver of treatments with a durable response. This is particularly important when comparing these durable therapies with conventional treatments [92].

### Changing Insurer's Financial Incentives

To avert the adverse selection problem, healthcare systems should get "insurers to compete to provide patients with access to effective therapies rather than incentivize them to avoid patients whose health may hang in the balance" [43]. In multi-payer systems, the performance-based annuity model

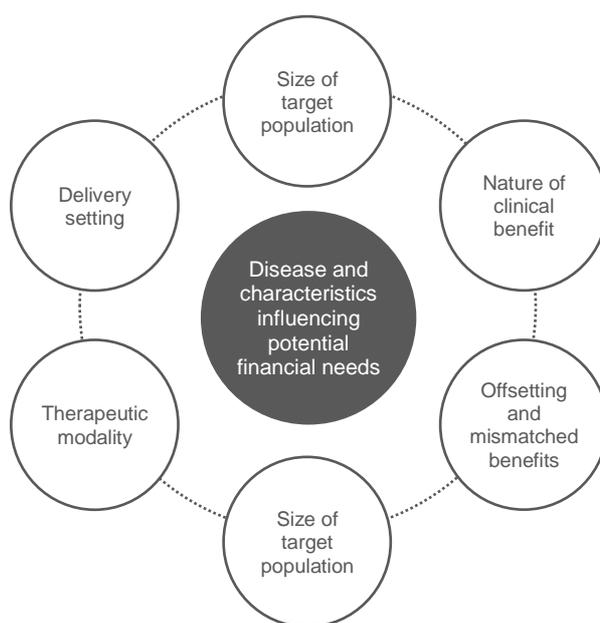


Fig. 3: Therapy Characteristics Influencing Precision Financing: Source: Adapted from [91]

can be augmented with a portability agreement, ensuring coverage [91].

Supplementary steps could include:

- a regulatory shift backstopping health plans with mandatory reinsurance programs, which would pay for individual outlier patients to counteract adverse selection to normalize good insurance coverage for durable and/or high-cost treatments [43];
- caps on patients' out-of-pocket expenses [43].

## Creating a Connected Digital Ecosystem

The advancement of precision medicine ought to benefit from the massive amount of data being generated through genome sequencing, experimentation and digital apps. Advances in machine learning promise to improve –omics-based medical diagnostic, but this requires the development of an innovative ecosystem that sustains a data value chain suitable for precision medicine innovation.

### 1 | Data quantity and quality

Access to relevant data is hindered by the fact that different types of individual-patient data reside in disparate, unlinked silos. Moreover, multi-omics, images, device data, and electronic health records that constitute main big data types in biomedical research are neither created nor stored in a uniform way. Medical records, for instance, may be biased [36]. Going forward, there is a need for **standardized data, interoperability** and electronic health records with unique patient identifiers [38]. With respect to data management, complex issues regarding informed consent, data portability, privacy protection for research conducted on biomedical big data, poor interoperability, lack of data curation, insufficient or poorly representative cohort need to be addressed. Interoperability, for instance, support the data-sharing demand of precision medicine which is critical as emerging tools enable more data, e.g., mobile apps bridging the gap between home and healthcare setting. Digital consent management contract— for instance blockchain-based solutions (<https://medrec.media.mit.edu/>) protecting privacy along with data integrity could be deployed.

### 2 | Governance

Blassime et al. [30] propose the **data cooperative model**—a model that enables direct control over personal data and democratization of the governance of data pools—to promote the requisite **integrated data stream** to accelerate research and its clinical translation. This model empowers citizens and communities to steer data use according to their motivation, preferences, concerns. This model may, however, run into the same challenges as with the **data donation model** [31], in particular, participant protection, representativeness, incentives to participate, and governance.<sup>2</sup>

In the absence of data cooperatives or where patients do not have direct control over their data, patients should be given an explicit opportunity to discuss their options with their providers about the use of their data and should be able to receive desired communications about how their information is used [35]. This will help build patient trust, and support precision medicine development through expanded use of patient data.

Critically, the imperative to share data is mounting. On the one hand, PM needs more genome data. On the other hand, machine learning techniques are more powerful with bigger training sets and more data. While big data partnerships are effectively being formed to enhance treatment,<sup>3</sup> greater collaboration along the data value chain is needed, calling for a reciprocal data access network [38].

### 3 | Translational enablers

1. **Advanced analytics.** Genomic sequencing, -omics data, precision diagnostics require the use of advanced machine learning techniques such as deep learning and cognitive computing which enable multi-view data analysis, while also enabling multidimensional data to be integrated with literature information, helping to advance the frontier of precision medicine research [32].
2. **Cloud computing and high-performance computing.** Given the proliferation of large volumes of data that cannot be handled using standard data management tools, the trend is to turn to cloud-based platforms, where advanced machine algorithms can be run, enabling discovery of new therapies [32][37].

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<sup>2</sup> <https://healthitanalytics.com/news/precision-medicine-genomics-require-strong-data-governance>

<sup>3</sup> <https://healthitanalytics.com/news/precision-medicine-big-data-partnerships-will-enhance-treatment>

3. Harness **synergies between big data analytics and conventional hypothesis-driven approaches** to medical science [33].
4. Foster **open science** precision medicine to meet the stringent model validation and experimental testing requirements necessary to accelerate precision medicine innovation [34].
5. Deploy validated **predictive models** to evaluate a patient's risk of developing a disease and to identify preventive measures or plan individualized treatment.

## Global Value Levers

### 1 | Stakeholder Collaboration

**Innovative collaborations among scientists, clinicians, and payers** can potentially accelerate the adoption of precision medicine tools and therapies. Such collaborations could include pairing clinical outcomes with payer cost and utilization data or implementing pragmatic clinical trials that provide opportunities to study precision medicine innovations within the context of the healthcare system [26].

**Patient engagement across the lifecycle.** Engaging with patients early on is a prerequisite to identifying what is of value to patients (incl. patient's preference).

**Pharma-payer interaction to ensure transparency of cost and pricing.** Pharmaceutical companies should seek advice from payers much earlier on the type of evidence they need to ensure reimbursement. Examples of innovative payer engagement strategies include (i) payer consultations, (ii) risk-sharing agreements, which can be either finance-based, outcomes-based or evidence-based, (iii) expertise based partnerships, involving either joint evidence generation or medication adherence projects or retrospective data analysis [39].

**Early collaboration between diagnostics and pharmaceutical companies** that encompasses the clinical trial phase would create opportunities to cogenerated clinical outcomes and health economic data, and develop a greater understanding of the clinical application and value of diagnostic tools prior to the acquisition of real-world evidence. This, in turn, would help create a more compelling case when looking to secure access to diagnostics for patients and their reimbursement, delivering benefits for both diagnostics and pharmaceutical companies [60].

**Earlier engagement with clinicians and laboratory professionals** would enhance understanding of the clinical application of diagnostic technology and its potential to positively impact patient outcomes. Where appropriate, this can lead to experts recommending the inclusion of a diagnostic in clinical guidelines, a factor that influences many market access decisions [60].

**Engaging with payers and laboratories earlier** in the process would ensure they had access to the clinical and economic data that would enable them to make value-based decisions about new diagnostics and allow potential issues to be identified and addressed [60].

### 2 | Regulation (licensing and payment)

Regulatory uncertainty is one of the major barriers to precision medicine development. Regulatory uncertainty pervades along the entire precision medicine value chain, encompassing reimbursement, co-development of therapeutics and diagnostics, unclear evidentiary requirements, regulation of diagnostics, clinical trials [51]. To the extent that they influence technology diffusion, reducing regulatory uncertainty could enhance precision medicine's value.

Regulation, in the form of specialty designations, e.g., Orphan Drug Designation, could provide valuable quality signals that could help ease the financing gap by making investment attractive to investors [50].

Evidence is also emerging for a greater role for policy to facilitate multi-stakeholder alignment at various levels, e.g., among payers to harmonize reimbursement, and providers to facilitate data flows [56].

Also to be taken into account is the role of regulatory agencies in establishing added therapeutic benefits of new drugs compared with existing, with impact on drug pricing [49].

# Precision Medicine across Health Systems

Governments across 14 countries have, together, invested US\$ 4billion in genomic-medicine. To ensure that genomic sequencing translates into treatments for high unmet needs, best-practices can be gleaned from learnings from the diversity of precision medicine approaches deployed.

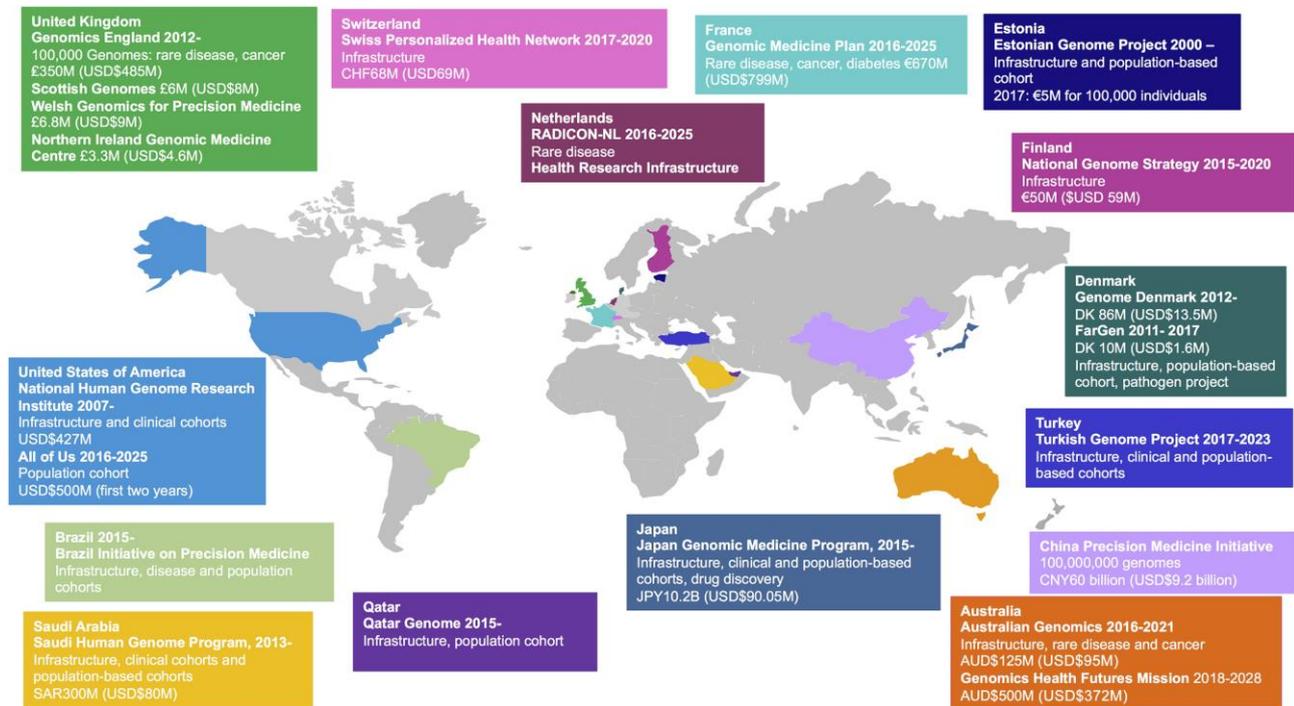


Fig. 4: Map of currently (2019) active government-funded national genomic-medicine initiatives. Source: [59]

Fig. 4 shows the map of currently active government-funded national genomic-medicine initiatives. The investment is primarily earmarked to genome-sequencing and infrastructure development, allowing large data repositories to be built. Switzerland has launched a Swiss Network of Personalized Health, of 118 M CHF for 2017-2020 (value differs on map). The private sector also joining in efforts. For instance, the US-based healthcare provider, Kaiser Permanente, is building a research biobank consisting of half a million people.

## 1 | Diversity of national approaches to PM

Stark et al. [59] highlight the diversity of approaches and current progress made toward meeting the challenges of integrating genomics into mainstream healthcare at a national level by focusing on the UK, France, Australia, and US. It notes the role of the degree of decentralisation and reviews the main initiatives implemented. The national genomic-medicine initiatives are also detailed in [57], and therefore not reproduced here.

## 2 | Value treatment in centralized and decentralized systems

There are two contrasting views as to whether value measurement should differ across centralized and decentralized systems. On the one hand, health economics and outcomes researchers generally measure value using the tool of CEA, which Garrison et al. [6] observe is an economic concept of value, and does not depend on whether value is being measured within a market-based or a single-payer healthcare system. CEA is patient-centric in building up the valuation from the impacts on patient length and quality of life.

In a market-based system, the individual—wearing the two hats of the plan subscriber and potential patient—is the ultimate decision-maker, making these decisions with the assistance of agents—the insurer and providers. Consumers making decisions about the purchase of private health insurance or out-of-pocket spending may vary in their objectives and preferences. As a result, they will choose different health plans that have different willingness-to-pay (WTP) for QALYs and so different cost-effectiveness thresholds [6]. Conversely, in a single-payer system as the United Kingdom, a social WTP threshold is used, based on which all citizens have equal access to the same benefit package.

On the other hand, since the CEA metric does not capture the complexity of value creation, Burkholder et al [12] highlight the need to “chart a course for better methods by identifying gaps and developing novel approaches that better align with the **decentralized [US] health system**, the movement toward patient-centeredness, and the emerging science of personalized medicine,” suggesting that different value treatments may be necessary.

### 3 | Market access

Access to novel drugs is restricted by the dearth of a comprehensive assessment of drugs and diagnostics in most countries. Besides cross-country differences in the assessment of therapeutics and diagnostics, there are intra-country differences in the treatment of therapeutics and diagnostics as illustrated in Table 2.

Decision Criteria	Description	Country (Rx)	Country (Dx)
Budget impact	HTA-based system focused on managing access with a high potential cost to drug budgets and the overall healthcare system	Italy, Spain	N/A
Cost-effectiveness	Established HTA-based system that primarily evaluates new drug/Dx based on quantifiable cost-effectiveness measures	UK	UK
Comparative clinical effectiveness	Reimbursement is dependent on added clinical value relative to a comparator drug/Dx	France, Germany, Japan	France, Japan
Competitive rationalizing/free market	Free market pricing exists, but extensive negotiation and discounting is required from both government and private payers to attain attractive formulary positioning	USA	Germany, Italy, Spain, USA
Patient pay	Strict price control and ongoing price-cutting	China	China

Table 2: Health technology assessment archetype model for therapy (Rx) and diagnostic (Dx). Source: Based on [60].

As evident from Table 2, Germany, Italy and Spain have **separate Rx-Dx assessment**, with the possibility that Rx is funded while DX is unfunded or funded with a delay. France has a **coordinated Rx-Dx assessment**, requiring highly aligned Rx and Dx departments. The UK is moving—under the NICE Diagnostics Assessment Programme—towards the gold standard of **joint Rx-Dx assessment**, as implemented in Australia, requiring highly aligned Dx and Rx clinical and economic data [58].

### 4 | Outcome-based pricing

“For now, the outcome-based pricing initiative has been centered on the U.S. marketplace, but other regions are beginning to follow suit. For example, the National Institute for Health and Care Excellence (NICE) in the UK determines if a new product provides greater benefits than others currently available at an acceptable cost. If they believe the benefits do not outweigh the costs, they can require price concessions to increase the benefit-to-cost ratio. Other countries are keeping a close tab on the outcome-based pricing and payment matrix, evaluating its impact on costs and outcomes, acutely aware that achieving accurate, real-time data is the best approach to achieving a sustainable business model across the entire value chain.” [44]

Since the US and the UK are located at the two extremes of the decentralisation-centralisation continuum, it follows that implementation of outcomes-based pricing is independent of health system types.

### 5 | Indication-Based Pricing (IBP)

“The feasibility of implementing indication-specific pricing (ISP) varies significantly by country, but some payers are already moving towards it.” - IQVIA<sup>4</sup> The feasibility of IBP in major markets is illustrated in Fig. 5. by Towse et al. [62], who also provides an extensive discussion of the merits and demerits of IBP in different countries.

In International Risk Governance Center’s workshop on the “Economics of Precision Medicine” (April 2018) IBP was discussed as a potential precursor to outcomes-based pricing. Based on the contemporary adoption of the outcomes-

<sup>4</sup> <https://www.iqvia.com/-/media/iqvia/pdfs/isporbarcelona2018posters/november-13/one-product-different-indicationsdifferent-prices.pdf?la=en&hash=D8D72076C6ABE3B429775FC147C4ADB21373179B>

based pricing and the feasibility of IBP across countries, IBP readiness is neither a necessary nor sufficient condition for advancing outcomes-based pricing.

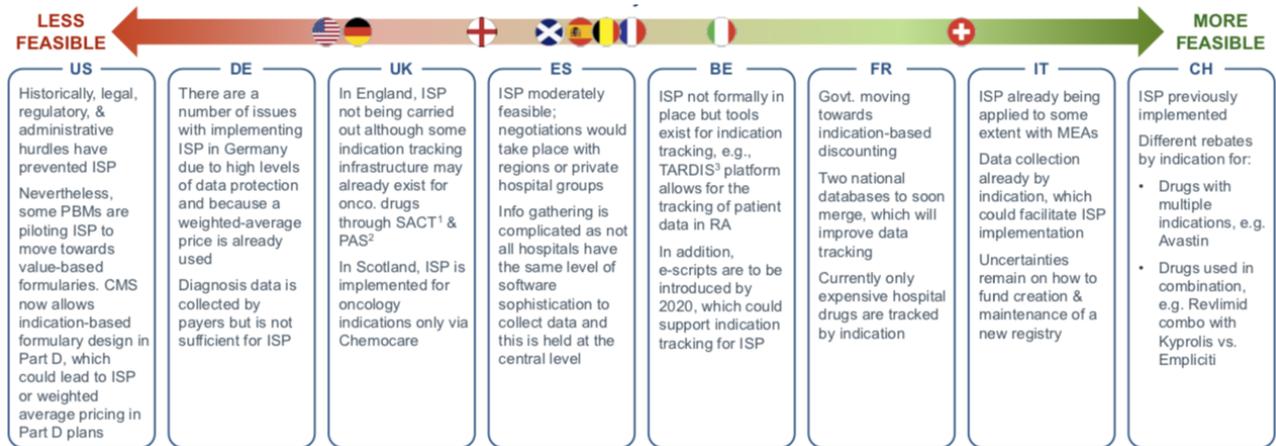


Fig. 5: Feasibility of Indication-Based Pricing Across Countries. Source: IQVIA

## 6 | Towards a “Global Learning Health System”

In the spirit of the intersectoral collaboration imperative for a “Learning Health System” highlighted by Ginsburg and Phillips [53], the time is nigh for international collaboration for advancing precision medicine. The need to shift the frontier beyond national boundaries has been expressed in the national genomic-medicine initiatives. Expanding genetic tests to more diverse groups would also help reduce health disparities [85].

## 7 | A global financing imperative

“A global imperative needs global financing. Producing the science and evidence to support personalized healthcare is costly, and if pricing and reimbursement policies within and across countries and between medicine and diagnostic development do not efficiently share these costs and reward value appropriately, then the global rate of innovation will be sub-optimal with a long-run adverse impact on population health.” - Garrison and Towse [41].

# Developing Precision Prevention

## Implications for Switzerland

While precision treatment is making headlines, the value of precision medicine also involves a shift towards more precision or predictive prevention. **Precision prevention** is a tailored approach that applies the same strategy as precision medicine<sup>5</sup> to reduce the risk of disease. As in the example in Fig. 6, the disease (herein, cancer) will be ideally averted before it starts by means of a custom-designed action plan that used patient-specific biological, epidemiological, behavioural and socioeconomic characteristics.

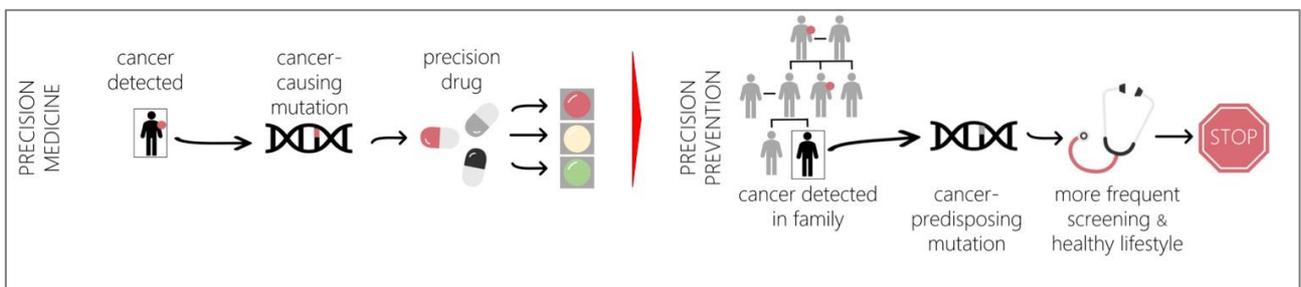


Fig. 6: From Precision Medicine to Precision Prevention. Source: Adapted from [71]

A recent study [77] estimates that over half of cancer-related deaths may be prevented by lifestyle changes, such as smoking cessation for lung cancer or public-health measures such as vaccination for pathogenic cancers. More generally, preventive medicine is three-tiered consisting of: **primary prevention** to maintain healthy conditions,

<sup>5</sup> i.e. the use of information about a person’s genes, environment and lifestyle to diagnose and treat disease through more accurate prediction of which treatment strategies for a particular disease will work in which groups of people.

**secondary prevention** to avert disease development, and **tertiary prevention** to halt disease progression. Predictive approaches can be used to identify individuals at risk (both current and future) as well as to provide recommendations for actions aligned with the prevention level. Although sound in theory, there are practical challenges—both scientific/clinical and economic—to precision prevention.

Preventive medicine strategies are hard to sell since cost savings are not immediate: some investment has to be incurred now in anticipation of preventing larger investments in treatment later.

## 1 | Value of Prevention

McGrath et al. [74] propose a 5-step process for **ascertaining the value of prevention**:

### Box 2 | A Precision Prevention Framework

1. Preliminary research on an area of interest, including identification of risk factors and biomarkers
2. Identify current prevention strategies
3. Identify populations in need of tailored intervention
4. Determine areas of ineffectiveness in current preventive measures for each specific population
5. Monitor the effectiveness of various tailored interventions

### Comparative cost, pricing and value of prevention vs. treatment.

See Goetzel [69] on “Do prevention or treatment services save money? The Wrong Debate” wherein he argues that “Instead of debating whether prevention or treatment saves money, we should determine the most cost-effective ways to improve population health.”

When evaluating prevention, it is important to distinguish between primary, secondary and tertiary prevention. More specifically, savings from primary and secondary prevention, and tertiary prevention and treatment costs, and the price paid for not preventing diseases should be established [76][84].

Trein et al. [79][80] analyze the governance challenges (i.e. the coordination of stakeholders) to develop an adequate public policy favouring prevention: citizens’ trust, legal protection against discrimination, and integration of genomic research in health systems.

## 2 | Precision prevention: challenges

Although prevention has been a hallmark of health systems, the notion of predictive prevention, enabled by advances in precision medicine and data analytics, raises some challenges or concerns:

1. The difficulty for patients to understand or accept a genetic test (see “‘We are all mutants now’: the trouble with genetic testing,” *The Guardian*, July 18 2017)
2. Because precision in precision prevention should refer to the individuals who are the target of the intervention, **excessive precision** may dilute the promises of precision prevention, especially in terms of cost-effectiveness [82]
3. A preventive measure which brings much benefit to the population offers little to each participating individual. The opposite is also true: a useful intervention for a single individual might be irrelevant at the population level. This gap between individual and population benefit is commonly known as the “**Prevention Paradox**.” [75] [82]
4. **Prevention carries the risk of being medicalized**. Accordingly, the lure of mirroring precision therapy with precision prevention should not be allowed to distract from the many opportunities for prevention at the population level [82]
5. As with all diagnostics tests, there are risks of false positives or inaccurate diagnostic

## 3 | Prevention financing

Davis et al. [63] discuss alternative methods for paying for preventive care—1) fee-for-service; 2) a periodic preventive health visit fee; 3) capitation; and 4) a preventive services account, highlighting the need for further assessment of these methods in terms of cost-effectiveness of services and payment approaches.

Amendments to reimbursement coding systems may be needed to integrate precision prevention in care delivery, taking into account that standards for acceptance of prevention may persist to be higher than for treatment [65].

## 4 | Navigating the Transition

“To fully deliver precision prevention programme, long-term, large scale studies that capture longitudinal clinical data and biosamples is required” [81]. To the extent that further advances are needed to effectively identify who should be targeted in precision prevention, precision medicine should not trump opportunities for classical public health approaches

to prevention [78]. Using precision and conventional measures of risk in parallel until evidence is established that predictive genetics-based risk scores are better could set in motion the transition [70].

Generating the scientific/clinical evidence for advancing precision prevention could further benefit from synergies in R&D for prevention and treatment [67]. For effective prevention, research should focus on causes, more than on symptoms, unravelling biological complexity [54].

## 5 | Swiss context

Despite having an extensive and expensive healthcare system, **Switzerland's spending on prevention is well below OECD's average**.<sup>6</sup> The significance of this fact is nuanced, since Switzerland also has an above-OECD average share of out-of-pocket expenses for both healthcare, in general, and prevention [68]. The burden of prevention is carried by individuals more than by the healthcare system. This may explain why in Switzerland (like in the US) cost concerns and lack of understanding of the benefits of regular screenings are barriers to preventive medicine [66]. Switzerland lacks a comprehensive legal basis for federal action to promote prevention, resulting in patchwork efforts at the cantonal levels. Because of the co-pay component of insurance, screening fees create a disparity in access to preventive medicine.

The Swiss Government launched in 2016, a multi-year **National Prevention Strategy targeting non-communicable diseases** [72]. The objective is to encourage more systematic prevention within care services and reach out to vulnerable groups, including low-income households.

Going forward, although the Swiss system is innovation-friendly, there is need for greater efficiency and transparency in the Swiss pricing and reimbursement system [61] as well as for robust evidence of preventive care benefits [64].

## Conclusion

The importance of re-evaluating value creation in the precision medicine era (and the role of precision medicine in creating value in health) cannot be overemphasized. The term 'value' involves a combination of economic, social and individual judgements, preferences and decisions, which differ across stakeholders. Indeed “Personalized medicine will have a rocky start with reduced markets, unless a clear understanding of value addition to customers... is quickly established.” - Tiriveedhi [20]

The path to delivering the promises of PM is difficult. Expectations should be better managed, in part because biological complexity and uncertainty is and will remain high. Moreover, genetic associations with diseases are subject to confounding bias of the environmental context in which the genes operate, resolving which requires linking multiple data sources and intersectoral collaboration.

### Key Takeaways

- Delivering value in precision medicine and health, more broadly, is a balancing act between pursuing value given standards of care and incentivising innovation to address unmet needs.
- Precision medicine—and the ecosystem that supports it—must embrace patient-centeredness and engagement, digital health, genomics and other molecular technologies, data sharing and data science to be successful [53]. It also requires individual responsibility of patients in their own health.
- The full realization of precision medicine's disruptive potential will require a multipronged scientific, clinical and policy agenda, creating a learning health system [53].
- Precision Global Health is a strategic, innovative, multi-level and transdisciplinary approach, which aims at equitably improving human health by addressing complex global health challenges, working with and for targeted populations for the identification of their specific needs and the delivery of sustainable and impactful tailored health interventions, in a learning system based on continuous and transparent evaluation of impact.

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<sup>6</sup> [https://www.swissinfo.ch/eng/us---swiss-health-series\\_how-two-countries-handle-illness-prevention/43833990](https://www.swissinfo.ch/eng/us---swiss-health-series_how-two-countries-handle-illness-prevention/43833990).

## Appendix: Evolving Industry Structure

PM ought to change industry structure in a number of ways, depending on the degree of product differentiation, regulation and scale/scope economies. These may affect value creation. Of note, precision medicine is not objectively delimited. What constitutes a precision medicine is determined by joint scientific and economic considerations.

**The rise of niche busters.** PM can result in oligopolies as developers target small population subsets with a small number of interdependent differentiated products—akin to me-too drugs, each commanding some market power. The outcome is the emergence of high-priced niche busters [29].

**Me-too innovations.** This mushrooming of me-too innovations is potentially valuable as long as treatment effects are uncorrelated across therapies [14]. This also suggests that although wasteful in traditional pharmaceutical model, me-too innovations could be more valuable in a world with personalized medicine.

**Biomarker cut-off value.** What constitutes a precision medicine can be strategically determined by choosing biomarker cut-off value. “By setting the companion diagnostic cut-off value, developers link science, the clinic and the marketplace to create a precision medicine. Selecting the cut-off value connects scientific understanding of both therapeutic response and biomarker performance to change the observed efficacy in the selected clinical trial population. This in turn has implications for pricing, especially when price is linked to patient benefit” [29].

Setting this value also accounts for the **dynamic effects on market size**. Effect on market size: 1. Reduction with companion diagnostics, 2. Increased market share as preferred treatment, 3. Higher treatment adherence, 4. New patients enter, 5. Treatment order effect. Also, need to account for the responder depletion effect.

**Product vs. price competition.** Although firms may want to differentiate their product so that it commands a high price, regulators may want to promote price competition on the grounds of inadequate differentiation. Firms’ ability to provide **credible evidence of differential treatment effects** is key to avoiding low prices [29].

**Economies of scale and scope.** Complexity of biomedical sciences, economies of scale and scope.

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**Abstract:** The majority of studies concluded that the PM intervention was at least cost-effective compared to usual care. However, the willingness-to-pay thresholds varied widely. Key factors influencing cost-effectiveness included the prevalence of the genetic condition in the target population, costs of genetic testing and companion treatment and the probability of complications or mortality.

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In this article, Porter advocates that considering patients as the main stakeholder of healthcare will improve value for all stakeholders, and provides suggestions on how to implement value-based healthcare. [Details are provided in the main text.]

[5] Caudle et al., 2018. PRN Opinion Paper: Application of Precision Medicine across Pharmacy Specialty Areas. *Journal of the American College of Clinical Pharmacy* 2: 288—302. doi: 10.1002/jac5.1107

**Key Takeaways:** The paper describes current and emerging aspects of precision medicine as it relates to clinical pharmacy across a variety of speciality areas of practice. **Abstract:** Clinical pharmacists have been incorporating precision medicine into practice for decades. Drug selection and dosing based on patient-specific clinical factors such as age, weight, renal function, drug interactions, plasma drug concentrations, and diet are expected as part of routine clinical practice. Newer concepts of precision medicine such as pharmacogenomics have recently been implemented into clinical care, while other concepts such as epigenetics and pharmacomicrobiomics still predominantly exist in the research area but clinical translation is expected in the future....

### Value Frameworks

[6] Garrison, L.P., Pauly, M.P., Willke, R.J., Neumann P.J., 2018. An Overview of Value, Perspective, and Decision Context: An ISPOR Special Task Force Report. *Value in Health* 21: 124—130. <https://doi.org/10.1016/j.jval.2017.12.006>

The paper defines “value” from an economic perspective, considering both the **gross value**—what someone would be willing to pay for access to and use of a healthcare technology—and its **net value**, taking account of “opportunity cost”—what they have to give up to get it. It discusses the relationship to perspective and decision context, i.e., how recently proposed value frameworks vary by the types of decisions being made and by the stakeholders involved. It describes the patient perspective on value both as a key stakeholder and as a health insurer purchaser. The paper discusses how value is relevant in the market-based US system of mixed private and public insurance, and different from its use in single-payer systems.

The paper then presents 5 VAFs that vary in the types of decisions they intend to inform, ranging from coverage, access, and pricing decisions to those defining appropriate clinical pathways and to supporting provider-clinicians shared decision making. Each of these value frameworks must be evaluated in its own decision context for its own objectives. Existing guidelines for cost-effectiveness analysis emphasize the importance of **clearly specifying the perspective from which the analysis is undertaken**. Relevant perspectives may include, among others, 1) the health plan enrollee, 2) the patient, 3) the health plan manager, 4) the provider, 5) the technology manufacturer, 6) the specialty society, 7) government regulators, or 8) society as a whole. **A valid and informative cost-effectiveness analysis could be conducted from the perspective of any of these stakeholders, depending on the decision context.**

- [7] Jena, A.B., Neves, L., Burkholder, R., 2018. *Do Value Frameworks Fully Capture the Value of Innovation?* Health Affairs Blog. <https://www.healthaffairs.org/doi/10.1377/hblog20180409.228386/full/>

The basic building block of most value frameworks is the increase in quality-adjusted life years (QALYs) of a given therapy compared to the standard of care. This approach generally takes the **perspective of an individual payer making spending decisions under short-term budget constraints**. However, this perspective may not align with the best long-term interests of the broader society. In its recent recommendations, the Second Panel on Cost-Effectiveness in Health and Medicine calls for cost-effectiveness analyses to take both **payer and societal perspectives**, to ensure that broader sources of societal value are accounted for. **To effectively capture value to society, dimensions of innovation are a necessary component.**

Operationally, this would involve conducting **health technology assessments not only from the viewpoint of payers but also from that of society**, with the recognition that the sources of value that payers may focus on may be appropriately different from the value components that are relevant to society at large. This is not to say that technology assessments should never be conducted from the perspective of payers—they should. However, these assessments should also specify what other sources of societal value might not be captured and ideally suggest the range of impacts that incorporating those sources of value may have on estimated levels of cost-effectiveness.

**Measuring the value that new medical therapies bring to society is complex** and not easily summarized by a single measure. A failure to do this in a comprehensive manner **risks underinvesting in therapies that create value for society**. The evaluation of value from a societal perspective, as recommended by the Second Panel on Cost-Effectiveness in Health and Medicine, is critical. **Without this perspective, myopic decision-making that leaves long-term benefits unrealized or under incentivizes future innovation is likely.**

Now is the time, while value frameworks are in their nascent stages, to cast a wide net to ensure that the societal value of therapies is accurately measured and recognized. Frameworks that are flexible and that consistently reflect broader dimensions of value of innovation should be developed; they should act as tools, not rules, for assessing the value of medical innovation.

- [8] Joshi, J.A., Miller-Sonet, E., Puckett, J.T., Glick, H.A., 2019. *Advocating for New Patient-Centered Tools for Value-Based Treatment Choices in Oncology.* *Journal of Clinical Pathways* 5(2): 44—47. <https://doi.org/10.25270/jcp.2019.03.00062>

**Abstract:** The cost of medical drugs continues to increase, and costs of novel therapies for oncology are particularly expensive—for patients as well as health systems in general. **Many healthcare stakeholders are concerned about financial toxicity for patients and how to ensure access to innovative therapies.** There is a large and growing consensus that costs and value should be important considerations in patients' and providers' cancer treatment discussions. Many leading organizations have created value frameworks to help assess treatment options and their relative value. The American Society for Clinical Oncology and the National Comprehensive Cancer Network have each created their own value frameworks, but many think that **patient preferences are not adequately integrated into these frameworks and that the metrics they employ do not produce reliable information.** We provide a brief assessment of these frameworks and how they further need to evolve to meet the needs of patients in a health system shifting to value-based care.

- [9] PMC, 2016. *Personalized Medicine and Value Assessment Frameworks: Context, Considerations and Next Steps.* Washington DC: Personalized Medicine Coalition.

**Adapted from the report introduction:** The report first highlights that value assessment frameworks (VAFs) do not sufficiently capture the value of personalized medicine, focusing instead on population health, thereby overlooking efficiencies in patient-level healthcare. It then proceeds to (1) describing the intersection of personalized medicine and VAFs; (2) providing an overview of U.S.-centered VAFs; (3) identifying areas of consideration related to personalized medicine that need to be accounted for in the VAF methodology; and (4) provides a synopsis of how VAFs may incorporate these considerations. The report also offers recommendations for refining VAF methods so that they can delineate the value of personalized treatments to both patients and healthcare system.

- [10] Slomiany, M., Madhavan, P., Kuehn, M., Richardson, S., 2017. *Value Frameworks in Oncology: Comparative Analysis and Implications to the Pharmaceutical Industry.* *American Health Drug Benefits* 10(5): 253—260.

As the cost of oncology care continues to rise, composite value models that variably capture the diverse concerns of patients, physicians, payers, policymakers, and the pharmaceutical industry have begun to take shape. The paper reviews the 5 of the most notable value frameworks in oncology that have emerged in recent years: ASCO Value Framework (version 2.0), the NCCN Evidence Blocks, MSKCC DrugAbacus, the (US) ICER VAF and the European Society for Medical Oncology Magnitude of Clinical Benefit Scale, using a side-by-side comparative approach in terms of the input, scoring methodology, and output of each framework. In addition, we gleaned stakeholder insights about these frameworks and their potential real-world applications through dialogues with physicians and payers, as well as through secondary research and an aggregate analysis of previously published survey results.

The frameworks differ in their respective focus on clinical trial elements, breadth of evidence, evidence weighting, scoring methodology, and value to stakeholders. There pervades a **varying level of awareness of, and use of, each of the value frameworks in clinical practice**. For example, although the ASCO Value Framework appears nascent in clinical practice, physicians believe that the frameworks will be more useful in practice in the future as they become more established and as their outputs are more widely accepted.

Along with patients and payers, who bear the burden of treatment costs, physicians and policymakers have waded into the discussion of defining value in oncology care, as well as pharmaceutical companies that **seek to understand the impact of these value framework**.

[11] Walter, E., 2019. **Approaches to Capturing Value in Oncology. *Recent Results for Cancer Research* 213: 85—108. [https://doi.org/10.1007/978-3-030-01207-6\\_7](https://doi.org/10.1007/978-3-030-01207-6_7)**

Abstract: This article sets out to describe different value frameworks in the field of new developments in oncology. Since the costs of new oncological therapies follow a steep path, their implementation and financing demand a thorough assessment. This is an ambitious task due to the complex nature of oncological treatments within overall health policy. Five value frameworks were reviewed: European Society for Medical Oncology (ESMO) Magnitude of Clinical Benefit Scale, American Society of Clinical Oncology (ASCO) Value Framework (version 2.0), National Comprehensive Cancer Network (NCCN) Evidence Blocks, Memorial Sloan Kettering Cancer Center DrugAbacus, and the Institute for Clinical and Economic Review Value Assessment Framework. They are all based on a large set of criteria. However, all these frameworks differ considerably in their outcomes. Among the main differences, one has to cite are the inclusion of costs and the use of different outcomes, as well as the fact that they address different target stakeholders, etc. Despite these shortcomings, the value frameworks serve the necessity to introduce more rationality in health decision making seen from the perspective of physicians, patients, and financing bodies.

Future perspectives: Value frameworks' main advantage therefore is the fact that they should enable more rationality in such processes and help to avoid excessive power struggles. However, more internationally harmonized priorities in the establishment and homogeneity in the approach of such value frameworks would be desirable.

For this purpose, **“meta-criteria” would have to be developed by international health organizations to elucidate the strengths and weaknesses of these value frameworks**. This, of course, cannot substitute national decision making since it is always affected by national peculiarities. Currently, the most commonly used “value” assessment for cross-discipline comparisons is the incremental cost-effectiveness ratio. Including cost aspects, not only anticancer drug costs but also total direct medical costs, would lead to a comprehensive application of the value frameworks since costs are the core issue after confirmation of the clinical benefit. Costs also comprise the crucial question of patient access to expensive treatments.

The value-based frameworks are an important element for encouraging discussions around price and value. In this stage of development, results can support oncologists, healthcare decision-makers, or health technology assessment organizations to choose from treatment alternatives. As a next step, the aspect of total costs and QoL should be incorporated in a broader view.

## Value Measurement

[12] Burkholder, R.J., Dougherty, S., Neves, L.A., 2018. **ISPOR's Initiative on US Value Assessment Frameworks: An Industry Perspective. *Value in Health* 21(2): 173—175.**

The authors highlight the **limitations of cost-effectiveness analysis (CEA)** (and, in particular, of C/QALY), disagreeing with its use as “the cornerstone for value assessment” in the context of coverage and reimbursement decision making. The QALY metric is a “one-size-fits-all” approach to healthcare decision making that is ill-suited to represent healthcare benefits within the complex nature of the US healthcare system and is increasingly pressured by changes in science and medicine. Patients do not receive treatments in isolation; the provision of healthcare is a complicated, multifaceted process with patients receiving care along an entire continuum—from diagnostic testing, to medication therapy,

hospitalization, and post-acute care. The value of each of these services may rely on steps taken before or after, as well as circumstances unique to each patient, including the existence of comorbid conditions and care-seeking behavior. The QALY metric is also discriminatory in nature to more vulnerable populations, does not often reflect true patient preferences or price changes, and cannot be tailored to real-world healthcare systems that vary in practice patterns and care delivery protocols. Therefore, the application of C/QALY CEA into real-world decision making will fail to yield clinically appropriate, patient-centered results.

The opportunity to drive the healthcare system to one based on value has never been greater, making the need for better methods more pressing than ever. The (US) Science and Technology Foundation (STF) should lead the way in charting a course for better methods by identifying gaps and developing novel approaches that better align with the decentralized US health system, movement toward patient-centeredness, and emerging science of personalized medicine. To meet these goals, value assessment must be more patient-centered, transparent, and adaptable.

**[13] Gavan, S.P., Thompson, A.J., Payne, K., 2018. The Economic Case for Precision Medicine. *Expert Rev Precis Med Drug Dev.* 3(1): 1–9. <https://doi.org/10.1080/23808993.2018.1421858>**

**Introduction:** The advancement of precision medicine into routine clinical practice has been highlighted as an agenda for national and international healthcare policy. A principle barrier to this advancement is in meeting requirements of the payer or reimbursement agency for healthcare. This special report aims to explain the economic case for precision medicine, by accounting for the explicit objectives defined by decision-makers responsible for the allocation of limited healthcare resources.

**Areas covered:** The framework of cost-effectiveness analysis, a method of economic evaluation, is used to describe how precision medicine can, in theory, exploit identifiable patient-level heterogeneity to improve population health outcomes and the relative cost-effectiveness of healthcare. Four case studies are used to illustrate potential challenges when demonstrating the economic case for a precision medicine in practice.

**Expert commentary:** The economic case for a precision medicine should be considered at an early stage during its research and development phase. Clinical and economic evidence can be generated iteratively and should be in alignment with the objectives and requirements of decision-makers. Programmes of further research, to demonstrate the economic case of a precision medicine, can be prioritized by the extent that they reduce the uncertainty expressed by decision-makers.

**[14] Hult, K.J., 2016. *Measuring the Potential Health Impact of Personalized Medicine: Evidence from MS Treatments.* NBER Working Paper 23900. <https://www.nber.org/papers/w23900>**

The potential of personalized medicine comes from its ability to either create treatments that address the heterogeneity across patients or in the ability to provide information to patients that can improve the health impact of existing treatments. This paper explores the potential magnitude of the latter effect for multiple sclerosis (MS) treatments.

The author finds that several factors influence the health impact of personalized medicine. Personalized medicine has a greater potential health impact when treatment effects are less correlated across treatments, the variance of the distribution of health impacts is larger, there is less noise in an individual's signal of their treatment effect, and there are more treatment options. These results suggest that there is significant potential for personalized medicine in MS due to the heterogeneity in the MS population, disease course, and treatment response and twelve disease-modifying therapies (DMTs) that vary in their efficacy and administration. Hult finds that personalized medicine has the potential to increase the health impact of MS patients by over 60 percent.

**[15] Jena, A.B., Julia Thornton Snider, Oliver Diaz Espinosa, Andy Ingram, Yuri Sanchez Gonzalez, Darius Lakdawalla, 2019. How Does Treating Chronic Hepatitis C Affect Individuals in Need of Organ Transplants in the United Kingdom? *Value in Health* 22(6): 669—676. <https://doi.org/10.1016/j.jval.2018.09.2923>.**

**Key Takeaway:** Treating CHC has large positive spillovers— amounting to more than £53 million in social value each year in the United Kingdom under the current opt-in organ donation policy—to uninfected individuals by reducing the need for liver transplants and allowing cured individuals to donate organs. These spillovers have not been included in traditional value assessments of CHC treatment.

**[16] Lakdawalla, D.N. et al., 2018. Defining Elements of Value in Health Care—A Health Economics Approach: An ISPOR Special Task Force Report [3]. *Value in Health* 21(2):131—139**

This report identifies and defines a series of elements that warrant consideration in value assessments of medical technologies. We aim to broaden the view of what constitutes value in healthcare and to spur new research on incorporating additional elements of value into cost-effectiveness analysis (CEA). Twelve potential elements of value are considered. Four of them—quality-adjusted life-years, net costs, productivity, and adherence-improving factors—are conventionally included or considered in value assessments. Eight others, which would be more novel in economic assessments, are defined and discussed: reduction in uncertainty, fear of contagion, insurance value, severity of disease, value of hope, real option value, equity, and scientific spillovers. Most of these are theoretically well understood and available for inclusion in value assessments. The two exceptions are equity and scientific spillover effects, which require more theoretical development and consensus. A number of regulatory authorities around the globe have shown interest in some of these novel elements. Augmenting CEA to consider these additional elements would result in a more comprehensive CEA in line with the “impact inventory” of the Second Panel on Cost-Effectiveness in Health and Medicine. Possible approaches for valuation and inclusion of these elements include integrating them as part of a net monetary benefit calculation, including elements as attributes in health state descriptions, or using them as criteria in a multicriteria decision analysis. Further research is needed on how best to measure and include them in decision making.

[17] Lee. T.H., 2010. Putting the Value Framework to Work. *The New England Journal of Medicine* 326(26): 2481—2483.

So how is the concept of value being translated into reality? As is often true in medicine itself, the critical first step is measurement. Provider organizations need to capture data on the outcomes that matter to patients, as well as the costs for a patient over meaningful episodes of care. These data are essential for assessing whether value is improving. This work is not easy, because the collection of such data has not been encouraged by the fee-for-service system and is hindered by the silos in the current organizational structure of medicine. Current information systems are designed to support clinicians in performing individual services for individual patients and to collect their reimbursement. Outcomes as important as death are not routinely recorded; functional-status outcomes (e.g., whether a patient with head and neck cancer can swallow or talk) are buried in free text and are not captured in analysable form.

[18] Lee et al. 2016. Developing a Measure of Value in Health Care. *Value in Health* 19(4): 323—325. <https://doi.org/10.1016/j.jval.2014.12.009>

The **quality measures** must be important, scientifically sound, and usable. The relative weights used in the composite can either represent empirical criteria, such as the measure’s reliability, validity, impact, evidence, and opportunity for improvement, or represent a value judgment, determined with input from patients, providers, and payers. Although most of these quality measures are available, the methods to combine them into a single index score are under-developed. Any approach that evaluates performance requires a benchmark for comparison. Finally, measures need to be presented in an understandable and meaningful way for different audiences.

The methods used to **measure cost** for the value equation are also immature. Three methods dominate cost measurement in the provider setting. One approach takes hospital charges, which are notoriously inaccurate, and multiplies them by a cost-to-charge ratio from the Medicare cost report. The second approach uses a cost accounting system, which incorporates a traditional activity-based costing (ABC) to allocate costs to various resource categories. The third approach uses the TD ABC described earlier.

These methods have their respective advantages and disadvantages, but the **marginal benefits and costs** have not been rigorously studied. **The need to measure value in healthcare is urgent.** Between 10% and 30% of hospitalized patients suffer preventable harm, 2 of 10 patients report receiving disrespectful care, and one-third of healthcare dollars are wasted—nearly \$1trillion or \$9000 per US household. We can begin this journey using current measures. Despite the existing challenges of measuring quality and costs, we believe our approach to measuring value in healthcare is the way forward in the near-term. Concurrent to maturing near-term approaches, research should push ahead with developing more ideal value measures.

[19] Love-Koh, J., Peel, A., Rejon-Parrilla, J.C. et al., 2018. The Future of Precision Medicine: Potential Impacts for Health Technology Assessment. *PharmacoEconomics* 36: 1439. <https://doi.org/10.1007/s40273-018-0686-6>

Innovation in precision medicine promises substantial benefits but will change the way in which some health services are delivered and evaluated. The shelf life of guidance may decrease, structural uncertainty may increase, and new equity considerations will emerge. As biomarker discovery accelerates and artificial intelligence-based technologies emerge, refinements to the methods and processes of evidence assessments will help to adapt and maintain the objective of investing in healthcare that is value for money.

Three types of precision medicine technologies are likely to become more widespread in clinical practice over the next decade: **'omics'-based biomarkers; complex artificial intelligence-based algorithms; and digital health applications.** These innovations will require health technology assessment and guideline-producing agencies to **adapt their methods and processes.** The paper presents the fast pace of discovery technological innovation, along with the potentially complex and uncertain treatment pathways patients in the case of UK.

**[20] Tiriveedhi, V., 2018. Impact of Precision Medicine on Drug Repositioning and Pricing: A Too Small to Thrive Crises. *Journal of Personalized Medicine* 8: 36.**

This is a review article in which the authors discuss the framework of value justification and changing pricing strategies, highlighting complex trade-offs that must be managed between innovation and diagnostic testing versus value-based pricing. In particular, the authors highlight that “Personalized medicine will have a rocky start with reduced markets, unless a clear understanding of value addition to customers and profit maximization to pharmaceutical companies, along with the potential complementary role of clinical laboratories as providers of molecular diagnostics, is quickly established.”

## Biomarkers and Diagnostics

**[21] Amur, S., La Vange, L., Zineh, I., Buckman-Garner, S., Woodcock, J., 2015. Biomarker Qualification: Toward a Multiple Stakeholder Framework for Biomarker Development, Regulatory Acceptance and Utilization. *State of the Art* 98(1): 34—46.**

**Abstract:** The discovery, development, and use of biomarkers for a variety of drug development purposes are areas of tremendous interest and need. **Biomarkers can become accepted for use through submission of biomarker data during the drug approval process.** Another emerging pathway for acceptance of biomarkers is via the **biomarker qualification program** developed by the Center for Drug Evaluation and Research (CDER, US Food and Drug Administration). **Evidentiary standards are needed** to develop and evaluate various types of biomarkers for their intended use and multiple stakeholders, including academia, industry, government, and consortia must work together to help develop this evidence. The article describes various types of biomarkers that can be useful in drug development and evidentiary considerations that are important for qualification. A path forward for coordinating efforts to identify and explore needed biomarkers is proposed for consideration.

**Conclusion:** With focused, coordinated attention and **prioritization of putative biomarkers for development**, coupled with greater clarity regarding the level of evidence needed to support qualification, attention to reproducibility of studies, and data quality, great strides can be taken to help **streamline medical product development.** The FDA called for this over a decade ago in the call to action for the Critical Path Initiative. While progress has been made, we still have more to achieve and it must be done collaboratively with government, academia, and industry at the table together to advance the needed science.

**[22] Deloitte, 2017. A Framework for Comprehensive Assessment of the Value of Diagnostic Tests.**

Diagnostic manufacturers need to understand, demonstrate, and clearly articulate how their offerings can lead not only to improved patient outcomes, but also create value to a variety of stakeholders. Different stakeholders care about and prioritise different but overlapping sets of value drivers against which they judge the benefits of a diagnostic test.

When assessing value, should be considered: scenarios of impact (against both qualitative and quantitative metrics); the unique characteristics of tests; the relevant timeframes associated with testing or impact of a test; any patient subgroup that is more likely to benefit from test.

**[23] Garfield, S., et al., 2016. Health Technology Assessment for Molecular Diagnostics: Practices, Challenges, and Recommendations from the Medical Devices and Diagnostics Special Interest Group. *Value in Health* 19: 577—587.**

Health technology assessments (HTAs) are increasingly used to inform coverage, access, and utilization of medical technologies including molecular diagnostics (MDx). Although MDx are used to screen patients and inform disease management and treatment decisions, there is no uniform approach to their evaluation by HTA organizations.

In effect, the few HTA programs that have MDx-specific methods, however, do not provide clear parameters of acceptability related to clinical and analytic performance, clinical utility, and economic impact. The case studies highlight similarities and differences in evaluation approaches across HTAs in the performance metrics used (analytic and clinical

validity, clinical utility), evidence requirements, and how value is measured. Not all HTAs are directly linked to reimbursement outcomes.

To improve MDx HTAs, organizations should provide greater transparency, better communication and collaboration between industry and HTA stakeholders, clearer links between HTA and funding decisions, explicit recognition of and rationale for differential approaches to laboratory-developed versus regulatory-approved test, and clear evidence requirements.

**[24] Graves, J.A., Garbett, S., Zhou, Z., Peterson, J., 2017. *The Value of Pharmacogenomic Information*. NBER Working Paper 24134. Online: <http://www.nber.org/papers/w24134>**

**From abstract:** “Despite a growing base of scientific discovery on genetic variation that predicts drug response, reimbursement for genetic testing among health systems and payers remains uneven. In large measure this is because the cascading impacts of genetic testing on individual and provider incentives and behavior, as well as downstream healthcare spending and outcomes, remain poorly understood. In this study, we couple evidence from a real-world implementation of pharmaco-genomic testing with a discrete event simulation model. We use this framework to evaluate the cost-effectiveness of various genetic testing strategies. We find that the cost-effectiveness of multiplexed genetic testing (e.g., whole genome sequencing) hinges on the ability of a health system to ensure that dense genotypic information **is routinely utilized by physicians**. Moreover, while much attention has been paid to lowering the cost of genetic tests, we demonstrate that in practice, **other scientific and behavioral factors**, focused on certain high-yield drug-gene pairs, are key to implementing precision medicine in ways that maximize its value.”

**[25] Grosse, S.D., 2014. Economic Analyses of Genetic Tests in Personalized Medicine: Clinical Utility First, Then Cost Utility. *Genetics in Medicine* 16(3): 225—227.**

“The primary constraint in understanding the economic value of genetic testing in medicine may not be lack of formal economic evaluations, but rather the unmet need for reliable, reproducible data on clinical outcomes. Demonstrated clinical utility is the essential foundation of reliable cost-utility estimates.” The paper highlights the following *prioritisation scheme* for economic value assessment:

- Evaluate genetic tests and applications for clinical effectiveness, ensuring that evidence levels are sufficiently high
- Use decision analytic models *without costs*, i.e., risk-benefit models, to identify factors that generate the highest net-benefit to patients
- Conduct a value of information analysis—an evaluation of economic gain from optimized coverage decisions resulting from more accurate predictions of effectiveness and cost effectiveness to prioritize investments
- Proceed to cost-effectiveness analysis based on the previous sections.

**[26] Kogan, J.N., Empey, P., Kanter, J., Keyser, D.J., Shrank, W.H., 2018. Delivering on the Value Proposition of Precision Medicine: The View from Healthcare Payers. *American Journal of Managed Care* 24(4): 177—179.**

The pace of discovery within the field of precision medicine has been remarkable, **yet optimal uptake of new genetic tests and genetically targeted therapies will occur only if payers recognize their value and opt to cover them. Coverage decisions require clear evidence of clinical effectiveness and utility and an understanding of how adoption will impact healthcare costs and utilization within a payer’s network.** Research in precision medicine has often not considered the payer’s perspective, and despite demonstrations of clinical effectiveness for many promising precision medicine innovations, coverage determinations have been deferred because relevant findings that payers can use to make informed decisions are lacking. Collaboration among payers, scientists, and clinicians is essential for accelerating uptake and value creation. By pairing clinical outcomes with claims and cost data and collaboratively conducting well-designed pragmatic clinical or observational studies, all stakeholders can learn from more meaningful and relevant outcomes.

**[27] Parkinson, D.R., et al., 2014. Evidence of clinical utility: An Unmet Need in Molecular Diagnostics for Patients with Cancer. *Clinical Cancer Research* 20(6): 1428—1444.**

This article defines and describes best practices for the academic and business community to generate evidence of clinical utility for cancer molecular diagnostic assays. Beyond analytical and clinical validation, successful demonstration of clinical utility involves developing sufficient evidence to demonstrate that **a diagnostic test results in an improvement in patient outcomes**. Practical criteria and steps for establishing clinical utility are crucial to subsequent decisions for reimbursement without which high-performing molecular diagnostics will have limited availability to patients with cancer and fail to translate scientific advances into high-quality and cost-effective cancer care.

### Factors contributing to lack of success of molecular diagnostic tests in the clinic:

- Method-specific issues
- Availability of multiple assays and methodologies for one target with a lack of material and method standards
- Lack of complete understanding of the clinical setting or scientific knowledge of the disease parameters by the developers
- Insufficient demonstration of analytical and clinical validation before commercialization
- Inadequate clinical trial designs or infrastructure needed to support assay implementation
- Lack of direct evidence that use of the assay leads to improved patient outcomes over other available solutions
- Lack of agreement among stakeholders on definitions and evaluation of evidence of utility

### Key steps toward demonstration of clinical utility / Best practices for demonstration of clinical utility

- Define the intended use of the new test and associate the assay result with a measurable clinical outcome.
- Consider regulatory and commercial implications of implementing an LDT versus an FDA-approved IVD when evaluating regulatory and business strategies
- Outline what will be needed to demonstrate clinical utility as part of assay implementation (e.g., components for long-term performance tracking).
- Anticipate the demonstration of clinical utility to support regulatory approval and payer clearance, including cost–benefit analysis,
- Anticipate the importance of costs in future test reimbursement decisions
- Carefully design clinical trials and specify an analysis plan to start generating evidence of clinical utility before regulatory approval and commercialization; work with partners to obtain access to appropriate sample and patient populations.
- Assemble chain of evidence (study data) to demonstrate utility.

[28] Philips, K.A., Sakowski, J.A., Trosman, J., Douglas, M.P., Liang, S-Y., Neumann, P., 2014. The Economic Value of Personalized Medicine Tests: What We Know and What We Need to Know. *Genetics in Medicine* 16(3): 251—257.

Personalized medicine is increasingly being developed and used in clinical care, and thus the need to assess its value is inescapable. There is much debate and uncertainty on which personalized medicine tests provide economic value and how to balance the need for innovative new technologies with affordability. Genomics has the potential to “bend the cost curve” by ensuring that the most effective treatment is used in the most appropriate patients—but that it is “too soon to know the extent of this potential benefit.” Decision-makers and stakeholders need information on which tests provide relatively higher value in order to make appropriate decisions about where to invest efforts in development and adoption.

Based on an analysis of the Tufts Cost Effectiveness Analysis Registry—where effectiveness is measured by QALY, the paper highlights that there are only few economic value assessment of tests and diagnostics because they lack widely accepted evidence of clinical utility. However, the lack of evidentiary thresholds should not impede innovation, but instead be aligned to the intended information use. The analysis culminates with the following policy implications:

- Information on clinical utility, economic value, affordability, and public health implications is essential for appropriately assessing new technologies.
- Methods are needed to prioritize and conduct early and rapid assessments of clinical utility and economic value, before widespread adoption of new technologies.
- It is critical to consider the true value of diagnostics and not impede the need for innovation because of the need to consider economic value.
- Balancing innovation and affordability is a shared responsibility.

## Industry Structure

[29] Berndt, E.R., Trusheim, M.R., 2019. *The Information Pharms Race and Competitive Dynamics of Precision Medicine: Insights from Game Theory in Economic Dimensions of Personalized and Precision Medicine*. Eds. Ernst R. Berndt, Dana P. Goldman, and John W. Rowe (p. 87—114)

Precision medicines inherently fragment treatment populations, generating small-population markets, creating high-priced “niche busters” rather than broadly prescribed “blockbusters”. It is plausible to expect that small markets will attract limited entry in which a small number of interdependent differentiated product oligopolists will compete, each possessing market power. Multiple precision medicine market situations now resemble game theory constructs such as the prisoners’ dilemma and Bertrand competition. The examples often involve drug developer choices created by setting the cut-off value for the companion diagnostics to define the precision medicine market niches and their payoffs.

Precision medicine game situations may also involve payers and patients who attempt to change the game to their advantage or whose induced behaviors alter the payoffs for the developers. The variety of games may predictably array themselves across the lifecycle of each precision medicine indication niche and so may become linked into a sequentially evolving meta-game. We hypothesize that certain precision medicine areas such as inflammatory diseases are becoming complex simultaneous multi-games in which distinct precision medicine niches compete. Those players that learn the most rapidly and apply those learnings the most asymmetrically will be advantaged in this ongoing information pharms race. Optimal societal roles for public and private sectors in creating, disseminating, and pricing information

Key takeaways:

- Game theoretic analysis of PM to answer the question as to whether PM can achieve sustainable commercial success and payer acceptance,
- Underlying science may support virtually unlimited differentiation, but economic forces may advance commoditization,
- Likelihood of commoditization increases with multiple product introduction in each PM scientific niches, and decreases with differentiation (i.e., supported by credible evidence),
- Comparative advantage in information race arises from fast learning and asymmetric application of learnings.

## Data and Analytics

[30] Blasimme, A., Vayena, E., Hafen, E., 2018. Democratizing Health Through Data Cooperatives. *Philosophy & Technology* 31(3): 473—479. <https://doi.org/10.1007/s13347-018-0320-8>

Massive amounts of data are collected and stored on a routine basis in virtually all domains of human activities. Such data are potentially useful to biomedicine. Yet, access to data for research purposes is hindered by the fact that different kinds of individual-patient data reside in disparate, unlinked silos. We propose that data cooperatives can promote much-needed data aggregation and consequently accelerate research and its clinical translation. Data cooperatives enable direct control over personal data, as well as more democratic governance of data pools. This model can realize a specific kind of data economy whereby citizens and communities are empowered to steer data use according to their motivations, preferences, and concerns. Policy makers can promote this model by recognizing citizens' rights to access and to obtain a copy of their own data, and by funding distributed data infrastructures piloting new data aggregation models.

[31] Bietz, M., Patrick, K. and Bloss, C., 2019. Data Donation As a Model for Citizen Science Health Research. *Citizen Science: Theory and Practice* 4(1):6 <https://doi.org/10.5334/cstp.178>

New computational and sensing innovations, coupled with increasingly affordable access to consumer health technologies, allow individuals to generate personal health information that they are then able to submit to a shared archive or repository. This paper presents data donation as a model for health-focused citizen science, with special attention to the ethical challenges and opportunities that this model presents. We also highlight some existing data donation projects curated by citizen scientists. After describing data donation in more detail, including its relationship to movements like the Quantified Self and research in personalized medicine, we report findings from the Health Data Exploration (HDE) Project's second annual Network Meeting, which was focused on data donation. These findings include identification of four challenges for the ethical conduct of health-focused data donation research: **participant protection, representativeness, incentives to participate, and governance**. We use these insights as a springboard for further discussion of specific issues, pointing both to the current state of the field and our suggestions about potential pathways for addressing some of the challenges.

[32] Cirillo, D., Valencia, A., 2019. Big Data Analytics for Personalized Medicine. *Current Opinion in Biotechnology* 58: 161—167.

Big Data are radically changing biomedical research. The unprecedented advances in automated collection of large-scale molecular and clinical data pose major challenges to data analysis and interpretation, calling for the development of new computational approaches. The creation of powerful systems for the effective use of biomedical Big Data in Personalized Medicine (a.k.a. Precision Medicine) will require significant scientific and technical developments, including infrastructure, engineering, project and financial management. We review here how the evolution of data-driven methods offers the possibility to address many of these problems, guiding the formulation of hypotheses on systems functioning and the generation of mechanistic models, and facilitating the design of clinical procedures in Personalized Medicine.

[33] Hulsen, T., Jamuar, S. S., Moody, A. R., Karnes, J. H., Varga, O., Hedensted, S., ... McKinney, E. F., 2019. From Big Data to Precision Medicine. *Frontiers in Medicine* 6:34. <https://doi.org/10.3389/fmed.2019.00034>

Abstract: For over a decade the term “Big data” has been used to describe the rapid increase in volume, variety and velocity of information available, not just in medical research but in almost every aspect of our lives. As scientists, we now have the capacity to rapidly generate, store and analyse data that, only a few years ago, would have taken many years to compile. However, “Big data” no longer means what it once did. The term has expanded and now refers not to just large data volume, but to our increasing ability to analyse and interpret those data. Tautologies such as “data analytics” and “data science” have emerged to describe approaches to the volume of available information as it grows ever larger. New methods dedicated to improving data collection, storage, cleaning, processing and interpretation continue to be developed, although not always by, or for, medical researchers. Exploiting new tools to extract meaning from large volume information has the potential to drive real change in clinical practice, from personalized therapy and intelligent drug design to population screening and electronic health record mining. **As ever, where new technology promises “Big Advances,” significant challenges remain.** Here we discuss both the opportunities and challenges posed to biomedical research by our increasing ability to tackle large datasets. Important challenges include the need for standardization of data content, format, and clinical definitions, a heightened need for collaborative networks with sharing of both data and expertise and, perhaps most importantly, a need to reconsider how and when analytic methodology is taught to medical researchers. We also set “Big data” analytics in context: recent advances may appear to promise a revolution, sweeping away conventional approaches to medical science. However, their real promise lies in their synergy with, not replacement of, classical hypothesis-driven methods. The generation of novel, data-driven hypotheses based on interpretable models will always require stringent validation and experimental testing. Thus, hypothesis-generating research founded on large datasets adds to, rather than replaces, traditional hypothesis driven science. Each can benefit from the other and it is through using both that we can improve clinical practice.

[34] Moreno et al. 2019. Open Science Precision Medicine in Canada: Points to Consider. *FACETS* 4: 1—10. <https://doi.org/10.1139/facets-2018-0034>

Abstract: Open science can significantly influence the development and translational process of precision medicine in Canada. Precision medicine presents a unique opportunity to improve disease prevention and healthcare, as well as to reduce health-related expenditures. However, the development of precision medicine also brings about economic challenges, such as costly development, high failure rates, and reduced market size in comparison with the traditional blockbuster drug development model. Open science, characterized by principles of open data sharing, fast dissemination of knowledge, cumulative research, and cooperation, presents a unique opportunity to address these economic challenges while also promoting the public good.

[35] Petersen, C., 2016. The Future of Patient Engagement in the Governance of Shared Data. *EGEMS (Wash DC)* 4(2):1214. <https://doi.org/10.13063/2327-9214.1214>

Background: The emerging healthcare system increasingly values patient engagement and shared decision-making between patients and their providers. The practice of these values is gaining importance as the patient-centered medical home model and personalized medicine come into greater use.

Opportunity for Improvement: Exploration of patient preferences about personal health data use for research and quality improvement is a fundamental element of the provider-patient relationship. Giving patients an explicit opportunity to discuss their options about use of their data and implementing a process that allows patients to receive desired communications about how their information is used can help build patient trust, a requirement for successful care partnerships.

Practice Advancement: Working to change organizational cultures that exclude patients from participation in important decisions related to personal health information use promotes a strong patient-provider relationship and, ultimately, lays the foundation for improved healthcare through expanded use of patient data.

[36] Prosperi, M., Min, J.S., Bian, J., Modave, F., 2018. Big Data Hurdles in Precision Medicine and Precision Public Health. *BMC Medical Informatics and Decision Making* 18: 139

The present work focuses on analyzing both the technical and societal hurdles related to the development of prediction models of health risks, diagnoses and outcomes from integrated biomedical databases. Methodological challenges that need to be addressed include improving semantics of study designs: medical record data are inherently biased, and even the most advanced deep learning’s denoising autoencoders cannot overcome the bias if not handled a priori by

design. Societal challenges to face include evaluation of ethically actionable risk factors at the individual and population level; for instance, usage of gender, race, or ethnicity as risk modifiers, not as biological variables, could be replaced by modifiable environmental proxies such as lifestyle and dietary habits, household income, or access to educational resources.

Conclusions: Data science for precision medicine and public health warrants an informatics-oriented formalization of the study design and interoperability throughout all levels of the knowledge inference process, from the research semantics, to model development, and ultimately to implementation.

**[37] Rose, N. 2019. Advancing Precision Medicine Using Cloud-Based Informatics. Genetic Engineering & Biotechnology News. [online] <https://www.genengnews.com/insights/advancing-precision-medicine-using-cloud-based-informatics/>**

Given the challenges associated with handling large volumes of multidimensional data using conventional data management tools, organizations are increasingly turning to platforms that allow them to get the most from their “big data.” In this article, we consider how the latest cloud-based informatics platforms are translating the goals of precision medicine into reality.

**[38] Avalere, 2013. Delivering Value in Healthcare: A Multistakeholder Vision for Innovation.** Online: [https://avalere.com/research/docs/031913\\_Dialogue\\_WhitePaper.pdf](https://avalere.com/research/docs/031913_Dialogue_WhitePaper.pdf)

**Key Takeaways:** There is a tension between pursuing value and supporting continued investments in new products that address the unmet needs of patients (innovation). Driving value in ways that align with innovation in life sciences with the value perspectives of patients and providers calls for a collaborative approach. The dynamic nature of pharmaceutical innovation (e.g., growing number of targeted therapies from PM) exacerbates the:

- Lack of stakeholder consensus on what constitutes values and how to support it;
- The challenge of ascertaining value in biomedical innovation, since understanding of clinical and economic value evolves over time and varies among and between different stakeholders.

The following four action domains to move to an ideal state are proposed:

<b>1. Data Infrastructure</b>	<b>2. Frameworks for Evaluating Evidence</b>
<ul style="list-style-type: none"> <li>• Standardized data</li> <li>• Reciprocal data access network</li> <li>• Unique patient identifiers</li> </ul>	<ul style="list-style-type: none"> <li>• New platforms for multi-stakeholder evidence need</li> <li>• Tools for evaluating evidence frameworks</li> <li>• Integration of patient perspectives in the research process</li> </ul>
<b>3. Evidence Communication</b>	<b>4. Coverage &amp; Payment</b>
<ul style="list-style-type: none"> <li>• Best practices in evidence communication</li> <li>• Guidelines for incorporating new information</li> <li>• Involving patients in translation and dissemination</li> <li>• Methods of communicating uncertainty about benefits and risks</li> <li>• Safe harbour for multi-stakeholder scientific discussions</li> </ul>	<ul style="list-style-type: none"> <li>• Pathways for innovation in novel provider payment models</li> <li>• Transparency of incentives in clinical pathways</li> </ul>

## Incentive Design

**[39] Akhmetov, I., Bubnov, R.V., 2017. Innovative Payer Engagement Strategies: Will Convergence Lead to Better Value Creation in Personalized Medicine? EPMA Journal 8(5): 5—15.**

As reimbursement authorities are gaining greater power to influence the prescription behaviour of physicians, it remains critical for life science companies focusing on personalized medicine to develop “tailor-made” payer engagement strategies to secure reimbursement and assure timely patient access to their innovative products. Depending on the types of such engagement, pharmaceutical and diagnostic companies may benefit by obtaining access to medical and pharmacy claims data, getting invaluable upfront inputs on evidence requirements and clinical trial design, and strengthening trust by payers, therefore avoiding uncertainties with regards to pricing, reimbursement, and research and development reinvestment. This article aims to study the evolving trend of partnering among two interdependent, yet confronting, stakeholder groups—payers and producers—as well as to identify the most promising payer engagement strategies based on cocreation of value introduced by life science companies in the past few years. We analyzed the recent case studies from both therapeutic and diagnostic realms considered as the “best practices” in payer

engagement. The last 5 years were a breakout period for deals between life science companies and reimbursement authorities in the area of personalized medicine with a number of felicitous collaborative practices established already, and many more yet to emerge. We suggest that there are many ways for producers and payers to collaborate throughout the product life cycle—from data exchange and scientific counseling to research collaboration aimed at reducing healthcare costs, addressing adherence issues, and diminishing risks associated with future launches.

**Conclusions** The presented case studies provide clear insights on how successful personalized medicine companies customize their state-of-the-art payer engagement strategies to ensure closer proximity with payers and establish longer-term trust-based relationships.

The paper provides 3 examples of innovative payer engagement strategies: (1) payer consultations; (2) risk-sharing agreements, which can be either finance-based, outcomes-based or evidence-based; (3) expertise based partnerships, involving either joint evidence generation or medication adherence projects or retrospective data analysis.

Illustration of best-practices of payer engagement

1. “Roche-Swiss Re” collaboration in China, facilitating access of a large number of cancer patients to innovative treatments
2. “VitrOmics-CZ-CPCT” partnership in the Netherlands: a private-public collaboration to address the problem of overtreatment in breast cancer
3. “Eli-Lilly-Humana” initiative in the USA – retrospective analysis of medical, pharmacy, and laboratory claims data for predictive analysis of diabetes care needs by patient group
4. “MolecularMD-Medco” partnership in the USA – a patient-centred initiative aimed at stratifying of patients into responsive and non-responsive
5. “Nuo Therapeutics—CMS” risk-sharing deal in the USA

**[40] Faulker et al., 2012. Challenges in the Development and Reimbursement of Personalized Medicine—Payer and Manufacturer Perspectives and Implications for Health Economics and Outcomes Research. A Report of the ISPOR Personalized Medicine Special Interest Group. *Value in Health* 15(8): 1162—1171.**

**Abstract:** Personalized medicine technologies can improve individual health by delivering the right dose of the right drug to the right patient at the right time but create challenges in deciding which technologies offer sufficient value to justify widespread diffusion. Personalized medicine technologies, however, do not neatly fit into existing health technology assessment and reimbursement processes.

Five key areas in which health economics and outcomes research best practices could be developed to improve value assessment, reimbursement, and patient access decisions for personalized medicine include: 1) research prioritization and early value assessment, 2) best practices for clinical evidence development, 3) best practices for health economic assessment, 4) addressing health technology assessment challenges, and 5) new incentive and reimbursement approaches for personalized medicine.

Key gaps in health economics and outcomes research best practices, decision standards, and value assessment processes are also discussed, along with next steps for evolving health economics and outcomes research practices in personalized medicine.

**[41] Garrison, L.P., Towse, A., 2017. Value-Based Pricing and Reimbursement in Personalized Healthcare. Introduction to the Basic Health Economics. *Journal of Personalized Medicine* 7(3): E10. <https://doi.org/10.3390/jpm7030010>**

‘Value-based’ outcomes, pricing, and reimbursement are widely discussed as health sector reforms these days. In this paper, we discuss their meaning and relationship in the context of personalized healthcare, defined as receipt of care conditional on the results of a biomarker-based diagnostic test. We address the question: “What kinds of pricing and reimbursement models should be applied in personalized healthcare?” The simple answer is that competing innovators and technology adopters should have incentives that promote long-term dynamic efficiency. We argue that—to meet this social objective of optimal innovation in personalized healthcare—payers, as agents of their plan participants, should aim to send clear signals to their suppliers about what they value. We begin by revisiting the concept of value from an economic perspective and argue that a broader concept of value is needed in the context of personalized healthcare. We discuss the market for personalized healthcare and the interplay between price and reimbursement. We close by emphasizing the potential barrier posed by inflexible or cost-based reimbursement systems, especially for biomarker-based predictive tests, and how these personalized technologies have global public goods characteristics that require global value-based differential pricing to achieve dynamic efficiency in terms of the optimal rate of innovation and adoption.

[42] Garrison, L.P., Finley Austin, M.J., 2007. **The Economics of Personalized Medicine: A Model of Incentives for Value Creation and Capture.** *Therapeutic Innovation and Regulatory Science* 41(4): 501-509.  
<https://doi.org/10.1177/009286150704100408>

Personalized medicine is a concept promoted as a new paradigm for healthcare delivery, with particular emphasis on more tightly linking genomics-based diagnostics and therapeutics. The analysis provided in this paper addresses the incentives to develop linked genomics based diagnostics and the broader public policy implications. Using a standard economic framework of an insurer-payer negotiating reimbursement with manufacturers of an innovative, targeted diagnostic and a companion patented therapeutic, several illustrative hypothetical scenarios are developed. The relative importance of the key economic factors is examined, including whether the reimbursement system is value or cost based, whether the therapeutic is already marketed, the strength of diagnostic intellectual property, and a current year versus longer time frame. The results suggest that health systems reforms that promote value-based, flexible reimbursement for innovative, patent-protected diagnostic and therapeutic products are critical to create stronger economic incentives for the development of personalized medicine.

[43] Geruso, M., Jena, A.B., Layton, T., 2018. **Will Personalized Medicine Mean Higher Costs for Customers.** *Harvard Business Review*

To ensure the financial viability of new medical innovation for patients, health insurance markets need to be regulated to eliminate the perverse financial incentives that limit patients' coverage.

If insurance markets function as they should — spreading risk across patient populations — then the costs of expensive specialized therapies should be spread across all enrollees, rather than rest on those patients who require treatment. In theory, this would make out-of-pocket payments for affected patients low, with the financial burden of treatments reflected in slightly higher premiums for all.

In reality, **patients frequently face significant out-of-pocket costs for expensive specialized medicines**, even under otherwise generous insurance policies. This is likely due to what economists call “adverse selection,” or the tendency of sicker, more expensive consumers to choose health insurance plans with more generous coverage. Because sicker patients are more likely to be unprofitable, insurers try to push them toward competitors' plans by designing plan benefits (e.g., provider networks, drug copays, and prior authorization requirements) to be unattractive to those who need more generous coverage.

Adverse selection in insurance markets is likely to worsen as personalized medicine grows (as the fixed costs of drug development and production are spread across smaller populations of patients, resulting in higher manufacturer prices for drugs like tisagenlecleucel), and as government public programs shift more individuals to private health plans, rather than offering coverage through one. The paper also discusses the need to change insurers' financial incentives.

[44] Miles, J., Steller, B., 2017. **Outcomes-Based Pricing Initiatives in the Healthcare Industry.** *Vistex*

Provides a high-level overview of outcomes-based pricing. “By linking drug prices with desired results, outcome-based pricing puts the focus on the patients while aligning all the players around the consequences for patients.” Such alignment is not always obvious and can vary from therapy to therapy.

The drug company essentially establishes a risk-sharing model that allows for higher reimbursements for better outcomes and lower reimbursements for reduced outcomes, such as failing to achieve the outcome documented in a clinical study. This relationship between pricing and outcomes ensures that payers receive the full value of the drugs or products, resulting in the form of a healthy patient. And providers benefit from improved outcomes that typically reduce the cost of care while minimizing readmissions.

Additionally, outcome-based pricing strategies may take on a variety of forms for various drugs and devices. Pricing should be reflective of the type of product and the therapy utilized. For example, many oncology-related therapies will most likely include a genomically-defined patient population sharing a common biomarker that demonstrates a higher likelihood of a positive outcome. Conversely, diabetes patients may not have a biomarker but may require a more holistic therapy that utilizes drugs, exercise and diet to enable a higher quality of life. In either case, the therapies are designed to improve the health of the patient, ensure a return to the productive lifestyle enjoyed before diagnosis, and reduce the long-term cost of healthcare.

[45] Pauly, M.V. 2017. **Cost Sharing in Insurance Coverage for Precision Medicine.** NBER Working Paper 24095.  
Online: <http://www.nber.org/papers/w24095>

**Abstract:** This paper describes current pattern of insurance coverage for precision medicines and, especially, companion diagnostics and explores what coverage would improve efficiency. We find that currently coverage is common for tests and treatments with clinical acceptance used at high volumes but is haphazard across both private insurers and Medicare for precision medicines in general. Analysis of the case of homogenous patient preferences finds that discovery and use of the test that converts an ordinary drug into a precision drug can either increase or decrease total spending, and might call for full or no coverage of test and treatments. Heterogeneity in marginal benefits from testing and treatment can call for partial coverage. Finally, varying threshold levels for diagnostic test results can lead to a demand curve to test and treatment that calls for partial cost sharing. Numerical examples and case studies of several test-treatment combinations illustrate these points.

**Conclusion:** Our review of coverage for genetic testing reveals a trend toward a more general acceptance of such tests as having clinical utility and therefore in principle appropriate candidates for insurance coverage. There is still a reluctance to cover tests deemed experimental and relatively high bars for the evidence that can make coverage routine—though in most cases the coverage usually follows rather than facilitates clinical practice.

Genetic testing to determine the effectiveness of treatment is still relatively new though growing rapidly. There does seem to be a common cycle in which three trends compete: Evidence for and use of genetic testing increase over time; insurance coverage (though present) imposes higher cost sharing; then test prices fall and coverage improves.

In principle, cost effectiveness studies could provide the basis for determining those tests so efficient that coverage should be 100%, but this determination may vary across consumers depending on their willingness to pay for health outcomes and avoiding side effects of treatment. So coverage may become broader but shallower.

The other conflicting influence is that new but initially expensive tests appear that do impose a financial burden but, with dubious evidence for their effectiveness or cost effectiveness, are generally not covered. Thus there is likely to be continued debate on how insurance should deal with both the testing and treatment associated with personalized medicine.

**[46] Seeley, E., Kesselheim, A.S., 2017. *Outcomes-Based Pharmaceutical Contracts: An Answer to High U.S. Drug Spending? The Commonwealth Fund.***

**Key Takeaways:** In response to high U.S. prescription drug prices, some pharmaceutical manufacturers and private payers have shown interest in outcomes-based contracts, in which rebate levels are tied to a specified outcome in the target population receiving treatment. Outcomes-based contracting can potentially prevent payers from wasting resources on medications that are not as effective outside clinical trials. Based on semistructured interviews with payers, manufacturers, and policy experts, it is concluded that the impact of these contracts on quality of care or costs is unclear, as current applicability is restricted to a small subset of drugs. Moreover, meaningful metrics to evaluate their impact are limited. Outcomes-based contracts are intended to shift pharmaceutical spending toward more effective drugs, but their impact is unclear. Voluntary testing and rigorous evaluation of such contracts in the Medicare and Medicaid programs could increase understanding of this new model.

**[47] Trusheim, M.R., Berndt, E.R., 2015. *The Clinical Benefits, Ethics and Economics of Stratified Medicine and Companion Diagnostics. Nature Drug Discovery Today 20(12): 1439—1450.***

The stratified medicine companion diagnostic (CDx) cut-off decision integrates scientific, clinical, ethical, and commercial considerations, and determines its value to developers, providers, payers, and patients. Competition already sharpens these issues in oncology, and might soon do the same for emerging stratified medicines in autoimmune, cardiovascular, neurodegenerative, respiratory, and other conditions. Of 53 oncology targets with a launched therapeutic, 44 have competing therapeutics. Only 12 of 141 Phase III candidates addressing new targets face no competition. CDx choices might alter competitive positions and reimbursement. Under current diagnostic incentives, payers see novel stratified medicines that improve public health and increase costs, but do not observe companion diagnostics for legacy treatments that would reduce costs. It would be in the interests of payers to rediscover their heritage of direct investment in diagnostic development.

Stratified medicine tightens the links among science, the clinic, and the marketplace. Setting the companion diagnostic cut-off value is a crucial shared connection among all three, with no easy rule of thumb to guide the choice. Each stratified medicine opportunity faces unique facts and circumstances that require balancing ethical, scientific, and financial concerns.

Today, stratified medicine economic incentives favor new medicine developers and the patients they serve. Payers benefit from more efficient new treatment for unmet medical needs, but likely face increased total costs for the resultant increase in overall public health, with little or no offsetting cost savings from companion diagnostics better stratifying legacy treatments. Diagnostic companies are generally paid for their services, but not sufficiently to invest independently

in companion diagnostic development. Current economics do not reliably signal true healthcare needs to therapeutic and diagnostic developers, and even less so to the discovery scientists at the beginning of the innovation value chain.

Improving the stratified medicine innovation chain through better economics requires incremental, but significant changes. Greater direct payer sponsorship of medical technology development has precedent in both civilian and military contexts, but seems unlikely for stratified medicine in the near term. Proponents of changes already occurring, such as alternative payment methods and accountable care organizations, hope that they will better connect healthcare decision making with healthcare technology providers. The introduction of improved information technologies from electronic health records, big data analytics, patient wearable devices, and improved data sharing in the sciences also promise improvements.

Companion diagnostics and the stratified medicines that they enable are a growing category of new and legacy therapies in oncology and other disease areas. Their ultimate success depends upon more than scientific discovery. They unite clinical benefits, ethical choices, and economic incentives in ways that significantly accelerate decision timing, decrease therapeutic outcome uncertainty, shift competition, and might increase ICER-justified product prices. Mechanisms to create, determine, and share value among all stakeholders from patients, providers, and payers to regulators, developers, and discovery scientists must also advance.

**[48] Vlaanderen, F. P., Tanke, M. A., Bloem, B. R., Faber, M. J., Eijkenaar, F., Schut, F. T., & Jeurissen, P., 2018. Design and Effects of Outcome-Based Payment Models in Healthcare: A Systematic Review. *The European Journal of Health Economics : HEPAC – Health Economics in Prevention and Care* 20(2): 217–232. <https://doi.org/10.1007/s10198-018-0989-8>**

[Abstract] Introduction: Outcome-based payment models (OBPMs) might solve the shortcomings of fee-for-service or diagnostic-related group (DRG) models using financial incentives based on outcome indicators of the provided care. This review provides an analysis of the characteristics and effectiveness of OBPMs, to determine which models lead to favourable effects.

Methods: We first developed a definition for OBPMs. Next, we searched four data sources to identify the models: (1) scientific literature databases; (2) websites of relevant governmental and scientific agencies; (3) the reference lists of included articles; (4) experts in the field. We only selected studies that examined the impact of the payment model on quality and/or costs. A narrative evidence synthesis was used to link specific design features to effects on quality of care or healthcare costs.

Results: We included 88 articles, describing 12 OBPMs. We identified two groups of models based on differences in design features: narrow OBPMs (financial incentives based on quality indicators) and broad OBPMs (combination of global budgets, risk sharing, and financial incentives based on quality indicators). Most (5 out of 9) of the narrow OBPMs showed positive effects on quality; the others had mixed (2) or negative (2) effects. The effects of narrow OBPMs on healthcare utilization or costs, however, were unfavourable (3) or unknown (6). All broad OBPMs (3) showed positive effects on quality of care, while reducing healthcare cost growth.

Discussion: Although strong empirical evidence on the effects of OBPMs on healthcare quality, utilization, and costs is limited, our findings suggest that broad OBPMs may be preferred over narrow OBPMs.

## Regulation

**[49] Eichler, H.-G.; Enzmann, H. & Rasi, G., 2019. Added therapeutic benefit and drug licensing. *Nature Reviews Drug Discovery* 18:651—652s. <https://www.nature.com/articles/d41573-019-00068-x>**

**Abstract:** One aspect of the ongoing debate about drug pricing is the added therapeutic benefit of new drugs compared with existing — and potentially cheaper — therapies. Here, we discuss the merits and pitfalls of proposals that are being discussed with regard to the role of regulatory agencies in establishing added therapeutic benefit.

**[50] Gorry, P., Useche, D., 2017. Orphan Drug Designations as Valuable Intangible Assets for IPO Investors in Pharma-Biotech Companies. *NBER Working Paper* 24021. <http://www.nber.org/papers/w24021>**

The paper attempts to explain the “Pisano Puzzle,” which relates to investment flows into the biopharmaceutical sector even though profits are hard to come by, focusing on the case of rare diseases. The paper investigates whether ODD applied prior to an IPO may be considered as a valuable intangible asset which influences the way investors perceive biotech firms’ potential through an increase in the amount invested at the time of the IPO in the US stock markets. The authors show that ODD represent a valuable intangible asset with a powerful certification and reputational component which attract IPO investors. This is due to **the signaling value and productive effects** (exclusionary and/or markets for technology effects). The promise of a 7-year market exclusivity and the 50% tax credit for clinical drug testing are

attractive enough for investors to balance the risk linked to targeting a niche market. While OD designations are more valuable than patents to attract IPO investors, it is **unclear which of market exclusivity or the tax refund is the more effective incentive measure**; is market exclusivity, limiting the competition and approval of another version of the same orphan drug, the most powerful signal for investors as it secures long-term monopoly profits, or are investors more sensitive to the tax-credit, the lowering of drug R&D costs, and the short-term balance sheet. We argue that IPO investors are more interested in the **competitive advantage related to the tax credit, and not that related to market exclusivity. Otherwise the patent portfolio would be more important for IPO investors than OD designations.** But a clear separation between the effects of these two incentives is not possible. The OD Act with its regulation and financial incentives succeeded in attracting private investments, and represents an opportunity for biotech companies, which depend on external finance. **If one could draw a parallel between rare and neglected diseases, Orphan-type legislation might provide a solution to attract investments to support drug development for tropical diseases, for example (Anderson, 2009).** This type of supply-side incentive seems to be stronger in attracting external investors than patent protection. Recently the FDA implemented a new support for stimulating the development of new antibiotics, the “Generating Antibiotics Incentives Now” or GAIN7. The new law provides an additional five years of exclusivity. It remains to be seen whether this legislation will succeed in attracting biotech companies and private investors. It could also be interesting to **compare the European Union and the US in terms of the signaling value of Orphan Drug Designation for investors.** Future studies should also examine more explicitly the trade-offs associated with alternative quality signals at different stages of the drug development and the relative importance of those signals.

[51] Knowles, L., Luth. W., Bubela, T., 2017. Paving the Road to Personalized Medicine: Recommendations on Regulatory, Intellectual Property and Reimbursement Challenges. *Journal of Law and the Biosciences* 4(3): 453–506. <https://doi.org/10.1093/jlb/lx030>

Abstract: Personalized medicine (PM) aims to harness a wave of ‘omics’ discoveries to facilitate research and discovery of targeted diagnostics and therapies and increase the efficiency of healthcare systems by predicting and treating individual predispositions to diseases or conditions. Despite significant investment, limited progress has been made bringing PM to market. We describe the major perceived regulatory, intellectual property, and reimbursement challenges to the development, translation, adoption, and implementation of PM products into clinical care. We conducted a scoping review to identify (i) primary challenges for the development and implementation of PM identified in the academic literature; (ii) solutions proposed in the academic literature to address these challenges; and (iii) gaps that exist in that literature. We identified regulatory barriers to PM development and recommendations in 344 academic papers. **Regulatory uncertainty was a cross-cutting theme** that appeared in conjunction with other themes including: reimbursement; clinical trial regulation; regulation of co-development; unclear evidentiary requirements; insufficient incentives for research and development; incompatible information systems; and different regulation of different diagnostics. To fully realize the benefits of PM for healthcare systems and patients, regulatory, intellectual property, and reimbursement challenges need to be addressed in lock step with scientific advances.

## Adoption and Diffusion

[52] Carlson, B., 2012. In Search of the Perfect Model. *Biotechnology Healthcare* Spring 2012: 20—23.

Carlson delves into the question of how to develop a value proposition in a healthcare market that is becoming increasingly elastic. He argues that “ If personalized medicine is going to fulfil its promise of better outcomes and lower overall costs, it has to be **systematically deployed in patient care. Pharmaceutical companies and diagnostics companies are mutually interdependent in the stratified medicine work.** The price of a companion diagnostic can be perceived as an obstacle to sales of the drug. And, biopharma companies have absorbed the price of companion diagnostic to maintain the sales momentum of their drug. Stakeholder alignment is one of the major issues, if not the number one issue, confronting personalized medicine. A valid business model for PM must include **consumer education and engagement.** This is suggestive that employers can take the lead.” He highlights the imperative to move beyond the herd mentality and the need for enough winners to create a stampede. “It’s not the technology, it’s the **business model.**”

[53] Ginsburg, G.S., Phillips, K.A., 2018. Precision Medicine: From Science to Value. *Health Aff (Millwood)* 37(5): 694—701. <https://doi.org/10.1377/hlthaff.2017.1624>

The paper provides a nice review of precision medicine and how to unleash the value from PM. In particular it delves into “the intersection of data science, analytics and precision medicine in creating a **learning health system** that carries out

research in the context of clinical care and at the same time optimizes the tools and information used to deliver improved patient outcomes.”

The paper highlights the components of precision medicine system in terms of patient willingness to share data—highlighting **data sharing as a high-payoff strategy**, and the optimal use of data by different stakeholders, including payer assessment of precision medicine interventions. The role of health information technology providers to enable a learning health system by creating a linkage between data science, digital health and precision medicine.

The paper emphasizes the need for global efforts to develop precision medicine as a science and healthcare strategy (highlighting key barriers) and proposes a five-pronged policy agenda: 1. Evidence generation, 2. Data sharing and infrastructure needs, 3. Incorporating genomic and other molecular data into clinical care and research; 4. Diagnostics, drug discovery and the economics of precision medicine; 5. Participant engagement and trust.

**[54] Hermosilla, M., Lemus, J.A., 2018. *Therapeutic Translation of Genomic Science: Opportunities and Limitations of GWAS (Genome-Wide Association Studies)*. NBER Working Paper 23989**

Many scientists predicted a swift revolution in human therapeutics after the completion of the Human Genome Project (“HGP”). This revolution, however, has been slow to materialize in spite of the scientific advances. We investigate the role of biological complexity in slowing down this revolution. For less complex diseases, we find a strong and positive association between cumulative knowledge and the amount of innovation. This association weakens as complexity increases, becoming statistically insignificant at the extreme. Our results suggest that biological complexity is, in part, responsible for the slower-than-expected unfolding of the therapeutical revolution set in motion by the HGP.

## International Comparisons

**[55] Kichko, K., Marschall, P., & Flessa, S. (2016). *Personalized Medicine in the U.S. and Germany: Awareness, Acceptance, Use and Preconditions for the Wide Implementation into the Medical Standard*. *Journal of Personalized Medicine* 6(2):15. doi:10.3390/jpm6020015**

Based on surveys in Pennsylvania (U.S.) and Bavaria (Germany), the paper assesses public and physician awareness, acceptance and use of Personalized Medicine (PM), as well as their opinions on PM reimbursement and genetic privacy protection in the U.S. and Germany. Findings: “Survey results, analyzed by means of descriptive and non-parametric statistic methods, have shown that awareness, acceptance, use and opinions on PM aspects in Pennsylvania and Bavaria were not significantly different. In both states there were strong concerns about genetic privacy protection and no support of one genetic database. The costs for Personalized Medicine were expected to be covered by health insurances and governmental funds. Summarizing, we came to the conclusion that for PM wide implementation there will be need to adjust the healthcare reimbursement system, as well as adopt new laws which protect against genetic misuse and simultaneously enable voluntary data provision.”

**[56] Kissam, S.M., Beil, H., Cousart, C., Greenwald, L.M., Lloyd, J.T., 2019. *States Encouraging Value-Based Payment: Lessons From CMS’s State Innovation Models Initiative*. *Milbank Quarterly* 97. DOI: 10.1111/1468-0009.12380**

Policy points:

- Six states received \$250 million under the federal State Innovation Models (SIM) Initiative Round 1 to increase the proportion of care delivered under value-based payment (VBP) models aligned across multiple payers.
- Multipayer alignment around a common VBP model occurred within the context of state regulatory and purchasing policies and in states with few commercial payers, not through engaging many stakeholders to act voluntarily.
- States that made targeted infrastructure investments in performance data and electronic hospital event notifications, and offered grants and technical assistance to providers, produced delivery system changes to enhance care coordination even where VBP models were not multipayer.

Findings: State policymakers leveraged existing state law, new policy development, and federal SIM Initiative funds to implement new VBP models in Medicaid. States’ investments promoted electronic health information going from hospitals to primary care providers and collaboration across care team members within practices to enhance care coordination. Multipayer alignment occurred where there were few commercial insurers in a state, or where a state law or state contracting compelled commercial insurer participation. Challenges to health system change included commercial payer reluctance to coordinate on VBP models, cost and policy barriers to establishing bidirectional data exchange among all providers, preexisting quality measurement requirements across payers that impede total alignment of

measures, providers' perception of their limited ability to influence patients' behavior that puts them at financial risk, and consumer concerns with changes in care delivery.

Conclusions: The SIM Initiative's test of the power of state governments to shape healthcare policy demonstrated that strong state regulatory and purchasing policy levers make a difference in multipayer alignment around VBP models. In contrast, targeted financial investments in health information technology, data analytics, technical assistance, and workforce development are more effective than policy alone in encouraging care delivery change beyond that which VBP model participation might manifest.

**[57] Panagiotara, A., Skoufas, E., Chalikiopoulou, C., Tsermpini, E-E., Bartsakoulia, M., Katsila, T., Patrinos, G.P., 2019. *Implementation of Genomic Medicine: An International Perspective in Principles and Practice of Medical Genetics and Genomics (Seventh Edition)*, Academic Press. Eds. Reed E. Pyeritz, Bruce R. Korf, Wayne W. Grody, Emery and Rimoin (p. 369-380). <https://doi.org/10.1016/B978-0-12-812536-6.00015-8>**

In the "omics" era, incorporation of genomic medicine into clinical practice is greatly anticipated following recent scientific and technological advances. Currently a multidisciplinary agenda that involves government officials, funding agencies, industry leadership, healthcare providers, biomedicine researchers, and the general public is of outmost importance to "translate" human discoveries into human health. But although groundbreaking scientific findings are being revealed, the clinical application of genomic medicine and its acceptance in healthcare cannot be envisaged without sound science and evidence-based facts. A series of challenges exist from both scientific and policy perspectives at a global level. This chapter presents an overview of the current genomic medicine initiatives, both national and worldwide, which once successfully completed will help to expedite implementation of genomic medicine practices into the clinic.

**[58] Sobrio, A., Ruzicic, A., Hoday, K., 2014. *Uptake Challenges: Are Healthcare Systems Ready for Personalised Medicines and Companion Diagnostics*. Pharmaceutical Market Europe.**

Highlights the market access challenge for novel drugs in countries where pricing and reimbursement of drugs and their companion diagnostics are not jointly evaluated.

**[59] Stark,Z., Dolman, L., Manolio, T.A., Ozenberger, B., Hill, S.L., Caulfied, M.J., Levy, Y., Glazer, D., Wilson, J., Lawler, M., Boughtwood, T., Braithwaite, J., Goodhand, P., Birney, E., North, K.N., 2019. *Integrating Genomics into Healthcare: A Global Responsibility*, *The American Journal of Human Genetics*, Volume 104, Issue 1, Pages 13-20, <https://doi.org/10.1016/j.ajhg.2018.11.014>.**

Genomic sequencing is rapidly transitioning into clinical practice, and implementation into healthcare systems has been supported by substantial government investment, totaling over US\$4 billion, in at least 14 countries. These national genomic-medicine initiatives are driving transformative change under real-life conditions while simultaneously addressing barriers to implementation and gathering evidence for wider adoption. We review the diversity of approaches and current progress made by national genomic-medicine initiatives in the UK, France, Australia, and US and provide a roadmap for sharing strategies, standards, and data internationally to accelerate implementation.

**[60] St Jean, N., Pinto, C., Tenente, I., Murray, G., 2018. *Collaboration is Key to Accelerating Diagnostics Access to Optimize Benefits of Precision Medicines*. *Personalized Medicine* 15(3): 157—161. <https://doi.org/10.2217/pme-2018-0018>**

Precision medicine is defining the future of healthcare. In addition to providing clinically meaningful benefits to patients, delivery of the right treatment to the right patient at the right time may offer budgetary efficiencies by reducing the costs of clinical time, service use and ineffective treatment associated with a less personalized, 'one-size-fits-all' approach [1]. Approximately one-third of all new drugs in development use genomic data to identify patients most likely to benefit from them [2,3]. A significant proportion of the new generation of novel targeted therapies arriving in the clinic require patients to have essential tests required by a therapy's indication, known as companion diagnostics, or tests that support treatment decisions but are not essential prior to prescription, known as complementary diagnostics.

As a result of this major change in the way pharmaceutical companies develop new medicines, there has been exponential growth of drug–diagnostic combinations seeking regulatory approval. Data from the US FDA show an increase from five to 63 approvals of drugs with associated diagnostics between 2006 and 2012. However, in only seven of these 63 drug–diagnostic combinations were the drug and the diagnostic approved at the same time. Growth in precision medicines continues, with a record of 16 new products approved by the FDA in 2017, representing a third of total approvals. However, a report from the Personalized Medicine Coalition citing these figures also acknowledges the

ongoing challenges, including diagnostic regulatory policy, coverage and reimbursement. Without diagnostics to guide the use of these novel targeted medicines, clinicians may be reluctant to prescribe them, and payers to fund them; as a result, limiting access to these important medicines, to the detriment of patients.

Why is there a mismatch in timelines for availability of precision medicines and diagnostics, and how can the current challenges facing clinicians, payers and pharmaceutical and diagnostics companies be overcome, in order to accelerate patients' access to the right medicines for them so that they can experience the real-world benefits of these precision treatment options?

**[61] Szucs, T., Weiss, M., Klaus, G., 2017. The Enigma of Value: In Search of Affordable and Accessible Healthcare. *European Journal of Health Economic* 18:667–670. <https://doi.org/10.1007/s10198-016-0857-3>**

In times of shrinking resources and pharmaceutical breakthrough situations, our value-assessing systems are stretched to their very limits. Assessing value is highly complex. Current value-assessment systems risk neglecting important factors, such as therapy duration, budget impact, or the importance of combination therapies. Especially when dealing with breakthrough therapies within high prevalence indications, these factors play an important role in healthcare spending. When it comes to assessing value in Switzerland, the system is innovation and access friendly; the price level of pharmaceutical products, however, is relatively high in comparison to neighboring countries. The Swiss pricing and reimbursement system can still improve in terms of efficiency and transparency.

**[62] Towse, A., Cole, A., Zamora, B., 2018. *The Debate on Indication-Based Pricing in the U.S. and Five Major European Countries*. London: Office of Health Economics Consulting**

The purpose of this report is to leave the reader with a better understanding of the state of the debate on the merits and demerits of moving from a price for a drug to a price for each use of a drug.

## Prevention

**[63] Davis, K., Bialek, R., Parkinson, M., Smith, J., Vellozzi, C., 1990. Reimbursement for Preventive Services: Can we Construct an Equitable System? *Journal of General Internal Medicine* 5(Suppl 2): S93. <https://doi.org/10.1007/BF02600851>**

This report examines alternative methods of paying for clinical preventive care services. First, the extent of coverage of preventive healthcare services in public and private health insurance plans is reviewed. Included in this review are Medicare, Medicaid, health maintenance organizations, and private health insurance plans. Second, four alternative methods for paying for preventive care are discussed. These options are: 1) fee-for-service; 2) a periodic preventive health visit fee; 3) capitation; and 4) a preventive services account. The report concludes with recommendations for constructing an equitable system for increasing access to preventive services. A multi-pronged approach is recommended involving improvements in public and private coverage of these services; development of a periodic preventive health visit fee payment mechanism; initiation of additional research and demonstration efforts designed to determine cost-effectiveness of services and payment approaches; and modifications to the current coding system that would lead to a more appropriate method for reimbursement of preventive care services.

**[64] Eisner, D., Zoller, M., Rosemann, T., Huber, C.A., Badertscher, N., Tandjung, R., 2011. Screening and Prevention in Swiss Primary Care: A Systematic Review. *International Journal of General Medicine* 4: 853–870.**

Prevention is a challenging area of primary care. In Switzerland, little is known about attitudes to and performance of screening and prevention services in general practice. To implement prevention services in primary care it is important to know about not only potential facilitators but also barriers. Primary care encompasses the activities of general practitioners, including those with particular interest and/or specializations (e.g., pediatrics, gynecology). The aim of this study was to review all studies with a focus on prevention services which have been conducted in Switzerland and to reveal barriers and facilitators for physicians to participate in any preventive measures.

Most studies focussing on screening and prevention activities in primary care addressed vaccination, lifestyle modification or cardiovascular disease prevention. Identified barriers and facilitators indicate a need for primary-care-adapted education and training which are easy to handle, time-saving and reflect the specific needs of general practitioners. If new prevention programs are to be implemented in general practices, RCTs of high methodological quality are needed to assess their impact.

[65] Faust , H.S., 2011. *Historical Perspectives on Structural Barriers to Prevention in Prevention vs. Treatment: What's the Right Balance?* Eds H.S. Faust and P.T. Menzel. <https://doi.org/10.1093/acprof:oso/9780199837373.003.0006>

Three main structural barriers limit the implementation of prevention in the US: (1) higher standards for acceptance of prevention than treatment or “cure” modalities; (2) a built environment favoring efficiency and expediency over health, and (3) lack of medical insurance coverage. In this chapter I examine the historical reasons for barriers (2) and (3), concentrating on the third, lack of medical insurance coverage. The Patient Protection and Accountable Care Act will help alleviate this barrier, but a lack of resources to implement PPACA, along with ongoing built environment issues, will continue to cause prevention to lag behind its optimal implementation.

[66] Ganzer, T., Wong Sak Hoi, G., 2018. *How Two Countries Handle Illness Prevention*. Online: [https://www.swissinfo.ch/eng/us---swiss-health-series\\_how-two-countries-handle-illness-prevention/43833990](https://www.swissinfo.ch/eng/us---swiss-health-series_how-two-countries-handle-illness-prevention/43833990)

[67] Gillman, M.W., Hammond, R.A., 2016. Precision Treatment and Precision Prevention: Integrating “Below and Above the Skin.” *JAMA Pediatrics* 170(1): 9–10.

Precision prevention can aim to change individual behavior, it can also target “precise” groups or entire communities by modifying care delivery systems, optimizing transmission through social networks, or instituting targeted policy or macroenvironmental changes that are different from one community to the next. Precision prevention often emphasizes the “how” (eg, the most cost-effective implementation approach) as much as the “what” (which behaviours to target) or the “why” (the biological mechanisms that mediate prevention effectiveness). We believe the nascent precision revolution can benefit both treatment and prevention alike. Three loci hold particular promise: mutual learning from each other’s research paradigms, sharing study designs, and transdisciplinary integration through innovative data analysis and modeling.

[68] Gmeinder, M., Morgan, D., Mueller, M., 2017. *How Much Do OECD Countries Spend on Prevention?* OECD Health Working Papers, No 101. Paris: OECD Publishing. <http://dx.doi.org/10.1787/f19e803c-en>

**Abstract:** OECD countries face the multiple challenges of rapidly ageing societies with the associated rise in chronic diseases and the ever-present threat from new or evolving communicable diseases. This is within the context of seeking better value for money from the health sector. While a growing body of evidence shows that many health promotion and disease prevention measures can improve health outcomes at relatively low cost, less has been documented – in an internationally comparable way – on how much countries actually invest in such activities and the drivers of prevention spending over the years. This is particularly pertinent in the context of fiscal sustainability and tight public budgets.

Using newly available data from across OECD countries, **this study examines the differences in spending on prevention both at an aggregate and detailed level.** This analysis **brings a fresh perspective and raises questions as to the optimal resource allocations within the sector.** Time series data is also scrutinized in conjunction with collated policy and public health developments from a number of countries to try to identify some of the drivers behind the observed prevention spending trends. In doing so, directions for further improvement in the underlying data as well as policy implications are discussed.

[69] Goetzel, R.Z., 2009. Do Prevention of Treatment Services Save Money? The Wrong Debate. *Health Affairs* 28(1): 37–41. <https://doi.org/10.1377/hlthaff.28.1.37>

Health improvements and cost savings are achievable by providing targeted, evidence-based, and cost-effective health promotion and disease prevention programs that reduce modifiable risk factors, often the cause of costly chronic diseases. Adopting commonsense health practices does not require expensive technology, medication, specialty training, or elaborate treatment facilities. Providing certain preventive services, mostly in clinical settings, does not save money, but neither do most medical treatments. The key question then, is what is the most cost-effective ways to achieve population health, and where to focus the resources to get the “biggest bang for the buck.”

[70] Greenland, P., Hassan, S., 2019. Precision Preventive Medicine—Ready for Prime Time? *JAMA Internal Medicine* 179(5): 605–606.

Prevention is one target for precision medicine. Predictive genetics-based risk scores should be compared with conventional measures, and should not be used in place of conventional measures until the evidence is established.

[71] Guerra, S. 2017. **Cancer Moonshot Musings Part 1: Precision Prevention**. Online: <http://sitn.hms.harvard.edu/flash/2017/cancer-moonshot-musings-part-precision-prevention/>

[72] Mattig, T., Chastonay P.A., 2017. **Switzerland's National Non-communicable Diseases Strategy**. *Annals of Chronic Disease* 2(1):1002

[73] Miller, G., Roehrig, C., Hughes-Cromwick, P., B., A.T., 2012. **What is Current Spend on Prevention as Compared to Treatment?** in *Prevention vs. Treatment: What's the Right Balance?* Eds. Halley S. Faust and Paul T. Menzel.

In this chapter we address the need for metrics and methods to measure spending on prevention as a basis for understanding the current distribution of funds between prevention and treatment and to promote discussion regarding the amount that should be spent on prevention. We develop a taxonomy of prevention and produce an estimate of the portion of the National Health Expenditure Accounts (NHEA) that is devoted to prevention activities. Our estimate suggests that roughly 8.6 percent of expenditures captured by the NHEA are devoted to prevention. The difference between this estimate and earlier estimates (that suggest that as little as 1 to 2 percent of national expenditures are devoted to prevention) indicates a need for a dialog on what activities should be included in the estimate and on methods for establishing the magnitude of the associated expenditures. In addition to developing this expenditure estimate, we sketch preliminary ideas for extensions of this work that include methods to expand the estimate beyond the NHEA, and methods to explore the relationships in the cost effectiveness of alternative allocations of expenditures among prevention interventions, treatment interventions, research into new preventive measures, and research into new treatments.

[74] McGrath, C., Palmarella, G., Solomon, S., Dupuis, R., 2017. **Precision prevention and public health**. *CPHI Data Briefs* 4. Online: [https://repository.upenn.edu/publichealth\\_databriefs/4](https://repository.upenn.edu/publichealth_databriefs/4)

The authors present a precision prevention framework to assess the effectiveness of various interventions.

[75] Rose, G. 2001. **Sick individuals and sick populations**. *International Journal of Epidemiology* 30: 417—432.

**Prevention Paradox:** "A preventive measure that brings much benefit to the population offers little to each participating individual." A large number of people at a small risk might give rise to more cases of disease than the small number at high risk.

[76] Russell, L.B., 2012. **Prevention vs. Cure: An Economist's Perspective on the Right Balance** in *Prevention vs. Treatment: What's the Right Balance?* Eds. Halley S. Faust and Paul T. Menzel. <https://doi.org/10.1093/acprof:oso/9780199837373.003.0003>

Three questions are addressed in this chapter: Does prevention reduce medical costs? Does the U.S. spend too little on prevention? Should it spend more (and if so, on what)? Since much of the evidence comes from cost-effectiveness studies, a brief explanation of how cost-effectiveness analysis is used to evaluate medical interventions is provided. The evidence, from hundreds of studies published over the last four decades, shows that most preventive interventions add more to medical spending than they save, even as they improve health. With prevention, as with so much else, it costs more to get more. Moreover, the U.S. spends considerably more on prevention than commonly thought (see chapter 2 of this volume), even without considering the vast array of preventive activities outside the medical sector. Prevention is not a solution to the healthcare cost problem. Each intervention needs to be evaluated individually and the goal should be to find the most effective mix of health services, the one that makes the best use of our resources to improve health and extend life, whether through prevention or treatment.

[77] Song, M., Giovannucci, E., 2016. **Preventable Incidence and Mortality of Carcinoma Associated with Lifestyle Factors Among White Adults in the United States**. *JAMA Oncology* 2(9):1154—1161. <https://doi.org/10.1001/jamaoncol.2016.0843>

The study shows that a substantial cancer burden may be prevented through lifestyle modification. Accordingly, primary prevention should be a priority for cancer control, despite recent findings that random mutations during stem cell divisions are a major contributor to human cancer.

**[78] Thomas, D.C., 2017. What Does “Precision Medicine” Have to Say About Prevention. *Epidemiology* 28(4): 479—483.**

Population-wide vs. targeted intervention. Although the genomics revolution has potential to transform prevention in addition to treatment, we still have a long way to go to more effectively identify who should be targeted. Environmental interventions like air pollution regulation cannot be targeted to any subgroup, genetic, or otherwise. Others, like antismoking campaigns, exercise, or diets, could in principle, but this might not be practical or cost efficient. The most efficient would be to identify those at high genetic sensitivity to avoidable exposures. But simply predicting genetic risks is not sufficient: we need evidence of G × E interaction. We should not let the enthusiasm for personalized medicine distract us from opportunities for classical public health approaches to prevention.

**[79] Trein, P., 2018. *Healthy or Sick? Coevolution of Health Care and Public Health in a Comparative Perspective*. Cambridge: Cambridge University Press.**

**Abstract:** The book analyses how policies to prevent diseases are related to policies aiming to cure illnesses. It does this by conducting a comparative historical analysis of Australia, Germany, Switzerland, the UK, and the US. It also demonstrates how the politicization of the medical profession contributes to the success of preventative health policy. The book argues that two factors lead to a close relationship of curative and preventative elements in health policies and institutions: a strong national government that possesses a wide range of control over subnational levels of government, and whether professional organizations (especially the medical profession) perceive preventative and non-medical health policy as important and campaign for it politically. The book provides a historical and comparative narrative to substantiate this claim empirically.

**[80] Trein, P., & Wagner, J., 2019. Four governance challenges for personalized health : a systematic literature review. [http://www.philipptrein.com/wp-content/uploads/2019/10/PH\\_Governance\\_Challenges.pdf](http://www.philipptrein.com/wp-content/uploads/2019/10/PH_Governance_Challenges.pdf)**

**Abstract:** Personalized health (PH) is an important driver for the advancement of public health, health care and medicine. In recent years, research around personalized health services has advanced and scholars have explored new possibilities for integrating personalized care and prevention into existing health systems. Against this background, it is important for researchers and policymakers to know about the governance challenges, i.e., the coordination of stakeholders to develop adequate public policies, related to PH. This paper presents the results of a systematic literature review on the governance of PH. In using a PRISMA protocol search, we analyze publications dealing with governance and policy making in the field of PH. We conducted two search iterations in Web of Science. The first one consists of 47 publications that constitute the main corpus of papers for this review, which we examine in detail. Through a second search, we have added 98 additional papers that complement the main corpus. Our analysis demonstrates that governing PH requires to address four interrelated governance challenges that concern policymakers and practitioners alike. The key issues that we highlight are about (1) harmonizing research infrastructures to augment the possibilities for collaborative research; (2) building trust among citizens to participate; (3) creating regulatory frameworks that organize collaboration and protect individuals against discrimination; and (4) integrating the results of genomic research in health systems to provide better health care and prevention.

**[81] Turnbull, C., Sud, A., Houlston, R.S., 2018. Cancer Genetics, Precision Prevention and a Call to Action. *Nature Genetics* 50: 1212—1818.**

The authors argue that “the time is nigh for the initiation of national population-testing programs to identify carriers of first-wave gene mutation.” denouncing the procrastination of waiting additional future ‘new genes’ to ‘add value’ to the population-screening proposition. This is because, “ ‘genetic economics’ of frequency penetrance clearly indicates that focused identification of carriers of first-wave-gene mutations is most impactful for cancer control. ... [And.] to fully deliver a precision prevention program, long-term, large-scale mutation studies that capture longitudinal clinical data and serial biosamples are required. ... Although great progress has already been made on the characterization and clinical applications of these genes, to fully deliver their value in cancer prevention, substantial and sustained investment in research platforms will be required to deliver the necessary long-term epidemiological, biological and clinical studies.”

**[82] Vineis, P., Wild, C.P., 2017. The Science of Precision Prevention of Cancer. *Lancet Oncology* 18: 997—998.**

Precision medicine has been proposed as a new frontier to tackle the emergence of non-communicable diseases. According to one definition, “Precision medicine is a revolutionary approach for disease prevention and treatment that takes into account individual differences in lifestyle, environment, and biology.” (NIH) Prevention is mentioned side-by-side with treatment. However, what is precision prevention? How can it be conceptualised? In this comment, we raise some key considerations relating to the development of a science of precision prevention of cancer.

**[83] Wallace, R.B., 2011. The Evidence Base for Clinical Prevention: An Incomplete Story. <https://doi.org/10.1093/acprof:oso/9780199837373.003.0004>**

In this chapter, I provide an overview of the nature and completeness of scientific evidence for clinical preventive interventions. While great strides have been made in disease prevention, there are many gaps in our ability to provide preventive modalities because of: (1) absent or incomplete understanding of the causes of many important conditions, (2) our lack of understanding of the impact of community vs. individual health behavior factors that might best impact factors that have been identified to cause disease, (3) poor understanding of where to administer interventions, (4) lack of effective administration techniques, (5) the unknown effectiveness of combined prevention modalities, and (6) limited understanding of providing prevention in the face of existing illness, including the unknown adverse effects of various prevention modalities in combination with medical treatments. Further, even when effective interventions are available, this effectiveness is only partial because of lack of effective methods and important logistical challenges in delivering them to properly targeted individuals and populations. While important research continues, there are still great gaps and limitations in attaining optimal population prevention, limitations that must be better understood when considering the apportioning of health system resources to clinical prevention versus treatment.

**[84] Institute of Medicine (US) Roundtable on Evidence-Based Medicine. Eds. Yong PL, Saunders RS, Olsen LA, The Healthcare Imperative: Lowering Costs and Improving Outcomes: Workshop Series Summary. Washington (DC): National Academies Press (US); 2010. 6, Missed Prevention Opportunities. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK53914/>**

- The price paid for not preventing diseases
- Cost savings from primary and secondary prevention
- Tertiary prevention and treatment costs

**[85] Smith et al., 2016. Using Genetic Technologies to Reduce Rather than Widen, Health Disparities. *Health Affairs* 35(8): 1367—1373. doi: 10.1377/hlthaff.2015.1476**

Evidence shows that both biological and nonbiological factors contribute to health disparities. Genetics, in particular, plays a part in how common diseases manifest themselves. Today, unprecedented advances in genetically based diagnoses and treatments provide opportunities for personalized medicine. However, disadvantaged groups may lack access to these advances, and treatments based on research on non-Hispanic whites might not be generalizable to members of minority groups. Unless genetic technologies become universally accessible, existing disparities could be widened. Addressing this issue will require integrated strategies, including expanding genetic research, improving genetic literacy, and enhancing access to genetic technologies among minority populations in a way that avoids harms such as stigmatization.

## Financing Curative Therapies

**[86] Barlow, J.F., Yang, M., Teagarden, J.R., 2019. Are Payers Ready, Willing, and Able to Provide Access to New Durable Gene Therapies? *Value in Health* 22(6): 642—647. doi:10.1016/j.jval.2018.12.004.**

**Abstract:** Access to new gene therapies may be impacted by payer ability to absorb the cost of coverage. Variation exists in awareness of new gene therapies and level of incorporation of new costs into future plan coverage. The sustainability of current financing mechanisms varies by payer segment, profitability, and size; smaller plans and Medicaid are likely to be impacted first. Government reinsurance, commercial reinsurance, and stop-loss insurance backstop current reimbursement models, dampening the need for urgent action. The tipping point for action may be severe premium inflation in stop loss and reinsurance. Payers are open to innovative financing models that improve financial predictability and reward clinical performance.

[87] Hlávka, J.P., Mattke, S., Wilks, A., 2019. **The Benefits of Deferred Payment in Congestive Heart Failure Gene Therapy.** Rand Corporation. [https://drive.google.com/file/d/10KVYyKQEHWKL0VP2B0UF9u7S\\_0rHMbof/view](https://drive.google.com/file/d/10KVYyKQEHWKL0VP2B0UF9u7S_0rHMbof/view)

[88] Mattke, S., Liu H.,S., Hoch, E., and Mulcahy A., W., 2016. **Avoiding the Tragedy of the Commons in Health Care: Policy Options for Covering High-Cost Cures.** Santa Monica, CA: RAND Corporation. <https://www.rand.org/pubs/perspectives/PE190.html>.

**Abstract:** In this Perspective, Mattke and his colleagues discuss the risk that strategic behavior by health insurers could unravel the market for curative therapies for chronic diseases. Because the cost of these cures is front-loaded but the benefits accrue over time, insurers might attempt to delay treatment or avoid patients who require it, in the hope that they might change insurers. The authors discuss policy options to remedy this potential free-rider problem through alignment of incentives at the patient level, coordination among payers, and government intervention. They present a framework to analyze policy options and real-world case studies. While implementing those policy options is far from easy, stakeholders need to collaborate in order to establish equitable mechanisms that fairly distribute the cost and benefits of high-cost cures.

[89] Mattke, S., and Hoch E., 2015. **Borrowing for the Cure: Debt Financing of Breakthrough Treatments.** Santa Monica, CA: RAND Corporation. <https://www.rand.org/pubs/perspectives/PE141.html>.

**Abstract:** Recent market entries of breakthrough pharmaceutical products have reignited the debate about the affordability of high-priced drugs for public and private payers worldwide. Payers had voiced concerns about such drugs before but, faced with a possible outcry of patients and advocates, grudgingly accepted them. But as more high-cost drugs reach the market and treat more-prevalent conditions, medical professionals and government ministers have complained that this "blank check" might not be sustainable. Concerns about short-term budget impact have led countries to restrict access to expensive drugs, even when they met cost-effectiveness criteria and could lead to long-term savings. This paper offers a research-grounded perspective on innovative financing mechanisms to facilitate access to expensive yet highly effective breakthrough medical treatments. The authors outline the scope of the problem; describe several policy and market options, including bond financing and linking repayment to real-world value generation; and describe real-world applications.

[90] MIT NEWDIGS, 2019. **Paying for Cures. FOCUS project.** <https://www.payingforcures.org/>

Emerging classes of durable therapies with short (sometimes single dose) treatment regimens and lasting benefits create significant healthcare financial challenges. One key challenge is the heightened importance of uncertainty regarding benefit level at the time of treatment. FoCUS has developed solutions to durable therapy financial challenges, including milestone-based contracts, performance-based annuities and an Orphan Reinsurer and Benefit Manager (ORBM). These solutions require changes to many existing policies and practices for implementation.

[91] MIT NEWDIGS, 2019. **Precision Financing Solutions for Durable / Potentially Curative Therapies. White Paper 2018 F201-V023.**

In light of the emergence of a few broad financing and reimbursement solutions for durable/potentially curative therapies in the US, this white paper emphasizes that each solution must be tailored to the specific context. These alternative mechanisms are discussed in some depth and illustrated by means of several use cases.

[92] Salzman, R., Cook, F., Hunt, T., Malech, H.L., Reilly, P., Foss-Campbell, B., Barrett, D., 2018. **Addressing the Value of Gene Therapy and Enhancing Patient Access to Transformative Treatments.** *Molecular Therapy* 26(12): 2717—2726. <https://doi.org/10.1016/j.ymthe.2018.10.017>

**Abstract:** Although high upfront costs for the high value of gene therapy have resulted in concerns about sufficient reimbursement to allow patient access to these therapies, the significant benefits of gene therapies will not be realized unless patients have access to them. Stakeholders are discussing these issues, and the payment models being developed for the newly approved gene therapies provide an early indication of the flexibility that will be needed from treatment manufacturers, payers, and policy makers to optimize patient access. Maximizing patient access to effective gene therapies is one integral part of the overall mission of the American Society of Gene and Cell Therapy, along with maximizing the quality of therapies and minimizing their costs. Several use cases are also presented.