Precision Reimbursement for Precision Medicine: Using Real-World Evidence to Evolve From Trial-and-Project to Track-and-Pay to Learn-and-Predict

Hans-Georg Eichler1,*, Mark Trusheim2, Brigitte Schwarzer-Daum1, Kay Larholt2, Markus Zeitlinger1, Martin Brunninger3, Michael Sherman4,5, David Strutton6 and Gigi Hirsch2

Basic scientists and drug developers are accelerating innovations toward the goal of precision medicine. Regulators create pathways for timely patient access to precision medicines, including individualized therapies. Healthcare payors acknowledge the need for change but downstream innovation for coverage and reimbursement is only haltingly occurring. Performance uncertainty, high price-tags, payment timing, and actuarial risk issues associated with precision medicines present novel financial challenges for payors. With traditional drug reimbursement frameworks, payment is based on an assumed randomized controlled trial (RCT) projection of real-world effectiveness, a “trial-and-project” strategy; the clinical benefit realized for patients is not usually ascertained ex post by collection of real-world data (RWD). To mitigate financial risks resulting from clinical performance uncertainty, manufacturers and payors devised “track-and-pay” frameworks (i.e., the tracking of a pre-agreed treatment outcome which is linked to financial consequences). Whereas some track-and-pay arrangements have been successful, inherent weaknesses include the potential for misalignment of incentives, the risk of channeling of patients, and a failure to use the RWD generated to enable continuous learning about treatments. “Precision reimbursement” (PR) intends to overcome inherent weaknesses of simple track-and-pay schemes. In combining the collection of RWD with advanced analytics (e.g., artificial intelligence and machine learning) to generate actionable real-world evidence, with prospective alignment of incentives across all stakeholders (including providers and patients), and with pre-agreed use and dissemination of information generated, PR becomes a “learn-and-predict” model of payment for performance. We here describe in detail the concept of PR and lay out the next steps to make it a reality.

From repurposing therapies based on a patient’s genetic profile1 to bespoke gene therapies and platform technologies for individual patients,2,3 upstream scientists and drug developers are accelerating innovations toward the goal of creating the right treatment for the right patient to be delivered at the right time and at the right site of care. The hoped-for benefit of these achievements are precision medicines that respond to the specific pathobiology of individual patients which, in turn, should lead to larger, more certain effect sizes compared to the one-size-fits-all drugs from the statin-era and even the current biological treatments, such as anti-TNF biologics and JAK inhibitors.4,5

Regulators are also innovating with the European Medicines Agency (EMA) introducing a Joint Action Plan for Advanced Therapeutic and Medicinal Products,6 and the Adaptive Pathways approach for early and progressive patient access to medicines.7 Similarly, the US Food and Drug Administration (FDA) has leveraged existing tools, such as Accelerated Approvals and Breakthrough Designation and with the 21st Century Cures Act introduced the Regenerative Medicine Advanced Therapy, created the Oncology Center of Excellence to enable a more unified, collaboration and patient-centered environment for cancer drugs, especially precision medicines that require coordinated therapeutic and diagnostic reviews.8 The FDA is also addressing the emerging needs of bespoke individualized therapies with new manufacturing guidance envisioning consortium-based development platforms.9,10

Payors are concerned about the wave of new treatments they will be asked to reimburse that have followed regulatory pathways designed to get patients access to innovations sooner, but require continued evidence generation post-launch. Payors acknowledge the need for change, especially for precision medicines and their companion diagnostics, but downstream innovation for coverage, reimbursement and patient access to novel treatments is only now, and haltingly, occurring.

Against this background, we here describe the concept of “precision reimbursement” (PR)11–14 to enable drug payments based

---

1Medical University of Vienna, Vienna, Austria; 2Massachusetts Institute of Technology Center for Biomedical Innovation, Cambridge, Massachusetts, USA; 3Dachverband der Sozialversicherungsträger, Vienna, Austria; 4Point32Health, Wellesley, Massachusetts, USA; 5Department of Population Medicine, Harvard Medical School, Boston, Massachusetts, USA; 6Merck & Co., Inc., Kenilworth, New Jersey, USA. *Correspondence: Hans-Georg Eichler (hgeichler@gmx.net)

Received February 25, 2021; accepted October 22, 2021. doi:10.1002/cpt.2471
on actual patient value received rather than what the healthcare system value hoped for. PR also aims to create evidence to target therapeutic regimens to more precise subpopulations for dosing, comorbidity management, and core response based on molecular, clinical, socioeconomic, or other factors, as well as combinations and sequences of treatments. PR more naturally considers longitudinal patient journeys within a disease.

Central to our argument is the notion that generation of real-world evidence (RWE) utilizing robust real-world data (RWD) will be the basis for PR. We also elaborate how RWE, coupled with the use of advanced analytics, including artificial intelligence (AI) and machine learning (ML), and end-user agreements will enable the move from conventional payment schemes, including simple track-and-pay forms of outcome-based payments, to creative learn-and-predict modes of PR that will not only help mitigate payer risks but at the same time improve patient outcomes by way of continuous learning and adaptation of practice pathways. Finally, we propose concrete actions by different stakeholders to enable PR.

**TRIAL-AND-PROJECT REIMBURSEMENT FRAMEWORKS**

Traditional drug reimbursement frameworks mostly evolved during the “blockbuster” era.15 Under these frameworks, the clinical benefit and effect size derived from (usually) randomized controlled trials (RCTs) that had been primarily designed for regulatory review, become the starting point for value assessment, price negotiations, and the definition of treatment-eligible populations (i.e., the population for which the drug cost will be covered or excluded by the payor). Once a price and population have been agreed, the product is paid for on a per-patient basis. Sometimes, safeguards, such as step-through therapy and pre-authorization requirements are put in place by payors.16 Of note, the treatment outcome is generally not recorded or evaluated ex post for the purpose of reimbursement, although, in some limited cases, payors have required evidence.

Relying on such conventional payment frameworks is feasible for drugs with large target populations where clinical benefit can be confidently estimated ex ante (i.e., before market launch), based on average effect sizes observed in RCTs. However, even in the presence of high-quality RCT evidence, this framework relies on the critical assumption that the external validity of RCTs is adequate and relevant to the target payor membership; this means that effects observed in a constrained research-setting (“efficacy”) will project the therapeutic benefit realized in the real-world setting of usual patients and usual care (“effectiveness”). When the clinical benefit realized for patients is not ascertained ex post, this payment framework bases drug reimbursement on an assumed RCT projection of real-world effectiveness data; hence, we consider it a “trial-and-project” strategy.

External validity of RCTs is affected by a range of factors, including how well the RCT sample matches the real-world patients, on-trial adherence and patient management relative to the real world, and outcome measures (e.g., reproducibility of complex scales or length of follow-up).17 Experience shows that external validity of trials across many therapeutic areas may be less than optimal or difficult to assess,18 giving rise to an efficacy-effectiveness gap,19 where RCT efficacy many times are not fully realized in clinical practice. Hence, in many cases, the payors’ trial-and-project strategy may not deliver, resulting in unnoticed opportunity cost; the risk then falls on the payor.

**NEW THERAPIES CREATE CHALLENGES FOR TRADITIONAL HEALTHCARE REIMBURSEMENT**

Reliance on average results from RCTs for pricing and access will become even more problematic in the context of precision medicine when, due to small numbers of patients available and/or ethical considerations, RCTs may not be feasible or are so small that projections to real-world populations effectiveness creates such large confidence intervals that a priori average results are not useful for value determination. Measuring effect size in precision medicine can be additionally complicated by uncertainty in durability of effect and for individualized treatments.3

Innovative precision medicines often come with additional challenges for payors: price tags to match, nonconventional administration schedules or treatment settings, and a range of uncertainties unresolved by their regulatory-oriented clinical trials. In addition, these therapies may serve significant underserved populations whose seeking of relief may create financial tsunamis for payors.20 Paradoxically, innovations for ultra-rare diseases can also create financial challenges for smaller payors due to their actuarial volatility. Furthermore, high price tags and limited types of “traditional” evidence may create conflict by limiting payors’ willingness to cover drugs in populations that were not explicitly studied but where there may be a reasonable likelihood of a positive response based upon the underlying biology. Rare, expensive events make budgeting difficult in small populations.

The development of cell- and gene-based therapies raises the possibility that (rare) diseases with severe unmet need may be significantly slowed down or cured after a single course of treatment. These therapies represent another foreseeable reimbursement challenge to current healthcare systems: upfront cost can be substantial and is often incurred all-at-once, but patient benefits are accrued over a longer period. Durability could extend for years or even a lifetime but may be unknown at the time of initial access discussions. Depending on healthcare environment, patients may move from payor to payor, so the benefit may occur in another payor when the original payor had paid the claim. This disrupts the normal payment paradigm for chronic treatments for chronic diseases, wherein reimbursement occurs in parallel with the recognition of benefits.21 However, this is not different from many other (non-drug) medical interventions with evidence gaps.

Thus, performance uncertainty, payment timing, and actuarial risk issues converge to present novel financial challenges for healthcare payors.14 Unsurprisingly, payors have been increasingly wary of covering for such drugs within their traditional trial-and-project frameworks.21 Their reluctance creates obstacles for timely patient access to precision medicines.

**TRACK-AND-PAY REIMBURSEMENT FRAMEWORKS**

In order to get a better grip on uncertainties about a drug’s performance and to mitigate the resulting financial risk, manufacturers and payors devised the concept of what we term “track-and-pay” frameworks. Such contractual arrangements became known...
under a range of different names, including pay for performance, performance-based managed entry agreements, value-based pricing, or risk-sharing agreements. (For detailed description and taxonomy of these arrangements, please refer to Wenzl et al.\textsuperscript{21}.) Whereas these arrangements may vary considerably from one case to the next (e.g., focus on population vs. patient-level), they are all based on a track-and-pay paradigm (i.e., the tracking of a pre-agreed treatment outcome which is linked to financial consequences).

The financial challenges that track-and-pay arrangements seek to address include:

- **Performance Risk**: At the time of initial pricing and reimbursement (P&R) negotiations, the net clinical benefit for any particular patient is uncertain, as is the duration of clinical benefit (e.g., for cell and gene therapies); therapeutic effects could wane quickly or extend for years or possibly even a lifetime. A system that would better distribute risk would adjust reimbursement for the actual patient value received, rather than provide a fixed amount for an expected patient benefit.
- **Payment Timing** (for durable treatments): Current healthcare systems are mostly organized around a “pay a constant price as you go” structure for treatments and therapies, not to cover one-time payments for durable therapies that offer multi-year benefits to patients.
- **Actuarial Risk**: The number of patients that will receive a high-priced therapy targeted to a very small group of eligible patients is hard to predict, which can result in financial volatility, especially for smaller insurance plans and self-insured employer health plans in the United States.

To mitigate those risks, track-and-pay makes use of a range of financial/contractual tools, including (multi-year) milestone-based contracts, performance-based annuities (for durable therapies), payment over time/installment financing, subscription, risk pools, and others. For an in-depth description of track-and-pay financial tools please refer to ref.\textsuperscript{22}.

This represents a major shift in the nature of the P&R framework: payment is not (or only partly) effected for the purchase of a drug and based on \textit{ex ante} assessment of effectiveness (as in the trial-and-project model) but for the clinical outcome that is observed after treatment.

One of the first and most controversial attempts at track-and-pay was the “UK multiple sclerosis risk sharing” arrangement, set up almost 20 years ago by the UK National Health Service.\textsuperscript{23} The scheme ran into a number of problems, was not generally considered a success, and raised the issue whether a definitive RCT would have been more valuable in terms of the evidence generated.\textsuperscript{24} The case may have contributed to a lack of enthusiasm for track-and-pay agreements; it also illustrates the opportunity for conducting some form of value of information analysis, which could inform the choice of future evidence generation (RCT vs. RWD) and payment approaches.

To date, performance-based Managed Entry Agreements in Europe and Asia remain rare and experimental.\textsuperscript{25} In the United States, only 10 out of 50 State Medicaid Plans even have authorization from the Centers for Medicare and Medicaid Services (CMS) to pursue Value-Based Purchasing agreements for prescription drugs (although this does not necessarily affect private payors). A recent Medicaid rule change hopes to expand that to all 50 states through a simplified process leveraging the current Medicaid Drug Rebate Program, but will not be operational until 2022 at the earliest.\textsuperscript{26} Similarly, US commercial payors and drug manufacturers have been cautious in implementing innovative payment models, however, there continues to be interest by many large payors to engage in these outcome-based payment models. A recent payor survey regarding new payment models for durable cell and gene therapies whose list prices can exceed $2 million,\textsuperscript{27} indicated that while most (60%) were likely to change their approach, 86% had not begun implementing.\textsuperscript{28}

Overall, the track record of such frameworks in several healthcare environments has been mixed; they are perceived as not addressing the issue of opportunity cost if there is fundamental mis-pricing of the clinical value, as well as being administratively burdensome, lacking transparency, and anticipated results are often not forthcoming or difficult to interpret.\textsuperscript{21} Issues of data infrastructure, data quality, and governance have hampered the execution of early track-and-pay agreements. An adequate data infrastructure that enables generation of robust, actionable clinical data is a sine qua non for the success of these types of contractual arrangements; so are governance rules for data access that address issues of consent and personal data protection. These exigencies have been extensively debated and assessed\textsuperscript{29,30} and will not be discussed here.

In spite of a number of obstacles, some track-and-pay arrangements have been successful in enabling timely access for patients to novel treatments and mitigating payors’ risk.\textsuperscript{31,32} Healthcare payors, like the Italian National Health Care System, with long-standing experience in the generation and use of RWE obtained from disease registries specifically for P&R purposes, report significant savings from their forms of track-and-pay agreements.\textsuperscript{33}

We are optimistic that current efforts to further develop the foundations of the health data ecosystem will increasingly enable the data generation side of reimbursement schemes based on clinical outcomes. The FDA Sentinel system has become established as a federated data collection capability across the disparate US healthcare collection of claims and medical record systems. Although constructed primarily for drug safety surveillance purposes, the FDA’s current strategic vision for it has expanded to also include “real-world data (RWD) sources used to evaluate medical product performance.”\textsuperscript{34} Another example is the Center for International Blood and Marrow Transplant Research (CIBMTR) outcomes tracking capability for cellular therapies. Originally established for stem cell transplants, it now is on a path to track 90% of CAR-T cellular treatments within its US network of transplant centers.\textsuperscript{35} To better support track-and-pay structures, a plethora of new private sector solutions have emerged in the United States, especially for cell and gene therapies.\textsuperscript{36} Although only the latter directly support track-and-pay, in combination they demonstrate the improving scale, scope, and efficiency of RWD platforms from single product registries to multiple therapy and therapeutic area capabilities integrating numerous fragmented sources.
However, whereas some of the hurdles encountered with early track-and-pay frameworks are solvable as experience accumulates and infrastructure improves, others are inherent to this approach and cannot be easily addressed, even when learnings from past failures are applied. We argue that inherent weaknesses of the track-and-pay approach include (i) the potential for misalignment of incentives, (ii) the risk of channeling of patients, and (iii) a failure to use the RWD generated to enable continuous learning about the treatment.

Lessons learned from over 2 decades of experience with “pay for performance” incentive models in clinical care (although not specifically focused on drug reimbursement) suggest they may be ineffective and, in some cases, destructive, when “implemented in a near-scientific vacuum.”

Without a deeper understanding of the clinical and socioeconomic drivers of variability, well-intended, outcomes-oriented compensation models can harm sicker and poorer patients and lead to poorer outcomes overall. The observed negative consequences are partly the result of factors outside providers’ control, but past experience suggests that misalignment of incentives across payors, providers, and patients plays a major role.

Misalignment of incentives results in behavioral changes of individual actors in the healthcare system that is prone to lead to the channeling of patients to or away from certain providers or treatments, with potentially detrimental effects for patients. In the context of track-and-pay schemes for precision medicines, misalignment could result from various sources within the coverage process, including co-pay (for patients), “buy and bill” drug markups (e.g., in some US hospital settings), contracts with financial penalties or bonuses at the hospital, practice, or individual physician level tied to quality targets, budget caps set by care type or care modality (for payers), and others.

May track-and-pay agreements for drug treatments also be susceptible to channeling of patients?

We recall that collection of reliable RWD and appropriate adjudication of events (where needed) are necessary for any outcome-based payment framework but are not sufficient to establish a causal relationship between treatment and outcome in an individual patient. This is because the observation of a (favorable) outcome in a given patient cannot answer the important question about the “counterfactual” (i.e., “what would have happened if this patient had received no treatment or if they had received a different treatment known to be effective?”). In some black-and-white instances, this may not be an issue. Consider a hypothetical genetic disorder that is well known to lead to certain death in the first 6 months of life in all untreated newborns while all children treated with a new gene therapy survive and thrive beyond their fifth birthday. All else being equal, it seems trivial to conclude that the treatment was effective. By contrast, consider a condition where a clinical outcome of interest is characterized by high interindividual variability and a high degree of fluctuation over time. In such “messy” scenarios, the difficulty arises when the treatment in question does not produce a complete and definitive cure but, for example, 20–30% improvement. An effect of that magnitude may well be relevant in the eyes of patients, but simply tracking the outcome in a few patients will not allow one to distinguish between a true treatment effect and the play of chance or basic fluctuation of disease severity. It follows that, even with adequate tracking of outcomes, payors will find themselves paying for some patients who experience little or no benefit from the treatment. This realization may be disappointing, but the issue is neither new nor should it be considered a showstopper. Under the conventional trial-and-project model, payors have always spent a considerable share of their funds for nonresponses, given the less than perfect effect sizes of most blockbuster drugs (e.g., the size of absolute risk reductions for cardiovascular preventions).

Hence, it is unrealistic to expect that any form of track-and-pay arrangement could fully eliminate payment for patients who experience little or no benefit from the treatment but it may improve the ratio of payment for patients experiencing treatment success vs. patients without treatment success. If this came to pass, payors would improve value-for-money and mitigate their financial risk. These types of agreements may also encourage payors to be less restrictive than they might otherwise be, for example, in cases where it is not entirely clear whether a specific patient meets the criteria for reimbursement.

However, that desired effect may be undercut in the presence of significant channeling of patients. In epidemiology, one form of this phenomenon is described as “confounding by indication” and may impact the robustness of comparative effectiveness analyses. In the current context, we define channeling of patients as the conscious or unconscious behavior in the healthcare system that results in certain (subgroups of) patients being directed toward or away from a given treatment, for reasons that are not intended by the pre-agreed outcome-based scheme. In some cases, channeling of only the most severe patients to a new treatment can result in seeing worse outcomes then the RCT data, leading to the misinterpretation that the innovation does not work as well as the RCT suggested. In other situations, channeling has been shown to produce negative consequences in health care when, for example, providers are incentivized to achieve certain outcomes for their patients. For outcome-based payment arrangements, channeling may lead to patients perceived to have a good prognosis and outcome to be preferentially prescribed a drug treatment, even when they might not need it, whereas patients with a poor expected outcome may not be prescribed the treatment. Thereby, some patients might be denied potentially beneficial treatment while payors get less than expected value for money. Simple track-and-pay contracts are not well-suited to minimize patient channeling.

Last, track-and-pay schemes are often not designed to use the RWD to generate RWE and to enable continuous learning about the treatment allocation process and the treatment effect. We consider this an inherent weakness because it wastes an opportunity to ensure optimal allocation of patients to the treatment and to refine general knowledge about benefits and risks of a drug.

PR intends to overcome the inherent weaknesses of simple track-and-pay schemes. In combining the generation of actionable RWD-generated RWE with prospective alignments of stakeholder incentives, PR becomes a learn-and-predict model of payment for performance.
THE CONCEPT OF PRECISION REIMBURSEMENT ENABLES LEARN AND PREDICT

We define PR as flexible, tailor-made contractual arrangements aligned among not only drug manufacturers and payors but also providers and patients that aim to address the specific exigencies of precision medicine. PR seeks to improve patient outcomes for appropriate treatment regimens; affordability for payors (public and private), providers, and patients; and the sustainability of innovation by manufacturers while continuously improving knowledge about the best use of a treatment in each patient’s context.

Precision Reimbursement pursues these goals by:

- Harnessing payment models to incentivize clinical use of therapies based on RWE to improve patient outcomes, enhance healthcare system sustainability, and account for value created by upstream innovation.
- Creating scalable PR models, based on iterative learning cycles, capable of implementing RWE findings while adapting to each finding’s characteristics and each stakeholder’s needs.
- Contributing RWD/RWE regarding the therapeutic use changes and outcomes.
- Rewarding RWD/RWE platforms for generating findings that inform treatment regimens by either direct financial support or through indirect mechanisms.

The elements of PR seek to align stakeholders by rewarding them for patient outcomes while concomitantly generating evidence to do so. PR focuses on a range of challenges, including financial challenges, definition of reimbursable population, data collection, effectiveness uncertainties, and behavioral uncertainties, as well as transparency and dissemination of learnings. PR can be conceptualized as an all-participant payment and reimbursement framework that spans beneficiary benefit design, provider budgets and reimbursement, payor treatment coverage and utilization management as well as drug contracting.

Key elements of reimbursement frameworks and the continuum from trial-and-project to track-and-pay to learn-and-predict are summarized in Table 1.

| Reimbursed population       | Effectiveness uncertainty | Behavior uncertainty | Incentives/disincentives | Data and evidence approach |
|-----------------------------|---------------------------|----------------------|--------------------------|----------------------------|
| Static coverage per label (or subset) | RCT projection, no ex post assessment | Over (under) prescribing and reimbursement | Driven by volume; per stakeholder | RCT and invoices/scripts |
| Static coverage per label (or subset) | Ex post outcome measurement and payment | Financial-motivated channeling with no mitigating actions | Drive by outcome; per stakeholder dyads | Siloed claims and medical records |
| RWE dynamically optimized within label | Baseline measurement plus ex post measurement | Evidence driven channeling with mitigating action | Driven by contextualized outcomes; aligned across stakeholders | Federated RWD and evidence generation |

The journey from bench to bedside normally progresses “from left to right” when depicted graphically (Figure 1).

Decisions and actions taken by companies to develop a given treatment, assessments, and licensing decisions taken by drug regulators, and P&R negotiations and decisions by healthcare payors are usually taken in sequential order. We argue that for PR to deliver its goals, planning must happen from right to left (Figure 1). It needs to start with a definition of what constitutes “successful” drug treatment. This is best defined by choosing a clinical end point that is both patient-relevant and sufficiently easy to observe and adjudicate. Arguably, the easiest end point would be survival (or all-cause mortality) at predefined milestones (e.g., annually) but, in many instances, functional end points may be needed, such as degree of vision impairment for genetic diseases of the eye, or a transfusion-free state for some types of hematologic gene therapies. We would expect biomarkers like laboratory-based end points or well-defined events like myocardial infarction to be more easily adjudicated than, for example, clinical rating scales or clinical progression of a disease but patients may advocate for more patient-relevant end points like health-related quality of life.

There is one caveat: if end points are specific to a drug manufacturer/payor dyad, then this will add inefficiency to the system. Providers will have to collect different end points depending on the drug and the payor; the resulting evidence will be inconsistent and therefore integration of evidence and learning will be impossible. The goal should be to agree on real-world clinical end points that are specific for a drug class/indication (e.g., disease activity scores in rheumatoid arthritis, HbA1c in diabetes, etc.) and therefore will be captured as part or routine care by the provider. We are hopeful that ongoing international efforts at standardizing outcomes measures may help improve technical efficiencies. Where legally possible, regulators could help catalyze broad agreement on a given end point (see below).

Building on an agreed end point, payors and the manufacturers need to agree on the key points of a future PR payment contract, including an outline of the RWD generation plan, as well as rules for end point adjudication.
Payor-manufacturer agreement is necessary but not sufficient to ensure alignment of all stakeholder interests and end-user inputs into the contract designs as well as the evidence planning will be key.\textsuperscript{44,45}

Patient preferences that affect treatment selection and adherence should be included as well as any associated patient disincentives from direct healthcare cost sharing (depending on healthcare environment) to out-of-pocket costs, such as travel to distant centers of excellence. Traditionally, some payment schemes use financial levers to encourage specific patient behaviors, such as using a high-value over a low-value drug; in a world of precision medicine, it is clear that what is high value vs. what is low value may be dynamic based upon one or more variables.

Addressing physician interests and incentives will be required to make PR a success. Under a PR contract, physicians will be at the frontline of RWD generation and bear the burden of above-normal documentation requirements.

Hence, every effort has to be made to reduce the need for additional documentation by making the patients’ electronic health records fit for purpose. Some payor organizations attempt to have medical registries planted on electronic health records coupled with patient consent for data analytics. This has the advantage of connecting specific registry data with longitudinal health data from the patient. Stand-alone RWD platforms for specific PR arrangements may be overly cumbersome for physicians in addition to being incomplete and having a conflictive ownership structure.

Physician interests also need to be considered to avoid inappropriate patient channeling. In some instances, physicians may be wary of perceived restrictions to their freedom to prescribe due to expected utilization management compliance or, where applicable, productivity targets. Hence, physician incentives, such as bonuses (where legally and administratively feasible) or exemption from pre-authorization requirements, should be built into the PR agreement.

Last, medical facility financial incentives arising from risk sharing (explicitly or implicitly through fixed annual budgets) to administrative costs from data reporting to inventory carrying costs need to be factored in.

Ideally, the planning process for PR should be drafted by the time pivotal clinical trials of a given product are started; having the RWD plan inform the design of pivotal premarketing trials would enable a continuum of learning from research setting to clinical practice setting by focusing on the same end point(s) of interest. Participation of drug regulators in the planning processes may be helpful to align evidence requirements and enable a single continuous development program, all the way to on-market utilization.

---

**Figure 1.** The road from bench to bedside vs. planning for precision reimbursement. The top part depicts the conventional road from bench to bedside, moving from left to right. The lower part seeks to illustrate that planning for precision reimbursement (PR) must move from right to left (i.e., starting with the end in mind). The planning starts with an agreement among stakeholders on an end point of interest that should be achieved by the drug (e.g., survival at predefined milestones, vision above a predetermined level for eye diseases, transfusion-free status for some hematologic conditions), followed by an agreement on a draft PR payment contract, a plan for RWE generation, and agreements on procedures for endpoint-adjudication, where needed. Finally, the pre-authorization clinical trials should be informed by the RWE generation plan, in order to enable a continuum of evidence from clinical trials to RWE. Note that deliberations and agreements on PR should ideally be in place before the pivotal premarketing trials are started (symbolized by the blue box joining the clinical development arrow around midway). P&R, pricing and reimbursement; RWE, real world evidence.
Generation of RWD

RWD have a long track record of use for safety evaluation of drug treatments. The example of Natalizumab illustrates the power of prospective collection of RWD to help identify and manage drug toxicity.46 RWD have also been used to demonstrate the RWE of drugs and for health economic analyses for many years. More recent efforts are exploring the use of RWD for the quantification of clinical benefit.47

The field is currently given a boost by the learnings from the coronavirus disease 2019 (COVID-19) pandemic: interrogation of patient baseline characteristics and outcomes of interest helped identification of clinical COVID-19 phenotypes, reflecting patient populations with different comorbidities, complications, and clinical outcomes. In turn, this information may help tailoring treatment regimens of hospitalized patients based on the clinical courses most likely for a patient given their a priori risk.48

Closer to the topic of PR, data held by Israel’s largest health-care organization were recently used to conduct an observational study to emulate a target trial of the causal effect of the BNT162b2 vaccine on COVID-19 outcomes49; newly vaccinated persons were matched in a 1:1 ratio to unvaccinated controls, enabling researchers to compare the outcomes in vaccinated persons with the “counterfactual” (as discussed above). The study has immediate relevance for PR: on the one hand, it demonstrates that good quality clinical and administrative claim level RWD held by a payor organization can generate important learnings about treatment effectiveness; on the other, it shows that simply tracking the outcome of interest in those patients who received a treatment is not enough to draw meaningful conclusions about the effects or the value of a given treatment, and may not be enough to detect patient channeling. What is needed is linkage of patient baseline variables with the clinical outcome and the construction of a suitable control group, ideally coupled to sensitivity analyses. This level of data generation, linkage, and analysis is not typically built into simple track-and-pay arrangements.

There is one additional challenge, though. The LEAPS consortium, a multistakeholder collaborative group organized by the Massachusetts Institute of Technology’s (MIT) NEWDIGS group has recently begun to apply advanced analytics to RWD, including both e-health records and insurance data, of patients with rheumatoid arthritis (RA) in the state of Massachusetts.

The pilot project had several objectives: (i) describe the RA patient population in Massachusetts using a 5 year cut of the All Payers Claims Database (APCD),50 (ii) describe patient journeys within RA, specifically with regard to therapy choices—selection, sequences, and switching, and (iii) create predictive algorithms and perform feature selection for RA Treatment Response. All of these objectives leveraged RWD to improve RA patient care. RA was chosen for this case study because there is a large number of therapeutic options but patient heterogeneity is high and responses to individual treatments are notoriously difficult to predict. Whereas the project showed that advanced analytics can be applied to RWD, it also showed that due to confounding and data gaps, observational hypotheses concerning different “archetypes” of patient journeys were difficult to map to and validate in RWD, patient cohort comparisons found limited differences, and time of follow-up was limited.51 The key learning from this pilot project was that the level of granularity of currently available RWD is likely insufficient to identify actionable opportunities even when the number of patients studied is large, at least in diseases characterized by high patient heterogeneity. For RWD to yield actionable RWE in the context of precision medicine (i.e., in small populations), we anticipate that the data sources need to be much more diverse and to include genomics and ideally other omics data. Such data are becoming available in a growing number of patients with diseases amenable to precision treatment but are not usually used for the purpose described above. Additionally, patient generated health data, socio-economic data, and social determinants of health will all add to the final predictive models.

Advanced analytics

We recall that data are not evidence. Organizations like the FDA have rightly defined and differentiated RWD from RWE52 and acceptance of RWE is a highly contentious issue in the scientific community. RWE, especially if nonrandomized, is more prone to confounding and bias and we re-emphasize that, wherever possible, RWE is to supplement and not supplant RCT evidence. However, where adequately powered RTCs are not feasible, treatment and reimbursement decisions need to be informed by RWE based on the best available analytic methods. AI and ML offer the potential to generate RWE and test hypotheses based on RWD53,54 with a view to optimize allocation of individual patients to a treatment that is likely best for them, or to detect or prevent inappropriate treatment channeling.

Various studies have developed ML models to predict treatment failure or to discover potential novel indicators of treatment failure. Sauer et al.55 created an ML model that identified relevant variables to treatment failure in tuberculosis and showed consistently high predictive performance. The significant features extracted that were associated with resistance to treatment may be used in improving routine care for patients. Advancements are concentrated on working toward increasing the clinical utility of ML to the delivery of regular patient care in the form of precision medicine.

ML models, even with no prior medical knowledge, can be leveraged for finding features/variables that may be correlated with, and/or contribute to, RA treatment response/failure. Building on this work, the MIT LEAPS team explored the potential to apply ML to RWD to identify clinically meaningful features associated with “responder” and “nonresponder” subpopulations. The team hypothesized, based on patient and physician input in LEAPS, that there are different “archetypes” of patient journeys that, if well-characterized, could provide useful insights to support shared clinical decision making about drug therapy selection, switching, sequencing, and stopping over time. Given the current lack of validated clinical predictive markers in RA, and, on average, only a 30% response to treatment with any biologic, such additional insights would be valuable to support prescribing decisions that provide earlier symptom relief, prevent further irreversible disease progression, and reduce payors’ costs for nonresponse.

Utilizing the APCD of Massachusetts and a previously validated administrative claims-based algorithm for response to medications
for RA, the LEAPS team applied a supervised ML approach to the RWD, designed to enable hypothesis generation related to subpopulations that are “responders” or “nonresponders” to specific product classes of RA therapeutics. Features, such as age group, gender, diagnosis codes, treatment codes, comorbidities, and procedures were extracted from the RWD sets and included in the model to predict RA treatment response. Upon applying the aforementioned ML models to perform classification, relevant and highly correlated features for treatment failure were extracted. The team implemented three ML predictive models, including Forward Stepwise Selection, Random Forest, and logistic regression with least absolute shrinkage and selection operator penalty (logistic LASSO) to the data. The models all performed relatively well with performance measures consistent with others published (e.g., Sauers et al.) despite the limitation of the administrative claims data and the sparseness of features.

The exercise has been unsuccessful in identifying actionable patient profiles but correctly confirmed previous analyses. This corroboration of prior analysis in an additional RWD set represents an important step toward the use of federated RWD and advanced analytics, both essential for catalyzing scalable approaches to learn and predict with greater economies of scale. The addition of clinical, genetic, and molecular data as well as advancements in high-throughput technologies and the quality of ML algorithms, will further strengthen the emergent predictive models.

Based on published and our own experience briefly described above, we submit that ML has reached a level of maturity that would allow it to be trialed in the context of payment contracts for above, we submit that ML has reached a level of maturity that would allow it to be trialed in the context of payment contracts for patients, including mitigation of patient channeling routes toward PR. Those payors who do not have a deep understanding of data analytics may remain skeptical of highly complex analyses. A more concerted and collaborative effort among payor organizations (where legally possible) could be a potential route toward PR. Those payors who do not have a deep understanding of data analytics may remain skeptical of highly complex PR approaches and may perceive the process to be skewed towards manufacturers’ viewpoints.

Second, payor organizations need to take steps to build the infrastructure and processes to utilize their own claims and health data and/or to partner with external organizations, such as academic centers, to query health data on their insured patients and help generate actionable RWE. Although some payer organizations may already be quite advanced at this, confidentiality, as discussed above, may limit general progress in the field. One benefit of collaborative approaches, such as that of the LEAPS consortium, is that added visibility and the potential for early wins will gain the attention of the many payors that have historically preferred to operate in the shadows after others have developed clear-cut solutions.

Manufacturers may also need to leave their comfort zone. As they have to become “co-financers of uncertainty,” the price (or rebates or installments) of a drug product at any given point in time will need to reflect uncertainties and must be allowed to fluctuate up or down over time in line with new information, and, in some instances, to vary from patient to patient. A PR scenario is truly a risk-sharing arrangement which may entail more uncertainty about future sales and revenues.

On a technical level, manufacturers will need to, at a minimum, mirror payors’ capacity and process building to enable successful negotiations of complex payment agreements. In a recent survey, US-payors expressed an expectation that where manufacturers
sought any form of PR, the onus was upon them to bring to payors that innovation, complete with clear plans for outcomes tracking and payment mechanics. 28 For the foreseeable future, at least, manufacturers will likely have to drive the transition to PR, while at the same time be willing to co-develop with payors some aspects of PR, such as RWD collection and analytics.

Providers (clinicians, tertiary care centers, community hospitals, outpatient centers, and more) are the primary generators of RWD and may in some cases support adjudication of events. Depending on healthcare environment, providers may need to be incentivized to play their part in PR. Besides these obvious roles, providers may need to support PR in another, less appreciated way: at the time of contract negotiation, some aspects of a PR contract, including timing of payments and thresholds of effectiveness, will need background data to contextualize the outcomes observed on-treatment. Ideally, such background information should come from (reasonably) comparable patients from the same or similar healthcare environments where the treatments are going to be applied. Hence, providers would be expected and need to be ready to also be the providers of extant data on natural history of the disease.

Although drug regulatory agencies have no role in PR, they can facilitate the evolution of PR by engaging with manufacturers, payors, and providers to discuss a postmarketing evidence generation plan that fulfills the information needs of all sides. Obvious candidates for such multistakeholder interactions would be drugs that are going through facilitated regulatory pathways, with extensive postapproval regulatory commitments. At present, payors see tension among available clinical trial results, the regulatory label, and parameters of performance-based contracting that manufacturers could bring. 58 Such disconnects are avoidable and can be addressed by planning from “right to left,” as discussed above and stylized in Figure 1. Some payor organizations are already open to such interactions with regulators 57 but participation of regulators will be required for end-to-end planning. 58 In so doing, regulators would not overstep their statutory role but fulfill their mission for public health—that is to enable access for patients to beneficial treatments.

Last, patient organizations and patient advocates, especially organizations dedicated to rare diseases, have a key role to play in advocacy, including for the use of patient health data for the specific purpose of PR. 59-61

Patients have the highest stakes in these developments, and may find that they are denied novel treatments unless their own data may be used to enable PR; it should be in the interest of patients and insurance policy holders to have their data leveraged by their public or private insurance body. Their advocacy needs to be balanced against safeguarding personal data protection and ensuring against discrimination based on diseases or needs for defined therapies. In the process, patient organizations may need to go up against overly narrow interpretations of data protection rules (or even advocating for legislative change, where necessary). That said, some patient advocacy groups, such as the Multiple Myeloma Foundation 62 and the Cystic Fibrosis Foundation 63 have been able to transcend these challenges and take a leadership role in collecting, curating, and managing valuable RWD repositories, fueling important therapeutic advances for their constituents.

Appropriate use of RWE may also help defuse the (sometimes heated) debate over statistical significance and clinical relevance between payors, manufacturers, and patients. Thus, patient advocacy groups need to be RWD-literate in order to become an objective and goal-oriented advisory body, especially with expensive products that produce only minimal clinical improvement.

Navigating different markets, legal, and administrative barriers

Depending on jurisdiction, even the best attempts from all stakeholders to implement PR may run into legal or administrative roadblocks. For example, in some countries with public healthcare systems, there are no legal provisions to allow for indication-based pricing, which may become relevant for precision medicines targeting different (sub-)indications. Another challenge to PR, specific to the United States, is the legally mandated Medicaid requirement for lowest price. Amending Medicaid Best Price regulations to support the adoption of PR has been identified as an urgent need. 64,65 We are aware that some aspects of PR may not work or need to work differently in some markets and for payers who may have different roles and objectives within their healthcare systems.

Building collaborative learning capabilities

Accelerating the evolution to learn-and-predict will require that we advance from thinking of RWD primarily for its utility in supporting individual, product-specific reimbursement transactions between a single payor and developer. Rather, PR must be powered by a learning health system where the latent knowledge within currently fragmented RWD is more fully exploited with greater efficiency and economies of scale. Building on emerging approaches of federated RWD architectures and leveraging advanced analytics, efficient RWE technical infrastructures are now within reach. The greatest challenge—and the greatest value—lies in aligning incentives across stakeholders in ways that are both patient-centered and economically sustainable for all parties.

CONCLUSIONS

There is little doubt that the upcoming wave of precision medicines coming to market will be associated with increasing complexity for the healthcare ecosystem, including payment for drugs. It is reassuring that recognition is growing among some payors that RWD capabilities are needed to efficiently implement solutions to enable patient access; awareness of this need is also gaining traction among other stakeholders. 58 We believe that some form of PR, as described here, will be the most promising avenue to achieving the goals of optimizing patient benefit and mitigating payor risk. From a technical perspective, the innovations required for the building blocks of PR, including enhanced RWD generation and analysis, are in place or within reach. However, stakeholders need to start addressing the strategic perspective: a collaborative approach to assembling the building blocks.

The evolution toward PR (and a learning healthcare system) is best orchestrated in a step-wise fashion, starting with dedicated pilot projects involving a coalition of willing stakeholders and well-selected product-indication pairs where implementation of the
concept seems feasible and will likely generate value. Now is the time to start the process.

ACKNOWLEDGMENTS
The authors thank Fiona Cai (MIT student) for her review of the advanced analytics section of the manuscript.

DISCLAIMER
The views expressed in this article are the personal views of the author(s) and may not be understood or quoted as being made on behalf of or reflecting the position of the organizations with which the author(s) is/are employed/affiliated.

FUNDING
No funding was received for this work.

CONFLICT OF INTEREST
D.S. owns shares of Merck & Co., Inc., Kenilworth, NJ, USA. M.T. reports other from MIT NEWDIGS consortium fees, during the conduct of the submitted work; other from Co-Bio Consulting LLC, personal fees from Merck & Co. and Novartis, outside the submitted work. G.H. and K.L. report other from MIT NEWDIGS consortium fees during the conduct of the submitted work. All other authors reported no competing interests for this work.

© 2021 The Authors. Clinical Pharmacology & Therapeutics published by Wiley Periodicals LLC on behalf of American Society for Clinical Pharmacology and Therapeutics.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

1. Wartman, L. & Cavallo, J.O. Without genomic sequencing, I would not be alive today. The ASCO Post <https://ascopost.com/issue/s/november-10-2018/without-genomic-sequencing-i-would-not-be-alive-today/> (2018). Accessed August 2021. Story of how Washington University genetics researchers identified the gene mutation driving the ALL (acute lymphoblastic leukemia) of their colleague Dr. Lukas Wartman to repurpose a kidney cancer to put the ALL into remission (wild-type FLT3 overexpression treated with sunitinib [Sutent]).

2. Kim, J. et al. Patient-customized oligonucleotide therapy for a rare genetic disease. *N. Engl. J. Med.* **381**, 1644–1652 (2019).

3. Tambauser, E. et al. Therapies for rare diseases: therapeutic modalities, progress and challenges ahead. *Nat. Rev. Drug Discov.* **19**, 93–111 (2020).

4. Eichler, H.G. et al. Randomized controlled trials versus real world evidence: neither magic nor myth. *Clin. Pharmacol. Ther.* **109**, 1212–1218 (2021).

5. Lautscham, G. & Mullner, S. Beyond oncology – precision medicine for autoimmune disease. Life science leader <https://www.lifescienceleader.com/doc/beyond-ontcology-precision-medicine-for-autoimmune-diseases-0001> (2017). Accessed August 2021.

6. European Commission DG Health and Food Safety and European Medicines Agency Action Plan on ATMPs. First published October 20, 2017, last revised July 10, 2020 <https://www.ema.europa.eu/en/documents/other/european-commission-dg-health-food-safety-european-medicines-agency-action-plan-advanced-therapy_en-0.pdf>. Accessed August 2021.

7. EMA website. Adaptive pathways <https://www.ema.europa.eu/en/human-regulatory/research-development/adaptive-pathways#:~:text=Adaptive%20pathways%20in%20medicine%20and,discussions%20on%20medicine’s%20development>. Accessed August 2021.

8. FDA Website. 21 Century Cures Act. Last updated January 1, 2020 <https://www.fda.gov/regulatory-information/sele selected-amendments-fdc-act/21st-century-cures-act>. Accessed August 2021.

9. Marks, P. & Witten, C. Toward a new framework for the development of individualized therapies. *Gene Ther.* <https://doi.org/10.1038/s41434-020-0143-y>. [e-pub ahead of print]

10. Woodcock, J. & Marks, P. Drug regulation in the era of individualized therapies. *N. Engl. J. Med.* **381**, 1678–1680 (2019).

11. Eichler, H.G. et al. From adaptive licensing to adaptive pathways: Delivering a flexible life-span approach to bring new drugs to patients. *Clin. Pharmacol. Ther.* **97**, 234–246 (2014).

12. Eichler, H.G. et al. Adaptive licensing: taking the next step in the evolution of drug approval. *Clin. Pharmacol. Ther.* **91**, 426–437 (2012).

13. Hirsch, G. et al. Adaptive biomedical innovation: evolving our global system to sustainably and safely bring new medicines to patients in need. *Clin. Pharmacol. Ther.* **100**, 685–698 (2016).

14. MIT NEWDIGS White Paper 2019F201V023 Precision Financing <https://newdigs.mit.edu/sites/default/files/MIT%20FoCUS%20Precision%20Financing%202019F201V023.pdf>. Accessed August 2021.

15. Trusheim, M., Berndt, E. & Douglas, F. Stratified medicine: strategic and economic implications of combining drugs and clinical biomarkers. *Nat. Rev. Drug Discov.* **6**, 287–293 (2007).

16. Hess, G.P. et al. PCSK9 inhibitor therapy: payor approvals and rejections, and patient characteristics for successful prescribing. *Circulation* **136**, 2210-2219 (2017).

17. Brønd, A.M., Straand, J. & Klovning, A. Clinical drug trials in general practice: how well are external validity issues reported? *BMC Family Pract.* **18**, 113 (2017).

18. Eichler, H.-G. et al. Bridging the efficacy-effectiveness gap: a regulator’s perspective on addressing variability of drug response. *Nat. Rev. Drug Discov.* **10**, 495–506 (2011).

19. MEDEV. Medicine Evaluation Committee. Reflection on national strategies for new medicines coming to the market. Brussels <https://www.medev.com.eu/images/Pdf_docs/MEDEV_National_strategies_for_new_medicines.pdf> (2020). Accessed August 2021.

20. Wenzl, M. & Chapman, S. Performance-based managed entry agreements for new medicines in OECD countries and EU member states: How they work and possible improvements going forward. OECD Health Working Papers, No. 115, OECD Publishing, Paris (2019).

21. Paying for Cures Toolkit, MIT NEWDIGS website <https://payingforcures.mit.edu/toolkit-overview/precision-financing-solutions/> (2020). Accessed August 2021.

22. The Department of Health Risk-sharing Scheme <https://mstrust.org.uk/department-health-risk-sharing-scheme>. Accessed August 2021.

23. COST. Performance-based managed entry agreements for new medicines in OECD countries and EU member states: How they work and possible improvements going forward. Brussels <https://www.cordis.europa.eu/innov政党/medleys请点击-newdigs.mit.edu/sites/default/files/2019F201V023.pdf>. Accessed August 2021.

24. Performance-based managed entry agreements for new medicines <https://www.oecd.org/health/health-systems/pharmaceuti c-managed-entry-agreements.htm>. Accessed August 2021.

25. Performance-based managed entry agreements for new medicines <https://www.oecd.org/health/health-systems/pharmaceuti c-managed-entry-agreements.htm>. Accessed August 2021.

26. Verma, S., Coster, J. & Guram, J. Value-based purchasing rule of print<https://doi.org/10.1038/s41434-020-0143-y. [e-pub ahead of print].

27. Novartis Press Release. AveXis Announces Innovative Zolgensma® Gene Therapy Access Programs for US Payors and Families <https://www.novartis.com/news/media-releases/avexis-announcements-creative-zolgensma-gene-therapy-access-programs-us-payors-and-families> (2019). Accessed August 2021.

28. Payor perspectives on financing and reimbursement of one-time high-cost durable treatments. MIT NEWDIGS White Paper: A
Survey on Payor Perspectives–2019F210v044 <http://newdir gs.mit.edu/sites/default/files/MIT%20FoCUS%20Payor%20Per spectives%202019F210v044.pdf>. Accessed August 1, 2021.

Oderkirk, J. Readiness of electronic health record systems to contribute to national health information and research. OECD Health Working Papers, No. 99, OECD Publishing, Paris (2017).

OECD. Health Data Governance: Privacy, Monitoring and Research (OECD Publishing, Paris, France, 2021).

Netherlands Cancer Institute website: Immunotherapy treatment accessible to cancer patients with a rare tumour profile; 14-06-2019 <https://www.nki.nl/news-events/news/immunotherapy-treatment-accessible-to-cancer-patients-with-a-rare-tumour-profil e/>. Accessed August 2021.

Barlas, S. Health plans and drug companies dip their toes into value-based pricing: the pressure is on P&T Committees to monitor utilization. P T. 41, 39-53 (2016).

Entela Xoxi: real world evidence data collection Italian experience on registries. Brussels <https://ec.europa.eu/health/sites/default/files/files/committee/stamp/2016-03_stamp4/4_real_world_evidence_aifa_presentation.pdf> (2016). Accessed August 2021.

FDA. Sentinel system five-year strategy 2019-2023. FDA <https://www.fda.gov/media/120333/download> (2019). Accessed August 2021.

Pasquini, M.C. & Tiffany, H. Cellular Therapy Registry Update. Slide 37. Presentation dated February 19, 2019 <https://www.cibmtr.org/Meetings/Materials/CRPDMC/Documents/2019/TCT%202019%20MPasquini%20slides%20Cell%20Therapy.pptx>. Accessed August 2021.

MIT FoCUS Project. Emerging market solutions for financing and reimbursement of durable cell and gene therapies. MIT NEWDIGS FoCUS White Paper. June 16, 2021 <https://newdir gs.mit.edu/sites/default/files/FoCUS-WP-CTG-Market-Solutions.pdf>. Accessed August 2021.

Berlowitz, D., Burgess, J.F. & Young, G. Introduction. JAMA Cardiol. 3, 143–145 (2018). Accepted for regulatory and health technology assessment.

Goettsch, W.G. Bridging the gap: Can International Consortium of Health Outcomes Measurement standard sets align outcomes accepted for regulatory and health technology assessment decision-making of oncology medicines. Pharmacol. Res. Perspect. 9, e00742 (2021).

MIT NEWDIGS website <https://newdir gs.mit.edu/programs-proje cts/focus>. Accessed August 2021.

Kalf, R.R.J., Vremen, R.A., Delnoij, D.M.J., Bouvy, M.L. & Goetsch, W.G. Bridging the gap: Can International Consortium of Health Outcomes Measurement standard sets align outcomes accepted for regulatory and health technology assessment decision-making of oncology medicines. Pharmacol. Res. Perspect. 9, e00742 (2021).

Trusheim, M. et al. The Janus initiative: a multi-stakeholder process and tool set for facilitating and quantifying adaptive licensing discussions. Health Policy Technol. 3, 241–247 (2014).

Hirsch, G. Leaping together toward sustainable, patient-centered innovation: the value of a multistakeholder safe haven for accelerating system change. Clin. Pharmacol. Ther. 105, 798–801 (2018).

Butzkueven, H. et al. Long-term safety and effectiveness of natalizumab treatment in clinical practice: 10 years of real-world data from the Tysabri Observational Program (TOP). J. Neurol. Neurosurg. Psychiatry 91, 660–668 (2020).

Franklin, J.M. et al. Emulating randomized clinical trials with nonrandomized real-world evidence studies. Circulation 143, 1002–1013 (2021).

Luszczek, E.R. et al. Characterizing COVID-19 clinical phenotypes and associated comorbidities and complication profiles. PLoS One 16, e0248956 (2021).

Dagan, N. et al. BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting. N. Engl. J. Med. 384, 1412–1423 (2021).

Center for Health Information and Analysis, Massachussetts. All-Payer Claims Database (MA APCD) Release 7.0 2013-2017 Documentation Guide (2018) <https://www.chiamass.gov/assets/docs/p/apcd-apcd-7.0-MA-APCD-Release-7.0-Documentation-Guide.pdf>. Accessed November 11, 2021.

Matza, M. et al. Rheumatoid arthritis treatment patterns in Massachussetts: Informative findings from insurance claims data [abstract]. Arthritis Rheumatol. 73(Suppl 10), (2021).

US FDA website. Real-world data (RWD) and real-world evidence (RWE) are playing an increasing role in health care decisions. July 16, 2021 <https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence>. Accessed August 2021.

McConnell, K.J. et al. Estimating treatment effects with machine learning. Health Serv. Res. 54, 1273–1282 (2019).

Künzel, S.R. et al. Metalearners for estimating heterogeneous treatment effects using machine learning. Proc. Nat. Acad. Sci. 116, 4156–4165 (2019).

Sauer, C.M. et al. Feature selection and prediction of treatment failure in tuberculosis. PLoS One 13, e0207491 (2018).

Curts, J. et al. Derivation and preliminary validation of an administrative claims-based algorithm for the effectiveness of medications for rheumatoid arthritis. Arthritis Res. Ther. 13, R155 (2011).

Reflection on national strategies for new medicines coming to the market. Brussels <https://www.medev.com.eu/images/Pdf_docs/MEDEV_National_strategies_for_new_medicines.pdf> (2020). Accessed August 2021.

EMA website. Minutes EMA – Payor Community meeting. September 19, 2017 <https://www.ema.europa.eu/en/documents/minutes/minutes-european-medicines-agency-payor-commu nity-meeting_en.pdf>. Accessed August 2021.

MIT NEWDIGS Research Brief 2019F203-v037-patient caregiver themes <http://newdir gs.mit.edu/sites/default/files/FoCUS %20Research%20Brief%202019F203v037.pdf>. Accessed August 2021.

MIT NEWDIGS Research Brief 2021F201-v052 Resource Navigation <https://newdir gs.mit.edu/sites/default/files/RB%20Resource%20Navigation%202021F201v052.pdf>. Accessed August 2021.

Schneeman, K. & Barton, V. Advancing models of patient engagement: patient organizations as research and data partners. Milken Institute Report <https://milkeninstitute.org/report/advancing-models-patient-engagement-patient-organizations-research-and-data-partners> (2018). Accessed August 2021.

Siwicki, B. Multiple myeloma foundation debuts CureCloud to advance precision medicine <https://www.healthcarenews.com/news/multiple-myeloma-foundation-debuts-curecloud-advance-precision-medicine> (2019). Accessed August 2021.

Cystic Fibrosis Foundation Patient Registry 2019 Annual Data Report Bethesda, Maryland. ©2020 Cystic Fibrosis Foundation <https://www.cff.org/Research/Researcher-Resources/Patie nt-Registry/2019-Patient-Registry-Annual-Data-Report.pdf>. Accessed August 2021.

Tools for implementation of precision financing solutions within Medicaid plans. November 20, 2019 <https://newdir gs.mit.edu/sites/default/files/Milestone-Based%20Contracts%20with%20Medicaid%20Plans%20%202019F211v047.pdf>. Accessed August 2021.

Verma, S., Coster, J. & Guram, J. Value-based purchasing rule for Medicaid Rx drugs: continuing to shift from FFS towards accountability. Health Affairs Blog <https://www.healthaffairs. org/do/https://doi.org/10.1377/hblog20211019.109892/full/> (2021). Accessed August 2021.