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Are Global Health Systems Ready for Transformative Therapies?

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ABSTRACT

Background: We have seen significant advancement in a range of health technologies, some with transformative or curative potential. Nevertheless, it is often unclear how global health systems recognize or reward innovation.

Objectives: To consider what is transformative, challenges for transformative therapies, and downstream health ecosystem effects.

Methods: A systematic review of publications in English between 2012 and 2018 was conducted with a focus on value assessment processes and health system effects of a range of breakthrough health technology categories. After screening 9012 records, 222 unique studies were identified. The study also included an analysis of 100 health technology assessments (HTAs) from 5 markets to consider how and in what ways global HTA bodies evaluate transformative therapies. Global sales and technology/procedure utilization data were also evaluated to gain insights into patient access and commercial impact.

Results: This article evaluated uncertainties around evidence of efficacy, safety, and duration of effect, as well as underlying study quality and methodological considerations in the target categories. Although many HTA evaluations had similar approaches to assessing parameters such as safety, there were significant differences across technology categories. Technology-driven trends also surfaced where global HTA and payer systems may not yet be prepared to recognize and reward emerging technology impacts, including use of next-generation diagnostic results to guide care, considering novel impacts on therapy sequencing and clinical pathway management, and changes in payment and health delivery models.

Conclusions: Some trends stemming from rapid evolution of breakthrough therapies will prompt reconsideration of our conventional value assessment and reward models, because health system measurement and management processes have not fully anticipated their effects.

Keywords: advanced therapies, cell therapy, curative, gene therapy, health technology assessment, managed care, precision medicine, rare disease, regenerative medicine, transformative.

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Introduction

Many first-in-class therapies are now entering the global marketplace, evolving at a rapid pace and fueled by increasing knowledge of genetics, systems biology, and computational science. The past 30 years have seen the development of many technologies that have been considered innovative, including precision medicine, rare disease treatments, immunotherapies, and other advancements.[1] More recently, emerging gene-editing approaches have the potential to enable a new generation of advanced therapies that have the potential to transform or cure diseases. Others question how much the value of innovation is truly realized by patients.[2] Technology evolution also influences our notions of clinical development and evidence-based practice, including at the system level.[3–5]

It is often unclear as to what extent the type and nature of technological innovation matters, or how key health stakeholders recognize or reward innovation. This article considers what is transformative, challenges for transformative therapies, and downstream health ecosystem effects.

Methods

A systematic literature review was conducted in PubMed, EMBASE, and gray literature to identify studies published from

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2012 to 2018. This time frame was selected to include the broadest net of sources that may consider transformative or curative effects, because it was viewed that a 5-year window may miss some key literature. Although discussion on using the terms "transformative" and "curative" has entered the technology debate only over the past several years, this does not mean that therapies that are transformative have emerged only during the past 2 to 4 years (eg, the first precision medicines and cell therapies have been approved for >20 years). Nevertheless, to capture the greatest concentration of therapies leveraging our knowledge of biomarkers, genetics, and cellular biology, we have opted to include a 7-year window. The following keywords were used: precision medicine, personalized medicine, gene therapy, cell therapy, cell or tissue therapy, innovation, curative, transformative, breakthrough, health technology assessment, reimbursement, commercialization, funding, funding mechanism, cost, cost and cost analysis, and high cost. Duplicate records were reviewed and articles were screened using the following criteria: (1) articles in English; (2) publication between 2012 and 2018; (3) focus on health technology assessment (HTA), reimbursement, or funding of therapies that may be viewed as breakthrough or transformative/curative; (4) human studies; and (5) clinical trial or review. Focus was on benefits/challenges or on value assessment, reimbursement, payment, and other health system effects of the following therapy types: advanced cell and gene therapy, precision medicine, immunotherapies, rare disease therapies, and next-generation diagnostics. See the Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram in Appendix Figure 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.04.1911 outlining search characteristics, and also Appendix Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.04.1911 presenting search strategy details.

The study also included an analysis of 100 HTAs from 5 markets—Australia, Canada, France, the United Kingdom, and the United States— spanning an initial set of 35 therapies approved by the US Food and Drug Administration (FDA) and the European Medicines Agency during 2017. Policy- or system-relevant changes in other markets from gray literature evaluation are also included for context around some issues as appropriate. This regulatory approval time frame was selected to enable evaluation of HTA and other uptake drivers. We excluded 14 therapies on the basis of the availability of HTAs and arrived at a set of 21 technologies. HTAs were evaluated for various factors, including uncertainties in clinical, economic, or other variables frequently considered in technology assessment. Nonprecision, rare disease, or advanced therapy oncology agents were also included to highlight potential differences in how various technology types are assessed. Global sales data from manufacturers' financial statements and product utilization via CodeMap®, a US coding and utilization platform, and the international Ipsos data set were also evaluated.

Results

After screening 9012 records, 222 unique studies were identified. Although individual study characteristics are not presented, a Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram depicting study selection is shown in Appendix Figure 1 and a search strategy is provided in Appendix Table 1 (both in Supplemental Materials).

What Is "Transformative" or "Curative"?

The term "transformative" has gained significant traction in recent years.[6] When stakeholders talk about transformative effect, they often mean leaps in improvement over existing alternatives.[7] Antibiotics, vaccines, initial monoclonal antibody treatments, the first precision medicines, and early enzyme-replacement therapies could all be viewed as transformative at time of launch. In this way, whether a technology is viewed as transformative is often relative, benchmarked against standard of care.

A 2018 payer study conducted by the National Association of Managed Care Physicians and the Alliance for Regenerative Medicine reported that a transformative effect includes full or partial disease stabilization for a significant period of time with minimum or no additional treatment.[8] Nevertheless, such a definition may not hold true for other technologies with the potential to transform care and outcomes, such as next-generation diagnostics that do not have direct effects.[9] There is no clear, single metric agreed upon as denoting transformative effect. Curative effect, on the other hand, can be more narrowly defined. The study reported that a curative treatment involves *no* other treatment for a period of years. About 35% of respondents indicated that curative effect should be for a lifetime, whereas 50% suggested that it should last 5 to 10 years; so the curative status centers more on the timing of effect.

Some markets such as those of France, Germany, and Japan have instituted approaches recognizing innovation and/or thresholds of benefit (eg, *Amélioration du Service Médical Rendu* ratings in France).[10] Although HTA agencies are beginning to acknowledge differences in technology types (eg, the Diagnostics Assessment Programme of the National Institute for Health and Care Excellence [NICE]), most have not developed explicit channels for addressing transformative or curative effect per se.[11–13] Even recent efforts to evolve next-generation value frameworks have not included explicit emphasis on transformative or curative effect.[14]

Although it is clear that transformative medicine is not marginal, studies addressing transformative effect indicate that health stakeholders find it difficult to assign a single definition or threshold of transformative effect for creating health policies. In scenarios in which transformative or curative therapies are given special consideration, it is currently unclear how such definitions would influence patient access.[15]

Technology Platform Influence on Perspectives of Value

First-in-class or innovative technology types or "platforms," whether transformative or not, can precipitate change in global value assessment, reimbursement, and delivery practices.[16,17] Table 1 presents the key factors that influence how new health technologies are addressed by health system decision makers. Appendix Figure 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.04.1911 lists various technology types and highlights differences in the ways they may be perceived as contributing value. The key point is that different technology types can bring different dimensions of value, some overlapping and some nonoverlapping. Both are derived from the literature assessment and experience of the Evidera Precision and Transformative Medicine Center of Excellence with more than 1100 emerging technology assets. Whether a therapy is perceived to have transformative effect is a factor of how and to what extent the technology addresses one or more of these dimensions. (Precision and Transformative Medicine Center of Excellence is a cross-organizational center focused on leveraging deep expertise in emerging and innovative health technologies, including regenerative and advanced therapies, precision medicine and diagnostics, orphan and rare disease treatments, immunotherapy and therapeutic vaccines, medical devices, and e-connective and smart technologies. The center has a standing Leadership Committee comprising senior executives and scientists spanning all

Table 1. Key factors that influence how new health technologies are addressed by health system decision makers.[4–17]

Core factors considered	Additional detail/underlying decision drivers
Nature of the disease	• Volume of the disease/population size • Availability of established alternatives • Chronic vs acute health effects • Severity of health effects (eg, mortality, morbidity, and quality-of-life risks)
What is assessed (ie, clinical, economic, patient-centric, or other effects)	• Extent to which the value assessment framework is appropriate to the technology type • Whether special technology-specific frameworks are applied that account for special value considerations/drivers • How a new technology has an impact on care efficiencies, processes, or financial flows
Who the decision maker is and their incentives for acceptance and uptake	• National vs regional HTA • National vs regional payer • Hospital or health system • Patient as the payer
Fit of the technology into reimbursement and payment systems	• Coding fit (ie, whether code is sufficiently descriptive or has appropriate associated payment level) • New or special payment scheme required for access • Ability of existing payment and cash flow models to accommodate the therapy
Source of funding for the therapy or service	• Payer vs hospital budget latitude • Alternative funding sources (eg, earmarked funds for special applications)
Affordability	• Degree to which cost may be outside the norm; per unit or aggregate • Budget impact and cost-effectiveness

Note. Findings are based on the literature review conducted and experience with HTA and payer stakeholder processes and requirements within the Evidera Precision and Transformative Medicine Center of Excellence.
HTA indicates health technology assessment.

internal business units and also draws from broader clinical and regulatory leadership members from the parent organization PPD, one of the largest global clinical research organizations.)

New health technologies continue to influence and challenge HTA practices. Challenges stemming from innovative platforms are presented in Table 2, and subjective ratings have been derived from the literature search and authors' experience in the International Society for Pharmacoeconomics and Outcomes Research's (ISPOR's) global, technology-focused special interest groups over the past 20 years.[18] Some areas have been explored by HTA agencies, including rare disease and oncology scenarios. Other challenges, such as integrating diagnostic aspects into precision medicine assessments, remain.[19–22,39] (The Precision Medicine Special Interest Group, the Medical Device and Diagnostics Special Interest Group, and the Rare Disease Special Interest Group of the ISPOR are global mixed stakeholder groups addressing specific technology thought leadership and educational issues for the organization.) As might be expected, few HTA agencies have evolved specific criteria for regenerative and advanced therapies that may offer transformative or curative effect. One notable exception is the recent NICE mock assessment on chimeric antigen receptor T-cell therapies.[40] In terms of reimbursement and payment, innovative technologies face one or more complex acceptance issues.

One example of a disruptive technology type is molecular diagnostics. Many issues surfaced during initial test launches, including disconnected HTA processes, unclear funding, limited familiarity with diagnostic evidence, uncertain use by physicians, and lack of value-based reimbursement.[16,23,41] Currently, next-generation diagnostics involving dozens or hundreds of biomarkers are poised to disrupt health provision further and raise issues some decision makers may be ill prepared to address.[9,24–26] Rapid expansion in rare disease treatments has also prompted change.[27] Special regulatory and HTA pathways have been created in some markets. Unique considerations have stimulated debate over HTA methods (eg, use of multicriteria decision assessment), evolution in patient-reported outcomes, modeling, and real-world data analysis.[28–31] Aggregate affordability has also been debated, with some markets instituting stringent management practices.[32–37]

These are just a few examples of how innovative technologies with attributes different from conventional therapies are influencing our expectations and shaping what we view as transformative.

Implications of Technology Type: Observations From HTA and Commercial Assessment

This section explores the extent to which different innovative or transformative technology applications are specifically recognized or rewarded in global technology assessment and commercial acceptance mechanisms.

As noted, we evaluated 21 technologies and associated HTAs from 5 global markets. Figure 1A,B highlights results by (1) technology category/focus and (2) core dimensions of value including efficacy, safety, and duration of effect and drivers of evidence quality/interpretability.[42-132] Appendix Table 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.04.1911 provides a list of indications included in the HTA analysis.

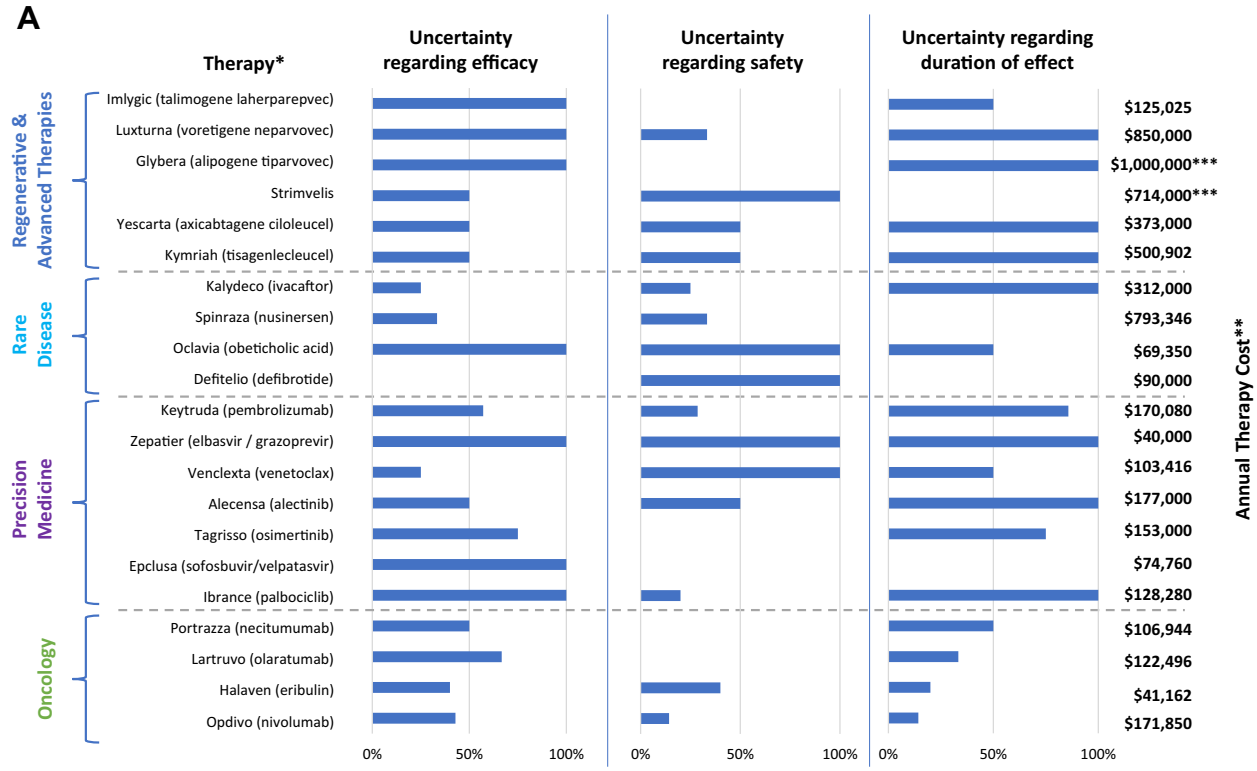
For therapies with transformative or curative intent, magnitude and duration of effect are core value drivers. In evaluating these variables, both regenerative and advanced therapies and precision medicines had a greater number of HTAs citing uncertainties around efficacy (~54% of products in these categories in >60% of HTAs in the set) in contrast to rare disease and non-precision oncology agents. Significant emphasis was placed on the efficacy of the 2 precision hepatitis C therapies, Zepatier™

Table 2. Key innovative HTA, reimbursement, and pricing challenges.[4–38]

HTA challenge	Technology examples	Reimbursement and payment challenge	Technology examples
1. Assessment body's process does not anticipate/acknowledge unique attributes that influence the technology value proposition	• Sensitivity, specificity, and predictive value of diagnostics used with precision medicine • Adaptive trial design for precision medicine scenarios that cut across multiple diseases • Physiological effects that go beyond typically measured outcomes (eg, persistence treatment in body, inability to turn off the therapy in the event of a safety issue, broader biometabolic effects of therapeutic vaccines) • Capacity or willingness to leverage multiple HTA frameworks tailored to technology types	1. Technology does not "fit" nor is anticipated by coding and reimbursement systems, placing innovative technology manufacturers and providers at risk for insufficient payment to cover costs	• Initial companion diagnostics and precision medicines • Next-generation diagnostics that include dozens or hundreds of biomarkers • E-connective or smart technology device applications or combination products • Multitarget precision medicines and highly individualized therapeutic vaccines • Regenerative and advanced cell and gene therapies, particularly those that involve complex procedural attributes that are more device-like
2. Unique technology attributes are understood, but evidence is not available and uncertainty around gap(s) has strong potential for clinical or economic impact	• Evidence of long-term durability of effect for regenerative and advanced therapies • Evidence of real-world effectiveness and safety for therapies with long-term duration of effect • Data on appropriate controls for single-arm oncology and IO therapies	2. Technology is reimbursed, but payment rates or disruption of existing provider business models creates a provider uptake barrier	• Alipogene tiparvovec for lipoprotein lipase deficiency
3. Technology scenario presents the process with a value scenario for which there is not yet a clear or consistent methodological "fix" or approach	• Clinical and economic methods and expectations adapted for niche populations (eg, rare disease and precision medicine) • Innovative precision medicine, oncology, and IO therapies launching with single-arm studies • Value of multitarget precision medicines in lieu of individually administered combination therapies • Lack of provisions for therapies with curative intent • Methods for evaluating therapeutic vaccines tailored to each individual's molecular configuration • Capacity or willingness to leverage multiple HTA frameworks tailored to technology types	3. Technology viewed as promising but viewed as having insufficient evidence at the time of launch and may be subject to managed entry, risk sharing, or conditional coverage arrangements, or categorized as research only/investigational	• Various PET radiopharmaceutical applications • Transcatheter aortic valve replacement • Novel transformative regenerative and advanced therapies launched from 2016 to present
		4. Technology represents a volume or cost concern that precipitates structured or complex patient access management by payers or other stakeholders	• Innovator transformative hepatitis C drugs • Aggregate impact of orphan/rare disease treatments • Combination oncology or immune-oncology therapies • Rapid expansion of molecular diagnostics
		5. Technology fits into a bundled payment model that does not enable separate technology payment from the procedure	• Cell therapies used as adjunct to hematopoetic stem cell transplant • Innovator implantable medical devices at higher price points than SOC or that do not align with an existing procedural payment
		6. Technology or delivery scenario does not "neatly" align with existing payment models	• Single administration regenerative and advanced cell and gene therapies • Companion diagnostics in some markets (eg, Canada, some EU markets)

EU indicates European Union; HTA, health technology assessment; IO, immuno-oncology; PET, positron emission tomography; SOC, standard of care.

Figure 1. (A) Percentage of study HTAs that noted uncertainty regarding efficacy, safety, and duration of effect for innovative therapies.[38,42-64,66-137] (B) Percentage of study HTAs that noted uncertainty regarding key clinical and economic attributes.[38,42-64,66-137] Percentage of HTAs that address key value assessment considerations for innovative therapies. n = 100 global HTAs from Australia, Canada, France, the United States, and the United Kingdom published in 2017 for therapies attaining regulatory approval in 2016 and 2017.



Percentage of HTAs that address key value assessment considerations for innovative therapies. n = 81 global health technology assessments from Australia, Canada, France, US, and UK published in 2017 for therapies attaining regulatory approval in 2016 and 2017.

*Some therapies may involve >1 technology category. HTA indicates health technology assessment.

(elbasvir/grazoprevir) and Epclusa® (velpatasvir/sofosbuvir), perhaps because of historical emphasis on hepatitis C budget impact and availability of alternatives.[138] Of the efficacy concerns most frequently cited, insufficient comparative data, lack of epidemiology/unclear patient population, and study design issues were the top factors influencing efficacy assessment.

Perhaps surprisingly, despite the novelty of cell and gene therapy, product safety was not noted as an area of HTA uncertainty with greater frequency versus other categories. In contrast, safety of nonprecision oncology agents was the least frequently noted in HTA reviews, perhaps reflecting better understanding of conventional oncology agent safety considerations.

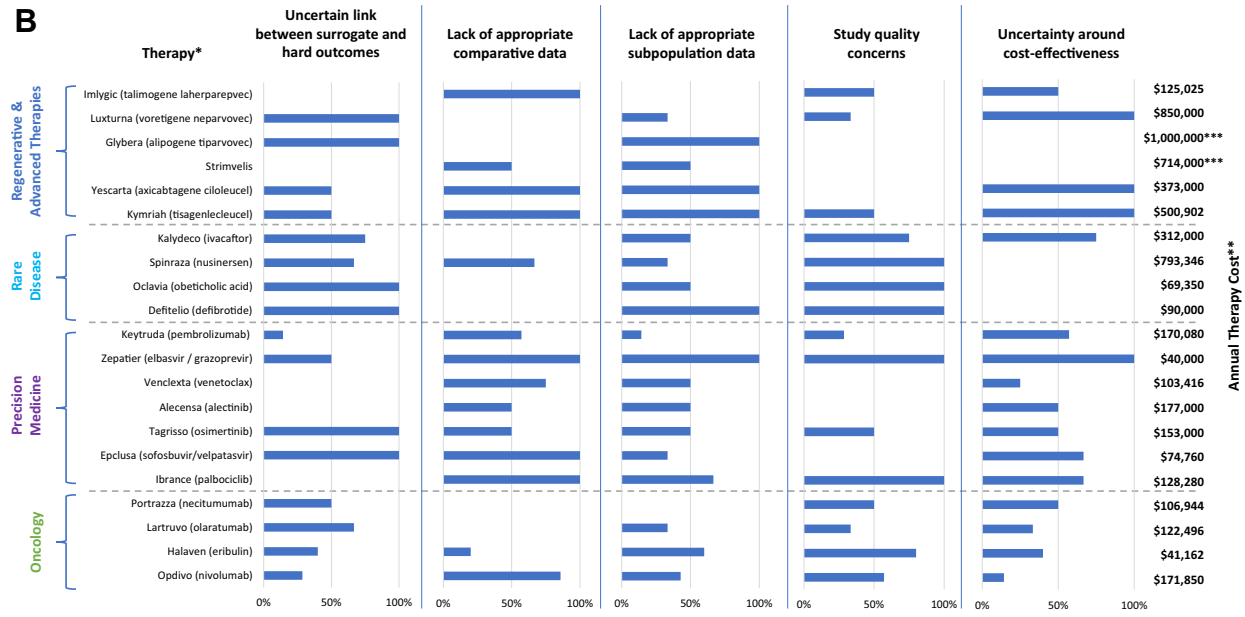
As may be expected, duration of effect was cited as a significant uncertainty among regenerative and advanced therapy agents considered, with the exception of Strimvelis, which reported an average of 7 years of follow-up data at the time of launch.[139] Interestingly, more than 70% of the precision medicine products considered included HTA uncertainty around duration of effect in more than 60% of HTA reports considered, when annual costs were in excess of $125 000. Duration of effect was not noted as a concern for most orphan and rare disease products, potentially because of perceptions of unmet need and lack of sufficient alternatives.

Several core dimensions that influence assessment of clinical effectiveness and cost-effectiveness were also considered. These dimensions included reliance on surrogate outcomes, availability of comparative data, uncertain population or subpopulation data, study quality, and uncertainty around cost-effectiveness estimates.

Nearly all the rare disease therapies (including those also regenerative and advanced therapies) included HTA concerns about the linkage between surrogate and "patient-relevant" or "final" health outcomes. This could be because many rare diseases are often fast-tracked, sometimes requiring reliance on surrogates for diseases with long deterioration periods, and not as well-characterized versus more prevalent diseases.[140] Limitations noted in HTAs included patient epidemiology, burden of disease, and natural history or longer term consequences of surrogates. This suggests that for rare disease therapies, irrespective of technology type, better characterization of the disease area and treatment effects are important to HTA acceptance. Many of the other treatments in the set were for oncology or hepatitis C, both of which have established trial endpoints.

Lack of comparative data was most frequently noted for precision medicines, with the second most frequent category being regenerative and advanced therapy. One reason could be uncertainties around the epidemiology of the biomarker population in comparison with the broader population.[141] Similarly, virtually all the rare disease HTAs cited uncertainty around patient population/subpopulations. Study quality and uncertain cost-

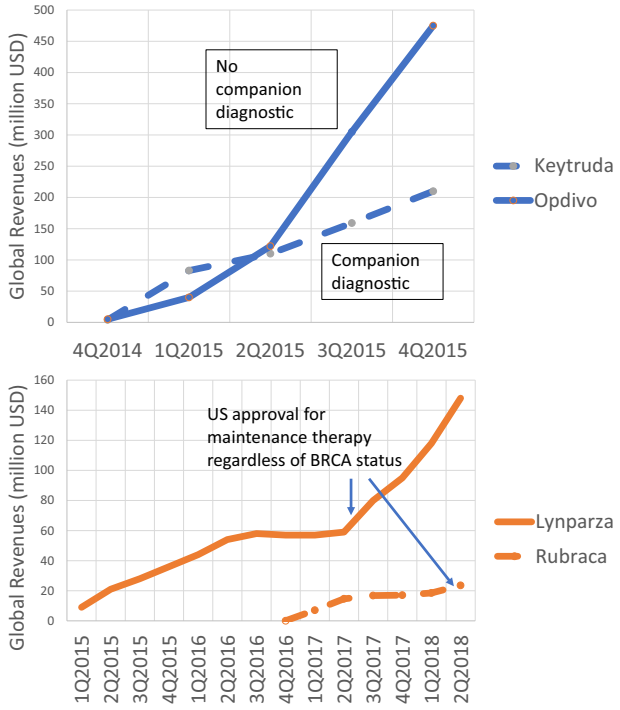
Figure 1. (*continued*).



Percentage of HTAs that address key value assessment considerations for innovative therapies. n = 81 global health technology assessments from Australia, Canada, France, US, and UK published in 2017 for therapies attaining regulatory approval in 2016 and 2017.

effectiveness were most frequently noted in regenerative and advanced therapy studies, with approximately 50% of products noting these concerns in 100% of available HTAs, including uncertainty around links between short- and long-term effects.

Figure 2. Uptake of PD-L1 inhibitor drugs or advanced melanoma and small cell lung cancer.[38,42-64,66-137]



PD-L1 indicates programmed death-ligand 1.
Source: Bristol Myers Squibb, Merck, AstraZeneca, and Clovis Oncology financial reports (SEC.gov).

Overall, there was no clear correlation between agent cost and degree of scrutiny across the core value dimensions. Nevertheless, uncertainties in clinical effectiveness and patient population often translated into HTA uncertainty around cost-effectiveness, as would be expected. It is worth noting that sometimes, despite uncertainty in clinical benefit, it may be possible to have sufficient certainty on whether a product is cost-effective. This is particularly true when the required threshold of clinical benefit has been met or exceeded with a high degree of certainty, or has clearly not been met. The former scenario was observed in the NICE favorable appraisals of Kymriah™ (tisagenlecleucel) for relapsed/refractory B-cell acute lymphoblastic leukemia[95] and Strimvelis for adenosine deaminase–deficient severe combined immunodeficiency.[91] Although there was uncertainty regarding the actual duration of therapeutic benefit in terms of patient survival for these technologies, they both met thresholds required to deem them cost-effective in their respective contexts.

This analysis also suggests that although the HTA bodies, with the exception of rare disease products, may not be applying a technology-specific analysis framework, there are common evidence gaps associated with certain technology types/applications, for example, the need to establish clear magnitude and duration of effect in regenerative and advanced therapies, comparative effect of precision medicines versus broader applications, and the need to characterize the disease situation in rare diseases. It is beyond the scope of this article to fully determine the extent to which HTA organizations take into account special value attributes of different technology types, but it is an important consideration in (1) the context of the active value framework development activities of ISPOR and other professional organizations and (2) implications for patient access and quality/cost efficiencies.[142]

Although the overarching purpose of the evaluation was to identify aggregate trends among HTAs, future work should consider detailed comparative analysis of HTAs to further elucidate specific differences in how specific decision bodies address technologies with transformative or curative effect. Considering trends among HTA archetypes may also be beneficial to further advance the dialogue.

Implications for Commercial Uptake

Commercial uptake was also considered on the basis of product sales and utilization analysis. This was not possible for most of the regenerative and advanced therapies in the set because sufficient data were not yet available. Examples that were identified were normalized to ensure comparability in trend analysis. One area in which evaluation was possible was implications of developing a product with a companion diagnostic as a precision medicine versus a broader development without one.

Health ecosystem externalities such as application of diagnostics can play a significant role in therapy uptake. Figure 2 compares uptake for Keytruda® (pembrolizumab) and Opdivo® (nivolumab), which are programmed death-ligand 1 (PD-L1) inhibitor immunotherapies for specific forms of cancer. Keytruda and Opdivo received initial FDA approval in September and December 2014, respectively, for advanced[143] or unresectable melanoma. Both were generally viewed to have transformative benefits to patients. In 2015, both product labels were expanded to include patients with metastatic non–small cell lung cancer. Both therapies were granted breakthrough therapy designation after demonstrating greater than or equal to 25% objective response rates in deadly forms of cancer that had progressed on previous therapies.[143]

Many factors influence revenue growth for new therapies, including regulatory approval timing, market size for approved indications, pricing, and promotional budgets. Before January 2016, these commercial considerations were similar enough between Keytruda and Opdivo to compare revenue curves. One key difference, however, is that during the period shown in Figure 2, Keytruda was approved for use in PD-L1+ patients (as determined by a companion diagnostic), whereas Opdivo could be prescribed regardless of PD-L1 expression status. Given that PD-L1 inhibition was a key component of the mechanism of action for both drugs, it could be posited that the therapy with a PD-L1 testing requirement could be perceived as more targeted and have faster uptake. Nevertheless, as shown in Figure 2, sales of the PD-L1 inhibitor therapy without a PD-L1 requirement were more than double that of the precision medicine. Other factors such as test turnaround time, interpretation, and reimbursement may also have played more subtle roles in physician uptake postlaunch.

It is also possible that lessening a requirement for diagnostic testing can enhance uptake of competing therapies. Figure 2 also shows uptake curves for Lynparza® (olaparib) and Rubraca® (rucaparib), which are poly(adenosine diphosphate ribose) polymerase inhibitors indicated for patients with ovarian cancer treated with 2 or more chemotherapies, and have a *BRCA* mutation as determined by an FDA-approved companion diagnostic. Lynparza was approved 2 years before Rubraca and had already reached a revenue "plateau" before the launch of Rubraca in December 2016. Despite added competition from Rubraca, revenue growth for Lynparza was revived by expanding the label to include maintenance therapy regardless of *BRCA* mutation. Revenue growth for Rubraca appeared to stall 6 months after launch, but is anticipated to rebound as a result of label expansion.

Although these examples do not enable general conclusions about the value of precision medicine, from a patient access and commercial perspective, it is possible to conclude that acceptance drivers are complex and may not always align to technology hypotheses. Even in scenarios in which benefits to a subpopulation or patient group have been demonstrated, acceptance and uptake can be nontransparent and counterintuitive. Similar challenges have been reported for early cell therapy products, where lack of reimbursement mechanisms has resulted in multiple product withdrawals in Europe, even after favorable HTA results.[144] In this sense, emerging as a transformative technology may actually be a disadvantage, in terms of both patient access and commercial viability.

Health Ecosystem Implications of Potentially Transformative Therapies

Although it is clear that innovative technologies face challenges at the product level, consideration of their health ecosystem effects is equally important. Table 3 presents 6 trends on the basis of the literature review, HTA analysis, and gray literature search where innovative technologies are poised to influence our health ecosystem, value assessment, and reward paradigms. These trends will influence or require further evolution of health economics and outcomes research, HTA, reimbursement, and access/resource management models.

Appendix Figure 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.04.1911 also characterizes the core distribution of systematic literature review citations that addressed (1) specific categories of HTA and market access challenges and (2) specifically noted key trends relevant to the global health ecosystem flowing from emerging technology introduction. It is clear from these results that although some emphasis has been placed on addressing technologies with transformative and curative impact, such focus has, to date, represented a very low percentage of topics on technology impact captured under this analysis. Overall, there is a reasonably even distribution of many of the trends. Similarly, only a small number of citations reflected emphasis on impact of technologies on clinical pathway/management and health system efficiencies, even though these arguably could represent areas of significant benefits. Not surprisingly, the greatest emphasis was on areas such as methods of assessment, requirements of preferences of technology assessment, challenges of fit in current reimbursement and payment models, and affordability. These topics more clearly align with current value assessment and uptake processes, but proportional emphasis suggests that (1) many issues that have health system impact are being discussed and (2) consideration of how to measure or harness technology impacts beyond current HTA, reimbursement, and payment models is in the earliest stages of evolution.

Conclusions

It is clear that whether a technology is dubbed transformative or curative, innovation will continue to influence and evolve our health ecosystem. Such technologies, in addition to pushing boundaries of the health system and delivery models, are also excellent at exposing limitations of our value assessment and reward structures. It has been noted that HTA is most developed in higher income countries, with more limited use of evidence-based processes in health policy decisions in lower income countries.[219–221] Although there is still a way to translate novel HTA approaches to evaluating transformative therapies in countries with well-established HTA systems, lower income countries still struggle to apply HTA to therapies now considered "standard/essential," which is likely a term goal without substantial improvements in health system architecture, resources, and market attractiveness to originators. Therefore, applications of the trends noted in this assessment are likely most relevant to the major global markets.

Table 3. Technology-driven trends poised to influence the global health ecosystem.[6,8,13,24,40,144-218]

Trend	Examples
1. Next-generation diagnostics and machine learning influence on precision medicine and patient management decision making	Our knowledge of the interconnection of biomarkers with disease is beginning to influence our approaches to value demonstration and reimbursement. The following highlights some key issues that have health ecosystem impacts: • *New clinical trial approaches* are emerging that differ from our conventional trial design practices. The US FDA has been a leader in this area, leveraging the 21st Century Cures Act to support movement to broader approaches that "shotgun" across multiple therapies and disease areas and enable submission of RWE alongside pivotal evidence.[145–147] So-called basket, blanket, and adaptive trials, which would have been challenging to implement even 5 y ago, are now being executed with increasing frequency on the basis of our knowledge of biomarkers.[148] Such approaches will also stimulate evolution of HTA practices, including clearer practices for incorporating RWE to support regulator and payer assessment. Several factors such as recalibrating methods to address smaller subpopulations, shift in our expectations for comparators, and methods for bridging evidence gaps are all developing.[149] Evolved clinical and HEOR solutions such as enrichment studies and evolution of RWE and indirect treatment comparisons are already being implemented.[150,151] • *Integration of next-generation diagnostics with smart decision analysis* (eg, AI and machine learning) will also further refine patient management approaches and move us toward iterative decision models. Applications may include therapy switching, comparative value and access tiering, sequencing, or integration with performance metrics. Vanguard efforts such as IBM's Watson, Human Longevity's Health Nucleus, and Cyft Analytics represent different approaches to incorporating biomarker data into decision platforms. How will our global health systems value and pay for such knowledge if it substantively improves care?
2. Updating our perceptions of value and approaches to value assessment	As new technologies enter the marketplace with different characteristics and decision drivers, our approach to evidence development has also begun to shift to better integrate patient-centric effects and evidence over the asset life cycle. In early asset development, changes such as inclusion of PRO and RWE in regulatory submissions and increased use of managed entry agreements to encourage further evidence development (eg, in Italy, the United Kingdom, and the United States) are 2 examples of this shift.[24,152] Some novel technology applications have significant potential to challenge our current views on value assessment, including the following: • *[Increasing personalization] therapeutic vaccines and multitarget precision medicine* that can be manufactured to better address an individual's specific genetic/biological "situation" and have potential to replace some combination therapies.[153] The most advanced technologies may enable multiple adaptations of the same product at different points in patient care (ie, the therapy evolves on the basis of the patient's biomarker composition).[154–156] How do HEOR methods and assessment approaches adapt to account for truly individualized treatments that involve iterative advancements that adjust for changes in disease state? • *[Increasing magnitude and duration of effect] regenerative and advanced therapies* offer the promise of profound magnitude and duration of effects that may be viewed as transformative or curative. These technologies have the potential to alter our perspective on therapy performance and raise the bar for value assessment (similar to introduction of monoclonal antibodies more than 25 y ago). Although methods are currently evolving to address uncertainty around duration of effect, it is clear that early data collection on duration of effect is key, and that postapproval requirements for additional evidence will apply.[157] It is as yet unclear how these technologies will impact (1) HTA expectations, (2) new payment models, or (3) evolution of new policies based on affordability, but they will push our perceptions on defining "good" outcomes.
3. Innovative therapy influence on therapy sequencing and clinical pathway management	As transformative therapies enter the marketplace, they have significant potential, including the following examples: • *Disruption of established care paradigms:* Single administration cell and gene therapies may have potential to leapfrog traditional recurrent dosing models. Similarly, next-generation precision medicines also have potential to change how physicians manage patients.[158,159] RWE will become increasingly important in assessment as care becomes increasingly individualized. • *Redefining our approaches to clinical pathway management:* Next-generation diagnostics, when combined with RWE and decision tools such as AI, have the potential to chart entire clinical pathways.[160] Management of access beyond individual assets focusing on sequence of care efficiencies will become more important as our ability to "tune" guidelines and pathways increases.
4. Transformative and curative technologies shifting the bar for acceptance	• *Redefining "good enough":* Therapies that are truly transformative can also shift the bar for acceptability.[161] Technologies entering the market today with evidence that would have been considered breakthrough a decade before can be at risk for rejection today.[162,163] Therapies such as Enbrel® (etanercept) (the first biological), Herceptin® (trastuzumab) (the first personalized medicine), Gleevec® (imatinib) (increased 5-y survival to 90%), and Harvoni® (ledipasvir/sofosbuvir) (one of the first curative treatments for hepatitis C) are all examples of technologies that have shifted our definition of "good."[164] Emerging cell and gene therapies have the potential to further raise the bar for acceptance. For example, entry of the gene therapy Strimvelis demonstrated transformative improvement in ADA-SCID, but also reflected the value of collecting detailed outcomes data from the earliest stages of the patient journey to prove lasting effect.[165–168] • Alternatively, particularly high-cost therapies face substantial acceptance challenges in scenarios where existing treatments, albeit imperfect, could be viewed as "good enough."[169–171] Although we remain in early days, various therapies including Glybera® (alipogene tiparvovec), Provenge® (sipuleucel-T), ChondroCelect™ (autologous cultured chondrocytes), and MACI™ (autologous cultured chondrocytes

continued on next page

Table 3. Continued

Trend	Examples
	on porcine collagen membrane) have faced varying degrees of market access challenges, flowing from various factors including mismatch between value story and pricing, lack of reimbursement "fit," and provider selection of alternatives.[172]
5. Evolution of new reimbursement and payment models to manage affordability	It is not unusual that innovative technologies have attributes that do not "fit" neatly into existing reimbursement systems developed well before our current explosion of novel innovations. When technologies have not been anticipated by reimbursement systems, both manufacturers and providers face economic disincentives that have an impact on patient access. The following text provides some examples of how reimbursement systems may be affected in the near term by transformative technology entrants. • *Pressure for expanded or more flexible reimbursement structures* will increase as the pace of technology outstrips our reimbursement and policy. This has long been a challenge for new medical devices.[13,173–175] The rapid expansion of rare disease therapies has also stimulated much debate and shift of focus toward solutions to manage aggregate cost impacts.[176–178] Similarly, cellular therapies involving multiple steps and technologies face similar challenges, as do smart and e-connective technologies not readily accommodated by today's systems.[6,179–182] As the volume of technologies with "goodness of fit" issues expands, our processes for establishing reimbursement will need to adopt more flexible updating approaches. • *Recognition of evidence as a journey not a destination*. Our reimbursement systems need to better recognize that evidence develops the continuum of the asset life cycle.[183,184] At present, our fledgling value- and performance-based systems would be challenged by this iterative approach, but acceptance of RWE in pre- and postapproval outcomes-based risk sharing reflects early movement in this direction. • *Pressure for novel payment models and focus on affordability* is another key impact flowing new technology introduction.[185,186] No topic has advanced the dialogue on how we pay for new technologies more than the recent debate over payment for single-administration gene and cell therapies.[187–189] Initial launch price points have ranged from several hundred thousand dollars to more than $1 million and must often be absorbed at the time of care.[167] Key ecosystem challenges include absorbing high-cost single payment and aggregate affordability.[40,156,190–194] Many solutions including staggered and long-term payment models (eg, amortization) have been debated. Of the 4 sentinel transformative therapies launched since mid-2016, all have engaged payers with typical risk-sharing agreements and only 1 has pursued staggered payment with US Medicare.[8] Several groups, including the Alliance for Regenerative Medicine, the National Association of Managed Care Physicians, MIT NEWDIGS, and the Duke Margolis Institute, are exploring alternative financing models.[195–197] It is too early to tell where the novel payment model and affordability debates will land, but it is safe to say that solutions will challenge our modern notions of evidence-based medicine and push closer to more innovative, iterative, and collaborative methods for realizing and rewarding value.
6. Novel technologies influence on health delivery models	Novel health technologies will also have a significant impact on provider operations. The following text illustrates some key implications for provider-side dynamics. • *Limited adoption and patient access to some therapies driven by reimbursement and payment hurdles:* Because most global reimbursement systems were not built with innovative technologies in mind, provider adoption can be hamstrung by uncertainty around reimbursement.[198,199] Two key historical examples include (1) recent cell and gene therapies that were successfully approved, but were withdrawn from the EU because of commercial challenges and (2) limited US adoption for the cell therapy Provenge®.[144,200–202] In both examples, value perspective and reimbursement markedly curbed physician uptake. Nevertheless, recent curative treatments for hepatitis C have been broadly successful despite cost concerns because their effect was viewed by some as transformative.[203] This suggests that product access strategies must not focus only on payer-level uptake drivers in value demonstration. • *Challenges and opportunities within value- and performance-based incentive structures:* Many global provider organizations are shifting to value and performance models that balance quality and cost.[204–207] As innovative technologies enter the marketplace, it is important to consider how they integrate with such reward structures. Technologies such as novel diagnostics and precision medicine have substantial potential to align with provider focus on value-based medicine.[208,209] This will also precipitate changes in how we think about HEOR and value assessment, as well as the questions we are trying to address around introduction of novel health technologies.[210] • *Innovative technology is the focus of new multistakeholder partnerships:* As health stakeholder incentives begin to blur, there is a focus on integrated partnerships that combine payers, providers, patients, and manufacturers.[211] These partnerships vary in focus, but some center on leveraging novel technology to help improve quality, cost, and efficiency.[213-215] The Cancer Moonshot is a key example combining multiple stakeholders to leverage next-generation tests and immunotherapies to improve cancer care.[212] Other examples include recent partnerships on rare disease patient identification and treatment best practices[214,215] and provider-side collaborations to support advanced therapies.[216] • *Changing the provider-patient interface:* Innovative health technologies are also poised to have an impact on the provider-patient interface.[217] Novel diagnostics, health decision tools, and smart applications are emerging that enable rapid, accurate, and patient-centric treatment and monitoring. In markets such as that of the United States, where financial responsibility is increasingly being on the patient, consumer choice may drive 50% of the health insurance market by 2020, suggesting that value demonstration must increasingly consider patient acceptance drivers.[218]

ADA-SCID indicates adenosine deaminase–deficient severe combined immunodeficiency; AI, artificial intelligence; EU, European Union; FDA, Food and Drug Administration; HEOR, health economics and outcomes research; HTA, health technology assessment; RWE, real-world evidence.

The following are some key considerations for additional focus:

- It is *difficult to realize the value of transformative or curative effect when we have not defined it.* Although it is clear that our current HTA and reimbursement processes do consider differences in technology effects, it is also clear that their (1) emphasis on how to address technologies with disruptive or transformative effects out of the norm of conventional technologies seems very limited and (2) consideration of implication/impact characteristics of specific technology types such as cell and gene therapies, next-generation tests, precision medicine, and smart technologies has much room to evolve. Some of the value attributes noted here, such as efficiencies in overall pathway management or long-term avoidance of treatment and certain health outcomes flowing from curative therapies, currently set outside of conventional HTA practices.

  Until we define the characteristics of technologies that require special consideration, it will be difficult to appropriately evolve new policies and approaches to fully harness their value. We also have potential to underrecognize some technology attributes that do warrant both a broader (in terms of health ecosystem impacts) and more specific (in terms of the dimensions of value offered by a new technology) set of definitions and alignment to next-generation HTA and patient access processes. Our current methodologies for broader value assessment spanning and incorporating HTA/payers, providers/health systems, and patients will also need to evolve in tandem to better reflect holistic impact beyond current clinical and economic assessments geared toward HTA/payer processes. Such avenues also open the door for novel product differentiation beyond our conventional lens.

  The commercial landscape is more subject to technology disruption than ever before. Incoming technologies should take stock of their relative value particularly if they represent true disruption in terms of value demonstration, reimbursement, or payment norms. In tomorrow's health ecosystem, manufacturer success will depend on early and iterative pursuit of comprehensive value demonstration and market access preparation. This includes both addressing shifting technology evolution and the evolution of acceptable value packages (eg, acceptance of alternative study designs and iterative integration of real-world evidence [RWE] across the life cycle). Payer and provider decision makers also face a constant stream of technologies, some of which will disrupt their value assessment, access, and payment systems in ways we are only beginning to realize.
- Evidence development is a continuum, but *our approaches to technology assessment, reimbursement, and payment are currently more static or punctuated. In the future, we will need to consider flexible and iterative models that capture and adjust for shifts in the evidence base over time.* Although policy changes such as acceptance of RWE via the 21st Century Cures Act begin to recognize the importance of considering evidence across the continuum, we are only at the beginning of revamping our conventional evidence-based approaches. Such redefinition would also ideally consider how we can evolve clinical pathways, guidelines, and pricing paradigms to reflect rapid evolution of high-impact technology solutions. These alterations in value assessment will have implications across the entire structure of health provision, including patient access, reimbursement, and payment models.

  Our approaches for recognizing and realizing value are geared more for individual asset assessment versus evaluation of relative impact. Our consideration of the broader pathway and delivery implications of innovative technologies will sharpen in tandem with health information system/data source, RWE, and rapid data analytics advancements and our ability to leverage them for improved decision making. Support of pilot approaches and sharing of results may also help us understand how to further achieve outcome and efficiency goals flowing from technology confluence.
- We need to *rethink incentive structures and system outputs to harness transformative technologies while ensuring affordability.* Assuming that technology advancement does bring truly transformative benefits, our uptake models and systems must be able to appropriately absorb them without unintentionally dampening meaningful technology evolution. This will require reassessment of multiple dimensions of our health system processes, incentives, and expectations. It will require discarding or reinventing processes that did not anticipate the rapid pace of health technology and data evolution and the systems to measure and manage it, which some may view as having flexibility limitations. Mapping our incentive structures and their alignment with stakeholder and system goals may illuminate which practice and policy levers are best suited to strike this balance, leverage true innovation, and achieve quality and cost goals.

  Collaboration among payers, providers, manufacturers, patients, and policy makers will be the key to realizing benefits of innovative technology impacts. There is significant potential to leverage novel stakeholder partnerships to evaluate implications of novel health technologies for broader health system change. We are already seeing this across a range of partnerships and pilots, including risk-sharing agreements, convergence of data pools/registries around disease categories, and increased emphasis on value-based care. As new partnerships emerge, it will be key to look beyond the implications of individual technologies to both platform and ecosystem effects.

Tomorrow's value assessment and reimbursement environment is poised to be shaped by various rapidly evolving technology platforms, some of which will overlap or integrate. As we enter the era of transformative and potentially curative medicine, it will be important to consider how and to what extent our HTA, reimbursement, and access processes may need to change to harness true transformative value when it presents itself. Reform efforts may benefit from taking into account different technology types and the dimensions of value to ensure that approaches for harnessing value are aligned with quality, affordability, and other goals.

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Supplemental Materials

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