WHITE PAPER

OUTCOMES-BASED CONTRACTING: A HELPING HAND FOR CELL AND GENE THERAPIES

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EXECUTIVE SUMMARY

- Outcomes-based contracts (OBCs) are arrangements where payment for a drug is tied to the achievement of one or more predetermined outcome
- Manufacturers and payers are implementing OBCs for cell and gene therapies to address the risk from high upfront costs and to distribute risk more evenly across stakeholders

In this whitepaper, Health Advances proposes a framework for understanding what situations provide the greatest incentives and opportunities for OBC implementation

- An ideal opportunity for an OBC is characterized by:
  - High upfront financial risk
  - Absence of long-term outcomes data
  - A competitive market

Measurable clinical value

- The drivers for implementation of OBCs will shift in importance as the cell and gene therapy landscape continues to evolve

Stakeholders today are highly motivated by the lack of long-term outcomes data

As data matures, competition will become a larger driving force in adoption of OBCs

- Long-term outcomes data will help shape future OBCs as pharma has the opportunity to use real-world data to influence the terms and introduce additional novel payment models further reducing risk and ensuring broader adoption of cell and gene therapies.

INTRODUCTION

To anyone watching, the story of rising healthcare costs in the US is not a new one. Prescription drug prices in particular have made headlines in recent years, from outrage over the 56-fold increase of anti-malarial drug daraprim, to controversy over the steady rise in price of EpiPen packs used to quell life-threatening allergic reactions. As Figure 1 illustrates, these examples are not isolated. In fact, a congressional report released by Senator Claire McCaskill found that the price of the 20 most frequently prescribed branded drugs covered under Medicare Part D rose by more than ten times the rate of inflation from 2012 to 2017[1]. The financial impact of branded drugs is considerable — ***although branded non-generics account for just 11% of drugs dispensed, they comprise 74% of overall drug spending***[2].

477%

The Increase in Price of Chest Pain Drug Nitrostat from 2012 to 2017[1].

Stakeholders at every level are pushing back against these rising costs with a variety of methods. Payers continually look for ways to regulate drug access with step-edits and preferential tiers for more affordable drugs. Patient groups like ***Patients for Affordable Drugs Now*** work to educate the public and advocate for policy change. Top ranking Democrats, including Senator Bernie Sanders, introduced the *Medicare Drug Price Negotiation Act* a bill that would allow the Department of Health and Human Services (HSS) to negotiate better deals with drug makers for patients covered by Medicare. While that particular bill stalled in committee, these efforts are indicative of a shrinking tolerance of rising healthcare costs. Adding insult to injury, this rise in costs has not appeared to significantly improve the quality of care Americans are receiving. To address the issues of cost and quality, payers and providers are moving towards models of value-based care (VBC). These models create financial incentives for providers to improve patient outcomes and reduce expensive re-hospitalizations or unnecessary procedures. To date, most VBC efforts have focused on providers and have not translated to impact on drug prices — but that is starting to change.

Outcomes based contracts (OBCs), sometimes referred to as outcomes-based agreements or risk-sharing agreements, are arrangements where drug payments are tied to achievement of predetermined clinical outcomes

within a specific period of time post-treatment. Typically, if a drug fails to meet the predetermined outcome target, the manufacturer provides a rebate, or in some cases, a full refund. Examples of OBCs already exist in the market across various therapeutic areas and in many countries. This includes heart failure drug Entresto, for which Novartis will provide a rebate if it fails to reduce the number of patient hospitalizations[3] and Takeda's Velcade, which is only reimbursed by NHS if treatment of a patient is measured to be effective[4]. While these OBCs are not new, they are rising in popularity. According to the University of Washington's Performance-Based Risk Sharing Agreement database, the cumulative number of drugs with an OBC has risen from 61 in 2006 to 492 worldwide in 2018[5]. In the US, OBC uptake has been more limited to date, accounting for just 45[6] of the existing agreements, but is similarly on the rise.

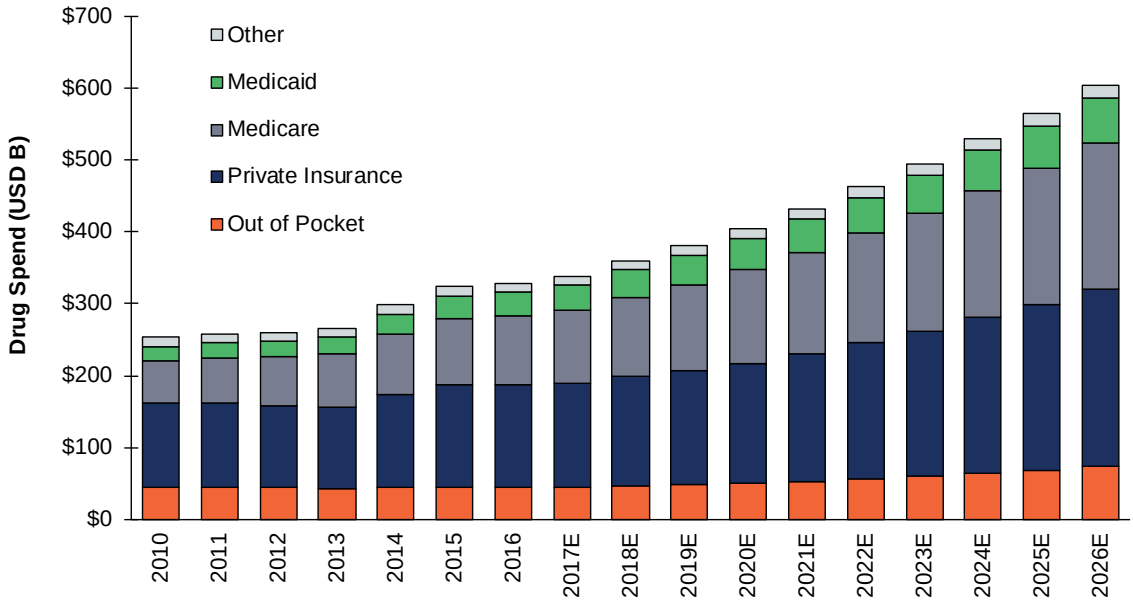

Figure 1: Rising Prescription Drug Spend

Source: Health Advances analysis, CMS 2014 NHE, Express Scripts 2016 Drug Trend Report.

The rise of OBCs and other novel contracting models coincides, and is likely driven in part by the major advancement of single-administration cell and gene therapies, often referred to as regenerative medicines. These therapies, such as ***Novartis's Kymriah, Kite's Yescarta, and Spark's Luxturna*** are genetically modified and designed to restore cell or gene function for durations much longer than traditional medicines. While the added convenience and clinical benefit these therapies offer is a huge win for patients, the high price point associated with single administration therapies poses a conundrum for manufacturers and payers. As a manufacturer, how do you price a single-administration cell or gene therapy to ensure commercial viability without causing payers to restrict access? As a payer, how do you manage financial and clinical risk when these drugs cost hundreds of thousands of dollars and lack long-term data on outcomes and durability? OBCs are one tactic manufacturers and payers are employing to relieve concerns on both sides. But is this a prudent approach? This paper will propose a framework for what constitutes a prime opportunity for OBC implementation and explore how regenerative medicine currently stack up within said framework. Moreover, this paper will strive to assess how this framework will evolve as these medicines increasingly become a part of standard care.

FRAMEWORK FOR OUTCOMES-BASED CONTRACTING IN CELL AND GENE THERAPY

The following section will define key criteria driving the shift towards outcomes based contracts for therapeutics, with an eye towards cell and gene therapies in particular.

1. Upfront Financial Risk — Will a Particular Patient Respond at All?

Key Takeaway: The massive upfront costs associated with single-administration therapies place payers at much higher risk relative to traditional therapies. OBCs can mitigate said risk.

Single administration cell and gene therapies represent a radical departure from traditional models of drug administration and payment. With that departure comes disruption of how payers typically budget for the patients they cover. Let's take a relapsed diffuse large B-cell lymphoma (DLBCL) patient as an example: traditionally payers would expect to pay for treatment with some combination of systemic chemotherapy and rituximab for some number of months until the patient stops responding. If the patient fails to respond to the initial dosing cycle, the payer is only out the cost of that very first cycle. With a single administration therapy like Yescarta (and in the absence of an OBC), a payer could end up on the hook for the full cost of therapy, a whopping $373K, even if that patient shows no response to Yescarta whatsoever.

OBCs address this upfront financial risk by providing large rebates for patients that fail to respond to a therapy in a predetermined way. It is worth noting that the overall budget impact of currently approved cell and gene therapies is miniscule compared to annual expenditure on large chronic conditions like diabetes or heart failure. Nonetheless, the immense per-patient cost posed by cell and gene therapies is enough to give payers pause; OBCs, are one way to soften the blow to payers and demonstrate faith in the product.

2. Absence of Long-Term Outcomes Data — Will the Value Endure?

Key Takeaway: The lack of long-term patient outcomes data for cell and gene therapies makes investment in these high-priced drugs risky. Will short-term clinical benefits translate to long-term value? Only time will tell.

One of the biggest challenges payers face in determining coverage is the daunting possibility that these therapies will not have durable benefits. While trials can demonstrate the near-term clinical value of these therapies, none of the pivotal trials in cell and gene therapy to date have matured enough to provide data beyond three years of follow up. The FDA has generously granted fast-track designation and expedited reviews of CAR-T products; a byproduct of this is limited longitudinal patient outcomes data at the time of launch.

Furthermore, the benefits of therapy in the long-term are not the only unknown. There are theoretical concerns about complications from viral vectors, secondary malignancies related to mutation of T-cells, and unanticipated harms that may be found as a larger number of patients receive treatment. The single-arm studies typically used in cell and gene therapy trials introduce the possibility of selection bias, further confounding payer estimates of ultimate risk. In its recent review, ICER concluded that CAR-T therapies Kymriah and Yescarta are cost-effective given the survival benefit these therapies imbue. However, the lack of long-term data forced ICER to extrapolate from 6 month data instead of the typical 4 year event-free survival. ICER was forced to cushion its conclusion stating that, "All of the uncertainties highlighted above make our comparative efficacy analyses versus standard therapy controversial."[vii]

The question of long-term clinical benefits and risks is unavoidable for truly innovative drugs like cell and gene therapies. As time goes on and the trial data for regenerative medicine matures, we expect this driver to shrink in significance. But for now, it plays a key role in the decision of manufacturers to engage in OBCs.

3. Competitive Market

Key Takeaway: OBCs have historically been used by manufactures to stand out in crowded, competitive markets. Competitive pressure exists in the cell and gene therapies space, but are driven by limited patient numbers rather than number of manufactures (for now).

Traditionally, manufacturers using outcomes-based contracts have played in a saturated or genericized market. A prime example of this is the overcrowded diabetes market. Providers and payers have come to believe that all DPP-IV inhibitors are the same and differentiation is insignificant. As such, major players such as Boehringer Ingelheim (BI), Novo Nordisk, Merck, and Lilly are engaging with payers and PBMs to establish favorable access in exchange for shared risk[viii] [ix] [x] [xi]. These manufacturers use OBCs to gain a competitive advantage and access to patients that would not have otherwise been possible.

While competition is not yet nearly as significant for cell and gene therapies in the current market, we expect this driver to grow in importance as more and more therapies move from clinical trials to the marketplace. Already Yescarta and Kymriah (both of which target CD-19) have overlapping indications and are competing for a very limited number of patients. With more than 100 CAR-T trials initiated in 2017 alone[xii], it is safe to say that competitive pressures will play a role in manufactures' decisions use OBCs.

4. Measurable Clinical Value

Key Takeaway: For OBCs to function properly, outcomes need to be measurable and clinically relevant. This may require additional endpoint development for some manufacturers.

The success of an OBC hinges on clear, well-defined outcomes. Without these, measuring success and determining payment can be challenging. To date, OBCs have been used in diseases with clear outcomes that can be measured in a short time-frame. For example, Lilly's OBC with Harvard Pilgrim for GLP-1 drug Trulicity hinges on the percentage of patients meeting their HbA1c target compared to patients on other drugs[xi]. Takeda's OBC with NHS for Velcade defined response by measuring patients' serum M protein after four cycles — rebates were issued for patients seeing less than a 50% reduction[xiii].

As obvious as this criteria sounds, fulfilling it may prove tricky for cell and gene therapies addressing conditions without any other disease-modifying therapies to date. For these opportunities, the more traditional and straightforward OBC model of comparing outcomes against patients on other drugs is not an option. Instead, manufacturers will need to develop and validate new measures and endpoints during clinical trials that can translate to OBCs post-FDA approval.

Furthermore, the best candidates for OBCs will offer high clinical value relative to standard of care therapies. Manufacturers need a high degree of assurance that their drug can reliably meet the agreed upon outcomes to enter an OBC confidentially. Similarly, payers need a high degree of confidence that the outcome measures chosen are clinically significant and worth the effort required to implement an OBC.

LUXTURNA, KYMRIAH, AND YESCARTA: HOW DO THEY FIT OUR FRAMEWORK

This section will explore how Luxturna, Kymriah, and Yescarta, profiled in Figure 2, check the boxes within our framework for OBC opportunity. These three therapies each represent a major milestone in the advancement of regenerative medicine. Spark's Luxturna, recently approved for a rare inherited form of retinal dystrophy, is the first gene therapy to be approved by the FDA and marketed in the US. Novartis's Kymriah's, initially approved for pediatric relapsed or refractory B-cell acute lymphoblastic leukemia (r/r B-ALL), is the first approved chimeric antigen receptor T-cell (CAR-T) therapy. Kite's Yescarta, approved for second line or later DLCBL is the first CAR-T therapy approved for adult patients.

		KYMRIAH (tisagenlecleucel)	YESCARTA (axicabtagene ciloleucel)	LUXTURNA voretigene neparvovec-rzyl
Company		NOVARTIS	GILEAD Kite Pharma	Spark Therapeutics
Initial Indication		R/R Pediatric B-ALL, R/R Adult BCL	R/R Adult BCL	Leber Congenital Amaurosis, RPE65 Mutations
List Price		$475K	$373K	$850K
Initial Pivotal Trial	*ID*	ELIANA	ZUMA-1	NCT00999609
	Phase	II	I / II	III
	*Pts. Evaluated**	63	101	20
	Data Available at Approval	3 months	7.9 months**	12 months
Approval		Aug 2017	Oct 2017	Dec 2017
Months from Pivotal Trial Start to Approval		~28	~33	~62
Primary Outcome Measure		ORR at 3 months	ORR at 12 months	MLMT at 12 months
Post-Marketing Commitment		1,000 patient study over 15 years	1,500 patient study over 15 years	

Figure 2: Kymriah, Yescarta, and Luxturna Overview

* Patients administered with therapy and eligible for evaluation, ** Median time frame.
Source: Heath Advances analysis, Datamonitor, company websites, Clinicaltrials.gov.

There are a few common threads between these three drugs. All three drugs cost substantially more than the standard of care (SOC) therapies — an immediate check for the Upfront Financial Risk box. Similarly, all three have demonstrated immense clinical improvement over SOC regimens in trial. Kymriah and Yescarta have more than tripled the complete response rates historically seen in r/r B-ALL and r/r DLBCL respectively. Luxturna has been able to improve eyesight as measured by multi-luminance mobility testing (MLMT) and full-field light sensitivity threshold (FST) in an indication that does not have a single other disease-modifying therapeutic option to date.

A concern among all three, however, is the lack of long-term data to confirm that the impressive results seen in trial will last much longer beyond said trial. The longest follow-up data available thus far is for Luxturna — a follow

up of its Phase III participants found that at 3 years post-treatment, patients maintained the benefit seen at 1 year post-treatment[xiv]. Follow up data for Kymriah and Yescarta are less mature (median follow up of 13.1 months[xv] and 15.4 months[xvi] respectively) but positive so far. Neither trial has reached median overall survival (OS) at the time of most recent follow up. This bodes quite well for patients, given that median OS for both indications seen in other trials is a mere 6 months[vii]. Information on how Luxturna, Kymriah, and Yescarta fit additional OBC opportunity criteria is summarized in Figure 3:

	KYMRIAH (tisagenlecleucel)		YESCARTA (axicabtagene ciloleucel)		LUXTURNA voretigene neparvovec-rzyl
Upfront Financial Risk	• List Price: $475K • Annual US Pediatric ALL Patients Eligible: 617 • Annual US DLBCL Patients Eligible: 6,223 • Annual budget impact: $3.3B	✓	• List Price: $373K • Annual US Patients Eligible: 6,223 but manufacturing capacity is only 5K • Annual budget impact: $1.9B	✓	• List Price: $850K • Annual US Patients Eligible: 350 per year for the next 5 years* • Annual budget impact: $298MM
Absence of Long-Term Data	• Kymriah persistence detected in patients up to 20 months • Median duration of remission not yet reached as of Jan 2018 data release	✓	• 42% of patients still responding at follow up (minimum one year post-infusion, median 15.4 months) • Median OS not yet reached as of Dec 2017 data release	✓	• 3-year follow up to Phase III trial found that patients maintained benefit seen at 1-year follow up
Competitive Market	• Limited therapeutic options • Besides HSCT, options are minimally effective or transient • Competes with Yescarta in DLCBL	–	• Limited therapeutic options • Besides HSCT, options are minimally effective or transient • Competes with Kymriah	–	• Luxturna is the first and only approved treatment for biallelic *RPE65* IRD
Measureable Clinical Value	• Response rates, and definitions based on cell count are clear and easily measured • ORR and CR rate of 83% • Relapse free survival probability of 75% and 64% at 6 and 12 months respectively	✓	• Response rates, and definitions based on cell count are clear and easily measured • ORR of 82%, CR rate of 58% vs historical CR rate of <15%	✓	• MLMT score is a newer endpoint designed by Spark; can be retested at any time • 65% of intent-to-treat group showed max improvement in MLMT** vs 0% of control group

Figure 3: Kymriah, Luxturna, and Yescarta OBC Opportunity

* ICER estimates that there are 1,750 eligible patients in the US and that treatment of these patients would be evenly distributed over five years, hence 350 per year.
** Patients able to pass the MLMT at the lowest tested lux level tested (1 lux) were considered to show maximal improvement.
Note: Used annual patients eligible calculated by ICER. MLMT = multi-luminance mobility test.
Source: Health Advances analysis, Spark, Novartis, Kite Pharma press releases. Source: Heath Advances analysis, Datamonitor, company websites, Clinicaltrials.gov.

Unsurprisingly, Luxturna, Kymriah, and Yescarta hit many of the criteria for a prime OBC opportunity. One key area of divergence from our framework is the competitive market criteria. Traditionally, OBCs have been concentrated in highly competitive disease areas such as diabetes, where implementing an OBC may help set a drug apart from

a number of similar competitors. These three drugs however, all target orphan indications with few, if any effective treatment options. While Kymriah and Yescarta won lead approvals in different patient populations, the two are now head to head in third line and later DLBCL patients. This pattern of unique initial approvals with subsequent movement into overlapping indications mirrors what we are seeing in the checkpoint inhibitor space and implies that we can expect a similar competitive dynamic in the future. Furthermore, Juno and Celgene's JCAR017 looms on the horizon, meaning that we could see three high profile CAR-T products targeting the same ~6K patients estimated to become eligible each year in the US. This doesn't even include the potential competition out of China, which as of May 2018, had 237 active CAR-T clinical trials[xvii], a lead over the US's 186.

So, if Yescarta checks just as many boxes in our framework criteria as Luxturna and Kymriah, why is it that Gilead/Kite does not appear to be pursuing an OBC for Yescarta? While CEO John Milligan has described Gilead as "open" to value-based pricing on a payer-by-payer basis[xviii], no agreements have been announced to date, in contrast to Luxturna and Kymriah. Details for Luxturna and Kymriah's OBCs (to the extent that information is publically available) is summarized in Figure 4. One potential explanation is that this is a strategic choice. Gilead may be expecting some insurers to be hesitant about engaging in an OBC when the per-patient financial risk is so high. By coming in at a substantially lower list price ($373K vs Kymriah's $475K), Kite is positioning Yescarta as the anti-CD19 option with less uncertainty in cost. This approach may be effective in earning Yescarta preferred status in among payers less willing to engage in the activities required to negotiate and execute an OBC.

	KYMRIAH® (tisagenlecleucel)	LUXTURNA™ voretigene neparvovec-rzyl
Parties Involved	CMS, Treatment centers	Harvard Pilgrim, Express Scripts, CMS
Assessment Timepoint(s)	• 30 days post-treatment	• Short-term: 30-90 days • Long-term: 30 months
Outcomes Measured	• Objective response per Lugano criteria	• Full-field light sensitivity threshold (FST) • Baseline FST will be established prior to Luxturna administration
Terms of Agreement	• Payment to CMS would occur only if patient responds to Kymriah within first 30 days	• If efficacy is not demonstrated within timeframe, Spark will offer rebates up to but not exceeding standard Medicaid rebate • Proposal for CMS would allow payment as an annuity rather than upfront lump sum
Notes	• CMS pilot was cancelled after backlash due to Novartis's $1.2 million payment to Michael Cohen	• Agreements are for specialty pharmacies and commercial payers • Payment negotiation for treatment centers will be left up to payers

Figure 4: Cell and Gene Therapy OBC Agreement Details to Date

Source: Health Advances analysis, FiercePharma. Informa, company press releases and websites.

And if recent sales are any indicator, this strategy may be paying off for Gilead. In the second quarter, Novartis reported $16MM in sales of Kymriah, falling slightly below analyst expectations of $20MM — and less than a fourth of Yescarta's $68MM second quarter sales[xix].This is not to say that payment and pricing strategy is the

only factor at play here; it is important to remember that Yescarta had a six month head start in the adult DLBCL indication. Furthermore Novartis has recently hit bumps in the road in expanding its manufacturing process to accommodate the higher dose required for adult patients that may have impacted sales[xx]. Regardless, the relative success of Kymriah and Yescarta over the next few years will be a fascinating look at how receptive payers and providers are to outcomes based contracting for regenerative medicine.

HOW WILL THE FRAMEWORK SHIFT IN THE FUTURE?

With the rapid evolution of the cell and gene therapy space, it is inevitable that the framework for OBCs and motivation to implement them will shift over time. While the upfront financial risk will remain a constant and central driver, we expect the relative importance of competition and absence of long-term data to shift as illustrated in Figure 5.

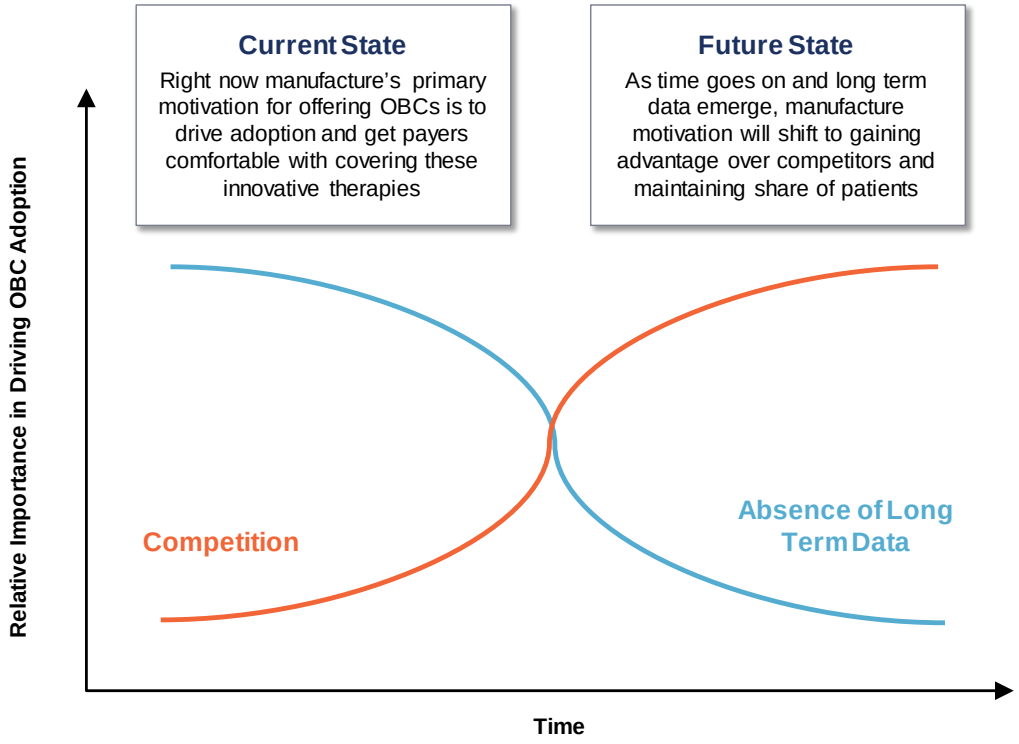

Figure 5: Future Shift in Framework

Source: Health Advances analysis.

At the risk of stating the obvious, the driving strength of absence of long-term data will diminish as cell and gene therapy data matures and eliminates said absence. Both Kymriah and Yescarta have 1000+ patient long-term follow up studies that will track results over the next 15 years[xxi] [xxii] to fulfill their post marketing requirements. In addition to providing critical information on unforeseen safety issues such secondary malignancy and other risks, these follow up trials will help establish baselines for durability of response. Ten years from now we will have a much larger body of evidence to inform expectations on patient response, lowering the incentive for manufacturers to engage in OBCs.

In contrast, the influence of competition will rise dramatically as more cell and gene therapeutic agents make it to market. The Alliance of Regenerative Medicine estimates that there are more than 870 companies active in the cell therapy, gene therapy, and tissue engineering space, responsible for 977 clinical trials as of Q2 2018[xxiii] illustrated in Figure 6. More than 50% of these trials are targeting oncology indications such as lymphoma, glioblastoma, breast cancer, and more. In addition to the rise in volume, we are seeing the pace of clinical development quicken for cell and gene therapies. Figure 7 illustrates how the average time to completion for cell and gene therapy trials has steadily sunk from 7.0 to 3.1 years over the last two decades. Furthermore, the stakes of winning any individual patient will be even higher due to the single administration nature of these therapies. In more traditional models of cancer treatment, patients have the opportunity to switch therapies for a variety of reasons including lack luster response, tolerability issue, copayments, etc. With drugs like Kymriah and Yescarta, the prospect of switching therapies or re-challenging is dubious at best. This means manufacturers will have even stronger incentive to make their agent preferred (relative to competitors) among payers and providers — as the first drug a patient gets could be the only drug. Outcomes-based contracting is one tool manufacturers will use to make that happen.

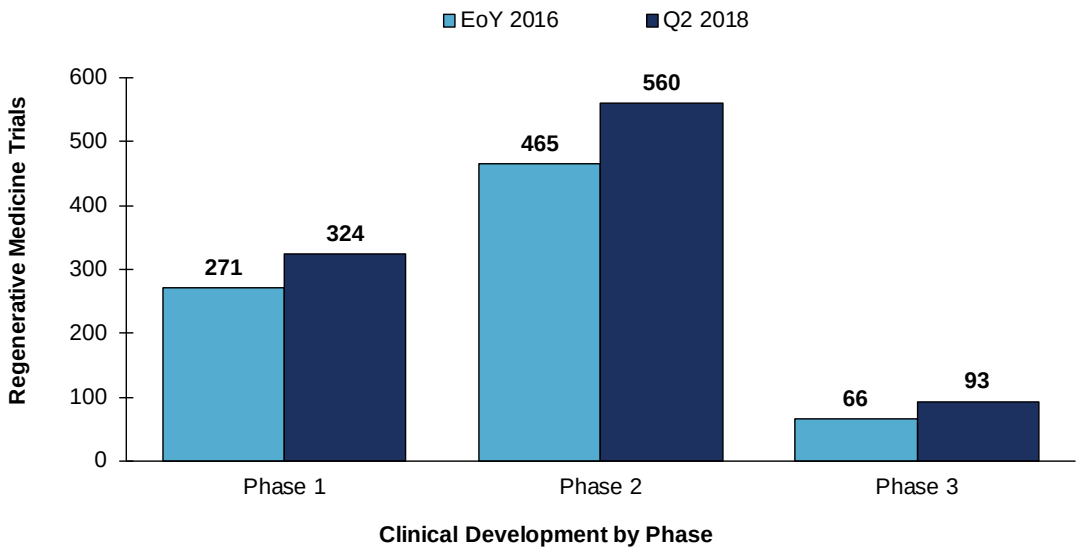

Figure 6: Increasing Regenerative Medicine Trials

Source: Health Advances analysis, Alliance for Regenerative Medicine Quarterly Reports.

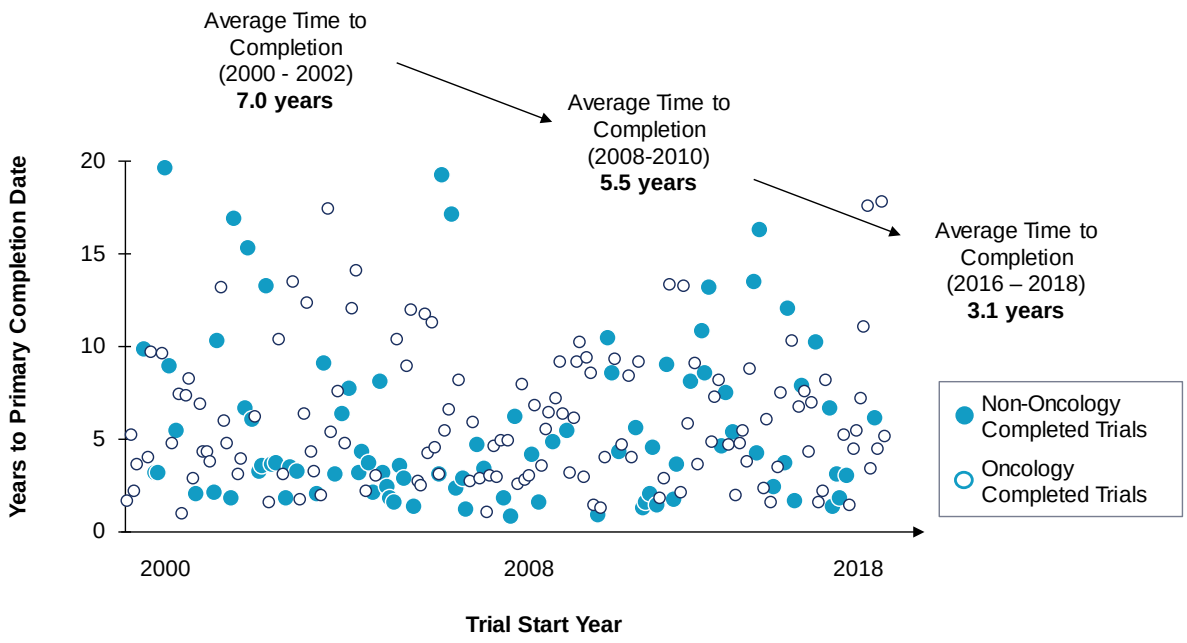

Figure 7: Time to Completion for Cell and Gene Therapy Trials

Note: Excludes China-only trials. Includes active and completed trials. For active trials, estimated primary completion date was used.
Source: Health Advances analysis, Clinicaltrials.gov, PharmaProjects.

Another fascinating question is how the risk dynamic for drugmakers and payers will change over time. The traditional model of oncology drug development goes as follows: Drugmakers start by targeting the clearest path to approval, which is typically the indication or patient segment where they believe the drug is most likely to work. Once initial approval is won, manufactures use label expansion trials to move into adjacent indications broadening their base of addressable patients. Take AstraZeneca's Lynparza (olaparib) for example. Lynparza won its original approval in ovarian cancer, but only for patients with specific mutations, namely germline *BRCA1* or *BRCA2*. Eventually Lynparza was approved for ovarian cancer patients regardless of *BRCA1/2* mutation status, and for a subset of breast cancer patients. Today, AstraZeneca has trials ongoing in a variety of solid tumor types[xxiv], all of which stand to expand the number of Lynparza-eligible patients even further. These trials include prostate cancer, gastric cancer, and even notoriously difficult to treat pancreatic cancer and glioblastoma.

AstraZeneca's approach to clinical development of Lynparza is a perfectly rationale one. Even if just a small percentage of pancreatic patients benefit from the drug, a large proportion of eligible patients will likely attempt the drug since treatment options are so limited. Under traditional payment models this is to the benefit of the manufacturer — while under an OBC this is not necessarily the case. Expansion to larger, more heterogeneous patient populations where response rates will likely be lower actually increases the per patient risk to manufactures. In other words, as it becomes less likely that any individual patient will respond, it also becomes less likely that the manufacturer will receive full payment for any individual patient. This dynamic means that Novartis, Spark, and any other drugmakers engaged in OBCs looking to expand labels will have strong incentive to develop or acquire diagnostics capable of identifying likely responders.

CONCLUSION AND FUTURE OUTLOOK

Recent success with cell and gene therapies is propelling the field faster and further than ever before. Despite the uncertainty of long-term benefits of these therapies, the pace of development continues to increase. However, this uncertainty creates financial risk for payers that are grappling with the unknown duration of efficacy of these expensive therapies.

Outcomes-based contracts aim to more evenly distribute this risk among payers and pharma manufacturers. Several players have engaged in OBCs that reimburse the payer for costs if the therapy fails. The parameters of these contracts are variable, and the industry is starting to experiment with new payment models, including monthly payments and payment linked to lifespan. These contracts, and their nuanced payment terms, will become increasingly important to product forecasts and revenue recognition.

Tracking and analyzing real-world data is the cornerstone to fulfilling the promise of OBCs. Many players are working on making real-world data useable at scale, including scrubbing, structuring, and bridging multiple sources (clinical, genomics, outcomes, and cost data). As the data industry matures, cell and gene therapy manufacturers will have the opportunity to use richer clinical and genomics data alongside companion diagnostics to better define the target patient population for each therapy. This data can also lead to better designing the terms of OBCs that will reduce financial risk while maintaining a strong position in an increasingly competitive space.

KEY QUESTIONS

Many questions still remain unanswered that will lead us to a better understanding of how these therapies can reach full adoption potential. Health Advances often helps its clients think about the future of cell and gene therapy, and tackle questions like these. If they resonate with you and you would like to discuss them, please contact us.

Structure of OBCs

- How will the structure and terms of an OBC sufficiently incentivize a manufacturer if their drug provides high clinical value under a growing body of evidence?
- What leverage will payers have under these scenarios?
- What is the anticipated development arc of short-term outcomes that predict long-term benefits?
- What happens when patients who received a therapy under a deferred payment outcomes-based agreement switch insurers?

Pricing

- How must pricing change to adapt to a high one-time cost across much larger target populations?

Opportunities

- Will patient registries play a larger role in tracking patients across different payers, or will other digital health tools rise to the challenge?
- What technologies (e.g., biomarker testing, predictive analytics, digital biomarkers) have a role to play in addressing these challenges?

Emerging Technologies

- What technological advances are needed in patient response detection to enable wider use of OBCs?
- How will emerging real-world data sets go on to shape OBCs for cell and gene therapy

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For further discussion on the future of OBCs for cell and gene therapy and strategic implications, contact ***Amanda Sani*** at ***asani@healthadvances.com***

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REFERENCES

[1] Homeland Security and Governmental Affairs Minority Staff Report (2018) Manufactured Crisis: How devastating drug price increases are harming America's seniors. HSGAC Senate website.

[2] Association for Accessible Medicines (2017) Generic Drug Access and Savings in the US. AAM Access Savings Report.

[3] Humer (2016) Insurer Cigna and Novartis set heart-drug price based on health outcome. Reuters website.

[4] Kudrin A (2012) Reimbursement challenges with cancer immunotherapies. Human Vaccines & Immunotherapies, 8(9): 1326-1334.

[5] University of Washington Performance Based Risk Sharing Database accessed on September 17, 2018.

[6] DataMonitor Healthcare (2018) Value-Based Reimbursement in the US 54.

[vii] Institute for Clinical and Economic Review (2018) Chimeric Antigen Receptor T-Cell Therapy for B-Cell Cancers: Effectiveness and Value Evidence Report.

[viii] Caffrey M (2018) Highmark Reaches Value-Based Contract for Empagliflozin, Fixed-Dose Combinations. The American Journal of Managed Care.

[ix] Lecher D (2017) Prime Therapeutics Signs Outcomes-Based Contract with Novo Nordisk for Type 2 Diabetes Drug Victoza (liraglutide). PRNewswire.

[x] Caffrey M (2016) Aetna, Merck Reach Value-Based Deal on Diabetes Drugs and Collaborate on Wellness. The American Journal of Managed Care.

[xi] Staton T (2016) Lilly's Trulicity joins pay-for-performance trend with Harvard Pilgrim deal. FiercePharma.

[xii] Townsend M (2018) The expansion of targetable biomarkers for CAR-T cell therapy. Journal of Experimental & Clinical Cancer Research

[xiii] Mayor (2006) Drugs "refund" scheme proposed for England and Wales. The BMJ.

[xiv] Spark Press Release (2017) Three-year Follow-up Phase 3 Data Provide Additional Information on Efficacy, Durability and Safety of Investigational LUXTURNA™ (voretigene neparvovec) in Patients with Biallelic RPE65-mediated Inherited Retinal Disease.

[xv] Novartis Press Release (2018) Novartis announces NEJM publication of updated analysis from ELIANA trial showing longer-term durable remissions with Kymriah(TM) in children, young adults with r/r ALL.

[xvi] Gilead Press Release (2017) Kite Announces Long-Term Data From Pivotal ZUMA-1 Study of Yescarta™ (Axicabtagene Ciloleucel) in Patients With Refractory Large B-cell Lymphoma.

[xvii] Yang (2018) Can China Ace the CAR-T Race? Scrip News.

[xviii] Morrison (2017) Gilead 'open' to considering value-based pricing for Yescarta with some payers. APM Health Europe.

[xix] Gilead Press Release (2018) Gilead Sciences Announces Second Quarter 2018 Financial Results.

[xx] Pagliarulo (2018) Novartis hits CAR-T manufacturing snag as Kymriah sales disappoint. Biopharma Dive.

[xxi] ClinicalTrials.gov. Accessed September 17, 2018. CD19 CART Long-term Follow Up (LTFU) Study.

[xxii] FDA.gov (2017) BLA Approval Letter for axicabtagene ciloleucel.

[xxiii] Alliance for Regenerative Medicine (2018) Q2 2018 Quarterly Data Report.

[xxiv] AstraZeneca website. Accessed September 20, 2018. Our Science: Our Pipeline.

GLOSSARY OF TERMS

ALL	Acute Lymphoblastic Leukemia
BCL	B-Cell Lymphoma
CAR-T	Chimeric Antigen Receptor T Cell
CD-19	Cluster of Differentiation 19
CMS	The Centers for Medicare and Medicaid Services
DLBCL	Diffuse Large B-Cell Lymphoma
DPP-IV	Dipeptidyl Peptidase IV
FDA	Food and Drug Administration
FST	Full-field Light Sensitivity Test
GLP-1	Glucagon-Like Peptide 1
ICER	Institute for Clinical and Economic Review
MLMT	Multi-Luminance Mobility Test
NHS	National Health Service
OBC	Outcomes-Based Contract
ORR	Overall Response Rate
OS	Overall Survival
PBM	Pharmacy Benefit Manager
R/R	Relapsed/Refractory
SOC	Standard Of Care
VBC	Value Based Care