Three Essays in Health Economics

Towards Alternative Payment Models for High-Value, High-Cost Medical Treatments

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Contents

Abstract

The emergence of high-cost treatments has accelerated the pace of discussions about alternative payment models that would simultaneously enable rapid patient access while ensuring sustainable health care spending. However, limited empirical research exists on the magnitude of the problem and the expected performance of such payment models.

The first paper presents a pipeline analysis of regenerative treatments in clinical trials. It finds that there are nearly 50 late-stage clinical trials that could produce regenerative drugs with potentially high prices. Alzheimer's disease poses the largest budget impact risk for U.S. payers, with new spending likely to exceed $50 billion annually. Spending on several other regenerative treatments, including treatments for traumatic brain injury, X-linked retinoschisis and congestive heart failure, could each exceed $5 billion annually.

The second paper studies a novel payment model linking a drug's performance to pre-negotiated price levels. Drawing on the Future Elderly Model (FEM), it estimates the clinical benefits of PCSK9 inhibitors under three different efficacy scenarios. It shows that an adaptive pricing approach has the potential to lower the cost per event avoided under a low-efficacy scenario, thus avoiding unnecessary spending, should the drug not meet clinical trial efficacy in the real world.

The third paper studies deferred payment in a gene therapy for congestive heart failure. It draws on a simulation of more than 91,000 Medicare fee-for-service beneficiaries over a period of 3 years and finds that deferred payment results in a 26.1% reduction of cardiovascular admissions and a 23.3% reduction of deaths over a three-year period, both relative to status quo payment and assuming a fixed budget constraint. Financial gains to payers and manufacturers are relatively minimal, with savings on avoided admissions amounting to just 0.3% of total spending, primarily due to the small share of expected cost savings on the total cost of therapy.

The dissertation finds that large budget pressures resulting from regenerative treatments will be driven by several specific indications, and tests how two different payment models could help address the uncertainty about clinical benefits and the high upfront cost of some emerging therapies.

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Introduction

The emergence of high-cost treatments has accelerated the pace of discussions about alternative payment models that would simultaneously enable rapid patient access while ensuring sustainable health care spending. Concerns about access and payment sustainability are particularly imminent in case of therapies with a regenerative or curative potential – while providing substantive clinical value, they may be delivered over a relatively short period of time, thus concentrating payment into a shorter timeframe than the accrual of clinical benefits. Given the structure of the U.S. health care system and constrained health care budgets, existing payment arrangements result in a limited willingness of public and private payers to reimburse therapies with either uncertain clinical potential or a long-term clinical benefit that may not benefit the payer after the patient switches to a different plan. In current literature, there is a limited understanding of solutions that would ensure that three conditions are met: 1) eligible patients have rapid access to breakthrough therapies, 2) public and private payers utilize their budgets in a cost-effective way, and 3) incentives for productive innovation in drug development are protected. This dissertation aims to provide an empirical foundation for discussions about the budget impact of curative therapies and to test two alternative payment models that have the promise of addressing the incentive mismatch of existing payment for medical treatments.

Incentives for new payment models for prescription drugs

Drug prices have traditionally increased faster than other products and concerns about price gouging on the prescription drug market in the United States have been voiced in recent years. Yet, there are also legitimate reasons for higher prices of some new therapies, which may result in a greater pressure to implement more efficient payment models. Two of these trends – the emergence of cures and the uncertainty of real-world effectiveness – are discussed briefly.

Emergence of cures

While new treatments have been entering health care markets over the last many decades, the last several years have seen several new drugs produce breakthrough treatments for previously incurable diseases. Moreover, many new drug candidates in stage II and III of clinical trials are

showing promise to be regenerative in nature (in contrast to chronic treatments) and might be delivered in just one or a few visits to a physician's office. In the first paper of this dissertation, I show that indications with potential regenerative treatments include Alzheimer's disease, acute myocardial infarction, hepatitis B, hemophilias, sickle cell disease and others. Collectively, their approval could upend the traditional payment model for prescription drugs, especially in cases where large numbers of patients will be eligible for the treatment immediately or when it may not be possible to determine the clinical benefit fully prior to launch.

The biggest shock experienced by payers so far followed the approval of a cure for Hepatitis C, offered at a list price of $84,000 for a 12-week regimen. Despite being cost-effective using traditional criteria, the immediate impact on payer budgets resulted in state Medicaid programs restricting treatment to only the most ill patients.[i] Limiting the adoption of these drugs could have had, unfortunately, negative spillovers: further spreading of the infection and additional medical costs incurred by patients not receiving the drug. In just the first two years on the market, Hepatitis C drugs accounted for $18 billion in new spending while the average cost per claim in Medicare Part D was $28,360 between 2014-2015, indicating significant discounts to the list price.[ii] Yet, even if all U.S. patients with Hepatitis C were treated at this price (which is unlikely), the aggregate budget impact would be $85 billion – hardly manageable to make available in a short time period. During the same period, out-of-pocket costs for Sovaldi were an estimated $6,608 per patient[iii], a high amount for the generally lower-income patient population.

Uncertainty about clinical effectiveness of approved treatments

The emergence of new therapies with uncertain real-world effectiveness has incentivized payers to consider innovative payment models.[iv] In cases of insufficient clinical trial evidence, payment may be offered in return for 'evidence development' – collecting further clinical outcome data while the drug is made commercially available – or can be outcome-based, where

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[i] Silverman, Ed. (2014). Illinois Med Director on Gilead Hep C Pill: "We Want to be Compassionate". *Wall Street Journal*. https://blogs.wsj.com/pharmalot/2014/07/31/illinois-med-director-on-gilead-hep-c-pill-we-want-to-be-compassionate/

[ii] Hoadley, Jack, Neuman, Tricia, et al. (2016). The Cost Of A Cure: Revisiting Medicare Part D And Hepatitis C Drugs. *Health Affairs Blog*. http://healthaffairs.org/blog/2016/11/03/the-cost-of-a-cure-revisiting-medicare-part-d-and-hepatitis-c-drugs/

[iii] Ibid.

[iv] Carlson, Josh J, Sullivan, Sean D, et al. (2010). Linking payment to health outcomes: a taxonomy and examination of performance-based reimbursement schemes between healthcare payers and manufacturers. *Health Policy*, 96(3), 179-190.

pre-negotiated rewards or discounts are applied based on clinical effectiveness in the real world.[v] Uncertainty about clinical effectiveness[vi] is expected to be an issue for many regenerative treatments, including cell and gene therapies, whose benefits may take many years to materialize. The FDA has issued guidance for gene therapy manufacturers to collect safety data for a period of 15 years, illustrating the magnitude of the challenge.[vii] Outcome-based agreements have been implemented in numerous cases in the U.S. but published evidence of them resulting in better value for money is scarce, barring the growing number of agreements implemented.

In the United States, the market entry of PCSK9 inhibitors to treat hypercholesterolemia was subject to uncertainty about the drugs' impact on lowering mortality and incidence of cardiovascular events, prompting payers like Cigna and Harvard Pilgrim to enter in outcome-based agreements[viii] Harvard Pilgrim, specifically, has agreed to rebates with Amgen should its drug, Repatha®, not meet specific clinical outcomes in the real world.[ix] In this dissertation, I present another approach to payment for drugs with uncertain clinical benefits like PCSK9 inhibitors.

Oncology is another large area with uncertainty about effectiveness: clinical benefits of many treatments, including cancer immunotherapies, are observed in smaller subsets of patients, and often, off-label use may produce variable outcomes.[x] The high cost of these treatments associated with a risky, but potentially significant clinical benefit (in best-case scenarios, a durable relapse) could make such treatments suitable candidates for performance-based reimbursement contracts.[xi]

Additional trends, such as increasing unit costs of new drugs – with new gene and cell therapies priced at more than $100,000 per course of treatment, and budget pressures – with U.S.

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[v] Ibid.

[vi] In contrast to clinical efficacy, which is observed in clinical trials.

[vii] FDA. (2006). Guidance for Industry: Gene Therapy Clinical Trials - Observing Subjects for Delayed Adverse Events. https://www.fda.gov/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/cellularandgenetherapy/ucm072957.htm

[viii] Sagonowsky, Eric. (2017). Amgen puts Repatha outcomes data to work in refund deal with Harvard Pilgrim. http://www.fiercepharma.com/pharma/amgen-inks-repatha-refund-arrangement-harvard-pilgrim

[ix] Ibid.

[x] Ramsey, S. D., & Sullivan, S. D. (2014). A new model for reimbursing genome-based cancer care. *Oncologist*, 19(1), 1-4. doi: 10.1634/theoncologist.2013-0392

[xi] Persson, U., & Jönsson, B. (2016). The End of the International Reference Pricing System? *Applied Health Economics and Health Policy*, 14(1), 1-8. doi: 10.1007/s40258-015-0182-5

per capita spending on prescription drugs exceeding $1,000[xii] – have also been discussed in literature.

Research objectives

In its first part, this dissertation aims to contribute evidence on the expected budget impact of novel therapies currently in late-stage development. The second part consists of two papers – simulations of the performance of two unique payment schemes in two specific indications: hypercholesterolemia and congestive heart failure. The first of these studies a novel payment model based on pre-negotiated, outcome-based pricing for PCSK9 inhibitors, a treatment already available in the United States, and the second simulates a deferred payment model for an assumed high-cost gene therapy to treat congestive heart failure. I conclude with policy recommendations.

[xii] OECD. 2017. Pharmaceutical spending. Retrieved from: https://data.oecd.org/healthres/pharmaceutical-spending.htm [Accessed September 1, 2017].

Paper I: Budget Impact of Regenerative Treatments

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Introduction

The advent of direct-acting antiviral drugs for Hepatitis C has led to a vivid debate about the affordability of so-called "cures" [1], i.e., pharmaceutical products that are expected to have a lasting or potentially regenerative effect on the trajectory of a chronic disease with a limited number of doses [2-5]. While eagerly awaited by patients and physicians, the high cost for a course of treatment, as much as $84,000 for 12 weeks of treatment with sofosbuvir (the first treatment to reach the market), combined with the sizeable treatment-eligible population led several payers to restrict access [6]. Importantly, these access restrictions were not imposed because of concerns about effectiveness or cost-effectiveness, but in an effort to manage the short-term impact on budgets.

Historically, drugs for chronic conditions, such as heart failure and diabetes, have aimed at disease control, i.e., halting or decelerating the progression of an illness. Treatment is typically life-long, implying a large number of doses per patient, and medicines are paid when dispensed. "Cures" or regenerative treatments, in contrast, try to fundamentally alter the disease process with a short treatment course, implying few doses per patient. Even if we assumed that the cost of the cure were comparable to the cumulative lifetime costs of maintenance treatment, the cost would be spread over a small number of doses. Thus, the per unit cost of such a treatment would be much higher and payment for treatment would be heavily frontloaded.

The budget impact of potential cures is unknown, yet concerns about its magnitude across different indications has prompted discussions about best ways to address it. For example, in the wake of the Hepatitis C shock, several experts have argued that the approach to payment for high-cost drugs should be rethought [7-8], with some who have proposed a deferred payment

model for regenerative treatments, which would lessen the immediate budget impact for payers [9-11]. Under such model, drugs are no longer paid for upfront, but over time and, in some cases, contingent on real-world performance [12-13]. For example, Spark Therapeutics, which has been developing a gene therapy for a hereditary form of blindness, SPK-RPE65, reportedly discussed "staggered-payment alternatives including pay-for-performance models that would spread costs over an extended period based on effectiveness" [14] while GlaxoSmithKline considered different pricing options, including flexible "payment terms over a number of years" for Strimvelis, its gene therapy for severe combined immunodeficiency (SCID) [15].

While conceptually attractive, implementing such payment models is a complex challenge for two reasons. First, patients and their outcomes have to be tracked over time to ascertain whether the conditions for continuing payment have been met. This is feasible if the required data are routinely collected and audited, such as data on hospital admissions which can be derived from insurance claims. However, outcomes that require dedicated collection of clinical data (e.g., tumor progression, or patient-reported outcomes like symptom control), necessitate complex agreements between patients, clinicians, payers and pharmaceutical companies to govern the collection, sharing, and audit of data. Moreover, multi-payer systems, like the U.S., face the additional challenge that patients might switch payers after having received a treatment, which introduces the need to resolve how data and payment responsibilities would be transferred between payers [16]. Second, deferred payment schemes could run afoul of several laws and regulations specific to the U.S. market [17].

Given the complexity and cost of setting up alternative payment models for regenerative drugs, the obvious question arises whether the need for them is great enough for stakeholders to make the investments that are necessary to implement them. Our paper aims to shed light on that very question. We analyzed the development pipeline for curative treatments to predict potential spending over the next seven years in the U.S. We also interviewed health plan executives to obtain their perspective whether new payment models are needed, given their expectations and our findings on the predicted increase in spending.

Methods

Pipeline review

We focused our search on the top 25 biopharmaceutical companies by sales (Roche, AbbVie, Johnson & Johnson, Amgen, Merck & Co, Celgene, Pfizer, Novartis, Gilead Sciences, Sanofi, GlaxoSmithKline, Allergan, Bristol-Myers Squibb, Shire, Eli Lilly, Novo Nordisk, AstraZeneca, Biogen, Boehringer Ingelheim, Valeant Pharmaceuticals, Takeda, Regeneron Pharmaceuticals, Otsuka Holdings, Teva Pharmaceutical Industries and Astellas Pharma). We reviewed their development pipelines for regenerative therapies as published on their websites. In addition, we searched ClinicalTrials.gov for clinical trials of cell or gene therapies in phases II or III that were conducted by any company by using key words "gene", "genetic" and "cell". We reviewed the status of each identified drug using ClinicalTrials.gov and company websites to eliminate programs that had been abandoned or likely discontinued (if no updates have been provided since 2014). Of note, we exclude oncology given the availability of budget impact analyses in the field, relative to other disease areas [18]. For example, it has been argued that initial CAR-T leukemia indications have an $18 billion potential alone, assuming a $200,000 cost of treatment [25]. Our search was conducted between January 2017 and March 2017.

Spending prediction

We used the pipeline review to predict annual expected spending on regenerative treatments for the U.S. over the next seven years. First, we obtained data on probability of technical success, i.e., the likelihood that a given drug will obtain regulatory approval, based on trial stage and therapeutic area from a dataset containing information for 7,455 development programs between 2006 – 2015 [19]. This estimate of technical success was used to incorporate the fact that many treatments fail during the clinical development process into the overall spending estimates. This study calculated phase transitions for FDA registration-enabling development programs, and classified these transitions by disease area [19]. Second, we projected date of market entry based on a 2014 Tufts study [20] that suggests an average time to market of 46.7 months from end of Phase 2 and 16 months from end of Phase 3. These results are based on a sample of 106 successfully approved drugs. We added an additional 12-month lag to account for the regulatory complexity that regenerative therapies are expected to face and the fact that some first-in-line

drug candidates may fail in trials. If more than one drug a given indication was being developed, we base our projections on the market entry for the candidate that is farthest along in the development process under the assumptions that it would have the largest budget impact.

We estimated the number of patients that are likely to be eligible for each drug based on published estimates for disease prevalence and incidence. For chronic conditions, we projected the number of prevalent cases at the time of expected market entry and added incident cases in each subsequent year. For acute conditions, we used annual incidence estimates. We then used the respective trial exclusion and inclusion criteria as well as estimates for the proportion of patients, which is sufficiently controlled with established treatment options– if applicable, to identify the subpopulation that will be eligible for the new treatment. Details on the estimation can be found in Appendix A.

For the candidates identified, we used hypothetical price assumptions based on the closest analogues:

- $50,000 per patient for regenerative treatments for Alzheimer's disease, antivirals and population disease therapies (applicable to degenerative arthritis, congestive heart failure, painful diabetic neuropathy, peripheral arterial disease, acute myocardial infarction, myocardial infarction, Parkinson's disease and traumatic brain injury), based on average price of specialty drugs [22],
- $250,000 per patient for cell therapy (applicable to severe hypoxic-ischemic encephalopathy), based on the potential cost of current stem cell transplants [23-25], and
- $1,000,000 per patient for gene therapies (applicable to all other indications, including hemophilia A and B, sickle cell disease, amyloidosis and others) based on expert estimates [14, 26] and the price of Glybera, the first commercialized gene therapy [27].

Finally, we projected market uptake by assigning two different launch curves: for indications with an established standard of care, we use the industry average of 6 years from launch to peak sales [21]. For indications without an established treatment option, we assume that peak sales are reached by year 3 and then decline by 10% annually, roughly mirroring a 12-year lifecycle of a novel therapy.

Payer interviews

We conducted semi-structured interviews with a convenience sample of eight medical directors at U.S health plans. The objective of these interviews was to derive insights into how payers were beginning to think about the potential fiscal challenges posed by the emergence of

regenerative therapies, and the potential implications these challenges could have on patient access. We asked the medical directors about their expectations for future growth in prescription drug spending by therapeutic area and type of treatment (e.g., regenerative vs not), their plans' current and anticipated responses to this trend, their perspectives on deferred payment models for regenerative therapies (including the potential designs of such models) as well as other insights related to alternative payment models for regenerative treatments. As a prompt, we asked interviewees about the possibility of introducing a payment model that would stretch payments over time and across payers to address the immediate budget impact and adverse selection, respectively, resulting from regenerative treatments. The interviews were conducted between February and March 2017.

Results

Projected Spending on Regenerative Drugs

We identified 48 regenerative drug candidates for 19 indications that fell into four broad categories: (1) Alzheimer's disease, (2) chronic viral infections, (3) common chronic conditions and (4) genetic disorders (Figure 1).

Figure 1: Current pipeline for curative pharmacologic treatments

Primary Indication	First Likely Candidate to Market	Sponsor	Estima-ted Launch	Primary Trial Comple-tion	Clini-cal Trial Phase	NCT Identifier	Other candidates
Alzheimer's Disease							
Alzheimer's Disease	Gantenerumab	Roche	2020	July 2018	III	NCT02051608	• CERE-100 • LY3202626 • C2N-8E12 • AMG 520 • CNP520/ CAD106 combo • Aducanumab • Crenezumab • Gantenerumab • Verubecestat • E2609 • LY3314814 • JNJ-54861911
Chronic Viral Infections							
Hepatitis B	GS-9620	Gilead	2021	May 2016	II	NCT02166047	
Hepatitis C	MK-3682B	Merck	2023	August 2018	II	NCT02613403	• MK-3682/MK-8408 • GSK2878175 • AL-335 • Danoprevir/ Ritonavir combo

| Common Chronic Conditions							
Acute Myocardial Infarction	MPC-25-IC	Mesoblast	2021	July 2018	II	NCT01781390	
Congestive Heart Failure	Ad5.hAC6 (RT-100)	NHLBI, and Renova	2019	January 2015	I/II	NCT00787059	
Degenerative Arthritis	TissueGene-C	Kolon Life Science	2018	October 2013	II	NCT01221441	
Myocardial infarction	Allogeneic Cardiosphere-Derived Cells (CAP-1002)	Capricor, NIH, and NHLBI	2022	September 2017	I/II	NCT01458405	
Painful Diabetic Neuropathy	VM202	ViroMed	2020	April 2018	III	NCT02427464	
Parkinson's Disease	AADC Gene Therapy	Jichi Medical University, Takara and Gene Tx Research Institution	2022	October 2017	I/II	NCT02418598	• CERE-120 • ProSavin
Peripheral Arterial Disease/ Vascular Disease	DVC1-0101 gene therapy	Kyushu University	201	October 2016	II	NCT02276937	• HGF Plasmid • PDA-002
Severe Hypoxic-ischemic Encephalopathy	HPDSC+HIE	New York Medical College and Celgene	2024	June 2019	II	NCT02434965	
Traumatic Brain Injury	SB623 cells	SanBio	2022	June 2017	II	NCT02416492	
Genetic disorders							
Beta-Thalassemia	LentiGlobin BB305	bluebird bio	2022	December 2017	I/II	NCT02151526	• TIGET-BTHAL
Hemophilia A	Factor VIII gene transfer	Spark Therapeutics	2024	August 2019	I/II	NCT03003533	• BMN 270 • SPK-8011
Hemophilia B	AAVrh10FIX gene therapy	Dimension Therapeutics	2022	September 2017	I/II	NCT02618915	• AAV5-hFIX • AskBio009 • DTX101 • SPK-9001
Sickle Cell Disease	Gene transfer	Children's Hospital Medical Center, Cincinnati	2022	July 2017	I/II	NCT02186418	• BB305 • SCD gene therapy
Stargardt Disease	SAR 422459	Oxford BioMedica	2021	November 2018	I/II	NCT01367444	
Usher Syndrome	UshStat	Sanofi	2019	April 2019	I/II	NCT01505062	
X-Linked Retinoschisis	rAAV2tYF-CB-hRS1	Biogen and Applied Genetic Technologies Corp.	2022	December 2017	I/II	NCT02416622	

Source: Authors' analysis of company websites and ClinicalTrials.gov

The pipeline review indicated that the majority of regenerative candidates currently under development were for common chronic conditions as well as genetic disorders, with additional

drug development programs in Hepatitis B and C and continuous development of Alzheimer's disease treatments.

We combined the population estimates and prices to estimate total annual expenditure on regenerative therapies in the U.S, adjusted based on the probability of regulatory approval given stage of development. Based on these calculations, we estimate that spending on regenerative treatments could reach $34 billion by 2023 on a risk-adjusted basis (**Error! Reference source not found.**).

Figure 2: Forecast of risk-adjusted spending on regenerative treatments
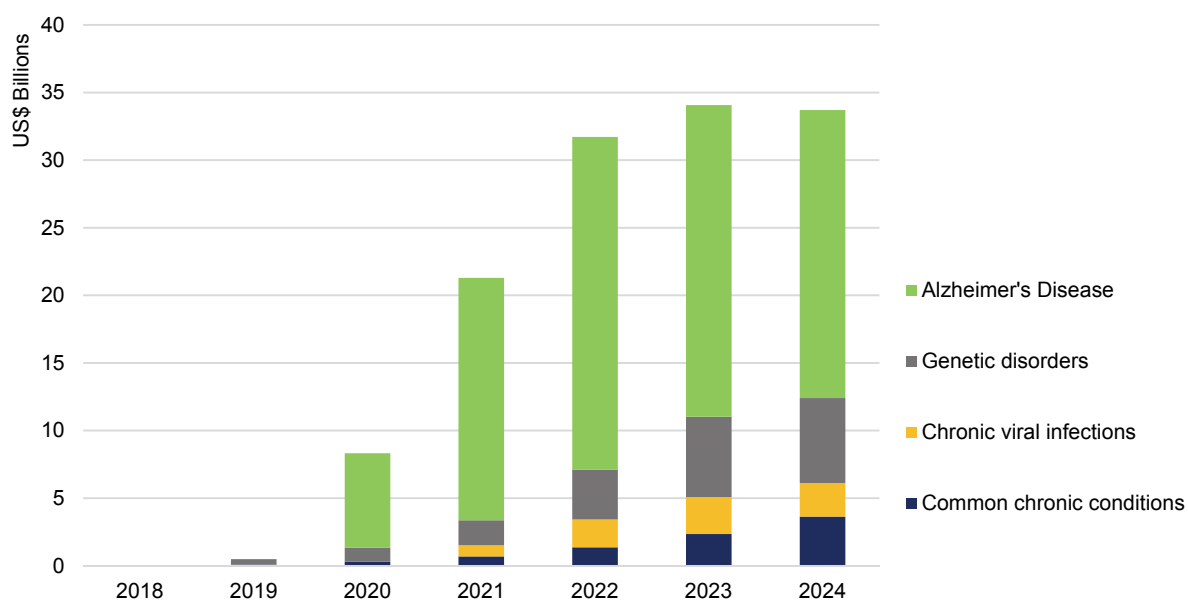
Source: Authors' analysis

The single largest contributor to this estimate would be treatment costs associated with a regenerative Alzheimer's disease therapy, because of the combination of a patient pool of over 3.5 million prevalent cases in mild phase and the current lack of any disease-modifying treatment. In spite of their likely high per patient costs, the small population numbers associated with gene therapies for hereditary disorders means that total expenditures would amount to just $6.3 billion by 2024. Risk-adjusted projections for outlays on treatments of common chronic conditions and chronic viral infections are only $3.6 and $2.5 billion, respectively, even though the theoretically eligible patient pools are quite large. We assume that only patients who do not

respond to standard of care and fall within trial inclusion criteria would receive the treatment. In case of Hepatitis C, for instance, we find that current treatment options yield a sustained virologic response in 98% of patients, leaving only 2% eligible for future drugs. Details on our calculations of eligible patient populations can be found in Appendix A.

In Figure 3, we provide a sensitivity analysis that estimates spending on regenerative treatments by year, but assumes a 100% probability of technical success for each leading regenerative candidate. This shows the potential budget impact if a curative therapy is approved in each of the indications analyzed.

Figure 3: Potential spending on regenerative treatments by indication (sorted by potential peak spending, in $ billion)

| Indication	Lead candidate (sponsor)	2019	2020	2021	2022	2023	2024
Alzheimer's Disease	Gantenerumab (Roche)		14.64	37.50	**51.47**	48.22	44.56
Hepatitis B	GS-9620 (Gilead)			3.02	7.47	**9.92**	9
Traumatic Brain Injury	SB623 cells (SanBio)				1.11	3.12	**5.84**
X-Linked Retinoschisis	rAAV2tYF-CB-hRS1 gene therapy (Biogen, Applied Genetic Technologies Corp)				1.61	4.1	**5.59**
Congestive Heart Failure	Ad5.hAC6 (RT-100) gene therapy (NHLBI, Renova)	0.41	1.25	2.5	3.5	4.35	**5.18**
Stargardt Disease	SAR422459 gene therapy (Oxford BioMedica)			1.3	3.32	**4.54**	4.24
Acute Myocardial Infarction	Revascularization and cell therapy (Mesoblast)					1.55	**4.36**
Usher Syndrome	UshStat gene therapy (Sanofi)	1.21	3.08	**4.23**	3.95	3.65	0.64
Peripheral Arterial Disease/ Vascular Disease	DVC1-0101 gene therapy (Kyushu University)			0.51	1.49	2.9	**3.94**
Sickle Cell Disease	Gene therapy (Children's Hospital Cincinnati)				0.96	2.44	**3.34**
Beta-Thalassemia	BB305 stem cells (bluebird bio)				0.9	2.29	**3.13**
Painful Diabetic Neuropathy	VM202 gene therapy (ViroMed)		0.18	0.53	1.02	1.39	**1.69**
Myocardial infarction	CAP-1002 (Capricor, NIH, NHLBI)				0.29	0.86	**1.66**
Hemophilia B	AAVrh10FIX gene therapy (Dimension)				0.32	0.82	**1.12**
Severe Hypoxic-ischemic Encephalopathy	HPDSC+HIE stem cells (New York Medical College, Celgene)						**0.99**
Degenerative Arthritis	TissueGene-C cell therapy (Kolon Life Science)	0.26	0.51	0.69	0.84	**0.98**	0.92
Hemophilia A	SPK-8011 gene transfer (Spark)						**0.83**
Parkinson's Disease	AADC gene therapy (Jichi Medical University, Takara, Gene Tx Research Institution)				0.03	0.09	**0.17**
Hepatitis C	MK-3682B (Merck)					0.01	**0.02**

These non-risk-adjusted projections suggest that annual spending on an Alzheimer's disease treatment could surpass $51 billion within 3 years from launch and remain at that level for several years given the high number of prevalent cases. A curative hepatitis B treatment could result in spending of close to $10 billion per year by 2023. Spending on several other regenerative treatments, including treatments for traumatic brain injury, X-linked retinoschisis and congestive heart failure, could each exceed $5 billion annually.

Payer Perspective

In our interviews with eight medical directors at U.S. health plans, respondents consistently expressed their expectation that spending on prescription drugs will increase by 10-15% annually over the next five years, based on their analysis of the drug development pipeline and industry reports. The trend was explained by market entry of drugs both for previously unmet needs and of new drugs for existing indications, with limited mitigation due to patent expirations or biosimilar entry.

As we show in Figure 4, all interviewees agreed that oncology will be a therapeutic area with disproportionate spending growth accelerated by combination therapies and potential breakthroughs like CAR-T cell therapy. Other areas that were mentioned by several payers were maintenance treatments for rare diseases because of high per-patient cost, and chronic hepatitis, and PCSK9 inhibitors because of large eligible patient pools.

Figure 4: Payers' expectations of high spending by disease area
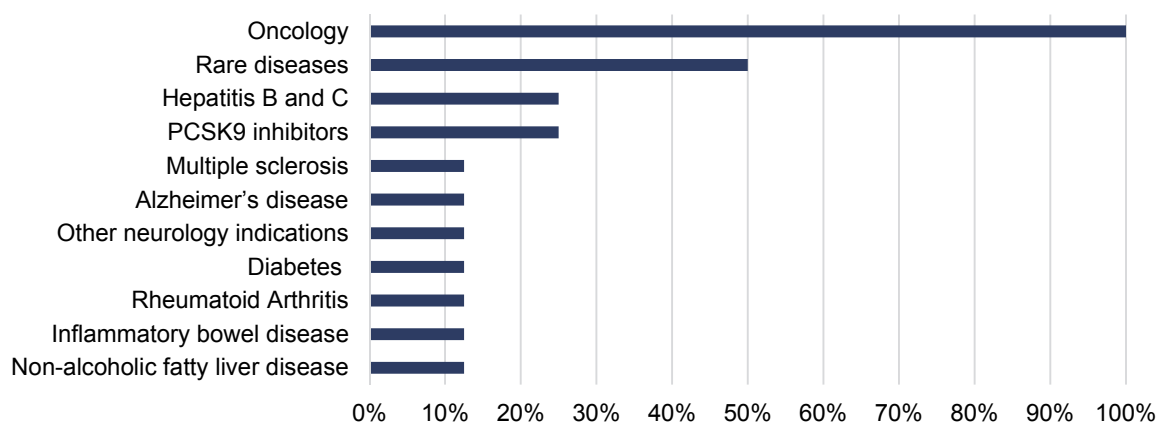
Several other indications were raised by just one medical director each. They included newer drugs for common conditions that would replace established, less costly alternatives (such as for multiple sclerosis and type 2 diabetes) and drugs for indications with no existing treatment, such as nonalcoholic fatty liver disease and Alzheimer's disease. Regarding regenerative therapies, medical directors indicated awareness of late-stage drug candidates primarily in Hepatitis C and of gene therapies for rare disorders, such as hemophilia and cystic fibrosis.

Payers expressed great concern about the sustainability of increased drug spending, as their scope for increasing premiums and/or shifting cost to members had narrowed, while they were keen to make new drugs accessible given their undisputed value. Besides tactical measures, such as trading favorable formulary placement for discounts and restricting coverage to label indications, results-based payment models have emerged as a preferred tool to reduce spending or at least improve value for money. Under these models, payers receive additional rebates from manufacturers if prespecified targets for effectiveness are not met. A typical agreement covers a period of one to three years and uses targets that are routinely captured in electronic data, such as hospital admission and lab values. While rebates reported were mostly single-digit, our interviewees expected the amounts at stake to increase as both sides gained more experience with such payment models.

Given limited concerns about the budget impact of regenerative drugs, our respondents had not considered payment models that would stretch payment over several years and link a large share of the payment to real-world performance. The sentiment was that most regenerative treatments, while expensive, would target ultra-rare diseases and either be absorbed as other randomly high claims or handled through their reinsurance coverage. But payers agreed that the emergence of regenerative drugs with longer effect duration and for larger patient groups might necessitate deferred payment models. As the experience with sofosbuvir has shown, these models would be particularly important for managing the budget impact when the drugs first come to market, as large number of prevalent cases will have to be treated. They also acknowledged that legal obstacles, established business models and a lack of collaboration between stakeholders would make the implementation challenging.

Discussion

Our analysis shows that a substantial number of regenerative treatments are currently in clinical development. This includes potential therapies for Alzheimer's disease, chronic viral hepatitis, common chronic conditions like degenerative arthritis and painful diabetic neuropathy, and rare genetic disorders ranging from Stargardt Disease to X-linked retinoschisis.

Given historical assumptions of clinical trial success, uptake trends, estimates for patient populations and per-patient price, we predict that spending on regenerative treatments could surpass $31 billion per year by 2022. This equates to less than 10% of net spending on prescription drugs that IMS predicts for that year [28]. In some cases, this spending would replace existing therapies; in others, the lack of treatment options would mean that regenerative therapies would represent new spending. IMS, for example, currently assigns a 'very low' probability of technical success to a potential Alzheimer's therapy, which implies that spending on that therapy, if approved, would be additive to their current forecasts [29].

Our estimates stand in contrast to dramatically higher forecasts issued by academics, think tanks, and private research groups. For instance, a 2017 report from the Institute for Clinical and Economic Research predicts that the cumulative budget impact of gene therapies for genetic conditions could be up to $3 trillion, even if just 10% of patients with a genetic condition were treated [30], while Smith (2017) [31] argued that the cost of drugs for rare diseases is "threatening the U.S. health care system" with potential spending of up to $350 billion annually if 10% of rare diseases became treatable. These estimates are typically based on general, system-wide assumptions, not a granular analysis of development pipelines and patient population pools. While our risk-adjusted estimates suggest only a modest budget impact of regenerative drugs, payers and other stakeholders must keep in mind that this projection is highly sensitive to assumptions about probability of technical success and uptake, and does not account for drugs that are currently in pre-clinical stages of development. If approved, several candidates could reach several billion dollars in annual sales and do so quickly, especially if they target an indication with no current treatment option and a large prevalent population. A recent study has confirmed that payers are concerned about the affordability of curative treatments for both rare and chronic diseases [34].

It is likely that the approval of disease-modifying therapies for Alzheimer's disease would be a seismic event, both in terms of clinical breakthrough and spending. The current paradigm

behind drug development is that Alzheimer's disease cannot be reversed at the stage of manifest dementia, but needs to be prevented by treating patients with early-stage memory loss. They will have to be tested for the presence of biomarkers indicative of the Alzheimer's pathology and then treated to avoid or at least delay the onset of full-blown disease in future years. This treatment paradigm creates a substantial near-term problem for payers: an estimated 5.5 million patients currently live in the U.S. with prodromal Alzheimer's disease [32] and we estimate about 3.5 million suffer from mild Alzheimer's disease. Given that there are currently no disease-modifying therapies currently available, a large proportion of this population would become immediately eligible for treatment. Even with a conservative assumption of $50,000 per patient treatment cost, annual spending could reach over $51 billion by 2021, which amounts to about three times the peak spending on direct-acting antiviral drugs for Hepatitis C [33]. As current spending projections do not seem to factor in an Alzheimer's disease therapy and only one of our interviewees mentioned it as a potential driver of spending, a large part of that amount might be additive.

Delaying or avoiding dementia would substantially reduce cost of medical care and, in particular, nursing home care, but those cost offsets would be realized only years or even decades later, and possibly to accrue to a payer that did not have to bear the cost of treatment. Current trials enroll patients as young as age 50, implying that commercial health plans would be exposed to the cost, but Medicare and Medicaid might benefit from the future savings. While the large number of previous failures of Alzheimer drug trials might lead payers to discount the likelihood of success event, the fact that at least 13 candidates are currently in mid-stage development and some have reported promising results suggests that the healthcare system may not be prepared for such an event. Greater dialogue is needed to ensure that patients can get access to breakthrough regenerative treatments while allowing to manage the costs of doing so.

Limitations

Our estimates for probability of technical success, time to market and uptake are informed by historical data on non-regenerative treatment, and future regenerative treatments could take a faster or slower path. Estimates for eligible populations are based on our interpretation of the inclusion and exclusion criteria of the respective clinical trials and published estimates, both of which could over- or underestimate the actual number of eligible patients. Our assumptions for

prices of regenerative treatments are subject to substantial uncertainty, as actual prices will depend on a complex interplay of factors like effect sizes in pivotal trials, cost of alternatives, cost offsets and the political environment. We base our estimates on the first drug that is likely to be approved in each indication while follow-on drugs could increase the eligible populations and thus increase projected spending, and we do not explicitly consider cost offsets new therapies may result in. Lastly, we did not include oncology treatments in our analysis, even though it is a major contributor to increased drug spending, as those have historically not been curative. If potentially curative treatments, like CAR-T, were approved for common malignancies, projected spending might increase substantially.

Conclusions

Our analysis suggests that risk-adjusted spending on regenerative drugs has largely been incorporated into current projections and that payers are likely to be able to cover these drugs without fundamentally different payment models from a financial perspective, even though they might prefer deferred payment models from a conceptual perspective. But the actual approval of an Alzheimer's treatment would become a disruptive event, given the large treatment-eligible population, the current lack of a disease-modifying treatment and the long latency until savings from reductions in medical and nursing home care materialize. Conceivably, the confluence of these three factors will make the introduction of a deferred payment model necessary to balance considerations of patient access and budget impact. Given the complexity of implementing such a model, manufacturers, payers and regulators would be well advised to start collaborating on the necessary building blocks, which could then be utilized for other treatments with front-loaded cost and long-term impact.

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Paper II: Three-Part Pricing for Drugs of Uncertain Efficacy

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Paying for value has risen to the top of the health policy agenda as society seeks ways to improve quality without substantial additional spending. Medicare in particular has made considerable progress in tying reimbursement to outcomes to pay providers.1 However, there has not been similar progress in pharmaceuticals. For decades, the United States has relied on a price-per-dose model, limiting access to innovative but expensive therapies.2

Tying reimbursement to outcomes offers one intriguing solution.[3] However, there are some fundamental challenges, especially for newly launched drugs where long-term efficacy is unknown, and where the benefits might accrue long after a patient has changed health plans. In this paper, we propose a novel pricing strategy – three-part pricing, or TPP – to overcome these hurdles.

The Case of Cholesterol Lowering Drugs

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors provide a useful example of how the model might work. PCSK9 inhibitors were introduced in 2015 with some controversy. The drugs could potentially benefit millions of patients who cannot manage their low-density lipoprotein cholesterol (LDL-C) using statins and other medications alone. The initial labels of evolocumab (Repatha®; Amgen) and alicrocumab (Praluent®; Sanofi/

Regeneron) were somewhat narrow; covering patients with familial hypercholesterolemia or those who required additional lowering of LDL-C beyond standard of care.[2,4] The use of evolocumab was expanded in 2017 to include adult patients with established cardiovascular disease who were at risk of myocardial infarction, stroke, and coronary revascularization.[3,5] An expansion of alirocumab's label is expected this year.[6,7]

Immediately upon launch, payers raised concerns about the overall costs of these drugs – with some projecting annual spending in the range of $50 to $100 billion.[8] The Institute for Clinical and Economic Review (ICER) in 2015 predicted the uptake for PCSK9 inhibitors could reach over 2.5 million patients within 5 years,[9] while several million patients could benefit from the new drugs under current labels.

However, uptake has been slow, despite positive trial results. This has been directly linked to coverage restrictions by payers.[10] As a result, only half of patients initially prescribed PCSK9 inhibitors in their first year of availability received coverage approval from payers, and one-third of approved prescriptions were not filled due to high patient copays.[11] Amgen reported $60 million in U.S. Repatha® revenues in the second quarter of 2017. Assuming a 34% discount to the list price, this amounts to only 25,000 patients treated in that quarter.

Much of the controversy surrounds long-term efficacy.[12] The FOURIER clinical trial, which resulted in expansion of the evolocumab label, did not fully resolve uncertainty about its long-term survival benefits, given the short (26-month) median follow-up. Efforts to address slow uptake have been piloted by payers such as Cigna[11] and Harvard Pilgrim[12] who have entered into outcome-based refund agreements with manufacturers; however, there is no evidence that these have led to higher uptake or made the drugs more cost-effective.[13]

The current state of affairs leaves everyone worse off. Slower adoption of PCSK9 inhibitors results in worse clinical outcomes for patients and limits the rate at which evidence about real-world outcomes can be collected.[11] This, in turn, hinders future negotiations to improve access to this therapy. Even substantial manufacturer discounts may not address the dilemma, especially if the drugs' long-term effectiveness is better than observed in clinical trials. Cardiovascular risk increases with the length of exposure to high LDL-C[14,15] and cost-effectiveness improves in real-world populations with higher baseline risk.

A Better Pricing Model to Accelerate Learning

We propose a three-part pricing (TPP) schedule to address the significant unmet need, high budget impact, and uncertainty about long-term effectiveness of PCSK9 inhibitors.[16] Compared to the status quo of price-per-dose, where prices are set high at launch until patent expiration, the pricing schedule under TPP has three phases during the drug's exclusivity period:

- **Evaluation**. During an evaluation phase, the price is set low to encourage adoption and develop real-world evidence rapidly;
- **Reward**. In the reward phase, prices are set based on the effectiveness established in the evaluation phase, which rewards manufacturers for their innovation;
- **Access**. In the access phase, prices are lowered to facilitate widespread adoption.

Figure 1 illustrates the status quo for PCSK9 inhibitors, starting from 2016 until expected exclusivity expiration in 2030. It shows a constant annual price (for a monthly or bi-monthly dosing regimen) of $9,598 from 2016 until generic competition reduces the price to $2,181 in 2030. The former is based on an assumed 34% discount to the list price, equal to the industry-wide discount average estimate, and the latter on an expected 85% reduction in price when exclusivity is lost.[17] In our modeling of TPP, we assume a three-year Evaluation Phase,[i] the drug is priced at 50% off list price to encourage rapid adoption. Pricing in the seven-year Reward Phase depends on the drug's performance in terms of reduced myocardial infarction and stroke risk during evaluation, and is calibrated to result in the same cost per event avoided (a composite of both events) under three different efficacy scenarios.

The price in the Access Phase is set at $3,635 (75% off the list price), to ensure the total cash flow to the manufacturer over the exclusivity period (2016 – 2030) is equal for expected efficacy in both TPP and status quo at a 3% discount rate.

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[i] Although we assume three years in this example, phase lengths may vary; for medicines with less uncertainty, shorter Evaluation Phases may be sufficient.

Figure 1: Three-Part Pricing of PCSK9 inhibitors
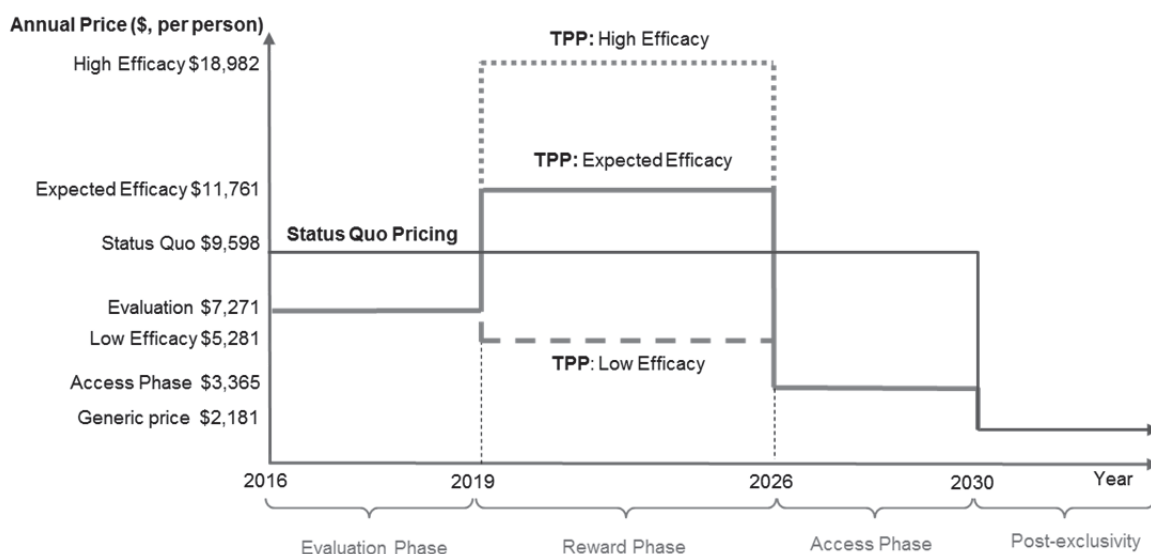
Based on our calibration, Reward Phase prices are $5,281 for low efficacy, $11,761 for expected efficacy, and $18,982 for high efficacy. Efficacy here is defined based on the reduction in risk of myocardial infarction (MI) and stroke observed in the pivotal FOURIER trial.[5] We assume a drug meets expected efficacy criteria when the risk reduction of MI ranges from 0.660 to 0.795 (median 0.730) or the risk reduction of stroke ranges from 0.735 to 0.845 (median 0.790). If the drug demonstrates real-world risk reduction that is better than this range, we classify it as high efficacy. We classify a drug as low efficacy when the real-world risk reduction for MI ranges from 0.795 to 1.000 (median 0.86) or for stroke from 0.845 to 1.00 (median 0.90).

The Model. We compare the results of TPP with the status quo pricing using the Future Elderly Model (FEM), an economic demographic microsimulation model, to estimate the health benefits of PCSK9 inhibitors among Americans aged 51 and older for each efficacy scenario. The FEM uses initial demographic characteristics and health conditions for each individual to project their medical spending, health conditions and behaviors, disability status, and quality of life. The model has been developed over time with support from the National Institute on Aging, the Department of Labor, the MacArthur Foundation, and the Centers for Medicare & Medicaid Services to study health care innovation in a wide variety of contexts.[18-20] Of particular note, the model has been used to study the benefits of innovation in heart failure treatment,[21] statin use,[22] and reduction in cardiovascular risk factors.[23]

A detailed discussion of our methods can be found in a technical appendix; below we provide an overview. We first identify the population eligible for PCSK9 inhibitors based on the FDA label and inclusion criteria for the pivotal FOURIER trial: those with familial hypercholesterolemia (defined as LDL cholesterol level higher than 190 mg/dl) and those with an existing cardiovascular condition and LDL cholesterol level of at least 70mg/dL while receiving cholesterol-lowering therapy. We do not assume that everyone is treated initially, consistent with the data observed to date, and we allow uptake to change once the real-world experience becomes available. Specifically, we estimate that uptake will rise gradually during the first two phases of TPP, reaching about 5% of eligible patients treated annually within 6 years of launch. During the final phase, we assume that uptake adjusts based on efficacy data: under low efficacy, uptake gradually decreases to 2.5% of the eligible patient population, and under high efficacy, uptake increases to 10% of the eligible population.

The key metric for evaluation of PCSK9 inhibitors is "cost per event avoided." The FOURIER trial demonstrated reduced incidence of myocardial infarction and stroke, both of which are simulated in the FEM. We simulate the entire population aged 51 years and older from 2016 onwards, accumulating information about individuals' health conditions (including incident disease cases) and total drug spending in each year—taking into account the disease risk reduction and the price of treatment, which reflects the annual per-patient cost of PCSK9 inhibitors.

Spending on PCSK9 inhibitors. Figure 2 shows the present discounted value of spending on PCSK9 inhibitors under different scenarios. As we show, TPP produces benefits for manufacturers, patients, and payers compared to the status quo. Under the status quo, spending varies modestly with efficacy, ranging from a low of $64.3 billion to a high of $84.4 billion. Spending with TPP varies more widely, from $34.7 billion to $114.7 billion. Importantly, if PCSK9 inhibitors exhibit low real-world efficacy, TPP avoids $30 billion in spending relative to the status quo. If the drug performs similarly as in the clinical trials, TPP generates comparable cash flow, but delivers revenues faster, enabling more immediate investment in further R&D. If real-world effectiveness is better than the clinical trials predict, spending is higher under TPP, reflecting the higher uptake in the high efficacy scenario with TPP relative to the status quo.

Figure 2: Discounted total revenues under different efficacy scenarios, in $ billion (3% discount)
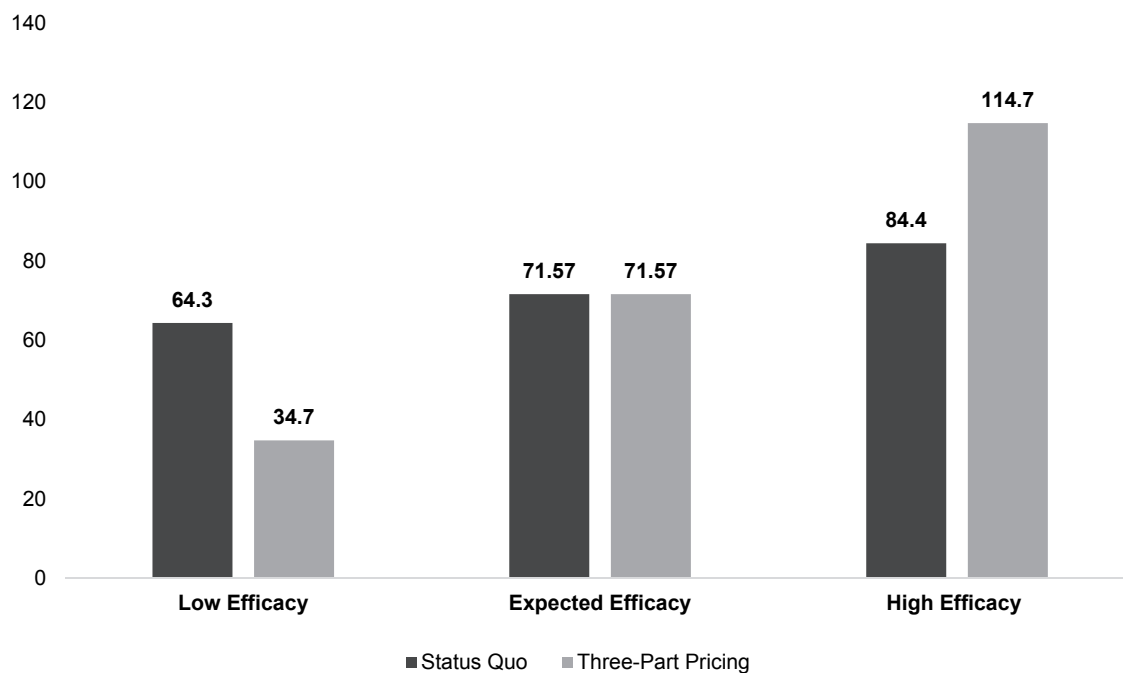
Cost per event avoided. The ultimate question, however, is how much health benefit we get for the PCSK9 inhibitor spending shown in Figure 2. In Figure 3, we examine the cost per event avoided. TPP lowers the cost per event avoided under both low and expected efficacy scenarios, and results in comparable cost per event avoided under high efficacy. In this way, TPP leaves society better off in terms of value per dollar spent, relative to status quo pricing.[ii]

[ii] We do not model cost-effectiveness in our model, given ongoing discussion about appropriate thresholds for different patient populations, but rather assume a generic discount to the list price to frame our price setting under Status quo pricing and associated spending on PCSK9 inhibitors.

Figure 3: Cost per event avoided under different efficacy scenarios for PCSK9 inhibitors

Implications

A three-part pricing approach offers several advantages over the status quo. If the drug's real-world effectiveness is better than in trials, more patients are treated, with the same cost per event avoided as the status quo. However, if real-world effectiveness is worse than expected, payers spend less on the drug (by about $30 billion), with a 50% lower cost per event avoided than under the status quo. Therefore, a pre-negotiated TPP price schedule would accelerate access and real-world evidence development at lower cost to society.

Some issues would need to be resolved in practice. First, TPP shifts some effectiveness risk to manufacturers, and it exposes payers to higher spending if the drug's effectiveness exceeds expectations. Hence, manufacturers may not accept the deal unless they are confident about their drug's performance, and payers may not want to risk greater spending even if the drug performs as expected. While both uncertainties exist in the status quo, TPP's design is conditional on the parties accepting higher risk exposure.

Second, collection of clinical outcomes during the Evaluation Phase could be hindered by several challenges, including reporting issues, adherence to therapy and data-sharing challenges among providers, payers and manufacturers. Provisions related to extra-low efficacy, under

which coverage would be stopped, should be in place. Such details have already been worked out in private agreements with plans like Harvard Pilgrim[24] and Cigna,[25] so this concern is likely not prohibitive.

Finally—and of most concern—a longer-term agreement such as TPP may weaken product competition and reduce benefits if another innovative therapy enters the market and provides greater value for money. Specific contractual provisions would be required to ensure the theoretical benefits of TPP are realized by all parties.

In sum, pay-for-performance has been difficult to achieve in the pharmaceutical sector. Most importantly, it has failed because manufacturers have little incentive to launch at a low price to encourage use as more evidence is collected about real-world, long-term effectiveness. We propose a three-part price schedule which could provide access at a lower price during an evaluation phase, and limit the period during which the innovator is rewarded in proportion to the clinical benefits delivered by a new therapy. The result is better access while still rewarding innovators. While TPP is not a panacea, in the case of PCSK9 inhibitors it offers lower cost per event avoided, and distributes risk between manufactures and payers based on the drug's performance. As such, it provides a promising alternative to existing payment models for high-cost therapies.

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Paper III: The Benefits of Deferred Payment in Congestive Heart Failure Gene Therapy

Jakub P. Hlávka

Introduction

The emergence of "curative" therapies that deliver long-term clinical benefits with a limited number of doses, possibly including some gene and cell therapies, is creating challenges for payers as the unit price of those products tends to be very high. Even if these treatments meet conventional thresholds for value for money, short-term budget constraints can lead to obstacles to access, such as in the case of the directly acting antiviral for Hepatitis C (Barua et al., 2015; Chhatwal, He, Hur, & Lopez-Olivo, 2017).

New payment approaches have been proposed to address this challenge, ranging from outcome-based agreements to reinsurance schemes and installment-based payment (Gottlieb & Carino, 2014; Hampson, Towse, Pearson, Dreitlein, & Henshall, 2018; S Mattke & Hoch, 2015; Schaffer, Messner, Mestre-Ferrandiz, Tambor, & Towse, 2018). In cases of curative and regenerative therapies, deferred (installment) payments are thought to have an advantage in shifting the financial profile of such payments to that of chronic treatments, and could even include a performance component to link payment to clinical outcomes in individual patients or patient cohorts (Hampson et al., 2018).

As we show in earlier work, regenerative therapies are currently under development for numerous indications potentially targeting large numbers of people (Hlávka & Mattke, forthcoming). In this paper, we study one potential design of a deferred payment model (DPM) and use gene therapy for congestive heart failure (CHF) as case study. By studying the financial and clinical properties of this payment model for payers, manufacturers and patients, we provide an empirical assessment of the financial and clinical properties this payment model produces relative to existing (status quo) payment model, generally associated with upfront payment.,

The choice of CHF as case study is motivated by the potentially large treatment-eligible population, as around 6.5 million people suffer from the disease in the United States alone (Benjamin et al., 2018). As the prognosis under standard of care remains poor – a 5-year mortality of nearly 50% (Hernandez, 2013) – a substantial share of these patients could be eligible for treatment. Specifically, several regenerative therapies have been under development for CHF, including a Phase IIb trial by Celladon of Mydicar, a gene therapy aiming at SERCA2a protein which is downregulated in a failing heart, which experienced a vector failure in 2015 (Ylä-Herttuala, 2015), and more promising Phase II results reported in 2017 by Renova Therapeutics for RT-100, its adenylyl cyclase type 6 (AC6) gene transfer (Renova Therapeutics, 2018). A phase III trial of RT-100 is expected to commence in 2018. RT-100 is a single-dose gene therapy delivered via an intracoronary injection during an outpatient procedure with the potential to improve the heart function (Renova Therapeutics, 2018).

Objective

This paper tests the clinical and financial properties of a deferred payment model in CHF gene therapy relative to status quo payment. It focuses on the perspective of three stakeholders: payers, who minimize per-patient spending, manufacturers, who maximize product revenue, and the patient population, which maximizes clinical benefits. In addition, we test the sensitivity of clinical and financial outcomes on payment design choices.

Design and methods

The analytical approach of this paper consists of three components: an empirical analysis of longitudinal data for cardiovascular admissions and mortality, a Markov transition model for patient progression under different payment scenarios, and a discounted cashflow forecast model.

Markov chain probabilities in the model were populated from a separate empirical analysis of CHF readmission by Mattke and Wilks (forthcoming). That analysis, using Medicare Provider and Analysis Review (MedPAR) 5% data files, calculated 30-day probabilities of death and repeat CHF admission. The analysis was limited to patients admitted with a primary diagnosis of CHF (ICD-9-CM 428.xx) who did not die during the admission and had not been admitted for

CHF in the preceding 12 months. The study ultimately tracked more than 91,000 Medicare fee-for-service beneficiaries over a period of 5 years (2009-2014), from the index admission until death, disenrollment, or the end of the study period.

The Markov transition model for patient progression under status quo and deferred payment calculates life-years gained and avoided cardiovascular admissions under DPM relative to status quo payment with an identical budget constraint. The key variable – the size of a down payment relative to the cost of the therapy – ranges from 25% to 75% of the total expected cost of therapy, which is estimated at $200,000 (Kish, 2017).[i] Our payment simulation is based on the assumption that avoided cardiovascular hospitalizations contribute to an increased annual budget for CHF patients (such cost offsets are designed to be the only change to otherwise fixed annual budgets, to ensure comparability with status quo payment), allowing more people to receive treatment. The average cost of cardiovascular hospitalizations avoided of $16,000 is based on Kilgore, Patel, Kielhorn, Maya, and Sharma (2017). The average cost of therapy is identical under both DPM and status quo payment on a per-patient basis over a period of 3 years. A longer payment model may not be practical due to a large attrition of patients with CHF given high mortality rates both with and without treatment, as we show later. Disenrollment (loss to follow-up) commonly denotes patient switching to Medicare Advantage plans, and is assumed constant under both payment models.

For treated patients, we assume a relative risk of any future cardiovascular admission of 0.70 compared to untreated patients (rounded downwards from the relative risk of a first heart failure admission achieved by sacubitril/valsartan (Entresto), a new therapy for CHF (McMurray et al., 2014)). Moreover, we assume an identical relative risk of mortality to that of Entresto for cardiovascular death, 0.80 (McMurray et al., 2014).

Payment under DPM consists of a down payment of differing amounts and monthly installments for each period when a patient is 'stable' (payment is suspended if a patient experiences a cardiovascular hospitalization and is halted once a patient dies). At the baseline, we assume an annual budget constraint of $1 billion – the amount associated with blockbuster therapies – which translates to about 15,000 patients treated in the first 3 years under fee-for-service payment arrangements. This is only a small fraction of the potential patient pool, but

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[i] We do not consider down payments smaller than 25% due to feasibility issues, and do not expect any down payment to exceed 75% of the total cost of care for practical purposes.

shows the magnitude of the potential benefit relative to the cost of therapy for a cohort of any size.

Figure 1 shows the general payment design as evaluated in this study.

**Figure 1: Design of a Deferred Payment Model for CHF**
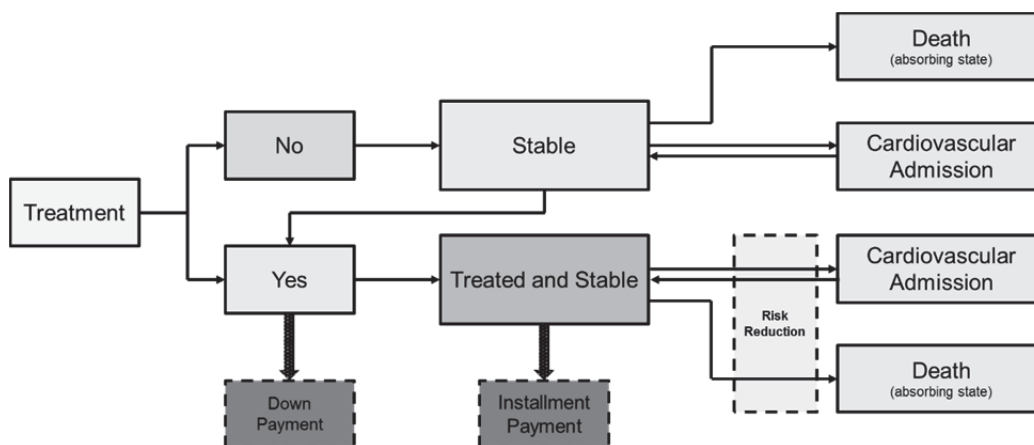
Third, we assess the financial effects of a DPM for manufacturers with a discounted cashflow forecast model. We calculate the cashflow using a discount rate of 5% and compare the cashflow resulting from status quo payment and different down payment scenarios under DPM, both with identical budget constraints, cost of therapy and relative risk reduction.

Results

Figure 2 shows monthly event probabilities for patients who have been discharged following a CHF diagnosis under standard of care. Patients are at the highest risk of cardiovascular admissions in the first several months following the index event, with monthly risk ranging from 14.7% in the first month to 5.1% one year after the index event. Similarly, mortality risk is the highest in the first several months following the index event, ranging from 8.4% in the first month to 2.3% a year after initial discharge. Total mortality in the first year is 33.6%, 20% in the second year, and 19.5% in the third year.

Figure 2: Post-discharge event probability for CHF patients with no treatment, by month since index event
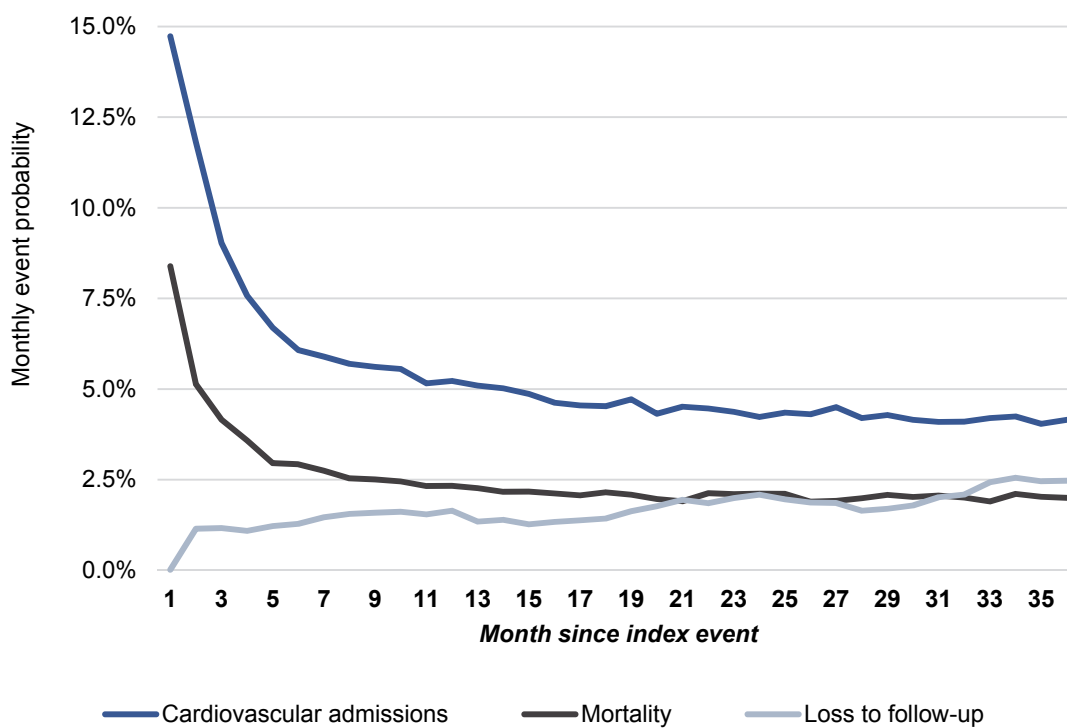
Note: Monthly data based on a 5% sample from based on Medicare Provider and Analysis Review (MedPAR) data (2009 – 2014).

The number of patients treated monthly under different payment scenarios is presented in *Figure 3*. Under all scenarios, deferred payment results in slightly more patients from the same cohort receiving gene therapy (ranging from 15,043 patients treated under a 25% down payment to 15,000 under status quo payment)[ii], and those patients receiving therapy sooner than under status quo.

[ii] Numbers of patients treated monthly in Figure 3 are rounded.

**Figure 3: Average monthly number of patients treated by year, by payment scenario (annual budget: $1 billion)**

Share of down payment on total cost of therapy or FFS payment

■ Treated per month (Y1)   ■ Treated per month (Y2)   ■ Treated per month (Y3)
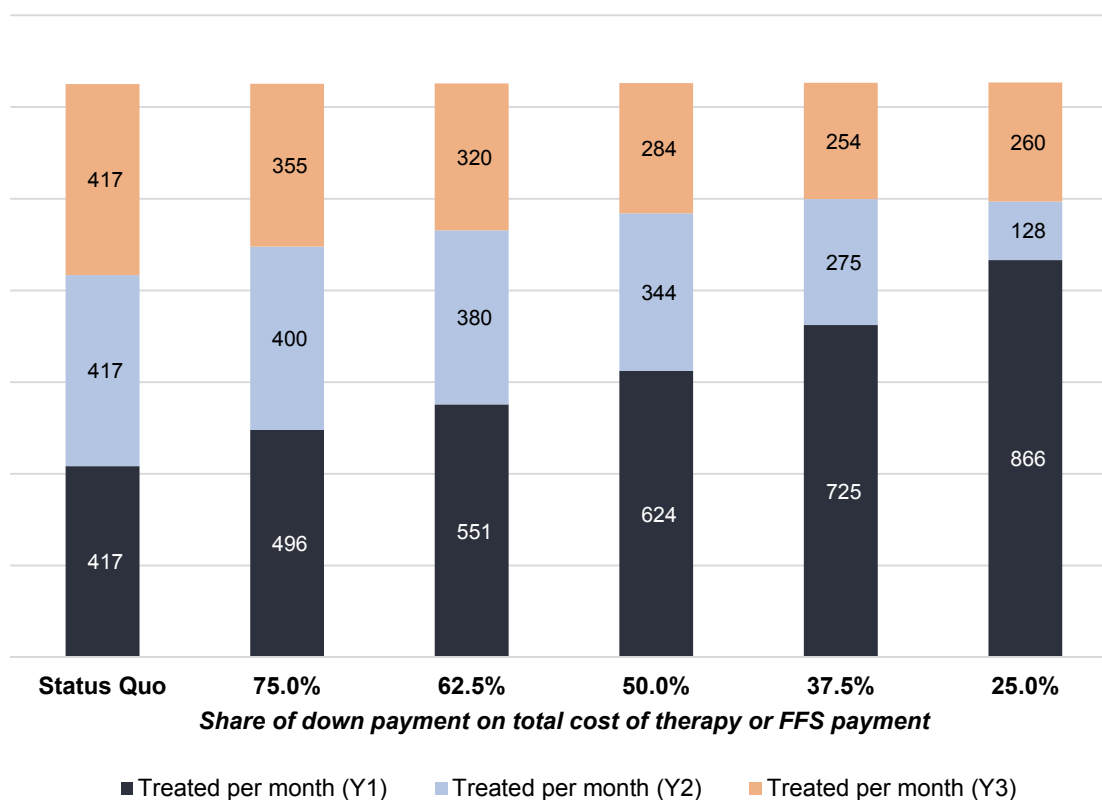
In *Figure 4*, the effect of individual payment models relative to no treatment is presented. The highest number of admissions and deaths are avoided under the lowest down payment of 25%, which translates into a 26.1% reduction of cardiovascular admissions relative to status quo payment and a 23.3% reduction of deaths over a three-year period, largely due to patients receiving treatment sooner than under status quo. In absolute terms, the implementation of DPM for gene therapy in CHF results in a 0.15% reduction in 3-year mortality (from 51.47% under status quo to 51.32% under DPM with the lowest down payment) and a 0.54% reduction in cardiovascular admissions (from 101,673 under status quo to 101,133 under DPM), with only about 16.5% of eligible patients receiving treatment. At an admission cost of $16,000 and annual budget constraint of $1 billion, the highest potential cost-savings due to admissions avoided under DPM relative to status quo payment are $8.64 million at the baseline.
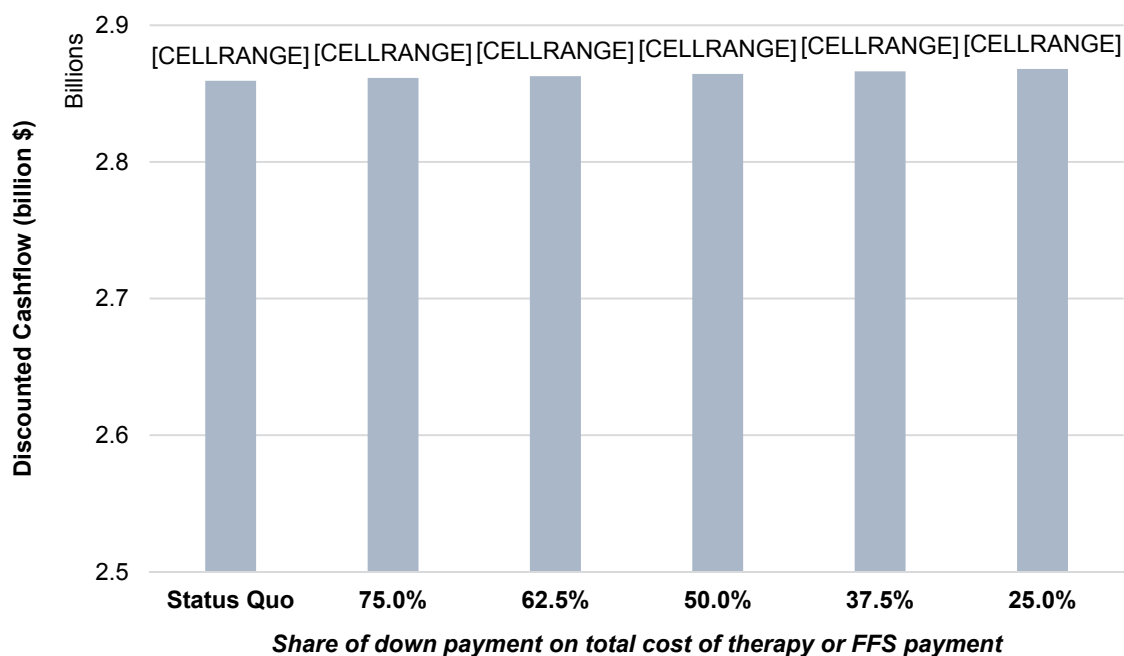
Figure 4: Clinical outcomes for CHF patients relative to no treatment, by payment scenario (annual budget: $1 billion)

Share of down payment on total cost of therapy or FFS payment

■ Admissions avoided ■ Deaths avoided
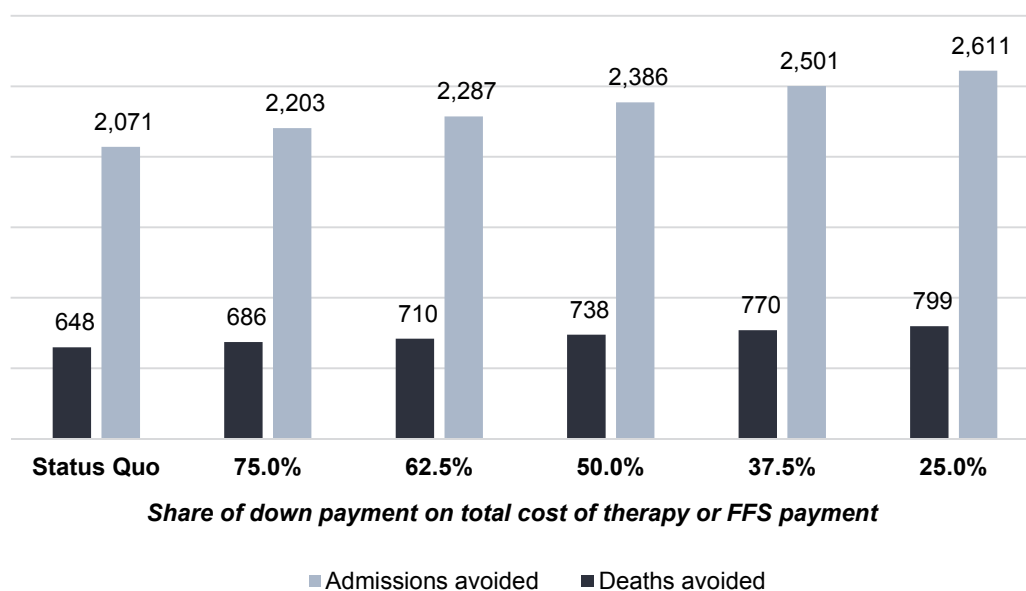
Relative to status quo payment, a 25% down payment in DPM under our base budget constraint ($1 billion annually) results in 345.2 life-years gained, an increase of 51.6%. The gain with a 75% down payment relative to status quo is 73.3 life-years gained, an increase of 11%. As a result of being treated earlier under DPM, fewer patients die in the 3-year period and societal benefits are derived from patients with CHF living longer beyond savings due to avoided admissions (a full summary of clinical benefits observed is presented in Figure A.1 in the Appendix).

Finally, we present the results of a discounted cashflow analysis that indicate small differences in total cashflow to the manufacturer under different payment scenarios and for different discount rates over a period of 3 years in *Figure 5*. Under the highest discount rate, the relative difference between DPM with the smallest down payment and status quo payment is just 0.31%. This result is primarily driven by model design: the difference in cashflow results from more patients being treated due to savings in hospital admissions under DPM relative to status quo.

Figure 5: Discounted cashflow over 3 years, by down payment
(annual budget $1 billion, discount rate of 5%)

[CELLRANGE] [CELLRANGE] [CELLRANGE] [CELLRANGE] [CELLRANGE] [CELLRANGE]

Share of down payment on total cost of therapy or FFS payment

Y-axis: **Discounted Cashflow (billion $)**, Billions, values: 2.5, 2.6, 2.7, 2.8, 2.9

X-axis categories: **Status Quo**, **75.0%**, **62.5%**, **50.0%**, **37.5%**, **25.0%**

Discussion

Previous research has indicated that implementing novel payment arrangements for prescription drugs, including performance-based payment, has been difficult (Neumann, Chambers, Simon, & Meckley, 2011). Yet, the arrival of cures and other regenerative therapies is continuing pressure on payers to come up with new payment models that would enable 'rapid adoption' of high-cost treatments (Gottlieb & Carino, 2014), and payers including the Centers for Medicare and Medicaid Services have been exploring "innovative pricing systems" that could achieve that (Centers for Medicare & Medicaid Services, 2017). In this paper, we present the first empirical assessment of both clinical and financial outcomes of deferred payment for patients, payers and manufacturers, using a hypothetical gene transfer in congestive heart failure as a test case.

We find that deferred payment does not result in substantial financial gains for payers or manufacturers, primarily because of the small share of expected cost savings on the total cost of therapy. In our model, nearly 13 admissions must be avoided for an additional patient to receive a costly treatment and benefit from a lower relative risk of cardiovascular hospitalization. The absolute impact on hospital admissions and mortality resulting from DPM is small, given an

annual budget constraint of $1 billion, with the cost of admissions avoided of less than $9 million over a period of 3 years under the most favorable scenario. Net gains of DPM may be eliminated once the costs of implementing the model are considered. In neither of our scenarios does DPM present a significant cashflow advantage to the manufacturer: under the most favorable conditions, the maximum cashflow gain is just over 0.3%.

The benefits of deferred payment in CHF would be mostly felt by patients: we find that DPM is associated with earlier treatment and a resulting improvement in clinical outcomes. The smallest down payment under DPM is associated with the highest relative improvement and reduces the number of admissions by over 26% and deaths by over 23% relative to status quo payment, while spending is held constant. Given our budget constraint and the size of the simulated cohort, approximately 16.5% of theoretically eligible patients would be treated over a period of 3 years.

Our results are robust to changes in relative risk for cardiovascular admissions and a change in the cost of therapy (as shown in the Appendix). An improvement in the relative risk of cardiovascular admission to 0.50 produces a 28.5% increase in the admissions avoided under the lowest down payment in DPM relative to status quo payment (Figure A.1.), and a decrease in the cost of therapy by 50% to $100,000 per patient allows over twice as many patients to receive treatment, resulting in 26.9% more cardiovascular admissions avoided under a 25% down payment relative to status quo (Figure A.2.). In case of a higher treatment effectiveness for cardiovascular admissions (RR=0.50), the total cost of admissions avoided in our model is $16.9 million, and in case of a reduced price of therapy ($100,000 per patient), the cost of admissions avoided is $17.8 million.

While we find that financial benefits of a DPM in a CHF gene therapy are relatively limited, it is possible that deferred payment will show a greater promise for treatments with higher cost offsets, such as a potential cure of hemophilia, a disease with significant maintenance therapy costs (Chen, 2016). Moreover, indications with large prevalent populations relative to incident cases may benefit more significantly from DPM as the budget impact of treating all eligible patients is concentrated into a shorter time horizon and could prevent a larger share of patients from receiving timely access to a new therapy (in contrast, CHF is a disease with a large number of incident cases). Our results, nevertheless, suggest that providing patients with earlier access to a high-cost therapy is a key benefit of deferred payment in CHF.

Limitations

Our analysis may be affected by several limitations. First, the patient population in our model is based on a sample of Medicare beneficiaries (commonly age 65 and older) – a sample which does not capture the full spectrum of CHF patients in clinical practice. In addition, the data includes patients with any heart failure, irrespective of their ejection fraction stage. Some of the treatments in late-stage trials aim at reduced ejection fraction heart failure patients who could experience different outcomes than the general CHF patient population. Third, we do not address implementation challenges, such as regulatory issues or the cost of implementing DPM in clinical practice. As a result, we are not able to determine the net costs and benefits of DPM relative to status quo payment. Fourth, our outcome of interest, cardiovascular admissions, is an imperfect proxy for the effectiveness of a gene therapy in CHF, given that patients with the disease suffer from multiple comorbidities and may be admitted for a number of cardiovascular conditions. We conclude, however, that relying on CHF admissions alone could underestimate the benefit of the therapy given the imperfect distinction between cardiovascular and heart failure admissions in claims data. Finally, we do not assume any prioritization in treatment by disease severity, thus assuming homogeneous risk reduction due to treatment across patients in our sample. In reality, it is possible that patients expected to benefit the most from treatment (such as those who would experience the largest improvement in survival or reduction in hospitalizations) would be treated first, thus increasing both clinical and financial gains of deferred payment observed in the real world relative to our findings.

Conclusions

While conceptually promising, deferred payment may not be a universal solution in payment for high-cost treatments such as a gene therapy in CHF. We find, however, that under the proposed design, DPM results in faster access to a restorative treatment for CHF, producing societal benefits, including a reduction in hospital admissions and mortality in contrast to status quo payment with the same budget constraint.

Deferred payment could, in addition, generate greater clinical and financial benefits if implemented in indications with high per-patient or cohort-level cost offsets due to receiving treatment sooner – ranging from indications with costly standard of care to those with large

prevalent patient populations relative to incident cases observed. Empirical research should be conducted to test these hypotheses and show under which conditions a DPM would produce greatest clinical and financial benefits.
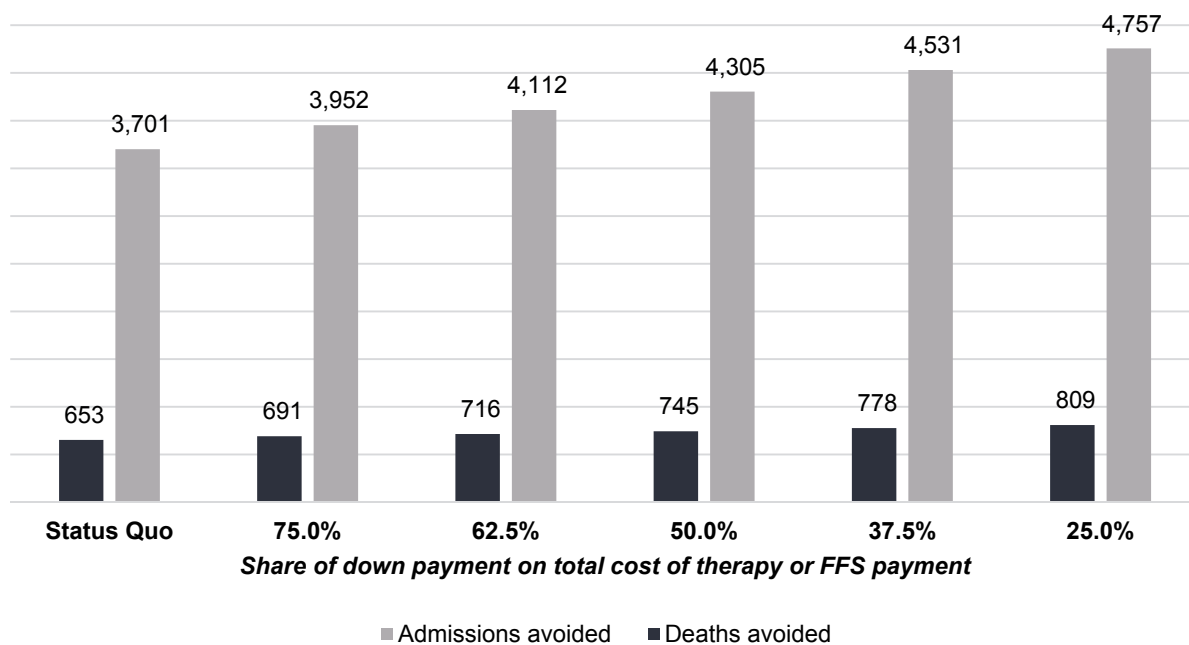
We conclude that deferred payment in CHF gene therapy is a creative solution that can expedite access to high-cost therapies and improve clinical outcomes, but its acceptance in clinical practice hinges on resolving challenges related to its economic viability.

Appendix

**Figure A.1: Events observed under different payment models (base scenario)**

Down Payment Size (DPM only)	Variable	No Treatment	Status Quo Payment	DPM	Life Years Gained (DPM relative to status quo payment)
25% ($50,000)	Deaths			51,317	345
	Loss to Follow up			25,102	
	Admissions			101,133	
	Patients Treated			15,043	
37.5% ($75,000)	Deaths			51,346	256
	Loss to Follow up			25,084	
	Admissions			101,242	
	Patients Treated			15,034	
50% ($100,000)	Deaths	52,116 24,852 103,744 0	51,468 25,026 101,673 15,000	51,378	181
	Loss to Follow up			25,067	
	Admissions			101,358	
	Patients Treated			15,025	
62.5% ($125,000)	Deaths			51,406	121
	Loss to Follow up			25,053	
	Admissions			101,457	
	Patients Treated			15,017	
75% ($150,000)	Deaths			51,430	73
	Loss to Follow up			25,042	
	Admissions			101,541	
	Patients Treated			15,011	

Figure A.2: Clinical outcomes under improved efficacy (risk reduction in admissions of 0.50)

Share of down payment on total cost of therapy or FFS payment

■ Admissions avoided ■ Deaths avoided

NOTE: This model assumes existing (baseline) assumption for the cost of therapy per patient ($200,000), and annual budget of $1 billion.

Figure A.3: Clinical outcomes under lower cost of therapy per patient ($100,000)

Share of down payment on total cost of therapy or FFS payment

■ Admissions avoided ■ Deaths avoided
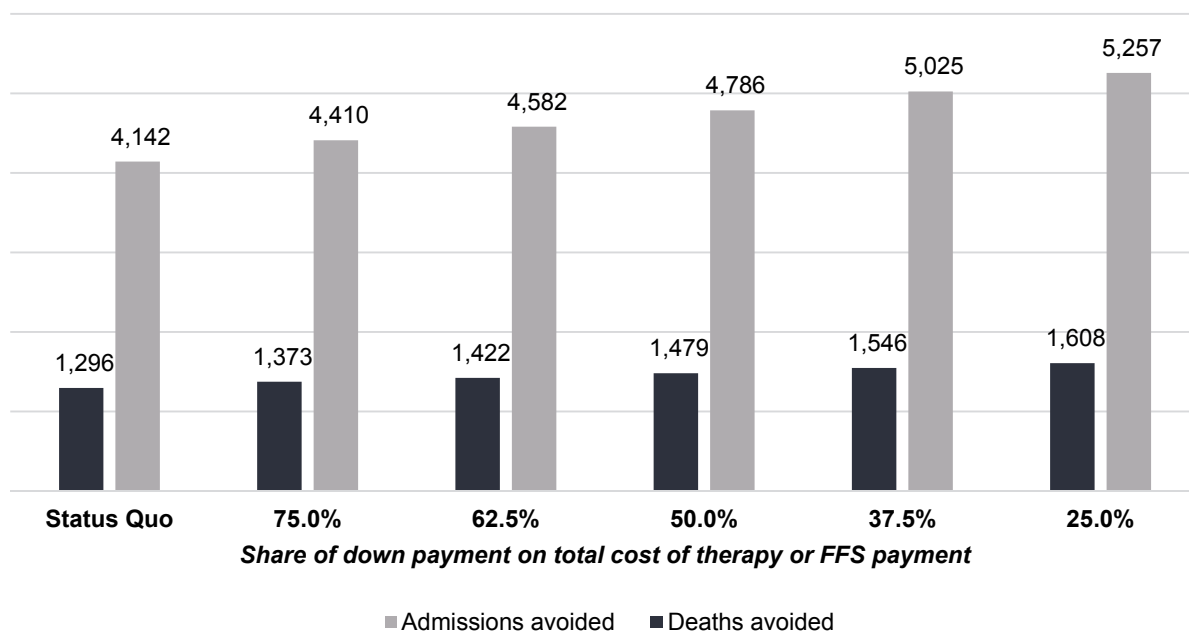
NOTE: This model assumes existing (baseline) assumption for risk reduction in admissions (RR = 0.70) due to treatment, and annual budget of $1 billion.

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Policy Implications

This dissertation has presented evidence about the estimated budget impact of selected regenerative therapies currently in late-stage clinical development, and simulated the performance of two alternative payment models for high-cost treatments in the context of the United States health care system.

The first paper shows that while budget pressures will not be insurmountable in case of all indications where new treatments will be launched, several specific indications will result in substantive budget impact for public and private payers, dominated by Alzheimer's disease.

The second paper shows that pre-negotiated pricing for a novel drug with uncertain real-world effectiveness, such as PCSK9 inhibitors for hypercholesterolemia, has the potential to reduce cost per event avoided, particularly when the drug fails to meet clinical trial efficacy in the real world.

The third paper shows that deferring payment in case of a congestive heart failure gene therapy results in a significant improvement of clinical outcomes as more eligible patients receive treatment sooner, even under a fixed budget constraint. Deferring payment, however, has negligible benefits for payers and manufacturers, which results in feasibility challenges that need to be overcome.

In general, the implementation of alternative payment models in the United States faces multiple challenges, ranging from regulatory hurdles to free-riding and patient switching. However, growing pressures on patients, payers and manufacturers are likely to encourage the adoption of such payment models. There are three key policy implications of this research.

Alternative payment models for medical treatments are becoming inevitable

As we show, multiple therapeutic areas are subject to a large budget impact once a regenerative treatment is approved and launched. Given the high prices of drugs that result in complete cures or significant improvements in patients' outcomes, and the budget constraints public and private payers experience today, access to even cost-effective treatments may be delayed without an alternative payment model in place. Our research shows that Alzheimer's

disease is the most critical indication, given the expected budget impact exceeding $50 billion annually, if approved. The need will be particularly high if the treatment is delivered over the course of one or a few visits, but clinical benefits are proven to last much longer. Other indications of concern are hepatitis B, traumatic brain injury, X-linked retinoschisis and congestive heart failure, whose potential spending could exceed $5 billion annually. Given the estimated approval timelines, the peak budget impact of newly approved therapies could be reached as soon as in 2023.

Clinical and cost implications differ by model and indication

Two payment simulations presented in this dissertation have shown different clinical and cost implications. These are driven both by model design and the unique characteristics of the diseases and treatments studied. In case of three-part pricing for PCSK9 inhibitors, cost per event avoided is reduced under low and expected effectiveness and remains virtually constant under high effectiveness. This results in a better value for money, and is expected to result in greater uptake and utilization. In contrast, deferred payment for gene therapy in congestive heart failure results in better clinical outcomes but limited financial gains for payers and manufacturers, mostly driven by small cost offsets resulting from avoided admissions. In other indications with higher cost of care, such as hemophilia and rare forms of blindness, deferred payment may prove to result in both better clinical outcomes as well as financial gains to payers while protecting innovation incentives to manufacturers.

Alternative payment models improve access and value for money

While we find that the two alternative payment models studied promise to improve access to novel treatments and value for money, they should not be expected to solve the broader challenge of the financial sustainability of the U.S. health care system. The launch of new regenerative therapies can expedite the utilization of more efficient payment models, such as the ones studied in this dissertation, but challenges related to budget pressures, equality in access to health care, or price transparency are unlikely to be resolved by these models alone.

Future research may expand on the application of these (and other) payment models for prescription drugs, consider the performance of these models in different indications, including

oncology, and consider some of the challenges identified in individual papers: regulatory and policy feasibility, issues related to patient switching, data collection and sharing, and the risk of free-riding. In the coming years, however, the need to consider new approaches to payment for high-cost, high-value treatments will only continue to increase.