Insurance Switching and Mismatch Between the Costs and Benefits of New Technologies

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ABSTRACT

OBJECTIVES: Many therapies have immediate costs but delayed benefits. Recent and anticipated transformative therapies may exacerbate these challenges. This study explored whether disconnects between short-term budget impacts and long-term costs and benefits, and among impacts on initial payers, downstream payers, and society, are expected for a range of such therapies and whether they are likely consistent or variable, with implications for potential policy responses.

STUDY DESIGN: Modeling.

METHODS: We modeled the impacts of 5 hypothetical therapies affecting different patient types: curative gene therapy for a childhood disorder, highly effective hepatitis C virus therapy, disease-modifying Alzheimer disease therapy, and cardiovascular disease therapy for both rare genetic and higher-risk prior cardiovascular event populations. We constructed disease-specific models, modifying best-available Markov analysis estimates for standard-of-care state transition rates, utilities, and costs. We disaggregated total healthcare impacts into impacts on initial versus downstream payers, dividing payers into 3 types: commercial insurers, Medicaid, and Medicare.

RESULTS: Although we found gaps between the impacts on initial and downstream payers in all examples, some substantial, the magnitude and reasons vary.

CONCLUSIONS: As scientific advances generate transformative therapies with substantial structural disconnects between "who pays" and "who benefits," creative approaches may be needed by manufacturers, payers, and others to ensure appropriate access to cost-effective therapies, adequate economic incentives for future development, and sustainable payer economics. Mechanisms may amortize high up-front costs over time, provide for transfers among payers, or a combination. Our research suggests that approaches should be tailored to specific disease and therapy characteristics to be effective.

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Scientific progress has transformed patient outcomes in many disease areas, leading to economic gains.[1] However, such therapies can challenge short-term payer budgets if benefits are not coincident with costs. Although this phenomenon is not new, recent and anticipated therapies may exacerbate these challenges. For example, sofosbuvir (Sovaldi), lauded as a breakthrough hepatitis C virus (HCV) treatment, has been restricted by some insurers concerned about short-term budget impacts, including by delaying access for patients with asymptomatic or milder disease whose costs would be paid later by Medicare.[2]

Disconnects between the impacts on different payers can be large in the United States, where commercial insurers, state Medicaid programs, and the federal Medicare program pay most costs. Given insurance switching by patients over time, payers covering initial costs may not benefit from all, or any, downstream cost offsets. Moreover, patients and families may highly value better health and quality of life, improved functional status and productivity, and longer life, whereas insurers may value lower costs most.

In 5 hypothetical examples, we modeled the mismatch between who pays for and who benefits from innovative therapies. Like others, we focused on patient movement over time across Medicaid, commercial insurance, and Medicare rather than contemporaneous switching among private insurers.[3] Our aim was to explore a widely acknowledged feature of US healthcare, namely that the fragmented insurance system creates potential disincentives for coverage of therapies with up-front costs and long-lived or delayed benefits, and whether the situation may be exacerbated for new clinically effective therapies that are also high-priced relative to the current standard of care (SOC). Rather than precise numerical estimates for specific diseases, we explored whether substantial disconnects may be expected under credible, but by no means the only possible, assumptions (and therefore the extent to which some cost-effective therapies with potential to improve length and quality of life may face heightened coverage disincentives); whether they vary across examples; and the implications for policy.

Some prior studies' results have illustrated payer disconnects for specific diseases; others have advocated specific policy responses. This study extends the literature by comparing disconnects across diseases subject to new transformative therapies and by exploring the implications for effectiveness of potential policy responses.

Disease Examples

We examined 5 disease states for which transformative therapies have been discussed or recently launched: highly effective HCV therapy; curative gene therapy for beta-thalassemia (BT), a rare childhood genetic disorder; disease-modifying therapy for patients with mild Alzheimer disease (AD); and cardiovascular disease (CVD) therapy for patients with the rare genetic disorder familial hypercholesterolemia (FH) and those with prior CVD. Several resemble, but do not purport to be identical with, recently introduced on-market therapies (HCV and cardiovascular therapies); others reflect areas that may produce breakthrough therapies (disease-modifying therapy for AD and gene therapy). These examples, although not exhaustive, were selected to represent diverse patient types (ie, pediatric, adult, and senior populations), clinical intervention models (ie, 1-time curative and ongoing disease-modifying therapies), and disease burdens (ie, highly certain ongoing chronic health management costs, probabilistic catastrophic hospitalization costs, and custodial and other costs from function deterioration). **Table 1** summarizes key characteristics across the examples.

TAKEAWAY POINTS

- Many therapies have financial costs and benefits at different times, creating gaps between initial and downstream payers when patients switch payers between the initial therapy payment and subsequent cost offsets.
- In modeling the potential impacts of 5 hypothetical new transformative therapies representing diverse patient types, clinical intervention models, and disease burdens, we found substantial and varying gaps between initial and downstream payer impacts.
- New creative mechanisms may be needed to ensure economic incentives for development of transformative therapies, appropriate patient access, and sustainable payer economics.
- Manufacturers and payers should tailor solutions to specific disease and therapy characteristics to be effective.

METHODS

To assess the net effect by payer type of each therapy, we constructed disease-specific analytic models and compared the present discounted value (PDV) of an individual's expected lifetime healthcare costs under the current SOC and the hypothetical new therapy, from the age an average patient initiates the latter (eg, gene therapy at age 2 years). We adopted this analytic frame to model payers' budget impact considerations associated with covering the new therapy for a patient of expected age. We also calculated improvements in quality-adjusted length of life associated with the new therapy and the incremental cost per quality-adjusted life year (QALY). This cost-effectiveness metric is provided as an indicator of social desirability. For US commercial payers, cost-effectiveness analysis is typically not an established coverage determination constraint, but budget impact analyses are important considerations. Therefore, we focused on budget impact in our analysis.

We first calculated the aggregate budgetary impact on all payers of the new therapy, including healthcare offsets due to morbidity improvements and additional healthcare costs due to extended life. We also incorporated the impact on elder care in the case of disease-modifying therapy for AD, including the net impact on both nursing home care and family caregiving. Second, we disaggregated these effects into those on a representative initial payer in the 3 main payer types and those on a representative downstream payer, restricting analysis to the most relevant payers (eg, 2-year-olds are generally covered by commercial insurance or Medicaid, not Medicare).

TABLE 1. Characteristics of Selected Disease–Therapy Combinations[a]

	Hepatitis C	Beta-Thalassemia	Alzheimer Disease	CVD: FH	CVD: Prior CVD
Patient population	Adults	Pediatric	Seniors	Adults	Adults
Disease-related burden	Cirrhosis, liver cancer, liver transplant	Chronic iron overload management (chelation, transfusion), CVD	Elder care costs	MI, stroke	MI, stroke
Timing of disease-related burden	Many years after viral exposure	Ongoing, from childhood	Increases with advanced age and disability	Early adulthood on	Mid-life through advanced age
New therapy type	1-time; curative	1-time gene therapy; curative	Ongoing; disease-modifying	Ongoing; disease-modifying	Ongoing; disease-modifying
Initial payer	Commercial insurance or Medicaid	Commercial insurance or Medicaid	Medicare	Commercial insurance or Medicaid	Commercial insurance or Medicaid

CVD indicates cardiovascular disease; FH, familial hypercholesterolemia; MI, myocardial infarction.
[a]Source: authors' analysis of clinical literature and summary of hypothetical therapy.

TABLE 2. Aggregate Cumulative PDV of Lifetime Net Healthcare Cost Impact Per Patient[a]

	Direct Therapy Cost [A]	Other Healthcare Cost Impacts		Subtotal Direct + Other Healthcare Costs [D = A+B+C]	Value of Additional QALYs [E = G × $100,000]	Total Impact [F = D+E]	Additional QALYs [G]	Incremental Cost per QALY [H = D/G]
		Morbidity Improvement [B]	Mortality Improvement [C]					
Hepatitis C	–$24,688	$25,184	–$12,536	–$12,039	$233,322	$221,282	2.33	$5160
Beta-thalassemia	–$499,941	$377,739	–$57,291	–$179,493	$2,092,798	$1,913,305	20.93	$8577
Alzheimer disease	–$81,196	$17,754	–$14,384	–$77,826	$142,602	$64,776	1.43	$54,576
CVD: FH	–$278,368	$28,602	–$19,402	–$269,168	$109,950	–$159,218	1.10	$244,809[b]
CVD: prior CVD	–$374,825	$28,978	–$30,231	–$376,078	$145,424	–$230,654	1.45	$258,608[b]

CVD indicates cardiovascular disease; FH, familial hypercholesterolemia; PDV, present discounted value; QALY, quality-adjusted life year.
[a]All figures are PDVs; future costs are discounted at 3% per year. Figures with negative signs indicate financial loss; others indicate financial gain. For Alzheimer disease, disease-related costs include elder care costs (ie, long-term care costs, home health costs, and the value of caregiver time). A per-QALY value of $100,000 has been reflected. Source: authors' model results.
[b]Incremental costs per QALY for CVD reflect those reported by Institute for Clinical and Economic Review in its review,[6] adjusted for an average 20% discount. Figures reported in **Table 3** and **Figure** for CVD correspond to these figures.

We modeled the impact of patients switching payer types as they age, rather than switching commercial insurance plans contemporaneously. Whereas approximately 1 in 8 nonelderly Americans with employer coverage switched health plans in 2010 (approximately 1 in 13 due to reasons other than job change), nearly all will transition to Medicare at age 65 years.[4] If recent and expected therapy breakthroughs suggest a continuing shift toward front-loaded costs and back-loaded benefits, the implications for both commercial insurance and Medicare may be far reaching. We explored the reasonableness of this modeling choice via several anonymized interviews with medical directors at large commercial payers who confirmed that, given prohibitions on pre-existing condition exclusions and the nature of geographic competition where leading plans may tend toward similar coverage, they generally expect that short-run losses from a therapy for patients who "switch out" roughly offset gains from those patients who have "switched in" and whose therapy costs were covered by other commercial payers. However, for the effects of switching over time as patients age, similar assumptions do not apply. Respondents were not interviewed about the effects of potential Affordable Care Act repeal or about actions that could affect the balance between commercial coverage and state exchanges.

Our analyses rely on best-available Markov-type models published by others, incorporating rates of patient transition from one health state to another and healthcare costs and patient utilities for each state. In order to compare the hypothetical new treatment with the current SOC, we adapted these models by varying parameters related to efficacy, cost, and age at therapy initiation, specific to the hypothesized intervention. We applied shared assumptions across the models for the percentage distribution of insurance type by age and sex from the literature. In calculating the total impact of the new therapy, we valued a QALY at $100,000; the impact on payers excludes this value, as there is no market to monetize the value of additional QALYs.[5] (Cost-effectiveness calculations exclude the value of additional QALYs, by definition.) Throughout, the value of all costs and savings was discounted at a 3% annual rate. For additional relevant disease-specific and shared assumptions, see the **eAppendix** (eAppendices available at **ajmc.com**).

RESULTS

Table 2 summarizes the aggregate impact of the different therapies. For the 2 CVD examples, the model relied on recently released calculations for patients aged 35 to 74 years (rather than a single age) with FH and a history of CVD.[6] Without direct access to the authors' health state-specific model, we calculated incremental cost per QALY from these figures (after adjusting for a modeled average 20% net price discount). Figures reported for the 2 CVD therapies in **Tables** 2 and **3**[7] and the **Figure** reflect these cost-effectiveness figures (rather than higher figures reflected in a PCSK9 inhibitor manufacturer's technology appraisal submission to the United Kingdom's National Institute for Health and Care Excellence).[8] Regardless, we focused on the difference between the impacts on the initial and downstream payers rather than their absolute levels.

Under our assumptions, all 5 therapies would increase discounted net healthcare costs. The magnitude of additional QALYs and the healthcare costs in additional years of life would vary, depending on patient and disease dynamics. Under the assumptions used, 3 therapies were highly cost-effective, with an incremental cost per QALY of $55,000 or less; the 2 CVD therapies were cost-effective at a value of about $250,000 per QALY (less, under manufacturers' estimates; translated from pounds to dollars without any other adjustment for differences in utilization or unit prices, the corresponding figures would be incremental costs per QALY of

TABLE 3. Cumulative PDV of Incremental Lifetime Net Healthcare Cost Impact Per Patient on Initial and Downstream Payers and Relative to $1 of Total Healthcare Cost Impact[a]

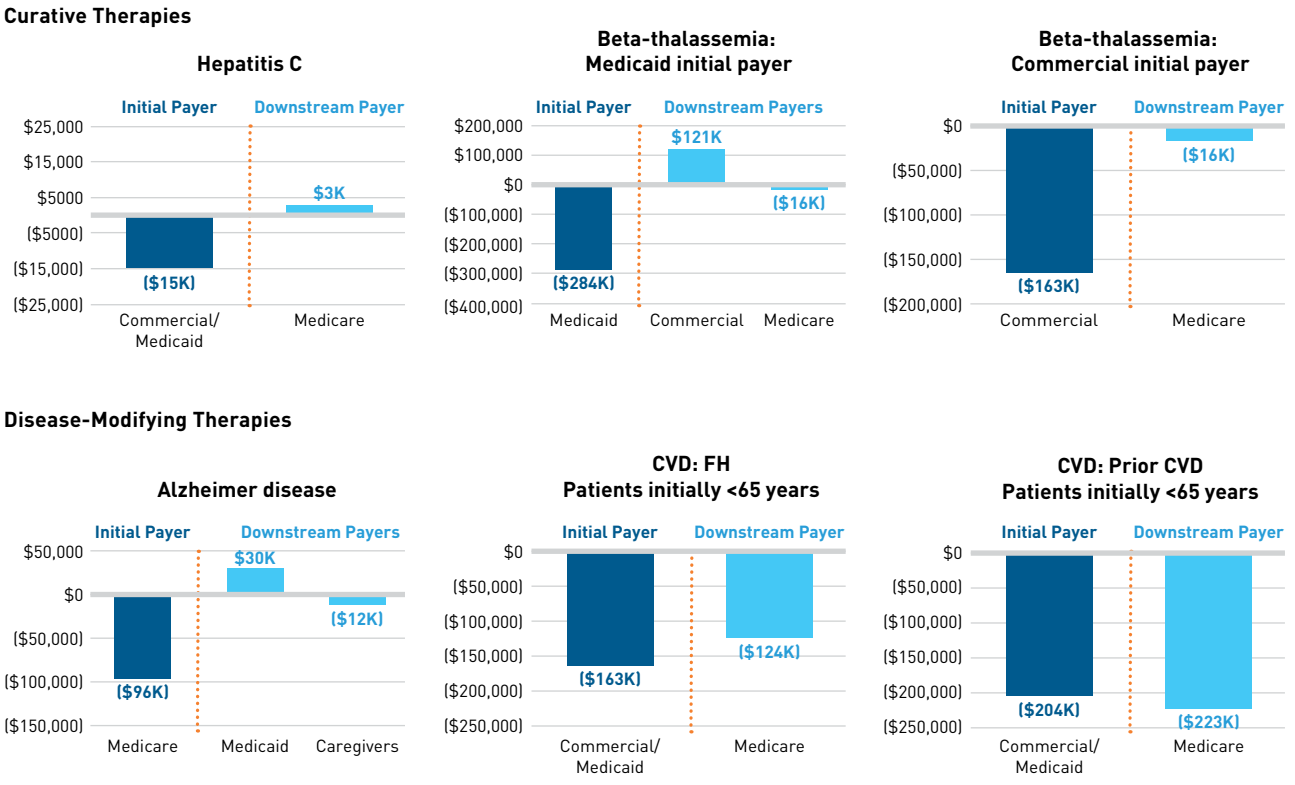
	PDV Healthcare Cost Impact	Impact Relative to $1.00 of Total Healthcare Impact
Hepatitis C		
Aggregate payer impact	–$12,039	–$1.00
Initial payer impact: commercial insurance/Medicaid	–$15,001	–$1.25
Downstream payer impact: Medicare	$2962	$0.25
Beta-thalassemia		
A. Aggregate payer impact	–$179,493	–$1.00
Initial payer impact: commercial insurance	–$163,351	–$0.91
Downstream payer impact: Medicare	–$16,142	–$0.09
B. Aggregate payer impact	–$179,493	–$1.00
Initial payer impact: Medicaid	–$284,012	–$1.58
Downstream payer impact: commercial insurance	$120,661	$0.67
Downstream payer impact: Medicare	–$16,142	–$0.09
Alzheimer disease		
Aggregate payer impact	–$77,826	–$1.00
Initial payer impact: Medicare	–$95,835	–$1.23
Downstream payer impact: Medicaid	$30,169	$0.39
Downstream impact: patients/caregivers	–$12,160	–$0.16
CVD: FH		
A. Aggregate payer impact (patients initially <65 years)[7]	–$288,383	–$1.00
Initial payer impact: commercial insurance/Medicaid	–$164,004	–$0.57
Downstream payer impact: Medicare	–$124,379	–$0.43
B. Aggregate payer impact (patients initially ≥65 years)[7]	–$167,902	–$1.00
Initial payer impact: Medicare	–$167,902	–$1.00
Downstream payer impact: N/A	–	–
CVD: Prior CVD		
A. Aggregate payer impact (patients initially <65 years)[7]	–$426,925	–$1.00
Initial payer impact: commercial insurance/Medicaid	–$204,378	–$0.48
Downstream payer impact: Medicare	–$222,547	–$0.52
B. Aggregate payer impact (patients initially ≥65 years)[7]	–$286,522	–$1.00
Initial payer impact: Medicare	–$286,522	–$1.00
Downstream payer impact: N/A	–	–

CVD indicates cardiovascular disease; FH, familial hypercholesterolemia; N/A, not applicable; PDV, present discounted value.
[a]Initial payer impact + downstream payer impact = aggregate payer impact. Figures represent difference between new therapy and standard of care. All figures are PDVs; future costs are discounted at 3% per year. Figures with negative signs indicate financial loss (ie, increases in costs); others indicate financial gain. Includes healthcare cost impacts only (therapy cost, mortality improvement effect, morbidity improvement effect). Figures correspond to impacts for a single patient covered by a given payer at the time of initial therapy intervention. Therapy intervention costs include initial and ongoing annual costs. For Alzheimer disease, disease-related costs include elder care (ie, long-term care, home healthcare, and the value of caregiver time). Assumptions incorporate those reported by others in corresponding Markov-type analyses.

$33,703 for FH and $67,701 for prior CVD). Our focus, however, was on disconnects across payers, and the Figure disaggregates the overall payer impact into impacts on initial and downstream payers. For HCV, BT, and AD, the financial impact on the initial payer was negative and the impact on at least 1 downstream payer type was positive. Table 3 reports these figures in dollar terms and, to allow for direct comparison, per dollar of aggregate payer impact.

Under our assumptions, treating BT costs the healthcare system nearly $180,000. The impact by payer varies depending on the initial insurer. When commercial payers are the initial insurers,

FIGURE. Cumulative PDV of Lifetime Net Healthcare Cost Impact Per Patient on Initial and Downstream Payers[a]



CVD indicates cardiovascular disease; FH, familial hypercholesterolemia; PDV, present discounted value.

[a]Includes therapy cost impacts, healthcare impacts due to changes in morbidity and mortality. Bars to the right of the dotted line (downstream payer) below the horizontal axis indicate when downstream payers experience financial loss; bars above the axis indicate financial gain. Source: authors' model results. Additional detail available in **eAppendix**. Omits results for CVD: FH and CVD: prior CVD for patients initially ≥65 years. In both cases, downstream payer is not applicable (see **Table 3**).

they face slightly lower financial impacts relative to aggregate healthcare costs, the difference being additional downstream Medicare costs from children now surviving to age 65. That said, most costs are paid by commercial payers. Children initially covered by Medicaid, however, are covered by private insurance when older (modeled at age 21). Thus, Medicaid pays all treatment costs and commercial insurers realize a gain, the net effect of more likely survival and lower per-patient costs. For every patient whose treatment at age 2 is paid by Medicaid, commercial insurers benefit by a cumulative PDV of $120,661.

Others also have analyzed the tension between long-term cost-effectiveness and the immediate budget impact of highly effective therapies for HCV and similarly find a disincentive for commercial insurer coverage, with results borne by Medicare and other downstream payers[7,9,10]; 1 study estimated roughly a 15-year payback period for private payer coverage.[3] Under our assumptions, initial commercial payers experience a cumulative PDV net cost of about $15,000 per patient. Medicare benefits from commercial payer coverage because patients avoid later expensive catastrophic events, such as liver cancer and transplants. These savings are greater than the additional costs incurred from patients living longer, for a gain of nearly $3000 per patient.

Slowing the progression of AD costs Medicare, both because it pays therapy costs and because patients live longer. However, it also reduces the need for nursing home care, thus saving Medicaid approximately $30,000 per patient. Families benefit from reduced needs for nursing home care, but experience additional caregiving burden during longer disease progression at home, for estimated increased net costs.

For patients initiating CVD therapy before age 65, commercial insurer and Medicaid costs are lower than the aggregate impact because many therapy costs occur after age 65. Although commercial insurers and Medicaid experience lower savings from avoided cardiovascular events, they also experience lower additional healthcare costs from longer life. For patients initiating therapy after age 65, Medicare experiences all therapy costs, healthcare cost offsets, and extra healthcare costs associated with extended life. For both populations, the net effect is negative, moreso for

patients with prior CVD than those with FH. Although the magnitude reflects the assumptions used by others (which have been critiqued[11]), the general pattern remains under other cost and disease transition assumptions.

DISCUSSION

Our research confirms that switching between payer types over time results in financial disconnects between initial and downstream payers across multiple hypothetical examples of highly effective new therapies with front-loaded costs and back-loaded benefits. Without mechanisms to monetize the downstream benefits of health improvements to others, returns from initial payers' investments are understated. In particular, switching from commercial to Medicare coverage at age 65 may result in systematic disincentives for some new therapies by commercial payers, depending on specifics relating to age at initial treatment, up-front therapy cost, and morbidity and mortality impacts.

Medicare may be a financial "winner" or "loser," depending on the balance between additional therapy cost, morbidity improvement savings, and extra healthcare costs from mortality gains. For HCV, we found (as have others) that Medicare benefits from initial payer coverage.[3] For BT, Medicare impacts are far in the future and somewhat negative. For disease-modifying AD therapy and the CVD therapies as modeled, Medicare would pay more. Depending on the magnitude of the effects and the numbers of patients treated, downstream Medicare impacts of commercial insurer decisions could be an important additional form of "spillover," documented in other contexts.[12] Commercial insurers face negative financial impacts across the examples when they are the initial payers, suggesting all therapies could face coverage disincentives, overlooking downstream cost offsets. Yet, from an aggregate healthcare cost point of view, the incremental cost per QALY as modeled is within standard acceptable ranges and well below for some, and investment would be socially desirable.

Absent direct social investment or subsidies, other approaches may address disconnects between privately incented and socially desirable outcomes. Two types of approaches, or a combination, may be relevant, depending on circumstances: mechanisms to align costs and benefits over time (for the same payer) and to help finance up-front therapy costs and mechanisms to share and align therapy costs and benefits across payers (eg, transfers between winners and losers). Several alternative financing proposals of the first type have been proposed, incorporating some form of cost amortizing to address challenges of high up-front costs. These include manufacturer–payer financing mechanisms (eg, manufacturer-issued debt secured by dedicated streams of contractual payments from commercial payers)[13,14]; changes in accounting rules and/or insurance regulations to allow payers to amortize some costs over longer time periods[14]; monthly annuity payments or manufacturer service fees linked to clinical milestones and/or continued efficacy, rather than single up-front or per-dosage charges[15]; or consumer credit or debt programs.[16,17] Such arrangements would be novel in biopharmaceutical reimbursement, but they are similar in some respects to financing expensive long-lived consumer medical devices, such as insulin pumps, that are used for chronic disease. Our results suggest that alternative financing mechanisms smoothing front-loaded costs over time could be relevant for 1-time curative gene therapy and highly effective HCV therapy, but they may be only partial solutions, as benefits and costs may still accrue to different payers. Disincentives for HCV therapies occur not only because initial costs for cure are high, creating short-term budget stress, but also because substantial downstream benefits accrue to others. Such mechanisms are likely less relevant for ongoing therapies, such as disease-modifying AD therapies or cardiovascular therapies, where costs are already spread over time.

The second types, cross-payer financial transfers and burden-sharing mechanisms between winners and losers, specifically address gaps between who pays and who benefits (rather than gaps in time between costs and benefits for the same payer). Transfers can address when costs to one payer type are offset by savings to another. For instance, up-front Medicaid cost burdens and future benefits to Medicare could be recognized by enhanced state Medicaid reimbursement rates or direct federal transfers. So-called burden-sharing proposals address when therapies are cost-effective but also cost-increasing, and a gap remains after transfers.

Transfers from one payer type to another theoretically could be appropriate for therapies such as those for BT, where Medicaid bears large up-front costs and commercial insurers experience substantial downstream benefits. However, proposals to smooth out therapy costs over time for the same payer will be easier to implement than proposals to transfer costs and benefits across payer types.[18] More generally, future innovative therapies may benefit from proposals tailored to their specific circumstances, including mechanisms to amortize costs over time or to transfer value from downstream winners to initial losers, or a combination (see **Table 4**). Although we find disconnects between initial and downstream payers in all examples, some substantial, the magnitude and reasons vary.

Limitations

As with all modeling studies, different price, timing, and effectiveness assumptions yield different results for cumulative payer PDVs (see eAppendix sensitivity analyses). Moreover, not all relevant societal benefits have been included in the models relied upon for cost-effectiveness inputs. For instance, educational attainment and lifetime productivity impacts, important benefits of curing childhood genetic diseases, are not included for BT. Similarly, the value of reducing future transmission to others is not included for HCV

TABLE 4. Potential Approaches Addressing Payer Challenges for Cost-Effective Transformative Therapies

	Types of Approaches	
	Financing therapy costs and aligning costs and benefits over time	**Aligning therapy costs and benefits across payers**
Financial focus	• Per-patient therapy costs create burden due to costs being front loaded	• Per patient benefits of therapy (eg, cost offsets) are not evenly distributed across payers • Gap between who pays and who benefits
Representative examples	• Manufacturer–payer debt instruments that smooth payments over time • Stop-loss reinsurance provisions for new therapy costs • Manufacturer monthly therapy service fees, rather than per dose charges	• Mechanisms to share therapy costs or benefits across payers and that follow patients as they switch payers • Enhanced federal Medicaid program reimbursement rates to states when Medicare later benefits from Medicaid coverage of certain therapies (sharing benefits across payers)
Characteristics of Modeled Therapies[a]		
Hepatitis C	✓ • Moderate therapy cost impact per patient on initial payer	✓ • Net healthcare cost to initial payer and moderate benefit to Medicare, per patient
Beta-thalassemia	✓✓ • Very high 1-time therapy cost impact per patient on initial payer	✓✓ • Large net healthcare cost per patient to Medicaid and large downstream benefit to commercial insurers
Alzheimer disease	× • Ongoing therapy; not a match	✓ • Large cost to Medicare and benefit to Medicaid (LTC), but transfers inappropriate when Medicaid is downstream payer
CVD: FH	× • Ongoing therapy; not a match	× • Impacts on initial and downstream payer are both cost increasing and of similar magnitude • Equalizing burden sharing not a major opportunity
CVD: prior CVD	× • Ongoing therapy; not a match	× • Impacts on initial and downstream payer are both cost increasing and of similar magnitude • Equalizing burden sharing not a major opportunity

CVD indicates cardiovascular disease; FH, familial hypercholesterolemia; LTC, long-term care.
[a]× indicates characteristic is not a match with the modeled therapy; check mark indicates a match; double check mark indicates a strong match. Source: authors' interpretation of model results.

and the benefits from sustained functioning and independence for patients and their families due to disease-modifying therapy are not included for AD. These benefits are not monetized but are real nonetheless, and including them could increase gaps between front-loaded costs and back-loaded benefits and/or improve cost-effectiveness. Second, for chronic therapies, we did not include changes in the new therapy's net price over time. Third, given pre-existing health condition coverage exclusion prohibitions, we applied average population-level insurance coverage statistics and did not incorporate disease-specific insurance coverage or switching rates. We modeled at the aggregate payer type level, and this assumption may not hold true for all plans (eg, smaller payers may face greater temptations to free-ride on others' prior coverage decisions) and patients (who may experience different switching rates post treatment). For simplicity, we assumed uniform therapy and medical costs across payer types; lower Medicaid prices could reduce Medicaid net PDVs relative to other payers. Fourth, our analyses reflect the limitations of the underlying Markov-type models (eg, constant age-specific mortality and transition rates over time), which may yield underestimated mortality benefits when extended over many years. To the degree that not all healthcare cost offsets from the new therapy are reflected in these underlying models, our calculations overstate net costs. For instance, cost offsets in heart failure and unstable angina are not included in the cardiovascular models and improvements in heart attack and stroke incidence may be understated, as they may reflect an assumed lower-risk treatment population than targeted.[11] Because our focus is on general dynamics under plausible (but by no means the only possible) assumptions, our findings are representative rather than precise conclusions about specific disease–therapy combinations or forecasts of the impacts of specific therapies. Finally, our calculations reflect the assumption that, for chronic conditions, downstream payers also cover the therapy (this limitation is not relevant to 1-time therapies, such as gene therapy).

CONCLUSIONS

As scientific advances generate breakthrough therapies with varying profiles, creative thinking and flexible solutions by manufacturers, payers, and others will be needed to address barriers to

realizing their benefits. Well-designed alternative financing or other mechanisms could help ensure economic incentives for future development, appropriate patient access, and sustainable payer economics for expensive but cost-effective transformative therapies. Although proposals have been suggested to address upfront cost barriers, proposed transfers from downstream winners to initial losers and burden-sharing mechanisms have received less attention. In some cases, both could be helpful, with the balance reflecting disease-specific circumstances. However, further research is needed to address practical and theoretical challenges, including defining why and under what circumstances Medicare would or would not incent private payer coverage, how to maintain incentives for private-sector coverage, and how and when to implement acceptable cross-payer transfers. The framework we used to disaggregate potential impacts on initial and downstream payers of new therapies, and to identify potential gaps between who pays and who benefits, may be a useful tool for manufacturers and others to map sources of potential coverage disincentives and develop and fine-tune such proposals before presenting them to payers. Failing to consider relevant disease-specific dynamics may mean the promise of new transformative therapies is not fully realized. ■

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eAppendix

ADDITIONAL DETAIL ON DISEASE-SPECIFIC MODEL ASSUMPTIONS AND OUTPUTS

We constructed disease-specific analytic models for each of five disease states for which important breakthrough therapies have been discussed, have recently been launched, or have the potential to be nearing market introduction in the coming years, given scientific advances:

- highly-effective hepatitis C therapy;
- gene therapy for a rare childhood genetic disorder (beta-thalassemia);
- disease-modifying therapy for Alzheimer's disease;
- cardiovascular disease therapy for patients with a rare genetic disorder (familial hypercholesterolemia, or FH); and
- cardiovascular disease therapy for a high-risk population (patients with prior cardiovascular disease, or prior CVD).

The disease-specific analytic models rely on recently-published Markov-type models by others which incorporate information on rates of patient transition from one health state to another (e.g., cirrhosis to liver transplant) and healthcare costs and patient utilities associated with each state, under the current standard of care. In order to compare the hypothetical new treatment with the standard of care, we adapted these Markov-type models by varying parameters specific to each example, such as the annual probability of a patient advancing from one disease-related state to the next as a result of the new treatment (for example, for the disease-modifying Alzheimer's disease therapy we assumed that the hypothetical therapy was administered to patients with mild cognitive impairment beginning at age 70, and that it slowed the rate of disease progression to each subsequent health state by half).

We assume that the hypothetical gene therapy is administered once at age 2 at a cost of $1 million, reflecting recent discussion [A1], and results in medical costs and longevity thereafter equal to the population average for the same age and sex. We assume that the disease-modifying AD therapy is administered to patients with mild cognitive impairment beginning at age 70 at a cost of $10,000 a year, and slows the rate of progression to each subsequent health state by half. Analysts have assumed costs between $5,000 and $20,000, depending on efficacy

and other factors; we selected an approximate mid-point to correspond with a slowing in the rate of disease progression rather than stasis or regression.[A2] We assume that hepatitis C patients are treated at age 55 at an average net price equal to a 50% discount from the current list price of sofosbuvir -- roughly the current price, net of discounts -- and approximately 95% of patients treated achieve therapeutic response.[A3]

When representing the expected future costs of individuals cured by hypothetical interventions, we assumed the average U.S. healthcare costs of males and females by age, adjusting as necessary for higher healthcare costs in the last year of life (as a multiple of baseline expected healthcare costs for males and females of the same age).[A4,A5] Other details and the survival and cost impact curves calculated for these three examples can be found in the following sections specific to each hypothetical therapy example.

For the two CVD examples, the model relies on recently-released calculations for patients age 35 to 74 (rather than a single age) with FH and a prior history of CVD, which were generated from the Cardiovascular Policy Model [A6]. Without direct access to the health state-specific model, we could not generate cost curves for these examples. Instead, we modified those reported figures to reflect an average net cost for the new therapy equal to a 20% average discount from the average list price for alirocumab and evolocumab (a current WAC list price of $14,350), and incorporated non–disease-related costs by age and sex using the same approach as for the three other examples.

We modeled at the payer-type level (i.e., commercial insurance, Medicaid, Medicare), rather than at the level of an individual payer, and applied average insurance rates by age and sex across all of the disease-specific models.

Key assumptions in the models are reflected in tables below, segmented into disease-specific assumptions (I.A, II.A, III.A, IV.A, and V.A) and shared assumptions across disease models for insurance coverage by age and sex, and average healthcare spending by age, sex and terminal versus non-terminal year of life (VI).

Model outputs include survival (I.B.1, II.B.1, III.B.1) and healthcare cost impact (I.B.2, II.B.2, III.B.2) curves for the standard of care and the hypothetical new therapy (figures are undiscounted; healthcare cost curves include the impacts of the hypothetical therapy on both

disease-related and non–disease-related healthcare costs, and exclude the incremental costs of the therapy interventions themselves).

Model outputs also include a summary table of cumulative present discounted value (PDV) of lifetime disease-related and non-disease-related healthcare costs, per initially-covered patient in each of the three main payer types, with and without the theoretical therapy intervention (I.B.3, II.B.3, III.B.3, IV.B.3, V.B.3, VII.A). Sensitivity analyses to key assumptions (i.e., price, age at treatment, therapeutic response) are presented in VII.B. In all tables, the value of all costs and savings are discounted at an annual rate of three percent.

As noted, as a result of the difference in the modeling approach described above, corresponding healthcare cost curves and sensitivity analyses for the CVD (FH and prior CVD) examples are not presented.

I. Beta-Thalassemia

A. Beta-Thalassemia Disease-Specific Assumptions

Table I.A.1
Key Beta-Thalassemia Model Assumptions

Model parameter	Value
Age of patients at therapy intervention	2
Distribution of patients by sex	
Female	50%
Male	50%
Distribution of patients by disease state at therapy intervention	
Alive without cardiac disease	100%
Alive with cardiac disease	0%
Proportion of treated patients achieving therapeutic response	
Theoretical therapy intervention	100.0%
Standard of care	0.0%
Costs of therapy	
Initial costs	
Theoretical therapy intervention	$1,000,000
Standard of care	$0
Ongoing annual costs	
Theoretical therapy intervention	$0
Standard of care[1]	$31,546
Discount rate	3%
QALY value	$100,000

Note:

1. Ongoing annual costs of standard of care therapy include drug and administration costs associated with infusional chelation therapy and medical costs associated with transfusions.

Source:

1. Delea TE, Hagiwara M, Thomas SK, et al. Outcomes, utilization, and costs among thalassemia and sickle cell disease patients receiving deferoxamine therapy in the United States. Am J Hematol. 2008;83(4):263-270.

Table I.A.2
Beta-thalassemia model mortality, healthcare costs, and health state utility assumptions

Disease state	Without therapeutic response		
	All-cause mortality multiplier	Annual per-patient β-thalassemia-related healthcare costs[1]	Health state utilities
Alive without cardiac disease	3.90	$19,863	0.61
Alive with cardiac disease	See Assumptions Table 3	$38,987	0.52

Disease state	With therapeutic response		
	All-cause mortality multiplier	Annual per-patient β-thalassemia-related healthcare costs[1]	Health state utilities
Cured	1.00	$0	1.00

Notes:

1. Costs for living patients without cardiac disease include incremental healthcare costs of β-thalassemia, excluding costs associated with infusional chelation therapy and transfusions. Costs for living patients with cardiac disease include incremental healthcare costs of β-thalassemia, as well as costs associated with β-thalassemia-related cardiac disease.

Sources:

1. Delea TE, Sofrygin O, Thomas SK, et al. Cost effectiveness of once-daily oral chelation therapy with deferasirox versus infusional deferoxamine in transfusion-dependent thalassaemia patients: US healthcare system perspective. Pharmacoeconomics. 2007;25(4):329-342.
2. Delea TE, Hagiwara M, Thomas SK, et al. Outcomes, utilization, and costs among thalassemia and sickle cell disease patients receiving deferoxamine therapy in the United States. Am J Hematol. 2008;83(4):263-270.

Table I.A.3
Beta-thalassemia model transition probability assumptions

Annual transition probabilities				
	Final disease state, without therapeutic response[1]			
Initial disease state	**Cured**	**Alive without cardiac disease**	**Alive with cardiac disease**	**Death**
Alive without cardiac disease	0.0%	95.4%	4.6%	0.0%
Alive with cardiac disease	0.0%	0.0%	84.0%	16.0%
Death	0.0%	0.0%	0.0%	100.0%

One-time transition probabilities (at time of therapy intervention)				
	Final disease state, with therapeutic response			
Initial disease state	**Cured**	**Alive without cardiac disease**	**Alive with cardiac disease**	**Death**
Alive without cardiac disease	100.0%	0.0%	0.0%	0.0%
Alive with cardiac disease	100.0%	0.0%	0.0%	0.0%

Note:

1. Annual probability of transition from no cardiac disease to β-thalassemia-related cardiac disease derived from Bentley et al. 2013. Annual probability of transition from β-thalassemia-related cardiac disease to death as reported by Delea et al. 2007.

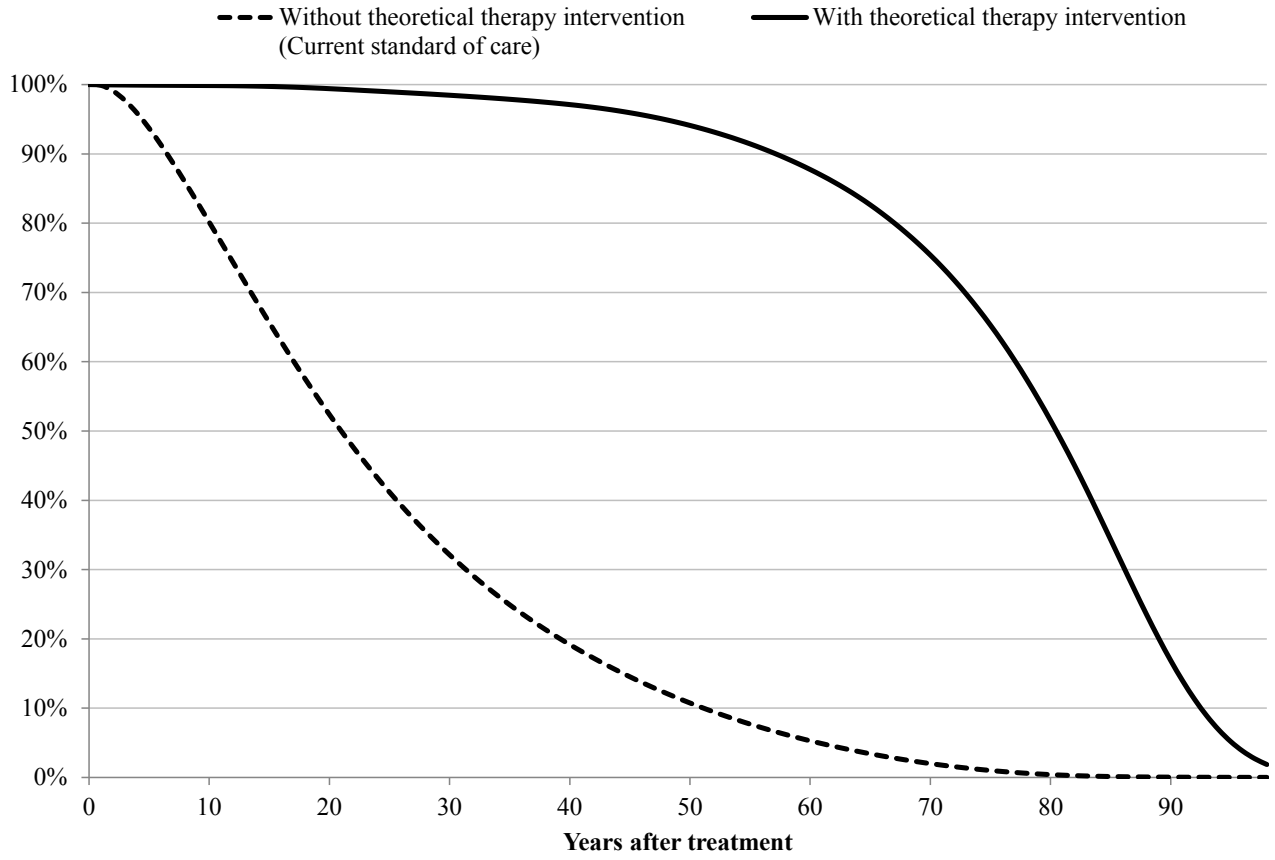
Sources:

1. Bentley A, Gillard S, Spino M, et al. Cost-utility analysis of deferiprone for the treatment of beta-thalassaemia patients with chronic iron overload: a UK perspective. Pharmacoeconomics. 2013;31(9):807-822.
2. Delea TE, Sofrygin O, Thomas SK, et al. Cost effectiveness of once-daily oral chelation therapy with deferasirox versus infusional deferoxamine in transfusion-dependent thalassaemia patients: US healthcare system perspective. Pharmacoeconomics. 2007;25(4):329-342.

B. Beta-Thalassemia Model Outputs

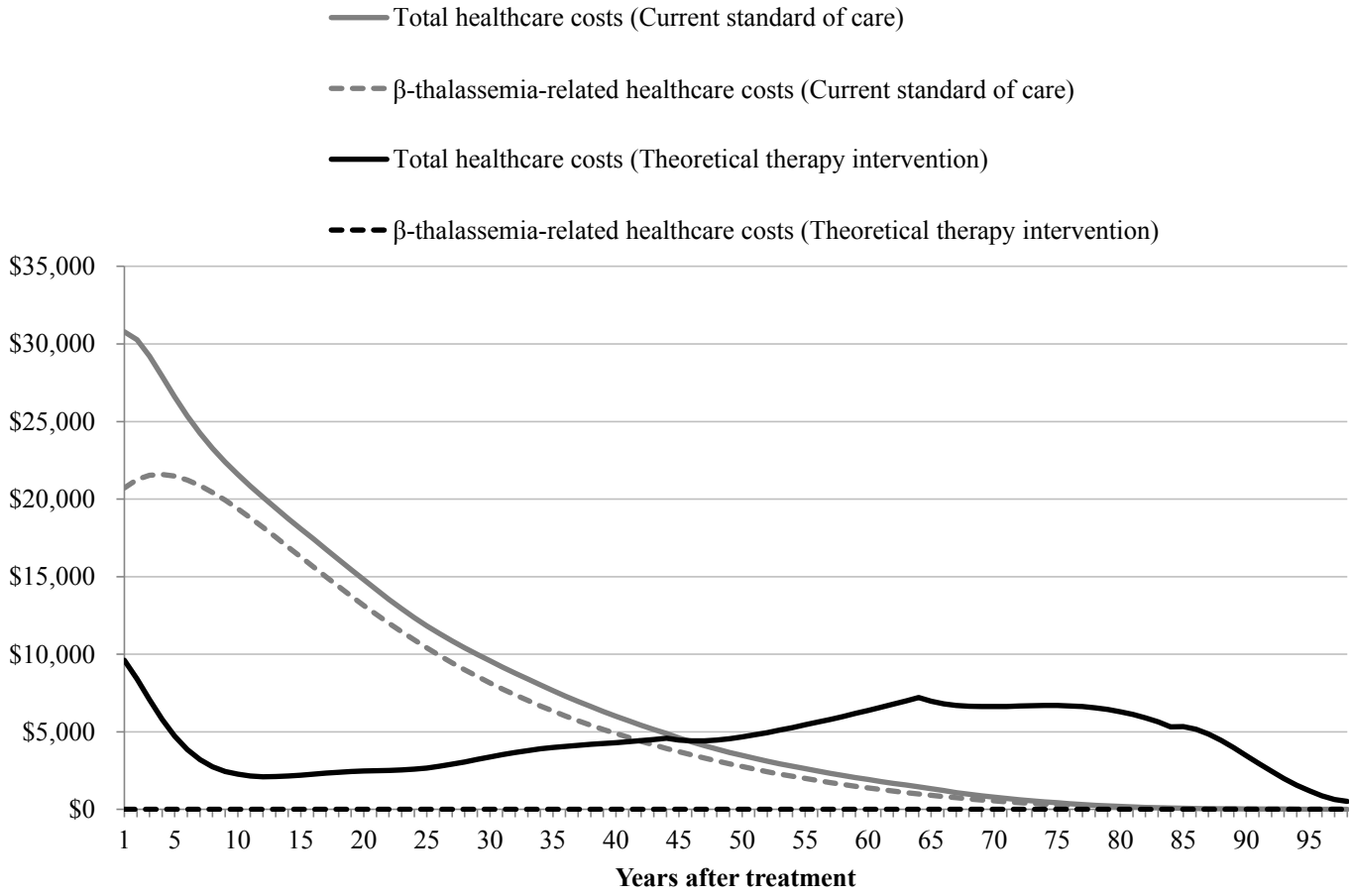
1. Cumulative probability of survival, with and without theoretical therapy intervention

Figure I.B.1
Beta-thalassemia cumulative probability of survival, with and without theoretical therapy intervention



2. Expected per-patient Beta-thalassemia-related and total healthcare costs, with and without theoretical therapy intervention, undiscounted (excludes therapy intervention spend)

Figure I.B.2
Expected per-patient β-thalassemia-related and total healthcare costs (undiscounted), with and without theoretical therapy intervention



3. Cumulative PDV lifetime Beta-thalassemia-related and non–Beta-thalassemia-related healthcare costs, per initially covered patient With and without theoretical therapy intervention, by payer type, discounted

Table I.B.1
Cumulative present discounted value (PDV) of lifetime net healthcare cost impact[1,2]
Per initially covered patient

Payer type	Lifetime		
	Without theoretical therapy intervention (Current standard of care)	With theoretical therapy intervention	Difference (SOC - new therapy)[3]
Commercial insurance			
Therapy intervention cost[4]	$498,749	$1,000,000	($501,251)
Healthcare costs			
β-thalassemia-related costs	$376,601	$0	$376,601
Non β-thalassemia-related costs	$76,329	$115,030	($38,701)
Subtotal (therapy intervention cost + healthcare costs)	**$951,679**	**$1,115,030**	**($163,351)**
Medicaid			
Therapy intervention cost[4]	$418,259	$1,000,000	($581,741)
Healthcare costs			
β-thalassemia-related costs	$311,983	$0	$311,983
Non β-thalassemia-related costs	$65,463	$79,717	($14,254)
Subtotal (therapy intervention cost + healthcare costs)	**$795,705**	**$1,079,717**	**($284,012)**
Total societal			
Therapy intervention cost[4]	$500,059	$1,000,000	($499,941)
Healthcare costs			
β-thalassemia-related costs	$377,739	$0	$377,739
Non β-thalassemia-related costs	$76,861	$134,153	($57,291)
Total (therapy intervention cost + healthcare costs)	**$954,660**	**$1,134,153**	**($179,493)**
Value of additional QALYs	($937,355)	($3,030,153)	$2,092,798
Total societal impact (Healthcare cost impact + years of healthy life gained)	**$17,305**	**($1,896,000)**	**$1,913,305**
Incremental cost per QALY			**$8,577**

Notes:

1. Represents a single patient covered by a given payer type at the time of therapy intervention. Cumulative present discounted value of lifetime net healthcare cost impact is calculated accounting for the probability that patients transition from the initial payer type to other payer types over time, but not accounting for patients transitioning to the initial payer type from other payer types.
2. All figures are PDV; the value of future costs is discounted at a rate of 3% per year.
3. Positive values indicate improvement in PDV.
4. Costs of therapy include both initial and ongoing annual costs.

II. Hepatitis C

A. Hepatitis C Disease-Specific Assumptions

Table II.A.1
Key Hepatitis C Model Assumptions

Model parameter	Value
Age of patients at therapy intervention	55
Distribution of patients by sex	
Female	30%
Male	70%
Distribution of patients by disease state at therapy intervention	
F0 - No fibrosis	17%
F1 - Portal fibrosis without septa	35%
F2 - Portal fibrosis with rare septa	22%
F3 - Numerous septa without cirrhosis	14%
F4 - Compensated cirrhosis	12%
Decompensated cirrhosis	0%
Hepatocellular carcinoma	0%
Liver transplant - Year 1	0%
Liver transplant - Year 2+	0%
Proportion of treated patients achieving therapeutic response	
Theoretical therapy intervention[1]	95.4%
Standard of care[2]	33.9%
Costs of therapy	
Initial costs	
Theoretical therapy intervention[3]	$42,171
Standard of care[3]	$17,483
Ongoing annual costs	
Theoretical therapy intervention	$0
Standard of care	$0
Discount rate	3%
QALY value	$100,000

Notes:

1. Among treatment-naive patients with no cirrhosis (69.5%), 96.0% of patients completing treatment achieve a therapeutic response and 0.5% of patients discontinue treatment. Among treatment-naive patients with cirrhosis (9.5%), 89.2% of patients completing treatment achieve a therapeutic response (no discontinuation). Among treatment-experienced patients with no cirrhosis (18.5%), 97.7% of patients completing treatment achieve a therapeutic response (no discontinuation). Among treatment-experienced patients with cirrhosis (2.5%), 100.0% of patients completing treatment achieve a therapeutic response
2. Among treatment-naïve patients (79%), 54.6% of patients completing treatment achieve a therapeutic response and 24.2% of patients discontinue treatment. Among treatment-experienced patients (21%), 16.5% of patients completing treatment achieve a therapeutic response and 64.6% of patients discontinue treatment.
3. Assumes WAC price, multiplied by total dosage and adjusted to account for treatment discontinuation; discounted by 50% (estimated average market discount).

Sources:

1. Institute for Clinical and Economic Review. The Comparative Clinical Effectiveness and Value of Novel Combination Therapies for the Treatment of Patients with Genotype 1 Chronic Hepatitis C Infection: A Technology Assessment. 30 Jan
2. Ditah I, Dith F, Devaki P, et al. The changing epidemiology of hepatitis C virus infection in the United States: National health and nutrition examination survey 2001 through 2010. J Hepatol. 2014;60(4):691-698.
3. U.S. Census Bureau, Population Division. Annual Estimates of the Resident Population by Single Year of Age and Sex for the United States: April 1, 2010 to July 1, 2013.

Table II.A.2
Hepatitis C mortality, healthcare costs, and health state utility assumptions

Disease state	Without therapeutic response		
	All-cause mortality multiplier	Annual per-patient hepatitis C-related healthcare costs[1]	Health state utilities
F0 - No fibrosis	1.00	$810	0.98
F1 - Portal fibrosis without septa	1.00	$810	0.98
F2 - Portal fibrosis with rare septa	1.00	$810	0.92
F3 - Numerous septa without cirrhosis	2.37	$2,150	0.79
F4 - Compensated cirrhosis	2.37	$2,516	0.76
Decompensated cirrhosis	See Assumptions Table 3	$29,795	0.69
Hepatocellular carcinoma	See Assumptions Table 3	$47,525	0.67
Liver transplant - Year 1	See Assumptions Table 3	$188,671	0.50
Liver transplant - Year 2+	See Assumptions Table 3	$41,090	0.77

Disease state	With therapeutic response		
	All-cause mortality multiplier	Annual per-patient hepatitis C-related healthcare costs[1]	Health state utilities
F0 - No fibrosis	1.00	$405	1.00
F1 - Portal fibrosis without septa	1.00	$405	1.00
F2 - Portal fibrosis with rare septa	1.00	$405	0.93
F3 - Numerous septa without cirrhosis	1.40	$1,075	0.86
F4 - Compensated cirrhosis	1.40	$1,258	0.83
Decompensated cirrhosis	See Assumptions Table 3	$29,795	0.69
Hepatocellular carcinoma	See Assumptions Table 3	$47,525	0.67
Liver transplant - Year 1	See Assumptions Table 3	$188,671	0.50
Liver transplant - Year 2+	See Assumptions Table 3	$41,090	0.77

Note:

1. Hepatitis C-related healthcare costs include only the costs of hepatitis C-related health care (i.e., the costs of care related to other conditions are excluded).

Source:

1. Institute for Clinical and Economic Review. The Comparative Clinical Effectiveness and Value of Novel Combination Therapies for the Treatment of Patients with Genotype 1 Chronic Hepatitis C Infection: A Technology Assessment. 30 Jan

Table II.A.3
Hepatitis C model transition probability assumptions

Annual transition probabilities

Final disease state, without therapeutic response

Initial disease state	Spontaneous resolution	F0 - No fibrosis	F1 - Portal fibrosis without septa	F2 - Portal fibrosis with rare septa	F3 - Numerous septa without cirrhosis	F4 - Compensated cirrhosis	Decompensated cirrhosis	Hepatocellular carcinoma	Liver transplant - Year 1	Liver transplant - Year 2+	Death
Spontaneous resolution	100.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
F0 - No fibrosis	0.2%	92.1%	7.7%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
F1 - Portal fibrosis without septa			92.6%	7.4%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
F2 - Portal fibrosis with rare septa				91.1%	8.9%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
F3 - Numerous septa without cirrhosis					89.3%	8.8%	1.2%	0.7%	0.0%	0.0%	0.0%
F4 - Compensated cirrhosis						94.2%	3.9%	1.9%	0.0%	0.0%	0.0%
Decompensated cirrhosis							84.0%	1.4%	1.7%	0.0%	12.9%
Hepatocellular carcinoma								55.6%	1.7%	0.0%	42.7%
Liver transplant - Year 1									0.0%	89.3%	10.7%
Liver transplant - Year 2+										95.2%	4.9%
Death											100.0%

Final disease state, with therapeutic response

Initial disease state	Spontaneous resolution	F0 - No fibrosis	F1 - Portal fibrosis without septa	F2 - Portal fibrosis with rare septa	F3 - Numerous septa without cirrhosis	F4 - Compensated cirrhosis	Decompensated cirrhosis	Hepatocellular carcinoma	Liver transplant - Year 1	Liver transplant - Year 2+	Death
Spontaneous resolution	100.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
F0 - No fibrosis	0.2%	98.8%	1.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
F1 - Portal fibrosis without septa			99.3%	0.7%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
F2 - Portal fibrosis with rare septa				99.0%	1.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
F3 - Numerous septa without cirrhosis					98.4%	1.0%	0.1%	0.5%	0.0%	0.0%	0.0%
F4 - Compensated cirrhosis						98.4%	0.3%	1.2%	0.0%	0.0%	0.0%
Decompensated cirrhosis							88.8%	1.0%	1.2%	0.0%	9.0%
Hepatocellular carcinoma								55.6%	1.7%	0.0%	42.7%
Liver transplant - Year 1									0.0%	89.3%	10.7%
Liver transplant - Year 2+										95.2%	4.9%
Death											100.0%

One-time transition probabilities (at time of therapy intervention)

Final disease state, with therapeutic response

Initial disease state	Spontaneous resolution	F0 - No fibrosis	F1 - Portal fibrosis without septa	F2 - Portal fibrosis with rare septa	F3 - Numerous septa without cirrhosis	F4 - Compensated cirrhosis	Decompensated cirrhosis	Hepatocellular carcinoma	Liver transplant - Year 1	Liver transplant - Year 2+	Death
Spontaneous resolution	100.0%										
F0 - No fibrosis	0.0%	100.0%									
F1 - Portal fibrosis without septa	0.0%	35.0%	65.0%								
F2 - Portal fibrosis with rare septa	0.0%	12.0%	58.0%	30.0%							
F3 - Numerous septa without cirrhosis	0.0%	0.0%	24.0%	46.0%	30.0%						
F4 - Compensated cirrhosis	0.0%	0.0%	9.0%	14.0%	22.0%	55.0%					
Decompensated cirrhosis	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	100.0%				
Hepatocellular carcinoma	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	100.0%			
Liver transplant - Year 1	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	100.0%		
Liver transplant - Year 2+	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	100.0%	
Death	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	100.0%

Additional disease state assumptions

24.0% of patients with no fibrosis (disease state F0) at therapy intervention will never progress to portal fibrosis without septa (disease state F1).

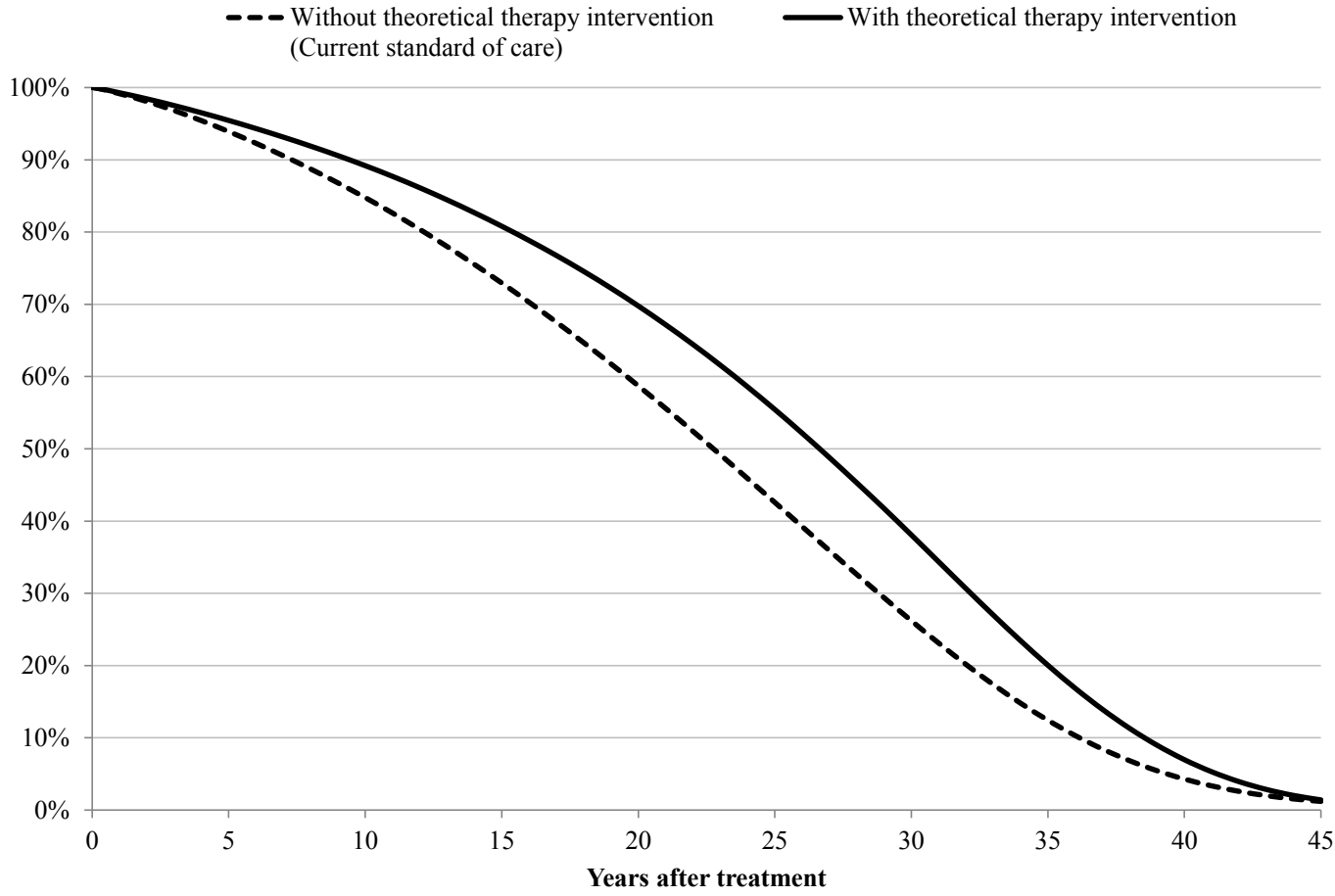
Source:

1. Institute for Clinical and Economic Review. The Comparative Clinical Effectiveness and Value of Novel Combination Therapies for the Treatment of Patients with Genotype 1 Chronic Hepatitis C Infection: A Technology Assessment. 30 J

B. Hepatitis C Model Outputs

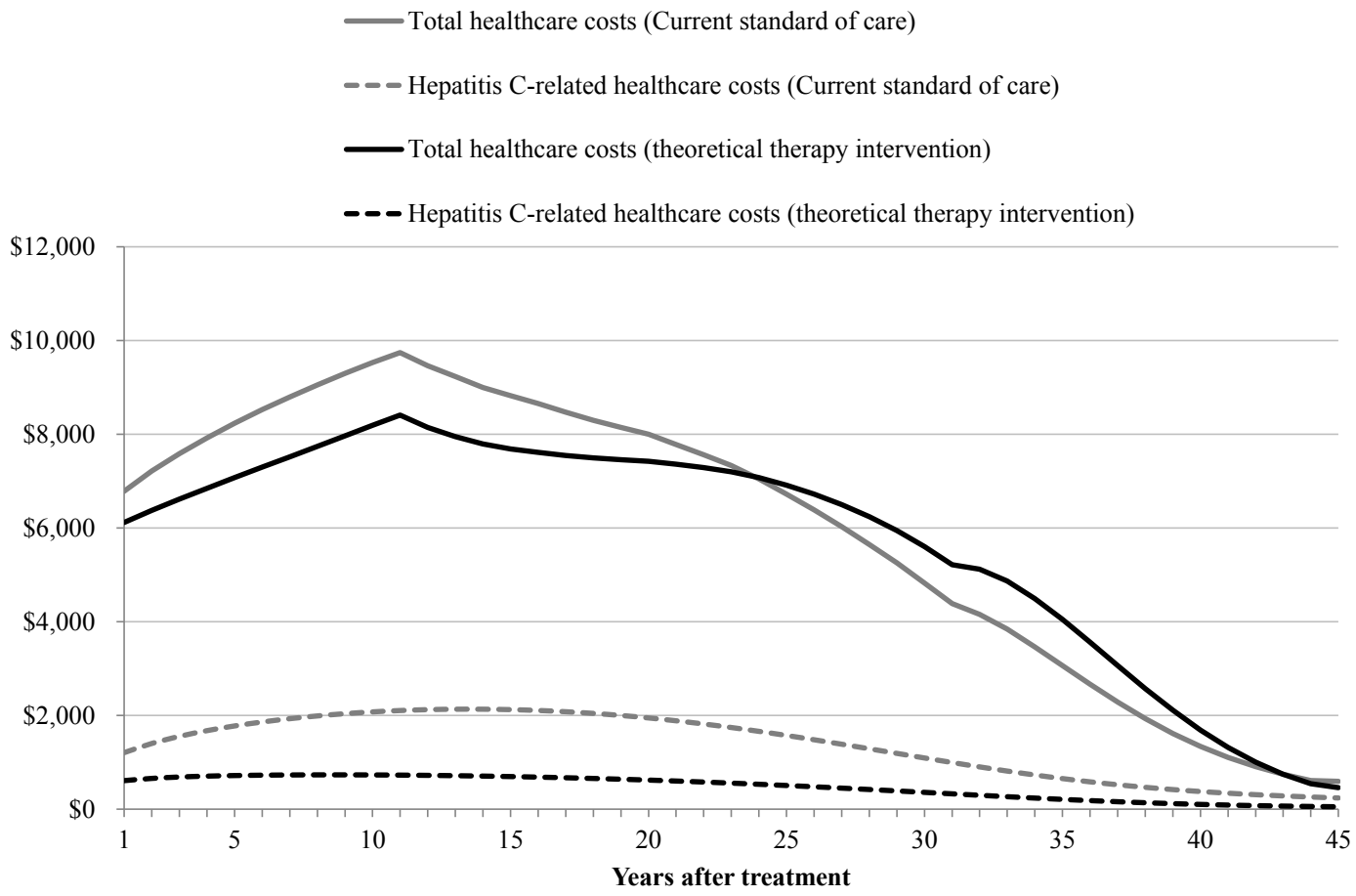
1. Cumulative probability of survival, with and without theoretical therapy intervention

Figure II.B.1
Hepatitis C cumulative probability of survival, with and without theoretical therapy intervention



2. Expected per-patient hepatitis C-related and total healthcare costs, with and without theoretical therapy intervention, undiscounted (excludes therapy intervention spend)

Figure II.B.2
Expected per-patient hepatitis C-related and total healthcare costs (undiscounted), with and without theoretical therapy intervention



3. Cumulative PDV lifetime hepatitis C-related and non-hepatitis C-related healthcare costs, per initially covered patient
With and without theoretical therapy intervention, by payer type, discounted

Table II.B.1
Cumulative present discounted value (PDV) of lifetime net healthcare cost impact[1,2]
Per initially covered patient

Payer type	Lifetime		
	Without theoretical therapy intervention (Current standard of care)	With theoretical therapy intervention	Difference (SOC - new therapy)[3]
Commercial insurance			
Therapy intervention cost[4]	$17,483	$42,171	($24,688)
Healthcare costs			
Hepatitis C-related costs	$15,185	$6,151	$9,034
Non hepatitis C-related costs	$57,052	$56,399	$652
Subtotal (therapy intervention cost + healthcare costs)	**$89,720**	**$104,721**	**($15,001)**
Medicaid			
Therapy intervention cost[4]	$17,483	$42,171	($24,688)
Healthcare costs			
Hepatitis C-related costs	$15,185	$6,151	$9,034
Non hepatitis C-related costs	$57,052	$56,399	$652
Subtotal (therapy intervention cost + healthcare costs)	**$89,720**	**$104,721**	**($15,001)**
Total societal			
Therapy intervention cost[4]	$17,483	$42,171	($24,688)
Healthcare costs			
Hepatitis C-related costs	$39,088	$13,904	$25,184
Non hepatitis C-related costs	$134,551	$147,088	($12,536)
Total (therapy intervention cost + healthcare costs)	**$191,123**	**$203,162**	**($12,039)**
Value of additional QALYs	($1,403,892)	($1,637,214)	$233,322
Total societal impact (Healthcare cost impact + years of healthy life gained)	**($1,212,769)**	**($1,434,051)**	**$221,282**
Incremental cost per QALY			**$5,160**

Notes:

1. Represents a single patient covered by a given payer type at the time of therapy intervention. Cumulative present discounted value of lifetime net healthcare cost impact is calculated accounting for the probability that patients transition from the initial payer type to other payer types over time, but not accounting for patients transitioning to the initial payer type from other payer types.
2. All figures are PDV; the value of future costs is discounted at a rate of 3% per year.
3. Positive values indicate improvement in PDV.
4. Costs of therapy include both initial and ongoing annual costs.

III. Alzheimer's Disease

A. Alzheimer's Disease-Specific Assumptions

Table III.A.1
Key Alzheimer's disease model assumptions

Model parameter	Value
Age of patients at therapy intervention[1]	70
Distribution of patients by sex[1]	
Female	67%
Male	33%
Distribution of patients by disease state at therapy intervention	
Mild	100%
Mild/moderate	0%
Moderate	0%
Severe	0%
Reduction in annual proportion of patients progressing to more severe disease states	
Theoretical therapy intervention	50%
Costs of therapy	
Initial costs	
Theoretical therapy intervention	$0
Standard of care	$230
Ongoing annual costs	
Theoretical therapy intervention	$10,000
Standard of care	$0
Discount rate	3%
QALY value	$100,000

Source:

Alzheimer's Association. 2015 Alzheimer's disease facts and figures. Alzheimers Dement.
1. 2015;11(3):332-384.

Table III.A.2

Alzheimer's disease model mortality, healthcare costs, likelihood of long-term care, costs of care, and health state utility assumptions

Disease state	All-cause mortality multiplier[1]	Annual per-patient Alzheimer's healthcare costs[2]	Likelihood of long-term care[3]	Annual per-patient long-term care costs[4,5]	Likelihood of home health care among patients living in the community[6]	Weekly per-patient home health care hours among patients receiving home health care[7]	Annual per-patient home health costs[4,8]	Weekly per-patient caregiver hours for patients living in the community[9]	Annual per-patient costs of caregiver time[4,10]	Health state utilities[4,]
Mild	1.00	$1,023	0.0%	$0	9.9%	15.7	$1,613	15.4	$13,686	0.68
Mild/moderate	2.52	$2,973	16.7%	$11,713	34.5%	45.3	$13,531	44.5	$33,179	0.53
Moderate	2.52	$2,973	49.6%	$34,788	34.5%	45.3	$8,187	44.5	$20,637	0.51
Severe	7.30	$3,195	86.1%	$60,388	34.5%	71.4	$3,562	70.2	$10,355	0.32

Notes:

1. Relative mortality risk as reported by Budd et al. 2011.
2. The yearly per-patient Medicare spending attributed to dementia as reported by Hurd et al. 2013 is assumed to be an average of per-patient Medicare spending for patients with mild/moderate or moderate Alzheimer's disease and per-patient Medicare spending for patients with severe Alzheimer's disease. Ratios between direct medical costs among patients with mild Alzheimer's disease, mild/moderate or moderate Alzheimer's disease, and severe Alzheimer's disease, based on Souêtre et al. 1999, are applied to the Hurd et al. 2013 spending estimate to estimate annual per-patient Alzheimer's disease-related healthcare costs among patients with mild, mild/moderate, moderate, and severe Alzheimer's disease.
3. Estimated proportion of patients in long-term care institutions as reported by Hux et al. 1998.
4. Annual per-patient long-term care costs, home health costs, costs of caregiver time, and health state utilities are weighted averages of the estimated costs and health state utilities for patients living in the community and patients living in long-term care.
5. The annual per-patient costs of long-term care at a private-pay rate are assumed to equal the median annual per-patient nursing facility costs as reported by Reaves et al. 2015 ($87,600). The annual per patient costs of long-term care at a Medicaid rate ($58,863) are estimated using the annual per-patient costs of long-term care at a private-pay rate and the ratio of the Medicaid reimbursement amount for a nursing home day to the private-pay cost of a nursing home day as reported by Weimer et al. 2009 (0.67). The annual overall per-patient costs of long-term care are estimated using a weighted average of private-pay and Medicaid rates, under the assumption that Medicaid spending accounts for 51% of total long-term care costs, as reported by Reaves et al. 2015.
6. For patients in the mild disease state, the proportion of patients living in the community who received home health care was assumed to be that observed by Zhu et al. 2008 among a sample of patients with mild Alzheimer's disease at baseline. For patients in the mild/moderate, moderate, and severe disease states, the proportion of patients living in the community who received home health care was assumed to be that observed among the same sample of patients four years after baseline.
7. For patients in the mild disease state, the average weekly home health care hours among patients receiving home health care were assumed to be as observed by Zhu et al. 2008 among a sample of patients with mild Alzheimer's disease at baseline. Weekly home health care hours among patients in more severe disease states were assumed to increase by the same proportion as the estimated average weekly caregiver hours reported by Weimer et al. 2009 for patients living in the community.
8. To estimate annual per-patient home health costs, estimated weekly home health care hours (accounting for the proportion of patients living in the community who received home health care) were multiplied by the cost of home health aide services as reported by Reaves et al. 2015 ($20.00) and by 52 weeks.
9. Average weekly caregiver hours for patients living in the community as reported by Weimer et al. 2009. For patients living in long-term care, Weimer et al. 2009 reported estimated average weekly caregiver time as 0.6 hours for patients in the mild disease state, 1.6 hours for patients in the mild/moderate and moderate disease states, and 2.2 hours for patients in the severe disease state.
10. To estimate the annual per-patient costs of caregiver time, estimated average weekly caregiver hours were multiplied by the median hourly wage as reported by the U.S. Department of Labor, Bureau o Labor Statistics ($17.09) and by 52 weeks.
11. Health state utilities as reported by Weimer et al. 2009.

Sources:

1. Budd D, Burns LC, Guo Z, et al. Impact of early intervention and disease modification in patients with predementia Alzheimer's disease: a Markov model simulation. Clinicoecon Outcomes Res.
2. Hurd MD, Martorell P, Delavande A, et al. Monetary costs of dementia in the United States. N Engl J Med. 2013;368(14):1326-1334.
3. Souêtre E, Thwaites RMA, Yeardley HL. Economic impact of Alzheimer's disease in the United Kingdom. Cost of care and disease severity for non-institutionalised patients with Alzheimer's disease. E J Psychiatry. 1999;174:51-55.
4. Hux MJ, O'Brien BJ, Iskedjian M, et al. Relation between severity of Alzheimer's disease and costs of caring. CMAJ. 1998;159(5):457-465.
5. Reaves EL, Musumeci MB. Kaiser Family Foundation. Medicaid and Long-Term Services and Supports: A Primer. 8 May 2015.
6. Zhu CW, Scarmeas N, Torgan R, et al. Home health and informal care utilization and costs over time in Alzheimer's disease. Home Health Care Serv Q. 2008;27(1):1-20.
7. Weimer DL, Sager MA. Early identification and treatment of Alzheimer's disease: social and fiscal outcomes. Alzheimers Dement. 2009;5(3):215-226.
8. U.S. Department of Labor, Bureau of Labor Statistics. Occupational Employment Statistics. May 2014 National Occupational Employment and Wage Estimates. 25 Mar 2015.

Table III.A.3
Alzheimer's disease model transition probability assumptions

Annual transition probabilities				
	Final disease state, current standard of care (first year)[1]			
Initial disease state	**Mild**	**Mild/moderate**	**Moderate**	**Severe**
Mild	69.1%	26.7%	3.9%	0.2%
Mild/moderate	24.1%	43.3%	23.4%	9.2%
Moderate	1.5%	19.1%	23.2%	56.2%
Severe				100.0%
	Final disease state, current standard of care (subsequent years)[2]			
Initial disease state	**Mild**	**Mild/moderate**	**Moderate**	**Severe**
Mild	62.7%	30.1%	6.8%	0.4%
Mild/moderate	13.0%	40.6%	27.0%	19.4%
Moderate	1.6%	14.6%	14.1%	69.7%
Severe				100.0%
	Final disease state, with theoretical therapy intervention[3]			
Initial disease state	**Mild**	**Mild/moderate**	**Moderate**	**Severe**
Mild	81.3%	15.1%	3.4%	0.2%
Mild/moderate	13.0%	63.8%	13.5%	9.7%
Moderate	1.6%	14.6%	49.0%	34.9%
Severe				100.0%

Notes:

1. Based on 6-month transition probabilities among patients treated with 10 mg donepezil per day and patients treated with placebo as reported by Stewart et al. 1998. Patients on the current standard of care treatment are assumed to transition between disease states with the same probabilities as patients treated with 10 mg donepezil per day for the first 6 months of the first year, and are assumed to transition between disease states with the same probabilities as patients treated with placebo in the second 6 months of the first year.
2. Based on 6-month transition probabilities among patients treated with placebo as reported by Stewart et al.
3. The theoretical therapy intervention is assumed to reduce the annual proportion of patients progressing to more severe disease states by 50% (compared with transition probabilities among patients treated with placebo), and is assumed to have no effect on the probability of regression to less severe disease states.

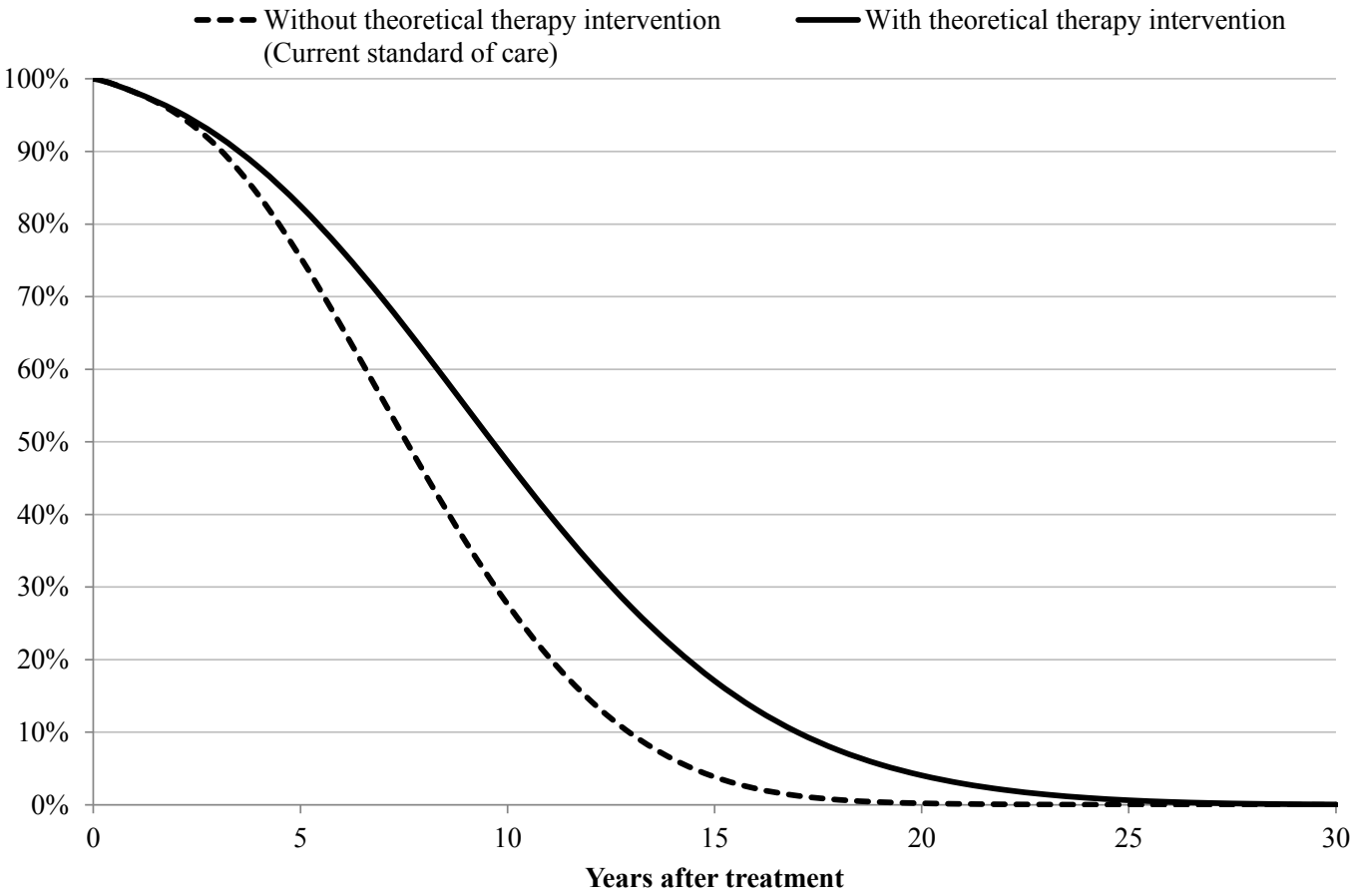
Source:

1. Stewart A, Phillips R, Dempsey G. Pharmacotherapy for people with Alzheimer's disease: a Markov-cycle evaluation of five years' therapy using donepezil. Int J Geriatr Psychiatry. 1998;13(7):445-453.

B. Alzheimer's Disease Model Outputs

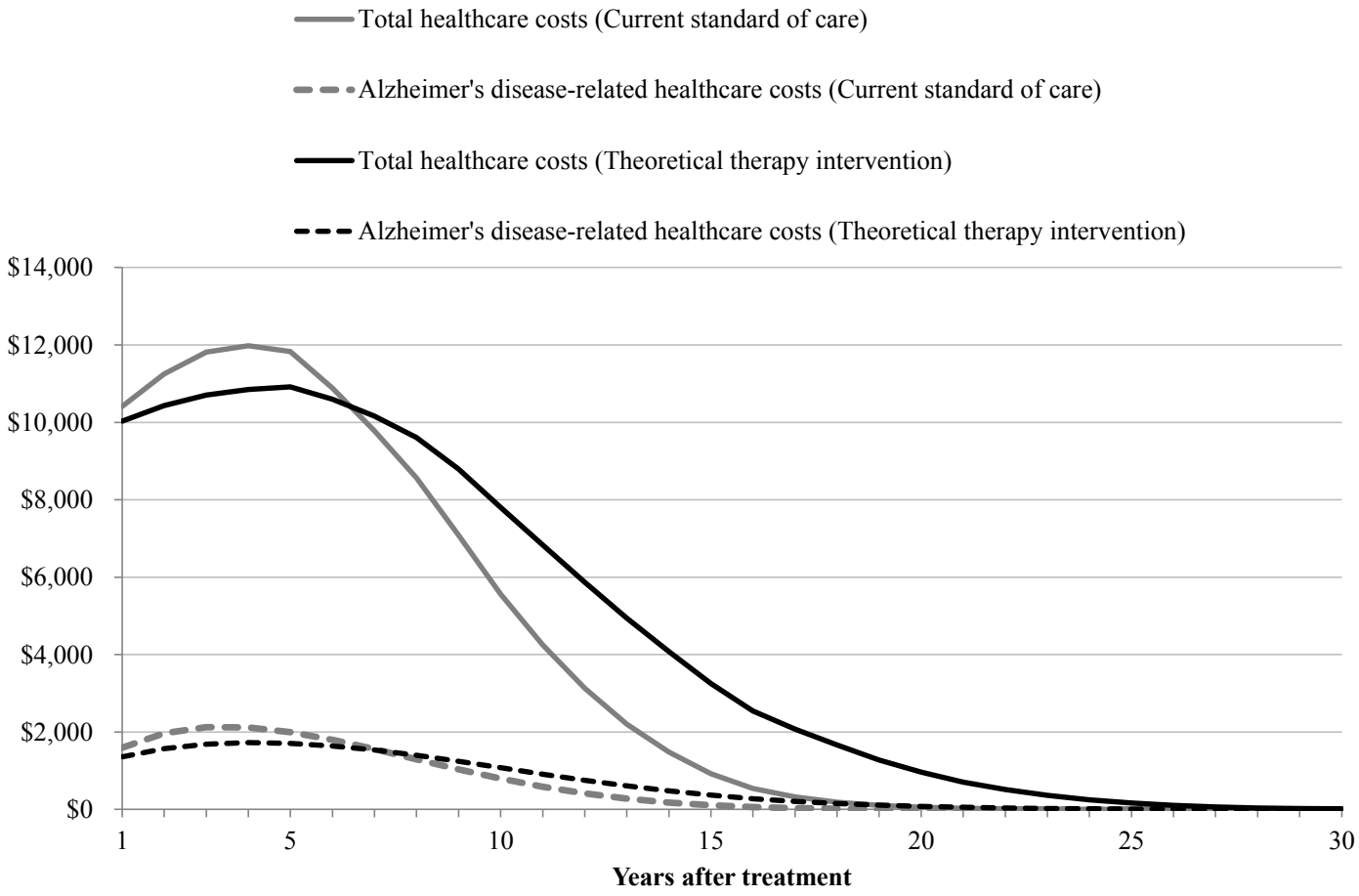
1. Cumulative probability of survival, with and without theoretical therapy intervention

Figure III.B.1
Alzheimer's disease cumulative probability of survival, with and without theoretical therapy intervention



2. Expected per-patient Alzheimer's-related and total healthcare costs, with and without theoretical therapy intervention, undiscounted (excludes therapy intervention spend)

Figure III.B.2
Expected per-patient Alzheimer's disease-related and total healthcare costs (undiscounted), with and without theoretical therapy intervention



3. Cumulative PDV lifetime Alzheimer's-related and non-Alzheimer's-related healthcare costs, per initially covered patient
With and without theoretical therapy intervention, by payer type, discounted

Table III.B.1
Cumulative present discounted value (PDV) of lifetime net healthcare cost impact[1,2]
Per initially covered patient

Payer type	Lifetime		
	Without theoretical therapy intervention (Current standard of care)	With theoretical therapy intervention	Difference (SOC - new therapy)[3]
Medicare			
Therapy intervention cost[4]	$230	$81,426	($81,196)
Healthcare costs			
Alzheimer's disease-related costs	$15,773	$16,028	($255)
Non Alzheimer's disease-related costs	$81,958	$96,343	($14,384)
Therapy intervention cost + healthcare costs	**$97,961**	**$193,796**	**($95,835)**
Long-term care costs	$0	$0	$0
Subtotal (therapy intervention cost + healthcare costs + long-term care and home health costs)	**$97,961**	**$193,796**	**($95,835)**
Total societal			
Therapy intervention cost[4]	$230	$81,426	($81,196)
Healthcare costs			
Alzheimer's disease-related costs	$15,773	$16,028	($255)
Non Alzheimer's disease-related costs	$81,958	$96,343	($14,384)
Therapy intervention cost + healthcare costs	**$97,961**	**$193,796**	**($95,835)**
Long-term care costs			
Medicaid	$90,562	$60,393	$30,169
Out-of-pocket	$87,010	$58,025	$28,986
Home health costs	$36,839	$43,029	($6,190)
Value of caregiver time	$115,004	$149,959	($34,955)
Total (therapy intervention cost + healthcare costs + long-term care, home health, and informal care c	**$427,376**	**$505,202**	**($77,826)**
Value of additional QALYs	($327,629)	($470,230)	$142,602
Total societal impact (Care-related cost impact + years of healthy life gained)	**$99,747**	**$34,972**	**$64,776**
Incremental cost per QALY			**$54,576**

Notes:

1. Represents a single patient covered by a given payer type at the time of therapy intervention. Cumulative present discounted value of lifetime net healthcare cost impact is calculated accounting for the probability that patients transition from the initial payer type to other payer types over time, but not accounting for patients transitioning to the initial payer type from other payer types.
2. All figures are PDV; the value of future costs is discounted at a rate of 3% per year.
3. Positive values indicate improvement in PDV.
4. Costs of therapy include both initial and ongoing annual costs.

IV. Cardiovascular Disease: Familial Hypercholesterolemia

A. FH Disease-Specific Assumptions

Table IV.A.1

Cost-effectiveness model results among patients aged 35-74 with familial hypercholesterolemia

Model parameter	Value
Number at risk (baseline cohort)	605,000
Outcomes associated with adding a PCSK9 inhibitor to current statin therapy	
Clinical outcomes	
Number of cardiovascular deaths averted	132,200
Number of nonfatal myocardial infarctions averted	111,100
Number of nonfatal strokes averted	80,900
Total incremental costs	
Drug costs	$210.52 billion
Drug costs (assuming 20% rebate)	$168.41 billion
Costs of other cardiovascular care	-$17.30 billion
Non cardiovascular disease-related costs	$11.74 billion
Per-patient incremental costs [1]	
Drug costs	$347,960
Drug costs (assuming 20% rebate)	$278,368
Costs of other cardiovascular care	($28,602)
Non cardiovascular disease-related costs	$19,402
QALYs gained	665,200
Incremental cost per QALY	
Excluding non cardiovascular disease-related costs (as reported by ICER)	$290
Excluding non cardiovascular disease-related costs (assuming 20% drug rebate)	$227
Including non cardiovascular disease-related costs (assuming 20% drug rebate)[2]	$245

Note:

1. Calculated based on estimates of total incremental costs and number of patients at risk as reported in the 2015 ICER PCSK9 Inhibitor Technology Assessment.
2. Calculated based on estimates of total incremental costs and QALYs gained as reported in the 2015 ICER PCSK9 Inhibitor Technology Assessment—difference is due to inclusion of non cardiovascular disease-related costs and the application of an assumed 20% rebate to drug costs.

Source:

1. Institute for Clinical and Economic Review. PCSK9 Inhibitors for Treatment of High Cholesterol: Effectiveness, Value, and Value-Based Price Benchmarks: A Technology Assessment. Final Report. 24

Table IV.A.2

Distribution of patient population treated with new therapy by age and sex, accounting for cumulative probability of survival over time [1]

Year[2]	Male						Female						Cumulative probability of survival[3]
	35-44	45-54	55-64	65-74	75-84	85-94	35-44	45-54	55-64	65-74	75-84	85-94	
Year 1	8.7%	17.8%	14.9%	7.3%	0.0%	0.0%	8.8%	18.4%	15.9%	8.4%	0.0%	0.0%	100.0%
Year 2	7.5%	16.9%	16.1%	7.3%	0.6%	0.0%	7.6%	17.5%	17.3%	8.4%	0.8%	0.0%	99.0%
Year 3	6.3%	16.0%	17.2%	7.6%	1.2%	0.0%	6.4%	16.5%	18.5%	8.7%	1.5%	0.0%	98.0%
Year 4	5.2%	15.0%	18.4%	7.8%	1.8%	0.0%	5.2%	15.5%	19.8%	9.0%	2.3%	0.0%	96.9%
Year 5	4.0%	14.1%	19.6%	8.0%	2.4%	0.0%	4.0%	14.5%	21.1%	9.2%	3.1%	0.0%	95.8%
Year 6	2.7%	13.1%	20.9%	8.2%	3.0%	0.0%	2.7%	13.5%	22.5%	9.4%	3.9%	0.0%	94.5%
Year 7	2.1%	12.4%	20.5%	9.3%	3.5%	0.0%	2.1%	12.8%	22.1%	10.7%	4.4%	0.0%	93.2%
Year 8	1.6%	11.7%	20.1%	10.5%	3.9%	0.0%	1.6%	12.0%	21.7%	12.0%	5.0%	0.0%	91.8%
Year 9	1.1%	11.0%	19.6%	11.6%	4.4%	0.0%	1.1%	11.3%	21.1%	13.2%	5.7%	0.0%	90.3%
Year 10	0.6%	10.2%	19.1%	12.8%	4.8%	0.0%	0.6%	10.5%	20.5%	14.7%	6.3%	0.0%	88.7%
Year 11		9.5%	18.4%	14.1%	5.2%	0.0%		9.8%	19.9%	16.2%	6.9%	0.0%	87.1%
Year 12		8.3%	17.7%	15.5%	5.3%	0.3%		8.5%	19.1%	17.8%	7.0%	0.5%	85.3%
Year 13		7.1%	16.9%	16.7%	5.6%	0.6%		7.3%	18.2%	19.2%	7.4%	1.0%	83.5%
Year 14		5.9%	16.1%	18.0%	5.8%	0.9%		6.0%	17.3%	20.8%	7.7%	1.4%	81.5%
Year 15		4.5%	15.3%	19.4%	6.1%	1.1%		4.7%	16.4%	22.4%	8.0%	1.9%	79.5%
Year 16		3.1%	14.5%	20.9%	6.4%	1.4%		3.2%	15.5%	24.2%	8.4%	2.3%	77.3%
Year 17		2.5%	13.9%	20.8%	7.4%	1.5%		2.6%	14.9%	24.1%	9.7%	2.6%	75.1%
Year 18		1.9%	13.3%	20.6%	8.5%	1.6%		2.0%	14.3%	23.9%	11.1%	2.8%	72.8%
Year 19		1.3%	12.7%	20.4%	9.6%	1.8%		1.3%	13.6%	23.7%	12.5%	3.1%	70.5%
Year 20		0.7%	12.0%	20.1%	10.8%	1.9%		0.7%	12.9%	23.4%	14.1%	3.4%	68.0%
Year 21			11.4%	19.8%	12.1%	2.0%			12.2%	23.0%	15.9%	3.6%	65.5%
Year 22			10.1%	19.4%	13.5%	2.1%			10.9%	22.6%	17.8%	3.7%	62.9%
Year 23			8.8%	18.9%	14.8%	2.3%			9.5%	22.0%	19.6%	4.1%	60.2%
Year 24			7.4%	18.4%	16.3%	2.5%			8.0%	21.4%	21.6%	4.4%	57.5%
Year 25			5.9%	18.0%	17.9%	2.7%			6.3%	20.8%	23.7%	4.7%	54.8%
Year 26			4.1%	17.6%	19.6%	2.9%			4.4%	20.2%	26.0%	5.1%	52.1%
Year 27			3.4%	17.3%	19.7%	3.6%			3.6%	19.9%	26.4%	6.2%	49.3%
Year 28			2.6%	16.9%	19.9%	4.3%			2.8%	19.5%	26.7%	7.4%	46.6%
Year 29			1.8%	16.5%	20.0%	5.0%			2.0%	19.0%	27.0%	8.7%	43.8%
Year 30			1.0%	16.0%	20.3%	5.8%			1.1%	18.5%	27.3%	10.0%	41.1%
Year 31				15.6%	20.5%	6.6%				18.1%	27.6%	11.6%	38.4%
Year 32				14.2%	20.6%	7.5%				16.6%	27.9%	13.2%	35.7%
Year 33				12.7%	20.9%	8.5%				14.9%	28.1%	14.9%	33.0%
Year 34				11.0%	21.2%	9.5%				12.9%	28.5%	16.9%	30.4%
Year 35				9.0%	21.7%	10.7%				10.6%	29.0%	19.0%	27.8%
Year 36				6.6%	22.5%	12.0%				7.8%	29.8%	21.4%	25.4%
Year 37				5.6%	22.8%	12.3%				6.7%	30.5%	22.2%	22.9%
Year 38				4.5%	23.2%	12.6%				5.4%	31.2%	23.0%	20.6%
Year 39				3.3%	23.7%	13.1%				4.0%	31.8%	24.1%	18.4%
Year 40				1.9%	24.1%	13.8%				2.2%	32.6%	25.4%	16.3%
Year 41					24.8%	14.6%					33.6%	27.0%	14.4%
Year 42					23.5%	15.6%					32.1%	28.8%	12.6%
Year 43					21.9%	16.9%					30.2%	31.0%	10.9%
Year 44					19.8%	18.6%					27.7%	33.9%	9.4%
Year 45					17.1%	20.9%					24.1%	37.8%	8.1%
Year 46					13.4%	24.2%					19.0%	43.3%	6.8%
Year 47					11.9%	25.3%					17.0%	45.9%	5.8%
Year 48					10.0%	26.6%					14.5%	48.9%	4.8%
Year 49					7.6%	28.3%					11.2%	52.8%	4.0%
Year 50					4.5%	30.9%					6.7%	57.9%	3.2%
Year 51						34.8%						65.2%	2.6%
Year 52						34.1%						65.9%	2.0%
Year 53						33.5%						66.5%	1.5%
Year 54						32.8%						67.2%	1.1%
Year 55						32.3%						67.7%	0.8%
Year 56						31.9%						68.1%	0.5%
Year 57						31.0%						69.0%	0.4%
Year 58						30.2%						69.8%	0.2%
Year 59						29.4%						70.6%	0.1%
Year 60						28.6%						71.4%	0.1%

Note:

1. The initial distribution of patients treated with the new therapy (PCSK9s) reflects the prevalence of familial hypercholesterolemia by patient age as reported by de Ferranti et al. 2014 and U.S. population estimates for individuals aged 35-74. Values represent the proportion of surviving patients in each age/sex category, by year, and account for both population aging and mortality.
2. The analytic horizon of the model presented in the 2015 ICER PCSK9 Inhibitor Technology Assessment is lifetime (defined as until patients reach 95 years of age).
3. For purposes of calculating distribution of ICER-reported incremental effects, mortality among the population of PCSK9-treated patients is assumed to be 30% higher than among the average population in the same age/sex category. Assumes all patients initially treated continue to be treated for all surviving years.

Sources:

1. de Ferranti SD, Rodday AM, Mendelson M, et al. What is the prevalence of familial hypercholesterolemia in the US? Circulation. 2014;130:A19656.
2. U.S Census Bureau, Population Division. Annual Estimates of the Resident Population by Single Year of Age and Sex for the United States: April 1, 2010 to July 1, 2013.
3. National Vital Statistics Report. Volume 63, Number 7. United States Life Tables, 2010. 6 Nov 2014.

B. FH Model Outputs

1. Cumulative PDV lifetime FH-related and non-FH-related healthcare costs, per initially covered patient

With and without theoretical therapy intervention, by payer type, discounted

Table IV.B.1

Cumulative present discounted value (PDV) of lifetime net healthcare cost impact[1-3]

Per initially covered patient

Payer type	Lifetime Difference (SOC - new therapy)[4]
Commercial insurance	
Therapy intervention cost[5]	($168,688)
Healthcare costs	
Cardiovascular disease-related costs	$7,580
Non cardiovascular disease-related costs	($2,374)
Subtotal (therapy intervention cost + healthcare costs)	**($163,482)**
Medicaid	
Therapy intervention cost[5]	($168,688)
Healthcare costs	
Cardiovascular disease-related costs	$7,580
Non cardiovascular disease-related costs	($2,374)
Subtotal (therapy intervention cost + healthcare costs)	**($163,482)**
Medicare[6]	
Therapy intervention cost[5]	($127,457)
Healthcare costs	
Cardiovascular disease-related costs	$20,171
Non cardiovascular disease-related costs	($16,697)
Subtotal (therapy intervention cost + healthcare costs)	**($123,983)**
Total societal (patients aged <65 at the time of treatment initiation)[7]	
Therapy intervention cost[5]	($296,145)
Healthcare costs	
Cardiovascular disease-related costs	$27,751
Non cardiovascular disease-related costs	($19,072)
Total (therapy intervention cost + healthcare costs)	**($287,466)**
Total societal (patients aged ≥65 at the time of treatment initiation)[7]	
Therapy intervention cost[5]	($182,773)
Healthcare costs	
Cardiovascular disease-related costs	$33,177
Non cardiovascular disease-related costs	($21,177)
Total (therapy intervention cost + healthcare costs)	**($170,773)**

Notes:

1. Represents an average patient covered by a given payer type at the time of therapy intervention. Cumulative present discounted value of lifetime net healthcare cost impact is calculated accounting for the probability that patients transition from the initial payer type to other payer types over time.
2. All figures are PDV; the value of future costs is discounted at a rate of 3% per year, as reported by ICER.
3. Costs per patient initially covered by either commercial insurance or Medicaid are calculated by dividing the costs attributable to patients initially treated prior to age 65 by the number of patients initially treated prior to age 65.
4. Positive values indicate improvement in PDV.
5. Costs of therapy include both initial and ongoing annual costs.
6. Values indicate the cumulative present discounted value of the lifetime net healthcare cost impact per patient initially covered by either commercial insurance or Medicaid.
7. Separate estimates of the impact on society are reported for patients initially covered by commercial insurance/Medicaid and patients initially covered by Medicare (i.e., patients aged <65 at the time of treatment initiation and patients aged ≥65 at the time of treatment initiation).

V. Cardiovascular Disease: Prior CVD

A. Prior CVD Disease-Specific Assumptions

Table V.A.1

Cost-effectiveness model results among patients aged 35-74 with a prior history of cardiovascular disease and LDL-cholesterol ≥70mg/dL on statin therapy

Model parameter	Value
Number at risk (baseline cohort)	7,271,000
Outcomes associated with adding a PCSK9 inhibitor to current statin therapy	
Clinical outcomes	
Number of cardiovascular deaths averted	2,733,300
Number of nonfatal myocardial infarctions averted	1,698,900
Number of nonfatal strokes averted	1,189,600
Total incremental costs	
Drug costs	$3,406.69 billion
Drug costs (assuming 20% rebate)	$2,725.35 billion
Costs of other cardiovascular care	-$210.70 billion
Non cardiovascular disease-related costs	$219.81 billion
Per-patient incremental costs [1]	
Drug costs	$468,531
Drug costs (assuming 20% rebate)	$374,825
Costs of other cardiovascular care	($28,978)
Non cardiovascular disease-related costs	$30,231
QALYs gained	10,573,800
Incremental cost per QALY	
Excluding non cardiovascular disease-related costs (as reported by ICER)	$302,256
Excluding non cardiovascular disease-related costs (assuming 20% drug rebate)	$237,819
Including non cardiovascular disease-related costs (assuming 20% drug rebate)[2]	$258,608

Note:

1. Calculated based on estimates of total incremental costs and number of patients at risk as reported in the 2015 ICER PCSK9 Inhibitor Technology Assessment.
2. Calculated based on estimates of total incremental costs and QALYs gained as reported in the 2015 ICER PCSK9 Inhibitor Technology Assessment—difference is due to inclusion of non cardiovascular disease-related costs and the application of an assumed 20% rebate to drug costs.

Source:

1. Institute for Clinical and Economic Review. PCSK9 Inhibitors for Treatment of High Cholesterol: Effectiveness, Value, and Value-Based Price Benchmarks: A Technology Assessment. Final Report. 24 Nov 2015.

Table V.A.2

Distribution of patient population treated with new therapy by age and sex, accounting for cumulative probability of survival over time [1]

Year[2]	Male						Female						Cumulative probability of survival[3]
	35-44	45-54	55-64	65-74	75-84	85-94	35-44	45-54	55-64	65-74	75-84	85-94	
Year 1	4.2%	16.9%	23.4%	22.9%	0.0%	0.0%	1.9%	5.2%	12.2%	13.3%	0.0%	0.0%	100.0%
Year 2	3.8%	15.9%	23.4%	22.7%	1.7%	0.0%	1.7%	4.9%	11.9%	13.1%	1.0%	0.0%	98.7%
Year 3	3.4%	14.7%	22.8%	23.0%	3.3%	0.0%	1.5%	4.6%	11.3%	13.2%	2.1%	0.0%	97.4%
Year 4	3.0%	13.6%	22.3%	23.1%	5.1%	0.0%	1.3%	4.3%	10.7%	13.3%	3.2%	0.0%	95.9%
Year 5	2.6%	12.4%	21.9%	23.3%	6.8%	0.0%	1.2%	4.1%	10.1%	13.3%	4.3%	0.0%	94.4%
Year 6	2.2%	11.2%	21.6%	23.4%	8.6%	0.0%	1.0%	3.8%	9.5%	13.3%	5.4%	0.0%	92.7%
Year 7	1.7%	10.0%	21.2%	23.5%	10.4%	0.0%	0.8%	3.5%	8.9%	13.3%	6.6%	0.0%	91.0%
Year 8	1.3%	8.8%	20.7%	23.6%	12.4%	0.0%	0.6%	3.2%	8.3%	13.3%	7.9%	0.0%	89.1%
Year 9	0.9%	7.5%	20.1%	23.5%	14.6%	0.0%	0.4%	2.8%	7.6%	13.2%	9.4%	0.0%	87.1%
Year 10	0.5%	6.2%	19.5%	23.6%	16.7%	0.0%	0.2%	2.5%	6.8%	13.2%	10.8%	0.0%	85.0%
Year 11		4.9%	18.8%	23.9%	18.8%	0.0%		2.2%	5.9%	13.3%	12.2%	0.0%	82.8%
Year 12		4.5%	17.9%	24.1%	18.7%	1.0%		2.0%	5.7%	13.0%	12.2%	0.8%	80.5%
Year 13		4.1%	16.8%	23.9%	19.2%	2.0%		1.9%	5.5%	12.5%	12.5%	1.6%	78.1%
Year 14		3.7%	15.8%	23.8%	19.6%	3.0%		1.7%	5.2%	12.1%	12.7%	2.4%	75.5%
Year 15		3.3%	14.7%	23.8%	20.1%	4.0%		1.5%	5.0%	11.7%	12.9%	3.1%	72.9%
Year 16		2.8%	13.6%	23.9%	20.5%	4.9%		1.3%	4.7%	11.2%	13.2%	3.9%	70.1%
Year 17		2.3%	12.4%	23.9%	21.1%	5.9%		1.0%	4.4%	10.7%	13.5%	4.8%	67.2%
Year 18		1.7%	11.1%	24.0%	21.7%	6.9%		0.8%	4.2%	10.2%	13.8%	5.6%	64.3%
Year 19		1.2%	9.8%	24.0%	22.3%	8.1%		0.6%	3.8%	9.5%	14.1%	6.6%	61.3%
Year 20		0.6%	8.3%	24.0%	23.2%	9.2%		0.3%	3.5%	8.8%	14.6%	7.6%	58.2%
Year 21			6.8%	23.8%	24.3%	10.3%			3.1%	8.0%	15.2%	8.6%	55.1%
Year 22			6.4%	23.3%	25.1%	10.3%			3.0%	7.9%	15.3%	8.6%	51.8%
Year 23			6.1%	22.7%	25.6%	10.8%			2.8%	7.9%	15.1%	9.1%	48.5%
Year 24			5.6%	21.9%	26.3%	11.3%			2.6%	7.8%	15.0%	9.4%	45.3%
Year 25			5.1%	21.1%	27.2%	11.9%			2.4%	7.6%	14.9%	9.9%	42.1%
Year 26			4.5%	20.1%	28.2%	12.5%			2.1%	7.5%	14.7%	10.4%	39.1%
Year 27			3.8%	18.9%	29.2%	13.3%			1.8%	7.3%	14.6%	11.0%	36.2%
Year 28			3.0%	17.6%	30.4%	14.3%			1.4%	7.1%	14.3%	11.7%	33.3%
Year 29			2.2%	16.1%	31.7%	15.5%			1.0%	6.8%	14.0%	12.6%	30.6%
Year 30			1.2%	14.3%	33.1%	17.0%			0.6%	6.5%	13.6%	13.8%	28.0%
Year 31				12.3%	34.5%	18.8%				6.1%	13.1%	15.2%	25.5%
Year 32				12.0%	34.3%	19.4%				5.9%	13.3%	15.1%	23.3%
Year 33				11.6%	34.0%	20.1%				5.8%	13.5%	15.1%	21.1%
Year 34				11.1%	33.6%	21.1%				5.5%	13.6%	15.1%	19.0%
Year 35				10.4%	33.1%	22.3%				5.2%	13.8%	15.2%	17.1%
Year 36				9.4%	32.5%	23.9%				4.8%	14.0%	15.4%	15.3%
Year 37				8.2%	31.7%	25.9%				4.2%	14.3%	15.8%	13.6%
Year 38				6.8%	30.8%	28.3%				3.5%	14.4%	16.3%	12.0%
Year 39				5.1%	29.6%	31.2%				2.6%	14.6%	17.0%	10.5%
Year 40				2.9%	28.2%	34.8%				1.5%	14.7%	17.9%	9.1%
Year 41					26.7%	39.3%					14.9%	19.2%	7.9%
Year 42					26.6%	38.8%					15.0%	19.7%	6.9%
Year 43					26.3%	38.4%					15.0%	20.3%	6.0%
Year 44					25.9%	38.1%					14.9%	21.1%	5.1%
Year 45					25.1%	38.3%					14.6%	22.1%	4.4%
Year 46					23.6%	39.0%					13.9%	23.6%	3.7%
Year 47					21.4%	40.4%					12.7%	25.5%	3.1%
Year 48					18.5%	42.4%					11.1%	27.9%	2.5%
Year 49					14.6%	45.5%					8.9%	31.1%	2.0%
Year 50					8.9%	50.2%					5.5%	35.4%	1.6%
Year 51						58.1%						41.9%	1.3%
Year 52						57.4%						42.6%	1.0%
Year 53						56.8%						43.2%	0.8%
Year 54						56.1%						43.9%	0.7%
Year 55						55.3%						44.7%	0.5%
Year 56						54.6%						45.4%	0.4%
Year 57						53.8%						46.2%	0.3%
Year 58						53.1%						46.9%	0.2%
Year 59						52.3%						47.7%	0.1%
Year 60						51.6%						48.4%	0.0%

Note:

1. The initial distribution of patients treated with the new therapy (PCSK9s) reflects the distribution of myocardial infarctions by patient age and sex as reflected in the CVD Policy Model simulation outputs for 2010 (model base year) reported in the 2015 ICER PCSK9 Inhibitor Technology Assessment and U.S. population estimates for individuals aged 35-74. Values represent the proportion of surviving patients in each age/sex category, by year, and account for both population aging and mortality.
2. The analytic horizon of the model presented in the 2015 ICER PCSK9 Inhibitor Technology Assessment is lifetime (defined as until patients reach 95 years of age).
3. For purposes of calculating distribution of ICER-reported incremental effects, mortality among the population of PCSK9-treated patients is assumed to be 10% higher than among the average population in the same age/sex category. Assumes all patients initially treated continue to be treated for all surviving years.

Sources:

1. Institute for Clinical and Economic Review. PCSK9 Inhibitors for Treatment of High Cholesterol: Effectiveness, Value, and Value-Based Price Benchmarks: A Technology Assessment. Final Report. 24 Nov 2015.
2. U.S Census Bureau, Population Division. Annual Estimates of the Resident Population by Single Year of Age and Sex for the United States: April 1, 2010 to July 1, 2013.
3. National Vital Statistics Report. Volume 63, Number 7. United States Life Tables, 2010. 6 Nov 2014.

B. Prior CVD Model Outputs

1. Cumulative PDV lifetime Prior CVD-related and non-Prior CVD-related healthcare costs, per initially covered patient With and without theoretical therapy intervention, by payer type, discounted

Table V.B.1

Cumulative present discounted value (PDV) of lifetime net healthcare cost impact[1-3]
Per initially covered patient

Payer type	Lifetime Difference (SOC - new therapy)[4]
Commercial insurance	
Therapy intervention cost[5]	($207,893)
Healthcare costs	
Cardiovascular disease-related costs	$6,448
Non cardiovascular disease-related costs	($2,933)
Subtotal (therapy intervention cost + healthcare costs)	**($204,378)**
Medicaid	
Therapy intervention cost[5]	($207,893)
Healthcare costs	
Cardiovascular disease-related costs	$6,448
Non cardiovascular disease-related costs	($2,933)
Subtotal (therapy intervention cost + healthcare costs)	**($204,378)**
Medicare[6]	
Therapy intervention cost[5]	($217,165)
Healthcare costs	
Cardiovascular disease-related costs	$21,281
Non cardiovascular disease-related costs	($26,664)
Subtotal (therapy intervention cost + healthcare costs)	**($222,547)**
Total societal (patients aged <65 at the time of treatment initiation)[7]	
Therapy intervention cost[5]	($425,058)
Healthcare costs	
Cardiovascular disease-related costs	$27,729
Non cardiovascular disease-related costs	($29,596)
Total (therapy intervention cost + healthcare costs)	**($426,925)**
Total societal (patients aged ≥65 at the time of treatment initiation)[7]	
Therapy intervention cost[5]	($286,351)
Healthcare costs	
Cardiovascular disease-related costs	$31,179
Non cardiovascular disease-related costs	($31,350)
Total (therapy intervention cost + healthcare costs)	**($286,522)**

Notes:

1. Represents an average patient covered by a given payer type at the time of therapy intervention. Cumulative present discounted value of lifetime net healthcare cost impact is calculated accounting for the probability that patients transition from the initial payer type to other payer types over time.
2. All figures are PDV; the value of future costs is discounted at a rate of 3% per year, as reported by ICER.
3. Costs per patient initially covered by either commercial insurance or Medicaid are calculated by dividing the costs attributable to patients initially treated prior to age 65 by the number of patients initially treated prior to age 65.
4. Positive values indicate improvement in PDV.
5. Costs of therapy include both initial and ongoing annual costs.
6. Values indicate the cumulative present discounted value of the lifetime net healthcare cost impact per patient initially covered by either commercial insurance or Medicaid.
7. Separate estimates of the impact on society are reported for patients initially covered by commercial insurance/Medicaid and patients initially covered by Medicare (i.e., patients aged <65 at the time of treatment initiation and patients aged ≥65 at the time of treatment initiation).

VI. Shared Assumptions (Across Disease Models)

A. Insurance coverage type by age, sex

Probability of enrollment in commercial insurance, Medicaid, and Medicare, by member age and sex

Age/sex	Probability of enrollment[1,2]		
	Commercial insurance	Medicaid	Medicare
Male			
0-5	0.60	0.40	0.00
5-10	0.60	0.40	0.00
10-15	0.60	0.40	0.00
15-20	0.60	0.40	0.00
20-25	0.87	0.13	0.00
25-30	0.87	0.13	0.00
30-35	0.87	0.13	0.00
35-40	0.87	0.13	0.00
40-45	0.87	0.13	0.00
45-50	0.87	0.13	0.00
50-55	0.87	0.13	0.00
55-60	0.87	0.13	0.00
60-65	0.87	0.13	0.00
65-70	0.00	0.00	1.00
70-75	0.00	0.00	1.00
75-80	0.00	0.00	1.00
80-85	0.00	0.00	1.00
85 and over	0.00	0.00	1.00
Female			
0-5	0.59	0.41	0.00
5-10	0.59	0.41	0.00
10-15	0.59	0.41	0.00
15-20	0.59	0.41	0.00
20-25	0.83	0.17	0.00
25-30	0.83	0.17	0.00
30-35	0.83	0.17	0.00
35-40	0.83	0.17	0.00
40-45	0.83	0.17	0.00
45-50	0.83	0.17	0.00
50-55	0.83	0.17	0.00
55-60	0.83	0.17	0.00
60-65	0.83	0.17	0.00
65-70	0.00	0.00	1.00
70-75	0.00	0.00	1.00
75-80	0.00	0.00	1.00
80-85	0.00	0.00	1.00
85 and over	0.00	0.00	1.00

Note:

1. Dual-enrolled members are assigned to a single payer based on the following assumed payer coverage hierarchy: Medicaid, Medicare, commercial insurance. Patients not covered by one or more of these payers are excluded
2. Medicare is assumed to cover no patients before age 65 and all patients after

Source:

1. 2014 Current Population Survey Annual Social and Economic Supplement.

B. Annual average per-patient healthcare costs for non-terminal, terminal year of life by age, sex

Sex/age	Annual per-patient healthcare costs	
	Non-terminal year of life	Terminal year of life
Male		
0-5	$5,227	$36,250
5-10	$4,767	$33,043
10-15	$2,597	$18,015
15-20	$2,238	$15,582
20-25	$2,165	$15,116
25-30	$1,981	$13,835
30-35	$2,119	$14,811
35-40	$2,522	$17,662
40-45	$3,090	$21,758
45-50	$3,631	$25,827
50-55	$4,316	$31,148
55-60	$5,442	$40,059
60-65	$6,852	$51,738
65-70	$7,562	$56,537
70-75	$8,006	$44,839
75-80	$9,175	$40,069
80-85	$10,717	$36,057
85 and over	$15,929	$35,820
Female		
0-5	$4,808	$33,332
5-10	$3,377	$23,404
10-15	$1,843	$12,780
15-20	$2,301	$15,967
20-25	$2,827	$19,638
25-30	$3,657	$25,425
30-35	$4,978	$34,643
35-40	$5,687	$39,655
40-45	$5,784	$40,476
45-50	$5,517	$38,844
50-55	$5,640	$40,031
55-60	$6,384	$45,776
60-65	$7,304	$53,335
65-70	$7,721	$55,240
70-75	$8,225	$44,053
75-80	$9,529	$39,628
80-85	$11,121	$35,459
85 and over	$15,773	$33,730

Sources:

1. Centers for Medicare and Medicaid Services, Office of the Actuary, National Health Statistics Group. Health Expenditures by Age and Gender.
2. Yamamoto DH. Society of Actuaries. Health Care Costs—From Birth to Death. June 2013.
3. Kaiser Family Foundation. The Rising Cost of Living Longer: Analysis of Medicare Spending by Age for Beneficiaries in Traditional Medicare. January 2015.

VII. Results Across Disease Models

A. Cumulative PDV of incremental lifetime net healthcare cost impact of new therapy per patient, aggregate payer impact, and impact on initial and downstream payers

		Healthcare Cost Effects				Impact Relative to $1.00 of Total Healthcare Impact
		Therapy Cost Effect	Morbidity Improvement Effect	Mortality Improvement Effect	Total Healthcare Impact	
Hepatitis C	Aggregate payer impact	($24,688)	$25,184	($12,536)	($12,039)	($1.00)
	Initial payer impact: comm'l ins /Medicaid	($24,688)	$9,034	$652	($15,001)	($1.25)
	Downstream payer impact: Medicare	-	$16,150	($13,188)	$2,962	$0.25
Beta-Thalassemia	Aggregate payer impact	($499,941)	$377,739	($57,291)	($179,493)	($1.00)
	Initial payer impact: comm'l ins	($501,251)	$376,601	($38,701)	($163,351)	($0.91)
	Downstream payer impact: Medicare	$1,310	$1,138	($18,590)	($16,142)	($0.09)
	Aggregate payer impact	($499,941)	$377,739	($57,291)	($179,493)	($1.00)
	Initial payer impact: Medicaid	($581,741)	$311,983	($14,254)	($284,012)	($1.58)
	Downstream payer impact: comm'l ins	$80,490	$64,617	($24,447)	$120,661	$0.67
	Downstream payer impact: Medicare	$1,310	$1,138	($18,590)	($16,142)	($0.09)
Alzheimer's Disease	Aggregate payer impact	($81,196)	$17,754	($14,384)	($77,826)	($1.00)
	Initial payer impact: Medicare	($81,196)	($255)	($14,384)	($95,835)	($1.23)
	Downstream payer impact: Medicaid	-	$30,169	-	$30,169	$0.39
	Downstream impact: patients/ caregivers	-	($12,160)	-	($12,160)	($0.16)
CVD: FH	Aggregate payer impact (patients initially aged <65)[9]	($296,145)	$27,751	($19,072)	($287,466)	($1.00)
	Initial payer impact: comm'l ins /Medicaid	($168,688)	$7,580	($2,374)	($163,482)	($0.57)
	Downstream payer impact: Medicare	($127,457)	$20,171	($16,697)	($123,983)	($0.43)

	Aggregate payer impact (patients initially aged ≥65)[9]	($182,773)	$33,177	($21,177)	($170,773)	($1.00)
	Initial payer impact: Medicare	($182,773)	$33,177	($21,177)	($170,773)	($1.00)
	Downstream payer impact: N/A	-	-	-	-	-

CVD: Prior CVD	Aggregate payer impact (patients initially aged <65)[9]	($425,058)	$27,729	($29,596)	($426,925)	($1.00)
	Initial payer impact: comm'l ins /Medicaid	($207,893)	$6,448	($2,933)	($204,378)	($0.48)
	Downstream payer impact: Medicare	($217,165)	$21,281	($26,664)	($222,547)	($0.52)
	Aggregate payer impact (patients initially aged ≥65)[9]	($286,351)	$31,179	($31,350)	($286,522)	($1.00)
	Initial payer impact: Medicare	($286,351)	$31,179	($31,350)	($286,522)	($1.00)
	Downstream payer impact: N/A	-	-	-	-	-

Source: Authors' model results.
Notes: Figures represent difference between new therapy and SOC. All figures are present discounted values (PDV); future costs are discounted at 3% per year. Positive values indicate improvement in PDV. Includes healthcare cost impacts only. Figures correspond to impacts for a single patient covered by a given payer at the time of initial therapy intervention. Therapy intervention costs include initial and ongoing annual costs. For Alzheimer's disease, disease-related costs include elder care costs (i.e., long-term care costs, home health costs, and the value of caregiver time). Assumptions incorporate those reported by others in corresponding Markov-type analyses.

B. Sensitivity Analyses to Key Assumptions

Beta-Thalassemia

	Base Case	Treatment at age 1	Treatment at age 3	80% of price *	120% of price *	80% of therapeutic response **
PDV Healthcare Cost Impact						
A. Initial Payer: Commercial insurance						
Aggregate Payer Impact	($179,493)	($178,137)	($181,434)	$20,507	($379,493)	($348,580)
Initial Payer Impact: Comm'l ins	($163,351)	($162,336)	($164,954)	$36,649	($363,351)	($314,152)
Downstream payer impact: Medicare	($16,142)	($15,802)	($16,480)	($16,142)	($16,142)	($34,427)
B. Initial Payer: Medicaid						
Aggregate Payer Impact	($179,493)	($178,137)	($181,434)	$20,507	($379,493)	($348,580)
Initial Payer Impact: Medicaid	($284,012)	($272,527)	($296,835)	($84,012)	($484,012)	($384,284)
Downstream payer impact: Comm'l ins	$120,661	$110,192	$131,881	$120,661	$120,661	$70,132
Downstream payer impact: Medicare	($16,142)	($15,802)	($16,480)	($16,142)	($16,142)	($34,427)
Impact Relative to $1.00 of Aggregate Payer Healthcare Impact						
A. Initial Payer: Commercial insurance						
Aggregate Payer Impact	($1.00)	($1.00)	($1.00)	N/A ***	($1.00)	($1.00)
Initial Payer Impact: Comm'l ins	($0.91)	($0.91)	($0.91)	N/A ***	($0.96)	($0.90)
Downstream payer impact: Medicare	($0.09)	($0.09)	($0.09)	N/A ***	($0.04)	($0.10)
B. Initial Payer: Medicaid						
Aggregate Payer Impact	($1.00)	($1.00)	($1.00)	N/A ***	($1.00)	($1.00)
Initial Payer Impact: Medicaid	($1.58)	($1.53)	($1.64)	N/A ***	($1.28)	($1.10)
Downstream payer impact: Comm'l ins	$0.67	$0.62	$0.73	N/A ***	$0.32	$0.20
Downstream payer impact: Medicare	($0.09)	($0.09)	($0.09)	N/A ***	($0.04)	($0.10)

* Base Case price is $1.0M

** Base Case assumes 100% of patients achieve therapeutic response.

*** Aggregate payer impact is positive with 80% of price assumption.

Hepatitis C

PDV Healthcare Cost Impact	Base Case	Treatment at age 50	Treatment at age 60	80% of price *	120% of price *	80% of therapeutic response **
Aggregate Payer Impact	($12,039)	($9,384)	($14,907)	($3,605)	($20,474)	($15,965)
Initial Payer Impact: Comm'l ins / Medicaid	($15,001)	($9,970)	($20,171)	($6,567)	($23,435)	($18,007)
Downstream payer impact: Medicare	$2,962	$585	$5,264	$2,962	$2,962	$2,042
Impact Relative to $1.00 of Aggregate Payer Healthcare Impact						
Aggregate Payer Impact	($1.00)	($1.00)	($1.00)	($1.00)	($1.00)	($1.00)
Initial Payer Impact: Comm'l ins / Medicaid	($1.25)	($1.06)	($1.35)	($1.82)	($1.14)	($1.13)
Downstream payer impact: Medicare	$0.25	$0.06	$0.35	$0.82	$0.14	$0.13

* Base Case price reflects 50% discount from list.

** Base Case reflects weighted average response rate of 95.4%.

Alzheimer's Disease

PDV Healthcare Cost Impact	Base Case	Treatment at age 65	Treatment at age 75	80% of price *	120% of price *	80% of therapeutic response **
Aggregate Payer Impact	($77,826)	($79,286)	($70,706)	($61,541)	($94,111)	($75,951)
Initial Payer Impact: Medicare	($95,835)	($108,750)	($81,587)	($79,550)	($112,120)	($86,877)
Downstream payer impact: Medicaid	$30,169	$40,769	$20,778	$30,169	$30,169	$21,718
Downstream payer impact: Patients / caregivers	($12,160)	($11,305)	($9,896)	($12,160)	($12,160)	($10,792)
Impact Relative to $1.00 of Aggregate Payer Healthcare Impact						
Aggregate Payer Impact	($1.00)	($1.00)	($1.00)	($1.00)	($1.00)	($1.00)
Initial Payer Impact: Medicare	($1.23)	($1.37)	($1.15)	($1.29)	($1.19)	($1.14)
Downstream payer impact: Medicaid	$0.39	$0.51	$0.29	$0.49	$0.32	$0.29
Downstream payer impact: Patients / caregivers	($0.16)	($0.14)	($0.14)	($0.20)	($0.13)	($0.14)

* Base Case price is $10,000 annually.

** Base Case assumes 50% reduction in state-specific rate of progression (i.e., 80% of therapeutic response corresponds to 40% reduction)

eAppendix References

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