Reconsidering the Economic Value of Multiple Sclerosis Therapies

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ABSTRACT

OBJECTIVES: To illustrate a more comprehensive view of value associated with medicines treating a highly severe illness and to apply these insights to estimate the costs and benefits of 3 treatments for multiple sclerosis (MS): Avonex, Tysabri, and Tecfidera.

STUDY DESIGN: Retrospective study spanning 2002 to 2013. We used economic theory to derive the value of therapy to patients with MS and to individuals who face the risk of contracting MS in the future, under the alternative assumptions that therapies were fully insured or paid for out of pocket.

METHODS: Models were parameterized through secondary data analysis and targeted literature review. Estimates of individual value were aggregated to the societal level using therapy-specific treatment prevalence rates. Aggregate consumer value was compared with manufacturer revenue.

RESULTS: In the baseline model, Avonex, Tysabri, and Tecfidera generated $46.2 billion of total value to consumers, almost one-third of which accrued to those without MS. The total value to consumers was double manufacturer revenue. Results were qualitatively robust to the use of alternate epidemiological and economic parameters. We found that value to the healthy is positively related to disease severity, and that value to both the sick and the healthy are larger when costs are shared via health insurance.

CONCLUSIONS: Theory predicts that treatments for severe disease provide "peace of mind" value to the healthy. Avonex, Tysabri, and Tecfidera have generated significant social value, a large majority of which accrues to consumers. Future economic valuations of medical technology should consider both the potential value to the healthy and the effects of insurance.

Am J Manag Care. 2016;22(11):e368-e374

The rising cost of healthcare in recent decades has been accompanied by an increasing interest in quantifying the value of medicine.[1,2] The cost of healthcare—unlike the costs of other goods—is often borne primarily by healthy consumers who are not currently using it. For example, premiums for private health insurance and taxes for public health insurance schemes are paid by the entire population, not just the patients who happen to be sick at a point in time. This raises a key question: What is the value of healthcare to the sick and to the healthy consumers who are paying for it?

The value of medical care to the sick is readily apparent, whereas the value to the healthy manifests in at least 2 ways. First, healthy individuals value medical technology because it will be available to them if they become sick in the future. The higher the likelihood of becoming sick with a particular disease, the more a healthy person values treatments for that disease. Second, new technology can provide peace of mind in the present, even to those who may never end up using it. The worse the disease, the more a healthy person values this peace of mind.[3-5]

To illustrate the "peace of mind" value, consider the analogy of a fire extinguisher in one's home: it provides value should the house catch fire by reducing the damage the fire would cause, and this value increases with the size of the potential loss. Awareness of this potential benefit provides immediate and continuous peace of mind from the protection against fire damage. This value is realized even if a fire never breaks out. Moreover, this peace of mind value increases with the size of the potential loss. A renter with few possessions may worry little about the risk of fire and thus derive few benefits from a fire extinguisher. In contrast, the owner of a home filled with priceless heirlooms might worry more and thus place higher value on the fire extinguisher. The "peace of mind" value is likely to be quantitatively meaningful, because evidence suggests that most consumers dislike risk and value reducing it.[6-10]

Medical technology provides peace of mind similar to that in the fire extinguisher example. To illustrate, consider a healthy individual today and another in 1990 who are concerned about the

prospect of a human immunodeficiency virus (HIV) infection. Both would experience anxiety, but the first individual would be anxious about the risk of complications and the inconvenience of a lifetime of medical treatment; the second individual would be anxious about death. The very real difference between these 2 levels of anxiety contributes to the value that healthy individuals have obtained from modern HIV and AIDS therapies. In other disease areas, the value of a new therapy to a healthy individual can be similarly characterized by decreased anxiety or fear of a diagnosis due to the therapy's ability to reduce the harm from a disease. This example illustrates that the peace of mind afforded by new medical technologies will be especially valuable for treatments that mitigate the consequences of the most severe diseases.[4,5]

TAKE-AWAY POINTS

Although many studies have assessed the social value of medical care to the sick, the value to the healthy who may use treatment if they become sick has been largely ignored. We used empirical estimations to parameterize an economic model that describes the value of 3 multiple sclerosis treatments to those who are healthy but face the risk of contracting MS in the future, as well as to the sick.

- When patients bear the full cost of treatment, the value of the 3 treatments to the sick totals $11.1 billion, while the value to the healthy is $8.9 billion.
- The value of therapy increases with the severity of the disease being treated.
- Insurance coverage has a complementary effect on the value of therapy: the total populationwide value of the 3 treatments increases to $46.2 billion when actuarially fair insurance is assumed.

Multiple sclerosis (MS) provides a useful case study of a severe disease, as it is the leading cause of nontraumatic neurologic disability among young adults.[11,12] In MS, the body's immune system attacks the central nervous system, creating brain lesions. During relapses, symptoms dramatically worsen and the disease can transition into a stage of progressive disability. MS patients suffer from fatigue and pain, as well as mobility and sensory problems.[13-15] Peak onset occurs between the ages of 20 and 40, often affecting healthy individuals in their prime years of productivity. Thus, MS onset imposes high medical costs and has severe consequences for quality of life and productivity, such as lost income.[13-15]

MS therapies also highlight the wider debate over the value of new medical technology. Some question the value of innovative drugs that help manage—but do not cure—debilitating and progressive diseases. Skepticism about the value of such drugs has been fueled by cost-effectiveness studies and a recent United Kingdom risk-sharing scheme.[16,17]

Our study uses an economic model developed by Lakdawalla, Malani, and Reif (2015)[4] to estimate the value of MS therapies to both healthy and sick individuals. We focus on 3 currently available MS therapies, incorporating their specific dates of introduction, magnitudes of health benefit, and prices: Avonex (interferon beta-1a intramuscular, introduced 1996), Tysabri (natalizumab, introduced 2004), and Tecfidera (dimethyl fumarate, introduced 2013).

METHODS

From an economic perspective, the value of a good is measured as the amount of other consumption that an individual is willing to sacrifice in exchange for it. These trade-offs are conventionally estimated in the framework of a "utility" model that explicitly estimates the value that consumers assign to different goods. A plethora of studies measure the value consumers assign to health relative to other goods,[18-23] and these measurements provide the empirical basis for utility models that estimate the trade-off between health improvements and other consumption. We followed this approach and estimated the value of the MS therapies of interest by constructing an economic model of the trade-off between consumption and health. Following the economic literature, we assumed that the quantity of consumption is determined by the income that remains after medical costs.

As we describe above, value may accrue not only to those suffering from an illness, but also to those who are currently healthy but still susceptible to future illness. We refer to these constructs as "value to the sick" and "value to the healthy." Both of these depend, in turn, on how the costs of therapy are incurred. Unlike standard goods, a portion of healthcare is often paid for by nonusers, via insurance. Insurance may increase the value of therapy for both the sick (by replacing direct costs with less costly insurance premiums) and the healthy (by reducing financial risk). Our study thus estimates the value of MS therapy from 4 perspectives: value to the sick and value to the healthy, first under the assumption that costs are fully borne by consumers (without insurance) and then assuming actuarially fair insurance, in which therapy costs are distributed across the entire risk pool (with insurance).[2,8] These perspectives are summarized in **Figure 1**. Prior efforts to estimate the value of new medical technologies have typically emphasized only 1 of these 4 perspectives: the value to the sick, without consideration of insurance.

The **eAppendix** (available at **www.ajmc.com**) formally describes the economic model developed by Lakdawalla, Malani, and Reif (2015),[4] which we used to measure value from each of these perspectives (utility model–based willingness-to-pay estimation). The value to the sick depends on: 1) health benefits of the therapy for those who are diagnosed with MS, as measured by incremental

FIGURE 1. Four Perspectives for the Value of MS Therapy

	Insurance State Perspective	
Health State Perspective	Sick, without insurance	Sick, with insurance
	Healthy, without insurance	Healthy, with insurance

TABLE. Baseline and Sensitivity Parameters

Parameter	Baseline	Sensitivities	Source
Income change: MS, relative to no MS	−37.1%	Bootstrap	MEPS analysis
Income change: therapy, relative to MS without therapy	41.4%		
Medical cost change: MS, relative to no MS	87.0%		Claims data analysis
Medical cost change, relative to MS without therapy			
Avonex	−11.2%		
Tysabri	−16.4%		
Tecfidera	−11.2%	−13.8%; bootstrap	
MS incidence rate (per 100,000 US population)	7.3	5.0	Mayr et al (2003)[29] Langer-Gould et al (2014)[28]
MS treated prevalence rate (per 100,000 US population)	Varies by drug and year: range = 0.03-16.76	Halved, doubled	Imputed from revenue data
Avonex: annualized QALYs without treatment	0.762	N/A	Inferred: Noyes et al (2011)[16]
Avonex: annualized QALYs with treatment	0.785	N/A	
Tysabri: annualized QALYs without treatment	0.585	N/A	Inferred: Thompson et al (2008)[30]
Tysabri: annualized QALYs with treatment	0.639	N/A	
Tecfidera: annualized QALYs without treatment	0.710	N/A	Inferred: Noyes et al (2011)[16] Zhang et al (2015)[31]
Tecfidera: annualized QALYs with treatment	0.814	N/A	
Relative value of health	Higher 0.845	Lower 0.700	Edwards (2008)[32]
Risk aversion among healthy individuals	Higher 1.78	Lower 0.15	Chetty (2006)[6]
Insurance load	0	16%	Karaca-Mandic et al (2011)[35]
Opportunity cost of drug development	0	$107M	DiMasi et al (2016)[34] Damodaran (2016)[33]

M indicates million; MEPS, Medical Expenditure Panel Survey; MS, multiple sclerosis; N/A, not applicable; QALY, quality-adjusted life-year.

quality-adjusted life-years (QALYs); 2) the health costs of MS, as measured by QALYs for individuals with and without MS; 3) the costs of therapy; 4) other medical costs with and without therapy; and 5) differences in consumer income, which determine the value of money to a consumer. We measured these both for MS patients receiving best supportive care (BSC) and for MS patients utilizing 1 of the 3 qualified drugs.

The value to the healthy depends on all 5 factors above, along with: 6) the incidence of MS, which measures the risk that healthy people will acquire the disease in any given year; and 7) the degree of consumer risk-aversion, which measures the value of risk-reduction to healthy consumers. In reality, some individuals are not materially at risk for MS, meaning that the population could consist of 3 groups: those with MS, healthy individuals at risk for MS, and healthy individuals not at risk for MS. This third group may never derive benefit from the actual use of the therapies. However, as the causes of MS are still not well understood,[24-26] healthy individuals cannot easily ascertain whether they fall into the second or third groups. Thus, for the purposes of our analysis, we pooled these groups together.

We used parameters in these 7 areas to construct separate economic utility models for each of the 4 perspectives described in Figure 1. Our models assume that the health state and drug utilization choice are constant for an individual within each year. These models are then used to estimate the annual value to consumers of using 1 of our 3 drugs of interest relative to BSC. The incremental value of the 3 drugs is given by the difference in value between using the drug and using BSC.

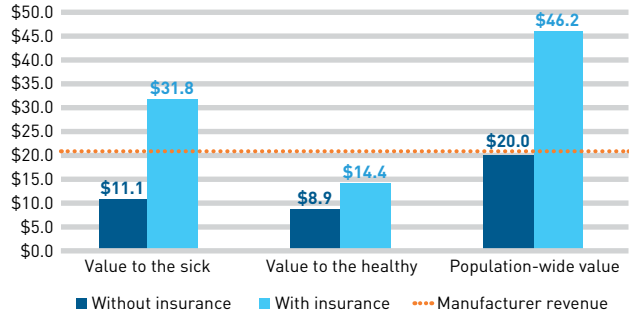
Finally, we aggregated the different estimates of incremental per-patient value to the societal level using disease prevalence and drug utilization rates. We added up the individual annual values of treatment over the period 2002 to 2013 (the years for which data on the therapies are available) to obtain the aggregate value of the 3 therapies. These aggregate values have been compared with manufacturer revenue to determine the share of value that returns to consumers. Complete details on economic model specification, parameterization, and sensitivity analyses are provided in the eAppendix.

RESULTS

Economic Model and Parameters

The **Table** summarizes the parameters obtained from our literature review and data analysis, which were used to calculate the social value of therapies. As detailed in the eAppendix, our analysis suggests that MS patients earn 37.1% less income than their non-MS counterparts; Avonex users earn 41.4% more income than their MS patient counterparts who are not using disease-modifying therapies (DMTs). Because of data limitations, we

FIGURE 2. Estimates of Total Lifetime Population-wide Value (by health state and insurance state) and Manufacturer Revenue for Avonex, Tysabri, and Tecfidera (2014 $B)[a]



$B indicates dollars in billions.

[a]Value numbers are net of therapy costs: positive value means consumers got more than they paid for and vice versa. The first pair of estimates shows the aggregate combined value to the sick with and without insurance. The second pair of bars portrays the value to the healthy, again with and without health insurance. The third pair of estimates ("population-wide value") sums the value to the sick and healthy, first without and then with insurance.

were unable to estimate income effects for Tysabri and Tecfidera directly. Instead, we assumed that the effects for those therapies were equal to that of Avonex. This conservative assumption likely understates the income effect of those therapies, because both of those products reduce relapse rates and disability progression more than Avonex does.

An MS diagnosis was also associated with a significant increase in non-DMT medical costs (87.0%), while the use of Avonex and Tysabri reduced annual medical costs by 11.2% and 16.4%, respectively. There were too few cases of Tecfidera usage in the claims data to identify an effect on medical costs (Tecfidera had a sample size of 137 compared with 9272 and 1223 for Avonex and Tysabri, respectively). As a result, we elected to use the Avonex cost offset parameter (–11.2%) for Tecfidera. This is a conservative approach, as Tecfidera was shown to reduce disability progression and relapse frequency more compared with interferons (including Avonex).[27] As a result of using this conservative estimate, our models likely underestimate the social value of Tecfidera. In the eAppendix, we describe a sensitivity analysis in which this value is set equal to the midpoint of the Avonex and Tysabri estimates (–13.8%).

To complete the economic model, we used established estimates from the literature for the health and risk-aversion parameters. The Table summarizes the baseline and sensitivity values used for the MS epidemiological parameters,[28,29] the QALY impacts of therapy,[16,30,31] and the economic parameters for the value of health.[6,32] In addition, the Table displays values used in sensitivity analyses that account for insurance loading and, separately, the cost of drug development borne by manufacturers.[33-35]

Estimates of the Value of MS Therapies

Figure 2 provides baseline estimates of value for all 3 drugs combined, aggregated over all years from 2002 through 2013. Aggregate value to the sick, when bearing the full cost of therapy, is estimated to be $11.1 billion. When actuarially fair insurance is available—so that the healthy and sick share the cost of treatment—value to the sick almost triples, to $31.8 billion. Conversely, value to the healthy without insurance is estimated to be $8.9 billion. When insurance is available, value to the healthy rises to $14.4 billion. This increase demonstrates the value of financial risk reduction that is obtained with insurance coverage.

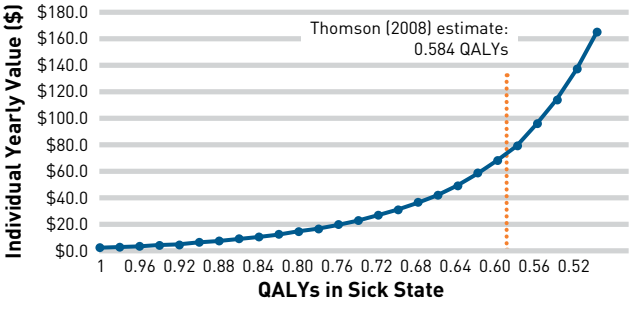
Based on an 80% national average insurance coverage rate, the total value of the 3 therapies is estimated to be $40.9 billion.[36] Overall, these results suggest that estimates of the value of medical technologies which ignore either the benefits that accrue to the healthy or the role of health insurance may be biased downward—perhaps severely so.

Impact of Disease Severity on Value to an Individual Insurance Enrollee

Conceptually, the value to the healthy should be higher when considering treatments for more severe diseases. For instance, an effective new treatment for a highly fatal disease provides significantly more peace of mind to the healthy than one for a mild skin condition. Our analysis confirms this intuition by re-estimating the value of 1 therapy (Tysabri) to a healthy individual with insurance, while incrementally varying the assumed severity of MS, holding other factors (including the absolute treatment effect) constant. The results are depicted in Figure 3.

If MS was not a severe disease, the value of Tysabri to a healthy individual would be small. This is evident on the left side of Figure

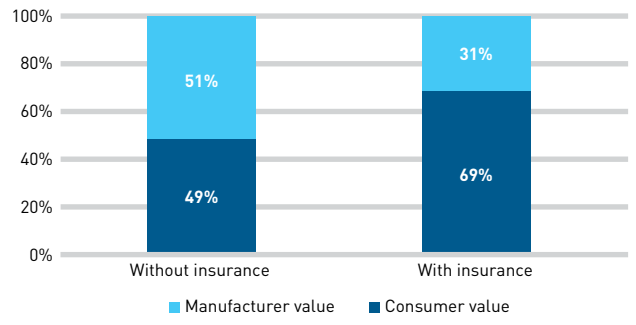
FIGURE 3. Value of Tysabri to a Healthy Individual, 2006, by Disease Severity[a]



QALY indicates quality-adjusted life-year.

[a]The x-axis portrays the QALY value of 1 year spent in the sick state. A value of 1 implies that 1 year spent with MS is identical to 1 year spent in perfect health. A value of 0.5 implies that 1 year spent with MS is worth the same as 0.5 years in perfect health, and so on.

FIGURE 4. Share of Lifetime Value Accruing to Consumers and Manufacturers, With and Without Insurance: Avonex, Tysabri, and Tecfidera Combined



3: as the assumed QALY of untreated MS approaches 1, the value of treatment to a healthy individual approaches 0. However, MS is a debilitating disease, with an estimated untreated QALY value of 0.584 for those patients who might be treated by Tysabri.[30] At this level, our model estimates the monthly value of Tysabri to a healthy individual to be $6.26. By contrast, we calculate that the actuarially fair per-member-per-month cost of insurance coverage of Tysabri is an order of magnitude smaller—about $0.48. This suggests that individual insurance enrollees gain more value from access to coverage than they lose due to the associated incremental insurance premium.

Significantly, the value of the treatment varies with disease severity, even when clinical effectiveness is held constant. Intuitively, a given improvement in clinical status is worth more to a patient suffering from a more severe disease. Therefore, singular focus on efficacy and/or effectiveness may ignore an important additional determinant of value.

Distribution of Surplus

Figure 4 portrays the relative share of lifetime value accruing to all consumers (both healthy and sick) and manufacturers, aggregated across the 3 therapies. When no insurance is available, an estimated 49% of value accrues to consumers ($20.0 billion—the "population-wide value" previously described), and 51% accrues to manufacturers as revenues ($21.2 billion). Because most individuals in the United States had health insurance during the time period of the study,[37] the values under full insurance are empirically relevant. When full insurance is assumed, the share of value accruing to consumers rises to 69% ($46.2 billion), with the remaining 31% accruing to manufacturers. We conservatively assumed that all revenues ($21.2 billion) accrue to the manufacturer as profits. In reality, costs are not 0, and as a result, the true share of value accruing to consumers will be larger than what we have estimated here. In the sensitivity analyses, we provide a revised estimate of the distribution of surplus that incorporates estimates of the opportunity cost of research and development.

Sensitivity Analyses

Our model relies on both epidemiological (eg, incidence rate) and economic (eg, risk aversion) inputs, obtained from the literature and from our original data analysis. Varying these inputs moderately alters the results presented above. For example, assuming the availability of health insurance, estimates of the share of overall value accruing to consumers range from 59% (when the relative value of health is reduced) to 75% (when the treatment prevalence rate is reduced). When using the lower bound for risk aversion (0.15), the share to consumers (assuming insurance coverage) is 62%. These results are presented in the eAppendix (exhibits A12 and A13).

In addition to relying on parameters retrieved from the literature, our model takes as inputs parameters obtained via novel data analysis—specifically the income and medical cost effects of MS (relative to no MS) and of therapy (conditional on MS). These parameters have associated error distributions, and we accounted for these distributions using bootstrap methods. We created 1000 weighted bootstrap samples from the Medical Expenditure Panel Survey and claims datasets and estimated the parameter of interest (population-wide value—the sum of aggregate value to the sick and aggregate value to the healthy) from each set of regression results. The results are qualitatively robust to the introduction of these error distributions: 95% of the resampled estimates show more aggregate value accruing to consumers than to the manufacturer. The distribution of bootstrapped estimates is presented in the eAppendix (exhibit A14).

At baseline, our model assumes that actuarially fair insurance is available; however, in reality, insurance always involves some loading cost to cover administrative overheads.[38] We therefore conducted a sensitivity analysis using an administrative load parameter of 16% (the median of the values reported by Karaca-Mandic et al [2011]).[35] Finally, our baseline estimates of manufacturer surplus do not take into account the costs of drug development, and therefore overestimate the percent of surplus accruing to the manufacturer. We calculate the annualized costs of new drug development, based on recent work by DiMasi et al (2016)[34] and recalculate the distribution of surplus. When subtracting these costs from manufacturer surplus, the consumer share of surplus increases from 49% to 51% and from 69% to 71% in the cases without and with insurance, respectively.

DISCUSSION

Severe diseases like MS reduce the health of the sick and inspire fear among the healthy who may be susceptible. Thus, it is important to understand the value that treating such diseases produces for each group. Although some recent economic research has described and estimated this "peace of mind" value to the healthy,[4] the concept has not yet been widely presented to the payer or health policy communities. The importance of insurance coverage in expanding the value of medical technology has been similarly neglected.

Our study demonstrates the empirical relevance of value to the healthy in the case of 1 severe illness—MS. When consumers are covered under actuarially fair health insurance, we estimate the aggregate value to the sick of the 3 therapies for MS to be $31.8 billion. Adding value to the healthy (with insurance) leads to a $46.2 billion estimate of population-wide value. The healthy therefore accrue 31.1% of the total consumer value from the 3 therapies. In this scenario, consumers derive 69% of the total value generated by the technology, while the manufacturer retains 31%.

The results of this study also illustrate the unique and complementary relationship between health insurance and medical technology. More generous insurance boosts the value of medical technology, and helps society extract greater value from new innovations. For sick patients, the introduction of actuarially fair health insurance increases the value of therapy to $31.8 billion compared with $11.1 billion when patients bear the full cost of treatment.

Note that the size of the additional value provided by insurance coverage varies depending on the efficiency of insurance. Our baseline model assumes that insurance allocates treatments efficiently. If, on the other hand, insurance leads to overuse or underuse of therapies, then the value of insurance would be lower. By similar logic, if there are other inefficiencies in the market apart from insurance (eg, agency problems that result in physicians failing to maximize the well-being of patients), the value of medical technology would fall in both the insured and uninsured cases. These points represent the more general observation that the value of medical technology is intimately linked to the efficiency of the institutions allocating it to patients.

Our estimates of consumer value and the consumer share of value are conservative in that they do not incorporate all sources of consumer value (eg, alleviated caregiver burden), nor do they consider manufacturer costs of production. Regardless, other severe diseases may display similar patterns, and this analysis may inform value assessments for technologies that treat them.

At the same time, some other severe diseases might also feature known risk factors— asbestosis is an extreme example, which occurs only for individuals occupationally or environmentally exposed to asbestos. In such cases, the healthy can be clearly divided into populations at risk, and populations not at risk. The "at-risk" group derives insurance value, while the "not-at-risk" group cross-subsidizes the value enjoyed by both the sick and the at-risk healthy. This pattern is worth exploring in future research.

Limitations

This study has several important limitations. First, it emphasizes 3 therapies for the treatment of MS (Avonex, Tysabri, and Tecfidera); the generalizability of our results to other MS treatments or to other disease areas is not yet clear. Second, although efforts were taken to minimize bias, the estimated cost and income effects were obtained through observational data analysis; if bias persisted in these estimates, it would extend to the main study findings as well. Third, owing to small sample sizes, we were unable to directly estimate the cost offset and income effects for Tecfidera or the income effects for Tysabri; we conservatively assumed these to be equal to the Avonex effects. Finally, the estimated QALY benefits of the 3 therapies were obtained from 3 different sources, rather than from a single head-to-head analysis.

CONCLUSIONS

This paper brings tools of economic analysis to bear on the question of value in healthcare. Our approach resolves 2 key omissions in prior valuations of MS therapies. First, this study quantified the role of insurance coverage in enhancing the value of therapy. Second, this study examined how MS therapies improve the outlook of those who face the risk of future MS onset, in addition to providing benefits to those who are already sick.[4] We found that accounting for these 2 factors more accurately depicts the estimated overall value of the therapies considered here.

Acknowledgments

The authors thank Sarah Beers, Oliver Diaz, Melissa Frasco, Barney Hartman-Glaser, Sarah Green, and Anshu Shrestha for excellent research assistance and technical support. They also thank Dr Lawrence Steinman for clinical advice.

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Source of Funding: Biogen.

Author Disclosures: Drs Shih and Sussell, and Ms Liu, and Ms Shim are employees of Precision Health Economics (PHE), a consulting firm that received research funding from Biogen. Dr Chung was an employee of PHE at the time this research was performed. Dr Meletiche and Mr Wakeford are employees of Biogen, which funded this research project. Dr Lakdawalla is chief strategy officer and holds equity at PHE.

Authorship Information: Concept and design (TS, CW, DM, DL); acquisition of data (YL); analysis and interpretation of data (TS, CW, JS, YL, JJS, DL); drafting of the manuscript (TS, JS, AC); critical revision of the manuscript for important intellectual content (TS, CW, DM, JS, AC, YL, JJS, DL); statistical analysis (TS, JS, YL, JJS); obtaining funding (CW, DM); administrative, technical, or logistic support (AC); and supervision (TS, CW, DM, JS, DL).

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eAppendix

Economic models

We utilized two related utility models to estimate the social value of multiple sclerosis (MS) therapies, following Lakdawalla, Malani, and Reif (2015).[4] The first model, which estimates what we refer to as "value to the sick," measures the value to individuals who are already diagnosed with MS. The second model estimates what we refer to as "value to the healthy" and measures the expected value to healthy individuals who may be diagnosed with MS in the future.

Value to the Sick

Conceptually, we think about utility at time t as taking the general form $u_t(g_t, h_t)$, where h_t is health at time t, and g_t is the amount of income spent on all other types of consumption. The willingness to exchange other consumption for health improvement is thus the value of that health improvement. Under the assumption that costs are borne by the sick (ie, the "without insurance" case), we formally denote the value of drug X to a sick individual in year t as $v^X_{SNI,t}$, given by:

$$u_t(y^w_t - C^w_t - C^s_t - w^s_t, h^s) = u_t(y^w_t - C^w_t - C^X_t - w^X_t - v^X_{SNI,t}, h^s + \Delta h^X) \quad (1)$$

where for each year t,

$u_t(g,h)$ One-year utility over consumption g and health h,

$v^X_{SNI,t}$ Value of therapy X to a sick individual in year t (no insurance)

y^w_t Income in healthy state (ie, does not have MS)

C^w_t Medical costs (annualized) in healthy state

C^s_t Medical costs (annualized) of MS under best supportive care (BSC) relative to healthy state

C^X_t Medical costs (annualized) of MS under treatment X (insurable), including the cost of therapy, relative to healthy state

w^s_t Income losses (annualized) of MS under BSC (uninsurable) relative to healthy state

w^X_t Income losses (annualized) of MS under treatment X (uninsurable) relative to healthy state

h^s Annualized quality-adjusted life-years (QALYs) of MS under BSC or prior drug, d years since initiation of drug utilization

Δh^X Annualized incremental QALYs to an individual with MS from treatment X

Equation (1) derives the value of X such that it equates the utility of individuals with MS utilizing BSC (left hand side) with MS patients utilizing X (right hand side). Throughout the study, we assume $u_t(g,h)$ takes the "Cobb-Douglas" functional form, which is defined as:

$$u_t(g,h) \equiv \frac{(g^\gamma h^{1-\gamma})^{1-\sigma} - 1}{1-\sigma} \text{ if } \sigma \neq 1$$

$$u_t(g,h) \equiv \ln(g^\gamma h^{1-\gamma}) \text{ if } \sigma = 1.$$

According to this functional form, parameters $\gamma \in (0,1)$ and $\sigma \geq 0$ affect the value of a therapy to healthy individuals. Specifically, γ relates to the marginal rate of substitution between consumption and health. Relative risk aversion, which describes the extent to which individuals will tolerate risk, is then given by:

$$R = 1 - \gamma(1-\sigma) > 0. \ (^{38})$$

Estimates from the economic literature suggest that a reasonable range for γ is between 0.155 and 0.443, while R ranges up to 1.78 or higher.[6,32] Intuitively, a higher level of relative risk aversion will lead to a higher valuation of treatments by the healthy, because it increases the impact that a difference between the healthy and sick states has on expected utility.

In the "with insurance" case, the value to the sick in year t, denoted $v^X_{CI,t}$, is given by:

$$u_t(y_t^w - \pi_r(C_t^w + C_t^s) - w_t^s, h^s) = u_t\left(y_t^w - \pi_r(C_t^w + C_t^X) - w_t^X - v^X_{CI,t}, h^s + \Delta h^X\right)$$

where π_r is the likelihood of using the drug of interest. That is, medical costs, including the price of the drug, are covered by actuarially fair insurance, with individuals only responsible for paying risk-adjusted premiums.

In the "without insurance" case, negative estimates of individual value to the sick are observed for some therapies in some years. Our model sets these values to zero, under the theory that consumers with a negative willingness to pay are free to opt out of purchasing the therapy (and thus to avoid incurrence of the negative value). We relax this assumption in a sensitivity analysis, and allow individual to incur negative value from therapies, perhaps due to irrationality. In the "with insurance" case, the estimated individual value to the sick is positive for all drugs and all years.

Both with and without insurance, the total value to the sick of therapy X in year t is then $V_{S,t}^{X} = \sum_{d=1}^{10} v_{S,t}^{X} \alpha_t^X$ where α_t^X is the estimated number of individuals in year t utilizing therapy X. Total therapy values over the lifetime of the drug through 2013 are provided by summing the discounted annual values of the drug.

Value to the Healthy

To determine the value of drug X for a healthy individual in year t, we assume the individual is considering only the risk of diagnosis in the current year t (ie, he or she does not consider risk of diagnosis in year $t+1$ until period $t+1$). The value to a healthy individual in year t is the amount the individual would pay in year t to ensure he or she could utilize therapy X (in place of the best alternative -- either best supportive care or the prior drug available) if he or she falls sick. We apply a model developed in Lakdawalla, Malani, and Reif (2015), which mathematically defines this value as the amount of consumption one would need to take away from the individual in order to make them indifferent to accessing the treatment versus not accessing it. We again consider two cases: the first where an individual must pay all medical and drug costs out-of-pocket ("without insurance"), and the second where these costs are covered under insurance ("with insurance"). Specifically, the value to the healthy without insurance is denoted v_{HNI}^{X} and defined by the following expression:

$$\begin{aligned}
&\pi_i u_t(y_t^w - (C_t^w + C_t^s) - w_t^s, h^s) + (1-\pi_i) u_t(y_t^w - C_t^w, h_t^w) \\
&= \pi_i u_t\left(y_t^w - (C_t^w + C_t^X) - w_t^X - v_{HNI,t}^X, h^s + \Delta h^X\right) \\
&+ (1-\pi_i) u_t\left(y_t^w - C_t^w - v_{HNI,t}^X, h_t^w\right)
\end{aligned}$$

and the value to the healthy with insurance as v_{HWI}^{X} as:

$$\begin{aligned}
&\pi_i u_t(y_t^w - \pi_r(C_t^w + C_t^s) - w_t^s, h^s) + (1-\pi_i) u_t(y_t^w - \pi_r(C_t^w + C_t^s), h_t^w) \\
&= \pi_i u_t\left(y_t^w - \pi_r(C_t^w + C_t^X) - w_t^X - v_{HWI,t}^X, h^s + \Delta h^X\right) \\
&+ (1-\pi_i) u_t\left(y_t^w - \pi_r(C_t^w + C_t^X) - v_{HWI,t}^X, h_t^w\right)
\end{aligned}$$

where other elements are as previously described and

π_i Risk of an MS diagnosis (incidence rate)

h^w QALYs in healthy state.

Utilities under the sick states are based on the annualized medical costs and health benefits to an individual who would be diagnosed in year t. The total value of drug X to the

healthy is then $\sum_t \frac{1}{(1+r)^{t-2014}} v^X_{HWI,t}\, m^X f_t$, where m^X and f_t are the fraction of MS patients using X and the population at risk in year t.

In isolated years, some estimates of the value to the healthy (without insurance) are negative. As with the estimates of value to the sick, these negative values are set to zero—again under the theory that individuals with a negative willingness to pay are free to opt out of purchasing the therapy and thus to avoid incurring negative value. Again, we perform a sensitivity analysis in which negative values are incurred by consumers. As with value to the sick, the estimated individual value to the healthy "with insurance" is positive for all drugs and all years.

The following Exhibit A1 summarizes how the model treats negative estimates of value to the sick and healthy under the different insurance specifications:

Exhibit A1: Treatment of Negative Willingness to Pay Estimates by Value Type and Insurance Assumption

	Value to the Sick	**Value to the Healthy**
Without Insurance	Set to zero (negative values allowed in sensitivity analysis)	Set to zero (negative values allowed in sensitivity analysis)
With Insurance	Not applicable – no negative values are estimated	Not applicable – no negative values are estimated

Economic model parameters

Health effects and health status

Both the therapy-specific estimates of the baseline QALY level for those suffering from MS, and of the QALY effects of the three disease modifying therapies (DMTs) were obtained from recent cost-effectiveness studies focused on US populations. Where possible, we used studies that compared the drug of interest to best supportive care (BSC). For Avonex, we found two such studies with similar annualized QALY benefits, but preferred the recent paper by Noyes et al. (2011), who utilize data from a large-scale longitudinal study.[16,39] We found only one study that fulfilled our criteria for Tysabri and only one cost-effectiveness study

incorporating Tecfidera.[30] Because the latter does not compare Tecfidera to BSC, we inferred Tecfidera's QALY benefits relative to BSC based on the reported benefits relative to Avonex.[31]

Health benefits as measured by QALYs were annualized based on aggregate QALYs as in cost-effectiveness studies. Specifically, we assume an annualized QALY, given by:

$$h^X = \frac{H^X r_h}{1-(1+r_h)^{-T}}$$

where H^X is the total QALYs over T years under treatment X, using discount rate r_h. Incremental QALYs were calculated as $\triangle h^X = h^X - h^{BSC}$, where h^{BSC} are the annualized QALYs under BSC.

Risk-aversion

Many previous studies have sought to quantify consumer risk aversion, but parameter estimates remain widely divergent. Chetty (2006) represents one of the most widely respected sources in the literature. He suggests a credible range for the coefficient of risk aversion from 0.15 to 1.78. Since some studies have estimated values greater than Chetty's upper bound,[7-10] we elected to use that upper bound value (1.78), with the lower value used in a sensitivity analysis.

Medical costs and income effects

For income and medical cost parameters, we use data from the Medical Expenditure Panel Survey (MEPS) and from a large claims database. The database includes health insurance claims under employer-provided insurance from more than 50 large US firms. Medical costs include payments for all inpatient, outpatient, emergency and pharmacy claims. We employed regression methods to estimate the income and medical cost impacts of both MS and of treatment. To mitigate differences in characteristics between MS and non-MS populations, we used regression methods on pre-screened populations based on their propensity to have MS, according to an individual's gender, race, age, educational attainment, and region. To eliminate unobservable person-level differences in health costs, we employ individual fixed-effects and measured how costs and income change for individual patients as a result of MS onset. We also measured—conditional on MS—the effects of DMT initiation on costs and income. Because we cannot fully control for bias due to unobservable characteristics, our results should not be interpreted as strictly causal. For example, our regression specification does not include

comorbidities. In addition, we note that approximately 15% of MS patients have a disease form that is not treatable by DMTs. This population is not differentiable in the data, which may bias our estimate of the income consequences of DMT utilization. To assess the degree to which estimates of aggregate social value are affected by uncertainty in these parameters, we use bootstrap techniques to construct confidence intervals for the value estimates. This process and the results are described below.

Income effects

We sought to estimate baseline income for the average person without MS, the change in income that accompanies MS onset, and the change in income that accompanies treatment with DMTs. We employed two strategies to eliminate confounding due to demographic differences between the non-MS, untreated MS, and treated MS groups. First, we used propensity score-matching to identify a non-MS population in MEPS with demographic characteristics (gender, race, age, educational attainment, and geographic region) similar to that of the MS population. We then regressed income on MS, DMT treatment, and demographic characteristics.

Patients were identified as having MS if they had an ICD-9 diagnosis of "340" in the current or any prior year. Because DMTs diffused widely starting in 2004, we generated two models: one using only years prior to 2003 and patients who did not report using a DMT, and another using only the years 2003-2013.

We predicted income from these models. Non-MS and non-DMT MS incomes were predicted using the regression model for years prior to 2003 (ie, prior to wide utilization of DMTs and identification of Avonex in the MEPS data). Finally, the impact of DMTs on income for those with MS was predicted using the model for years 2003-2013 (ie, following the introduction of DMTs).

From MEPS, we utilized all household Full Year Jobs Files from 1996 to 2013. All persons aged 16 and older in MEPS are asked to report on jobs held. From this, we created a patient-year level jobs file containing the entire MEPS population, with individuals identified by MS diagnosis and by DMT treatment. These attributes were used as covariates in each of the propensity estimation and regression models described in this appendix.

To estimate the relationship between an MS diagnosis and income, we compared MS individuals to individuals without MS. We prescreened the analytic population to include

individuals with similar likelihoods based on demographics. Specifically, we utilized a logit model to estimate the likelihood of an MS diagnosis based on race, gender, geographic region, age, and education. Observations were eliminated when the likelihood of MS was outside the 10^{th}-90^{th} percentiles in likelihoods for the actual MS population. The following regression model was then estimated:

$$income_{i,t} = \alpha + \beta_1 demographics_{i,t} + \beta_2 MS_{i,t} + \epsilon_{i,t}$$

where $income$ is an individual's full annual income, $demographics$ is a matrix of demographic variables and MS indicates a current MS diagnosis. The coefficient β_2 provides the relationship between MS and income. The relative effect of MS was estimated as β_2 relative to the predicted average income of the non-MS population.

Exhibit A2: MS and income, regression results

	Income, if employed (2014 $)		**Employed** (odds ratios)		**Income** (2014 $)	
Current MS diagnosis	-2481.7	-2488.5	-1.61***	-1.98***	14796.9***	15210.6***
	(4793.4)	(3677.7)	(0.2)	(0.2)	(2422.4)	(2234.4)
Demographics	N	Y	N	Y	N	Y
Education Level	N	Y	N	Y	N	Y
Geographic Region	N	Y	N	Y	N	Y
Constant	49069.1***	8269.7***	0.80***	-1.45***	41379.6***	10836.5***
	(288.4)	(550.9)	(0.012)	(0.038)	(240.8)	(350.7)
N (unweighted)	332718	332718	357457	357457	353496	353496
R-square	0	0.22	N/A	N/A	0	0.22

Standard errors in parentheses, * p<0.05 ** p<0.01 *** p<0.001

Demographics include gender, race, ethnicity

Exhibit A3: MS and income, relative effects

	Income, if employed (2014 $)	**Employed** (odds ratios)	**Income (>0)** (2014 $)
Healthy population			
Average predicted	44265	69.10%	40949.97
SE	(127.9)	(0.12%)	(117.4)

Effect of MS			
Absolute	-2,489	-32.8%***	-15210.6***
SE	(3677.7)	(2.80%)	(2234.4)
p-value	0.499	0	0
Relative	-5.62%	-47.52%	-37.14%

* p<0.05 ** p<0.01 *** p<0.001

We find that compared with peers of similar demographic, educational, and geographic characteristics, those with MS have incomes about $15,000 lower, equivalent to a 37% reduction relative to the predicted income for individuals without MS. The income loss is largely due to loss of employment, constituting a relative reduction of nearly 48% for MS patients.

To estimate the relationship between DMT use and income, we included only individuals with a current MS diagnosis. Similarly to the above, the analytic population was prescreened based on the likelihood of taking a DMT, given an MS diagnosis. We then applied the following regression:

$$income_{i,t} = \alpha + \beta_1 demographics_{i,t} + \beta_2 \sum individual\_DMTs_{i,t} + \epsilon_{i,t}$$

where $individual\_DMTs$ are individual dummies for utilization of each DMT and no other DMT that year. The individual components of β_2 provide the relationship between individual DMT utilization and income, relative to those not using DMTs (there was one observation of an individual using more than one DMT in the same year, which we excluded in our analysis). These effects were defined relative to the average income of non-DMT-using MS patients.

Exhibit A4: Avonex and income regression results

	Income (2014 $)
Use of only Avonex in year	11542.1*
	(-5496.4)
Use of other DMTs	Y
Constant	27991.6***
	(-2792.4)
N (unweighted)	228135
R-sq	0.23

Standard errors in parentheses, * p<0.05 ** p<0.01 *** p<0.001
Controls include demographics, education level, and geographic region.

Exhibit A5: DMT and income, relative effects

	Income (2014 $)
MS population	
Average predicted	27870
SE	(-1456.3)
Avonex treatment	
Absolute	11542*
SE	(-5,496)
Relative	41.40%

* p<0.05 ** p<0.01 *** p<0.001

Our results suggest that Avonex utilization is associated with an income improvement of about $11,500, or a 41% increase relative to individuals with MS who are not using DMTs. While we pre-screen and control based on demographics, education, and geographic location, lack of random assignment for Avonex utilization may bias these results.

Due to small sample sizes, Tysabri and Tecfidera were not identified in the MEPS data. However these drugs reduce disability progression and relapse frequency at least as well as Avonex.[27] We thus conservatively assumed that the relationship between these two drugs and relative improvements in income is equivalent to that estimated for Avonex.

In the utility model, we utilized the predicted income of the average healthy individual and the relative income effect of MS as in Exhibit A3. We also utilized the relative income impacts of DMT treatment as in Exhibit A5. Absolute estimated incomes were multiplied by three to reflect the time value of leisure.

Medical cost parameters

We used a large claims database spanning 2004-2013 to estimate total annual medical costs for MS patients, excluding the direct DMT cost. Because claims data are longitudinal, we observed patients' medical costs over time, eliminating the need to identify a non-MS comparison population. We used regression models to estimate the total annual medical costs of individuals with MS before and after diagnosis, and after utilization of a DMT.

Specifically, after constructing a patient-year level file containing medical and pharmacy costs, we estimated the relationship between an MS diagnosis and total annual medical costs as:

$$Cost_{i,t} = \alpha + \gamma_i + \gamma_t + \beta_1 age_{i,t} + \beta_2 Diagnosis_{i,t} + \epsilon_{i,t}$$

where individuals are indexed by *i*, $Cost_i$ is the total medical cost an individual pays in period t, γ_i and γ_t are person and yearly fixed effects, $age_{i,t}$ is the age of the individual at year t, $Diagnosis_{i,t}$ is an indicator for whether individual i has been diagnosed with MS by year t. Here we included the longitudinal history of all individuals who had an MS diagnosis at some point, prior to utilization of any DMT. β_2 provides the relationship between an MS diagnosis and medical costs, where again we then define the impact relative to the predicted total cost prior to an MS diagnosis. The inclusion of person-fixed effects results in an estimate of costs *after* utilization of a drug compared to costs *prior* to initiating drug utilization, for the same individual.

Regression results are shown in Exhibit A6, with relative results shown in Exhibit A7. An MS diagnosis was associated with a significant increase in medical costs, equivalent to an 87% increase in annual non-DMT medical costs relative to the period prior to diagnosis.

Exhibit A6: MS and medical costs, regression results

	Total annual medical costs (2014$)
MS diagnosis in year	8048.3***
	(571.4)
Year categories	Y
Age categories	Y
Constant	15705.1***
	(2433.3)
N	72571
R-sq	0.49

Exhibit A7: MS and medical costs, relative effects

	Total annual medical costs (2014$)
Healthy population	
Average predicted	9,248
SE	4390.2
Effect of MS	
Absolute	8048.3
SE	571.4
p-value	0.000
Relative	87%

Similarly, we analyzed the following regression only on individuals with an MS diagnosis to determine the role of DMT utilization:

$$Cost_{i,t} = \alpha + \gamma_i + \gamma_t + \beta_1 age_{i,t} + \beta_2 any\_DMT_{i,t} + B_3 \sum individual\_DMTs + \epsilon_{i,t}$$

where $individual\_DMTs$ are dummies for the use of only a given DMT during the year, so the incremental effect of an individual DMT on medical costs is given by its corresponding value in matrix B_3 plus β_2. Relative impacts are defined in relation to the predicted average cost for the non-DMT MS population.

Regression results are provided in Exhibit A8 with full drug effects provided in Exhibit A9. Use of Avonex and Tysabri led to statistically significant decreases in medical costs for MS patients, with effects relative to MS patients not using DMTs of -11% and -16%, respectively. There were too few cases of Tecfidera use in the data to identify a cost offset for that therapy. In order to parameterize the model, we assumed that the cost offset effect for Tecfidera is equal to that of Avonex as was done with the estimation of income effects for Tysabri and Tecfidera. (This approach is conservative because Tecfidera reduces disability progression and relapse frequency at least as well as Avonex[27]; the estimated Avonex parameter is therefore a reasonable estimate of the cost offset effect of Tecfidera).

As noted above, approximately 15% of patients with MS have forms not treatable by DMTs. We therefore calculated the absolute and relative effects of DMTs on medical costs, using the 10th percentile of the regression estimates for the Avonex and Tysabri variables. The results are provided in Exhibit A10. The estimated reduction in medical costs due to treatment

reduced from $1936 to $1899 per year for Avonex and from $2840 to $2789 for Tysabri. Using the 10th percentile led to a negligible change in the relative reduction in medical costs due to treatment. While we calculated the corresponding change in total social value and its distribution among consumers and manufacturers, the results are nearly identical to the baseline case and are therefore not reported here.

Exhibit A8: DMT use and medical costs, regression results

	Total annual medical costs (2014$)	
Use of any DMT	-1072.9*	762.8
	(535)	(805.5)
Use of only Avonex in year		-2698.6**
		(834.5)
Use of only Tysabri in year		-3603.2*
		(1622)
Use of only Tecfidera in year		not directly estimated; assumed equal to Avonex cost offset
Use of other DMTs	**N**	**Y**
Constant	28241.6***	27843.5***
	(2131.8)	(2128.7)
N (unweighted)	98296	98296
R-sq	0.49	0.49

Standard errors in parentheses, * p<0.05 ** p<0.01 *** p<0.001

All regressions include year, age and person FEs

Costs are net of DMT costs

Exhibit A9: DMT use and medical costs, total drug effects, absolute and relative

	Total annual medical costs (2014 $)
MS population	
Average predicted	17282.01
SE	-4554
Avonex treatment	
Absolute	-1935.76
SE	(677)
p-value	0.004
Relative	-11%
Tysabri treatment	
Absolute	-2840.37
SE	(1662)
p-value	0.087
Relative	-16%
Tecfidera treatment	
	not directly estimated; assumed equal to Avonex cost offset

Exhibit A10: DMT use and medical costs, total drug effects, absolute and relative, using the 10th percentile of the regression estimate

10th percentile of coefficient ($)	
Avonex	-2661.57
Tysabri	-3551.57
Tecfidera	-1313.91
Avonex treatment	
Absolute ($)	-1898.77
Relative (%)	-11%
Tysabri treatment	
Absolute ($)	-2788.77
Relative (%)	-16%
Tecfidera treatment	
	not directly estimated; assumed equal to Avonex cost offset

Epidemiological parameters

Our model uses two epidemiological parameters: the incidence rate for MS and the drug- and year-specific treated prevalence rates. We obtained estimates of MS incidence rates from the literature:[28,29] For our baseline model, we use an incidence rate from Mayr et al. (2010). They compute incidence for US Caucasians, as well as a regional incidence estimate. We choose the former, because it is lower and thus more conservative as an estimate of national incidence. We also test a lower incidence in our sensitivity analyses.

The total number of users of each therapy was estimated to be the therapy-specific US revenues reported by the manufacturer, divided by the estimated annual cost of the therapy. Therapy costs were obtained from claims data analysis. The treated prevalence rate was calculated as this estimated number of users divided by the US population. In sensitivity analysis, we explore the effects of halving and doubling these rates.

Drug costs, market shares, and revenues

Annual DMT costs were obtained from claims data, using appropriate NDC or HCPCs codes. We focused on patients who were adherent to a given drug (claimed 80% or more of a yearly supply), and estimated the yearly drug cost as actual drug cost inflated to a 100% adherent level. To overcome error from small sample sizes, we used the average cost over two-year bins. The results are shown in Exhibit A11. Market share estimates were obtained by combining the cost estimates described above with estimates of total MS prevalence and with drug-specific annual revenue values from Biogen Inc.'s publicly available 10-K reports for the time period in question. Specifically, the market share for drug X in time period t was estimated as follows:

$$Share_{Xt} = \frac{AR_{Xt} / UC_{Xt}}{AP_t}$$

Where

AR_{Xt} Biogen's aggregate revenues (US) for drug *X* in year *t*

UC_{Xt} The yearly unit cost estimate for drug *X* in time *t* (described above)

AP_t The aggregate prevalence of MS in the United States in year t (eg, the total number of cases)

The numerator in this expression is an estimate of the total number of individuals with MS using the therapy in question; this number divided by the total number of individuals with MS is thus an estimate of market share.

We also include an additional sensitivity analysis in which we estimate the manufacturer's cost of production based on work by Dimasi et al (2014), who find that the average cost of developing a new drug is approximately $1.395BN (2014). Multiplying this cost of drug development by the cost of capital in the pharmaceutical industry, estimated to be 0.0772 (Damodaran, 2016), provides the annualized opportunity cost of capital. We assume a constant real average cost of drug development and a 3% discount rate. Further, we assume that the cost of capital is additive between the three drugs.

Exhibit A11: Treatment Prevalence Rate Based on Analysis of Therapy Price and Manufacturer Revenue (Treated Cases per 100,000 Population)

Year	Avonex	Tysabri	Tecfidera
2002	15.15	N/A	N/A
2003	16.01	N/A	N/A
2004	18.47	0.03	N/A
2005	18.62	0.05	N/A
2006	16.39	0.27	N/A
2007	17.22	1.07	N/A
2008	14.26	1.86	N/A
2009	15.58	2.18	N/A
2010	13.51	2.09	N/A
2011	14.66	2.69	N/A
2012	10.60	2.01	N/A
2013	11.16	4.38	3.94

Sensitivity Analyses

Impacts of changes to parameters obtained from the literature

Exhibits A12 and A13 show how estimates of value vary in response to changes in the parameters for MS incidence, MS prevalence, risk aversion, preferences for health (relative to consumption), and when including a non-zero insurance load, the cost of capital to manufacturers, or allowing for negative values of therapy. The specific parameters values used to obtain these results are described in Exhibit 2. Exhibit A12 presents results of the sensitivity analyses under the "without insurance" assumption; Exhibit A13 presents results assuming full insurance.

Exhibit A12: Sensitivity Analysis: Effects of Changes to Epidemiological and Economic Input Parameters on Estimates of Value, Without Insurance (2014 $BN)

	Value to the Sick (A)	**Value to the Healthy** (B)	**Population-Wide Value** (C=A+B)	**Manufacturer Profit** (D)	**Share Accruing to Consumers** (E = C/(C+D))
Baseline	11.1	8.9	20.0	21.2	49%
Lower incidence	11.1	6.1	17.2	21.2	45%
Higher treated prevalence	23.6	8.9	32.5	45.0	42%
Lower treated prevalence	5.3	8.9	14.2	10.1	59%
Less risk averse	11.1	2.1	13.2	21.2	38%
Lower value of health	8.0	2.8	10.8	21.2	34%
Tecfidera cost offset = midpoint of Avonex and Tysabri estimates	11.1	8.9	20.0	21.2	49%
Non-zero insurance load	11.1	8.9	20.0	21.2	49%
Cost of drug development	11.1	8.9	20.0	21.2	51%
Negative values of therapy allowed	9.9	6.4	16.3	21.2	43%

Exhibit A13: Sensitivity Analysis: Effects of Changes to Epidemiological and Economic Input Parameters on Estimates of Value, with Insurance (2014 $BN)

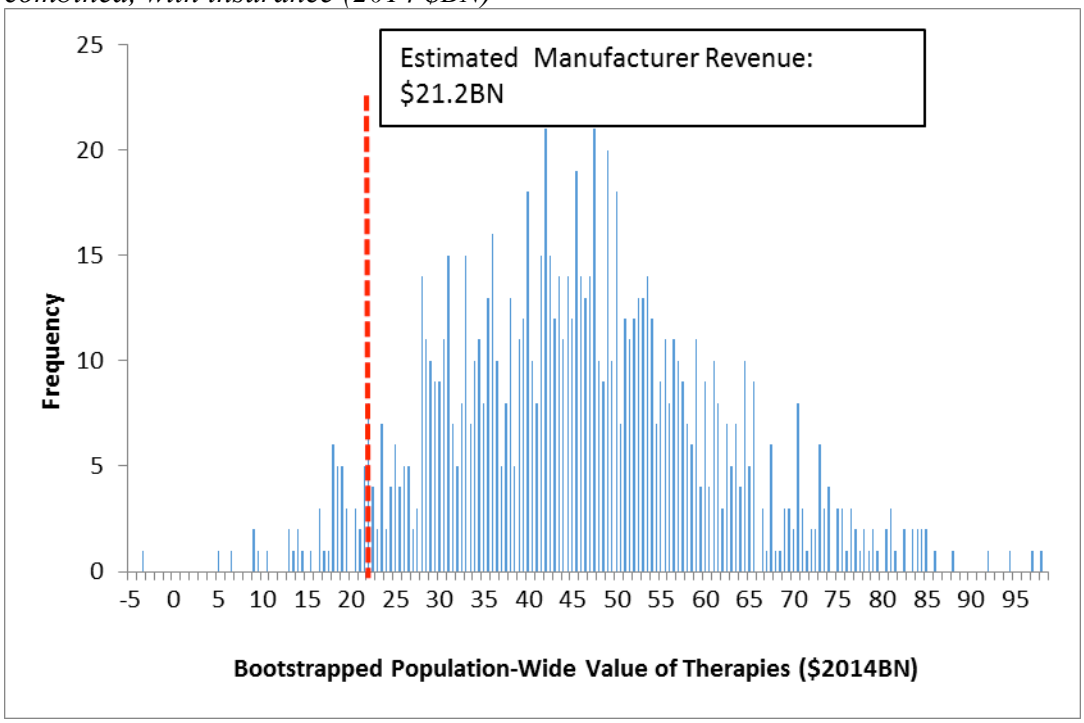
	Value to the Sick (A)	**Value to the Healthy** (B)	**Population-Wide Value** (C=A+B)	**Manufacturer Profit** (D)	**Share Accruing to Consumers** (E = C/(C+D))
Baseline	31.8	14.4	46.2	21.2	69%
Lower incidence	31.8	9.0	40.8	21.2	66%
Higher treated prevalence	67.6	11.6	79.1	45.0	64%
Lower treated prevalence	15.1	15.8	30.9	10.1	75%
Less risk averse	31.8	3.5	35.3	21.2	62%
Lower value of health	26.8	3.6	30.3	21.2	59%
Tecfidera cost offset = midpoint of Avonex and Tysabri estimates	31.8	14.4	46.2	21.2	69%
Non-zero insurance load	31.8	13.9	45.7	21.2	68%
Cost of drug development	31.8	14.4	46.2	19.2	71%
Negative values of therapy allowed	31.8	14.4	46.2	21.2	69%

Impact of variance in parameters obtained from regression modeling

Four model parameters – the effects of MS on income and medical costs, and the effects of treatment on income and medical costs conditional on MS – were estimated through regression analysis using MEPS data. The baseline analysis presented in the main body of this report uses the point estimates from these regressions but does not account for their error distributions. To examine the sensitivity of study findings to this source of variation, we bootstrapped these parameters. Specifically, we generated instances of these four parameters for 1,000 resampled distributions, fitted a survey regression applying survey weight and primary sampling unit (PSU) information, and then estimated aggregate measures of value using these 1,000 parameter quadruples in place of the actual regression coefficients. This allowed us to describe the error distributions for the estimate of aggregate value, which is shown below in Exhibit A14.

As expected, the mean of the bootstrapped values (total lifetime population-wide value of $46.1BN) is close to the estimate from the baseline model ($46.2BN). The 95th and 90th percentile confidence intervals for the estimate are ($18.4BN - $79.4BN) and ($22.1BN - $73.3BN), respectively. In 95% of the simulations, the estimated value accruing to consumers is greater than the estimated manufacturer profits ($21.2BN).

Exhibit A14: Distribution of Bootstrapped Values for Lifetime population-wide value of all drugs combined, with insurance (2014 $BN)



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