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MEASURING THE POTENTIAL HEALTH IMPACT OF PERSONALIZED MEDICINE:
EVIDENCE FROM MS TREATMENTS

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ABSTRACT

Individuals respond to pharmaceutical treatments differently due to the heterogeneity of patient populations. This heterogeneity can make it difficult to determine how efficacious or burdensome a treatment is for an individual patient. Personalized medicine involves using patient characteristics, therapeutics, or diagnostic testing to understand how individual patients respond to a given treatment. Personalized medicine increases the health impact of existing treatments by improving the matching process between patients and treatments and by improving a patient's understanding of the risk of serious side effects. In this paper, I compare the health impact of new treatment innovations with the potential health impact of personalized medicine. I find that the impact of personalized medicine depends on the number of treatments, the correlation between treatment effects, and the amount of noise in a patient's individual treatment effect signal. For multiple sclerosis treatments, I find that personalized medicine has the potential to increase the health impact of existing treatments by roughly 50 percent by informing patients of their individual treatment effect and risk of serious side effects.

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1 Introduction

Pharmaceutical treatments in the United States are homogeneous products that are tightly regulated by the FDA to ensure that the dosage and delivery are consistent across each prescription. However, differences across patients—including genetics, age, comorbidity, preferences, and environment—and differences across diseases—such as severity and progression—cause the impact of a treatment to vary across patients. Patients respond to the same dosage differently, from how their bodies process and react to the treatment to the side effects that arise.[1]

This heterogeneity is often not apparent when assessing the impact of innovations because clinical trials and cost-effectiveness research focus on the average treatment effect, even if this effect varies significantly across patients. To understand the potential impact of heterogeneity across treatments, consider two treatments in the same disease category where the health impact of each treatment measured in quality-adjusted life years (QALYs) across the patient population is an independent normal distribution with a mean of one QALY and a standard deviation of one.[2] If patients match with the treatment that provides the highest individual health impact, then the total impact across all patients is over 56 percent higher than if patients are randomly assigned a treatment.[3]

Personalized medicine is a growing field that addresses the heterogeneity in treatment effects across patients by targeting or tailoring treatments to individuals based on their characteristics. Personalized medicine has the ability to create novel treatments, such as treatments that target specific genes or proteins, and the ability to guide patients to the most efficacious treatment through diagnostic testing or data-driven analysis.[4]

Understanding the potential impact of incorporating patient heterogeneity in biology, environment, and behavior, the United States announced a $215 million Precision Medicine Initiative in 2015.[5] The purpose of this initiative is to provide funding for research in personalized medicine, including building a research cohort to collect individual level data to help develop more effective treatments and funding cancer genomics, one of the leading research fields in personalized medicine.[6]

We are just beginning to understand the potential impact of precision medicine. Goldman *et al.* (2013) present a framework for understanding the value of diagnostic tests. In a case study of rofecoxib, a non-

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[1]See discussions and examples in Basu *et al.* (2014), Kravitz *et al.* (2004), and Segal *et al.* (2012).

[2]QALYs are a frequently used measure of either disease burden or treatment effect that includes the quality and quantity of life lived by the patient.

[3]The maximum of two independently distributed normal distributions with mean μ and a standard deviation of one is distributed as a Gumbel or Extreme Value Type 1 distribution which has a mean of $\mu + \frac{1}{\pi} > \mu + 0.56$.

[4]Examples of targeted treatments include human epidermal growth factor receptor 2 (HER2) in breast cancer, epidermal growth factor receptor (EGFR) in colorectal cancer, and BRAF inhibitors for melanoma. See Hutchinson *et al.* (2015).

[5]See www.whitehouse.gov/precisionmedicine.

[6]See Chin *et al.* (2011).

steroidal anti-inflammatory drug that was withdrawn from the market, they show that diagnostic testing can have a large social value by avoiding unnecessary treatment and identifying patients who would not otherwise be treated. Basu (2013) discusses the difference between passive personalization, which is a form of learning by doing where patients and physicians learn about patient-specific treatment effects through a trial and error process, and active personalization, which involves biomarker and genetic tests that inform patient-specific treatment effects.

Egan and Philipson (2014) discuss the role of passive personalization in measuring adherence. They create a dynamic model to argue that personalized medicine has the capacity to expedite this search process which reduces over-adherence and increases under-adherence.

The goal of this paper is to present a framework for understanding the potential health impact of personalized medicine and to compare it to the health impact of other types of pharmaceutical innovations.[7] I present a theoretical framework for measuring the health impact of personalized medicine by modifying the model of Hult (2014). The model in this paper measures the value of two types of personalized medicine: allocating patients to treatments based on individual treatment effects and identifying individual risk to serious side effects from a treatment. The health impact of these types of personalized medicine depends on the number of treatments, the variance in the health impact within a treatment, the noise in a patients signal of their treatment effect, and the correlation of treatment effect across the different treatment options.

To understand the value of personalized medicine, consider two examples. First, consider a multiple sclerosis (MS) patient deciding which first line therapy to take. If that patient chooses a therapy on which they will eventually fail (meaning they have a suboptimal response and switch to a different therapy), that patient experiences a relapse rate five times higher compared with their second therapy (Rio *et al.*, 2012). These patients stay on their unsuccessful first treatment for almost as long as they stay on their successful treatment (3.9 years versus 4.2 years). For diseases like multiple sclerosis where the disease progression is irreversible and failing on a treatment produces similar results to taking no treatment at all, the effect of choosing an ineffective treatment can be significant and permanent.

Second, consider an MS patient deciding which second line therapy to take. Two second line options are Tysabri, a treatment with the highest efficacy but the risk of a potentially fatal side effect, and Gilenya, a treatment with lower efficacy but with much less severe side effects. When personalized information is used to inform a patient of their individual side effect risk level (which ranges from less than 1 in 10,000 to 1 in 89), high risk patients are able to avoid being exposed to the potentially fatal side effect while low-risk patients are able to take more efficacious treatments than they would have without personalized information

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[7]This paper focuses on pharmaceuticals, but the implications of the paper are also relevant for medical devices and other medical treatments.

(Sorensen *et al.*, 2012).

I measure the relative impact of personalized medicine compared with the introduction of new treatments in a case study of MS treatments. I find that the potential health impact of personalized medicine for MS patients would increase the health impact of existing treatments by 21 percent by improving the ability to match patients with the treatment that provides the largest treatment effect and by 30 percent by properly identifying the risk of a patient to serious side effects, which can prevent a patient from taking the treatment that provides the largest treatment effect. I end with a discussion of the incentives for firms to invest in and the return to personalized medicine.

This paper is organized as follows. Section 2 discusses the different types of pharmaceutical innovation, which include novel, follow-on, and personalized innovations. Section 3 discusses the theory of how to measure the value of personalized innovations. Section 4 is a case study of disease-modifying therapies in Multiple Sclerosis to illustrate the return to personalized medicine. Section 5 discusses the value of and the incentive for firms to engage in personalized medicine. Section 6 concludes.

2   Types of Pharmaceutical Innovations

There are three main types of pharmaceutical innovations: novel innovations, follow-on innovations, and innovations in personalized medicine. Novel innovations are the approval of a chemical entity that has not already been approved by the FDA and is the part of the pharmaceutical treatment that is responsible for the pharmacological action of the treatment. These approvals are either a new molecular entity (for smaller chemically synthesized molecules) or a new biologic (for larger treatments extracted from biological sources). Novel innovation is a necessary precursor for follow-on innovation and personalized medicine. However, novel innovation in its original form often extracts only part of the potential health impact of the new molecule because it generally provides only one treatment which has not been adapted to the heterogeneity of the treatment population or to the learning that takes place from treatments being on the market. Follow-on innovations and personalized medicine develop the molecule into a more efficacious or desirable treatment for patients.

Follow-on innovations take already FDA-approved molecules and create new treatments by changing the dosage, formulation, indication, active ingredient, or by combining two molecules.[8] Roughly 70 percent of all FDA approved innovations are and over half of all prescriptions use follow-on innovations (Hult 2014). Follow-on innovations make three main types of improvements. First, they can create a new treatment by combining existing molecules. Second, they can make existing treatments either more effective or better

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[8]A follow-on innovation that contains a new active ingredient means that it contains the same active moiety but includes a different enantiomer, racemate, salt, ester, complex, chelate, or clathrate.

tolerated. Third, they can expand the number of treatment options available and expand the availability of treatment to subgroups of the population.[9] The main focus of these innovations is to expand the treatment population, reduce treatment burden, or increase efficacy for a group of patients. For instance, HIV/AIDS treatments in their original form were unable to be taken by pediatric, elderly, and pregnant patients. With follow-on innovation, all of these patients groups now have a variety of treatment options, including oral pellets that can be mixed into children's food or intravenous treatments for patients that cannot take the pill regimen.[10]

The third type of innovations are innovations in personalized medicine, which take follow-on innovations a step further by creating directed treatments or diagnostics tests from the characteristics of an individual patient. These innovations can create new treatments, create datasets or diagnostic tests to determine the best treatment considering individual treatment effects, and identify individual treatment burdens for patients.

Improve Matching and Reduce Searching One way in which personalized medicine improves the health outcomes of patients is that it can inform a patient about which treatment will either be more efficacious or have a lower burden of treatment through diagnostic testing or patient databases.[11] If a patient learns of their individual treatment effect, it can direct the patient towards a treatment that makes them better off than if they do not have any individual specific information.

Consider the two treatment options shown in Figure 1. This figure plots the distribution of patient outcomes for the treatment efficacy and burden of two treatments, treatment 1 (represented in blue) and treatment 2 (represented in red). The indifference curves (IC) show the efficacy and burden combinations for which patients are equally well off, so a patient is indifferent between receiving the treatment effect of any points along the same IC. Patients are better off with higher efficacy and lower treatment burdens so they are better off on indifference curves closer to the upper left of the graph. A patient with no information about his individual treatment effect would be indifferent between these two treatments.

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[9]Examples of follow-on innovations include the creation of CART treatments used in HIV/AIDS which combine three different molecules in a treatment that reduces pill burden and potential drug interactions; Fetzima, a SNRI drug used to treat major depressive disorder, was approved as a new active ingredient using a different orientation of the molecule in milnacipran HCI (Savella) which is used to treat fibromyalgia; and Norvir, an HIV/AIDS treatment, received a new formulation which eliminated the need for refrigeration, reduced the number of drug and food interactions, and provided extended release for drugs.

[10]See UNAIDS (2015).

[11]As a simplification, throughout this paper I treat the patient as the person who decides what treatment to take when this decision is heavily influenced by the physician.
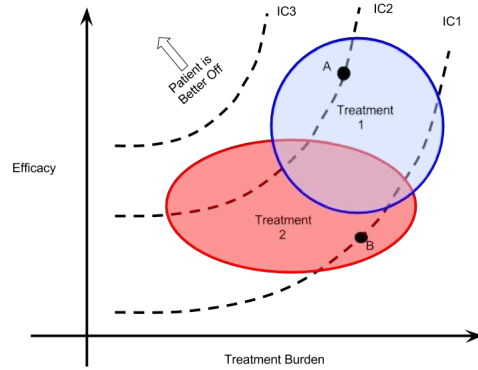
Figure 1: Improve Matching and Reduce Searching

However, if a patient learns from diagnostic testing that they receive the efficacy and treatment burden at point A for treatment 1 and the efficacy and treatment burden at point B for treatment 2, then the patient is better off taking treatment 1 than treatment 2.

There are different ways that a patient can learn about their individual treatment effect, which can broadly be categorized as passive and active personalized medicine.[12] In passive personalized medicine, a patient or their physician learns about a patient's individual treatment effect through learning-by-doing. So a patient may try different treatments and learn his treatment effect or the physician may learn about how different patients respond to different treatments from experience. Passive personalized medicine can be thought of as a dynamic process of a patient searching over treatments or making the decision to continue taking a given treatment.[13]

Passive searching has several costs including opportunity costs, side effects, and financial costs. For example, if a patient has an aggressive form of MS, taking a treatment that the patient does not respond to can cause irreversible damage and disability and allow the disease to progress to a form of MS that is less responsive to therapy (see Rush *et al.*, 2015). In addition for MS patients, taking less efficacious but milder treatments at an early stage of the disease can increase the risk of serious side effects for a patient who takes more efficacious treatments at a later stage of treatment. Therefore, when patients have to passively search over treatments, a patient with a more aggressive disease will be more prone to serious side effects than a patient who can be matched to the more efficacious treatment earlier (see Saheer and Berger, 2012). Finally, MS patients may develop neutralizing antibodies taking one treatment that makes other treatments ineffective. For example, if a patient takes either Betaseron (interferon beta 1-b), Extavia (interferon beta

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[12]See a discussion of passive and active personalization in Basu (2013).
[13]Egan and Philipson (2016) describe it as an optimal stopping problem as a patient learns his individual treatment effect as he takes a treatment.

1-b), or Glatopa (glatiramer acetate), that patient may develop neutralizing antibodies that will block the biological activity of the other two treatments.

In active personalized medicine, physicians give patients a diagnostic test or use patient databases to learn how an individual patient may respond to a treatment. In the MS examples above, this would include a test that determines the aggressiveness of a patient's MS or susceptibility of developing neutralizing antibodies to determine which course of treatment is best for that patient.

Risk Assessment Another way that personalized medicine impacts health is through risk assessment. Some treatments have very serious side effects for a fraction of the patient population. For example, Tysabri, an MS treatment, has a side effect of progressive multifocal leukoencephalopathy (PML) for up to 0.013 percent of patients. PML is a devastating disease that has a mortality rate up to 50 percent within months and potentially severe neurological disabilities for those who survive.[14] The risk of PML was enough to get Tysabri pulled from the market within four months of FDA approval. However, Tysabri is the most efficacious treatment for MS patients. The ability to identify patients with higher risk factors can reduce the odds of getting PML from 0.013 to less than 0.001 percent.
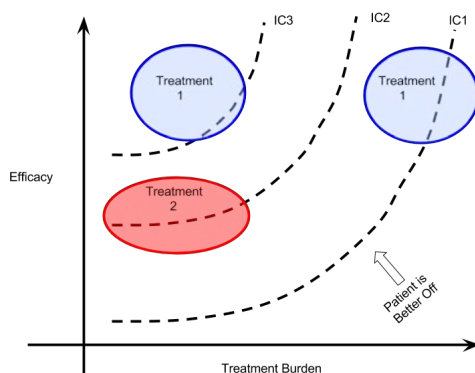
Figure 2: Risk Assessment

For example, Figure 2 shows two treatments, treatment 1 in blue and treatment 2 in red. Treatment 1 has a potentially serious side effect (which increases the treatment burden) as shown by the two blue distributions. The treatment 1 distribution on the left is for those patients who do not have the side effect, and the treatment 1 distribution on the right is for those patients who have the side effect. Without any information about their side effect risk factor, patients would choose treatment 2. However, if patients can

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[14]See https://www.tysabri.com/en_us/home/about/safety-side-effects.html.

identify whether they would have the serious side effect from treatment 1, then patients could incorporate this information in their treatment decision. In this bifurcated outcome, the health impact of treatment increases on average.

3   Measuring Health Impact

In this section, I describe a model from Hult (2014) that describes how to measure the health impact of pharmaceutical treatments, and I discuss an extension of the model to incorporate patient heterogeneity and the potential health impact of personalized medicine.

3.1   Health Impact of Novel and Incremental Innovation

The health impact of a novel or incremental innovation is how much it increases the patient population's length and quality of life. Innovations affect health through three channels: adherence, quantity measured as the number of users, and efficacy measured in QALYs.

The health impact of treatment t on individual i (h_{it}) is:

$$h_{it} = a_{it}e_{it}$$

where a_{it} is the adherence and e_{it} is the efficacy conditional on being fully adherent for patient i with treatment t. Health impact is a one-dimensional measure of the total impact of a treatment incorporating efficacy as well as the treatment burden, such as side effects or burden of administration. A negative value for h_{it} means that a patient is worse off taking the treatment relative to not taking the treatment, and the more positive the value for h_{it} the better off the patient is taking the treatment.

Summing across all patients who take treatment t ($i \in T$), the aggregate health impact of treatment t, H_t, is:

$$
\begin{aligned}
H_t &= \sum_{i \in T} h_{it} = \sum_{i \in T} a_{it}e_{it} \\
&= q_t \bar{h}_t = q_t \bar{a_t}\bar{e}_t
\end{aligned}
$$

where q_t is the quantity measured as the number of users. If 100 people take a drug with a 60 percent adherence rate that adds one QALY on average, then the health impact of the drug is 60 QALYs.[15]

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[15] $100 * 0.6 * 1$ QALY $= 60$ QALYs.

To measure the increase in health impact produced by treatment t, which is how treatment t increases health impact relative to the standard of care (SOC) that existed before the innovation, I construct $\Delta H_t^{innovation}$:

$$\Delta H_t^{innovation} = \frac{\partial h_t}{\partial q}\Delta q + \frac{\partial h_t}{\partial a}\Delta a + \frac{\partial h_t}{\partial h}\Delta e$$

$$= \Delta q_t a_t e_t + \Delta a_t q_t e_t + \Delta e_t q_t a_t$$

$$= \Delta q_t h_t + \Delta h_t q_t$$

where q_t is the average quantity of treatment t per year, Δq_t is how treatment t changes the quantity relative to the standard of care (SOC), Δa_t is how treatment t changes the adherence rate relative to the SOC, and Δe_t is how treatment t changes efficacy relative to the SOC. Hence, the health impact of treatment t is the effect of the change in the quantity, adherence, and efficacy relative to what would be used instead of that treatment. For instance, if a treatment with 100 users and an efficacy of one QALY increases the adherence rate relative to the previous SOC by five percentage points, then the health impact of that innovation is $0.05 * 100 * 1 = 5$ QALYs. If that drug innovation had an adherence rate of 60 percent and also increased efficacy by 5 percent, then the health impact would be $5 + 0.05 * 100 * 0.6 = 5.3$ QALYs.

3.2   Potential Health Impact of Personalized Medicine

To understand the effect of innovations in personalized medicine, consider patient i who receives a health impact (h) measured in quality-adjusted life years (QALYs) and has the choice between two treatments, treatment A and treatment B. The health impact for the two treatments is distributed as a bivariate normal:

$$h \sim N\left(\begin{bmatrix} \mu_A \\ \mu_B \end{bmatrix}, \begin{bmatrix} \sigma_A^2 & \sigma_{AB} \\ \sigma_{AB} & \sigma_B^2 \end{bmatrix}\right)$$

where μ_t and σ_t^2 are the mean and variance of each treatment $t \in \{A, B\}$ and σ_{AB} is the covariance between A and B. The covariance between treatment effects is important because the more correlated effects are across treatments, the lower the value of identifying individual treatment effects.

Impact of Individual Treatment Effect on Searching   Information about the patient's individual treatment effect can come from numerous sources, including disease severity and progression, genetics, environment, and comorbid conditions. In this section I do not distinguish learning through passive or active

learning, as they have the same effect. For simplicity in this section assume $\mu_A > \mu_B$.[16]

If a patient has no information about their individual treatment effect, then the patient chooses the treatment t with the highest μ_t because the patient's expected health impact for each treatment is $E[h_t] = \mu_t$. In this scenario, each patient chooses treatment A, and the average treatment effect across all patients is $\bar{h}_1 = max_{t \in \{A,B\}}(\mu_t) = \mu_A$.[17]

With perfect information, a patient knows his exact h for each treatment so he simply chooses the highest h_t. In this scenario, the average treatment effect across all patients is

$$\bar{h}_2 = \mu_A \Phi(\eta) + \mu_B \left(1 - \Phi(\eta)\right) + \theta \phi(\eta)$$

where $\theta = \sqrt{\sigma_A^2 + \sigma_B^2 - 2\sigma_{AB}}$, $\eta = \frac{\mu_A - \mu_B}{\theta}$, and $\phi(\cdot)$ and $\Phi(\cdot)$ are the pdf and cdf of a standard normal distribution respectively (Nadarajah and Kotz, 2008). Note that $\bar{h}_2 \geq \bar{h}_1$, so patients are not worse off having perfect information about their individual treatment effect.[18]

The third scenario is patients receive a noisy signal of their individual treatment effect from t. For a patient who has treatment effect h_t from treatment t, that individual gets a signal $s_t \sim N(h_t, \sigma_s)$. In this scenario, patients choose the treatment with the highest signal s_t, and the average treatment effect across all patients is $\bar{h}_3 = max_{t \in \{A,B\}}(s_t)$. Receiving an inaccurate signal means that a patient can choose a treatment with a lower treatment effect (h_t). Across the population, patients get a greater health impact with perfect information compared to either a noisy signal or no information ($\bar{h}_2 \geq \bar{h}_3$ and $\bar{h}_2 \geq \bar{h}_1$) but having a noisy signal does not necessarily make the patient better off than having no signal ($\bar{h}_1$ can be greater than, less than, or equal to $\bar{h}_3$).

As a result, the maximum potential health impact of personalized medicine in this market is:

$$\begin{aligned} \Delta H^p &= q \Delta h^p \\ &= q \left(\bar{h}_2 - \bar{h}_1\right) \end{aligned}$$

With a noisy signal the maximum potential health impact of personalized medicine is:

$$\begin{aligned} \Delta H^p &= q \Delta h^p \\ &= q \left(\bar{h}_3 - \bar{h}_1\right) \end{aligned}$$

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[16]In this framework, generics and biosimilars can be thought of as treatments with the same distribution and perfect correlation with the branded treatment. Therefore, having a generic option does not provide an increase in health impact. If a generic uses a different formulation or delivery mechanism, then it would not necessarily be perfectly correlated with the branded version.

[17]Throughout this section, I assume patients are risk neutral.

[18]The max of two or more independently distributed normals generalizes to the Gumbel distribution, or type 1 extreme value distribution, which for two standard normals has a mean of $\frac{1}{\sqrt{\pi}} \approx 0.56$.

where $\frac{\partial \bar{h}_3}{\partial \sigma_{AB}} \leq 0$ and $\frac{\partial \bar{h}_3}{\partial \sigma_s} \leq 0$. Therefore, the less correlated the different treatment outcomes and the less noise that a patient has about his treatment effect, the larger the health impact of personalized medicine for improving the matching of patients to treatments.

For this paper the relevant comparison is how much personalized medicine can increase the total health impact compared to how patients and physicians choose treatments in the real world:

$$\Delta H^p = q \left(\bar{h}_3 - \bar{h}_{actual} \right) \tag{1}$$

To understand the effect of a patient's knowledge of his individual treatment effect, consider an example where the distribution of h across two treatments A and B is:

$$(h_A, h_B) \sim N \left(\begin{bmatrix} 1.5 \\ 1 \end{bmatrix}, \begin{bmatrix} 1.5 & \sigma_{AB} \\ \sigma_{AB} & 1 \end{bmatrix} \right)$$

and patients receive a noisy signal of their individual treatment effect observe:

$$s_t \sim N (h_t, 1) \ \forall t \in \{A, B\}$$

Figure 3 illustrates the average treatment effect for different covariances between the two treatments (σ_{AB}) for the three scenarios discussed: patients have no information about their individual treatment effect, patients have full information about their individual treatment effect, and patients have a noisy signal of their individual treatment effect.
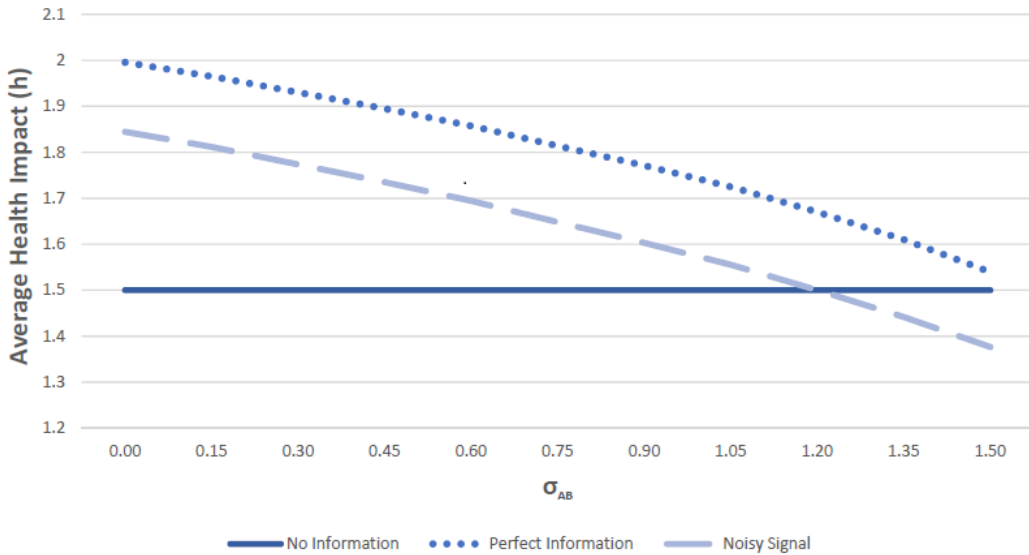

Figure 3: Average Treatment Effect by σ_{AB} and Patient Signal

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In this example, perfect knowledge of an individual's treatment effect increases the health impact by up to 33 percent relative to patients choosing the treatment with the highest average health impact. The largest increase in health impact comes when the treatments are uncorrelated and there is no health impact when the treatments are perfectly correlated. With a noisy signal, the increase in health impact with uncorrelated treatment effects drops to 23 percent and is negative with perfectly correlated treatment effects.

Impact of Individual Treatment Effect on Risk Assessment   The impact of risk assessment is similar to treatment effect of searching except the health impact of treatment A (h_A) comes from a multimodal normal distribution. This distribution represents the two possible outcomes that occur depending on whether the patient does not get the serious side effect (state 1) or the patient does get the serious side effect (state 2). Therefore:

$$\mu_A = p\mu_{A1} + (1-p)\mu_{A2}$$

and

$$\sigma_A^2 = p\sigma_{A1}^2 + (1-p)\sigma_{A2}^2 + \gamma$$

where $\gamma = p(1-p)(\mu_{A1} - \mu_{A2})^2$ and $A1$ represents treatment A in state 1 and $A2$ represents treatment A in state 2.

Consider a patient choosing between treatment A and treatment B where a patient knows his individual treatment effect for each treatment in each state in the world such that $h_{A1} > h_B > h_{A2}$.[19] With no individual information about p, the probability a patient is in state 1 (no serious side effect) versus state 2 (serious side effect), the patient may have information about $\bar{p}$, the average share of patients in state 1 in the patient population. A patient then chooses treatment A if:

$$\bar{p} > \frac{h_B - h_{A2}}{h_{A1} - h_{A2}}$$

and treatment B if the inequality holds in the other direction.[20] As a result, all patients choose either treatment A or treatment B based on $\bar{p}$ and the average health impact of the different treatments.

If a patient has information about his individual probability of getting the serious side effect, p_i, then he chooses treatment A if:

$$p_i > \frac{h_B - h_{A2}}{h_{A1} - h_{A2}}$$

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[19]It is straightforward to adapt this example to the case where the patient has no information or noisy information about his health impact and makes his choice based on either the treatment average across the population (μ) with no information or the treatment signal (s) with noisy information.

[20]The patient chooses treatment A if $\bar{p}h_{A1} + (1-\bar{p})h_{A2} > h_B$.

and treatment B if the inequality holds in the other direction. As a result, for the case when $\bar{p} > \frac{h_B - h_{A2}}{h_{A1} - h_{A2}}$, patients with p_i such that:

$$\bar{p} > \frac{h_B - h_{A2}}{h_{A1} - h_{A2}} > p_i$$

would choose treatment A in the case of no information and treatment B in the case of full information about p.[21] This patient is better off in the case of full information by $p_i h_{A1} + (1 - p_i) h_{A2} - h_B > 0$. Summing over all patients the increase in health effect is:

$$\Delta H^p = \sum_{i \in \left\{ p_i < \frac{h_B - h_{A2}}{h_{A1} - h_{A2}} \right\}} p_i h_{A1} + (1 - p_i) h_{A2} - h_B \tag{2}$$

4   Case Study in MS

MS is a good case study for understanding the value of innovations in personalized medicine because there is profound heterogeneity in the MS population, disease course, and treatment response (Lucchinetti *et al.*, 2000). MS is a chronic condition that occurs when the body's immune system attacks the central nervous system and damages or destroys the nerve's protective covering, causing flare-ups that range from dizziness to paralysis and cognitive loss.[22] There are currently more than 400,000 patients with MS in the United States with almost $14 billion in annual spending on MS treatments, which makes it the fourth largest specialty pharmacy class in the US.[23]

Currently, physicians can rely on clinical trials data, biomarkers, and passive searching to determine the best course of treatment. Clinical trials data in MS is useful at the group level, but it is viewed as insufficient to influence individual treatment decisions and "few biomarkers have made their way into clinical practice" in MS (Derfuss 2012). As a result, there is very little predictive power about how a patient will respond to an individual treatment (Derfuss 2012). Passive searching, while frequently used, is costly because, as previously discussed, it can cause irreversible damage and disability, increase disease progression, increase future side effects, and increase the probability that a patient will be unresponsive to alternative treatments.

There are twelve disease modifying therapies (DMTs) available in the US to treat MS, which are listed in Table 4. The purpose of these treatments is to reduce the number of flare-ups that patients suffer, and they do not cure the underlying disease. These treatments can broadly be categorized in two ways: by line of treatment and mode of administration. Figure 4 shows the typical line of treatment for each DMT,

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[21]The case when $\bar{p} < \frac{h_B - h_{A2}}{h_{A1} - h_{A2}}$ and $\bar{p} < \frac{h_B - h_{A2}}{h_{A1} - h_{A2}} < p_i$ is symmetric.

[22]There are four disease courses for MS patients, clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS), primary progressive MS (PPMS), and progressive relapsing MS (RPMS). 85 percent of MS patients have RRMS, which is the focus of this case study (Trapp and Nave, 2008).

[23]See Pietrangelo and Higuera (2015) and IMS (2015).

where first line treatments are safer treatments with lower efficacy and lower treatment burden, second line treatments are more aggressive treatments that feature higher efficacy but also higher treatment burden, and third line treatments feature the highest efficacy but also have potentially life-threatening side effects. Most of the first line treatments are referred to as ABCRE treatments which represents Avonex, Betaseron, Copaxone, Rebif, and Extavia.

First, second and third line therapies
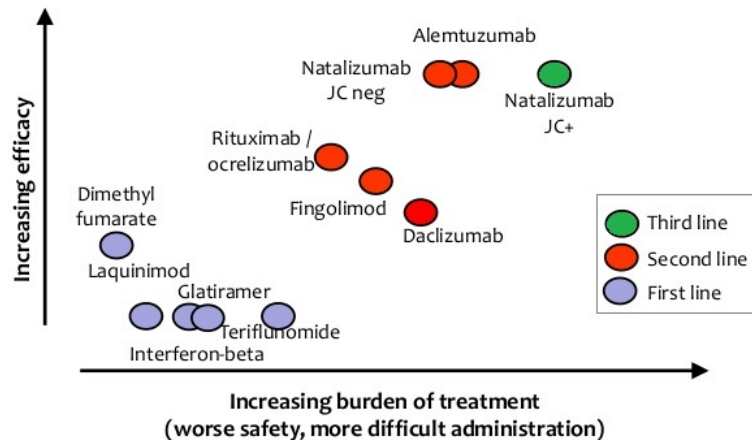
Source: Coles (2015)

Figure 4: Market for MS Treatments

The other way the market is divided is by the mode of administration. There are three modes of administration: injection, infusion, and oral. The ABCRE treatments are all injectable (either with intramuscular or subcutaneous injection) and injectables were the only option from 1993 to 2004.

In 2004, Tysabri, a more efficacious treatment that is administered through infusion was introduced. Tysabri plays an important role in the MS market because it is not only the most efficacious treatment, but it has been linked to a rare and highly fatal brain disease PML. Tysabri was approved by the FDA in 2004 as the first infusion treatment and was almost six times more efficacious than any existing treatment. By February 2005, the treatment was withdrawn from the market after three patients developed PML. In February 2006, Tysabri returned to the market with conditions including mandatory patient registration in a database, follow-ups every six months, and MRI evaluation prior to initiation.

In 2010, oral treatments were introduced which reduced the burden of treatment administration yet have among the lowest adherence rates of any MS treatment.

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4.1 Data

There are three main types of data necessary to estimate the health impact of MS treatments: the distribution of QALYs for each treatment t (previously denoted as μ_t and σ_t), the covariance in treatment outcomes between treatments ($\sigma_{t_1 t_2}$), and the patient count estimates for each treatment (q_t). The data appendix provides additional details about the data.

The QALYs estimates are taken from published clinical studies, most of which are summarized in the Tufts Medical Center Cost-Effectiveness Analysis Registry (CEAR).[24] CEAR includes over 4,800 pharmaceutical cost-utility analyses in the peer-reviewed medical literature. It is intended to be a comprehensive dataset of all cost-utility articles analyzed by trained professionals, who rate the quality of the study and provide information about the quality level and quality relative to the standard of care found in the study. Of the 24 MS studies that use MS DMTs, I rely on the 15 that are for RRMS patients (which composes 85 percent of all MS patients). CEAR rates the studies on a scale from 1 to 7 depending on the quality of the analysis. All of the MS clinical studies used from the CEAR dataset have a rating above average. The efficacy measures are relative to a patient taking no DMT, so a QALY of zero means that the treatment provides no benefit relative to not taking any DMT.

The estimates of the covariance between treatment outcomes are more difficult to measure because clinical studies generally provide information about how a patient responds to one treatment, not how each patient responds to multiple treatments.[25] However, there are observational studies that measure the treatment effect of patients before and after a treatment failure, which is when a patient experiences a suboptimal response to a treatment and switches to a substitute treatment.[26] These studies show how a patient responded to two different treatments conditional on the patient failing at least one of the treatments, but do not show how many patients would have been successful on both treatments.[27] Appendix 3 describes how the covariance estimates were constructed.

The patient count estimates come primarily from published reports that use Symphony Health Solutions and IMS data.

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[24] I assume the distributions of QALYs from clinical studies is equal to distributions of all patients in the disease category, that the QALY measure incorporates all side effects as well as treatment efficacy, and that QALY measures incorporate adherence and are not conditional on adherence.

[25] See Basu and Philipson (2011) for a discussion of the effect of the joint distribution of treatment effects.

[26] See, eg., Rio et al. (2012) and Gajofatto *et al.* (2009).

[27] A patient's response to their second treatment may be affected by the first treatment. For example, I previously discussed the effect of neutralizing antibodies which could be produced during the first treatment and make the second treatment less effective.

4.2 Health Impact

I measure the actual or potential health impact of seven events in the history of MS treatments: (1) the innovation of Betaseron, the first MS DMT, (2) the innovation of the other ABCRE DMTs, (3) the potential impact of improved matching between ABCRE treatments, (4) the innovation of oral DMTs, (5) the potential impact of improved matching between oral DMTs, (6) the innovation of infusion DMTs, and (7) the potential benefit of risk assessment for Tysabri.

1. Innovation of Betaseron   Betaseron, approved in 1993, was the first DMT for MS. As shown in Table 4, Betaseron provides patients with 0.34 QALY relative to no DMT, has an adherence rate of 52 percent, and has a market share of 10 percent (or roughly 23,400 patients per year).

To measure the health impact of Betaseron, I compare the market for MS with no DMT and a but-for world where Betaseron is the only DMT. I assume that in this but-for world all interferon patients and 63 percent of Copaxone patients (the share of actual Copaxone patients that are tolerant of interferon treatments) would be on Betaseron (Bergvall *et al.* 2014). .[28] As a result, the introduction of Betaseron provided 0.34 QALYs of treatment for 76 percent of the market (or 178,000 patients) for a total health impact of roughly 61,000 QALYs.

2. Innovation of other ABCREs   After Betaseron's entry to the market, the other ABCRE treatments (Avonex, Copaxone, Rebif, and Extavia) hit the market between 1996 and 2009. The introduction of these treatments had several effects. First, they expanded the market by the 21 percent of the market (or 63 percent of actual Copaxone patients) who could take Copaxone but not an interferon. Second, the introduction of the other ABCRE treatments made higher efficacy and adherence treatments available. For instance, Copaxone, with an efficacy of 0.41 QALY and an adherence rate of 55 percent, has a higher efficacy and adherence rate than Betaseron.

To determine the increase in health impact from the other ABCRE treatments, I measure the share of patients who failed or did not fail on treatment.[29] Failure is defined by either switching to a different first line treatment or switching to a second line treatment after being on treatment for less than 2 years. I assume that patients who failed their treatment received a health impact similar to a patient who was randomly assigned a treatment (h_1) and a patient who did not fail their treatment received a health impact similar to a patient who was assigned their optimal treatment (h_2).

The introduction of the ABCREs increased the health impact of MS treatments by 22,000 QALYs or a 36 percent increase in the total health impact.

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[28] There are four interferon treatments, Avonex, Betaseron, Extavia, and Rebif, which compose 55 percent of the market)

[29] These shares are taken from Gajofatto *et al.* (2009).

3. Potential of ABCRE Heterogeneity Using the distribution of health impact for each of the treatments (shown in Table 1) and the covariance table found in Appendix 3, I estimate the potential impact of personalized medicine to match patients to their highest individual treatment effect across the different ABCRE treatments.

I assume that the individual health impact from Avonex and Rebif (which are both interferon beta 1-a) and from Betaseron and Extavia (which are both interferon beta 1-b) are perfectly correlated because they are the same molecule. Since Avonex and Rebif have different modes of administration, this assumption provides a conservative estimate of the potential impact of heterogeneity.

	Mean	Standard Deviation
Avonex	0.20	0.08
Betaseron	0.34	0.14
Copaxone	0.41	0.20
Extavia	0.34	0.14
Rebif	0.20	0.08

Table 1: Distribution of Health Impact of ABCRE Treatments

The health impact of the actual distribution of patients across treatments increases the health impact by 63 percent relative to patients being randomly distributed across treatments. The maximum potential health impact given this distribution provides an 18 percent or 14,000 QALY increase compared to how patients and physicians choose treatments in the real world.

4. Innovation of Oral Treatments The three oral treatments, Aubagio, Gilenya, and Tecfidera, entered the market between 2010 and 2013. These treatments altered the MS landscape by offering an alternative form of treatment administration. They also offered improved efficacy over the existing ABCRE treatments for early line patients. The oral treatments expanded the market by the six percent of oral treatment patients that were not on any MS treatment before taking an oral treatment.[30] In addition, the oral treatments increased the maximum health impact by a first line treatment by 0.19 QALY.

As a result, the introduction of the oral treatments increased the health impact by 18 percent over ABCRE treatments which resulted in an increase of 15,000 QALYs.

5. Potential of Oral Treatment Heterogeneity As with the ABCRE treatments, properly matching patients with treatments considering patient heterogeneity has a potential to increase the health impact of treatments. The distribution of health impact across the oral treatments is listed in Table 2.

The health impact of the current distribution of patients across treatments increases the health impact by 100 percent relative to patients being randomly distributed across treatments. The maximum potential

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[30]See MS in America (2014).

	Mean	Standard Deviation
Gilenya	0.60	0.27
Aubagio	0.32	0.34
Tecfidera	0.59	0.23

Table 2: Distribution of Health Impact of Oral Treatments

health impact given this distribution provides am 18 percent increase over the current distribution. As a result, personalized medicine that improves the ability of patients to identify the oral treatments with the highest impact can improve the average health impact of these patients by 17,700 QALYs.

6. Innovation of Infusion Treatments The innovation of infusion treatments, especially Tysabri, not only brought a new form of treatment administration to the market but also an increase in efficacy. The infusion treatments increased the market by 3 ppts since 35 percent of infusion patients were new to the market (in other words they were not patients that would have been on another treatment in the absence of the infusion treatments) and infusion treatments compose 9 percent of the market (Biogen, 2008). In addition, the infusion treatments provide 1.70 QALY over the next highest treatment in terms of efficacy.

As a result, the infusion treatments increased the total health impact by 60 percent or almost 58,000 QALYs.

7. Potential of Tysabri Risk Assessment As discussed previously, Tysabri not only brought an increase in efficacy but also the potential for a very serious side effects.[31] Tysabri's PML side effect was not known at the time of the FDA approval. Instead, the treatment was on the market for almost three months when Biogen, the maker of Tysabri, learned about one confirmed and two suspected cases of PML. As a result, Tysabri was temporarily pulled from the market until it was allowed to be reintroduced to the market roughly one and a half years after learning about the PML side effect.

Since the PML side effect was learned after Tysabri was on the market, I back out the effect that PML has on Tysabri consumption to measure the potential effect of a PML diagnostic test. First, prior to learning about PML, industry analysts expect Biogen sales to exceed 87,000 patients per year which amounts to over 40 percent of market share.[32] Second, when information about Tysabri's link to PML came out, Biogen's stock dropped 44 percent or $10 billion which is consistent with an expected market share of Tysabri above 33 percent.[33] Third, before the information about Tysabri's link to PML was known, industry projection

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[31] It was recently discovered that Tecfidera also poses a PML risk.

[32] Wall Street Journal (2005). Tysabri was expected to sell over $2 billion per year at $23,000 per year. For a market with 210,000 patients, which is roughly the market size in 2009, this would amount to over 40 percent of the market.

[33] See http://www.fool.com/investing/high-growth/2005/03/08/after-the-crash-is-biogen-idec-a-buy.aspx. If Avonex was responsible for the entire $12 billion remaining market share, had 40 percent market share, and had a nearly identical price to Tysabri, this suggests that Tysabri's market share would be in excess of 33 percent market share

models predicted that Tysabri would have a market share that rose from 15 percent in 2005 (the treatment's first full year on the market) and would stay around 35 percent through 2015.[34] Finally, these estimates are consistent with an estimate based on physician perceptions. If the only patients in the current market that are prescribed Tysabri are patients with physicians who feel the benefits of Tysabri outweigh the costs (roughly 65 percent of physicians) and are JCV negative (55 percent of patients), then Tysabri's 9 percent market share would be over 25 percent in a world with perfect information about a patient's PML risk.[35]

All of these examples suggest that Tysabri would have a market share between 25 and 40 percent of the market with a diagnostic test that provides perfect information about a patient's PML risk. To be conservative and allow for the introduction of other treatments that were not on the market in 2005, I assume Tysabri would have a 20 percent market share if it did not have any PML side effect. By comparison the number of PML cases in the US from 2005 to 2015 was 165.[36]

As a result, a perfect PML diagnostic test that could correctly identify the PML side effect would have allowed over 12 percent of the MS market to take Tysabri while restricting it to the hundreds of patients that were subjected to PML.[37] The health impact of putting 12 percent of the market that is not at risk for PML onto Tysabri relative to the treatment with the next highest health impact (0.60 for Gilenya compared with 2.30 for Tysabri) would increase the total health impact by almost 47,000 QALYs or 30 percent from the current market.[38]

Although conservative in the 20 percent market share, this estimate serves as an upper bound for a PML diagnostic test since the diagnostic test would not perfectly sort patients. The health impact of an actual diagnostic test would depend on its accuracy.

Breakdown Table 3 breaks down what share of the total health impact discussed in the previous sections, come from each of the seven events.

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[34] http://www.fool.com/investing/small-cap/2004/12/07/spin-the-medicine-bottle.aspx

[35] http://i.bnet.com/blogs/tysabri-confidence-survey_figure-2.jpg

[36] http://wasmain.nationalmssociety.org/site/DocServer/PML._MS_Summit_2015.pdf?docID=75816.

[37] There is already a diagnostic test on the market for JCV. In a step toward incorporating personalized medicine into MS treatments, in 2012, the FDA approved the Stratify JCV Antibody ELISA test, which helps identify patients who are more prone to PML. This diagnostic test tells if a patient is anti-JCV antibody positive or negative. If the patient is anti-JCV antibody negative, they have a lower than 1 in 1,000 risk of developing PML. If the patient if anti-JCV antibody positive, that risk is between 6 and 13 in 1,000 depending on prior treatments. However, 70 to 90 percent of the population has the JCV virus, so the test is not very informative about a patient's actual risk factors (Holland and Nall, 2015). However,this test was not on the market for most of the period of interest so the vast majority of MS patients did not have access to JCV diagnostic test before taking Tysabri.

[38] Lemtrada is currently the second highest treatment on the market, but it has not been on the market long so it would not have a significant impact during the 2005 to 2015 time period.

Health Impact as a Share of Total Health Impact

Noval and Incremental Innovation

Innovation of Betaseron	26%
Innovation of ACRE	9%
Innovation of Oral Treatments	6%
Innovation of Infusion Treatments	25%
Total	66%

Potential Impact of Personalized Medicine

Within ABCRE Treatments	6%
Within Oral Treatments	8%
Potential of Tysabri Risk Assessment	20%
Total	34%

Table 3: Health Impact by Type of Innovation as a Share of Total Health Impact

This breakdown shows that personalized medicine events in MS have the potential to increase the health impact of treatments by over 50 percent (=0.34/0.66). The potential health impact of personalized medicine is split between improving the matching process of patients to treatment through the individual treatment effect and risk assessment for serious side effects.

Betaseron had the largest impact even in large part because it was the first treatment on the market and the infusion treatments had the second largest impact because they were had the highest efficacy. The potential impact of a Tysabri risk assessment shows that Tysabri would have by far the largest health impact if the PML risk were better identified.

The impact of perfectly sorting patients on both ABCRE and oral treatments is roughly equivalent to the impact of the seven treatments (Avonex, Copaxone, Rebif, Extavia, Gilenya, Aubagio, and Tecfidera).

5 Value of and Incentives to Engage in Personalized Medicine Innovation

Up to this point, this paper has focused on the health impact of personalized medicine. In this section, I discuss the value of this personalized medicine, defined as the health impact divided by the cost of creating the innovation, as well as the incentive for individual firms to engage in R&D in personalized medicine.

It is difficult to measure the R&D cost of creating personalized medicine because R&D costs are generally not observed and there are so many different ways to create personalized medicine. There are three broad ways to categorize innovations in personalized medicine: innovations that create new treatments, innovations create a diagnostic test for existing treatments, and innovations that predict a patients response to a treatment through data on patient characteristics.

For innovations that create new treatments, the cost to create an innovation in personalized medicine is likely to be even higher than the cost of a standard novel innovation. For a standard novel innovation, where new molecules cost in excess of $2.5 billion, a large share of the cost comes from the clinical trials that are required for FDA approval (DiMasi *et al.*, 2016). For personalized innovations, the clinical trials are more complex because there is a narrower patient population that respond to the targeted therapies, which increases the cost of patient recruitment, and standard protocols may need to be enhanced to determine the safety and efficacy of each treatment, including improved diagnostic and data collection (PhRMA, 2015).

For innovations that create a diagnostic test, the cost of creating a personalized innovation is likely to be a cheaper but potentially still a risky form of R&D. Rough estimates put the developement costs at $250 million to $300 million, or roughly 10 to 12 percent of the cost of a new treatment (McKinsey and Company, 2013). Even after Tysabri was pulled from the market for the potential of PML and foregoing potential revenues in excess of $1 billion per year, it took nearly seven years to get the first PML diagnostic test approved by the FDA. However, the cost of this diagnostic test is likely to be significantly less than the cost of funding a novel, competitive treatment for Tysabri.

Innovations that predict a patients response to a treatment through data on patient characteristic are likely to be significantly cheaper to develop. For example, the Rio Score is a scoring system that combines patient characteristics, including clinical and MRI parameters, to predict whether a patient will fail on a treatment (Rio *et al.*, 2009).[39] After one year of therapy, 92 percent of patients with a Rio Score of 2 or 3 failed on their treatment while 8 percent of patients with a Rio Score of 0 or 1 were failed their treatment (Hyun *et al.*, 2015). Tests like these are far cheaper forms of innovations but can have significant effects on health impact.

It is well documented that profit is a major driver of a firm's decision to engage in pharmaceutical innovation.[40] Firms have different incentives regarding the incentive to engage in personalized medicine

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[39]The Rio Score is the count of how many of the following conditions are met: (1) more than 2 active T2 lesions on an MRI, (2) at least 1 relapse, and (3) and increase of EDSS score by at least 1 point sustained over at least six months. Failure was defined as having any of the following: switched therapy due to failure, clinical relapse, or EDSS progression.

[40]See Acemoglu and Linn (2004).

depending on how the personalized information affects expected profits. Profits for treatment t are:

$$\Pi_t = q_t(p_t - c_t) - r_t$$

where q_t is the number of patients, p_t is the price per patient, c_t is the cost per patient, and r_t is the R&D cost of t. The main effect of personalized medicine is through the number of patients.

Personalized medicine that affects the active or passive searching over treatments has two effects on profits. First, there is a redistribution of patients between treatments. Consider the extreme case of switching from no information about individual treatment effects to perfect information about treatments effects, the redistribution moves patients away from the treatment with the highest average treatment effect (which all patients would take) to the other treatment depending on the distribution of each treatment and the correlation of the treatments. This redistribution gets more complicated when there is more noise in a patient's signal of his individual treatment effect.

The second effect is that information can cause the total number of patients on treatment to change. For instance, in the market for infusion MS treatments, more patients could start treatment because they know they will not get PML and some patients may stop taking treatment because they learn they are at risk for PML and are not satisfied with the other treatments on the market.

For risk assessment, there is a strong incentive for firms to engage in personalized medicine when their product has an uncertain side effect risk. The reason, as discussed previously in this paper, is that uncertainty about a potentially serious side effect can cause patients to avoid a product. For example, Biogen, the firm that produces Tysabri, forgoes in excess of $1 billion per year by patients avoiding the treatment due to the potential of PML.[41] It is no surprise that Biogen is the firm behind the Stratify JCV Antibody ELISA test as well as investing in other research topics including a PML vaccine and two anti-PML treatments.[42]

6   Conclusion

The potential of personalized medicine comes from its ability to either create treatments that address the heterogeneity across patients or in the ability to provide information to patients that can improve the health impact of existing treatments. This paper explores the potential magnitude of the latter effect for MS treatments.

I find that several factors influence the health impact of personalized medicine. Personalized medicine has

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[41]The $1 billion estimate comes from the potential of Tysabri loosing over 10 percent of the $14 billion annual MS market.
[42]http://www.xconomy.com/boston/2009/11/19/tysabri-the-ms-drug-haunted-by-deadly-side-effect-doesnt-look-so-deadly-anymore/4/.

a greater potential health impact when treatment effects are less correlated across treatments, the variance of the distribution of health impacts is larger, there is less noise in an individual's signal of their treatment effect, and there are more treatment options.

These results suggest that there is significant potential for personalized medicine in MS due to the heterogeneity in the MS population, disease course, and treatment response and twelve DMTs that vary in their efficacy and administration. I find that personalized medicine has the potential to increase the health impact of MS patients by over 50 percent.

One extension of this work is understanding the value of me-too innovations or evergreening, which are innovations that are considered to be slight modifications of existing treatments. The conventional wisdom is that these innovations provide little to no value and waste resources (see, eg., Collier, 2013). With personalized medicine, me-too innovations can provide a health impact even if they have a lower average treatment effect than similar existing products if the treatment effects are not well correlated across treatments. This result suggests that me-too innovations are more valuable in a world with personalized medicine.

Three areas for future research in personalized medicine are, first, estimating the R&D costs to get a better understanding of the value of investments in personalized medicine. Second, using data of how and why patients switch between treatments to understand the value of improving the ability to match patients to treatments in a dynamic method, similar to Egan and Philipson (2014). This type of analysis is ideally suited to patient level data that includes a patient's treatment history and the disease progression over time. Third, there are currently eight established biomarkers and at least six potential biomarkers in MS and it would be valuable to understand how much health impact could be gained if these biomarkers could be more effectively integrated into determining individual treatment effects (Derfuss 2012).

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Appendix 1: MS Treatments

Treatment	Company	Molecule	Year of FDA Approval	Mode of Administration	Health Impact (QALY)	Standard Deviation of Health Impact	Adherence	Market Share (2005-2015)
Betaseron	Bayer	Interferon beta-1b	1993	Subcutaneous injection	0.34	0.14	52%	10%
Copaxone	Teva	Glatiramer Acetate	1996	Subcutaneous injection	0.41	0.20	55%	33%
Avonex	Biogen	Interferon beta-1a	1996	Intramuscular injection	0.20	0.08	62%	28%
Rebif	Serono/ Pfizer	Interferon beta-1a	2002	Subcutaneous injection	0.20	0.08	59%	17%
Tysabri	Biogen	Natalizumab	2004	Infusion	2.30	-	75%	8%
Extavia	Novartis	Interferon beta-1b	2009	Subcutaneous injection	0.34	0.14	52%	0%
Gilenya	Novartis	Fingolimod	2010	Oral	0.60	0.27	55%	0%
Aubagio	Sanofi	Teriflunomide	2012	Oral	0.32	0.34	55%	0%
Tecfidera	Biogen	Dimethyl Fumarate	2013	Oral	0.59	0.23	55%	4%
Lemtrada	Sanofi	Alemtuzumab	2014	Infusion	1.54	-	93%	1%
Plegridy	Biogen	Pegylated interferon beta-1a	2014	Subcutaneous injection	0.20	0.08	62%	0%
Glatopa	Sandoz	Glatiramer Acetate	2015	Subcutaneous injection	0.41	0.20	55%	0%

Sources: Listed in Appendix 2.

Table 4: Summary of MS Treatments

Notes: ABCRE treatments are shown as solid lines and all other treatments are shown as dashed lines. Extavia, Gilenya, Glatopa, Lemtrada, and Plegridy are not shown due to low market shares.
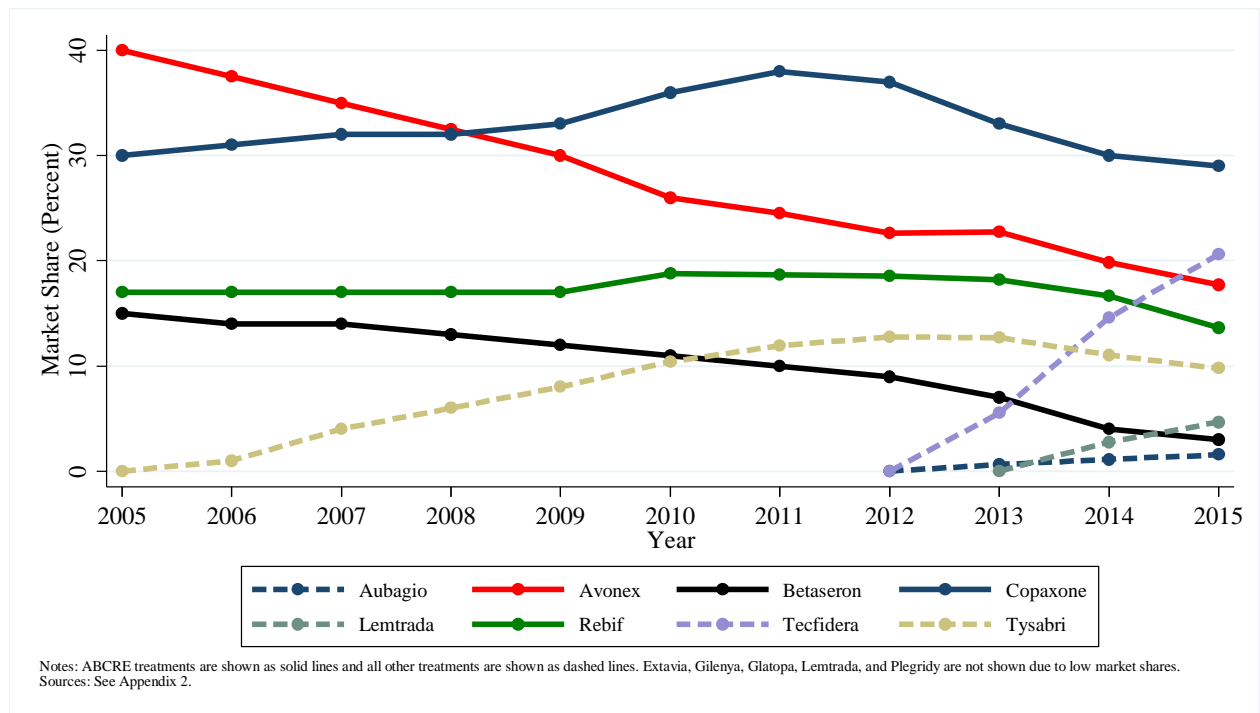Sources: See Appendix 2.

Figure 5: Market Share of MS DMTs, 2005-2015

Appendix 2: Data

Health Impact/Efficacy Data For the efficacy measurement, I mainly use the Tufts Medical Center Cost-Effectiveness Analysis Registry (CEAR). CEAR includes over 4,800 pharmaceutical cost-utility analyses

in the peer-reviewed medical literature. It is intended to be a comprehensive dataset of all cost-utility articles analyzed by trained professionals, who rate the quality of the study and provide information about the quality level and quality relative to the standard of care found in the study. The dataset lists the drug's name or active ingredient; the drug's disease class, which can be uniquely mapped into my 19 disease classes; and the year of the study. The dataset includes fifteen studies that list the QALY of treatments for all ABCRE treatments and Tysabri. I take the average across studies for treatments that have multiple studies. For the oral treatments, I use estimates from Pistoresi (2015) and for Lemtrada, I use an estimate from the Scottish Medicines Consortium (2014).

The estimates of standard deviations are taken from estimates in Prosser *et al.* (2003) and Pistoresi (2015).

Adherence Data Adherence is a measure of whether patients are taking their treatment as prescribed and with the proper frequency. A patient is generally defined to be adherent if he possesses medication for at least 80 percent of the time they are active on treatment. I get adherence estimates from published studies in medical journals. Specifically, for all ABCRE treatment, I use adherence estimates from Halpern *et al.* (2011), which estimates adherence rates from 6,680 MS patients from 2000 to 2008 on ABCRE treatments. For oral and infusion treatments, I use estimates from Dionne *et al.* (2015) which compares adherence rates for 209 MS patients. These rates are generally consistent with those found in other published studies including Treadaway (2009), Devonshire *et al.* (2011), and Reynolds (2010).

Patient Count Data I take patient count estimates published estimates from Symphony Health Solutions.[43] Since these data are in revenues, I convert them to patients using cost estimates from Hartung *et al.* (2015). I supplement this data with estimates published from Biogen documents, the producer of Avonex, Plegridy, Tecfidera, and Tysabri, published by the SEC which primarily use IMS data.[44]

Appendix 3: Covariance Estimation

I estimate the covariance between treatment impacts using two observational studies of patients who switch therapies (Gajofatto *et al.*, 2009 and Rio *et al.*, 2002). The covariance could also be estimated using a micro-level dataset that tracks a patient's treatment and response to treatment such as the Sylvia Lawry Centre MS Patient Database.

I estimate two covariances with this data. First, I estimate the covariance in treatment outcomes between

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[43]See http://symphonyhealth.com/wp-content/uploads/2013/06/Tecfidera.inThought.4Mar.pdf.
[44]See Biogen (2008).

a patient on two different interferons. Second, I estimate the covariance in treatment outcomes between a patient on an interferon and Copaxone. I do not have data on oral treatments so I assume that oral treatments have the same covariance as an interferon with Copaxone. Since I do not have the patient's treatment impact in QALYs, I use the covariance between treatment failure as a proxy. I define treatment failure for the second treatment as patients free from relapse. Table 5 shows the share of patients from Gajofatto *et al.* (2009) that fall into each combination of treatment pair and treatment result (failure/success). I observe aggregate counts of patients who fail or not on their first treatments. However, I do not observe what a patient who has a success with their first treatment would do on a second treatment. As a result I assume that the probability of success on treatment A given the success of treatment B is proportional to the probability of failure on treatment A given failure of treatment B.

First Treatment	Result on First Treatment	Second Treatment	Result on Second Treatment	Share of Patients
Copaxone	Failure	Interferon	Success	6%
Copaxone	Failure	Interferon	Failure	1%
Copaxone	Success	Interferon	Success	12%
Copaxone	Success	Interferon	Failure	1%
Interferon	Failure	Copaxone	Success	2%
Interferon	Failure	Copaxone	Failure	2%
Interferon	Success	Copaxone	Success	38%
Interferon	Success	Copaxone	Failure	38%
				100%
Interferon 2	Failure	Interferon 1	Success	16%
Interferon 2	Failure	Interferon 1	Failure	9%
Interferon 2	Success	Interferon 1	Success	48%
Interferon 2	Success	Interferon 1	Failure	26%
				100%

Table 5: Failure Correlation Calculation

The resulting covariances are list in Table 6.

Treatment 1	Treatment 2	Correlation	Covariance
Interferon A	Interferon B	0.13	0.03
Interferon	Copaxone	0.10	0.02

Table 6: Failure Correlation Calculation