NON-ADHERENCE AND PERSONALIZED MEDICINE:

A POSITIVE AND NORMATIVE ANALYSIS

by

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Abstract:

Non-adherence in health care results when a patient does not initiate or continue care that a provider has recommended. Previous researchers have identified non-adherence as a major source of waste in US health care, totaling approximately 2.3% of GDP, and have proposed a plethora of interventions to raise adherence. However, health economics has provided little explicit analyses of the important and dynamic demand behavior that drives non-adherence, and it is often attributed to uninformed patients. We argue that whereas providers may be more informed about the population-wide effects of treatments, patients are more informed about the individual value of a treatment. We interpret a patient's decision to adhere to a treatment regime as an optimal stopping problem in which patients learn the value of a treatment through experiencing it. We derive strong positive and normative implications resulting from interpreting non-adherence as an optimal stopping problem. Our positive analysis derives an "adherence survival function," depicting the share of patients still on treatment as a function of time, and predicts how various observable factors alter it. Our normative analysis derives the efficiency effects of non-adherence and the conditions under which adherence is too high or low. We consider the efficiency implications of this analysis for common adherence interventions. We argue that personalized medicine, by replacing learning through experience with a companion diagnostic, speeds up our leaning process and raises efficiency through cutting over-adherence. We assess the quantitative importance of these implications by calibrating the degree of over- and under-adherence for one of the largest US drug categories, cholesterol-reducing drugs. Contrary to frequent normative claims of under-adherence, our estimates suggest the ex-post efficiency loss from over-adherence is over 80% larger than from under-adherence, even though only 43% of patients fully adhere.

Section 1: Introduction

Improving adherence to prescribed medical treatments remains a universally agreed-upon and widespread challenge in health care. In the United States, estimates show that non-adherence is wasteful;[2] the New England Healthcare Institute (2009) estimates that the annual cost of non-adherence in the United States is approximately $290 billion, equating to about 13% of total health care spending, or 2.3% of GDP. Improving medical adherence through both private and public interventions has been identified as a crucial step toward improving health outcomes and lowering health care costs.[3] Recent technological advancements have targeted medical adherence, for example, electronic and educational messaging systems (Baum 2013, Comstock 2013, Vollmer et al. 2011), as well as technology designed to help providers identify non-adherent patients (Lesselroth et al. 2011). In the United States, The Patient-Centered Outcomes Research Institute (PCORI), the Agency for Healthcare Research and Quality, and the National Institutes of Health, among other government bodies, dedicate substantial funding to support research on raising medication adherence (Pharmaceutical Research and Manufacturers of America 2013). An enormous literature outside of economics on the prevalence of non-adherence and its consequences has driven these efforts. Indeed, since 1996, an estimated more than 25,000 peer-reviewed medical articles have been published on patient adherence or compliance (Chernew 2008). The overall implicit concern of this vast literature is that adherence is too low and that private or public interventions are needed to raise adherence. Although many analysts stress inadequate patient adherence in both economic and medical circles, one should be cautious about bystanders' claims of under-consumption.

[2] See Bosworth et al. (2011) for further discussion.
[3] See Black et al. (1987), Feldman et al. (1998), Flack et al. (1996), Haynes et al. (1996), Hershey et al. (1980), Mallion et al. (1998), and Nelson et al. (1980).

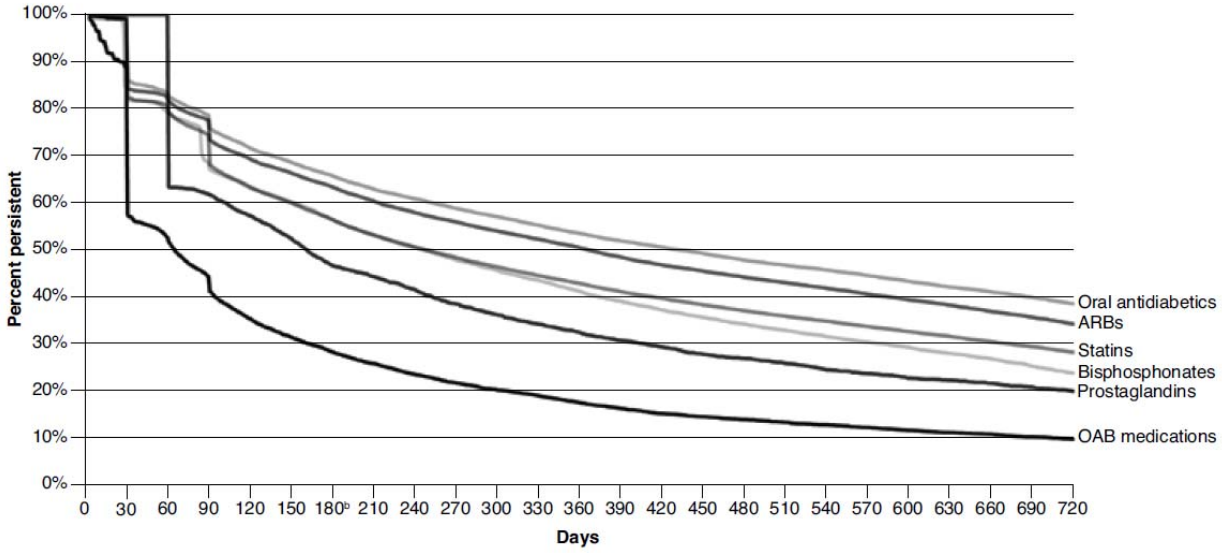
Despite the great concerns regarding under-adherence, little explicit economic analysis examines the dynamic demand behavior resulting in non-adherence that offers predictions about the conditions under which it is more likely to occur than not. Without an empirical validation of such a positive theory, making credible normative claims that adherence is too low is difficult. To this end, this paper provides an explicit analysis of non-adherence and derives its positive and normative implications.

We interpret non-adherence as an optimal stopping problem for a patient learning about her individual value of a therapy. Although providers recommending treatments are likely more informed about the population-wide effects of these treatments, patients experiencing a treatment are more informed about its individual specific value. This individual value of treatment incorporates how the patient trades off patient-specific treatment effectiveness, side effects, and costs of care. In our analysis, a patient's prior beliefs about a treatment coupled with the patient's experience with the treatment drive initiation and subsequent adherence. The patient behavior mimics the common-sense approach of using a treatment, assessing its value, and discontinuing if it is not valuable. Non-adherence is thus inherently a dynamic demand behavior that requires an explanation of why people initiate but then discontinue therapy.

Our positive analysis of non-adherence as an optimal stopping problem offers many testable implications. As patients learn about the treatment, they will become more informed over time, implying that good patient–treatment matches last, but bad ones do not. More precisely, we derive an "adherence survival function" depicting the share of patients still on treatment as a function of time, and show how various observable factors affect adherence. We predict that non-adherence occurs early in the sense that adherence decisions stabilize with sufficient learning about treatment value. We also predict that education has non-trivial effects

on adherence because it interacts with patient-level treatment effects; more educated individuals adhere longer to valuable care, but shorter to what turns out to be invaluable care for them.[4] In addition, we predict that the quality of providers and their communication with patients are likely to affect short-run rather than long-run adherence behavior. Figure 1 below depicts adherence behavior that the medical literature reports across several treatment classes. It displays the general pattern that non-adherence occurs early, which we interpret as patients learning about treatment value over time.

FIGURE 1: ADHERENCE SURVIVALS ACROSS TREATMENT CLASSES (YEAW ET AL. 2009)



Notes: Figure 1 illustrates observed adherence patterns for prostaglandin analogs, statins, bisphosphonates, oral antidiabetics, angiotension II receptor blockers (ARBs), and overactive bladder (OAB) medications. This figure is taken directly (Figure 2) from Yeaw et al. (2009).

Non-adherence that such patient learning drives produces many surprising normative implications. In particular, we argue that separating ex-ante from ex-post efficient adherence is

[4] Such effects are the analog to uneducated individuals adhering more to smoking after it was discovered that cigarettes had the "side-effect" of inducing cancer.

important. When learning about personalized treatment value, patients act in an ex-ante optimal fashion given their treatment beliefs. However, adherence may be ex-post inefficient in that some patients adhere to what turns out to be non-valuable care for them, whereas others do not adhere to what turns out to be valuable for them. Therefore, those who turn out to not value care display ex-post over-adherence, and those who do value care display ex-post under-adherence . We argue that such over-adherence vanishes over time as patients eventually learn that they do not respond to the therapy. However, under-adherence is permanent if the patient does not re-adhere.

This analysis has strong implications for the effects of private and public interventions aimed at altering adherence behavior. We distinguish between interventions that have symmetric versus asymmetric effects on responders and non-responders. We stress the indeterminate welfare effects of interventions with symmetric effects, such as copay reductions to raise adherence, because they customarily raise adherence of both groups. We stress the unrecognized but intimate relationship between personalized medicine and ex-post efficient adherence. Testing for treatment value before undertaking therapy involves changing the therapy from an experience good, for which consumption experience is required to determine its quality, to a search good, for which it is not. Personal medicine essentially speeds up our learning process and is an asymmetric intervention that eliminates inefficient adherence for both responders and non-responders. The value of personalized medicine is the highest when learning through experience is costly relative to learning through a diagnostic, which explains its emergence in cancer care, where over-adhering to the wrong therapy may be fatal. The fact that personalized medicine reduces harmful over-adherence is in direct contrast to the common belief that adherence is generally too low.

To assess the quantitative importance of these implications, we calibrate the ex-post efficiency effects in the case of the cholesterol-reducing drug simvastatin (Zocor). Interestingly, our calibration results imply the vast majority of the efficiency loss comes from over-adherence, as opposed to under-adherence, even though less than half of patients adhere. In particular, we find that the ex-post efficiency loss from over-adherence is over 80% larger than that from under-adherence. In this context, we stress that the common argument that patients under-adhere because they do not understand the treatment benefits seems unsatisfactory, because those perceived benefits presumably made them start the therapy in the first place.

This paper relates to several strands of previous analysis. A large literature on health care demand starts with Grossman (1972), but we are not aware of any explicit analysis of the dynamic demand behavior that is inherent in non-adherence. Elsewhere (Seabury et al. 2014), we have provided a partial review of the vast empirical health services research literature on the extent of non-adherence. This paper relates most closely to, and may be viewed as the direct post-marketing analog of, Philipson and Hedges (1998) and Philipson and Desimone (1997), who analyze the effects of attrition in clinical trials when patients learn about treatments from their own experience when investigators learn about population-wide effects from aggregate data. The paper also relates to later structural estimation papers such as Crawford and Shum (2005) and Dickstein (2014), but their papers do not consider the positive or normative analysis of adherence behavior discussed here. Goldman et al. (2007) and Chernew et al. (2008) report estimates of negative price elasticities for this type of health care demand. In the general economics literature, this paper is most closely related in spirit and structure to the labor literature on job turnover (Jovanovic 1979), where matching workers to jobs is the analog of matching patients to treatments.

The paper is briefly outlined as follows. Section 2 sets up the model and derives the implied adherence survival functions. Section 3 discusses the large set of positive implications regarding the effects of observable factors on the adherence survival function. Section 4 discusses the normative implications for efficient adherence and the role of personalized medicine in terms of an asymmetric adherence intervention. Section 5 calibrates the size of efficiency effects for the cholesterol-reducing drug simvastatin. Lastly, Section 6 concludes with a discussion of several future research avenues that the explicit analysis of this type of demand behavior suggests.

Section 2: Non-Adherence as an Optimal Stopping Problem

In this section we derive the positive implications of interpreting non-adherence as an optimal stopping problem when a patient learns about her own personal treatment value given prior knowledge about population wide effects.[5] Following Philipson and Desimone (1997), we assume the patient decides whether to initiate the treatment regime with limited information regarding the value of the treatment. By initiating treatment, the patient learns if she values the treatment and then decides to continue to adhere or stop the treatment depending on whether or it is valuable. We are interested in the observable conditions under which so called *primary* adherence occurs, the patient initiates the treatment, as well as when *secondary* adherence occurs, the patient continues after initiation.

We assume that there is a continuum of patient types or true quality levels or treatment effects denoted by q and distributed according to $F(\cdot)$. These treatment effects correspond to the patient-specific "quality" of the product the treatment represents. This level of quality represents

[5] Our model is similar in spirit to Jovanovic's (1979) and Ljungqvist and Sargent (2006) analysis of job turnover.

all health related outcomes and throughout the paper is interpreted as a *net benefit* index of inclusive of treatment effectiveness, side effects, and any other effects on a patient's health. For example, the quality may represent quality-adjusted-life-years (QALY) net of side effects.

The health of the patient in a given period reflects the quality of the treatment plus some idiosyncratic shock (noise) according to

$$h_t = q + \varepsilon_t$$

Thus, the observable health of the patient depends on the unobservable quality of treatment q as well as other unobservable factors, ε_t. For example, a reduction in pain or body temperature may be due to a treatment or the body healing itself naturally. Patients only observe health outcomes, h_t, and do not separately observe q and ε_t. Thus, the patient cannot infer treatment quality immediately from their health outcomes but learns it over time.

The period utility from the treatment is given by $U(h_t, p)$ where

$$U(h_t, p) = h_t - \gamma p$$

The parameter γ represents patient's health consumption trade-off. Utility is distinct from the effectiveness or health; effective treatments may have little value and low adherence by a patient not concerned with the condition being treated. If not on treatment, the patient has access to an alternative treatment with per period utility (h_A, p_A) where both h_A and p_A are known with certainty.[6]

Patients have a prior over the quality of the treatment, $F_0(\cdot)$. We assume that each patient's initial prior beliefs reflect the true distribution of treatment heterogeneity such that $F_0(\cdot) = F(\cdot)$. This may be interpreted as patients agreeing with providers, perhaps through provider communication, about the population wide effects of treatments before learning about

[6] In the Appendix, we derive the analog implications for the case of multiple treatments which we interpret to include partial adherence levels of a single treatment.

their individual value of care. For example, this prior may be the result of knowing summary statistics of the distribution of treatment effects from the labeling of the product, obtained from clinical trials in the approval process. We denote a patient's prior at time t as $F_t(\cdot\,|\vec{h}_t)$ where $\vec{h}_t$ is the history of personal health outcomes on the treatment. Under the maintained assumption that treatment quality and noise/shocks are normally distributed, $q \sim N(\mu, \sigma^2)$ and $\varepsilon_t \sim N(0, \sigma_\varepsilon^2)$, standard normality results imply that a patient's posterior distribution over their treatment effect is given by

$$F_t(q, \vec{h}_t) = N\left(\omega_t \bar{h}_t + (1-\omega_t)\mu_0, \left[\frac{t}{\sigma_\varepsilon^2} + \frac{1}{\sigma_0^2}\right]^{-1}\right), \omega_t = \frac{\sigma_0^2}{\frac{\sigma_\varepsilon^2}{t} + \sigma_0^2} \quad (1)$$

where the patient's initial priors are $F_0(\cdot) = N(\mu_0, \sigma_0^2)$.

The patient optimally updates his beliefs about the quality of the treatment based on weighting the average health outcomes, $\bar{h}_t$, and his initial prior. With each observation the patient places more weight on his treatment experience and less on his prior. In addition, his posterior variance decreases after each treatment experience over time. In other words, the longer a patient has been in treatment, the more he learns about the quality of the treatment and the more his belief is informed by his own experience rather than any beliefs prior to initiating the treatment, such as the population-wide beliefs offered by the provider.

Given these beliefs about the personal treatment effect, the patient's value function after t rounds of treatments is given by

$$V(h_t, \vec{h}_t, F_0) = U(h_t, p) + \beta \max\left\{E\left[V(h_{t+1}, \vec{h}_{t+1}, F_0)\,|F_t\right], \frac{U(h_A, p_A)}{1-\beta}\right\}$$

The patient elects to adhere to treatment only if the expected value of staying on the treatment is larger than going on the alternative treatment from there on. The future is discounted according the parameter β which may induce differential adherence across treatments with differences in

timing of benefits and costs. For example, a patient may adhere perfectly to a pain medicine while adhering poorly to a cholesterol reducing drug given the immediate benefit of the former and delayed benefit of the latter.

Once a patient elects to forgo treatment for the alternative treatment, he will find it optimal to continue the standard care in all proceeding periods.[7] Patients will never find it optimal to "re-adhere" to the treatment regime. As before, because of the future option value of continuing treatment, a patient may elect adhere to treatment even if the expected future period return is lower than that of the alternative treatment.

It is well established that the optimal stopping behavior for this type of learning is characterized by a treatment performance threshold (Gittins and Jones 1974, Gittins and Jones 1979).[8] This implies that non-adherence occurs when the average experience on treatment $\bar{h}_t$ is below a certain threshold level, here denoted z_t. In other words, a patient remains in treatment as long as their average treatment experience, $\bar{h}_t$, is greater than the threshold z_t. The optimal stopping rule or threshold, z_t, is a function of the patient's prior mean and variance as well as the distribution of the treatment/signal noise.

Adherence behavior conditional on patient type (q) is characterized by survival function $S(t|q)$ which reflects the proportion of type q individuals remaining in treatment at time t.

$$S(t|q) = \Pr(h_1 > z_1, \bar{h}_2 > z_2, \dots, \bar{h}_t > z_t|q)$$

The overall survival function of adherence thus results from aggregating over all types

[7] Suppose patients potentially found it optimal to reenter treatment. Consider the patients decision to continue treatment after receiving n rounds of treatment

$$\max\left\{E\left[V\left(h_{n+1}, \vec{h}_{n+1}, F_0\right)\middle|F_n\right], V(h_A, \vec{h}_n, F_0\right\}$$

If a patient opts for the alternative treatment he does not learn any additional information about the treatment regime. Thus if a patient opts for the alternative treatment he will do so in all proceeding periods. This was originally shown in Bradt, Johnson and Karlin (1956).

[8] See also Gittins et. al (2011) and Powell and Ryzhov (2012) for a general discussion of characterizing stopping problems.

$$S(t) = \int S(t|q)dF(q)$$

For such a survival function, the degree of primary non-adherence or non-initiation corresponds to the magnitude $1 - S(1)$ while secondary non-adherence or discontinuation corresponds to $S(1) - S(t)$.

Section 3: Positive Implications about Factors Driving Non-Adherence

In this section we discuss the many testable implications of interpreting non-adherence as optimal stopping when patients learn about individual treatment value.

3.1 Treatment Duration and Adherence

In our analysis, learning about the quality of the treatment takes place initially but eventually the patient learns its value with great precision. More precisely, as treatment progresses a patient's observed average treatment effect $\bar{h}_t$ converges to the true individual specific quality of the treatment, q. As the number of periods t increases, the posterior variance converges to zero and once the patient knows the true treatment quality, they elect to adhere to the treatment if and only if they value it over the alternative treatment, $U(q, p) \geq U(q_A, p_A)$.

The hazard rate out of treatment is defined as the fraction of remaining patients that quit the treatment in a given period, or $\frac{S(t)-S(t+1)}{S(t)}$. Since patients eventually learn about treatment quality with great precision, this implies the hazard rate of non-adherence converges to zero over time. Our model then predicts that the level of adherence $S(t)$ flattens out and converges to some level $\lim_{t\to\infty} S(t) = S^*$.

3.2 Costs and Adherence

There are two primary costs of treatment: the monetary cost of treatment p and the opportunity cost of treatment incurred by forgoing an alternative treatment. The cost of treatment

naturally lowers the value of treatment and raises non-adherence by raising the optimal stopping threshold; $\frac{dz_t}{dp} > 0$. This simply says that demand is downward sloping. This rise in price may be either due to higher co-pays, premiums, or other forms of time or monetary costs that contribute to the total cost of care.

In the health policy literature, a common argument is since price (premium or copay) are a barrier to adherence, it should be cut when adherence is price-sensitive. However, we here note that this pricing policy is the exact opposite to optimal insurance design under moral hazard. Standard arguments about moral hazard imply that there is excessive adherence without copays. In sum, moral hazard implies there is over-adherence rather than under-adherence.

The other cost of treatment is the opportunity cost in terms of alternative care which represents the outside option in our stopping problem. Thus, it is straightforward to show that the better the outside options, the lower the adherence. This implies that the price of the alternative treatment raises adherence while the quality of alternative treatment lowers adherence; $\frac{\partial z_t}{\partial p_A} < 0, \frac{\partial z_t}{\partial q_A} > 0$.

3.3 Treatment Quality and Adherence

A basic implication of our analysis is that better performance leads to higher adherence both on the individual level as well as on an aggregate level relating to overall product quality.

On an individual level, our analysis implies that a patient's treatment experience drives adherence behavior. In our framework, if a patient experiences treatment outcomes $\vec{h}$ that are uniformly larger than another set of treatment outcomes $\vec{h}'$, then he will adhere longer with the first experience. In our particular learning environment based on normality assumptions, the first

set of experiences would imply a larger average health outcome throughout, which in turn would imply a higher posterior mean, thus resulting in higher adherence.

On an aggregate level, differences across treatments in terms of their overall quality are represented by differences in the mean quality of the treatment μ.[9] These population-wide effects of treatments are often estimated in clinical trials conducted to gain approval for marketing. At any given time, the performance threshold driving optimal stopping is decreasing in the average quality of the treatment, $\frac{\partial z_t}{\partial \mu} \leq 0$.[10] In fact, an increase in the average quality of the treatment raises adherence through two channels. It lowers the performance threshold as well as increases the fraction of patients that perform above any given threshold.

3.4: Education, Provider Communication, and Adherence

Education affects a patient's ability to assess and learn and in particular the Bayesian learning assumed here. We interpret more educated and informed as a patient's beliefs being closer to the truth than when less educated.

There are at least three ways in which having such more truthful beliefs may come about. First, traditional education, as measured a years of regular schooling, may enable the patient to better understand treatment information. Second, the patient may have more specialized education in health- or treatment related matters for a given disease, sometimes referred to as "health-literacy". Health literacy often comes from longer exposure to a chronic disease for which education takes place over the course of having the disease. Third, effective provider-

[9] Aggregate effectiveness should be distinguished from so called "cost-effectiveness" of care which is more loosely related to larger adherence. Cost-effectiveness is not perfectly related to adherence because patients may trade off cost versus effectiveness differently than one to one, that is, the utility $U(h,p)$ may differ from a ratio. Other reasons include unmeasured quality dimensions that affect patient utility and adherence, or prices that do not correspond to the full cost of care faced by the patient.

[10] See section 6.4 in Gittins (1989) and Corollary 1 in Yao (2006) for further details.

patient communication about treatments may affect the accuracy of patient beliefs[11]. However, it is important to stress that although a provider may communicate his expertise in the *population-wide effects* of the treatment, here features of the distribution $F(\cdot)$, the patient has the ultimate expertise in the *individual value* of the treatment after experiencing it, his quality level q. Providers will not have expertise in how a given patient trades off various aspects of the treatment after learning about it, such as side-effects, efficacy, or the full costs of compliance and treatments.[12]

For all three scenarios, consider when educated individuals have beliefs closer to the truth than uneducated individuals. In particular, consider when the true mean is μ, educated individuals hold prior mean μ_{EO} and uneducated individuals hold prior μ_{UO} such that $\mu_{UO} > \mu_{EO} = \mu$. This says that uneducated individuals are overly optimistic about the treatment. From our previous discussion of the impact of priors on adherence, it follows that adherence falls with education in this case. However, if uneducated patients are overly pessimistic about treatment ($\mu_{UO} < \mu_{EO} = \mu$), education raises adherence. In other words, if education means having beliefs closer to the truth it may either be positively or negatively related to adherence.

Regardless of the form of education, more accurate initial beliefs about a treatment through education will not have a marginal effect on adherence in the long run. This is because ultimately the patient will learn whether the treatment works for him or not which will drive

[11] There are of course other factors that may drive provider effects on adherence. One is through reimbursements incentives, e.g. fee-for-service medicine may discourage adherence when it means less future care. Another way is that high quality providers may have a direct effect on adherence without communication. If a doctor from a well-known medical institution prescribes a treatment, the patient may believe in the treatment more than if a resident or nurse from a community hospital prescribed it.

[12] In particular, doctors may incorrectly argue that patients under-adhere because doctors are often only focused on health outcomes as opposed to the patients that must weigh all aspects of care and pay the price.

adherence. A patient's posterior beliefs are determined more and more by treatment performance over time regardless of the patient's prior beliefs.

3.5: Treatment Heterogeneity and Noise

A patient's health outcome in a given period is a function of treatment heterogeneity ($q \sim N(\mu, \sigma^2)$) and the ability to infer treatment quality from health or so called noise ($\varepsilon_t \sim N(0, \sigma_\varepsilon^2)$). Treatment heterogeneity, captured by the true and prior variance σ^2, and the treatment noise, captured by σ_ε^2, impact learning and thus adherence. Both have offsetting effects on overall adherence and thus their impact on adherence is indeterminate.

3.5.1 Heterogeneity in Treatment Quality and the Option Value of Care

Heterogeneity in treatment value (σ^2), including effectiveness and side effects, has opposing effects on adherence. On the one hand, the patient's outside option to adopt the alternative treatment allows patients to partake in the upside of treatment value without the downside making the payoff of treatment resemble an equity call option. The option value of treatment rises in heterogeneity because non-adherence limits the downside. Other things constant, an increase in treatment heterogeneity lowers the patients stopping threshold, $\frac{\partial z_t}{\partial \sigma^2}<0$.[13] On the other hand, treatment heterogeneity not only impacts the threshold z_t but it also impacts the distribution of treatment experiences observed by the patients. In particular treatment heterogeneity raises the number of patients experiencing bad outcomes. [14] As a consequence, heterogeneity has offsetting effects on adherence and produces an indeterminate effect on adherence.

[13] See Theorem 1 in Yao (2006) for details on the proof.

[14] Consider the trivial example where treatment is known to be valuable for all individuals; $U(q,p) > U(h_A, p_A)$, $\sigma^2 = 0$ and $\sigma_\varepsilon^2 > 0$. If $\sigma^{2\prime} > 0$, the ex-ante value of treatment rises but it would no longer be the case that all individuals find it valuable to stay in treatment. There exists h' such that $U(h', p) < U(h_A, p_A)$ since $h \sim N(\mu, \sigma^{2\prime})$. Heterogeneity raises the value of treatment but produces an ambiguous effect on adherence.

3.5.2 Noise in the Learning about Treatment Quality from Health

Treatment noise also has offsetting effects on adherence. On the one hand, a greater variance of treatment noise makes it harder for patients to discern between the true treatment effect and the treatment noise. In other words, treatment noise ultimately slows the learning process of patients. Other things constant, an increase in the variance of the treatment noise lowers the value of continuing treatment and increases the stopping threshold such that $\frac{\partial z_t}{\partial \sigma_\varepsilon^2} > 0$.[15] On the other hand, treatment noise interacts with treatment quality in driving adherence. To illustrate, consider the extreme case without noise (σ_ε^2=0). In the setting without noise, the fraction of those who benefit ($U(q,p) > U(q_A, p_A)$) adhere while the rest leave. At the opposite extreme, nothing is learned about treatment from adhering (σ_ε^2 is very large). In this case, if the average value is positive then everyone adheres, otherwise no-one adheres. These extreme cases illustrate how the impact of treatment noise on adherence interacts with the true value of the treatment. The end result is that, the effect of noise on adherence is indeterminate.

3.6: Comorbidities and Adherence

A patient undergoing a given treatment may be undertaking other treatments due to multiple diagnoses or comorbidities. There are three ways in which comorbidities may affect adherence in our analysis. First, the effectiveness of a treatment may depend critically on the patient's comorbidities and the associated treatments. For example, the effectiveness of one drug may be partially subdued or enhanced when taken in conjunction with another drug.

Secondly, comorbidities may make it harder for patients to infer treatment value from health outcomes. This is because when the patient is on several treatments due to comorbidities, the patient does not know whether it is the treatment itself, the comorbidities, or the treatment for

[15]See Lemma 1 in Yao (2006) for details on the proof.

comorbidities that may be causing a given health outcome. In other words, comorbidities raise the variance of the treatment noise σ_ε^2. As discussed, a rise in the variance of the treatment noise produces an indeterminate effect on adherence.

Lastly, comorbidities may affect adherence by making it marginally more taxing on a patient, both financially and mentally, to undertake multiple treatments for multiple morbidities. For example, it may be more taxing to remember when to take eight medicines rather than one. This would be reflected by a higher total price p (including time costs) in our analysis and clearly lowers adherence.

The overall effect of comorbidities on adherence will be determined by the relationship of these three effects.

Section 4: Normative Implications for Efficient Adherence

In this section we discuss the efficiency implications of non-adherence.[16] Inefficient adherence transpires as the direct result of heterogeneous and unknown personalized treatment effects. The process in which individuals learn about their own value of the treatment creates the potential for both under and over-adherence.

4.1 Ex-ante vs Ex-post Efficient Adherence

Ex-ante efficient behavior occurs if an individual cannot be made better off given their individual information at a given point in time. By definition, our stopping behavior is ex-ante

[16] Both medical and economic discussions of adherence often state that patients do not adhere enough, although there is no explicit criteria discussed defining whom and why a patient should adhere. In some sense, our theory suggests an explanation of this normative claim by third party bystanders about the under-consumption of patients; the selection effect inherent in learning means that those that adhere do better than those who do not adhere. With the inherent upward bias in adherence effects under optimal learning, it maybe ill-advised to argue everyone should adhere.

efficient unless there are external effects across patients that are not internalized (we discuss such issues in the conclusion). *Ex-post efficient* adherence behavior occurs when only those who actuality truly value the treatment adhere to it. Let q^* be threshold level of health or treatment quality (the same thing ex-post) which makes the patient is indifferent between the treatment and the alternative treatment

$$U(q^*, p) = U(h_A, p_A)$$

Naturally, the reservation level of health q^* is increasing in the price of the treatment and the health of the alternative treatment but decreasing in the price of the alternative treatment; $\frac{\partial q^*}{\partial p} > 0$, $\frac{\partial q^*}{\partial h_A} > 0$, and $\frac{\partial q^*}{\partial p_A} < 0$.

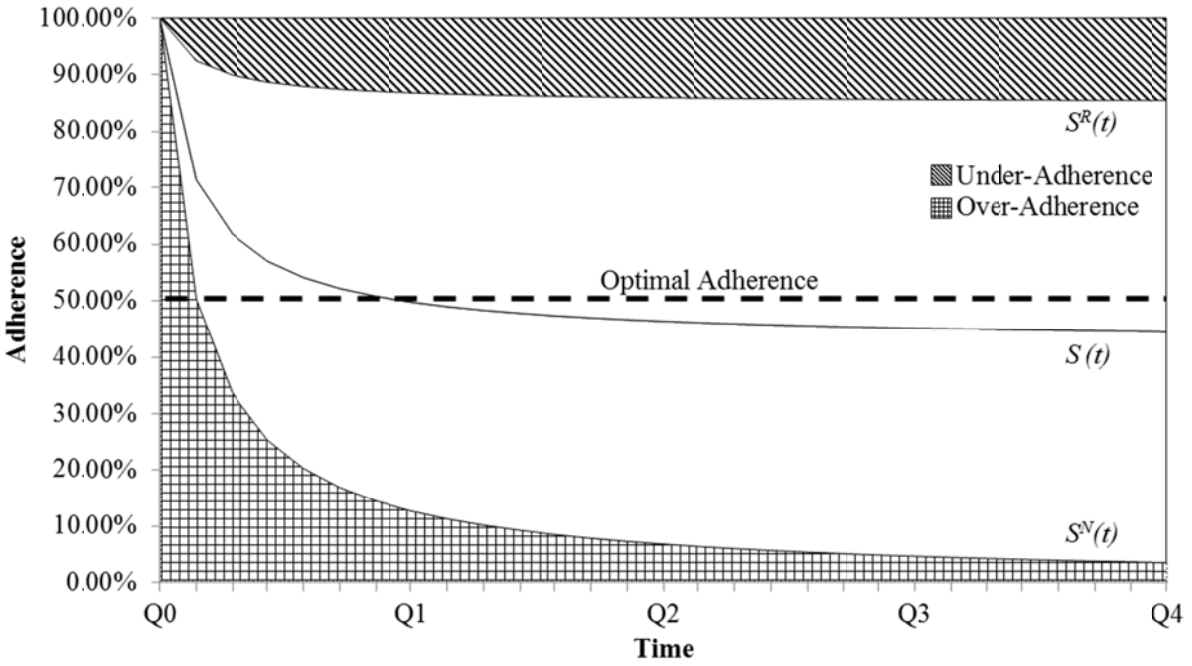
It is ex-post efficient for patients ("responders") with personalized treatment effects above this reservation level to be on treatment; $q > q^*$. Therefore, there are two types of ex-post inefficiencies. The first inefficiency is under-adherence. Even though treatment is valuable for a fraction $1 - F(q^*)$ of patients, some of those patients will stop treatment because of incorrect inferences about treatment value. The second type of inefficiency is over-adherence. Treatment is not valuable for the fraction $F(q^*)$ of patients that do not respond ("non-responders") where $q < q^*$. Some non-responders may initially adhere to the treatment before learning that it is not valuable for them.

Figure 2 illustrates the general pattern of ex-post inefficient adherence. The survival curve $S^R(t)$ reflects the proportion of responders that adhere for each period. It is the survival function for individuals that respond to treatment; $q > q^*$. Treatment is valuable for responders thus it is efficient for all of those individuals to adhere. Under-adherence by responders is reflected by the fact that the survival curve $S^R(t)$ is not equal to one; $S^R(t) < 1, \forall t > 0$. The shaded area above represents $S^R(t)$ reflects the proportion of responders that inefficiently under-

adhere to treatment. Inefficient under-adherence occurs because some of the patients experiencing poor initial performance on the treatment leave even though it is in fact valuable.

The survival curve $S^N(\cdot)$ reflects the proportion of non-responders that adhere at each period. Treatment is not valuable for non-responders, thus $S^N(\cdot)$ represents inefficient adherence. It is the survival function conditional for those who do not respond to treatment, $q < q^*$. The shaded area underneath the curve $S^N(\cdot)$ represents the fraction of non-responders that inefficiently adhere to treatment. Such inefficient over-adherence is reflected by a positive survival curve for this group. Inefficient adherence occurs because of either the option value of treatment and/or because they experienced good initial performance on the treatment. However, sooner or later all of them will learn that the treatment is invaluable such that non non-responders adhere; $\lim_{t\to\infty} S^N(t) = 0$.

FIGURE 2: ADHERENCE BEHAVIOR BY RESPONDERS AND NON-RESPONDERS



Notes: The non-responders survival function, $S^N(t)$ present adherence for those for whom treatment is not valuable. The responders survival function, $S^R(t)$ represents adherence for those for whom treatment is valuable.

By our previous discussion that showed that true treatment quality raises adherence, the figure depicts that efficient adherence is always larger than inefficient adherence; $S^N(t) < S^R(t), \forall t$. The overall solid survival curve is the mixture of the two conditional survival functions with the mixture weights given by the fraction of true responders and non-responders:

$$S(t) = F(q^*)S^N(t) + \big(1 - F(q^*)\big)S^R(t)$$

It follows that in the short-run, there will be both under-adherence for true responders and over-adherence for true non-responders. However, in the long run there will always be under-adherence because there are responders who drop out and will never find it optimal to re-adhere. The dotted line in Figure 2 reflects the optimal adherence level which is simply the fraction of the population that responds to treatment $1 - F(q^*)$. After the first quarter of treatment, the overall population survival function $S(\cdot)$ remains inefficiently below the optimal level of adherence. The survival function among responders $S^R(\cdot)$ is decreasing and inefficiently remains below one. It asymptotes to a stable level since learning makes the non-adherence hazard vanish over time. The survival function $S^N(\cdot)$ of true non-responders efficiently goes to zero as non-responders learn that the treatment is not worthwhile for them.

This previous discussion concerned the inefficiency in quantities, that is, who is on the treatment or not compared to who should be. The monetary value lost from under- and over-adherence results from how much the foregone therapy is valued. Let the reservation price for the treatment beyond the going price for an individual of type q be denoted $r(q)$ and defined by

$$U\big(q, p + r(q)\big) = U(q_A, p_A)$$

Thus the sign of $r(q)$ reflects whether the treatment is truly valued or not relative to the alternative treatment. It follows directly that higher performing treatments have a higher

reservation price, $r'(q) > 0$, and that the price is negative for those who do not respond $r(q) \leq 0$ if $q < q^*$. The dollar value of the welfare loss at time t can then be written as

$$Welfare\ Loss\ at\ t = L_O(t) + L_U(t) = \int_{-\infty}^{q^*} -r(q)S(t|q)dF(q) + \int_{q^*}^{\infty} r(q)[1 - S(t|q)]dF(q)$$

The first term $L_O(t)$is the loss in welfare at time t from over-adherence; those who do not value the treatment but still adhere to it. The second term $L_U(t)$ is the loss in welfare at time t from under-adherence; those who value the treatment but stopped adhering.

Given the welfare loss at each period, the present value of the total welfare loss over time is the discounted value of the loss from both forms of inefficiencies

$$L = \int_0^{\infty} \beta^t [L_O(t) + L_U(t)]dt$$

The important aspect of this overall welfare loss is that over-adherence is front-loaded while under-adherence that is back-loaded as displayed in Figure 2 above. This results from the fact that non-adherence occurs early during learning and vanishes in the long run. Therefore, in present value terms over-adherence often matters more than under-adherence. This is part of the reason we find that efficiency losses from over-adherence dominate under-adherence in our later calibration results for cholesterol lowering drugs. More generally, the importance of front-loaded over-adherence for overall efficiency is in contrast to common arguments of the importance of raising adherence.

4.2 Welfare Effects of Adherence Interventions

We separate adherence interventions into those that have symmetric- versus asymmetric effects on responders and non-responders.

4.2.1 Adherence Interventions that do not affect Learning

Adherence interventions often target treatment costs or other treatment parameters rather than target the patent learning process. However, by doing so the adherence intervention affects true responders and non-responders symmetrically by raising adherence for both groups. As a canonical illustration of such symmetric interventions that do not affect learning, consider price-based interventions that lower the time- or dollar expense of treatment. However, lowering price raises adherence for both responders and no-responders which implies that over-adherence is increased while under-adherence decreased; $\frac{\partial L_O}{\partial p} > 0$ and $\frac{\partial L_U}{\partial p} < 0$. This implies counteracting effects on the overall welfare loss given by

$$\frac{dL}{dp} = \int_0^\infty \beta^t \left[\frac{\partial L_O(t)}{\partial p} + \frac{\partial L_U(t)}{\partial p} \right] dt$$

Therefore, any intervention that raises adherence behavior by the two groups symmetrically will have indeterminate effects on ex-post efficiency. On the other hand, this will likely be the norm as it is extremely difficult to make adherence interventions operate differently across the two groups.

The long-run effects of interventions not based on learning that raise adherence are easier to sign. In the long run, we discussed over-adherence must go to zero when those truly not responding eventually learn that they should not adhere. Therefore, in the limit the welfare loss must fall from an intervention that raises adherence

$$\lim_{t\to\infty} \frac{\partial L_O(t)}{\partial p} = 0 \Longrightarrow \lim_{t\to\infty} \frac{dL(t)}{dp} < 0$$

4.2.1 Adherence Interventions that affects Learning

An optimal intervention would have asymmetric effect on adherence, raising adherence among responders while decreasing adherence among non-responders. One such asymmetric

adherence intervention is personalized medicine. Personalized medicine, by use of so called companion diagnostics, aims to provide patients with better information about treatment value before undertaking treatment. The companion diagnostic is taken before treatment and is aimed at better diagnosing the value of the treatment given the disease, as opposed to the disease itself. In other words, the companion diagnostic essentially "speeds up" the patient learning process. Personalized medicine replaces learning about the treatment value from health experience with learning about the treatment value from a diagnostic test. It thereby changes the therapy from being a so called experience good, for which consumption is necessary to determine its quality, to a search good, for which it consumption is not necessary to determine its quality.

Consider the scenario where a companion diagnostic prior to treatment provides a potentially noisy signal $d = q + \eta$ of the personalized value of the treatment. However, learning from the diagnostic may be imperfect just as learning from health experience may be, through a noisy test distributed according to $\eta \sim N(0, \sigma_\eta^2)$. With a perfect companion diagnostic (i.e. $\sigma_\eta = 0$ and $d = q$), the test is fully informative and true responders always adhere to treatment and non-responders never initiate treatment. Thus, this idealized form of personalized medicine produces an *asymmetric* effect on adherence of the two groups. In this case, personalized medicine eliminates all ex-post inefficient adherence.

$$\sigma_\eta = 0 \quad \Rightarrow \quad S^R(t) = 1 \;\&\; S^N(t) = 0 \;\; \forall t \quad \Rightarrow \quad L = 0$$

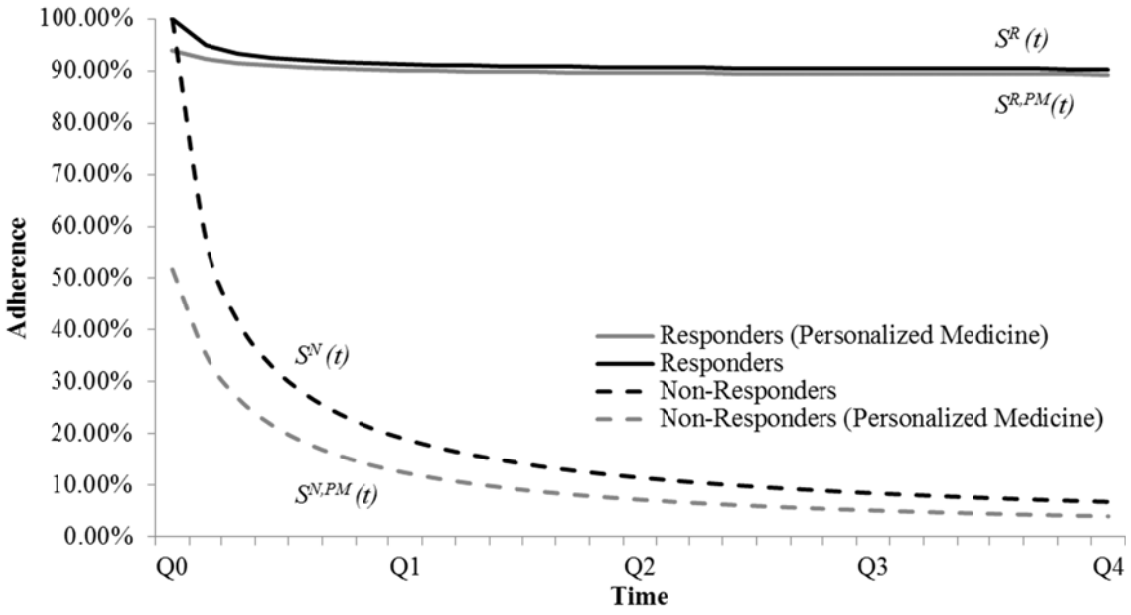
Thus, in our framework, the upper bound on the value of personalized medicine is given by the ex-post efficiency loss L discussed previously.[17] An implication is that for classes where learning about treatment quality through experience is very costly relative to learning through a companion diagnostic, we would expect personalized medicine to emerge. This is one

[17] We have elsewhere discussed other value aspects of personalized medicine using evidence from COX-2 inhibitors, see Sood et al. (2013).

explanation of why companion diagnostics have emerged in oncology where learning through treatment experience may induce premature mortality. One of the primary benefits of personalized medicine is that it reduces over-adherence; this is in stark contrast to the common belief that there is too little adherence.

Consider now when the companion diagnostic, just as treatment experience, provides imperfect information about treatment quality as represented by $\sigma_\eta > 0$. Figure 3 compares adherence behavior of responders and non-responders with personalized medicine relative to the baseline case without personalized medicine. The gray survival functions reflect the survival functions for responders and non-responders ($S^{R,PM}(t)$ and $S^{N,PM}(t)$) with personalized medicine while the black correspond to the survival functions in the baseline case without personalized medicine.

FIGURE 3: NOISY COMPANION DIAGNOSTIC AND ADHERENCE



Notes: The gray curves $S^{N,PM}(t)$ and $S^{R,PM}(t)$ represent the survival functions for both non-responders and responders with personalized medicine. The black curves $S^N(t)$ and $S^R(t)$ represent the survival functions for both non-responders and responders in the baseline case without personalized medicine.

Personalized medicine, even with imperfect tests, provides patients with better knowledge of their personal treatment effect at any given moment, even prior to treatment. Thus with personalized medicine, it is no longer the case that everyone initiates treatment. Both responders and non-responders fail to initiate treatment though non-responders fail to initiate at a much higher rate. This is indicated in Figure 3 as the gray survival functions for both responders and non-responders are less than one at time zero, $S^{N,PM}(0) < 1$ and $S^{R,PM}(0) < 1$. Similar to the optimal stopping rules described earlier, there exists a stopping threshold z_0 such that patients test into and initiate treatment if $d > z_0$ and test out of treatment if $d < z_0$. Responders are more likely to receive signals suggesting that treatment is effective $U(d, p) > U(h_A, p_A)$ and test into treatment while non-responders are more likely to receive information suggesting treatment is ineffective. This example shows how even imperfect personalize medicine could greatly reduce the number of patients inefficiently adhering. Although some responders inefficiently drop out of treatment earlier ($S^{N,PM}(t) \leq S^{N}(t)$), at each period fewer non-responders adhere to treatment with personalized medicine ($S^{R,PM}(t) \leq S^{R}(t)$).

Section 5: Calibrating Adherence Inefficiencies: The Case of Simvastatin (Zocor)

In this section we calibrate our model of non-adherence to assess the welfare losses induced by ex-post inefficient adherence. We show how this is feasible given readily available data. We consider adherence associated with cholesterol lowering treatments taken by adult males. More specifically, we consider old males taking the drug simvastatin (Zocor) as a cholesterol lowering treatment regime. Our main result is that even though a majority of these patients do not adhere fully, the welfare loss of over-adherence dominates that of under-

adherence. In particular, the loss due to over-adherence is over 80% larger than the loss due to under-adherence.

In our framework, we interpret simvastatin as the unknown treatment while the alternative is not taking any treatments. Our interpretation assumes that the sole objective of the treatment is to lower low-density lipoprotein cholesterol (LDL-C). The per-period (quarterly) benefit of simvastatin h_t represents the patient's percentage point decline in LDL-C levels relative to their initial baseline levels. The percentage point decline in LDL-C levels of a patient in a given period reflects the true personalized treatment effect plus some idiosyncratic shock according to

$$h_t = q + \varepsilon_t$$

where $q \sim N(\mu, \sigma^2)$ and $\varepsilon \sim N(0, \sigma_\varepsilon^2)$. Our calibration is for 58 year old males and we assume that patients expect to live the average life expectancy of 23 years without treatment but longer if responding to the simvastatin treatment.[18]

Patients observe their cholesterol levels through lab tests and update their adherence decision on a quarterly basis. We assume patients learn their true value of treatment fully after one year of treatment. Therefore, patients continue with the treatment after a year (hazard rate goes to zero) if and only if they are true responders i.e. $(U(q,p) > U(q_A, p_A) = 0)$ for the remainder of their lives.

Calibrating our model requires knowledge of the distribution of treatment effects, (μ, σ^2), how well the symptoms reflect treatment or signal noise (σ_ε^2), the costs of treatment (p), and the utility parameters (β, γ). Clinical trial data often provide information on the treatment quality and noise parameters. In particular, the treatment mean and variance, (μ, σ^2), is often

[18] We calculate life expectancy according to the 2009 CDC National Vital Statistics Report and the Social Security Administration.

directly reported from such trials and individual longitudinal data can be used to estimate the noise distribution (σ_ε^2).

Table 1 summarizes the parameters values used in calibrating the model for simvastatin. We use clinical trial data on the distribution of effectiveness of simvastatin from (Bays et al. 2004). On average, the simvastatin treatment therapy in the Bays et al. study lowered LDL-C levels by 37.00% over a quarter relative to no treatment (placebo).[19] In the context of our model this implies $E[h] = E[q] = \mu = 37.00\%$ and $h_A = q_A = 0.00\%$. We use simvastatin treatment cost estimates from Hoadley et al. (2012) who using Medicare Part D data find that the median out of pocket cost paid by users for a one quarter supply of branded simvastatin was \$231.25.[20,21] The health consumption trade-off parameter γ represents a patient's willingness to pay to lower his cholesterol for one quarter. As described in the Appendix A2, this parameter is calculated using data on the longevity gains from simvastatin (Jönsson et. al 1996) valued in terms of dollars using standard value-of-life estimates (Murphy and Topel 2005). We calculate that a patient is willing to pay one dollar to lower his LDL-C levels by a bit more than a sixth of a percentage point, 0.17%, per quarter. We calibrate the remaining parameters β and σ_ε to match observed adherence patterns for simvastatin as described in the Appendix. The calibrated health discount factor is 0.90 which is line with the estimates from Moore and Viscusi (1988) and

[19] Patients studied in Bays et al (2004) received dosages of 10-80 mg respectively of simvastatin per day.
[20] Hoadely et al. (2012) find that the median 30-day out of pocket cost for branded Zocor was \$71 in 2008. We convert their cost estimates into the cost of a one quarter supply in 2014 by scaling the cost by 3.257 to account for the quantity and inflation. We account for inflation according to the BLS inflation calculator [http://www.bls.gov/data/inflation_calculator.htm]. We find similar cost estimates using CVS Pharmaceutical data from GoodRx.com . GoodRx reports estimated cash price of a one month dosage (taken daily) of 20mg simvastatin Zocor at CVS Pharmacy is \$38. Assuming that each patient receives 30mg of simvastatin daily implies the cost of a one quarter dosage is then \$171.

Viscusi and Moore (1989).[22] The noise parameter implies that an adhering patient's cholesterol level varies naturally from quarter-quarter with a standard deviation of $\sigma_\varepsilon = 7.40\%$.[23]

TABLE 1: MODEL PARAMETER VALUES USED IN CALIBRATION

Parameters	Value
Parameters from the Literature:	
Mean Effectiveness of Simvastatin (Zocor) Therapy (μ)‡	37.00% per quarter
SD of Effectiveness of Simvastatin (Zocor) Therapy (σ)‡	14.80% per quarter
Cost of Simvastatin (Zocor) Therapy (p)	$231.20 per quarter
Health Consumption Trade-Off (γ)	0.17% per dollar
Calibrated Parameters:	
Treatment Noise (σ_ε)	7.40% per quarter
Discount Factor (β)	0.90

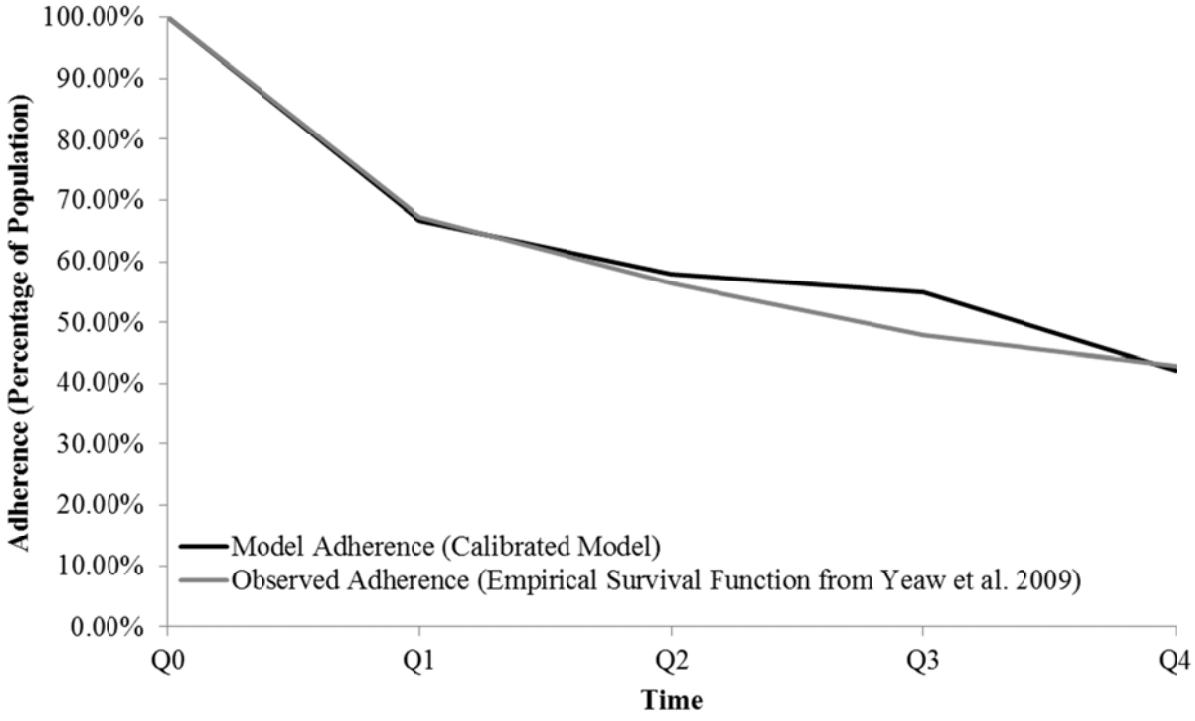
‡ These parameter values are from the clinical study Bays et al. 2004. Effectiveness measures the percentage point drop in low density lipoprotein cholesterol (LDL-C) over one quarter relative to the initial baseline level.
We calculate the cost of Zocor using the observed median out of pocket cost as calculated in Hoadley et. al (2012). See footnote 17 to see how the cost estimate is adjusted for inflation and dosage.
The discount factor and treatment noise are calibrated to fit the empirical survival function for statin adherence estimated in Yeaw et al. (2009).
The health consumption trade-off parameter represents a patient's willingness to pay to lower their cholesterol in percentage points. We calculate the health consumption trade-off parameter as described in the text using existing value of a statistical life year (VSLY) estimates and the longevity benefits of simvastatin.

Figure 3 below displays the adherence survival function from the calibrated model. We calculate the survival function by simulating 10 million hypothetical patients the parameter values displayed in Table 1. The solid black line reflects the survival function corresponding to the calibrated model while the solid gray line reflects the observed adherence survival function

[22] See Moore and Viscusi (1990) for further discussion on estimating discount rates for health outcomes.
[23] Note that in principle, the degree to which health symptoms reveal treatment quality (signal-to-noise ratio) could be estimated using longitudinal clinical trial data on health outcomes. When such data is available, one would not need to observe adherence data in order to calibrate the noise distribution, thereby allowing for out-of-sample predictions about future post-approval adherence behavior from trial data obtained pre-approval.

as reported in Yeaw et al. (2009). The calibrated survival function exhibits a correlation with the observed empirical survival function of 0.94.

FIGURE 4: CALIBRATED ADHERENCE SURVIVAL FUNCTION



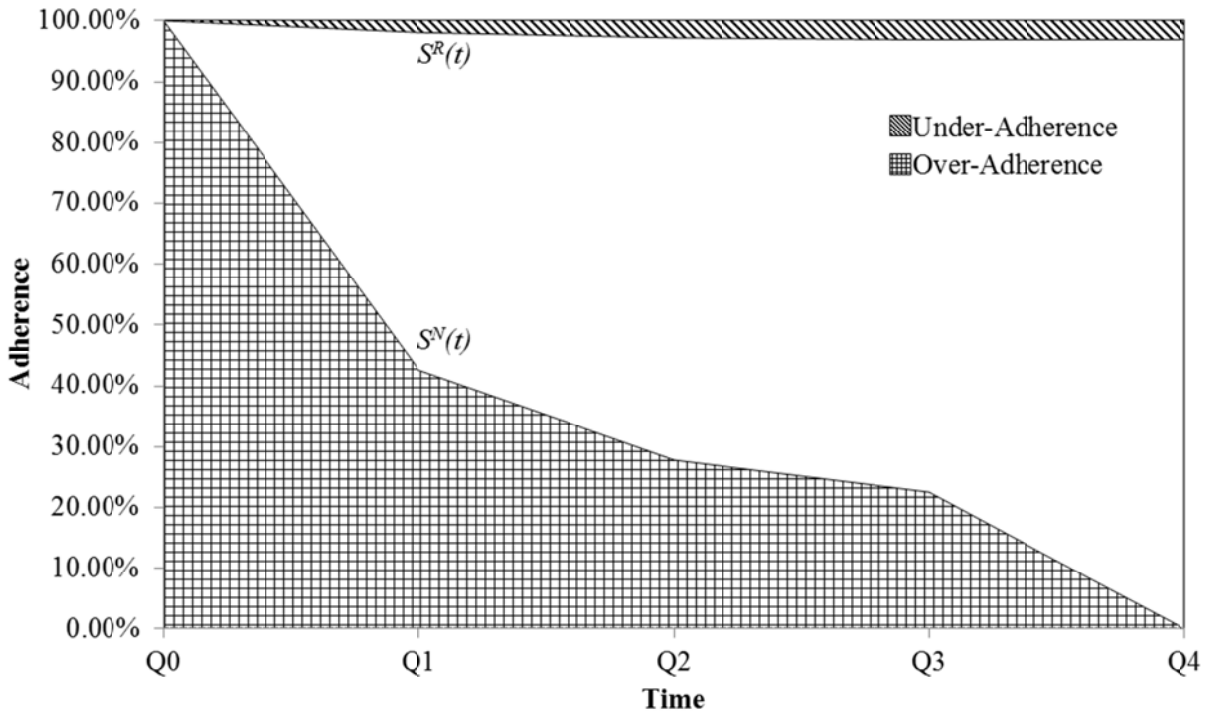
Notes: Figure 4 illustrates the calibrated survival curve corresponding to the parameter values in Table 1 and the empirical survival curve estimated in Yeaw et al. (2009).

Both the observed and calibrated adherence to simvastatin is relatively low; the majority of patients do not adhere to the treatment in the long run. In particular, the parameter values imply that the simvastatin treatment is adhered to by only 42.91% of those prescribed in the long-run. The large degree of non-adherence is driven by the discounting of the fairly modest longevity effect of the treatment which is in addition discounted substantially because it occurs in the future. The calibrated discount factor of 0.90, which as discussed is in line with previous estimates (Moore and Viscusi 1990), implies that patients are not willing to trade off current

consumption for these small health benefits occurring in the distant future. In addition, the more the patients discount the future, the less weight patients place on the discussed option value of treatment. Overall, these simple facts suggest that low adherence to statins seem less puzzling than commonly discussed in both the economics and public health literatures.

The calibrated model for simvastatin allows us quantify ex-post inefficient adherence behavior and separate the inefficiencies driven by over-adherence vs under-adherence. Figure 5 below displays the calibrated survival functions for non-responding and responding simvastatin users using the parameter values of Table 1. The figure illustrates the overall cumulative effect of these two types of inefficiencies when the flows are aggregated up and weighted over time.

FIGURE 5: CALIBRATED UNDER-AND OVER-ADHERENCE



Notes: Figure 6 illustrates the calibrated survival curves for responders, $S^R(t)$, and non-responders, $S^N(t)$, corresponding to the parameter values in Table 1.

These two survival functions suggest that over-adherence may be more problematic than under-adherence. About 42% of true non-responders still take simvastatin after one quarter. However, as discussed, over-adherence vanishes as patients learn treatment as opposed to under-adherence that cannot be recovered. In the long run, only about 3.1% of true responders under-adhere to the treatment.

The calibrated model also allows us to dollarize the welfare losses associated with this inefficient adherence. Consider a patient adhering to the simvastatin treatment inefficiently which occurs whenever the health benefits do not exceed the cost of care; $\frac{1}{q}\gamma < p$. The associated welfare loss of over-adherence is equal to the cost treatment minus dollarized health effect.

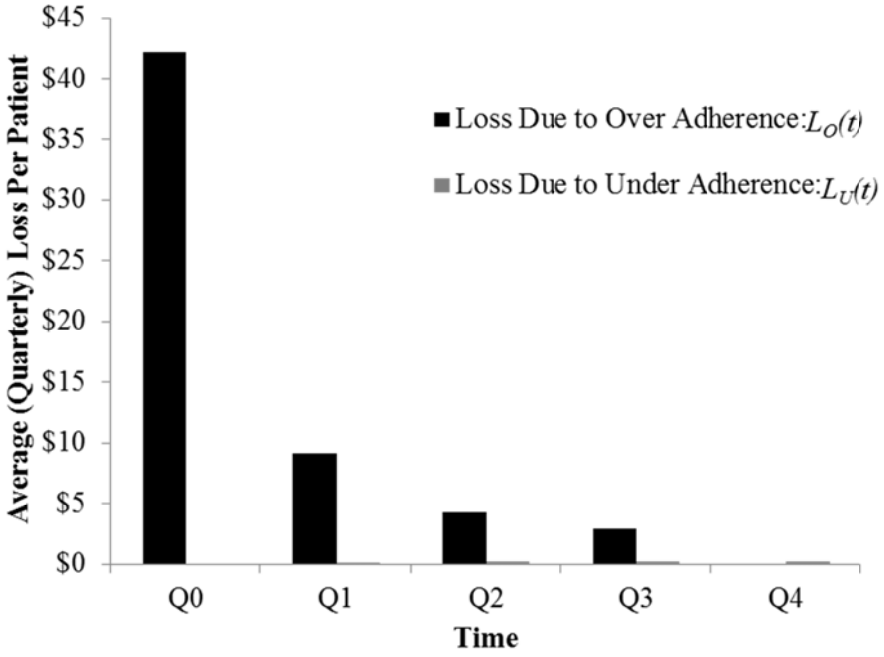
$$Quarterly\ Loss\ Due\ to\ Over\ Adherence = L_O = p - \frac{1}{\gamma}q$$

An analogous expression applies to those who truly value the new treatment but do not adhere

$$Quarterly\ Loss\ Due\ to\ Under\ Adherence = L_U = \frac{1}{\gamma}q - p$$

Figure 6 below displays the calibrated welfare losses from over- and under-adherence using these methods.

FIGURE 6: CALIBRATED WELFARE LOSSES FOR SIMVASTATIN



Notes: Figure 6 illustrates the welfare loss due to over and under adherence corresponding to the parameters in Table 1. The loss due to over adherence at each period is calculated as sum of $p - \frac{1}{\gamma}q$ across all adhering non-responders normalized by the total number of patients. The loss due to of under adherence is calculated as the sum of $\frac{1}{\gamma}q - p$ across all non-adhering responders normalized by the total number of patients.

The black bars in Figure 6 represent the average welfare loss per patient in a given quarter stemming from over-adherence by patients for whom the simvastatin treatment is not valuable. The gray bars represent the average loss per-patient from under-adherence by patients for whom the simvastatin treatment is indeed valuable. As discussed, the loss from over adherence vanishes with time as patients learn that the treatment is not valuable. Since individuals never re-enter treatment, the loss from under-adherence rises over time but converges to a steady state level in perpetuity as those who value the treatment eventually stay on. The initial welfare loss due to over-adherence is $42.18 per patient-quarter but declines to zero as

non-responders drop out of treatment. Conversely, the loss due to under-adherence is initially zero as everyone exhibits primary adherence but is $0.21 per patient-quarter in the long run. In present value terms, the total loss due to under-adherence is $6.52 per patient and for over-adherence is $57.87 per patient.[24] As discussed in the theoretical analysis, the larger present value effects of over-adherence steams from that it is front loaded in time as opposed under-adherence that is back-loaded. The total per capita loss due to inefficient adherence (over-adherence plus under-adherence) is $64.39. To put these numbers in perspective, a quantity of 94.1m simvastatin prescriptions were dispensed in the US in 2010 and the total spending on lipid regulators was $18.7bn (IMS Health 2011). The potential aggregate losses due to inefficient adherence are thus on the order of billions of dollars. Regardless, the major finding is that over-adherence losses greatly dominate under-adherence ones for statins, especially in present value terms.

Section 6: Concluding Remarks and Future Research

Little explicit positive and normative analysis exists in health economics on the dynamic demand behavior implicit in non-adherence, which is often associated with uninformed patients. We analyzed the implications for adherence behavior stemming from patients learning about personalized treatment value. Although providers may be more informed about the population-wide effects of treatments, patients may be more informed about their own value of care in terms of how they trade off effectiveness, side effects, costs of care, and compliance. We derived the optimal stopping problem, which corresponds to non-adherence under personalized patient learning, and characterized its observable determinants. The model produces strong normative

[24] This is calculated using an annual discount factor of 0.90 and assuming that non-adhering patients live 23 years.

implications resulting from such non-adherence, and calibrates the welfare losses implied for the cholesterol-reducing therapy simvastatin (Zocor). The calibration results suggest that losses due to over-adherence are over 80% larger than losses from under-adherence, even though only 43% of patients adhered to the therapy.

Our analysis is in contrast to traditional analysis of adherence, which almost uniformly assumes it should be raised. This traditional view may be interpreted as a special case of our analysis in which the entire population truly benefits from treatment but patients misconceive the benefits of treatment. In this case, factors that raise or lower adherence also raise or lower ex-post efficiency, and which is often an implicit assumption of much of the existing policy analysis of adherence. However, when not everyone benefits from treatment, as potentially revealed by the fact that some patients do not adhere, factors that raise adherence may lower ex-post efficiency, and factors that lower adherence may raise such efficiency. This broken link between greater adherence and efficiency is central to assessing the value of adherence interventions under patient learning.

We conclude by discussing some of the shortcomings of the analysis, and address issues that future theoretical or empirical research on adherence may consider.

External Effects and Non-adherence

We only considered adherence from the private-choice perspective of the patient. However, privately optimal adherence may not be socially optimal when adherence behavior confers external effects. For example, adherence to treatments for infectious diseases such as TB may involve positive externalities and thus may be inefficiently low when non-infected individuals benefit from adherence by infected patients. Classes of drugs such as antibiotics or antiretrovirals raise an additional issue—that of the negative externality that non-adherence

imposes on everyone else because of population resistance to the treatment. Or external effects may operate through insurance premiums when non-adherence raises the total cost of care through cost offsets (Goldman and Philipson 2007, Chandra et al. 2010). Pigouvian subsidies to stimulate adherence under positive external effects may then be relevant and may be implemented through lower copays or other methods that raise adherence. More careful analysis of the role of adherence programs is needed in the context of external effects.

Selection and the Effects of Adherence on Health

Medical studies stress the importance of adherence because of the positive impacts on a patient's health. For example, many analysts think patients need to be better educated about treatments for breast cancer given that compliance is poor but the health benefits seem substantial. However, our analysis directly implies that those that adhere perform better than those that do not, and thus the adherence effects are overestimated when optimal stopping occurs because of poor performance. The basic view of the medical community—that patients under-consume care—needs to be evaluated not from the average experience but from the patient-specific experience. This selection also affects the optimal targeting of adherence interventions; low levels of adherence may reveal preferences that imply small effects for adherence interventions.

Insurance Design and Adherence

Future analysis may consider optimal insurance design when patient learning drives adherence. One direct way in which insurance design may affect adherence is through copays, as generally recognized in the literature and as implied by the analysis above.

An interesting recent health policy literature exists on so-called value-based insurance design (VBID), which discusses copay design across treatments and services. However, to our

knowledge, that policy literature does not explicitly discuss the optimality criteria that determine whether copays should be set high or low (i.e., the *definition* of V in VBID). Without an explicit definition of the value V in VBID, determining whether high or low copays are good or bad in a normative sense and may thus lead to inefficient recommendations is impossible.

This policy literature is in contrast to the economic analysis of the value of insurance designs in which the value V is defined as economic efficiency (see Pauly, 1968, and Zeckhauser, 1970, for copay design for single treatments, and Goldman and Philipson, 2007, for multiple ones). When value is defined as economic efficiency, the implied VBID is that copays should be lower for less price-elastic treatments, because the insurance it enables is less counteracted by inefficiently high demand. Indeed, the VBID induced by the traditional economic analysis implies that marginally changing copays to alter adherence would result in inefficient adherence. It is not clear why suggested benefit re-designs of the more recent policy literature on VBID, often arguing that copays should be raised or lowered to alter adherence, affects efficiency favorably or any other definition of V (Pauly 1968).

A better understanding of how patient learning affects VBID is a useful area for future research. For experience goods such as medical treatments, initially low prices may indeed efficiently subsidize learning. Our analysis has several implications for optimal copay designs that future research may be able to address. One possibility is the value of temporary copay rebates to prevent under-adherence by those who benefit from care. Of particular important is an understanding of the role of pharmaceutical samples being provided free of charge in mitigating inefficient adherence.

Provider or Manufacturer Reimbursement and Optimal Adherence

If optimal learning drives adherence, the implications for the effects of various reimbursement policies set by payers to affect providers and manufacturers are strong. If patients are not adhering to poorly working therapies, reimbursements are not spent on poorly performing care. The patient learning process affects the impact of so-called "pay-for-performance" schemes as well as explicit therapy stopping rules undertaken by providers or payers. In particular, stopping rules imposed externally on patients only make those patients worse off in our framework. In addition, patient stopping rules mimic "risk contracting" or pay-for-performance to manufacturers, under which they only receive payment when a therapy performs well at a population level. Patient learning implies such types of reimbursements may have small effects because payers do not pay for ineffective care when patients do not adhere to it.

Structural Estimation of Trial Attrition to Predict Post-approval Adherence

The structural model of adherence discussed implies strong relationships between so-called "real-world" versus clinical trial performance of treatments, sometimes distinguished by the names efficacy versus effectiveness. However, attrition behavior in clinical trials may stem from the same type of behavior analyzed here (Philipson and DeSimone 1999). The central testable empirical implication of that past analysis as well as the adherence analysis here is that past performance drives current hazard rates into non-adherence. This prediction may be tested by longitudinal outcomes data in trials and data on both adherence and health outcomes in real-world settings, the latter of which may become more abundant as data on insurance claims and electronic medical records are merged.

Because of this similarity in behavior, under some conditions, one can estimate the structural parameters from only having attrition behavior from clinical trial data. The parameters can then be used to predict or forecast out-of-sample post-marketing adherence behavior. In

other words, structural estimation of attrition behavior in trials can allow for counter-factual predictions of future real-world adherence and effectiveness.

In summary, we believe more explicit theoretical analysis of non-adherence would better expand our understanding of this important type of dynamic health care demand. Empirical testing of explicit theories seems needed before we can make credible normative claims about the efficiency gains of various private or public interventions aimed at raising adherence.

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Appendix

A1. Multiple Treatments and Partial Adherence on a Single Treatment

This Appendix generalizes the discussion to the case when the quality of more than one treatment is unknown to the patient. Instead of two treatment alternatives, one uncertain treatment and one certain alternative treatment, the more general setting with K uncertain treatment alternatives is considered. One can think of the K treatments as completely different treatments or alternatively as different levels of adherence with the same treatment.

Multiple uncertain treatments involve a so called multi-armed bandit problem in statistical decision theory. We assume that each of the K treatment alternatives produces a personalized health benefit which is a function of the treatment quality, q^k, and an idiosyncratic noise term ε_t^k,

$$h_t^k = q^k + \varepsilon_t^k, k = 1,2, \dots K$$

The personalized quality of treatment k is distributed i.i.d. across individuals from the distribution $q^k \sim F^k(\cdot)$. As before, each treatment generates utility $U(h_t^k, p_k) = h_t^k - \gamma p_k$.

Patients' prior belief over the quality at time t for treatment k id denoted $F_t^k(\cdot\,|\vec{h}_t^k)$ where $\vec{h}_t^k$ is the history of experienced personal health outcomes on treatment k. This formulation assumes that treatment qualities for a patient are distributed conditionally independently across the treatment alternatives.[25] Further we assume that each patients initial prior reflects the true distribution of treatment heterogeneity, $F_0^k(\cdot) = F^k(\cdot)$. Under the maintained assumption that the prior and shocks are normally distributed,$F^k(q) \sim N(\mu^k, \sigma_k^2)$ and $\varepsilon_t^k \sim N(0, \sigma_{k\varepsilon}^2)$, standard

[25] See Pandey et al. (2007), Rusmevichientong and Tsitsiklis (2010) and Dickstein (2014) for a discussion of multi-armed bandit problems with correlated arms.

normality results imply that a patient's posterior distribution is optimally updated according to the previous equation (1) the single treatment case.

The patient's adherence problem now involves selecting the optimal treatment regime among the K alternatives each period. The value function of a patient adhering to treatment option k at time t is

$$V\left(h_t^k, \boldsymbol{H}_t, \overrightarrow{F_0}\right) = U\left(h_t^k, p_k\right) + \beta \max\left\{E\left[V\left(h_{t+1}^1, \boldsymbol{H}_{t+1}, \overrightarrow{F_0}\right)\middle|\overrightarrow{F_t}\right], \ldots, E\left[V\left(h_{t+1}^k, \boldsymbol{H}_{t+1}, \overrightarrow{F_0}\right)\middle|\overrightarrow{F_t}\right]\right\}$$

Here, $\boldsymbol{H}_t$, represents the matrix of outcomes across the K different treatments and the vectors $\overrightarrow{F_0}$ and $\overrightarrow{F_t}$ represent the patient's prior and posterior distributions over the K different treatment alternatives. The previous discussion with a single uncertain treatment ($k = 1$) and a certain alternative treatment ($k = 2$) corresponds to $K = 2$ with $\sigma_2^2 = 0$.

The optimal adherence rule generalizes to selecting the treatment alternative with the highest Gittins index (Gittins and Jones 1974, Gittins and Jones 1979, Gittins et al. 2011). The Gittins index, I_t^k, for a particular treatment k at time t corresponds to the level of utility generated by some hypothetical known alternative treatment for which the patient is indifferent between treatment and the alternative treatment in the simple two treatment alternative case.[26]

$$\frac{I_t^k}{1-\beta} = E\left[U\left(h_{t+1}^k, p_k\right) + \beta \max\left\{E\left[V\left(h_{t+2}^k, \vec{h}_{t+2}, F_0\right), \middle|F_{t+1}\right], \frac{I_t^k}{1-\beta}\right\}\middle|F_t\right]$$

The Gittins Index Theorem (Gittins and Jones 1974, Gittins and Jones 1979) shows that in each period, patients optimally adhere by selecting the treatment alternative with the highest Gittins index at that time. The Gittin's Index Theorem essentially reduces the K multi-armed bandit problem into a set of K single-armed bandit problems.

[26] See Powell and Ryzhov (2012) for a full discussion of Gittins indices.

Implications for Non-Adherence among Multiple Treatments

Computing Gittins indices correspond directly to the single armed bandit problem and optimal stopping rules described for the two treatments govern optimal adherence. Furthermore, since Gittins indices in the multiple treatment framework are computed using the simple two treatment framework (with one known treatment alternative), the comparative statics discussed generalize to the multiple treatment setting. For example, the Gittins index for a particular treatment k is increasing in the perceived quality of treatment μ^k while decreasing in the cost of treatment p_k. Similarly, conditional on the perceived quality of treatment, the Gittins index for an alternative k is increasing in the variance of treatment quality σ_k^2 while decreasing in the variance of the treatment noise $\sigma_{k\varepsilon}^2$.

Implications Partial Adherence on a Single Treatment

The multiple-treatment framework allows one to assess behavior involving partial adherence. Different levels of adherence, such as fractions of prescribed medications taken, can be thought of as separate treatments in the multiple treatment framework. Consider a patient facing the option of fully adhering versus partially adhering to a treatment regime. On one hand, fully adhering to the treatment regime likely generates superior and less noisy health outcomes relative to partial adherence. Both of these attributes (higher mean and lower treatment noise variance) make full adherence an attractive alternative relative to partial adherence. On the other hand, partial adherence is likely at substantially lower cost than full adherence, whether in direct treatment costs or time costs of compliance. Because of its lower cost and greater variance of treatment effectiveness, patients may find it optimal to partially rather than fully adhere to

treatment. The general point is that whatever effects that one believes are true for different levels of adherence can be viewed as multiple treatments with different health outcomes and costs.

A2. Model Calibration

A calibration of our model requires knowledge of the distribution of treatment effects, (μ, σ^2), how well the symptoms reflect treatment or signal noise (σ_ε^2), the costs of treatment (p), and the utility parameters (β, γ). We pull estaimes of the cost and effectiveness of simvastatin directly from the data. We use a combination of data and economic theory to calculate/calibrate the remaining parameters $(\gamma, \beta, \sigma_\varepsilon^2)$.

The health consumption trade-off parameter γ represents a patient's willingness to pay to lower his cholesterol for one quarter. The value of lowering cholesterol is induced from the value of the longevity increase it generates. In particular, is parameter is calculated using data on the longevity gains from simvastatin priced out to dollars using standard value-of-life estimates. Based on the results from the Scandinavian Simvastatin Survival Study (S4)[27], Jönsson et. al (1996) find that simvastatin treatment raised longevity by an estimated 0.377 undiscounted life years. These estimated longevity effects are in line with the results from the Heart Protection Study Collaborative Group (2006) study. This implies that taking simvastatin for an average 58 year old male increases his life expectancy from roughly 81 to 81.377 years.[28,29] Standard existing estimates of the value of a life year at 81 $(VSLY_{81})$ is about $230,000 in 2014 (Murphy

[27] Patients were given 20-40mg of simvastatin daily over a roughly five year period (5.4 years on average). Over the whole course of the study, simvastatin lowered LDL-C levels by 35% on average (Pederson et al. 1994). These findings are similar to those in Bays et. al 2004 study.
[28] The average age in S4 study for males was 58 .1 years old (Pederson et al. 1994). The average age in the Bays et al. (2004) study was 56 years old.
[29] We calculate life expectancy according to the 2009 CDC National Vital Statistics Report and the Social Security Administration.

and Topel (2006)).[30] Under the assumption that the only benefit of simvastatin is increased longevity, we equate the discounted stream of health benefits $\frac{1}{\gamma}\mu$ (expressed in dollars) with the longevity benefits.

$$\sum_{t=0}^{23\times 24} \beta^{0.25t} \frac{1}{\gamma}\, \mu = \beta^{23} VSLY_{81} \times 0.377 \qquad (2)$$

The value of lowering cholesterol can then be induced from the value of the longevity increase it generates. In particular, given our parameter estimates of the parameters μ, $VSLY_{81}$, and β above, the health consumption trade-off parameter satisfying equation (2) is $\gamma = 0.17\frac{\%}{\$}$. In other words, patients are willing to pay one dollar to lower their LDL-C levels by a bit more than a sixth of a percentage point, 0.17%, per quarter.

The calibrated parameters in the model are the discount factor β and the treatment noise σ_ε. We calibrate β and σ_ε to match observed adherence patterns for simvastatin. Using claims data, Yeaw et al. (2009) implicitly estimate the adherence survival function we discussed for the cases of statins.[31] We calibrate β and the ratio $\frac{\sigma_0}{\sigma_\varepsilon}$ to minimize squared differences between the calibrated and empirical adherence survival function at each quarter for the first year.[32] The calibrated health discount factor is 0.90 which is line with the estimates from Moore and Viscusi (1988) and Viscusi and Moore (1989).[33] The calibrated ratio $\frac{\sigma_0}{\sigma_\varepsilon}$ is 2.00. This implies that an

[30] See Figure 2(b) in Murphy and Topel (2006). Since Murphy and Topel's value of life year estimates are expressed in USD 2000 we adjust them by a factor of 1.38 to express the estimate in USD 2014 according to the BLS [http://www.bls.gov/data/inflation_calculator.htm].
[31] Although Yeaw et al. examine adherence to all statins, not just simvastatin, studies have shown that any of the statins available in the US are effective for moderate (up to 35%) LDL-C cholesterol reductions (Smith et al. 2009).
[32] More precisely, we calibrate the values of β and $\sigma_0/\sigma_\varepsilon$ by implementing a grid search over the parameter space $\beta \in \{0.90, 0.95, 0.99\}$ and $\sigma_0/\sigma_\varepsilon \in \{0.50, 0.75, 1.00, 1.25, 1.50\}$.
[33] See Moore and Viscusi (1990) for further discussion on estimating discount rates for health outcomes.

adhering patient's cholesterol level varies naturally from quarter-quarter with a standard deviation of $\sigma_\varepsilon = 7.40\%$.[34]

[34] Note that in principle, the degree to which health symptoms reveal treatment quality (signal-to-noise ratio) could be estimated using longitudinal clinical trial data on health outcomes. When such data is available, one would not need to observe adherence data in order to calibrate the noise distribution, thereby allowing for out-of-sample predictions about future post-approval adherence behavior from trial data obtained pre-approval.