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HEALTH CARE ADHERENCE AND PERSONALIZED MEDICINE[*]

by

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May 11, 2016

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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 research identifies non-adherence as a major source of waste in US health care, totaling approximately 2.3% of GDP, and has proposed a plethora of interventions to raise adherence. However, health economics provides little explicit analyses of the important dynamic demand behavior that drives non-adherence, and it is often casually attributed to ill-informed or naïve patients. We argue that whereas providers may be more informed about the population-wide effects of treatments, patients are more informed about the individual-specific value of treatment. We interpret a patient's decision to adhere to a treatment regime as a simple optimal stopping problem in which patients learn the value of a treatment through treatment experience. 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 impact adherence. 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 including personalized medicine which we argue is intimately linked to adherence issues. Personalized medicine replaces the learning through treatment experience with a diagnostic test, and thereby speeds up the learning process and cuts over-adherence and raises under-adherence. We assess the quantitative implications of our analysis 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 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;[1] 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.[2] 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. 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 it.

Despite the great concerns regarding under-adherence, little explicit economic analysis examines the dynamic demand behavior resulting in non-adherence that offers predictions about

[1] See Bosworth et al. (2011) for further discussion.
[2] 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).

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.

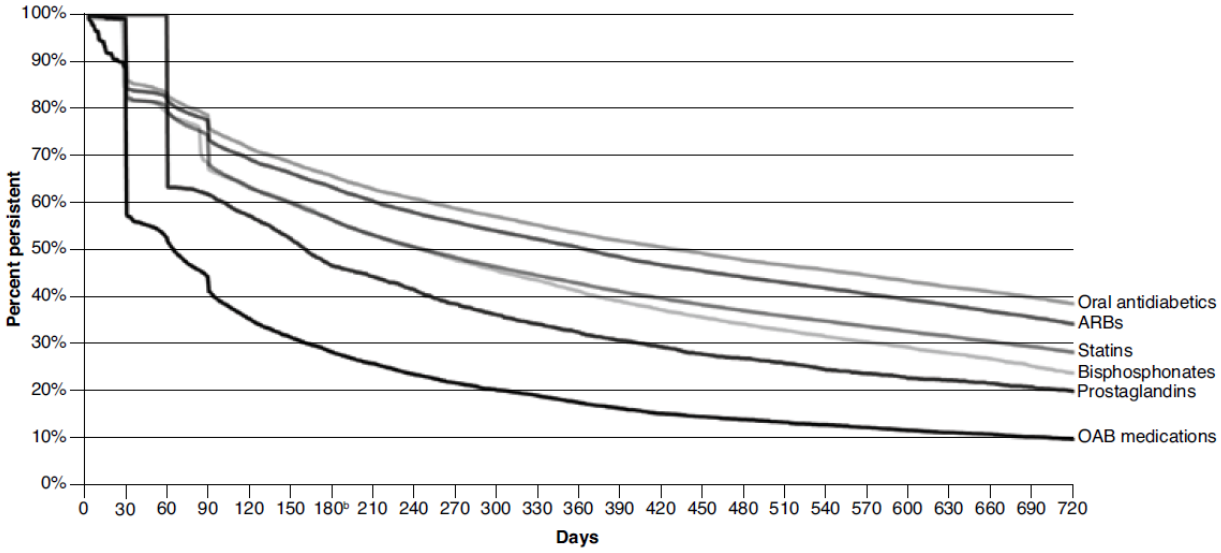
We interpret non-adherence as a simple optimal stopping problem for a patient learning about his individual value of a therapy. Although providers recommending treatments are likely more informed about the *population-wide* effects of these treatments, patients experiencing a treatment are more informed about the *individual* specific value of treatment. This individual specific 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. Patients use a treatment, assess its value on an ongoing basis, and discontinue treatment 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. Learning about treatment value provides one natural explanation.[3] In this context, the common argument that patients under-adhere because they do not understand the benefits of treatment seems unsatisfactory, because those perceived benefits presumably made them start the therapy in the first place.

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

[3] Lien et al. (2010) discusses clinical evidence supporting the view that treatment performance drives adherence in this manner.

over time, implying that good patient–treatment matches last, but bad patient-treatment matches do not last. 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. Figure 1 below depicts the common type of empirical adherence behavior reported in the medical literature across several treatment classes. It displays the general pattern that non-adherence occurs early but then stabilizes, 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. Figure 1 is taken directly (Figure 2) from Yeaw et al. (2009). Details for each drug cohort are as follows. Prostaglandin analogs, such as Xalatan (Latanoprost) are used to manage glaucoma. Statins, such as Lipitor (Atorvastatin), are used to lower cholesterol levels. Biophosonates, such as Fosamax (Alendtronate Sodium), are used to treat osteoporosis. Oral antidiabetics, such as Glucophage (Metformin) are used control blood sugar levels for patients with Type 2 diabetes. Angiotension II Receptor Blockers, such as Hyzaar (Losartan Potassium and Hydrochlorothiazide), are used to treat hypertension. OAB medications, such as Detrol LA (Tolterodine Tartrate) are used to treat overactive bladders.

Our positive analysis predicts that non-adherence occurs early as displayed in Figure 1 because adherence decisions stabilize with sufficient learning about treatment value. In addition,

we find that adherence as conventionally measured may sometimes be increasing in price. 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 individually valuable care, but shorter to non-valuable care.[4] Patients may learn about treatment quality in other ways than through personal experience, such as from communication with providers or through diagnostic tests in personalized medicine, and we also analyze how these impact adherence behavior. We conclude our positive analysis by illustrating how medical innovation impacts adherence over time.

Non-adherence driven by patient learning produces many surprising normative implications. In particular, we argue that separating ex-ante from ex-post efficient adherence is 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 treatment for them, whereas others do not adhere to what turns out to be valuable treatment for them. Therefore, adhering patients who do not value treatment display ex-post over-adherence, and non-adhering patients who value treatment display ex-post under-adherence. We argue that such over-adherence vanishes over time as patients eventually learn that they do not value the therapy. However, under-adherence is permanent if the patient does not re-adhere. In general, we argue that these type I and II errors in adherence have been previously ignored but are central to assessing efficiency effects and also to explain new innovations such as those in personalized medicine.

Our analysis has strong implications for the effects of private and public interventions aimed at altering adherence behavior. We distinguish between interventions that have symmetric

[4] For example, uneducated individuals adhered longer to smoking after it was discovered that cigarettes had the "side-effect" of inducing cancer.

vs. asymmetric effects on patients making type I and II errors in their adherence behavior. 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 through the use of companion diagnostics 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. Companion diagnostics in personalized medicine essentially converts experience goods to search goods by speeding up the learning process and is an asymmetric innovation that eliminates both type I and II errors in adherence. The emergence of innovations in personalized medicine is therefore *explained by* learning as central to adherence and the efficiency gains of eliminating type I and II errors. In particular, the value of personalized medicine is higher when learning through experience is costly relative to learning through a diagnostic, which explains its emergence in cancer care, where type I and II errors in adherence may be fatal. The fact that much of the rationale of personalized medicine seems to be to reduce harmful over-adherence is in direct contrast to the common belief that adherence is too low.

To assess the quantitative importance of these implications, we calibrate the efficiency effects of these type I and II errors in the case of the cholesterol-reducing drug Zocor (simvastatin). 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, even though only 43% of patients eventually adhere.

This paper relates to several strands of previous analysis. There is a large literature on health care demand (e.g. Grossman 1972), but we are not aware of any theoretical positive and normative 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 Philipson and Hedges (1998) and Philipson and Desimone (1997) who analyze attrition in clinical trials when patients learn about treatments from their own experience in the same way investigators learn about population-wide effects from aggregate data. Non-adherence driven by learning after the trial is thus analog to attrition driven by learning in the trial. The paper also relates to later structural estimation papers such as Crawford and Shum (2005), Chan and Hamilton (2006), Fernandez (2013), and Dickstein (2014), but these papers are not concerned with the positive or normative analysis of adherence behavior addressed 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. Indeed, there appears to be many analogies between optimal matching issues in economics and personalized medicine.

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 and the role of personalized medicine as an asymmetric adherence intervention. Section 5 calibrates the amount of over-and under-adherence for the

cholesterol-reducing drug Zocor. Lastly, Section 6 concludes with a discussion of a large set of 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 a simple optimal stopping problem when a patient learns about his 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 the current experience suggests it valuable or not. 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 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

$$h_t = q + \varepsilon_t$$

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

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. For symptomatic disease, the health outcome is observed directly by the patient and for asymptomatic disease it is observed through lab results conveyed to the patient. For example, the value of statin therapy is assessed by cholesterol tests conveyed to the patient. Either way, 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 rather learn about the quality of treatment 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 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

[6] In Section 3.8, we derive the analog implications for the case of multiple treatments which we interpret to include partial adherence levels of a single treatment.

clinical trials in the approval process. We denote a patient's prior at time t as $F_t\left(\cdot \middle| \vec{h}_t\right)$ 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

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

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

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

The patient elects to adhere to treatment if and 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. [8] 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).[9] 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, discount rate β, as well as the variance 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.

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

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

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

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] In the case of multiple treatment options or the case when the value of the alternative treatment is not known with certainty, as discussed in the Appendix A1, the patient may find it optimal to re-adhere to the initial treatment regime.

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

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

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

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 usually seems to refer to adherence conditional on initiation or $S(t)/S(1)$. For example the adherence behavior depicted in Figure 1 in the Introduction concerns this type of secondary adherence.[10]

Section 3: Positive Implications about Factors Driving Non-Adherence

In this section we discuss the many testable implications of interpreting non-adherence as an optimal stopping problem when patients learn about their 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 about the quality of treatment 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 the patient knows the true treatment quality. 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, $U(q,p) \geq U(q_A, p_A)$. This implies that the hazard rate out of treatment, defined as the fraction of remaining patients that quit the treatment in a given period $\left(\frac{S(t)-S(t+1)}{S(t)}\right)$, converges to zero over time. Our model then predicts that the level of adherence

[10] Sometimes the quantity S(t)/S(1) is referred to as *persistence* in the empirical and medical adherence literature, referring to the fraction of patients that refill prescriptions, differentiating it from secondary adherence, referring to fraction of days during the treatment period the prescription was followed.

$S(t)$ flattens out and converges to some positive level $\lim_{t\to\infty} S(t) = S^* > 0$. This implication is consistent with the often reported empirical finding that so called "incident users" who are new to therapy have larger non-adherence rates than so called "prevalent users" who are already on therapy.

In terms of the timing of non-adherence, an implicit implication of our analysis is also that learning must precede non-adherence. In other words, symptoms or lab results that reveal treatment quality must be observable before a patient exits therapy. For example, if side-effects take say three months to manifest themselves for a treatment treating an asymptomatic disease, then a large amount of non-adherence in the first couple of months would invalidate our analysis. The timing of non-adherence should match *when* patients learn about the quality of treatment.

3.2 The Effect of Prices and Income on 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 may rise either due to higher co-pays, premiums, the time-cost of adherence, or other forms of time or monetary costs that contribute to the total cost of care. Such a price increase naturally lowers the value of treatment and lowers the adherence survival function by raising the optimal stopping threshold; $\frac{dz_t}{dp} > 0$. For primary adherence, it's governed by whether the value function at initiation is larger than the permanent adoption of the alternative treatment: $V > U(q_A, p_A)/(1-\beta)$. Since the left-hand side falls in the price p and the right hand side does not, primary adherence falls in price. This simply says that demand is downward sloping in its own price.[11]

[11] 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 that implies larger copays for price-elastic demand. Standard

However, secondary adherence may not be down-ward sloping in its own price. As usually defined as the adherence conditional on initiation, $S(t)/S(1)$, secondary adherence may potentially rise as opposed to fall with price depending on whether the denominator falls more than the numerator. This will depend on the type of patient heterogeneity present. For example, consider when differential prior beliefs in the treatment value determine the level of primary adherence. An increase in price lowers primary adherence but those still initiating believe more in the treatment than those that initiated before the price increase. This would imply a potentially offsetting positive selection effect on secondary adherence counteracting the direct negative price effect on initiation.[12] For example, if the treatment lost patent expiration and went generic, the resulting lower prices would imply larger primary adherence but potentially lower secondary adherence.

The other cost of treatment is the opportunity cost in terms of alternative care that represents the outside option in our stopping problem. 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; $\frac{\partial z_t}{\partial p_A} < 0, \frac{\partial z_t}{\partial q_A} > 0$. Analog arguments imply that primary adherence falls in the value of alternative care, whether through it having a higher quality or lower price, but that secondary adherence may rise or fall with the value of alternative care.

arguments about moral hazard imply that there is excessive adherence without copays. In short, moral hazard implies there is over-adherence rather than under-adherence.

[12]The selection generating these non-standard price-effects on secondary adherence are similar to the empirical findings of Cardon and Showalter (2015) who find that advertising lowers adherence.

To consider the effect of income on adherence in this setting, we assume that health is normal good that is valued more highly by wealthier patients. In this case, a wealthier patient may be represented as having a lower price in terms of the utility loss from foregone consumption represented by a lower parameter value for γ. It is straightforward to show that adherence is decreasing in $\gamma, \frac{\partial z_t}{\partial \gamma} > 0$.

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.[13] 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, $\frac{\partial z_t}{\partial \mu} \leq 0$.[14] In fact, an increase in the average quality of the

[13] 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 vs. 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.

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

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 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 (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. Other things constant, an increase in treatment heterogeneity increases the value of learning about treatment and lowers the patients stopping threshold, $\frac{\partial z_t}{\partial \sigma^2}<0$.[15] 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.[16] As a consequence, heterogeneity has offsetting effects on adherence and produces an indeterminate effect on adherence.

Treatment noise (σ_ε) impacts the speed at which patients learn about treatment quality and also produces offsetting effects on adherence.[17] To illustrate, consider the extreme case

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

[16] 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.

[17] 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. 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 $\frac{\partial z_t}{\partial \sigma_\varepsilon^2} > 0$ (See Lemma 1 in Yao 2006 for further details). On the other hand, treatment noise interacts with treatment quality in driving adherence.

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. The end result is that the effect of noise on adherence is indeterminate.

3.5: Education and Adherence

Learning about treatment quality may occur in other ways than through experiencing it, such as from education or communication with providers. In particular, we examine how education affects a patient's ability to assess treatment quality in the particular Bayesian learning framework assumed here.

We consider when a more educated patient has more accurate beliefs about the true value of the treatment than a non-educated patient. 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 corresponds to having beliefs closer to the truth, education may either be positively or negatively related to adherence.

Regardless of why patients may have more accurate prior beliefs about a treatment, various forms of 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 adherence. A patient's posterior beliefs are determined more and more by treatment performance over time (the weight w goes to unity) regardless of the patient's prior beliefs.

3.6 Provider Communication and Adherence

Providers, such as nurses and doctors, play a critical role not only in the diagnosis and prescription process but also in the patient's adherence decision. The model is easily extended to incorporate the role of providers by considering how providers impact a patient's prior beliefs about treatment as well as how patients update those beliefs based on treatment experience. A provider may have expertise in and educate patients about the *population-wide effects* of the treatment, here $F(\cdot)$, but the patient has the ultimate expertise in the *individual value* of the treatment after experiencing it, here q. In particular, providers do not have expertise in how the patient trades off side-effects, efficacy, or the full time costs of compliance.[18]

A patient's prior beliefs may be partially or totally determined by his medical provider. In the context of the model, providers may provide patients with a noisy signal about the personal effectiveness of treatment $s, s \sim N(q, \sigma_s)$. The patient then incorporates this information into his beliefs such that his beliefs prior to treatment are now

$$F_0(q; s) = N(\mu_0^s, \sigma_0^s)$$
$$= N\left(\omega s + (1-\omega)\mu_0, \left[\frac{1}{\sigma_s^2} + \frac{1}{\sigma_0^2}\right]^{-1}\right), \omega = \frac{\sigma_0^2}{\sigma_s^2 + \sigma_0^2}$$

The patient then updates his beliefs based on treatment experience given his new prior beliefs (μ_0^s, σ_0^s). Better providers may be characterized by providing less noisy signals about the effectiveness of treatment (i.e. smaller σ_s) such that patients of better doctors have more precise

[18] 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.

beliefs about the effects of the treatment. However, as discussed, more precise priors may increase or decrease adherence. Thus more knowledgeable providers do not necessarily lead to more adherence. If there are agency issues, providers may provide biased information to steer patients towards more highly reimbursed treatments (American College of Physicians 1990, Engelberg et al. 2014, Wazana 2000).[19] However, in the long run the effect of the doctor's bias on patient beliefs disappears. As illustrated by eq. (1), the patient's treatment experience dominates the patient's biased prior beliefs. In other words, our model suggests that the agency problem between patients and doctors is muted in the long run when patients can learn treatment quality over time.

3.7: 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. Second, comorbidities may make it harder for patients to infer treatment value from health outcomes.[20] Last, comorbidities may affect adherence by making it marginally more taxing on a patient, both financially and mentally, to undertake multiple treatments for multiple morbidities. 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.

3.8 Medical Innovation and Treatment Adherence

[19] Consider when the provider provides more positive information about a more highly reimbursed treatment. Hence, rather than providing a signal s~N(q,σ_s), doctors may provide patients with a biased signal s_b~N(q+b,σ_s), b>0. If patients are aware of the bias, then this will not impact their adherence decision. If patients are unaware of the bias then the bias results in overly optimistic patients and an increase in short-run adherence.

[20] 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 comorbidities that may be causing a given health outcome. In other words, comorbidities raise the variance of the treatment noise σ_ε^2.

Medical innovation improves the number and quality of treatment options for a given disease over time. Since we argued that treatment quality raises adherence it may seem that innovation should raise adherence. However, the introduction of a new medical treatment impacts adherence through two channels. First, adherence to *a given individual* treatment which may fall as innovation provides substitute treatments. However, the overall adherence to *any treatment in the class* treating the disease may rise with medical innovation as a heterogeneous patient population matches with more individually suitable treatments. Looking at individual treatments adherence falls, although class adherence rises.

More precisely, consider K uncertain treatment alternatives[21] which each have 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 $U\left(h_t^k, p_k\right) = h_t^k - \gamma p_k$.

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.[22] 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

[21] The K treatments could be completely different treatments or alternatively different levels of adherence with the same treatment in case of considering partial adherence.
[22] 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 updated according to the previous updating equation (1) in the single treatment case.

The patient's adherence problem now involves a multiple-bandit problem of 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. [23]

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.[24]

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

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.

[23] The previous discussion with a single uncertain treatment ($k = 1$) and a certain alternative treatment ($k = 2$) corresponds to $K = 2$ with $\sigma_2^2 = 0$.
[24] See Powell and Ryzhov (2012) for a full discussion of Gittins indices.

Consider now the implication of a new medical innovation becoming available. We argue that it will weakly increase class adherence while weakly decrease adherence to the individual treatments within the class. A simple proof by contradiction illustrates this result. It must be the case that no patients currently adhering to the drug class would leave the drug class after the introduction of the new treatment. Assume for contradiction that a set of patients currently adhering to some Treatment A stop adhering to the drug class after the introduction of Treatment B in the same class. Those stopping Treatment A, elect to forgo treatment for some outside option denoted Treatment O. It must be the case that prior to the introduction of Treatment B that the Gittins Index of Treatment A is greater than Treatment O for those patients. Upon the introduction of Treatment B, it must then be the case that the Gittins Index of Treatment O is greater than the Gittins Index for Treatment A for those patients. However, the introduction of Treatment B does not impact either the Gittins Index for Treatment A or Treatment O. Hence, the introduction of Treatment B would not induce patients to switch from Treatment A to Treatment O or vice versa. Class adherence is weakly increasing with the introduction of the new treatment.

Section 4: Normative Implications for Efficient Adherence

In this section we discuss the efficiency implications of non-adherence.[25] Inefficient adherence transpires as the direct result of type I and II errors in adherence as the process in

[25] 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.

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 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 actually truly value the treatment adhere to it. As is well known, improvements in ex-post efficiency will lead to increased ex-ante efficiency but not vice versa so we will focus on the former here.

Let q^* be threshold level of health or treatment quality at which the patient is indifferent between the treatment and the alternative treatment

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

We will refer to individuals who value treatment, such that $q > q^*$, as "valuers" and the remaining group as "non-valuers". Naturally, the reservation level of health q^* is increasing in the price of the treatment and the quality 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 $\frac{\partial q^*}{\partial p_A} < 0$.

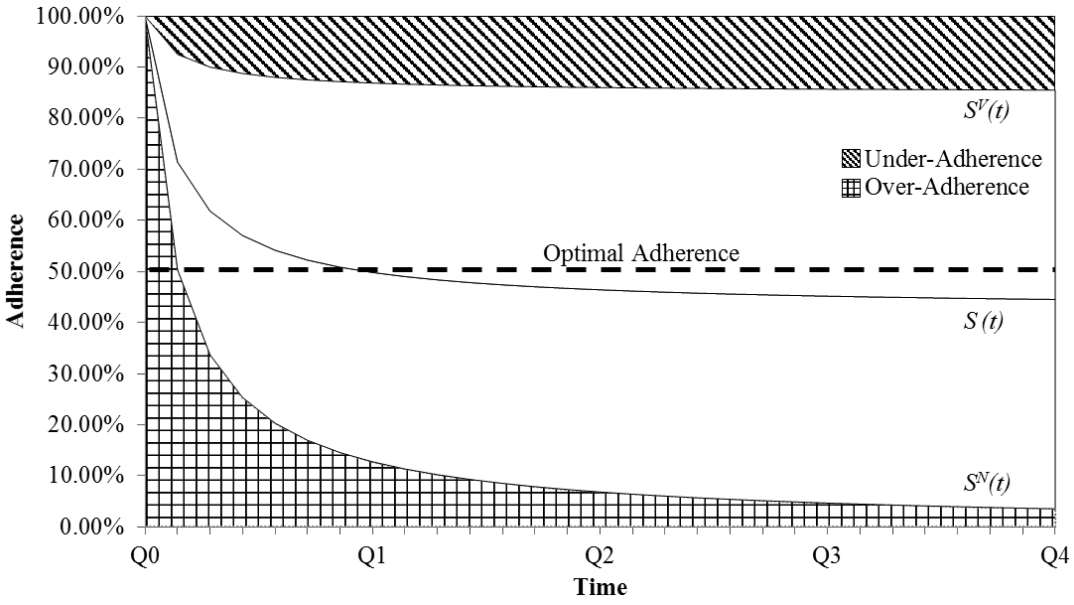
It is ex-post efficient for valuers to be on the treatment but ex-post inefficient for non-valuers to be on the treatment. Therefore, there are two types of ex-post inefficiencies. The first inefficiency is under-adherence. Even though treatment is valuable for a fraction $1 - F(q^*)$ of patients, some 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 non-valuers even though they 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 $S^V(t)$ reflects the proportion of valuers that adhere for each period. Under-adherence by valuers is reflected by the fact that the survival curve $S^V(t)$ is not equal to one. The shaded area above represents $S^V(t)$ thus reflects the proportion of valuers 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-valuers that adhere at each period. Treatment is not valuable for non-valuers, thus $S^N(\cdot)$ represents inefficient adherence. The shaded area underneath the curve $S^N(\cdot)$ thus represents the fraction of non-valuers that inefficiently adhere to treatment. Such inefficient over-adherence is reflected by a strictly positive survival curve for this group. Inefficient adherence occurs because of either the option value of treatment and/or because the patient experienced good initial performance on the treatment. However, sooner or later all of the non-valuers will learn that the treatment is invaluable such that no non-valuers adhere; $\lim_{t\to\infty} S^N(t) = 0$.

FIGURE 2: ADHERENCE BEHAVIOR BY VALUERS AND NON-VALUERS



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

Because true treatment quality raises adherence, as discussed previously, adherence by non-valuers will always be lower than that by valuers, $S^N(t) < S^V(t)\ \forall t$, as depicted in Figure 2. The overall solid survival curve is the mixture of the two conditional survival functions with the mixture weights given by the fraction of true valuers and non-valuers:

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

It follows that in the short-run there will be both under-adherence for valuers and over-adherence for non-valuers. However, in the long run there will always be under-adherence because there are valuers 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, $1 - F(q^*)$, assumed half in the Figure. In the long run, the overall adherence survival function $S(\cdot)$ goes below the optimal level of adherence because non-valuers all disappear and valuers who leave never return. It asymptotes to a stable level since learning makes the non-adherence hazard goes to zero. The survival function $S^N(\cdot)$ of non-valuers goes to zero as non-valuers 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 reservation price is positive for valuers and negative for non-valuers. The dollar value of the welfare loss at time t can then be written as the total loss of the two groups

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

The first term $L_N(t)$is the loss in welfare at time t from non-valuers over-adhering; those who do not value the treatment but still adhere to it. The second term $L_V(t)$ is the loss in welfare at time t from valuers under-adhering; 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 groups

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

The important aspect of this overall welfare loss is that over-adherence is front-loaded while under-adherence is back-loaded as displayed in Figure 2. Therefore, in present value terms over-adherence often matters more than under-adherence which 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- vs. asymmetric effects on valuers and non-valuers.

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 valuers and non-valuers 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 valuers and non-valuers which implies that over-adherence is increased while under-adherence decreased; $\frac{\partial L_N}{\partial p} > 0$ and $\frac{\partial L_V}{\partial p} < 0$. Any intervention that affects adherence behavior by the two groups symmetrically will have indeterminate effects on ex-post efficiency.[26] On the other hand, this will likely be the norm as it is extremely difficult to make adherence interventions operate differently across valuers and non-valuers.

4.2.1 Adherence Interventions that affects learning and personalized medicine

An optimal intervention would have an asymmetric effect on adherence, raising adherence among valuers while decreasing adherence among non-valuers. One such asymmetric adherence intervention is personalized medicine. Personalized medicine, which we here identify 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"

[26] 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.

the patient learning process. The emergence of personalized medicine is therefore *explained by* learning being central to adherence. In particular, 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 (similar to the provider case discussed in Section 3.6. However, learning from the diagnostic may be imperfect just as learning from health experience may be, through a noisy test distributed according to $\eta \sim N(0, \sigma_\eta^2)$. It is straightforward to show the analog threshold property in optimal stopping with diagnostics as before; patients will test into treatment with such a diagnostic if it is above a threshold, $d > x$ and test out of the treatment if they are below it, $d \leq x$.

The sign of the normative welfare effect of having access to a companion diagnostic is clear. A companion diagnostic always raises ex-ante welfare as the patient can always choose not to use it, and be as well off as without the diagnostic.[27] The magnitude of this positive welfare gain depends on the quality of the diagnostic and is highest with a fully accurate diagnostic. Consider a fully accurate companion diagnostic represented by $\sigma_\eta = 0$ and thus the diagnostic reveals the quality fully; $d = q$. In this case the diagnostic is fully informative and true valuers always adhere to treatment and non-valuers never initiate treatment. Thus, the threshold level of the diagnostic is the reservation level of quality defining whether a treatment is valuable, $x = q^*$.

[27] It is often argued that the contraction of treatment demand that follows from personalized medicine when patients test out of treatment will result in lower profits. However, the new *combined* product with a companion diagnostic always raises patient welfare so should be able to be sold at higher prices than the treatment alone.

True valuers test into treatment and non-valuers test out of it thereby producing an *asymmetric* effect on adherence of the two groups. The diagnostic raises adherence by valuers and lowers it for non-valuers. The positive welfare effect is maximized by an accurate diagnostic in the sense that personalized medicine eliminates all ex-post inefficient adherence.

$$\sigma_\eta = 0 \Rightarrow S^V(t) = 1,\ S^N(t) = 0\ \forall t \Rightarrow L = 0$$

This implies that an upper bound on the value of personalized medicine is given by the ex-post efficiency loss *L* discussed and this bound is obtained for a fully accurate test.[28] An implication of this value of personalized medicine 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 explanation of why companion diagnostics have emerged primarily 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 in the treatment classes where learning through experience is costly relative to testing; this is in stark contrast to the common belief that there is too little adherence overall.

Although these normative implications of personalized medicine are clear, the positive implications of how personalized medicine affects adherence behavior are less clear. If we consider the case of a perfect test, it follows directly that secondary adherence rises with personalized medicine as everyone testing into therapy know they value it. However, primary adherence may rise or fall with personalized medicine. This is because some patients that initially did not adhere may test into therapy, thereby expanding the market for the treatment.[29] On the other hand, some patients who adhered may test out of therapy, thereby contracting the

[28] We have elsewhere discussed other value aspects of personalized medicine using evidence from COX-2 inhibitors, see Sood et al. (2013).
[29] This is the case for so called "rescue diagnostics" that are developed to test patients out of any side-effects preventing a drug from getting FDA approval.

market for the treatment. Thus the overall effect on primary adherence is indeterminate and depends on the relative sizes of the two groups.[30]

For imperfect companion diagnostics, it is straightforward to show that both primary and secondary adherence may rise or fall with personalized medicine. As opposed to the case with a fully accurate diagnostic, secondary adherence does not always rise with personalized medicine for reasons similar to the non-standard price effects on secondary adherence. With an imperfect test just as with price effects, both the denominator and the numerator of the ratio of secondary adherence $S(t)/S(1)$ are affected by the personalized medicine.

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

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 adult males taking the drug Zocor (simvastatin) 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 Zocor 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 Zocor

[30] This is assuming the indicated population remains the same. Alternatively one could redefine the adherence and the indicated population based on the diagnostic test.

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 Zocor treatment.[31]

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 valuers 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 lab results reflect Zocor or other factors (signal noise σ_ε^2), the costs of treatment (p), and the utility parameters (β, γ). Note that 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 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 Zocor. We use clinical trial data on the distribution of effectiveness of Zocor from Bays et al. (2004). On average, the Zocor treatment therapy in the Bays et al. study lowered LDL-C levels by 37.00%

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

over a quarter relative to no treatment (placebo).[32] In the context of our model this implies $E[h] = E[q] = \mu = 37.00\%$ and $h_A = q_A = 0.00\%$. We use Zocor 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 Zocor was $231.25.[33] 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, the trade-off parameter γ is calculated using data on the longevity gains from Zocor (Jönsson et. al 1996) valued in terms of dollars using standard value-of-life estimates (Murphy and Topel 2005). Jönsson et. al (1996) find that simvastatin treatment raised longevity by an estimated 0.377 undiscounted life years. 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 Zocor as described in the Appendix. The simple intuition of why these parameters, such as σ_ε, drive the shape of the adherence survival function is that with immediate learning the survival function would be a step-function and with no learning. The calibrated health discount factor is 0.90 which is in-line with the estimates from Moore and Viscusi (1988) and Viscusi and Moore (1989).[34] The noise parameter implies that an adhering patient's cholesterol level varies naturally for other reasons than the treatment from quarter-quarter with a standard deviation of $\sigma_\varepsilon = 7.40\%$.[35]

[32] Patients studied in Bays et al (2004) received dosages of 10-80 mg respectively of simvastatin per day.
[33] 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.
[34] See Moore and Viscusi (1990) for further discussion on estimating discount rates for health outcomes.
[35] 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

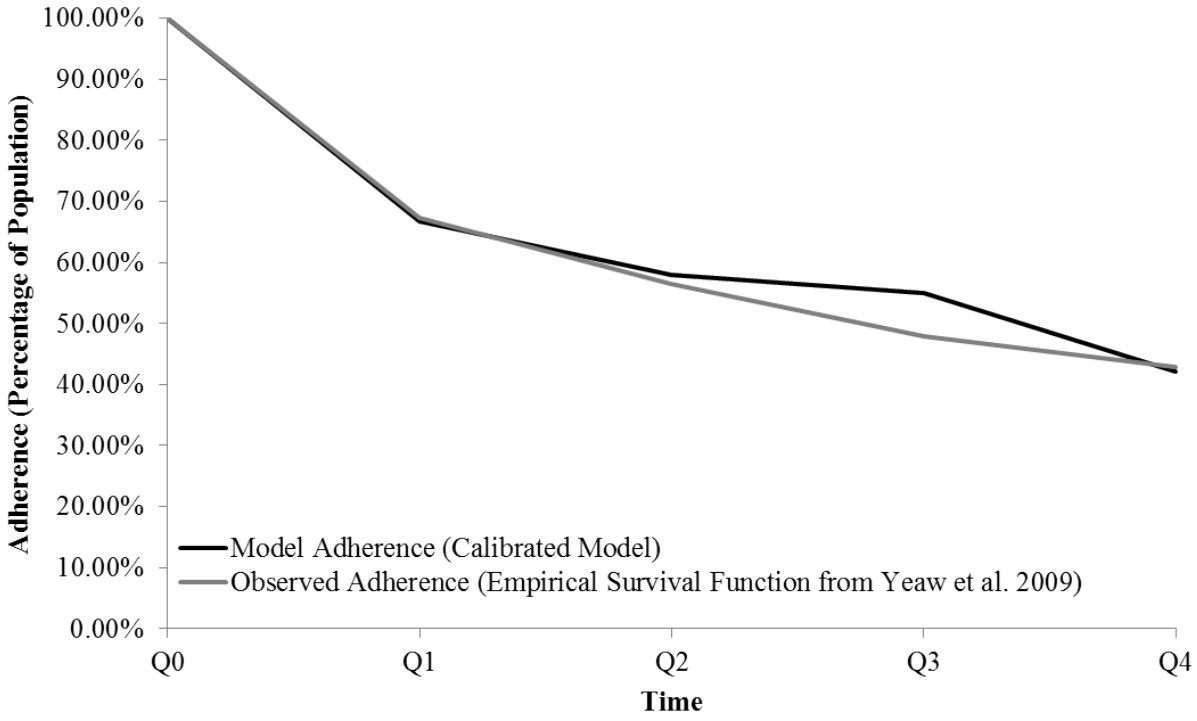
TABLE 1: MODEL PARAMETER VALUES USED IN CALIBRATION

Parameters	Value
Parameters from the Literature:	
Mean Effectiveness of Zocor (μ)	37.00% per quarter
SD of Effectiveness of Zocor (σ)	14.80% per quarter
Cost of Zocor (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

Notes: The mean and standard deviation of the effectiveness of Zocor 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 23 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 Zocor.

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.

FIGURE 3: CALIBRATED ADHERENCE SURVIVAL FUNCTION



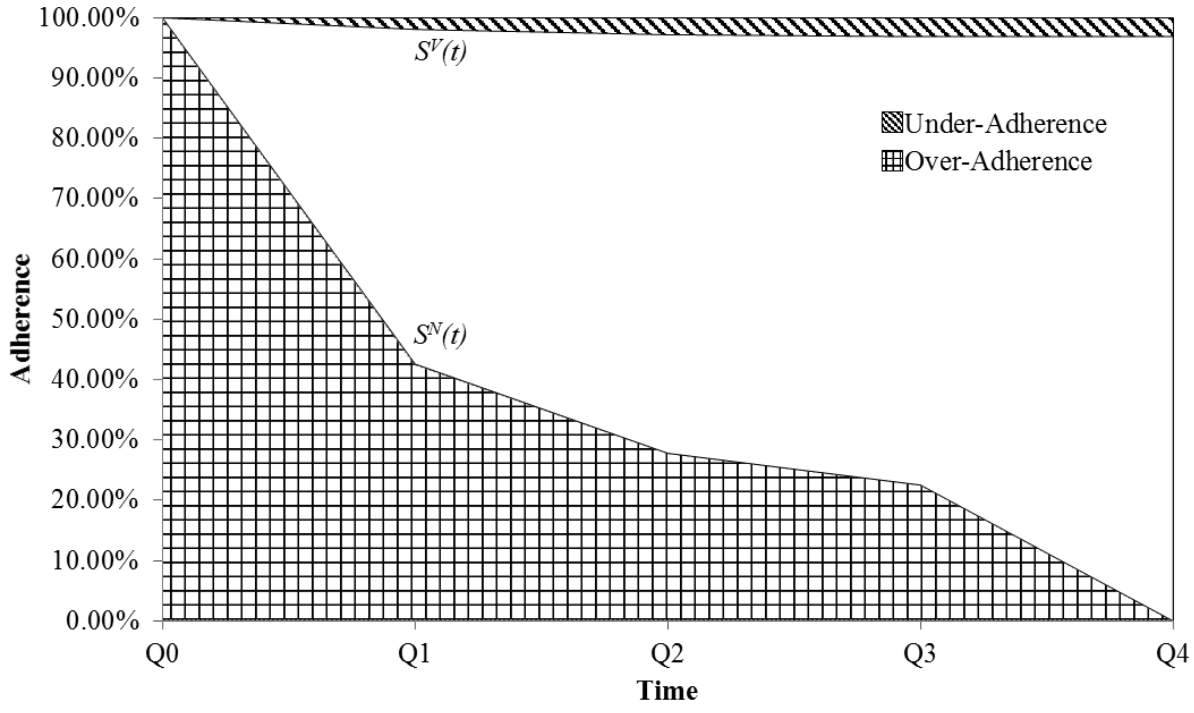
Notes: Figure 3 illustrates the calibrated survival curve corresponding to the parameter values in Table 1 and the empirical survival curve estimated in Yeaw et al. (2009).

Figure 3 above displays the adherence survival function from the calibrated model. We calculate the survival function by simulating 10 million hypothetical patients using 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 as reported in Yeaw et al. (2009). The calibrated survival function exhibits a correlation with the observed empirical survival function of 0.94.

The calibrated model for Zocor allows us quantify ex-post inefficient adherence behavior and separate the inefficiencies driven by over-adherence vs. under-adherence. Figure 4 below displays the calibrated survival functions for non-valuers and valuers 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. These two survival functions suggest

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

FIGURE 4: CALIBRATED UNDER-AND OVER-ADHERENCE



Notes: Figure 4 illustrates calibrated survival curves. The non-valuers survival function, $S^N(t)$, illustrates adherence for those individuals for whom treatment is not valuable/inefficient. Similarly the valuers survival function, $S^V(t)$, illustrates adherence for those individuals for whom treatment is valuable/efficient.

The calibrated model also allows us to dollarize the welfare losses associated with this inefficient adherence. Consider a patient adhering to the Zocor 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.

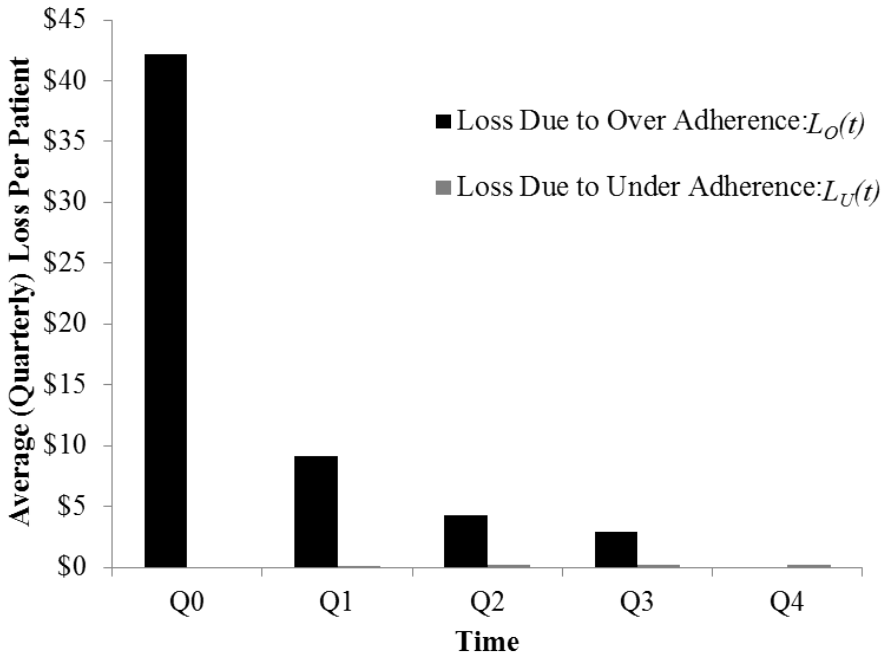
$$Quarterly\ Loss\ Due\ to\ Over\ Adherence = L_O = p - \frac{1}{\gamma}q$$

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

FIGURE 5: CALIBRATED WELFARE LOSSES FOR ZOCOR



Notes: Figure 5 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-valuers 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 valuers normalized by the total number of patients.

The black bars in Figure 5 represent the average welfare loss per patient in a given quarter stemming from over-adherence by patients for whom the Zocor treatment is not valuable. The gray bars represent the average loss per-patient from under-adherence by patients for whom the Zocor 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-valuers 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.[36] 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, 94.1m Zocor 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.

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

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 thereby often associated with ill-informed or naïve 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 positive and normative predictions from interpreting adherence as an optimal stopping problem. We showed how to use readily available data to calibrate the welfare losses stemming from type I and II errors in adherence by considering the cholesterol-reducing therapy 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. In addition, we evaluated the efficiency effects of personalized medicine, a technological advance we argued was explained by role of patient learning and adherence.

Our analysis is in contrast to traditional analysis of adherence, which almost uniformly simply 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 the treatment but patients misconceive these benefits. More precisely, this occurs when the true share of patients who do not value the treatment is zero ($F(q*) = 0$) but prior treatment beliefs are inconsistent with this ($F_0(q*) > 0$). In this case, factors that raise or lower adherence also raise or lower ex-post efficiency, which is often an implicit assumption of much of the existing policy discussions of adherence. However, when not everyone benefits from treatment, as 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, such as personalized medicine.

We believe the analysis raises a host of important research questions that can be addressed in future research.

Behavioral Adherence vs. Therapeutic Adherence

Most of empirical analysis of adherence has centered on the demand for medical products after they have been prescribed by providers. However, the same type of behavior applies to *behavioral* recommendations by providers that usually concern behaviors that improves health, such as weight reduction. Many patients do not adhere to such behavioral recommendations by providers partly because they bear the costs of adhering that providers do not. Even if they engage in primary adherence, they may not adhere later by not following diet or exercise regimes in the long run. Even though data constraints make it harder to study behavioral adherence, e.g. it does not show up in claims data, more research is needed to understand differences between the two forms of adherence. The more wide spread use of electronic medical records that may facilitate empirical analysis of these issues.

Pay for Performance and Performance-Based Adherence

If optimal learning drives adherence, it greatly impacts how care is altered by various pay for performance or risk-contracting policies set by payers to affect providers and manufacturers. If patients do not adhere when a therapy does not perform, reimbursements are not spent on poorly performing care. Put differently, when patients *themselves* engage in "pay for performance" as implied by our analysis, pay-for-performance reimbursements by payers to

manufacturers may have small effects as payers do not pay for ineffective care when patients do not adhere to it. The patient stopping rules implied by our analysis mimic the population-wide-pay-for-performance schemes on the individual level from payers to manufacturers, under which manufacturers only receive payment when a therapy performs well at a population level.

External Effects and Non-adherence

We only considered adherence from the privately optimal 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 tuberculosis 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 a similar issue – adherence confers a positive externality by preventing resistance. 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 implemented through lower copays or other methods that raise adherence. However, such Pigouvian subsidies do not discriminate across type I and II errors. Therefore, careful analysis of the role of adherence promotion 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 policy analysts think patients need to be better educated about treatments when compliance is poor but the health benefits are substantial. However, our analysis directly implies that those that adhere perform better than those that do not, and thus the

effect on health is upward-biased 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. In addition, standard forms of selection bias could be present, such as otherwise healthier patients, regardless of treatment, being the ones that adheres the most. Both forms of selection also affect the optimal targeting of adherence interventions; low levels of adherence may reveal preferences that imply small effects for adherence interventions.

Structural Estimation of Trial Attrition to Predict Post-approval Adherence

The structural model of adherence discussed implies strong relationships between "real-world" vs. clinical trial performance of treatments. However, attrition behavior in clinical trials may stem from the same type of behavior analyzed here (Philipson and DeSimone 1999). One implication of that past analysis as well as the adherence analysis here is that past performance lowers the hazard rates into non-adherence. This prediction may be tested by longitudinal data in both trial and real-world adherence settings. The latter form of data may become more abundant as merged data on insurance claims (measuring adherence) and electronic medical records (measuring performance) are more readily available in the future. Because of this similarity in behavior one can estimate the structural parameters from only having attrition behavior from clinical trial data. The parameters can then be used 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. The complementary role of empirical testing of explicit theories seems needed before one 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

In Section 3.8 we extend our learning based model of non-adherence to the case with multiple treatment alternatives. Here we generalize the main implications discussed in Section 3 for multiple treatments.

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 for 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 vs. 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 estimates 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 Zocor priced out to dollars using standard value-of-life estimates. Based on the results from the Scandinavian Simvastatin Survival Study (S4)[37], 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 Zocor for an average 58 year old

[37] 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 (Pedersen et al. 1994). These findings are similar to those in Bays et. al 2004 study.

male increases his life expectancy from roughly 81 to 81.377 years.[38,39] Standard existing estimates of the value of a life year at 81 ($VSLY_{81}$) is about $230,000 in 2014 (Murphy and Topel (2006)).[40] Under the assumption that the only benefit of Zocor 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.[41] 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.[42] The calibrated health discount factor is 0.90 which is line with the estimates from Moore and Viscusi

[38] The average age in S4 study for males was 58 .1 years old (Pedersen et al. 1994). The average age in the Bays et al. (2004) study was 56 years old.
[39] We calculate life expectancy according to the 2009 CDC National Vital Statistics Report and the Social Security Administration.
[40] 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].
[41] 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).
[42] 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 $\sigma_0/\sigma_\varepsilon \in \{0.50, 0.75, 1.00, 1.25, 1.50\}$.

(1988) and Viscusi and Moore (1989).[43] The calibrated ratio $\frac{\sigma_0}{\sigma_\varepsilon}$ is 2.00. This implies that an adhering patient's cholesterol level varies naturally from quarter-quarter with a standard deviation of $\sigma_\varepsilon = 7.40\%$.[44]

[43] See Moore and Viscusi (1990) for further discussion on estimating discount rates for health outcomes.

[44] 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. e