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The Timing and Probability of Treatment Switch under Cost Uncertainty: An Application to Patients with Gastrointestinal Stromal Tumor

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ABSTRACT

Background: Cost fluctuations render the outcome of any treatment switch uncertain, so that decision makers might have to wait for more information before optimally switching treatments, especially when the incremental cost per quality-adjusted life year (QALY) gained cannot be fully recovered later on. **Objective:** To analyze the timing of treatment switch under cost uncertainty. **Methods:** A dynamic stochastic model for the optimal timing of a treatment switch is developed and applied to a problem in medical decision taking, i.e. to patients with unresectable gastrointestinal stromal tumour (GIST). **Results:** The theoretical model suggests that cost uncertainty reduces expected net benefit. In addition, cost volatility discourages switching treatments. The stochastic model also illustrates that as technologies become less cost competitive, the cost uncertainty becomes more dominant. With limited substitutability, higher quality of technologies will increase the demand for those technologies disregarding the cost uncertainty. The results of the empirical application suggest that the first-line treatment may be the better choice when considering lifetime welfare. **Conclusions:** Under uncertainty and irreversibility, low-risk patients must begin the second-line treatment as soon as possible, which is precisely when the second-line treatment is least valuable. As the costs of reversing current treatment impacts fall, it becomes more feasible to provide the option-preserving treatment to these low-risk individuals later on.

Keywords: cost uncertainty, decision analysis, economic evaluation, health economics, switch treatments.

Introduction

For some diseases, patients receive a sequence of treatments. These may involve different drugs or different dosages of the same drugs. The decision regarding whether to move a patient to the next treatment in a sequence may be based on patient characteristics or patient history, and therefore subject to variability. If it is accepted that adoption decisions should be made with consideration of the associated decision uncertainty, then we may say that models submitted to decision makers should do two things: estimate expected net benefit (NB) and characterize decision uncertainty. If this dual purpose of models is accepted, failure to fulfill the latter requirement will limit its value for decision making and leave the decision maker without a key element of information.

The decision to adopt a particular technology should be based on the expected NB so that when comparing mutually exclusive treatment strategies for a particular disease, the optimal strategy is simply the one with the highest expected NB [1]. Nevertheless, decisions based on the expected NB are appropriate only if there is also some consideration of whether current evidence is sufficient for allocating health care resources, based on an assessment of the consequences of decision uncertainty [2]. If the decision uncertainty and the consequences of adopting a suboptimal treatment strategy are large, the decision maker may require further evidence on which to base the adoption decision [3].

For example, adopting some medical technologies restricts the use of certain medical technologies in the future, and explains the lack of consensus about when to start therapy in HIV patients [4,5]. Some advocate fighting HIV with a powerful combination of drugs as early as possible in the course of the disease to prevent the disease from progressing. Others are concerned that starting therapy at early stages may lead to the development of viral resistance to these drugs and related compounds and the disease may progress to an advanced stage more rapidly, while other clinicians advocate waiting until the disease reaches a more advanced stage to initiate treatments so that future options can be preserved. This problem of current decisions affecting future options has received considerable theoretical attention in the literature on economic investments. The higher the uncertainty about future outcomes, the more individuals will gain from waiting for more information before committing to investment (or dis-investment) whenever there are significant sunk costs [6]. This result is a prediction of the "option-pricing" approach to the analysis of irreversible investment under uncertainty [7–9]. Analogously, benefits associated

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with actions that preserve treatment choices in the future, above and beyond the direct value associated with those actions, are referred to as the option value of the intervention [10].

For many physicians the observation that current medical treatment decisions have repercussions for the treatment of health conditions in the future is an obvious one that is often considered in their clinical decision making. Such considerations form no part of health care technology assessment calculations, leading to potentially significant mischaracterizations of the treatment value. While it is difficult to systematically assess the size of the bias induced from ignoring option values, the only empirical study in the health domain found an increase in consumer willingness-to-pay of approximately 53% when option values were considered [11].

Using the option-pricing approach for the analysis of irreversible treatment choices under uncertainty is important because the health sector is one in which there is tremendous uncertainty about the demand for future medical technologies. When we begin treating a population of individuals, we do not know what additional conditions they will develop in the future. Because new diseases are constantly emerging, we do not even necessarily know the nature of these future conditions. Higher life expectancy prospects for new conditions to arise, especially those associated with aging such as cancer and dementia, make the option value of the interventions a key variable of the valuation equation. Ignoring option values during the drug approval and reimbursement setting process could result in disincentives to create socially valuable technologies. Finally, unlike many private investment decisions, decisions taken by national health systems may be effectively irreversible for political reasons. Palmer and Smith [12] focus on the timing of health investments and whether it makes sense to delay the adoption of a new technology in anticipation of the exogenous arrival of new information about its value. While the prospects for delaying investments have potentially important implications for decision making, delay is often not feasible in this setting, especially on the time scale under which we expect new information to arrive. When analyzing situations in which current treatment decisions have irreversible implications for the treatment of future diseases, and decision makers are choosing between competing interventions with differing temporal consequences, Zivin and Neideill [10] find that irreversibility raises the value of treatment modalities that preserve future treatment options. Introducing some reversibility, however, can either increase or decrease the option value, depending on the distribution of patient types. These authors also examine the relationship between these values and the biological and economic parameters that characterize any given set of technologies. Meyer and Rees [13] analyze the treatment decision at a general level. They determine optimal threshold values for initiating the intervention, and derive comparative statics results with respect to model parameters. In particular, an increase in the degree of uncertainty over the patient's health state, in most cases, makes waiting more attractive. This may not hold, however, if the patient's health state has a tendency to improve.

This article follows the theory very closely to develop a dynamic stochastic model for the optimal timing of a treatment switch. Its main value addition consists in the concrete application to a problem in medical decision taking, that is, to patients with unresectable gastrointestinal stromal tumor (GIST). In the stochastic model, we assume two lines of treatment in treating a chronic disease and we consider the problem of a patient who is using the first-line treatment but the decision maker is contemplating switching to a second-line treatment that consists of higher doses of the drug used in the first-line treatment and then provide a more advanced drug. The patient will use the new line treatment only if such a move is deemed beneficial in the medium and long term. That, in turn, will depend on the perceived evolution of cost. The higher the uncertainty regarding the cost of a new treatment, the more likely it is that a favorable situation will turn into an unfavorable one, and the more the patient will gain from waiting for more information before committing to the new treatment whenever the incremental cost per quality-adjusted life-year (QALY) gained cannot be fully recovered later on.

With the aim of empirically testing this study's option-pricing model, an empirical application uses data from a modeling exercise that compared alternative treatment pathways for patients with unresectable GIST who failed to respond to imatinib 400 mg/d [14]. The study of Hislop et al. [14] assessed the effectiveness and cost-effectiveness of imatinib at escalated doses of 600 and 800 mg/d following progression of disease at a dose of 400 mg/d, compared with sunitinib, or the provision of best supportive care (BSC) only for patients with unresectable and/or metastatic GISTs. Several studies have reported further disease control after progression on an initial imatinib dose of 400 mg/d with dose escalation of imatinib to 800 mg/d, and this has also become common practice [15,16]. However, it should be noted that current National Institute for Health and Care Excellence guidelines for imatinib do not actually recommend dose escalation for patients with unresectable and/or metastatic GISTs who progress on an initial dose of 400 mg/d [17] but suggest that clinical decisions be made on an individual case-by-case basis, reflecting uncertainty regarding optimal practice.

Three studies [18–20] compared imatinib with BSC. The study by Wilson et al. [18] used the manufacturer submissions (Novartis model) and compared imatinib and BSC, but in the imatinib group allowed for escalation of doses from 400 to 600 mg/d for those who failed to respond or were intolerant to imatinib at the 400 mg/d dose. The study by Mabasa et al. [20] noted that patients included from retrospective cohorts in their analysis were given imatinib 400 mg/d until disease progression, and later were allowed escalated doses of between 600 and 800 mg/d. Six of 56 patients in the imatinib group of patients considered in this economic evaluation were then allowed to switch to sunitinib therapy. The economic evaluation by Huse et al. [19] considered imatinib at 400 mg/d. Two studies [21,22] compared both imatinib and sunitinib with BSC for patients who had failed or become resistant to imatinib 400 mg/d.

The empirical application of this study assumes that patients in the first-line treatment are being treated with 400 mg/d and the second-line treatment consists of dose escalation of imatinib to 600 mg/d followed by sunitinib. Empirical results suggest that the existence of an option value means that the first-line treatment may be the better choice when considering lifetime welfare. Thus, under irreversibility, low-risk patients must begin the second-line treatment as soon as possible, which is precisely when the second-line treatment is least valuable. As the costs of reversing current treatment impacts fall, it becomes more feasible to provide the option-preserving treatment to these low-risk individuals later on.

This article is organized as follows. The following section develops the stochastic option-pricing model, specifying the two feasible treatments and examining the effect of cost shocks on both the timing of treatment switching and the NB of each treatment. The next section presents the probability and expected time of treatment switch. The discussion of the results with an empirical application is presented in the following section. Conclusions are discussed in the last section.

The Model

In this section, we develop a model to illustrate the role that uncertainty and irreversibility can play in determining the decision regarding whether to move a patient to the next treatment