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Innovative Applications of O.R.

Using a partially observable Markov chain model to assess colonoscopy screening strategies – A cohort study

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ABSTRACT

Colorectal cancer (CRC) is notoriously hard to combat for its high incidence and mortality rates. However, with improved screening technology and better understanding of disease pathways, CRC is more likely to be detected at early stage and thus more likely to be cured. Among the available screening methods, colonoscopy is most commonly used in the U.S. because of its capability of visualizing the entire colon and removing the polyps it detected. The current national guideline for colonoscopy screening recommends an observation-based screening strategy. Nevertheless, there is scant research studying the cost-effectiveness of the recommended observation-based strategy and its variants. In this paper, we describe a partially observable Markov chain (POMC) model which allows us to assess the cost-effectiveness of both fixed-interval and observation-based colonoscopy screening strategies. In our model, we consider detailed adenomatous polyp states and estimate state transition probabilities based on longitudinal clinical data from a specific population cohort. We conduct a comprehensive numerical study which investigates several key factors in screening strategy design, including screening frequency, initial screening age, screening end age, and screening compliance rate. We also conduct sensitivity analyses on the cost and quality of life parameters. Our numerical result demonstrates the usability of our model in assessing colonoscopy screening strategies with consideration of partial observation of true health states. This research facilitates future design of better colonoscopy screening strategies.

Introduction

Colorectal cancer (CRC) ranks third in incidence among cancer diseases and second in cancer-related death in the U.S. (Jemal, Bray, & Center, 2011). Nonetheless, CRC is often cured if detected early, e.g., the 5-year survival rate for localized CRC is 90% while the survival rate is only 12% if the cancer has spread to distant locations (Howlader et al., 2012). However, there are often no symptoms when CRC is in its early stages. Fortunately, with improved fiber optic technology, enhanced understanding of CRC natural history, and more intelligent screening strategies, it is increasingly possible to detect polyps including precancerous adenomas early, predict their progression accurately, and thus reduce CRC incidence and mortality. Furthermore, slow precancerous adenoma progression allows intelligent application of screening to detect and remove adenomas before they become cancerous.

Colonoscopy is the most accurate CRC screening test as it provides a visual diagnosis of the entire colon and rectum. It can detect precancerous adenomas and remove them immediately before they become cancerous. This adenoma removal procedure, also called polypectomy, can significantly reduce patients' cancer risks. The American College of Gastroenterology (ACG) recommendations imply that colonoscopy is the preferred cancer screening method (Rex et al., 2009). The ACG further suggests that other cancer detection tests are less preferred but should be offered to patients who decline colonoscopy. In addition to colonoscopy, several CRC screening methods are currently used in practice. These include fecal testing for occult blood (i.e., g-FOBT, FIT, and i-FOBT), fecal DNA testing, flexible sigmoidoscopy, and computed tomographic colonography (virtual colonoscopy). Guidelines from the U.S. Multisociety Task Force (Levin et al., 2008) and the U.S. Preventive Services Task Force (U.S. Preventive Services Task Force, 2008) recommend some of the above alternative screening methods that are less invasive and less expensive than colonoscopy. However, these methods are only good at detecting preclinical cancer but not adenomas. Hence, their value is only significant in low risk populations. Therefore, our main objective is assessing colonoscopy screening strategies using an innovative mathematical model.

We consider two classes of colonoscopy screening strategies: fixed-interval screening strategy and observation-based screening

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strategy. With a fixed-interval screening strategy, patients are recommended to take the screening tests in a fixed time interval regardless of their cancer risks. An observation-based screening strategy, however, specifies the timing of the next screening based on the previous screening result. Intuitively, a well designed observation-based screening strategy should be more desirable than a fixed-interval screening strategy since it determines screening intervals based on an individual's cancer risk rather than treating all patients the same. Thus, designing a good observation-based screening strategy is an important research question.

We develop a discrete-time partially observable Markov chain (POMC) model with a detailed description of precancerous adenoma states and a set of age-dependent transition probabilities estimated from a large longitudinal clinical data set for a specific population cohort. Traditionally, Markov models are used to represent the transitions among the true adenoma states. However, the true adenoma states can rarely be observed with complete accuracy due to limitations of the technology and insufficient experience of the practitioner who performs the test. For example, based on Rex et al. (1997), only about 70% of small adenomas (size less than 5 mm) are detected by a single colonoscopy. Thus, we use belief states to capture the likelihood of each true state being occupied. We update the belief states in a Bayesian manner based on the latest colonoscopy findings and the disease progression, i.e., natural history. By using a detailed description of precancerous adenoma states, the state space of our POMC model becomes much larger compared to the existing Markov models in the literature. Furthermore, by incorporating incomplete adenoma detection and removal, optimization of screening strategies with the POMC model becomes extremely challenging computationally. Therefore, we focus on assessing the cost-effectiveness of the screening strategies and investigating the effects of several key factors in the strategy design, including screening frequency, initial screening age, screening end age, and partial compliance to screening tests.

Our work is among the first that applies POMC modeling to assess colonoscopy screening strategies. Our main contributions are twofold. First, we incorporate inaccurate observations of health states and update the belief state based on the colonoscopy test results in a Bayesian manner. Such incorporation of partial observability has not been seen in the literature of economic analysis for CRC screening. Second, we conduct comprehensive cost-effectiveness assessment and compare fixed-interval and observation-based colonoscopy screening strategies. Although our results may lack generalization because our parameter estimations are based on a specific population cohort, the modeling framework is valuable and can be easily adapted to assess colonoscopy screening strategies for any other cohort once its clinical data is available.

The remainder of this paper is organized as follows. In section 'Literature review', we provide literature review on both well-accepted and recent economic studies and decision models on CRC screening strategy design. In section 'Model development', we present our POMC model and describe the belief update and outcome measures. In section 'Parameter estimation and experiment design', we describe our data sources, parameter estimation, and experimental design. We report numerical studies with a baseline case study and several sensitivity analyses in section 'Numerical results'. Conclusions and future research directions are presented in section 'Conclusions and future work'.

Literature review

Long duration of CRC progression at the precancerous stages and availability of various screening methods motivate the development of accurate CRC disease models and the analysis of cost-effectiveness for CRC screening. Pignone et al. (2005) and Zauber et al. (2012) summarized most existing CRC models which can be divided into two categories: discrete-event based models and Markov based models. Discrete-event simulation models (Cubbage, 2004; Ness, Holmes, Klein, & Dittus, 2000; Roberts, Wang, Klein, Ness, & Dittus, 2007; Tafazzoli, Roberts, Ness, Klein, & Dittus, 2009; Loeve, Boer, van Oortmarssen, van Ballegooijen, & Habbema, 1999; Loeve et al., 2000; Rutter, Zaslavsky, & Feuer, 2010; Wilschut et al., 2011) simulate a population of individuals from birth to death. Each simulated individual experiences a series of events, including colorectal adenoma incidence, growth, and transition, CRC staging, CRC or non-CRC induced deaths, CRC screening tests, and adenoma removals. The cost and effectiveness outcomes can be obtained via the simulation. Discrete-event simulation models suffer from complexity that hinders transparency as well as the need of extensive data for calibration. Markov based models (Frazier, Colditz, Fuchs, & Kuntz, 2000; Sonnenberg, Delco, & Inadomi, 2000; Vijan, Hwang, Hofer, & Hayward, 2001; Song, Fendrick, & Ladabaum, 2004; Ladabaum, Song, & Fendrick, 2004; Heitman, Hilsden, Au, Dowden, & Manns, 2010; van Rossum et al., 2011; Sobhani, Alzahouri, Ghout, Charles, & Durand-Zaleski, 2011; Hedden et al., 2012; Lucidarme et al., 2012), on the other hand, specify CRC-related health states individuals may occupy during their lifetimes and use the Markovian property to guide state transitions in a discrete fashion. The occurrence of CRC screening alters the state transition from natural disease progression. These Markov chain-based models differ in CRC-related health states definition, state transition probability, time horizon, and outcome parameters, but all of them assume the health states of a person are explicitly observed, which is not necessarily valid due to the asymptomatic nature of early-stage CRC. It is worth noting that three models have been approved by the Cancer Intervention and Surveillance Modeling Network (CISNET), which represents the state of the art for the CRC screening models (National Cancer Institute, 2012). They are MISCAN-Colon model (Loeve et al., 1999; Loeve et al., 2000), Sim-CRC model (Frazier et al., 2000), and CRC-SPIN model (Rutter & Savarino, 2010).

Through literature review, we identify two important issues that, to the best of our knowledge, are not fully addressed in the existing CRC screening strategy assessment literature. The first issue is the assessment of observation-based colonoscopy screening strategies. Even though the current guideline developed by the U.S. Preventive Work Force has recommended the observation-based strategies for patients with different colonoscopy screening results in terms of the number of precancerous adenomas and the size of each of the adenomas (Levin et al., 2008), we have not witnessed any study that assesses the cost-effectiveness of the observation-based strategies and their variants. To achieve this, a more detailed description of the CRC natural history model is required, which implies an expansion of the state space in the existing Markov based models and requires more complicated model calibration with detailed colonoscopy observation data. In addition, adenoma removal via polypectomy is a unique feature associated with colonoscopy, which requires the incorporation of reverse transitions in the model. The other issue is the partial observability of patients' health states from colonoscopy screening tests. Most previous Markov-based cancer screening models assume patients' health conditions can be fully observed, which is not realistic. Maillart, Ivy, Ransom, and Diehl (2008) and Ayer, Alagoz, and Stout (2012) incorporated partial observability in the design of mammography screening strategy, and Zhang, Denton, Balasubramanian, Shah, and Inman (2012a, 2012b) proposed partially observable Markov decision process (POMDP) models to study prostate cancer screening decision making. All of these models either for breast cancer or prostate