

Medical decision making: open research challenges

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In recent decades there have been many advances in methods for the prevention, diagnosis, and treatment of diseases. These advances have resulted in improved health care for many patients, including longer lifespan and a better quality of life. They have also increased the complexity of medical decisions and created an opportunity for industrial and systems engineering (ISE) and operations research (OR) methods to assist medical decision making. This article summarizes some of the active areas of research and describes several examples of open problems.

Keywords: Medical decision making, disease screening, treatment

1. Introduction

Many advances have been made in methods for preventing, diagnosing, and treating diseases. These new innovations have resulted in increased life expectancy and improvements in the quality of life for many patients. However, they have also increased the complexity of medical decision making. In many cases physicians and patients must balance the potential harm and benefit of medical interventions. Often the complexity of these decisions is compounded by uncertainty in future outcomes such as adverse events associated with diagnostic tests or long term effects of treatment. As a result of these challenges there are numerous opportunities for the application of industrial and systems engineering (ISE) and operations research (OR) methods to assist in medical decision making.

Historically, medicine has been an empirical scientific discipline, centered around hypothesis generation and testing through randomized control trials (RCTs). However, not all research questions can be answered through RCTs. For instance, RCTs are often too costly to conduct, deemed unethical by institutional internal review boards, or subject to unavoidable sources of bias. Furthermore, in some cases the time required to conduct an RCT is prohibitive due to the likelihood of changes in standards of care or other factors that may confound the results of an RCT.

As a result of challenges in conducting RCTs, and the recent availability of unprecedented amounts of data about the disease incidence and progression, the use of quantitative models is gaining acceptance. Methods such as decision analysis, Markov decision processes, mathematical programming, simulation, and statistical process control, to name a few, have found applications in medicine. This has led to emerging research opportunities for ISE and related fields to play a role in helping to advance basic knowledge in many areas of medical decision making.

The purpose of this article is to highlight some examples of successful ISE applications and to point out open research challenges and opportunities related to medical decision making. It is not intended to be an exhaustive survey of the current state of the art (extensive surveys related to medical decision making can be found in Pierskalla and Brailer (1994), Brandeau *et al.* (2004), Schaefer *et al.* (2004), Zhang *et al.* (2011)). Rather, this article provides some specific examples of recent research and emerging opportunities related to the prevention, detection, and treatment of diseases.

The remainder of this article is organized as follows. In Section 2 we present several examples of stakeholders in the decision making process. In Sections 3 to 5 we provide examples of ISE methods applied to disease prevention, detection, and treatment decisions, respectively. In Section 6 we give some examples of ISE methods that have been translated into practice. Finally, in Section 7 we present

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some conclusions about the state of current research along with opportunities for the future.

2. Decision maker perspectives

Applications of ISE methods to medical decision making often seek to find an optimal choice among alternatives. For example, selecting the best sequence of screening tests to diagnose a disease, or the best medication regimen or surgical intervention to treat or cure a disease. These problems require an explicit definition of the criteria associated with the decisions. The criteria are determined by the stakeholder perspective. In medical decision making there are four commonly considered perspectives: patient, physician, third party payer, and societal.

The criteria of the stakeholder is influenced by the health system in which they reside. For example, if patients have third-party health insurance that covers all or most health-care expenditures, then the most relevant criteria are those related to the effects of treatment. Treatment effects can be positive (longer life expectancy, a reduction in chronic conditions, or improved quality of life) or negative (short-or-long term side effects, disablement, or death). A common way to quantify the tradeoff between the pros and cons of treatment is through the use of quality adjusted life years (QALYs), which is a numeric measure for a year of life between 0 (death) and 1 (perfect health). Estimates of QALYs can be elicited through patient surveys and are commonly used for treatment evaluation and health policy investigations (see Packer (1968) and Fanshel and Bush (1970) for a review of the use of QALYs).

The physician perspective is often assumed to be aligned with that of the patient. In practice, decisions are often made through a shared patient-physician decision making process. When third-party payer or societal perspectives are considered, costs become part of the criteria. The decision of which costs to include in a study can be challenging. For example, costs may include the direct cost of drug treatment, hospital billing for procedures, the cost of follow-up visits to monitor treatment (e.g., laboratory testing of cholesterol levels following initiation of cholesterol lowering medication), or to evaluate recovery (e.g., outpatient visits to a surgeon in the weeks and months following surgery). In some cases the cost burden may be on members of a patient's family and friends, or on a patient's employer due to leave from work. From the third-party payer perspective there is a tradeoff between the immediate cost of medical treatment (e.g., blood pressure lowering medications) and long term potential cost savings associated with avoiding serious health outcomes (e.g., heart attack or stroke).

The societal perspective, which simultaneously considers the patient, physician, and third-party payer perspectives, involves the consideration of multiple criteria. Quantitative analysis requires a factor, sometimes referred to as *willingness-to-pay*, which defines the monetary value

of QALYs. A commonly used estimate in the U.S. is \$50,000/QALY; however, the most appropriate value is widely debated (Rascati, 2006). Often researchers will explicitly consider multiple criteria and employ the concept of an *efficient frontier* to determine candidate solutions that are not dominated. Identifying the gap between the optimal solution for the patient/physician and the third-party payer perspective informs the debate about optimal decision making.

3. Disease prevention

The benefits of disease prevention are summarized by the idiom "an ounce of prevention is worth a pound of cure." Advances in the state of knowledge about risk factors for disease have created new opportunities to help individuals avoid or delay disease onset and progression. However, these advances have also added to the complexity of medical decisions. ISE methods can assist in making decisions about how best to prioritize risk factors, select preventative treatment options, and estimate the effects of prevention programs for individual patients as well as for entire populations.

An important aspect of prevention is educating patients about risk factors such as smoking, obesity, cholesterol, and blood pressure control. All of the above are well established risk factors for cardiovascular disease, a leading cause of death in many parts of the world. While the benefits of controlling risk factors are clear, success in prevention at the population level can be costly. For many patients, their primary care physician is the likely source of information about the importance of prevention. However, physician time is costly and limited, leaving decision makers with the open questions of how to prioritize educational activities and how to optimize the timing of interventions.

Mason *et al.* (2011) studied the benefits of adherence improving educational interventions in the context of cholesterol lowering medications. The authors found that the optimal time to initiate statin treatment is influenced by the likelihood of patient adherence. They present cost-effectiveness analysis on the evaluation of hypothetical adherence improving interventions designed to improve the likelihood a patient takes their daily dose of medication. They find that interventions can increase expected QALYs for patients, and may reduce overall costs to the health system by avoiding costly health outcomes.

Vaccination is another important topic that is central to disease prevention. There are many challenges related to the delivery of vaccines to a population. First, there are often multiple delivery methods including monovalent and multivalent vaccines with varying costs and benefits. Second, some vaccines have conflicts with others and some have special scheduling requirements, such as multiple doses that must be administered within a minimum or maximum time window. Third, for some diseases there is uncertainty about

the future evolution of epidemic strains, resulting in questions about selecting the best design. Pediatric or childhood vaccination is the most common means of mass vaccination. OR researchers have developed models to aid in the selection of a vaccine formulary, pricing of vaccines, and the design of vaccination schedules. Jacobson *et al.* (1999) proposed an integer programming model with the goal of finding the lowest cost formulary subject to constraints based on clinical recommendations for childhood immunization.

Some diseases, such as seasonal flu, evolve over time, necessitating regular vaccination. This leads to challenging decisions about how to design vaccines. For example, Wu *et al.* (2005) proposed a continuous-state discrete-time dynamic programming model for the design of the annual flu vaccine. In their model, the state is represented by the antigenic history, including previous vaccine and epidemic strains. The decision variable (action) is the vaccine strain to be selected, and the reward represents the efficacy of the vaccine.

Researchers have also contributed to problems related to the intentional infection of a population. For instance, Kaplan *et al.* (2003) analyzed bio-terror response logistics using smallpox as an example. The authors developed a system of ordinary differential equations (ODEs) incorporating scarce vaccination resources and queueing of people for vaccination.

Controlling risk factors over the course of a patient's lifetime is important for preventing some common chronic diseases. For example, high cholesterol and blood pressure increase the likelihood of heart disease. Better control of these factors may help avoid or delay heart attack and stroke. Common interventions involve improvements in lifestyle (e.g., diet and exercise) or the use of medication. In recent decades numerous medications have come on the market such as statins for cholesterol control, and ACE inhibitors for blood pressure control. Trading, off the benefits and costs of these medications can be challenging and depends on the decision maker's perspective. From the patient perspective the benefits are a reduced probability of heart attack and stroke; however, this must be assessed against the downside of medication including patient copay, side effects, and possible consequences of long term exposure to the drug. From the third-party payer perspective, considerations include the full cost of medication, which can vary widely depending on whether it is a generic or a brand name, and the cost savings from avoiding major health outcomes such as heart attack and stroke, including immediate costs of emergency care, and long-term follow-up costs.

4. Disease screening and surveillance

Diseases historically were detected when symptoms manifested themselves. For many diseases, including various forms of cancer, this meant detection in late stages, when limited treatment options were available. More recently, efficient screening and surveillance methods have been de-

veloped for a large number of diseases. These tests can help achieve early detection, resulting in improved quality of life and/or reduced morbidity. These can be broken into two groups: noninfectious and infectious diseases. In this section we provide examples of each.

There are now effective means of screening for many noninfectious chronic diseases including several types of cancer. For example, breast cancer is commonly screened with mammography, a medical imaging test that can help radiologists identify suspicious masses in need of biopsy. Recent debate about the best frequency for mammography has been vigorous due to the potential for false-positive findings leading to unnecessary biopsy and anxiety for patients. Stochastic models that incorporate the partially observable nature of a patient's health status have been used to study alternative breast cancer screening protocols (Maillart *et al.*, 2008). Ayer *et al.* (2011) developed a partially observable Markov decision process (POMDP) model to determine patient-specific mammography screening schedules. A recent study by Alagoz *et al.* (2010) summarizes applications of ISE methods for cancer screening and open research opportunities related to cancer screening.

Colorectal cancer is another example of a disease for which effective screening methods exist. There are numerous tests including fecal occult blood test (FOBT), flexible sigmoidoscopy, and colonoscopy. While the latter is often considered the "gold standard" it is also the most expensive and most risky for the patient. Optimally combining the available methods to screen a population has been studied using simulation (Tafazzoli *et al.*, 2009). The authors present a net benefit analysis to compare alternative screening strategies including newly proposed screening strategies that employ virtual colonoscopy. Erenay *et al.* (2011) developed a POMDP model for optimizing colorectal cancer screening and surveillance via colonoscopy. The authors found that women with a personal history of colorectal cancer should be screened more aggressively than similar men. Furthermore, they estimate the optimal stopping age for colonoscopy screening.

Testing is often done to monitor patients that have been diagnosed with cancer to detect a potential recurrence following treatment. This is referred to as *surveillance* in the medical literature. Prostate specific antigen (PSA) tests can be used for this purpose for prostate cancer. For example, Lavieri *et al.* (2009) developed a stochastic model to determine the optimal time to initiate treatment for prostate cancer patients based on a patient's PSA level. Bladder cancer is another cancer for which surveillance is common. Typically bladder cancer patients receive regular cystoscopies over some or all of their remaining lifetime. A cystoscopy is a diagnostic test in which a urologist inserts a cystoscope through the urethra into the bladder to look for signs of recurrence. The procedure can be painful and can cause anxiety for patients. Currently there is wide variation in the recommended frequency of cystoscopies based on published guidelines.

Disease screening is also important for monitoring the progression of infectious diseases in a population where early detection of outbreaks may significantly limit the overall impact. A detailed review of the mathematics of infectious diseases is provided in Hethcote (2000). Intervention strategies for infectious diseases can include (a) vaccination strategies that limit incidence of disease (b) contact reducing interventions such as quarantine or travel restrictions and (c) transmission reduction strategies such as the use of face masks and frequent hand washing.

Blood tests are commonly used for screening. However, blood testing a large population is costly. Wein and Zenios (1996) proposed models for pooled testing of blood products for HIV screening. Optimization of pooled testing involves decisions such as discarding of samples in the pool and the division of the pool into sub-pools. The authors show that such methods may increase efficiency in the use of screening resources.

5. Treatment decisions

Many diseases now have treatment options that can cure or delay the progression of the disease. In some cases treatment decisions are one-time decisions, but in other cases treatment decisions recur, often involving the coordination of multiple treatment types to achieve control of one or more risk factors.

Liver transplant decisions, often treated as one-time decisions, have received significant attention in the ISE literature. In the case of live donor transplants, such as liver transplants, there exists an optimal timing decision that involves maximizing the pre- and post-transplant lifespan of an individual patient. Alagoz *et al.* (2004) studied a Markov decision process to maximize expected quality adjusted lifespan of patients with end stage liver disease. The states of their model were defined by the patient's health states. The authors establish a number of structural properties, including the existence of an optimal threshold type policy. Results are presented based on model parameter estimates from a large population of patients with end stage liver disease.

In some cases there are multiple treatments, with different advantages and disadvantages. One example is prostate cancer, which can be treated with prostatectomy (surgical removal of the prostate), external beam radiation, brachytherapy (implantation of radioactive seeds in the prostate), and active surveillance. Active surveillance is a recent treatment protocol that can involve medical treatment and regular biopsies to monitor the progression. Sanda and Kaplan (2009) provide an excellent description of the decision process for a particular patient diagnosed with low risk prostate cancer. The authors point out that there is no single treatment option that is uniformly considered to be the best. Rather, the decision maker must consider many factors including the risk of mortality from treatment, variation in the likelihood of future recurrence, and

the side effects of treatment including sexual dysfunction and urinary incontinence.

Many diseases involve complex drug treatment decisions, particularly chronic conditions for which treatment decisions are made over long time frames. For example, patients with diabetes must carefully weigh the costs and benefits associated with treatment of multiple risk factors including blood sugar, blood pressure, and cholesterol control. Mason *et al.* (2011) use an MDP model to study the optimal timing of treatment options under uncertainty about future health states. Simultaneous control of multiple risk factors presents challenges, including a combinatorially large health state space resulting from the dependence of health states on treatment history.

Another important application area is the design of intensity modulated radiation therapy (IMRT) plans for the treatment of cancer. Such planning problems involve decisions such as the optimal selection and intensity of external beams with the goal of balancing the goals of ensuring a high dose to the tumor while minimizing radiation close to critical structures. The design process naturally divides into three sub-problems, those being: 1) the selection of the beams that will be used in the treatment, 2) deciding on the amount of radiation to deliver along those beams, and 3) optimizing the delivery of the treatment. The preponderance of the literature addresses one of the three problems, but the modern trend is to combine these to better optimize the overall treatment, see Matthias *et al.* (2008) for a detailed discussion of these topics.

6. Translation to practice

Although research on advanced ISE methods is at a relatively early stage, there are some examples of success in practice. Often the translation of these methods to practice is through the development of a software based decision support system to aid patients and/or physicians in making decisions. The following are some examples.

Mathematical programming methods have been successfully implemented to aid clinical decision making for brachytherapy for prostate cancer. Lee and Zaider (2008) report on a successful implementation of a discrete optimization model for optimizing the location of radioactive seeds in 3-dimension to maximize the delivery of radiation to a prostate tumor. The authors report benefits including improved local tumor control and reduced normal tissue complication. The particular model studied is computationally challenging as a result of a dense constraint matrix. As a result, the authors develop and adapt specialized methods to efficiently solve the resulting discrete optimization problems Lee and Zaider (2003).

Recent studies report the successful use of ISE methods for decision making related to prostate cancer screening and treatment. Liberatore *et al.* (2009) report on the use of analytic hierarchy process (AHP) to help with decisions about whether or not to undergo screening for prostate

cancer. They combined the use of a health educator with the AHP process to identify variables most significantly associated with the decision process. Simon (2009) describes a model that was used to help patients decide among multiple treatment options. They use multi-attribute utility theory to quantify preferences and uncertainty to help patients compare treatment alternatives. Their model was made available through a decision support system that was provided online.

A third example involves the application of mathematical programming methods for a decision support system to aid decision making for designing childhood vaccination plans. Engineer *et al.* (2009) present a dynamic programming approach to compute feasible schedules for physicians that must provide a vaccination plan for children that have fallen behind on their required vaccinations. The authors present a case study of two different real life scenarios. They also summarize the use of the tool in practice based on its dissemination to physicians through the U.S. Centers for Disease Control and Prevention.

At the population health level there are a number notable examples of successful practice related to ISE models. Kaplan (1989) made seminal advances related to recommendations for HIV needle-exchange policy. A number of authors report findings from models that have influenced the decision making process for bioterrorism response events (see Kaplan *et al.* (2002), Wein *et al.* (2003), Wein (2005), Wein (2008), for examples). Lee *et al.* (2006, 2009) report on a successful collaboration with Centers for Disease Control and Prevention (CDC) investigators to recommend a new national mass dispensing policy for biological attacks and infectious disease outbreaks.

7. Open opportunities

New trends in medicine will provide opportunities for the development and application of ISE methods, and we identify several examples of emerging research areas.

7.1. Personalized medicine

Personalized medicine, which is noted to be the future of medicine Liebman (2007), emphasizes the customization of healthcare interventions for individual patients using each person's unique clinical, genetic, genomic, and environmental information. Personalized medicine may lead to alternative interventions for patients and therefore may require the use of advanced mathematical modeling such as large-scale optimization to choose the best intervention. For instance, as Alagoz (2011) notes, the use of personalized medicine will increase the number of possible cancer screening policies (i.e., specification of what age to start and end screening and how often to screen) that need to be evaluated.

With the sequencing of the human genome and the desire to detect hard-to-treat diseases for early and suc-

cessful intervention (e.g., pancreatic cancers, brain tumors, Alzheimers' Disease), biomarkers are developing rapidly. Feltus *et al.* (2003) described predictive models for early cancer diagnosis. Mathematical programming techniques can also be powerful tools for classification and disease prediction (Lee and Wu, 2007). However, significant challenges remain in the solution strategies for large-scale and multi-group instances.

7.2. Patient behavior

An important issue in medical decision making is understanding the influence of patient behavior. One example is patient compliance to medical recommendations, which can significantly influence any recommendations about medical decisions. As World Health Organization (WHO, 2003) reports, "Adherence to therapies is a primary determinant of treatment success. Poor adherence attenuates optimum clinical benefits and therefore reduces the overall effectiveness of health systems." It is therefore crucial to consider the effect of poor adherence in optimizing medical decisions and tailoring clinical recommendations based on patient behavior.

Patient behavior can mean more than just compliance and adherence. There is significant research being done by clinicians and social scientists on behavioral models. This is also a potential area of application for ISE methods where medical and behavioral sciences need to be integrated. In particular, there is a need to develop mathematical models that represent human behavior to better understand its role in medical decision making.

7.3. Natural history of disease

Most medical decision making studies require data-driven mathematical models to represent the progression of a particular disease without any intervention, i.e., the natural history of a disease if left untreated. Because there is typically no clinical data about the natural history of diseases such as breast cancer or end stage liver diseases, it is necessary to develop and use a theoretical natural history model. Such models often require calibration using observational data that is often influenced by various sources of bias. The accurate estimation of the natural history of a particular disease based on observational data is important since it establishes a baseline. However, little research has been done to develop generalizable approaches that use observational data. In the future ISE methods may provide ways to estimate natural history models.

7.4. Future medical interventions

Most medical decision making studies estimate disease progression and treatment outcomes using current available treatment options, and they assume that treatment options remain constant in the future. On the other

hand, medical research and development often leads to new and improved therapies, such as in HIV and organ transplantation. As a result, in some cases where innovations are anticipated in the near future ISE studies using stochastic models in medical decision making such as Shechter *et al.* (2010) are needed to consider how the uncertain availability may affect decisions.

7.5. Burden of treatment

The preponderance of medical studies focus on the benefits of treatment, and little has been done to assess the impact of treatment on a patient's quality of life. For example, a common criteria used to evaluate alternative medical decisions is QALYs. However, little has been reported in the medical literature on the effect of medical interventions on the quality of life. Few studies report on the disutility of invasive interventions such as colonoscopy, mammogram, or medical interventions such as cholesterol or blood pressure lowering medications. Consequently, in many cases it is difficult or impossible to accurately assess the pros and cons of medical interventions. Furthermore, little research exists to quantitatively evaluate the disutility associated with increasingly complex medical treatment regimens that may involve a dozen of more daily medications. Thus, there is a need for new methods and their application to provide more accurate inputs for medical decision making models.

7.6. Decision aids

As evidenced by the many examples in the previous section, ISE models and methods are being developed for many types of medical decision making problems. However, the benefits will not be realized unless patients and physicians can easily use and understand the tools. This can be challenging given that the models and methods themselves may employ advanced concepts related to deterministic or stochastic models that most patients and physicians are not familiar with. Furthermore, the way in which the decision and available options are framed can significantly influence patient choice. Therefore decision aids must be constructed to limit potential sources of bias. Decision aids must also attempt to explain what is unknown about the possible risks and/or benefits of a particular medical intervention without overwhelming the patient with unnecessary information.

7.7. Interdisciplinary medicine

Currently many areas of medicine specialize in certain diseases or parts of the body. For example, cardiologists have expertise in heart disease, gastroenterologists in diseases of the gastrointestinal system, and so on. In recent years it has become apparent that many medical conditions cut across disciplines. For example, a patient with Lupus, a disease of the immune system, may require regular visits with a cardiologist, urologist, dermatologist, and other special-

ists. As a result, interdisciplinary decision making based on shared information is becoming an important part of medical decision making. This has created challenges in optimizing communication among multiple caregivers that provide care at different stages of treatment during the cycle of a disease. Improved communication will provide the ability to form interdisciplinary teams giving decisions collectively for the path of treatment that patients need to follow. However, the resulting problems will be challenging due to their increased complexity, resulting in greater challenges in model validation and larger scale in terms of computational effort.

7.8. Integration of prevention, screening, and treatment decisions

Sections 3–5 covered a number of examples related to prevention, screening, and treatment of diseases. Most of these considered a single domain separately, i.e., prevention, detection, or treatment of a particular disease. However, these goals are not independent; they each have an impact on a patient's outcomes such as quality adjusted lifespan and total cost of healthcare. For example, the optimal policy for prevention of a disease is likely to be highly dependent on the optimal policy for screening, and ultimately the disease treatment. Furthermore, there are interactions across diseases. For example, whether or not to screen for a particular disease may depend on the overall health of a patient and whether it is likely to affect that patient. A good example is prostate cancer, which has a high prevalence but low mortality, particularly for older patients with comorbidities, such as heart disease.

8. Conclusions

This article summarizes active areas of research and open challenges for future research related to the applications of ISE methods to medical decision making. Among the future challenges will be the development of new models for capturing personalized genetic information, patient behavior, and the integration of decisions related to prevention, detection, and treatment. These new directions are anticipated to lead to practical applications that improve the health and quality of life of patients and the efficiency of health systems. These new research directions also hold the promise of new methodologies that can be directed to other important problems.

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