PERSONALIZED SCREENING POLICIES FOR CERVICAL CANCER PREVENTION

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ABSTRACT

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INDUSTRIAL ENGINEERING Ph.D DISSERTATION, JULY 2021

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Keywords: Cervical cancer screening, Optimal policy, Partially observable Markov decision processes, POMDP, Cotesting, Cervical cytology, HPV-DNA testing

Since the introduction of the first cervical cancer screening method, i.e., Pap smear, the disease burden has declined steadily and the outlook for women with cervical cancer has improved significantly. However, the reduction in mortality and incidence of the disease has not been uniform across the globe. While in the developed countries the disease is under control, in many low resource settings, the disease continues to inflict major health problems. Through organized screening programs, the abnormal changes in cervical cells can be detected at earlier and more treatable stages. Yet, determining the optimal frequency and type of screening test remains a challenge for the policy makers who want to balance the benefits and costs. To overcome this challenge, in many countries screening policies are presented in the form of general guidelines that dictate the frequency for the whole population, regardless of their risk profile. Essentially, since guidelines do not have the flexibility to address the individual patient's risk profile prior to a screening decision, they fail to distinguish between different types of patients. Recently, personalized medicine (PM) has been adopted to answer this differentiation problem. Personalized medicine links the disease condition of an individual to the risk profile which helps to design a targeted treatment for a patient's specific health condition. The application of PM has recently been extended to the screening decisions for many cancer types including cervical cancer.

In this study, we propose a personalized partially observable Markov decision process (POMDP) approach to address the questions regarding the screening type and frequency at different ages for cervical cancer patients with different risk profiles. As a sequential decision making tool, POMDPs provide a rich framework to study further questions such as the impact of the patient's risk profile and the false outcomes of the screening tests on the screening decisions. Specifically, we propose two POMDP models that incorporate the risk of the disease as well as the effect of test characteristics on the screening decisions. The first model considers a reduced state space with cotesting of cytology and HPV-DNA testing as a single combined test for screening as opposed to waiting. This constitutes a small model which can be solved exactly. The second model, uses cytology and HPV-DNA testing as two separate decisions along with the wait decision. We also expand the state space of the model for accurate representation of the natural history of the disease. Due to the large size of this model, exact methods are not applicable, and we propose an approximate solution method to solve the problem. Our results suggest that screening the whole population with the same frequency leads to health disparities and that screenings need to be tailored to the specific risk profile of the patients to improve the expected quality adjusted life years (QALYs) of the patients. Our results also confirm that screening programs will experience a paradigm shift towards HPV-DNA testing as the standalone testing for cervical cancer in accordance with what is proposed in the literature.

ÖZET

SERVİKAL KANSER ÖNLENMESİNDE KİŞİSELLEŞTİRİLMİŞ TARAMA POLİTİKALAR

MALEK EBADI

ENDÜSTRİ MÜHENDİSLİĞİ DOKTORA TEZİ, TEMMUZ 2021

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Ilk serviks kanseri tarama testinin kullanıma sunulmasından bu yana, bu kanserin hastalık yükü istikrarlı bir şekilde azalmıştır. Bununla birlikte, mortalite ve hastalık insidansındaki azalma dünya genelinde eşit ölçüde olmamıştır. Gelişmiş ülkelerde bu hastalık kontrol altındayken, birçok üçüncü dünya ölkeside büyük sağlık sorunları yaratmaya devam ediyor. Organize tarama programları ile servikal hücrelerdeki anormal değişiklikler daha erken ve daha tedavi edilebilir aşamalarda tespit edilebilir. Bununla birlikte, tarama testinin optimal sıklığını ve türünü belirlemek, fayda ve maliyetleri dengelemek isteyen politika yapıcılar için bir zorluk olmaya devam etmektedir. Bu zorluğun üstesinden gelmek için, birçok ülkede tarama politikaları, risk altındaki nüfusa tarama testinin zamanı ve türü hakkında bilgi içeren kılavuzlar biçiminde sunulmaktadır. Ancak kılavuzlar, tarama kararını etkileyen önemli faktörleri ele alma esnekliğine sahip değildir ve bir tarama kararından önce her bir hastanın risk profilini dikkate almamaktadır. Buna ek olarak, sağlık hizmetlerinde, bireyin hastalık durumunu risk profiline bağlayan ve hastanın durumunun daha iyi anlaşılmasını sağlayan kişiselleştirilmiş tıbba yönelik yükselen bir eğilim vardır. Kişiselleştirilmiş tıp kavramı, son zamanlarda rahim ağzı kanseri de dahil olmak üzere birçok kanser türü için tarama kararlarını kapsayacak şekilde genişletilmiştir.

Bu çalışmada, serviks kanseri için tarama tipi ve aralığı ile ilgili soruları ele almak için kişiselliştirilmiş kısmen gözlemlenebilir Markov karar süreci (POMDP) yaklaşımını öneriyoruz. Sıralı karar verme aracı olarak, POMDP'ler, hastanın risk profilinin etkisi ve tarama testlerinin yanlış hata oranlarının serviks kanseri için tarama kararları üzerindeki etkisi gibi diğer soruları incelemek için zengin bir çerçeve sağlar. Spesifik olarak, bu çalışmada test özelliklerinin tarama kararları üzerindeki etkisinin yanı sıra hastalık riskini de içeren ve dolayısıyla kişiselleştirilmiş tıp alanına katkıda bulunan iki POMDP modeli öneriyoruz. Önerilen ilk model, cotesting'i (cytology ve HPV-DNA testlerini birlikte uygulanması) tarama için tek başına bir test olarak kabul eder ve optimal çözüm metodları ile tarama politikaları elde etmek için çözülür. İkinci modelde, tarama testleri olarak cytology ve HPV-DNA testleri öngörülmüş ve modelin büyük olması nedeniyle yaklaşık bir çözüm yöntemi kullanılır. Sonuçlarımız, tüm popülasyonu aynı sıklıkta taramanın sağlık eşitsizliklerine yol açtığını ve taramaların hastaların spesifik risk profiline göre uyarlanması gerektiğini göstermektedir. Literatürle uyumlu olarak, bu çalışma serviks kanseri için tarama programlarının bağımsız test olarak HPV-DNA testine doğru yönelmesini göstermiştir.

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LIST OF ACRONYMS/ABBREVIATONS

ACS American Cancer Society 21

ASCCP American Society for Colposcopy and Cervical Pathology 21

ASCP American Society for Clinical Pathology 21

CC Cervical cancer 9

CCEMC WHO Cervical Cancer Elimination Modelling Consortium 10

CIN Cervical Intraepithelial Neoplasia 11

CIN1 Cervical Intraepithelial Neoplasia of degree 1 (Low-grade neoplasia) 11

CIN2 Cervical Intraepithelial Neoplasia of degree 2 (Medium-grade neoplasia) 12

CIN3 Cervical Intraepithelial Neoplasia of degree 3 (High-grade neoplasia) 12

CIN3+ Collectively referred to CIN3 or worse as CIN3+ 50

CKC Cold knife conization 16

FDA US Food and Drug Administration 14

GP Gaussian process 74

GPR Gaussian process regression 68

HIV Human Immunodeficiency Virus 10

HPV Human Papilloma Virus 10

HSIL High grade squamous intraepithelial lesion 12

LBC Liquid-based cytology 18

LEEP Loop electrosurgical excision procedure 15

LSIL Low grade squamous intraepithelial lesion 12

MDP Markov decision process 26

Pap test Papanicolaou test (cytology-based method for CC screening) 18

PM Personalized medicine 23

POMDP Partially observable Markov decision process 25

PWLC Piecewise Linear and Convex 45

QALE Quality-Adjusted Life Expectancy 65

QALY Quality-Adjusted Life Year 28

QOL Quality of life 28

RBF Radial Basis Function 74

SEER Surveillance, Epidemiology, and End Results Program 79

TBS The Bethesda System 12

USPSTF US Preventive Services Task Force 21

VIA Visual inspection with acetic acid 18

WHO World Health Organization 9

1. INTRODUCTION

1.1 Chapter Overview

This chapter introduces the research area and outlines the rationale for the present study. The chapter begins with an overview of the problem and presents motivation of the research. Then, it highlights the scope of the research and introduces the research questions explicitly. The chapter ends with an overview of the research methodology and a chapter by chapter overview of the thesis.

1.2 Problem Statement and Motivation for This Research

Prevention and treatment of the cancers of any type impose huge financial costs on the healthcare systems. Therefore, healthcare leaders and policy makers aim to minimize the cancer cases using different preventive methods.

Cervical cancer is among the cancer types with high mortality, especially in low resource settings. Globally, cervical cancer is the fourth most common cancer type diagnosed among women (Buskwofie et al., 2020). In 2018, a total of 570000 new cases of cervical cancer and 311,000 deaths linked to cervical cancer were reported worldwide. During the next decade, the annual disease incidence and mortality rates are expected to increase (Holmström et al., 2021).

Observed incidence rates of cervical cancer vary substantially across different populations. In low- and middle- income countries, cervical cancer is ranked as the second most common cancer type, accounting for approximately 85% of the new

cases worldwide (Small Jr et al., 2017). A disproportionate fraction of reported annual death due to cervical cancer is observed among medically under-served populations that do not have proper access to healthcare services (i.e., vaccination and regular screening), resulting in significant cancer health disparities. It is estimated that 90% of the total deaths due to cervical cancer occurs in countries ranked low in the Human Development Index. According to the World Health Organization's predictions, by 2030, a 27% increase in cervical cancer mortality in low-income countries will be realized (Sung et al., 2021).

Fortunately, the understanding of oncogenesis associated with the development of cervical cancer has evolved over the years. It is now well established that an infection with oncogenic Human papillomavirus types is closely associated with the malignant transformation of cervical cells and development of cervical cancer. This has lead to a variety of strategies to accelerate the elimination of cervical cancer as a public health problem including preventive methods (Tulay & Serakinci, 2016).

Preventive methods against cervical cancer have been classified into three categories: *primary prevention*, *secondary prevention* and *tertiary prevention*. Primary prevention concerns prevention in the asymptomatic phase, where the aim is to prevent the disease, and reduce the exposure to risk factors before their biological onset. Immunization through vaccination is an example of primary preventive methods. Secondary prevention refers to the prevention of clinical disease through early detection prior to the emergence of symptoms that, if left undetected, would likely become clinically important. Secondary prevention is often referred to as *screening*. Tertiary prevention refers to preventing the progression of clinically manifested existing disease in those who are already affected by the disease. Tertiary prevention aims to improve quality of life, reduce disability, and impact of complications by providing treatment or rehabilitation (Burthold, 2007) .

In May 2018, the WHO announced a global plan of action to engage health institutions and mobilize resources to eliminate cervical cancer over the next decades (Gultekin et al., 2019). One of the fundamental steps in the action plan is to establish vaccination programs combined with a high-quality surveillance and monitoring system through screening. The complexity of operationalizing this call requires collaborative and interdisciplinary effort. While addressing the global health questions, many important strategic and operational decisions have to be made. For example, choosing between policy A or policy B, determining cost-effective interventions, finding the optimal way to allocate a limited budget across multiple competing options, or deciding on the feasibility of a new intervention such as a vaccination program, noting that many of these decisions require evaluation of long-term outcomes

(Bradley et al., 2017).

The WHO's call has been responded by the operations research (OR) community in various ways ranging from studies covering the logistics related to the provision of services, the allocation of resources or the operations of health facilities. Using advanced analytical methods (e.g. simulation, optimization, decision analysis), OR community provides better understanding of complex systems and facilitates decision-making. In the context of healthcare, OR is particularly useful for analyzing complex global health issues due to its orientation towards improving efficiency, cost-effectiveness and decision-making. Especially, in settings with limited resources where the burden of disease is high and health systems are functioning poorly, the impact of OR in improving healthcare performance and equity for communities and populations is fundamental (Bradley et al., 2017; Myskja & Steinsbekk, 2020). Therefore, we believe that this is a highly opportune time to harness the power of data analytics and optimal control policies to design targeted approaches to address the observed health disparity in medically-underserved populations and resource-constrained settings in the context of cervical cancer.

Additionally, rapidly emerging new medical technology and advancement of genetic medicine methodologies come with new questions for the research community that require new set of techniques to handle the complexity accompanying them. Recently, there is a tremendously increasing trend towards personalized medicine. Among the healthcare community, there is a common agreement that the underlying heterogeneity of disease evolution observed in many diseases suggests that strategies for monitoring or preventing those diseases, must be tailored or *personalized* to the individual's unique physiological, biochemical, genomic, and behavioral profile. Examples of personalized medicine include cell transplant therapies for certain types of cancer and mutation-specific medicines to treat fibrosis and personalized screening policies for many types of cancer (Goetz & Schork, 2018). This poses another challenge/opportunity for OR researchers and policy makers alike to integrate personalized interventions with healthcare decision making processes.

1.3 Scope of This Dissertation and Research Questions

The current research concentrates on the secondary preventive method (i.e., screening) against cervical cancer. Screening test is a tool for identification of women with

early disease within a broad population and pursues the objective of diagnosing the disease at a pre-symptomatic or early symptomatic stage, since at those stages treatment has a higher chance of changing the natural pathway of the disease. Using the test helps the decision maker to gain information about the real but unobservable health state of the patients. Screening tests may also be further classified as primary screening tests (such as Pap smears) or secondary diagnostic tests (such as biopsy test) (Cassels, 2012; Croyle, 1995; Saquib et al., 2015; Wilson et al., 1966). Secondary diagnostic tests are excluded from the scope of this research.

There are two commonly used primary screening tests, namely cytology testing and HPV-DNA testing for cervical cancer. It is possible to conduct these two tests simultaneously, also called cotesting. These tests are introduced and discussed in detail in Chapter 2. Unfortunately, none of the primary screening tests for cervical cancer are 100% accurate; these tests may produce false-negative or false-positive results. In other words, using the test provides only partial information about the hidden health state of the patient where tests with lower errors result in stronger belief that the real state overlaps with the state that the test indicates. Hence, decision makers need to consider the differences in test characteristics before making an screening decision.

The effectiveness of screening increases with the frequency of screening rounds; when the re-screen interval is short, abnormalities are less likely to escape detection. However, it is generally recognized that screening too frequently is linked to diminishing returns (Bedell et al., 2020; Last & Breslow, 2012). An immediate question that arises here is what should be the frequency of screenings? In many countries standards and guidelines are developed to specify the time and type of screening tests for the population. For instance, the guidelines of the American Society for Colposcopy and Cervical Pathology (ASCCP) state that women aged 21-20 need to undergo cytology screening every 3 years and women aged 30-65 need to be screened with HPV-DNA (or cotesting) every 5 years. Such guidelines are easy to understand and implement by the practitioners but they also have shortcomings such as ignoring the differences in risks of patients and ignoring the previous test results. In such a setting, screening the whole population with the same frequency may result in overdiagnosis of patients who do not need medical intervention and also under-treatment of those who are screened late.

In light of the above discussion, we pose the personalized cervical cancer screening decision process in terms of finding the series of actions, given the different observations that the screening tests produce over time. In addition, decisions must be adjusted to the risk factors of the patients including risk of cancer and age of the

patient at the time of screening and also capture the effect of the test characteristics. It is nevertheless noteworthy that with increasing age of the patients, the incidence rates of infection change and the disease evolves differently. Therefore, the best action at the current age (screen with a specific test or wait until next decision epoch) may not be the best action in the future. Decision making in such a complex environment requires sophisticated modeling techniques that suit well to the problem at hand and are able to address different aspects of the problem.

Specifically, the research questions addressed by this dissertation include: Given the age and risk profile of the patient,

1.1 At what age screening must begin?

1.2 Which screening test must be conducted?

1.3 What is the optimal screening frequency? Given the previous screening results, what should be the length of rescreen interval?

1.4 At which age screening should be stopped?

1.4 Conceptual Framework of This Research

Obviously, addressing these research questions and developing personalized model for cervical cancer screening policy requires sequential decision making techniques. Among the sequential decision making techniques, partially observable Markov decision processes (POMDPs) have recently been suggested as a suitable model to formalize the planning of personalized medical intervention and are increasingly being used particularly in screening and treatment decision-making. The applicability domain of POMDPs in medical decision making arena is diverse; examples can be seen in organ transplantation, epidemic control, drug infusion, diabetes, ischemic heart disease, Parkinson's disease and many cancers including colorectal, breast, prostate, and cervical cancer. In addition to the POMDP models, cost effectiveness analysis has been also a common approach in making a screening decision which is a useful method to study the effect of implementing certain policies.

POMDPs provide a rich framework to model problems where there are two layers of uncertainty; the first layer of uncertainty refers to the uncertainty of the underlying state (i.e, real heath state of an individual) and the second layer of uncertainty

refers to the action outcomes and the future state after taking an action. Such models provide useful tools to handle inaccurate observations made after conducting an action. Consequently, POMDP models are commonly used in cancer screening context where the state of the cancer is unknown, the screening tests used to identify the real health state are not perfectly accurate (i.e., the decision maker has a belief of the real health state), and probabilistic transitions among the health states occur over time.

We model the personalized screening decision making for cervical cancer as a finite-horizon partially-observable Markov decision process (POMDP) framework, which iteratively optimizes the choice of screening actions given the current information including risk, prior observations, and age of the patient. In the current research, we assume the patient perspective. From the patient's point of view, the most important factor to consider in screening decision making is the health outcome of the decision. This perspective has the underlying assumption that, the screening decision maker (i.e., physician) acts in the best interest of the individuals being considered for screening. In this setting, for obvious reasons, evaluation of the desirability of a decision is solely based on the desirability of the health outcomes.

Solving POMDP problems using the optimal solution methods is feasible for only small problems, due to computational complexity inherent to such problems. For large POMDP problems multiple approximate solution methods have been proposed in the literature. The current study uses both optimal and approximate methods to solve the POMDP models developed for screening decision making.

1.5 Contributions and Organization of This Dissertation

The contributions of this research study are as follows:

The models presented in this research promote the concept of personalized care by providing patient-specific policies for cervical cancer screening in contrast to the current practice of non-tailored guidelines. After giving the background of the disease in **Chapter 2**, we provide a review of the approaches in the literature for evaluating or designing policies for personalized disease prevention in **Chapter 3** .

From a methodological point of view, the current research is the first study to address cervical cancer screening as a partially observable Markov decision process

(POMDP). In **Chapter 4**, we present our first proposed model for a personalized optimal screening policy for cervical cancer. The proposed model in this chapter is distinguished from the subsequent one in the screening test and solution methodology. Specifically, cotesting is the only screening test considered while due to the small size of the problem, the model is solved using an optimal solution methodology. Our results suggest that contrary to the guidelines, screening frequency varies with the risk profile of the patient.

A second novelty of the current research is associated with the approximate solution methods developed for solving complex POMDP problems. In **Chapter 5** we introduce the second personalized cervical cancer screening where the screening tests include cytology and HPV-DNA testing. Due to the large size of the problem, an approximate grid-based solution method is employed to solve the problem. It is often the case that value at a nongrid point is required when computing the value of a grid point. The proposed interpolation based classical methods in the literature use linear programming for this purpose which restricts the grid size to a few thousand points. This study employs Gaussian process regression method in combination with the grid based solution method to make inference at those points. While similar studies in the literature reported intractability of using a large grid representation, Gaussian process regression approach enables using a finely meshed grid and therefore, improved solution accuracy compared to the interpolation based methods. Our results in this chapter shows that in line with the recent studies HPV-DNA testing can be safely used as a stand-alone test. In addition to the screening policy, a detailed discussion about the sensitivity of the model outputs with varying parameters is provided.

However, the contributions presented in this study are not limited to the methodological approach. In addition to being able to solve a complex stochastic decision process, our models provide patient specific screening policies as a function of the patient's risk. Moreover, our analysis can be adjusted to further study the possible effect of socio-cultural factors that contribute to the development of infection and disease. In this context, our model can produce screening policies for specific patient subgroups with potential health disparities. We expect the performance of the screening policy to improve as a result.

Finally, the policies presented in this research can be framed into policy trees or in more advanced forms such as spreadsheets or applications which are intuitive to understand and hence, facilitate interpretation of the policies for both physicians and patients. By this means, patients have a better understanding of their health and as a consequence, they can be more involved in the process of shared decision-making.

In **Chapter 6** we provide further discussions about the strength and limitations of our study and an outline of plans for future research in this area.

2. MEDICAL BACKGROUND

2.1 Chapter Overview

This chapter presents a synopsis of the cervical cancer, incidence and mortality rates associated with it. It outlines the course of the disease development and the importance of early detection. The chapter subsequently describes the preventive methods including the primary prevention by vaccination, secondary prevention by screening and tertiary prevention by treatment. In the screening section, along with the contribution of the screening programs to the disease control, the role of the population level screening programs and the characteristics of different screening tests are outlined. The chapter concludes by emphasizing the significance of personalized screening.

2.2 Cervical Cancer

2.2.1 Cervical Cancer: State of the Art

With more than one million women suffering globally, cervical cancer (CC) continues to be one of the most common cancer types among females. According to the World Health Organization (WHO), cervical cancer is currently the fourth most frequent cancer in women worldwide (Arbyn et al., 2020). Despite the medical and

clinical advancements, the incidence and mortality of cervical cancer remains high. Every year, more than half a million women are diagnosed with cervical cancer and among the diseased population over 340000 cases result in death worldwide (Cohen et al., 2019). In addition, the trend in the number of incidences and deaths is constantly increasing. The estimates published by the WHO Cervical Cancer Elimination Modelling Consortium (CCEMC) shows that the annual number of new cases of CC is expected to rise from 570000 to 700000 between 2018 and 2030, while the annual number of deaths is expected to increase from 311000 to 400000 (WHO, 2021b).

Cervical cancer occurs in the cervix. Inside and outside surface of the cervix (called endocervix and ectocervix respectively) are covered by layers of skin-like cells. Cervical cancer refers to the state when either type of these cells turns cancerous. More precisely, the Squamous cells covering the ectocervix can cause squamous cell carcinoma and the Glandular cells covering the endocervix can lead to adenocarcinoma. Most of the cervical cancers occur in transformation zone where two cell types join each other and they are mainly of squamous cell cervical cancer type (Wang et al., 2020).

The main cause of cervical cancer is the change in genetic expression of cervical cells caused by long-lasting infection of Human Papilloma Virus (HPV). Specifically, HPV infected body produce certain type of proteins that turn off genes which have the functionality of suppressing abnormal cell growth (Clark & Trimble, 2020; Wilson et al., 2018).

Among several other risk cofactors, age of the patient at sexual debut and immunodeficiency play a major role in the etiology of cervical cancer (Martin-Hirsch & Wood, 2011; Rodríguez et al., 2008). In the vast majority of women younger than 25 years, the transformation zone is placed on the ectocervix, causing the cervix to be more exposed to potential HPV infections, while only less than 2% of adult females older than 64 years continue to have this condition (Autier et al., 1996). Consequently, younger females are at increased risk of HPV infections. Immunosuppression associated with human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome is another risk factor for HPV infection. Several studies demonstrate that the prevalence of HPV is 5-8 folds higher among HIV-positive women, persistent infections are more frequent resulting in an increased risk of pre-invasive cervical lesions (Moscicki et al., 2019; Myers & Ahmed, 2018).

2.2.2 Human Papilloma Virus

Clinical evidences have shown that nearly in all of the cervical cancers an infection by HPV is present (Walboomers et al., 1999; Wilson et al., 2018). HPV targets epithelial basal cells, and HPV-associated diseases are primarily transmitted through sexual contact and in many cases, the infection with HPV occurs shortly after the onset of sexual activity (Heitmann & Harper, 2012) with a peak incidence between the age of 15 to 25 Eun & Perkins (2020).

HPV spans a wide range of strains (Jones et al., 2011). Very specific strains of HPV are persistent in the body while the majority of the other strains are acute (nonpersistent) and harmless (Alizon et al., 2017). It is known that 70% to 90% of HPV cases, typically those caused by the low risk HPV types such as Types 6 and 11, clear their infections naturally within a few years (Al-Daraji & Smith, 2009) and only a portion of people infected with low risk HPV will develop clinical symptoms. These symptoms are in form of skin warts or minor abnormalities which are spontaneously eliminated by the immune system without any medical intervention (Alsaleh & Gumel, 2014). Infection with high-risk HPV types, such as Types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82, on the other hand, can persist for many years, causing cell abnormalities, cervical intraepithelial neoplasia (CIN) and cervical cancer (Elbasha et al., 2008). HPV Types 16 and 18 account for over 70% of cervical cancer cases globally (WHO, 2021a). Furthermore, high-risk HPV types cause pre-cancerous *intraepithelial neoplasia* in males, resulting in various cancers such as anal and penile cancers (Anic & Giuliano, 2011; Elbasha & Dasbach, 2010).

2.2.3 Natural History of the Disease

The natural history of disease is represented as a sequence of transitions between mutually-exclusive health states, where the health state of a woman is represented by the states in natural history model. Figure 2.1 shows the natural history of cervical carcinogenesis in an individual woman. Generally, health states are defined to include HPV infection status (HPV- or HPV+), grade of cervical intraepithelial neoplasia (CIN) and stage of cancer including local, regional and distant.

Depending on the extent and severity of dysplastic features, the spectrum of cervical intraepithelial neoplasia (CIN) is traditionally divided into three histopathological categories, namely: CIN1, CIN2 and CIN3. In CIN1 (mild dysplasia), cells with

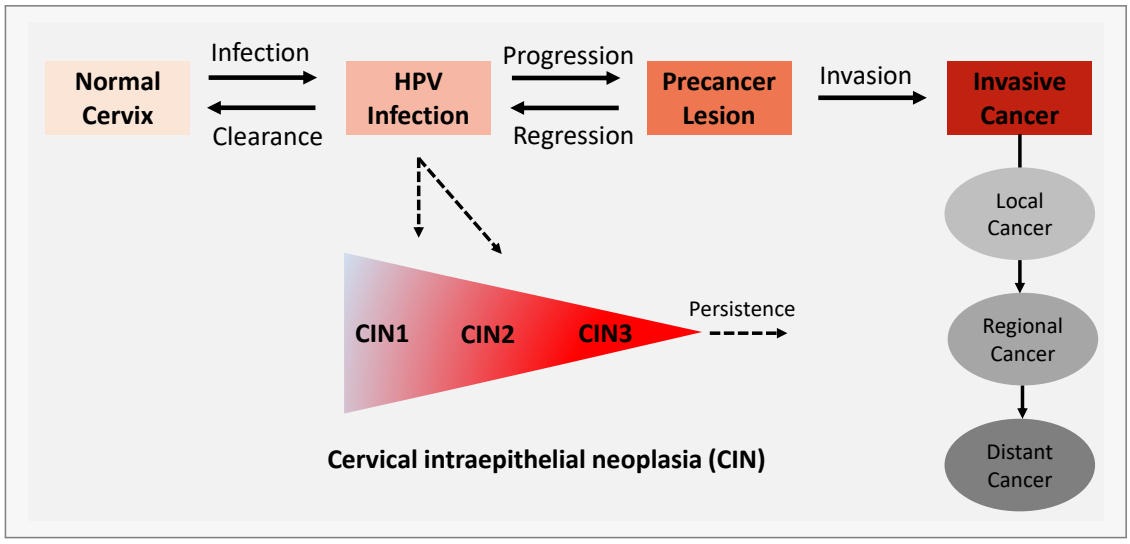


Figure 2.1 Natural history of cervical carcinogenesis. Source: Kim et al. (2008)

malignant changes are limited to the superficial layer of the cervical epithelium. Most CIN1 lesions are likely to disappear without treatment. However, a small percentage may progress to high-grade CIN, namely CIN2 (moderate dysplasia) and CIN3 (server dysplasia, which sometimes are also known as cervical carcinoma in situ). This high grade CIN is characterized by more severe dysplastic changes and higher degree of epithelial basal cell involvement (Gravitt & Winer, 2017). The risk of progression to carcinoma in situ and invasive cervical cancer increases significantly with worsening CIN grades (Daling, 1996). However, there is controversy on whether cancer and CIN3 are always preceded by stepwise transition from HPV infection into CIN1 and then into CIN2. Despite studies which suggest that a persistent HPV infection may lead to CIN3 or cancer without detectable low grade CIN (CIN1 and CIN2), it is commonly accepted that the classical pathway of stepwise progression is still valid (Bedell et al., 2020; Massad, 2008).

To ensure a uniform analysis and a consistent interlaboratory terminology for the reporting of cervicovaginal cytology specimens, The Bethesda System (TBS) defined a framework to use specific terminology for the cervical findings. According to terminology of TBS, CIN1 findings are labled as *low grade squamous intraepithelial lesion* (LSIL)) that reflects mostly transient HPV infection and associated cellular alterations, whereas *high grade squamous intraepithelial lesion* (HSIL) is the terminology introduced for histological abnormalities and high grade precancerous lesions and encompasses CIN2 and CIN3 (Zhu et al., 2017).

Table 2.1 provides the description of the invasive cancer stages. According to classification systems defined by TBS, invasive cancer refers to a family of four stages characterized by the severity and spread of abnormal cervical cells.

Table 2.1 The stages of cervical cancer in the natural history model according to TBS

No Cancer	**Precancerous Lesions**		**Cancer**	
	Stage[1]	Description	Stage	Description
No infection with virus (HPV-) HPV+, no CIN	CIN1	Lesion level 1	stage I	Cancer is confined in the cervix only.
	CIN2	Lesion level 2		
	CIN3 [2]	Lesion level 3		
			stage II	Cancer has spread beyond the cervix but has not spread to the pelvic wall or to the lower third of the vagina.
			stage III	Cancer has spread to the lower third of the vagina and/or may have spread to the pelvic wall, and/or has caused kidney injury.
			stage IV	Cancer has spread to the bladder, rectum, or other parts of the body.

[1] CIN1, CIN2, CIN3 refer to cervical intraepithelial neoplasia stage 1, 2, 3.
[2] In the literature, CIN3 is acknowledged to be identical to carcinoma insitu stage.

2.2.4 Significance of Early Detection

Cervical cancer has a long pre-clinical phase. A woman may be infected with HPV without knowing it while the virus remains symptomatically nonexistent for several years before it develops into cancer (Bennett et al., 2018). It is estimated that approximately 10 to 20 years elapse from HPV infection until the changes in cells genetic expression caused by the virus transform the cervix tissue to show the signs of a pre-cancer stage, which may then progress to invasive cancer. During this time a patient may feel perfectly healthy. Unfortunately, symptoms usually only appear when the disease has already progressed to cancerous stages. However, early abnormalities are easily treated and most of times the consequences of HPV infection can be radically eliminated with minimally invasive interventions (Huh et al., 2015; Kim et al., 2017; Landy et al., 2018).

The relatively long latency period from infection with the virus until the infected cells becoming cancerous, creates a precious opportunity for diagnosis or to delay the progression to invasive cancer by performing clinical interventions (Silkensen et al., 2018). To this end, a regular and effective screening program is required to detect abnormalities before they become cancerous. There is strong evidence that the mortality of the disease has decreased sharply in the countries where regular population-based screening programs are implemented. Correlational studies in the

United States, Canada, and several European countries comparing cervical cancer data over time have shown that even when using inaccurate tests, implementing serial testing over decades contributes significantly to the reduction in the incidence of invasive cervical cancer (Kessler, 2017; Massad, 2008). In addition, case-control studies have shown that there is a strong negative association between screening and invasive cancer. Whether screening by itself is the causative factor in this finding requires evidence from randomized controlled trials. Nonetheless, a large body of supportive evidence accumulated to date in the literature has promoted adoption of a routine screening nationwide (Sasieni et al., 2009).

2.3 Preventive Methods

2.3.1 Primary Prevention: Vaccination

Primary preventive methods against CC include uptake of vaccine and delivering training/education to minimize the risky behavior of the individuals. Recent advances have allowed the development of highly efficacious prophylactic vaccines for certain types of HPV. In particular, the Food and Drug Administration (FDA) has approved the use of three anti-HPV vaccines, GlaxoSmithKline's bivalent (HPV16/18) Cervarix, as well as Merck's quadrivalent (HPV 16/18, and nononcogenic HPV 6/11) Gardasil4 and the nonavalent (HPV16/18/31/33/45/52/58) Gardasil9, against some of the most common HPV types (Bedell et al., 2020; Institute, 2013; Kawana et al., 2012; Naud et al., 2011; Villa et al., 2006). After the October 2016 meeting of the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices, the recommended schedule was changed to vaccinating all boys and girls between the ages 9 and 14 with a series of two doses of HPV vaccine, 6 months apart; individuals older than 15 and younger than 26 are recommended to receive three doses of the vaccine (Foxx et al., 2018; Meites et al., 2017).

The introduction of HPV vaccines has brought about significant changes in screening (Barroeta et al., 2017). Recommendation for HPV vaccination have a positive impact on disease prevention, and herd immunity effects already being reported

(e.g., free vaccination program in Australia that started in 2007 (Machalek et al., 2017)). Hence, as vaccination rates increase across the nation (Karen Lewis, 2016; Society, 2017), screening policies may be adjusted considering the reduced risk of transmission, which may allow the transfer of resources from screening to HPV vaccination efforts, which should provide additional boost toward the Healthy People 2020 objective of increasing HPV vaccine completion rates for females ages 13-15 years to 80% (McGhee et al., 2017). therefore, effective prevention, control and management of HPV-related diseases and in particular, cervical cancer must involve comprehensive strategies that promote the combined application of vaccination as the primary prevention and screening as the secondary prevention of cervical cancer.

2.3.2 Tertiary Prevention: Treatment

Not all of the lesions require treatment; CIN1 (LSIL) is often spontaneously resolved via immune system and reverts back to the normal state without medical intervention. One review found that approximately 62% of CIN1 regress in 24 months, 22% persist as CIN 1, and 16% progress to CIN 3 (Vasef & Auerbach, 2019). Therefore, for women with CIN1 close surveillance or observation rather than treatment is recommended (Santesso et al., 2016; Zhu et al., 2017). However, CIN 2 and CIN3 (HSIL) are less likely to regress without appropriate treatment. Especially, lesions associated with persistent high risk HPV strains have a higher risk of progression to malignancy if left untreated (Insinga et al., 2007). One long-term retrospective analysis demonstrated that, during a minimum follow-up period of 12 years, 71% of women with CIN3 (carcinoma in situ) developed invasive cervical carcinoma (Weidner et al., 2009).

Therefore, for women with CIN2 or CIN3 lesions, treatment with one of the standard methods is required (Stanley, 2010). As a general practice, treatment methods are personalized based on the patients' age, fertility desires, the type of cancer (squamous cell or adenocarcinoma), the exact location of CIN or cancer, and stage of the cancer and colpopathologic findings (Khan & Smith-McCune, 2014).

Available treatments for CIN2 and CIN3 include excisional treatment (also called cone biopsy) and ablative treatment. In excisional treatment, the abnormal tissue is removed while in ablative treatment abnormal tissue are destroyed (Hu et al., 2019).

Excisional treatment includes:

- Loop electrosurgical excision procedure (LEEP) in which a thin wire with an

electric current is used to remove the abnormal cells.

- Cold knife conization (CKC) in which using a scalpel, the physician removes a cone-shaped piece of the cervix where the abnormal cells were found.
- Laser conization uses a carbon dioxide laser as a knife to make bloodless cuts to remove the tissue.

Ablative treatment includes

- Cryotherapy in which the physician uses an instrument that freezes off the abnormal tissue.
- Laser ablation in which high energy X-rays destroys abnormal tissue.
- Thermoablation in which extreme temperatures (thermal) are used to destroy (ablate) cancer cells.

Currently, WHO recommends using cryotherapy for the treatment of CIN2-positive patients in low-resource settings. Estimates of the cure rate varies depending on the treatment method. Thermoablation has an estimated cure rate of 95% for CIN2-positive. Cure rate of LEEP and cryotherapy for CIN2 and CIN3 range from 77-93% (Bedell et al., 2020).

For treating invasive cancer (metastatic cervical cancer), depending on the stage of the cancer and spread of malignancy, one of the standard treatment methods with or without chemotherapy can be used. Complete removal of cervix (hysterectomy) as a primary treatment for CIN2 or CIN3 is rarely recommended, but it is an option for recurrent CIN, invasive cancer or incomplete treatment with excision or ablation(Dolman et al., 2014; Martin-Hirsch et al., 2010; Santesso et al., 2016).

2.4 Cervical Cancer Screening

2.4.1 Significance of Cervical Cancer Screening

Preventive HPV vaccines even though very effective are not enough to prevent cervical cancer. From the medical point of view, the uptake of HPV vaccine provides

partial immunity against certain high risk strains of HPV. The fact that cervical cancer is linked to many types of HPV while the available vaccines do not target all known high-risk HPV types and there are significant problems with their adoption imply that control and prevention efforts against HPV and cervical cancer will continue to involve screening protocols for the foreseeable future (Castle et al., 2012; Polman et al., 2019; Schiffman et al., 2017).

In contrast to vaccination, screening helps to detect abnormalities or precancer in apparently healthy asymptomatic population in order to prevent the development of cervical cancer (Polman et al., 2019). There is now substantial and consistent evidence that the incidence of the disease has decreased sharply in the countries where regular population-based screening programs are implemented (Pileggi et al., 2014). Evidence suggest that more than 50% of all new cervical cancers are in women who have never been screened or have not been screened in the last 5 years(CDC, 2020). According to Bedell et al. (2020), only one screening after age 35 reduces the risk of dying from cervical cancer by 70% and the same risk can be reduced by more than 85% if screening is continued in every 5 years. Hence, screening should remain unquestionably in practice to prevent the disease even for the women who have received vaccination.

2.4.2 Importance of Screening in Poor Societies

Globally, screening is either not administered at all or ineffectively administered in many resource-challenged regions of the world. Approximately 90% of the 270,000 deaths from cervical cancer in 2015 occurred in low- and middle-income countries (LMIC) (Siegel et al., 2019). According to WHO, in low- and middle-income countries, the incidence of CC is approximately twice as high and the mortality rates are nearly three times as high as those in high-income countries and the five-year survival rate is significantly lower (55% versus 65%) (Gelband et al., 2016; WHO, 2021b). Moreover, in those countries, the burden of cervical cancer is significantly (over ten-fold) greater than affluent countries (Lemp et al., 2020).

The observed differences among countries are the result of multiple factors, which include both cultural and socio-economical elements that affect both the dynamics of HPV epidemics as well as the effectiveness of surveillance actions. Contrary to the developed countries where educational programs, effective guidelines and prevention programs have decreased the incidence and mortality rates, many developing countries due to the absence, or inadequate investment to offer screening program

with wide enough coverage or to diagnose and treat CIN in women with positive test result are still bearing very high costs for cervical cancer (Heller et al., 2018; Nayar et al., 2018; Toliman et al., 2018; Vu et al., 2018). More specifically, in 2008, the overall uptake of screening was reported 19% in low-income and middle-income countries, compared with 63% in high-income countries. Disparity in vaccination coverage is even worse; as of May 2020, national HPV vaccination programs have been implemented in less than 30% of LMICs, compared with more than 80% in high-income countries (Sung et al., 2021). In high-income countries by 2014, an estimated $33 \cdot 6\%$ of eligible individuals aged 10–20 years had received the full course of the HPV vaccine, compared with $2 \cdot 7\%$ in LMICs (Bruni et al., 2016; Gakidou et al., 2008; Simms et al., 2019). Consequently, in the absence of comprehensive preventive methods in resource-poor settings, effective control and prevention mechanisms including patient-tailored screenings programs are promising in reduction of the overall disease burden.

2.4.3 Cervical Cancer Screening Tests

Screening policies for cervical cancer generally use both primary and secondary tests. Currently, there are four main primary screening tests used for cervical cancer screening: Visual inspection with acetic acid (VIA), Cytology screening (including conventional Pap test and liquid-based cytology (LBC), molecular HPV-DNA testing, and cotesting (Mustafa et al., 2016).

In VIA an acetic acid solution is applied to the cervix, which causes abnormal tissue to change color. Although very unreliable, this method is still practiced in many rural areas in less developed countries. In cervical cytology testing a smear is collected from the endocervix for later analysis by microscope. Cervical cytology checks for the presence of precancerous abnormalities (Aref-Adib & Freeman-Wang, 2016). HPV testing on the other hand, refers to a broad class of testing methods which rely on identification of HPV viral DNA by analysis of the genetic material obtained from a tissue smear (Leal Jr & Gulley, 2017). Specifically, qualitative methods detect only the presence of HPV DNA; quantitative methods estimate the viral load as the quantity of the virus in a given volume and some methods detect the degree of integration of HPV into the host genome (Hartmann et al., 2016).

Co-testing, refers to the simultaneous application of cytology and HPV-DNA tests, the two primary tests most commonly used worldwide. Selection of the appropriate screening method depends on multiple attributes including age, prior screening

records, availability of resources and test characteristics defined by its sensitivity and specificity (Stumbar et al., 2019). Unfortunately, none of the primary screening tests are perfectly accurate.

If during the primary screening tests any abnormality is found, a secondary diagnostic (confirmatory) test is conducted. This procedure involves a magnifier tool called Colposcope to detect the right location of the abnormal cells, followed by examination of a sample of tissues by a pathologist, called Biopsy. Secondary diagnostic tests are used for triage purposes which includes the process of sorting the patients based on their abnormal findings observed in the primary screening tests and hence, their need for immediate medical treatment. Secondary diagnostic tests are known to be almost perfectly accurate if the samples are adequately taken. Otherwise, Biopsy might provide misleading results. A positive result on a secondary test leads to the initiation of a treatment phase. Triage and management of colposcopy/biopsy findings are outside the scope of this research.

2.4.4 Characteristics of the Screening Tests

Primary tests used in cervical cancer screening are not perfectly accurate. Therefore, the choice of preferred screening test for any screening program among many other factors, also depends on the test characteristics defined by the sensitivity and specificity which in turn can be measured based on the number of false-positive and false-negative test-outcomes. Screening outcomes are defined as false-negative (FN) when an individual is misclassified as disease-free for the disease she/he is screened. In contrast, screening outcomes are defined as false-positive (FP) when an individual is misclassified as having a disease when in reality she/he is disease-free. There are important potential adverse effects associated with errors in the interpretation of screening tests. Individuals misclassified as FP may undergo unnecessary and costly follow-up examinations and treatments and hence can suffer severe psychological consequences, discomfort and anxiety (Maxim et al., 2014). However, false negative diagnosis is of greater significance and can have serious health consequences since the disease may progress to a more severe state until the next screening (Edoh et al., 2018).

Sensitivity of a test refers to the probability of correctly detecting a positive individual, and specificity of a test refers to the probability of correctly detecting a healthy person (Zhu et al., 2010).

$$specificity(\%) = \frac{TN}{TN+FP}$$
$$sensitivity(\%) = \frac{TP}{TP+FN}$$

Precise data on the sensitivity and specificity of screening tests are lacking due to methodological differences in the study design including the triage and the presumed positive/negative thresholds. However, it is generally recognized that a cytology test has a higher specificity but lower sensitivity compared to the HPV-DNA testing (Johnson et al., 2019). Several recent meta-analysis studies have reported very low sensitivity for a single Pap test, varying between 20-80%. Similar to the case of Pap test, more recent liquid based cytology screening has also a low sensitivity that ranges between 50 and 70%. Although reliable data are lacking, specificity is probably greater than 90% (Ronco et al., 2014; Wang et al., 2020). In contrary to cytology testing, the estimates of sensitivity for HPV-DNA testing are generally more than 90% (Bedell et al., 2020; Kulasingam et al., 2002; Nanda et al., 2000). Systematic reviews including 20 studies have reported a pooled sensitivity of 90.5% (95% confidence interval, 88.1-92.6) and specificity of 55.1% (95% confidence interval, 53.5-56.8). Two other systematic reviews have reported a range of 75.4% to 95.0%, for sensitivity and a range of 63.0% to 97.0% for specificity (Burger et al., 2011; Macedo et al., 2019; Mustafa et al., 2016; Verdoodt et al., 2013).

Lower sensitivity of cytology test results in higher number of false negatives; hence, missing many precancerous lesions. To compensate this shortcoming, if a standalone cytology based screening is followed, more frequent screenings at shorter intervals must be exercised to increase reassurance against precancers (Basu et al., 2017; Ronco et al., 2016). Conversely, HPV-DNA testing is more sensitive and hence more suitable to detect precancerous lesions which may be missed by cytology screening. HPV testing also allows extending screening intervals longer than those by cytology screening (Dijkstra et al., 2016; Kitchener et al., 2011). However, the increased sensitivity of HPV testing comes at the cost of the twofold number of screen-positive results compared to cytology testing (Benard et al., 2017), which subsequently increases the cost by too many unnecessary follow-up tests and treatment (Demarco et al., 2020; Tjalma, 2018; Wentzensen et al., 2016). Achieving a reasonable trade off becomes even more challenging knowing that in many cases the precancerous lesions which are missed by cytology and found by HPV testing are clinically important (Castle et al., 2012). Therefore, in some countries, the guidelines recommend screening by HPV testing as an adjunct to cytology testing to maintain high sensitivity at longer intervals.

Ideally, primary screening tests should be highly sensitive so that the test does not miss diseased individuals, and secondary diagnostic tests (such as biopsy) be highly specific to rule out healthy patients that were wrongly classified by primary testing as positive cases (Kim et al., 2008). In addition, the test characteristics create a dilemma regarding the cost and benefit expected from selecting a certain primary screening test. In communities where literally the majority of patients take regular tests at regular intervals, the cost associated with a less specific test (such as for instance HPV-DNA) outweighs the cost of a possible delayed treatment associated with a less sensitive test (e.g. cytology). Hence, cytology is preferable. On the other hand, in countries where patients take the tests in an unsystematic way, screening with a highly sensitive test (HPV-DNA) reduces the chance of missing the disease in patients who are falsely diagnosed as negative (Kulasingam et al., 2002; Ronco & Rossi, 2018). Since neither test is dominant, many guidelines have included co-testing in their recommendations to increase the chance of correct diagnosis.

2.4.5 Screening Guidelines

In many developed countries, the specifications of a routine screening programs for the entire population are provided by the government or national health organizations in the form of guidelines. Guidelines are country specific and different guidelines are designed for the needs of each country. For cervical cancer, there is no common screening modality recommended by the guidelines in different countries. Depending on the resources, countries exercise standalone cytology or standalone HPV testing or cotesting. In some cases, the choice depends on the discretion of the clinicians to decide on the favored approach (Ebell et al., 2018).

In the US, many national health organizations including the American Cancer Society (ACS), American Society for Colposcopy and Cervical Pathology (ASCCP), American Society for Clinical Pathology (ASCP), and US Preventive Services Task Force (USPSTF) provide screening guidelines. Table 2.2 summarizes the current guidelines of US (Salina Zhang et al., 2019; Smith et al., 2019).

In 2020, the American Cancer Society (ACS) updated its previous recommendations. According to the new guideline, individuals are strongly recommended to initiate screening at age 25 years and preferably undergo primary HPV-DNA testing every 5 years until age 65; if HPV-DNA testing is not available, then they should be screened with cotesting every 5 years or cytology alone every 3 years (Fontham et al., 2020).

Table 2.2 Summary of screening guidelines

	ASCCP		USPSTF	
POPULATION	**RECOMMENDED SCREENING METHOD (updated 2015)[4]**	**MANAGEMENT OF ABNORMAL SCREEN RESULTS (updated 2019) [5]**	**RECOMMENDED SCREENING METHOD (updated 2018)[6]**	**MANAGEMENT OF ABNORMAL SCREEN RESULTS**
Aged <21 y	No screening		No screening Grade: D	
Aged 21-29 y	Cytology alone every 3 y	if age<25 management according to 2006,2012 ASCCP/ACS/ASCP[1] guidelines [7]and if aged 25-65 management according to 2019 risk based consensus guidelines [9]	Cytology alone every 3 y Grade: A	Management according to 2006,2012 ASCCP/ACS/ ASCP guidelines [7] 2015 ASCCP/SGO[2]interim guidelines [8]
Aged 30-65 y	Cotesting every 5 y Cytology alone every 3 y HPV DNA every 5 year[3]		Cotesting every 5 y Cytology alone every 3 y HPV DNA every 5 y Grade: A	
Aged >65 y	No screening if adequate prior negative screens		No screening if adequate prior negative screens Grade: D	
After hysterectomy	No screening		No screening Grade: D	
HPV vaccinated	Same as unvaccinated		Same as unvaccinated	

[1] American Society for Colposcopy and Cervical Pathology, American Cancer Society, American Society for Clinical Pathology
[2] The Society of Gynecologic Oncology
[3] Added after 2015 interim update
[4,8] Huh et al. (2015); Saslow et al. (2012)
[5,9] Perkins et al. (2020)
[6] Curry et al. (2018)
[7] Saslow et al. (2012); Wright Jr et al. (2007)

As the first basic step population-based screening has to identify the target population that should be screened (Dillner, 2019). Type of the screening, optimal interval until re-screen and the ideal age to initiate and stop screening based on the risk-benefit trade off analysis are the subsequent questions to answer. There is an enormous ongoing research on the criteria for the selection of ideal candidates to screen (Loud & Murphy, 2017). There is also debate among the health researchers about the appropriate intervals for screening and acceptable risk thresholds (Smith et al., 2019). Theoretically, an ideal screening interval for a population-based screening program must result in detecting all cases of treatable precancers allowing for extremely few undetected invasive cancers. Creating such a delicate balance is crucial in that screening too frequently will only detect many HPV infections with low risk of progression into cancer, causing costly overtreatment. On the other hand, screening too infrequently increases the possibility that a large number of precancers develop into invasive cancers which otherwise could be prevented (Silver et al., 2016). In many population-based screening programs, the recommended age to start undergoing routine screening is the age at which the cancer risk begins to rise. Screening is stopped at an age at which there is no significant evidence that screening further will improve the health outcome (Wentzensen et al., 2016).

2.4.6 Personalized Screening

There are several advantages to following guidelines, including simplicity of implementation and effectiveness in reducing mortality. While guidelines create a distinct advantage by reducing the disease burden in many countries, they also suffer from several drawbacks. First, it is widely acknowledged that screening the whole population with the same intensive frequency is costly to the healthcare system and requires considerable availability of diverse resources and infrastructure (Gelband et al., 2016). Second, it must be recognized that the clinical understanding of cervical cancer is not static, rather it is exposed to fast-paced changes with the new emerging technologies (Smith et al., 2019). Consequently, the population based guidelines very often evolve with the emergence of new data and evidence regarding the natural history of the disease and the optimal screening strategies (Stumbar et al., 2019). In the United States, since the introduction of the first guideline, the guidelines have gone through several revisions (Silver et al., 2018). This creates complexity and challenges to implement such guidelines in a context where a long chain of patients, healthcare providers, clinicians, gynecologists as well as healthcare payers have to continuously adapt to the frequent updates of the recommendations from the multiple guidelines (Lees et al., 2016).

Recently, personalized medicine as an alternative to the guidelines has gained attention in the medical and public health community and is being incorporated into the cancer screening programs. Ayer & Chen (2018) characterize personalized medicine (PM) as interventions focused on individual patients in contrast to one-size-fit-all population based guidelines. According to the authors, the differentiating characteristics of PM is based on restricting the treatment to those who are more likely to benefit from a particular intervention and leaving the rest out of intervention scope. The primary objectives of PM among others include guidance with respect to the selection of optimal intervention, avoid adverse effects, and minimizing the overall healthcare cost. The current approaches in PM are classified as *modeling of the disease* and *artificial intelligence approaches*. They further classify modeling approaches into sequential decision making models and onetime decision models. Other studies including the ones by (Konecny, 2015) and (Robertson & Ladabaum, 2019) address the required settings and the challenges to shift from population based guidelines to personalized screening programs.

In 2020, ASCCP published personalized follow-up management for the patients already diagnosed with an abnormal result. Notice that the personalized follow-up plan is implemented when the patient leaves the regular population level screening when an abnormal result is identified. In other words, patients with a normal primary screening result need to continue regular screenings provided by the guidelines of primary screening. The personalized follow-up plan, identifies the current

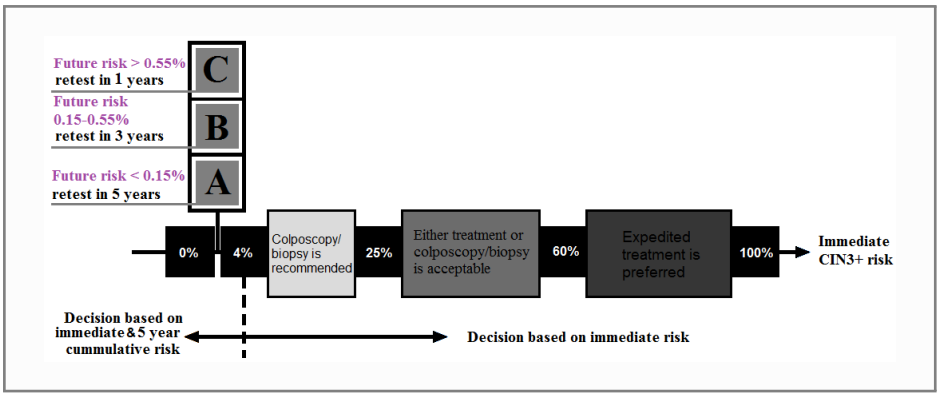


Figure 2.2 Management of abnormal results based on ASCCP clinical action thresholds

and five-years future risk of developing cancer. As it is shown in Figure 2.2, the immediate and future actions depends on the current and future risk. This type of personalized plans are called risk-action threshold policies, in that the risk threshold specifies the appropriate action to implement.

2.4.7 Conclusion

The primary objective of the current research is to develop personalized screening policies for cervical cancer patients. The approach adopted in this thesis is similar to that of ASCCP management plan to follow-up abnormal result. However, contrary to the ASCCP that established followup policies for the patients already diagnosed with abnormal findings, we aim to develop a personalized primary screening policy for the asymptotic populations who are entitled to undergo routine screening checks. Our proposed personalized cervical cancer screening model is characterized by its ability to distinguish patients based on the individual attributes including risk of cancer and age of the patient as well as other factors such as test characteristics parameterized by sensitivity and specificity of the test.

Personalized screening for cervical cancer policy considers risk of cancer for each individual separately contrary to the guidelines that adopt policies based on the risk for general population. Negative test results may imply longer rescreen interval and positive tests may required more aggressive screenings. From the guidelines perspective, information encoded in a sequence of three negative test result is considered to be equal to the information encoded in a single negative test as both cases lead to a rescreen at a fixed interval length of, e.g., 5 years with cotesting. In contrast, the records of the previous screening results are not marginalized under personalized

screening plans which substantially account for the prominence of the personalized models. Of course, this approach requires sophisticated risk estimation models that can utilize gained information about the risk factors and convert that knowledge into risk estimates. To implement this step we employ the proposed risk estimation models in the literature.

Another distinctive feature of personalized policies relates to the fact that the decision maker can pick the appropriate screening tests based on the test performance in cancer detection. As discussed in Section2.4.4, each screening test has its unique characteristics with potentially dissimilar implications for the timing of the next screening and choice of the future screening type. This research considers three screening modalities, namely, cytology testing, HPV-DNA testing and cotesting as the main primary screening tests against CC. It's also worth noting that the current evidence indicates no clinically important differences between conventional Pap test and liquid-based cytology Curry et al. (2018). Therefore, this study uses cytology testing as a reference to any of these cytology based testing methods.

Additionally, for the implementation of a personalized screening policy, it is of crucial importance to develop models that are flexible enough to make use of the risk information, test performance and other factors affecting the disease. Among the promising methodologies, partially observable Markov decision process (POMDP) provide a rich framework for sequential decision-making under partial information that suits perfectly to the problem at hand. In the following section, we provide a detailed review of methodologies that can be used for screening policy making including POMDP models which we use in the current study for modeling and analysis purposes of cervical cancer screening policies.

3. REVIEW OF THE METHODOLOGIES FOR THE PLANNING OF DISEASE PREVENTION

3.1 Chapter Overview

In recent years, numerous studies in the literature focused on the design and planning of screening and treatment decision making problems for various types of diseases including heart disease, cancer and diabetes using well suited simulation or sequential decision making models. This chapter aims to present a review of the approaches and discuss the various aspects of each approach used by authors in dealing with such problems. Specifically, we first provide a review of the operations research applications in healthcare decision making and focus on two commonly used design and planning approaches namely cost effectiveness studies and Markov decision process (MDP) respectively. A generalization of MDP problems with partial observability namely, partially observable Markov decision process (POMDP) has also been used frequently in the literature since it fits well into the problem of screening decision making where the screening tests are imperfect. We provide an extensive review of such models in this chapter.

3.2 Overview of Medical Decision Making

The previous chapter established that the prospect of applying personalized interventions into cancer screening decision making problem is partly associated with the suboptimality of the guidelines. According to Burthold (2007) guidelines are generally premised on fundamental logical fallacies and unrealistic assumptions. As

an alternative to the guidelines, personalized interventions are gaining more ground especially in screening programs.

The problem of developing and evaluating screening policies has been addressed in the literature in various ways. Güneş & Örmeci (2018) present a detailed analysis of disease screening problems and operations research applications on different aspects of the problem. Steimle & Denton (2017) provide a review of state-of-the-art models and methods that have been applied to chronic diseases. Their study also includes a tutorial about how to formulate and solve these problems emphasizing some of the challenges specific to chronic diseases such as diabetes, heart disease, and cancer.

3.3 Cost-effectiveness Analysis

Many studies in the literature for different cancer types focus on cost-effectiveness models. These models help to understand and evaluate different preventive policies in terms of their health and economic consequences. Simulation models have been developed as a useful tool for their ability to reproduce the natural history of the disease. In many chronic diseases, the evolution of disease can be represented using a Markov chain and in theory, one can devise many distinct screening policies and compare/contrast them against the one in practice. Generally, by simulating the process, cost effectiveness analysis focuses on the potential effect of certain decision rules of the hypothesized policies on the health and cost outcomes.

Cost effectiveness analysis (CEA) has important applications in health policy around the globe. Many countries including the UK, Australia, and Canada require economic evaluations before approving new healthcare technologies or interventions. CEA helps to compare the relative value of alternative strategies and identify those that create high-value care. The need for CEA especially arises when different competing policies exist. For instance, in the United States, the complexity created by the possibility of choosing between various test combinations, screening frequencies, and ages to switch from one screening strategy to another requires clear understanding of the outcomes that following each strategy may bring about.

The outcomes of the CEA are usually summarized in cost-effectiveness ratios (CER), where the costs in the numerator are related to a single measure of effectiveness in the denominator. The effectiveness can be any pertinent clinical marker such as life years gained (LYG). Incremental cost-effectiveness ratio (ICER) refers to the

case when comparisons between two interventions are made. ICER indicates the marginal health effect gained by spending dollars on a strategy compared to an alternative one, and is expressed as cost per unit of effect. Cost-utility analysis refers to the analysis of cost per one unit of an additional quality adjusted life year (QALY) (Edoh et al., 2018; Kraemer, 2007). According to Weinstein et al. (1996), QALY is the only approved benchmark for health outcomes recommended by the U.S. Panel on Cost-Effectiveness in Health and Medicine. QALY varies between 0 and 1 where a QALY of 1 is equivalent with one year of perfect health and score of 0 equivalents death. For instance, 4 years lived with a quality of life (QOL) of 0.25 yields a QALY of 1 (Vergel & Sculpher, 2008).

Ayvaci et al. (2012) used an MDP framework for evaluating the cost-effectiveness of breast cancer diagnostic decisions after an abnormal mammography where the diagnostic decisions are subject to the budget constraints. Authors demonstrated that the total expected QALYs improve as the level of funding increases, but with diminishing returns in the allocated resources arguing that short-term follow-ups are the immediate candidates for elimination when the resources are scarce. They showed that contrary to the recommendations of USPSTF women at their 40's need to undergo mammography screenings, and the most benefits in terms of QALY improvement can be achieved in this age group.

Li et al. (2014) developed a partially observable Markov chain (POMC) model in order to assess the cost-effectiveness of colonoscopy screening strategies. In their model, they estimated state transition probabilities based on longitudinal clinical data from a specific population cohort. Their research answers multiple questions including screening frequency, initial screening age, screening end age, and screening compliance rate.

In the context of cervical cancer, policy making from the perspective of CEA has been more common in the literature than other methodologies. Examples of systematic reviews of the literature in these streams include studies by Gervais et al. (2017); Schiller-Frühwirth et al. (2017), and Koleva-Kolarova et al. (2015). According to ASCCP guidelines for CC screening presented in Table 2.2, patients aged 21-29 are recommended screening with cytology every 3 years. After age 30, they can switch to HPV-DNA testing every 5 years. Using CEA, the cost and health consequences of such transition can be studied. Specifically, Sawaya et al. (2019) considered the cost-effectiveness of 12 cervical cancer screening strategies in the United States including ASCCP guidelines. Authors concluded that for women aged 21-29 years who are currently undergoing cytology screening every 3 years, continuing screening every 3 years with cytology testing or switching to a low-cost HPV-DNA testing

every 5 years after age 30 confers a reasonable balance of harms, benefits, and costs.

As the selected studies suggest, CEA primarily involves a comparison of intervention options for health policy or medical decision making. Consequently, application of the CEA methodology in sequential decision making has restrictions. A survey of literature shows that the dominant methodology in modeling sequential decision process has been Markovian models. In the remaining part of this chapter, we focus on the Markovian models namely, MDP and POMDP models.

3.4 Planning Preventive Policies Using Markovian Models

Generally, preventive decisions are characterized by repeated choice paradigms. Therefore, Markovian models are widely used by the researchers of medical decision making to formulate and analyze the influence of different preventive actions. In particular MDP and POMDP modeling approaches are commonly used. (PO)MDPs are suitable frameworks for modeling sequential decision-making in situations where the outcomes are partly uncertain such as the progression of the disease and partly under the control of the decision maker through the decision to perform a certain preventive action such as screening.

Schaefer et al. (2005) present an overview of MDP models in the context of medical decisions including screening and treatment. Their study reviews selected applications of MDPs to a variety of medical decisions including treatment, screening, organ transplantation and drug infusion decisions in the literature. Alagoz et al. (2010) provide a review of MDP models applied to different chronic diseases and address the challenges and opportunities of applying them for medical decision making.

Multiple examples of applying personalized MDP models that capture the general characteristics of the patients including age, education or the disease specific characteristics in different disease contexts can be found in the literature. Alagoz et al. (2004) developed an MDP model to study the form of optimal policies for the timing of living-donor liver transplantation. Authors argued that variations in individual's disease progression can lead to significant differences in the optimal policies for identical patients in different disease groups, underlining the importance of patient specific attributes in developing care plans.

Chhatwal et al. (2010) addressed the problem of follow-up for the women based on

their abnormal mammography finding, where the decision process is designed to include the mammographic features and demographic factors of the women undergoing screenings. They formulate the biopsy decision problem as a finite horizon MDP and use a mammography Bayesian network to estimate the breast cancer risk based on patient's individual risk factors. Their optimal policy infers that the risk threshold for biopsy in older patient should be higher than that of a younger patient.

As an extension to the the previous study, Burnside et al. (2012) addressed the problem of optimal risk threshold to recommend breast biopsy by an MDP model where the optimal biopsy threshold depends on the patient's breast cancer risk. By incorporating demographic risk factors and mammographic findings into a logistic regression model, they estimate the patient's cancer risk. Authors argued that 2% is the optimal breast biopsy threshold for women of age between 42 and 75. For patients younger than 42, biopsy thresholds are lower than for older patients. Another extension of the study by Chhatwal et al. (2010) can be found in Alagoz et al. (2013) where the authors considered the eligible patients for short-interval follow-up after an abnormal mammography finding. Similar to Burnside et al. (2012), they maintained that the biopsy threshold increases with age, also confirming 2% risk as the best threshold for a short term follow-up of breast cancer patients.

Denton et al. (2009) used an MDP model to optimize the starting time of cholesterol lowering medication for patients with diabetes. This study has been taken further by Mason et al. (2012) by introducing the adherence level of the patients to the recommendations in the model. To study the influence of adherence on the optimal timing of treatment initiation, the authors use an MDP model, in which 4 standard thresholds of adherence in the literature define the so-called adherence states in the Markov chain. The transitions among adherence states occur if a treatment phase starts. The objective function in the MDP model includes both minimization of expected total costs and maximization of expected QALYs. Their result show that adherence-improving interventions can increase expected QALYs by as much as 1.5 years.

Yaylali & Karamustafa (2019) modeled obesity levels using an MDP model to observe the effect of obesity on cancer and mortality risks. Their gender-specific results suggest that obese patients for all obesity levels should undergo surgery to improve their health outcomes and to decrease cancer risk. Önen et al. (2019) addressed the question of whether the population based screening for Alzheimer's disease is necessary. They formulate an MDP model whose objective function combines QALY and costs. A numerical implementation of the MDP model showed that in the baseline case, the optimal policy is not to employ a population-wide screening program.

POMDPs have also been used for medical decision making. A survey of the recent literature exhibits the rising trend in the usage of personalized POMDP frameworks for medical decision making, and specifically for screening and treatment decisions in different cancer types. While in the MDP models it is assumed that the outcome of actions are perfectly observable to the decision maker, POMDP models are not restricted to such assumptions. Consequently, in the settings where the action outcomes are partially observable, such as the case of screening tests for cervical cancer, POMDP models provide more realistic framework compared to MDP models.

In the literature, a plethora of papers have been put forward to develop policies for disease prevention using POMDP framework. Vargas et al. (2015) studied optimal treatment decisions for breast cancer and proposed a dynamic decision model to determine optimal breast cancer treatment decisions that included both the impact of overtreatment and the potential delay in cancer detection. Goulionis & Koutsiumaris (2010) developed a POMDP model for the problem of treating patients with early prostate cancer. They used a procedure that take advantage of special problem structure, and provide optimal policies to stochastic and dynamic decisions naturally arise in finding optimal disease treatment plans.

Consistent with the real world practice, Ibrahim et al. (2016) suggested a two stage solution approach to the problem of personalized anticoagulation treatment of patients who are using warfarin. In the first stage, the physician gains inference about the reaction behavior of the patient to warafin. They model this stage as a POMDP, where the inference is achieved through the consecutive belief updates inherent in POMDPs. The second stage involves, a phsycian's decision about the optimal dose to prescribe to a patient considering the patients sensitivity to warafin, which is modeled as an MDP. They studied the required length of the initiation phase, and the effect of the physician's initial belief about the patient's sensitivity on the length. Their results show that, the risk reduction is higher when the initiation phase is shorter. Their results suggest that the initial belief about the sensitivity has a critical impacts on the required length for the initiation phase, such that higher sensitivity results in lengthy initiation phase.

Gan et al. (2019) addressed the challenge of comparing treatment regiments for opioid use disorder (OUD) using different wearable devices. They argue that the contrary to the traditional urine test to evaluate the patient response to a treatment option, wearable devices are more effective tests. The devices are assumed to have yet noisy behaviour and patients are not complying to the treatments fully. The decision maker is also subject to limited budget level. For such setting, they construct a POMDP model with budget constraints to study the value of different

devices in OUD treatment. Their result suggest that under a moderate budget level, for patients with low or moderate adherence level wearable devices are valuable.

One of the early studies to use POMDP model to evaluate a screening policy is the one by Maillart et al. (2008) to assess different policies of screening for breast cancer. Authors formulated a POMDP model that incorporated age-based dynamics of the breast cancer and the accuracy of the test results with mammography as the only detection tool. They measured the value of a screening policy by lifetime mortality risk of a patient under that particular policy. Using this metric, authors argued that to achieve an efficient policy, screening should start relatively early in life and continue relatively late regardless of the screening intervals adopted.

Zhang et al. (2012) addressed by a POMDP model the problem of policy making for prostate cancer in an environment with two decision makers: patient and payer, each having a different metric to evaluate the goodness of an intervention. From the patient's perspective, the metric is QALY and from the payer perspective, the metric is cost. They combine the two angles in a so-called "societal perspective", which concerns maximizing a net monetary benefit that combines the total cost of a policy and the QALY weighted by the willingness-to-pay value.

Ayer et al. (2012) proposed a POMDP model to personalize mammography screening decisions. They considered self detection or mammography as the two methods of disease detection. In their model, 5 stages of the disease and a death state were represented, and the age-dependent progression of the disease as well as the accuracy of mammography tests were taken into account. Using patient's perspective, their model aims to maximize QALY. One important aspect of their study is that they incorporate several personal risk characteristics of women in their model, making it more realistic. They report promising results including reduction in the number of mammograms and false results, and increase in the total QALY gain. Additionally, the authors derived sufficient conditions that ensure the existence of a threshold value for cancer risk over which it is optimal to conduct the mammogram. In a similar study, Erenay et al. (2014) considered the problem of optimizing colonoscopy screening for colorectal cancer prevention and surveillance, with a model that aims at maximizing QALY throughout the patient lifetime.

Witteveen et al. (2018) addressed the problem of follow up screening tests for patients treated for breast cancer. They argue that optimal schedule is correlated with age. To investigate the effect of age and decrease the number of unnecessary follow-ups, they develop a POMDP model to determine optimal follow-up strategies based on the cancer recurrence risk for patients in four different age groups. The age effect is captured by risk prediction model. Their result showed that the highest

recurrence risk is in the second year after diagnosis. Hence, more intensive follow-up tests are scheduled afterwards. For patients younger than 50, they recommended slightly more aggressive follow-up than the current schedule with five year intervals. Their optimal policy also suggested less screenings for patients older than 50. Similar to the study of Witteveen et al. (2018), Otten et al. (2017) addressed the problem of reducing unnecessary follow ups for patients who are treated for breast cancer. They maintained that the optimal follow-up policy depends on the personal risk characteristics of a patient. Their result are confirming the results of the former study about intensifying screenings at peak risky period.

Tomer et al. (2019) discussed the problem of rigorous biopsy screening mostly unnecessary for the low-risk prostate cancer patients who are enrolled in active surveillance programs and undergo frequent screenings on fixed intervals. Due to complexities associated with Biopsy testing, the adherence level to the scheduled screenings are low and hence, the risk of undetected disease increase. To address this problem, they develop personalized screening schedules. To target the right group of patients and their schedule, they collect the information of antigen levels from the patient's historical data and their history of biopsy results. Their results suggest that if a patient carries the risk of a slow growing PC, two less screening than the current schedules should be conducted. For a faster growing cancer risk, one less than the current schedules is recommended. For the case when the risk can not be predicted, they recommend a hybrid approach.

Most of the studies in cancer screening planning assume that the patients are fully complying with the screening recommendations. In reality, however, patients exhibit heterogeneity in adhering to the prescriptions. An adherence issue arises when patients undergoing screening tests are not showing up according to the scheduled procedures. Personalized POMDPs are capable to incorporate heterogeneous behavior of the patient into decision making process. Examples of such studies include works by Ayer et al. (2016) and Li et al. (2015). Ayer et al. (2016) develop a POMDP model for planning breast cancer screening which incorporates the uncertainty about patient adherence. They demonstrate that low adherence results in more aggressive screening intervals. Study of Li et al. (2015) considers a setting where the patients undergoing screening tests for colorectal cancer are not complying fully. Authors suggested approach includes an adherence parameter that represents the individual rate at which a patient complies with the recommendations. For different rates, they propose the corresponding optimal policy. The results suggest more aggressive screenings than the currently practiced guidelines for the patients with low compliance. Both studies suggest that low adherence results in shorter screening intervals and more aggressive screenings than those recommended by the current guidelines.

Few studies have considered the potential effect of limited resources on the decision process. Cevik et al. (2018) developed a constrained POMDP (CPOMDP) where there is a budget restriction on the number of screenings which can be recommended. They assume that one round of screening consumes one unit of budget. This way, their budget constraint is transformed into the total number of screenings that can be performed during a certain planning period. They study the impact of the resource restriction in two settings: first for the patients within the same risk group, where the resource is optimally allocated for different age groups. Second among the patients from different risk groups. For the first setting their results demonstrate that not always the limit number of resource is exhausted. Moreover, the resources are used less intensively at lower age and more intensively as the patient gets older. For the second setting, the result suggest more screening is assigned to average risk (AR) patient versus high risk (HR) patient due to the difference in the corresponding population size. Moreover, the proportion of the tests assigned to the HR patients increases as the imposed limit becomes tighter.

The problem of policy making for cervical cancer screening at an individual level was first addressed by Akhavan-Tabatabaei et al. (2017). In their study, the authors developed an MDP model aiming at determining optimal screening policies for cervical cancer prevention while minimizing a cost function that includes the cost of prevention and treatment procedures, as well as the cost associated with loss of life quality due to wrong decisions that delay screening. In the model, considering the age of the patient, the most recent test result and diagnosis, and HPV contraction risk, the authors obtain optimal policies to decide when and which screening test is to be conducted. An important limitation is that the model relies on the assumption that the tests are 100% accurate, thus not adjusting for the test characteristics and the possibility of false result. Accounting for the sensitivity and specificity may reduce the number of unnecessary follow-ups on the one hand, and the number of missed opportunities to detect the disease early and initiate the treatment phase on the other hand. The second limitation of the model is that only pap and colposcopy tests are considered as methods of detection, while recently published guidelines by different institutions recommend the use of both cytology and HPV-DNA tests as primary detection tests.

The application of POMDPs to medical decision making is not a straightforward task, primarily due to their high computational complexity (Schaefer et al., 2005). The computational complexity of POMDPs is attributed to *curse of dimensionality* and *curse of horizon*. Curse of dimensionality refers to the difficulty of solving problems with too many states and/or actions. Curse of horizon refers to the difficulty of implementing iterative steps of dynamic programming as the horizon increases.

In the past years, research community has made extensive efforts on the computational aspects of POMDP problems. Generally, the proposed solution methods can be classified into exact and approximate solution methods where the exact algorithms aim to efficiently compute optimal solutions and approximation algorithms aim to compute larger and more complex problems.

Even though the exact solution algorithms provide optimal solutions, dynamic programming step inherent to current exact algorithms require an intractable amount of memory. Despite many attempts to make this process more efficient, the time and space complexities of POMDP algorithms remain serious challenges. Therefore, use of the exact methods has been restricted to problems with few states and actions. A survey of studies using exact methods including studies by Ayer et al. (2012); Cevik et al. (2018); Li et al. (2015); Otten et al. (2017,2) reveals that exact methods are unable to handle problems with large state/action spaces. To bridge this limitation of exact algorithms researchers have shown interest in approximate methods that compromise optimality for reasons of tractability. Approximation algorithms can operate with a limited memory for problems with too many state/actions, however, they provide weak theoretical results.

3.5 Conclusions

This chapter has reviewed some of the studies that addressed decision making problems in connection with disease prevention. In the context of preventive methods against different forms of cancer, several models have been developed, each associated with strengths and limitations, and each equipped with features suited to address different policy questions. Our review shows that along with the cost-effectiveness and simulation models, a huge pool of studies in the literature have used MDP or POMDP models as the general framework of analysis. Generally, the popularity of personalized POMDP models relies on the power of these models to reflect the real world. Since many chronic disease evolve with time, POMDP models provide a suitable framework to reflect the disease progression/regression in the state space of the model, while preventive actions can be utilized to change the course of the disease.

This research employs a POMDP approach for personalized screening policy making for cervical cancer. In Chapter 4 we propose a POMDP model where the screening

action is considered to be only a cotesting test which is approved and recommended by many of the US guideline organizations. We use a compact state space representation where precancerous lesions of any grade are bundled into one state. Since the state and action space are small, we use an exact solution algorithm to solve the problem. In Chapter 5, we expand the state space and use a model with 10 states and the screening actions are considered to be screening with cytology and HPV-DNA tests. The expansion of the state space is primarily motivated by difference in the progression and regression rates observed in the precancerous lesions states. Since the problem size is large, we use an approximate solution method to solve the problem.

4. PERSONALIZED SCREENING POLICY WITH COTESTING

4.1 Chapter Overview

This chapter presents a personalized optimal screening policy for cervical cancer where the screening action includes cotesting. It briefly introduces the problem and subsequently provides details about the formulation of the model. The chapter subsequently discuss the optimal solution algorithm used to solve the problem and derive the optimal policy. The result section compares and contrasts the findings in the POMDP model with the current practices and guidelines. Finally, it concludes with a discussion of our findings and risk-QALY improvement trade-off.

4.2 Introduction

In recent years, after the approval of cotesting as a primary screening into a screening policy, many countries have started to adapt it as the primary screening test. In the US, following the 2003 approval of cotesting for routine screening by the US Food and Drug Administration, cotesting gained more popularity among the patients. One particular clinical trial in a private hospital showed that the usage of cotesting increased from less than 10% in 2006 to 78% in 2013 (Silver et al., 2018). The shift from cytology testing to cotesting was partially motivated by the lower degree of assurance that a 3-year interval following a negative cytology testing can effectively reduce cancer risk. Studies also suggest that, compared to a single round of cytology testing, a single round of HPV-DNA testing more effectively reduces the incidence of CC within 5 years and mortality within 8 years (Castle et al., 2012).

Introduction of cotesting as the primary screening test has created controversy in regard to the frequency and management of the findings. Studies have shown that following a negative cotesting, the risk of cancer is twice as large at 5 years as it is at 3 years (Kinney et al., 2015). Other studies however suggest that from a cost effectiveness perspective, a 5-year screening interval for cotesting results in a reasonable balance between benefits and harms while screening more frequently does not substantially improve benefit but increases the number of screening tests and follow-up interventions (USPSTF, 2018). Management of the cotesting results with HPV-positive and cytology-negative which is the most common finding in cotesting is also a matter of on-going debate among researchers and functions as a major challenge to the widespread use of cotesting (Schiffman et al., 2011).

Even though, there are studies maintaining that the added sensitivity of cotesting compared to HPV testing alone is minimal (Curry et al., 2018), evidence suggest that cotesting offers more assurance and hence gained more popularity. Moreover, such studies are based on observations from only a few screening outcomes (Whitlock et al., 2011) and do not compare cotesting with HPV testing for more than 2 rounds of screening (Salina Zhang et al., 2019). With regard to the aggressive follow-up interventions associated with cotesting, few authors argued that there is little if any concrete evidence indicating that colposcopy/biopsy procedures will increase for women undergoing cotesting, if currently recommended cotesting guidelines are followed (Nayar et al., 2018).

To better address the above mentioned challenges, we introduce in this chapter a personalized model that can incorporate the cancer risk as well as test characteristics to create a patient-tailored screening program. Since a number of studies address the positive effect of applying cotesting as the primary screening test (Kinney et al., 2011; Wright et al., 2015), we consider cotesting as the primary screening test for the personalized screening programs.

The most similar studies in the literature to ours include the studies by Ayer et al. (2012) and Akhavan-Tabatabaei et al. (2017). Our approach is similar to the former study, but in a different disease context. The later study presents an MDP model for cervical cancer screening policies in Colombia. Their optimal policy shows how frequently patients in different age groups with different risk profiles must undergo screening. Despite similarities in the context, our model differs in multiple aspects. Our model addresses making screening decisions using a POMDP approach, which is capable of incorporating the sensitivity and specificity of the screening tests. We consider cotesting as the primary screening test whereas the intervention modality in their study is cytology and colposcopy. Finally, in their model the intervention

outcomes are measured in terms of monetary costs, while the objective function of our POMDP model maximizes the quality-adjusted life years (QALY), which is a measure of health outcome that varies between 0 and 1.

To the best of our knowledge, the present work is the first study to apply the POMDP approach to cervical cancer screening, incorporating the patient's risk characteristics and history of screening into the decision making process. We implement our model and compare the optimal policy against multiple real-world guidelines and scenarios and present insights on the frequency of screenings and its relation to the risk and QALY gain or loss.

4.3 Model Formulation

Over a certain period in a patient's lifetime, the decision maker (e.g., physician) aims to choose an optimal action from the feasible set of actions such that the expected total reward is maximized. We model this problem as a discrete-time finite horizon partially observable Markov decision process (POMDP) while at any point in time, the state of the patient evolves according to the underlying Markov chain. We model the natural history of the disease starting with the state of *no-cancer* `(NC)`, which represents all the possible cases when the patient is perfectly healthy, has no HPV infection nor any cervical lesions. Newly infected patients or patients with a persistent HPV infection may develop *precancerous-lesions*. We denote the state of such patients with `(PL)`. HPV infections/precancerous lesions may regress to the healthy state or progress to a more severe disease state and lead to *invasive-cancer* denoted by state `(IC)`. The complete set of states and the underlying Markov chain are depicted in Figure 4.1. We explain and motivate the remaining states in the Markov chain while discussing the decision process in our model. The decision process can be described as follows: in each of the decision epochs in the planning horizon, for the patients in any of the states `(NC)`, `(PL)` or `(IC)`, the decision maker faces a decision problem: either to test or wait. Consistent with most of the guidelines, we assume that the planning horizon in our model starts from age 21 and ends at age 69, and decisions are made annually. In many countries 21 is the earliest age to start screening for cervical cancer, and screening stops at age 69. We use t to denote the decision epochs and as a convention $t = 0$ corresponds to age 21. We use N to denote the terminal age when the decision process ends (N corresponds to $t = 49$ and age 70); the last decision will be made at $N - 1$, i.e., at

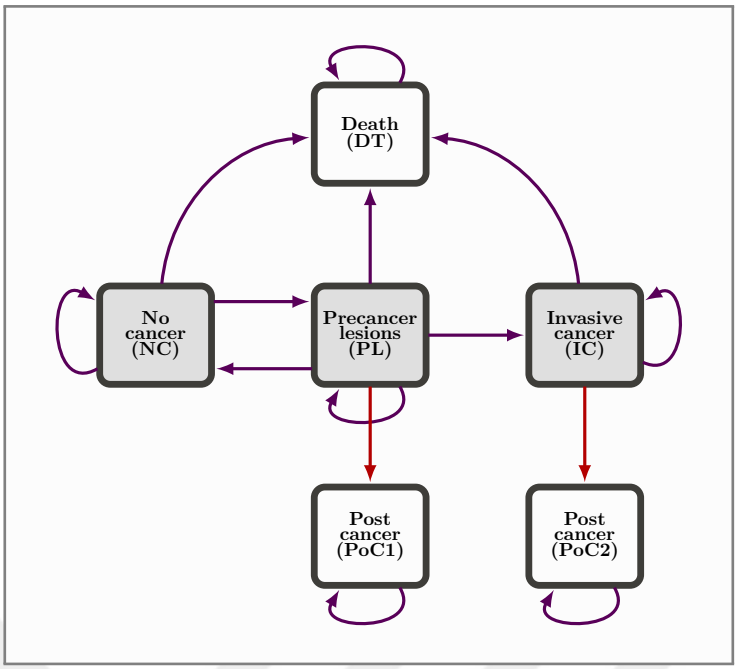


Figure 4.1 State transition diagram.

$t = 48$.

At decision epoch t, if *wait* action is decided, the next decision will be made at $t+1$. Otherwise, if *cotesting* is conducted and the result is negative, the patient waits again until $t+1$. If the test is positive, a diagnostic test, i.e., *biopsy* (Bx), which is assumed to be perfectly accurate, is conducted. Biopsy reveals the correct state of the patient. If she has no cancer (state `(NC)`), the biopsy result will be negative. If she has lesions (state `(PL)`), the biopsy will show precancerous lesions. Similarly, if the patient has invasive cancer (state `(IC)`), the biopsy will show cancer. Those patients whose biopsy results show either precancerous lesions or invasive cancer enter the post-cancer states and start the corresponding treatment. We represent the treatment states for precancerous lesions with `(PoC1)` and for invasive cancer with `(PoC2)`. For patients who undergo treatment, the follow up procedure includes more aggressive screenings (Kocken et al., 2011). Hence, we assume that those patients leave the decision process once they enter `(PoC1)` or `(PoC2)`. In all states `(NC)`, `(PL)` and `(IC)` patients may die from noncancerous reasons. Additionally, patients in state `(IC)` may die from cancer. An absorbing *death* state `(DT)` will represent all such transitions. Figure 4.2 shows the decision process at epoch t. The decision maker will face the same problem at $t+1, t+2, \ldots$ until the decision horizon is reached (i.e., $t = N$). After a cotesting, the outcome of the test will help us to gain information about the actual state of the patient. However, despite its increased sensitivity compared to standalone cytology and HPV-DNA testing, cotesting does not provide exact information about the state. That is, when the

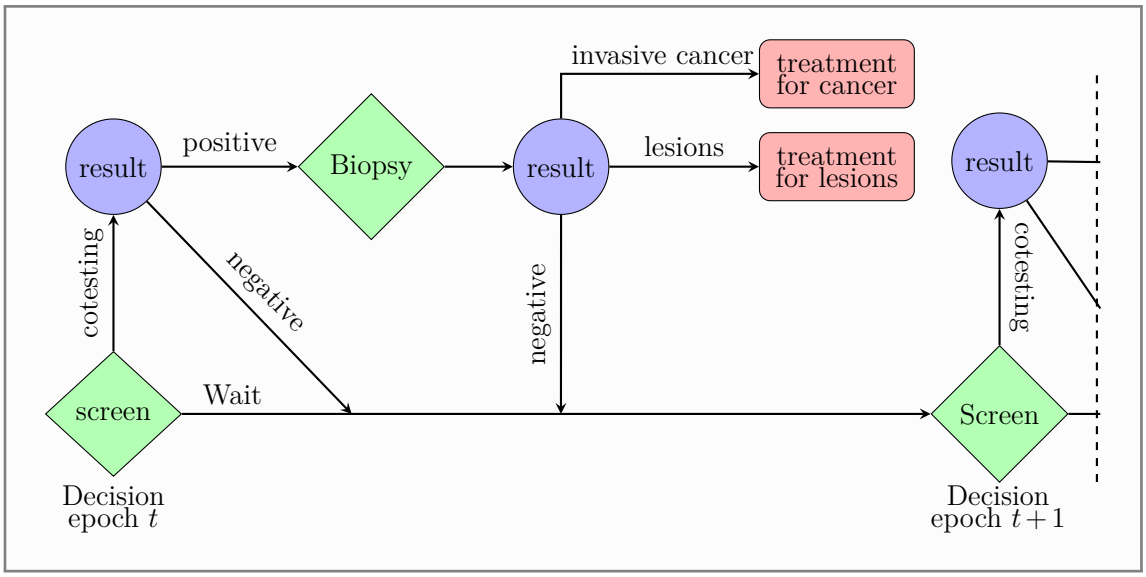


Figure 4.2 Timeline of the decision process.

test outcome is positive, still there is little yet non-negligible chance that the test is falsely alarming the existence of the disease, while in reality the patient is disease free. Similarly, a negative test outcome does not provide 100% confidence against the existence of the disease. As a result, even though the test outcome provides good indication of the real state of the patient, the true state might be different than the one revealed by the test. To account for this uncertainty caused by the test performance, a common approach is assigning probabilities of occupying each state accordingly. These probabilities form the so-called *belief states*, corresponding to the partially observable states. For instance, a belief state $b_t = [0.9, 0.065, 0.035]$, shows that the probability of being in state `(NC)` at a given time t is 0.90 (i.e., $P(NC) = 0.9$), the probability of being in `(PL)` is 0.065 (i.e., $P(PL) = 0.065$), and the probability of being in `(IC)` is 0.035 (i.e., $P(IC) = 0.035$). It must be noted that states `(PoC1)`, `(PoC2)` and `(DT)` are observable states. The components of the POMDP model are listed and described below.

State space: $\mathcal{S} = \mathcal{S}_d \cup \mathcal{S}_a$ including partially observable states $\mathcal{S}_d$ and absorbing states $\mathcal{S}_a$. where $\mathcal{S}_d = \{NC, PL, IC\}$ and, $\mathcal{S}_a = \{PoC1, PoC2, DT\}$. For simplicity, we use numbers $1, \cdots, 6$ to denote the states `NC, PL, IC, PoC1, PoC2,` and `DT`, respectively.

Action space: $\mathcal{A} = \{\text{CT, W}\}$, $a_t \in \mathcal{A}$ denotes the action taken at time t. CT stands for *cotesting* and W stands for *waiting* until the next decision epoch. Death and post-cancer states are absorbing and no decision is associated with these states.

Observation space, Ω: is the set of all observations. After conducting an action a, an immediate observation θ is received. We assume that cotesting will result in

either a positive ($CT+$) or a negative ($CT-$) result. Hence, $\Omega = \{\theta_{CT}, \theta_W\}$ with $\theta_{CT} = \{CT-, CT+\}$ and $\theta_W = \emptyset$.

Transition function, $T_t(s, s', a, \theta)$: defined by $p_t^{a,\theta}(s'|s)$, which denotes the conditional probability of ending up at state s' at time $t+1$ given that at time t, the states is s, action a is conducted and an immediate observation θ is obtained. Transition probabilities vary with the age of the patient. Younger patients are more prone to new infections, and at the same time the regression rate of the infections is also higher at younger ages. With increasing age, the infection rate of the patient decreases, but the progression rate of the persistent infections into invasive cancer increases. Death due to both cancerous and noncancerous reasons occur at a higher rate with the increasing age of the patient.

Observation function, $O(\theta, s, a)$: defined by $k^a(\theta|s)$, which denotes the conditional probability of observing an outcome θ upon taking an action a in state s. In cancer screening, observation probabilities are determined by test sensitivity and specificity (Otten et al., 2020). As an example, $k^{CT}(CT-|s=1)$ is the probability of observing a negative cotesting when the patient is disease free. This probability is equivalent to the specificity of the test denoted by $spec(CT)$. We also use $sens(CT, s)$ to denote the sensitivity of the test in state s, noting that the sensitivity depends on the state of the patient (Molani et al., 2019; Otten et al., 2020). Similarly, we use the following relations to specify the observation probabilities in our model:

$$
\begin{aligned}
&k^{CT}(CT-|s=1) = spec(CT),\\
&k^{CT}(CT+|s=1) = 1 - spec(CT)\\
&k^{CT}(CT-|s=x) = 1 - sens(CT, s) \quad x \in \{2,3\}\\
&k^{CT}(CT+|s=x) = sens(CT, s) \quad x \in \{2,3\}.
\end{aligned}
$$

Sensitivity and specificity of screening tests may vary with age (Leinonen et al., 2009); however, due to the lack of reliable data, we assume that they are independent of age.

Belief space, $\mathcal{B}$: which denotes the entire space of belief states.

$\mathcal{B} = \{b \in \mathbb{R}^{|\mathcal{S}_d|} : b(s) \geq 0, \sum_s b(s) = 1\}$. Given three partially observable states $1, 2$ and 3 in our model, the belief space is a two-dimensional simplex (triangle), as shown in Figure 4.3. Immediate rewards, $r_t(s, a, \theta)$: which represents the reward of being in a state s, taking an action a and receiving an observation θ. Consistent with the literature, we reward the implementation of each action by its consequent quality-adjusted life years (QALYs). Sonnenberg & Beck (1993) argued that on average, transitions occur halfway through each decision epoch and proposed the

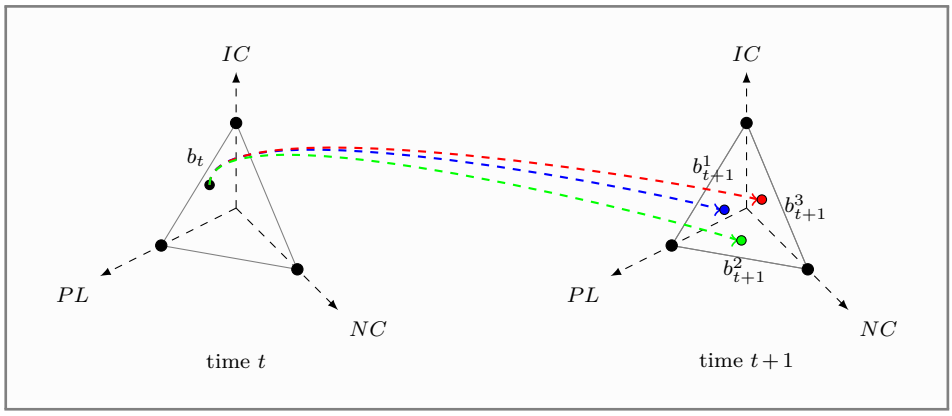


Figure 4.3 Belief simplex and update of belief states.

half cycle correction method. In this method, it is assumed that if the patient dies between two decision epochs, half the length of the cycle contributes to the expected number of QALYs (Otten et al., 2020). By doing so the reward of action W is obtained from $r_t(s, W, \emptyset) = P(\text{alive at t}|s) + 0.5 * P(\text{dies at t }|s)$. While assigning rewards for a screening test, it is common to incorporate the discomfort due to medical interventions into the reward function (Ayer & Chen, 2018; Otten et al., 2020). The calculation of rewards for action CT relies on the disutility score due to the discomfort caused by conducting a cotesting and possibly disutility of a biopsy test if cotesting turns out positive. Let $\zeta_t^{(a,\theta)}(s)$ be the disutility associated with a screening action with outcome θ for the true health state s at time t, and ζ_t^{Bx} denote the disutility of biopsy testing,

$$r_t(s, CT, CT-) = r_t(s, W, \emptyset) - \zeta_t^{(CT,CT-)}(s) \quad for \quad s \in \mathcal{S}_d$$
$$r_t(s, CT, CT+) = r_t(s, W, \emptyset) - \zeta_t^{(CT,CT+)}(s) - \zeta_t^{Bx} \quad for \quad s \in \mathcal{S}_d$$

Lump sum rewards, $R_t(s)$: denote the post treatment life expectancy. For patients who have been treated for cervical cancer, the screening program of asymptomatic population are not considered. For those patients, despite treatment, the risk of developing a post-treatment recurrent cancer remains high. Those patients undergo close surveillance with more frequent screenings every six months (Kocken et al., 2012). Therefore, we assign a lump sum treatment reward in the absorbing states 4 and 5. Let $e_t(s)$ denote the life expectancy of a patient in state s at time t. The lump sum reward $R_t(s)$ can be calculated by:

$$R_t(s) = \begin{cases} e_t(s) & \text{if} \quad s \in \{4, 5\} \\ 0 & \text{if} \quad s = 6 \end{cases}$$

Terminal reward, $r_N(s)$: We define the terminating reward $r_N(s)$, $s \in \mathcal{S}$ to represent

the reward of ending up at state $s \in \mathcal{S}$. Terminal rewards are equal to the life expectancy of the patients at terminal time N. For $t = 49$,

$$r_N(s) = \begin{cases} e_t(s) & \text{if} \quad s \in \{1,2,3,4,5\} \\ 0 & \text{if} \quad s = 6 \end{cases}$$

Belief update function, $\tau(b,a,\theta)$: While the decision at time t was based on b_t, conducting action a and receiving test result θ provides new information to the decision maker to make his decision at time $t+1$. For any belief state b_t, after performing an action and receiving the observation at time t, the updated belief state at time $t+1$ denoted by $b_{t+1} = \tau(b,a,\theta)$ can be calculated from the Bayesian belief update:

$$b_{t+1}(s') = \begin{cases} \dfrac{\sum_s b(s) p_t^{a,\theta}(s'|s)}{\sum_s \sum_{s'} b_t(s) p_t^{a,\theta}(s'|s)} & \text{if} \quad a = W \\ p_t^{CT,CT+}(s'|1) & \text{if} \quad a = CT, \theta = CT+ \\ \dfrac{\sum_s b_t(s) p_t^{a,\theta}(s'|s) k^a(\theta|s)}{\sum_s \sum_{s'} b_t(s) p_t^{a,\theta}(s'|s) k^a(\theta|s)} & \text{if} \quad a = CT, \theta = CT- \end{cases} \tag{4.1}$$

Figure 4.3 shows the belief space and updated belief state for each action and observation pair.

Value function, $J_t^*(b)$: represents the maximum total expected QALY at belief state b at time t. If at time t, the patient is in one of the absorbing states with probability one, then the value equals the lump sum reward of that state.

$$J_t^*(b) = \begin{cases} R_t(4) & \text{if} \quad b_t(s) = [0,0,0,1,0,0] \\ R_t(5) & \text{if} \quad b_t(s) = [0,0,0,0,1,0] \\ 0 & \text{if} \quad b_t(s) = [0,0,0,0,0,1] \\ J_t(b) & \text{if} \quad b_t(s) = [b'|0,0,0]\ ,\ b' \neq [0,0,0] \end{cases} \tag{4.2}$$

where $J_t(b) = \max\{J_t^W(b), J_t^{CT}(b)\}$ and the boundary condition at the end of the horizon is:

$$J_N(b) = \sum_{s \in \mathcal{S}_d} b(s) r_N(s) \tag{4.3}$$

$J_t^W(b)$ and $J_t^{CT}(b)$ are computed using the following equations:

(4.4)

$$J_t^W(b) = \sum_{s \in \mathcal{S}_d} b(s) \Big(r_t(s, W, \emptyset) + \sum_{s' \in \mathcal{S}_d} p_t^{W,\emptyset}(s'|s) J_{t+1}(\tau[b, w, \emptyset]) \Big), \quad t = 1, \cdots, N-1$$

(4.5)

$$
\begin{aligned}
J_t^{CT}(b) = \sum_{s\in\mathcal{S}_d} b_t(s)\Big[k^{CT}(CT-|s)\Big(r_t(s,CT,CT-) + \sum_{s'\in\mathcal{S}_d} p_t^{CT,CT-}(s'|s). \\
J_{t+1}(\tau[b,CT,CT-])\Big)\Big] \\
+ b_t(1)\Big[k^{CT}(CT+|1)\Big(r_t(1,CT,CT+) + \sum_{s'\in\mathcal{S}_d} p_t^{CT,CT+}(s'|1). \\
J_{t+1}(\tau[b,CT,CT+])\Big)\Big] \\
+ \sum_{s=2}^{3} b_t(s)\Big[k^{CT}(CT+|s)\Big(r_t(s,CT,CT+) + \sum_{s'\in\mathcal{S}_d} p_t^{CT,CT+}(s'|s)R_{t+1}(s)\Big)\Big], \\
t = 1,\cdots,N-1
\end{aligned}
$$

Defining The Value Function in Terms of Alpha Vectors and Solving The POMDP Model:

The value functions given in Equations (4.4) and (4.5) can be computed using Bellman's dynamic programming. One approach is the backward recursions of value iteration (Hauskrecht, 2000). However, it should be noted that both equations are defined over the belief simplex, $\mathcal{B}$, which is a continuum with uncountably many belief states. Hence, it is computationally intractable to use this method for computing the value of each and every belief state in $\mathcal{B}$. Furthermore, as it can be seen from Figure 4.3, the number of action-observation histories grow exponentially with the planning horizon; this problem is also known as the curse of history (Pineau et al., 2003). Therefore, for POMDP problems, the classic dynamic programming recursions have often been considered impractical (Krishnamurthy, 2015).

Sondik (1971) and Smallwood & Sondik (1973) were the first to explore the structure of the POMDP value function and showed that the optimal value function is piecewise linear and convex (PWLC) in belief at every time t. This means that, for any time t, the value function $J_t^*(b)$ can be represented using a finite set of $|\mathcal{S}_d|$-dimensional vectors (hyperplanes). Those vectors are called alpha vectors. Using alpha-vector representation, the value iteration algorithm reduces to the computation of the alpha-vectors for every time t. In other words, instead of evaluating the value function over a continuous space of belief states, one only needs to find the set of vectors $\Gamma_t = \{\alpha_t^j\}_{j=1}^{|J_t|}$, such that

$$
J_t^*(b) = \max_k \{\sum_{s\in\mathcal{S}_d} b_t(s)\alpha_t^k(s)\} \quad \text{for some } \{\alpha_t^1, \alpha_t^2, \ldots, \alpha^{|J_t|}\} \tag{4.6}
$$

where each α_t^j is a vector of dimension $|\mathcal{S}_d|$, i.e., $\alpha_t^j = [\alpha_t^j(s)], s \in \mathcal{S}_d$. Equation (4.6) infers that the value at a certain belief state b_t is obtained by taking the maximum of the dot product of b_t with each vector in Γ_t. The merit of the algorithm is that given Γ_t, we can generate the set of alpha vectors, which together constitute the value function at time $t+1$, i.e., Γ_{t+1} (Walraven & Spaan, 2019). Furthermore, each alpha vector is associated with an action $a(\alpha_t^j) \in \mathcal{A}$, and the reflection of each optimal alpha vector over the belief space creates a partitioning over which the action associated with the vector is the optimal action. For the belief state b_t, the value-maximizing alpha vector from the set Γ_t, denoted as $\alpha_t^{l^*(b)}$ can be obtained from $\alpha_t^{l^*(b)} = \text{argmax}_k\{\sum_{s\in\mathcal{S}_d} b_t(s)\alpha_t^k(s)\}$. The optimal policy $\pi : \mathcal{B} \mapsto \mathcal{A}$ is a mapping from belief $b_t \in \mathcal{B}$ into an action $a_t \in \mathcal{A}$. The policy at b_t is given by $\pi(b) = a(\alpha_t^{l^*(b)})$. This implies that the set of alpha vectors encodes both the value and the optimal policy (Porta et al., 2006).

An example of the PWLC value function with the optimal alpha vectors in two-state POMDP is illustrated in Figure 4.4. The x-axis represents the belief space over the core state space with two states s_1 and s_2. The belief space is a one-dimensional unit interval and each point on the horizontal x-axis is a belief state. The y-axis is the value of each belief state. The belief space is covered with five alpha vectors, $\alpha^1, \alpha^2, \alpha^3, \alpha^4$, and α^5, while only four vectors contribute to the optimal value function. At any belief state b_t, the optimal value $J_t^*(b)$ is the upper surface of four vectors $\alpha^1, \alpha^2, \alpha^3$ and α^5. We also use $\alpha_t^{l(b,a)}$ to denote the value-maximizing alpha

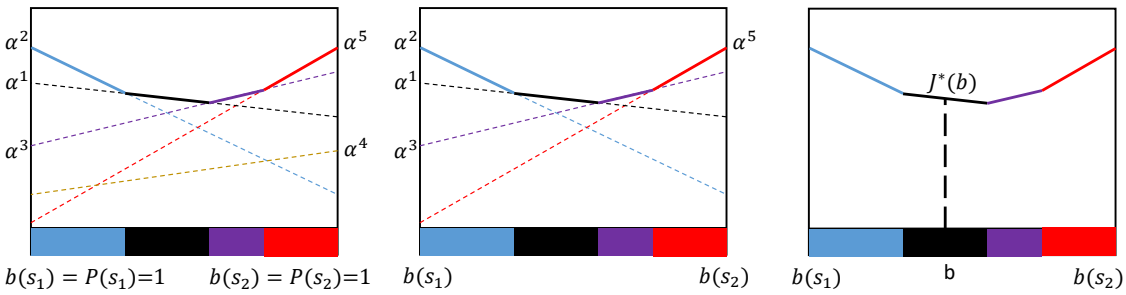


Figure 4.4 Alpha vectors over belief space in a two-state partially observable Markov decision process (POMDP); bold segment of the alpha vectors constitute a piecewise linear and convex (PWLC) value function. α^4 is a redundant vector and can be eliminated.

vector for a belief given an action a. We proceed to write $\alpha_t^{l(b,W)}$ and $\alpha_t^{l(b,CT)}$.

$$\alpha_t^{l(b,W)}(s) = r_t(s, W, \emptyset) + \sum_{s'\in\mathcal{S}_d} p_t^{W,\emptyset}(s'|s)\alpha_{t+1}^{\iota(b,W,\emptyset)} \tag{4.7}$$

(4.8)

$$\alpha_t^{l(b,CT)}(s) = \begin{cases} k^{CT}(CT-|s)\Big(r_t(s,CT,CT-) + \sum\limits_{s'\in\mathcal{S}_d} p_t^{CT,CT-}(s'|s)\alpha_{t+1}^{\iota(b,CT,CT-)}\Big) \\ +k^{CT}(CT+|s)\Big(r_t(s,CT,CT+) + \max\limits_k \Big(\sum\limits_{s'\in\mathcal{S}_d} p_t^{CT,CT+}(s'|s)\alpha_{t+1}^k\Big)\Big), s=1 \\ k^{CT}(CT-|s)\Big(r_t(s,CT,CT-) + \sum\limits_{s'\in\mathcal{S}_d} p_t^{CT,CT-}(s'|s)\alpha_{t+1}^{\iota(b,CT,CT-)}\Big) \\ +k^{CT}(CT+|s)\Big(r_t(s,CT,CT+) + \sum\limits_{s'\in\mathcal{S}_d} p_t^{CT,CT+}(s'|s)R_{t+1}(s)\Big), s=2,3 \end{cases}$$

where

(4.9)

$$\iota(b,a,\theta) = \begin{cases} \operatorname*{argmax}\limits_k \Big\{\sum\limits_{s\in\mathcal{S}_d} b(s) \sum\limits_{s'\in\mathcal{S}_d} p_t^{a,\theta}(s'|s)\alpha_{t+1}^k\Big\} & \text{if } (a,\theta)=(W,\emptyset), \\ \operatorname*{argmax}\limits_k \Big\{\sum\limits_{s\in\mathcal{S}_d} b(s)k_t^a(\theta|s) \sum\limits_{s'\in\mathcal{S}_d} p_t^{a,\theta}(s'|s)\alpha_{t+1}^k\Big\} & \text{if } (a,\theta)\in\{(CT,CT-), \\ & \qquad (CT,CT+)\}. \end{cases}$$

Multiple exact solution algorithms for POMDPs, including Sondik's one-pass algorithm (Sondik, 1971), Cassandra's witness algorithm (Cassandra et al., 1994), Monahan's enumeration algorithm (Monahan, 1982), Cheng's linear support algorithm (Cheng, 1988), and Cassandra's incremental pruning (Cassandra et al., 2013) have been proposed in the literature. These solution methods differ mainly in the way that they generate the alpha vectors at time $t+1$ given the set of alpha vectors at time t. It can be seen from Equations (4.7) and (4.8) that alpha vectors at time t are formed by a transformation of the vectors at time $t+1$. Smallwood & Sondik (1973) showed that the transformation preserves the PWLC property of the value function. To compute Equations (4.7) and (4.8), one needs to use Equation (4.9) to find the optimal alpha vector at time $t+1$ for belief state b_t. The well-known algorithm of Monahan (1982) simplifies the solution procedure by generating all possible alpha vectors instead of checking the maximizing alpha vector for every pair of action and observation. Enumerating all the possible alpha vectors creates a maximum of $|\mathcal{A}||\Gamma_t|^{|\Omega|}$ vectors for Γ_{t+1} (Braziunas, 2003). Of course, many of the generated vectors are dominated by other vectors and are not useful. Therefore, in the pruning phase, the algorithm eliminates the vectors that are not part of the value function by checking whether there exists a belief point where that specific vector is dominant or not. Such vectors are easily identified using a direct linear programming (LP) approach. The most straightforward LP method introduced by

Monahan (1982) is defined as: for $\alpha_t^i, \alpha_t^j \in \Gamma_t$,

$$
\begin{aligned}
\max \quad & \sigma \\
\text{s.t.} \quad & \sum_{s \in \mathcal{S}_d} b_t(s)\Big(\alpha_t^i(s) - \alpha_t^j(s)\Big) \geq \sigma, \quad \forall j, \alpha_t^j \neq \alpha_t^i \\
& \sum_{s \in \mathcal{S}_d} b_t(s) = 1, \\
& b_t(s) \geq 0, \qquad \forall s \in \mathcal{S}_d
\end{aligned} \tag{4.10}
$$

Other pruning methods including Lark's filtering algorithm (White, 1991), Skyline algorithm (Raphael & Shani, 2012) and accelerated pruning method (Walraven & Spaan, 2017) can also be found in the literature.

For POMDP problems with a small set of states, actions and observations, Monahan's algorithm is proven to be efficient, as implemented in studies by Ayer et al. (2012) and Cevik et al. (2018) to solve the POMDP models for breast cancer screening policies and by Otten et al. (2017,2) to solve the POMDP model developed for the follow up planning of the patients already treated for breast cancer. Li et al. (2015) also applied this algorithm to solve their proposed POMDP model for the colorectal cancer screening policies.

We also implement Eagle's reduction (Eagle, 1984) phase, which is speeding up the pruning phase by eliminating element-wise dominated vectors. In Figure 4.4, α^4 is not element-wise dominated by α^2, but it is element-wise dominated by α^1 and α^3. Hence, it can be eliminated from the set of alpha vectors.

The solution procedure is summarized in 1. Our model is coded in MATLAB, and implemented on a machine with Intel(R) Core(TM)i7-8700 processor. We use Gurobi to solve the linear programming problems.

4.4 Results

In this section, we present our computational examples and show how our proposed decision making process is implemented. We then compare our results with the recommendations of the guidelines and discuss the trade-offs. At the end of the section, we also test the sensitivity of our results to the input parameters. The sources of the input data used in our computational experiments are presented in the Appendix A.

Algorithm 1 Compact representation of solution method with Monahan's algorithms and Eagle's reduction phase

2.1 **Initialization:** $\alpha_N(s) = r_N(s), \forall s \in \mathcal{S}_d$, $\Gamma_N = \{\alpha_N\}$

2.2 **For** $t = N-1$**, until** $t = 0$**, do:**

2.3 **Apply Monahan's enumeration phase:** Generate all the possible alpha vectors (using Equations (4.7) and (4.8), without trying to find the maximizing vector from $t+1$) and mark the generated vectors. Create the set $\Gamma_t = \{\alpha_t^1, \alpha_t^2, \alpha_t^3, \cdots, \alpha^{|J_t|}\}$.

2.4 **Apply Eagle's reduction phase:**

- For every marked vector α^i in Γ_t, do
- Unmark the vector and check if there exists a vector α^j s.t. $\alpha^i \leq \alpha^j, \forall s \in \mathcal{S}_d$, if so, remove α^i from Γ_t.

2.5 **Apply Monahan's pruning phase:**

- Mark the remaining vectors in Γ_t after Eagle's reduction phase.
- For every marked vector in Γ_t, do
- Unmark the vector and use Equation (4.10) to check if LP has a solution $\sigma \leq 0$, if so, remove α^i from Γ_t. Otherwise, there exists a belief state at which α^i is useful.

4.4.1 Optimal Belief-Based Screening Policy

We begin with an example that helps to illustrate how the optimal policy is generated for any patient. Suppose a patient at age 21 with $b_0 = [0.99, 0.0071, 0.0029]$, meaning that she has a 0.71% chance of being in state 2 and 0.29% chance of being in state 3. Based on her age and risk profile, she is expected to undergo screening at age 21. Determining the sequence of following actions throughout the patient's lifetime requires the knowledge of the current and subsequent action's outcome. If the test result is negative, b_0 is accordingly updated with $(a, \theta) = (CT, CT-)$. The output b_1 is then multiplied by each alpha vector in the set of alpha vectors of $t = 1$ created using the procedure explained in Algorithm 1 of Section 4.3. This procedure is repeated for every t until the terminal decision epoch.

Under the POMDP policy, for a patient whose belief state at age 21 is $b_0 = [0.99, 0.0071, 0.0029]$, nine screenings with cotesting are recommended throughout her lifetime at ages 21, 25, 30, 35, 44, 49, 55, 63 and 67.

Patients who start late to screen are exposed to higher risks of lifetime cancer. According to Table 4.1, a perfectly healthy patient with belief state $b_0 = [1, 0, 0]$ at age 21 who has no history of screening ends with an increased risk of developing infections or lesions. Waiting until age 41 leads to the belief state $b_{20} = [0.714, 0.251, 0.035]$.

Table 4.1 Impact of starting late to screen on the health state of a 41 year old patient who has been healthy at age 21.

Age	$b_t(1)$	$b_t(2)$	$b_t(3)$
21	1	0	0
22	0.971	0.026	0.003
23	0.944	0.050	0.006
$\vdots$	$\vdots$	$\vdots$	$\vdots$
41	0.714	0.251	0.035

Generating the optimal policy for a patient who was perfectly healthy at age 21, but has not undergone any screening until age 41, is similar to those starting at age 21 with the only difference that the initial belief state of the patient at age 41 would be equal to $b_{20} = [0.714, 0.251, 0.035]$. According to our POMDP policy, screening for such a patient involves six cotestings. That is only one less than the screening frequency for a low risk patient who starts screening at age 21.

High risk of cancer is not solely correlated with a late start of screening rounds. Sexually active young patients are also subject to higher risks of new or persistent infections. In this part, we aim to evaluate the impact of the patient's initial risk profile on the optimal screening policy. We consider three patients starting at age 21 with distinct risk profiles, i.e., low risk, medium risk and high risk. Their initial belief vectors are as follows:

- Low risk patient: $b_0 = [0.995, 0.0029, 0.0021]$,
- Medium risk patient: $b_0 = [0.99, 0.0071, 0.0029]$,
- High risk patient: $b_0 = [0.75, 0.2, 0.05]$.

One of the risk measures introduced by the medical community of cervical cancer is the risk of being in any of the states of severe cervical dysplasia (in-situ) and invasive cancer, which together are referred to as *CIN3+* risk. In our POMDP model *CIN3+* risk is equivalent to the belief of being in states 2 and 3. We also introduce two additional measures of risk in our study: five-year and lifetime average risk of cancer, which are the arithmetic means of the *CIN3+* risks. Figure 4.5 illustrates the difference in the 5-year average *CIN3+* risks for three cohorts of patients with low, medium and high risk.

Even though the initial *CIN3+* risk between three groups is considerably different (i.e., 0.005 for low risk, 0.01 for medium risk, and 0.25 for high risk patients), the

observed gap in risk is not directly reflected on the number of screenings. That is, 25 times higher risk of cancer for a high risk patient compared to a medium risk patient, leads to only 30% more screenings. Average re-screen interval length is the longest for low risk patients. This observation can possibly be explained by the higher length of the time which is required for the low risk patients to develop a large enough risk of cancer to enter the screen-required zone. For each patient group, the optimal age of screening is depicted in Figure 4.5. Our analysis also shows that for the high risk patients, the lifetime average risk of cancer is considerably higher than low risk patients. The impact of the patient's risk profile on the screening schedule and the lifetime average risk of cancer is summarized in Table 4.2.

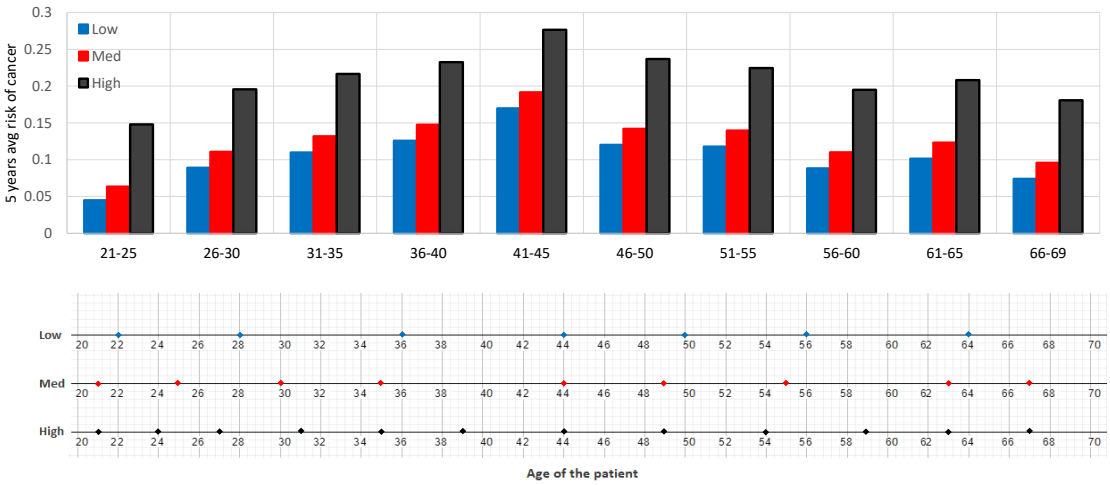


Figure 4.5 Five-year average risk of cancer for patients with different risk profiles. Colored dots show the screening ages of each risk profile.

Table 4.2 Impact of the patient's risk profile on the cancer risk and screening schedule.

Risk Profile	**Lifetime No. of Screenings**	**Avg. Screening Interval Length**	**Lifetime Avg. Risk of Cancer**
Low risk	7	6.86	0.0849
Medium risk	9	5.33	0.125
High risk	12	4	0.209

4.4.2 Comparison of Multiple Policies and Guidelines

To evaluate the performance of our POMDP model, we compare its resulting optimal policy with a set of static policies or guidelines.

No screening: The base case for our comparison is a patient with the same risk of cancer as given in Section 4.4 who has performed no screening tests during her lifetime and all of the actions are assumed to be a W action. We call this *no screening* policy.

Modified US practice: represents a policy that recommends screening with cotesting every five years. Screenings start at the age of 21 and end at age 65. We have modified the US guidelines to make them comparable with our cotesting action, since they start with cytology at age 21, repeating every three years until 30, and shifting to cotesting until age 65 with cotesting repeated every 5 years.

Aggressive plan: In order to show that the policies with more frequent screening do not necessarily improve the QALY, we define a screening policy called *aggressive plan*. Under this plan, a patient is screened first at age 21 and repeats screening every three years until age 66.

Alternative policy 1: In order to study the effect of age at which screenings are conducted, we defined a static policy with the same number of screenings as suggested by our optimal POMDP policy (i.e., nine screenings throughout the lifetime), but distributed at equal intervals.

Alternative policy 2, and Alternative policy 3: Closely related to the real-world scenarios in which patients start late to undergo screening, we defined two static policies under which patients wait until age 41 and 51, respectively, to begin screening. Under *Alternative policy 2*, the patient starts screening at age 41 as her first screening round and continues screening every 5 years until age 66. Under *Alternative policy 3*, the patient starts screening at age 51 as her first screening round and continues screening every 5 years until age 66. Such patients carry a higher risk of remaining undetected. Hence, their lifetime risk of cancer might be higher than those who start early.

In the following part, the focus of the comparison analysis will be on both the expected QALY gains under the POMDP policy with other practices and on the lifetime risk of developing cancer under the POMDP policy with those of the other static policies.

QALY-Based Policy Comparison

To maximize the expected QALY gains throughout the patient's lifetime, the POMDP policy chooses optimal actions at every age of the patient. The sequence of such actions for a specific patient is discussed in Section 4.4.1.

Under *no screening*, assuming that such a patient survives until age 70, we observe that the expected QALY gain will be 56.346, whereas the POMDP policy creates 57.228 QALY gains, an approximate 1.57% increase relative to the *no screening* policy. We also observe that *Alternative policy 1* creates 57.05 QALYs and is outperformed by POMDP policy. *Aggressive plan* with the highest screening frequency, creates 57.156 QALYs, lower than that of POMDP policy. Table 4.3 presents the expected QALY gain under various policies for a 21 years old patient.

Table 4.3 Comparison of performance across different policies for a 21 year old patient with no test history.

	Start Age	**Screen Interval Length**	**Screen Rounds**	**Stop Age**	**Exp. False Results**	**Exp. QALY Gain**	**Improve In QALY**(%)
No screening	-	-	0	-	0	56.346	-
Modified US practice	21	5	10	66	0.18	56.119	0
Aggressive plan	21	3	16	59	0.252	57.156	1.4
Alternative policy 1	21	6	9	69	0.162	57.075	1.3
Alternative policy 2	40	5	6	66	0.108	57.004	1.18
Alternative policy 3	50	5	4	66	0.072	56.824	0.87
POMDP policy	23	variable	9	67	0.162	57.228	**1.57**

Comparison of Lifetime Cancer Risk across Different Policies

The POMDP model can also be used to study the risks associated with the current guidelines or benchmark practices. Figure 4.6 illustrates the risk performance of different policies considered. As expected, the risk of doing nothing and waiting is outranking all the other policies. Therefore, *Alternative policy 2* and *Alternative policy 3* accrue a higher risk until age 40 and 50, respectively, which start to decline as soon as the screening begins. Compared to the other policies, including our POMDP policy, *Alternative policy 2* and *Alternative policy 3* behave similar to *no screening* and carry a significantly higher risk until the first screening round. Moreover, one can conclude that *Alternative policy 2* exposes the patient to a lower lifetime cancer risk compared to *Alternative policy 3* as it is observed in Figure 4.6, yet there is not much risk difference between *Alternative policy 2* and *Alternative policy 3* after age 52 until 70. In fact, two patients with the same initial risk, one

following *Alternative policy 2* and the other following *Alternative policy 3* end up at age 70 with the same risk even though in the latter case the patient starts screening 10 years later.

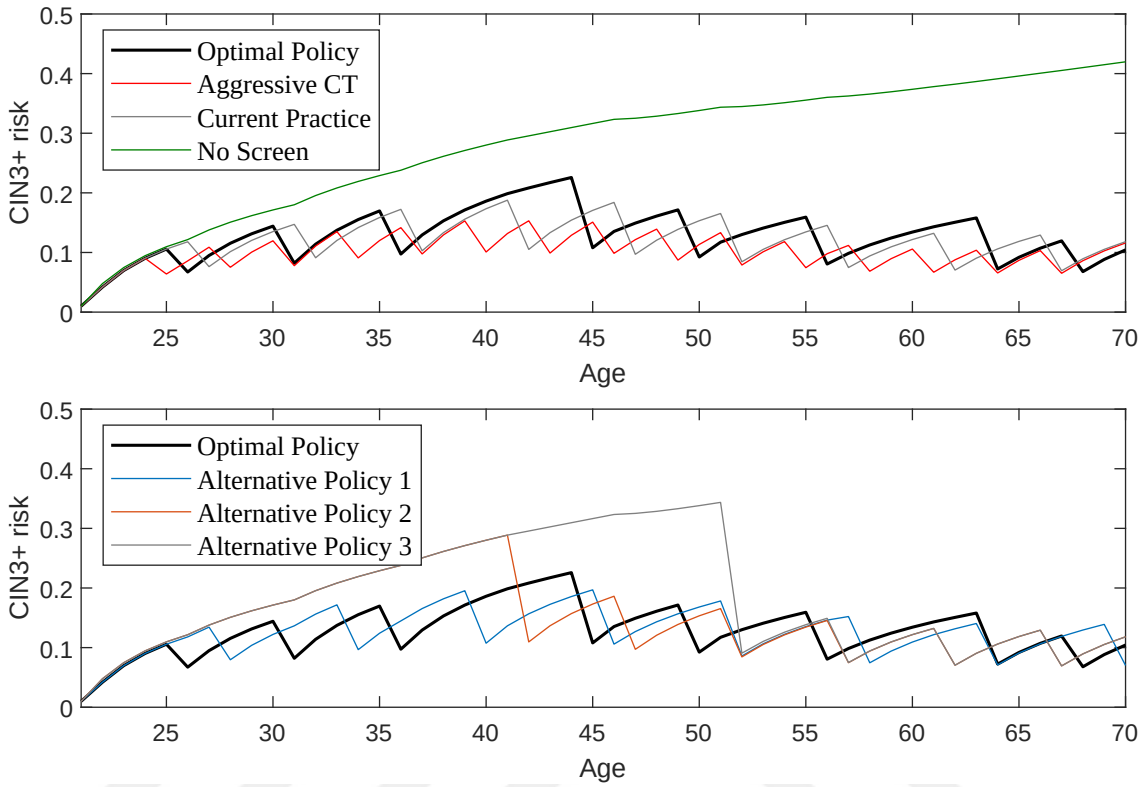


Figure 4.6 Lifetime risk of cancer under different policies.

4.4.3 Sensitivity Analysis

In this section we analyze the model's behavior with respect to different initial belief states. In other words, this study aims to investigate how our personalized POMDP model behaves while varying the initial belief. This can be interpreted as follows: For a pool of patients at age 21 with different initial cancer risk, what will be the life expectancy? To answer this question, we are looking at two sets of initial belief points.

- **Set** 1: high risk patients who are 99% healthy and their invasive cancer risks vary between 0.25% and 0.90%. This case is shown with a red line in Figure 4.7.
- **Set 2:** medium risk patients who are 99.3% healthy and their invasive cancer risks vary between 0.05% and 0.70%. This case is shown with a blue line in Figure 4.7.

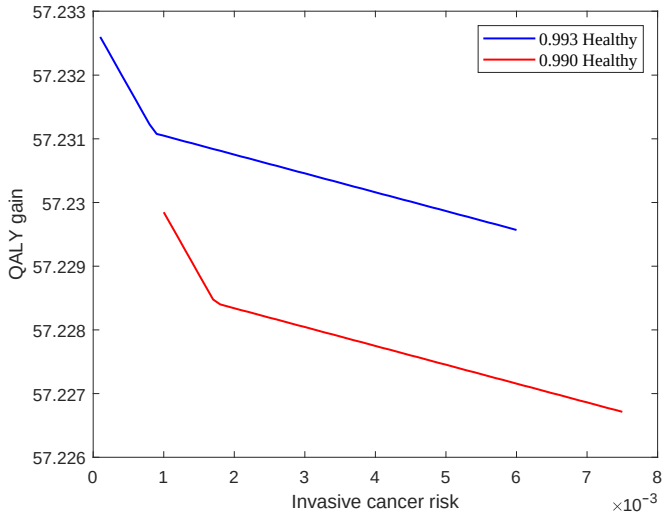


Figure 4.7 Quality adjusted life years (QALY) gained under different starting belief points.

As it is shown in Figure 4.7, one intuitive interpretation is that healthier patients are expected to gain more life expectancy under the POMDP model. For the patients in Set 1, the higher the risk of invasive cancer, the lower the expected QALY gain. The sudden drop in both graphs can be attributed to the age factor in QALY gain. That is, younger patients on average are gaining more life expectancy up to a certain age.

4.5 Discussion

"One size fits all" screening guidelines have recently been challenged by the newly introduced personalized screenings. In this study, using a POMDP approach, we developed a personalized screening policy for cervical cancer, which stratifies risk and generates a policy to follow. We showed that our proposed POMDP policy compared to the guidelines, in addition to being more patient representative, improves the life expectancy of the patients. The objective function of our POMDP model maximizes the quality adjusted life years (QALY), which indirectly includes the lifetime risk of cancer as part of the life-quality of the patient. Excessive testing increases the chance of false positive results, which in turn reduces the life quality of the patient due to unnecessary follow ups. By maximizing QALY, we simultaneously reward the lifetime cancer risk reduction and penalize the impact of false positive results. Therefore, the proposed policy by our POMDP model balances the benefits of the

testing and the disutility of excessive testing and hence, results in a slightly higher lifetime cancer risk but increasing the overall life-quality of the patient.

Early screening and detection is critical to reducing the future cancer risk of the patients. As we show by one instance, starting screening at the age of 21 versus 41 can relatively reduce the cancer risk while applying only one extra screening on the patient in her lifetime. This highlights the impact of starting screening at an early age on the healthcare system both in terms of effectiveness and costs. Our analysis of the impact of the patient's risk profiles on the screening frequency and the five-year average risk of cancer shows that the screening frequencies are not proportionate to the cancer risk.

One of the important observations made from our result is the lower QALY gain of aggressive plans compared to the POMDP policy. Therefore, we can safely conclude that performing more frequent screening does not necessarily lead to higher total QALY gains. Such policies, besides being more costly, could be less reliable too. Reliability of a policy is reduced when the policy results in a higher number of false results. False results of the tests, namely false negative and false positive results are crucial factors to consider while studying the performance of a specific policy and they can be considered as the secondary performance measures. Our results suggest that even though aggressive screening practices result in QALY close to that of the POMDP model, this is achieved with the increase of false test results compared to the POMDP policy.

Our analysis of lifetime risk exhibits that even though no policy is dominant in reducing the lifetime risk, it is clear that the POMDP policy has a slightly higher risk, which can be explained by the lower number of screening tests compared to most of the practices considered. We observe that, as the screening interval gets longer, the risk increases. Therefore, policies with longer screening intervals including the POMDP policy create higher risks. Another important observation made in risk analysis is that the policies that start their first screening later, end in relatively similar risk when the patient reaches age 70. This is due to the fact that a test with negative outcome hugely impacts our belief that the patient is healthy in reality.

A major issue that pervades most of the similar studies is the lack of reliable or abundance of conflicting data. Post treatment survival rates for different treatment types, which is common for cervical lesions and cervical cancer, are rarely studied in the literature. It should be noted that an important aspect of the recommendations obtained by a POMDP solution is how accurately a generated belief state represents the state of the patient. In this regard, an important limitation of this study is the lack of a risk estimation module similar to the Framingham Risk Score for

cardiovascular disease or the Gail model for breast cancer.

Future research will consider the problem of a generative model for belief states, which receives two types of inputs: the disease attributes and biomarkers specific to HPV and cervical carcinoma, which altogether shape the body of knowledge of the decision maker. Identifying pertinent biomarkers requires the assistance of a cytopathologist, which will render a more reliable belief state if such information is supplied to the generative model. The second type relates to the patient attributes. The more such attributes are included, the more precise the belief estimates will be. In addition, by taking over the role of the Bayesian belief update approach, the generative model approach can remove the dependency on a pure probabilistic update procedure.

5. PERSONALIZED SCREENING POLICY WITH CYTOLOGY AND HPV DNA TESTING

5.1 Chapter Overview

The previous chapter addressed personalized screening policies for cervical cancer with cotesting. In this chapter, we focus our attention on the policies when the screening includes cytology testing and HPV-DNA testing as two separate tests. The chapter begins with an introduction to the problem and highlights the proposed approach to address the research question. The chapter continues with model formulation and presents a detailed review of the approximate solution methods. It subsequently presents the parameterization of the model. The results section provides risk-action threshold policies and sensitivity analysis of the model parameters. Finally, the chapter concludes with the implementation of the policy and provides a discussion on the strengths and limitations of the model.

5.2 Introduction

Given the inherent deficiency of cytology testing in finding the positive cases of cancer, HPV-DNA testing developed initially as an adjunct to cytology screening and was used for triage of the patients with cytology positive. Since recently, the guidelines of cervical cancer screening included either cytology or cotesting, and HPV-DNA testing were not recommended as a standalone test. After the introduction of HPV-DNA test, many clinical trials attempted to study the significance of this test that accordingly helped to improve the understanding of the performance

of HPV testing. The data coming out of these studies were consistently showing that HPV testing has a a higher sensitivity and reproducibility with increased negative predictive value compared to the cytology testing, thus leading to a scientific and clinical interest in primary HPV-DNA testing as a method for cervical cancer screening. In 2015, after the joint interim update of the ASCCP guidelines, HPV-DNA has been added to many guidelines. Since then, many guidelines aligned their recommendations to include HPV-DNA testing every 5 years and therefore, testing for the presence of high-risk HPV has become an integral part of new screening strategies (Lees et al., 2016; Maver & Poljak, 2020; Tota et al., 2017).

With emerging technologies and biomarkers, and the advancements in the molecular techniques of high risk HPV testing, a number of studies maintain that cytology as an adjunct test to HPV-DNA testing does not improve the performance of screening, and suggest that cotesting/cytology can be safely replaced with standalone HPV DNA testing. These studies suggest that the sensitivity of cytology testing is low which is a drawback for population based screening aiming to find the most possible cases of abnormalities. Adding to the challenge is the low specificity of HPV-DNA testing. Since HPV infections are common and most of the infections are transient, HPV-DNA testing has a higher false-positive rate compared to cytology testing, and as a consequence, more women will be sent for additional but unnecessary followups (Castle et al., 2018; Gupta et al., 2017; Ogilvie et al., 2017).

In addition to the type of screening test, there is a continuous search for the most appropriate screening frequency if either test is employed, especially in low-resource countries. The commercial availability of low-cost HPV-DNA test in some resource-limited countries raised further question regarding whether implementing HPV-DNA testing as a standalone test every five years provides the best safety against the cancer. To address these questions, we considered a setting where the screening includes cytology and HPV-DNA testing as two separate tests. Similar to the previous chapter, we aim to develop a personalized risk-tailored model for screening decisions that can capture the differences in the test performance to find abnormalities. In the next section, we provide the details of the proposed model.

5.3 Model Formulation

The decision process in our model proceeds as follows. At every decision-epoch, the physician (decision-maker) is faced with three options: screen the patient with cervical cytology (referred as cytology), screen with HPV DNA testing or wait until the next annual decision epoch. The decision of the physician is made based on the patient's current risk of cervical cancer. We also assume that both the patient and the physician are risk neutral and that the patient will adhere to the decision made by the physician. If the patient undergoes either of the two cervical screening tests, the physician will examine the test results subsequently. If the result is negative, she will return for screening next year. On the other hand, if the test result turns out to be positive, it is followed up by a biopsy test. A biopsy test result may find no abnormal cells, which means that HPV is not present and the patient is perfectly healthy, meaning that the initial screening results have been false positive. Biopsy may also find infection with HPV, abnormal cells (dysplasia) or cancer. Biopsy results enable the oncologist to specify the grade of observed dysplasia, which may be mild (CIN1), moderate (CIN2), or severe (CIN3). Hence, it is reasonable to assume that biopsy can detect the exact health state of the patient. If the result of the biopsy is CIN2, CIN3 or cancer, the woman starts treatment and quits the decision process. Consequently, the patient continues the decision process after a negative cytology or HPV-DNA test, a biopsy with no referral to treatment following a positive cytology or HPV-DNA test, or a recommended *Wait* action. The decision process ends either when the patient starts treatment following a biopsy with referral to treatment or if she dies.

We formulate this problem as a discrete-time, finite horizon POMDP in which the objective of the patient/physician is to maximize the patient's total expected QALYs. Next, we describe the notation used to build our model and the formal definition of the POMDP model.

Decision epochs: $t \in T = \{0, 1, \ldots, N\}$ where $N < \infty$. Time $t = 0$ corresponds to age 21 and the last decision will be made at age 69, at decision epoch $N - 1 = 48$. As such, $t = 0$ represents age 21 and $t = N$ represents age 70). The current guidelines of USPSTF and ASCCP do not recommend screening for the patients below the age of 21.

Core state space: $\mathcal{S} = \mathcal{S}_d \cup \mathcal{S}_a$. $\mathcal{S}_d = \{1, 2, 3, 4, 5, 6\}$ refers to the disease states at which decision process continues and $\mathcal{S}_a = \{7,8,9,10\}$ to refer to the absorbing states at which the decision process ends. $s_t \in \mathcal{S}$ represents the true health state at time

t. We define disease states in our model following the natural history models of cervical cancer presented in the literature. In particular, disease states 1 through 6 represent healthy patient, infected with HPV, CIN1, CIN2, CIN3 and invasive cancer, respectively. States 7, 8 and 9 are post-biopsy states in which the patient receives treatment. Treatment begins if the screening test result is positive and the diagnostic biopsy result denoted as $BX \in \{4,5,6\}$. Hence, states $7,8$ and 9 represent treatment states for disease states 4, 5 and 6, respectively. State 10 represents death due to cancer or other causes. The threshold for the onset of treatment in our model is CIN2. (Castle et al., 2007) argue that treating CIN2 provides an additional margin of safety, even though it may result in over-treatment in some cases. Women diagnosed with CIN1 will frequently undergo spontaneous regression of the dysplasia without treatment. Therefore, monitoring for progression without treatment is currently the standard practice and recommendation of the majority of guidelines. The underlying Markov chain of our POMDP model is shown in Figure 5.1. We remark that the disease states $\mathcal{S}_d$ are not directly observable to the decision maker, whereas the absorbing states $\mathcal{S}_a$ are perfectly observable.

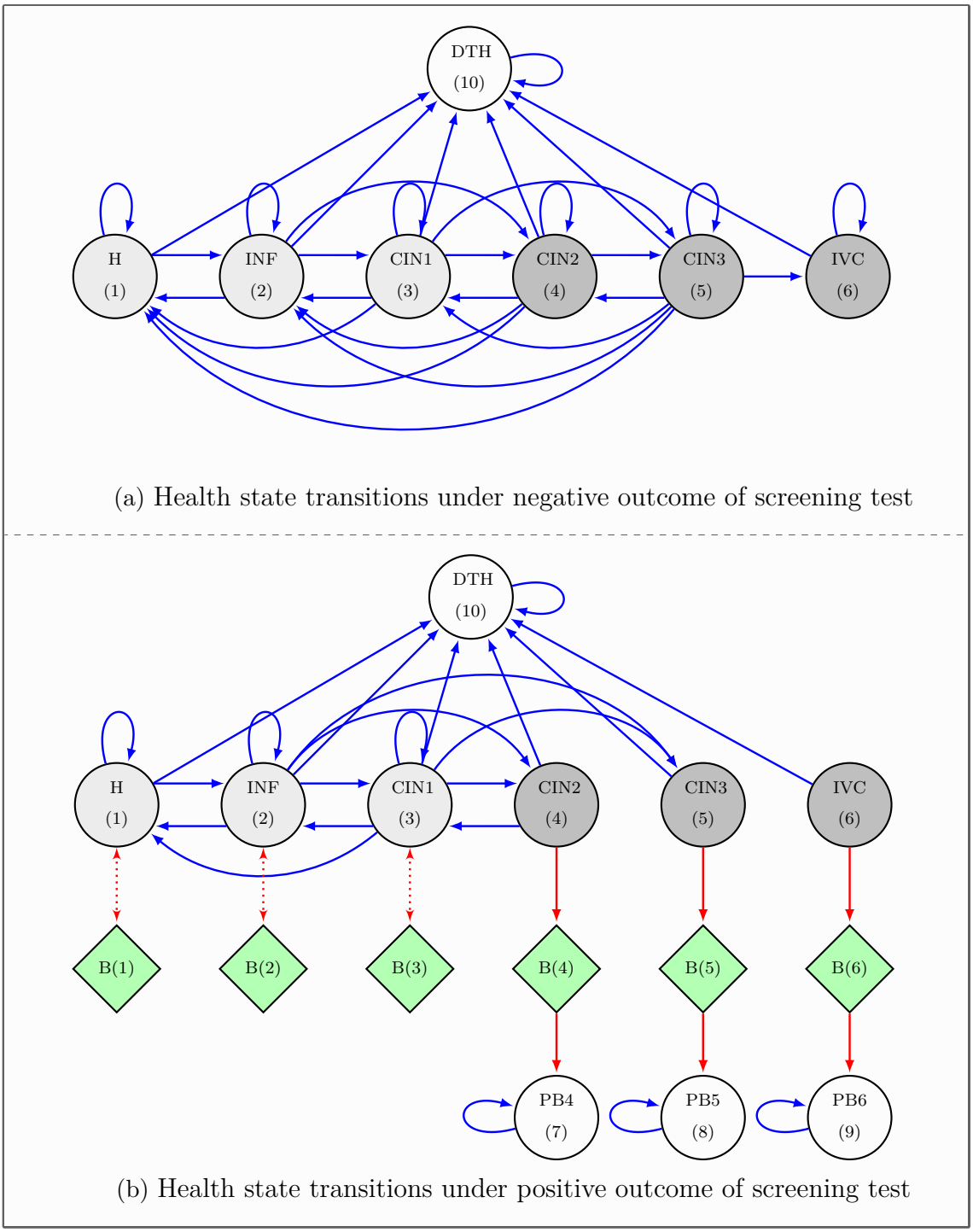
Action space: $\mathcal{A}_d = \{W, C, H\}$ where W represents "*Wait*," C represents "*Cytology*," H represents "*HPV DNA*" action. $a_t \in \mathcal{A}_d$ denotes the action taken at time t.

Observation space: $\mathcal{Z}$ denotes the set of observations where $\mathcal{Z} = \mathcal{Z}_W \cup \mathcal{Z}_C \cup \mathcal{Z}_H$. The notation $z_t \in \mathcal{Z}$ represents the observation made at time t. Naturally, $\mathcal{Z}_W = \emptyset$.

Cervical cytology testing can find lesions or cancer. When performing a cytology, the possible outcomes are: negative, atypical squamous cells of undetermined significance (ASCUS), atypical glandular cells (AGC), CIN1, CIN2, CIN3, squamous cell carcinoma (SCC) and adenocarcinoma (AC), where CIN1, CIN2 and CIN3 indicates presence of lesions with different grades (CIN1 indicates LSIL and CIN2 and CIN3 are collectively refered to as HSIL), and SCC and AC are advanced cancer indicators. The HPV-DNA test is either negative (H-) or positive (H+).

Note that in the patients with abnormal cervical cytology, or ASCUS, is the most common observed abnormality (Hasçiçek[1] et al., 2018). However, administering ASCUS result in standalone cytology testing lack uniformity. Current guidelines of ACS/ASCCP/ASCP recommend routine screening or triage test in one year (Ismail et al., 2020). For simplicity, we assume that NILM and ASCUS are negative cytology results. Similarly, LSIL, ASC-H, AGC, HSIL and SCC are positive cytology results. That is, $\mathcal{Z}_C = \{C^-, C^+\}$ and $\mathcal{Z}_H = \{H^-, H^+\}$.

Observation probability: $k_t^a(z|s)$ denotes the probability of observing z at time t, given that the core state is $s \in \mathcal{S}_d$ and action a is taken. That is, $k_t^a(z|s) = \Pr\{z_t =$



(a) Health state transitions under negative outcome of screening test

(b) Health state transitions under positive outcome of screening test

Figure 5.1 Health state transitions in the natural history of the disease under positive and negative outcome of the screening tests

$z|s_t = s, a_t = a\}$. The observation probabilities are assumed to be stationary. We assume HPV-DNA can detect existence of an infection with virus, as well as lesions and cancer. Hence, an H^+ in state 1 is a false positive. Cytology finds lesions or cancer. A cytology result either in form of ASCUS or worse for women without any histologic abnormalities is considered as a false positive Chuck (2010). In other

words, a C^+ in states 1 and 2 is a false positive. The sensitivity of cytology test depends on the threshold at which the test result will be considered as positive. Since we assumed the positivity threshold is set at ASC-H, the the sensitivity is the probability of at least ASC-H de Kok et al. (2018). We define sens$(a|s)$ and spec$(a|s)$ as the sensitivity and specificity of action a in state s at time t. Table 5.1 summarizes the observation model in our problem.

Table 5.1 Parameterization of observation probabilities for cytology and HPV DNA testing

State (s)	$K(C^-\|s)$	$K(C^+\|s)$	$K(H^-\|s)$	$K(H^+\|s)$
1	spec(C|1)	1- spec(C|1)	spec(H|1)	1- spec(H|1)
2	spec(C|2)	1-spec(C|2)	1-sens(H|2)	sens(H|2)
3	1-sens(C|3)	sens(C|3)	1-sens(H|3)	sens(H|3)
4	1-sens(C|4)	sens(C|4)	1-sens(H|4)	sens(H|4)
5	1-sens(C|5)	sens(C|5)	1-sens(H|5)	sens(H|5)
6	1-sens(C|6)	sens(C|6)	1-sens(H|6)	sens(H|6)

Transition probability: $p_t^{a,z}(s'|s)$ denotes the probability that the state of the patient will be s' at time $t+1$, given that her state is s at time t, action a is taken and an immediate observation z is made. That is, $p_t^{a,z}(s'|s) = \Pr\{s_{t+1} = s'|s_t = s, a_t = a, z_t = z\}$. We assume that transition probabilities are time dependent and that death due to cervical cancer may happen only after patient reached state 6. We also assume that once invasive cancer develops, the disease does not regress. We define q_t and u_t as the probabilities of all cause death and death due to cervical cancer during period t, respectively. Using this notation, for all $s \in \mathcal{S}_d$, $a \in \mathcal{A}$, and $t \in \mathcal{T}$, we have

$$p_t^{a,z}(10|s) = \begin{cases} q_t & \text{if} \quad s \in \mathcal{S}_d \backslash \{6\} \ , \\ q_t + u_t & \text{if} \quad s = 6 \ . \end{cases} \tag{5.1}$$

Belief space: $\mathcal{B}(\mathcal{S}_d)$ denotes the space of all probability distributions over the partially observable disease state space, $\mathcal{S}_d$. Any element of $\mathcal{B}(\mathcal{S}_d)$ is called a belief state, which is a six dimensional vector denoted by b. That is, $b_t = [b_t(1), b_t(2), \ldots, b_t(6)]$, where $b_t(s)$ represents the conditional probability of occupying state $s \in \mathcal{S}_d$ at decision epoch t given the initial belief b_0 and the entire history experienced so far. That is, $b_t(s) = \Pr\{s_t = s|I_t\}$ for all $s \in \mathcal{S}_d$, and accordingly, $\sum_{s \in \mathcal{S}_d} b_t(s) = 1$. To act optimally in POMDPs, without the knowledge of the core state of the process, the decision maker has to either record the entire history of action and observations or use a sufficient statistics of the entire history.

The best known sufficient statistics for the history in POMDPs is the belief state Bertsekas & DP (1976). The following result is also readily established. For any fixed sequence of actions $a_1, a_2, \ldots, a_N \in \mathcal{A}$, the sequence of the belief states $\{b_t\}_{t=0}^{N}$ is a Markov process. Therefore, b_t can be viewed as the state of the discrete time MDP (Sondik, 1971). In other words, POMDP is converted into a belief state completely observable MDP problem. Furthermore, b_{t+1} can be computed from b_t using the Bayes' rule.

Updated belief state: The function $\tau_{t+1}[b_t, a, z]$ defines the updating of belief states as a result of observations. We define $\tau_{t+1}[b, a, z] = [\tau_{t+1}[b, a, z](s')]$, where $\tau_{t+1}[b, a, z](s')$ represents the probability of occupying state $s' \in \mathcal{S}_d$ at time $t+1$, given that the decision maker's belief about the patient's health state was b_t, action taken was $a \in \mathcal{A}$, and $z \in \mathcal{Z}$ was observed at time t. Throughout the text, we interchangeably use $b_{t+1} = \tau_{t+1}[b, a, z]$ for simplicity.

If $a_t = W$, the updated belief state is the product of the probability that the patient will transition at time $t+1$ to state $s' \in \mathcal{S}_d$ given that at time t she is in any possible state $s \in \mathcal{S}_d$, and action W is taken. Then,

$$\tau_{t+1}[b_t, a, z](s') = \sum_{s \in \mathcal{S}_d} b_t(s) p_t^{W,\emptyset}(s'|s) \quad \text{for all } s' \in \mathcal{S}_d \ . \tag{5.2}$$

If $a_t = C$ or $a_t = H$, the updated belief state is the conditional probability $P(s'|s, b, a, z)$, which represents the probability of being in state $s' \in \mathcal{S}_d$ at time $t+1$, given that at time t there is a belief b_t, action $a_t \in \mathcal{A}$ is taken, $z \in \mathcal{Z}$ is observed and a transition from state $s \in \mathcal{S}_d$ to $s' \in \mathcal{S}_d$ occurs.

(5.3)

$$\tau_{t+1}[b_t, a, z](s') = \begin{cases} \frac{\sum_{s \in \mathcal{S}_d} b_t(s) K_t^a(z|s) p_t^{a,z}(s'|s)}{\sum_{s \in \mathcal{S}_d} b_t(s) K_t^a(z|s)} & \text{if } (a,z) = (C, C^-) \text{ or } (H, H^-) \\ p_t^{W,\emptyset}(s'|1) & \text{if } (a,z) = (C, C^+) \text{ or } (H, H^+), BX = 1 \\ p_t^{W,\emptyset}(s'|2) & \text{if } (a,z) = (C, C^+) \text{ or } (H, H^+), BX = 2 \\ p_t^{W,\emptyset}(s'|3) & \text{if } (a,z) = (C, C^+) \text{ or } (H, H^+), BX = 3 \end{cases}$$

The probability tree associated with the belief update procedure is given in Figure B.2 in the Appendix B.

Immediate rewards: $r_t(s, a, z)$ denotes the expected reward of taking action $a \in \mathcal{A}$ in state $s \in \mathcal{S}_d$ and getting an observation $z \in \mathcal{Z}$ at time t. Many of the studies with focus on dynamic policy making for screening decisions use quality adjusted life years (QALY) as the metric to quantify the quality-of-life gains from medical interventions. In our model, we use QALYs to parametrize the immediate rewards.

When the action is wait, we set the immediate reward as

(5.4)

$$r_t(s,W,\emptyset) = P(\text{alive during } t|s) + 0.5 * P(\text{dies during } t|s) - \epsilon_t(s) \ , \quad \text{for } s \in \mathcal{S}_d \ ,$$

which is a slightly modified version of the approach used in (Ayer et al., 2012). The term $\epsilon_t(s)$ can be regarded as the utility penalty for living with a virus, lesion or cancer, depending on the state, s. Subtracting $\epsilon_t(s)$ can be justified as follows. q_t (the probability of non-cancer death) is the same in all the states $s \in \mathcal{S}_d \backslash \{6\}$ while obviously, the QALY of a patient is not the same as that of a patient in those states. To account for this, we introduce a disutility parameter. $\epsilon_t(s)$.

$$r_t(s,W,\emptyset) = \begin{cases} 1 - 0.5q_t - \epsilon_t(s), & \text{if } s = \{1,2,3,4,5\} \ , \\ 1 - 0.5(q_t + u_t) - \epsilon_t(6), & \text{if } s = 6 \ . \end{cases} \tag{5.5}$$

When the action is screening, the QALY scores are obtained from those of wait action minus the disutility scores $\alpha_t^{(a,z)}(s)$ and $\beta_t(s)$, where $\alpha_t^{(a,z)}(s)$ represents the disutility associated with taking action $a_t = a$ with outcome $z_t = z$ when $s_t = s$ and $\beta_t(s)$ represents disutility of *biopsy* when $s_t = s$.

$$r_t(s,C,C^-) = r_t(s,W,\emptyset) - \alpha_t^{(C,C^-)}(s), \qquad \text{if} \quad (a,z) = (C,C^-) \tag{5.6}$$

$$r_t(s,C,C^+) = r_t(s,W,\emptyset) - \alpha_t^{(C,C^+)}(s) - \beta_t(s), \qquad \text{if} \quad (a,z) = (C,C^+) \tag{5.7}$$

$$r_t(s,H,H^-) = r_t(s,W,\emptyset) - \alpha_t^{(H,H^-)}(s), \qquad \text{if} \quad (a,z) = (H,H^-) \tag{5.8}$$

$$r_t(s,H,H^+) = r_t(s,W,\emptyset) - \alpha_t^{(H,H^+)}(s) - \beta_t(s), \qquad \text{if} \quad (a,z) = (H,H^+) \tag{5.9}$$

Lump sum rewards: $R_t(s)$ denotes the reward obtained when entering an absorbing state $s \in \mathcal{S}_a$. Patients in $s \in \mathcal{S}_a \backslash \{10\}$ have started treatment and regular screenings are no longer a feasible action for them. Hence, we use a lump sum reward that represents the post treatment quality adjusted life expectancy (QALE) of the patients from time t onward.

Terminal stage reward: $R_N(s)$ denotes the QALE of patients in state $s \in \mathcal{S}$ at time N. Note that if the patient is in state $s \in \mathcal{S}_a$ at time N, post treatment QALE will be used.

Order of events: The order in which these events occur are illustrated in Figure 5.2. At the beginning of year t, a decision $a_t \in A_t$ is taken based on the current belief state b_t. Depending on the action chosen, $z \in \mathcal{Z}$ is observed and a health state transition occurs during the year t. At the end of the year, the belief state is updated to $\tau[b,a,z]$. The solution of a POMDP is in form of a policy $\pi : \mathcal{B} \mapsto \mathcal{A}$ which maps every belief state $b \in \mathcal{B}$ into an action $a \in \mathcal{A}$. Executing a policy $\pi(b)$ induces a value

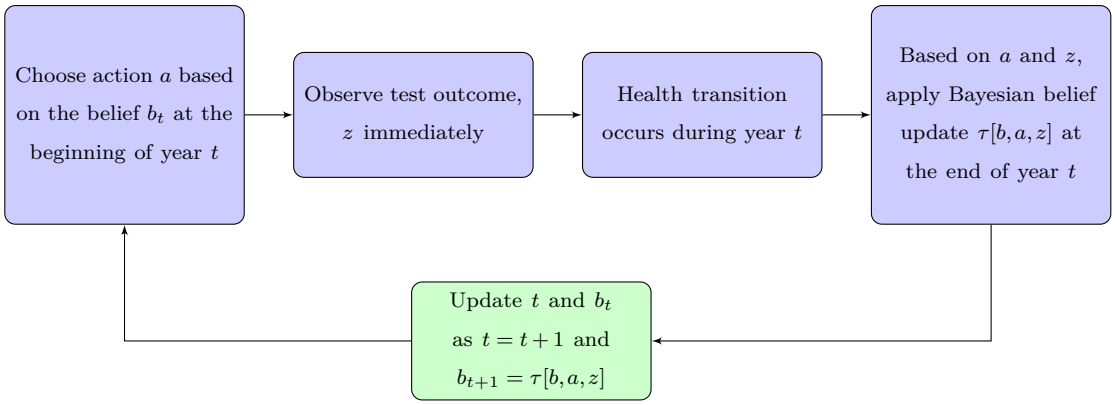


Figure 5.2 Order of the events in the POMDP model

function $V^\pi(b) : \mathcal{B} \mapsto \mathbb{R}$ which represents the expected total reward if starting from belief state b the policy π is followed.

$$V^\pi(b) = E_\pi\Big[\sum_{t=0}^{\infty} r_t(b_t, \pi(b_t)) | b_0 = b\Big] \tag{5.10}$$

where $r_t(b_t, \pi(b_t)) = \sum_{s\in\mathcal{S}} r_t(s, \pi(b_t))b_t(s)$. A policy π which maximizes V^π is called an optimal policy π^*. The optimal value function V^* maximizes Equation 5.10, and satisfies the Bellman stochastic dynamic program. We proceed to write these equations in our model.

Value function: $V_t^*(b_t)$ denotes the value function at belief state b_t, which is the optimal long-run average total QALYs a patient with b_t is expected to live beyond period t. We define the observable states using the following belief notation: $b^7 = [0,0,0,0,0,0,1,0,0,0]$, $b^8 = [0,0,0,0,0,0,0,1,0,0]$, and $b^9 = [0,0,0,0,0,0,0,0,1,0]$. Note that $R_t(10) = 0$ for $t \leq N$. The value function at terminal stage N can be expressed as follows.

$$V_N(b_N) = \begin{cases} \sum_s b_N(s)R_N(s), & \forall s \in \mathcal{S}_d \ . \\ \sum_s b^i(s)R_N(s), & \forall s \in \mathcal{S}, i \in \{7,8,9\} \ . \end{cases} \tag{5.11}$$

If a patient is in one of the absorbing states $\mathcal{S}_a$, the state of the patient is completely observable. Moreover, the patient is out of the screening decision process. Therefore, the recursive dynamic programming iterations are not applied in those states. Then, for absorbing observable states 7, 8, and 9, we have

$$V_t(b^i) = R_t(b^i) \ , \qquad i \in \{7,8,9\} \ . \tag{5.12}$$

When the patient is not in an observable state, her state is represented by a belief

state vector, b_t, with the value function

$$V_t(b_t) = \begin{cases} \max\left\{V_t^W(b_t), V_t^C(b_t), V_t^H(b_t)\right\}, & t = 1, 2, \cdots, N-1 \ . \\ \max\left\{V_t^C(b_t), V_t^H(b_t)\right\}, & t = 0 \ . \end{cases} \tag{5.13}$$

where

$$\begin{aligned} V_t^W(b_t) &= \sum_{s \in \mathcal{S}_d} b_t(s)\Big[r_t(s, W, \emptyset) + \sum_{s' \in \mathcal{S}} p_t^W(s'|s) V_{t+1}(\tau_{t+1}(b_t, W, \emptyset))\Big] \\ &= \sum_{s \in \mathcal{S}_d} b_t(s)\Big[r_t(s, W, \emptyset) + (1 - p_t^W(10|s)) V_{t+1}(\tau_{t+1}(b_t, W, \emptyset))\Big] \end{aligned} \tag{5.14}$$

After a positive screening test (i.e., C^+ or H^+), for patients in states 4, 5 and 6, biopsy will determine the exact state and hence, the next state will also be known. For instance, for a patient in state 4, the next state will be either 7 or 10. Therefore, $(1 - p_t^{a,a^+}(10|4))$ can be substituted with $p_t^{a,a+}(7|4)$. Note that value of belief state corresponding to observable death state is zero. For screening test actions $a \in \{C, H\}$, the expression $V_t^a(b_t)$ is written as follows.

$$\begin{aligned} V_t^a(b_t) \ = \ & \sum_{s \in \mathcal{S}_d} b_t(s) k^a(a^-|s)\Big[r_t(s, a, a^-) + (1 - p_t^{a,a^-}(10|s)) V_{t+1}(\tau_{t+1}(b_t, a, a^-))\Big] \\ & + \sum_{s=1}^{3} b_t(s) k^a(a^+|s)\Big[r_t(s, a, a^+) + (1 - p_t^{a,a^+}(10|s)) V_{t+1}(\tau_{t+1}(b_t, a, a^+))\Big] \\ & + b_t(4) k^a(a^+|4)\Big[r_t(4, a, a^+) + p_t^{a,a+}(7|4) V_{t+1}(b^7)\Big] \\ & + b_t(5) k^a(a^+|5)\Big[r_t(5, a, a^+) + p_t^{a,a+}(8|5) V_{t+1}(b^8)\Big] \\ & + b_t(6) k^a(a^+|6)\Big[r_t(6, a, a^+) + p_t^{a,a+}(9|6) V_{t+1}(b^9)\Big] \ . \end{aligned} \tag{5.15}$$

The above defined POMDP model presents significant computational challenges. In the next section, we describe the solution methodology we have used to obtain an optimal age- and risk-dependent screening policy for cervical cancer.

5.4 Solution Methodology

In this section, we first briefly explain the existing optimal solution methods and the complexity of using those methods on problems with large state space and then

we present common approximate solution methods in the literature. We provide a detailed discussion on the grid based solution method which we use in our problem to break down the complexity of dealing with continuous belief space. Approximating the value function over the discretized belief space requires the knowledge of the value at non-grid points generated by the belief update function. In the final part of this section, we explain the convex interpolation method and introduce our proposed Gaussian process regression (GPR) method that helps to make such approximations.

5.4.1 Grid Based Approximate Solution

Exact solution methods for finite-horizon POMDP problems exploit the fact that the value function is piecewise linear and convex in belief (Sondik, 1971) to generate a finite set of hyperplanes over the belief simplex, resulting in a finite number of regions over which the action associated with the hyperplane covering that region is the optimal action. The hyperplanes at time t are used to generate hyperplanes at time $t+1$ using dynamic programming (DP) iterations. Many of the exact value iteration methods differ in the way that this step is performed. Constructive methods such as Sondik's one-pass algorithm (Sondik, 1971), Cheng's relaxed-region method (Cheng, 1988) and Littman's witness method (Littman, 1996) consider only useful hyperplanes to generate hyperplanes at time $t+1$. On the other hand, enumerative methods such as Monahan's exhaustive method (Monahan, 1982) and Eagle's dominance-exhaustive method (Eagle, 1984) generate all possible combinations of hyperplanes at time $t+1$ and prune the dominated ones. Constructive methods use linear programming (LP) to find useful hyperplanes, and enumerative methods use LP to prune the dominated ones. Both methods are subject to computationally intensive LP problems when the size of the problem or the planning horizon is large. Applications of such methods in the literature of health decision making can be found in Ayer et al. (2012); Cevik et al. (2018); Li et al. (2015); Otten et al. (2020); Witteveen et al. (2018) and Zhang et al. (2012).

In general, computing exact solutions for POMDP problems is cumbersome and therefore, a great deal of efforts has been made to design approximate solution methods for POMDP problems. Heuristic methods such as the most likely state MDP method and the Q-MDP method rely on solving the underlying MDP problem and ignoring partial observability (Spaan, 2012). Petousis et al. (2019) used Q-MDP method to solve their POMDP model designed for lung cancer screening. Silver & Veness (2010) introduced partially observable Monte-Carlo planning (POMCP),

which combines a Monte-Carlo update of the agent's belief state with a Monte-Carlo tree search from the current belief state. Policy iteration methods, on the other hand, generate an infinite-horizon policy in each iteration and iteratively improve the generated policies. Such methods have been addressed in various studies including Hansen (1998) and Poupart & Boutilier (2004).

More popular approximate solution methods include point-based and grid-based approximation methods. Point-based value iteration (PBVI) method introduced by Pineau et al. (2003) focuses on reachable belief states, which are successors of the initial belief state b_0 at some point of time. This method computes the hyperplanes only for those reachable belief states and proceeds by expanding the initial set of beliefs in every iteration. The procedure is repeated until either the solution reaches the desired accuracy or the solution time reaches a limit.

In this study, we apply a grid based approximation method, and therefore, discuss the method in details. The grid-based approximation method uses the idea of discretizing the continuous belief space into a finite number of points called *grid points*. The value function is then calculated at the grid points using backward recursion, rather than over the entire continuous belief state space. The value function at non-grid points is approximated using the value function evaluations at the grid points, via some interpolation method. Early applications of the method appear in studies by Scarfet al. (1967) and Kakalik (1965). For a more complete discussion of grid-based approximation methods, see (Lovejoy, 1991b; White, 1991).

A very simple gridding scheme is to divide the belief space into a certain number of equidistant intervals. In the simplest case of a one dimensional state space, where the domain $\Omega = (0,1)$ is an interval, a grid having the *resolution* of e will divide the belief simplex into e equally-spaced intervals where each interval will have the length $\Delta x = 1/e$. Over a three-dimensional belief space, for example, the grid points would be generated as shown in Figure 5.3. We define $\mathcal{G}$ and $|\mathcal{G}|$ to be the set of grid points and the cardinality of the grid set, respectively. Let $\mathcal{M} = \{1,2,\ldots,m\}$ denote the index set of $\mathcal{G}$. We can write the set of grid points as $\mathcal{G} = \{g^1, g^2, \ldots, g^m\}$ given $|\mathcal{G}| = m$.

Gridding methods that use the same set of grid points over all decision epochs are called "fixed" gridding methods. In contrast, "variable" gridding methods update the gridding scheme from one epoch to the next. Within each decision epoch, the grids may be either uniform or nonuniform. Uniform grid has the same resolution over the entire belief space. Selection of a gridding strategy depends on the application and the objectives of meshing. Finely meshed grids obviously provide a better approximation for the value function but at the cost of relatively high computational

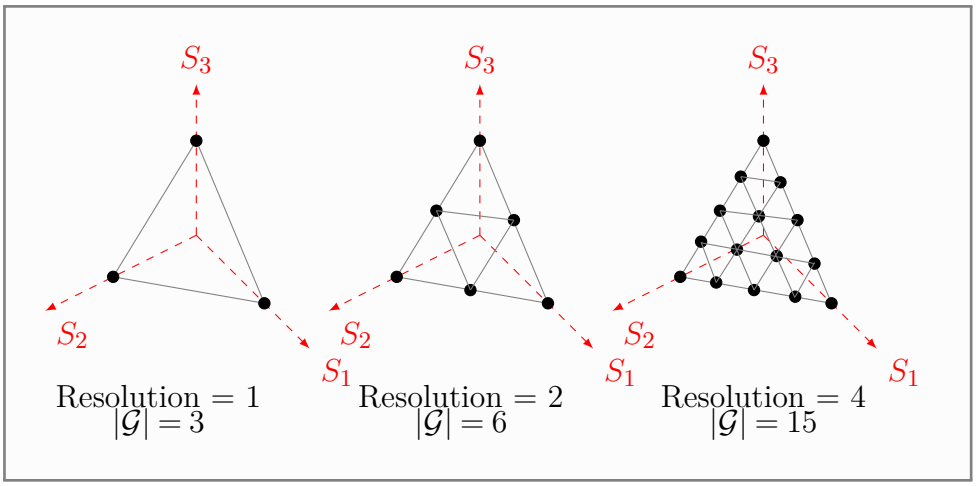


Figure 5.3 Grid point generation over a three-dimensional belief simplex using different resolutions

time. A reasonable compromise is to use different grid resolutions in different regions of the belief space, since typically, the belief trajectory only travels through a very small subset of the entire belief space (Theocharous & Kaelbling, 2004). In order to estimate the reachable belief space for a given initial belief distribution, Ahmadi et al. (2019) propose a switched system representation for the belief evolutions of POMDPs and use tools from control theory to overapproximate the reachable beliefs in terms of sub-level sets of Lyapunov functions. Examples of recent application of grid based approximation in the literature are Sandıkçı et al. (2013) and Cevik et al. (2018). Sandıkçı et al. (2013) consider minimum bandwidth when searching for the reachable belief states. Band belief vectors has the property that nonzero elements appear consecutively. In other words, adjacent grid points are close to each other in the consecutive one dimensional ordering as well. They argue that for a cancerous patient, it is highly likely that the patient occupies two consecutive states rather than otherwise. That is if the states are healthy, infected and cancerous, it is more sensible to assume that higher belief scores are given to healthy and infected states unless the patient is already diagnosed with cancer. Despite the reported success of this approach in their specific problem, applying this method in our problem, due to the minimal set of band points, was not feasible. Cevik et al. (2018) accumulate the beliefs of not being healthy into one dimension and create a nonuniform grid with higher resolutions assigned to healthier region. This approach resorts intensively to the regions that are more reachable, and yet the possibility of having both nonzero score for the other belief states are still considered. In their specific small size problem with three partially observable states, this approach is shown to be applicable. Unfortunately, this approach is again not computationally feasible for our case. The dynamic programming algorithm requires that the value function at all reachable belief states be computed for stage t before computing the value func-

tion for stage t-1. Since the set of grid points may not include all of the reachable belief states at a given stage, various approaches has been proposed to estimate the value function at non-grid points using an interpolation of the the value function evaluations at grid points. Interpolation methods include nearest neighbor approximations, kernel regression methods, and using a convex combination or weighted average (Hauskrecht, 2000). Using a convex combination mainly involves expressing any non-grid belief point b_t as a convex combination of the grid points in $\mathcal{G}$, and using the weights to obtain an estimate for the value function at b_t. In addition to that, the weighting procedure assigns nonzero weights to points which are far from the point's neighborhood. Zhou & Hansen (2001) suggested the use of the following LP to obtain the best weights to approximate the value function.

$$\min \left\{ \sum_{j=1}^{|\mathcal{G}|} \lambda_j V_t(g^j) : \sum_{j=1}^{|\mathcal{G}|} \lambda_j g^j(s) = b_t(s) \; \forall \, s \in \mathcal{S}_d, \; \sum_{j=1}^{|\mathcal{G}|} \lambda_j = 1, \; 0 \leq \lambda_j \leq 1 \; \forall \, j \in \mathcal{M} \right\}$$

But this approach still presents significant computational challenges as the number of the grid points increases. Specifically, for a grid set of size above 3000 points, solution time of the POMDP problem for the whole planning horizon using LP method for finding interpolation weights can be in the order of several hours. Among the studies in the literature, Cevik et al. (2018) and Sandıkçı et al. (2013) used this method of interpolation, but with fewer than 1500 and 1000 grid points, respectively.

To limit the error in our computations, we wanted to significantly increase the number of grid points. This required the use of more contemporary methodologies to construct an approximation for the value function over the continuous belief space. In the next section, we describe more details on the Gaussian process regression models we used to solve the problem with almost 700,000 grid points.

5.4.2 Inference of Value At Non-Grid Points

Gaussian Process Regression (GPR) is a Bayesian method for statistical inference. Before starting with GPR, we give a quick review of the linear regression with Bayesian approach.

5.4.3 Overview of Linear Regression With Bayesian Approach

Let $\mathcal{D} = \{(x_i, y_i) : i = 1, 2, \cdots, n\}$ denote the set of n observations, where x and y are real valued scalars. The objective is to create a model $f(x) = \beta_0 + \beta_1 x$ and use it to make prediction of y_* at a new input point x_*. Often, it is assumed that the observed values y differ from the function values $f(x)$ by additive noise ϵ, according to the following relation, for $i = 1, 2, \cdots, n$,

$$\begin{aligned} y_i &= f(x_i) + \epsilon_i \\ &= \beta_0 + \beta_1 x_i + \epsilon_i \end{aligned}$$

where we assume that the noise terms ϵ_i's are independent and identically distributed and $\epsilon_i \sim \mathcal{N}(0, \sigma_\epsilon^2)$. In matrix notation:

$$f(x_i) = \mathbf{x}_i^\intercal \mathbf{w}, \quad \text{and} \quad y_i = \mathbf{x}_i^\intercal \mathbf{w} + \epsilon_i$$

where

$$\mathbf{x}_i = \begin{bmatrix} 1 \\ x_i \end{bmatrix}, \quad \mathbf{w} = \begin{bmatrix} \beta_0 \\ \beta_1 \end{bmatrix}$$

The matrices can be setup as,

$$\mathbf{y} = \begin{bmatrix} y_1 \\ y_2 \\ \vdots \\ y_n \end{bmatrix}, \quad \mathbf{X} = \begin{bmatrix} 1 & x_1 \\ 1 & x_2 \\ \vdots & \vdots \\ 1 & x_n \end{bmatrix}, \quad \mathbf{w} = \begin{bmatrix} \beta_0 \\ \beta_1 \end{bmatrix}, \quad \epsilon = \begin{bmatrix} \epsilon_1 \\ \epsilon_2 \\ \vdots \\ \epsilon_n \end{bmatrix}$$

Under the Bayesian approach, a prior distribution will be fitted over the unknown parameters $\mathbf{w}$.

$$p(\mathbf{w}) = \mathcal{N}(0, \Sigma_p),$$

where Σ_p denotes the covariance matrix of the weights $\mathbf{w}$.

It can be shown that, the likelihood function is also Gaussian.

$$p(\mathbf{y}|\mathbf{X}, \mathbf{w}) = \mathcal{N}(\mathbf{X}^\intercal \mathbf{w}, \sigma_\epsilon^2 \mathbf{I}),$$

where $\mathbf{I} = diag(\mathbf{1}_n)$ is an identity matrix of size n.

Under the Bayes rule, the posterior distribution will be:

$$\begin{aligned} p(\mathbf{w}|\mathbf{X},\mathbf{y}) &\propto p(\mathbf{y}|\mathbf{X},\mathbf{w})p(\mathbf{w}) \\ &= \mathcal{N}\Big(\bar{w} = \frac{1}{\sigma_\epsilon^2}\mathbf{A}^{-1}\mathbf{X}\ \mathbf{y}, \mathbf{A}^{-1}\Big) \end{aligned}$$

where $\mathbf{A}_{D\times D} = \Sigma_p^{-1} + \sigma_\epsilon^{-2}\mathbf{X}\ \mathbf{X}^\intercal$. Notice that, the posterior distribution is Gaussian with mean $\bar{w}$ and covariance matrix A^{-1}.

Suppose using the n observations made for input x, (i.e., $x_{1:n}$) and output y, (i.e., $y_{1:n}$), we aim to predict the output y_* for a new input point x_*. Given the inference made for the weights $\mathbf{w}$ by posterior distribution, we can write posterior predictive distribution for f_* as,

$$\begin{aligned} p(f_*|\mathbf{x}_*,\mathbf{X}\ ,\mathbf{y}) &= \int p(f_*|\mathbf{x}_*,\mathbf{w})p(\mathbf{w}|\mathbf{X},\mathbf{y})d\mathbf{w} \\ &= \mathcal{N}\Big(\bar{f}_* = \frac{1}{\sigma_\epsilon^2}\mathbf{x}_*^\intercal\mathbf{A}^{-1}\mathbf{X}\ \mathbf{y}, \mathbf{x}_*^\intercal\mathbf{A}^{-1}\mathbf{x}_*\Big) \end{aligned}$$

Notice that the predictive distribution is also Gaussian where the predictive variance is a quadratic form of x_* with the posterior covariance matrix $\mathbf{A}^{-1}$, which indicates that the predictive uncertainties increase with the magnitude of the test input x_*. Finally, a good prediction for y_* is the expected value of $f_* = y_* - \epsilon_* = f(\mathbf{x}_*)$. By choosing an appropriate basis function (polynomial or nonpolynomial), the model can be modified to fit to the shape of the data.

5.4.4 Gaussian Process Regression

Gaussian process regression (GPR) is a Bayesian statistical approach used for learning functions and making inference when the shape of the function is unknown, or the analytical evaluation of the function is costly.

Let $\mathcal{D} = \{(\mathbf{x}_i, y_i) : i = 1, 2, \cdots, n\}$ denote the set of n observations, where $\mathbf{x} \in \mathcal{X} \subset \mathbb{R}^D$, and y are real valued scalars. Let $f : \mathbf{x} \mapsto \mathbb{R}$ be a function from the input space to the reals. Let $\mathbf{X}_{D\times n} = [\mathbf{x}_1, \mathbf{x}_2, \cdots, \mathbf{x}_n]$ and $\mathbf{y} = [y_1, y_2, \cdots, y_n]^\intercal$.

In GPR, we model the relationship between $\mathbf{x}$ and y as follows:

$$y = f(\mathbf{x}) + \epsilon.$$

Notice that in linear regression, we fitted distributions over weight parameters $\mathbf{w}$.

In GPR, a distributions over functions $f(.)$ is fitted, where for any point $\mathbf{x}$, the function value at $\mathbf{x}$ denoted as $f(\mathbf{x})$ is a random variable. In general, GPR relies on the assumption that the prior probability distribution of a random vector is multivariate normal, with a particular mean vector and covariance matrix.

Definition 5.1 *A random function $f : \mathcal{X} \mapsto \mathbb{R}$ is a Gaussian process (GP) if for any finite collection of input points $\mathbf{X} = \{\mathbf{x}_i \in \mathbb{R}^D, i = 1, \cdots, n\}$, the corresponding random vector $\mathbf{f}$ is multivariate Gaussian distributed.*

$$\begin{bmatrix} f(\mathbf{x}_1) \\ \vdots \\ f(\mathbf{x}_n) \end{bmatrix} \sim \mathcal{G}\left(\begin{bmatrix} m(\mathbf{x}_1) \\ \vdots \\ m(\mathbf{x}_n) \end{bmatrix}, \begin{bmatrix} k(\mathbf{x}_1, \mathbf{x}_1) & \cdots & k(\mathbf{x}_1, \mathbf{x}_n) \\ \vdots & \ddots & \vdots \\ k(\mathbf{x}_n, \mathbf{x}_1) & \cdots & k(\mathbf{x}_n, \mathbf{x}_n) \end{bmatrix} \right)$$

This can be represented as,

$$\mathbf{f} = \left[f(\mathbf{x}_1), \cdots, f(\mathbf{x}_n) \right]^{\intercal} \sim \mathcal{G}(m(\mathbf{X}), K(\mathbf{X}, \mathbf{X}))$$

Gaussian process is completely defined by its mean and covariance function. That is, for any $\mathbf{x} \in \mathcal{X}$,

$$f(\mathbf{x}) \sim \mathcal{GP}(m(\mathbf{x}), k(\mathbf{x}, \mathbf{x}'))$$

where

$$m(\mathbf{x}) = E[f(\mathbf{x})]$$

$$cov[f(\mathbf{x}), f(\mathbf{x}')] = E[(f(\mathbf{x}) - m(\mathbf{x}))(f(\mathbf{x}') - m(\mathbf{x}'))]$$

Very often, the mean function is assumed to be constant, either zero or the mean of the training dataset. Therefore, the model is fully controlled by covariances, where

$$cov[f(\mathbf{x}), f(\mathbf{x}')] = k(\mathbf{x}, \mathbf{x}')$$

Notice that, the covariance between the outputs is written as a function of the inputs. This means that the kernel covariance function $k(\mathbf{x}, \mathbf{x}')$ defines the behavior of the function values $f(\mathbf{x})$ and $f(\mathbf{x}')$ corresponding to the input points $\mathbf{x}$ and $\mathbf{x}'$. Any covariance kernel function works as long as it satisfies semi-positive definite and symmetric property. However, any choice of the kernel covariance function, implies certain underlying assumptions about the model. For example, ensuring smoothness of the functions is an important aspect of the kernel choice, implying that the similarity of the inputs is reflected in the similarity of the outputs. Squared exponential kernel, also known as Radial Basis Function (RBF) is a commonly used kernel function which ensures that the correlation between two points decays

exponentially with the distance between them.

$$k(\mathbf{x},\mathbf{x}') = \sigma_f^2 \exp\left[-\frac{1}{2}\sum_{l=1}^{d}\frac{(\mathbf{x}-\mathbf{x}')^2}{\ell^2}\right] \tag{5.16}$$

This kernel function has two hyperparameters: signal variance, σ_f^2, and lengthscale, ℓ. Obviously, the maximum allowable covariance is σ_f^2, which is attained when $\mathbf{x}=\mathbf{x}'$ implying perfect correlation between $f(\mathbf{x})$ and $f(\mathbf{x}')$. If $\mathbf{x}$ and $\mathbf{x}'$ are further away, then $k(\mathbf{x},\mathbf{x}')$ will converge to 0. The length scale ℓ is an additional leverage that controls how quickly the correlation between two points should decay as their distance increases.

Sampling From a Gaussian Process

Even though in the function-space view, a random function represents a vector of infinite size, in practice, drawing samples is conducted for only a finite set of points by using a multivariate normal distribution with a covariance matrix generated by the kernel function. By computing the covariance between all n points in $\mathbf{X}$ using Equation 5.16, we can form the $n\times n$ covariance matrix $K(\mathbf{X},\mathbf{X})$. By choosing prior mean function $m(\mathbf{x})=0$, we can then sample values of f at n inputs collected in $\mathbf{X}$ from the GP by sampling from a multivariate normal distribution, $\mathbf{f}\sim\mathcal{G}(\mathbf{0},k(\mathbf{X},\mathbf{X}))$, where $\mathbf{f}=\left[f(\mathbf{x}_1),\cdots,f(\mathbf{x}_n)\right]^{\mathsf{T}}$. Note that $\mathbf{f}$ is a sample of the function values and not observations values as it is noise free. To sample observations $\mathbf{y}$, an additional and independent sample of the noise term ϵ must be added.

An example of such samples is shown in Figure 5.4, panel (a).

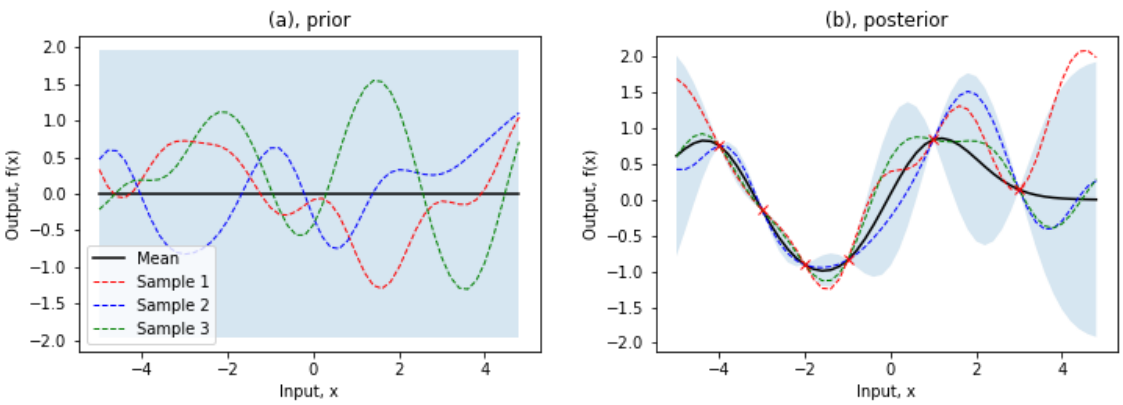


Figure 5.4 Prior and posterior using squared exponential kernel with $\ell=1$ and $\sigma_f=1$. Panel (a) shows three functions randomly drawn from a GP prior. Panel (b) shows three random functions drawn from the posterior, using 6 noise free observations. The shaded area represents the 95% confidence region.

Prediction Using Noise-free Observations

Suppose the n observations are noise free, that is $\mathcal{D} = \{(\mathbf{X}, \mathbf{f})\}$ and our aim is to make predictions for m new inputs collected in $\mathbf{X}_*$. By definition, the joint prior distribution of the training outputs, $\mathbf{f}$, and the test outputs $\mathbf{f}_*$ according to the prior is

$$\begin{bmatrix} \mathbf{f} \\ \mathbf{f}_* \end{bmatrix} \sim \mathcal{N}\left(\mathbf{0}, \begin{bmatrix} K & K_* \\ K_* & K_{**} \end{bmatrix}\right)$$

where $K_* = K(\mathbf{X}, \mathbf{X}_*)$ denotes the $n \times m$ matrix of the covariances evaluated at all pairs of training and test points. Similarly K_{**} denotes the $m \times m$ matrix of the covariances between the test points. The conditional distribution

$$\mathbf{f}_* | \mathbf{X}_*, \mathbf{X}, \mathbf{f} \sim \mathcal{G}(K_* K^{-1} \mathbf{f}, K_{**} - K_* K^{-1} K_*^\intercal)$$

Prediction Using Noisy Observations

Suppose we have collected observations $\mathcal{D} = \{(\mathbf{X}, \mathbf{y})\}$ and we aim to make predictions for new points $\mathbf{X}_*$. Since the observations $\mathbf{y}$ and function values $\mathbf{f}_*$ follow a joint multivariate Gaussian distribution, we can write,

$$\begin{bmatrix} \mathbf{y} \\ \mathbf{f}_* \end{bmatrix} \sim \mathcal{N}\left(\mathbf{0}, \begin{bmatrix} K + \sigma_\epsilon^2 \mathbf{I} & K_* \\ K_* & K_{**} \end{bmatrix}\right)$$

Therefore, the conditional distribution

$$\mathbf{f}_* | \mathbf{X}, \mathbf{y}, \mathbf{X}_* \sim \mathcal{G}\Big(K(K + \sigma_\epsilon^2 \mathbf{I})^{-1} \mathbf{y}, K_{**} - K_*(K + \sigma_\epsilon^2 \mathbf{I})^{-1} K\Big)$$

The best estimate for $\mathbf{f}_*$ is the mean of this distribution:

$$\bar{\mathbf{f}}_* = \mathbb{E}[\mathbf{f}_* | \mathbf{X}, \mathbf{y}, \mathbf{X}_*] = K(K + \sigma_\epsilon^2 \mathbf{I})^{-1} \mathbf{y}$$

and the uncertainty in our estimate is captured in its variance:

$$cov(\mathbf{f}_*) = K_{**} - K_*(K + \sigma_\epsilon^2 \mathbf{I})^{-1} K$$

The covariance kernel function contains unknown hyper-parameters such as the length-scale ℓ, signal variance σ_f^2, and noise variance σ_ϵ^2. The values of these hyper-parameters need to be inferred from the data. Tuning the hyper-parameters of the covariance kernel function is done by maximizing the log marginal likelihood of the observed data. Given the data $\mathcal{D} = \{(\mathbf{X}, \mathbf{y})\}$ and hyper-parameters $\theta = (\ell, \sigma_f^2, \sigma_\epsilon^2)$,

the log marginal likelihood is

$$\log p(\mathbf{y}|\mathbf{X},\theta) = -\frac{1}{2}\mathbf{y}^{\intercal}\mathbf{K}_y\mathbf{y} - \frac{1}{2}\log|\mathbf{K}_y| - \frac{n}{2}\log 2\pi$$

where $\mathbf{K}_y = K(\mathbf{X},\mathbf{X}) + \sigma_\epsilon^2\mathbf{I}$ is the covariance matrix of the noisy output values $\mathbf{y}$. A gradient-based optimizer can be used to maximize the marginal likelihood.

In our model, we have a finite grid point set $\mathcal{G} = \{\mathbf{x}_1, \mathbf{x}_2, \ldots, \mathbf{x}_n\} \subset \mathbb{R}^6$. We have made observations of value function at the grid points, namely, $f(\mathbf{x}_1), f(\mathbf{x}_2), \cdots, f(\mathbf{x}_n)$ where $f(\mathbf{x})$ is the continuous response vector. The goal is to predict the value of the non-grid points using the already observed values at the grid points. We use GP regression method to make these predictions, as defined in Algorithm 2. We use MATLAB's *RegressionGP class* to train a GPR model, (using *fitrgp*). Using the trained model, we predict responses for new predictor data (using *predict*).

Algorithm 2 Grid Based POMDP Solution with GPR Predictions

3.1 **Inputs:** Transition and observation probabilities, rewards.
3.2 **Output:** $\widetilde{V}_t(g), t \in \{0, 1, \cdots, N\}, g \in \mathcal{G}$.
3.3 **For t ← N down to 0**
3.4 **For all grid points** $g \in \mathcal{G}$
    If $t = N$
        Calculate $V_N(g)$ (Eq.: 5.11)
    Else if $t = N-1:1$, **then,**
        Update grid point belief for every (a,o), i.e., $\tau[g,a,o]$ (Eq.: 5.2, 5.3)
        Obtain prediction $\widetilde{V}_{t+1}(\tau[g,a,o])$ using GPR
        Calculate $\widetilde{V}_t^W(g), \widetilde{V}_t^C(g), \widetilde{V}_t^H(g)$ (Eq.: 5.14, 5.15)
        Calculate $\widetilde{V}_t(g) = \max\{\widetilde{V}_t^W(g), \widetilde{V}_t^C(g), \widetilde{V}_t^H(g)\}$ (Eq.: 5.13)
        Fit a GPR to obtain predictors $\widetilde{V}_t(b)$, for any belief state, b
    Else
        Follow steps 1 and 2 for $t \neq N$ (lines 6,7). Obtain $\widetilde{V}_t^C(g), \widetilde{V}_t^H(g)$ (Eq.: 5.15)
        Calculate $\widetilde{V}_t(g) = \max\{\widetilde{V}_t^C(g), \widetilde{V}_t^H(g)\}$ (Eq.: 5.13)

In our problem, the size of the state space does not permit using uniform grids with reasonable resolution. Instead, we generated a finely-meshed grid in regions that patients are most likely to occupy and a relatively sparse mesh over the remaining regions of the belief state space. These regions were identified with a simulation model. Using a pool of 100000 patients, we simulated the updating of belief states using randomly selected actions and observations. The outcome of this simulation provides an estimate of the reachable belief states during the planning horizon.

Finally, to ensure a sufficient grid resolution, we conducted a grid-convergence analysis, which indicated a convergence of the solutions for grid sizes above 440,000 grid points. The results we present in the next sections were obtained using 691,025

grid points at every iteration of the DP algorithm. The optimal objective function value (optimal expected QALYs for a healthy patient at age 21) and its convergence for different fixed grid sizes are shown in Figure 5.5. We solved our model using a computer with Intel(R) Core(TM) i7 − 8700 CPU @ 3.20 GHz with 64 GB of RAM.

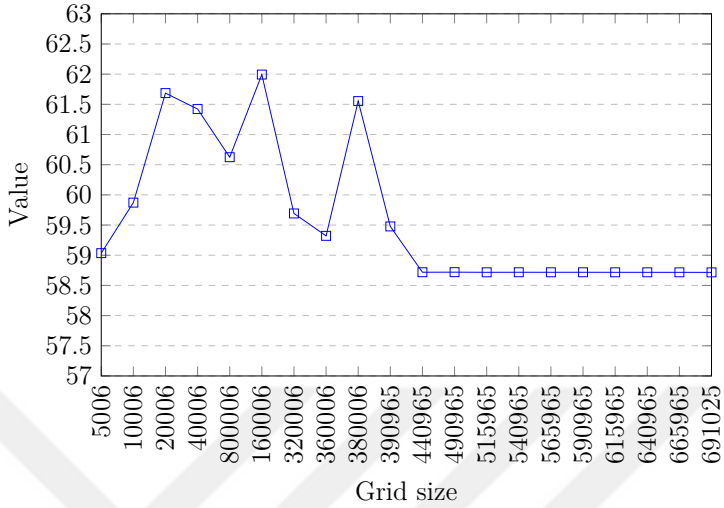


Figure 5.5 Convergence of the optimal expected QALY for a healthy 21-year old patient as a function of grid size

5.5 Parameterization of the Model

In this section, we present the sources of the parameters we used to obtain the optimal screening policy given in the next section. Table B.1 presents a comprehensive list of parameters and associated inputs and sources of the parameters.

The annual transition probabilities were collected from multiple sources with focus on clinical cohort studies in the literature. In case of multiple inconsistent data, we obtained an ensemble estimate from pooled weighted data. Monthly rates were converted to annual and calibrated such that the sum of the probabilities of disease regression, progression, persistence, and death is equal to one. Marcellusi (2017) presents a detailed discussion about the calibration of transition probabilities in Markov models. Campos et al. (2014) and Taguchi et al. (2020) present mathematical models for the parameterization of the model when the longitudinal data are available. Gopalappa et al. (2018) present a general methodology for parameterizing a Markov processes model for cancer onset and progression for the countries where longitudinal cancer registry data are not available. Transition probabilities in our

model are age-dependent. This assumption is consistent with observed higher progression of HPV infection and higher regression of neoplasia including CIN1, CIN2 and CIN3 at younger ages, and higher lesion progression rates at older ages (Mandelblatt et al., 2002).

For the absorbing states we assume that $p_t^{W,\emptyset}(s'|s) = 1$ if $s' = s \in \mathcal{S}_a$, and zero otherwise. When the test result is negative, transition probabilities follow $p_t^{H,H-}(s'|s) = p_t^{C,C-}(s'|s) = p_t^{W,\emptyset}(s'|s)$ for $s \in \mathcal{S}_d$ and $s' \in \mathcal{S}$. For the case of a positive test, it must be noted that biopsy result will determine the exact state. Practically, patients for whom the biopsy indicates their states as 2 or 3 are not treated. Even in case of a treatment, according to Chuck (2010), the partial immunity against high risk strains remains very low. Therefore, due to the recurrent nature of the disease, it is reasonable to assume that those patients remain under the routine screening program. That is, for $s \in \{1,2,3\}$, $p_t^{C,C+}(s'|s) = p_t^{C,C-}(s'|s)$, $s' \in \mathcal{S}_d \cup \{10\}$. For states $s \in \{4,5,6\}$, the patient will transition into $s' \in \{7,8,9\}$ if she remains alive, which happens with probability $1 - p_t^{C,C+}(10|s)$. Age-specific cancer incidence rates were derived from Cancer Institute's Surveillance, Epidemiology, and End Results Program (SEER).

We use the observation model given in Table 5.1 to find the observation probabilities required in our model. We calculate the sensitivity and specificity for both conventional and liquid based cytology by taking the weighted average of values from most recent studies using an ASCUS+ threshold. Observation probabilities expressed in terms of sensitivity and specificity are highly variable in the literature and vary in wide ranges. Therefore, we conduct an extensive study on the sensitivity of our model results on those parameters. The observation probabilities used in our base model as well as two scenarios constructed for sensitivity analysis are presented in Table 5.2 in Section 5.6.

Consistent with the literature, we use quality-adjusted life year (QALY) as the measure of rewards for each state. QALY captures both the length and quality of life. Calculation of QALY is done by multiplying a health related quality of life (hrQOL) score for a specific health state with the length of time spent in that state. hrQOL is a generic measure of utility for residing in each health state where the utility is a number between zero (worst health state, i.e., dead) and one (perfect health state) (de Kok et al., 2018). It is important to note that, mainly in the literature of cost effectiveness analysis, QALYs refer commonly to the total expected quality adjusted life years. In our model, our interest is finding yearly basis QALY scores. When only one year is considered, QALY is equivalent to the utility of being in each heath state. As such, QALY represents the utility of living one year in each

relevant health state.

Often, the utility/disutility data reported in the literature is conflicting and vary widely (de Kok et al., 2018). The estimated disutilities for HPV-related health outcomes are based on several sources in Balasubramanian et al. (2010); Chesson et al. (2008); Conway et al. (2012); de Kok et al. (2018); Insinga et al. (2007); Mo et al. (2017). For a perfectly healthy patient in state 1, it is reasonable to assume that $\epsilon_t(1) = 0$. For the disutility of CIN1, CIN2 and CIN3, we take the weighted average of the values reported in the literature. For the disutility of the invasive cancer, we use the average of local, regional, and distant cancer states. The reported disutility of invasive cancer varies between 0.25 and 0.45 (Kulasingam & Myers, 2003; Mo et al., 2017). For the base model, we select the following set of disutility scores. $\epsilon_0(s) = [0, 0.02, 0.1, 0.13, 0.14, 0.35]$. We assume that the health state disutilities $\epsilon_t(s)$ are age-dependent. To model a gradual change, we assume they are increasing every five years with 0.002 units for $s \in \{2, 3, 4, 5, 6\}$.

In addition to the disutility of living with an infection or lesion, we incorporated the disutility of screening and disutility of a possible false result into our model. The disutility of screening may arise from different sources including physical discomfort during or after the screening procedure or psychological impact observed in forms of anxiety and distress (Croyle, 1995; Maissi et al., 2005). As such, $\alpha_t^{(a,z)}(s)$ encapsulates two types of disutilities. Disutility of discomfort due to screening itself, and possible disutility due to side effects of a false test result. In the literature, it is common to express disutility of screening in terms of quality-adjusted days lost (QADL). In the literature, the reported QADL due to the screening discomfort varies from a few days up to three weeks. In our analysis, we specify it as ten days. In the case of a false negative test, false reassurance and delayed treatment lead to disutility. However, there is no specific enumeration of such disutilities in the literature. Therefore, in our analysis, we do not include disutility of a false negative. Some analyses also include disutility associated with a positive screening test result (Kim et al., 2008). For a false positive test, disutilities are mostly associated with severe psychological impacts. The disutility of a false positive reported in the literature varies between 0.02 and 0.048 (Balasubramanian et al., 2010). In our analysis, we specify it as 0.0411. We also assume that QADL due to true positive is three days.

According to the literature, with increasing age, the risk and side-effects of biopsy also become more harmful. Wang (2017) suggests that the disutility associated with biopsy is inversely proportional to the age-specific EQ-5D scores. EQ-5D is a utility-based measure of health status and is widely used in clinical and economic evaluation of health care. These scores reflect varying negative impacts of biopsy

on women's health at different ages. For EQ-5D scores in case of a cervical cancer, we use the estimates of Hanmer et al. (2006).

Several studies in the literature reported long term side effects of treating cervical cancer, including physical and psychological distress, and sexual disruptions (Greimel et al., 2009; Sun et al., 2005; Wenzel et al., 2005). However, the literature lacks specific quality adjusted life (QoL) loss due to such complications. In addition to that, the patient in states $s \in \{7, 8, 9\}$, receive different treatment modalities, making it more difficult to specify numeric disutilities for those states. Therefore, we use the approach presented by Ayer et al. (2012). Using this method, we obtain the age-specific mortality for patients treated for cervical cancer from the SEER data, and we apply the method described by Arias et al. (2019) to convert the post-treatment death probabilities into age-specific life expectancy. Note that this approach is only taking the post-treatment life expectancy into account without considering the quality of life spent in a possible imperfect health state.

The calculation of the terminal stage rewards, i.e., $R_N(s)$ for the states $s \in \{7, 8, 9\}$ follows the same method explained in lump sum reward section. For the states $s \in \mathcal{S}_d$, we multiply the life expectancy of the population at time N, i.e., 16.7 with the disutility scores of the relevant health states, $\epsilon_N(s)$ to obtain the quality adjusted life years lost for each health state $s \in \mathcal{S}_d$. Finally, we subtract them from the age-specific life expectancy of the population to obtain the age specific quality adjusted life expectancy (QALE) for the relevant health states.

5.6 Results

In this section, we present the optimal risk-action thresholds for the optimal screening policy obtained for the parameter settings described above. In addition, we solve the model under different assumptions for a sensitivity analysis.

5.6.1 Risk-Action Thresholds for an Optimal Screening Policy

Figure 5.6 depicts the optimal testing actions at the set of gridded belief states b_t such that the probability that the patient is healthy, $b_t(1) = 1 - b_t(5) - b_t(6)$ and

$b_t(2) = b_t(3) = b_t(4) = 0$ for patients at ages 21, 34, 37, 54, 61 and 67. The x-axis in Figure 5.6 corresponds to the probability of an existing in situ cancer, i.e., $b_t(5)$, and the y-axis shows the probability of invasive cancer, i.e., $b_t(6)$. The regions colored in dark blue correspond to the belief states where the optimal action is to wait and the light blue regions correspond to the belief states where the optimal action is to conduct an HPV DNA test. We see that the optimal actions at the plotted belief states were only wait and HPV DNA test (more discussion on this observation is included below).

The process of finding the optimal action for a given patient with a certain age involves finding the belief state of the patient on the corresponding graph. Consider a 21 year-old patient with an initial belief state, $b_0 = [0.865, 0.135, 0, 0, 0, 0]$. For this patient, the optimal action is to wait since her cancer risk falls within the wait region in Figure 5.6. Her updated risk in the next decision epoch (i.e., at age 22) using Equation 5.2 will be $b_1 = [0.8834, 0.1047, 0.0119, 0, 0, 0]$, which may possible yield a different testing action. Progressing in this fashion, we find the next epoch with a recommended testing action.

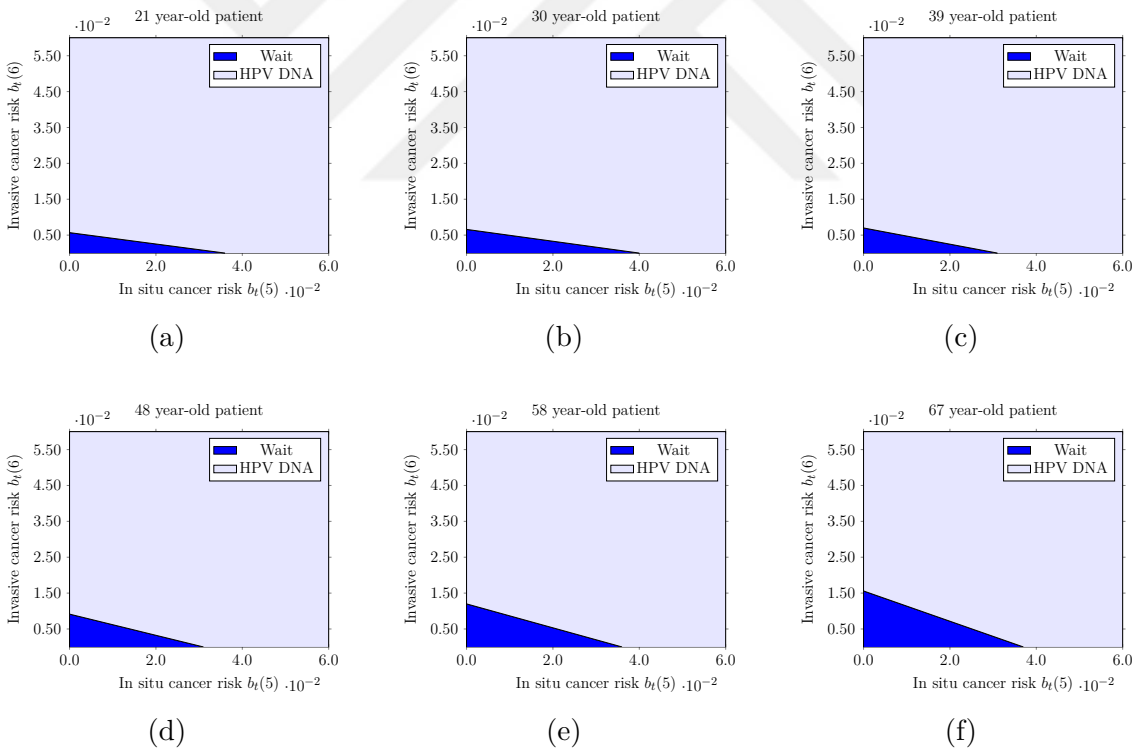


Figure 5.6 Risk-action threshold for cervical cancer screening at different patient ages

Figure 5.6 allows us to observe how the risk-action thresholds change as a function of patient's age. First, note that the testing threshold for invasive cancer risk, i.e., $b_t(6)$ for $b_t(5) = 0$, increases monotonically with age. This is intuitive since the disease is only expected to get worse after this health state. In comparison, we see the

risk-action threshold show more interesting behavior on the x-axis, which represents the in situ cancer risk. The risk-action thresholds provided by the optimal screening policy is a result of two types of behavior at different ages: (i) annual risk of infection, (ii) probability of spontaneous regression of CIN1, CIN2 and CIN3 lesions versus progression to invasive cancer. At younger ages, patients have a higher annual risk of infection with HPV and probability of infections progressing to a low-grade lesion, but they also enjoy a higher rate of spontaneous regression of lesions. As patients age, the risk of infection goes down, but it becomes more likely for existing CIN2 or CIN3 lesions to progress to invasive cancer. As a result of carefully considering the trade-off between these two types of behavior, the optimal screening policy allows us to avoid over-diagnosis (and consequently, over-treatment), which is an ongoing issue discussed heavily in the literature (Esserman et al., 2013,1).

5.6.2 Sensitivity Analysis

Under what conditions does cytology become preferable?

The assumed parameters of our baseline model imply that cytology is rarely recommended under the optimal screening policy; among the plotted belief states in Figure 5.6 cytology was never the recommended testing action.

Recent studies suggest that compared to cytology test, HPV testing finds more cases of CIN3 or cancer (Schiffman & Solomon, 2013) and provides greater protection against cervical cancer (Ronco et al., 2014). In addition, Grimes et al. (2020) argued that HPV testing conducted every five years yielded lower cancer risk compared to cytology test at every three years. In this regard, our POMDP model generates screening actions that are consistent with the current literature.

However, it is widely recognized that cytology test is highly subjective and there is a high variability in detection rates across hospitals. Studies suggest a considerable proportion of diagnostic errors are attributed to laboratory error that are primarily influenced by variations in the expertise and procedures of different cytopathology laboratories (Last & Breslow, 2012). In one study the liquid based cytology specimens were evaluated in four large regional US cytology laboratories in a routine fashion. Despite the fact that the participants' age and the prevalence of high risk HPV positivity were similar between the laboratories, there was a 2.6-fold variation in the percentage of cytology specimens that were diagnosed as abnormal at the four laboratories. Same study suggested that in contrast to the large variability

observed between laboratories in the performance of cervical cytology, variability in the performance of HPV-DNA testing for the detection of CIN2+ is lower, where the positive predictive value varied between 10 and 13.2 (Sørbye et al., 2017; Wright Jr et al., 2014).

Additionally, it is important to note that the accuracy of HPV test depends highly on the correct sampling of cells. Currently, precisely determined adequate amount of cells required for DNA analysis has not been established. As a result, due to the varying HPV loads in the collected samples, the sensitivity of the HPV testing differs across various laboratories (Coutlée et al., 2005). In addition, HPV DNA testing is currently more costly. Therefore, countries with lower cytology screening cost prefer adoption of cytology as the primary screening test (de Kok et al., 2012).

The sensitivity analysis in this section considers such variations in the performance of both cytology and HPV-DNA testing. A relevant question in such a setting would be how much of a variation in the sensitivity and specificity of the cytology/HPV-DNA test would cause cytology testing to be the preferable mode of testing. To answer this question, we conducted a sensitivity analysis by varying the relevant assumptions that we used in the baseline model solved above. Specifically, we defined the following two scenarios.

- *Scenario 1:* for scenarios with lower accuracy (than baseline) of HPV DNA testing, we assumed $\text{spec}(H|1) = 0.820$ and $\text{sens}(H|2) = 0.899$.
- *Scenario 2:* for scenarios with higher accuracy (than baseline) of cytology testing, we assumed $\text{sens}(C|3) = 0.803$, $\text{sens}(C|4) = 0.647$, $\text{sens}(C|5) = 0.649$, $\text{sens}(C|6) = 0.704$.

These scenarios are presented in Table 5.2 along with the sensitivity and specificity parameters used in the baseline model. The values in red are the parameters changed in comparison to the baseline model.

Table 5.2 Observation probabilities for Cytology and HPV DNA testing

	Baseline Model				Scenario 1				Scenario 2			
s	$K(C^-\|s)$	$K(C^+\|s)$	$K(H^-\|s)$	$K(H^+\|s)$	$K(C^-\|s)$	$K(C^+\|s)$	$K(H^-\|s)$	$K(H^+\|s)$	$K(C^-\|s)$	$K(C^+\|s)$	$K(H^-\|s)$	$K(H^+\|s)$
1	0.895	0.105	0.835	0.165	0.895	0.105	0.820	0.180	0.895	0.105	0.835	0.165
2	0.875	0.125	0.085	0.915	0.875	0.125	0.101	0.899	0.875	0.125	0.085	0.915
3	0.213	0.787	0.106	0.894	0.213	0.787	0.106	0.894	0.197	0.803	0.106	0.894
4	0.366	0.634	0.127	0.873	0.366	0.634	0.127	0.873	0.353	0.647	0.127	0.873
5	0.364	0.636	0.156	0.844	0.364	0.636	0.156	0.844	0.351	0.649	0.156	0.844
6	0.310	0.690	0.201	0.799	0.310	0.690	0.201	0.799	0.296	0.704	0.201	0.799

Figure 5.7 and Figure 5.8 show the corresponding risk-action thresholds for Scenario 1 and Scenario 2, respectively. Not surprisingly, we see that scenarios 1 and 2 result in cytology being the preferred mode of testing, albeit at a very small frac-

tion of belief states. In particular, our sensitivity analysis shows that specificity of cytology must be at least 0.90 so that cytology is an optimal action at age 21.

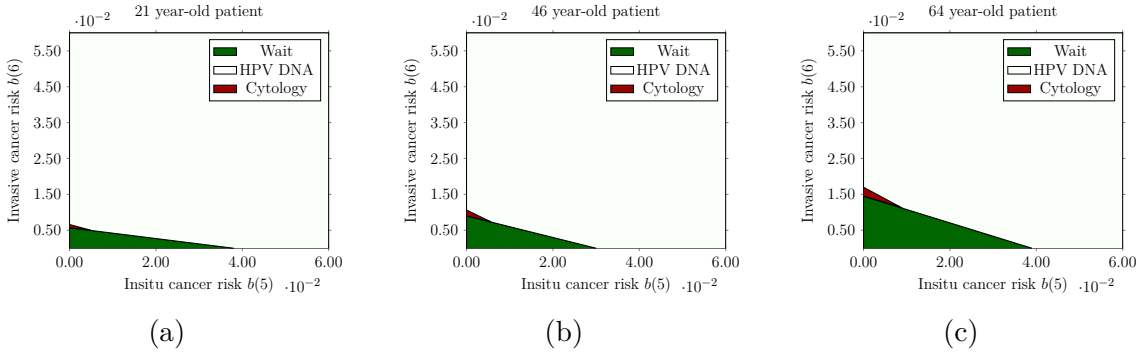


Figure 5.7 Sensitivity analysis: risk-action threshold for scenario 1

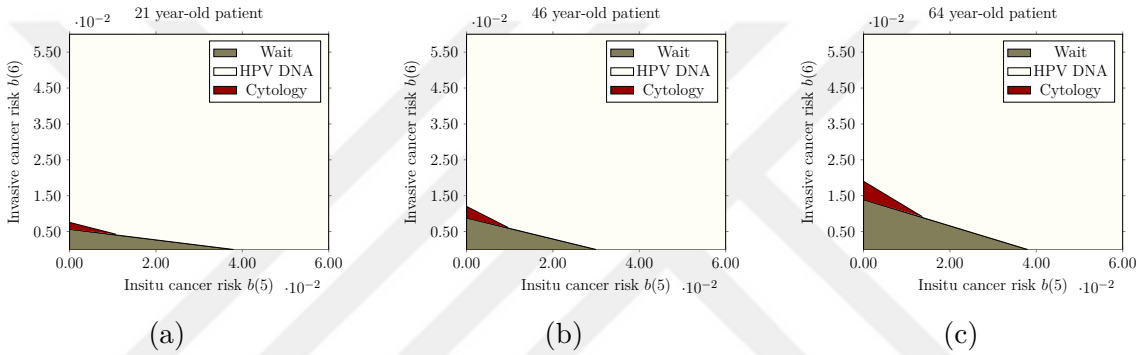


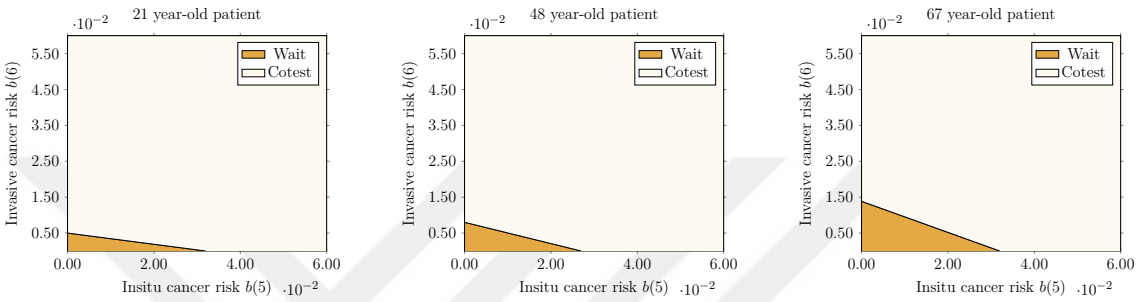
Figure 5.8 Sensitivity analysis: risk-action threshold for scenario 2

How does the optimal screening policy change with the use of cotesting (i.e., testing both with HPV DNA and cytology)?

Cotesting is one of the recommended screening modalities by ASCCP and USPSTF guidelines. With its improved sensitivity and specificity, it allows the patients to undergo screening at longer intervals (Schiffman & Solomon, 2013). According to both guidelines, cotesting is recommended at every five year interval. Both guidelines recommend HPV standalone testing every five years as well. Considering this surprising fact, we aim to understand the extent to which cotesting improves the performance of screening as a result of the increased sensitivity obtained through the use of both tests. In our analysis, we select maximum of sensitivity and specificity from either test as the sensitivity and specificity of cotesting, while the rewarding structure of cotesting remains the same as HPV testing in the base model. The result of this study for three ages namely 21, 48, and 67 is presented in Figure 5.9.

According to our results, compared to the base model, under the cotesting scenario, testing region is slightly expanded meaning that over the newly expanded region, patients with small risks who would have to wait under the base model should now

undergo cotesting. This property of the cotesting is probably the cost of the additional accuracy that comes with conducting cytology and HPV tests simultaneously. It is commonly accepted that a positive result in either arm leads to conducting colposcopy or biopsy (Grimes et al., 2020). Therefore, conducting cotesting for patients without cytologic abnormalities who have positive HPV tests will lead to unnecessary follow ups for many cases in which HPV infection would be likely to clear (Schiffman & Solomon, 2013). Similar to the base model, smaller expansion along the y-axis implies that, the tolerance of the model against invasive risk is lower compared to insitu cancer risk independent of the screening tests considered.



(a) (b) (c)

Figure 5.9 Sensitivity analysis: risk-action threshold for cotesting

5.7 Discussion

The real implementation of a POMDP policy follows certain steps which we describe them in detail in this section. In addition, the outcome of the implementation can be measured using different performance measures, such as expected number of false negatives/positives or expected number of screenings. In this section, we also explain the simulation analysis which we conducted in order to evaluate the performance of our POMDP model and compare it to the other guidelines or practices.

5.7.1 Risk Stratification and Patient's Initial Belief, $b_0(s)$:

For generating a screening policy, it is important to know that whether a patient at the time of visit has an oncogenic HPV infection, precancer lesions or cancer. To

simplify the risk estimation for the patients following routine screening, we assume that the probability of having lesions or cancer at the time of first visit is negligible. Therefore, for such patients, we focus only on predicting the risk of an oncogenic HPV infection. We define *risk of infection* as the probability that a woman at the time of visit has already an oncogenic HPV infection or not. Quantifying such risk depends on various demographic and behavioural variables as well as genetic biomakers (Ley-Chavez & Higle, 2018). Collectively, such variables are called risk factors which influence the probability of contracting an HPV infection. The known demographic risk factors for HPV infection include age, education level, country of birth, race, below poverty index, and marital status also being a smoker or not and use of oral contraceptives. The known sexual behavior risk factors include age at first intercourse, number of lifetime sex partners, number of recent sex partners, and history of chlamydia, genital herpes, and genital warts (Kahn et al., 2007; Moscicki et al., 2001; Sellors et al., 2003).

Several studies have addressed the problem of risk estimation for the cervical cancer patients using the Statistical methods; examples can be found in Castle et al. (2007); Cheung et al. (2017); Demarco et al. (2018) and Landy et al. (2018). However, these studies focus on the cancer risk for the patients with an abnormal test result. In order to calculate infection risk, we use the predictive logistic regression model of Ley-Chavez & Higle (2018). Let X denote the event that the patient is infected. We use $P_t(X;\omega)$ to denote the likelihood function of the infection or simply risk for a given set of characteristics $\omega = \{$age, marital status, below poverty index, and number of lifetime partners$\}$ at time t. Note that the risk factors may vary during the patient's lifetime. We define the following indicator variables:
$I_1 = 1$ if the patient's age is $21-29$ and 0, otherwise.
$I_2 = 1$ if the patient's age is $29-69$ and 0, otherwise.
$I_3 = 1$ if the patient is not married and not living with a partner and 0, otherwise.
$I_4 = 1$ if the patient is below poverty index and 0, otherwise.
$I_5 = 1$ if the patient's lifetime number of partners if above 4 and 0, otherwise.

$P_t(X;\omega)$ can be computed as follows:

$$P_t(X;\omega) = \frac{1}{1+e^{-y}} \tag{5.17}$$

where $y = -1.88 - 1.094I_1 - 1.29I_2 + 0.541I_3 + 0.621I_4 + 0.577I_5$.

Therefore, using Equation 5.17, the initial belief b_0 can be approximated as

$$b_0 = [1 - P_t(X;\omega), P_t(X;\omega), 0, 0, 0, 0]$$

Table 5.3 shows the estimates of the initial belief for patients with different risk factors. Among the cases considered, a patient who is bellow 29, is single and had more than 4 partners has the highest risk.

Table 5.3 Initial belief based on patient's risk factors

Patient	Age	Marital Status	Below Poverty	Partners>4	Initial Belief, b_0
1	21	Single	False	True	[0.865,0.135,0,0,0,0]
2	25	Single	False	False	[0.919,0.081,0,0,0,0]
3	27	Married	False	False	[0.951,0.049,0,0,0,0]
4	43	Single	False	False	[0.933,0.067,0,0,0,0]
5	56	Married	False	False	[0.960,0.040,0,0,0,0]
6	65	Married	True	False	[0.927,0.073,0,0,0,0]

5.7.2 Comparison with other guidelines and practices

We compared the base POMDP model against different set ups using various performance metrics. Table 5.4 summarizes the result of the simulation analysis within simulated populations of 100000 women. The simulation begins with 21-year-old healthy patients. The health state transitions are randomly generated using age dependent transition probabilities from our data. The outcome of each test result is also generated randomly using the corresponding probability distributions of state dependent test sensitivity and specificity. As it is shown in the table, in terms of TQALY, base model achieves the highest value where the improvement over no screening case and ASCCP guideline amounts to 5.9% and 4.29%. Patients under the base policy are expected to undergo 14.7 screenings which is the highest amongst the cases considered. Despite higher frequency of screenings in base model, cotesting model achieves the minimal lifetime cancer risk, which is a direct consequence of increased test accuracy, however, the disadvantage of cotesting is that the number of false cytological results are higher. It can also be observed that cotesting model is more advantageous in reducing the number of false positives, while ASCCP model achieves the least number of false negatives, which can be related to the lower number of screenings compared to base model. The result of the optimal policy in our

Table 5.4 POMDP vs current guideline: simulation of 100000 21-year-old healthy -patients

		No screening	ASCCP guideline	Base model	Cotesting model
Healthy patients	Expected TQALYs	58.198	58.38	60.266	58.991
	Avg. No. of screening	-	9.102	14.7[1]	12.756
	Avg. lifetime risk of cancer	4.38%	0.4%	0.2%	0.1%
	Avg. No. of False Negatives	-	0.139	0.23	0.334
	Avg. No. of False Positives	-	1.22	1.36	0.924

[1] On average 3.88 cytology testing is produced.

base case POMDP is presented in the Appendix B. It is important to note that the policy obtained is different than those recommended by ASCCP guidelines in the sense that POMDP policies are risk based policies whereas the ASCCP policies are frequency based policies. According to our optimal policy, patients start the first screening at age 31, assuming that the patient at age 21 is perfectly healthy. Regarding the screening intervals after age 30, our POMDP policy recommends more aggressive screenings at smaller intervals than ASCCP guidelines.

5.7.3 Conclusion and Future Work

This chapter addressed the problem of identifying optimal screening actions as a function of a patient's age and current risk for cervical cancer using cytology and HPV-DNA testing modalities. For the proposed personalized POMDP model, due to the larder problem size, we used an approximate solution technique namely grid based approximation method to solve the problem. We adopted Gaussian process regression method for inference of unknown values. and showed that the method can perform significantly faster compared to the other existing methods in the literature. Using the published studies in the literature, we calibrated our model to the best available data on age-specific transition probabilities, test accuracy and QALY scores. After solving our model, we conducted sensitivity analysis and compared our model results with the current guidelines. Our results, in accordance with the current practice and recommendations from the guidelines shows that the future of the cervical cancer screening will be more leaned towards the HPV DNA testing methods.

The screening policy can be launched on a mobile application or decision support systems to facilitate the navigation as it has been recently done by ASCCP. The

tables generated by ASCCP for the risk based follow up and management of patients are easily read by the users using a simple app and website. This avoids complexity in interpretations and facilitates patient's involvement into the decision process Chapman & Sonnenberg (2003).

6. SUMMARY AND FUTURE RESEARCH

6.1 Summary of Findings

In this thesis, we developed a stochastic sequential decision making model to produce screening policies for the patients exposed to the risk of cervical cancer. By including patient's characteristics such as age and current risk, our model contributes to the body of literature in the field of personalized medicine and healthcare decision making. Considering that the risk of the disease is high during a certain period of patient's lifetime, within this period, our model aims to inform the patient about whether to screen or to wait until next year.

The sequentially made decisions are subject to two types of uncertainties: the uncertainty about the health state of the patient when she visits a physician, and the uncertainty about true outcome of the test. To model this problem, due to uncertain nature of the health state and the unreliability linked to the test results, we used a discrete time finite horizon POMDP model. The advantage of using this model is that first, the decision maker does not need to record the history of the action (i.e., test or wait) and observation (i.e., test negative or test positive) sequences. Second, the model has the capability to use the disease specific information of the patient such as age or risk factors, as well as the performance metrics of the test used to screen the patient to make better decisions. Better decisions in our model correspond to decisions which maximize the number of healthy-years that the patient is expected to live. More specifically, one year living a relatively poor health state is not equal to one year living in perfectly healthy state. These differences are reflected in the QALY metric. Through our POMDP model, using DP iterations, we pick actions such that the expected total QALY values over the planning horizon is maximized.

Our results in Chapter 4 suggest that early screening and detection is critical to reducing the future cancer risk. As we show by one instance, lifetime cancer risk reduction due to early start to screening outweighs additional screenings required. Our analysis of the impact of the patient's risk profiles on the screening frequency and the five-year average risk of cancer shows that the screening frequencies are not proportionate to the cancer risk. For instance, 20% higher cancer risk does not translate to the same percentage of increase in the screening frequencies. Additionally, we showed that performing more aggressive screenings does not necessarily lead to higher total QALY gains which can be attributed to the fact that excessive testing increases the chance of false positive results, which in turn reduces the life quality of the patient due to unnecessary follow ups and decreases the reliability of the policy. Our analysis of lifetime cancer risk exhibits that cancer risk is reduced with the increase in the number of screenings. Consequently, the POMDP policy has a slightly higher risk, which can be explained by the lower number of screening tests compared to most of the practices considered. It is important to point out that, low frequency implies that the screening interval are longer, and therefore, the cancer risk increases meaning that the policies with longer screening intervals including the POMDP policy lead to higher risks. Another important observation made in risk analysis is that the policies that start their first screening later in time, end up in relatively similar risk when the patient reaches the end of planning horizon. This rather peculiar behavior can be attributed to the fact that a cotesting with negative outcome hugely impacts our belief that the patient is healthy in reality.

In Chapter 5, we showed that screening with HPV-DNA testing outperforms cytology testing. This is an important observation since many recent studies reported that cytology testing will be replaced by the HPV-DNA testing in relatively short time (Bhatla & Singhal, 2020; Fontham et al., 2020; Vale et al., 2021). Our results also suggest that, adding a cytology test as an adjunct to HPV-DNA testing (cotesting) results in similar risk-action threshold policies. This implies that the added value of conducting cotesting is negligible compared to HPV-DNA testing. This finding suggest that the HPV-DNA testing can be safely used as a stand-alone test without compromising from the patient's quality adjusted life expectancy.

It is important to note that, our POMDP model can be easily manipulated to address the sub-populations with health disparities or those linked with economic or social disadvantage. Another advantage of the POMDP model is its flexibility to consider settings in which the prevalence of the disease is different. In case of a different infection rate for such special groups, the POMDP model can be adjusted to include transition probabilities. This enables a more tailored screening plan and therefore, more reliable policies for such sub-populations.

Finally, the policies presented in this research can be framed into policy trees (as shown in Figure B.3 in the appendix) or in more advanced forms such as spreadsheets or applications which are intuitive to understand and hence, facilitate interpretation of the policies for both physicians and patients. By this means, patients have a better understanding of their health and as a consequence, they can be more involved in the process of shared decision-making.

6.2 Limitations

While our model is useful for finding personalized screening decisions, it is important to consider the limitations of our analysis. One limitation of our study is the diversity of the required input data sources. The inputs in our numerical analysis are obtained from various published studies in the literature. In addition, due to the complexity of conducting longitudinal studies, long-term data about the health transitions and activities of an individual are rarely available in the literature. The majority of the studies reporting inputs are cross-sectional studies where the inputs are outcomes of short-term observations. Therefore, it is necessary to carefully analyze the model outputs. To do so, we conduct sensitivity analysis on the parameters of the model including sensitivity and specificity values associated with the screening tests to measure the robustness of the model performance. Another limitation of our study is that we do not provide sensitivity analysis for the transition probabilities.

Furthermore, implementing national screening programs is a multifaceted problem that will require among others resource availability, trained personnel, government initiative to set up the framework, and aid of insurers and stakeholders. In a real setting, some of these players may have discordant objectives. For instance, insurers or third-party payers who intend to regulate the coverage with minimum cost, may be unwilling to support a specific screening plan. Therefore, a crucial point to acknowledge is that while in many developed countries, the cost is not much of a concern for screening decision making, in many less developed countries, cost is still an important factor for such decisions. One of the principles in the guidelines on the principles and practice of screening for disease published by WHO in 1968 states that the total cost of detecting a case should be economically balanced with the medical expenditure as a whole. This principle clearly highlights the significance of considering cost aspect of screening policies that can not be disregarded (Edoh et al., 2018). It is therefore important to assess the model outputs when the cost of

screening is also included as a parameter into the model.

6.3 Directions for Future Research

As a future work, this study can be extended in multiple ways. One is to explore the possible existence of overdiagnosis/undertreatment and its effect on the patient's quality adjusted life expectancy. Due to the variations in the incidence rate of the HPV among sub-populations of a community, it is likely that certain subgroups receive unproportional screening or treatment compared to what is required. It is well established that the incidence rate of the disease among populations with insufficient access to healthcare services are significantly higher than those with enough access to the medical resources. For example, in the United States, Hispanic women have the highest cervical cancer incidence rate, which is considerably higher than the national incidence rate. While this study uses the average incidence rate for the whole population, it is important to acknowledge that subgroups representing the incidence rates above or below the population average will not receive their best possible screenings. Therefore, adjusting the POMDP model to account for such differences leads to creating policies which fit best to the needs of subgroups with their specific risk profiles.

Additionally, according to the literature, there is no consensus on whether treating patients with cervical intraepithelial neoplasia of grade 2 (i.e., $CIN2$) is reasonable or not. A number of studies have maintained that many of the $CIN2$ cases will regress without the need for any treatment. It is therefore possible that treating patients in state $CIN2$ may lead to overdiagnosis, while otherwise, they would have regressed without treatment intervention. Hence, further analysis is required to study the health outcome of one option against another.

As an extension to the current study, we also aim to address the possible effect of the GPR errors on the optimal policy. Making predictions from a Gaussian process regression model with known covariance function requires huge computational power for the problems with too many data points, which is the case in this study. In problems with the larger number of test points requiring Gaussian inference, computing the inverse of the kernel covariance matrix becomes intractable. Many attempts have been made to accelerate the computational process for the fitting and especially for the kernel approximations. However, using kernel approximation

methods increases fitting errors. Depending on the magnitude of the error, the optimal decision may vary from one action to another, which accordingly impacts the future actions. Therefore, we believe that it is required to study the potential influence of fitting errors on the optimal policy, that will contribute to the richness of the current study.

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APPENDIX A

Source of Inputs Used in Chapter Four

The primary source of inputs in our model is the literature of cervical cancer, which is summarized in Table A.1.

Table A.1 Source of model parameters.

Parameter	**Source**
State transitions	JC et al. (2016), Campos et al. (2014)
Sensitivity and specificity of cotesting	JC et al. (2016)
Probability of cancerous death	JC et al. (2016)
Probability of noncancer death	McLay et al. (2010)
Disutility of Biopsy	Velanovich Velanovich (1995), Hanmer et al. (2006)
Survival rates	SEER data Siegel et al. (2019)
Life expectancy	SEER data Siegel et al. (2019)
Quality of life	US life tables Arias et al. (2019)

Based on the method explained in Arias et al. (2019) and the US life tables, we use the following terminating rewards in our calculations; $r_T(1) = 11,\ r_T(2) = 11,\ r_T(3) = 9.75,\ r_T(4) = 10,\ r_T(5) = 10,\ r_T(6) = 0$. The method estimates the age-specific life expectancy based on the current state and mortality rate. According to the table, the life expectancy of a patient at age 69 who is in state 1 is 11 years.

For the *cotesting* action, we use the following scores as the disutility in our model. One day for a negative test result, two weeks for a true positive test result and four weeks for a false-positive test result. We assume the initial disutility of doing biopsy is 2 weeks Ayer et al. (2012), which is increasing over time, meaning that disutility of biopsy for older patients is higher. This is mainly due to the increased risk of adverse side effects of biopsy in older ages. We assume that the disutility associated with biopsy is inversely proportional to the age-specific EQ-5D scores, a utility-based measure of health status widely used in clinical and economic evaluation of health care. These scores reflect varying negative impacts of biopsy on women's health at different ages. We use the estimates of Hammer et al. Hanmer et al. (2006). Table A.2 summarizes the age-specific EQ-5D scores and our estimates of disutility of biopsy.

Similar to the approach proposed by Ayer et al. Ayer & Chen (2018), we use the age-specific post cancer mortality rates from SEER data and apply the method

described in Arias Arias et al. (2019) to calculate these rewards. The mortality rate data in SEER is reported based on the cancer stage of localized, regional and distant. According to our definition of states in our Markov chain, those stages are part of our cancer state 3. Hence, we combine all those stages into one stage. Table A.3 summarizes the data related to the test characteristics used in our model.

Table A.2 Age dependent disutility of biopsy.

Age Group	**20–29**	**30–39**	**40–49**	**50–59**	**60–69**	**70–79**	**80–89**
EQ-5D values	0.913	0.893	0.863	0.837	0.811	0.771	0.724
Disutility of biopsy (weeks)	2	2.04	2.12	2.18	2.25	2.37	2.52

Table A.3 Data related to test characteristics and observation probabilities.

Age	**Sens(CT,2)**	**Sens(CT,3)**	**Specificity CIN3+ Threshold**	$k^{CT}(CT-\|s)$			$k^{CT}(CT+\|s)$		
				States					
				1	**2**	**3**	**1**	**2**	**3**
21–69	0.625	0.991	0.991	0.991	0.375	0.009	0.009	0.625	0.991

APPENDIX B

Uniform Grid Generation

Freudenthal algorithm, (Lovejoy, 1991a): Let S denote the set of states in the Markov chain. Suppose $|S| = n$. Let q be any positive integer representing the desired resolution. Form the set $\mathbb{V}$ of all vectors v such that $v(1) = q$ and $v(1) \geq v(2) \geq \cdots \geq v(n) \geq 0$.

$\mathbb{V}$ can be represented as

$$\mathbb{V} = \left\{ v \in I_+^n | v(1) \geq v(2) \geq \cdots \geq v(n) \right\}$$

It is easy to verify that the cardinality of set $\mathbb{V}$, denoted as $|\mathbb{V}|$ is given by,

$$|\mathbb{V}| = \binom{q+n-1}{n-1}$$

Define the $n \times n$ nonsingular matrix

$$\mathbf{Q} = \begin{bmatrix} 1 & -1 & 0 & & 0 & 0 \\ 0 & 1 & -1 & & 0 & 0 \\ 0 & 0 & 1 & \cdots & 0 & 0 \\ & & & \vdots & & \\ 0 & 0 & 0 & \cdots & -1 & 0 \\ 0 & 0 & 0 & & 1 & -1 \\ 0 & 0 & 0 & & 0 & 1 \end{bmatrix}$$

Then, for any $v \in \mathbb{V}$,

$$\mathbf{Q}v = (v(1) - v(2), v(2) - v(3), \cdots, v(n-1) - v(n), v(n))$$

Let $v' = \mathbf{Q}v$. Form the set $\mathbb{V}'$ of all vectors v',

$$\mathbb{V}' = \left\{ v' \in I_+^q | q = \sum_i^n v'(i) \right\}$$

For any $v' \in \mathbb{V}'$, the grid point $\pi = \frac{1}{q} v'$, where $\pi = (\pi(1), \pi(2), \cdots, \pi(n))$.

The set of all grid points Π formed in this way can be represented as,

$$\Pi = \{\pi = \frac{1}{q}v' | v' \in \mathbb{V}', \sum_{i}^{n} \pi(i) = 1, \pi(i) \geq 0\}$$

Example:

As an illustration, consider the case when the MC has 3 states and the desired resolution $q = 2$. The set $\mathbb{V}$ is composed of the vectors: $v_1 = (2,2,2)^\intercal, v_2 = (2,2,1)^\intercal, v_3 = (2,2,0)^\intercal, v_4 = (2,1,1)^\intercal, v_5 = (2,1,0)^\intercal, v_6 = (2,0,0)^\intercal$.

Multiplying the 3×3 matrix

$$\mathbf{Q} = \begin{bmatrix} 1 & -1 & 0 \\ 0 & 1 & -1 \\ 0 & 0 & 1 \end{bmatrix}$$

with the vectors $v \in \mathbb{V}$, results in set $\mathbb{V}'$ with the vectors: $v'_1 = (0,0,2)^\intercal, v'_2 = (0,1,1)^\intercal, v'_3 = (0,2,0)^\intercal, v'_4 = (1,0,1)^\intercal, v'_5 = (1,1,0)^\intercal, v'_6 = (2,0,0)^\intercal$.

Therefore, the grid set Π has the following grid points obtained by multiplying $1/2$ with the vectors $v' \in \mathbb{V}'$: $\pi_1 = (0,0,1)^\intercal, \pi_2 = (0,0.5,0.5)^\intercal, \pi_3 = (0,1,0)^\intercal, \pi_4 = (0.5,0,0.5)^\intercal, \pi_5 = (0.5,0.5,0)^\intercal, \pi_6 = (1,0,0)^\intercal$. Notice that the set Π has the same cardinality as $\mathbb{V}$.

Figure B.1 illustrates the transformation of the vectors in set $\mathbb{V}$ into grid points in set Π.

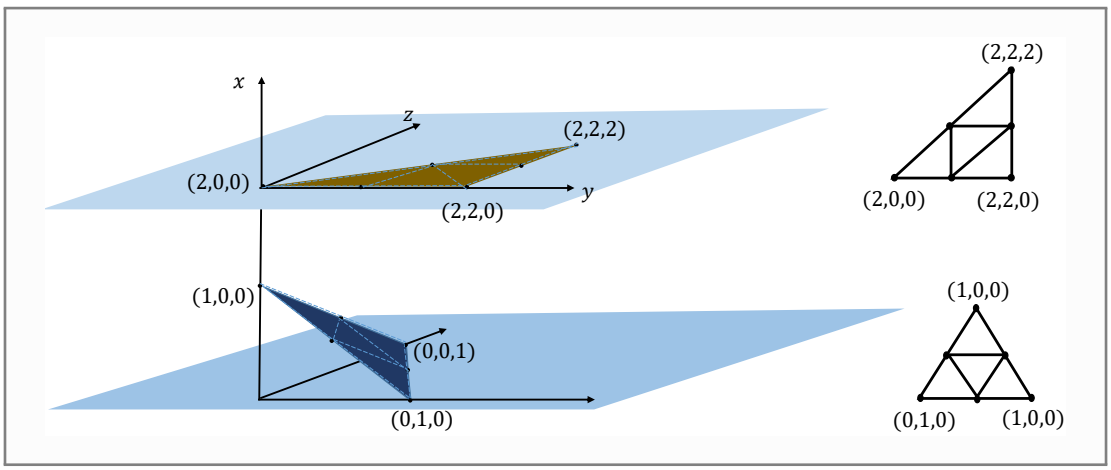

Figure B.1 Uniform grid generation using Freudenthal algorithm.

Probability Tree

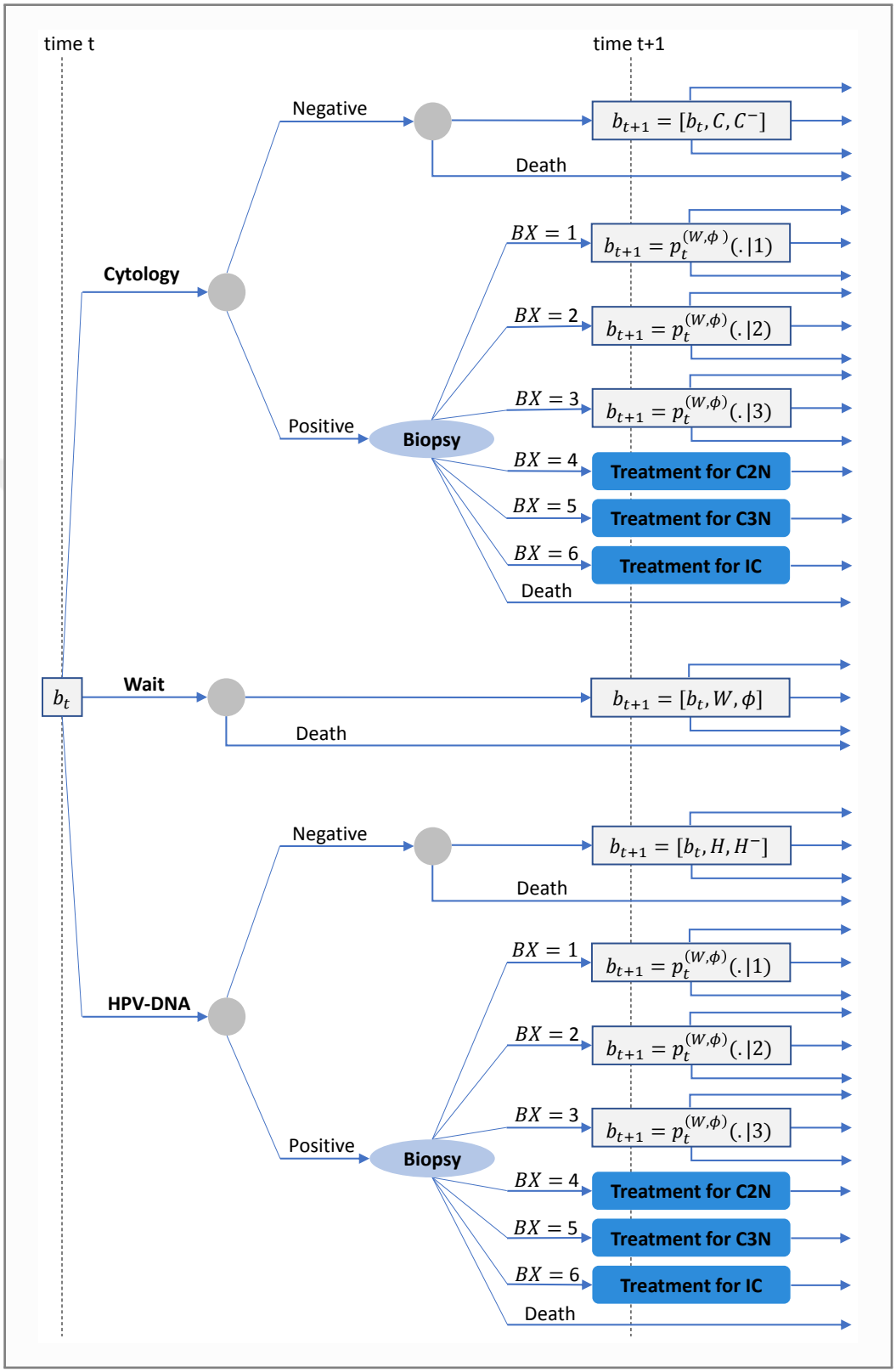

Figure B.2 Probability tree and decision process with actions wait (w), cytology testing (C), and HPV-DNA testing (H).

Source of Inputs Used in Chapter Five

Table B.1 Parameters used in the model and the sources

Parameter	Base Score	Source
Transition probabilities[1]		
Progression from HL to IF		Mandelblatt et al. (2002)
		Bergeron et al. (2008)
20-24 years	0.088	
25-34 years	0.059	
35-49 years	0.050	
50-64 years	0.034	
65+ years	0.0053	
Regression from IF to HL		Kulasingam et al. (2012)
15-24years	0.7	Insinga et al. (2011)
25-29years	0.5	
30-39years	0.25	
40-49years	0.15	
50+ years	0.05	
Progression from IF to C1N		Mandelblatt et al. (2002)
20-24 years	0.088	
25-34 years	0.059	
35-49 years	0.050	
50-64 years	0.034	
65+ years	0.0053	
Regression from C1N to HL		Bergeron et al. (2008)
12-24 years	0.4666	Insinga et al. (2011)
25–29 years	0.3333	
30–39 years	0.2666	
40–49 years	0.18	
50+ years	0.0666	
Regression from C1N to IF		Mandelblatt et al. (2002)
20-24 years	0.088	Insinga et al. (2011)
25-34 years	0.059	
35-54 years	0.050	
50-64 years	0.034	
65+ years	0.0053	
Progression from C1N to C2N		Bergeron et al. (2008)

continued

Parameters used in the model and the sources

Parameter	Base Score	Source
16–34 years	0.0297	
35+ years	0.1485	
Progression from C1N to C3N		Bergeron et al. (2008)
all	0.0301	
Regression from C2N to HL		Kulasingam et al. (2012)
20-24years	0.0213	Insinga et al. (2011)
25-29 years	0.0144	
30+ years	0.015	
Regression from C2N to IF		Myers et al. (2000)
20-24years	0.0870	
25-29 years	0.0939	
30+ years	0.0933	
Regression from C2N to C1N		Kulasingam et al. (2012)
20-24 years	0.0213	
25-29 years	0.0144	
30+ years	0.015	
Progression from C2N to C3N		Bergeron et al. (2008)
16–34 years	0.0389	
35–44 years	0.0797	
45+ years	0.1062	
Regression from C3N to HL		Kulasingam et al. (2012)
20-24years	0.0087	
25-29 years	0.0156	
30+years	0.015	
Regression from C3N to IF		Myers et al. (2000)
20-24years	0.0496	
25-29 years	0.0427	
30+ years	0.0433	
Regression from C3N to C1N		Kulasingam et al. (2012)
20-24 years	0.0087	
25-29 years	0.0156	
30+ years	0.015	
Regression from C3N to C2N		Bergeron et al. (2008)
all	0.0135	
Progression from C3N to IC		Campos et al. (2014)

continued

Parameters used in the model and the sources

Parameter	Base Score	Source
21 – 29 years	0.0464	Mandelblatt et al. (2002)
30 – 34 years	0.0557	Kulasingam et al. (2012)
35 – 39 years	0.0603	Armstrong & Guest (2020)
40 – 44 years	0.1299	
45 – 49 years	0.1392	
50 - 54 years	0.1488	
55 - 59 years	0.1526	
60 - 64 years	0.1614	
65+ years	0.1697	
Persistence [7]	($\star$)	Complementary prob.
Age- and sex-specific average annual all-cause mortality		Mandelblatt et al. (2002)
20–24 years	1.3 per 1000	
25–29 years	1.6	
30–34 years	1.6	
35–39 years	1.9	
40–44 years	2.5	
45–49 years	3.6	
50–54 years	2.5	
55–59 years	7.2	
60–64 years	11.6	
65–69 years	17.5	
70+	69.5	
Age-specific average annual invasive cancer mortality (% per year)[2]		Insinga et al. (2009)
15–29 years	16 per 100	Campos et al. (2014)
30–39 years	16.83	
40–49 years	19.5	
50–59 years	21.57	
60–69 years	25.47	
70+	36.83	
Sensitivity		
Cytology		Insinga et al. (2009)
		Chuck (2010)

continued

Parameters used in the model and the sources

Parameter	Base Score	Source
		de Kok et al. (2012)
		Mandelblatt et al. (2002)
C1N	0.787	Solomon et al. (2001)
C2N	0.634	de Kok et al. (2018)
C3N	0.636	Termrungruanglert et al. (2018)
IC	0.690	Pista et al. (2019)
HPV-DNA testing		de Kok et al. (2018)
IF	0.915	Mandelblatt et al. (2002)
C1N	0.894	Pista et al. (2019)
C2N	0.873	Chuck (2010)
C3N	0.844	Solomon et al. (2001)
IC	0.799	Ley-Chavez (2012)
Specificity		Ley-Chavez (2012)
Cytology		Mandelblatt et al. (2002)
HL	0.895	Chuck (2010)
IF	0.875	de Kok et al. (2018)
HPV-DNA testing		Ley-Chavez (2012)
		Mandelblatt et al. (2002)
		Chuck (2010)
		de Kok et al. (2018)
HL	0.835	
Disutilities		
Health specific disutility $\epsilon_t(s)$		
IF	0.02	
C1N	0.1	Marcellusi (2017)
C2N	0.113	Insinga et al. (2007)
C3N	0.13	Marcellusi (2017)
IC	0.2	
False positive[5]	0.041	
QADL[6]		
Screening		
Cytology	10 days	
HPV DNA	10 days	
True positive[3]	3 days	
Biopsy		Hanmer et al. (2006)

continued

Parameters used in the model and the sources

Parameter	Base Score	Source
20-29 years, EQ-5D = 0.913	2 weeks	
30-39 years, EQ-5D = 0.893	2.04 weeks	
40-49 years, EQ-5D = 0.863	2.12 weeks	
50-59 years, EQ-5D = 0.837	2.18 weeks	
60-69 years, EQ-5D = 0.811	2.25 weeks	
70-79 years, EQ-5D = 0.771	2.37 weeks	

[1] All transition probabilities in the table (except mortalities) are multiplied by (1 - annual probability of death), so that sum of the transition probabilities is 1.

[2] Average of LCC, RCC and DCC which stand for local, regional and distant cervical cancer respectively.

[3] C^- in states {3,4,5,6} or H^- in states {2,3,4,5,6}

[4] C^+ in states {3,4,5,6} or H^+ in states {2,3,4,5,6}

[5] C^+ in state {1,2} or $H+$ in state {1}

[6] Quality adjusted days lost

[7] ($\star$) Persistence = $\Big[(1-(\text{regression} + \text{progression})\Big]$

Graphical Representation of The Optimal Policy

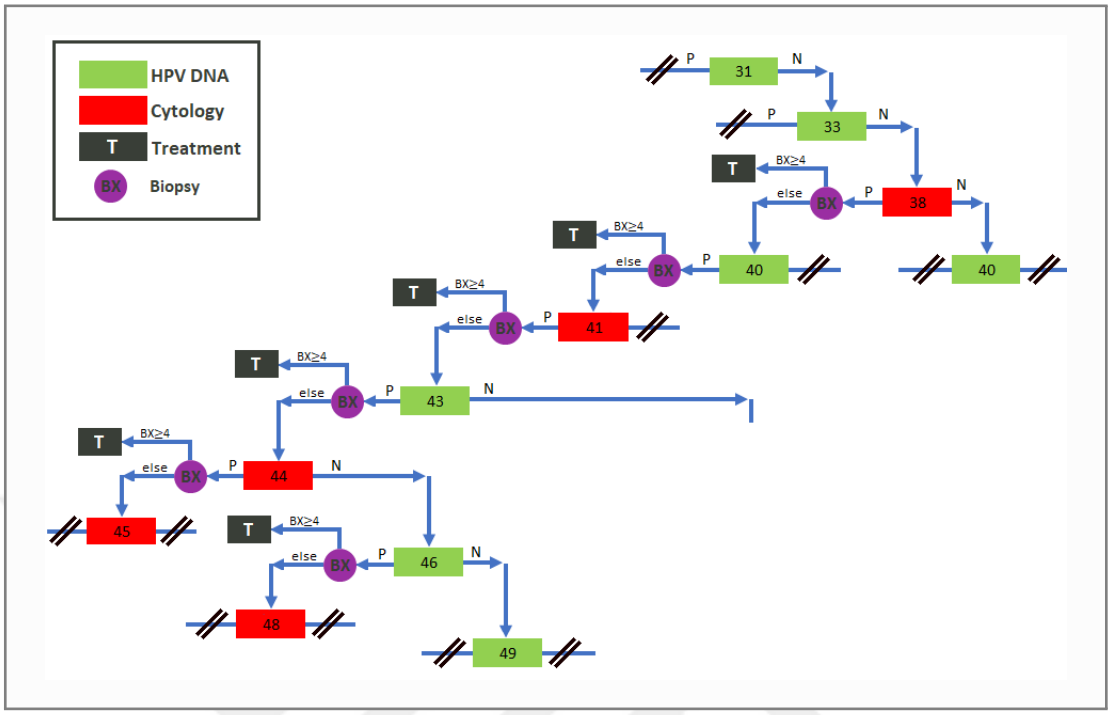

Figure B.3 Policy obtained by POMDP model