Chapter 13
Dynamic Bayesian Network for Cervical Cancer Screening

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Abstract In this chapter we will present the application of dynamic Bayesian networks to cervical cancer screening. The main goal of this project was to create a multivariate model that would incorporate several variables in one framework and predict the risk of developing cervical precancer and invasive cervical cancer. We were interested in identifying those women that are at higher risk of developing cervical cancer and that should be screened differently than indicated in the guidelines.

13.1 Introduction

Cervical cancer is the fourth most deadly cancer in women worldwide.[1] The introduction of the Papanicolaou test (also known as a Pap smear or a Pap test) for cervical cancer screening has dramatically reduced the incidence and mortality of cervical cancer. According to Ries et al. [15], screening for cervical cancer with the Pap test led to a 70 % drop in incidence of cervical cancers between 1950 and 1970 and a 40 % drop between 1970 and 1999 in the USA. Despite this fact, cervical cancer has not been eradicated, even in countries where the programs for cervical cancer screening exist. Prophylaxis has reduced the incidence and mortality of cervical cancer, although there is still need for improving the management of cervical cancer screening, for example, by means of identifying groups of women that are at higher risk of developing cervical cancer and that should be screened differently than indicated in the guidelines.

There are several studies that addressed the management of cervical cancer. Cantor et al. [7] presented several decision-analytic and cost-effectiveness models that could be applied to guide cervical cancer screening, diagnosis, and treatment decisions. One of the decision-analytic models was a Markov model for the natural history of high-risk strain of human papillomavirus (hrHPV) infection and cervical carcinogenesis [14]. The model assesses life-time risk of cervical cancer as well as approximates the

[1] World Health Organization (http://globocan.iarc.fr/), accessed on July, 2014.

A. Hommersom and P.J.F. Lucas (eds.), *Biomedical Knowledge Representation*, LNAI 9521, DOI 10.1007/978-3-319-28007-3_13

age-specific incidence of cervical cancer. A similar model was built for the German population [18]. The model was a Markov model for evaluating a life-time risk and life-time mortality of cervical cancer. Another group of tools for cervical cancer screening are cost-effectiveness models. Most of these cost-effectiveness models refer to investigation of an optimal scenario for cervical cancer screening based on two tests: Pap test and testing for the presence of hrHPV, e.g., [5, 10, 13].

There are many published studies that report risk assessments for cervical cancer, e.g., [8, 11, 12]. All these approaches have a major weakness, i.e., to our knowledge, most of these studies assess the risk based on the current results of patient screening tests and usually do not include any patient history record such as previous results of screening and diagnostic tests, or other clinical findings. In our project we were interested in building a multivariate model that would incorporate several variables in one framework and that would predict the risk of developing cervical precancer and invasive cervical cancer over time. One of the approaches that can address these challenges are dynamic Bayesian networks that were described in the introduction of this part of the book.

13.2 Medical Domain

In this section we will present a few important facts about cervical cancer, its risk factors, symptoms, and causes. We will also discuss screening for cervical cancer and describe screening data that we have used to build a dynamic Bayesian network model for cervical cancer risk assessment.

13.2.1 Cervical Cancer

Cervical cancer is one of the few cancers for which we know the cause. The most important risk factor in the development of cervical cancer is an infection with a high-risk strain of DNA human papillomavirus. In fact, the HPV infection by itself is the most frequent sexually transmitted disease in the world and in most cases this infection does not cause any clinical symptoms. The hrHPV infection is responsible for all cervical cancer cases, however, the relationship between the hrHPV infection and a development of cervical cancer is not deterministic, and only a small percentage of women that are infected with hrHPV will develop a cervical cancer. Furthermore, most cervical cancers are caused by a persistent hrHPV infection. There is still unknown why some women are good hosts to the hrHPV virus and why the infection leads in their case to a development of cervical cancer. Other risks of developing cervical cancer include smoking, oral contraceptives, or chlamydia infection. Cervical cancer rarely causes any clinical symptoms until it reaches a late stage. One of the few late stage cervical cancer symptoms is a vaginal bleeding.

There are two types of cervical cancer [1]. The first type of cervical cancer involves these cases that develop over years and progress to larger precancerous lesions. This

type of cancer is usually preventable by screening. By cervical precancer we mean an abnormal tissue on the cervical surface or in endocervical canal. These lesions can progress to invasive cervical cancer, therefore, if a lesion is detected during screening, it is usually removed by one of the surgical procedures that prevents the lesion from becoming cancerous and from a spread to other body organs. Unfortunately, the screening is less effective for the cancer type 2 and to be detected usually requires more frequent screening. The cancer type 2 includes rapidly progressing cancers, cervical cancers in younger and elderly women, and the cases of glandular cervical cancer that usually arise in endocervical canal.

13.2.2 Screening for Cervical Cancer

An important part of cervical cancer management is its screening. Most of the cervical cancers develop over years, therefore, screening can be effective even if the screening tests are not 100 % sensitive or specific. There are two major cervical cancer screening tests: (1) the Pap test and (2) the hrHPV test. A primary screening test in the USA is the Pap test. The Pap test is based on the analysis of cells sampled from the surface of the cervix, thus, in some countries it is simply known as a cytology test. Abnormal Pap test result suggests the presence of potentially premalignant or malignant changes in the cervix. Therefore, a woman with an abnormal Pap test result usually is directed to a further examination and to a possible preventive treatment. Recommendations for how often a Pap test should be performed vary, depending on a screening program, between once a year and once every five years. The second screening test is the hrHPV testing and it is often used as a complementary to Pap testing. While the Pap test shows possible changes in the cervix, the hrHPV test shows whether there is an infection present. Unfortunately, the hrHPV test result by itself does not tell anything about any previous infections.

In the last few years the HPV vaccine was introduced to the public. Up to date there are two vaccines available and they cover two strains of the hrHPV viruses (HPV16 and HPV18) that can lead to the development of cervical cancer. It is important to notice that the current vaccine does not provide a complete prevention for a cervical cancer. There are around 15 strains of the hrHPV virus that can lead to cervical cancer. Also, the vaccine is not effective if it is used in women infected already with the hrHPV virus [6].

13.2.3 Screening Data

The cervical cancer screening data available to us were collected during 8 years (2005–2012) at Magee-Womens Hospital, University of Pittsburgh Medical Center, USA. The data contained 791,092 Pap test results while 24.7 % of these results were accompanied by hrHPV test results. Our data contained mainly the results of screening tests. Thus, diagnostic tests were recorded only for around 10 % of

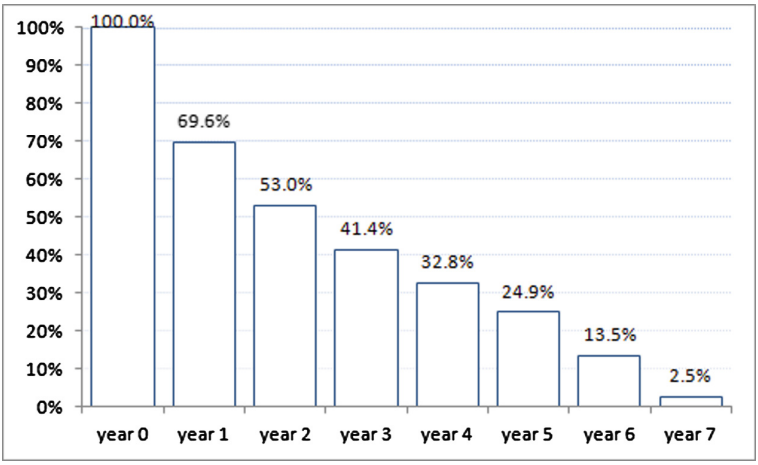

Fig. 13.1 The percentage of follow-up cases (Pap test results) available for each year in the Magee-Womens Hospital population.

screening tests, i.e., around 10 % of Pap test results were followed by a histopathological examination. The data were collected by means of advanced technologies such as liquid-based cytology (a new Pap test with a higher sensitivity than the conventional Pap smear test) and testing for the presence of the hrHPV virus. Furthermore, Pap test interpretations were assisted with a computer-based system that identifies abnormal cells [20]. The data contained also some clinical information such as the history of infections, cancers, or use of contraceptives. Our database registered also HPV vaccine status, although there were only 2,040 patient cases with HPV vaccine status recorded. Furthermore, histopathological examination results in our database were in a free text format. Therefore, these data entries required additional pre-processing, i.e., we had to convert these findings into dictionary entries.

While building any model based on time series data, the follow-up becomes a crucial issue. Our model focuses on assessing the prediction for cervical precancer and cervical invasive cancer, therefore, in our analysis we excluded vaginal Pap test results. The reason for this was that majority of women with vaginal Pap test results are those who had hysterectomy procedure performed in the past and had their cervix removed. We also excluded these patients that have only one Pap test performed and did not have any follow-up data recorded. This led us to the analysis of 575,936 cytology test results belonging to 170,560 patients. Figure 13.1 captures additional information on the follow-up data. *Year 0* in the figure indicates the year when a patient for the first time showed up for a screening test. Of all patients who appear in *year 0*, 69.6 % appeared for follow-up screening in *year 1*, while 53.0 % appeared in *year 2*, etc. Only 2.5 % of all patients appeared in *year 7* (this corresponds to 4,285 patients).

13.3 Pittsburgh Cervical Cancer Screening Model

We have built the Pittsburgh Cervical Cancer Screening Model (PCCSM) [2, 4]. The main goal of this project was to create a model that would incorporate several variables in one framework and predict the risk of cervical precancer and invasive cervical cancer. We were interested in identifying those women that are at higher risk of developing cervical cancer and that need more frequent screening or a reference to a diagnostic procedure such as a colposcopy. The PCCSM model is a dynamic Bayesian network, its structure was built based on textbooks and the expert knowledge[2] and then parameterized by means of the cervical cancer screening data collected at Magee-Womens Hospital.

13.3.1 Graphical Structure

The current version of the PCCSM model consists of 15 nodes that belong to four groups: (1) screening tests: Pap test and hrHPV test; (2) diagnostic or therapeutic procedures such as biopsy, cone biopsy, leep procedure, endocervical curettage, or hysterectomy; (3) patient history findings: menstrual history, cancer history, a use of contraception, HPV vaccine status; and (4) demographic variables: age and race. These variables has been chosen by the expert, although a procedure of selecting the model's variables was mainly driven by a set of medical finding recorded in the Magee-Womens Hospital electronic record system.

All variables were categorical, thus, we represented them in the model as the nodes with discrete values. The variable *Age* was discretized into three intervals: *below 30*, *between 30 and 50*, and *50 and up*. This discretization was suggested by our expert and it corresponds to three different cervical cancer risk groups. While modeling the node representing the Pap test we have distinguished 9 states. Our data on Pap test interpretations follow the Bethesda classification[3] and, in fact, the number of possible interpretations for the Pap test is even higher than modelled in the PCCSM. However, we grouped and merged some of the interpretations. For example, *Suspicious Malignant Cells*, *Positive Malignant Cells*, *Squamous Cell Carcinoma*, and *Adenocarcinoma* were merged into one state *SUSP/POS Malignant Cells*. This merge was performed mainly because of the lack of sufficient data for these categories. Similarly, we merged several interpretations of histopathologically verified diagnoses of cervix, for example, different types of cervical cancers: *Squamous Carcinoma*, *Adenocarcinoma*, or *Adenosquamous Carcinoma* were represented as one state and named as *Cervical Cancer*.

[2]The second author of this article is the expert of the PCCSM model.

[3]The Bethesda classification is a system for reporting Pap test interpretations. It was developed during the American Society for Colposcopy and Cervical Pathology Consensus Conference that took place in Bethesda, MD, USA [19]. The main goal of this meeting was to establish a standardized terminology in cytology diagnostic reports.

Table 13.1 Selected nodes of the PCCSM model along with their states

Node	States
Pap test	*Negative*, *ASCUS*, *LSIL*, *AGC*, *ASC-H*, *HSIL*, *SUSP/POS Malignant Cells*, *No Primary Interpretation*, *NA*
hrHPV test	*Negative*, *Positive*, *NA*
Cervix	*Benign*, *CIN1*, *CIN2*, *CIN3/AIS*, *Cervical Cancer*, *Metastatic Cancer in Cervix*, *NA*
HPV vaccine status	*Complete*, *Incomplete*, *NA*

Table 13.1 presents a list of possible results for two screening tests (Pap and hrHPV), a cervix status represented by the node *Cervix*, and a clinical finding describing HPV vaccine status. For example, the Pap test is described by 9 possible states: one state indicating a negative result, 6 states representing abnormal results, one state modeling the unsatisfactory result (*No Primary Interpretation*), and one state describing the result that is not available (*NA*).

A dynamic Bayesian network approach allows us to model a medical knowledge in the framework of a directed graph. While modelling the knowledge of cervical cancer screening we distinguished two types of relationships:

$$riskfactor \rightarrow disease \rightarrow screeningtest$$
$$riskfactor \rightarrow disease \rightarrow diagnostictest$$

$$cervix_t \rightarrow cervix_{t+1}$$
$$cervix_t \rightarrow cervix_{t+2}$$

While the first type of a relationship captures a static knowledge, the second type of a relationship shows a temporal knowledge. Figure 13.2 presents the graphical structure of the current version of the PCCSM model. The graphical structure of the model consists of two types of arcs: (1) regular arcs that model a static knowledge by means of probabilistic relationships between the variables in the same time step and (2) temporal arcs that model the relationships between the variables in different time steps. For example, the relationships between *Age*, *Cervix*, and *Pap test* capture a static knowledge and take place in the same time step. While a temporal relationship is represented by an arc with a label. For example, a label *2* in the node *Cervix* indicates a delay of an influence that takes two time steps.

Nine nodes out of 15 are temporal variables, i.e., they are repeated for each time step. In the GeNIe interface,[4] such nodes are placed within so called *Temporal Plate* (see Fig. 13.2). Five nodes were modeled as initial conditions and they represent patient clinical history record such as *History of contraception*, *History of Cancer*,

[4]The introduction to this part of the book contains a brief description of dynamic Bayesian networks with the examples presented in the GeNIe software.

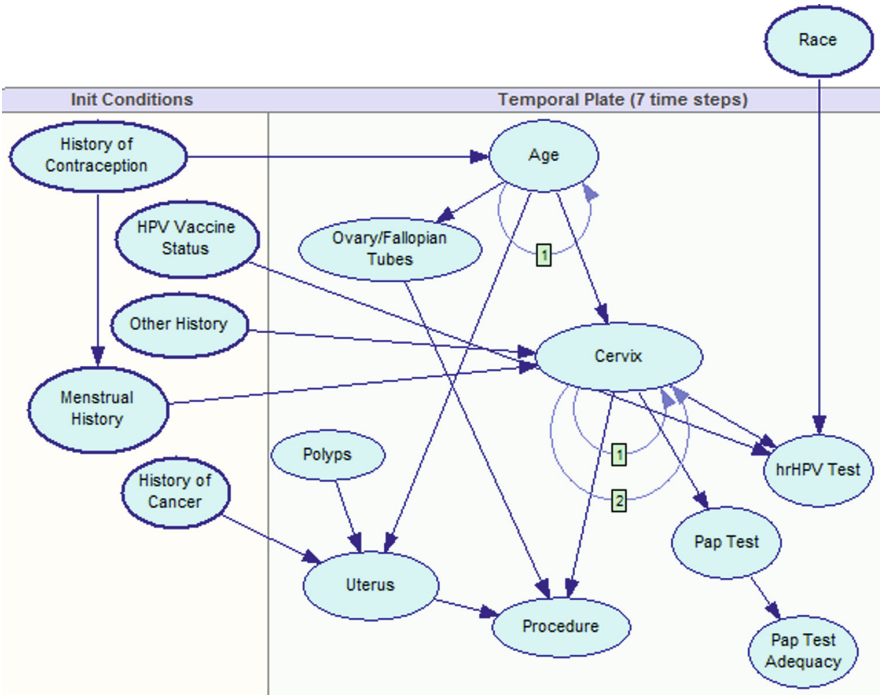

Fig. 13.2 Pittsburgh Cervical Cancer Screening Model

Menstrual History, the HPV *Vaccine Status*, and *Other History* (see the panel *Init Conditions* in Fig. 13.2). Another variable that does not change over time is *Race*. These static nodes are indicated in Fig. 13.2 by a bold border.

Most of the relationships modeled in the PCCSM model are causal, however, we also learned some of the relations from the data. For example, the relationship between *History of contraception* and *Age* was learned from the data. The average number of parents per node is 1.1, while the average number of states per node is 5.9. The node with the highest number of states is the one representing the *Pap test* and it consists of 9 states.

Figure 13.3 shows a version of the PCCSM model that is unfold for three time steps. To demonstrate the relationships between the variables in different time steps, we limited the model to four temporal nodes and five static nodes.

13.3.2 Time Granularity

The time step that we had chosen in the PCCSM model was one year. This is a consequence of cervical cancer screening guidelines in USA, recommending a woman

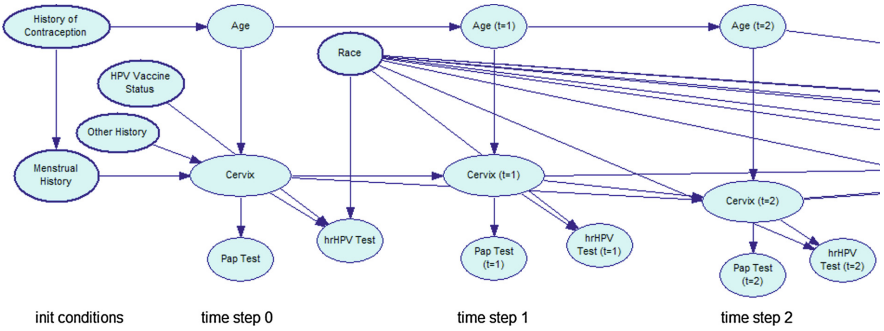

Fig. 13.3 Unfold version of the PCCSM model; a simplified version limited to 9 out of 15 nodes

to come for her Pap test examination once a year. In fact, these recommendations were recently changed to less frequent screening [17].

For each patient in the data set we defined the initial time as $t = 0$. Initial time indicates the year when the woman got registered in our database, i.e., usually when she showed up for the Pap test for the first time. While preparing the screening data for learning the parameters of the model, for each woman and for a particular model variable, we have chosen only one result per time step. For example, if a woman had more than one Pap test performed during a period of one year, we have chosen the most abnormal interpretation of this test.

13.3.3 Numerical Parameters

One of the feature of real world data is their incompleteness. Especially, in medical data collected over time we can expect missing entries. This is also a characteristic of our data. Figure 13.1 confirms that we do not have a complete follow-up data. In the PCCSM, we treated a missing value as an additional state and we modeled it explicitly as a possible state of a node. For example, if there was no Pap test result, we have modelled it as the state *not available* (*NA*). Please, note that each of the three nodes listed in Table 13.1 has the state *NA*. Similarly, if there was no diagnostic test result associated with a particular screening test result, we associated it with the value *not available*. Our data are screening data and 82 % of all screening test results are negative, i.e., they usually correspond to healthy women.

Another characteristic of our data is that they do not contain many cases of invasive cervical cancer. The reason for this is that if a woman is screened frequently enough, usually she will not develop an invasive cervical cancer due to treatment procedures that would be conducted if the presence of any precancerous cells will be detected on screening test results. Around 50 % of all women with cervical cancer in our database were not screened and did not have any previously recorded data.

We have learned the numerical parameters of the PCCSM model from the cervical cancer screening data collected at Magee-Womens Hospital. To learn the numerical parameters of the model we have applied the EM algorithm implemented in the SMILE library [9]. The resulting model has 2,414 independent numerical parameters.

13.4 Application of PCCSM

In this section we will present two applications of the PCCSM model: (1) the PCCSM as cervical cancer risk assessment tool and (2) the PCCSM as personalized aid for follow-up decision making.

13.4.1 Cervical Precancer and Invasive Cervical Cancer Predictions

The main outcome measure of the PCCSM model is the risk of developing cervical precancer or invasive cervical cancer. This risk is expressed by a posteriori probability calculated by the PCCSM model. The important advantage of dynamic Bayesian network approach is that it allows for looking at risk predictions for cervical precancer and invasive cervical cancer from different perspectives. Figure 13.4 presents the impact of patient history record on the cervical cancer risk assessments.

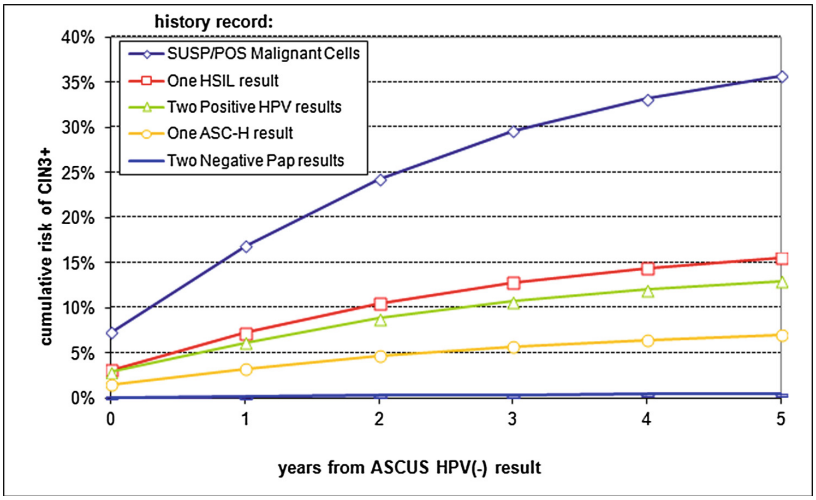

Fig. 13.4 The PCCSM risk assessments for cervical precancer and invasive cervical cancer (*CIN3+*) given history record

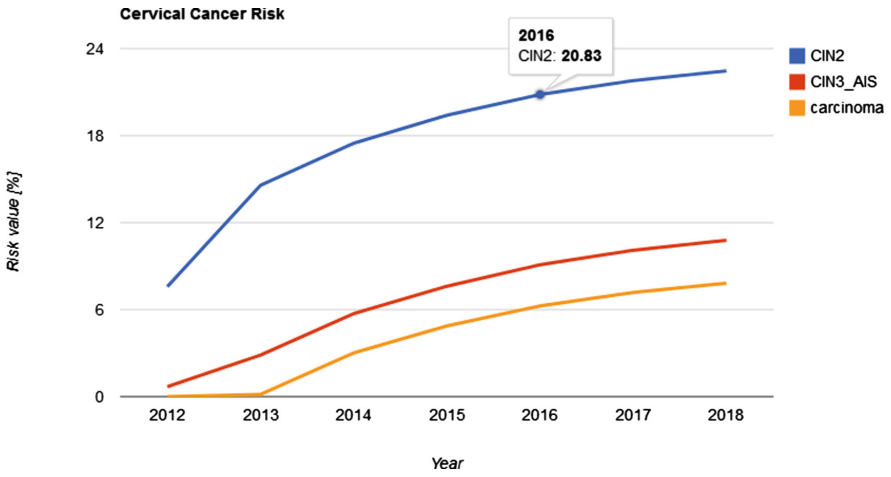

Fig. 13.5 A web-based interface of the PCCSM model: Risk assessments for cervical precancer (CIN2, CIN3/AIS) and invasive cervical cancer (carcinoma) over time

The figure captures quantitative risk predictions of precancer and invasive cervical cancer *(CIN3+)*[5] over the time period of five years for patients that in *year 0* had an abnormal Pap test result *(ASCUS)*[6] and a negative hrHPV test result. The five curves represent five groups of women with different history record. The PCCSM model allowed for identifying those risk categories that are crucial for follow-up planning, e.g., patients that are at higher risk of developing cervical cancer should be screened more often than patients that are at lower risk. For example, women with two negative Pap test results in the past (represented by a bottom curve in Fig. 13.4) are in a different risk category than women that had suspicious or positive malignant cells in the past (represented by a top curve in Fig. 13.4) even if they have the same screening test results in *year 0* (i.e., the *ASCUS* result for a Pap test and negative hrHPV test result).

13.4.2 Personalized Aid in Clinical Management and Follow-Up Decision Making

The PCCSM model allows for individualized management of patients and computes patient-specific risk based on the patients characteristics such as history data, demographics, and current screening test results. We have built a prototype web-based

[5] *CIN3+* stands for Cervical Intraepithelial Neoplasia grade 3 and indicates a severe dysplasia and worse including invasive cervical cancer.

[6] *ASCUS* stands for Atypical Squamous Cells of Undetermined Significance and indicates mild cellular abnormality in the cervix.

interface that helps to interact with the model [16]. This interface allows for entering patient data and saving them in patient data repository. The user of this tool can upload patient data and assess the risk prediction for cervical precancer and invasive cervical cancer. Figure 13.5 depicts one of the screen shots of this interface. The figure presents cumulative values of risk of developing cervical precancers (*CIN2*[7], *CIN3/AIS*) and invasive cervical cancer (*carcinoma*) over time. These results were calculated for a specific patient: a woman that at the beginning of the follow-up was 29, there were two years of follow-up data available: double ASCUS results for Pap test and double positive results for the hrHPV test. The PCCSM model shows that this woman will have a 20 % risk of developing *CIN2* within four years.

13.5 Conclusions

In this chapter we have introduced the PCCSM model for cervical cancer screening. The PCCSM model allows for calculating the predictions of cervical precancer and invasive cervical cancer. It incorporates various variables in one framework and allows for looking at these predictions from different perspectives, including the perspective of patient history record. The model is capable of identifying groups of patients that are at higher risk of developing a disease. These quantitative predictions can be helpful in establishing the optimal timing of a follow-up screening.

We plan to use the PCCSM model in a routine medical practice as a quality control tool in high risk case selection for rescreening [3]. This can have a noticeable effect on the quality of medical care in our laboratory. Under the Clinical Laboratory Improvement Amendments of 1988 (CLIA 88), laboratories in USA are required to rescreen negative Pap test results. The challenge here is how to select negative Pap test slides for targeted high risk quality control rescreening. The process of high risk case selection at Magee-Womens Hospital is currently based on a simple identification of cases with an abnormal prior history, e.g., if a woman had a positive hrHPV test result or abnormal tissue result in the past, she is considered to be a high risk case and is selected for rescreening. We believe, that this process could be further improved by the PCCSM model.

Acknowledgments. We would like to thank Karen Lassige for her help in retrieving the data from the hospital database. We also acknowledge Magee-Womens Hospital cytology manager Nancy Mauser for her assistance in reviewing individual cytology reports and the lead cytotechnologist Jonee Matsko for her assistance in identifying cytology-histology correlates. Our study was approved by the Institutional Review Board, Magee-Womens Hospital, University of Pittsburgh (IRB#: PRO09070454).

Bayesian network models were created and tested using SMILE, an inference engine, and GeNIe, a development environment for reasoning in graphical probabilistic models, both developed at the Decision Systems Laboratory and available at https://dslpitt.org/genie/.

[7] *CIN2* stands for Cervical Intraepithelial Neoplasia grade 2 and indicates moderate dysplasia that usually regresses.

References

1. Austin, R.M., Zhao, C.: Type 1 and type 2 cervical carcinomas: some cervical cancers are more difficult to prevent with screening. Cytopathology **23**(1), 6–12 (2012)
2. Marshall Austin, R., Oniśko, A., Druzdzel, M.J.: The pittsburgh cervical cancer screening model. a risk assessment tool. Arch. Pathol. Lab. Med. **134**, 744–750 (2010)
3. Austin, R.M., Oniśko, A., Druzdzel, M.J.: Bayesian network model analysis as a quality control and risk assessment tool in cervical cancer screening. J. Lower Genital Tract Dis. **12**(2), 153–179 (2008)
4. Austin, R.M., Oniśko, A., Druzdzel, M.J.: Patient history dependent risk assessments for cervical pre-cancer and invasive cancer using the pittsburgh cervical cancer screening model. J. Am. Soc. Cytopathol. **1**(1), S3–S4 (2012)
5. Bidus, M.A., et al.: Cost-effectiveness analysis of liquid-based cytology and human papillomavirus testing in cervical cancer screening. Obstetricians Gynecologists **107**(5), 997–1005 (2006)
6. Brotherton, J.M., et al.: Early effect of the HPV vaccination programme on cervical abnormalities in Victoria, Australia: an ecological study. Lancet **377**, 2085–2092 (2011)
7. Cantor, S.B., et al.: Decision science and cervical cancer. Cancer **98**(9), 2003–2008 (2003)
8. Castle, P.E., et al.: Risk assessmenmt to guide the prevention of cervical cancer. Am. J. Obstet. Gynecol. **197**, 356.e1–356.e6 (2007)
9. Decision Systems Laboratory, University of Pittsburgh, GeNIe and SMILE Software. https://dslpitt.org/genie/
10. Goldie, S.J., Kim, J.J., Wright, T.C.: Cost-Effectiveness of Human Papillomavirus DNA testing for Cervical Cancer Screening in women aged 30 years or more. Obstetricians Gynecologists **103**(4), 619–631 (2004)
11. Katki, H.A.: Cervical cancer risk for women undergoing concurrent testing for human papillomavirus and cervical cytology: a population-based study in routine clinical practice. Lancet Oncol. **12**(7), 663–672 (2011)
12. Khan, M.J., et al.: The Elevated 10-Year Risk of Cervical Precancer and Cancer in women with Human Papillomavirus (HPV) Type 16 or 18 and the Possible Utility of Type-Specific HPV Testing in Clinical Practice. J. Natl. Cancer Inst. **97**(14), 1072–1079 (2005)
13. Kim, J.J., Wright, T.C., Goldie, S.J.: Cost-effectiveness of alternative triage strategies for atypical squamous cells of undetermined significance. JAMA **287**, 2382–2390 (2002)
14. Myers, E.R., et al.: Mathematical model for the natural history of Human Papillomavirus infection and Cervical Carcinogenesis. Am. J. Epidemiol. **151**, 1158–1171 (2000)
15. Ries, L.A., Eisner, M.P., Kosary, C.: SEER Cancer Statistics Review, 1973–1999. National Cancer Institute, Bethesda (2002)
16. Sadkowski. J.A.: Computer-based system for cervical cancer risk assessment (in Polish). MA thesis. Bialystok, Poland, Faculty of Computer Science, Bialystok University of Technology, October 2011
17. Saslow, D., et al.: American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. CA Cancer J. Clin. **62**(3), 147–172 (2012)
18. Siebert, U., et al.: The German Cervical Cancer Screening Model: development and validation of a decision-analytic model for cervical cancer screening in Germany. Eur. J. Public Health **16**(2), 185–192 (2006)
19. Solomon, D., et al.: The 2001 Bethesda system: terminology for reporting results of cervical cytology. JAMA **287**(16), 2114–2119 (2002)
20. ThinPrep imaging system product insert. Marlborough, MA: Cytyc Corporation. http://www.thinprep.com/pdfs/thinprep_package_insert_imaging.pdf. Accessed 31 October 2013