The application of Bayesian network modelling for the early diagnosis and prediction of the medical condition Endometriosis

Rachel Collins
190706089
Professor Norman Fenton
MSc Computing and Information Systems

***Abstract*— Bayesian networks (BNs) are graphical models that can combine knowledge with data to represent the causal probabilistic relationships between a set of variables and provide insight into the processes underlying disease progression, closely resembling clinical decision-making. The aim of this study is to develop a BN causal model for the early diagnosis and prediction of endometriosis.**

Keywords— Endometriosis; Bayesian network causal model; diagnostic model; risk factors; medical idioms

I. Introduction

Endometriosis is relatively common and potentially debilitating gynaecological disorder that affects 6-10% of women of reproductive age (Rogers, et al., 2013). It is present in about a quarter of women who are infertile (Chen, et al., 2019). Endometriosis is a long-term condition defined as the presence of endometrial-like tissue outside the uterus and it is associated with a chronic and inflammatory reaction. Symptoms of endometriosis can include dysmenorrhoea (painful periods), dyspareunia (pain experienced during intercourse), non-cyclical pelvic pain and subfertility (Farquhar, 2000). The standard diagnosis is based on visualisation and histological examination of the lesions. The wide variety of symptoms of endometriosis often leads to wandering and medical diagnostic delay; it can take an average of four to eleven years for diagnosis with severity of symptoms and probability of diagnosis increasing with age (Akter, et al., 2019; Bérubé, et al., 1998). The cause for delay of diagnosis and treatment may be due to invasive laparoscopic procedures alongside histologic confirmation being the gold standard diagnostic confirmation of the condition and physicians treating the symptoms rather than the condition. It is estimated that affected individuals lose 10.8 hours of work weekly due to this condition and report a decreased quality of life (Rogers, et al., 2013). A better understanding and approach to diagnose this condition would allow better management of these patients.

This paper intends to assess risk and prediction of endometriosis in a Bayesian causal model approach, by building a Bayesian Network (BN) and structuring it with use of medical idioms elicited from expert knowledge and data available, with the aim of improving upon the current statistical models and aid decision-making for professionals. It will primarily function as a diagnostic model for the prediction of suspected endometriosis and probability of an individual being formally diagnosed. It will also offer insight into the impact endometriosis has on the quality of life of the individual.

II. Literature Review

A. Endometriosis and Machine Learning

The use of both supervised and unsupervised machine learning has been applied to biology studies and the prediction of endometriosis (Tarca, et al., 2007; Wölfler, et al., 2005). Biological patterns have been analysed by various machine learning tools; decision tree, partial least squares discriminant analysis (PLSDA), support vector machine, and random forest to classify endometriosis (Akter, et al., 2019; Lu, et al., 2015). Machine learning techniques have been utilised to explore associations between persistent organic pollutants and deep endometriosis (Matta, et al., 2020). However, this author found limited studies focusing on the signs and symptoms, most often observed in a primary care setting, associated with endometriosis as predictors for diagnosis. Furthermore, this author found Bayesian Networks had been applied as cancer prediction tools but were not utilised for the prediction on Endometriosis as a condition (Reijnen, et al., 2020; Roy, et al., 2015).

Literature was reviewed which claimed to be using Bayesian approaches but were not centred on the concept of casual Bayesian Network models. Correlated modelling framework to estimate ROC curves and the associated area under the curves was applied to the diagnostic performance of physicians in their diagnosing of endometriosis which suggested that clinical information may play a more important role in physicians' diagnostic performance than their experiences (Chen, et al., 2019). Endometriosis phenotypes were learned from patient-generated data through unsupervised learning (Urteaga, et al., 2020). Bayesian network meta-analyses were used to assess the role traditional Chinese medicine has in the treatment of endometriosis (Dong, et al., 2019).

The use of big data and machine learning algorithms, in which there is the belief of the ability to discover all properties and relationships for prediction and decision-making, may not be appropriate in the analysis of healthcare due to the limited nature of relevant data, the inconsistency of clinician reporting and recording of symptoms in clinic and hospital settings (Fenton & Neil, 2019). Therefore, the use of BN causal models, which can account for unobserved variables, would be a valuable method to use for the prediction of endometriosis in a clinical setting.

B. Bayesian Approach to Endometriosis

It must be noted that the literature reviewed involved case control studies that compare incidence of diagnosis, or risk of endometriosis, and control groups. This data is used to calculate odds ratio and confidence interval. Odds ratio is a measure that describes the odds of a patient developing the condition provided a certain criterion is met. It measures the strength of association between two events:

$$Odds\ Ratio\ (OR) = \frac{D_E/H_E}{D_N/H_N} \qquad (1)$$

where D_E represents patients who have the condition (endometriosis) and have had a certain sign/symptom, H_E is number of patients who are healthy but have the sign/symptom, D_N the patients who do not have the sign/symptom and do not have the condition, and H_N the patients who are healthy and do not have the sign/symptom. Given an odds ratio, a conditional probability table $B|A$ can be populated, where A can symbolise the sign/symptom and B the disease, as shown in Table 1.

Table 1. Odds ratio probability table

	$B = 1$	$B = 0$
$A = 1$	p_{11}	p_{10}
$A = 0$	p_{01}	p_{00}

The treatment and use of odds ratios can massively exaggerate the probability of the disease. It is not just the existence of potential confounding variables that can compromise the simple ‘odds ratio’ measure of risk factors. These odds ratios do not account for multiple cause and effects or the dependencies of interacting variables. It assumes that the exposure of the variable is the sole explanation for the condition. Yet, in randomised controlled trials (RCTs), often utilised in medical studies, it is impossible to control for all confounding variables. Odds ratio cannot work for the prediction of endometriosis as the aetiology of the condition is unknown (Farquhar, 2000). By using a Bayesian network for analysis, multiple observations and interventions can be applied and account for potential unobserved data.

C. Risk factors associated with Endometriosis

The aetiology of endometriosis has been studied and theorised since 1927 when John A Sampson presented his hypothesis, to the American Gynaecological Society, that the cause was due to retrograde menstruation; the uterine contents reaching the ovaries and the surrounding tissue via a retrograde flow of the menstrual contents through the fallopian tubes (Dastur & Tank, 2010). This theory is now viewed as a sign of endometriosis rather than the cause, as not all women who experience retrograde menstruation develop the condition (Bérubé, et al., 1998). Accordingly, there is general consensus among experts that the cause of endometriosis is still unknown (Bérubé, et al., 1998; Farquhar, 2000; Harris, et al., 2018). As a result, the study of risk factors associated with endometriosis is the focus of many, oftentimes contradictory, studies.

Reports show that there is an increased frequency of the disease among women of higher socio-economic status. Whilst socio-economic status can be viewed an indicator of the lifestyle habits that are associated with an increased risk of endometriosis, such as reproductive pattern, body mass, physical activity and diet (Parazzini, et al., 2017), there is argument that this status, which is closely linked to race and ethnicity, may impact the diagnosis of endometriosis through a patient’s ability to access healthcare (Bougie, et al., 2019).

Diet has often been studied as a potential area of risk for the contraction of endometriosis. There are conflicting studies surrounding the association of consumption of red meat, ham and trans fats with the risk of developing endometriosis (Parazzini, et al., 2013). A 2004 Italian study by Parazzini et al. (2004) reports the risk of endometriosis is significantly higher (OR 2.0, 95% CI 1.4–2.8, Ptrend = 0.0004) for women reporting high meat and ham consumption compared with women reporting a lower intake (OR 1.8, 95% CI 1.3–2.5, Ptrend = 0.001). However, this result was not replicated in a 2011 Trabert et al. (2011) study that summarised that there was no association between endometriosis risk and number of servings per week of red meat. The contradiction indicates further studies are required. Currently, there is no concrete evidence of associations between smoking and caffeine intake and the risk of developing endometriosis (Parazzini, et al., 2017). There is evidence of an association between alcohol consumption and endometriosis risk, but further studies are required to clarify whether alcohol is exacerbating an existing disease or is related to the severity of the disease (Parazzini, et al., 2013).

There is an association between exposure to violence during childhood and adolescence and endometriosis risk, a cohort study using data collected from 60,595 premenopausal women from 1989 to 2013 revealing a 79% increased risk of laparoscopically-confirmed endometriosis for women reporting severe-chronic abuse of multiple type (Harris, et al., 2018).

There is increasing evidence that patients with endometriosis have a higher risk of developing other chronic diseases. Endometriosis patients have a higher risk of ovarian and breast cancers, cutaneous melanoma, asthma, some autoimmune, cardiovascular, and atopic diseases, and a decreased risk of cervical cancer (Kvaskoff, et al., 2014). These findings necessitate the need for improved screening practices and better care and management for diagnosed patients. Women with endometriosis have an increased risk of Irritable Bowel Syndrome (IBS). There is an association between endometriosis and rheumatoid arthritis and psoriasis which supports the idea that endometriosis includes immunological factors (Parazzini, et al., 2017). Case studies have shown a greater prevalence of endometriosis among women with asthma, allergies, and allergic rhinitis (Kvaskoff, et al., 2014).

Studies do show that predictors of a diagnosis of endometriosis variables reflect the patterns that clinicians observe in a GP setting. A study by Burton et al. (2017) used primary care data to identify patterns of symptoms over time that appeared to be useful pointers to the diagnosis of endometriosis. This study argues that symptoms, such as distinct episodes of gynaecological pain and combinations of gynaecological pain on one occasion with menstrual symptoms or lower gastrointestinal symptoms on another, provide patterns that can be incorporated into diagnostic support systems (Burton, et al., 2017). The presence of endometriosis manifests into specific features of pain, menstrual bleeding, ovarian symptoms including cysts, and

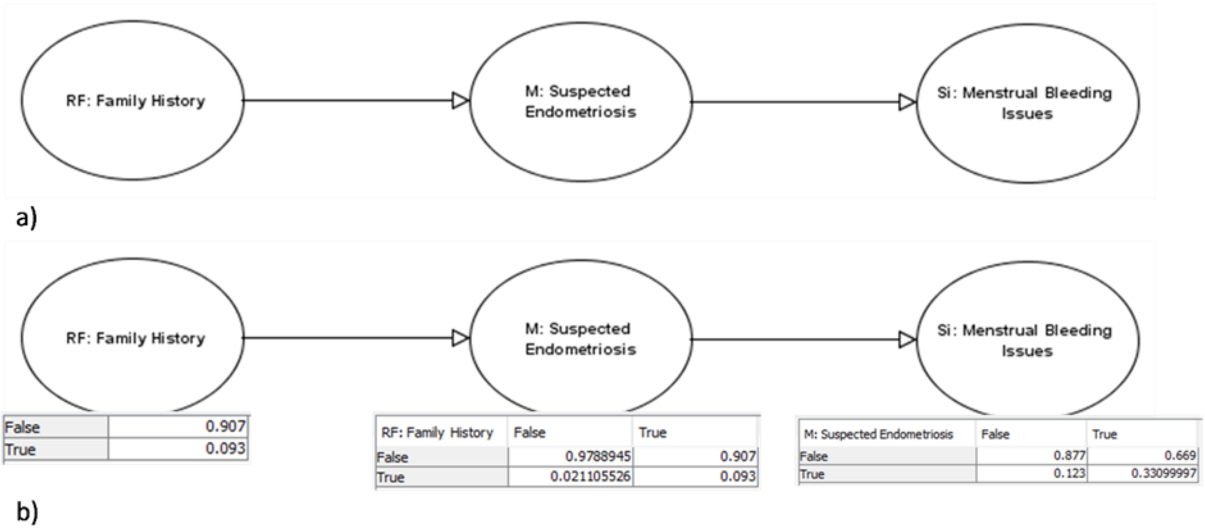


Figure 1. a) A three-node Bayesian Network casual model. b) A three-node Bayesian Network causal model with Node Probability tables displayed.

subfertility and in the non-specific features of fatigue, gynaecological issues including vulvo-vaginal symptoms and pelvic inflammation, and lower gastro-intestinal issues including pain, bloating and irritable bowel syndrome (Burton, et al., 2017). During the literature evaluation, it became evident that many studies identifying the 'risk factors' associated with endometriosis where in fact identifying the signs and symptoms associated with the condition. It became an important focus of this study to separate risk factors from symptoms to correctly apply the direction of influence.

III. Methodology

A. Bayesian Networks

A causal model is a precise specification of how each variable is influenced by its parents in a Directed Acyclic graph (Pearl, 2009). The model is developed with nodes representing different variables with direct edges representing either a causal, or influential, relationship. For example, in Figure 1 a), Family History is the parent of Suspected Endometriosis, indicating that family history has a causal impact on the probability of Endometriotic disease. In Figure 1 b), the Node Probability Table (NPT) is displayed representing the conditional probability distribution of each node, given the influence of its parent. As Family History is without parents it is referred to as a *root node* and its NPT is the probability distribution of itself (Fenton & Neil, 2019). The Bayesian Network is fully parameterised once all Node Probability tables are supplied. From this, Bayesian probabilistic reasoning, in which the prior belief about a certain hypothesis is updated considering new evidence, can be performed. *Prior probability* is the term used for the initial belief; the updated belief is termed *posterior probability*.

A benefit of using a Bayesian Network in the building of medical applications is that once evidence is entered the unobserved variables in the model are updated. This is achieved by two reasoning methods: forward reasoning and backward reasoning. Forward reasoning follows the direction of the arc whereas backward reasoning is counter the direction. When the Bayesian Network structure represents the true causal relationships, rather than simple associations, they are referred to causal reasoning and diagnostic reasoning, respectively.

B. Data and Selection of variables

A serious hurdle in practical application of probabilistic methods is the effort that is required of model building and, in particular, of quantifying graphical models with numerical probabilities (Druzdzel & Díez, 2004). As reported medical symptoms can vary significantly between hospitals and general population, it is recommended that models are built using population studies. As defined by Holt & Weiss (2000), 'definite endometriotic disease' includes ovarian endometriomas, pelvic endometriotic lesions over 5mm deep and pelvic endometriotic lesions with adhesions not attributable to other causes. Studies without clinical confirmation of the condition were excluded. Where available, data was collected from various population-control studies including Burton et al.'s (2017) case-control study using primary care electronic health records to isolate early pointers towards a diagnosis of endometriosis, Bérubé et al.'s (1998) study of endometriotic feature in infertile women, and Trabert et al.'s (2011) study of diet and risk of endometriosis, where diagnosis of endometriosis had been diagnostically made by laparoscopic procedure. Data to inform about the impact of socio-economic on the access of health care was

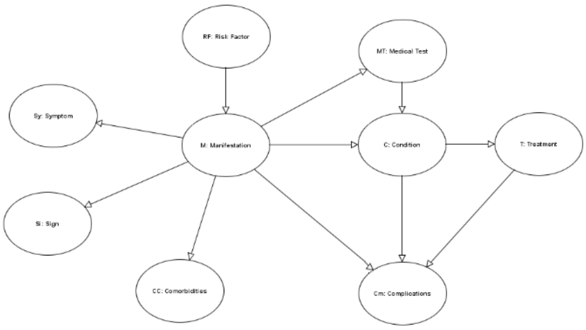


Figure 2. How medical idioms can be used to construct a Bayesian Network causal model.

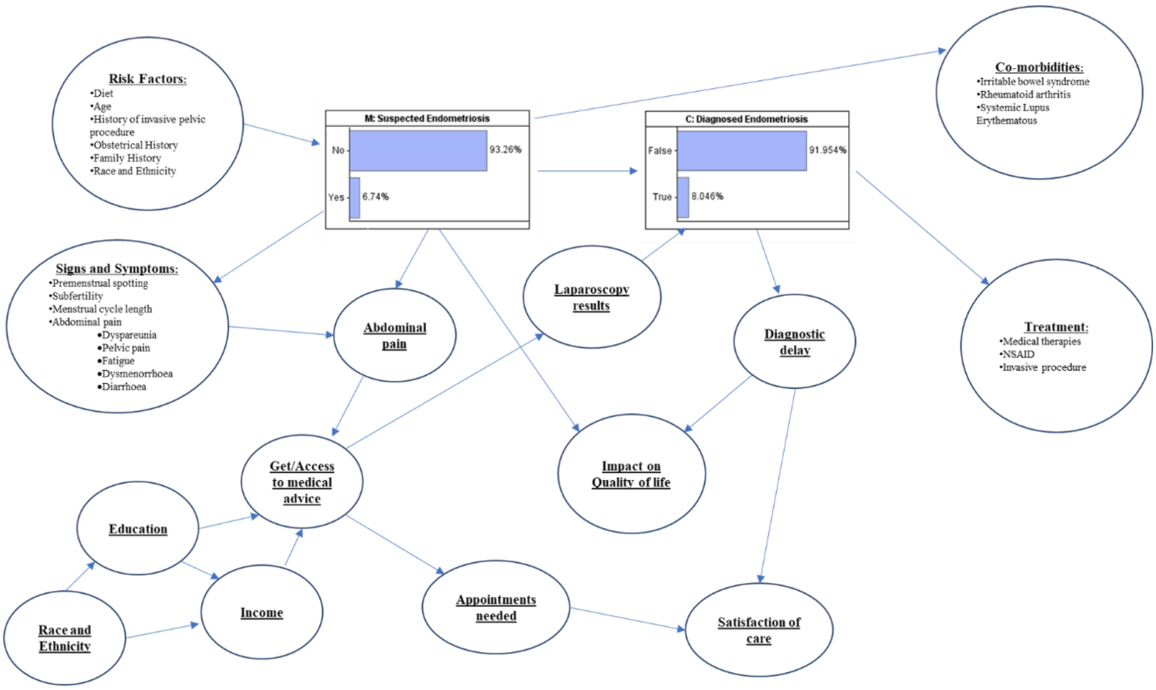


Figure 3. Endometriosis diagnosis model schematic.

taken from Williams et al.'s (2010) study 'Race, Socioeconomic Status and Health: Complexities, Ongoing Challenges and Research Opportunities.' Data regarding the patient's satisfaction with care received and the impact endometriosis has on their quality of life was taken from a study exploring a patient's journey to an endometriosis diagnosis (Lamvu, et al., 2020).

C. *Medical Idioms*

The method of following applicable and reusable medical reasoning patterns, proposed by Kyrimi et al., was used to produce the diagnostic Endometriosis BN causal model. The use of medical idioms has been identified as a method that helps bridge the barriers between medical knowledge and decision science as it simplifies the task of data gathering and construction of the Bayesian network (Kyrimi, et al., 2020). It is important to use classifications that represent the information that clinicians would normally use for describing a condition, therefore there is benefit in using medical idioms, such as Condition (C), Manifestation (M), Risk factors (RF), Treatment (T), Co-morbidities (CC) and Complications (Cm), to construct the model as shown in Figure 2. To fully assist with clinical decision-making, it is necessary for the medical BN to capture all relevant clinical variables and follow the causal mechanisms of the medical problem as reflected in the human reasoning process (Kyrimi, et al., 2020). The model was constructed using AgenaRisk software.

D. *Implementation*

Figure 3 displays the diagnostic Endometriosis BN causal model schematic . The starting point for building the model was to create the manifestation, 'M: Suspected Endometriosis.' The manifestation idiom models the uncertain causal relationship between the condition and the related manifestation variables, i.e. sign, symptoms and medical tests (Kyrimi, et al., 2020). The condition should exist before the effects are manifested; therefore, it was necessary to ascertain the marginal probability of suspected endometrioses from relevant risk factors.

Risk factors are part of a condition's aetiology, as with many medical conditions, it is difficult to detect and correctly identify the underlying cause of endometriosis (Kvaskoff, et al., 2014). Risk factors are comprised of observable attributes, characteristics or exposures that increase a likelihood of developing a medical condition, or a manifestation of it. The risk factor idiom models the uncertain relationships between an observable risk factor and the variables it affects (Kyrimi, et al., 2020). Diet studies have been characterised by weaknesses as the data collected is generally elicited from questionnaires and require patients to recall their eating habits, a retrospective assessment by the patient can lead to measurement errors. Furthermore, different dietary patterns from different countries has led to contradictory results. Trabert et al.'s (2011) case-control study on diet and risk in endometriosis has been included in the endometriosis model due to its size and population-based design. This study found decreased endometriosis risk with increased intakes of total fat and dairy and increased risk associated with higher intake of β-carotene, a red-orange pigment found in plants and fruit such as carrots and sweet potato, and fruit (Trabert, et al., 2011). Bérubé et al.'s (1998)

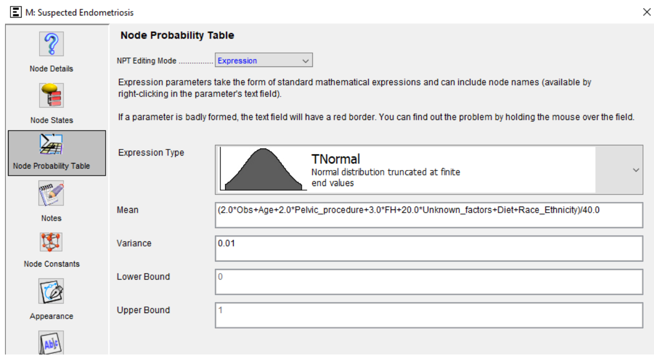


Figure 4. M:Suspected Endometriosis Node Probability table

study of characteristics related to endometriosis in infertile women found the prevalence of minimal or mild endometriosis was higher in women aged 25 years or older. Women who had ‘gravida >0, para =0’ pregnancies, i.e. pregnancies that did not survive to a gestational age of 24 weeks, were more likely to have endometriosis (Bérubé, et al., 1998). Ashrafi et al.’s study evaluating the risk factors associated with endometriosis in infertile women confirms these risk factors and adds family history of endometriosis (OR: 4.9, CI: 2.1-11.3, P<0.0001) and history of pelvic surgery (OR: 1.9, CI: 1.3-.7, P<0.001) as potential risk factors (Ashrafi, et al., 2016). Figure 5 shows the risk factor nodes as parent nodes to the ‘*M: Suspected Endometriosis*’ node. In this instance ranked nodes were used to avoid having to manually define the Node Probability Table of ‘*M: Suspected Endometriosis’* cell by cell. Ranked nodes have order-preserving meaning, in this case ‘worst-to-best’ with regards to the level of risk. When a node is specified as such, no matter what the state labels or how many states a node has, there is an assumption that there is an underlying numerical scale that goes from 0 to 1 in equal intervals (Fenton & Neil, 2019). The ranked node ‘*M: Suspected Endometriosis’* is defined as a weighted sum, where the weight has been defined by the empirical evidence regarding each risk factor. To produce the NPT, a truncated Normal distribution is used, this is a flexible distribution that can accommodate a wide range of BN fragments involving a ranked node with ranked parents, as shown in Figure 4. The marginal probability of suspected endometriosis is 6.74%, reflecting its prevalence in the general population (Overton, et al., 2007). When all risk factors are true/highest this probability increases to 16.406%, as shown in Figure 10. A parent node *‘RF: All unknown causal factors’* is included with a high weighting compared to the other risk factors. This node will never be observed, it represents the confounding variables and at its maximum level would ensure ‘*M: Suspected Endometriosis’* is true.

To ascertain the manifestation of the condition in the Endometriosis model, ‘*M: Suspected Endometriosis*,’ the observable consequences of the condition were added; symptoms, signs, and medical tests. Figure 5 shows the presence of endometriosis manifests into premenstrual spotting, subfertility, dyspareunia, pelvic pain, fatigue, dysmenorrhoea, and diarrhoea and menstrual cycle length. Symptoms (Sy) are subjective feelings which are apparent only to the patient and cannot be measured or quantified by the clinician. Pain and fatigue are symptoms that require self-reporting from the patient. In contrast, signs (Si) are objective indications that are observable to the clinician. The sign and symptom nodes are, again, ranked nodes that are children to ‘*M: Suspected Endometriosis*.’ Throughout most studies analysing features of endometriosis, abdominal and pelvic pain was identified as the principle symptom of the disease (Burton, et al., 2017; Grundström, et al., 2016; Rolla, 2019). The ‘*Sy: Abdominal pain’* node is a ranked node describing pain as ‘low’, ‘medium,’ or ‘high.’ It is the child of ‘*M: Suspected Endometriosis*’ and symptoms relating to pain. It is the parent of ‘*Get medical advice’*, the greater the level of pain the more likely the patient is to seek medical care, be referred for a test and therefore be diagnosed with endometriosis.

The condition in the Endometriosis model is the diagnosed ailment of endometriosis; ‘*C: Diagnosed Endometriosis.*’ It is a Boolean node, stating true or false, the probability of a patient being diagnosed with endometriosis. It is the child node of ‘*M: Suspected Endometriosis’* and *‘MT: Laparoscopy results*.’ Diagnosis can be true only with laparoscopy results confirming endometriosis, with or without suspected endometriosis being true. It is the parent node to the treatment nodes as treatment can only commence when diagnosis is made.

The medical test (MT) idiom indicates the procedure performed to diagnose the medical condition (Kyrimi, et al., 2020). Diagnosis of endometriosis is made following a laparoscopic inspection of the pelvis. It is considered the gold standard for confirmatory diagnosis, with histologic conformation after biopsy (Rolla, 2019; Parasar, et al., 2017). A study by Wykes et al. (2004) endeavoured to provide precise diagnostic accuracy estimates. It was concluded that the overall sensitivity was 94% and specificity was 79% for the accuracy of diagnosis by laparoscopy. This data is inputted in a labelled node ‘*MT: Laparoscopy results,*’ a child

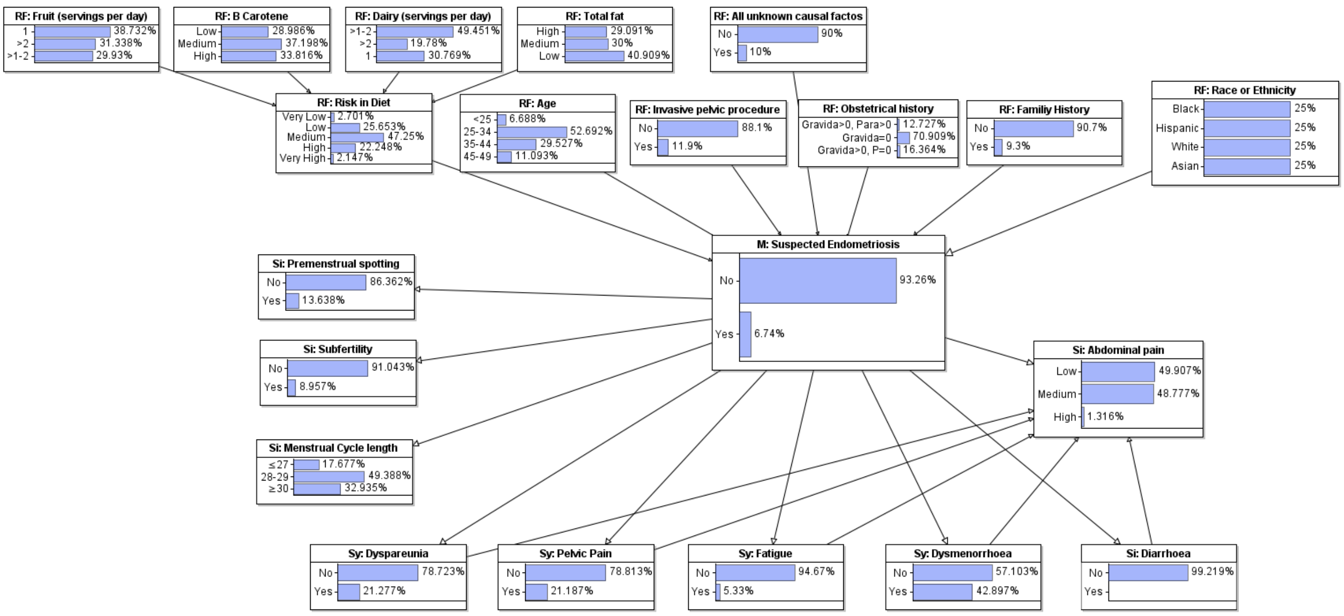


Figure 5. Diagnostic endometriosis model displaying risk factors, signs and symptoms associated with the condition.

node of '*M: Suspected Endometriosis*,' and *'Get medical advice*,' and a parent node to '*C: Diagnosed Endometriosis.'* The inaccuracy of each manifestation variable is accounted for as a false positive and false negative rate, however the reliability of the patient reporting their symptom, or the accuracy of the clinician performing tests, can be another source of inaccuracy (Kyrimi, et al., 2020). It was important, therefore, to introduce an accuracy node, a manifestation reliability idiom, for the experience of the laparoscopist conducting the examination. It was reported in 2002 that experienced laparoscopists have an 86% accuracy and less experienced laparoscopists have a 41% accuracy when compared to histologic biopsy results (Wood, et al., 2002). A labelled node was used '*Accuracy of Laparoscopist'* to indicate the level of experience and when the node probability table of '*MT: Laparoscopy results'* was updated to reflect this it revealed a 63.5% probability that a patient will be diagnosed with endometriosis.

The treatment (T) idiom represents the clinical management to treat the condition (Kyrimi, et al., 2020). In their first year following diagnosis of endometriosis, 55.5% of patients are prescribed medical therapies (Cea Soriano, et al., 2017). The most prescribed medication were combined oral contraceptives (COCs). Medical therapies also includes progestogen-only pills (POPs), implants, and injections, gonadotropin-releasing hormone (GnRH), copper and non-specific intrauterine devices (IUDs) among others. Pain medication was prescribed to 44.9 % of patients (Cea Soriano, et al., 2017). Non-steroidal anti-inflammatory drugs (NSAIDs), to treat pain, were also commonly prescribed. This list includes codeine, tramadol, and opioids. 48.3% of patients with confirmed endometriosis require invasive treatment, with most of this treatment taking place in the first three years following diagnosis. The most common surgical treatment is surgery to the ovaries and/or salpinges, also referred to as fallopian tubes. 19.7% of patients require further invasive treatment following an initial procedure (Cea Soriano, et al., 2017). 28.7% of patients underwent hysterectomy during their initial invasive procedure, 44.2% underwent hysterectomy following recurrent invasive procedures (Cea Soriano, et al., 2017). The treatment nodes can be identified by 'T' before the node name, for example '*T: Medical Therapy.*' These nodes are binary and are child nodes from the parent node '*C: Diagnosed Endometriosis*.' Recurrent treatment, invasive procedures that has occurred after an initial invasive procedure has already been performed, has been given the indicator 'Tr', for example '*Tr: Hysterectomy.*'

The race and ethnicity of the patient has long been touted as a risk factor for endometriosis with black women less likely to be diagnosed with endometriosis and Asian women more likely to be diagnosed when compared to white women. However, in women presenting with infertility, there was no significant difference in endometriosis prevalence between white and black women (Bougie, et al., 2019). It seems likely that race and ethnicity may influence the ability to access healthcare and obtain appropriate management for endometriosis through a combination of socio-economic issues (Williams, et al., 2010). Regardless, this causes an implicit and explicit bias among the medical community, which can influence a patient's chance of a timely and accurate diagnosis of endometriosis, depending on their ethnicity. Statistical data was taken from the United States Census Bureau (2009) to create ranked nodes displaying education, income, and access to medical to generate a node to indicate whether a patient would be able to access medical care regardless of the probability of suspected endometriosis, Figure 3.

The determine the satisfaction of care a patient will have on their diagnostic journey a ranked node with a weighted mean was created, '*Satisfaction with care*.' It is the child node of '*Appointments before referral for testing'*, '*M: Suspected Endometriosis*,' and '*Diagnostic delay after initial consultation with GP.*'

Finally, nodes representing impact on area of life important to the patient were created. *'Interference with starting_raising a family*'; a ranked node whose parents are '*RF: Subfertility*,' '*M: Suspected Endometriosis*,' and '*Diagnostic delay*'; and ranked nodes '*Interference with Education or Career*' and '*Interference with social life*'; whose parents are both '*M: Suspected Endometriosis*' and '*Diagnostic delay*.' Finally, these interference nodes alongside '*M: Suspected Endometriosis'* are parents of *'Negative impact on Quality of Life'* to determine how patients with endometriosis are affected in their day-to-day living. The information was pulled from study exploring a patient's journey to an endometrioses diagnosis (Lamvu, et al., 2020).

IV. Results

The final diagnostic BN causal model for endometriosis can be seen below in Figure 6, a larger image is available in Appendix A Figure 8. The primary objective of the model is to calculate the probability of having suspected endometriosis by observing risk factors, signs, and symptoms of the condition. The model then calculates the probability of the patient being surgically diagnosed with the condition. The secondary objective of the model is to predict the satisfaction of the patient from the care that they receive, and the impact endometriosis has on their quality of life. Scenarios and their results have been outlined below.

A. Diagnosis and Treatment results

Images of the model displaying diagnosis results can be viewed in Appendix B. Prior to any observed risk factors, the risk of suspected endometriosis is 7%, as seen in Figure 6, reflecting the prevalence of endometrioses is the general population. When risk factors including diet, age, previous invasive pelvic procedure, obstetrical history and family history are observed the risk of endometriosis rises to 16%, as shown in Figure 10. A node representing all unknown causal factors has been included. This node will never be observed, but if observed to be true, will ensure the probability of endometriosis is true.

When all signs and symptoms are observed the probability of endometriosis is not in doubt, the probability produced is 99.69%, the level of abdominal pain is high at 80% and the likelihood of the patient seeking medical advice rises to nearly 70%, as shown in Figure 12. The probability of being diagnosed with endometriosis is dependent on being referred for a laparoscopic scope and the accuracy of the laparoscopist. Figure 12 shows that without observations the probability of being diagnosed with endometriosis is 44%. If 'get medical advice' is observed to be true, the probability of being diagnosed increases to 63%, as shown in Figure 13. If an experienced laparoscopist is observed this figure rises to

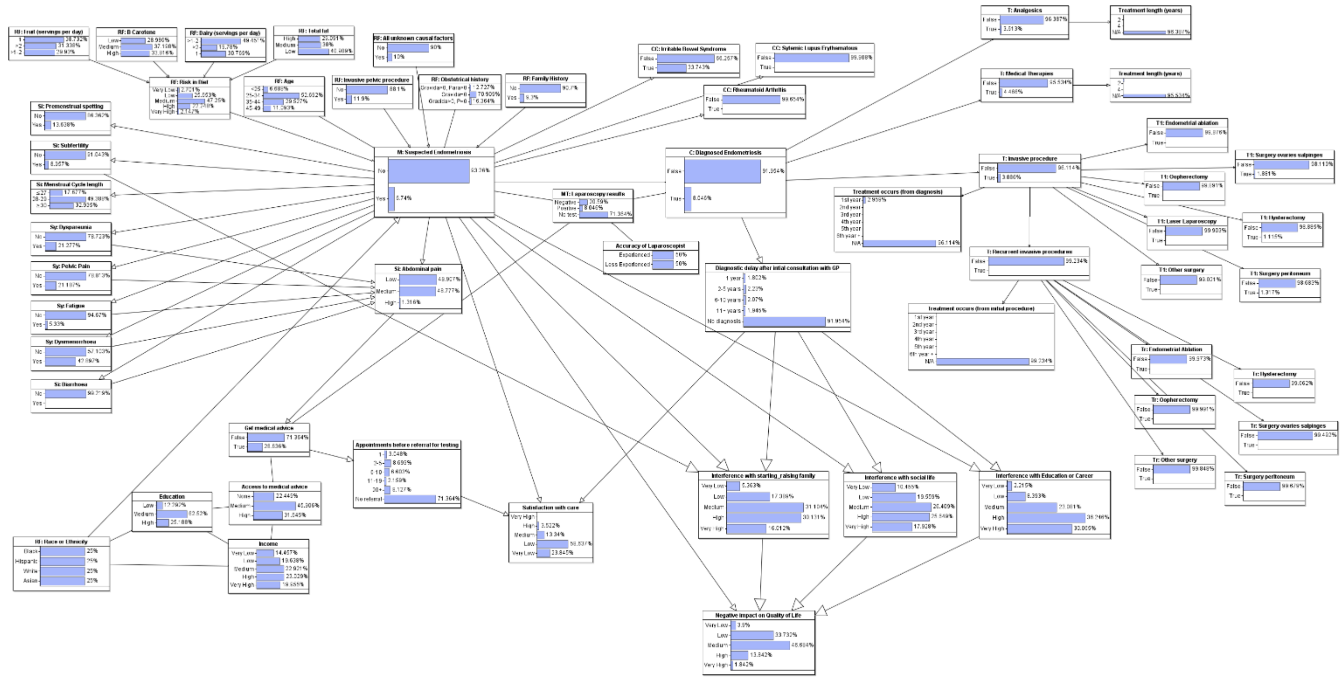


Figure 6. Full endometriosis diagnostic model.

86%, an unexperienced laparoscopist observed drops the figure to 41%, Figure 14.

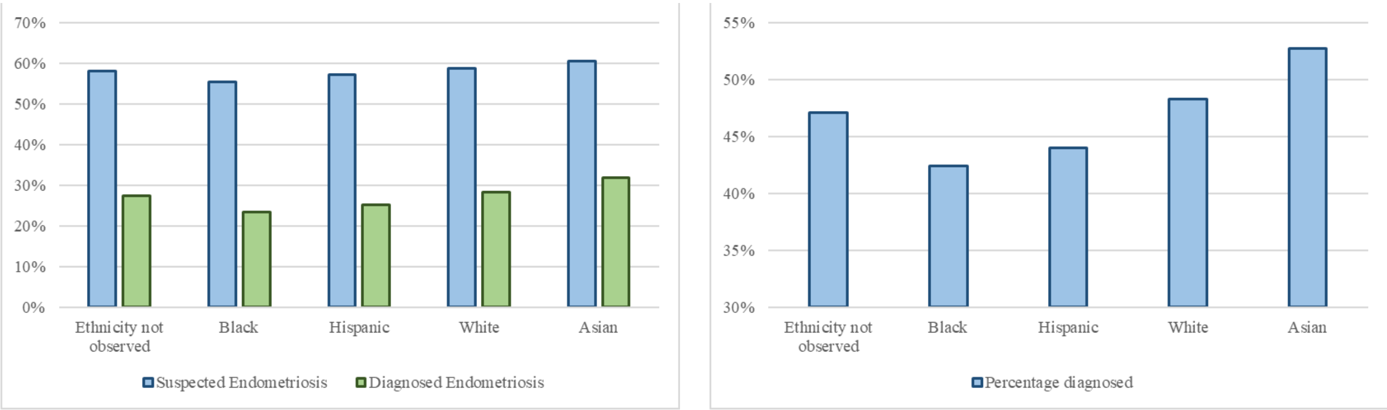
Once diagnosis is observed to be true the most likely treatment is medical therapies, most often combined oral contraception, at 56%, Figure 15. Analgesic treatment lies at 45%, and invasive procedure probability is 48%. By observing the treatment categories, medical therapy and analgesic treatment regularly take place over 5 years. The most likely invasive procedure a patient will undergo is surgery to the ovaries and salpinges, at 48%. This is followed by peritoneum surgery, the lining of the abdominal cavity, at 34% and hysterectomy, the removal of the uterus, at 29%. It is important to note that there is a 20% chance that the patient will have to undergo recurrent invasive procedures Figure 16. When recurrent procedure is observed, the probability of surgery to the ovaries and salpinges is again the highest at 66%. This is followed by hysterectomy, at 44%, indicating that the delay may be due to factors such as wishing to produce children.

B. Race and Ethnicity factors

The impact of race and ethnicity to the risk and potential diagnosis of endometriosis can be viewed in figures attached in Appendix C. Figure 17 a) shows that the probability of suspected endometriosis is 55% when 'Black' has been observed in the '*RF: Race or Ethnicity'* node. This figure rises to 57% when 'Hispanic' is selected, 59% when 'White' is selected, and 60% when 'Asian' is selected, as shown in Figure 17 b) and Figure 18, a) and b). This rise in risk reflects the influence of race or ethnicity on the prevalence of endometriosis, as discussed in literature above. Yet, the probability of receiving a confirmed diagnosis of endometriosis is also affected by race and ethnicity. The probability of confirmed endometriosis is 23% when 'Black' is observed, 25% when 'Hispanic' is observed, 28% when 'White' is observed and 32% when 'Asian' is observed. Figure 7 a) displays these figures on a bar chart. At first glance, the figures displayed on the chart look proportional to each other. However, when the percentage of patients with suspected endometriosis who are successfully diagnosed with endometriosis is calculated, it becomes evident that patients with a Black and Hispanic background are less likely to get a successful diagnosis. Black patients are successfully diagnosed 42% of the time compared to Asian patients, who have a 53% probability of being diagnosed. This result shows that education, income, and access to healthcare have a direct influence on whether a patient will be diagnosed with endometriosis.

C. Satisfaction with care

Please refer to Appendix D for figures relating to this scenario. When a patient does get medical advice there is a 30% probability that they will have to attend two to five appointments before being referred for testing, Figure 13. The second highest outcome from this observation is over 20 appointments before referral (28%). This is delay is likely due to the physician treating the symptoms rather than the condition and leads to frustration and lack of satisfaction with care for the patient (Lamvu, et al., 2020). When a patient is diagnosed with endometriosis there is a 28% probability that it occur two to five years following their initial consultation with a general practitioner. There is a 24% probability a patient will have to wait eleven or more years for diagnosis. Satisfaction with care falls the longer a patient must wait for referral or diagnosis, there is a 59% probability that a patient will have a high level of satisfaction when diagnosed in two to five years. This drops to an 81% probability of low level of satisfaction when diagnosis is delayed to eleven years or more, as shown in Figure 19 and Figure 20. Figure 20 also shows the negative impact on the quality of life coming from having endometriosis, the level of pain experienced and its impact on starting and/or raising a family, the impact on learning and/or the patients career, and its impact on the patient's social life.



a) b)

Figure 7. a) Suspected endometriosis probability compared with diagnosed endometriosis probability, grouped by race or ethnicity. b) Percentage of patients with endometriosis who get diagnosed, grouped by race or ethnicity.

V. Discussion/Conclusion

In this study, it was illustrated how a Bayesian Network causal model can be used to aid clinical decision-making for the diagnosis of endometriosis by observing signs and symptoms of the condition. Due to its graphical nature, the interactions between the different variables built into the network are directly visualised and follow clinical reasoning through the use of medical idioms. A diagnostic model was achieved with supplementary analysis of socio-economic factors that may help or hinder possible diagnosis. Insight has also been provided into the impact endometriosis has on the patient's quality of life, the impact on education and career, social life, and family life.

An area of the model which can be improved upon is the treatment the patient receives. The treatment of endometriosis can vary according to the symptoms, severity of the condition and the desire of the patient to maintain their fertility. The treatment of the condition has not been utilised to its full potential within this model.

It is noted that by observing just a few symptoms means that '*M: Suspected Endometriosis'* is almost certainly true. As a result, the data collected may be tainted by confirmation bias. This may also expose a problem with the way endometriosis is currently being diagnosed, i.e. the condition is being defined by the symptoms. Yet, it is important to note that many women with endometriosis are asymptomatic, may not seek medical care or may opt-out of surgical intervention. This bias was somewhat alleviated by including *'Sy: Abdominal pain'* to act as the main interdependent agent between symptoms and as the main indicator for a patient to seek medical aid. Considering endometriosis as a possible diagnosis in women who present with abdominal pain may improve its recognition in primary care settings.

The results from the socio-economic section of the model exploit the hidden, or latent, casual variables that account for the lower rate of diagnosis for patients from a black racial background compared with patients identifying as white and Asian. The socio-economic aspect of the model demonstrates that observed racial disparities in health reflect the differences in socio-economic circumstances among racial groups. This information can be used to inform policy-makers of the importance of access to healthcare, regardless of income levels, for the treatment and wellbeing of those who have the condition. The model outputs low levels of quality of life for individuals who have endometriosis but who have not received a formal diagnosis.

VI. Future Work

The model created is primarily a diagnostic model calculating the probability of a patient having, and subsequently being diagnosed, with endometriosis. It also explores the reality of how endometriosis affects the patient's quality of life. Whilst treatment probabilities are included, the model is considered a diagnostic rather than an intervention model. To make this a dynamic model it would benefit by being extended to a two-stage model by creating a link between pre-procedure symptoms and post-treatment outcomes. Further research will need to be undertaken to associate range of symptoms with the stage of endometriosis, stage 1-2 (minimal to mild) or stage 3-4 (moderate to severe), as this classification alongside consultation with the patient to ascertain their fertility options and requests will be needed to complete the decision-making process.

The complications and co-morbidities associated with endometriosis can be expanded upon as the model advances. Of interest is the prevalence of mental health issues arising from levels of pain experienced by the patient and the disregard exhibited by clinicians when treating this symptom and subsequent delay of associating it with endometriosis. To be given an explanation for their problems is almost as important as getting a cure for certain individuals (Grundström, et al., 2016).

The model would benefit from a user-centric interface if rolled out to clinicians, to aid decision-making, and policymakers, to illustrate the disadvantages experienced by lower-income workers in their access to medical care.

References

Akter, S. et al., 2019. Machine Learning Classifiers for Endometriosis Using Transcriptomics and Methylomics Data. *Frontiers in genetics*, 10(September), pp. 1-17.

Bérubé, S., Marcoux, S., Maheux, R. & Endometriosis, C. C. G. o., 1998. Characteristics Related to the Prevalence of Minimal or Mild Endometriosis in Infertile Women. *Epidemiology*, Volume September, pp. 504-510.

Bougie, O. et al., 2019. Influence of race/ethnicity on prevalence and presentation of endometriosis: a systematic review and meta-analysis. *BJOG: An International Journal of Obstetrics and Gynaecology,* 126(9), pp. 1104-1115.

Burton, C. et al., 2017. Pointers to earlier diagnosis of endometriosis : a nested case-control study using primary care electronic health records. *British Journal of General Practice.*

Chen, Z., Hwang, B. S. & Kim, S., 2019. A correlated Bayesian rank likelihood approach to multiple ROC curves for endometriosis. *Statistics in Medicine,* Issue 38, pp. 1374-1385.

Dastur, A. E. & Tank, P. D., 2010. John A Sampson and the origins of Endometriosis. *The Journal of Obstetrics and Gynaecology of India,* 60(4), pp. 299-300.

Druzdzel, M. J. & Díez, F. J., 2004. Combining knowledge from different sources in causal probabilistic models. *Journal of Machine Learning Research,* 4(3), pp. 295-316.

Farquhar, C. M., 2000. Clinical review Extracts from "Clinical Evidence" Endometriosis. *BMJ,* Volume 320, pp. 1449-1452.

Fenton, N. & Neil, M., 2019. *Risk Assessment and Decision Analysis with Bayesian Networks.* 2nd ed. Boca Raton: CRC Press.

Harris, H. R. et al., 2018. Early life abuse and risk of endometriosis. *Human Reproduction,* 33(9), pp. 1657-68.

Holt, V. & Weiss, N., 2000. Recommendations for the design of epidemiologic studies of endometriosis. *Epidemiology,* Volume 11, pp. 654-659.

Kvaskoff, M. et al., 2014. Endometriosis: A high-risk population for major chronic diseases?. *Human Reproduction Update,* 21(4), pp. 500-516.

Kyrimi, E. et al., 2020. Medical idioms for clinical Bayesian network development. *Journal of Biomedical Informatics,* 108(103495).

Lu, Y. et al., 2015. Shared genetics underlying epidemiological association between endometriosis and ovarian cancer. *Human Molecular Genetics,* 24(20), pp. 5955-5964.

Parazzini, F. et al., 2004. Selected food intake and risk of endometriosis. *Human Reproduction,* 19(8), pp. 1755-1759.

Parazzini, F. et al., 2013. A metaanalysis on alcohol consumption and risk of endometriosis. *American Journal of Obstetrics and Gynecology,* 209(2), pp. 106.e1-106.e10.

Parazzini, F. et al., 2017. European Journal of Obstetrics & Gynecology and Reproductive Biology Epidemiology of endometriosis and its comorbidities. *European Journal of Obstetrics and Gynecology,* Volume 209, pp. 3-7.

Parazzini, F., Vigano, P., Candiani, M. & Fedele, L., 2013. Diet and endometriosis risk: A literature review. *Reproductive Biomedicine Online,* Issue 26, pp. 323-336.

Pearl, J., 2009. *Causality: Models, Reasoning, and Inference.* 2nd ed. New York: Cambridge University Press.

Reijnen, C. et al., 2020. Preoperative risk stratification in endometrial cancer (ENDORISK) by a Bayesian network model: A development and validation study.. *PLoS Med,* 5(17), pp. 1-19.

Rogers, P. A. W. et al., 2013. Defining future directions for endometriosis research: Workshop report from the 2011 World Congress of Endometriosis in Montpellier, France. *Reproductive Sciences,* 20(5), pp. 483-499.

Roy, D. et al., 2015. Integrated Bioinformatics , Environmental Epidemiologic and Genomic Approaches to Identify Environmental and Molecular Links between Endometriosis and Breast Cancer. *International Journal of Molecular Sciences,* Volume 16, pp. 25285-25322.

Trabert, B. et al., 2011. Diet and risk of endometriosis in a population-based case-control study. *Br J Nutr,* 105(3), pp. 459-467.

Urteaga, I., McKillop, M. & Elhadad, N., 2020. Learning endometriosis phenotypes from patient-generated data. *npj Digital Medicine,* 3(88), pp. 1-14.

Williams, D. R., Mohammed, S. A., Leavell, J. & Collins, C., 2010. Race, Socioeconomic Status and Health: Complexities, Ongoing Challenges and Research Opportunities. *Ann N Y Acad Sci,* February(1186), pp. 69-101.

Wood, C., Kuhn, R. & Tsaltas, J., 2002. Laparoscopic diagnosis of endometriosis. *Australian and New Zealand Journal of Obstetrics and Gynaecology,* 42(3), pp. 277-281.

A. Appendix A

MODEL IMAGES

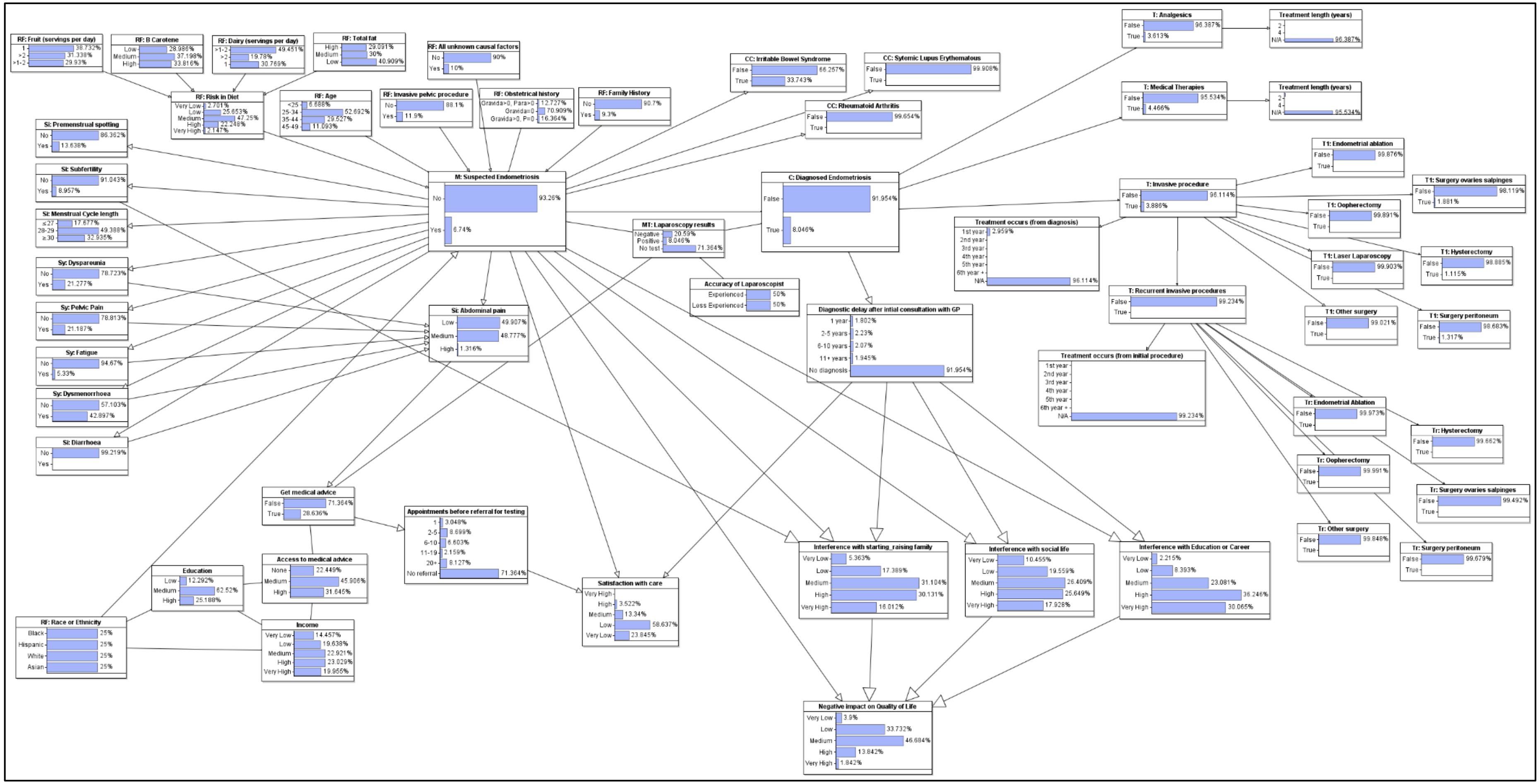


Figure 8. Full Endometriosis Diagnostic Bayesian Network model.

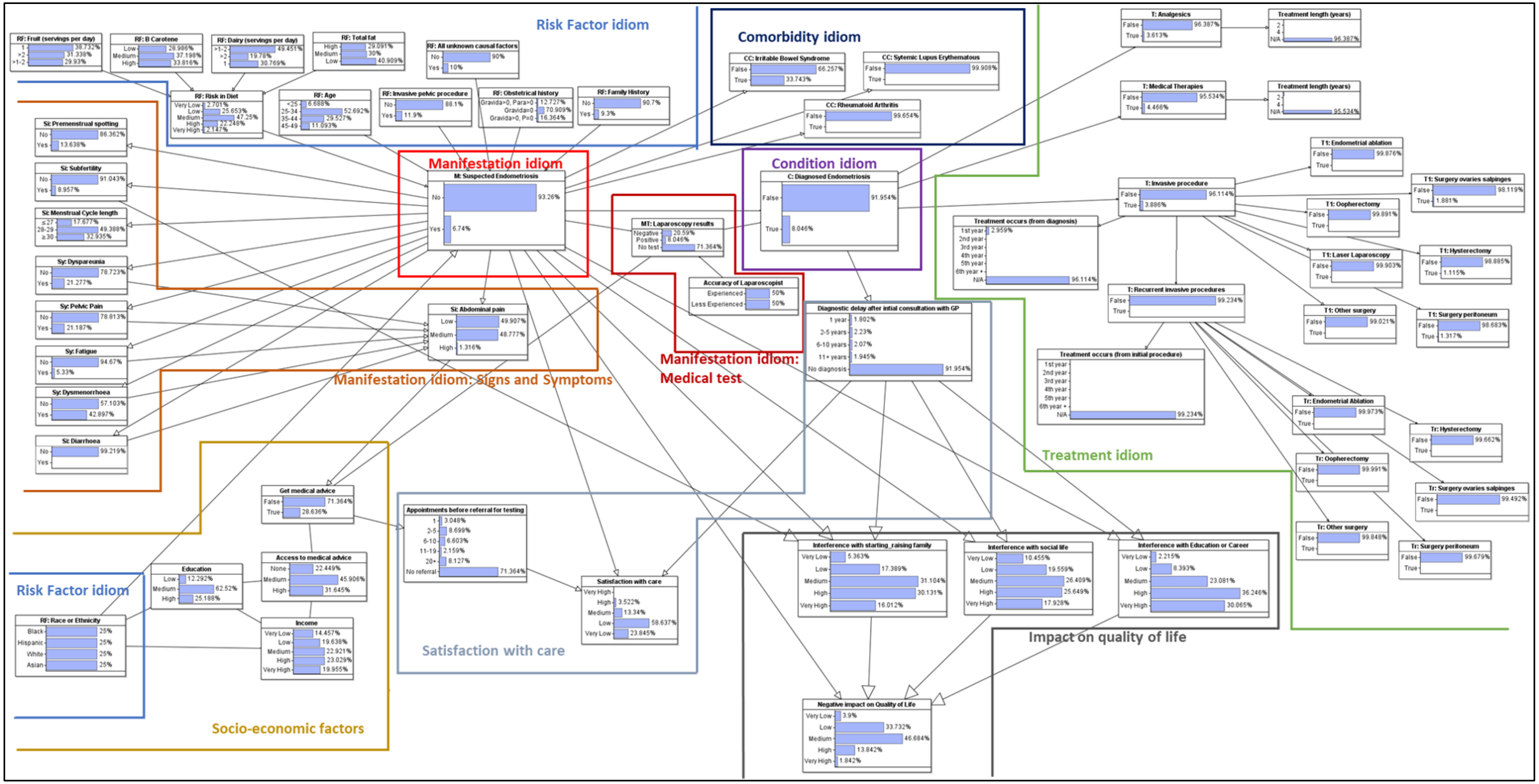


Figure 9. Full Endometriosis diagnostic model with medical idioms indicated.

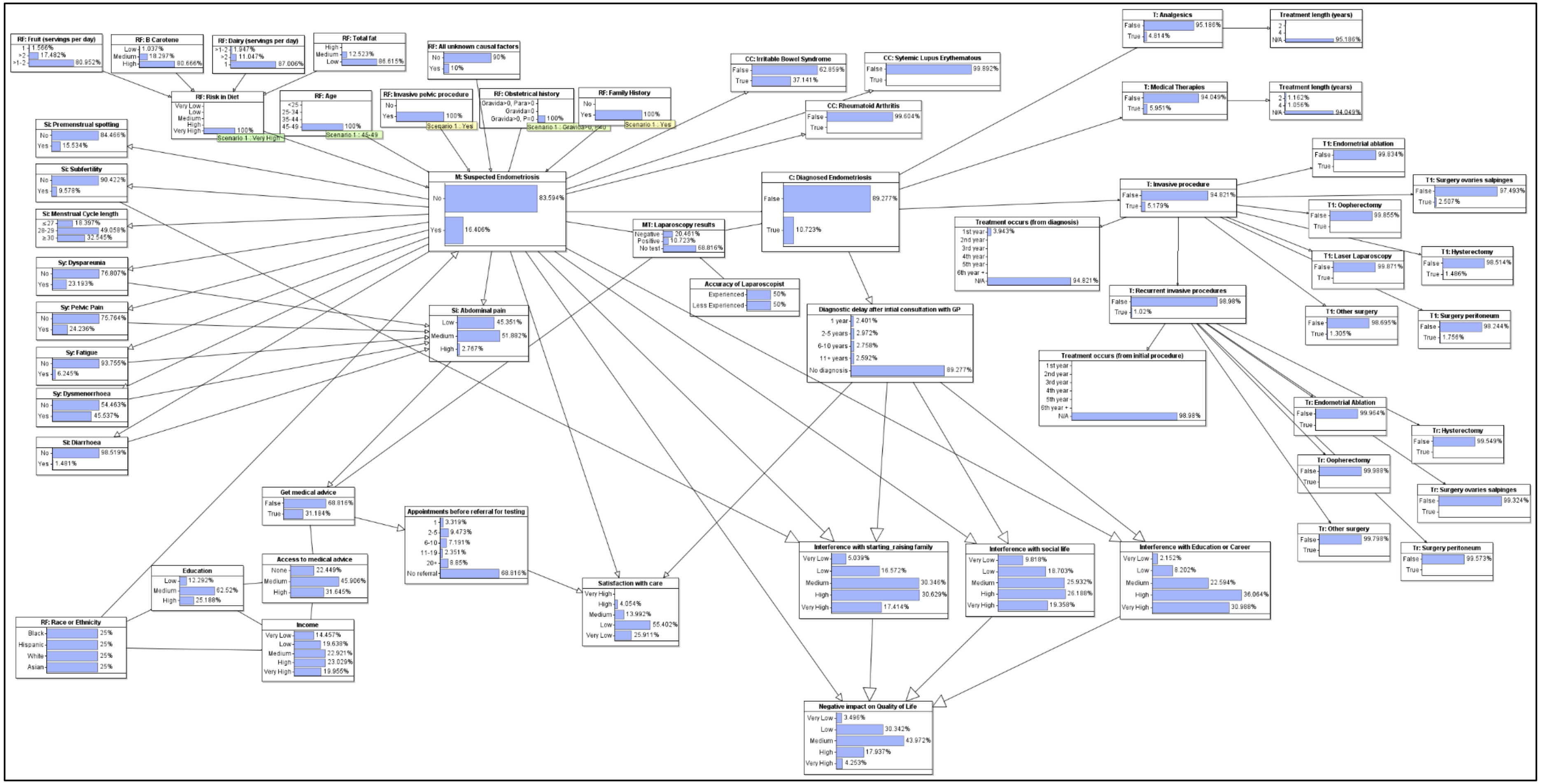


Figure 10. Endometriosis diagnostic model showing all risk factors observed.

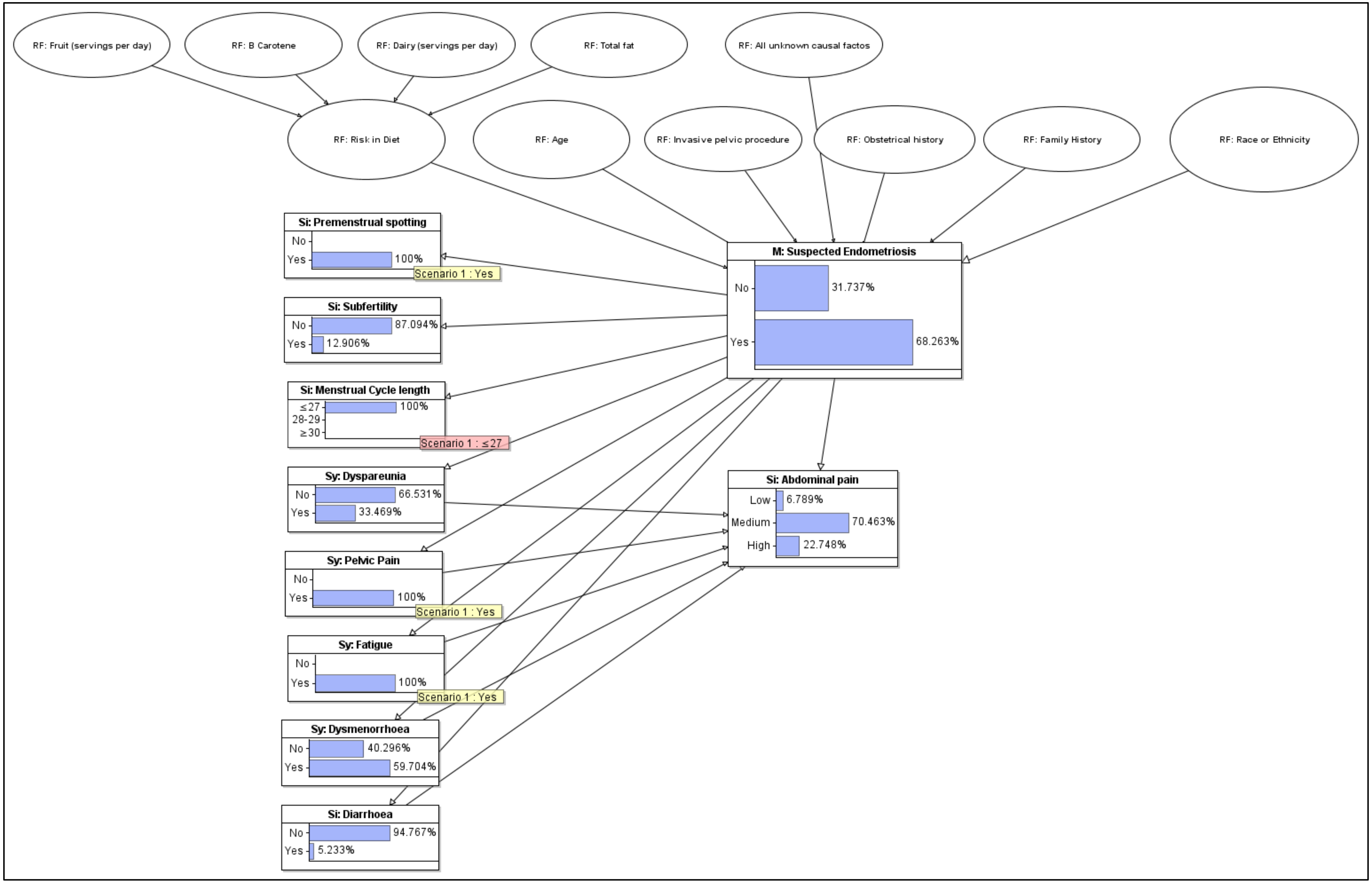


Figure 11. Section of Endometriosis diagnostic model showing how selecting a few symptoms can lead to M: Suspected Endometriosis to be largely true.

B. Appendix B

DIAGNOSIS AND TREATMENT RESULTS

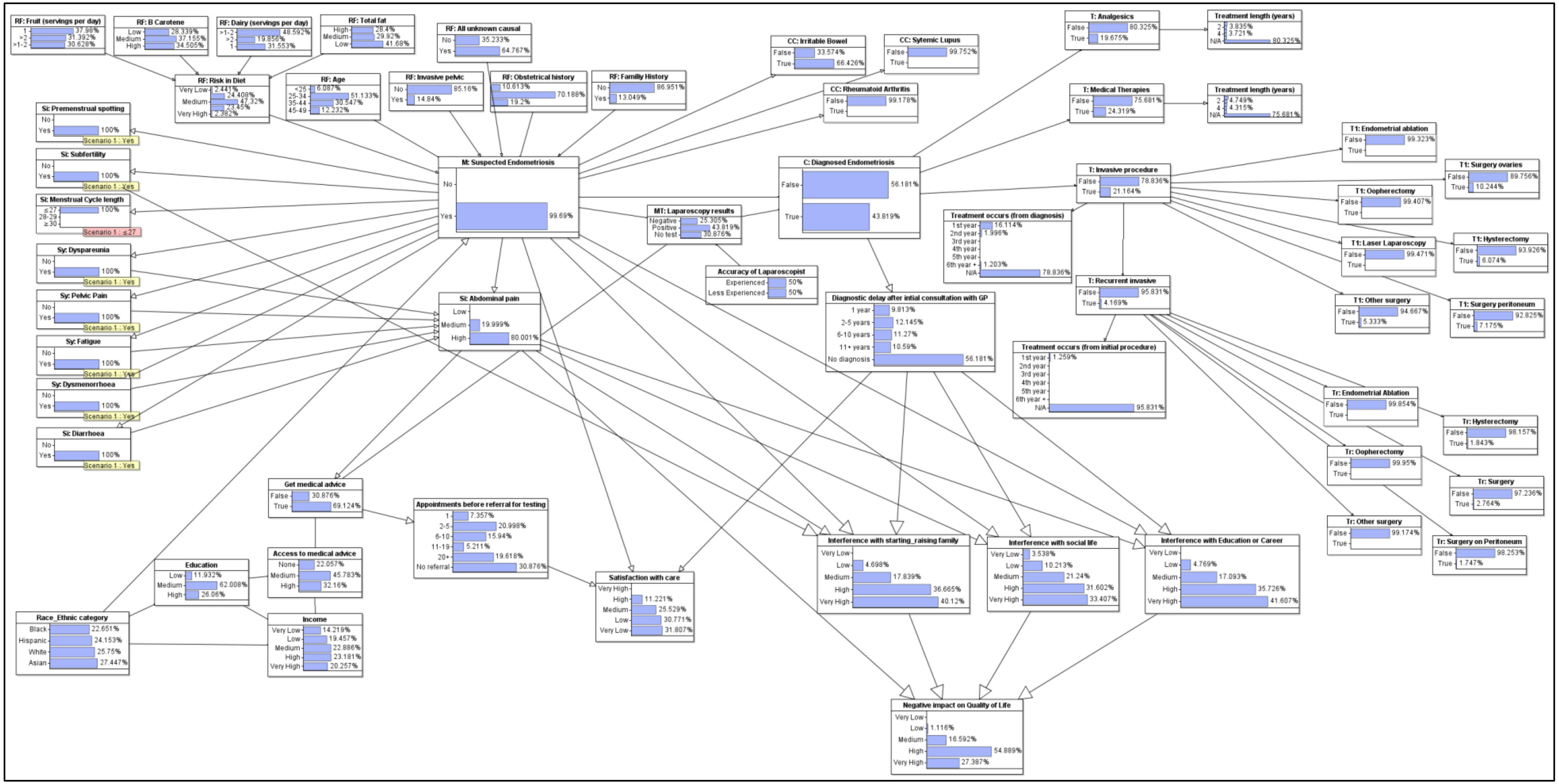


Figure 12. Endometriosis diagnostic model with all signs and symptoms observed.

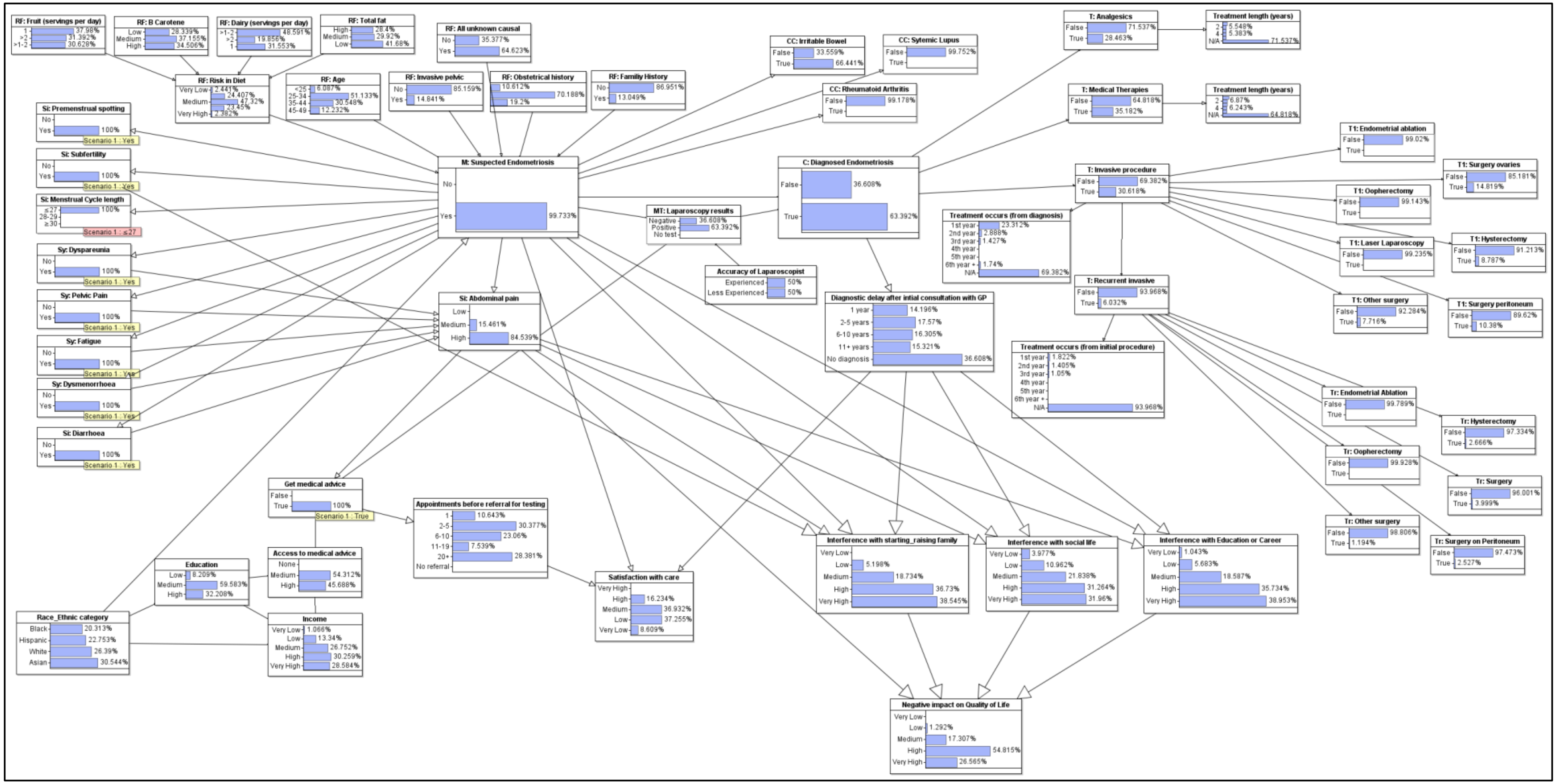
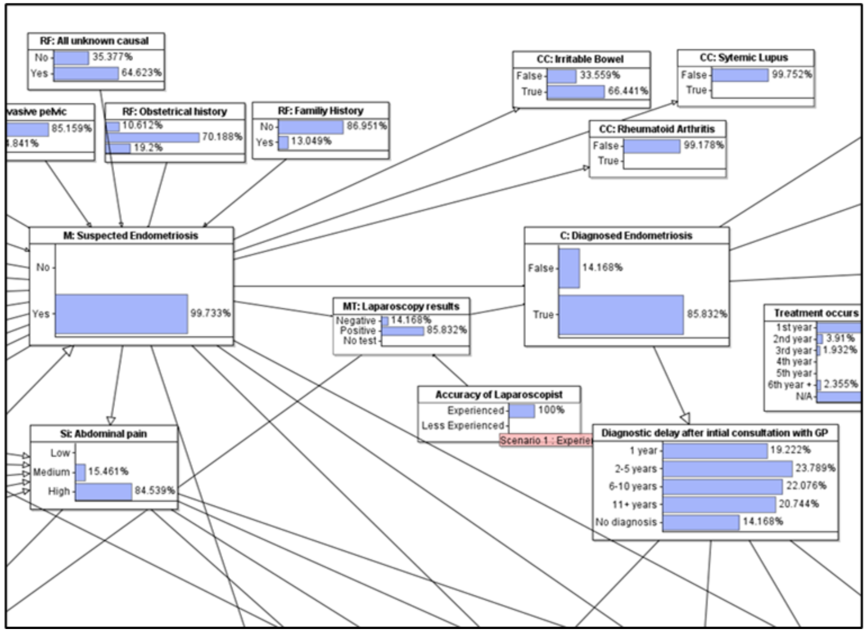
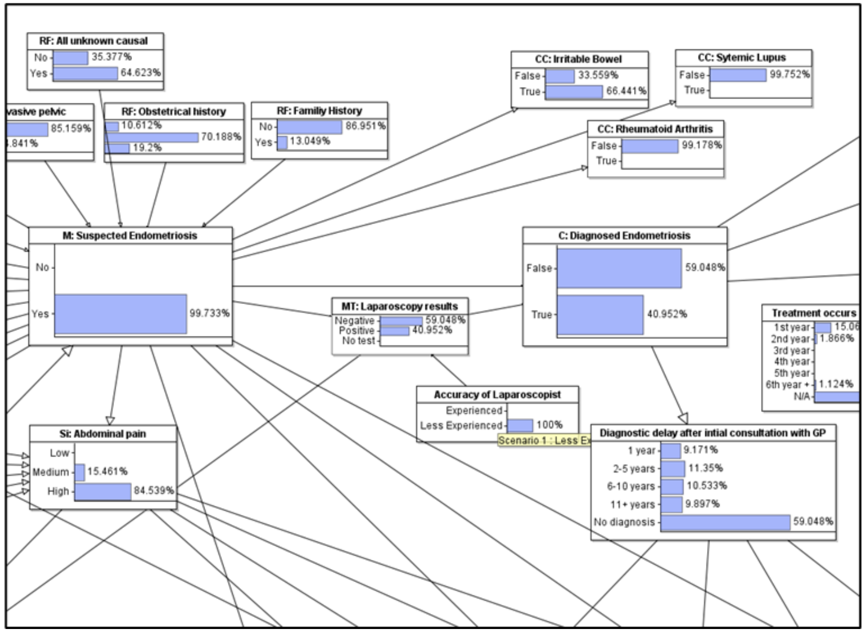


Figure 13. Endometriosis diagnostic model with 'Get medical advice' observed.



a)



b)

Figure 14. a) Endometriosis diagnostic model with experience laparoscopist observed. b) Endometriosis diagnostic model with less experienced laparoscopist observed.

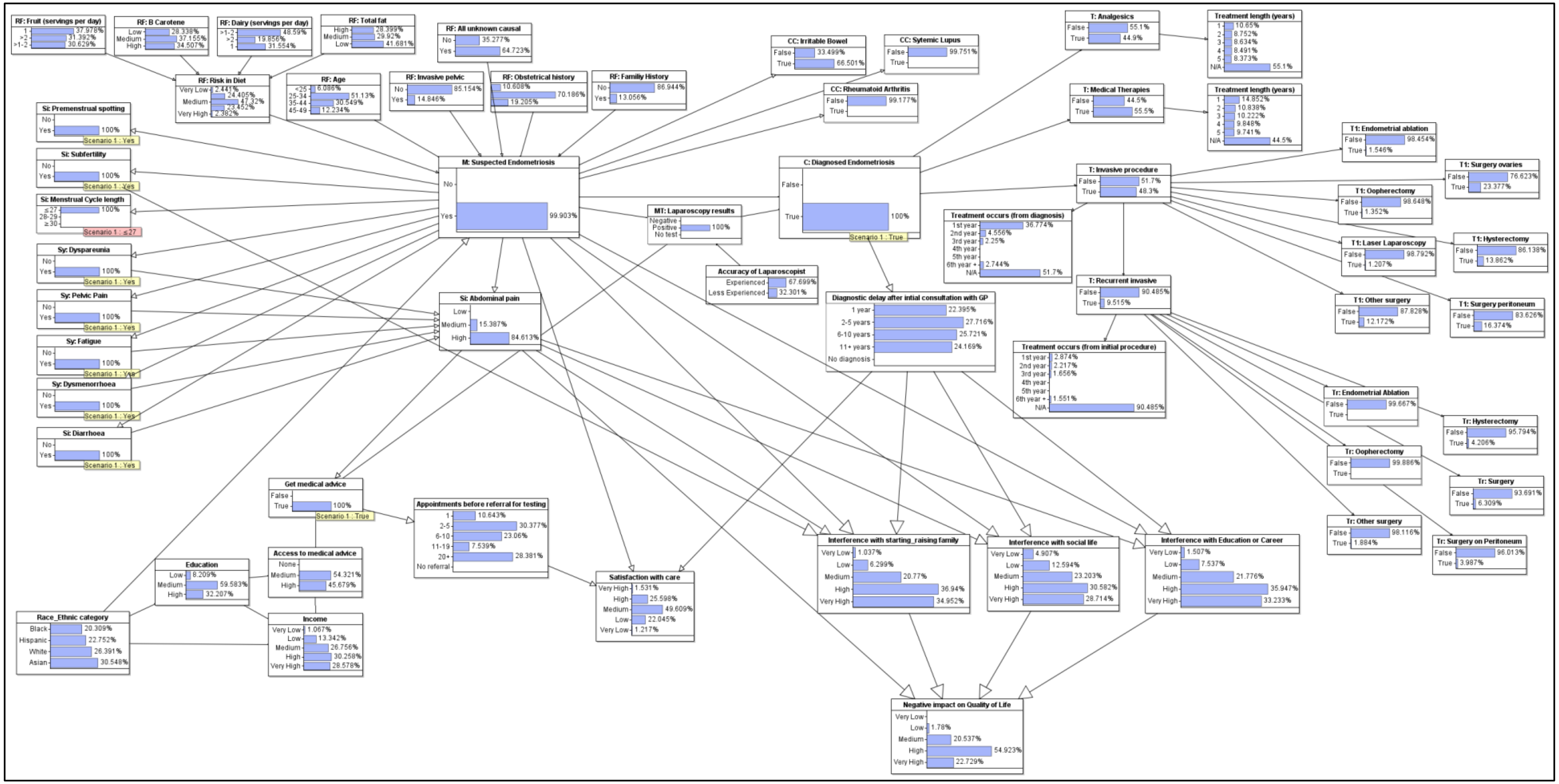
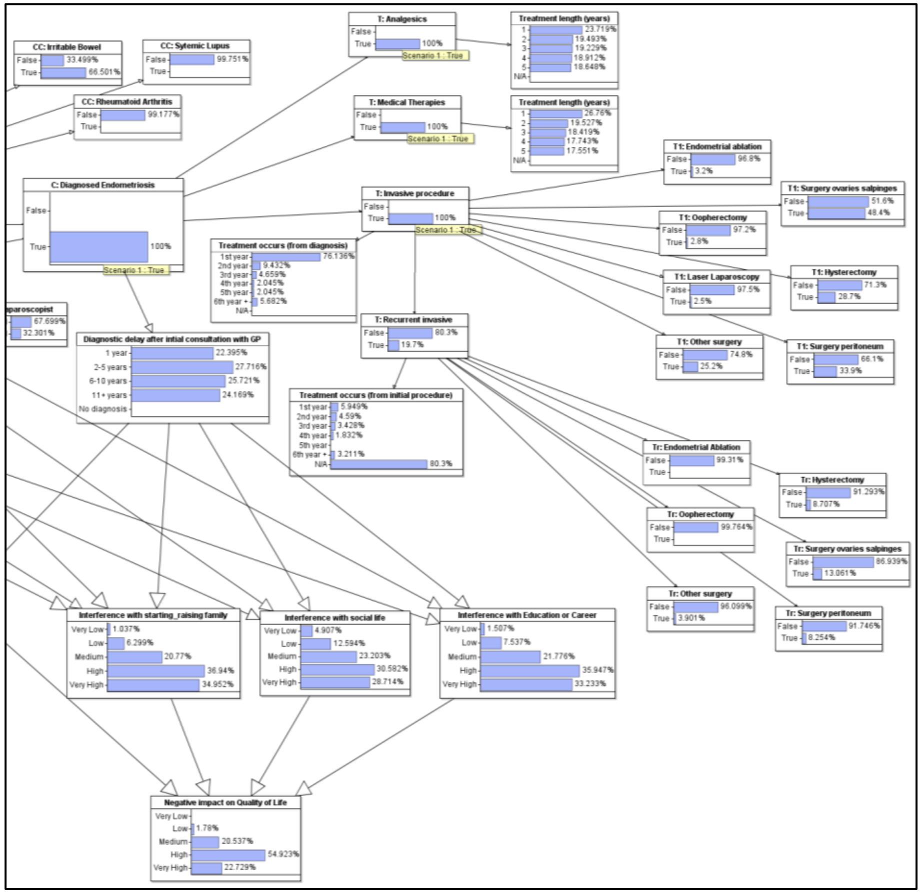
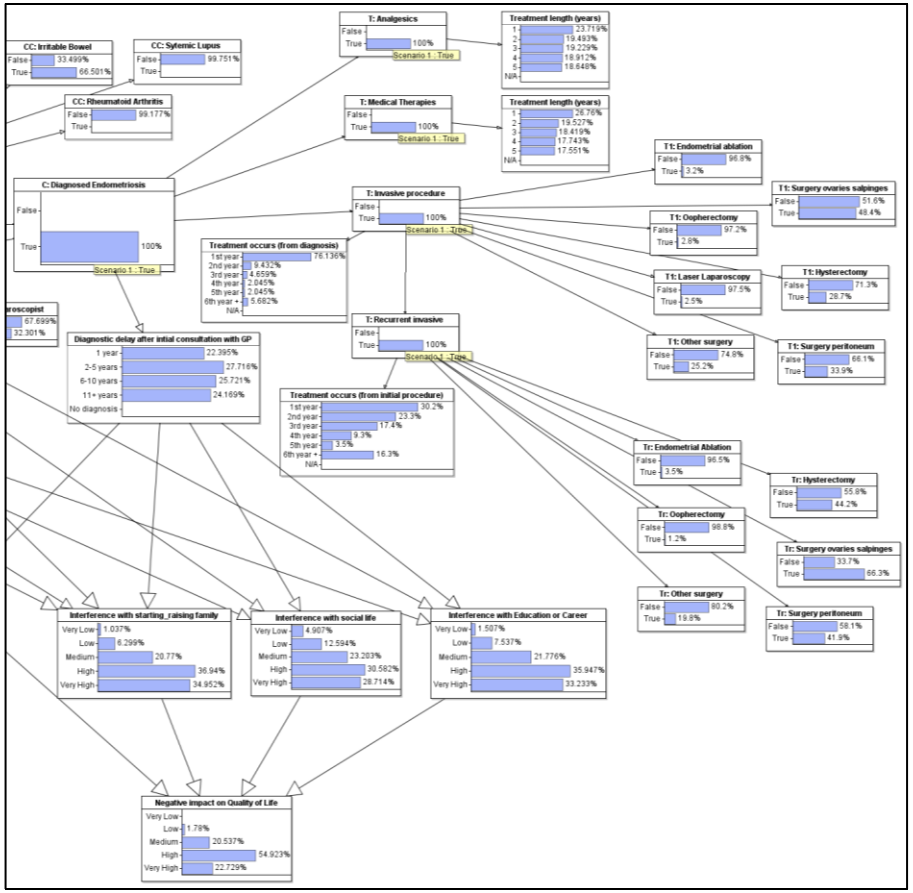


Figure 15. Endometriosis diagnostic model with 'Diagnosed Endometriosis' observed as true.



a)

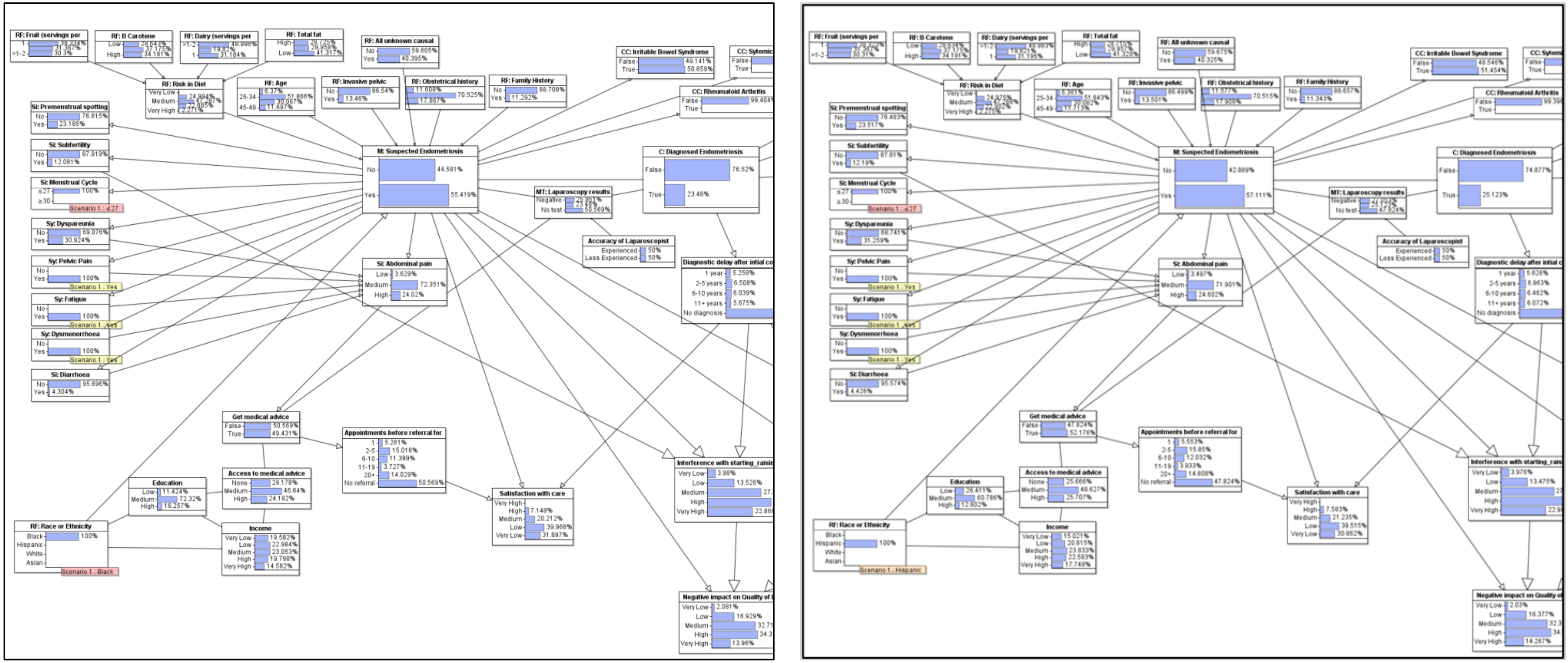


b)

Figure 16. a) Endometriosis diagnostic model with treatments observed. b) Endometriosis diagnostic model with Recurrent invasive procedures observed

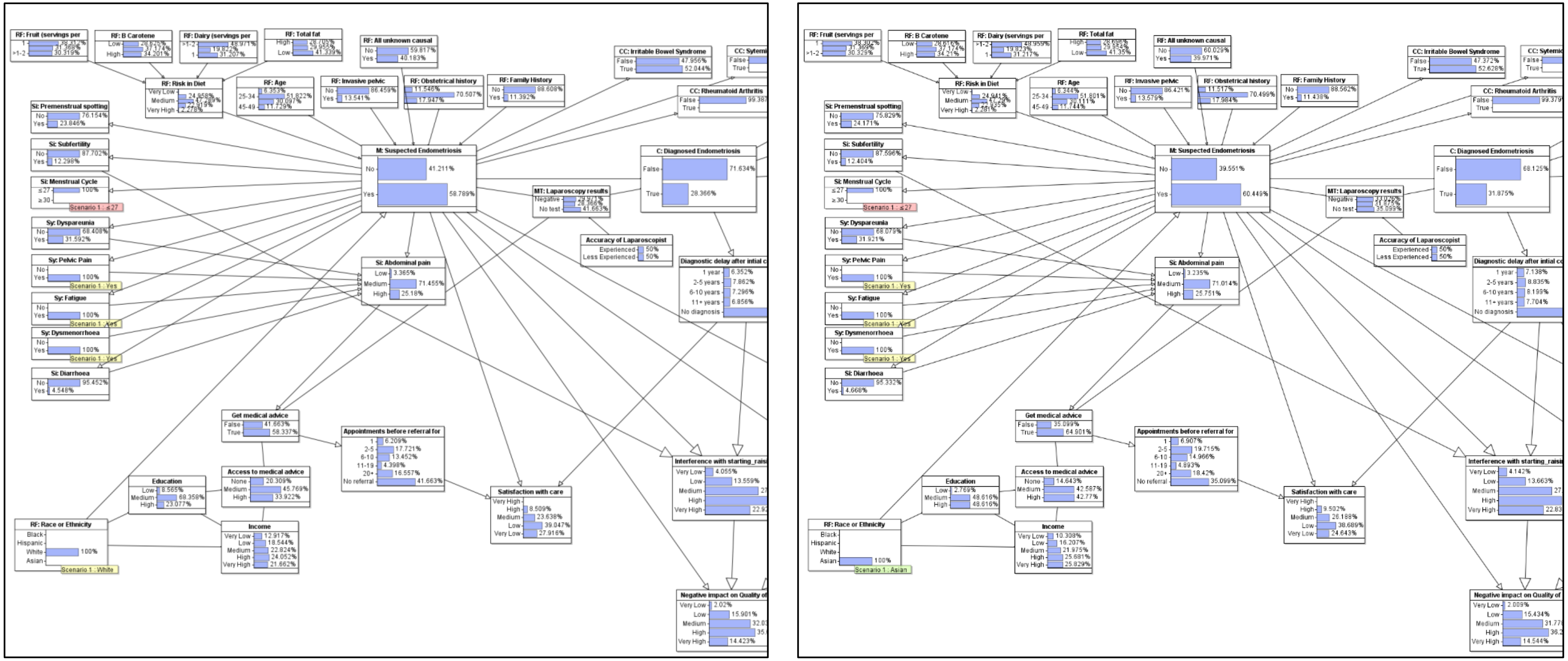
C. *Appendix C*

RACE AND ETHNICITY FACTORS



a) b)

Figure 17. a) Suspected endometriosis probability 55%, Diagnosed endometriosis probability 23% when 'Black' observed in Race or Ethnicity node. b) Suspected endometriosis probability 57%, Diagnosed endometriosis probability 25% when 'Hispanic' observed in Race or Ethnicity node



a) b)

Figure 18. *a) Suspected endometriosis probability 59%, Diagnosed endometriosis probability 28% when 'White' observed in Race or Ethnicity node. b) Suspected endometriosis probability 60%, Diagnosed endometriosis probability 32% when 'Asian' observed in Race or Ethnicity node*

D. Appendix D

SATISFACTION WITH CARE

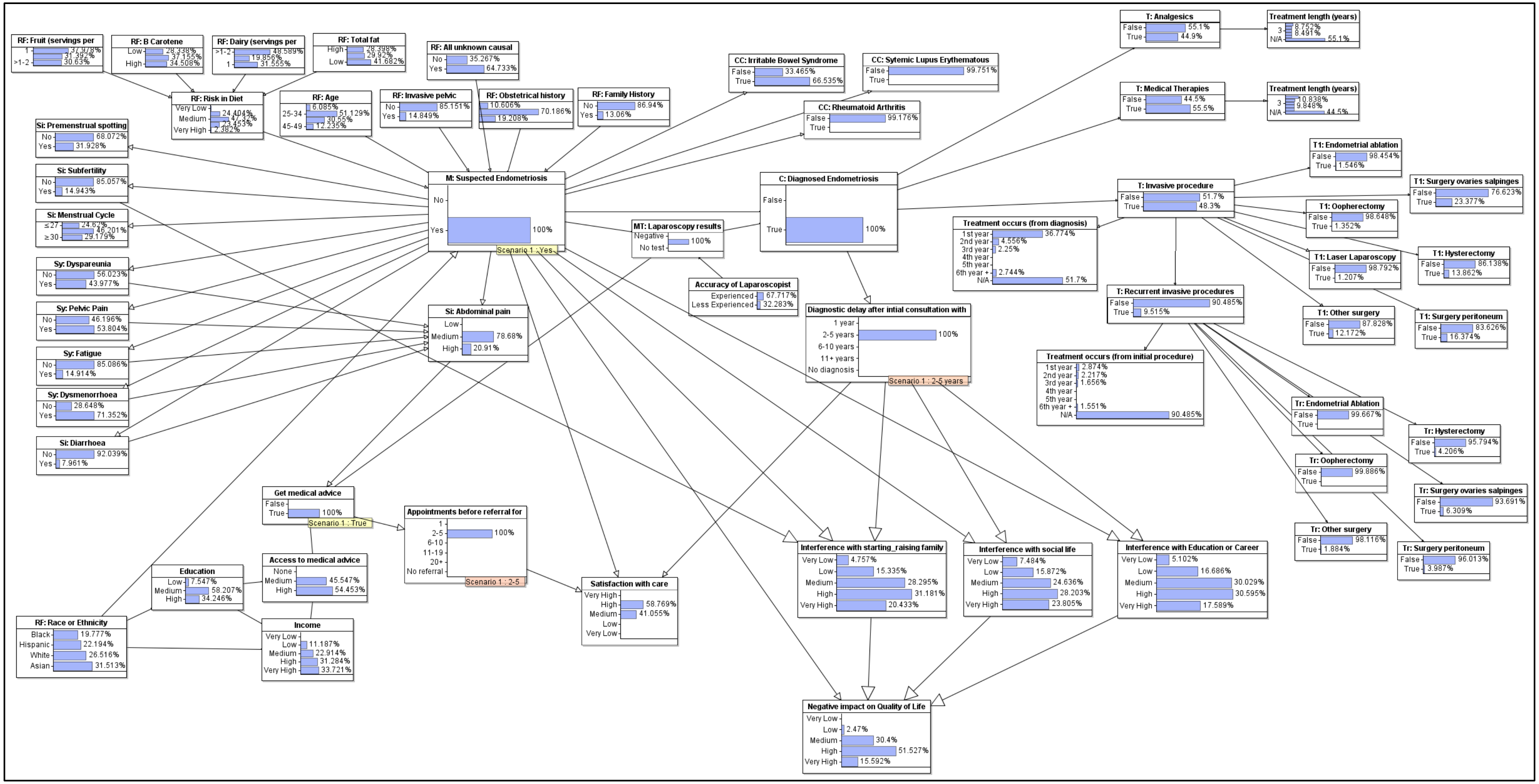


Figure 19. Endometriosis diagnostic model with '2-5' observed for 'Appointments before referral' and '2-5 years' for 'Diagnostic delay'.

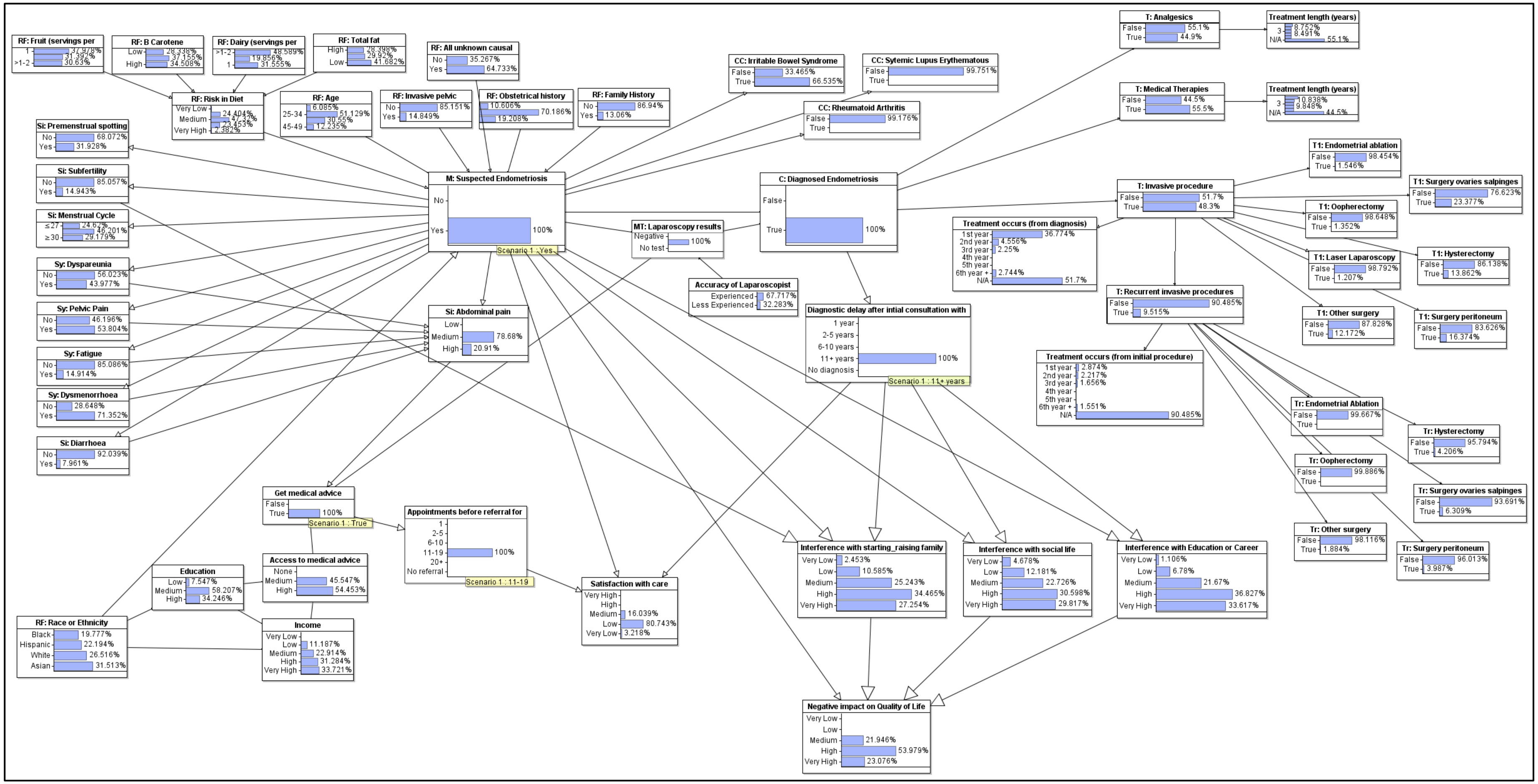


Figure 20. Endometriosis diagnostic model with '11-19' observed for 'Appointments before referral' and '11+ years' for 'Diagnostic delay'.

MSc Project - Reflective Essay

Project Title:	The application of Bayesian network modelling for the early diagnosis and prediction of the medical condition Endometriosis
Student Name:	Rachel Collins
Student Number:	190706089
Supervisor Name:	Professor Norman Fenton
Programme of Study:	MSc Computing and Information Systems

For my MSc project, I elected to create a diagnostic Bayesian Network (BN) causal model for the diagnosis of endometriosis. Endometriosis is a debilitating, yet common, gynaecological condition that affects 6-10% of women of reproductive age (Rogers, et al., 2013). I was especially interested to investigate this topic having known people affected by the condition who have suffered in pain for years without a diagnosis, adequate treatment, or reassurance from their medical professional. I felt confident creating a BN causal model following my undertaking of Professor Fenton's 'Risk and decision-making for data science and AI' module in my second semester at Queen Mary, University of London. I completed my project by creating a BN causal model that can be used to aid clinical decision making for the diagnosis of endometriosis. The model also calculates the probability of the individual being formally diagnosed by factoring in suspected endometriosis, accuracy of laparoscopic procedures, and the individual's access to medical advice.

<u>Analysis of strengths and weaknesses</u>

The first hurdle I had to overcome was encountering the range of conflicting studies investigating the risk factors associated with endometriosis. I initially felt overwhelmed by the sheer weight of content available and had to create a structure for myself to adequately review as much as possible within the time frame. I found I lost time reading papers that were not helpful or were actively trying to forward an agenda or product, before being able to swiftly identify what I required. I encountered inconsistencies in the way clinicians and primary care centres reported symptoms and diagnosis. Effort was spent collating and matching these symptoms. It then became quite evident that 'risk factors' associated with endometriosis included areas of risk and signs and symptoms. Time needed to be spent separating causal influences among the associations to correctly construct the model.

I could not find other authors who had used BN causal models for the prediction of endometriosis. As a result, I felt confident that I had found an area of research that needed to be filled. However, as a drawback, I found I had nothing to compare my study to, for reassurance that was heading in the right direction. Similarly, the onset of nationwide self-isolation protocols made me feel somewhat isolated from my peers and I think that lack of support from them was truly missing during this period. I had to use my communication skills to use calls with Professor Fenton effectively.

As I created my model from data extracted from published studies, I had to be confident that their results were correct. I was concerned that many of the studies I used for my model would be susceptible to confirmation bias, as no matter how much the knowledge of the outcome is resisted it cannot help but influence the result. This is reflected in my model by 'Suspected Endometriosis' becoming almost certainly true when only a few symptoms are observed. I tried to counteract this aspect by introducing an 'abdominal pain' node to create some interdependencies between the symptoms. However, this may be a weak point within the model and would benefit from further study into how symptoms interact and influence each other.

The possibility of cofounding variables was also a concern of mine. Some of these were identified, such as the influence of socio-economic factors in the access of patients to medical care however, I am sure more exist (Williams, et al., 2010).

Presentation of possibilities for future work

If I had more time on this project, I would want to increase the scope of the model by developing it into a dynamic model, i.e. the evolution of the model through time. To do this I would need to build a second stage or iteration following two years of treatment, in which treatment observed would have an influence upon the symptoms exhibited by the patient, it would provide a view of the observational impact of the intervention. If this could be created I, and clinicians, could take advantage of counterfactual reasoning to ascertain the outcome of treatment types and aid with the decisions that need to be made (Pearl & Mackenzie, 2019).

This scope could be increased again to develop the model into an influence diagram whereby there is at least one decision node, which could be 'Hysterectomy,' a form of treatment. The influence diagram would also include utility nodes, which in this example could include 'cost: loss of fertility', 'cost: cost of procedure' and 'benefit: reduced rate of recurrence' which would influence an overall utility node to indicate the benefit to the patient, or policymaker.

Finally, if provided with more time, I would like to build a user-centric interface, using Java API, to sit over the model to allow the clinician to interact with the model in a comfortable manner.

Critical analysis of the relationship between theory and practical work produced

In a BN causal network, each node represents some variable of interest and the arc between the two nodes represents an influential, or causal, relationship. This definition has been reflected in my model, however due to an aspect of the software used, the direction of influence cannot always be easily recognised in the images produced. A schematic of the model was included in the report to assist with reader understanding. Bayes theorem is extended to perform necessary probability updating between variables from the information in the node probability tables (NPTs). This data was extracted from observation studies.

By creating a BN causal model, I could overcome basic flaws and limitations of other commonly used approaches when analysing endometriosis by utilising a simple causal approach to risk assessment. For example, observational studies collect vast amounts of data on the topic of interest. As a result, they become susceptible to Simpson's paradox, in which a co-founder variable changes the outcome of results when observed, and supressed data, as clinicians collect considerable data on the condition and patients diagnosed with endometriosis yet have little data on patient's not diagnosed with the condition. To fix the problem of Simpson's paradox you need to make sure equal number of subjects and equal number in all subcategories. Controlling for even a few possible cofounders means you run out of possible subjects. By creating a casual model, I can simulate a randomised control trial (RCT) to resolve the issue simply by breaking the link between dependencies. Unfortunately, I was unable to fulfil this area of the model due to time constraints. It would be a beneficial area to explore is widening the scope to include a second iteration involving treatments as described above. I would like to fully develop the model along Pearl's ladder of causation: association, intervention, and counterfactuals.

From my studies, I understand that problem framing for risk is a crucial element. Risk is an event that can have negative consequences. In causal analysis, risk is defined as an event that can be characterised by a causal chain of events involving a trigger, risk event and consequence. In my model this is represented by risk factor -> suspected endometriosis -> symptom, another example is race/ethnicity of patient -> income -> access to medical advice.

A crucial graphical feature of a Bayesian network is that it informs as to which variables are not linked, therefore capturing our expectations about which pairs of variables are not directly dependent (Fenton & Neil, 2019). Yet, as mentioned above, the interdependencies between symptoms of endometriosis have not been researched extensively so this may be an incorrect assumption. Therefore, a common causal factor, 'abdominal pain' was introduced to explain the causal relationships.

I successfully created a diagnostic BN causal model for endometriosis by structuring it with use of medical idioms elicited from expert knowledge and data available (Kyrimi, et al., 2020).

<u>Awareness of legal, social, ethical issues, and sustainability</u>

I am acutely aware that there are negative and positive impacts when using technology and artificial intelligence (AI) algorithms within the health sector, and society at large. There needs to be an awareness and responsibility about how algorithms, AI, and data collection impact various parts of the public. Issues surrounding the protection of personal data and questions concerning accountability and responsibility when accessing and storing that data are becoming more significant.

There is a risk that ethical issues are framed within technical terms rather than addressing the moral significance of technology advancements. For example, ethical issues are framed as making machine-learning systems more usable and reliable or issues relating to privacy and data protection. Yet it is also important to ascertain whether all members of society, including minority groups, are being represented in this conversation as technology continues to develop. An EDPS advisory group, in 'Towards a Digital Ethics' list concerns about the balance of power between governments, individuals and large technology companies. Without understanding the perspectives of different groups in society we risk alienating and harming the values and needs of the majority at the expense of the minority. It would be beneficial to produce a single, theoretical framework of principles and values aimed at protecting individual's data and autonomy rather than relying on a 'code of conduct' put forward by individual companies.

From my research, there are concerns about algorithmic bias, it is often assumed human decision-makers are being replaced by algorithms. Yet, bias is often built into the algorithm by the builder either subconsciously or because of using expert knowledge, which is biased. For example, the role of race as a risk factor in my Endometriosis model, or inherent bias in a recent A-level results algorithm benefiting students from public schools and penalising students in state/comprehensive schools (Elsom, 2020).

The IEEE Standards Association developed a set of general principles to guide ethical governance. Widespread agreement that AI should not be used to harm people or undermine their fundamental rights. These principles should also respect values such as fairness, privacy, and autonomy. They may also provide a means of holding individuals and organisations accountable. Assumptions need to be identified and knowledge gaps filled around capabilities of technology to allow principles to be practiced.

Conclusion

To conclude, I have successfully created a diagnostic BN causal model for the medical condition endometriosis. I aimed to use my organisational and communication strengths to use my time wisely and effectively. I aimed to transfer the knowledge I gained during my taught modules to this project. There is scope to advance the model from the start I have given it, to include counterfactual reasoning. I was aware of the social, ethical, legal and sustainability issue surrounding advancements in AI and technology and tried to account for them in my work.

References

Burgess, J. P., Floridi, L., Pols, A. & van den Hoven, J., 2018. *EDPS Ethics advisory group. Towards a digital ethics,* s.l.: EDPS.

Elsom, D. J., 2020. *Inbuilt biases and the problem of algorithms,* s.l.: Guardian News & Media Limited.

Fenton, N. & Neil, M., 2019. *Risk Assessment and Decision Analysis with Bayesian Networks.* 2nd ed. Boca Raton: CRC Press.

Kyrimi, E. et al., 2020. Medical idioms for clinical Bayesian network development. *Journal of Biomedical Informatics,* 108(103495).

Pearl, J. & Mackenzie, D., 2019. *The Book of Why: The New Science of Cause and Effect.* London: Penguin Books.

Rogers, P. A. W. et al., 2013. Defining future directions for endometriosis research: Workshop report from the 2011 World Congress of Endometriosis in Montpellier, France. *Reproductive Sciences,* 20(5), pp. 483-499.

Whittlestone, J. et al., 2019. *Ethical and societal implications of algorithms, data, and artificial intelligence: a roadmap for research,* London: Nuffield Foundation.

Williams, D. R., Mohammed, S. A., Leavell, J. & Collins, C., 2010. Race, Socioeconomic Status and Health: Complexities, Ongoing Challenges and Research Opportunities. *Ann N Y Acad Sci,* February(1186), pp. 69-101.