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Project Title: Evaluating poor outcome for Manitoba women with epithelial ovarian cancer.

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SUMMARY: (no more than 250 words single spaced)

Relative survival rates for ovarian cancer (OvCa) in Manitoba were recently reported as some of the lowest in Canada. To investigate accurate survival rates for Manitoba OvCa patients from 2004-2010, we constructed a database seeded with complete, manually extracted data. We identified factors in the patient journey from suspicion to treatment, which may be delaying diagnosis and subspecialist referral. Descriptive and inferential statistics were used to identify and compare different groups within the patient population. Significant differences in variables (age, stage, histotype, income) were found between patients who were referred to CancerCare Manitoba (CCMB) or not, and between those who presented to the emergency room or elsewhere. CCMB patients who first presented to the ER were found to have worse outcomes, despite being referred and diagnosed more quickly than those presenting elsewhere. This was attributed to more severe disease in these patients. The utility of the Risk of Malignancy Index (RMI) triage tool was assessed in terms of time to diagnosis and referral. It was found that severity of disease at presentation played a larger role in these timelines than completeness of RMI workup. The poor outcomes seen are due to the high amount of late stage patients that present to the ER or are not referred to CCMB. Reducing the number of these patients would require detection of less progressed disease at early stages. At the conclusion of the study we propose recommendations for primary care providers to better recognize and triage early stage OvCa cases with low suspicion.

Student Signature

Supervisor Signature

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INTRODUCTION & BACKGROUND

A recent report indicated that 5-year relative survival of ovarian cancer patients in Manitoba ranged from 28.8-37.1% (1). This was significantly lower than survival rates for Canadian women in other health jurisdictions (38.2-41.9%). We sought to identify factors in the Manitoba population or health care system that may contribute to these potentially alarming statistics.

As part of the International Cancer Benchmarking Partnership (ICBP), Coleman *et al.* reported the relative survival rates of several types of cancers compared amongst 12 jurisdictions in 6 countries of similar health care systems and wealth (Australia, Canada, Denmark, Norway, Sweden, and the UK) during the time period of 1995-2007 (1). This included Manitoba, British Columbia, Alberta, and Ontario. They reported 5-year survival rates for ovarian cancer in Manitoba as 32.7% from 1995-1999, 37.1% from 2000-2002, and 28.8% from 2005-2007. The Canadian survival rates during the same time periods were 38.2%, 38.4%, and 41.9% respectively (1). These statistics may lead one to conclude that women diagnosed with ovarian cancer from 2005-2007 may expect approximately 10-15% better 5-year survival if they were diagnosed in Canadian provinces other than Manitoba. Coleman *et al.* postulated that clinical factors may play a role in these survival rates, such as public awareness of cancer, diagnostic delay, stage, comorbidities, and access to treatment. Beyond the treatment offered for a particular cancer, the effectiveness of the health care system overall contributed to relative survival, as was investigated in this large multi-jurisdiction analysis (1).

Publication of these results raised questions about the efficiency of recognition, referral, and quality of care at CancerCare Manitoba (CCMB) as compared to other provinces in Canada. However, it assumes that all cancer registries across Canada collect data to the same standards and level of entirety. The North American Association of Central Cancer Registries (NAACCR) has put forth methods to assess the completeness of case ascertainment of individual Cancer Registries (2). Cancer registries with incomplete capture of incident tumors can lead to biased estimates, especially of incidence, prevalence, and survival (2). NAACCR regularly evaluates provincial cancer registries, including the Manitoba Cancer Registry, which has received the highest gold rating in quality of data capture since 2004, where other provinces have had inconsistent ratings over the same time period, ranging from gold, to silver, to 'rating not achieved' (3). Since the data considered in the Coleman *et al.* paper was taken from provincial cancer registries, which may not have met the same standards, this should be considered when comparing Manitoba to other provincial registries.

Epithelial ovarian cancer (OvCa) has the highest mortality rate of all types of ovarian cancer. Recent research has shown that the majority of these malignancies found on the surfaces of the ovary, may in fact originate from other structures of Müllerian origin, specifically the fallopian tube and peritoneal surfaces (4). For this reason, these malignancies were included in our dataset, and in this thesis, 'ovarian cancer' and 'cancers of ovarian origin' will be used in reference to all of them. Epithelial malignancies of Müllerian origin also correspond to the different recognized OvCa histotypes: serous, mucinous, endometrioid, clear cell, transitional, undifferentiated, and mixed epithelial tumors (5). Serous tumors can also be divided into borderline, low and high grade serous carcinomas although this distinction was not made in this report (5). Although these histotypes have been subdivided in certain parts of my thesis to assess associated variables in unclassified cases, in general they are considered together as epithelial ovarian cancers. Non-epithelial ovarian tumors (germ cell, sex cord-stromal or metastatic) are less common, and have different epidemiological patterns, natural histories, and treatments (5). For these reasons they were excluded from my report.

In earlier stages, OvCa tumours can exert local mass effects causing abdominal distention, pain, bladder compression, hydronephrosis, or constipation (6). Metastasis involves both lymphatic spread (to the pelvic and para-aortic lymph nodes) and shedding of malignant cells

into the peritoneal cavity to implant on the peritoneal surfaces of the abdominal wall and organs (6). Both of these processes may contribute towards generation of ascites, and intraperitoneal inflammation, causing worsening symptoms, as well as organ compression leading to functional compromise (6). Death in OvCa patients results from dysfunction of abdominal organs (liver, bowel, kidney) leading to severe abdominal symptoms (nausea, vomiting, distention) (6). Despite the breadth of knowledge around the histotypes and natural history, there is no effective screening test to detect OvCa at earlier, more curable stages.

The Society of Obstetricians and Gynaecologists of Canada (SOGC), Gynaecologic Oncologists of Canada (GOC), and Society of Canadian Colposcopists (SCC) released joint clinical practice guidelines in 2009 detailing their recommendations for management of pelvic/ovarian masses (7). They insist that the diagnosis of OvCa should be on the differential diagnosis of any woman with suspicion of an ovarian mass (7). OvCa should be especially considered in postmenopausal women (50-55 years old), or in the perimenopausal period (3-5 years before and after menopause) (6). Although the majority of ovarian masses in premenopausal women will be benign, steps should be taken to ensure that is the case (7). In those with seemingly benign/functional disease on imaging (e.g. functional cysts), it is prudent to repeat imaging to ensure resolution, and to monitor patients for worsening symptoms. One must also keep in mind that benign disease can occur simultaneously with malignancy (7).

A careful characterization of patient symptoms including pelvic/abdominal pain, urinary urgency/frequency, abdominal distention/bloating, early satiety, nausea/vomiting, or changes in bowel movements is imperative. A detailed family history of malignancy must be obtained, and a thorough physical exam should be done in considering malignancy (7). The guidelines recommend that if a physician has a reasonable suspicion of OvCa based on history and physical exam, a serum CA-125 level measurement and a transvaginal pelvic/transabdominal ultrasound should be considered to assess the malignant potential of an ovarian mass via calculation of a Risk of Malignancy Index (RMI) score. There are multiple versions of this scoring system, but the RMI II scoring system was used for the cases in this thesis. The RMI score is calculated by multiplying three OvCa risk factors: the ultrasound score, menopausal score, and serum CA-125 level (U/mL) (7). The ultrasound score depends on the presence or absence of 5 features suggestive of a malignant pelvic mass (solid areas within the mass, loculations within the mass, ascites, bilaterality of lesions, and intra-abdominal metastasis) (7). The menopausal score accounts for the higher risk of malignancy in postmenopausal women (7). Finally, an elevated CA-125 level has been shown to be relatively suggestive of OvCa with variable sensitivity and specificity (8). The calculated RMI score is either above or below the cut-off of 200 (‘high’ or ‘low’), where scores over 200 indicate the patient is at high risk of OvCa (7). This scoring system can be used by any physician in Manitoba as an effective way to stratify the risk of OvCa in their patient. The final recommendation put forth in these guidelines is that any patient with high clinical suspicion of OvCa (high RMI score, or blatant OvCa with any level of investigation) should be referred to a gynecologic oncologist (GynOnc) for assessment (7).

The lack of screening tests available for OvCa and the non-specific symptoms play a role in the large proportion of cases diagnosed at later stages, and the poor survival outcomes documented. For the ~2800 women diagnosed with OvCa in Canada this year, ~1750 will die (9). In 2012, the Canadian Cancer society estimated that 80 Manitoban women will die while ~90 women will be diagnosed with OvCa; the age-standardized incidence calculated from the data in this thesis was 12.65/100,000 (~77.5 women diagnosed). OvCa diagnosed at later stages (defined by the International Federation of Gynecology and Obstetrics [FIGO] as Stage III or IV) is shown to have worse outcomes (10). In 2012, only 32% of Manitoba OvCa cases were diagnosed at Stage I with the majority (57.7%) diagnosed at Stage III/IV (11). This makes OvCa the 5th most common cause of cancer-related death amongst Manitoba women (9).

A comprehensive electronic database based on retrospective data detailing the demographics, treatment, and outcomes of women with OvCa treated in Manitoba did not exist before this project was started. Data specific for this project was seeded into the database during the first term of the B.Sc. (Med) program and throughout Med II. Analysis of survival rates and specific factors that might affect outcome were initiated during the second term. This study will aim to calculate accurate survival rates for OvCa patients in Manitoba, using up-to-date, manually extracted data, as well as identify any factors contributing to particularly poor outcomes in subgroups of this cohort. The utility of the RMI as a triage tool will be assessed in analyzing its association with diagnostic and referral timelines, as well as outcomes.

MATERIALS & METHODS

DATABASE FORMATION & STUDY COHORT With institutional research ethics board approval (HREB H2012:145), a database for this purpose was created using the CAISIS system (a web-based oncology data manager), available in the Cancer Registry at CancerCare Manitoba. All research was conducted in CancerCare Manitoba using secured computer system and paper charts. Patient consent was not sought for this study because it is a retrospective chart review, and will not alter the management of the study subjects. All materials pertaining to patient identification were kept strictly confidential. A unique code was assigned to each patient in the database. All paper charts were kept in a locked filing cabinet in a locked office in a security-controlled building and were never taken offsite for review. The findings presented omit all personal identifiers that may potentially link a patient to the study.

Invasive epithelial OvCa cases diagnosed between January 1, 2004 and December 31, 2010 were identified through the Manitoba Cancer Registry using the following ICD-O-3 codes: C48.1-C48.8, C56, and C57 (peritoneum, ovary, fallopian tube, uterine ligaments, other and unspecified female genital organs). The morphologies of sex cord-stromal and germ cell were excluded. Patients residing, or treated outside of Manitoba, were also excluded. The total cohort used in subsequent analysis included 687 patients. December 31, 2014 was considered the end-of-study date, which included the most up-to-date information in the Cancer Registry.

DATA COLLECTION Data extracted from the Registry included record type (chart or report only), morphology codes, age at diagnosis, FIGO staging, postal code at diagnosis, treatment information, and death date. Postal codes were used to identify residence at diagnosis and were also converted into income quintiles (stratified into urban and rural; Winnipeg and Brandon were considered urban) (12). Data extracted from electronic and paper charts (maintained by CancerCare Manitoba) included dates and details of physician encounters prior to, and after diagnosis, dates and details of diagnostic imaging procedures, dates and values of serum CA-125 levels, as well as additional treatment information. Physician notes from encounters included signs and symptoms, which identified when OvCa could first be suspected. The type of physician at each encounter was also identified.

ANALYSES Analyses were performed on OvCa cases that had chart information available. Descriptive statistics were calculated for all patients, and included a comparison of chart with report only patients. RMI was calculated using diagnostic information between the first date of suspicion and the date of diagnosis. The frequency of physician encounters from suspicion to diagnosis was calculated, and the series of physician types encountered from suspicion to diagnosis were also tabulated.

Several predictors were used in the multivariable logistic regression analysis of patients presenting to the emergency room (ER), and in the multivariable quantile regression of the time from suspicion to diagnosis, and in the time from suspicion to CCMB referral (assumption of normality could not be met for the latter two analyses). These predictors were age at diagnosis, FIGO stage at diagnosis, histotypes, year of diagnosis, income, symptoms at first presentation,

and whether the GynOnc encounter was before or after diagnosis. First presentation in the ER was also used as a predictor for the time period regression analysis. The predictors of GynOnc encounter and treatment were time-varying, to account for their changing status post-diagnosis. Overall survival post-diagnosis was analyzed using time-varying Cox regression models. Survival analyses were stratified by early- and late-stage cancer, due to the large heterogeneity between those groups, and the strong relationship between stage and treatment. Survival was measured as either a death recorded prior to, or on, the end-of-study date, or the individual was censored at the last physician encounter, or end-of-study date.

Analyses were conducted using R version 3.2.1. The rms package was used for logistic and Cox regression models. The quantreg package was used for quantile regression models. Restricted cubic splines were used for continuous predictors that violated the assumption of linearity. Predicted values from restricted cubic splines adjusted for other covariates at their mean were plotted. The proportional hazard assumption [hazard ratio (HR)] was evaluated using Schoenfeld residuals. Other diagnostics were performed using residual and influence plots. Likelihood ratio testing was used for model building. The RMI II scoring system was used and was calculated by RMI = ultrasound score x menopausal score x serum CA-125 level (U/mL) based on the SOGC guidelines (7).

RESULTS

During the time period of the BSc (Med) project, the database as described was successfully designed, and I was responsible for seeding the data for the 601 chart patients with information from the various sources. In cooperation with the health outcomes analyst and supervisors, I chose the direction of the study, which outcomes to analyse, and their interpretation in the context of previously published results. While most of the current findings were exploratory (and frequently non-significant), the direction and magnitude of the risk ratios were intriguing and will set the direction for further analysis. The database has far-reaching potential and can now be accessed for future research projects related to OvCa, such as correlations of patient outcome from changes in clinical management over time.

Chart vs Report Only Patients In light of the 2011 Coleman *et al* (1) publication highlighting the poor OvCa outcomes in Manitoba, we decided to separate our cohort into those who were referred to CCMB (“chart” patients), and those whom CCMB were notified of their OvCa only by report of malignant neoplasm, or report of their death (“report only” patients). This allowed us to look for any differences in patient demographics affecting outcome free from referral bias. The combination of the data from the Manitoba Cancer Registry and the data I extracted manually also provided a more accurate survival analysis of the cohort overall compared to the dataset used for the analyses reported in the Coleman paper (1).

For analysis of survival (Figure 1), the Kaplan-Meier curve showed survival of report only patients over time is significantly worse compared to chart patients. 3-year survival for the entire cohort was 45.2% (1-year survival 67.4%). When the report only patients were removed, the 3-year survival of chart patients was 48.8% (1-year survival was 72.9%). In fact, these results are comparable to the best survival for Canadian women as reported in Coleman *et al.* (1).

Table 1 shows the characteristics seen in report only and chart patients. Several significantly different characteristics were identified. Report only patients were diagnosed at a mean age of 79.2 years, 15.8 years older than that of chart patients. 34.9% of report only patients were diagnosed with OvCa at an unknown stage (as compared to 11.8% of chart patients), and 47.7% were most commonly diagnosed with ‘unclassified epithelial’ morphology. There was a prevalence of late stage disease in the chart patients (53.3%), whereas many of the report only patients had unknown stage (34.9%).

53.5% of report only patients received no treatment (no cancer-specific chemotherapy or surgery), while the most common treatment for those receiving intervention was surgery alone (32.6%). Of note with respect to presenting symptoms (as recounted by patients at CCMB admission), abdominal distention (30.0%) and abdominal pain (39.1%) were the top two most commonly seen in the chart cohort. Statistical significance was not determined for these characteristics due to the small sample size. We also looked at urban/rural place of residence that showed no statistically significant difference between chart and report only patients.

For the subsequent results and analysis contained in this thesis, chart patients will be used exclusively as these represent the most complete data sets, and allow us to use GynOnc encounter as the endpoint in the patient journey.

ER vs Non-ER Patient Presentations Along with recognizing the differences between chart and report only patients, there were also different groups recognized within the chart patients themselves. Dividing this group into those where the initial point of suspicion was in the ER ("ER patients") as opposed to any other healthcare setting ("non-ER patients") allowed me to test differences in the diagnostic or referral process, and see any corresponding differences in outcome. Hereafter, 'initial point of suspicion' may be referred to as 'presentation'.

As shown in Table 1, a large proportion of chart patients presented to the ER (29.0%); in fact, patients who were living in Winnipeg had significantly higher odds (2.2 fold) of presenting to the ER than those who were living outside of Winnipeg (Table 2). Further descriptive output showed that there were implications and associations applying to patients who present to the ER. In particular, significant differences in survival can be seen in Figure 2 where ER patients do much worse than non-ER patients over time. As well, late stage patients who presented to the ER were 1.5 times more likely to die than those who presented in a different setting ($p = 0.0018$).

Some of the reasons contributing to the poor outcome in ER patients are similar to those implicated in poorer report only patient survival: symptomatic patients presenting with terminal disease, and refusing further workup or treatment. This was indicated by a higher amount of ER patients without histotype classification. The odds of a patient who presented in the ER having unclassified disease are higher than that for a non-ER patient. This is shown by the significantly lower odds ratios for an ER patient, relative to a non-ER patient, to have OvCa classified as serous or clear cell/endometrioid subtypes compared to unclassified (Table 2). Late stage ER patients with classified disease had a reduced risk of death compared to those with unclassified epithelial OvCa [serous HR: 0.71 ($p = 0.0155$), clear cell/endometrioid HR: 0.407 ($p = 0.0067$)].

Histotype classification usually requires histology (of a surgical specimen or core biopsy) as the method of diagnosis. Cytology can be done in the ER, or clinical setting (non-ER), with sampling of ascites or pleural fluid, and can indicate that the malignant cells are of epithelial origin only. Table 3 shows both the initial method of diagnosis ("Diagnosis Method"), as well as diagnosis confirmation (updated diagnostic proportions if a more accurate method was used later on in the case) for ER and non-ER patients. A scenario where there is no diagnostic confirmation after cytology, often applies to late stage ER patients with a poor prognosis. This is seen in the 14.6% of chart cases with no diagnostic confirmation beyond cytology (Table 3). Late stage patients were 1.5 times more likely to present to the ER than elsewhere ($p = 0.0018$). Many of the ER patients presented with late stage, and diagnosed with unclassified morphology, both of which are associated with worse outcomes in my study.

Key Timelines & Physician Encounters in the OvCa Patient Journey Time to diagnosis and to GynOnc encounters are crucial to minimize for OvCa patients as the disease can progress significantly in a short period of time, and it is known that treatment by GynOnc rather than other specialists has been linked to better outcomes (13). Two time periods in the patient journey were measured for both ER and non-ER patients, and any significant variables were identified.

Suspicion is defined as the point at which the patient presented to a health care provider with a related symptom or there was an incidental physical/imaging sign of OvCa detected. The time period from point of suspicion to point of diagnosis (referred to as the 'diagnostic period') was compared between the two groups of patients (Figure 3). The median time until diagnosis for an ER patient was 7 days, as compared to 51 days for non-ER patients. At 30 days post suspicion, 73.6% of ER patients were diagnosed, as compared to 35.6% of non-ER patients. Improved incidence of diagnosis is seen at 60 days post suspicion, with 85.6% of ER patients and 55.3% of non-ER patients diagnosed.

The term 'referral period' refers to the time between point of suspicion until referral to GynOnc. The median referral period for ER patients was 18 days, whereas non-ER patients had a longer referral period of 49 days. 67% of ER patients, and 32.9% of non-ER patients had been seen by GynOnc within 30 days of suspicion. At 60 days, this incidence had increased to 80.5% of ER patients, and 58.2% of non-ER patients (Figure 4).

As part of characterizing the journey of an OvCa patient living in Manitoba, it was useful to know the frequency of encounters, and what types of physicians were encountered during these time periods. An encounter may be defined as a visit with any practitioner, on an emergent or non-emergent basis, leading to further referral, return visits, or neither. In general, it was observed that the majority of patients were diagnosed by GynOnc, (53.7%), and only 4.7% were not seen by GynOnc at all. 71.9% of the OvCa patients were diagnosed within 2 encounters (24.5% were diagnosed after 1 encounter) (Table 4). In the cases of 2 encounters, usually a family doctor or emergency physician referred the patient to a GynOnc by whom they were subsequently diagnosed (Table 5). In the cases of 1 encounter, most typically an emergency physician or a family doctor did the patient workup, which in itself was diagnostic of OvCa. Although many patients followed these typical, ideal journeys to diagnosis, 28.1% of patients required at least 3 encounters before diagnosis, and 49.3% of patients had a referral pattern different than those listed in Table 5.

Use of Risk of Malignancy Index in Manitoba OvCa Patients The worse outcomes associated with ER patients, coupled with their high prevalence in our chart cohort, emphasize the need to identify OvCa earlier, to prevent these patients becoming emergently symptomatic with extensive disease. One tool put forth to help detect OvCa in patients with low clinical suspicion (often at earlier stage, in the non-ER setting), is the RMI. To assess the effectiveness of the RMI in our non-ER patients, we were able to describe how many had a complete RMI workup resulting in a high (>200) or low (</=200) score, or had an incomplete RMI workup before they were diagnosed. A "complete RMI workup" refers to both CA-125 level measured and diagnostic imaging (CT Scan, ultrasound, or MRI of the abdomen and/or pelvis) completed, and the score calculated. 'Incomplete RMI workup" refers to only one of these investigations done before diagnosis. Of importance to note in my report, the RMI data was captured at any point from suspicion to diagnosis, and some of the cases may have had their RMI testing "completed" by the GynOnc after referral. This may be causing an underestimate in the use of RMI testing in the community by primary care practitioners (PCPs).

Table 6 shows the proportion of non-ER cases in these categories, and which test had been done in those with incomplete RMI scoring. 56.0% of non-ER patients had a complete RMI workup before diagnosis (43.3% scored high). Of the non-ER patients with an incomplete RMI workup, most commonly only imaging was done (27.9%), whereas a much smaller amount had only CA-125 measured (2.3%). 13.8% of non-ER patients had no RMI workup before diagnosis.

We next assessed whether degree of RMI workup lengthened/shortened time periods in the non-ER patient journey (Table 7). Of statistical significance, those with an incomplete RMI workup were diagnosed 69.0 days faster, and patients with no RMI workup were diagnosed 94.0

days faster, than those with a complete low RMI score. Completeness of RMI workup played no significant role in shortening the length of the diagnostic period.

We also wanted to investigate whether a positive RMI workup shortened the referral period. That is, if family doctors were able to recognize positive workup for OvCa, were they referring their patient to GynOnc sooner? Cases with high RMI score were referred on average 20 days sooner after their first RMI test (imaging or CA-125) than those with a complete low RMI score (p = 0.0233). The same was seen for the time from last test (CA-125 or imaging) to GynOnc referral, where patients with a complete high RMI score were referred on average 8 days sooner than those with low RMI score (p = 0.0212).

DISCUSSION

Our goal was to evaluate survival data for Manitoba women with OvCa and determine if there were identifiable factors that might contribute to poor outcome. Surprisingly, my analysis showed that survival for OvCa patients was equivalent to the best outcomes previously reported for Canadian women. As part of my analysis I discovered poorer survival in report only patients and chart ER patients. Both groups were associated with late stage, aggressively symptomatic OvCa, and often lack any diagnostic workup or surgery in favour of palliation. In assessing factors amongst the chart patients, I identified differences between ER and non-ER patients. We showed significantly shorter diagnostic and referral periods for the ER patients, and although unrelated to outcome, was an indication of the severity of disease.

How do we actually compare to previously published data? Our analysis included both revised 3-year and 1-year survival rates using current, manually extracted data allowing comparison to the statistics reported in Coleman *et al.* (14). The 5-year survival rate reported for Canada in 2005-2007 was 41.9%, which is indirectly comparable to the 45.2% 3-year survival in Manitoba calculated in my thesis (14). The 1-year survival in Manitoba that they reported was 68.0% from 2005-2007; over a similar time period in my study the results were essentially the same (67.4% 1-year survival calculated for the entire cohort) (14). These comparisons allow me to infer that the true Manitoba OvCa patient survival may be similar to that in Canada overall, if not better when only patients receiving care from GynOnc at CCMB are considered. To make further comparisons with other Canadian registries, proof of complete data capture (such as done for my dataset) would need to be accomplished in similar studies in other jurisdictions.

What are the trends in Chart and Report Only Patients? The stark survival differences between chart and report only patients can be attributed to several different factors. Many of these report only patients were not seen at CCMB because they presented with terminal disease and multiple comorbidities, declining further referral to a specialist and instead choosing observation or palliation for their end stage disease. Supporting this is the large amount of unknown stage and unknown morphology in report only patients. Precise staging of OvCa requires surgery to sample the pelvic mass, lymph nodes and/or other peritoneal organs. Determining the origin of the malignant cells, and possibly further identifying the histotype also requires sampling techniques and/or surgery which can be invasive and painful beyond their diagnostic and potentially therapeutic intentions. Tissue of origin can be determined on the pathologic/cytologic analysis of a surgical specimen, tissue biopsy, and possibly by pleural fluid or ascites. Determining histotype requires a tissue biopsy or surgical specimen. Determining histotype would not affect palliative treatment choices or prognosis in cases where the patient is not interested in pursuing interventional treatment (often in cases where the OvCa is highly progressed at presentation). In these cases, these procedures may not be in the best interest of the patient. Cases diagnosed on the basis of cytology are more likely to be unclassified epithelial as histotype can not be classified. Adding to this is the large number of cases diagnosed initially by cytology that were not confirmed diagnostically with histology (neither surgical intervention

nor biopsy were attempted to retrieve a specimen). Further supporting the reasons for lack of workup and intervention, was the prevalence of 'no treatment' for report only patients. This is again likely a reflection of many report only patients refusing intervention for their OvCa as often seen in end stage disease. Surgery alone in report only patients could be a reflection of palliative debulking by surgeons outside of CCMB, or a surgery on suspicion of a different disease with incidental OvCa diagnosis, and a refusal of CCMB referral. Alternative to declining referral, these report only patients may have died before diagnosis and/or referral. Both of these circumstances are more common with advanced age.

The majority of both report only and chart patients live inside Winnipeg, which is in concordance with census data (15). The same proportion of both chart and report only patients living in an urban versus rural setting implies that there is equal access to specialized care and consistent referral practices throughout the province. If, for instance there were poor rates of referral for suspected OvCa cases amongst rural patients, we would expect to see a higher proportion of report only cases in the rural cohort as compared to the urban. It is also reassuring to see no large disparities in access to CCMB between patients of different income quintiles.

What is typical of the OvCa patient journey in MB? What is the ideal journey? The most common journey was that of patients diagnosed by GynOnc after referral from their family doctor. This model in which OvCa is suspected in the community within one encounter, and the patient is referred to a subspecialist for characterization of disease and delivery of treatment is ideal. It gives the greatest opportunity for detecting OvCa at early stages where emergent attention is not required. This helps to relieve some of the congestion on emergency services and offers the earliest opportunity for intervention.

There were also patients referred to GynOnc by a general obstetrician/gynecologist (ObGyn). Many of these patients are those who underwent routine surgery with an ObGyn for seemingly benign gynecologic pathology, but were instead found to have malignant disease after assessment by Pathology. These cases were referred to GynOnc for adjuvant chemotherapy and monitoring for recurrence. Another subgroup, seen by GynOnc after diagnosis, were those who presented with severe symptomatic disease to the emergency department. In these situations, immediate diagnostic CT imaging can suggest features of OvCa, or a sample of ascitic fluid can confirm OvCa via cytology.

The high frequency of GynOnc visits within 2 encounters is reassuring that the recognition and referral systems for OvCa are operating efficiently in Manitoba, especially from the emergency room. However, there were a small proportion of cases for which this same system failed. For instance, one patient in our study visited the ER several times before a referral was made to GynOnc for diagnosis. Another visited their family doctor, or walk-in doctor, several times before presenting to the ER to finally be worked up for OvCa. There are also multiple cases where patients were referred to one or more specialists such as gynecologists, general surgeons, or gastroenterologists before being tested for OvCa (Imaging and CA125). Although these cases are few, they represent instances in which the diagnosis was not considered early enough to warrant proper work up. The speed with which OvCa is recognized and treatment initiated cannot be understated in improving outcomes (7).

With improved province-wide recognition and referral of early stage OvCa patients to the GynOnc service at CCMB, we would expect to see an increase in the proportion of cases diagnosed within 2 encounters: patients presenting symptomatically or with incidental signs of OvCa to their PCP (low index of suspicion), who then initiates the workup for OvCa, and/or refers to CCMB with an already high index of suspicion.

This discussion point regarding encounters brings to light one of the limitations in our study. In a minimal amount of cases, the exact dates of first suspicion (first healthcare encounter) were

not known because they were not included in any of the online, or paper charts. In these cases the best estimate of date of encounter was entered using information from referral letters, admitting history/physical, or imaging dates. To solve this problem by using the most accurate dates, Manitoba Health billing information from all physicians encountered by patients during the diagnostic and referral periods would be used (access was not granted during the time period of the study, however is currently being extracted). The exact dates corresponding to the billed encounter from these physicians would be the exact date of all encounters, giving a more accurate referral and diagnostic period.

Why are there so many ER presentations? A higher proportion of all ER presentations were in Winnipeg, which is reflective of how there are more hospital emergency departments in close proximity to women living in Winnipeg than those outside of Winnipeg. In the rural setting, workup for OvCa is more commonly done by PCPs as there is typically better access to these physicians than an emergency department. This may also be attributed to the fact that the majority (57.4%) of the entire cohort is urban as opposed to rural. Also, we do not know if these differences are from a disproportionate amount of PCPs in the urban versus rural setting.

Other factors beyond population distribution contribute to the prevalence of ER presentations. Some of the women presenting to the ER may not have a regular PCP. In a 2013 Statistics Canada report, 11.8% of Canadian women reported not having a regular medical doctor, with the most common reason being that they had not looked for one. Most commonly, women without a regular medical doctor reported going to walk-in clinics if they needed medical care, and the next being to a hospital emergency room (unchanged since 2009) (16). Of the patients who do have a PCP yet still presented in the ER, in some cases the PCP may have failed to recognize the early signs and symptoms of OvCa, or the patient may not have shared their pertinent symptoms/concerns during the visit.

Why are ER patients being diagnosed and referred so quickly? Despite the push for PCPs to find and diagnose OvCa at early stages, the time from presentation until diagnosis and until GynOnc encounter is significantly shorter for the patients who present to the ER. This is due to several related reasons. First of all, patients presenting to the ER are often very symptomatic with many signs of significant intra-abdominal/pelvic disease. These signs and symptoms increase the suspicion of the ER physicians, encouraging a fast and thorough workup for potential abdominopelvic malignancies, including OvCa. Furthermore, the diagnostic imaging and CA-125 testing used to detect OvCa is much more readily available for an ER physician, reducing the time needed to workup the patient. It can take weeks to months for a patient to get a non-emergent ultrasound or CT scan ordered by a PCP, prolonging both referral and diagnostic periods. In May 2015, the average wait time for any non-emergent ultrasound in Manitoba was 9 weeks, and just over 10 weeks for adult ultrasound at a Winnipeg hospital (17). Regardless of an ultrasound, any PCP can order a serum CA-125 level as part of the RMI, which if elevated would be grounds for referral to GynOnc alone regardless of severity of disease. However, CA-125 level may be elevated for a variety of reasons including endometriosis, pelvic inflammatory disease, or uterine fibroids (more commonly in premenopausal women) (6). This enforces how important diagnostic imaging is in the initial diagnosis of OvCa (in conjunction with CA-125), and highlights wait time problems with non-emergent ultrasounds in Manitoba.

There may also be specific advantages for ER patients in that if the patient is ill enough to warrant admission to hospital, an in-house consult with GynOnc may be requested. From this point the patient may be admitted under the GynOnc service or will be given an immediate clinic appointment (statistically shorter referral and subsequent diagnostic period).

Why are the ER patients doing so poorly? Obvious differences in patient survival were seen between women presenting to the ER or elsewhere. Patients presenting to the ER have worse long-term survival, especially with a diagnostic period shorter than the median. Although this

may seem counter-intuitive, from a clinical perspective it makes sense as women with more aggressive and late-stage symptomatic disease are more likely to come to the ER. Cases with a shorter diagnostic period have more obvious/easily detectable OvCa as they likely presented with later stage disease. This tendency of ER patients to present with later stage disease is associated with poorer outcomes, irrelevant of the length of time to diagnosis or GynOnc encounter. This argument can be made in the same way as why report only patients have poorer survival relative to chart patients, through the relationship between late or unstaged disease, with unclassified histotype, all translating to more severe disease at presentation and poorer prognosis. Also, we have seen that more of the non-ER patients had classified disease, with presentation at an early stage, and better outcomes as compared to ER patients.

What is the Utility of RMI for Manitoba OvCa patients? Several of our findings regarding the utility of implementing RMI in non-ER patients support its use as a triage tool when assessing patients with a low clinical suspicion of OvCa to increase detection at earlier stages. Greater awareness of OvCa amongst PCPs may also help this cause. One of the most significant findings in the RMI analysis is the small amount of OvCa cases with an RMI score below the threshold of significance (RMI </= 200). This highlights the effectiveness of the RMI to increase post-test probability in case of suspected OvCa, as very few cases have a low RMI score. This is in agreement with published literature on the specificity of the RMI II scoring system (83% positive predictive value, and a 92% specificity when an RMI cut-off of 200 was used) (8). However, these points must be regarded in light of one of the limitations of our study in that we do not have the RMI scores of women referred with suspected OvCa, but were instead found to have benign disease.

The larger proportion of incomplete workups that were imaging-only vs. CA-125-only in non-ER patients may indicate a lack of awareness about the utility of CA-125 among PCPs, or more likely the findings on imaging were significant enough to warrant immediate referral. Some of these cases also represent those worked up and treated surgically by an ObGyn. The diagnostic imaging on these patients likely showed a benign condition, and referral to GynOnc, or a CA-125 measurement, was not necessary before generalist surgery. The question could be raised as to whether a CA-125 level should be drawn on every peri/postmenopausal woman with signs of functional ovarian lesions on ultrasound, although given the cost of CA-125 and the significantly higher prevalence of benign ovarian cysts in these women, routine measurement of CA-125 levels may not be feasible (18). However, if malignant features are detected on ultrasound, CA-125 must be drawn to increase suspicion of OvCa (7).

Another contributing factor toward why there are incomplete RMI cases is the fact that we are using a partially incomplete data set. We would expect approximately 95% of all patients to be captured with some portion of the RMI workup done (only 5% with no RMI workup at all). However, in our study 15% of the entire cohort had no RMI workup at all before diagnosis (we are only capturing ~85%). This 15% includes those that were diagnosed initially at autopsy, or by histology or cytology alone, but it also includes some cases from which we did not capture the dates and details of the investigations. These cases would have been considered as ‘no’ RMI workup, or ‘incomplete’, and affect all subsequent data output.

It is clear that severity of disease is a more important factor than RMI scoring in the diagnosis and referral of a patient with a high suspicion of OvCa. For example, non-ER patients with an incomplete RMI workup were diagnosed almost 70 days sooner than patients with a complete, low RMI score. These patients had a high initial suspicion of OvCa at presentation, which was then established by one test before referral to GynOnc. We have seen that if there is high enough suspicion of OvCa, referral is necessary and should not be delayed by a PCP going through the RMI workup. In fact, delaying diagnosis and treatment by a GynOnc may possibly

lead to worse outcomes in these patients. The GynOnc team will accept patients with even minimal suspicion of OvCa to workup and decide on treatment internally.

Conclusions and Recommendations With this evidence, I propose that the RMI should be reserved as a tool for PCPs when they are assessing patients with a low clinical suspicion of OvCa. Patients presenting in the non-ER setting, with mild symptoms that are not obvious for OvCa, can be sent for ultrasound imaging and CA-125 serum testing to either rule out or increase the probability of OvCa as the cause of their disease. If the RMI score is high, these patients need to be urgently referred to GynOnc as my analysis showed that even early stage patients with high RMI score were significantly (3.3 times) more likely to die than those with a low RMI score (Table 8).

Such mild and non-specific symptoms as identified in the SOGC guidelines (urinary urgency/frequency, abdominal distention/bloating, nausea/vomiting, early satiety, changes in bowel movements, and pelvic/abdominal pain) along with positive findings on family/gynecologic history and physical exam should encourage the use of the RMI by PCPs. This is especially true given the prevalence of abdominal distention and pain seen in our patients at presentation (30.0% and 39.1% respectively). There is evidence that these guidelines leading to RMI workup are being underutilized. Partial proof of this may be inferred by the large amount of ER presenting cases, as well as the cases with multiple healthcare encounters before diagnosis.

Due to the non-specific nature of the symptoms, PCPs may not often consider OvCa as the cause of these symptoms. It may be the case that PCPs in Manitoba have limited awareness of the SOGC guidelines when investigating an OvCa patient. While there are popular online databases often used by PCPs (e.g. UpToDate) that offer evidence-based details about OvCa, enhanced awareness to even consider OvCa is necessary. Therefore, regular education about OvCa epidemiology and symptoms for PCPs currently practicing and during residency training might enhance consideration of OvCa, ultimately resulting in improving detection of cases with low clinical suspicion.

It is also important for PCP's to have a Manitoba-specific resource to access when they have patients with low suspicion of OvCa. CCMB has several cancer-specific algorithms as part of the "In Sixty" initiative. This initiative is designed to shorten the time from first point of suspicion to treatment, to 60 days or less. PCPs have easy online access to documents detailing important signs and symptoms, risk factors, diagnostic algorithms, and ideal workup/treatment timelines for several of the more common cancers in Manitoba (lymphoma, colorectal, lung, prostate, and breast cancer). These documents are a great tool to recognize and diagnose these cancers, as well as to help PCPs navigate the CCMB system efficiently. Unfortunately, such a resource does not yet exist for OvCa in Manitoba. If such a resource were to be created, it would contain information about the RMI as a triage tool to be used by PCPs in cases with lower clinical suspicion. I would urge CCMB to put together such a document of recommendations and disease awareness for distribution to, and regular online use by PCPs in Manitoba. Figure 5 is a proposed draft of such a summary for use with patients of different levels of suspicion, based on the evidence generated in this report and existing guidelines (NB: not an official CCMB document) (6,7). Such an initiative would not only help to detect women with OvCa at earlier stages but may also reduce the burden of benign cases unnecessarily seen at CCMB.

These initiatives towards increased awareness and use of triage tools are especially important moving forward given the predictions that from 2028-2032 there will be 3650 new cases of OvCa in Canada annually, which is ~53% increase in average annual new cases from 2003-2007. (9) In Manitoba there is a projected 23% increase in average annual new cases over the same time periods (9). Initiating these recommendations now to educate new and existing PCPs will prepare them and the healthcare system for this anticipated burden.

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Table 1. Descriptive statistics comparing "chart" and "report only" patients at presentation.

Variable		Chart N = 601 Count	%	Report only N = 86 Count	%
Age	mean (SD)	**63.41 (14.46)**		**79.22 (11.46)****	
Stage	I	**137**	**22.80**	**6**	**6.98**
	II	**73**	**12.15**	**6**	**6.98**
	III	**200**	**33.28**	**17**	**19.77**
	IV	**120**	**19.97**	**27**	**31.40**
	Unknown	**71**	**11.81**	**30**	**34.88**
Histotype (Morphology)	Serous Carcinoma	223	37.10	3	3.49
	Unclassified Epithelial	169	28.12	41	47.67
	Clear Cell	36	5.99	0	0.00
	Endometrioid	46	7.65	1	1.16
	Mucinous	48	7.99	1	1.16
	Other*	79	13.14	40	46.51
Residence	Winnipeg	345	57.40	47	54.65
	Outside Winnipeg	256	42.60	39	45.35
Income^	NF	**11**	**1.83**	**10**	**11.63**
	R1-R3	**137**	**22.8**	**26**	**30.23**
	R4-R5	**93**	**15.47**	**7**	**8.14**
	U1-U3	**236**	**39.27**	**35**	**40.7**
	U4-U5	**124**	**20.63**	**8**	**9.3**
ER	Yes	174	28.95	-	-
	No	427	71.05	-	-
Abdominal pain	Yes	235	39.1	-	-
	No	366	60.9	-	-
Abdominal distension	Yes	179	29.78	-	-
	No	422	70.22	-	-

*other epithelial-stromal, and miscellaneous and unspecified
^R=rural; U=urban; 1=poorest quintile; 5=richest quintile
**Bolded values were significantly different ($p < 0.0001$)

Table 2. Comparison between patients that appear in the ER at first suspicion versus not (chart patients only).

		Multivariable Model			
Variable		OR	95% CI		*p*
Histotype (Morphology)	Serous Carcinoma	**0.317**	0.20	0.51	<.0001
	Unclassified Epithelial	1			
	Clear Cell / Endometrioid	**0.193**	0.09	0.40	<.0001
	Mucinous	0.551	0.26	1.18	0.1251
	Other*	0.851	0.47	1.53	0.5885
Residence	Winnipeg	**2.246**	1.50	3.37	0.0001
	Non-Winnipeg	1			

*other epithelial-stromal, and miscellaneous and unspecified

Table 3. Amount of chart patients (ER and non-ER) diagnosed by different methods, and changes in proportion after diagnostic confirmation.

Method	Initial Diagnosis		Diagnosis Confirmation	
	Count	%	Count	%
Autopsy	1	0.17	1	0.17
Death certificate	0	0.00	0	0.00
Clinical	0	0.00	0	0.00
Serum CA-125 Level	14	2.33	10	1.66
Cytology	257	42.76	88	14.64
Radiology	42	6.99	33	5.49
Histology	287	47.75	469	78.04

Table 4. Amount of chart patients with different numbers of healthcare encounters between suspicion and diagnosis.

Number of Encounters	Frequency	%
1	147	24.46
2	285	47.42
3	120	19.97
4	37	6.16
5	12	2.00

Table 5. Five most common chart patient journeys from suspicion to diagnosis.

Physician Encounters in Journey from Suspicion to Diagnosis	Freq	%
Family Physician → GynOnc	124	20.63
ER	72	11.98
ER → GynOnc	54	8.99
Family Physician	45	7.49
Family Physician → ObGyn→ GynOnc	28	4.66

Table 6. Frequency of RMI information by ER status at presentation (N = 601 chart patients).

Score	Non-ER		ER	
	Count	%	Count	%
Complete				
200+	185	43.33	69	39.66
<=200	54	12.65	9	5.17
Incomplete				
CA-125 only	10	2.34	7	4.02
Imaging only	119	27.87	58	33.33
None	59	13.82	31	17.82

Table 7. Median difference in time from suspicion to diagnosis among non-ER chart patients with different RMI scores.

		Median Time Difference (days)	95% CI		*p*
Intercept		**101.0**	44.59	157.49	0.0005
RMI Score	</=200	(reference)			
	200+	-39.0*	-97.8	19.7	0.1924
	Incomplete	**-69.0**	-125.4	-12.6	0.0165
	None	**-94.0**	-152.5	-35.6	0.0016

*negative values indicate fewer days from suspicion to diagnosis

Table 8. Cox regression model of early stage chart patients with different RMI scoring/ workup at diagnosis.

RMI Score		HR	95% CI		*p*
Complete	</=200	1			
	200+	**3.255**	1.56	6.80	0.0017
	Incomplete	2.080	0.925	4.68	0.08
	None	2.211	0.89	5.48	0.0864

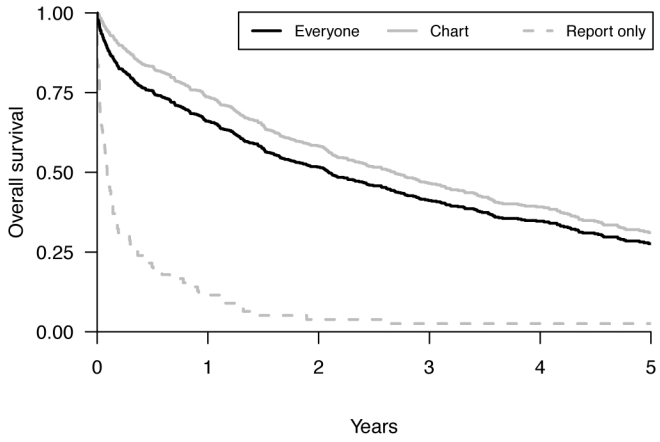

Figure 1. Kaplan-Meier curve illustrating overall survival for the Manitoba OvCa patient cohort diagnosed between 2004-2010. Chart patients had considerably better survival over time than report-only patients ($p < 0.0001$). Everyone = entire cohort, Chart = patients referred to CCMB (N = 601), Report only = patients without CCMB referral, but died of OvCa (N = 86).

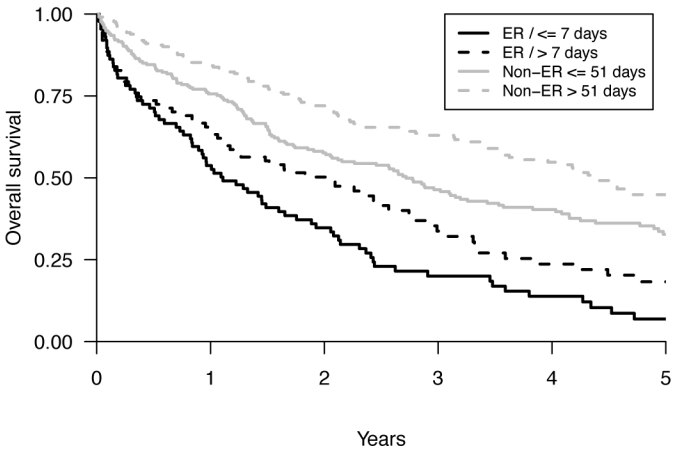

Figure 2. Kaplan-Meier curve illustrating overall survival for OvCa patients presenting in the emergency room (ER) or elsewhere (Non-ER). ER patients exhibited poorer survival than non-ER patients ($p < 0.0001$). “Days” indicates median time until diagnosis.

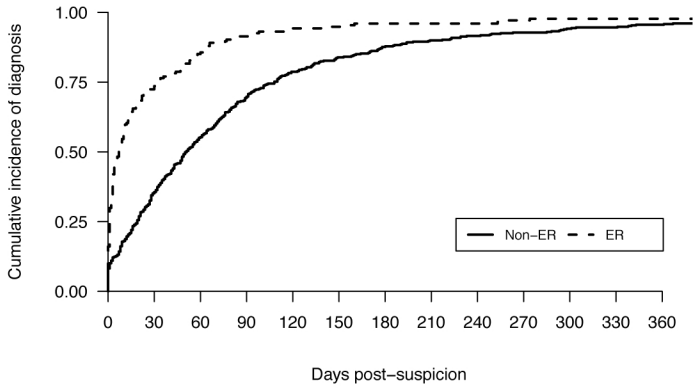

Figure 3. Cumulative incidence of diagnosis for OvCa patients presenting in the ER or elsewhere (Non-ER). Incidence of diagnosis was measured over time (days) from point of initial suspicion. Patients presenting in the ER were diagnosed sooner than those presenting elsewhere ($p < 0.0001$).

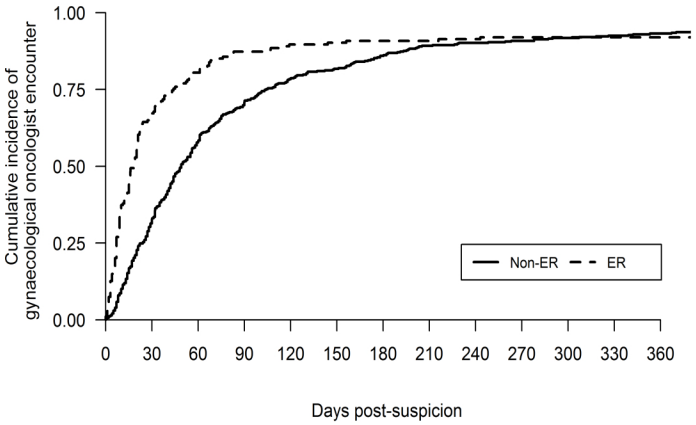

Figure 4. Cumulative incidence of GynOnc encounter for OvCa patients presenting in the ER or elsewhere (Non-ER). Incidence of GynOn referral was measured over time (days) from point of presentation. Similar to incidence of diagnosis, patients presenting in the ER were referred sooner than those presenting elsewhere ($p = 0.0063$).

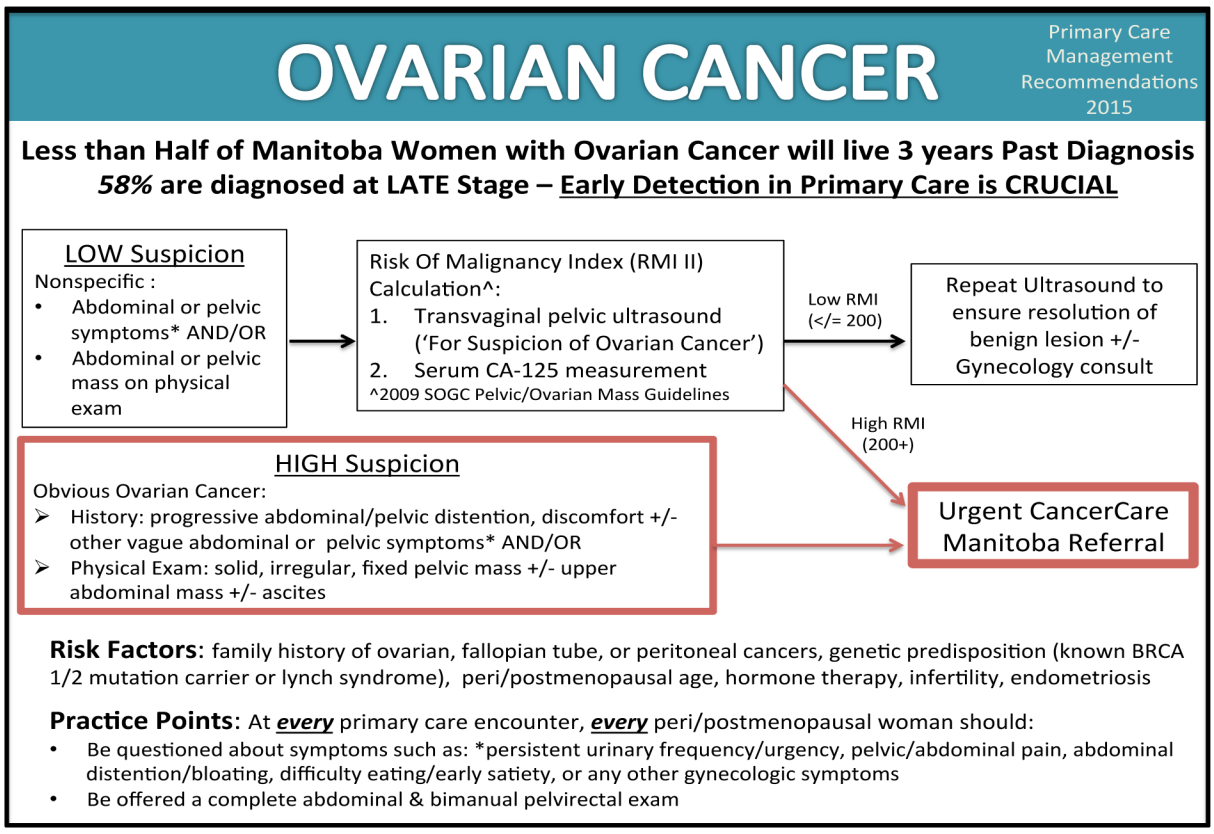

Figure 5. Proposed draft of primary care OvCa management recommendations for patients with different levels of suspicion. Guidelines formulated on the basis of evidence generated in this thesis and exisitng guidelines. NB: Not an official CCMB document.