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Performance characteristics of a brief Family History Questionnaire to screen for Lynch syndrome in women with newly diagnosed endometrial cancer

Lua Eiriksson [a], Melyssa Aronson [b], Blaise Clarke [c], Golnessa Mojtahedi [d], Christine Massey [e], Amit M. Oza [f], Steven Gallinger [g,h], Aaron Pollett [i,j], Helen Mackay [k], Marcus Q. Bernardini [d,l], Sarah E. Ferguson [d,l,*]

[a] Division of Gynecologic Oncology, Juravinski Hospital and Cancer Centre, Department of Obstetrics and Gynecology, McMaster University, 699 Concession St., Hamilton, Ontario L8V 5C2, Canada
[b] Zane Cohen Centre for Digestive Diseases, Familial GI Cancer Registry, Mount Sinai Hospital, 600 University Ave., Toronto, Ontario M5G 1X5, Canada
[c] Division of Pathology, Princess Margaret Hospital/University Health Network, 610 University Ave., Toronto, Ontario M5G 2M9, Canada
[d] Division of Gynecologic Oncology, Princess Margaret Hospital/University Health Network, 610 University Ave., Toronto, Ontario M5G 2M9, Canada
[e] Department of Biostatistics, Princess Margaret Hospital/University Health Network, 610 University Ave., Toronto, Ontario M5G 2M9, Canada
[f] Division of Medical Oncology, Princess Margaret Hospital/University Health Network, 610 University Ave., Toronto, Ontario M5G 2M9, Canada
[g] Division of General Surgery, Princess Margaret Hospital/University Health Network, 610 University Ave., Toronto, Ontario M5G 2M9, Canada
[h] Familial GI Cancer Registry, Mount Sinai Hospital, 600 University Ave., Toronto, Ontario M5G 1X5, Canada
[i] Pathology and Laboratory Medicine, Mount Sinai Hospital, 600 University Ave., Toronto, Ontario M5G 1X5, Canada
[j] Department of Laboratory Medicine and Pathobiology, University of Toronto, 27 King's College Circle, Toronto, Ontario M5S 2J7, Canada
[k] Division of Medical Oncology, Princess Margaret Hospital/University Hospital Network, 610 University Ave., Toronto, Ontario M5G 2M9, Canada
[l] Department of Obstetrics and Gynecology, University of Toronto, 27 King's College Circle, Toronto, Ontario M5S 2J7, Canada

HIGHLIGHTS

- We have developed a sensitive screening tool called brief Family History Questionnaire (bFHQ).
- It is a patient-administered screening test to identify women with endometrial cancer at risk for Lynch syndrome.
- bFHQ may be useful in identifying cancer patients who should undergo genetic assessment.

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ABSTRACT

Objective. The brief Family History Questionnaire (bFHQ) was developed to identify endometrial cancer patients whose family histories suggest Lynch syndrome (LS). We compared the bFHQ, extended Family History Questionnaire (eFHQ) and dictated medical records (DMRs) to determine which family history screening strategy is superior in identifying LS in unselected women with newly diagnosed endometrial cancer that have undergone universal germline testing.

Methods. Prospective cohort study recruited women with newly diagnosed endometrial cancer to evaluate screening strategies to identify LS. Participants completed bFHQ and eFHQ, had tumor assessed with immunohistochemistry (IHC) for mismatch repair proteins (MMR) and micro-satellite instability testing and underwent universal germline testing for LS. The sensitivity, specificity, positive and negative predictive values (PPV, NPV) were compared between the family history screening strategies as well as IHC.

Results. 118 of 182 eligible patients (65%) consented; 87 patients (74%) were evaluable with both family history and germline mutation status. Median age was 61 years (range 26–91). All 7 patients with confirmed LS were correctly identified by bFHQ, compared to 5 and 4 by eFHQ and DMR, respectively. The sensitivity, specificity, PPV and NPV values of bFHQ were 100%, 76.5%, 25.9% and 100%, respectively, performing similar to IHC testing. While eFHQ was more specific than bFHQ (86.7% vs. 76.5%, $P = 0.007$), 2 cases of LS were missed.

Conclusions. The patient-administered bFHQ effectively identified women with confirmed LS and is a good screening tool to triage women with endometrial cancer for further genetic assessment.

* Corresponding author at: M700-610 University Avenue, Toronto, Ontario M5G 2M9, Canada. Fax: +1 416 946 2288.
E-mail addresses: lua.eiriksson@jcc.hhsc.ca (L. Eiriksson), maronson@mtsinai.on.ca (M. Aronson), blaise.clarke@uhn.on.ca (B. Clarke), golnessa.mojtahedi@nyu.edu (G. Mojtahedi), cmssyc@gmail.com (C. Massey), amit.oza@uhn.ca (A.M. Oza), steven.gallinger@uhn.ca (S. Gallinger), apollett@mtsinai.on.ca (A. Pollett), helen.mackay@uhn.ca (H. Mackay), marcus.bernardini@uhn.on.ca (M.Q. Bernardini), sarah.ferguson@uhn.on.ca (S.E. Ferguson).

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Introduction

Lynch syndrome (LS) is an inherited cancer susceptibility syndrome, characterized by familial clustering of cancers such as colorectal and endometrial cancers. LS is inherited in an autosomal dominant fashion with genetic defects in DNA mismatch repair genes (e.g., *MLH1*, *MSH2*, *MSH6*, *PMS2*, *TACSTDI/EPCAM*) [1–7]. The lifetime risk of cancer in patients affected with LS is 20–83% for colorectal cancer, 33–61% for endometrial cancer, and 9–12% for ovarian cancer, in addition to other LS-associated cancers, such as gastric, hepatobiliary, urinary tract, small bowel, and brain cancers [8–12].

LS is one of the most commonly inherited cancer susceptibility syndromes, accounting for 3% and 2.3% of unselected colorectal and endometrial cancer patients, respectively [13–17]. The identification of LS carriers is important, since appropriate colorectal cancer screening and prophylactic gynecologic surgeries may provide survival benefits [18–20]. In patients diagnosed with endometrial cancer, the identification of LS is particularly significant, since endometrial cancer is the sentinel cancer in 50–60% of patients [21,22], often with a lead-time of 8 to 10 years prior to the next cancer diagnosis [21]. In some studies, the incidence of endometrial cancer has been found to exceed that for colorectal cancer in women with LS [8,11,12].

In the absence of universal screening of endometrial cancer cases by immunohistochemistry (IHC) for mismatch repair (MMR) protein expression or microsatellite instability (MSI) testing, patients suspected of LS are identified by family history, prompting referral to genetic counseling. In patients who meet defined clinical criteria, tumors are tested for loss of MMR protein expression using IHC or MSI testing. Germline testing for pathogenic mutations in MMR genes is then initiated in the setting of IHC deficiency of MMR proteins or high levels of MSI [23].

The challenge in identifying women with endometrial cancer who should undergo screening for LS is that current criteria are colorectal cancer-based, such as the Amsterdam II (AMS II) and revised Bethesda guidelines [24,25]. Both are also dependent on obtaining a detailed family history. Using these tools alone, up to two-thirds of LS mutation carriers presenting with endometrial cancer would not be identified [17,22,26,27]. Therefore, a reliable approach to identify endometrial cancer patients at risk for LS is needed to ensure that they benefit from genetic counseling and further genetic testing.

In Ontario, Canada, universal IHC testing and MSI testing are currently not funded. While this is under evaluation at the level of the Ministry of Health and Long Term Care (MOHLTC) as well as at the level of Cancer Care Ontario, patients with histories suggestive of LS are only eligible for genetic counseling and consideration for genetic testing if they satisfy the Ontario Ministry of Health (OMOH) testing criteria [28], which encompasses the AMS II and Society of Gynecologic Oncology (SGO) 20–25% criteria (Fig. 1) [29]. The SGO 20–25% criteria were developed with a focus on gynecologic malignancies, have demonstrated greater sensitivity in identifying LS in women with endometrial cancer, and are less restrictive than AMS II criteria [22]. In addition to inclusion of the AMS II and SGO 20–25% criteria, the OMOH criteria are less stringent with respect to the required number of 1st degree relatives affected and provide a more exhaustive list of LS-associated malignancies. In order to

CRITERIA	OMOH	SGO 20-25%
Amsterdam II Criteria: • ≥3 relatives with LS-associated cancer[a] • 1 should be 1st degree relative of other 2 • ≥2 successive generations affected • ≥1 diagnosed age <50 years	•	•
Amsterdam II-like Criteria: • ≥3 affected relatives one with CRC and the other 2 with any combination of LS-associated cancer[b] • 2 of the 3 in a 1st degree relationship • ≥2 successive generations affected • ≥1 diagnosed age <50 years	•	
S/M* colorectal cancer with LS-cancer[b], 1 diagnosed age <55 years	•	
Patient with colorectal cancer age <35 years	•	
Colorectal cancer age <50 years with 1st/2nd degree relative with an LS-cancer[a], age <50 years	•	
Tumors with mismatch repair (MMR) defect: • Microsatellite instablity • Loss of expression of MLH1, MSH2, MSH6, PMS2	•	•
1st/2nd degree relative with MMR gene mutation	•	•
S/M endometrial and colorectal cancer, 1 diagnosed age <50 years		•
S/M ovarian and colorectal cancer, 1 diagnosed age <50 years		•

Referral for genetic counseling based on satisfying any one "•" criteria; *S/M = synchronous or metachronous; [a]colorectal, endometrial, small bowel, ureter, renal pelvis, sebaceous adenoma/carcinoma/ and/or keratocanthoma; [b]colorectal, endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, brain, sebaceous gland adenoma/carcinoma and keratoacanthoma, small bowel

Fig. 1. Society of Gynecologic Oncology (SGO) 20–25% and Ontario Ministry of Health (OMOH) guidelines for Lynch syndrome referral.