The identification of Lynch syndrome in British Columbia

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OBJECTIVE: To determine the prevalence of Lynch syndrome mutations in a Canadian hereditary cancer clinic population, and to determine the effectiveness of the program's referral criteria and testing algorithm.

METHODS: A retrospective chart review of all patients who were referred for and received genetic counselling at the BC Cancer Agency's Hereditary Cancer Program for a family history of colon cancer from August 1, 2004, to September 1, 2006, was performed. Charts were reviewed for referral criteria met, cancer history, whether testing was offered and the outcome of testing.

RESULTS: Lynch syndrome was confirmed or highly suspected in 14.3% of index test patients (eight of 56) by the identification of a deleterious mutation or variant likely to be deleterious in either of the *hMLH1* or *hMSH2* mismatch repair genes. In the program, the two most effective criteria were a personal diagnosis of two or more primary Lynch syndrome-related cancers (one diagnosed at younger than 50 years of age) or two first-degree relatives with a Lynch syndrome-related cancer (both diagnosed at younger than 50 years of age). The respective positive predictive values of these two criteria were calculated to be 66.7% (95% CI 40% to 93%) and 58.3% (95% CI 30.4% to 86.2%).

CONCLUSIONS: The Hereditary Cancer Program developed and successfully implemented an approach that selected individuals at risk for Lynch syndrome with a significant pretest probability of mutation of 14.3%. Improved ascertainment of families with Lynch syndrome will require greater physician awareness of referral criteria, program advances in the testing algorithm and a population-based approach to screening incident colon cancers.

Key Words: *Colon cancer, Genetic testing; Hereditary; HNPCC; Lynch syndrome*

Le dépistage du syndrome de Lynch en Colombie-Britannique

OBJECTIF : Déterminer la prévalence des mutations du syndrome de Lynch dans la population qui fréquente les cliniques canadiennes de cancer héréditaire ainsi que l'efficacité des critères d'aiguillage et de l'algorithme de dépistage du programme.

MÉTHODOLOGIE : Les auteurs ont procédé à une analyse rétrospective des dossiers de tous les patients aiguillés entre le 1er août 2004 et le 1er septembre 2006 pour recevoir du counseling génétique et qui l'ont reçu au programme de cancer héréditaire de la *BC Cancer Agency* en raison d'antécédents familiaux de cancer du côlon. Ils ont examiné les dossiers afin d'examiner si les critères d'aiguillage étaient respectés, de connaître l'évolution du cancer, de déterminer si le dépistage était offert et les résultats du dépistage.

RÉSULTATS : Chez 14,3 % des patients de référence à l'étude (huit sur 56), on a confirmé ou hautement présumé la présence du syndrome de Lynch par le dépistage d'une mutation délétère ou d'une variante susceptible de l'être dans les gènes de réparation mal appariés *hMLH1* ou *hMSH2*. Dans le programme, les deux critères les plus efficaces étaient un diagnostic personnel d'au moins deux cancers primaires liés au syndrome de Lynch (dont un diagnostiqué à moins de 50 ans) ou un cancer lié au syndrome de Lynch chez deux parents du premier degré (tous deux diagnostiqués à moins de 50 ans). Les auteurs ont calculé les valeurs prédictives positives respectives de ces deux critères et sont parvenus à 66,7 % (95 % IC 40 % à 93 %) et 58,3 % (95 % IC 30,4 % à 86,2 %).

CONCLUSIONS : Le programme de cancer héréditaire a mis sur pied et implanté avec succès une démarche pour sélectionner des individus vulnérables au syndrome de Lynch ayant une probabilité de mutation de 14,3 % avant le dépistage. Pour mieux évaluer les familles ayant un syndrome de Lynch, les médecins devront être davantage sensibilisés aux critères d'aiguillage, aux avancées du programme à l'égard de l'algorithme de dépistage et à une démarche pour dépister les cancers du côlon incidents en population générale.

The Hereditary Cancer Program (HCP) at the BC Cancer Agency (Vancouver, British Coumbia [BC]) provides genetic counselling and testing to the population of BC for inherited cancer predisposition. Hereditary colon cancer is the second most frequent reason for referral to the HCP after hereditary breast and ovarian cancer syndrome. Clinical genetic testing for the most common form of hereditary colorectal cancer (CRC) – Lynch syndrome – has been available at the HCP since August 2004. The first aim of the present study was to describe the effectiveness of the referral criteria and testing algorithm in the identification of Lynch syndrome in BC in the two-year period since the inception of this testing. The second aim was to determine the prevalence of Lynch syndrome mutations in a Canadian hereditary cancer clinic population. This will establish a baseline with which to benchmark future improvements in the rate of ascertainment of Lynch syndrome.

Lynch syndrome is the term now used in place of hereditary nonpolyposis colorectal cancer (HNPCC) syndrome to describe families with a germline mutation in a DNA mismatch repair gene. HNPCC was a confusing term applied to heterogenous families meeting different family history criteria (eg, Amsterdam I, Amsterdam II) (1,2), regardless of genetic etiology. Furthermore, the term excluded single cases and was a misleading descriptor, given the significant extracolonic cancer risks and the presence of polyps, albeit with a much smaller number than in the hereditary polyposis syndromes.

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TABLE 1
Criteria for identifying Lynch syndrome: Amsterdam criteria I and II, and Bethesda guidelines

Amsterdam criteria I
Requires three or more relatives with CRC in addition to the following:
1. One affected patient should be a first-degree relative of the other two;
2. Two or more successive generations affected;
3. At least one CRC diagnosed at younger than 50 years of age; and
4. Familial adenomatous polyposis excluded. Tumours should be verified by pathological examination
Amsterdam criteria II
Requires three or more relatives with Lynch-associated cancer* in addition to the following:
1. One affected patient should be a first-degree relative of the other two;
2. Two or more successive generations affected;
3. One or more affected relative received diagnosis at younger than 50 years of age; and
4. Familial adenomatous polyposis excluded. Tumours should be verified by pathological examination
Revised Bethesda guidelines
1. CRC diagnosed in a patient who is younger than 50 years of age;
2. Presence of synchronous, metachronous CRC or other Lynch-associated tumour;
3. CRC diagnosed in a patient who is younger than 60 years of age, with the presence of tumour infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation or medullary growth pattern;
4. CRC diagnosed in a patient with one or more first-degree relatives with a Lynch-associated tumour, with at least one of the cancers being diagnosed at younger than 50 years of age; and
5. CRC diagnosed in a patient with two or more first- or second-degree relatives with Lynch-associated tumours, regardless of age

**Endometrial, stomach, ovarian, pancreas, ureter and renal pelvis. CRC Colorectal cancer. Data adapted from references 5, 13 and 14*

Lynch syndrome is a dominantly inherited susceptibility to CRC that accounts for up to 5% of all CRCs (3). Lynch syndrome causes up to an 80% lifetime risk of CRC, with an average age at diagnosis of 44 years (4). There is a 40% to 60% lifetime risk of endometrial cancer, with an average age at diagnosis of 46 years (4). Other cancers associated with Lynch syndrome include small bowel, ovarian, renal pelvis, ureter and gastric cancer (5). Given the high lifetime risk of CRC associated with Lynch syndrome, regular colonoscopic surveillance beginning at age 25 is recommended to reduce the morbidity and mortality of cancer in these families (6).

Lynch syndrome is caused by a mutation in one of four mismatch repair genes (7-11): *hMLH1, hMSH2, hMSH6* and *hPMS2*. Mutations in the *hMLH1* and *hMSH2* genes account for approximately 90% of families with Lynch syndrome, while mutations in the *hMSH6* gene account for approximately 10% (12). Mutations in the *hPMS2* gene (8) are expected to be rare and clinical genetic testing has only recently become available. Genetic testing is costly and complex. The identification of families in whom genetic testing for Lynch syndrome should be considered has traditionally been based on family history criteria, which have evolved over time to improve sensitivity (5,13,14) (Table 1).

An online survey of Canadian genetic counsellors in March 2007, demonstrated significant variability in the eligibility criteria and the genetic testing algorithm for Lynch syndrome.

TABLE 2
Criteria for identifying Lynch syndrome in British Columbia: 'A blend of Bethesda and Amsterdam'

1. Personal history of colorectal cancer diagnosed before 40 years of age
2. Personal history of, or close family memeber with, two or more primary HNPCC-related cancer diagnoses, at least one younger than 50 years of age and at least one colorectal cancer
3. Two first-degree relatives with HNPCC-related cancer, both diagnosed at younger than 50 years of age and at least one colorectal cancer
4. Three or more cases of HNPCC-related cancers, involving more than one generation, with at least one case of colorectal cancer and at least one case dignosed at younger than 50 years of age

Data adapted from the BC Cancer Agency. HNPCC Hereditary nonpolyposis colorectal cancer

We are not aware of any publications describing the yield of Lynch syndrome testing in Canadian hereditary cancer clinics. Jasperson et al (15) recently performed a retrospective review of 71 probands who underwent Lynch syndrome assessment ascertained through a United States cancer genetics registry. In this study, Lynch syndrome mutations were detected in 25.4% (n=18). A clinic's overall effectiveness in identifying families with this condition depends on many factors, including the specific referral criteria and the testing algorithm.

METHODS

Patient selection

All subjects included in the study were patients who had received genetic counselling at the BC Cancer Agency's HCP due to their family history of colon cancer. The progeny database was searched for all cases with a clinic date between August 1, 2004, and September 1, 2006, and with a syndrome diagnosis of "HNPCC" or "colon". Familial adenomatous polyposis or other polyposis syndromes were excluded from the present analysis. Research ethics board approval was obtained to review all charts for referral criteria met, cancer history, whether testing was offered and the outcome of testing.

The HCP criteria are shown in Table 2. As long as an individual's family meets the criteria for genetic testing, he or she is eligible for a genetic counselling appointment, even if this individual, the consultand, is not eligible for genetic testing.

Before the genetic counselling appointment, a three-generation cancer family history is collected and attempts are made to confirm all reported cancer diagnoses in relatives by pathology records. Based on this information, the genetic counsellor provides a hereditary cancer risk assessment (low, moderate or high) and offers genetic testing if eligibility criteria are met. The benefits, drawbacks and limitations of genetic testing are explained by the genetic counsellor as part of the informed consent process.

Genetic testing

Index testing refers to testing in the first affected individual of a family and preferentially starts with the screening of a colorectal tumour for microsatellite instability (MSI) and/or loss of MLH1 or MSH2 protein expression – the characteristic tumour features in Lynch syndrome (16) – as determined by immunohistochemistry (IHC). Microsatellite stability of the tumour-derived DNA is assessed with respect to constitutional DNA derived from peripheral blood at five loci recommended by the National Cancer Institute (17). The presence or absence of MLH1 and MSH2 expression in paraffin-embedded tumour tissue by IHC is

established using commercially available antibodies (16). The likelihood of Lynch syndrome is exceedingly low if tumour test results are normal, with genetic testing on a blood sample not generally indicated in these cases. Tumours that show MSI, or that are deficient in the MLH1 or MSH2 protein, are triaged for further testing by sequencing of the *hMLH1* or *hMSH2* genes obtained in a blood sample.

Once a mutation is identified in the index patient, presymptomatic testing (mutation specific) is available to at-risk relatives, affected or unaffected, and is performed by targeted genetic sequencing of a blood sample.

RESULTS

From August 2004 to September 2006, a total of 294 individuals from 207 families underwent genetic counselling for Lynch syndrome assessment. Of these, 47 individuals (16.0%) from 19 families were referred for presymptomatic testing because a Lynch syndrome mutation had already been identified in the family. The majority of referrals (36%) were from the category 'family members, self or other genetics programs', 27% were from oncologists, 26% from family doctors and 11% from 'other'. The large majority of patients were women (71.4%) and the average age at the time of referral was 48.4 years (range 16 to 82 years).

Among the 294 patients, 40% had a personal history of CRC (n=118), with an average age at diagnosis of 56.5 years (range 22 to 82 years). Other cancers in these patients included endometrial (n=15), ovarian (n=12), stomach (n=2), small intestine (n=3), hepatobiliary (n=1), genito-urinary tract tumours (n=8), brain (n=1) and cancers listed as 'other' (n=64). Of the 118 patients with CRC, nine had multiple CRCs (7.6%) and 13 (11%) had a second extracolonic primary cancer that is part of the Lynch syndrome spectrum (five cases of endometrial cancer, three cases of genito-urinary tumours and one case each of ovarian, stomach, small intestine, hepatobiliary and brain cancer). Of all patients, 32% met the Amsterdam I criteria, 36% met the Amsterdam II criteria and 29% met the Bethesda criteria.

Figure 1 shows the patient flow in the present study population. Of the 294 patients seen, 46% were eligible for genetic testing. Of the 122 patients who consented to testing, 78 were offered index testing and 44 were offered mutation-specific testing for the mutation previously identified in their family. The uptake of testing in the latter group was 95.7% (95% CI 89.8% to 100%) and among index patients was 88.6% (95% CI 82.0% to 95.3%). Of the 44 presymptomatic tests, 25 patients inherited the specific mutation present in their family (seven MLH1 and 18 MSH2). The remaining 19 individuals did not carry the mutation.

The analysis of index testing is based on the 56 cases with disclosed results. Only five cases did not begin with tumour testing because tissue blocks were unavailable. Twenty-four per cent of tumour test cases (n=12) had abnormal tumour results (either MSI, with or without abnormal IHC) (Figure 1). Germline mutations were identified in five of these cases (42%) and a variant was identified in two additional cases. All cases with a mutation or variant had evidence of MSI and an abnormal IHC result corresponding to the genetic result. Of five other MSI cases, none have been confirmed to have germline Lynch syndrome mutations. Some of these cases underwent further investigation (Table 3).

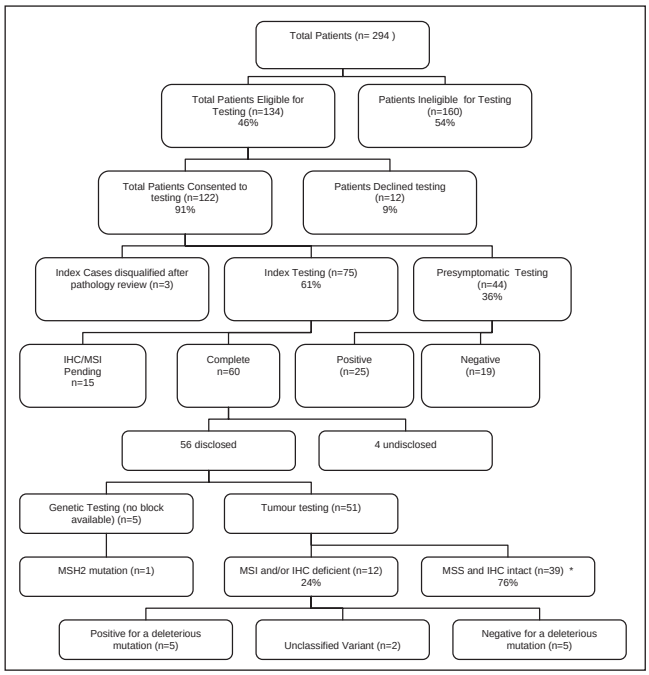

Figure 1) *Flow chart of Lynch syndrome assessment yield. *Two cases failed microsatellite instability (MSI) testing due to DNA degradation. In both cases, however, immunohistochemistry (IHC) was intact for MLH1 and MSH2, and germline genetic testing was normal for both genes. MSS Microsatellite stability*

The remaining 39 patients who underwent tumour analysis had normal results (76%) and no further testing was planned (Figure 1). Of these, nine patients met Amsterdam I criteria (23%). The term 'familial CRC Type X syndrome' has been proposed for families that are Amsterdam-positive but have no evidence of a germline mismatch repair mutation. In these families, the age of CRC diagnosis is typically later, the penetrance of CRC among relatives is reduced and the excess of extracolonic cancers are not seen, compared with Lynch syndrome families (18).

In total, a mutation was detected in the *MLH1* gene in two patients and in the *MSH2* gene in four patients, for an overall yield of Lynch syndrome in index patients of six of 56 (10.7%). In addition, two patients were found to carry 'unclassified variants' in the *MLH1* gene (*MLH1* p.I32N and *MLH1* p.R265S). Both of the tumours in these cases demonstrated MSI and were deficient for the MLH1 protein. Neither of them demonstrated the somatic *BRAF* (V-raf murine sarcoma viral oncogene homologue B1) gene mutation, which is an effective screening tool to identify noninherited or sporadic MSI-high CRC (19). Both cases had a family history of cancer that met Amsterdam criteria, which further suggests that these variants may represent pathogenic changes. If the unclassified variant cases are included, eight of 56 (14.3%) of the index cases tested were diagnosed with Lynch syndrome.

Performance of HCP criteria

The HCP currently uses four criteria that represent a blend of the Bethesda guidelines and the Amsterdam criteria. The performance of the various criteria is shown in Table 4. The reported values measure the extent to which the eligibility criteria predict whether Lynch syndrome is present in the group

TABLE 3
Cases with an abnormal tumour test result (n=12)

Case	Personal cancer history, age (years)	Fulfills Amsterdam criteria I or II	Microsatellite instability	IHC		Germline testing		Other testing requested
				MLH1	MSH2	*MLH1*	*MSH2*	
1	Colorectal, 71 Renal cell cancer, 71	No	High	Intact	Intact	Not requested	Not requested	IHC for MSH6 and PMS2
2	Colorectal, 24	No	High	Absent	Intact	No mutation	Not requested	*BRAF* MLPA
3	Colorectal, 31	No	High	Absent	Intact	No mutation	Not requested	*BRAF* MLPA
4	Colorectal, 33	No	High	Intact	Intact	Pending	Pending	IHC for MSH6 and *PMS2* MLPA
5	Colorectal, 37	No	High	Intact	Intact	No mutation	No mutation	IHC for PMS2 and MSH6
6	Colorectal, 40	Yes	High	Intact	Absent	N/A	Mutation	No
7	Colorectal, 32	Yes	High	Absent	Intact	Mutation	N/A	No
8	Colorectal, 33	Yes	High	Intact	Absemt	N/A	Mutation	No
9	Colorectal, 44 and synchronous thyroid, 42	Yes	High	Absent	Intact	Mutation	N/A	No
10	Colorectal, 59 (synchronous tumours) Small intestine, 59 Transitional cell carcinoma, renal pelvis, 41	Yes	High	Intact	Absent	N/A	Mutation	No
11	Colorectal, 37	Yes	High	Absent	Intact	Unclassified variant	N/A	No
12	Colorectal, 50 Endometrial, 51	Yes	High	Absent	Intact	Unclassified variant	N/A	No

*BRAF V-raf murine sarcoma viral oncogene homologue B1 gene; IHC Immunohistochemistry; MLPA Multiplex ligation-dependent probe amplification; MS(L)H Mismatch repair proteins/genes; N/A Not applicable; PMS2 Postmeiotic segregation increased 2 (*Saccharomyces cerivisiae*) gene*

TABLE 4
Summary of performance criteria

Criteria	Sensitivity*		Specificity†		PPV‡		NPV§	
	%	95% CI	%	95% CI	%	95% CI	%	95% CI
Amsterdam I	63	29–96	79	67.7–90.7	33	9.5–57.2	93	84.7–100
Amsterdam II	100	100–100	75	62.8–87.3	40	18.5–61.5	100	100–100
Bethesda guidelines	100	100–100	21	9.3–32.3	17	6.4–28.3	100	100–100
HCP1: Personal history of colorectal cancer diagnosed at younger than 40 years of age	50	15.4–84.6	50	35.9–64.1	14	1.3–27.2	86 14	72.8–94.7 5.3–27.2
HCP2: Two primary Lynch cancers (one colorectal cancer), with one diagnosed at younger than 50 years of age	100	100–100	92	84.8–99.5	67	40–93.3	100	100–100
HCP3: Two first-degree relatives with Lynch cancers (one colorectal cancer), with both diagnosed at younger than 50 years of age	88	64.6–100	90	80.9–98.2	58	30.4–86.2	98	93.3–100
HCP4: Three or more Lynch cancers (at least one colorectal cancer), with one younger than 50 years of age	Not possible to evaluate							

*Data are based on a total of 56 index patients. Six mutations and two unclassified variant results are combined in the present analysis.*Sensitivity measures the eligibility criteria's ability to identify carriers who use a genetic testing service. It only applies to carriers and reveals nothing about noncarriers. Sensitivity is between 0 and 1, with a higher value indicating a better service; †Specificity measures the eligibility criteria's ability to exclude noncarriers who use a genetic testing service. It only applies to noncarriers and reveals nothing about carriers. Specificity is between 0 and 1, with a higher value indicating a better service; ‡The positive predictive value (PPV) measures the proportion of carriers among people who are eligible for a genetic testing service. It only applies to eligible people and reveals nothing about ineligible people. PPV is between 0 and 1, with a higher value indicating a better service (The PPV is also called the post-test likelihood of being a carrier given eligibility); §The negative predictive value (NPV) measures the proportion of noncarriers among people who are ineligible for a genetic testing service. It only applies to ineligible individuals and reveals nothing about eligible subjects. NPV is between 0 and 1, with a higher value indicating a better service. The NPV is the converse of the post-test probability of being a carrier given ineligibility (ie, 1-NPV). HCP Hereditary Cancer Program*

for whom testing was performed at the HCP. This group is very different from the general population, and the performance measures reported here should not be compared with those in other groups or populations. However, the performance measures can be compared with one another for each of the eligibility criteria in the HCP dataset. Figure 2 shows the sensitivity, positive predictive value (PPV), specificity and negative likelihood ratio with 95% CIs for each criterion.

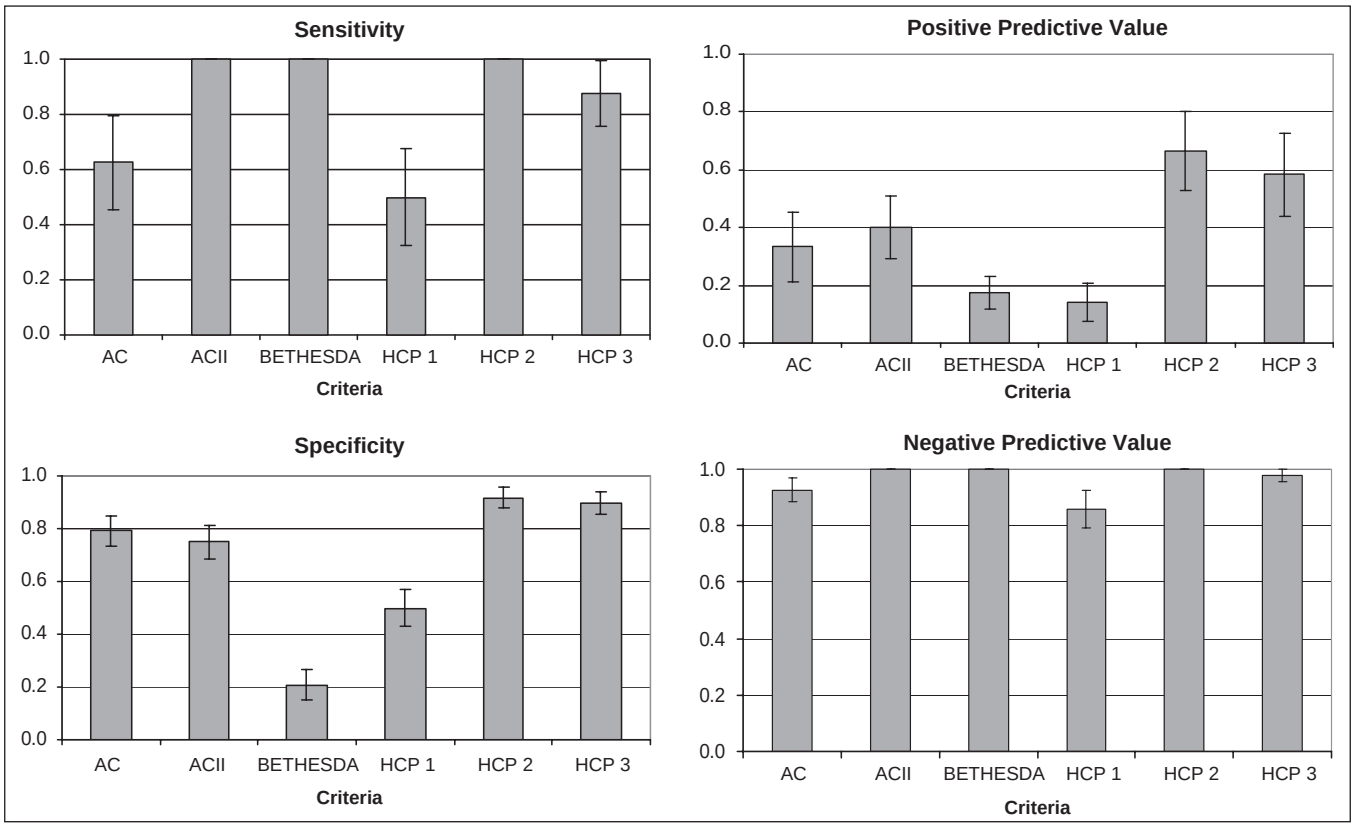

Figure 2) *Performance criteria. AC Amsterdam criteria I; ACII Amsterdam criteria II; Betheseda Bestheda guidelines; HCP Hereditary Cancer Program*

The Amsterdam II criteria, Bethesda guidelines and the HCP criterion 2 identified all eight patients with mutations or unclassified variants. The average sensitivity of the eligibility rules (excluding HCP criterion 4) was 0.833 and none of the individual criteria provided significantly different sensitivity than the average (χ^2 tests comparing observed and expected value; all P>0.05). The average PPV of the eligibility rules (excluding HCP criterion 4) was 0.383 and none of the individual criteria provided a significantly different PPV from the average (χ^2 tests comparing observed and expected values, all P>0.05).

DISCUSSION

A two-year period following the start of clinical genetic testing for Lynch syndrome in BC was evaluated. This represents a clinical stream of patients selected initially for referral into the HCP and subsequently selected for tumour analysis and/or genetic testing. The overall yield of Lynch syndrome mutations was 10.7% in individuals who underwent index testing. If the two variants in the *MLH1* gene were included, the yield increased to 14.3%. Among the 294 individuals assessed for Lynch syndrome (including the 47 patients referred for presymptomatic testing for the known mutation in the family), the overall prevalence of Lynch syndrome mutations was 11.2% (n=33). Excluding the presymptomatic testing referrals, Lynch syndrome was confirmed by a mutation (or strongly suspected with two unclassified variants in *MLH1*) in 3.2% (eight of 247) of all individuals who came for genetic counselling. This yield reflects the real-world scenario of a hereditary cancer clinic and the overall effectiveness of this strategy in detecting Lynch syndrome.

There are several important limitations to the present study. The index test study population includes only eight probands with a Lynch syndrome mutation or unclassified variant. The population that attended an appointment was a self-selected group and was likely different from the population of referred patients who did not follow through with an appointment. There are many reasons why an individual may decide not to follow through on a referral including health, anxiety, not understanding the purpose of the referral, fear of having a genetic risk assessment or the potential for life-insurance discrimination.

Second, the present report highlights obstacles in the ascertainment of new Lynch syndrome families in a real-world clinical scenario; not meeting test criteria, patient refusal of testing, and lack of available tumour tissue blocks. These obstacles are likely to affect mutation-positive and mutation-negative cases equally.

Third, five of 12 cases with abnormal MSI and/or IHC results did not reveal a mutation in *MLH1* or *MSH2*, some of which are undergoing further testing by multiplex ligation probe amplification to detect large gene rearrangements of *MLH1* and *MSH2*, *BRAF* testing to investigate somatic hypermethylation of MLH1, and by further evaluation for MSH6 mutations via IHC and/or *MSH6* gene sequencing. While these cases may be due to sporadic methylation of the *MLH1* gene promoter, as in 15% of all CRCs (20), it is also possible that they were caused by a mutation in *MSH6* or *PMS2*, or by an undetected mutation in *MLH1* or *MSH2*, which would

result in an underestimation of the Lynch syndrome yield. A limitation of the current testing algorithm at the HCP is that IHC for the MSH6 and PMS2 proteins is not currently part of routine tumour analysis.

In the present study, HCP criteria 2 (individual with two or more primary Lynch syndrome cancers, with at least one being colorectal and one diagnosed at younger than 50 years of age) and 3 (Lynch syndrome cancer younger than 50 years of age in two first-degree relatives, with at least one being CRC) outperformed both Amsterdam I and II criteria as well as the Bethesda guidelines, if both high sensitivity and PPV were sought (Figure 2). HCP criterion 2 identified all cases and HCP criterion 3 identified seven of eight. In a meta-analysis conducted by Kievit et al (21), the sensitivity of the Amsterdam I and Amsterdam II criteria were 54% to 91% and 78%, respectively. The PPVs were 61% and 46%, respectively. The high sensitivity and low PPV of the Bethesda criteria in our population are similar to previous reports (22). The 33% PPV of the Amsterdam criteria in our study is lower than the 50% to 92% reported in other studies (23-25). This may be due to the fact that our program does not require confirmation of diagnoses by pathology reports before offering testing. A more detailed review of records may have shown that some of these families did not meet the Amsterdam criteria.

Endometrial cancer is the sentinel Lynch syndrome cancer in some families. A limitation to the testing algorithm in BC described in the present study is that it required colorectal tumour tissue for preliminary MSI and IHC testing, thereby precluding testing in endometrial-only Lynch syndrome families. Seventy-five per cent of endometrial tumours in Lynch syndrome demonstrate MSI compared with 25% to 45% of sporadic endometrial cancer, making MSI an effective pre-screening tool for Lynch syndrome (26). Lu et al (27) found a 32% positive predictive value for Lynch syndrome in MSI-high endometrial cancers diagnosed at younger than 50 years of age. The clinical utility of MSI in other Lynch syndrome tumours, such as sebaceous adenomas, has also been proposed and is under current evaluation.

FUTURE DIRECTIONS FOR THE IDENTIFICATION OF LYNCH SYNDROME IN BC

The population of BC is currently estimated to be 4.380 million (Statistics Canada, 2007). Using a background Lynch syndrome mutation prevalence of one in 531 (28), this would yield an estimated 8249 Lynch syndrome patients. The provincial clinical database includes slightly more than 100 patients with confirmed Lynch syndrome mutations (42 *MLH1* mutation carriers, 52 *MSH2* carriers and three *MSH6* carriers).

In 2008, an important step was taken toward population-based screening for Lynch syndrome in the province. All newly diagnosed colorectal cancers for individuals younger than 50 years of age can now be referred for MSI analysis by any physician, regardless of family history and without referral to the HCP. If the next step was for MSI to become part of routine reporting on all newly diagnosed CRCs in individuals younger than 50 years of age, this testing would be expected to have close to a 100% sensitivity in identifying Lynch syndrome, based on the high prevalence of MSI in Lynch tumours. Alternatively, IHC for the MSH2, MLH1, PMS2 and MSH6 proteins could be offered. This would provide similar sensitivity and also provide data for direct genetic testing. However, because loss of MSH2 expression in a CRC almost invariably indicates a germline mutation, there is a greater need for informed consent for IHC as opposed to MSI testing.

There are approximately 200 cases of CRC diagnosed in individuals younger than 50 years of age in BC each year. Using a prevalence of mutations of 8.7% in unselected CRC diagnosed at younger than 50 years of age (29), if MSI testing was performed on all cases, up to 16 new patients with Lynch syndrome may be identified per year. We used a simulation model (30) to determine the effect of additional Lynch syndrome genetic testing for all CRC cases diagnosed in individuals younger than 50 years of age in BC. Simulations indicated that the additional testing strategy would increase sensitivity by approximately 4.0%, increase PPV by approximately 0.3% and decrease specificity by approximately 0.1%.

Currently, approximately 15% of all referrals to the HCP are for hereditary colon cancer as opposed to 77% for hereditary breast and ovarian cancer, a condition for which our program has offered testing since 1999. This study provides a baseline analysis of the yield of Lynch syndrome testing in BC by which future improvements will be benchmarked. Improving the effectiveness of identifying Lynch syndrome in BC can be achieved with a two-pronged approach: greater physician education of Lynch syndrome/awareness of the HCP's service and a population-based approach to screening incident colorectal cancers in patients younger than 50 years of age.

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