

# Validation of predictive models for germline mutations in DNA mismatch repair genes in colorectal cancer

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Lynch syndrome is defined by the presence of germline mutations in mismatch repair (MMR) genes. Several models have been recently devised that predict mutation carrier status (Myriad Genetics, Wijnen, Barnetson, PREMM and MMRpro models). Families at moderate-high risk for harboring a Lynch-associated mutation, referred to the BC Cancer Agency (BCCA) Hereditary Cancer Program (HCP), underwent mutation analysis, immunohistochemistry and/or microsatellite testing. Seventy-two tested cases were included. Twenty-five patients were mutation positive (34.7%) and 47 were mutation negative (65.3%). Nineteen of 43 patients who were both microsatellite stable and normal on immunohistochemistry for MLH1 and MSH2 were also genotyped for mutations in these genes; all 19 were negative for MMR gene mutations. Model-derived probabilities of harboring a MMR gene mutation in the proband were calculated and compared to observed results. The area under the ROC curves were 0.75 (95%CI; 0.63–0.87), 0.86 (0.7–0.96), 0.89 (0.82–0.97), 0.89 (0.81–0.98) and 0.93 (0.86–0.99) for the Myriad, Barnetson, Wijnen, MMRpro and PREMM models, respectively. The Amsterdam II criteria had a sensitivity and specificity of 0.76 and 0.74, respectively, in this cohort. The PREMM model demonstrated the best performance for predicting carrier status based on the positive likelihood ratios at the >10%, >20% and >30% probability thresholds. In this referred cohort, the PREMM model had the most favorable concordance index and predictive performance for carrier status based on the positive LR. These prediction models (PREMM, MMRpro and Wijnen) may soon replace the Amsterdam II and revised Bethesda criteria as a prescreening tool for Lynch mutations.

In Canada and the United States, colorectal cancer (CRC) is the third most common diagnosed cancer and the second leading cause of all cancer deaths.<sup>1,2</sup> Among those affected, up to 15% of CRC cases can be attributed to individuals with inherited susceptibilities, most notably the familial adenomatous polyposis (FAP) and the hereditary nonpolyposis colorectal cancer (HNPCC) syndromes.<sup>3</sup>

The HNPCC syndrome is more common than FAP, accounting for up to 5% of all CRC diagnoses; whereas FAP accounts for less than 1%.<sup>3</sup> Multiple adenomatous polyps, often greater than 100 arising at an early age, characterize the FAP phenotype. The clinical manifestation of the HNPCC syndrome phenotype is not as apparent as its FAP counterpart. Patients with HNPCC are often asymptomatic until pre-

sentation. The diagnosis of the HNPCC syndrome was based upon clinical criteria until the genetic basis of the syndrome was identified in the 1990s. Some families with HNPCC syndrome harbor inactivating mutations in mismatch repair genes (MMR), namely *MLH1*,<sup>4,5</sup> *MSH2*,<sup>6</sup> *MSH6*<sup>7,8</sup> and *PMS2*.<sup>9</sup> Abnormalities in these MMR genes result in DNA errors during replication, often marked by accumulation of microsatellite instability (MSI).<sup>10</sup> Alternatively, loss of MMR gene expression in tumors is a hallmark of this syndrome.<sup>11</sup> The term "Lynch syndrome" has been used to designate the HNPCC patients who harbor MMR gene mutations. This designation distinguishes those HNPCC patients or families that have tumors that are proficient in DNA mismatch repair, namely "familial colorectal cancer, type X."<sup>12</sup> It is important to identify individuals with the Lynch syndrome as they may benefit from genetic counseling and increased surveillance. Moreover, it may identify family members with an increased risk for CRC.

The identification of families at risk for the Lynch syndrome, the utilization of molecular evaluation and appropriate clinical management pose significant challenges for clinicians and researchers. Universal germline testing of all index CRC cases is not feasible as Lynch mutations are rare and family histories for CRC are common, thus making this both expensive and time consuming. Therefore, it is necessary to

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