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Informations

Review

Genetic mutation risk calculation in Lynch syndrome inheritance: Evaluating the utility of the PREMM$_{1,2,6}$ model in Lyon: The first French study

Souria Aissaoui [1,2,3], Charline Cartellier [3,4], Thomas Seytier [1,3], Sophie Giraud [1,2], Alain Calender [1]

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1. Hôpital Édouard-Herriot, 5, place d'Arsonval, 69003 Lyon, France
2. Centre hospitalier Lyon Sud, 165, chemin du Grand-Revoyet, 69310 Pierre-Bénite, France
3. French association of genetic counselors, 16, rue de Lorraine, 13008 Marseille, France
4. Centre hospitalier métropole Savoie, place Lucien-Biset, 73000 Chambéry, France

Correspondence:
Souria Aissaoui, hôpital Édouard-Herriot, 5, place d'Arsonval, 69003 Lyon, France.
Souria.aissaoui@chu-lyon.fr

Calcul du risque de mutation génétique dans le cadre du syndrome de Lynch : évaluation de l'utilité du logiciel PREMM1.2.6 à Lyon : 1ère étude française

Keywords
Familial cancer management
Genetic diagnosis
Lynch syndrome
Multidisciplinary decision-making
Risk assessment

Summary

Lynch syndrome is due to germline mutations in mismatch repair genes: *MLH1, MSH2, MSH6* and *PMS2*. It is characterized by an increased risk of various cancers including colorectal and endometrial cancers. Early diagnosis of these patients allows for appropriate surveillance and improves survival rates. Differentiating between patients who should undergo genetic testing and those for whom it is not necessary is difficult despite various established criteria (Amsterdam and Bethesda). Often, health professionals meet in multidisciplinary committees (MDC) to discuss patient cases regarding Lynch syndrome. In this study, we evaluated if the prediction model PREMM$_{1,2,6}$ could be used to enhance MDC decision-making and whether it should be included in our own routine practice and in those of other French teams. Using the prediction model in our cohort would have avoided 12% of the analyses recommended by our MDC. Furthermore, all patients with a mutation in one of the *MMR* genes would have been detected. In addition, according to the model, we should have provided 20% more genetic testing, which suggests that the decision-making criteria used by the professionals in our MDC, was too restrictive. These results suggest that PREMM$_{1,2,6}$ should be used in current practice to validate the decisions of the MDC before genetic testing is performed in complex cases. The model should be added as a major quality criterion for genetic testing, along with somatic tests, as previously reported in the literature.

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Introduction

Lynch syndrome is one of the most common diseases that predispose to colorectal cancer. A mutation in one or more *MMR* gene is responsible. In order to provide high-quality care management for patients and their family, genetic counseling is imperative. Decision-making for a given case is not always easy. In complex cases, multidisciplinary committees (MDC) are organized to help professionals optimize decision-making regarding genetic analysis and patient/families follow-up. In France, 76% of hospitals have instituted MDCs to consult in digestive cancers predisposition cases. In our center in Lyon, the MDC meets once-monthly [1].

The MDC meetings bring together oncogeneticists, gastro-enterologists, internal medicine physicians, genetic counselors, pathology and genetic biologists, surgeons and gynecologists. They influence medical management decision-making regarding each specific case so that the joint decision is most beneficial for the patient and the family when a predisposition to cancer is suspected.

Many models of genetic mutation risk calculation exist, notably three whose performances seem to be highest: MMRpredict [2], MMRpro [3], and PREMM$_{1,2,6}$ [4]. MMRpredict can only be used for patients with colorectal cancer. While it takes into account somatic testing, it does not incorporate endometrial cancer or the others cancers of Lynch-spectrum, nor cancer cases from 2nd degree relatives. MMRpro requires more time to implement as it considers the whole family. However, it only takes into account colorectal and endometrial cancers of the Lynch spectrum, and somatic testing.

In our investigation, we chose to use PREMM$_{1,2,6}$ because of its statistical strength and its rapidity and simplicity of use. Previous studies have shown that the PREMM$_{1,2,6}$ prediction tool is the only one that captures all cancers of the Lynch spectrum of 1st and 2nd degree relatives. It also allows risk calculation in healthy individuals. Contrary to the two other tools, it does not take into account somatic tests (microsatellite instability and immuno-histochemistry). The 5% threshold of a good positive predictive value of mutation detection is still retained. A comparative synthesis of different risk calculation softwares is shown on *table I*.

Different strategies for analysing clinical cases have been proposed in the literature, including somatic tests, informatics-based prediction tools and genetic analysis. Our study aimed to evaluate if this kind of tool would be beneficial to our current practice. Would using prediction risk calculation models, especially PREMM$_{1,2,6}$ enhance decision-making within our oncogenetic MDC? We explored whether and how PREMM$_{1,2,6}$ could be integrated our practice in Lyon.

We evaluated the decisions made by our MDC based on the calculation of mutation risk according to PREMM$_{1,2,6}$. We compared, in our cohort, PREMM$_{1,2,6}$ analysis (with a 5% PPV threshold of mutation risk) with the decisions made by the MDC and with the genetic result (when known) to look for concordance.

To our knowledge, no previous studies have been conducted to assess the condition and benefits of this tool associated with MDC experts. Our aim is to examine the evaluation of MDC and the improvement of quality decision-making for a family suspected of having Lynch syndrome. This initiative falls within the framework of quality control of the MDC, and assesses the performance of PREMM$_{1,2,6}$ to determine if it should become a new tool for decision-making in our genetics center.

Methodology

Cohort

The cases included in this study were patients affected by colon cancer or healthy relatives with a putative genetic predisposition, according to criteria published for the two major consensus conferences focusing on HNPCC-related digestive cancers [5,6], and discussed within our MDC from 2004 to 2012.

In total, 240 individual cases were initially selected. Risk calculation using PREMM$_{1,2,6}$ was possible for 175. The remaining cases were those in which familial polyposis or familial gastric cancers were suspected. Multidisciplinary committees discussed *MMR* gene analysis for 165 patients. Genetic testing was performed via PCR-based sequencing and large rearrangements study of the four *MMR* genes (*MLH1, MSH2, MSH6, PMS2*). *EpCAM* gene testing was also performed. We calculated the gene mutation rate and analyzed the PREMM$_{1,2,6}$ model's efficiency in our cohort.

Genetic risk calculation via PREMM$_{1,2,6}$

PREMM$_{1,2,6}$ is freely available on the following link http://premm.dfci.harvard.edu/.

For each case, this predictive model provides a mutation risk for each gene *MLH1*, *MSH2*, and *MSH6* individually and a cumulative value for an overall risk mutation for all 3 genes combined. We used the 5% relevant threshold for validation of gene analysis as recommended by the model's designers. Criteria taken into account in this tool are described in *box 1*.

Statistical analysis

For evaluating MDC decisions, statistical analysis was performed on the cohort of patients for whom genetic test indication was discussed (n = 165).

For evaluating PREMM$_{1,2,6}$ mutation rate values (threshold of detecting mutation: 5%), statistical analysis was performed on the cohort of patients for whom genetic results were available (n = 55):

- true positive: patients for whom gene test has been validated by PREMM$_{1,2,6}$ and a mutation has been identified;
- false positive: patients for whom gene test has been validated by PREMM$_{1,2,6}$ but no mutation has been identified;
- true negative: patients for whom gene test has not been validated by PREMM$_{1,2,6}$ and no mutation has been identified;