Myriad myRisk® Hereditary Cancer
Specifications for Clinical/Family History Analysis
Myriad Genetic Laboratories, Inc.
Effective: December 1, 2017

THE MYRIAD myRISK MEDICAL MANAGEMENT TOOL SHOULD ONLY BE USED AFTER REVIEW OF THE FOLLOWING SPECIFICATIONS

Overview of the Clinical/Family History Analysis

The myRisk® Management Tool (MMT) provides cancer risk levels based on an analysis of genetic test results and a summary of medical society management recommendations based on a combined analysis of germline DNA-based testing and, when possible, personal clinical factors and personal/family cancer history. The material below provides details regarding the clinical/family history analysis. Technical Specifications for the germline DNA-based testing are available at: https://new.myriadpro.com/documents-and-forms/technical-specifications/.

The clinical/family history is assessed for applicable medical society guidelines relevant to the screening and prevention of breast, colorectal, melanoma, pancreatic, and prostate cancer. The National Comprehensive Cancer Network (NCCN) is the default source for all of the reported medical management recommendations. Other professional/medical groups may be cited in addition to NCCN, or in cases where there are no applicable NCCN recommendations.

The clinical/family history analysis identifies applicable medical management guidelines based on the information submitted by the ordering healthcare provider on the Test Request Form (TRF). Information included in other documents (e.g., pedigrees, pathology reports) submitted by the healthcare provider may also be considered if it is readily identifiable and does not contradict information on the TRF, which is regarded as the definitive source of information. Information provided on the TRF or in other documents submitted by the healthcare provider is not verified by Myriad. The medical society management recommendations summarized in the MMT may be significantly different if details provided on the TRF for cancer and colorectal polyp diagnoses, ages, family relationships or other factors were incorrect, omitted, ambiguous or have since changed. The Clinical & Family Cancer History Information page of the report should be reviewed to determine if the clinical/family history information used in the analysis accurately reflects the information on the TRF.

The clinical/family history assessment provided on the MMT is for the purpose of identifying potential medical management strategies to reduce the risk of future cancers due to a personal or family history suggestive of increased risk due to inherited or other risk factors. This summary does not include management recommendations related to treatment of a previous or existing cancer, polyps or other premalignant lesions. Patients with a personal history of cancer, benign tumors or pre-cancerous findings may be candidates for long term surveillance and risk-reduction strategies beyond what is necessary for the treatment of their initial diagnosis. The general recommendations summarized in the MMT may require modification based on the patient's personal medical history, surgeries and other treatments.

Methodology for Clinical/Family History Assessment

Breast Cancer (Tyrer-Cuzick Model)[i]

The Tyrer-Cuzick Version 7.02 model is used to estimate a five year risk and remaining lifetime risk for breast cancer. A Tyrer-Cuzick risk estimate is only provided for women under the age of 85 who: 1) have no personal history of breast cancer, 2) do not carry any deleterious or suspected deleterious mutations in genes currently known to be associated with breast cancer risk, and 3) do not report any relatives known to carry a mutation in a hereditary cancer gene. Tyrer-Cuzick is not calculated if the provider indicates on the Test Request Form that the Tyrer-Cuzick risk estimate is not appropriate for the patient. Appropriate medical management recommendations from NCCN are summarized for women with a Tyrer-Cuzick remaining lifetime breast cancer risk estimate of 20% or higher. Women with a remaining lifetime risk for breast cancer higher than the general population risk, but below the 20% threshold, may also be candidates for modified medical management at the discretion of their healthcare provider.

The Tyrer-Cuzick model estimates a woman's breast cancer risk using information about hormonal factors (age of menarche, age of first live birth, menopausal status, use of hormone replacement therapy, body mass index), personal history of benign breast disease (past diagnoses of hyperplasia, atypical hyperplasia, lobular carcinoma *in situ*) and family history of breast and ovarian cancer.

Tyrer-Cuzick estimates of breast cancer risk can vary significantly based on the accuracy, completeness, and specificity of the data provided, and the way in which that data is applied to the model. The estimate provided on the MMT may be higher or lower than what would be calculated by other users. In some cases, Myriad may need to modify the information provided on the TRF to comply with the model's requirements, i.e., an age provided as "50's" could be converted to "55+", or an age provided as "<50" could be converted to "49". In other cases, values may be entered into the model as "Not specified" if they are ambiguous or fall outside of expected ranges. Additionally, Myriad is unable to include nieces, nephews, and relatives beyond first- and second-degree in the Tyrer-Cuzick analysis due to limited information about the family structure. The information used for the calculation is displayed on the Clinical & Cancer Family History Information page of the report. If there are concerns about the way in which Myriad calculated the Tyrer-Cuzick risk estimate, the risk estimate can be recalculated using the application available for download at http://www.ems-trials.org/riskevaluator/, or with the on-line tool available at http://ibis.ikonopedia.com/.

Colorectal Cancer

Information regarding the patient's family history of colorectal polyps and colorectal cancer is used to assess the applicability of recommendations for altered medical management. Information regarding the patient's personal and family history of colorectal polyps, colorectal cancer, and other cancers is also used to assess the possibility that a patient is at risk for Lynch syndrome (using Amsterdam II Criteria), Familial Adenomatous Polyposis, or Attenuated Familial Adenomatous Polyposis. The assessment for Lynch syndrome with the Amsterdam II Criteria is limited because Myriad does not have sufficient information about the family structure to fully assess the relevance of nieces, nephews, and relatives beyond first- and second-degree. Patients identified as being at risk for Lynch syndrome or a polyposis condition may be appropriate for further evaluation by healthcare providers with expertise in these conditions.

Pancreatic Cancer

Information regarding the patient's family history of pancreatic cancer is used to assess the applicability of recommendations for consideration of pancreatic cancer screening, which may only be available through clinical trials.

Prostate Cancer

When provided on the TRF, information about relatives with prostate cancer, or African ancestry, is used to assess the applicability of recommendations for modified risk-benefit discussions concerning the utility of prostate cancer screening.

Melanoma

Information regarding relatives with diagnoses of melanoma is used to assess the applicability of recommendations for skin screening.

Summary Interpretations

"***CLINICAL HISTORY ANALYSIS: BASED ON THE CLINICAL HISTORY PROVIDED, MODIFIED MEDICAL MANAGEMENT GUIDELINES WERE IDENTIFIED"*:** Includes cases where it was possible to identify a medical society guideline for modified medical management based on the clinical details provided. The provider is encouraged to consult the cited guideline and determine the most appropriate course of action.

***"CLINICAL HISTORY ANALYSIS: NO MODIFIED MEDICAL MANAGEMENT GUIDELINES WERE IDENTIFIED BASED ON THE CLINICAL HISTORY PROVIDED"*:** Includes cases where it was not possible to identify a medical society guideline for modified medical management based on the clinical details provided. This may include cases where the patient potentially met criteria for modified medical management, but the analysis was incomplete due to missing or ambiguous details about cancer diagnoses, ages, family relationships or other factors.

Changes to the Interpretation of the Clinical/Family History Analysis and Issuance of Amended Reports

Clinical/family history assessments provided are based on the versions of medical society guidelines cited on the MMT. These guidelines undergo frequent revision, and there may be cases where updated guidelines have been issued that are not yet cited. Therefore, recommendations summarized on the MMT should always be checked against the most recent published versions available directly from the relevant medical society.

Myriad does not issue an amended MMT when guidelines change. Myriad does not issue an amended report for changes in the patient's personal or family history, other than in cases where the MMT was initially generated with an error due to Myriad incorrectly documenting or applying the clinical history provided on the TRF.

Additional Resources for Information Regarding the Clinical/Family History Analysis

If you have questions about these specifications, either in general, or in regard to how the analysis was performed for a specific patient, please contact Myriad Medical Services by calling 800-469-7423, X3850, or by emailing helpmed@myriad.com.

---

[i] Amir E, et al. J Med Genet (2003) 40:807-14. PMID: 14627668.