Guideline Endorsement MOTAC-5

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Cancer Care Ontario Sequence Variants in Hereditary Cancers Guideline: An Endorsement of the 2015 Standards and Guidelines for the Interpretation of Sequence Variants: A Joint Consensus Recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology

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This document describes the CCO-MOTAC endorsement of the 2015 Standards and Guidelines for the Interpretation of Sequence Variants: A Joint Consensus Recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. The original publication is available at https://www.acmg.net/docs/standards_guidelines_for_the_interpretation_of_sequence_variants.pdf

An assessment conducted in November 2023 deferred the review of Guideline Endorsement MOTAC-5. This means that the document remains current until it is assessed again next year. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

Guideline Endorsement MOTAC-5 is comprised of 2 sections. You can access the full report here:
https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/43301

Section 1: Guideline Endorsement
Section 2: Endorsement Methods Overview

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For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
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Section 1: Guideline Endorsement

ENDORSEMENT

The Molecular Oncology and Testing Advisory Committee of Cancer Care Ontario endorses the recommendations of *Standards and Guidelines for the Interpretation of Sequence Variants: A Joint Consensus Recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology*, published by the American College of Medical Genetics and Genomics (ACMG) regarding inherited cancers, as modified by the endorsement process described in this document. Caveats and clarifications about the recommendations as they pertain to Ontario are discussed below (Table 1-1).

All recommendations in the ACMG/Association for Molecular Pathology guideline that refer to the Health Insurance Portability and Accountability Act (HIPAA) in the United States should apply to the Personal Health Information Protection Act (PHIPA) to reflect Ontario legislation. Similarly, the Ontario counterpart of Clinical Laboratory Improvement Amendments (CLIA) is the Institute for Quality Management in Healthcare (IQMH).

Additional update in March 2022

Additional refinements and tools have been developed for a consistent implementation of the ACMG/Association for Molecular Pathology guideline[1]. The ClinGens Sequence Variant Interpretation Group (https://www.clinicalgenome.org/working-groups/sequence-variant-interpretation/) supports the refinement and the evolution of the guideline through providing recommendations and tools for consistent implementation.

[1] Harrison SM, Biesecker LG, Rehm HL. Overview of Specifications to the ACMG/AMP Variant Interpretation Guidelines. Curr Protoc Hum Genet. 2019;103(1):e93.

Table 1-1: Caveats and/or Clarifications of Specific Elements from the ACMG/AMP Guidelines on Sequence Variants

Section	ACMG/AMP Guidance	Caveat/clarification for Ontario context
Literature and database use	When using databases, clinical laboratories should (i) determine how frequently the database is updated, whether data curation is supported, and what methods were used for curation; (ii) confirm the use of Human Genome Variation Society nomenclature and determine the genome build and transcript references used for naming variants; (iii) determine the degree to which data are validated for analytical accuracy (e.g., low-pass next-generation sequencing versus Sanger-validated variants) and evaluate any quality metrics that are provided to assess data accuracy, which may require reading associated publications; and (iv) determine the source and independence of the observations listed.	While it is recognized that it is not always possible to determine methods or frequency of curation for public databases, laboratories should adhere to these principles to the extent this is possible.
PS4 PM2 BA1 BS1 BS2 variant frequency and use of control populations	In general, an allele frequency in a control population that is greater than expected for the disorder is considered strong support for a benign interpretation for a rare Mendelian disorder (BS1) or, if over 5%, it is considered as stand-alone support (BA1).	For some disorders, very high frequencies (>5%) may be found in specific populations due to founder effect, and may be associated with some clinical risk. This possibility should be assessed through a careful consideration of available literature and other information, if possible.
PP1 BS4 segregation analysis	On the other hand, lack of segregation of a variant with a phenotype provides strong evidence against pathogenicity. Careful clinical evaluation is needed to rule out mild symptoms of reportedly unaffected individuals, as well as possible phenocopies (affected individuals with disease due to a nongenetic or different genetic cause).	Incomplete penetrance, variable expressivity and later age of onset should be considered when establishing evidence against pathogenicity.
PP4 using phenotype to support variant claims	In general, the fact that a patient has a phenotype that matches the known spectrum of clinical features for a gene is not considered evidence for pathogenicity given that nearly all patients undergoing disease-targeted tests have the phenotype in question. If the following criteria are met, however, the patient's phenotype can be considered supporting evidence: (i) the clinical sensitivity of testing is high, with most patients testing positive for a pathogenic variant in that gene; (ii) the patient has a well-defined syndrome with little overlap with other clinical presentations (e.g., Gorlin syndrome including basal cell carcinoma, palmoplantar pits, odontogenic keratocysts); (iii) the gene is not subject to substantial benign variation, which can be determined through large general population cohorts (e.g., Exome Sequencing Project); and (iv) family history is consistent with the mode of inheritance of the disorder.	Age of onset of a disease should also be taken into consideration.
Variant reanalysis	For reports containing variants of uncertain significance in genes related to the primary indication, and in the absence of updates that may be	Laboratories are encouraged to develop policies around the steps to be taken when a variant

	proactively provided by the laboratory, it is recommended that laboratories suggest periodic inquiry by health care providers to determine whether knowledge of any variants of uncertain significance, including variants reported as likely pathogenic, has changed. By contrast, laboratories are encouraged to consider proactive amendment of cases when a variant reported with a near-definitive classification (pathogenic or benign) must be reclassified. Regarding physician responsibility, see the ACMG guidelines on the duty to recontact.	undergoes reclassification such that clinical management decisions would be changed. Any such policies should be developed with input from the associated genetic clinic.
Evaluation and reporting variants in GUS based on the indication for testing	Genome and exome sequencing are identifying new genotype–phenotype connections. When the laboratory finds a variant in a gene without a validated association to the patient's phenotype, it is a GUS. This can occur when a gene has never been associated with any patient phenotype or when the gene has been associated with a different phenotype from that under consideration. Special care must be taken when applying the recommended guidelines to a GUS. In such situations, utilizing variant classification rules developed for recognized genotype–phenotype associations is not appropriate.	Generally, GUS should be considered as research findings, and not at the same level as clinically actionable and validated genes.

Abbreviations: ACMG, American College of Medical Genetics and Genomics; AMP, Association for Molecular Pathology; GUS, genes of uncertain significance

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Section 2: Endorsement Methods Overview

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC is a provincial initiative of CCO supported by the Ontario Ministry of Health and Long-Term Care (OMHLTC). All work produced by the PEBC is editorially independent from the OMHLTC.

BACKGROUND FOR GUIDELINE

The Molecular Oncology and Testing Advisory Committee (MOTAC) of CCO recognized that guidance around interpretation of sequence variants in patients with hereditary cancers was necessary.

GUIDELINE DEVELOPERS

This endorsement project was sponsored by MOTAC. MOTAC is comprised of geneticists, pathologists, medical oncologists, and clinical hematologists (see Appendix 1 for membership) and served as the Expert Panel for this endorsement. The project was led by a small Working Group comprised of clinical and medical geneticists practicing in Ontario, who were responsible for reviewing the recommendations in *Standards and Guidelines for the Interpretation of Sequence Variants: A Joint Consensus Recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology* in detail and making an initial determination as to any necessary changes, drafting the first version of the endorsement document, and leading the response to the external review. The Working Group members are noted in Appendix 1. All members contributed to the endorsement process, refinement of the endorsement document, and approval of the final version of the document. Conflict of interest declarations for all Guideline Development Group members are summarized in Appendix 1, and were managed in accordance with the *PEBC Conflict of Interest Policy*.

CHOICE OF GUIDELINE FOR ENDORSEMENT

The American College of Medical Genetics and Genomics (ACMG)/Association for Molecular Pathology (AMP) guideline was identified a priori by MOTAC and was determined to be a good candidate for endorsement by the Working Group due its acceptability in Ontario, scope, and relevance. Further, the Working Group felt that investing extensive effort to replicate the ACMG/AMP guideline would not be justified given the number of experts involved in its creation.

DESCRIPTION OF ENDORSED GUIDELINE

The recommendations regarding the classification of germline sequence variants were developed by the ACMG, the AMP, and the College of American Pathologists in 2013. The recommendations were developed through expert opinion, consensus, and community input and are applicable to variants in all Mendelian genes.

ENDORSEMENT PROCESS

The Working Group reviewed the *Standards and Guidelines for the Interpretation of Sequence Variants: A Joint Consensus Recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology* in detail, and reviewed each recommendation of that guideline to determine whether it could be endorsed, endorsed with changes, or rejected. This determination was based on the agreement of the Working Group with the interpretation of available evidence presented in the guideline, and whether it was applicable and acceptable to the Ontario context, and feasible for implementation.

All recommendations from the original ACMG/AMP guideline requiring caveats or clarifications as they pertain to Ontario are summarized in Table 1-1. All references to the Health Insurance Portability and Accountability Act were modified to refer to the Personal Health Information Protection Act to reflect Ontario legislation. Similarly, references to the Clinical Laboratory Improvement Amendments were modified to refer to the Institute for Quality Management in Healthcare.

ENDORSEMENT REVIEW

Members of MOTAC reviewed the draft endorsement and seven of the eight members voted (87.5% response rate). Of those that voted, all (100%) approved the endorsement.

MOTAC will review the endorsement on an annual basis to ensure that it remains relevant and appropriate for use in Ontario

ACKNOWLEDGEMENTS

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- Melissa Brouwers, Jennifer Hart, Rachel Healy, and Sheila McNair and for providing feedback on draft versions.
- Sara Miller for copy editing.

References

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405-424.

Appendix 1: Affiliations and Conflict of Interest Declarations

Name	Affiliation	Conflict of Interest
Working Group		
Harriet Feilotter Molecular Geneticist Chair of MOTAC	Kingston General Hospital Queen's University Kingston, ON	None declared.
Tracy Graham Genetic Counsellor	Sunnybrook Odette Cancer Centre Toronto, ON	None declared.
Victoria Mok Siu Clinical Geneticist	London Health Sciences Centre Western University London, ON	None declared.
Marsha Speevak Molecular Geneticist	Credit Valley Hospital University of Toronto Toronto, ON	Has signed out NIPT (prenatal screening) reports for LifeLabs Genetics on a few occasions.
Tracy Stockley Molecular Geneticist	University Health Network Toronto, ON	None declared.
Duvaraga Sivajohanathan Health Research Methodologist	McMaster University Program in Evidence-Based Care, Cancer Care Ontario Hamilton, ON	None declared.
Molecular Oncology and Testing Advisory Committee – Expert Panel		
Suzanne Kamel-Reid Molecular Geneticist	University Health Network Toronto, ON	None declared.
Michael Rutherford Molecular Pathologist	Hôpital Régional de Sudbury Regional Hospital Sudbury, Ontario	None declared.
Janet Dancey Clinician	Cancer Centre of Southeastern Ontario Queen's University Kingston, ON	None declared.
Andrea Eisen Medical Oncologist	Sunnybrook Health Sciences Centre Toronto, ON	Received a research grant from Genomic Health in 2015-2016.
Christopher Howlett Pathologist	London Health Sciences Centre London, ON	None declared.
Brian Leber Clinical Hematologist	Juravinski Cancer Centre Hamilton, ON	Has received $5000 or more to act in a consulting capacity within the past five years from Novartis Canada, Medical Advisory Boards.
Trevor Pugh Molecular Geneticist	Princess Margaret Cancer Centre University of Toronto Toronto, ON	Has received a training grant from Boehringer Ingelheim within the past five years for a fellow to train in circulating tumour DNA analysis.

Bryan Lo Clinician	Ottawa Hospital Ottawa, ON	Was employed as a research fellow at Genentech from 2007-2014 and has received research grants from Amgen and Roche within the past five years.