CCMG-CCGM National Office
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Committee: CCMG Clinical RNA-seq Working Group
Document: Terms of Reference (ToR)
Dates: Prepared by the Committee, December 14, 2023
Revised by the Working Group: October 2024
Approved by the Board of Directors: December 9, 2024

Brief Background for Formation of Working Group:

Clinical implementation of whole exome sequencing (WES) has revolutionized genetic diagnostics of individuals suspected of having a Mendelian disorder [28475856]; however, the diagnostic yield rarely exceeds 50%, leaving many patients without a genetic diagnosis [29323667].

Inconclusive WES can be partially attributed to the challenges concerning variant detection, prioritization, and interpretation [29242613]. Although many in silico tools have been developed to predict the effect of a variant on transcription, splicing, or RNA stability, their accuracy remains poor to establish a firm diagnosis. RNA-seq, which allows systematic identification of aberrant transcripts, enables validation of variants of uncertain significance (VUS) potentially affecting the transcript, re-interpretation of VUS when linked to an aberrant transcript event, and discovery of pathogenic variants not covered by WES. Approximately 30% of splicing VUSs could reach either a likely pathogenic or likely benign classification from RNA-seq analysis [33743207] and RNA-seq has increased diagnostic rates by 8-36% across a variety of rare disorders [31160820; 30827497; 31607746; 33001864].

Routine clinical implementation of RNA-seq requires robust and efficient computational workflows, establishment of quality controls, and adequate RNA source from various specimen types and sequencing depth. With the increasing adoption of RNA-seq in clinical laboratories, there is a need for comprehensive clinical guidelines. The CCMG Laboratory Practice Committee has agreed that a working group should be formed to develop guidelines for clinical RNA-seq.

Mandate:

The purpose of this CCMG working group is to develop and publish an evidence-based guideline for clinical RNA-seq for germline and somatic conditions. For areas with no or little evidence, expert opinion will be provided. The guideline will clearly indicate sections that are based on evidence or expert opinion.

These recommendations will promote consistency in RNA-seq validation, testing, and reporting across Canada. Therefore, representation from across Canada is important to achieve a broad Canadian viewpoint.

Timeline

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December 2023: Submission of ToR document for board approval.

March/April 2024: Volunteers identified to sit on the working group.

April/May 2024: Initial planning meeting with full working group.

December 2025: Completion of draft document.

February 2026: Circulation to Laboratory Practice Committee (and other committees as deemed appropriate by the Board of Directors) for review and feedback.

May 2026: Circulation to CCMG membership for review and feedback.

June 2026: Submit for publication.

Membership

- 5-6 CCMG laboratory scientists with experience/expertise in molecular genetics
- 1 CCMG Clinical Geneticist
- 1 Medical Oncologist
- 1 Pathologist
- 1 CCMG Genetic & Genomic Diagnostics (GGD) Fellow-in-training
- 1-2 Genomic/technical specialist(s) with experience/expertise in RNAseq
- 1 Bioinformatician with experience/expertise in RNAseq
- A representative from the CCMG Board of Directors
- A medical writer

Appointment and term of chair

- Two co-chairs will be selected for this working group.

Conduct of Meetings

- The co-chairs will convene regular zoom meetings with approximately one meeting held each month or more frequent if required.
- Quorum for decisions will be at least 50% of members.
- Draft minutes will be prepared and circulated to members for comment, ideally within 10 working days of the meeting.

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Reporting

- The co-chairs will report to the CCMG Board of Directors via the Board representative for monthly updates.
- After completion of the manuscript, it will be submitted to CCMG Board of Directors to seek feedback from appropriate CCMG committees.
- The final manuscript will be submitted to CCMG Board of Directors for approval before submitting to the Journal.