Cancer Care Ontario

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Somatic Cancer Panel Reporting in Ontario

Introduction

As the use of panel testing for molecular oncology expands in Ontario clinical labs, there is an opportunity to develop a standardized approach for the generation of clear, concise reports to reduce variation in report content and format. This standardization will support clinical management decisions by providing clear summaries of genomic findings that can be easily understood by experts and non-experts.

This report outlines the recommended components to be included in any somatic cancer panel report, as well as additional items to be considered moving forward to improve / standardize cancer panel reporting across the province. To support this initiative, the Somatic Cancer Panel Reporting Working Group (Working Group) was established. The Working Group was comprised of laboratory geneticists, pathologists with experience in massively parallel sequencing as well as staff from Cancer Care Ontario's (CCO) Pathology and Laboratory Medicine Program (PLMP). The purpose of the working group was to establish a standardized approach to:

- Variant reporting for somatic cancers
- Determine which findings and associated quality metrics should be included in a report
- Report formatting, including layout and content

Need for Standardization

The standardization of pathology reporting has been shown to improve the overall quality of pathology reporting and benefit clinical management of patients (1). Pathology reports are often the primary tool for test results to be communicated to health care providers, and can be an important resource for patients (2). As a result, it is crucial that these reports convey complex information in a comprehensive and concise way (3). Evidence has indicated that complex, lengthy and poorly formatted test reports can negatively impact patient management and disease prevention (2). Although some guidelines exist for reporting genes in the context of hereditary diseases, there is a lack of guidance on how somatic variants should be reported. Due to their complex nature and tumour heterogeneity, result interpretation of somatic variants is not always straightforward (4). There is a need to standardize how somatic variants are reported throughout the province, to ensure results are presented in a clear, concise and consistent manner (5).

Methods

Members of the working group represented molecular testing centres across the province. Members provided de-identified multigene panel reports and additional samples were pulled from the literature. The reports were analysed, itemized and compared. Common features were identified and used to develop a recommended report layout for review and discussion by the working group. Sections and features that were not common were discussed by the working group to determine if and how to

incorporate into the recommendations. The working group characterized report elements as either required or non-required based on standards, guidelines and consensus of best practice.

The recommendations were circulated to the CCO Molecular Oncology Testing Advisory Committee (MOTAC), the Pathology and Laboratory Medicine Program Committee, the CCO Complex Malignant Hematology Community of Practice and CCO Cancer Leads for review, and the feedback received was incorporated.

Recommendations

Essential Components of a Cancer Panel Report

The Institute for Quality Management in Healthcare (IQMH) has laboratory requirements that must be met by accredited Ontario laboratories which include elements of reporting from clinical assays. The "Somatic Cancer Panel Reporting in Ontario" report is intended to be used by laboratories as a supplement to the IQMH guidelines, as it provides more detailed discussion of elements that apply specifically to the reporting of somatic variants from targeted panel assays. These additional suggestions are based on working group consensus and available literature.

IQMH elements that are required to be reported are shown in **bold**. Non-bolded items provide additional clarity and assist with the readability and usability of the report.

A. PATIENT, LABORATORY and GENERAL INFORMATION

1. **Patient name or identifier, on each page of the report**
2. **Patient date of birth**
3. **The identification of the laboratory and any referral laboratories.**
4. **The page number in relation to the total number of pages**

B. SPECIMEN INFORMATION

1. **Sample type**

The type of specimen and, if relevant, its source, should be clearly indicated. Where appropriate, information about the proportion of tumour cells in the specimen should be provided.

2. **Specimen identification number**

May also be referred to as accession number.

3. **Specimen time stamps**

(1) Arrival time in lab – where appropriate, not mandatory.
(2) **Collection date**

(3) **Received date**
(4) **Final report sign out date**

4. Additional reports to refer to

Where appropriate, ancillary reports with findings that relate to the results in the cancer panel report should be mentioned. As an example, a test for a patient with recurrent cancer where a genomic variant is identified that was also identified in the diagnostic sample should refer to the original report.

C. INDICATION FOR TESTING

Indication for testing provides important information and context to optimally interpret molecular panel results. When the indication for testing is provided, molecular results should be interpreted within the context of the stated indication. If this information is not provided, it is recommended that lab directors attempt to acquire this information. If this is not practical, the report should include a statement explaining the general condition for which the interpretations are based.

D. RESULTS / INTERPRETATION

1. Variants identified

Clinically significant variants must be reported. Generally, for somatic assays, the terms clinically significant or clinically actionable should be used, instead of the terms pathogenic or likely pathogenic. The definition of clinically significant can be variable, based on the indication for testing, the type of specimen or assay being performed, the variants identified or the intent of treatment, and therefore must be developed with clinical input.

It is not required to report variants of unknown clinical actionability, although it is recommended.

a) **Gene in which variant was identified**
   i. The correct gene designation provided through the HUGO Nomenclature committee (HGNC) should be used
   ii. Legacy names should be included where these are in common use
b) **Transcript identification**
   i. The specific transcript against which the genomic data are aligned must be identified using the unique GenBank reference number, including the version number.
c) Specific exons in which variants is found
d) **Appropriate Nomenclature** according to the Human Genome Variation Society guidelines
   i. Variant nomenclature may be checked using programs such as Mutalyzer and Alamut.
e) **Variant allele fraction where relevant for variants being reported**

2. Interpretation of variants

Some level of interpretation must be made. It is recommended that labs work with clinicians to determine how much information they would like to receive. Basic interpretation should include whether the gene is known to be mutated in the relevant condition, the types of mutations (if known) in the gene that have clinical impact, and any functional evidence for clinical actionability in the relevant condition.

In cases where the potential for a germline variant exists (i.e. the mutated gene is known to result in a hereditary form of disease, and the variant allele fraction is consistent with a germline variant), a statement should be made suggesting that germline testing be considered for the family, including a referral to clinical genetics.

3. Databases Used

Databases may be used to categorize variants, however this is not required. If a database is used, it **should be one that provides detailed information on the methods used to curate and update data** (i.e in the form of a publication that can be cited)**.**

Examples of curated databases have been included below. The use of these and any other databases should be reviewed for appropriateness on a case by case basis:

- Clinical Interpretations of Variants in Cancer (CIViC): https://civicdb.org/home
- OncoKB : http://oncokb.org/#/
- ClinVar: https://www.ncbi.nlm.nih.gov/clinvar/
- PMKB: https://pmkb.weill.cornell.edu/
- Variant Interpretation for Cancer Consortium (VICC): https://cancervariants.org/
- Catalogue of Somatic Mutations in Cancer (COSMIC): https://cancer.sanger.ac.uk/cosmic

4. Drug recommendations

It is not required to make drug recommendations, and should only be done when the reason for referral was to predict response to targeted therapy.

5. Available clinical trials

It is not required to suggest available clinical trials.

E. METHODS

1. Technology Used

Technology used to perform analysis must be described. If ancillary or orthogonal testing is done through reflex testing, these methods should also be described.

2. DNA / RNA Source

3. Genomic regions analyzed in the assay

a) **Genes included in the assay**
   a. **For targeted panels, all genes tested must be listed on the final report.** See methods section for additional information on reporting of variants.

b) **Transcript identification**
   i. The specific transcript against which the genomic data are aligned must be identified using the unique GenBank reference number, including the version number.

c) **Coding Region**

i. The report should include the specific regions of genes that were investigated by the panel assay. This may include whole coding regions, portions of non-coding regions, or specific exons or parts of exons and these should be clearly stated. If this information is too cumbersome for the report, it could be made available in a "test information sheet" that could be available electronically to referring physicians and other labs as needed.

d) **Nomenclature**

Gene Nomenclature should be based on the Human Genome Organisation (HUGO).

5. Limit of detection, specified for different types of variants

6. Sensitivity and specificity of the assay, specified for different types of variants

F. COMMENTS / DISCLAIMER

1. **Specimen is Suboptimal**

When the specimen is suboptimal, it is recommended to specify this. Specific regions of the assay that did not meet quality metrics should be specified.

2. **Regions with inadequate depth of coverage**

3**.** Sample mix-up

Including a disclaimer relating to the potential for sample mix-up is not mandatory, but should be discussed and decided by each laboratory.

4. References

It is recommended, but not mandatory, that references are included when primary publications are used for information provided in the report. Databases used for variant classification should be referenced. Where applicable, include a specific Record ID.

G. REPORT STRUCTURE / FORMAT

Reports should be as concise as possible, and where appropriate links to additional information (such as websites) can be used. Varying font size can be used to emphasize information (6). The overall result and/or conclusion must be clearly visible (5).

Future Considerations

1. Molecular, cytogenetic and pathology information needs to be available and coordinated to ensure the best patient management. This information should be integrated in a comprehensive manner to facilitate alignment with other laboratory and clinical information. Recommendations from this report should be incorporated into the design of a comprehensive, integrated report which combines all the necessary information needed to provide optimal patient care.

2. This report is a first step towards establishing standards in molecular reporting for tumour panel testing. Standardized reporting, including information in an extractable format, will allow analysis of complex molecular results as they relate to patient outcomes and clinical phenotype. Ideally the standard molecular report format can eventually make use of standard clinical coding language (such as SnoMed) to allow for the sharing of information with other national and international healthcare systems.

3. The creation of standardized language for reporting molecular clinical variant interpretation would also simplify the process of submission of genomic data (variants and clinical interpretations) to large public databases that would be enhanced by the addition of high quality, high volume, and well annotated data.

4. As the number of genes on panels expands, the length of panel reports will also grow. The current method of reporting will become cumbersome and will reduce readability by users of the report. In the future, labs may choose to summarize operational and repetitive information in a "Test Information Document". The "Test Information Document" could be housed on a website, and the hyperlink could be referred to in the original report. Guidance on what information can be included in the "Test Information Document" will be needed in the future.

References

1. Does standard structured reporting contribute to quality in diagnostic pathology? The importance of evidence-based datasets. **Ellis, D. W. and Srigley, J.** 2016, Virchows Archive, pp. 51 - 59.

2. *Hereditary cancer gene panel test reports: wide heterogeneity suggests need for standardization .* **Makhnoon, Sukh, et al.** 2018, Genetics in Medicine, pp. 1438 - 1445.

3. *Reporting Results of Molecular Tests.* **Treece, Amanda L. , et al.** May 2017, Archives of Pathology and Laboratory Medicine, Vol. 141, pp. 658 - 665.

4. *The ins and outs of molecular pathology reporting.* **Tack, Veronique, et al.** March 2017, Virchows Archiv, pp. 199 - 207.

5. *General Genetic Laboratory Reporting Recommendations.* **Smith, Kath, et al.** 2015, Association for Clinical Genetic Science.

6. *Toward harmonization of clinical molecular diagnostics reports: findings of an international survey.* **Payne, Deborah A., et al.** May 2018, Clinical Chemistry and Laboratory Medicine, pp. 78 - 99.

Appendix A – Working Group Membership

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