

Meeting report series

Report of the 2nd DSC Working Group on Sequencing teleconference

27 November 2013

Organization

Organized by: IRDiRC Scientific Secretariat
Teleconference

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REPORT

The Diagnostics Scientific Committee (DSC) reviewed on September 10th the report of the previous teleconference of this WG and discussed the possible actions proposed by the WG. The feedback for each topic is summarized below, with the discussion of the WG that followed.

Development of guidelines

Recommendation by the DSC

The DSC recommends the compilation of all the guidelines available and to compare them to provide recommendation for use in the next 6 months.

Report on the headlines of the Eurogentest NGS guidelines

EuroGentest is already compiling guidelines with the participation of some members of this WG. It was proposed that the members of the WG will review the guidelines published by EuroGentest for comments and recommendation to the DSC within the next 6 months.

A draft guideline was compiled based on several existing guidelines (ACMG; CDC document, Dutch guidelines, document from clinical molecular society in UK, draft Australian guidelines) and discussed in a meeting in November. The purpose is to propose practical but not too technical guidelines.

Layout of the guidelines

- ▶ Diagnostics and clinical utility: emphasis that diagnostic NGS should only be performed when useful
- ▶ Informed consent: from the laboratory standpoint, looking at the responsibility of the laboratory; propose different levels of consent
- ▶ Technical validation: chapter both technical (analytical chemistry, analytical sensitivity, etc.) and practical.
- ▶ Reporting: emphasis on this topic; propose a structured report including an one-page summary, annexes and discussion on cluster
- ▶ Incidental findings: develop a clear distinction between unsolicited findings (unexpected finding inside the gene panel; to be reported) and secondary findings (beyond the gene panel).

Each chapter follows the same organization: why this chapter, viewpoints, statements and references to other guidelines for point discussed.

Highlights on the guidelines

- ▶ Diagnostic utility is based on Dutch guidelines; emphasize that laboratory should write down a diagnostic routine before they start

- ▶ Defining the gene core list: specialists other than geneticists (cardiologists, neurologists, etc.) should be included to define the gene core list
- ▶ Want to introduce a scoring system for panel and exome at the sequencing level. Propose 3 types:
 - Type A: run exome sequencing + gene panel extraction + fill gap with Sanger
 - Type B: run exome sequencing + gene panel extraction + fill some gap based on clinical evidence
 - Type C: run exome sequencing + panel extraction without adding anything with Sanger sequencing

Scoring system should be linked to the gene core list. This is a technical tool that could help healthcare system to compare quality and depth of the test.

Topics raised during the discussion:

- ▶ The topic of certification is not addressed in the guidelines. Several existing certifications are of interest:
 - ISO 27001 Information technology – Security techniques – Information security management systems – Requirements
 - ISO 15189 Medical laboratories – Particular requirements for quality and competences
 - ISO 13485 Medical devices – Quality management systems – Requirements for regulatory purposes.
- ▶ Disease-targeted test: a minimum set of gene is necessary and gene included in panel should meet a high level of evidence of gene-disease association (ClinGen started a program of evidence-based review process). It would be useful to be able to transfer data of Exome/genome sequencing obtained for diagnostic to research purpose (gene discovery, report of unclassified variant, etc.).

Inquiring the implementation of clinical exome/genome sequencing in other countries

Recommendation of the DSC

The DSC approves the idea as they agree that IRDiRC should recommend the reimbursement of genetic testing by national health system. They suggest identifying one person in each country to evaluate the approach of the country on the implementation of clinical exome/genome sequencing.

Questionnaire to evaluate the approach of countries on the implementation of clinical exome/genome sequencing

The purpose of the questionnaire is to investigate existing NGS activities in different countries including which countries what is done about implementing genetic testing in clinical setting and reimbursement by national health system. The idea is to find countries that can be used as example and encourage other to follow the example (need to mobilize patients rather than scientists).

2 aspects of the projects:

- ▶ Preparation of the questionnaire, knowing that there will be a huge heterogeneity between countries
- ▶ Finding the right contact person in each country, as uniformly as possible between countries (national societies?)

Although the survey will bring useful information, members of the WG are aware that it will practically difficult to influence the politic of countries.

- ⇒ Members agreed to wait for the outcomes of the Genomic Medicine VI meeting sponsored by the NHGRI, schedule on Jan 8-9, 2014 to further discuss the project. The idea is to see if the US approach can be expended to Europe to collect data. Some members of this WG will participate to this meeting.

Classification of variants

Recommendation of the DSC

The DSC is interested by this topic but this is not a priority for this WG who should identify and collaborate with other initiatives.

Comments from the WG

The American College of Medical Genetic (ACMG), in collaboration with the College of American Pathologists (CAP) and the Association for Molecular Pathology (AMP) is working on drafting guidelines for the interpretation of sequence variants. The first draft should be ready by March 2014. Inputs from a variety of stakeholders where obtained through 2 surveys and 2 open forums. Committee drafting these guidelines agreed to 5 levels of classification with respect to Mendelian disease variant classification (Pathogenic, Likely pathogenic, Uncertain significance, Likely benign and Benign).

- ⇒ Members of the WG agreed to wait for the publication of these guidelines and to recommend a position to IRDiRC members in regard to these guidelines (acceptation or suggest modifications).

Conclusion

It was important to get the feedback from the DSC.

The WG should focus on the following 2 tasks:

- ▶ Review the EuroGentest guidelines for recommendations
- ▶ Questionnaire on the implementation of high volume sequencing methods into diagnostics setting by each country

Next meeting

The following meeting should be scheduled at the end of January - beginning of Feb when the Eurogentest guidelines will be available and that the NHGRI workshop was held.