Oncologists Review of ctDNA EGFR Mutation Testing Reports

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INTRODUCTION

GenQA is an External Quality Assessment (EQA) provider for Genomics which assesses laboratory tests and the interpretative content of reports.

GenQA provided an EQA for the testing of circulating tumour DNA (ctDNA) for EGFR mutations in lung cancer patients.

The submitted reports were anonymously reviewed by a panel of Consultant Oncologists to identify the elements which were clear and unambiguous, and those misleading and may cause patient harm if misinterpreted. The findings were shared with the laboratories to improve the reporting standard of liquid biopsy test results.

METHODS

• In 2018, nine laboratories performed ctDNA testing for EGFR mutations in lung cancer patients in the United Kingdom, and all took part in the EQA and this report review.
• The EQA reports submitted for two clinical cases were anonymised and sent to the reviewers to be rated for:
  ➢ Ease of finding the result,
  ➢ Understanding the test methodology,
  ➢ Clarity of the interpretation and
  ➢ The clinical case was accurate.
• The reviewers were requested to highlight text which they found to be comprehensive, and content which was confusing or inaccurate and provide comments which in their view would improve the reports.
• Individual laboratory reviews were provided to the laboratories.

RESULTS AND DISCUSSION

Case 1

Clinical scenario: A patient progressing on first line EGFR TKI therapy with the primary EGFR mutation and a resistance mutation detected in the plasma sample.

Plasma testing result: c.2573T>G p.(Leu858Arg) at an allelic frequency of 10% and c.2689C>T p.(Thr903Met) at an allelic frequency of 1.25%.

Expected interpretation: The detection of the primary c.2573T>G p.(Leu858Arg) variant demonstrates that tumour DNA is present in the plasma sample. The detection of the c.2689C>T p.(Thr903Met) variant indicates that the patient is eligible for treatment with a third generation EGFR TKI which are targeted to the p.(Thr903Met) mutation.

Examples of reports which scored highly by the reviewers (figures 1 and 2). The expert displayed as figure 3 was identified by the reviewers as being “unhelpful” and “not required” as it suggests that a biopsy is also required after testing ctDNA despite reporting the correct result.

Figure 1: Case 1 example A of a highly scoring report

The EGFR T790M mutation, and original EGFR-TKI sensitizing mutation, L858R, were detected in the ctDNA sample from this patient. This is consistent with the disease progression noted in this patient and indicates that Wafar may benefit from treatment with next generation EGFR-TKIs targeted to T790M.

Figure 2: Case 1 example B of a highly scoring report

Conclusion: A T790M mutation has been detected in this sample in addition to the original L858R mutation. This patient may respond to third generation EGFR TKIs which target the acquired T790M mutation.

Figure 3: Case 1 example C of a low scoring report

GENERAL OBSERVATIONS FROM REVIEWERS

The reviewing Oncologists highlighted unhelpful report content as follows:

➢ Use of the commercial drug name rather than the generic name;
➢ Describing the TKI as being “novel” which led one of the Oncologists to speculate that the patient may be eligible for a trial for a new currently unlicensed drug;
➢ The majority of reports did not specifically mention that the third generation EGFR TKIs target p.(Thr903Met) specifically (when detected i.e. case 1);
➢ Reporting that the EGFR TKIs “would” benefit the patient. This was interpreted as being misleading and the word “might” would have been preferable;
➢ The variant allelic frequency was deemed to be not clinically relevant and many oncologists would not understand it. Although it was noted that in time, this may become more relevant for response prediction;
➢ Method specific metrics e.g. Semi Quantitative Index (SQI) was not clinically relevant and was not required on the report.

CONCLUSIONS

• Many laboratories report ctDNA in a variety of formats using language with varying degrees of clarity.
• Standardisation of reporting would help improve care standards for patients by limiting the risk of misinterpretation.

Figure 5: Summary of recommendations following the Oncologist’s review of ctDNA EGFR reports