Urgent Field Safety Notice

MY-FSN-RDS-Molecular Lab-2021-011

RDS/**cobas**® EGFR Mutation Test v2
Version 2

cobas® EGFR Mutation Test v2: Potential for False Mutation Detected results for exon20 Insertion

Product Name	**cobas**® EGFR Mutation Test v2
GMMI / Part No **Device Identifier**	**Roche Identifier: 07248563190** Device Identifier: 00875197005448
Production Identifier (Lot No./Serial No.)	Not Applicable (not kit lot specific)
SW Version	Not Applicable (not SW Version lot specific)
Type of Action	Field Safety Corrective Action (FSCA)

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Description of Situation

Dear Valued Customer,

Roche received complaints from customers reporting the generation of false Mutation Detected results for the EGFR exon 20 insertion (EGFR Ex20Ins) mutation when using the cobas® EGFR Mutation Test v2 (GMMI: 07248563190). This notification is an update to the previous version of MY-FSN-RDS-MolecularLab-2021-011, issued in 2021.

Investigation Result

In a majority of the escalated cases, it was noted that end users were extracting DNA from more than one 5-micron (µm) FFPET (formalin-fixed paraffin-embedded tissue) section or from sections with varying thicknesses.

The cobas® DNA Sample Preparation Kit (M/N 05985536190) Instructions for Use, which provide the specific instructions for the isolation of DNA from FFPET specimens, specify to use one 5-µm thick FFPET section for sample preparation.

The cobas® EGFR Mutation Test v2 Instructions for Use indicate:
- Each DNA stock must have a minimum concentration of 2 ng/µL to perform the cobas® EGFR Mutation Test v2. If the concentration of a DNA Stock is < 2 ng/µL, repeat the deparaffinization, DNA isolation, and DNA quantitation procedures for that sample using two 5-µm FFPET sections.
- If the DNA stock is still < 2 ng/µL, request another FFPET sample section from the referring clinical site.

During in-house testing using customer-provided FFPET samples, an EGFR Ex20Ins false Mutation Detected result was reproduced for one FFPET sample, which was processed following the validated sample preparation method from the Instructions for Use.

The generation of false Mutation Detected EGFR Ex20Ins results with plasma specimens has not been excluded.\

Based on the investigation, other mutations detected with the cobas® EGFR Mutation Test v2 (Ex19Del, S768I, L858R, T790M, L861Q and G719X) are not affected as these mutation channels use a different result interpretation concept than the EGFR Ex20Ins mutation channel.

Root Cause Analysis

The likely cause for the increased false EGFR Ex20Ins Mutation Detected results at customer sites was pefabloc modification of the Z05 AS-1 polymerase enzyme, one of the raw materials used in the assay reagent. The modification of the Z05 AS-1 polymerase enzyme by pefabloc resulted in earlier Ct values and increased variability in the non-specific amplification of EGFR Ex20Ins mutation. The resulting earlier Ct values, coupled with increased variability, led to an increase in the EGFR Ex20Ins false Mutation Detected results.

Recent feasibility studies have resulted in the manufacture of additional experimental batches of enzyme and Master Mixes to conduct additional testing to conclude the investigation. We anticipate the completion of these studies in 3Q2022. Upon completion of the studies, corrective and preventive actions will be identified, and then implemented as appropriate. The timeline for the implementation of any corrective/preventive actions is not yet defined.

Despite extensive root cause investigative testing, a definitive root cause for the early Ex20Ins Ct values and increased variability in the non-specific amplification of Ex20Ins mutation could not be determined. Ct results for false positive Ex20Ins Mutation Detected results were earlier and more variable for all batches of EGFR MMX3 v2 that used a specific lot of stock Z05 AS-1 polymerase enzyme (raw material). It is plausible that the earlier Ex20Ins Ct values,

coupled with the increased variability in Ct results, led to an increase in false positive Ex20Ins Mutation Detected results and the complaints in the field.

The investigation also identified additional contributing factors that may increase the frequency of the false positive EGFR Ex20Ins mutation call, including an off-label quantitation method (e.g., Qubit), which may under quantitate the amount of DNA relative to the validated method, resulting in the addition of DNA that is more concentrated than expected. In addition, the complexity of the enzyme manufacturing process as well as off-label practices such as the use of non-validated DNA quantitation methods (e.g., fluorometer).

Risk Assessment

Frequency of Occurrence

As of 18-Aug-2021, sixteen (16) escalated cases have been confirmed to be related to this issue. In a subset of these escalated cases, end users reported an increase in their Ex20Ins Mutation Detected rates.

EGFR Ex20Ins mutations occur in ~2-3% of all non-small cell lung cancer (NSCLC) cases, representing ~10-12% of all cancers with documented EGFR mutations (https://doi.org/10.1016/j.ctrv.2020.102105).

Detectability

False Mutation Detected Ex20Ins results can be detected if sequencing or other PCR-based tests are performed.

Severity

A false Mutation Detected EGFR Ex20Ins result could lead to harm to patients depending on several scenarios described below, some of them being unlikely or extremely unlikely to occur:

(i) A standalone false Mutation Detected EGFR Ex20Ins result may lead to:

A. Inappropriate administration of amivantamab (Rybrevant®, US FDA approved in May-2021; EU EMA conditional marketing authorization approved in October-2021; Health Canada conditionally approved in April-2022) or mobocertinib (Exkivity®, US FDA approved in September-2021), delaying Standard of Care (SOC) therapy (chemotherapy or immunotherapy) by 2-3 months;
B. Delay of SOC immunotherapy (or combination therapy) in countries where no anti-EGFR Ex20Ins targeted therapies are approved and medical guidelines recommend against administration of immunotherapy in the presence of any EGFR mutation.

(ii) A false Mutation Detected EGFR Ex20Ins result in combination with a sensitizing (e.g., Ex19Del, L858R) or resistance (T790M) EGFR mutations, in rare cases, might lead to:

A. Ineffective treatment (amivantamab or mobocertinib), if available, rather than an appropriate therapy with an EGFR tyrosine kinase inhibitor (TKI). However, it is likely the physician would prescribe the appropriate EGFR TKI rather than amivantamab or mobocertinib;
B. Delay of SOC therapy in patients who have progressed on an EGFR TKI (including osimertinib) by 2-3 months.

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Actions taken by Roche Diagnostics

Roche continues the root cause investigation. To reduce the potential for observing Ex20Ins false positive results, Roche plans to implement a new functional release method and specification for the Z05 AS-1 polymerase enzyme raw material to screen batches prior to utilizing the raw material in EGFR V2 test kit manufacturing. In parallel, Roche will implement a software update to the EGFR v2 tissue ASAP with modified Ex20Ins cut-off values to further reduce the risk of reporting false positive Ex20Ins Mutation Detected results.

The timelines for these actions will be communicated in due course, once they are available for implementation.

Actions to be taken by the customer/user

Customers must follow the **cobas**® DNA Sample Preparation Kit (M/N 05985536190) IFU for sample input. If an Ex20Ins Mutation Detected result is generated with the **cobas**® EGFR Mutation Test v2, customers must confirm the result with another method (e.g., sequencing or other PCR-based tests).

Until the implementation of the updated SW ASAP at customer sites, Clinical Laboratories must not report out EGFR Ex20Ins Mutation Detected results generated with the cobas EGFR Mutation Test v2 unless the results are confirmed with another clinically validated orthogonal method (e.g. sequencing or other PCR-based tests)

Clinical laboratories should consider the availability and approval status of amivantamab in their country as well as eligibility for immunotherapy as part of SOC in the presence of any EGFR mutation when determining the date range of test result reports (TRR) of the **cobas**® EGFR Mutation Test v2 that must be reviewed retrospectively, and should follow local guidelines and procedures.

Clinical laboratories located in the United States may consider reviewing results generated since May 2021 (Amivantamab was approved by the US FDA for NSCLC patients with EGFR Ex20Ins on May 21, 2021). TRRs with Ex20Ins mutation detected may be considered for confirmatory testing using sequencing or other PCR-based tests, upon the discretion of a CAP/CLIA laboratory director.

Communication of this Field Safety Notice

This notice must be passed on to all those who need to be aware within your organization or to any organization/individual where the potentially affected devices have been distributed/supplied. (If appropriate).

Please transfer this notice to other organizations/individuals on which this action has an impact. (If appropriate).

Please maintain awareness of this notice and resulting action for an appropriate period to ensure the effectiveness of the corrective action. (If appropriate).

Please complete and return the Customer Acknowledgement Receipt within 2 business days to acknowledge your reading and understanding of this notice.

We apologize for any inconvenience this may cause and hope for your understanding and your support.

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Contact

If you have any questions, please do not hesitate to contact your sales representative or our Customer Call Centre: **1800 88 8881**

Thank you.

Best regards,

ROCHE DIAGNOSTICS (M) SDN. BHD.

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Customer Acknowledgement Receipt

Roche Diagnostics Malaysia
Fax Back: +603 7967 2399
Email: malaysia.diagnostics@roche.com

Attention: Customer Partner Team

Re: MY-FSN-RMD-2021-011: cobas® EGFR Mutation Test v2: Potential for False Mutation Detected results for exon20 Insertion

I acknowledge I have received the notification on MY-FSN-RMD-2021-011: cobas® EGFR Mutation Test v2: Potential for False Mutation Detected results for exon20 Insertion and will proceed to perform the instructions as listed in MY-FSN-RMD-2021-011.

Thank you.

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Name:

Organization:

Stamp:

Date: