Urgent Field Safety Notice
SBN-RDS-Molecular Lab-2021-011

RDS/**cobas**® EGFR Mutation Test v2
Version 1

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**	GMMI: 07248563190 Device Identifier: 00875197005448
Production Identifier (Lot No./Serial No.)	Not Applicable (not kit lot specific)
SW Version	Not Applicable
Type of Action	Field Safety Corrective Action (FSCA)

Dear Valued Customer,

Description of Situation

Roche received complaints reporting the generation of false Mutation Detected results for the exon20 insertion (Ex20Ins) mutation when using the **cobas**® EGFR Mutation Test v2.

In a majority of the escalated cases, it was noted that end users were extracting DNA from more than one 5-micron (µm) FFPET 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 tissue specimens for the **cobas**® EGFR Mutation Test v2, specify to use one 5-µm 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 test. 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.

The root cause investigation is currently ongoing. During in-house testing, using customer-provided FFPET samples, an 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. Based on the observed data, the false Mutation Detected Ex20Ins results presented as low-positive samples.

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

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 positivity 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 mutation (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 Ex20Ins result could lead to harm depending on several scenarios described below, some of them being unlikely or extremely unlikely to occur:

- A standalone False Mutation Detected Ex20Ins result may lead to:
    - Inappropriate administration of amivantamab (US FDA approved in May-2021), delaying Standard of Care (SOC) therapy (chemotherapy or Immunotherapy) by 2-3 months. The amivantamab impacts are not applicable in countries where the drug is not available.
    - Delay of SOC immunotherapy in select ex-US countries, where there is disapproval of immunotherapy administration in the presence of any EGFR mutation based on local guidelines and regulations.

- A False Mutation Detected Ex20Ins result in combination with a sensitizing EGFR mutation (e.g., Exon 19 deletion, L858R) at the time of diagnosis, in rare cases, might lead to ineffective treatment (amivantamab) rather than appropriate therapy with an EGFR TKI. However, it is likely the physician would prescribe the appropriate EGFR TKI, rather than amivantamab.

- Although extremely unlikely, a False Mutation Detected Ex20Ins result in combination with a sensitizing mutation in patients who have progressed on an EGFR TKI (including osimertinib) could lead to delay of SOC by 2-3 months.

- While extremely unlikely, theoretically, a False Mutation Detected Ex20Ins result in combination with a resistance EGFR T790M mutation at progression on an EGFR TKI could lead to an ineffective therapy (amivantamab), delaying treatment with osimertinib by 2-3 months.

Actions taken by Roche Diagnostics (if applicable)
Roche continues the root cause investigation.

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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).

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 (if appropriate)

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).>

The following statement is mandatory in FSNs for EEA countries but is not required for the rest of the World:

The undersigned confirms that this notice has been notified to the appropriate Regulatory Agency.

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

<closing salutations>,

Contact Details

To be completed locally:
Name
Title
Company Name
Address
Tel. +xx-xxx-xxxx xxxx
Email name@roche.com