QIAGEN GmbH
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40724 Hilden, Germany

Acknowledgment of Receipt Form

Please complete this form and email it to **quality.communications@qiagen.com** by 28 July 2022 using the following acknowledgement text (it will be equivalent to your signature):

"I hereby acknowledge that I have received, read, and understood the included Urgent Field Safety Notice for *therascreen* FGFR RGQ RT-PCR Kit (24), REF 874711, for *in vitro* diagnostic use (IVD), dated July 2022. We have taken the necessary actions as suggested by this notice.

We acknowledge that this document may be presented to regulatory or administrative bodies globally according to mandatory legislation."

Laboratory name:

Address:

Contact name:

Title:

Phone number:

Date:

Signature:

July 2022

Urgent Field Safety Notice

REF 874711 *therascreen* FGFR RGQ RT-PCR Kit (24), LOTs 172017804 and 169046610

To the attention of Lab Director/Manager, Medical Director, Risk Manager, Safety Officer

Dear *therascreen* FGFR RGQ RT-PCR Kit customer,

QIAGEN has identified an increased occurrence rate of false positive results obtained with the *therascreen* FGFR RGQ RT-PCR Kit lots 172017804 and 169046610. For a proportion of samples with the Overall sample result "FGFR Alteration Detected", the result could be a false positive..

Potential risks associated with the issue

The issue can potentially lead to a false positive sample result that could subsequently be incorrectly reported from the laboratory. A false positive result could lead to the risk of the patient being exposed to an inappropriate or suboptimal anti-cancer treatment and/or unnecessarily experiencing side effects.

Detailed description of the issue

Only samples with an overall sample result "FGFR Alteration Detected" (as per *therascreen* FGFR FFPE MDx Analysis Report) are affected. In the affected runs, the Run Controls pass correctly (leading to a valid result for the sample), while an artefact in one or more of the mutation assays might cause an incorrect valid mutation positive result for individual sample. The software for the interpretation of all mutations claimed in the assay does not distinguish such artefacts from a real amplification obtained with a valid mutation positive sample.

The investigation at QIAGEN demonstrated that all targets/Amino acid variants/Fusion IDs are affected, except for Amino acid variant p.S249C (c.746c>C on Exon 7).

The increased occurrence rate of false positive results obtained with the affected lots was detected within the context of ongoing clinical trials. The investigation by QIAGEN revealed that approximately 2.7% of all samples tested and with valid results obtained with lots equivalent to the affected lots gave a false positive result. In the context of the corresponding clinical trials, with a prevalence of FGFR alterations in bladder cancer of 30%, the detected false positive rate results in a specificity of 96% and a Positive Predictive Value of 91% for the affected lots.

At this stage, any positive result showing "FGFR Alteration detected" for targets other than p.S249C (c746C>C on Exon 7) should not be reported, and a retest for confirmatory result should be performed.

The following are acceptable results:

- Sample Results with the Overall sample result "No Alteration Detected" are not affected by this issue and are correct.

- "FGFR Alteration Detected" results with Individual target result for p.S249C (c.746c>C on Exon 7) are not affected and can be regarded as correct. This includes results for samples with or without additional individual other target results.
- Kit lots of REF 874711 with lot numbers lower than LOT 169046610 are not affected.

Actions to be taken by the customer

- For the continued use of REF 874711 *therascreen* FGFR RGQ RT-PCR Kit LOT 172017804, please note the following criteria:
    - Samples with the Overall sample result "No Alteration Detected" should be regarded as correct and no further actions are needed.
    - Samples with the "FGFR Alteration Detected" results with Individual target result S249C Mutation Detected can be regarded as correct. This also includes samples with additional alterations detected.
    - All other "FGFR Alteration Detected" results aside from S249C Mutation Detected should be disregarded and a retest for confirmatory positive result should be performed using the extracted RNA if available, or re-extracted if it is not.
    - The following results should be assigned to the affected samples after the retest:
        - Retest result is positive for the same target(s)/ alteration(s): regard the result for the corresponding sample as positive.
        - Retest result is positive for different target(s)/ alteration(s) in the retest compared to the initial result: regard the result as indeterminate.
        - Retest is negative: the result for the corresponding sample should be regarded as negative
        - Retested sample is within an invalid run: repeat the run.
        - Result for individual sample is invalid in the retest: regard the result as indeterminate.

Table 1. Overview of affected results

Overall sample result	Individual target result	Affected of the issue	Action to be taken by customer
No Alteration Detected	n/a	no	n/a (correct result)
FGFR Alteration Detected	S249C Mutation Detected	no	n/a (correct result)
FGFR Alteration Detected	S249C Mutation Detected and additional individual target results	no	n/a (correct result)
FGFR Alteration Detected	One or more individual target results that don't include S249C	yes	Disregard result for this sample. Retest for confirmatory positive result

Table 2. Overview interpretation of retest results

Retest result	Individual target result in retest	Result to be assigned after retest
FGFR Alteration Detected	Same target(s)/ alteration(s) as within initial test	FGFR Alteration Detected, "positive result"
FGFR Alteration Detected	Different target(s)/ alteration(s) as within initial test	Indeterminate result
No Alteration Detected	n/a	No Alteration Detected
Invalid run	n/a	n/a, repeat the run
Invalid individual sample result	n/a	Indeterminate result

- If you have concerns about previously generated mutation positive results obtained with the affected lots, the criteria listed in the tables can be used for the review.

- Forward this information to all individuals and departments within your organization who are using REF 874711 *therascreen* FGFR RGQ RT-PCR Kit.
- If you are not the end user, please forward this notice to the product end user.
- Review this notice with your laboratory/medical director.
- Complete the Acknowledgement of Receipt Form attached to this letter by 28 July 2022 and email it to **quality.communications@qiagen.com**.
- **Actions for Commercial Partners:**
    - Forward this notice to your customers.
    - Follow-up on the Acknowledgement of Receipt with all of your customers.
    - Confirm the completion of the follow up of the Acknowledgement of Receipt of your customers to **quality.communications@qiagen.com**.

Actions taken by QIAGEN

QIAGEN is working on identifying and correcting the root cause of false positivity. QIAGEN is working with regulatory authorities following notification and any update on mitigation measures will be promptly communicated.

If you have any questions or concerns, please contact your local QIAGEN Technical Service Department:

QIAGEN Subsidiaries
www.qiagen.com/de/about-us-old/contact/global-contacts/subsidiaries

QIAGEN Commercial Partners and Importers
www.qiagen.com/de/about-us-old/contact/global-contacts/distributors-and-importers

We sincerely apologize for any inconvenience this may cause and thank you in advance for your cooperation.

With kind regards,

QIAGEN
www.qiagen.com