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External Quality Assessment for *FGFR3* testing in Urothelial / Bladder cancer

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Background & Objective

Bladder cancer is the ninth most commonly diagnosed cancer worldwide with both incidence and mortality rates increasing, urothelial carcinoma is the most common sub-type.[1,2] FGFR Kinase Inhibitors were approved by the European Medicines Agency (EMA) in 2024 for treatment of metastatic urothelial carcinoma patients with susceptible *FGFR3* variants. We have piloted a global external quality assessment (EQA) scheme for urothelial / bladder cancer *FGFR3* testing to assure quality of diagnostic services.

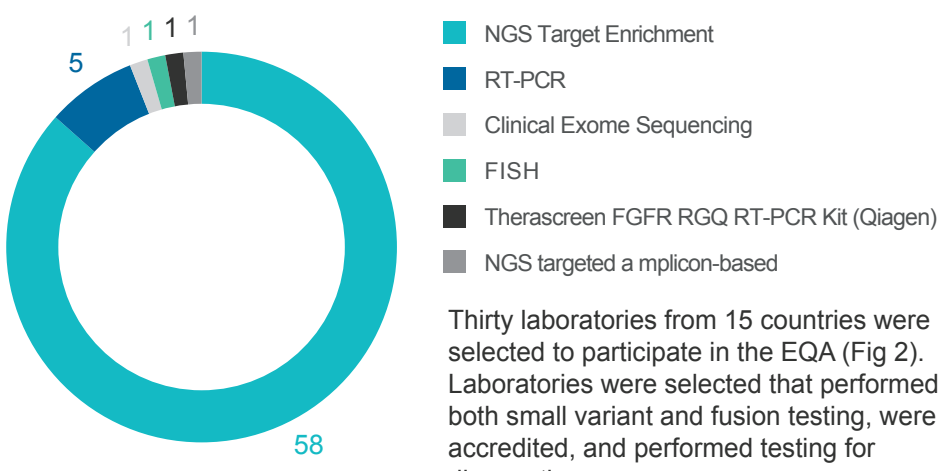
Methods

A survey was sent to over 2000 molecular pathology laboratories and thirty were selected to participate in the pilot EQA. Three formalin fixed paraffin embedded (FFPE) samples with mock clinical referrals were sent for *FGFR3* small variant or fusion testing and laboratories were instructed to use their routine test methodologies. One sample contained an *FGFR3* variant NM_000142.5:c.746C>G p.(Ser249Cys), one contained an *FGFR3* fusion FGFR3::BAIAP2L1 and one had no clinically relevant variants. Anonymised clinical reports were returned and assessed for *FGFR3* genotyping accuracy, result interpretation in the context of therapy, and clerical accuracy.

Results

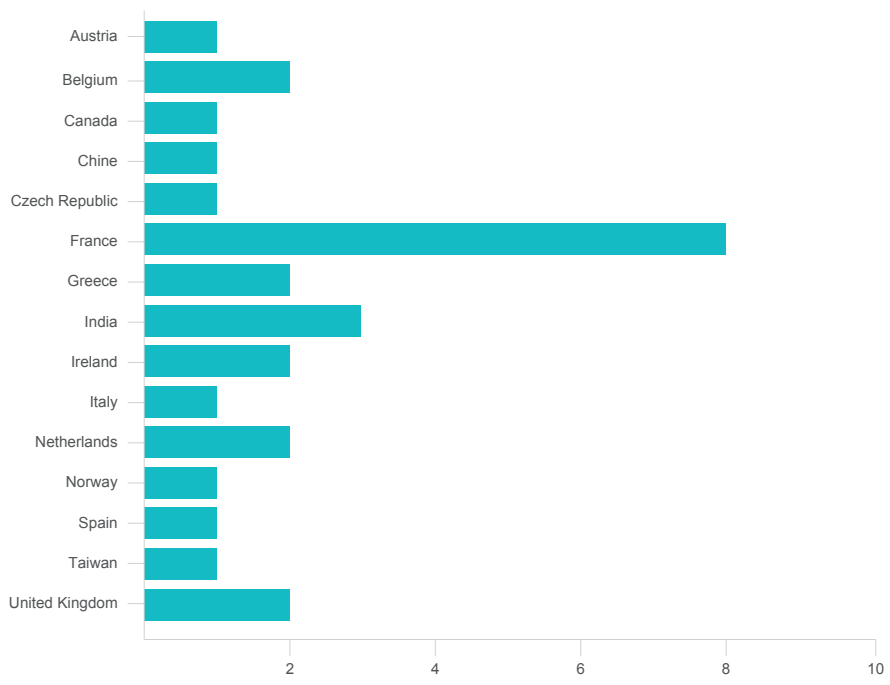
The survey was completed by 67 laboratories from 20 countries, with the highest applications from France and Italy. Of the applicants, 87% (58/67) performed targeted NGS, 7% (5/67) performed RT-PCR and 6% (4/67) used other methods for FGFR analysis (Fig 1).

Fig 1. Survey results for methods employed for FGFR analysis



Thirty laboratories from 15 countries were selected to participate in the EQA (Fig 2). Laboratories were selected that performed both small variant and fusion testing, were accredited, and performed testing for diagnostic purposes.

Fig 2. Participating countries



Of the thirty laboratories selected to participate in the pilot EQA, 27 returned results. All laboratories used NGS based methodologies (Fig 3 and 4).

Figure 3. Methodology used for detection of *FGFR3* short variants in pilot EQA

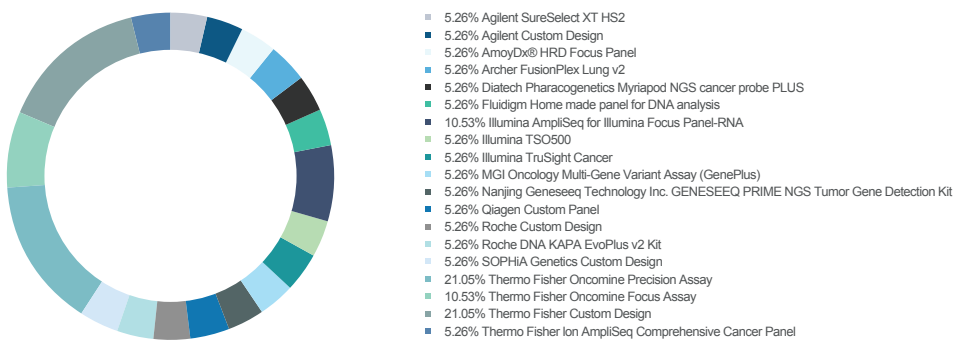
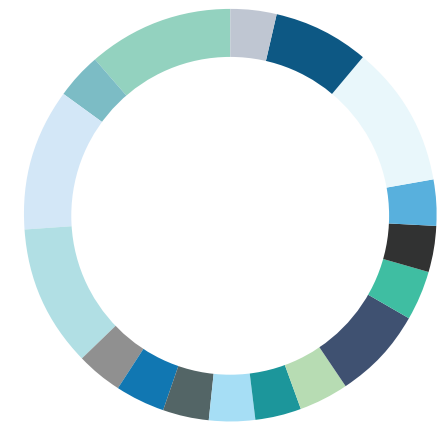
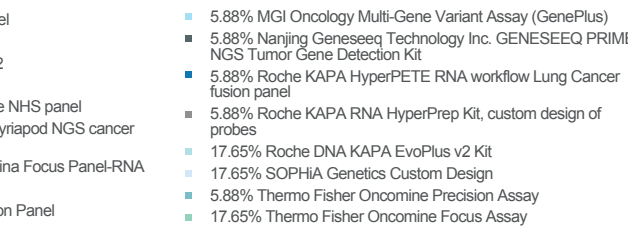


Figure 4. Methodology used for detection of *FGFR3* fusions in pilot EQA





Overall, the standard of genotyping was high. Three laboratories reported false positive results (3/27, 11.1%), with an overall error rate of 3.9% (3/77 reports) (Table 1).

Table 1. Summary of pilot EQA genotyping results

Category	Case 1 No clinically actionable variants or fusions	Case 2 *FGFR3* variant NM_000142.5:c.746C>G p.(Ser249Cys)	Case 3 *FGFR3:BAIAP2L1*	Totals
Number of cases completed	25	26	26	77
Number of laboratories with full marks	21	23	13	57
Number of critical errors	2	0	1	3
Error rate (%)	8.0	0	3.85	3.90

There was some variation in nomenclature used for reporting of the fusion; 33% (9/27) laboratories did not use internationally recognised nomenclature. Two laboratories received deductions for reporting the fusion incorrectly; one reported the incorrect exon for the fusion partner, and one laboratory used HGVS nomenclature with incorrect cDNA co-ordinates for the reference sequence provided.

Urothelial / Bladder cancer patients whose tumour harbours an actionable *FGFR3* variant or fusion are eligible for FGFR tyrosine kinase inhibitor therapy, although this may not be licensed in all countries. The majority of laboratories commented on FGFR inhibitor therapy but this information was missing from some reports.

Conclusions

Evidence from EQA shows that the introduction of a new test is usually accompanied by a high diagnostic error rate. This pilot EQA indicated that genotyping accuracy was good but there are improvements to be made for laboratories performing *FGFR3* testing for Urothelial cancer, and that there is a need for harmonisation, particularly in reporting of fusions.

Sponsorship

This EQA was supported by Johnson and Johnson.

References

1. International Agency for Research on Cancer (IARC) GLOBOCAN 2022 https://worldbladdercancer.org/news_events/globocan-2022-bladder-cancer-is-the-9th-most-commonly-diagnosed-worldwide/
2. Saginala, Kalyan et al. “Epidemiology of Bladder Cancer.” Medical sciences (Basel, Switzerland) vol. 8,1 15. 13 Mar. 2020, doi:10.3390/medsci8010015