# Artificial Intelligence (AI) Assisted Detection of FGFR3 Alterations In Bladder Cancer From Scanned Whole Slide Images (WSI) of H&E Sections

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## Background:

Fibroblast growth factor receptor (FGFR) screening in bladder carcinoma allows the identification of patients targetable by FGFR inhibitors. Overall, 26.7% of urothelial carcinomas have been reported to have FGFR3 alterations. Anecdotal experience of pathologists suggested there may be a morphologic signal for FGFR alterations.[1] We aimed to develop an AI assisted screening system for an FGFR3 phenotype based on H&E whole slide images (WSI) of bladder carcinoma.

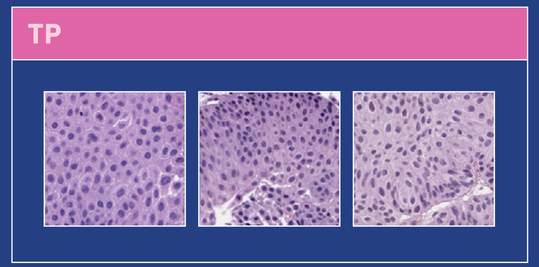
## Methods:

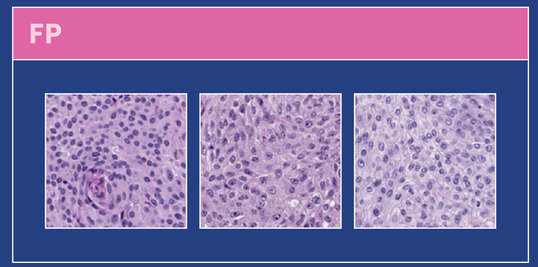
The FGFR3 detection system used a deep neural network for the detection of bladder carcinoma based on multiple instance learning (MIL) with a SE-ResNet50 CNN backbone, to identify bladder carcinoma regions in WSI. Using these regions, the FGFR3 model was trained and evaluated using 8-fold cross validation on 1051 WSI of primary and metastatic bladder carcinomas, 25.8% of which had FGFR3 alterations (FGFR3 p.S249C p.R248C p.Y373C mutations and FGFR3-TACC3 fusions) based on data from the MSK-IMPACT cohort.

## Results:

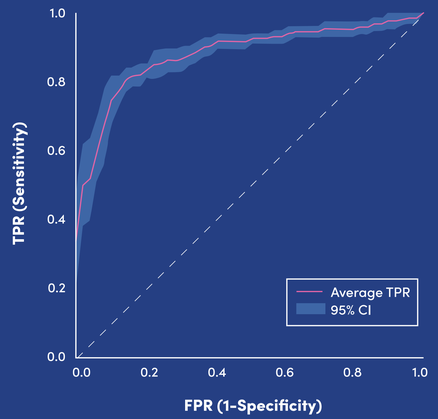
On the MSK-IMPACT cohort the FGFR3 AI model achieved a mean AUC of 0.88±0.02 on primary tumors.[2] Specific targetable alterations commonly observed achieved a stratified AUC performance of 0.84±0.02 for FGFR3 p.S249C, 0.75±0.06 for FGFR3 p.R248C and 0.82±0.08 for FGFR3 p.Y373C. On male patients the system had an AUC of 0.84±0.02 and on females of 0.89±0.05. On the TCGA dataset, which was not used for training, the system achieved 0.933 sensitivity and 0.495 specificity in identifying FGFR3 alterations in 297 bladder cancer WSI.

A disproportionate number of the false positive and false negative cases are upper urothelial tract primary tumors. These tumors have unique genomic profiles relative to the bladder tumors.[3] We observed that a combination of class 3 BRAF mutation with a RAS/MEK hotspot mutation is enriched in the false positive which points to an overlapping phenotype. In false negative cases, the tumors trended towards having high tumor mutation burden. In situations of high TMB, including cases with MSI high and POLE hypermutation status, the FGFR hotspot mutations may be incidental mutations or not act as the primary driver of proliferation, in which case the phenotype learned by the model may not be manifest. Within the false positive cases, alterations such as FGFR3-MRFAP1L1 fusion and FGFR3-TNIP2 fusion were present. These alterations were not part of our initial label definition.




### Internal Validation Dataset




## Conclusion:

We developed an effective AI system for detecting phenotypes associated with FGFR3 abnormalities that may be targetable by FGFR inhibitors. This system may allow cost and time savings in comparison to existing assays to screen bladder carcinomas for additional diagnostic testing.

### Bibliography:

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