Cholangiocarcinoma Testing

Background

Cholangiocarcinoma is a rare cancer that develops from the epithelial lining of the bile ducts. It is classified as intrahepatic or extrahepatic, based on the location of the primary tumour [(1)]. Cholangiocarcinoma is an aggressive disease with a poor prognosis [(2)].

FGFR2

Fibroblast growth factor receptor 2 FGFR2 gene fusions or rearrangements are present in approximately 10-15% of cholangiocarcinomas and may lead to tumour formation [(3)].

NICE recommend the use of Pemigatinib for treating relapsed or refractory advanced cholangiocarcinoma with a FGFR2 gene fusion or rearrangement. https://www.nice.org.uk/guidance/ta722

IDH-1

Isocitrate dehydrogenase 1 IDH-1 R132 point mutations are commonly found in intrahepatic cholangiocarcinoma and generate high levels of R-2-hydroxyglutarate, which commonly inhibits DNA repair, metabolism and other cellular processes [(4)]. NICE have recently recommended the use of Ivosidenib for treatment of IDH-1 mutant cholangiocarcinoma. https://www.nice.org.uk/guidance/indevelopment/gid-ta11113

NTRK1, NTRK2, NTRK3

Neurotrophic tyrosine receptor kinase NTRK 1, 2 and 3 gene fusions are less common than FGFR2 and IDH-1 aberrations, found in ~1.3% of cholangiocarcinoma patients [(5)].

NICE guidelines recommend the use of NTRK TKIs for advanced or metastatic cancers, irrespective of where in the body the cancer starts. https://www.nice.org.uk/guidance/ta644/chapter/1-Recommendations ; https://www.nice.org.uk/guidance/ta630/chapter/1-Recommendations

The AWMGS will use fluorescence in situ hybridization (FISH) to test for FGFR2 gene rearrangements, DNA-based NGS for IDH-1 codon R132 mutation status and RNA-based NGS for NTRK1, NTRK2 and NTRK3 whole gene fusion analysis.

AWMGS
All Wales Medical Genomics Service

Test	TAT (calendar days)
FISH test for FGFR2 rearrangements	14
DNA NGS test for IDH-1 point mutation	14
RNA NGS test for NTRK1, NTRK2, NTRK3 gene fusion	14

Contact Details
All Wales Genomics Laboratory,
Institute of Medical Genetics,
University Hospital of Wales,
Heath Park,
Cardiff CF14 4XW
Tel: 029 2074 2641
Fax : 029 2074 4043
lab.genetics@wales.nhs.uk
https://www.medicalgenomicswales.co.uk/
Accredited to ISO 15189:2012
(8988)

Sample Requirements

FGFR2 FISH:

1 H&E stained slide with area of highest neoplastic cell content CLEARLY circled
3 x 3-4µM sections (singly mounted) on charged/adhesion slides
Or
2 x air-dried cytospin prepared samples on charged/adhesion slides for FISH testing
Note: Cytospin cells should be air-dried and no fixative used. If a sample has been placed into a cytological fixative prior to the cytospin slides being created, please make AWGL aware on the request form

IDH1 DNA NGS:

1 H&E stained slide with area of highest neoplastic cell content CLEARLY circled
60µM (preferably 6x10µM) air dried unstained sections mounted on slides

NTRK1, NTRK2, NTRK3 RNA NGS:

1 H&E stained slide with area of highest neoplastic cell content CLEARLY circled
50µM (preferably 5x10µM) air dried unstained sections mounted on slides

All samples must be accompanied by request form
Consent for testing is assumed when request for test received

References:

(1) Khan, S. A., Davidson, B. R., Goldin, R. D., Heaton, N., Karani, J., Pereira, S. P., & Wasan, H. (2012). Guidelines for the diagnosis and treatment of cholangiocarcinoma: an update. *Gut*, *61*(12), 1657-1669.
(2) Blechacz, B. (2017). Cholangiocarcinoma: current knowledge and new developments. *Gut and liver*, *11*(1), 13.
(3) Neumann, O., Burn, T. C., Allgäuer, M., Ball, M., Kirchner, M., Albrecht, T., ... & Kazdal, D. (2022). Genomic architecture of FGFR2 fusions in cholangiocarcinoma and its implication for molecular testing. *British Journal of Cancer*, *127*(8), 1540-1549.
(4) Wu, M.J., Shi, L., Merritt, J., Zhu, A. X., & Bardeesy, N (2022). Biology of IDH mutant cholangiocarcinoma. *Hepatology,* 75(5), 1322-1337.
(5) Westphalen, C. B., Krebs, M. G., Le Tourneau, C., Sokol, E. S., Maund, S. L., Wilson, T. R., ... & de Braud, F. (2021). Genomic context of NTRK1/2/3 fusion-positive tumours from a large real-world population. *NPJ Precision Oncology*, *5*(1), 69.