Next Generation Sequencing of Thyroid Cancers

Overview

Thyroid cancer *(TC)* is a rare cancer, affecting the thyroid gland situated at the base of the neck. There are around 135 new diagnoses of thyroid and endocrine cancers every year in Wales.

Thyroid cancer is the most common type of endocrine cancer. Well-differentiated thyroid carcinomas (DTC) are the most common type, comprising 90% of diagnoses. DTCs are split into four subtypes.

Well-differentiated thyroid carcinomas (DTCs)	Percent of DTCs
Papillary thyroid cancer (PTC)	80-85%
Follicular thyroid cancer (FTC)	5-10%
Medullary thyroid carcinomas (MTC)	5-9%
Anaplastic carcinomas	1-2%

NICE guidelines for advanced RET fusion-positive thyroid cancer and advanced RET mutation-positive medullary thyroid cancer (MTC) are currently in development. RET variants have been found in 10-20% of people with a papillary thyroid cancer[(1)].

NTRK1 (OMIM 191315) fusions are expected to occur in 5% of papillary thyroid cancers. NTRK3 (OMIM 191316) fusions are expected to occur in 2% of sporadic papillary thyroid cancers [(2)].

Variants in the BRAF gene (OMIM 164757) occur in about 40-45% of papillary thyroid cancer cases and such variants are linked to poorer prognosis[(3)].

Test Information

The All Wales Genomics Laboratory utilises the Illumina TruSight Oncology 500 (TSO500) High Throughput DNA/RNA assay for next generation sequencing using the Illumina NovaSeq 6000™ to identify nucleotide variants and gene rearrangements (fusions) in patients with solid tumours including TC. More information on this service is available here.

Note: if <50ng of DNA is obtained from the FFPE sample provided, an alternative NGS panel will be utilised for testing. This provides hotspot analysis of the majority of the same clinically relevant genes to the tumour type, but overall is a less comprehensive gene analysis.

Table 1. Thyroid Cancer DNA Gene Panel

Gene	Hotspots/Screen	Regions covered
BRAF	Hotspots	Exon 15 (covers p.599, p.600, and p.601 which account for ~98% of known BRAF variants)
KRAS	Hotspots	Exons 2, 3 and 4 (covers p.12, p.13, p.59, p.61, p.117, p.146).
NRAS	Hotspots	Exons 2, 3 and 4 (covers p.12, p.13, p.59, p.61, p.117, p.146).
TP53	Screen	Whole gene sequence
RET	Screen	Whole gene sequence
HRAS	Hotspot	Exons 2 and 3

Table 2. Thyroid Cancer RNA Gene Panel

Gene	Regions covered
RET	Whole gene
EGFR	Exons 1-8 for EGFR vIII structural variant
NTRK1 **NTRK2** **NTRK3**	Whole gene

NTRK1 (OMIM 191315), NTRK2 (OMIM 600456), and NTRK3 (OMIM 191316) genes fusion testing is available by FISH as required for eligible patients, please refer to the clinical guidance and use the NTRK FISH request form.

Interpretation:
For thyroid cancer samples, the AWGL report is non-interpretative and provides only genetic variant information with no diagnostic, prognostic or treatment implications highlighted.

This test is performed to evaluate somatic variants within tumour samples and is not designed to assess for germline variants within the targeted genes.

DNA assay sensitivity/specificity may be reduced in specimens containing <10% tumour nuclei.

RNA assay sensitivity/specificity may be reduced in specimens containing <30% tumour nuclei.

Specimen Requirements

For information on sending FFPE samples refer to the CYSGODI service information sheet.

Please use the FFPE solid tumour request form and complete all fields.

Links for further information:

Orphanet www.orpha.net
EDDNAL www.eddnal.com
OMIM www.omim.org
Genetic Test Registry www.ncbi.nlm.nih.gov/gtr Cancer Research UK www.cancerresearchuk.org

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References

(1) Elisei R, Cosci B, Romei C, et al: Prognostic significance of somatic RET oncogene mutations in sporadic medullary thyroid cancer: A 10-year follow-up study. J Clin Endocrinol Metab 93:682-687, 2008

(2) Kumar-Sinha, C., Kalyana-Sundaram, S. & Chinnaiyan, A.M. Landscape of gene fusions in epithelial cancers: seq and ye shall find. Genome Med 7, 129 (2015).

(3) Liu, C., Chen, T. & Liu, Z. Associations between BRAFV600E and prognostic factors and poor outcomes in papillary thyroid carcinoma: a meta-analysis. World J Surg Onc 14, 241 (2016).

Consent for genetic testing and DNA storage is assumed when a test request and samples are received