Test Information Sheet - CYmru Service for Genomic Oncology DIagnoses – CYSGODI

The All Wales Genetic Laboratory (AWGL) has been a UK leader delivering precision medicine molecular pathology services for cancer patients since 2009. The drive to continue to improve, standardise and future-proof the genomic service we provide to patients has led the laboratory to launch the **CYSGODI** service which replaces the current solid tumour next generation sequencing multi-gene panel (PanCancer Panel), and in due course will incorporate the current haemato-oncology next generation sequencing multi-gene panel (TruSight Myeloid Sequencing Panel).

The following information is designed as an introduction to how the panel works, the range of findings that can be reported and a timeline for implementation of the panel.

Service Details

The **CYSGODI** service uses the TruSight Oncology 500 High-Throughput assay which facilitates the simultaneous detection of single nucleotide variants, copy number variants, structural variants (gene fusions), MSI and TMB from DNA in 523 genes and RNA in 55 genes. The assay also allows flexible batching of samples from 16 to 192 samples per sequencing flow cell on the NovaSeq 6000. Further flexibility is provided by the ability of the assay to concurrently sequence DNA and RNA extracted from formalin fixed paraffin embedded tissue (FFPE), bone marrow and leukaemic blood samples.

It is important to note that variants from all 523 genes will NOT be reported for individual tumour types.

Implementation of the **CYSGODI** service will future proof the somatic next generation sequencing service as emerging biomarkers are included in the assay. It will also enable Welsh patients and clinicians access to appropriate clinical trials.

The full gene list and further information on the assay can be found here
https://emea.illumina.com/content/dam/illumina/gcs/assembled-assets/marketing-literature/trusight-oncology-500-data-sheet-1170-2018-010/trusight-oncology-500-and-ht-data-sheet-1170-2018-010.pdf

Implementation Plan

A phased implementation of the **CYSGODI** service is planned:

- **August 2021**: Replacement of the PanCancer Panel with TruSight Oncology 500 for referrals of lung cancer, colorectal cancer, melanoma, gastrointestinal tumours, thyroid tumours and gliomas.
- **October 2021**: Launch of a new genomic service for prostate cancer and angioimmunoblastic T cell lymphoma
- **January 2022**: Transfer of the TruSight Myeloid Sequencing Panel to TruSight Oncology 500 for referrals from patients with a myeloid malignancy or chronic lymphocytic leukaemia.
- **February 2022 onwards**: addition of new tumour types, new haematological referrals and validation of MSI and TMB as required.

Solid Tumour Specific Gene Panel

The NHS England Genomics Test Directory (TD) was published in 2018, AWMGS is committed to providing equitable genetic testing to cancer patients in Wales. The TD specifies the gene panel content to be reported for different tumour types for patients in England which in turn is based on those targets which will influence management. This includes those which help to establish the correct diagnosis, predict prognosis, or to identify NICE treatments. Genes which do not influence management are currently not included in the TD. Therefore, following a consultation with service users, the gene panel content for some tumour types has changed to bring the gene panels in line with national guidelines. Tumour specific panel content is shown below:

Tumour Site	DNA Targets	RNA Targets
Lung	*EGFR* (exons 18-21); *BRAF* (exons 11 & 15); *KRAS* (exons 2-4)	ALK RET ROS1 NTRK1 NTRK2 NTRK3 EGFR MET
Melanoma	*BRAF* (exons 11 & 15); *KIT* (exons 9, 11, 13, 14, & 17); *NRAS* (exons 2-4)	NTRK1 NTRK2 NTRK3
Glioma	*IDH1* (codon 132 exon 4); *IDH2* (codon 172 exon 4); *BRAF* (exon 15); *EGFR* (exon 18-21); *ATRX* (whole gene), *H3F3A* (exon 2); *TERT* (promoter region c.-124; c.-126); *PTEN* (whole gene); *TP53* (whole gene); *CDKN2A* (whole gene)	BRAF MET NTRK1 NTRK2 NTRK3
GIST	*KIT* (exons 9, 11, 13, 14 & 17), *PDGFRA* (exons 12, 14 & 18)	NTRK1 NTRK2 NTRK3

Colorectal	*KRAS* (exons 2-4); *NRAS* (exons 2-4); *BRAF* (exons 11& 15); *PTEN* (whole gene); *TP53* (whole gene); *EGFR* (exons 18-21); *PIK3CA* (whole gene)	NTRK1 NTRK2 NTRK3
Thyroid	*BRAF* (exon 15); *KRAS* (exons 2-4), *NRAS* (exons 2-4); *TP53* (whole gene); *HRAS* (exons 2 & 3); *RET* (whole gene)	NTRK1, NTRK2, NTRK3

The NHSE TD is reviewed periodically, and any changes in reporting requirements will be actioned accordingly.

Sensitivity and Specificity

The DNA sequencing gene panel has a minimum validated sensitivity of 98.8% and specificity of 99.2% for the detection of gene rearrangements within FFPE solid tumour samples when >40ng FFPE-derived DNA is used.

The RNA-sequencing gene panel has a minimum validated sensitivity of 97.9% and specificity of 98.7% for the detection of gene rearrangements within FFPE solid tumour samples when >40ng FFPE-derived RNA is used.

Referring a Patient

There is ***no change*** to the process or sample requirements for referring samples to this service. Please refer to the solid tumour referral form for instructions:https://medicalgenomicswales.co.uk/images/Request-Forms/PD-GEN-ReqTumAnDRA_-electronic_form.pdf

Limitations

The **CYSGODI** service is not intended for use to detect cancer related germline variants, however, due to the cross-over between hereditary cancer genetic mutations and somatic variants found within cancers, we can analyse the same gene, but we are using tools to only consider somatic variants which are not suitable for detection of germline variants specifically. It is therefore possible that some variants found within the cancerous tissue indicate that the patient may have a germline (inherited) variant, this is known as an incidental finding. However, the presence of a germline variant cannot be confirmed without further testing.

If a report indicates that there is a possible germline variant, Clinical Genetics have outlined the following approach for oncologists:

- Speak with the patient further to explain that there is a possible germline finding in their molecular cancer results and agree the course of action they wish to take next.

It is possible that the patients family history has already shown known cancer-causing variants present in the family, therefore this finding will come as no surprise to the patient, e.g. in ovarian high grade cancer

patients in whom a variant in the BRCA gene is a contributing cause in the cancer, as well as being indicative of treatment options and prognostic information.

- Contact the on-call duty genetic counsellor to explore the next steps and whether a referral to medical genetics is required to confirm the germline finding.
- Organise a confirmation test directly, where you are confident to do so, by completing the relevant referral form and providing the required blood sample
- If a germline variant is confirmed a referral to clinical genetics will need to be arranged for further discussion about the implications for the patient and wider family.

About the Genetic Report

The final report clinicians receive has been designed to meet their needs with findings laid out simply in the following sections:

- Result summary outlines clinically actionable results relevant for the tumour type which the test was requested for
- Interpretation provides more detail on the test undertaken and specific genetic markers identified and classified within the report
- Technical information ensures we are ISO 15189 compliant and provides the variants nomenclature in line with HGVS, which clinicians may wish to refer to when considering eligibility for clinical trials
- Other information clarifies the somatic nature of the test and if applicable, will identify any suspected germline mutation

Reporting times

The reporting time for this test is 14 calendar days.

**** As this test is new to the laboratory's testing repertoire, it has not currently been assessed by UKAS against the ISO15189 standards and is therefore not within the scope of accreditation held by the laboratory****