Laboratory Genetics and Molecular Pathology Newsletter

August 2023

Scottish Strategic Network for Genomic Medicine

This network "brings genomics expertise and interest from across the NHS, academia, industry and the third sector together under a single network to provide a seamless, fully considered, sustainable and scalable genomics service for Scotland. The network supports the planning, finance and improvement of service change to achieve better patient outcomes and more efficient service delivery models in Scotland." (https://www.nss.nhs.scot/specialist-healthcare/national-networks/what-are-national-networks/strategic-networks/). Several work streams are already underway to improve and increase the available genomic services, and a publication setting out the intention for genomic medicine in Scotland has recently been published (https://www.gov.scot/publications/genomics-scotland-building-future/). The full strategy document will be published in the near future.

Since our last newsletter there have been many changes and improvements to the services available from Laboratory Genetics in the NHSG laboratory, some of which are described below.

Repatriation of genomic testing services from NHSE

The Scottish Genomic Network Laboratories continually develop, improve and increase the scope of genetic testing for the patients of Scotland. A recent initiative has been the repatriation of genetics testing for conditions where patient samples were previously sent to English laboratories for testing. The network laboratories developed a Scottish delivery model that distributes this large workload between the four member laboratories. Here in NHSG, Laboratory Genetics have undertaken testing in several specialist areas – inherited eye disorders, chromosome breakage syndromes, inherited metabolic and gastrohepatology disorders. In addition, we undertake testing for rare paediatric cardiomyopathies and inherited haematological malignancy syndromes. Since the implementation phase in late 2019, these services have undergone further improvements including the use of Whole Exome Sequencing (WES) for some of the indications. This repatriation exercise has been hugely successful, ultimately leading to the availability of timely, comprehensive services for the relevant patient populations of Scotland, alongside cost savings across the NHS.

Prostate cancer – a new cohort of patients benefitting from genomic testing

Following discussions with the Scottish Cancer MDT Group, a new service is being piloted for the cohort of patients with early onset prostate cancer and/or a significant

family history of prostate cancer. Individuals with prostate cancer under the age of 50 and others with metastatic prostate cancer and a family history of cancer (including prostate cancer) may be tested in this pilot project, where a panel of key genes known to be involved in the development of prostate cancer are sequenced. Results can inform future cancer risks in the individual and family members, and may also influence treatment options. This service went live in April 2021, and has been run as a pilot for 2 years to assess the effectiveness and clinical utility of the programme. The assessment of this pilot is now underway.

Implementation of NGS panel for the management of patients with haematological malignancies

In our last newsletter we described the development of an NGS panel to assist in the diagnosis and subsequent management of patients with myeloid malignancy, such as Acute Myeloid Leukaemia (AML) and Myelodysplastic Syndrome (MDS). The panel was designed following a period of consultation with the Scottish clinical community and collaboration with network laboratories in NHS Lothian and NHS Greater Glasgow & Clyde. The results generated identify a number of specific biomarkers that may be targeted with certain therapies, and also inform alternative treatment options, in addition to refining diagnosis and providing prognostic data to assist with patient management. The panel is now routinely implemented in service, with good clinical engagement and feedback received.

In the time since its introduction, an additional NGS panel has also been developed to identify specific gene fusion events that are also clinically significant in this group of patients, as well as other types of acute leukaemia, and again improve patient care by further informing treatment options. This panel also offers the benefit of streamlining laboratory processes resulting in staff time savings.

Solid tumour NSG fusion panels

As NGS technology continues to be embedded into routine healthcare, further improvements have been made with implementation of an NGS panel for the identification of gene fusion biomarkers in solid tumours, including lung and thyroid cancers. The panel enables the detection of specific gene fusion events that are known to drive cancer, and represent biomarkers for personalised therapeutic options in this group of patients. This panel enables the detection of additional biomarkers which future proofs the assay, as additional treatments become available. Similar to other assays, this assay has enabled laboratory processes to be streamlined in the laboratory whilst also increasing the number of biomarkers able to be identified simultaneously.

DPYD testing for cancer patients

Pharmacogenomics is an increasing area of importance within healthcare, and identifying patients who have inherited genetic variants that can predispose them to harmful toxicity to their treatment regime can be a vital aspect of their care. Fluoropyrimidines (FPs) are chemotherapy drugs that are commonly used in adjuvant

and palliative treatment for many types of cancer including colorectal, gastric, breast and head and neck cancer. Treatment with FPs is generally well tolerated, however approximately 10-40% of FP treated patients develop side effects ranging from vomiting and severe diarrhoea to fatal toxicity in extreme cases. Testing for DPYD genetic variants prior to the initiation of therapy to avoid this toxicity, now provides clear patient safety benefit. Having been first introduced as a test for patients in NHS Grampian and NHS Highland on a pilot basis in 2019, DPYD testing is now provided as standard of care for all patients who are likely to be offered FP-based chemotherapy. Over 600 patients per year now benefit from this improvement in care in the Grampian and Highland regions.

Improvements to existing services

We have also made improvements to a number of our existing services including Chronic Lymphocytic Leukaemia, Primary Immune Deficiencies, microarray testing and BRCA testing in serous ovarian tumours.

- ***Chronic Lymphocytic Leukaemia***

Non-functional TP53 is an important adverse prognostic marker in CLL. Identification of the sequence variants that lead to abnormal TP53 has typically been undertaken using Sanger sequencing. We have now transitioned to an NGS assay which allows greater sensitivity in the detection of low levels of specific biomarkers in liquid biopsy and tumour material. The information gained from the NGS assay affords our clinical colleagues an improved accurate assessment of *TP53* status in the tested sample, leading to improved informed decision making regarding treatments in patients with CLL. Additionally this method also improves laboratory workflow, resulting in staff time savings.

- ***Primary Immune Deficiencies***

Since the last newsletter, further improvements to this service have been enabled. We implemented a new NGS assay in the summer of 2020, which has increased the number of genes that can be examined and also includes new key genes. In addition the new assay enables copy number variations of the relevant genes to be assessed. Combined, these contribute to improving the clinical utility of the panel, and ultimately improving patient care. The referrals to the service continue to increase year on year, and we have established excellent links with our clinical and laboratory colleagues across the discipline to provide a comprehensive service.

- ***Microarray testing***

A range of sample types are processed using microarray technology, and in early 2020 we transitioned to a new platform enabling the detection of higher resolution DNA copy number variation across the genome. A major advantage of our new array system is the SNP probe content, which allows for the identification of uniparental isodisomy (UPD) and has the ability to help expose clinically significant recessive mutations.

As well as its use for germline analysis, our laboratory has now expanded the remit of microarray testing to include somatic analysis. Patients with a new diagnosis of Acute Lymphoblastic Leukaemia are now tested by array analysis, which provides information on ploidy changes and the copy number status of key gene regions, as

well as loss of heterozygosity where clinically relevant. Array testing has also replaced our centromeric FISH service for renal cell carcinoma patients, which enables the detection of whole chromosome gains and losses across the entire genome.

- ***Serous Ovarian Tumours***

BRCA1 and BRCA2 gene testing in individuals affected with serous ovarian cancer can stratify patients for specific therapies including PARP inhibitors (PARPi). Recent developments have identified that a wider group of ovarian cancer patients may benefit from this treatment - in addition to patients with BRCA1/BRCA2 gene mutations (in either germline or tumour material), those with ovarian tumours demonstrated to harbour a broader range of mutations (homologous recombination deficient) may also benefit. Testing for these is now also available via the NHSG Genetics Laboratory in eligible patients.

NHSS Test directories for genomic testing

Our laboratory led on a project to develop genomic testing directories for rare and inherited disease, and molecular pathology within Scotland. These initial versions have now been adopted by the SSNGM for further and ongoing update and document control. They represent a comprehensive and single point of reference for the genomic testing currently available in Scotland in the rare and inherited disease and molecular pathology fields (https://www.nss.nhs.scot/specialist-healthcare/specialist-services/genetic-and-molecular-pathology-laboratories/).

New and ongoing developments

As part of the work of the SSNGM, funding has recently been secured to implement new testing pathways of a number of cancer indications. These include endometrial, thyroid, prostate cancers and also the availability of NTRK gene fusion testing. Implementation of these testing pathways is underway.

Furthermore, testing pathways for additional indications will be realised in early 2024 (lymphoid NGS panel, AML disease monitoring, and additional neuropathology testing).

User feedback

In addition to our newsletter, we have also created an online form to gather user feedback. We would appreciate if you could take the time to click on the link below and complete the provided form to gain feedback on our services. The survey will close on Friday 29th September.

Genetics and Molecular Pathology Laboratory Feedback Form