CYP ONCOLOGY WHOLE GENOME SEQUENCING (WGS) TESTING; FOLLOW UP AUDIT FOR THE NORTH WEST CHILDREN'S CANCER ODN

Samantha Aldridge, Jessica Goncalves, Davina Hartley, Katharine Field, Charlotte Lloyd, Bernadette Brennan, Helene Schlecht, Rachel Hart, Kat Cooper, Minou Oostveen and Lisa Howell

Introduction

Advancements within genomics continue to have significant impact on the ability to diagnose and treat children and young people with cancer. Last year, the North West Children's Cancer Operational Delivery Network (NWCCODN) presented a baseline audit of whole genome sequencing (WGS) for children with cancer across the region*. This highlighted the low numbers performed and some of the reasons behind this. Subsequent changes to practise were implemented, including utilising research practitioners to facilitate discussion, receive consent, sample collection and tracking. We have now re-audited our current WGS practise within the region. We have identified data fields of interest and collated the data over the different time periods and the 2 PTCs. Our joint cohort now amounts to around 270 patients, demonstrating that our WGS testing has increased significantly, enabling us to interrogate results in a more meaningful manner. Sufficient numbers now exist to further add to the national data regarding practise and impact for patients. Demonstrating and understanding the impact of WGS testing is vitally important in providing optimal care for our patients and increasing knowledge. Challenges currently exist in the access to and sharing of this data, which we believe is a necessary part of this nationally offered service. ODN initiated projects can provide valuable resource for service development and patient benefit and enable multi-professional collaboration.

Objectives

- To demonstrate the impact of dedicated resource for WGS
- To create and interrogate a meaningful repository of data relating to WGS.
- To identify any improvement in turnaround times
- To identify limitations in testing including factors related to failed tests

*Scan to see last year's poster

Method

In house databases and tracking systems of WGS patients were created in the 2 PTCs. We submitted a data request to the GLH. The data available from the GLH was limited due to GDPR, resource and systems issues and required significant input and time from the Bio-Scientist. We reviewed the numbers, trends, turn around times and reasons for none testing for the entire 4yr cohort (some data items were only available for 1 PTC). We analysed cases by tumor type and explored results in terms of pathological variants in both somatic and germline samples, with particular interest in cases where there was impact on diagnosis, treatment or screening

Results

270 children in the North West had WGS over a 4 year period.

Figure 1: Percentage of AHCH patients with WGS

Tumour Group		No. of Diagnoses	% with WGS	Change in %
Leukaemia	21-23	77	53.2%	↑44.1%
	24	37	97.3%	
Solids	21-23	55	27.3%	↑36.7%
	24	50	64.0%	
CNS	21-23	47	8.5%	↑32.0%
	24	37	40.5%	

Figure 2: No of WGS By Disease Group & PTC

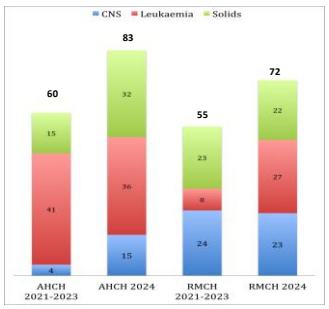
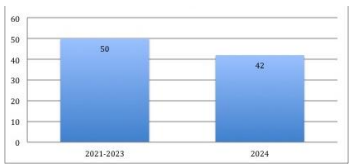


Figure 3: Mean Time from 2nd sample received into GLH to GTAB



Other Relevant Observations

- Tumour testing failed in only 11 patients
- Sample collection after the start of chemotherapy did not have an impact on failure rate (1 fail in a completely necrotic WT)
- Patients not having surgery at the PTC (AHCH); 6/16 Bone tumours and 6/6 Liver tumours had WGS – required team liaison
- 25 patients had WGS sent at the time of relapse
- Diagnostic M codes were used appropriately in the majority of cases
- 4/147 families at AHCH declined testing
- Very few cases had insufficient tissue after SOC

Figure 4: Pathogenic WGS findings and their clinical impact

Tumour type	Actionable finding	Clinical Impact
Somatic findings		
Undifferentiated sarcoma	Tumour signature associated with exposure to UV light	Change of diagnosis to Melanoma
Low grade glioma (Diffusely infiltrating astrocytoma	BRAFV600E mutation	Targeted treatment with Dabrafenib and Trametinib
Choroid plexus carcinoma (relapse)	BRCA1 and BRCA2 LOH	Targeted treatment with Olaparib
Low grade glioma	FGFR1 variant	Small molecule tyrosine kinase inhibitor
Wilms tumour Relapsed LCH	BRAFV600E mutation	Targeted treatment with Dabrafenib/MEK inhibitors
Infant type hemispheric glioma Neuroblastoma	ALK fusion	Targeted treatment with ALK inhibitor
Primary mediastinal B cell Lymphoma	High TMB	Checkpoint inhibitor
HGG	DST-ROS1 fusion	Targeted treatment with Entrectenib
Probable MCRNLMP	High TMB (24.59)	Checkpoint inhibitor
Pleomorphic Xanthoastrocytoma	TPR-NTRK fusion	Targeted treatment with Larotectinib
Medulloblastoma	PMS2 with high TMB (13.71)	Targeted treatment with Nivolumab and Lipilimumab
Germline findings		
Fibromellar Hepatocellular Carcinoma	Heterozygous BRIP1 gene	Risk of ovarian cancer in female family members
Rosette-forming glioneuronal tumour	Heterozygous NF1	
Relapsed B-ALL Neuroblastoma Low grade glioma	ATM variant	Risk of breast cancer in female family members
Renal cell carcinoma	FH c.431G>T p.(Gly144Val) variant	Genetic referral
ALL ALL	BRCA1 variant	BRCA1 cancer susceptibility, particularly breast and ovarian cancer
Wilms tumour	BRCA2 variant	BRCA2 cancer susceptibility, particularly breast and ovarian cancer
ALL	DICER1 variant	Genetic referral
T-LBL	CDKN1B variant	Genetic referral
ALL	DDX41 variant	Predisposition to myeloid neoplasms
Phaeochromocytoma	VHL variant	Genetic referral
High grade astrocytoma	Biallelic PMS variant	Cause CMMRD and associated cancer risk
ALL	Monoallelic PMS2 variant	Variants cause Lynch Syndrome. Risk of PMS2-associated cancers
ATRT	SMARCB1 variant	Genetic referral

Discussion & Conclusion

Dedicated staffing resource and pathways led to significantly increased numbers of patients offered WGS. This also led to the creation of in-house databases and tracking systems for audit purposes. Without this resource the numbers of patients offered WGS would fall significantly, as would the data available. The proportion of CNS tumour and leukaemia patients differ significantly between the centres, suggesting a different team approach. WGS is obtained almost 100% of leukaemia patients in AHCH. We had concern regarding tumours managed at super-regional centres, our small numbers indicate that rates of WGS may be more challenging to obtain for bone tumour patients. Turn around time within the GLH has reduced by a mean of 8 days to 42 days. Our understanding is that this varies across the country and may be important for timely patient management. Challenges remain in accessing relevant data from the GLH. This limits the ability to judge impact and learning at a local and national level and is particularly relevant for the more rare tumour types. In house databases were required to assess the impact for each centre. In a number of patients, WGS identified changes which led to an altered diagnosis and not previously known cancer predisposition syndromes. Both WGS and SOC testing picked up recognised alterations relevant for diagnosis and risk stratification. This rich data source provides the opportunity to collaborate with colleagues elsewhere, to maximise learning from WGS results in CYP with cancer. Further steps include examining demographic data to expose any inequalities in accessing the WGS service as well as looking at the variants of uncertain significance identified.

NHS North West NHS Genomic Laboratory Hub
NHS Manchester University NHS Foundation Trust
NHS Alder Hey Children's NHS Foundation Trust
North West Children's Cancer Operational Delivery Network