Whole Genome Sequencing for Paediatric Oncology Patients in Wales

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Childhood cancer genetic testing in Wales.

- Cancer caused almost a quarter of all deaths in children in 2021 in the UK Children's Cancers | Cancer Research UK.
- Current standard of care (SOC) genetic testing to predict prognosis, diagnosis or identify potential treatments for cancers in Wales can involve multiple genetic tests and multiple invasive procedures per patient.
- Tests target one area of the genome or certain types of variant (mutation) only across the genome. They may not detect all variants present in the cancer genome.
- Cancer patients could wait a long time for diagnosis, prognosis or access to potential treatments.

Childhood cancer genetic testing in Wales.

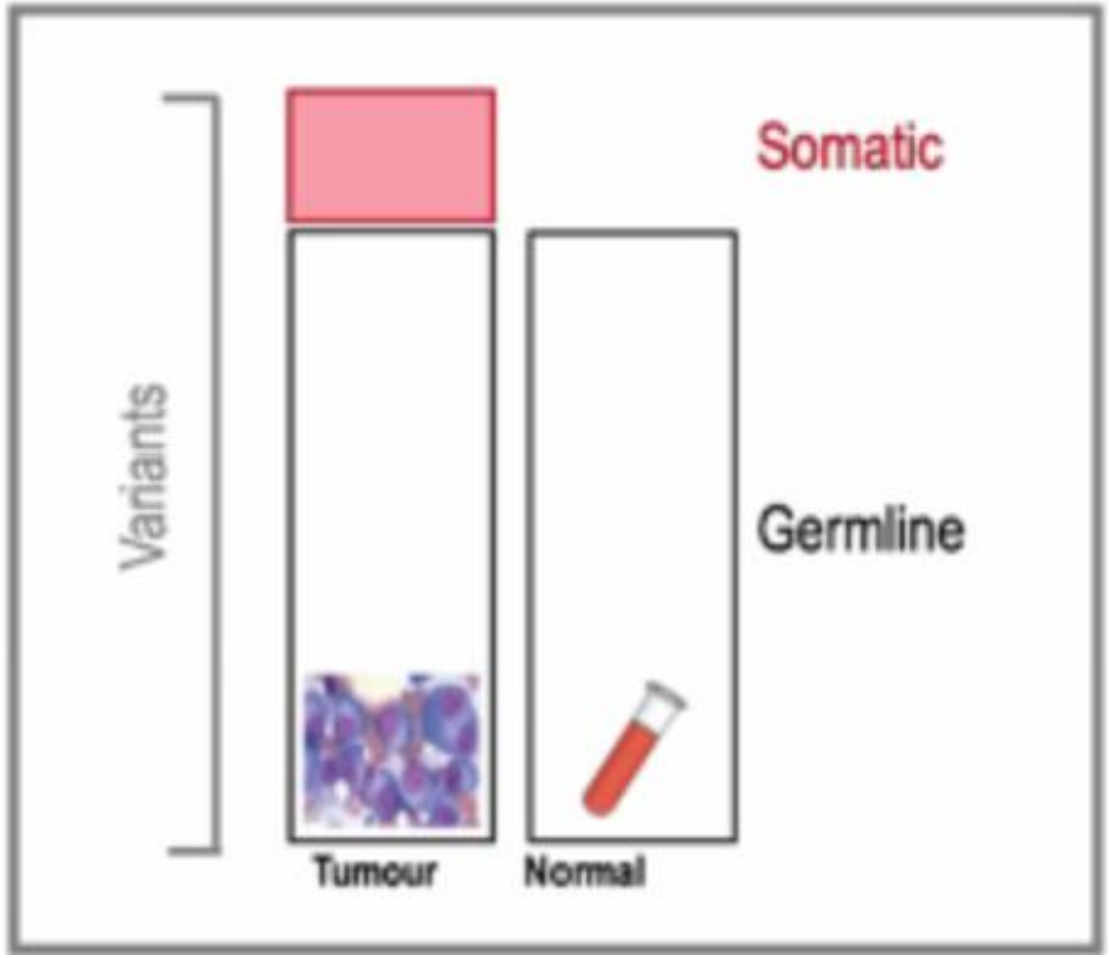
- Currently separate genetic testing for cancer cell variants (somatic) and germline (present from birth) variants at the All Wales Genomics Laboratory (AWGL). Tests are dependent on particular cancer referral and patient and family history.
  - Germline variants may influence clinical management of the patient and wider family.

Genomics delivery plan for Wales 2022-2025

- Genomics Delivery Plan for Wales (gov.wales) - Public health strategy for delivery of care for the people of Wales.

- Offer more comprehensive genomic profiling to patients with newly diagnosed cancer.

WGS Background



Whole Genome Sequencing

- DNA sequencing method that enables analysis of an entire genome (Illumina, Nakagawa et al., 2015).
- Potential to detect a variety of genomic variants in one test - structural variants, copy number alterations, protein coding variants including single nucleotide variants (exonic) (SNVs), non-coding variants (intronic). (Nakawaga et al., 2015).
- AWGL already uses whole genome sequencing of blood samples to detect germline genetic variants in rare disease patients (WINGS).
- Cancer WGS can detect somatic (cancer cell) and familial (cancer predisposition genes) variants in one test through paired testing of tumour and germline DNA.

Why WGS in childhood cancer

In a published study, thirty-six children, were recruited through the East of England Genomic Medicine Centre (East-GMC) as part of the 100,000 genomes project.

- 23 different solid tumour types.
- WGS provided clinical utility, beyond standard-of-care assays by:
  - refining (2/36) or changing (4/36) diagnoses,
  - providing prognostic information (8/36),
  - defining pathogenic germline mutations (1/36)
  - revealing novel therapeutic opportunities (8/36)

Of the 52 somatic and germline variants reported, 14 (27%) were previously known via standard-of-care management. 38/52 (73%) variants were novel (Trotman et al., 2022).

There is currently no standard provision for WGS testing for Welsh paediatric oncology patients. WGS offered to all paediatric oncology patients in England.

Patient story

- Gene test spared baby unnecessary chemotherapy - BBC News
- Genetic test rules out cancer for baby Oliver | CUH

A newborn baby was spared unnecessary chemotherapy when WGS revealed a suspected cancerous lump on his leg was benign.

"The thoughts of all this consumed us. It changed our lives," said Sara (mother). Parents readying themselves initially for Oliver's chemotherapy and surgery.

WGS revealed a mutation which changed the diagnosis of Oliver's tumour from cancer into a **benign tumour** type called myofibroma.

'"**Astonishing result'-** "I had been expecting cancer. I was so relieved". Dr Behnjati.

We would not have been able to pick this up by any other test - genetic or otherwise," Dr Behnjati.

Whole Genome Sequencing for Paediatric Oncology Patients in Wales.

- **Aim:** Validate a whole genome sequencing (WGS) pipeline for paediatric oncology patients at diagnosis, relapse, progression or where all standard of care treatment options are exhausted (<25years)
- **How:** Collect samples for WGS from patients undergoing standard of care testing with a prospective consent form.
    - Standard of care samples & additional sample types

Project approach

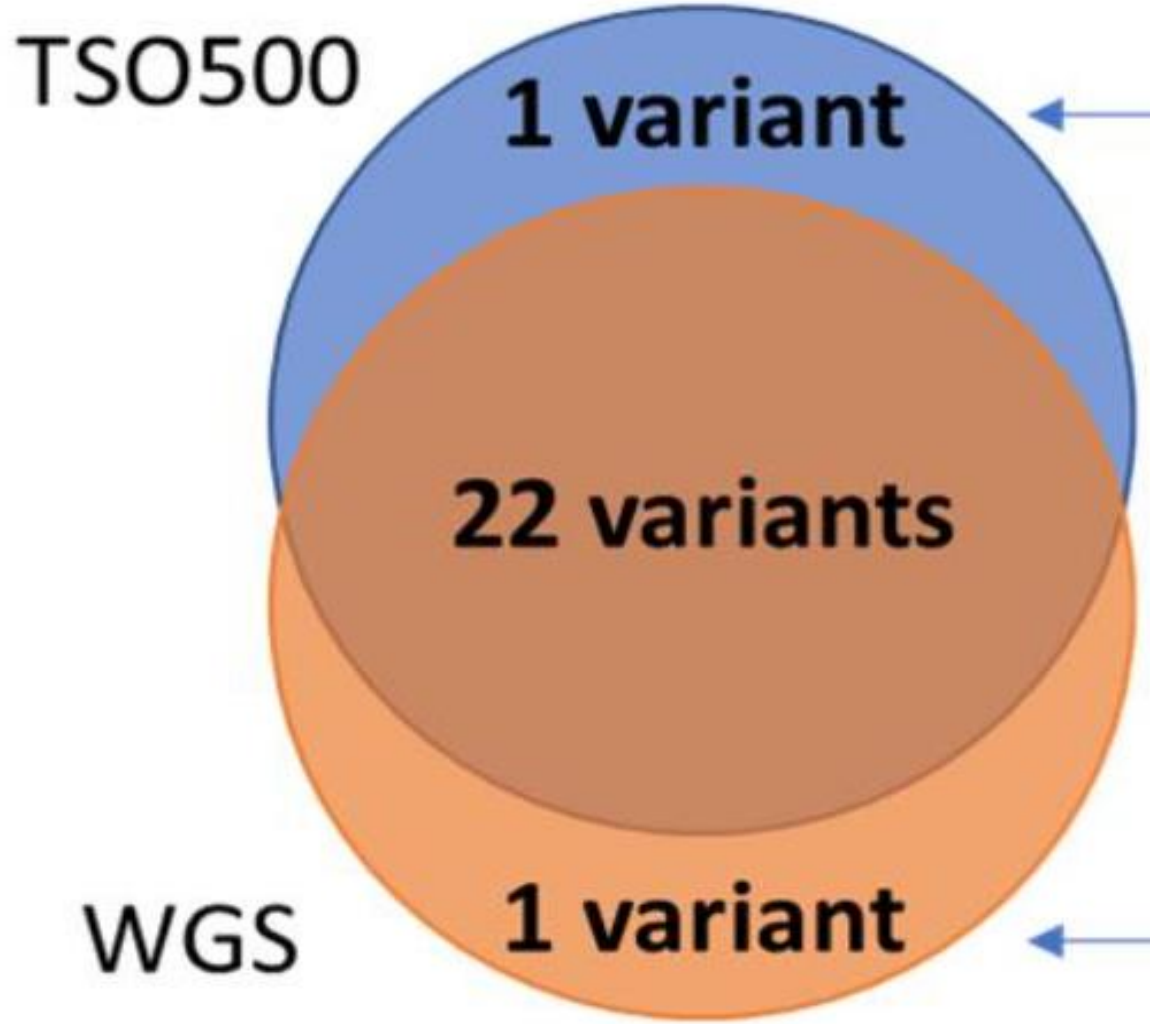
- Multi-disciplinary approach with clinical colleagues, industry and other UK genomics laboratories.
- Appropriate sample types (Tumour and Germline) collected from up to 60 paediatric oncology patients
  - Extract DNA from required samples
  - Sequence DNA on Novaseq.
- Assess quality of sequenced DNA - compare against the required quality of sequenced DNA (QC parameters) for existing WGS testing within AWGL.

Project approach

- Develop new WGS bioinformatics pipeline for Tumour and Germline samples.
- Analyse samples collected and assess concordance of WGS testing variant (mutation) status against known standard of care (SOC) testing results.
  - Identification of WGS variants not detected by SOC testing and confirmation using other genetic methods or onward referral to another laboratory for confirmation by WGS

Paediatric Oncology WGS- Results

- 45 sets of patient samples collected, 25 sequenced – all need analysis- working on analysis pathway.
- 44/45 sets of patient samples passed DNA extraction QC parameters for WGS.
- 25/27 sequencing runs met quality parameters (One run repeated twice).
- 10/12 sequencing runs met initial bioinformatics quality parameters including coverage (One run repeated twice).



All SNVs (single nucleotide variant) with greater than 5% VAF (Variant allele frequency) detected in a **cancer cell line** using TSO500 DNA panel (in house cancer panel) were also detected using WGS.

Outcomes and impact

- Implementation of a WGS technical pathway in house with sufficient quality DNA from paediatric oncology samples and matched germline samples.

- Includes pathways for samples that not usually taken from these patients as part of routine standard of care genetic testing
  - Fresh frozen solid tumour samples (somatic)
  - skins (germline)- taken routinely at the same time as a diagnostic bone marrow sample).

GPW Patient and public sounding board

17th April - Genomics Partnership Wales, Patient and Public sounding board.

- ✓Presentation of project background.
- ✓Discussion of scenarios (Focus groups)
- ✓Qualitative data will be thematically analysed.

Main themes from patient and public sounding board discussions.

- **Benefits**
  - Clinical significance of results to patients and wider family.
  - Broader scope for results including potential for further treatment options for the patient.
  - ‘Information is power’
- **Concerns**
  - How will results be shared with the wider family if of significance to them.
  - Making the consent form easily readable – laymen’s terms.
  - Unexpected/uncertain information and support provided.

Next steps

- Genomic data analysis of samples sequenced (see project approach).
- Further define analysis protocol and reporting requirements.
- GTAB/MDT – genomics tumour advisory board discussions in place with the working group.

Implementation and future aspirations

- Validation used to justify a business plan for the implementation of WGS for childhood cancer samples as an All Wales service.

- Technology, and reporting process for the paediatric oncology WGS project can be used for other cancers (Adult Sarcoma and adult Brain Tumour).

Thank you for listening.

References

1. Nakagawa H, Wardell CP, Furuta M, Taniguchi H, Fujimoto A. Cancer whole-genome sequencing: present and future. Oncogene. 2015 Dec 3;34(49):5943-50
2. Trotman J, Armstrong R, Firth H, Trayers C, Watkins J, Allinson K, Jacques TS, Nicholson JC, Burke GAA; Genomics England Research Consortium, Behjati S, Murray MJ, Hook CE, Tarpey P. The NHS England 100,000 Genomes Project: feasibility and utility of centralised genome sequencing for children with cancer. Br J Cancer. 2022 Jul;127(1):137-144.
3. Green RC, Berg JS, Grody WW, Kalia SS, Korf BR, Martin CL, McGuire AL, Nussbaum RL, O'Daniel JM, Ormond KE, Rehm HL, Watson MS, Williams MS, Biesecker LG; American College of Medical Genetics and Genomics. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. Genet Med. 2013 Jul;15(7):565-74. doi: 10.1038/gim.2013.73. Epub 2013 Jun 20. Erratum in: Genet Med. 2017 May;19(5):606. PMID: 23788249; PMCID: PMC3727274.

Websites: Children's Cancers | Cancer Research UK.
Genomics Delivery Plan for Wales (gov.wales).
Illumina | Whole Genome Sequencing (2024). Available at: Whole-Genome Sequencing (WGS) (illumina.com)