UKCGG & CanGene-CanVar Virtual Consensus workshop on Whole Genome Sequencing for Paediatric Cancer care 14th July 2022: Summary

Background

- Paired germline and tumour-based whole genome sequencing has the potential to offer timely identification of potentially targetable drivers of disease, facilitating improved diagnosis and prognostication of disease as well as facilitating genomically-informed treatment decision-making. Furthermore, considering the significant contribution of heritable risk factors to paediatric cancer predisposition, this paired approach enables rapid identification of underlying constitutional genomic aberrations, which, in turn, will allow more accurate estimation of future disease risk, and facilitate early detection and risk-reducing strategies in the proband and their at-risk relatives.
- In 2019, genomic services in England were reconfigured as part of the nationally commissioned **Genomic Medicine Service** (GMS), which is now served by seven **Genomic Laboratory Hubs** (GLHs). Seven NHS **Genomic Medicine Service Alliances** (GMSAs) align with these regions, with the aim of facilitating collaboration and education to ensure appropriate rollout and use of genomic testing
- With the aim of ensuring consistent and equitable service across England, indications for somatic and germline genetic testing have been standardised in a set of documents known as the **NHS Genomic Testing Directories**
- As outlined in these directories, paired germline and tumour-based whole genome sequencing is available for certain indications, after appropriate pre-test counselling of patient and completion of record of discussion by trained personnel.
- The test directory is a dynamic document, and changes may be implemented in response to input from stakeholders/public consultation
- Reconfiguration of services in Scotland, Wales and Northern Ireland is underway, with a view to aligning test types and indications with the NHSe directories.
- The most recent iteration of the NHSe National Test Directories (April 2022) indicates that paired germline and tumour-based whole genome sequencing will be available for all malignant tumours* diagnosed in paediatric (aged up to 25 years of age) patients (*excluding certain subtypes of sarcoma)
- The samples required for whole genome analysis include a fresh-frozen tumour sample, as well as a sample representative of constitutional DNA. In most cases, the preferred source of constitutional DNA is lymphocyte-derived DNA, from whole blood, but in certain cases (e.g. patients with haematological disease or prior history of an allogenic stem transplant, alternative sources may be required, such as fibroblasts from skin, or buccal epithelial cells from a buccal scrape).
- Analysis of data arising from WGS completed via the cancer pathway is undertaken by targeted rather than agnostic approach, with tiered application of virtual panels of genes associated with the cancer of interest and overall cancer risk.
- Anecdotally, there have been reports of challenges in implementing pathways to enable WGS, as well as challenges related to reporting of germline findings. Furthermore, different regions reported varying degrees of success in implementation of this new pathway.
- To address these issues, the UK Cancer Genetics Group (UKCGG), in collaboration with CanGene-CanVar organised a national workshop, held via Zoom on 14th July 2022. UK Cancer Genetics Leads

and Genetic Counsellors, Somatic and Germline Clinical Scientists, Pathologists, Paediatric Oncologists and Clinical Nurse Specialists were invited to attend. Please see appendix 1 for list of registered delegates.

- This document is designed to be a reflective summary of the understanding and discussions from the meeting on 14th July 2022. Further information, slides and recordings of the presentations are available at https://www.ukcgg.org/information-education/ukcgg-consensus-meetings/ .

Organising Committee

Helen Hanson
Ruth Armstrong
Emma Woodward
Beverley Speight
Beth Torr
Terri McVeigh

Aims of the workshop

In the interest of time and to maximise utility of the meeting, the remit of the workshop was limited to the following aims:

1. To review utility and limitations of WGS for detection of genomic aberrations driving cancer development
2. To review current challenges in implementation of WGS pathways in different regions
3. To establish current practice and agree future best practice regarding reporting of additional constitutional findings (i.e. findings likely unrelated to patient's known diagnosis), including uncertain variants and recessive traits
4. To outline indications and pathways for orthologous genetic testing where clinical suspicion of an underlying heritable genetic condition persists following uninformative WGS
5. To discuss novel clinical referral pathways that need to be developed and implemented, including where and how urgent post-test genetic counselling can be undertaken.
6. To consider the potential impact on resources and existing clinical pathways of the application of urgent pathways and carrier screening within the NHS.
7. To identify knowledge gaps and the potential for national, collaborative, interdisciplinary research projects and service/registry development.

Workshop format

A series of talks from invited expert speakers were delivered on the day to provide context-specific information to delegates. Slides from and recordings of those presentations not including sensitive patient data are available here (https://www.ukcgg.org/information-education/ukcgg-consensus-meetings/).

Thereafter, a number of related polls were conducted, with proposed statements for best practice in different scenarios. There were a total of 60 active participants. Each poll was closed when at least half of delegates had submitted a response, mindful of the interdisciplinary nature of the audience and considering that not all questions were relevant for all attendees. Consensus was deemed to be reached when ≥80% respondents selected "Yes", "Agree/Strongly Agree" in response to the statement posed; unless an argument was proposed requiring revision to the wording of the statement, after which the poll was repeated with the revised wording to generate final decision. For single best answer questions, consensus for "best" option was considered if ≥80% selected that option.

Presentations

- Pre-workshop survey results – *Dr Helen Hanson, St George's University Hospitals NHS Foundation Trust*

- *What is a WGS test, what can we detect and what can we miss? *Dr Patrick Tarpey, East Genomic Laboratory Hub, Cambridge University Hospital NHS Foundation Trust*
- *Challenges in implementation of WGS from a pathology perspective. *Dr John Taddross, Cambridge University Hospital NHS Foundation Trust*
- Challenges in implementation of WGS from a germline perspective. *Dr Ruth Armstrong, Cambridge University Hospital NHS Foundation Trust and Dr Emma Woodward, Manchester Centre for Genomic Medicine*
- Clinical utility and implementation challenges of WGS from a Paediatric Oncology perspective – *Dr Sam Behjati, Cambridge University Hospital NHS Foundation Trust*
- *Consent and Confidentiality*, Dr Alison Hall, PHG Foundation*
- *Interpretation, Reporting and Unexpected Findings Guidelines, *Ms Sandra Hing and Ms Rachel Mein, NHS England*
- *Overview of ACGS best practice guidelines on variant classification and reporting, *Dr Terri McVeigh, Royal Marsden NHS Foundation Trust*

(*recording available)

Before polling sessions, participants were invited to unmute and provide an insight into local issues in their GLH.

Polling Sessions

- Polling session 1 - Themes: Additional Findings and Carrier Status.
- Polling session 2 - Themes: Indications for orthologous testing and consideration for Clinical Genetics referral following WGS

Agreed Consensus and Recommendations from workshop

(Please note, percentages are rounded up to nearest whole number, so occasionally totals may appear >100%.)

Table 1: Legend

Acronym	Term
WGS	Whole Genome sequencing
pWGS	Paediatric Whole Genome Sequencing
GTAB	Genomic Tumour Advisory Board
TAB	Tumour Advisory Board
GPV	Germline (likely) Pathogenic variant (i.e. PV or LPV -see below)
CPG	Cancer Predisposition Gene
P(V)	Pathogenic (variant)
LP(V)	Likely pathogenic (variant)
VUS	Variant of Uncertain Significance
NHSe	NHS England

Additional Findings

1. GPVs in CPGs that may not be related to the child's cancer diagnosis, but for which there are clear management implications (e.g. surveillance/risk reducing options) for child or other family members should be included in the WGS report & shared with family (43 respondents) - **Strongly agree (72%)/agree (28%), Consensus 100%**
2. Following GTAB agreement to report a GPV(s) in GPGs that may not be related to the child's cancer diagnosis, but for which there are clear management implications, the patient should be

referred to Clinical Genetics for discussion of potential implications (45 respondents) – **Strongly agree (84%)/Agree (16%), Consensus 100%**

Recessive Traits

3. The WGS referral form and/or pre-TAB data gathering should include information on whether there is consanguinity in a family (40 respondents) – **Strongly Agree (48%)/Agree (45%)/Uncertain (8%). Consensus 93%**
4. Carrier status for GPV in a recessively inherited CPG, not related to the child's cancer diagnosis, should be reported where parents are consanguineous following GTAB discussion (40 respondents) – **Strongly Agree (23%)/Agree (63%)/Uncertain (15%). Consensus 86%**
5. Carrier status for GPV in a recessively inherited CPG, not related to the child's cancer diagnosis, should be reported where carrier frequency >1 in 70 following GTAB discussion (37 respondents) - **Strongly agree (54%) / Agree (38%)/Uncertain (3%)/Disagree (5%). Consensus 92%**

Implementation of WGS

6. Which of these suggestions do you think is most important for Clinical Genetics to focus on over the next two years? (ranked) (27 respondents)

   Ranked in order of greatest importance
   1. GTAB presence
   2. Increased staffing
   3. Involving GCs/genomic practitioners
   4. Education

Interpretation of results

7. Prior to a GTAB, scientists writing reports should ideally have pre-reporting access (via pre-TAB/email) to germline scientific/clinical expertise when deciding if variants are of significance in the germline setting - **Strongly agree (64%)/Agree (33%)/Disagree (3%). Consensus 97%.**

GTAB composition

8. Indicate which of the following should be represented at GTAB meetings (multiple choices) (35 respondents)
   a. Somatic scientist (**consensus - 100%)**
   b. Paediatric Oncologist/member of treating team (**consensus - 100%**)
   c. Clinical Geneticist/Genetic Counsellor (**consensus - 100%**)
   d. Pathologist (**consensus - 94%**)
   e. MDT coordinator (**consensus - 91%**)
   f. Germline scientist (**consensus - 83%**)

VUS reporting, indications for Clinical Genetics referral ± further testing

9. Consideration of orthologous testing is <u>best</u> undertaken at which of the following (multiple choices) (25 respondents)
   a. Paediatric Oncology MDT (0%)
   b. Discussion w Genetics (8%)
   c. Pre-TAB (0%)
   d. GTAB (12%)
   e. Any of the above depending on clinical scenario (**consensus - 92%**)
10. Indications for referral to genetics post WGS with no actionable germline findings, include, but

are not limited to: two or more cancers in child, consanguineous parents, strong family history of cancer, excessive treatment toxicity, syndromic features. (27 respondents) – **Strongly Agree (56%)/Agree (41%)/Uncertain (4%). Consensus 97%.**

11. Following GTAB discussion, VUS in CPG related to clinical diagnosis should be reported where further investigations have potential to change the classification to LP/P, with the patient referred to Clinical Genetics for further assessment (34 respondents) – **Strongly Agree (71%)/Agree (29%). Consensus 100%.**
12. In which of the following scenarios would you report a VUS that is unlikely to be related to the clinical diagnosis?
    a. VUS with 5 evidence points and potential up-classification from further investigation of child (**consensus - 84%**)
    b. VUS with 5 evidence points and potential up-classification from further investigation of family (**consensus - 81%**)
    c. VUS with 5 evidence points and potential up-classification from national/international data **(69% - consensus NOT reached)**
    d. VUS with <5 evidence points **(0%, taken as consensus NOT to report**)
    e. None of the above **(0%, taken as consensus that it is inappropriate to omit all VUS)**
    f. All of the above **(9%, taken as consensus that it is inappropriate to report all VUS)**

Storage of data

13. Where carrier status is not reported, there should be a mechanism in place to access information in adulthood (37 respondents) - **Strongly agree (51%)/Agree (38%)/Uncertain (8%)/Disagree (3%). Consensus 89%**
14. Where germline VUS are not reported, do you think the data should be systematically saved and searchable for review/ re-interpretation in future? (30 respondents) – **Yes (97%)/No (0%)/Uncertain (3%). Consensus 97%.**
15. Where germline VUS are not reported but systematically saved in a searchable way, how should this be held? (25 respondents)
    a. Locally (0%)
    b. Nationally (**84%** - **consensus**)
    c. GP (0%)
    d. Uncertain (12%)
    e. Other (4%)

Next steps

- A UKCGG CanGene-CanVar National Multidisciplinary Team meeting (21st July 2022) was held on theme of Whole Genome Sequencing in Childhood Malignancy.
- BSGM will host a virtual “lunch and learn” session on the theme of “BSGM guidance on Genetic Testing in Childhood” on 27th July 2022
- We plan to write up the consensus statements from this meeting as part of a publication.
- Further work is needed to establish how we can capture data related to those variants not routinely reported robustly on a prospective basis. We hope the findings from this meeting can be leveraged to support applications for additional resources related to this.
- The development of standardised patient information for scenarios not otherwise covered in existing educational resources (e.g. Understanding a VUS) will be progressed in conjunction with patient charities and UKCGG.
- The development of educational materials will be progressed with the Genomics Education Programme of Health Education England.
- During the meeting, it was acknowledged that collection of fresh frozen samples was a challenge for some centres in the implementation of WGS. However, for centres where paediatric oncology takes place on a single site, or where fresh frozen samples have been collected for other purposes

for many years (e.g., Hirschsprung's), pathway implementation has been more straightforward. It was recognised that with expansion of WGS to include Adolescents and Young Adults aged up to 25, further consideration regarding implementation of WGS in patients in transitional/adult services is required given that fresh frozen samples are not routinely collected in this setting and that these patients may be managed in multiple, rather than centralised settings

- Work is ongoing in Northern Ireland, Scotland and Wales to develop similar pathways aligned with that suggested by the NHSe directories.
- A Wellcome Connecting Science event 'Implementing whole genome sequencing in paediatric oncology practice' is planned for Thursday 20 October 2022

Appendix 1 - List of registered delegates and their affiliations

Name (Original Name)	Organisation	Job Title
Adele Timbs	Oxford University NHS Foundation Trust	Clinical Scientist
Aditi Vedi	Cambridge Stem Cell Institute	Consultant Paediatric Oncologist
Alan Donaldson	UHBW	Consultant in Clinical Genetics
Alison Hall	PHG Foundation	Senior Humanities Advisor
Amelia heaford	St Georges Hospital, London	Consultant Paediatric Pathologist
Amy Ruffle	Leeds	Consultant Paediatric Oncologist
Barnaby Clark	King's College Hospital	Clinical scientist
Beth Torr	Institute of Cancer Research	Scientific Programme Manager
Bev Speight	Addenbrooke's	Genetic Counsellor
Bianca DeSouza	Imperial NHS Trust and Northwest Thames Regional Genetics Service	Consultant in Clinical Genetics
Ceri Hogg	Cardiff and Vale UHB	Early Phase Paediatric Oncology Research CNS
Christine Bell	NHS Grampian	Deputy Head Genetics and Molecular Pathology Laboratory Services
Corina Moldovan	The Newcastle upon Tyne Hospitals	Consultant Paediatric Pathologist
Cristina Sau	NHS Tayside	Macmillan Genetic Counsellor
Delyth Badder	North Bristol NHS Trust	Consultant Paediatric Pathologist
Edmund Cheesman	Royal Manchester Children's Hospital	Consultant Paediatric Pathologist

Emma Woodward	MCGM	Consultant Clinical Geneticist
Farah Kanani	Birmingham Women's Hospital	Consultant Clinical Geneticist
Gemma Gunn	University Hospitals of Leicester NHS Trust	Genomic Medicine Lead, Clinical Nurse Specialist
George Burghel	North West GLH	Principal Clinical Scientist
Hector Conti	All Wales Medical Genomics Service	Specialist Clinical Geneticist
Helen Hanson	St George's University Hospitals NHS Foundation Trust	Consultant in Clinical Genetics
Ilana Weintroub	North West Thames Regional Genetics Service	Genetic Counsellor
Jackie Cook	Sheffield Children's Hospital	Consultant Clinical Geneticist
Jacqueline Dunlop	NHS Tayside	Principal Genetic Counsellor
Jamie Trotman	Cambridge University Hospitals NHS Foundation Trust	Clinical Scientist
Jane Lim	St George's Hospital	ST3 Paediatric and Perinatal Pathology
Jennie Murray	NHS Lothian	Consultant in Clinical Genetics
Jenny Adamski	Birmingham Children Hospital	Consultant Paediatric Oncologist
Jenny Turnbull	Nottingham Children's Hospital	Consultant Paediatric Oncologist
Jeremy Pryce	St. George's Hospital	Consultant Paediatric Pathologist
John Tadross	Cambridge University Hospitals	Consultant Pathologist
Judith Pagan	NHS Lothian - WGH	Clinical Scientist
Julian Barwell	University Hospitals of Leicester	Consultant Clinical Geneticist
Kathryn Urankar	North Bristol Trust	Consultant Neuropathologist
Kelly Kohut	St George's University Hospitals NHS Foundation Trust	Lead Consultant Genetic Counsellor
Laura Yarram-Smith	North Bristol NHS Trust	Principal Clinical Scientist
Leena Bhaw	King's College Hospital	Pre-Registration Clinical Scientist
Lisa Walker	Oxford University Hospitals	Consultant in Cancer Genetics

Louise Hooker	Wessex Cancer Alliance	Clinical Advisor Children and Young People
Louise Izatt	Guy's and St Thomas' NHS Foundation Trust	Consultant in Clinical Genetics
Lowri Hughes	NHS	Principal Clinical Scientist
Lucinda Sanders	University Hospital of Leicester	Consultant in Paediatric and TYA Haematology
Lucy Hanington	Oxford University Hospitals	ST4 in Clinical Genetics
Lucy Side	University Hospitals Southampton	Consultant Clinical Geneticist
Lynsey Williams	St George's Hospital, London	ST1 Histopathology
Madeleine Adams	Children's Hospital for Wales	Consultant Paediatric Oncologist
Mark Brougham	NHS Lothian	Consultant Paediatric Oncologist
Michelle Davies	C&V UHB	CNS - Research and Genetics
Miranda Durkie	Sheffield Diagnostic Genetics Service	Deputy head of rare disease
Monica Hamill	Institute of Cancer Research	Research Genetics Counsellor
Munaza Ahmed	GOSH	Consultant Clinical Geneticist
Neeta Lakhani	University Hospitals of Leicester	SpR Clinical Genetics
Neslihan Boz	St George's Hospital NHS Trust	Histopathology Registrar
Nicola Balatoni	LTHT	GLH Programme Specialist Nurse
Noha Eltawil	Birmingham Women's Hospital	pre-registration Clinical Scientist
Paola Angelini	The Royal Marsden Hospital	Paediatric oncology consultant
Patricia OHare	RBHSC	Consultant Paediatric Oncologist
Patrick Tarpey	East GLH	Scientific Lead: Solid Cancer
Paul Roberts	Leeds THT	Consultant scientist
Philippa Thomas	Cambridge University Hospitals NHS Foundation Trust	Pre-Registration Genetic Counsellor
Rachael Mein	NHS England	Senior Laboratory Advisor
Rachel Burnell	University Hospital Southampton	Clinical Nurse Specialist
Rachel Harrison	Nottingham University Hospitals	Consultant in Clinical Genetics

Rebecca Dodds	NHS	Clinical Scientist
Rhian White	All Wales Medical Genomics Service	Consultant Clinical Scientist
Richard Martin	Northern Genetics Service	Consultant Clinical Geneticist
Rosalyn Jewell	Yorkshire Regional Genetics Service	Consultant Clinical Geneticist
Rosemarie Davidson	NHS Greater Glasgow & Clyde	Consultant in Clinical Genetics
Ross Laxton	KCH	Laboratory lead - Molecular Neurpoathology
Ruth Armstrong	East Anglian Medical Genetics Service	Consultant Clinical Geneticist
Ruth Cleaver	Royal Devon University Healthcare NHS Foundation Trust	Consultant in Clinical Genetics
Ruth Young	NHS	Clinical Scientist
Sam Behjati	Wellcome Sanger Institute / Addenbrooke's	Group Leader / Hon Consultant Paediatric Oncologist
Sandra Hing	NHS England	Senior Scientific Advisor
Sarah Darko	Oxford University Hospitals NHS Foundation Trust	Clinical Scientist
Sarah Farndon	Bristol Royal Hospital for Children	Paediatric Oncology Consultant
Sarita Depani	Great Ormond street hospital	Consultant Paediatric Oncologist
Serrgey Popov	UHW	Paediatric pathologist
Shaun Wilson	OUH	Consultant Paediatric Oncologist
Shirley Heggarty	BHSCT	Clinical Scientist
Shirley Hodgson	SGUL	Prof of Cancer Genetics
Sianan MacParland	NI Regional Genetics Service	Genetic Counsellor
Simon Paine	Nottingham University Hospitals NHS Trust	Neuropathologist
Smitha Nevis	King’s College Hospital	Pre-registration clinical scientist
Sunita Dhir	University Hospital of Leicester	Consultant Paediatric Oncologist
Tasha Morley	Sheffield Teaching Trust	Research Sister
Terri McVeigh	Royal Marsden NHS Foundation Trust	Consultant Clinical Geneticist
Vicki Lee	Sheffield children's hospital	Consultant Oncologist
Yvonne Wallis	West Midlands Regional Genetics Laboratory	Consultant Clinical Scientist

Zita Reisz	King's College Hospital, NHS Foundation Trust	Neuropathology Clinical Fellow
Zosia Miedzybrodzka	NHS Grampian	Honorary consultant clinical geneticist