

Next-generation sequencing panel for solid tumour cancers in children

Medtech innovation briefing

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Summary

- The **technology** described in this briefing is a next-generation sequencing (NGS)-based panel, used to sequence genetic mutations in solid tumour cancers in children.
- The **innovative aspects** are that it was developed with input from a wide range of experts, so it is highly optimised and tailored specifically to solid tumours in children.
- The **intended place in therapy** would be in addition to standard care, or as a replacement to less extensive gene testing, to expand the level of genomic analysis in children with solid tumour cancers.
- The **main points from the evidence** summarised in this briefing are from 1 UK analytical validity and diagnostic accuracy study that included a total of 132 samples, in a genomics laboratory, using clinical samples from laboratories worldwide. This showed that the NGS panel detected 94 of 95 (98.9%) well-characterised genetic abnormalities in 33 clinical specimens and 13 cell lines.
- **Key uncertainties** around the evidence or technology are that the technology is still in early development, so the evidence base is not fully established. Further evidence generation is planned and in progress.
- The **cost** of the NGS panel varies according to sample throughput, but is estimated to be £346 to £651 per patient (excluding VAT). The **resource impact** would be initially cost-

incurring, but using the NGS panel could lead to the development of targeted therapies using biological agents or targeted drugs for cancer in children.

The technology

The next-generation sequencing (NGS)-based panel for solid tumour cancers in children is an in-house laboratory test, not a commercial product. It was developed at the Centre for Molecular Pathology at The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust and validated in-house for clinical application, following the standardised framework published by [Mattocks et al. \(2010\)](#).

The test provides a genetic profile from a sample of solid tumour tissue for a range of childhood cancers including glioma, medulloblastoma, bone sarcomas, soft tissue sarcomas, renal tumours and neuroblastoma. The test reports whether there are mutations within each target gene in the tissue sample, and may identify whether the child with cancer is eligible for any suitable clinical trial to have targeted treatment.

The current NGS panel design, which is being continually developed, includes 92 genes which are either recurrently altered in childhood cancers, or have clinical implications in adult cancers (and potentially childhood cancers). Specialist genetic sample processing techniques are used to identify mutations in these genes. The test takes 10 working days to complete from receipt of tumour material in the laboratory to final reporting of results.

Innovations

The NGS panel was developed with input from a wide range of clinical and scientific experts. It is highly optimised and tailored specifically to solid tumour cancers in children.

Ongoing clinical trials could contribute to developing molecular stratification approaches to treating cancer in children.

Current NHS pathway or current care pathway

Companion diagnostic tests designed to identify targeted genetic variations in tumour DNA are routinely used for some cancers in adults. However, childhood cancers are biologically different to adult cancers, and there are no targeted therapies available in the NHS. As such, diagnostics are not part of standard care pathway for treating cancer in children.

Targeted therapies are offered to children with cancer only in the context of clinical trials. Children with cancers that do not meet the inclusion criteria of clinical trials may be offered surgery, chemotherapy or radiotherapy, then palliative care for when all other treatment options have been exhausted.

Population, setting and intended user

The NGS panel is intended for use in a clinically accredited laboratory. Because of the relatively low numbers of children with cancer, the test would likely be run from a small number of laboratories that provide a service to centres involved in diagnosing and treating cancer in children. A sample from the tumour, together with corresponding germline DNA or whole blood, would be sent from the laboratory of the referring centre to the laboratory providing the test. The test laboratory would then prepare a formalin-fixed paraffin embedded (FFPE) clinical sample block, run the test and provide the results to the referring pathologist. The results would be used to help decide whether the child is eligible for enrolment in a clinical trial.

Staff using the NGS panel need training in the test, alongside general competency training in line with Good Clinical Laboratory Practice (GCLP) regulations. This would be provided by the test laboratory. The test is in scope for the NHS Genomic Laboratory Services on which NHS England has recently developed a specification for engagement with stakeholders.

Costs

Technology costs

Costs obtained from the Centre for Molecular Pathology at The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust vary depending on volume and turnaround time. Table 1 shows the total in-house costs, including the cost of using an Illumina Nextseq 500 NGS sequencer. The panel can be run in batches of 20 paired samples at most, or in smaller batches for faster turnaround or when sample numbers are limited.

Table 1 Cost per sample for NGS panel testing

| Description | Cost per sample (20 samples, full capacity) | Cost per sample (5 samples, faster turnaround) |
|------------------------|---|--|
| Reagents only | £204 | £325 |
| Reagents and overheads | £271 | £413 |

| | | |
|--|------|------|
| Reagents, overheads and labour* | £346 | £651 |
| * Including all necessary maintenance contracts, data analysis and labour costs, but no additional NHS administrative costs. | | |

Costs of standard care

Diagnostic tests such as the NGS panel are not part of standard care for cancer in children in the NHS.

Resource consequences

Cancer in children is relatively rare, but around 1,000 children with cancer could be eligible for NGS panel testing each year ([Childhood cancer registration in England, 2016](#)).

The resource impact would be cost-incurring at first. However, the NGS panel would mainly use existing laboratory resources and remove the need for expensive sequential testing to inform eligibility decisions for clinical trials in children with solid tumour cancer. Based on the costs outlined in table 1, sequencing all solid tumour cancers in children may cost between £342,194 and £643,839 per year (excluding administration costs).

The genetic information obtained may lead to the development of molecular stratification strategies in paediatric oncology, targeted therapies using biological agents or targeted drugs for children. These would be alternatives to surgery, chemotherapy, radiotherapy and other current treatments in children with solid tumour cancers.

Regulatory information

Laboratories running NGS panel tests must meet United Kingdom Accreditation Service (UKAS) Clinical Pathology Accreditation (CPA) or [ISO15189:2012](#) (Medical laboratories – Requirements for quality and competence) standards.

The Royal Marsden NHS Foundation Trust that currently offers this test meets the standards (CPA number 2898), with ISO15189:2012 inspection due in December 2017.

All equipment, including the Illumina [Miseq](#) and [Nextseq500](#) sequencers are kept in service contract and routine maintenance is logged as per ISO regulation. The Nextseq500 sequencer is CE

marked to Electromagnetic Compatibility (EMC) Directive 2014/30/EU, Low Voltage Directive 2014/35/EU and Radio Equipment Directive (RED) 2014/53/EU.

Equality considerations

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. In producing guidance and advice, NICE aims to comply fully with all legal obligations to: promote race and disability equality and equality of opportunity between men and women, eliminate unlawful discrimination on grounds of race, disability, age, sex, gender reassignment, marriage and civil partnership, pregnancy and maternity (including women post-delivery), sexual orientation, and religion or belief (these are protected characteristics under the Equality Act 2010).

Age is a protected characteristic under the Equality Act 2010. The NGS panel is designed specifically to sequence genes in solid tumour cancers in children. All patients with cancer are considered disabled from the point of diagnosis.

Clinical and technical evidence

For this technology, a variation from the [interim process and methods statement](#) was made. No literature search was done. Instead, experts and relevant charities provided the most relevant or best available published evidence relating to the clinical effectiveness of the technology. Further information about how the evidence for this briefing was selected is available on request by contacting mibs@nice.org.uk.

Published evidence

This briefing summarises 1 analytical validity and diagnostic accuracy study of 132 samples. This study was done at The Royal Marsden NHS Foundation Trust using clinical samples obtained from laboratories globally. Reported outcomes were:

- limit of detection
- precision
- panel sensitivity
- range of variant allele frequency detected

- performance and variant detection comparison in paired fresh frozen and FFPE clinical DNA samples
- detection of known variants
- detection of rearrangements.

The study concluded that the NGS panel detected 94 of 95 (98.9%) well-characterised genetic abnormalities in 33 clinical specimens and 13 cell lines (including single nucleotide variants, insertions or deletions, amplifications, rearrangements and chromosome losses).

Table 2 summarises the clinical evidence as well as its strengths and limitations.

Overall assessment of the evidence

The technology is still in development, so the published evidence base is limited in terms of quantity. Evidence on the analytical validity and diagnostic accuracy of the first version of the test (which included 78 genes) is available, and a number of clinical trials are ongoing or planned. The current version, which includes 92 genes, has been verified but the results were not publically available at the time of preparing this briefing.

Table 2 Summary of selected studies

| <u>Izquierdo et al. (2017)</u> | |
|---------------------------------|---|
| Study size, design and location | Analytical validity and diagnostic accuracy study of 132 samples from laboratories worldwide. London, UK. |
| Intervention and comparator(s) | Intervention: in-house, NGS panel comprising 78 genes involved in childhood cancers. Samples included: Horizon Discovery cell blends (n=4), childhood cancer cell lines (n=15), FFPE clinical samples (n=83) and FF clinical samples (n=30). Comparators: cell blends containing known SNVs (n=528) and small indels (n=108) were used to determine panel sensitivities of $\geq 98\%$ for SNVs and $\geq 83\%$ for indels, and panel specificity of $\geq 98\%$ for SNVs. |

| | |
|--|---|
| <p>Key outcomes</p> | <p>Panel sensitivity</p> <p>All background SNVs and cancer-specific SNVs were detected, resulting in a sensitivity of over $\geq 98\%$. 90 of 108 background indels and 15 of 17 cancer-specific indels were detected, resulting in a sensitivity of $\geq 83\%$.</p> <p>Panel specificity</p> <p>The specificity of cancer-specific SNVs was $\geq 98\%$. PPV was $\geq 98\%$ and NPV was $\geq 98\%$. There were insufficient true-negative indels (n=3) to determine specificity for indels.</p> <p>Detection of known variants</p> <p>100% of the 90 known genetic variants in 41 samples (in 13 cell lines, 14 FFPE and 14 FF samples) were detected.</p> <p>Detection of rearrangements</p> <p>94 of 95 (98.9%) well-characterised genetic abnormalities in 33 clinical specimens and 13 cell lines (including SNVs, indels, amplifications, rearrangements and chromosome losses) were detected by the panel.</p> |
| <p>Strengths and limitations</p> | <p>The study is written up transparently, with supplementary data available for independent scrutiny. Despite small numbers and low prevalence of these cancers in children, the use of paediatric clinical samples from an international collaboration should yield more generalisable findings than a smaller, single-centre study design.</p> <p>However, as of December 2017, the work was still undergoing peer review at the OncoTarget journal.</p> <p>The authors note that validation of the panel for the detection of rearrangements (translocations) was limited by small sample size (5 FFPE sarcoma samples), so further work is in progress at this stage.</p> |
| <p>Abbreviations: FF, fresh frozen; FFPE, formalin-fixed paraffin embedded; indels, insertions or deletions; NGS, next-generation sequencing; NPV, negative predictive value; PPV, positive predictive value; SNV, single nucleotide variants.</p> | |

Recent and ongoing studies

The NGS panel is currently being used for the following studies:

- BEACON: a randomised phase IIb trial of bevacizumab for refractory and relapsed neuroblastoma in children. EurodraCT identifier: [2012-000072-42](https://www.eurodra.org/clinical-trials/2012-000072-42). Status: ongoing.

- CRISP: a phase IB of crizotinib for ALK-, ROS1- or MET-positive malignancies in children. EurodraCT identifier: [2015-005437-53](#). Status: ongoing.
- BIOMEDE (Biological Medicine for Diffuse Intrinsic Pontine Glioma Eradication). ClinicalTrials.gov identifier: [NCT02233049](#). Status: recruiting.
- eSMART (European Proof of Concept Therapeutic Stratification Trial of Molecular Anomalies in Relapsed or Refractory Tumours). ClinicalTrials.gov identifier: [NCT02813135](#). Status: recruiting.
- FaR-RMS (Frontline and Relapse study in Rhabdomyosarcoma). Status: awaiting full approval.

The NGS panel forms the genetic testing basis for an ongoing study at the Royal Marsden Hospital (NGS sequencing CCR4924) and the national [CCLG METEOR trial](#). It is also being used in the Children with Cancer UK-funded [IMPACT trial](#) and as part of the Cancer Research UK [Stratified Medicine Programme 2](#).

Specialist commentator comments

Comments on this technology were invited from clinical experts working in the field and relevant patient organisations. The comments received are individual opinions and do not represent NICE's view.

All specialist commentators were familiar with or had used the NGS panel before. One is responsible for updating and implementing the NGS panel.

Level of innovation

Applying NGS technology to a range of childhood cancers was thought to be a novel concept. Other NGS tumour panels are available, but these are mostly for adult cancers and specific childhood cancers.

Potential patient impact

The specialist commentators identified faster identification of causative mutation for disease in some children as a potential patient benefit. Not every mutation will be associated with a specific drug or intervention, but the evidence generated from the NGS panel may be used to identify novel therapeutic targets.

One commentator felt that adopting the NGS panel could lead to longer survival through more personalised cancer treatment. Another commentator gave a specific example of identifying ALK mutations, which could redirect treatment to crizotinib. They also highlighted that the main advantage of the panel is that there is no need to guess which target gene to test, because this panel tests for all of the targets simultaneously.

Potential system impact

The specialist commentators identified a number of system benefits, including more accurate diagnoses. The NGS panel test is more expensive than some individual gene tests, but it removes the need for multiple sequential testing. It can also discover gene variants that are not detectable at all using current methodologies, in a reasonable and clinically useful turnaround time. In addition, 1 commentator noted that the panel provides a unified assay that avoids the need to purchase multiple platforms and conduct serial gene tests. The equipment required for the NGS panel will be equally applicable to all gene testing. Centralisation of testing would reduce turnaround times and reduce costs, because it is more cost effective to test several samples simultaneously.

One specialist felt that, if the NGS panel were adopted, changes would be needed to local pathology pathways (for example, to ensure that the correct tissue is taken at the correct time). They also observed that the published evidence focuses on somatic mutations, and that identifying incidental germline genetic mutations may pressure tertiary clinical genetics services later in the pathway. However another specialist commented that quantifying the potential cost impact is not possible given the limited evidence base.

General comments

The specialist commentators felt that gene panel testing may eventually become standard of care, with 1 claiming the NGS panel to be the future of diagnostics. However, the commentators advised individual gene testing should be kept for quality purposes and special cases where a triage approach might be effective and timely. The expert involved in developing the technology commented that it successfully demonstrates rapid and efficient assessment, and that this has driven demand.

Patient organisation comments

Two representatives from the [Christopher's Smile](#) charity, 1 individual patient expert who is also a consumer member from the [National Cancer Research Institute Children's Cancer & Leukaemia](#)

Clinical Studies Group (NCRI CCL CSG) and 1 representative from the Abbie's Army charity, provided comments on the NGS panel test as summarised below.

Christopher's Smile recognises the importance of personalised medicine and supports the chief medical officer's 2016 annual report, which promotes the need for accurate, quick, cost-effective testing to determine the genetic abnormalities that cause cancer. The charity funded the preclinical development and validation of the NGS panel technology and, although large clinical trials are still underway, the charity believes that it should now become part of standard care as a diagnostic tool. The opportunity to collect sequencing data is a huge potential benefit: adopting the NGS panel would build evidence to show that specific drug targets in adults also occur in children, which may persuade some companies to make drugs available for research in children earlier in the pipeline. Data from the NGS panel test will be critical when planning and assessing the treatment plans for cancer in children.

The individual patient expert agrees that genomic sequencing of childhood cancers should become standard practice in the UK, stating that the UK is already behind in terms of sequencing these tumours. Sequencing of tumours at both diagnosis and relapse will also help unlock additional areas of research, exploring and understanding the changes that occur with the tumour, which may in turn be used to develop new ways of treating these diseases.

Abbie's Army focuses on diffuse intrinsic pontine glioma (DIPG), a childhood cancer with a survival rate of less than 1%. A meta-analysis of 1,000 children with high-grade gliomas and DIPG revealed at least 10 disease and biological subgroups ([McKay et al. 2017](#)). The charity agrees that clinical treatments must keep pace with the science and that the NGS panel is the starting point. The benefits of a more personalised therapeutic approach have been seen in the BIOMEDE trial, the results of which are due to publish in 2018.

Specialist commentators

The following clinicians contributed to this briefing:

- Dr Paul Brennan, consultant in clinical genetics, Northern Genetics Service, and deputy clinical director of integrated laboratory medicine, Newcastle upon Tyne Hospitals NHS Foundation Trust. Dr Brennan is clinical programme director for the North East & North Cumbria NHS Genomic Medicine Centre, with a specific remit around enrolment of cancer patients, including children, into the 100,000 Genomes Project.
- Dr Mike Hubank, head of clinical genomics (research), The Royal Marsden NHS Foundation Trust. Dr Hubank has done occasional consultancy work for Roche Diagnostics (which provides

reagents for the NGS panel). Dr Hubank joined the organisation which developed the original NGS panel technology; he is responsible for updating and implementing the panel and running it as part of the METEOR clinical trial and for other purposes at the Royal Marsden Hospital.

- Professor Louis Chesler, consultant oncologist for paediatric cancer biology, the Centre for Molecular Pathology at The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust. No relevant conflicts of interest.

Additional reviewer:

- Dr Angela Silmon, chief executive officer, NewGene. No relevant conflicts of interest.

The following patient organisations contributed to this briefing:

- Christopher's Smile
- An individual patient expert who is also a consumer member from the National Cancer Research Institute Children's Cancer & Leukaemia Clinical Studies Group
- Abbie's Army.

Development of this briefing

This briefing was developed for NICE by Newcastle and York External Assessment Centre. The [interim process and methods statement](#) sets out the process NICE uses to select topics, and how the briefings are developed, quality-assured and approved for publication.

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