Tumour agnostics: realising the potential of precision medicine

Policy issues and recommendations

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Our increasing understanding of cancer genomics is enabling the development of new kinds of targeted cancer therapies. Such treatments are able to more precisely and specifically target cancer cells, increasing the chances that the treatment will be effective, and reducing the likelihood of harmful side-effects for the patient.

Planned moves towards a 'genomics first' approach to cancer testing and treatment planning will be critical to making the most of these new opportunities for improved care and outcomes through precision medicine. To achieve this, supportive policy developments are needed.

Roche Products Ltd sponsored the charitable think tank PHG Foundation to conduct research into the most important policy issues posed by the current and potential future use of tumour agnostic medicines and genomic testing in the NHS.

A series of interviews and an expert stakeholder roundtable have helped to inform the research and recommendations outlined in this paper.

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An introduction to tumour agnostic therapies

Tumour agnostics are a new type of targeted cancer therapy; they are cancer drugs that target specific cancer-associated genomic alterations, regardless of the type or sub-type of tumour. Such drugs can also be described as tissue agnostic, histology agnostic or histology independent. They represent a genomics-led approach to cancer, using the molecular profile of the tumour to inform treatment decisions - ideally from the point of initial diagnosis, as opposed to later in cancer pathways (for example, if standard treatments have proved ineffective).

Patients with quite different tumour types, but with shared genomic tumour features, may benefit from the same tumour agnostic therapies. For example, a patient with a lung cancer, and another with a breast cancer may have the same genetic alteration, and therefore receive the same therapy, whereas two lung cancer patients may have different alterations, and therefore need different therapies.

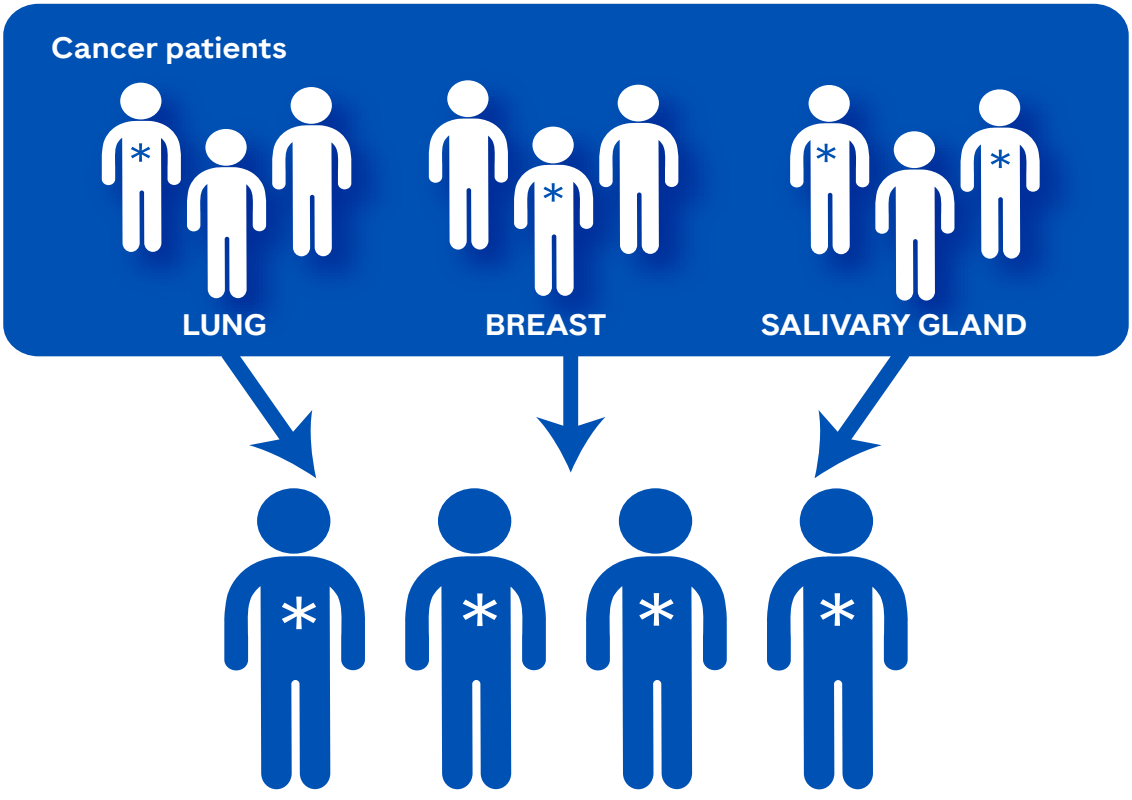
Tumour agnostics can only be used when the presence of a relevant genomic alteration in the tumour is confirmed, which means that appropriate testing must become routinely available to be used for their widespread adoption.

A challenge to patient identification lies in the variation of biomarker prevalence across all tumour types, an example being *NTRK* gene fusions which have a very high prevalence in rare cancers, such as secretory breast cancers (92%), but much lower levels in more common cancers, such as lung (0.1-3.3%), resulting in similar numbers of patients within each cancer type.

Importantly, in cancer types where there is low prevalence of genomic variants targeted by tumour agnostic therapies, patients with the target alteration (who could benefit from treatment with the corresponding tumour agnostic drug) may go undetected without easy access to routine genomic testing.

Tumour agnostic therapies

Patients with different types of cancer (e.g. lung, breast and salivary gland) may all be eligible for treatment with the same tumour agnostic therapy



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Tumour agnostics in clinical practice

In England and Wales, two tumour agnostic treatments have been recommended for use by the National Institute for Health and Care Excellence (NICE), under conditional approval within the cancer drugs fund. One is for use in Scotland. Both drugs can be used to treat solid tumours with genomic changes called *NTRK* fusions when there are no further satisfactory treatment options available: one in adults and children over 12, the other in both adults and children.

In England, genomic tests to detect *NTRK* fusions are listed on the NHS National Genomic Medicine Service Test Directory, with the tests delivered by Genomic Laboratory Hubs (GLHs). The Test Directory is regularly updated as new genomically guided treatments are approved; it includes a range of tests, the simplest of which are for a single defined genetic variant in a specific gene. Panel testing is the simultaneous detection of multiple pre-defined genetic targets of interest. Whole Genome Sequencing (WGS) is the complete sequencing of the entire genome followed by analysis for any genetic variant of potential interest.

Cancer genomic testing can include targeted mutation tests for single genes, panel testing for an agreed set of genomic alterations known to be associated with a specific tumour type, and WGS for some tumour types. Patients may only receive genomic testing when this information is needed for a clinical decision.

All clinically actionable genomic variants (i.e. those in the Test Directory) will be reported; this is designed to enable equity of access to tests with proven clinical utility across England.

When to carry out the genomic test is not currently indicated in the NICE clinical guidelines on use of these therapies, and there is significant variation across tumour types in terms of where in the clinical pathway genomic testing is applied. Although moving genomic testing earlier in the pathway would not lead to tumour agnostic therapies being used as a first-line treatment (as this would not be in line with their approved uses), it would allow therapy selection across all tumour types to be data-led, and should therefore be considered.

Planned moves towards a ‘genomics first’ approach to cancer testing are likely to change the delivery of some cancer pathways. The expected use of first-line Next Generation Sequencing (NGS) panel genomic testing in England and Wales for somatic (non-heritable) cancer variants is likely to maximise patients’ access to tumour agnostic therapies. This is because it would enable all locally advanced solid cancers to be consistently assessed for genomic variants relevant to potential treatment choices at the point of diagnosis. Once the NGS service in England is fully established, it is estimated that 100,000 solid tumours will be tested per year.

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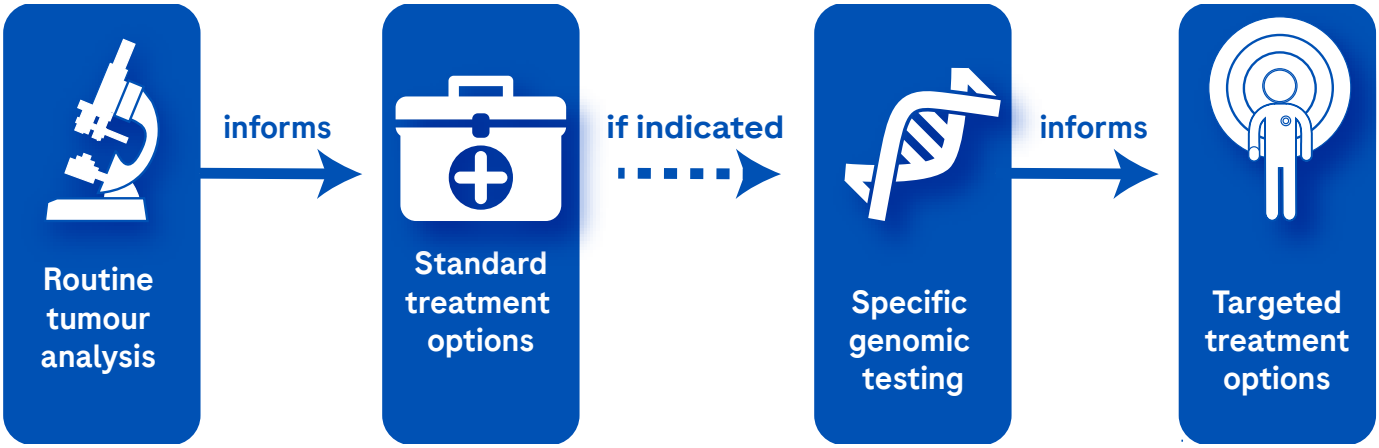
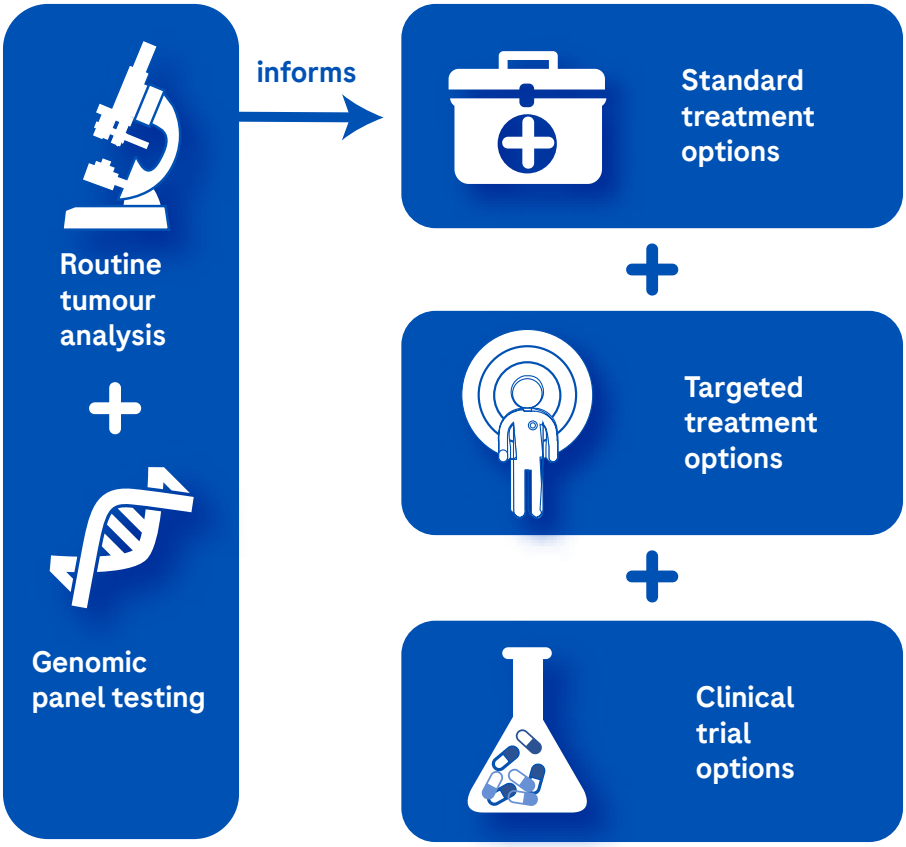
Current approach



Genomics first approach



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What next for tumour agnostics?

While only a small number of tumour agnostic therapies have currently been approved for clinical use in (or beyond) the UK, it is an area of active research and development. Further gene targets have been identified and many are being explored in a research or clinical trial setting, for example variants in the *ALK, RET, RAF, KRAS, ROS1, and ERBB2* genes. Some tumour agnostic drugs initially approved for individual indications have the potential for subsequent approval for wider use.

Clinical trials to investigate tumour agnostic drugs typically follow the basket trial design, rather than the standard Randomised Controlled Trial (RCT) design. This is because the recruitment of a significant number of patients with a specific tumour type and the relevant rare alteration would take unfeasibly long. Instead, in basket trials patients with any tumour type can be recruited, as long as they have a genomic variant hypothesised to inform response to treatment. This is useful because it increases the potential pool of participants (for example, to include rare cancer types), which might otherwise be too small to permit normal randomised control trial approaches. Challenges associated with basket trials can include the lack of a comparator arm and the involvement of multiple cancer types, making it harder to prove clinical efficacy, particularly where drugs could differ in their effectiveness between different clinical indications.

Consideration is being given to alternative trial designs that allow ongoing evidence gathering and interim data analysis, and options to adapt trial design in response to findings. Long-term clinical follow up and assessment in real-world settings could help to inform risk-benefit calculations in relation to these therapies. Models for effective regulation and reimbursement of these drugs are required in terms of supporting decision making and funding their availability.

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Policy issues and recommendations

Genomic testing in the NHS

Tumour agnostics are increasingly referred to as 'histology independent therapies', but this term is potentially misleading from a clinical perspective, as it incorrectly implies that tumour tissue analysis is redundant in cancer diagnosis and decision-making. 'Targeted therapies' may be a better term.

There are difficulties in harnessing the full potential of tumour genomic testing being undertaken (and the genomic information generated), and practice varies. Some clinicians only want to receive information on clinically actionable genomic variants, whilst others prefer results from a larger panel, potentially allowing them to enrol patients into relevant clinical trials.

Because the GLHs are not routinely commissioned to provide this additional form of genomic information from tumour analysis, some opportunities for patients (i.e. eligibility for clinical trials) may be missed. NHS England is exploring how to ensure an equitable approach to analysing genes being studied in clinical trials.

Recommendations

- **A consistent categorisation of tumour agnostic therapies should be agreed and applied across research, regulation and clinical practice.**
- **A consistent approach to 'genomics first' panel testing for tumours should be established across the NHS, including pathways for tumour sampling, handling and consistent storage and sharing of the information generated. Patient consent should also be obtained to allow long-term storage and sharing of the genomic information generated.**
- **Clear distinction is needed between clinically actionable test results, and additional test results that could inform clinical trial eligibility or other research purposes. Ideally, both categories of tests should be undertaken, with 'future-proofing' of cancer panel testing to include agreed research variants and genomic signatures.**
- **Potential routes to the use of medicines in non-licensed indications where a relevant molecular (genomic) target is identified should also be considered through existing NHS routes to allow formalised data collection to assess clinical effectiveness.**

Research and development

There is a compelling need for ongoing development of new precision medicine therapies, and for improved approaches to enable prompt, easy national recruitment of eligible cancer patients into relevant clinical trials.

Whilst experts agree on the importance of maintaining a clear distinction between clinical practice and clinical research with respect to tumour genomics, it is also felt that the information from clinical genomic testing should be used to inform and enable clinical trials of potential new treatments for patient benefit.

Recommendations

- **Genomic and clinical information should be readily available and searchable via patient electronic health records, and enable automatic flagging of clinical trial eligibility and invitation to participate for relevant patients across the UK. A UK clinico-genomic database should be created to harness the rich datasets currently available, to help understand how targeted treatments used today can help inform and improve care for future patients.**
- **Approaches to regulation and evaluation need to keep pace with the evolution of adaptive clinical trial designs. This will help to establish suitable evidence requirements for targeted treatments that are used in smaller and more specific patient sub-groups, and allow for reassessment as more evidence emerges.**

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Supporting health professionals and patients

A 'genomics first' approach to cancer in the NHS will require changes in how health professionals assess and plan treatment for cancer patients, and may necessitate further training, guidance and support on how to use and interpret genomic testing. In this context, it is important to note the difference between routine genomic panel test results linked to the use of specific therapies, useful for most patients, and WGS-based analysis of tumours that are more complex, or where standard testing and treatments have been exhausted. The latter approach, requiring a specialist review of findings, is appropriate for a minority of patients only, where there is clinical utility.

There is a need for clear and easily accessible guidance on the timing of testing and clinical pathways for the use of tumour agnostic therapies. The Clinical Pathway Initiative (a collaboration between NHS England and NHS Improvement, Health Education England and the Academy of Medical Royal Colleges to help integrate genomic medicine into clinical practice) could support this. However, as new therapies emerge there may well be a need for more rapid expansion and revision of oncology pathways.

Recommendations

- **Consideration must be given to the growing resource requirements that a move towards precision medicine will necessitate – especially the increasing need for complex forms of genomic analysis, and widening use of multi-disciplinary teams' reviews to inform clinical management of cancer patients.**
- **Demand for established forms of testing typically remains high among health professionals even when new forms of testing can or should replace them. Implementation of new forms of testing and treatment pathways will therefore require considerable support to achieve the change, acknowledging that not all services will be able to move at the same speed, but patients need to continue to receive treatment during this period.**
- **The process of ordering genomic tests should be streamlined, online and easily accessible for all relevant health professionals in oncology.**
- **Collaborative approaches between patients and health professionals are needed to boost awareness of how, when and where it is appropriate to use tumour agnostic and other precision medicine treatments to best effect, and confidence in adopting new approaches. For this to be possible, patients must have easy access to clear information and support.**
- **Efforts to boost health professional awareness of 'genomics first' approaches to tumour analysis and the potential impact on decision-making (including for common tumour types with multiple therapeutic options) are needed. Suitable GeNotes (genomic notes for clinicians produced by Health Education England) resources could contribute to this, provided all relevant health professionals in oncology are aware of them.**

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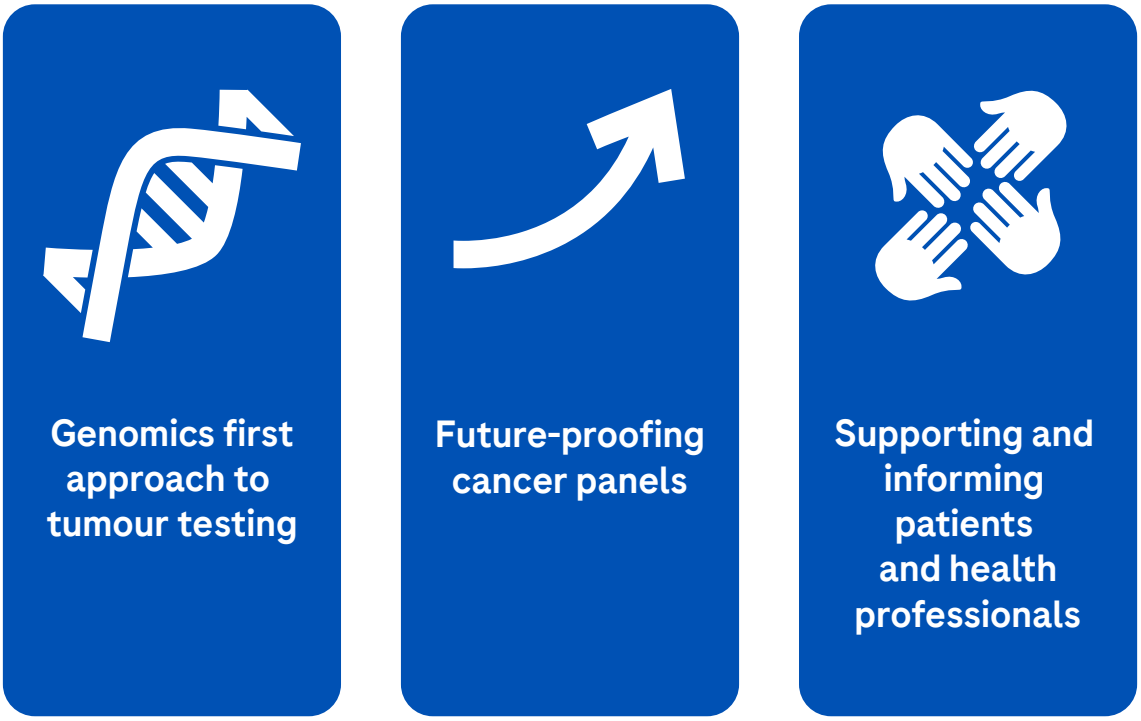
Summary policy recommendations



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Conclusions

The advent of increasingly targeted treatments for cancer offers exciting new scope to harness complex genomic and biomedical data to improve outcomes and experiences for patients. Tumour agnostic therapies are an excellent example of one of these new, targeted cancer medicines.

In order to ensure that all those patients across the UK who could benefit from the use of proven tumour agnostic and other targeted therapies are provided with equitable access to testing to inform treatment decisions, some challenges will need to be addressed.

In particular, an NHS approach is needed that considers genomics as an integral part of cancer diagnosis and analysis, and enables effective communication and collaboration across different health professional disciplines, and with patients.

Agreement and concerted action from all precision medicine stakeholders – including policy and decision-makers, regulators, patients and families, academic and industry researchers, health professionals and scientists – will be needed to successfully address the issues identified here, most notably:

- **A consistent NHS 'genomics first' approach to tumour genomic panel testing should be established, including pathways for sampling and testing, and systems for information storage and sharing.**
- **NHS cancer panel testing should be 'future-proofed' to maximise research utility, by including clearly distinct results on clinically actionable genomic variants, and on additional genomic variants to inform clinical trial eligibility and planning.**
- **Health professionals and patients should work together to improve awareness of new opportunities arising from genomic testing for tumour agnostics and other targeted treatments.**

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Roche in personalised medicine

Roche is a pioneer in pharmaceuticals and diagnostics, focused on advancing science to improve people's lives.

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We are a committed, long-term partner to the NHS and will continue to support the health service to ensure personalised medicine is a routine part of care.

Acknowledgements

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