CANCER RESEARCH UK POLICY STATEMENT: PATIENT ACCESS TO MOLECULAR DIAGNOSTICS AND TARGETED MEDICINES IN ENGLAND

SEPTEMBER 2018

SUMMARY

Thanks to scientific advances, it is now possible to detect specific molecular changes or genetic mutations in some patients’ cancer cells. Such changes help the cell to survive and grow, but drugs which can ‘target’ these variations can offer patients improved response rates, better outcomes and reduced side-effects compared to conventional chemotherapy.

Identifying these variations in a patient’s cancer, and using these findings to inform their treatment options (rather than simply looking at where in the body the cancer is growing), is known as ‘stratified’ or ‘precision’ medicine. This approach aims to achieve the best possible treatment outcomes by matching a patient with the medicine that works best for them, though further research will be required before every patient’s treatment can be guided in this way.

Many mutations which can be targeted with these medicines can be identified through ‘molecular diagnostic’ or ‘genomic’ testing. Swift and equitable access to these tests is therefore fundamental to ensuring patient access to targeted medicines. These tests are the focus of this policy statement.

Cancer Research UK (CRUK) has previously found many patients are missing out on molecular diagnostic tests. For example, we estimate that in 2014, around 16,000 patients with colorectal or non-small-cell lung cancer did not receive molecular diagnostic tests; of these patients, 3,500 could have benefitted from a ‘targeted’ medicine. The 2015 Cancer Strategy for England highlighted this issue and called for NHS England to “transform access to molecular diagnostics to guide treatment for cancer”.

We have heard anecdotally that there has been some progress since then in access to tests for some specific mutations such as EGFR, ALK and BRAF. This has been driven partly by NHS England’s decision to directly pay for some of these tests (including tests for ALK and BRAF mutations) under the terms of the National Tariff since 2016/17. However, there is no new data to suggest the situation is resolved, and NHS England acknowledges that inequitable patient access to genomic testing remains a problem.

Significant and promising changes in the national policy approach to genomic medicine are now underway. NHS England is planning to launch its Genomic Medicine Service in October 2018, which will establish seven new Genomic Laboratory Hubs (GLHs) and a National Genomic Testing Strategy. This will help to coordinate the national approach to providing molecular diagnostic tests. We support this approach and see it as in line with the ambitions in the Cancer Strategy. It is now important to make sure that this Service realises its potential to facilitate equitable access to molecular diagnostic tests and targeted medicines.

This statement outlines CRUK’s perspective on how access to these tests – and to targeted medicines – could be improved across England, including key priorities for the new Genomic Medicine Service. It will focus primarily on how to ensure the Service keeps up to date with scientific and technological progress, and the enablers that will ensure swift and equitable patient access to these technologies in future.
This statement does not include recommendations on the challenges that precision medicine poses to the NICE appraisal process, or about pricing and reimbursement. Our full policy position on access to new medicines covers these issues and will shortly be available on our website. This statement also does not cover testing for inherited gene mutations that can increase the risk of developing certain types of cancer (so-called “predictive” genetic testing).

RECOMMENDATIONS

- The Department of Health and Social Care (DHSC) and NHS England should use the Genomic Medicine Service launch to improve patient access to multiplex panel tests. They should ensure they continue to balance preparing for the future integration of Whole Genome Sequencing into mainstream services, and serving the needs of patients today through the provision of less complex diagnostic tests.
- In taking forward the previous recommendation, NHS England should also clarify how they will update the National Genomic Testing Strategy (detailing all cancer genomic tests available in the NHS in England) in the future, including how they will engage with external experts and other bodies such as NICE.
- DHSC and NHS England should ensure the operation of the Genomic Medicine Service enhances research into precision medicine, including improving patient access to clinical trials for new targeted medicines.
- Health Education England should complete detailed genomics workforce planning as soon as possible, with wide engagement from clinical experts, to ensure adequate provision of the key workforce roles required for a more genomics-focused approach to patient care.
- NHS England Specialised Commissioning should begin paying for all cancer molecular diagnostic testing directly, as soon as is feasible. This would streamline the process and reduce uncertainty, which could be a barrier to uptake.
- NHS England and Public Health England must ensure uptake of molecular diagnostic tests is monitored accurately. The new National Genomics Informatics System should be used to build up a picture of molecular diagnostic activity within each of the GLH regions, so that any variation in uptake can be quickly identified and investigated.
- NHS England and DHSC should continue to work with additional stakeholders, including Health Education England, to improve awareness and understanding of genomic healthcare among healthcare professionals and the wider public.
BACKGROUND

THE CHANGING SCIENTIFIC LANDSCAPE

Cancer drugs play a crucial role in many patients’ treatment. There have been exciting advances in drug development over recent years, with a shift towards precision medicine and drugs which can “target” specific molecular changes and genetic mutations in cancer cells. Such medicines can treat the disease more effectively (and with fewer side effects) than conventional chemotherapy.

For example, among patients with lung cancer that has a mutation in the EGFR gene, as many as 80-90% show evidence of response to targeted treatments, compared to only 20-40% responding well to non-targeted chemotherapy. Because of the shift towards more targeted treatment, rather than cancer being seen as a single site diagnosis it is increasingly defined by a combination of biological factors known as biomarkers (such as a specific genetic mutation).

CRUK has long been a leader in precision medicine, launching the first Stratified Medicine Programme in 2010 which tested the feasibility of running a genetic pre-screening programme within existing NHS infrastructure. Following the success of this programme, CRUK now funds pioneering clinical trials such as the National Lung Matrix Trial, which is seeking to understand which targeted treatments should be given to which patients based on the genomic make-up of their tumour. Patients with different biomarkers are allocated a different drug as part of their treatment, as shown in Figure 1 below.

Figure 1: National Lung Matrix Trial setup

CRUK has also recently launched PRECISION-Panc, which seeks to understand the genomic make-up of patients with pancreatic cancer, and TRACERx, which will uncover how the genomic make-up of patients with non-small cell lung cancer evolves over time.

PRECISION MEDICINE IN CLINICAL PRACTICE

There has been a dramatic increase in the use of precision medicines over recent years. Although breast cancer was highly segmented even in the early 2000s, the use of biomarkers to stratify patients has increased rapidly over the past 10 years and targeted medicines are now widely used in the NHS in many types of cancer. This trend is set to continue, with targeted drugs making 90% of the late phase pipeline in 2016. Of the 14 New Active Substance cancer therapies launched in 2017, all were targeted therapies and seven were associated with biomarkers which could be identified by molecular diagnostic testing.
Because a particular biomarker may occur in tumours in multiple different parts of the body, this shift also means that new medicines are increasingly being marketed for multiple types of cancer (‘indications’). For example, as of July 2018, one drug – pembrolizumab – had been approved by NICE for use in the NHS in England in six indications, and was being considered for use in a further sixteen indications. More than 50% of major cancer medicines marketed in 2014 were for multiple indications; by 2020 this is expected to reach 75%14.

Access to molecular diagnostic tests is fundamental to this treatment approach, since these tests can identify biomarkers that can be targeted with a precision medicine. They can also be used to identify if a patient could be suitable to participate in clinical research. A 2017 global survey of oncologists found that the highest rates of biomarker testing were achieved for oestrogen-receptor-positive and progesterone-receptor-positive breast cancers, BRAF mutations for melanomas, and 17P mutations for chronic lymphocytic leukaemia (CLL)15.

Without access to the appropriate tests, patients cannot receive targeted medicines and so may miss out on innovative, evidence-based treatment options that could benefit them. It is therefore crucial that patients have equitable and fast access to these tests across the country.

CURRENT ACCESS TO MOLECULAR DIAGNOSTIC TESTS

Molecular diagnostic tests generally fall into three categories:

- **Single biomarker tests**: these tests will look for the presence of one specific mutation in a tumour sample, such as EGFR for lung cancer. Some single tests are paired with a specific targeted drug; these are known as ‘companion diagnostics’ and currently must be approved separately to the drug.

- **Panel tests**: these tests will look for the presence of several specific mutations at once, without the need to take multiple samples from a patient. As research finds new mutations that could be targeted and new tests to detect them, panels can become broader and more cost-effective. Some larger panels can include a range of tests, only some of which are clinically relevant but with others that are of interest for research purposes.

- **Whole Genome Sequencing (WGS)**: this involves analysing the entire sequence of DNA in a tumour sample. WGS will provide information on all present mutations – some clinically relevant and many more of unknown significance. It takes about a day to sequence one human genome; however, the analysis takes much longer16. The 100,000 Genomes Project, managed by Genomics England, has returned whole genome analysis for cancer within three weeks17, though it is not clear if this speed could be replicated on a larger scale with more samples.

The use of molecular diagnostic tests has increased over recent years: for example, between 2011 and 2014, testing activity in England increased by 51% per year for lung cancer, colorectal cancer and melanoma collectively. However, past CRUK research has found there is still a gap in access to tests. In a 2015 report (summarised in Figure 2 below), we found that:

- Over 24,000 molecular diagnostic tests were not undertaken in 2014, based on estimated demand in England.
- Around 16,000 eligible patients with non-small cell lung cancer and colorectal cancer in England missed out on molecular diagnostic tests, and therefore exploration of all possible treatment options.
- Around 3,500 of these patients would have been eligible for a targeted medicine and therefore missed out on the associated benefits, including longer progression-free survival or overall survival and avoidance of side effects from treatment that may not work for them.
- However, there was no gap in melanoma testing.

**Figure 2: Molecular diagnostic testing gap, 2014**

There has been no new data since that suggests these problems have been resolved. Anecdotal evidence suggests that the pathways for some single biomarker tests such as BRCA and EGFR are now well-established at the local level in some areas, but that access to newer tests – and panel tests in particular – remains poor.

At the time of the analysis in 2015, it was felt that the most significant cause of this gap was unclear funding arrangements and the lack of a nationally-led approach to molecular diagnostic testing, together with limited awareness of molecular diagnostic testing among health professionals. Recognising this, the 2015 Cancer Strategy for England called for a new approach – with regional hubs coordinating access to tests across the country – and a yearly review of molecular diagnostics capacity.
This approach has now been taken forward by NHS England and a National Genomic Medicine Service is set to launch in October, with seven regional Genomic Laboratory Hubs (GLHs) at its core. We support this approach; however, there is more to do to ensure it succeeds and remains fit for the future. It is also crucial that there is an ongoing, coordinated effort to support uptake of molecular diagnostic testing and targeted medicines.

**ADDITION AND AVAILABILITY OF MOLECULAR DIAGNOSTIC TESTS**

**ADOPTING NEW MOLECULAR DIAGNOSTIC TESTS**

In the past, decisions about which molecular diagnostic tests for cancer to use in the NHS have largely been reactive, driven by NICE appraisals of targeted medicines. Moreover, the approval process for companion diagnostics has not been well-aligned with regulatory approval for the associated medicines.

As part of the new Genomic Medicine Service, NHS England is developing a National Genomic Testing Strategy. This will contain a list of tests which will be offered routinely on the NHS, via the seven GLHs. We support this approach, which will ensure a wide and standardised range of tests are available across the country.

We welcome NHS England’s commitment to update the Strategy on an annual basis, and to work with colleagues in the devolved nations to “implement a clear and transparent process for the future evaluation of new genomic tests.” We would welcome further clarity on this point, and how NHS England intends to ensure the health service can respond quickly to new advances in diagnostic technology, molecular pathology and targeted medicines. The process should prioritise:

- Ongoing dialogue with the research community and with industry as part of regular horizon-scanning
- Alignment with NICE’s assessments of specific targeted medicines
- Ensuring that new panel tests are adopted where these can replace existing individual molecular tests, or can incorporate a greater number of tests.

**NHS England should clarify how they will update the National Genomic Testing Strategy in the future, including how they will engage with external experts and other bodies such as NICE.**

**SINGLE TESTS, PANEL TESTS OR WHOLE GENOME SEQUENCING?**

The most appropriate testing mechanism will depend on the specific cancer type being investigated. However, in the immediate term we encourage DHSC and NHS England to focus on improving access to panel tests via the Genomic Medicine Service. Panel tests require fewer samples to be taken than individual biomarker tests, which has a positive impact on patient experience and can also be cost saving. Panel tests also have a much quicker turnaround time than WGS, since analysis is more straightforward.

In the longer term, however, there is likely to be a growing emphasis on WGS, as a greater number of identifiable molecular and genetic variations become clinically relevant. This approach was advocated in the Chief Medical Officer’s 2017 Annual Report ‘Generation Genome’, and we support continued investment in long-term WGS capacity in the NHS for both clinical and research purposes.
However, when conducting molecular analysis to guide a cancer patient’s treatment options, there are several reasons why WGS is unlikely to be the best option in the short term:

- The quickest return of WGS to date is three weeks. For most patients this is too long to be clinically justifiable, especially for those with rapidly advancing disease and in the context of the existing 62-day referral to treatment target.
- There are currently major gaps in key staffing groups, including bioinformaticians (who collect and analyse genomic and other complex biological data), so services could struggle to meet a growing demand.
- WGS is currently more expensive than panel-based tests.

Reflecting these points, the 2015 Cancer Strategy argued that a WGS-led approach was “not yet appropriate for most types of cancer other than in a research setting.” Attempting to move to a WGS-centred system too quickly would risk failing to provide the best quality care to patients in the here and now. The move towards larger panels and WGS must be done on a timescale that is clinically-led and brings the greatest possible patient benefit.

We therefore advocate a parallel capability development approach, with panel tests used as the default tool while WGS capacity increases and the time/cost burden decreases. Single biomarker tests should also be used in specific cases, for example where a panel test’s longer turnaround time makes it inappropriate because of anticipated rapid disease progression.

We are pleased to see the expectation set out in the “final draft” National Genomic Test Directory for Cancer that testing will be delivered “wherever possible” on panels. Likewise, we welcome the flexible approach to the supplementary use of single biomarker tests outlined in the directory where there is a need for rapid turnaround or high-sensitivity testing. This ambition and pragmatism must be carried forward into the final version of the Directory for 2018/19, and future updates.

**DSHC and NHS England should use the Genomic Medicine Service launch and development of a Genomic Testing Strategy as an opportunity to promote equitable patient access to panel tests. They should ensure they continue to balance preparing for the future integration of Whole Genome Sequencing into mainstream services, and serving the needs of patients today through the provision of less complex diagnostic tests.**

**PRECISION MEDICINE RESEARCH**

Research is the key to improving outcomes for people affected by cancer. Many of the newest medicines entering clinical trials are targeted treatments and the expansion of molecular diagnostic provision through the Genomic Medicine Service offers significant research opportunities. The NHS should put this ambition at the heart of the Service’s operation and ensure the following:

- Results from molecular diagnostic testing processed under the new Service should be used to flag patients who are eligible to participate in clinical trials. This could make access to clinical trials more equitable across the country.
- The data collected through the Genomic Medicine Service should be used to its full potential to drive progress in research. This will require not only strong data security safeguards, but also ongoing communication with patients and the public to build awareness of how their data can be used to improve healthcare services and drive scientific advances.

**DHSC and NHS England should ensure the Genomic Medicine Service is used to enhance precision medicine research, including improving patient access to clinical trials for targeted medicines.**
UPTAKE OF MOLECULAR DIAGNOSTIC TESTS

WORKFORCE

It is crucial that there is adequate provision of key workforce roles specific to precision medicine. Previous research has found major skills gaps in the UK for such roles, including bioinformaticians, clinical geneticists, and genetic counsellors\(^27\). The gap in the genomics workforce was highlighted in Health Education England’s Cancer Workforce Plan (Phase 1), in which HEE committed to ensuring the NHS has “sufficient staff with the right skills to deliver access to cancer genomic analysis [and] the stratification of treatments” and to undertake further analysis\(^28\).

This work should be undertaken as soon as possible, including wide engagement with clinical experts – as was also recommended by the Science and Technology Select Committee\(^29\). Initially, this work should focus on addressing short-term shortages such as those noted above, in order to bolster the NHS’ immediate capacity to deliver a more genomics-focused approach to patient care.

There are also a number of ongoing explorations of the long-term implications of genomics for the NHS workforce, including the Topol Review and Phase 2 of HEE’s Cancer Workforce Plan. It is crucial that these pieces of work are well-aligned, and that they set out a clear set of actions to ensure medical students are attracted to genomics-related specialties to secure the long-term workforce pipeline on which the Genomic Medicine Service will be reliant\(^30\).

Health Education England should complete detailed genomics workforce planning as soon as possible, with wide engagement from clinical experts, to ensure adequate provision of the key workforce roles required for a more genomics-focused approach to patient care.

FUNDING

The gap in access to molecular diagnostic testing CRUK identified in 2015 was largely attributed to unclear funding arrangements. Since there was no funding specifically set aside for molecular diagnostic tests, it was often paid for via local pathology or oncology budgets and covered under broader payments from the NHS England National Tariff Payment System\(^31\). This uncertainty was cited as a major barrier to uptake\(^32\).

The 2016/17 Tariff moved towards national commissioning; six molecular tests for cancer were listed and the cost of providing them directly covered under NHS England’s standard contracts with hospitals. This was a positive step in terms of clarifying funding arrangements for some of the most widely used molecular tests. CRUK worked with ABPI, BIVDA and NHS England to develop a factual guide aimed at helping to inform clinicians and pathologists of these new arrangements\(^33\).

Under the new Service, payment to the GLHs will initially continue to be administered at the local level (with the exception of WGS, which will be directly reimbursed by NHS England), with hospitals’ costs covered as part of broader national tariff payments. We are concerned that this could increase the workload for clinicians at the local level, and continue the uncertainty about funding flows which restricted access in the past.

We are aware that NHS England are planning to pay directly for all cancer molecular diagnostic testing by 2021. We welcome this commitment and urge NHS England to do this as soon as is feasible – prior to 2021 if this is possible.

NHS England Specialised Commissioning should begin paying for all cancer genomic testing directly, as soon as is feasible. This would streamline the process and reduce uncertainty.
DATA

The NHS holds several world-leading data sources. However, there is more still to be done to improve how they are used to drive progress. While the uptake of targeted treatments is recorded in Public Health England (PHE)’s Systemic Anti-Cancer Therapy (SACT) dataset, there is limited data on the uptake of molecular diagnostic tests.

There is currently insufficient data available to build up an accurate picture of molecular diagnostic activity across the country and allow for assessment of whether patients are missing out (and how many if so). This must be a priority for the new Genomic Medicine Service and the development of the new National Genomics Informatics System (NGIS).

By tracking molecular diagnostic activity in this way, any existing or emerging discrepancies in access or uptake within each of the GLH regions across England can be identified and rectified. NHS England and PHE should collaborate on this and should build on existing data held by bodies including PHE and the UK Genetic Testing Network (UKGTN). This data should be used to ensure there is equitable and appropriate patient access to tests – including panel tests and WGS – across the country.

**NHS England and PHE must ensure uptake of molecular diagnostic tests is monitored accurately. The NGIS should be used to build up a picture of molecular diagnostic activity within each of the GLH regions, so that any variation in uptake can be quickly identified and investigated.**

PATIENT AND CLINICIAN AWARENESS

Research has found a significant gap between the level of public understanding of genomics, and how scientists and health professionals generally discuss genomics. This threatens to undermine the success of precision medicine in the NHS by damaging public trust. This is particularly true for data: research has found that the public consider genomic data more risky than other forms of medical data.

It is vital that patients are made aware of how their data could be used, both for their individual care and in a research context, to improve healthcare and services. NHS England must consider how to increase public understanding and acceptance of genomic medicine, to ensure patients will consent to share their genomic data in this way and to facilitate a research environment which can promote further advances in genomic understanding which will ultimately benefit patients.

It is also essential that health professionals receive the appropriate education, training and resources to build their knowledge of precision medicine. Clinician awareness is fundamental to ensuring molecular tumour analysis is embedded into patients’ care pathway and so delivering patient access to molecular diagnostics (and subsequent targeted medicines).

Health Education England’s ongoing Genomics Education Programme has helped to advance healthcare professionals’ knowledge in this area, but from March 2018 will see its budget reduced to £1 million per year, compared to the average £5 million per year over the period 2014-18. Building on this Programme, NHS England and HEE should work with medical schools and Royal Colleges to help inform the development of professionals still in training, and ensure short course options are available for professionals already in the workforce.

Appropriate tools should also be provided to assist clinical decision-making. For example, we welcome plans to develop a tool within the new National Genomics Informatics System, to signpost clinicians to the appropriate diagnostic tests based on clinical information about the patient. This should help to promote equal access to individual tests across the country.
NHS England and DSHC should continue to work with additional stakeholders, including Health Education England, to improve awareness and understanding of genomic healthcare among healthcare professionals and the wider public.

For further information or to discuss this statement please contact duncan.sim@cancer.org.uk

REFERENCES


9 Ibid


31 Concentra (2015), op. cit.
33 Ibid