MOLECULAR DIAGNOSTIC PROVISION IN ENGLAND

FOR TARGETED CANCER MEDICINES (SOLID TUMOUR) IN THE NHS

A report for Cancer Research UK by Concentra

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CONCENTRA

CANCER RESEARCH UK

CONTENTS

SUMMARY AND RECOMMENDATIONS

We are now in an era where medicines are targeted at genetic mutations and other biomarkers in a patient's cancer. These targeted medicines can improve outcomes for certain patient groups, providing greater progression free survival or overall survival and avoidance of undesirable side effects from treatment that may not work for them. Some targeted medicines are already available on the NHS with many more in the pipeline. Although at present many cases of cancer will become resistant to targeted medicine and resume their growth, it is clear that this area is key part of the future for cancer drug treatment.

Molecular diagnostic tests assess the makeup of a patient's cancer to help identify the best course of treatment, including whether that patient is eligible for a targeted medicine. They can also be used to identify if a patient could be suitable to participate in clinical research and also as prognosis tools. It is therefore important that all patients that could benefit receive molecular diagnostic tests to ensure they get the best treatment for their cancer and that all appropriate options are explored.

Molecular diagnostic testing has been available in the NHS for some time. However, in England it has been shown previously that access to testing has been variable[i]. A commitment to develop a national commissioning structure for molecular diagnostics was made in the 2011 cancer strategy for England[ii]. However, it seems little progress has been made to improve equal access to these tests[iii]. This type of testing is becoming standard of care for patients internationally[iv], and if the NHS falls behind in this area, it could have an impact on our cancer outcomes and on the UK's position as a leader in clinical research.

Cancer Research UK commissioned this work to understand the evidence around provision of a subset of molecular diagnostic testing in England. While testing is done for a variety of reasons, this report focuses on molecular diagnostic testing for solid tumours for which an approved targeted medicine is routinely available on the NHS. To undertake this work a survey was sent to all labs that conduct testing across England.

In 2014:

- Over **24,000** molecular diagnostic tests were not undertaken, based on estimated demand in England[1].
- 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[2] 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.
- There was no gap in melanoma testing – important lessons can be learned from this case study.

Between 2011 and 2014, testing activity in England increased by 51% per year for lung cancer, colorectal cancer and melanoma collectively. As this is a snapshot, it is likely that activity has changed since then. However, it is very unlikely that demand has been met.

A lack of funding is seen as the most significant cause of the gap in molecular diagnostic testing, along with poor awareness of targeted medicines and associated molecular diagnostic testing among clinicians and multi-disciplinary teams (MDTs). This can have an impact on cancer outcomes. Depending on cancer indication and medicine, patients

[1] Data on incidence and the associated histological subtype was provided by Cancer Research UK Statistical Information Team. From this, demand was calculated by estimating disease stage and associated line of treatment with the Cancer Research UK stratified medicine team and interviews with oncologists. Only molecular diagnostics associated with regularly funded medicines in England were included.

[2] This does not account for patients with co-morbidity that could potentially make treatment, and therefore testing, not clinically appropriate.

can experience up to 10 months extra progression free survival (disease control) through having targeted medicines, and potentially better overall survival.

Most labs that responded use tests that produce individual molecular biomarker results (e.g. an EGFR result), which are relatively cost-effective when a single biomarker result is needed. However, some labs are using panels, which provide results for multiple molecular biomarkers for one sample. As research identifies new targetable mutations and new tests are developed to detect them, panels could be broadened and become the standard of testing. The use of panels is clearly the future and these will become more cost-effective as further biomarkers become clinically relevant (i.e. a targeted medicine is available for that indication). It is therefore important that in providing a solution to the current gap in testing, support is also provided to 'future-proof' the service to account for the emergence of new, targeted medicines that are in the pipeline.

It is estimated that £13.32 million per year is required to fund current testing activity for solid tumours in England, to bridge the gap to meet demand and to provide a 'future proof' service for molecular diagnostic testing[3]. This figure is likely to be an underestimate, as it does not account for costs of equipment, training, hospitalisation costs due to toxicity and test development and validation, which vary significantly from lab to lab, and should therefore be seen as a starting point.

Provision of molecular diagnostic testing will improve outcomes for patients, and a solution to fill the gap in testing is needed urgently. But this is also crucial to provide a service that makes the NHS fit for the future, which leads the way in providing the most up to date care to all patients as new research findings continue to emerge.

RECOMMENDATIONS

- NHS England should make funding available to support the adequate provision of molecular diagnostic tests, now and in the future, to ensure all eligible patients have access to these tests in a timely manner.
- Commissioning of cancer molecular diagnostics in the NHS should be coordinated at the national level by NHS England:
  - National commissioning policies should be developed to ensure equal access to high quality tests, and that results are provided in a timely manner to inform clinical decision making.
  - Policies should be suitably flexible to enable labs to move from individual tests to panel-based tests as these become cost effective with minimal impact to reimbursement.
  - Leadership at the national level within NHS England should proactively support the uptake of clinically relevant biomarkers, horizon scan for emerging biomarkers and support their adoption when appropriate.
- Public Health England, through the National Cancer Intelligence Network, should routinely collect and report data on cancer molecular diagnostic activity in national datasets, and these data should be linked to other data on chemotherapy, such as the SACT dataset.

[3] As there is no formal commissioning or payment structure for molecular diagnostic testing in England, any current spending in the NHS for this activity is not taken into account.

INTRODUCTION

Many targeted cancer medicines have already been approved for routine use in the NHS and many more are in the development pipeline. It is therefore important that the right mechanisms are in place to ensure all patients that could benefit can access these medicines. A body of research is emerging which examines the superior impact of targeted treatment compared to standard chemotherapy in some cancers. 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[v].

Cancer molecular diagnostic testing techniques are used to analyse genetic mutations and biomarkers in a patient's cancer. Molecular diagnostics provide important information to help inform decision making on the best course of treatment, including whether that patient should have a targeted medicine. They can also spare patients from undesirable side effects of treatments that would not work well for them, and increase the range of treatment options available to patients. There is growing evidence that molecular diagnostics can be used as a prognosis tool in cancer patients – for example, certain molecular diagnostic tests can provide information about a cancer in its early stages and indicate whether aggressive early management will be necessary[vi]. Finally, some molecular diagnostics can be used to monitor treatment response and cancer progression.

Patients who do not receive molecular diagnostics cannot be considered for targeted medicines, as clinicians do not have all the information available to them to inform decision-making. As well as the potential impact on patient outcomes such as progression free (disease control) or overall survival, the impact on patient experience can be significant. Patients' choices may be limited as every treatment option will not have been considered, and they may experience side effects from chemotherapy that could have been avoided. In short, when eligible cancer patients do not receive molecular diagnostics they may miss out on the benefits that targeted medicines offer.

PURPOSE

Cancer molecular diagnostics play an important role in patient experience and outcomes. Therefore it is important to assess the extent to which they are being utilized within the NHS and determine whether there are any gaps in provision. Cancer Research UK commissioned this work to update the baseline of evidence for provision of cancer molecular diagnostics in the NHS and assess whether there is a gap in provision.

This is also timely as an independent cancer taskforce has developed a new cancer strategy for England, to which this evidence was submitted.

This report provides a view of current provision, demand, and the level of unmet demand for cancer molecular diagnostics across England. This report then assesses the consequences of the unmet demand and potential causes. Finally, the report assesses options to close the gap.

METHODOLOGY

To develop a view of current provision of cancer molecular diagnostic testing we sent a survey to 25 labs known to be part of the UK National External Quality Assessment Service's (UK NEQAS) molecular genetics quality assurance scheme which assesses solid tumour molecular diagnostic testing. The survey was also sent to an additional 31 labs known to provide cytogenetic or haematology testing and who may have recently developed molecular genetics services.

Based on experience, we hypothesized that the most significant gap in cancer molecular diagnostic testing would be found within solid tumour molecular diagnostic testing. Therefore, while effort was made to collect data on cytogenetic and haematology testing, we asked labs to prioritise providing data for solid tumour molecular diagnostic testing which forms the basis of this report.

- Overall for solid tumour testing, 15 out of 25 labs responded, covering a catchment population of 34.3 million out of a total population of 53.5 million[4].

All labs were asked to provide data on catchment population, longitudinal data on test volume per tumour per test, reimbursements, referral volumes, test platforms (including information on panels, if used), turnaround times, retest rate, and cost. A list of the data requested can be seen in the Appendix. This information was requested for molecular diagnostic tests on solid tumours as well as cytogenetic and haematology tests (data on cytogenetic testing was provided by 13 labs; data on haematology tests was provided by 10 labs.)

The survey was distributed via email in February 2015 and remained open for collection of results for two months. The survey was closed on April 12th, 2015. Responses were collated into a single database for analysis. Responses on test volumes were scaled up on the basis of the catchment population vs. country population to estimate total provision of testing within England[5].

Significant effort was made to collect responses from labs conducting the highest volumes of solid tumour cancer molecular diagnostic tests. Labs with the highest volumes were identified through engagement within the molecular diagnostic testing community – most notably heads of labs – and responses were received from all labs identified within the community as major solid tumour testing sites, including the labs in England selected to provide solid tumour molecular diagnostic testing for Cancer Research UK's Stratified Medicine Programme.

Labs that did not respond either chose not to, or do not conduct molecular diagnostic testing for cancer.

Current testing demand was established through desk research[vii] and interviews with clinicians and healthcare statisticians[viii]. For each funded lung, melanoma, and colorectal targeted medicine in England, the team determined the population and associated number of patients, then considered histological subtype, disease stage and other testing guidance as advised by NICE to estimate a subpopulation requiring associated cancer molecular diagnostics. The impact of non-cancer related morbidity on test volume (potentially making treatment and therefore testing clinically inappropriate in some patients) was not factored into estimates of current demand for tests.

Gaps in provision of cancer molecular diagnostics were determined by subtracting current provision from current demand using 2014 provision and demand figures (based on 2012 incidence figures – as incidence in these cancers is currently increasing and projected to increase[ix], the estimated gap in provision is likely to be underestimated).

Consequences of the gap in cancer molecular diagnostic testing were assessed on the basis of varying patient journeys and quantified by comparing progression free survival (disease control), as reported in treatment studies, of the average patient receiving and not receiving targeted medicines as determined in clinical trials.

Causes of the gap in cancer molecular diagnostic testing were developed on the basis of interview based fact finding, and options to close the gap were developed and assessed using data provided by labs through the survey (for example, cost per test).

[4] Catchment population was self-reported by labs. The catchment population of the associated Trust was used in cases where labs did not report a catchment population.

[5] This assumes no variance in molecular diagnostic testing rates throughout England. Evidence suggests there is in fact variance in testing access; however, we have ensured coverage of major testing labs as identified by heads of labs within the testing community, thus we believe this scaling of test volume is conservative as it is likely that this assumption over-estimates testing provision.

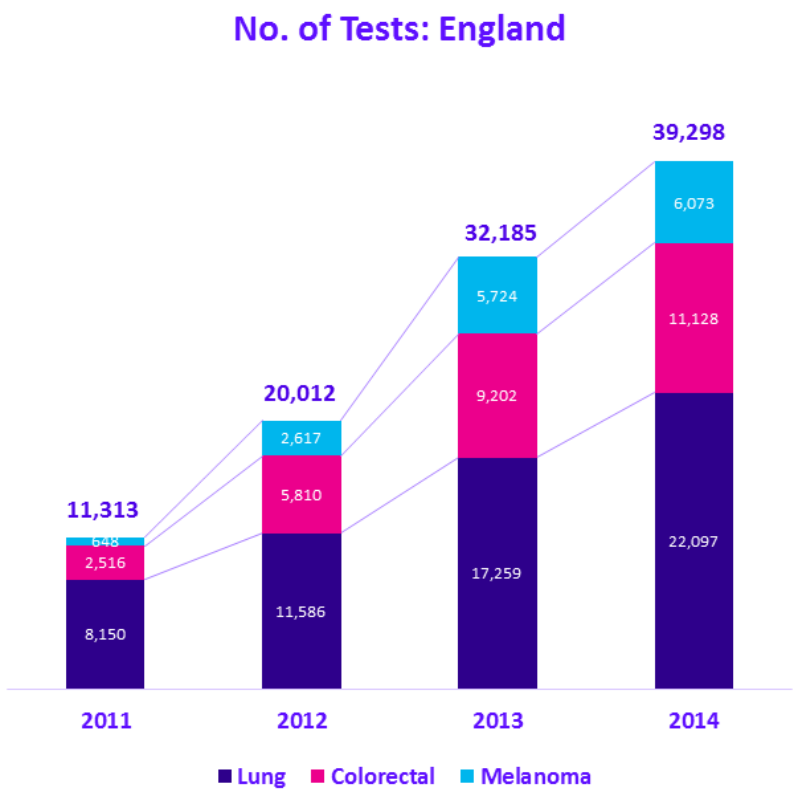
THE GAP IN MOLECULAR DIAGNOSTIC TESTING FOR SOLID TUMOURS

Solid tumour molecular diagnostic testing for lung, colorectal and melanoma cancer patients in England is growing. 39,298 tests were conducted for NHS practice in 2014 in England. However, for the same year and population there was demand for 59,294 single biomarker cancer molecular diagnostic tests to assess cancer patients as per NHS guidelines, leaving a substantial gap in testing.

This gap means that, due to some patients having multiple tests e.g. both EGRF and ALK testing for lung, at least 15,929 patients in England in 2014 missed out on molecular diagnostic testing (see "Consequences of the Gap" section page 16 for further detail). For these patients, this means every option was not explored and the treatment they received may not have been optimal. If they were tested, some of these patients would have fit the criteria for targeted medicines and could have benefited from them. It is estimated that 3,552 patients that could have accessed targeted medicines if testing volume met demand.

PROVISION OF MOLECULAR DIAGNOSTIC TESTING

Lab survey results from England indicated that 39,298 solid tumour molecular diagnostic tests were conducted for patients in 2014. These tests were used to inform whether patients should receive targeted lung, colorectal, and melanoma cancer medicines approved by NICE (England), as well as medicines listed on the Cancer Drugs Fund[6]. Total test volume has steadily grown at an average of 51% per year since 2011, with the majority of testing on non-small cell lung cancer.



Solid tumour cancer molecular diagnostic provision figures were provided by 15 labs via a lab survey. Figures from England have been scaled up by 1.56. Scaling was conducted to create a full picture of testing across these entire countries. Scaling factors were determined by dividing the total catchment population of all labs within England into the total population. Catchment population was self-reported by 12 labs in the survey. Catchment for the remaining 3 labs was estimated by using the catchment of the Trust in which the lab resides. Clinically relevant biomarkers reported were defined as those associated to targeted medicines for melanoma and lung and colorectal cancer approved by NICE (England) as well as medicines listed on the Cancer Drugs Fund. These include EGFR and ALK for lung cancer, KRAS and NRAS for colorectal cancer, and BRAF for melanoma.

[6] See "Consequences of the Gap" section for patient numbers.

In 2014 the pharmaceutical company funding colorectal testing made the decision to reduce the testing they funded to a smaller patient subpopulation; it is expected to show in the England data from 2015. NHS England does not explicitly fund molecular diagnostic tests, and there is no fee-per-test tariff. To date testing has been paid through three channels:

- Local Trust funding (e.g. pathology or oncology budgets), which does not enable labs to control cost as funds are not allocated to specific tests and, if ordered, must be conducted despite type, cost, and budget impact
- Grant and research funds, which are not available at all testing locations and may be restricted in their use
- Pharmaceutical companies, who have funded some labs to conduct cancer molecular diagnostic tests for a limited period (termed "pump priming") as their associated medicines have been introduced into the market

EMERGING CANCER MOLECULAR DIAGNOSTIC TESTS

Reported test provision figures only include tests associated to targeted cancer medicines approved by NICE as well as medicines listed on the Cancer Drugs Fund. However, survey data indicated approximately 4,600 additional tests were conducted to further assess patients. For example, while only EGFR and ALK tests are required for certain lung cancer patients, survey results showed BRAF and PIK3CA tests are also ordered by some practitioners.

There are also use cases for cancer molecular diagnostics beyond assessing whether a patient should receive a targeted medicine, for example, MSI tests are used to determine whether patients' colorectal cancer may be hereditary, and to assess patients for chemotherapy.

Additionally, there are several cancer molecular diagnostics currently in research but expected to emerge into practice with the introduction of new targeted medicines. For example, MET testing is indicated in the label for two medicines currently being evaluated.

This raises several important questions: Who is responsible for horizon scanning for emerging tests? Who is responsible for collecting the evidence? How do emerging tests become a new standard? How do they become funded?

Additional molecular diagnostic tests were reported as being used in practice for lung, melanoma, and colorectal cancer assessment: lung tests: KRAS, BRAF, PIK3CA; melanoma tests: NRAS, KIT; colorectal tests: BRAF, PIK3CA, MSI.

DEMAND FOR MOLECULAR DIAGNOSTIC TESTING

In 2014, there was demand for 59,294 cancer molecular diagnostic tests in England. 61% of total demand for testing is for tests associated with lung cancer, 37% for tests associated with colorectal cancer and 2% for tests associated with melanoma. This equates to an estimated 35,588 patients requiring molecular diagnostic tests.

Variation in testing demand between cancer types is determined by incidences, histological subtype, disease stage and the number of associated tests. Total demand for testing increases with the introduction of new clinically relevant tests, often associated with new medicines, and whether those tests are already performed to inform selection of other medicines (see "Gap in molecular diagnostic testing" subsection below for additional explanation).

Patient Population	Incidence	Histological Subtype	Disease Stage	Line of Treatment	Required Molecular Analysis	Testing Demand
Lung – NSCLC	34,889	All	III-IV	First Line	EGFR	23,131
Lung – NSCLC	34,889	Non-squamous	I[7]	Second Line	ALK (1 test in total)	12,790
Colorectal	36,387	All	IV[8]	Second Line	KRAS, NRAS*(2 tests in total)	21,832
Melanoma	11,850	All	III-IV	First Line	BRAF (1 test in total)	1,541
					TOTAL	**59,294**

Table 1: Calculations for number of individual gene tests required for the above disease indications based on current approvals and guidelines.

** Extended RAS testing for CRC (KRAS + NRAS) has been factored in.*

Patient Population	Incidence	Histological Subtype	Disease Stage	Approved for Use	Testable Population
Lung (EGFR) – NSCLC	34,889	85%	78%	100%	23,131
Lung (ALK) – NSCLC, non-squamous	34,889	47%	78%	100%	12,790**
Colorectal (KRAS/NRAS)	36,387	100%	30%	100%	10,916
Melanoma (BRAF)	11,850	100%	13%	100%	1541
				Total	35,588

Table 2: Figures used in determining testable population from total incident population.

This table records the calculations behind the estimates of the total testable patient population for each disease indication in England based on incidence, % of patients with the relevant histological subtype, disease stage and associated therapies that are available through NICE approval or the Cancer Drug Fund. Incidence figures are from Cancer Research UK. All remaining figures have been extracted from NICE guidance.

***The two NSCLC testable populations overlap. This overlap (of 12,790 patients) has been removed when estimating total testable patient population and patients eligible for targeted cancer medicine.*

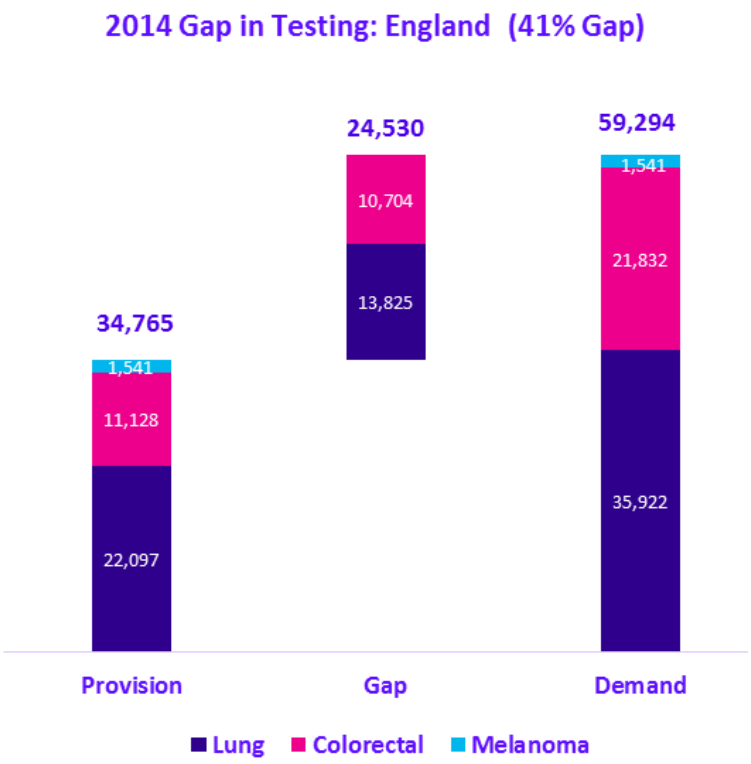
KRAS mutation analysis in lung cancer has been identified as an area of significant variability in both laboratory practice and clinical opinion. Whilst the presence of a KRAS mutation is not currently considered an independent predictive or prognostic marker, determining the KRAS genotype is necessary to inform clinical trial eligibility for patients with lung cancer. After careful deliberation it has been excluded from the calculation of testing demand in order to restrict this to what is absolutely necessary for delivering currently available treatments and standard of care.

[7] Discussions with oncologists and pathologists suggest there are differences in opinion as to when ALK testing should take place i.e. at stage I or stage III-IV within the clinical community.

[8] Demand estimated per NICE guidance; however we are including patients with stage IIB and above being tested for KRAS and NRAS mutations as there is a high probability of the patients progressing to stage IV. There is value in having data available as tumours are not typically re-biopsied.

GAP IN MOLECULAR DIAGNOSTIC TESTING

Subtracting 2014 provision of testing (34,765 tests[9]) from 2014 demand (59,294 tests) reveals a gap in testing provision of 24,530 tests. This unmet testing demand means that patients are not being considered for routinely available targeted medicines from which they could benefit, and therefore may be missing out on treatment that would be optimal for their cancer[10].



The gap in testing has been calculated by subtracting estimated testing demand from testing provision as reported earlier in this report.

Dividing the gap estimate by the demand estimate shows a gap of 41% in England. In absolute numbers the gap is largest in lung cancer. There was no evidence of a gap in melanoma testing – an impressive fact from which important lessons can be learned (see "closing the gap in melanoma testing" case study below).

[9] This figure is lower than the reported total provision of tests in 2014 of 39,298 due to catch up testing on melanoma, which has been removed to keep this estimate of the testing gap conservative; see "closing the gap in melanoma" case study below for additional detail

[10] Test volume is calculated with numbers populated in the survey for NICE approved and CDF listed medicines.

CASE STUDY: CLOSING THE GAP IN MELANOMA TESTING

In February 2012 BRAF testing became clinically relevant to assess patients with stage 4 malignant melanoma following approval of a targeted medicine for this indication. This created a demand over the next 12 months for 1,541 BRAF tests in England. Provision data shows that testing began before the associated medicine became available, and no gap in testing is evidenced in 2012, 2013 or 2014 data. These results were achieved through adequate funding and pre-launch capacity development, and catalysed by the small size of the melanoma clinical community and significant support it provided.

In anticipation of medicines launch in 2012, a pharmaceutical company implemented testing recommendations from the melanoma clinical community, including funding establishment of a quality assured network of labs in 2011 prior to launch and funding testing once the medicine was available. Thus testing capacity was already in the system as soon as testing became clinically relevant and funding for the test – from the pharmaceutical company – was immediately available. This explains high levels of testing prior to launch of the associated targeted medicine and ensured testing demand was met.

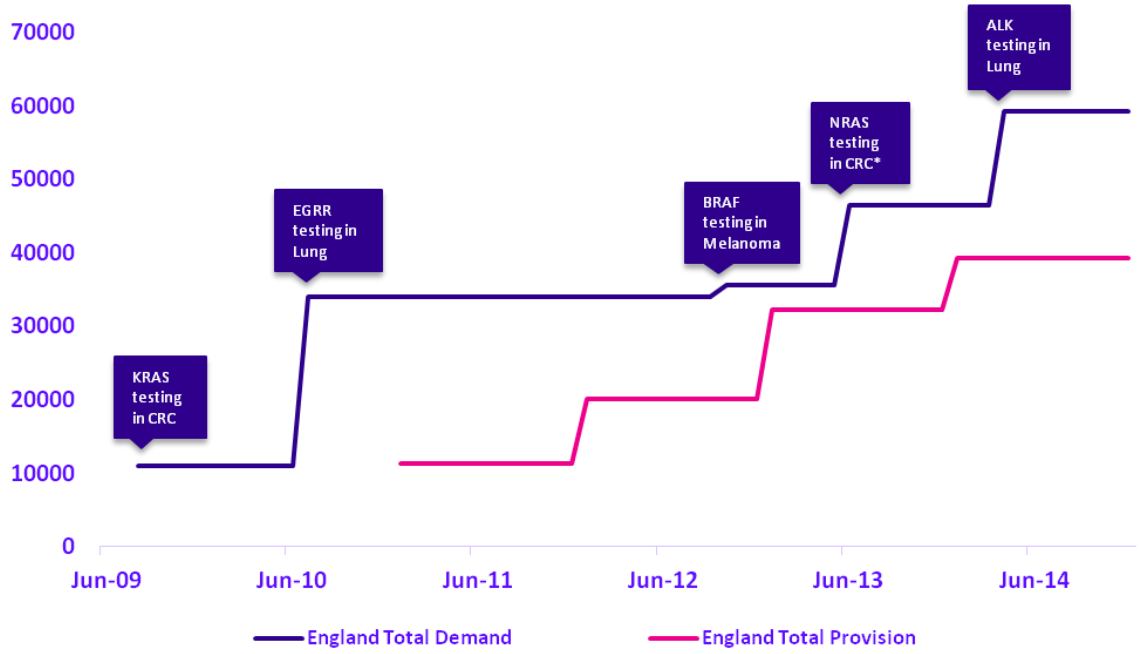
The success of this funding and pre-planning was catalysed by the small size of the community and the support it provided. Patients with malignant melanoma are treated by a small number of specialist multi-disciplinary teams. This is beneficial as the size of the community enabled rapid communication of pre-launch recommendations, support for implementation, launch awareness and awareness of the availability of funding for the test. It has also been noted that the strong knowledge base within the community enabled rapid momentum and subsequent improvements in the testing pathway. For example, an expert panel discovered that patients with malignant melanoma as early as stage IIB could benefit from testing, and developed an algorithm which was successfully implemented into the patient pathway.

See Gonzalez, D., "BRAF mutation testing algorithm for vemurafenib treatment in melanoma: recommendations from an expert panel", British Journal of Dermatology.

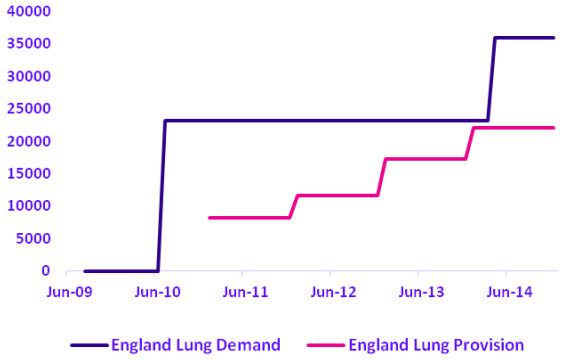
As already noted, demand for cancer molecular diagnostics grows when a new targeted medicine with a new associated biomarker is funded, or when a biomarker becomes clinically relevant for a new patient subpopulation for a regularly funded targeted medicine. A testing gap emerges when provision of testing for a biomarker does not increase sufficiently to meet this demand. For example, EGFR testing became clinically relevant in 2010 to assess patients for a new targeted medicine for lung cancer. In England, demand for this test "jumped" to include the relevant patient subpopulation – in this case all non-small cell lung cancer patients – amounting to about 23,000 tests per year. Supply of EGFR testing in lung cancer has grown since this point. However, although provision has increased, it still does not nearly meet the demand for testing. A similar gap is found in molecular diagnostic testing for colorectal cancer.

However, demand does not always increase with introduction of new medicines. Several additional targeted medicines for non-small cell lung cancer patients have emerged since the first medicine in 2010; these medicines also required an EGFR test to assess the same patients for suitability. Therefore demand for EGFR testing did not increase with the introduction of these new medicines because these tests were already conducted on the relevant patient population. Rather, the EGFR test results became more valuable for each patient, and they could now be used to assess patients for multiple targeted medicines, providing more options to patients and clinicians.

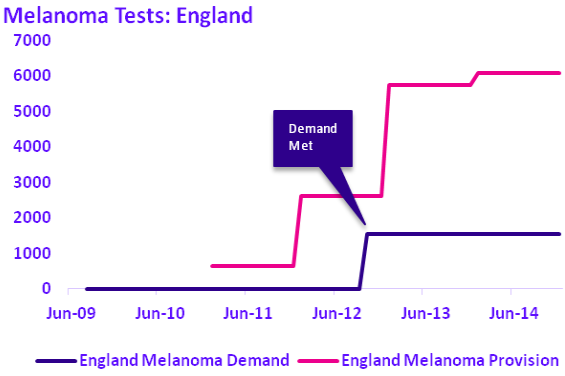
Provision and Demand: Number of Tests in England



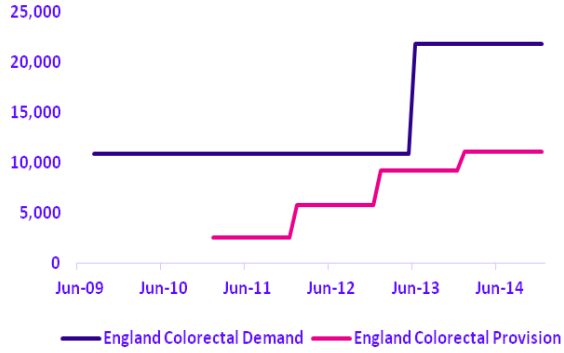
Lung Tests: England



Melanoma Tests: England



CRC Tests: England



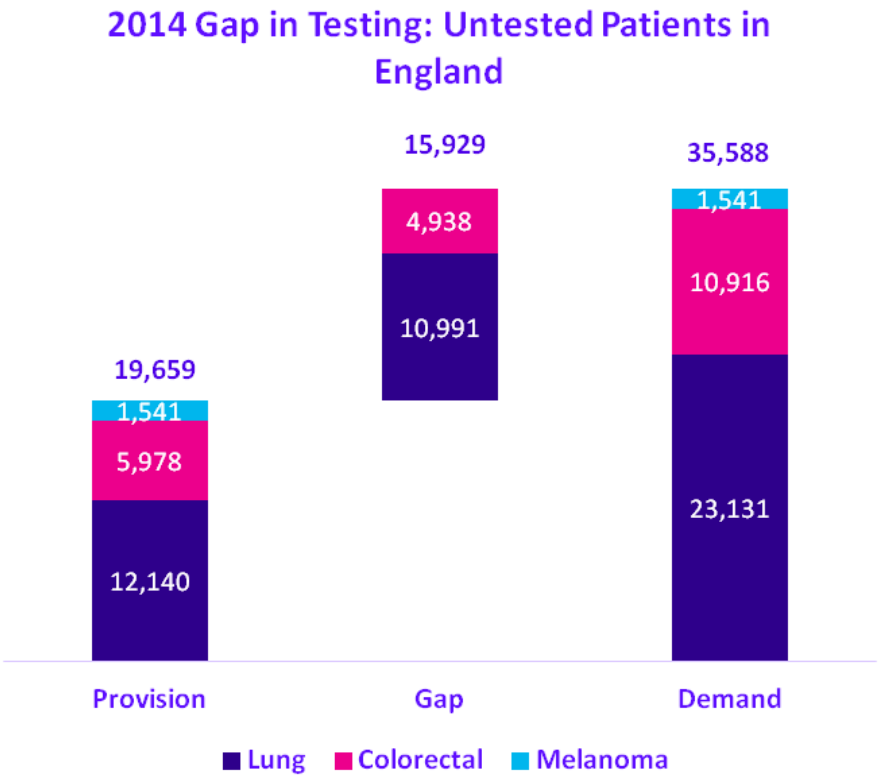
**Extended RAS testing for CRC (KRAS + NRAS) has been factored in from ~2013.*

The timeline for demand is based upon the approval of treatments by NICE or the Cancer Drugs Fund requiring each test. Provision figures are based on reported survey data from 15 labs across England and have been scaled to population level, as reported earlier in this report. Labs provided provision volume on an annual basis. This accounts for the step increases in the provision figures on the charts. The step increases in demand figures are due to the binary nature of test demand: before an associated medicine is regularly funded there is no demand for a test. As soon as an associated medicine is regularly funded there is a "jump" in demand equal to the size of the patient population eligible for the test based on the regulatory guidelines of the associated medicine. Melanoma provision is higher than demand as the initial back-log of testing is being addressed.

CONSEQUENCES OF THE GAP IN MOLECULAR DIAGNOSTIC TESTING FOR SOLID TUMOURS

The gap in cancer molecular diagnostic testing means that patients are missing out. Without molecular diagnostic tests all treatment options for a patient are not explored and therefore patients do not know whether they have had the best course of treatment for their condition. Patients who would have fit the profile for targeted medicines but do not receive molecular diagnostic tests to assess this also miss out on increased effectiveness associated with that treatment, including potentially fewer side effects, reduced hospital time[x], and ultimately extended progression free survival (disease control) or overall survival.

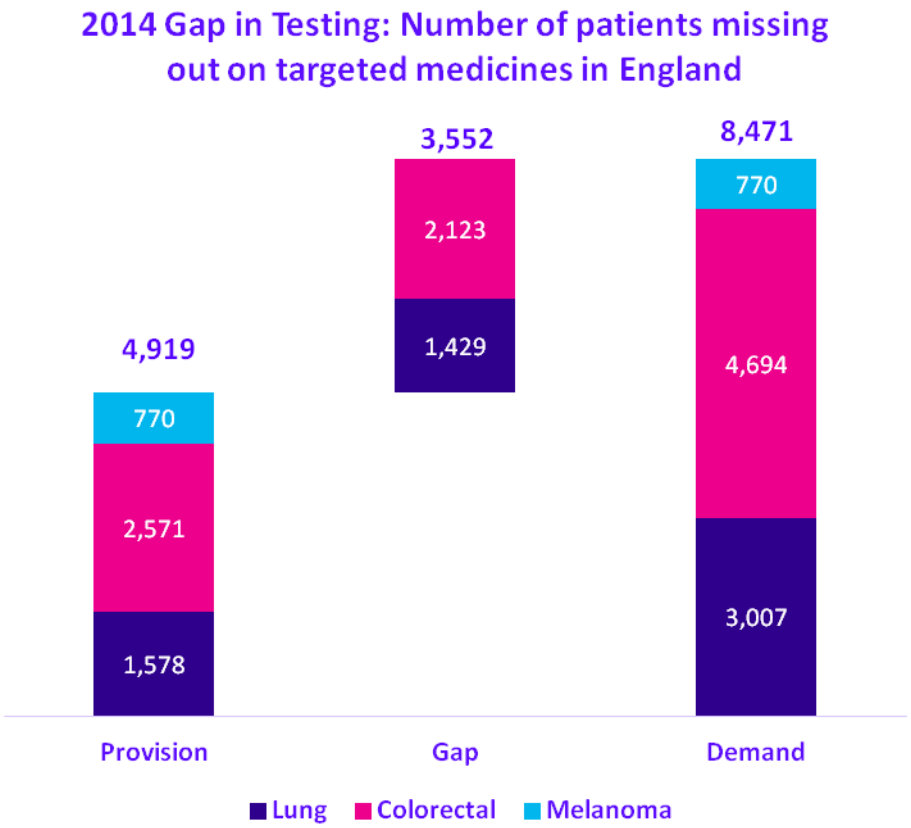
With an estimated 19,659 patients being tested and an estimated demand of 35,588 patients in need of testing there is an estimated untested population[11] of 15,929[12] patients missing out on molecular diagnostic tests in England– 45% of the patient eligible population in lung and colorectal cancers in 2014 (see figure below). These figures assume all testing for England's population was conducted within that country. The estimated gap in provision is likely to be underestimated as it is based on 2012 incidence figures and incidence in these cancers is currently increasing and are projected to increase[ix].



To calculate patient figures from test provision and demand figures reported earlier in this report the largest single test volume for each patient subpopulation was utilized. Because the same population within each cancer type will receive multiple tests i.e. both EGFR and ALK testing this is necessary to prevent counting patients twice (with the exception of melanoma, which only has one clinically relevant test). For lung cancer, EGFR test numbers were used; for colorectal cancer, KRAS numbers were used; for melanoma, BRAF numbers were used. This logic was applied to demand and provision figures. The gap is calculated by subtracting provision figures from demand figures.

[11] Defined as the number of patients whose incidence (2012 figures), histological subtype and disease stage require molecular diagnostics to consider them for routinely funded targeted medicines.
[12] There is overlap in testing for each tumour and to avoid duplicating patient numbers we have included numbers for EGFR testing in lung, KRAS testing for Colorectal and BRAF testing in Melanoma.

Based on mutation rates[13] it is estimated that there are 3,552 patients that could have received targeted medicines if the testing gap was closed[14]. This equates to 42% of the relevant patient population.



Test results for tested patients will indicate whether targeted medicine may be appropriate for each patient. To estimate this population the untested population has been multiplied by the rate at which patients tests results indicate eligibility for a targeted medicine. To be conservative, when a range is given we have used a low estimate (e.g. 13-20% of patients test positive for EGFR; we have used 13%). At least 13% of lung tested lung cancer patients and 43% of tested colorectal cancer patients are eligible for targeted medicines according to NICE guidance. 50% of tested melanoma patients are eligible for targeted medicine according to estimates provided by two practicing pathologists, including a specialist in melanoma molecular diagnostics.

3,552 patients in England could have received targeted medicines if the testing gap was closed

[13] For example, approximately 5% of NSCLC patients with Adenocarcinomas are ALK-positive and therefore eligible for the targeted medicine

[14] The untested population is multiplied by the percent who have the molecular aberration and then by the population who would receive treatment.

PATIENT CASE STUDY

The major reason behind patients not receiving molecular diagnostic testing is lack of funding for tests and lack of awareness by their oncologist or multi-disciplinary team (MDT) (see 'Closing the gap in molecular diagnostic testing' below). The hypothetical case study below follows four identical patients as their oncologists and MDTs experience these issues while selecting the course of treatment for their patients. Discussions with oncologists and pathologists have shown differing opinions as to when ALK testing should take place and when different methodology i.e. immunohistochemistry (IHC) or FISH should be used, demonstrating inconsistency in ALK testing.

All patients are non-small cell lung cancer patients that have not responded to first line therapy.

Patient A had an oncologist and MDT who decided to test their cancer for the ALK rearrangement at initial diagnosis (this is termed 'reflex testing').

Once relapse was confirmed following first line therapy, the MDT consulted the ALK test results.

Results indicated the cancer was ALK-positive.

Patient B had a molecular pathologist advising their MDT. The MDT decided not to test their cancer for the ALK rearrangement at initial diagnosis.

Once relapse was confirmed following first line therapy, the MDT decided to conduct an ALK test. The molecular pathologist knew where to send the sample and ensured results were obtained quickly.

Results indicated the cancer was ALK-positive.

Patient C's oncologist and MDT did not discuss testing their cancer for the ALK rearrangement at initial diagnosis.

Once relapse was confirmed following first line therapy, the MDT wanted to test their cancer for the ALK rearrangement, but they were unsure how long it would take to obtain a result and how much it would cost.

Their cancer was ALK-positive, but their oncologist and MDT did not know it.

Patient D's had a molecular pathologist advising their MDT. The MDT decided not to test their cancer for the ALK rearrangement at initial diagnosis.

Once relapse was confirmed following first line therapy, the MDT decided to conduct an ALK test.

Patient's condition deteriorated whilst waiting for test results.

Their cancer was ALK-positive, but their oncologist and MDT did not know it in time.

The patient was quickly moved onto a targeted medicine as a second line therapy. Body scans indicated 7.7 months of progression free survival (disease control) – the mean experienced by patients in a trial study.
http://www.nejm.org/doi/full/10.1056/NEJMoa1408440

The patient was moved onto chemotherapy as a second line therapy. Body scans indicated 3.0 months of progression free survival (disease control)– the mean experienced by patients in a trial study.
http://www.nejm.org/doi/full/10.1056/NEJMoa1408440

PROGRESSION FREE SURVIVAL IMPACT

One way of measuring the consequences of the gap in molecular diagnostic testing is through estimating foregone progression free survival (PFS) (disease control). Each targeted medicine confers a different benefit in terms of PFS; without access to cancer molecular diagnostic tests, patients are unable to be considered for targeted cancer medicines and therefore miss out on these benefits.

	Tumour	Untested Patients	Untreated Eligible Patients	Average PFS Increase (Months)[15]
England	Lung EGFR	10,991	1,428	9.7[xi]
	Lung ALK	2,834	85.02	4.7[xii]
	Colorectal	4,938	2,123	0.8 (~5)[15, xiii]
	Melanoma	0	0	4.2[xiv]

Table 3: Estimates of potential detrimental effect on PFS through patients not receiving appropriate molecular diagnostic analysis

It is important to note that progression free survival is only one method of measuring potential treatment benefit. Other benefits already stated include improved patient experience through exploration of all treatment options, reduced side effects; reduced time spent in hospital[xvv], and increased probability of response to treatment if the patient's tumour is appropriate for targeted medicine. Additionally, resistance to targeted medicines may develop over time, and the average progression free survival figures reported in clinical trials may disguise individual outlying patients who experience a sustained response to a targeted medicine. They may also not express the benefit of surviving to move to a subsequent line of a different novel medicine that may become available.

[15] PFS figures are based on those referenced within treatment studies by NICE, although emerging literature may show differences in PFS associated with some drug types. For example, Cetuximab for colorectal cancer is being re-reviewed by NICE based on new clinical evidence which shows PFS of between 3 – 7 months[xvi, xvii]. As the clinical evidence ranges from 3-7 months, an average of 5 months has been provided in the table alongside an average of the current PFS range stated within NICE guidance.

CLOSING THE GAP IN MOLECULAR DIAGNOSTIC TESTING FOR SOLID TUMOURS

Lack of funding is the most significant cause of the gap in molecular diagnostic testing. Funding is consistently cited as a limiting factor to the uptake of targeted medicines. A 2014 study by Cancer Research UK, the Royal College of Pathologists, and the ABPI Pharmaceutical Oncology Initiative which surveyed stratified medicine stakeholders revealed that stakeholders within and outside the NHS, providers and commissioners, and those within all agree that commissioning models are the most significant challenge to implementation of targeted medicine for NHS cancer patients. In a 2014, ABPI survey of clinicians and laboratory professionals 85% of respondents listed "reimbursement of diagnostics and drugs" as needed to achieve full implementation of molecularly targeted medicine[xvii].

The gap in cancer molecular diagnostic testing is also caused by limited awareness of targeted medicines and their associated molecular diagnostics. A 2014 survey of molecularly targeted medicine stakeholders focused on clinicians and laboratory professionals indicated limited awareness of molecularly targeted medicine – only 30% of respondents listed themselves as having "High" or "Expert" awareness of uses and applications of targeted medicine in their professional area[xix]. Testing will not occur if oncologists and MDTs do not order it, and they will not order it if they are not aware of it.

As already noted, some targeted medicines are funded and routinely available in England. However the molecular diagnostic tests required to assess patients for these medicines are not explicitly funded. Testing has been paid through local lab budgets, grants, and pump priming by pharmaceutical companies. While these funding channels have helped introduce and build capacity for cancer molecular diagnostics, none constitute a sustainable solution to close the gap:

- Local Trust funding is insufficient to keep up with rapid changes in testing technologies and volume
- Research and grant funds are not available to all pathology and genetics labs and are often restricted
- Pharmaceutical funding ("pump priming") eventually ceases once testing capacity is developed. Additionally, as more targeted medicines enter the market and use the same biomarkers, pharmaceutical companies will not be able to only fund biomarkers associated to their medicines as multiple companies will have medicines which use the same biomarkers. This has already happened for KRAS testing for targeted colorectal cancer medicines, and EGFR testing for targeted lung cancer medicines.

OPTIONS TO CLOSE THE GAP

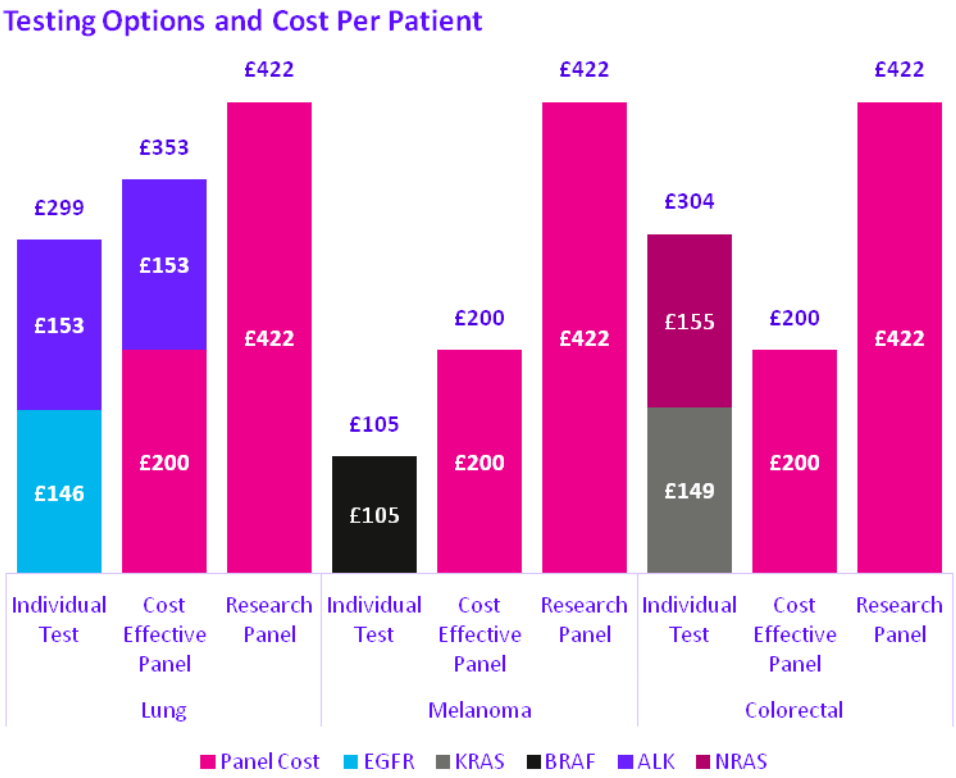
Fully funding cancer molecular diagnostic demand is the only sustainable way to close the gap. There are four options for closing the gap through funding different testing methods:

- Individual tests
- Panels with several clinically relevant (or soon-to-be clinically relevant) tests
- Larger "research" panels with clinically relevant tests and research tests
- Whole genome sequencing

At present while genome sequencing is cost-prohibitive and most of the information gathered in the process is not yet clinically relevant. Most labs currently use individual tests which produce a result for an individual molecular biomarker (for example, a BRAF result). However, labs are increasingly moving towards panel tests which provide results for multiple molecular biomarkers.

When results for a single biomarker are required individual tests are most cost effective: an individual NRAS or KRAS test costs around £150. However, as more biomarkers become clinically relevant panel testing becomes a more cost effective option: a panel that provides NRAS and KRAS results simultaneously costs about £200 (or £100 for each

result vs. £150 for each result if individual tests are used). Larger panels have been used especially in research and are able to return up to 60 results, lowering the cost per result to less than £10, although nearly all of the results provided are for research purposes and not yet clinically relevant, and collection of additional results carry additional cost -- for the panel itself and also for interpretation, storage and administration of the many results.



The cost of individual solid tumour molecular diagnostic tests was determined using mean reported costs for each test from 9labs (max: £300, min: £85). Cost effective panel costs for each tumour type was determined using mean reported cost from 4 labs (max: £200, min: £200). Research panel cost was determined using mean reported cost from 3 labs (max: £550, min: £300).

Note: Non-small cell lung cancer adenocarcinomas require ALK testing which currently needs to be conducted as an individual test; for this reason the cost of ALK testing has been added to the cost of "Cost Effective" panel. ALK testing is included on some research panels so the cost of the individual test has not been added to the cost of the lung research panel; however a panel-based ALK test it is not yet recommended for practice according to a practicing pathologist with specialty in lung molecular diagnostics.

While cost effectiveness is an important consideration in assessing options to close the testing gap, it is also important to horizon scan and to consider how options to fully fund testing will be effected as the targeted cancer medicine landscape changes. The number of clinically relevant biomarkers will expand as new medicines become regularly funded and as more uses are found for existing biomarkers. It is important that a commissioning policy creates appropriate incentives to ensure that testing is adequate in the short-run but also flexible in the long-run. In some cases individual tests are already more expensive vs. panel test, and as more biomarkers become clinically relevant eventually panel testing will be the most economical option for all tumour types. However, not all tests can be put on panels. For example, currently the best available ALK lung cancer test uses a methodology that is incompatible with panels. Therefore while panels will reduce testing cost as more biomarkers become clinically relevant, they cannot be the only solution and commissioning policy needs to be suitably flexible to accommodate this.

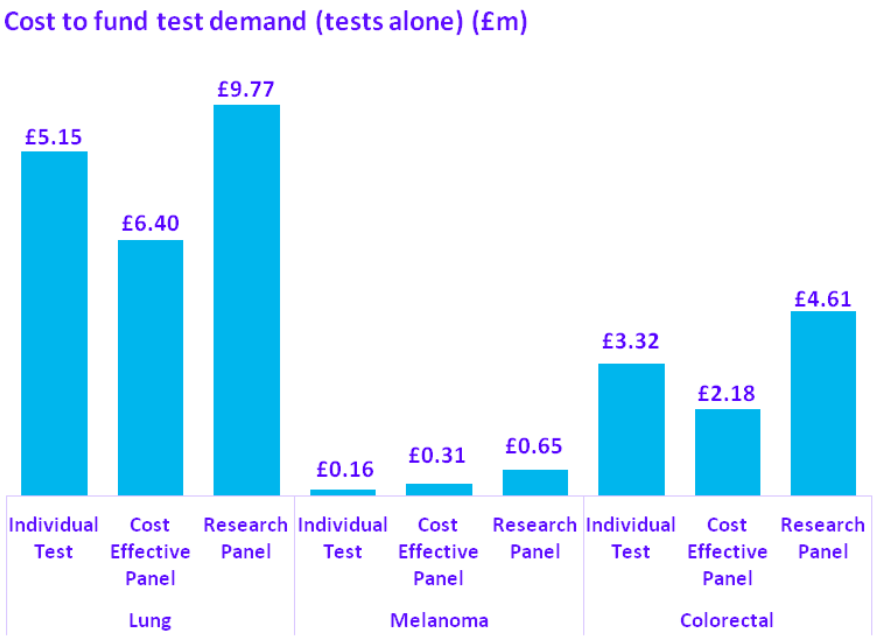
With these variables in mind, it is possible to 'future-proof' a molecular diagnostic service by providing funding for tests that are clinically relevant now, as well as those in the development pipeline. This would enable the service to provide all patients with the tests they need, while allowing it to develop the capacity required to provide the new tests when they become clinically relevant. For example, MET testing in Melanoma is on the near-term horizon, as is BRAF testing in lung cancer. The consequences of a lack of capacity in the system when a new test becomes clinically relevant have already been observed in colorectal cancer: NRAS testing very quickly became clinically

relevant, though because future proof methods were not in place the system struggled to implement NRAS testing quickly as it was unprepared for the new test, which created a testing gap that has still not been closed[xix].

Considering the trade-offs between individual tests, which will increasingly become less cost effective as more biomarkers become clinically relevant, and research panels, which collect a significant number of biomarkers but only return a few results which are clinically relevant, a balance can be found by funding smaller panels that include several clinically relevant and tests on the near-term horizon, while allowing funding to be suitably flexible such that it can also be applied to individual tests where need (e.g. ALK testing, as already noted).

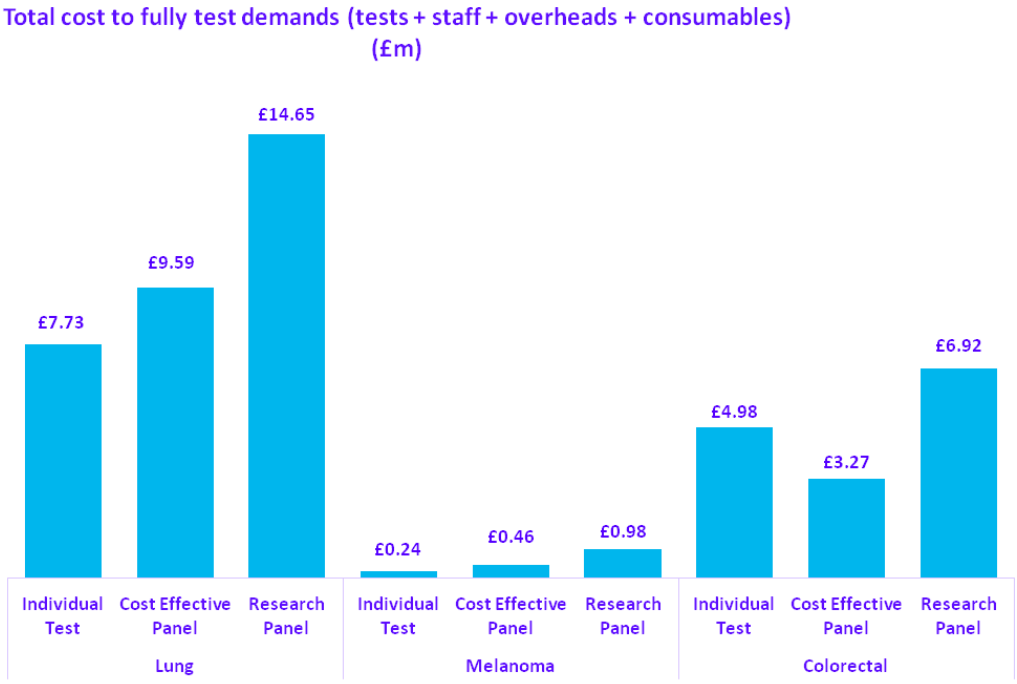
THE COST OF CLOSING THE GAP

Cost estimates for fully funding molecular diagnostic provision can be generated by multiplying the number of tests required to meet testing demand for each cancer type by the costs of each test. Doing so produces a view of the annual funding requirement to cover the cost of the tests themselves following the recommendation of funding small panels with allowance for individual tests where needed. In total £8.89 million would be required annually to fund the test costs alone, using a panel testing approach, for molecular diagnostics in England - melanoma (£0.31m), lung (£6.40m) and colorectal cancer (£2.18m) (see figure below).



Figures are calculated by multiplying the patient population eligible for each test by the associated cost of each test method.

In addition to the costs of the tests themselves, consideration needs to be made for other key cost drivers, namely the cost of the lab personnel who conduct the testing and the associated consumables and overhead costs. In 2014 Cancer Research UK, the Royal College of Pathologists and the ABPI Pharmaceutical Oncology Initiative worked in partnership to develop a Cancer Molecular Diagnostics Implementation Planning and Commissioning Toolkit (CMD ImPACT)[xx]. This toolkit has enabled labs providing testing for targeted cancer medicine to create detailed estimates of the cost of providing these tests. Experience with the toolkit has indicated that total cost of providing a test tends to be around 1.5 times the cost of the test itself (inclusive). Therefore, scaling the cost estimates we have already calculated by a factor of 1.5 enables us to estimate the total cost of fully funding molecular diagnostics for targeted cancer medicines.



Figures are calculated by multiplying estimated total test cost reported earlier in this report by a factor of 1.5, which is the observed scaling factor that estimates the total cost of provision (e.g. including test cost, plus lab staff cost, consumables, and lab overheads) based on the total cost of a test. This factor was calculated based on multiple uses of the CMD ImPACT toolkit provided through the Royal College of Pathologists as used within pathology labs in England.

Funding the total cost of provision for molecular diagnostics across England using a panel testing approach would require £13.32 million in annual funding - melanoma (£0.46m), lung cancer (£9.59m) and colorectal cancer (£3.27m). This would cover the cost per test, including reagents, consumables, staff time, and overheads. However, these estimates are conservative and do not include costs of equipment, training, hospitalisation costs due to toxicity, parallel germline testing and test development and validation, which vary significantly from lab to lab. These additional costs should be taken into account when developing a commissioning solution for testing provision.

As there is no formal commissioning or payment structure for molecular diagnostic testing, any current spending in the NHS for this activity is not taken into account. These estimates should therefore be taken as the starting point for amount needed to fund current testing activity, to bridge the gap to meet demand, and to provide a 'future proof' service.

CONSIDERATIONS FOR COMMISSIONERS

There is a crucial need for national leadership in commissioning cancer molecular diagnostics. The "closing the gap in melanoma testing" case study shown earlier in this report illustrates that, given appropriate funding, planning, and involvement from the clinical community gaps in cancer molecular diagnostic testing can pre-empted and avoided. Importantly, melanoma testing was funded by a pharmaceutical company; had this not been the case evidence suggests that a gap in melanoma testing would exist, and as already discussed test funding from pharmaceutical companies may not always be an option, and has not fully closed the gap in any other case save BRAF testing in melanoma.

At approximately £13.32 million to fully fund provision of lung, colorectal, and melanoma molecular diagnostics the cost is not insurmountable. As molecular diagnostics are required to assess patients for medicines which are routinely available, funding the diagnostics "unlocks" targeted medicines for patient groups. Funding cancer

molecular diagnostics would be a strategic investment in improving patient experience and outcomes, including superior impact and avoidance of undesirable side effects.

However, funding molecular diagnostics would not only unlock targeted medicine for certain patient groups. From a commissioning perspective it can also unlock value within the system by improving results per pound spent, for example by reducing the cost of treatment per responding patient, which is the key concern of both patients and the healthcare system. Consider the following example[xi]:

Consider a group of 100 non-small cell lung cancer patients who have the EGFR mutation

If the patient population receives molecular diagnostic testing through which they discover that they have the EGFR mutation, then:	**If the patient population does not receive molecular diagnostic testing so they do not know that they have the EGFR mutation, then:**
Erlotinib – a targeted cancer medicine – is prescribed	Docetaxel chemotherapy is prescribed
Erlotinib has a tumour reduction rate of 80-90%	Docetaxel has a response rate of 20-40%
The average duration of treatment is 4.2 months	The average duration of treatment is 6.4 months
Erlotinib has a cost of £1,632 per month	Docetaxel has a cost of £850 per month
The total cost to treat all patients is £685,440	The total cost to treat all patients is £544,000
Respondents gain on average 9.7 months of progression free survival	Respondents gain on average 5.2 months of progression free survival
See NICE guidance on Erlotinib[xi] and FDA approval of Erlotinib	Based on a recent randomised control trial[xxi]. Alternative chemotherapies may be used within the clinic setting i.e. pemetrexed and cisplatin whereby duration of treatment and associated costs may vary.
Total cost per responder: £7,616 - £8,568 Monthly cost per responder: £1,813 - £2,040	Total cost per responder: £13,600 - £27,200 Monthly cost per responder: £2,125 - £4,250
Cost of treatment for non-responding patients: £68,544 - £137,088	Cost of treatment for non-responding patients: £326,400 - £435,200

CONCLUSION

A cancer patient's outcome and experience can be affected by accessing regularly funded targeted cancer medicines. For certain patient groups the medicines offer a higher response rate, and those that respond experience greater progression free (disease control). Additionally the treatment journey may be enhanced: avoidance of undesirable side effects and less time in hospital.

As molecular diagnostic tests are the only way to access targeted cancer medicines, eligible patients who do not receive these tests are missing out – missing out on the knowledge of whether their cancer is suitable for targeted medicine, and for some missing out on the benefits of targeted medicine.

From this perspective the gap in provision of molecular diagnostic testing is significant and cause for concern. In England alone 15,929 patients were untested each year, which keeps about 3,552 patients from accessing targeted cancer medicines and their associated benefits.

This report has been based on NICE approved medicines and those approved through the Cancer Drugs Fund, thus may not reflect subsequent changes and the testing currently taking place in the clinics. Moreover, we are now in an era of personalised treatments, with many more targeted medicines in the development pipeline. The NHS must be in a position to capitalise on this and ensure funding and services are in place to both address current shortfalls and prepare for the future. The tests are relatively affordable – much less than the cost of the medicine itself – and should be fully funded in England.

Molecular diagnostic testing in melanoma has shown that demand for molecular testing can be anticipated, planned, and addressed so that there is no gap in testing when targeted cancer medicines become available. What is needed is leadership to:

- Provide funding to support the adequate provision of molecular diagnostic tests, now and in the future, to ensure all eligible patients have access to these tests in a timely manner.
- Commission cancer molecular diagnostics in the NHS at the national level.
- Routinely collect and report data on cancer molecular diagnostic activity in national datasets, for example linked to the SACT dataset in England.

Addressing these areas will improve patient outcomes and make the benefits of targeted medicine a reality for thousands more patients, now and in the future.

APPENDIX

DATA REQUESTED IN LAB SURVEY

Data was requested for somatic genetic cancer testing conducted for NHS practice only.

Labs were asked to report their name, contact details, and catchment area (excluding out of area referrals).

Data was requested for the following tumour / test combinations:

- Lung: EGFR, KRAS, BRAF, ALK, and PIK3CA
- Colorectal: KRAS, BRAF, PIK3CA, NRAS, MSI
- Melanoma: BRAF, NRAS, KIT
- Gastrointestinal stromal tumour (GIST): PDGFRA, KIT

For each tumour / test combination the following data was requested:

- Total test volume: calendar year 2011, 2012, 2013, 2014.
- Reimbursement: Is test currently reimbursed? By who?
- Out of area referrals: calendar year 2014 volume for first, second, third, fourth, and fifth-highest referring sites. Proportion of volume within Trust vs. outside referrals (%).
- Platform: primary testing method.
- Performance: average turnaround time (days), re-test rate (%).
- Price: price charged for each test.
- Panels: Panels/genes used. Price charged each panel.

GLOSSARY

- ABPI – The Association of the British Pharmaceutical Industry
- CDF – Cancer Drugs Fund
- MDT – Multidisciplinary team
- NCSLC – Non-Small Cell Lung Cancer
- NEQAS – UK National External Quality Assessment Service
- NHS – National Health Service
- NICE – National Institute for Health and Care Excellence
- PFS – Progression Free Survival
- SACT – Systemic Anti-Cancer Therapy Dataset

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