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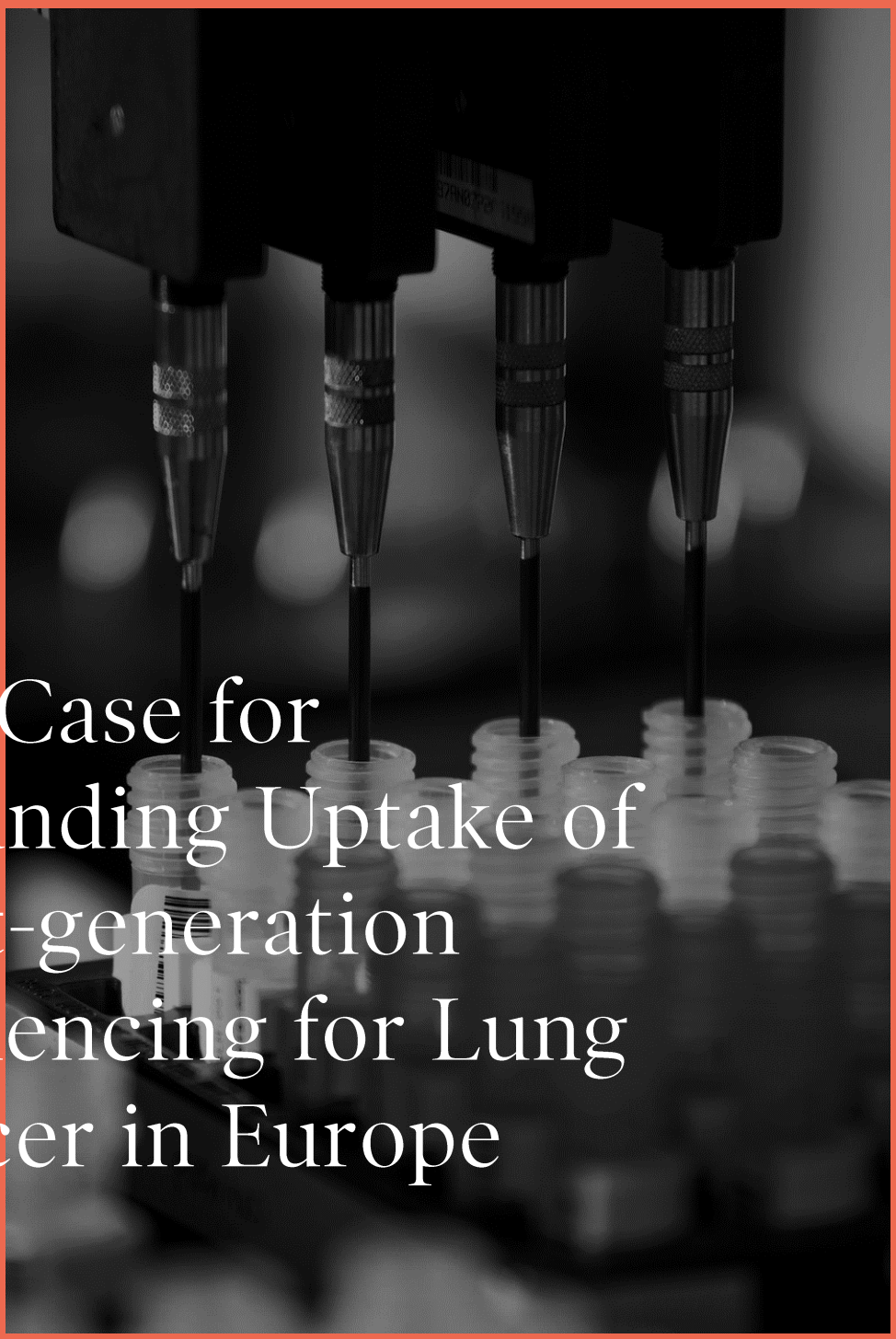

The Case for Expanding Uptake of Next-generation Sequencing for Lung Cancer in Europe

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MAY 2023

Chris Sampson
Edward Oliver
Priscila Radu
Tanja Podkonjak
Lotte Steuten

ohe.org

Takeda

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Chris Sampson
Office of Health Economics, London, UK

Edward Oliver
Office of Health Economics, London, UK

Priscila Radu
Office of Health Economics, London, UK

Tanja Podkonjak
Takeda, Zurich, Switzerland

Lotte Steuten
Office of Health Economics, London, UK

OFFICE OF HEALTH ECONOMICS **CONSULTING**

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Corresponding Author:
Chris Sampson
csampson@ohe.org

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For further information please contact:

Professor Lotte Steuten
Deputy Chief Executive, OHE
Honorary Visiting Professor in Economics at City, University of London

Tel +44 (0)207 747 1441
Email lsteuten@ohe.org

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Executive Summary

Next-generation sequencing (NGS) efficiently generates comprehensive and actionable information on molecular tumour profiles. NGS testing is especially relevant in lung cancer; targeted therapies can be two to three times more effective than cytotoxic chemotherapy for non-small-cell lung cancer (NSCLC) (Gutierrez et al., 2017). In 2020, guidance from the European Society for Medical Oncology recommended NGS testing for advanced cancers such as lung cancer. Despite these recommendations, uptake of NGS has been slow in Europe, and access is heterogenous (Lazzari et al., 2020). Gaps in funding and implementation mean that many patients with lung cancer cannot benefit from the use of NGS testing and the advanced precision treatments it facilitates.

This report explores the status of access and uptake for NGS testing for lung cancer in Europe. We develop the health economic case for NGS testing and identify barriers and opportunities for widespread access to NGS testing for patients with lung cancer in Europe.

We conducted a targeted literature review, extracting information on the clinical benefit of biomarker testing, cost-effectiveness and economic analyses, barriers to access and uptake of NGS, and policy relating to personalised medicine in Europe. We also established an Advisory Group with expertise in pathology, oncology, genomics, and health economics, who contributed to our evidence generation and interpretation. In addition, we conducted case studies for France, Italy, Spain, and England to identify local barriers and opportunities and to provide context for our review findings.

Clear and consistent clinical guidance on when to use NGS testing is lacking in Europe, and we observed heterogeneity across countries in terms of reimbursement and infrastructure. There is a wealth of evidence supporting the **clinical value** of NGS testing in lung cancer, with broad agreement on the mechanisms by which it can improve patient outcomes. Evidence also demonstrates the potential for **efficiency and cost savings** arising from the use of NGS testing. While there are few European cost-effectiveness studies of NGS in lung cancer, research has revealed efficiency in tissue use, health care resource use, and time-to-results. In addition to clinical and economic benefits, genomic testing is associated with **broader elements of value**, especially the 'value of knowing'.

We specify three objectives to support the broader uptake of NGS testing for lung cancer in Europe: i) the introduction of appropriate **pricing and reimbursement** mechanisms, ii) the **standardisation** of testing and care pathways, and iii) the development of **infrastructure**. In line with these objectives, we specify a set of six recommendations:

1. Inclusion of NGS for lung cancer in national minimal care provision
2. Reimbursement of NGS testing according to its value
3. Adoption of national standards for sample analysis and reporting
4. Development of local clinical guidelines
5. The rollout of national initiatives to map referral pathways
6. Introduction of national education and awareness programmes

Access to NGS testing for lung cancer is variable across Europe, despite recommendations for its use and comprehensive support for its clinical value. NGS testing can provide significantly more information than sequential single gene testing, with efficiency savings in terms of time and resources and significant value to patients. The prevailing barriers and opportunities for broader uptake differ across countries, but there are generalisable objectives and policy initiatives that can facilitate progress.

Introduction

Over the past 20 years, innovative targeted treatments and diagnostics have ushered in a new era of precision oncology (The Lancet, 2021). Care for cancer patients can be uniquely tailored to an individual patient's characteristics and needs. The development of new targeted medicines is a crucial part of this potential for improvement in patient care. But the cornerstone of these advancements is a greater understanding of the human genome (Quinn et al., 2022).

Massive parallel sequencing – such as next-generation sequencing (NGS) – was developed early in the 21st century and represented a step-change in the genomic information that could feasibly be obtained from patients seeking care. NGS is a multi-panel sequencing technique that simultaneously evaluates and characterises the nucleic acid sequences of hundreds or thousands of genes, often at a relatively lower cost than a sequential single-gene testing (SGT) approach (Pruneri et al., 2021). In recent years, NGS has become widely used in oncology to determine mutations in tumour tissue samples, particularly in metastatic cancer diagnosis (Cainap et al., 2021).

The information obtained through NGS testing is used to inform diagnosis, prognosis, and treatment planning and review. NGS has the potential to be relevant at multiple points throughout the patient pathway, and any applications that can be supported by evidence will be considered within the scope of this report (Coquerelle et al., 2020). Access to NGS can help physicians match treatments to the genomic driver alterations of an individual's specific cancer. In principle, personalised therapies that target genomic drivers specific to underlying tumours can improve patient outcomes and support a more efficient allocation of resources (Tan et al., 2018).

In 2020, the European Society for Medical Oncology (ESMO) issued guidance recommending NGS testing for advanced cancers, including lung cancer (Mosele et al., 2020). This was the first time a European scientific society gave recommendations on the use of NGS, intending to harmonise decision-making on its use for patients with metastatic cancer (ESMO, 2020). The authors argued in favour of NGS testing in part because of the benefits associated with requiring only a small amount of tissue, which can avoid the need for multiple biopsies. The recommendation also acknowledged the advantage of NGS in enabling patients with rare mutations to benefit from certain therapies (ESMO, 2020).

ESMO's push for innovation reflects developments in some settings. For example, between 2015 and 2019, 3,717 patients in Germany with advanced non-small-cell lung cancer (NSCLC) were recruited to the CRISP (Clinical Research Platform into Molecular Testing, Treatment, Outcome) registry at the start of systemic therapy. Of these patients, 90.5% were tested for biomarkers, and the most common testing methods were immunohistochemistry and NGS (Griesinger et al., 2021). However, the uptake of NGS has been otherwise slow in Europe, and access remains heterogenous (Horgan et al., 2022). Due to gaps in the implementation of this technology, many patients with lung cancer may not benefit from NGS testing and the advanced precision treatments it facilitates.

In principle, NGS is well-suited to the rapidly changing field of lung cancer care. Yet, a compelling case for broader access to NGS testing for lung cancer in Europe, grounded in research, has not been articulated. There is a need to understand stakeholders' perspectives on the value of NGS testing in lung cancer and identify the barriers to access and uptake. Where barriers exist, research can support decision-makers in implementing appropriate solutions and fostering existing opportunities. In particular, prevailing reimbursement policies and mechanisms are likely to influence the comprehensiveness of NGS access, and these policies should align with the health economic case for NGS. With this understanding and guidance, efforts in research and policy-making can be more

effectively leveraged, helping to realise patient benefits, improve population health, enhance care delivery, and make more efficient use of health care resources.

In this report, we describe research conducted to explore the health economic case for broader uptake of NGS testing in lung cancer in Europe. We provide evidence-based recommendations that can guide and inform decision-making by policymakers and other stakeholders at various levels of government and health care delivery.

The objectives of this report are as follows:

1. Understand the status of access and uptake of NGS testing for lung cancer in Europe
2. Develop the health economic case for widespread access to NGS testing
3. Identify barriers and opportunities for broader access to NGS testing for patients with lung cancer in Europe

Our approach

Our research included a literature review, stakeholder engagement, and country-specific case studies. This approach enabled us to represent the most recently available science, supported by the latest insights from a wide range of stakeholders and contextualised by the experience of four European countries.

Literature review

We performed a targeted literature review to identify published literature on the clinical and economic value of NGS in lung cancer – both evidenced and hypothesised – and the status of access and uptake in Europe. We sought to review clinical studies and reviews, cost-effectiveness and economic analyses, clinical guidelines, and policy-relevant reports. Our review focused on lung cancer patients and, where possible, Europe. We searched PubMed, Google Scholar, the Trip database, and the ESMO and Professional Society for Health Economics and Outcomes Research, known as ISPOR, presentation databases. Search terms were specified to identify records relating to biomarker screening with NGS. Studies pertaining to other genomic sequencing techniques or countries outside of Europe were included in the review if they were informative to our scope.

We employed an iterative search strategy, identifying studies and reports published before December 2022. One researcher conducted searches and screened citations, and the strategy was iteratively updated following discussion within the OHE team. We extracted quantitative estimates and descriptive information on NGS in the context of (but not always limited to) lung cancer, relating to the following:

- Drivers of clinical and patient benefits
- Drivers of cost and resource use
- Cost-effectiveness or budget impact
- Barriers to access and uptake
- Policies or guidelines on personalised medicine in Europe
- The burden of illness impact of personalised medicine

Stakeholder engagement

We convened an Advisory Group with representatives from different disciplines and countries and with various perspectives relating to our project's aims. The group consisted of 9 members, with experts in pathology, oncology, genomics, and health economics, as well as payer and patient representatives. Members from France, Italy, Spain, the UK, and the US were included, with several attendees working internationally.

The first Advisory Group meeting was held in July 2022 and focused on discussing the findings from our literature review. With support from the Advisory Group, we tested our interpretation of the

evidence, identified gaps in research, and planned the design of our case studies. The second meeting was held in September 2022 and focused on specifying the drafted overall health economic value case and the case study findings. At the second meeting, the group reviewed and prioritised our proposed recommendations.

Case studies

We selected four countries for in-depth case studies. We gathered additional data and information on clinical treatment guidelines, the perceived value of NGS testing for lung cancer, barriers and opportunities for expanding uptake, and existing initiatives to improve testing.

The countries chosen by the project team were France, Italy, Spain, and England. These were selected to provide learnings from countries with distinct experiences, as judged by the team's existing knowledge and experience. The selected countries capture different market archetypes and levels of implementation of NGS. This approach ensured that our recommendations were not only evidence-backed but also considered the implications of the different types of barriers associated with different health systems (e.g. centralised national systems vs decentralised regional systems).

The sources retrieved in the literature review and discussed by the Advisory Group were leveraged to identify the opportunities and barriers to widespread access to NGS in each of the four countries. We held a series of meetings with members of local Takeda teams in each country, including medical, market access, and advocacy team representatives. In these meetings, project findings were presented for discussion and attendees were invited to contribute their knowledge about the local context and the policy priorities. The knowledge gained from these meetings informed the ongoing literature review and interpretation by providing additional references and insights from specific countries. The findings from the case study investigations were then shared and validated with the Advisory Group members from each respective country.

The Case for NGS Testing

The evidence identified in our literature review provides a clear case for broader access to NGS testing in lung cancer. Our review of the evidence and engagement with stakeholders supports the following three pathways for value generation: i) clinical value, ii) cost and efficiency, and iii) broader elements of value, as summarised in Figure 1. The following sections summarise key value elements for each part of the case, our assessment of the strength of evidence, and its overall importance.

Clinical value	Cost and efficiency	Broader value
There is broad agreement on the accuracy of NGS testing and the mechanism for improved patient outcomes in lung cancer. The evidence base is robust, especially in NSCLC.	NGS testing in lung cancer can be associated with cost and efficiency savings. Preliminary evidence suggests that NGS testing can be cost-saving over sequential single-gene testing.	Genomic testing generates value beyond the usual scope of cost-effectiveness analysis. These benefits may be realised by patients or across the health system.
✓ Reliable identification of mutational drivers ✓ Enabling personalised treatments ✓ High sensitivity and specificity for small amounts of sample	✓ Lower total testing costs ✓ Efficient sample use ✓ Shorter time-to-results and diagnosis ✓ Improved cost-effectiveness	✓ Reduced uncertainty about treatment efficacy ✓ Real option value for terminal cancer ✓ Physicians' knowledge of cancer drivers
The evidence base is robust, especially in non-small-cell lung cancer.	Evidence has only recently started to develop on the cost-effectiveness of NGS testing.	These benefits can be challenging to quantify, and there is a lack of empirical studies.

FIGURE 1: THE HEALTH ECONOMIC VALUE CASE FOR NGS TESTING IN LUNG CANCER

NGS is clinically superior

The clinical advantages of using NGS testing are the foundation for our case for broader adoption of the technology. As the evidence presented in this section demonstrates, NGS is, in many contexts, clinically superior to either a) no genetic testing or b) sequential single-gene testing in the management of lung cancer.

Lung cancer is mutation dense and has more predictive genes that may influence treatment decisions than any other cancer type (Saarenheimo et al., 2021). Therefore, the most important clinical benefits are achieved through an effective precision therapy that targets a tumour's mutational driver. By indicating genetic alterations in tumours, effective use of NGS testing can allow for more focused and highly personalised treatment for key gene targets such as epidermal growth factor receptor (*EGFR*), anaplastic lymphoma kinase (*ALK*), and programmed death ligand-1 (*PDL-1*) (Hernandez, Churchill and Walton, 2021; Malone et al., 2020; Phillips et al., 2021; Massard et al., 2017; Paz-Ares et al., 2022). ESMO recommendations further highlight the ability of NGS to provide a valuable analytical tool for detecting dominant genetic alterations in metastatic cancers (Mosele et al., 2020).

A substantial body of research emphasises the high sensitivity and specificity associated with NGS testing, even with low amounts of sample (Vaughn et al., 2018). This view was supported by the experts who contributed to our study. NGS can simultaneously detect multiple alterations from a single assay, which is an important reason why NGS is considered superior to other technologies generally used in practice, such as PCR. Alternative techniques are bound by their limitations in scalability, as they often require more significant amounts of sample that are not always available from biopsies (Vaughn et al., 2018). A study by Lazzari et al. (2020) found that collected tissue is inadequate for molecular analysis for about 23% of patients due to difficulties in tissue collection. Therefore, working efficiently with small sample sizes is a crucial advantage of NGS.

Researchers have demonstrated the superior analytic performance of NGS testing compared with other assays. For example, Surrey et al. (2019) found that NGS was significantly better than non-NGS assays when identifying *BRAF* and *EGFR* variants. Compared to alternatives, such as quantitative polymerase chain reaction (qPCR), NGS assays can better identify clinically significant mutations and provide more information on specific tumours (Tønnesen, Lade-Keller and Stougaard, 2021). Furthermore, recent research presented at the World Conference of Lung Cancer revealed that PCR methods are expected to miss about 49.1% of *Exon20* insertion mutations, otherwise identified by NGS. This mutation accounts for up to 10% of all *EGFR* mutations in NSCLC (Bauml et al., 2021). Some researchers have suggested that the potential for NGS testing with low tumour content is still to be thoroughly evaluated, especially in the context of routine clinical practice (de Biase et al., 2013; Xu et al., 2016).

The evidence cited above demonstrates the clinical efficacy and technical superiority of NGS testing over alternative testing methods such as PCR and SGT. Other research reveals the clinical effectiveness of genomic testing in general, and NGS testing specifically, and the patient benefits arising from its use. For NSCLC, targeted therapies are two to three times more effective than cytotoxic chemotherapy (Gutierrez et al., 2017). Analysis of mortality rates in the US shows that NSCLC mortality has declined faster than the incidence rate, with a 6.3% annual decrease from 2013 to 2016, compared with an annual decline in incidence of 3.1% from 2008 to 2016 (Howlader et al., 2020). This is partly attributable to the use of therapies that target the *EGFR* biomarker. Conversely, the decline in mortality associated with small cell lung cancer was found to be entirely due to the decrease in incidence.

Research has revealed a rapid reduction in lung cancer patients identified at stage IV since 2013, which was when targeted therapies were first approved. Researchers attribute this earlier identification – and the concurrent improvement in prognosis and health outcomes – to the development of targeted therapies for the treatment of NSCLC and the approval of early-screening programmes (Liang, Liu and He, 2020). Research is also beginning to reveal similar improvements in early-stage NSCLC, where targeted therapies are incorporated into adjuvant and neoadjuvant therapies (Herbst et al., 2020; Forde et al., 2018). Targeted therapies first approved for other tumour types have also demonstrated clinical benefit in alterations existent in NSCLC. For example, the combination of dabrafenib (Tafinlar®) and trametinib (Mekinist®) was initially approved for *BRAF* V600E mutations in metastatic melanoma but is now also approved for *BRAF V600E* mutations in NSCLC (Nellesen et al., 2018). NGS is a crucial tool to identify the targets for these specialised therapies effectively and quickly, using small amounts of tissue sample.

Targeted therapies for precision oncology are developing rapidly, increasing the value of NGS testing. As recently as 2019, Aran and Omerovic (2019) remarked that there was no effective approved drug for people with advanced NSCLC who harboured *KRAS* mutations. Since then, sotorasib – a small-molecule *KRAS G12C* inhibitor – was launched. The National Institute for Health and Care Excellence (NICE) recommended the drug for use in the Cancer Drug Fund in England and Wales in March 2022 (NICE, 2022). This adds another actionable target that NGS can identify, thus increasing its clinical

value by enabling potentially improved outcomes for these patients. Sotorasib was authorised under Project Orbis, an international collaboration for the timely regulatory assessment of promising oncology drugs, highlighting the innovative nature of new drugs in this context (Nakajima et al., 2022). As the number of actionable targets increases, the number of patients who stand to benefit increases. For this reason, researchers and members of our Advisory Group have argued that the value of NGS testing for lung cancer will continue to increase over time.

Much of the evidence identified in our review and described above focuses on NSCLC. Members of our Advisory Group noted that using NGS in small-cell lung cancer should not be ignored and that test results can guide treatment planning by avoiding ineffective therapies. Evidence in this context is more limited, but research has shown how NGS panels can detect oncogenic driver mutations in small-cell lung cancer (Jin et al., 2021).

There is also support for NGS in new and emerging applications, such as in gene fusion analysis (Bruno and Fontanini, 2020) and NGS-based liquid biopsy (Zhang, Zhou and Wu, 2017). NGS testing has also been considered for applications other than diagnosis. Studies have suggested that NGS testing could provide insights into tumour evolution during the course of the disease, thus expanding the scope for incorporating advanced biomarker testing into the clinical toolkit (Kerr et al., 2021). Evidence to support novel applications and use in clinical practice beyond diagnosis is limited. Nevertheless, in addition to the patient benefit associated with targeted therapies, it is essential to acknowledge the clinical value of NGS to physicians. NGS provides a better understanding of the disease being treated and supports more effective and less uncertain clinical decision-making. In practice, as discussed by our Advisory Group, this can manifest as the avoidance of ineffective therapies that may cause unintended harm to patients.

The clinical value and improvement in patient outcomes associated with NGS testing underpin the health economic case for broader access and uptake in lung cancer. It has the most robust evidence base and is generalisable to different healthcare systems. Health care professionals, commissioners, and policymakers can be confident about the clinical effectiveness and value of NGS testing to patients and physicians. A clear understanding of the clinical value of NGS can support the development of clinical guidelines for when, how, and whom to test, as well as how to uniformly report the results of NGS testing and facilitate patient education and shared decision-making. Understanding the clinical case for NGS also provides the basis for value-based pricing and reimbursement of NGS testing, a matter to which we return later in this report.

Our literature review revealed broad agreement and validation of the clinical benefit of NGS testing in lung cancer. Consultation with our Advisory Group mirrored this perspective, with a clear consensus that the clinical case for NGS testing in lung cancer is robust and well-evidenced. Advisory group members emphasised that clinicians and pathologists were increasingly in agreement that routine lung cancer care should fully incorporate NGS testing.

NGS can increase efficiency

The efficient delivery of effective care programmes is a priority for decision-makers, healthcare professionals, and patients. Efficiencies can manifest in various ways, including reductions in healthcare expenditures, shorter timelines, and reduced waste of scarce resources. NGS testing has been demonstrated or hypothesised to increase efficiency in all of these respects.

There is a growing body of research exploring the costs associated with NGS testing. A systematic review found cost estimates ranging from $555 to $5,169 for whole-exome sequencing, and from $1,906 to $24,810 for whole-genome sequencing (Schwarze et al., 2018). Our case for the efficiency

of NGS is based primarily on a comparison with sequential SGT, which identifies biomarkers by testing for each potential gene individually and is the standard of care in several European countries (Malapelle et al., 2021). The ability to evaluate and characterise the nucleic acid sequences of thousands of genes simultaneously differentiates NGS from other biomarker tests (de Alava et al., 2022).

Sequential SGT takes time, and tissue exhaustion is a genuine concern in diagnostic pathways for lung cancer. While there is little evidence available to quantify savings, NGS testing can, in principle, make more efficient use of tissue, as some researchers have argued (Pennell et al., 2019a; Penault-Llorca et al., 2022). NGS testing is associated with similar or shorter diagnosis times compared to sequential testing techniques, especially when testing for all relevant biomarkers associated with NSCLC (Pennell et al., 2019b; Simarro et al., 2019). In an Italian study, Pruneri et al. (2021) showed that NGS testing can reduce hospital costs by up to €879 per patient in advanced NSCLC compared to targeted sequencing with SGT. These cost savings were driven by more efficient use of consumables and professional time, compensating for increased equipment costs (Pruneri et al., 2021).

Studies have assessed the cost-effectiveness of genomic testing using strategies other than NGS. For example, in a study with French NSCLC patients, Loubière et al. (2018) showed that molecular testing before treatment initiation can be cost-effective. Only recently has research turned to the economic evaluation of NGS testing. As such, evidence of the cost-effectiveness of NGS for lung cancer care in Europe is limited. Nevertheless, the available evidence points to NGS testing being cost-effective in lung cancer care, either now or in the near future.

De Alava et al. (2022) analysed the cost-effectiveness of using NGS panels to detect genetic molecular subtypes and oncogenic markers in patients with advanced NSCLC. The study was conducted in a Spanish referral hospital, and NGS was compared to sequential SGT of the same oncogenic markers included in the NGS panel. Despite incrementally higher total diagnostic costs (€18,590) with NGS, the authors argue that using NGS was a cost-effective strategy compared to sequential SGT, costing €617 per additional patient eligible for targeted treatment. When the authors estimated the costs and benefits of follow-on treatment, over a lifetime horizon, they found that the overall cost impact was an additional €47,432 per patient for NGS testing. This corresponded to an additional cost per quality-adjusted life year (QALY) gained of €9,084, which would be highly cost-effective in Spain.

A recent study by Wolff et al. (2022) reports a model-based cost-effectiveness analysis comparing the use of NGS and sequential SGT for patients with stage IV NSCLC in the Netherlands. The authors found that NGS was associated with lower testing costs and identified additional targets in 20.5% of cases. Additionally, this study found improved outcomes related to targeted treatment, implying that the NGS test can be considered cost-effective, with a cost-per-QALY gain of €69,614, which is below the recommended Dutch threshold of €80,000 per QALY (Wolff et al., 2022). Another modelling study focussing on Dutch patients argued that whole-genome sequencing would likely be cost-effective in the near future (Simons et al., 2023). Recent evidence on costs and cost-effectiveness from Canada (Sheffield et al., 2022) and the US (Zou et al., 2022) is also favourable.

A crucial dynamic in the cost-saving potential of NGS is that, compared with sequential SGT, NGS testing will be cost-saving at a break-even point corresponding to the number of tests in SGT. In the study by Pruneri et al. (2021), the estimated cost saving increased with the comprehensiveness of the sequencing. The authors estimated a break-even point in terms of the number of patients needed to test and found that, in most scenarios, NGS was cost-saving for any number of patients. The more molecular alterations sought, the more likely it is that NGS will be cost-effective. This is because NGS allows for testing a more comprehensive range of molecular alterations in a single run (Pruneri et al., 2021). The NGS panel in de Alava et al. looked at nine mutations following PD-L1 immunohistochemistry (IHC) testing, while the sequential testing analysed eight of the same biomarkers, excluding HER2 (de Alava et al., 2022). Based on this sequence of tests and their costs, NGS testing can cost less than sequential testing when targeting more than five genetic alterations.

> NGS testing can cost less than sequential testing when targeting **more than 5 genetic alterations**

Funding for genetic testing (including NGS) must consider the need for additional human resources associated with developing proficiency in testing, such as bioinformaticians. Despite the need for these investments in infrastructure, the literature supports the long-term return on these investments. It has been found that NGS-based approaches reduce personnel costs and overall time spent when compared to SGT (Pruneri et al., 2021). A study by the French Cancer Institute has highlighted the potential cost savings that arise from molecular testing due to reduced ineffective prescribing (Nofziger et al., 2014). A report from the European Commission describes how a one-off investment of €1.7 million in *EGFR* mutation testing in France drove a cost saving of approximately €70 million ("based on the median treatment period of 8 weeks") by identifying NSCLC patients who would respond to treatment with gefitinib or erlotinib (Draghia-Akli, 2012).

> An investment of **€1.7 million** in *EGFR* mutation testing drove a cost **saving of €70 million** by identifying NSCLC patients who would respond to treatment with gefitinib

Under the circumstances described in the research cited here, NGS represents a more efficient approach to testing than sequential SGT, reducing costs and resource use. A nascent but growing body of evidence linking testing costs and targeted treatment outcomes supports the cost-effectiveness of NGS testing. Important studies such as Pruneri et al. (2021) highlight the potential economies of scale that may be realised as a greater number of patients and a greater number of mutations are targeted.

NGS generates broader value

In adopting a traditional health technology assessment (HTA) perspective, the value generated by NGS testing tends to rely on the health benefits associated with the targeted treatments that it facilitates. However, this risks overlooking the broader value of these innovative technologies. In this section, we argue that NGS testing *in and of itself* is of value to patients and the wider healthcare system.

It is important to consider benefits beyond health. For example, Regier et al. (2018) draw particular attention to the value associated with the information provided by NGS, regardless of any health improvement arising from its use.

One example of broader value can be observed in a study of the preferences of NSCLC patients undergoing genomic testing in Australia. In this study, patients preferred tests that were not followed by further testing and therefore didn't require additional biopsies. The results also show significant preferences for tests that have actionable outcomes. This indicates that the value goes beyond the value of the treatment and includes the knowledge that the treatment is informed by evidence relating to the patient's specific tumour (Fifer et al., 2022). As an advanced diagnostic instrument, NGS presents additional challenges to utility valuation due to the breadth of information yielded (Regier et al., 2018). Failing to estimate patients' preferences correctly could result in under- or over-valuation of the technology.

Garau et al. (2013) described the value of reduced uncertainty about diagnosis and treatment in the context of molecular diagnostics. They show that comprehensive and informative test results provide value to the patient independent of the expected treatment outcomes. This element of value – the 'value of knowing' – is expanded upon by Towse and Garrison (2017), who also discuss the value of hope and real option value in the context of precision cancer medicine. By reducing uncertainty, a diagnostic such as NGS can increase the patient's and clinicians' confidence in treatment efficacy. This can also facilitate compliance and improved uptake of targeted therapies (Towse and Garrison, 2017). The value of knowing is widely discussed in the health economics literature but is not routinely quantified or included in HTA.

If a treatment can extend life, it allows patients to benefit from future medical advances. This value element is known as 'real option value' and is particularly relevant to lung cancer because of the high rate of innovation. Real option value is widely discussed in oncology because therapeutic progression can be non-linear. In this scenario, willingness-to-pay should theoretically be greater than the amount equal to the value of life gains by also providing the option of benefiting from future treatments (Towse and Garrison, 2017). For example, in treating *ALK*-positive NSCLC, the real option value is significant; improvements to survival or disease progression allow for additional health gains from future innovation and may lead to an 11% increase in estimated QALYs when incorporated into value assessment (Lee et al., 2022).

The value of hope, which has been widely discussed in the context of precision medicine, is recognised as representing the value that patients, particularly cancer patients, place on a therapy or care pathway that opens up a wider spread of outcomes that may offer a longer period of survival (Hauber et al., 2020). Researchers have described the value of 'hopeful gambles', which may be preferred over standard treatment with a similar average life expectancy, but with a reduced spread of outcomes; patients highly value low probabilities of extended survival (Lakdawalla et al., 2012). Monetised estimates for the value of hope, as it pertains to cancer, have been provided by Reed et al. (2021), who found that study participants' choices implied a valuation of $5,975 for a 5% chance of long-term survival and $12,421 for 10% chance of long-term survival.

Evidence from studies of treatments for NSCLC has shown that adopting a societal perspective – incorporating patient risk benefits and the real option value – can significantly change the value of treatments by capturing the added benefits outside of the payer's perspective (Shafrin et al., 2018). These wider societal benefits extend beyond the traditional payer-centric concept of value (i.e. direct treatment costs and measurable health outcomes) to incorporate the value of knowing and the value of information relevant to the patient and wider society.

The value of knowing, the value of hope, and real option value all describe additional elements of value that can be derived from broader access to NGS testing (and the targeted treatments that they support). These elements of value are not routinely quantified and have not been quantified in the context of lung cancer. Nevertheless, they should not be ignored in the health economic case for broader uptake of NGS testing in Europe.

In addition to these patient benefits that extend beyond narrowly-defined health benefits, broader access to NGS testing in lung cancer further benefits the wider health system. In particular, NGS testing can generate scientific spillovers in several respects. The benefit accrued from medical advances cannot entirely be attributed to those making them (Towse and Garrison, 2017). By providing complete information on genome sequencing, Members of our Advisory Group highlighted that NGS testing potentially enhances the knowledge base of which mutations are associated with which tumour types. This information can further be used in research and clinical studies to improve patient outcomes and potentially extend to additional indications.

Barriers to access and uptake

US and European clinical guidelines have recommended testing for patients with advanced lung cancer for multiple targetable genomic alterations. Despite this, the pace of adoption of NGS testing for lung cancer in Europe has been relatively slow, and there is widespread heterogeneity in access. This section describes the main barriers to access to NGS testing in Europe, borrowing examples from our case study countries to provide additional context. These barriers have been grouped into three key areas: i) reimbursement and funding, ii) testing standards and market failures, and iii) policy and guidance.

Reimbursement and funding

In Europe's social insurance and public tax-funded health systems, access to care generally relies on its reimbursement and national or regional commitments to funding. Our research has revealed that a lack of reimbursement and funding is the most significant barrier to access in several European countries.

A significant concern about funding and reimbursement relates to inequities in access to care. The Italian National Health Service provides coverage for specific health services; diagnostic tests are only reimbursed if they are included in the lists agreed upon at national or regional levels (see Box 1). This can result in significant geographical variation in patient access (Pinto et al., 2021). NGS testing is particularly heterogeneous in Italy, with regional differences in distribution, infrastructure, and expertise. Research has shown that only 2% of biomarker tests in Italy are performed with the most

advanced technology (compared to the European average of 10%) (Marchetti et al., 2021; IQNPath, ECPC, and EFPIA, 2021).

In some settings, NGS reimbursement is restricted to partial coverage of the cost. In France, NGS testing has not yet been reviewed for reimbursement by the Haute Autorité de Santé (HAS). Reimbursement is provided by a distinct funding pathway called the *Référentiel des actes Innovants Hors Nomenclature* (RIHN) (see Box 2). This composes a list of innovative technologies, including biomarker tests, which, according to members of our Advisory Group, has grown enormously since 2015. The large number of innovative tests this fund now covers means that reimbursement has reduced to less than 50% of the cost of NGS testing (Hofman et al., 2020). This limitation is expected to remain until NGS is recommended within the HAS open funding envelope. With only 50% of the test reimbursed in France, hospitals must cover the remainder and, as a result, are more selective about which patients they put forward for this testing procedure, thus restricting access to patients who could benefit. French pathologists in our Advisory Group highlighted that this has led to a lot of uncertainty towards incorporating new or innovative tests into RIHN funding, presenting a challenge for comprehensive NGS panels.

Italy

Health system overview:

- The National Health System in Italy is responsible for providing coverage for specific health services
- Diagnostic tests are only reimbursed if they are included in the lists agreed upon at national or regional levels

Status of NGS uptake:

- NGS testing is particularly heterogeneous in Italy, there are regional differences in distribution as well as in infrastructure and expertise
- Only 2% of biomarker tests are performed with the most advanced technology compared to the European average of 10%
- Since NGS testing does not currently fall in the basket of health services offered by the Italian National Health Service, it is not reimbursed at the national level

Barriers and challenges to uptake:

- Organisational divide between small and large centres
- The larger centres can generally manage increased complexities and have greater productivity
- Additionally, they are more likely to be associated with a Molecular Tumour Board (MTB) which provide further advice on interpreting the results of the genomic testing as well as guidance on the appropriate next steps in the treatment pathway

Opportunities to improve access:

- MTBs provide a great opportunity in Italy for establishing comprehensive quality control nationwide – there are also system efficiency gains to be achieved by reviewing genomic information in multidisciplinary teams.

BOX 1: ITALY CASE STUDY SUMMARY

Without guaranteed reimbursement from the health service, individual hospitals, or the centres performing the diagnoses, are expected to cover the cost of NGS testing for lung cancer. In some countries, this lack of reimbursement has resulted in a reliance on funding from the pharmaceutical industry. Pharmaceutical companies play a significant role in financing the use of NGS in Spain. A study by the Spanish Society of oncological medicine (SEOM) found that a pharmaceutical company funded the testing of at least one biomarker in more than 50% of centres providing genomic testing (SEOM, 2019). Thus, both France and Spain have similar funding and reimbursement challenges. Our Advisory Group highlighted that the funding pressures are forcing many hospitals to turn to private testing suppliers and that barriers to full genomic sequencing are forcing many clinicians to rely on less comprehensive PCR results.

Partial reimbursement and funding are also a challenge in Italy, where NGS testing does not fall in the basket of health services offered by the Italian National Health Service. As such, it is not reimbursed nationally (Pruneri et al., 2021). Lombardi is the only region in Italy with a reimbursement tariff covering NGS testing (Pruneri et al., 2021). Members of our Advisory Group highlighted the lack of a diagnosis-related group (DRG) code for NGS across Italy as a barrier to reimbursement, suggesting that while some regions offer partial cost coverage of around €200-300, the test cost is likely to be closer to €2,000.

Testing standards and market failures

France

Health care system overview:
- The process of reimbursement is regulated by the French Ministry of Health
- A recommendation from the Haute Autorité (HAS) is needed for full funding

The status of NGS testing:
- Molecular diagnostic tests in France are performed in a network of 28 platforms across the country with support from the French National Cancer Institute (INCa) and the Ministry of Health
- NGS testing is currently funded by the RIHN which provides coverage for a growing list of innovative technologies

Barriers and challenges to access:
- NGS testing is yet to be incorporated into the HAS open envelope and so reimbursement is limited to 50%
- As hospitals must take a hit of the remaining cost of NGS testing, they must be strategic about which patients they put forwards for the technology
- Bottle necks of testing causes many to rely on private suppliers who often swap out NGS testing for less comprehensive PCR tests

Opportunities for wider uptake:
- French National Cancer Institute (INCa), in partnership with the Digital Health Technology is working to standardise the reporting of genomic tests results through a structured and interoperable NGS model report
- INCa has set up working groups with pathologists, molecular geneticists, and clinicians to produce recommendations for somatic testing in colon cancer, lung cancer and melanoma (INCa, 2019)
- Statement from the Minister of Health that some testing acts will be released from the RHIN envelope.

BOX 2: FRANCE CASE STUDY SUMMARY

Supply-side challenges hinder the realisation of the full value of NGS testing in lung cancer. In our research, these were observed most plainly in the England case study (see Box 3). In England, NGS testing is commissioned by the NHS and covered by the National Genomic Test Directory for Cancer (National Genomic Test Directory Cancer, 2021). NICE clinical guidelines recommend that all patients with advanced lung cancer should be tested for somatic driver alterations, before systemic treatment, for optimal treatment selection. However, there is a considerable gap between the recommended standard of care, in terms of the frequency of molecular testing of those eligible for molecular testing, and implementation (National Lung Cancer Audit, 2020).

Time-to-results remains a significant issue among UK clinicians, with the median turnaround time for EGFR mutation analysis estimated at 18 days (National Lung Cancer Audit, 2020). Our Advisory Group highlighted variable time-to-results and opaque supply chains in the testing pathway as features that discourage clinicians from referring patients to NGS testing. Members of the Advisory Group suggested that these problems exacerbate patients' uncertainty in their outcomes and may also lead doctors to not use NGS testing if they believe the cancer is too advanced. Delays in the delivery of results may also be sufficient to cause doctors to consider alternative forms of treatment for the patient while awaiting information on mutational targets. Some countries, however, are showing positive improvements in time-to-results – in Spain, where NGS testing is not widely available, one study revealed that NGS panel results were available in nine days on average. In contrast, the determination of all biomarkers with sequential SGT took 17 days on average (de Alava et al., 2022). However, given that in Spain testing is not as widely available, the results of this study could be driven by sampling bias (for example, if only select academic centres have access to NGS testing as opposed to broader access as in the case of England). This is consistent with research

England

Health system overview:

- Funding for molecular tests is conditional on their approval by NICE
- NHS England National Genomic Test Directory Cancer 2021-2022 specifies which genomic tests are commissioned

Status of NGS uptake:

- Commissioned by the NHS and covered by the National Genomic Test directory for cancer
- NICE guidelines recommend testing in advanced lung cancer for somatic driver alterations
- Low uptake of molecular testing observed when compared to expected figures

Barriers and challenges to uptake:

- There is large variation in time to results with a median turn-around time of 18 days
- Poor tissue management in pathology supply chains means that tissue wasting renders many biopsies unutilised
- Lack of clinician awareness regarding the existence or availability of certain diagnostic tests can prevent patients from accessing the right treatment

Opportunities to improve access:

- The Genomic Education Programme, supported by Health Education England (HEE), provides educational materials for healthcare professionals to teach and encourage the use of genomic testing
- Implementation of Genomic Laboratory Hubs spread across England and Wales simplifies the care pathway for cancer patients and reduces geographical inequalities

BOX 3: ENGLAND CASE STUDY SUMMARY

from outside of Europe, which suggests that issues with time-to-results can be addressed by implementing adequate infrastructure (Tan et al., 2020).

Time-to-results is not the only barrier to NGS uptake that arises from the testing process. To obtain NSCLC tissue, patients undergo burdensome procedures, such as needle biopsies or endoscopic or surgical procedures. Biopsy represents a particular challenge in lung cancer; it can be difficult for patients to tolerate and is only effective in 10-30% of patients with metastasised NSCLC (Koole et al., 2022). Initial immunohistochemistry may be needed to confirm NSCLC and its subtype before genomic sequencing techniques, thus requiring sufficient material of good quality (Kerr et al., 2021). However, in most cases, especially in those with advanced lung cancer, the diagnostic material will only contain a small amount of the required tumour cells, on which all diagnostic tests must be performed. Using this sample to diagnose and classify tumour type can compromise further molecular testing such as NGS (Dietel et al., 2016). Tissue wasting presents a challenge because the invasive nature of tissue biopsy means that re-biopsy is frequently unfeasible or too demanding for the patient to endure (Gobbini et al., 2020). Because of the risks associated with tissue sampling in lung cancer patients, the diagnostic pathway should be optimally planned to reduce the number of procedures needed to obtain enough material for diagnostic and treatment planning (Saarenheimo et al., 2021).

Spain

Health care system overview:

- The Spanish National Health System is decentralised, giving regional authorities the autonomy to organise their own budget and infrastructure and make decisions on what services to offer outside of the minimum requirements set at national level (HealthManagement.org, 2010)

The status of NGS testing:

- No standard procedure or national guidelines are available for the use of NGS at the national level, resulting in a 'post-code lottery'
- NGS is available in various centres and hospitals and the majority of NGS testing (78%) is done in public sector hospitals
- To date, only two autonomous regions are known to reimburse NGS

Barriers and challenges to access:

- Lack of guidance at national level leads to inequality in access. It therefore falls to individual regions are responsible for establishing guidelines around use and reimbursement
- In some larger regions, such as Madrid, the decisions are taken at hospital or borough level. This heterogeneity often leads to disparities within regions , with individuals living in more affluent areas potentially benefiting from greater access to these services

Opportunities for wider uptake:

- The Spanish Lung Cancer Group (GECP) has launched the "Atlas" project that aims to provide NGS biomarker analysis to 1000 patients (GECP, 2022)
- The SEOM and SEAP, two major Spanish Scientific Societies, have been trying to highlight areas of concern which can be addressed to improve uptake of NGS in the country (SEOM and SEAP, 2022)
- The CASSANDRA Project, supported by various scientific societies with the aim to explore the feasibility of cancer screening in Spain (SEPAR, 2022)

BOX 4: SPAIN CASE STUDY SUMMARY

There is a lack of published evidence on testing standards. However, our Advisory Group members identified it as a critical issue. Some healthcare providers are keen to keep testing in-house, partly because it enables them to monitor how testing is conducted. Members of our Advisory Group explained that the content and format of test reporting can be highly variable in some settings – especially in the UK – and that reports are often not easily interpreted by clinicians or patients. Advisory Group members stated that, in some cases, test reports can provide patients with misleading information about their prognosis. In France, where policy-making has previously ensured that reporting is standardised, standards are now perceived to be threatened by the privatisation of testing services.

Variation in policy and guidance

Our review of the literature and engagements with the Advisory Group highlighted an absence of comprehensive policies and guidance documents that would support the proper implementation of NGS testing into routine clinical care. This has led to low physician knowledge and awareness, heterogeneity in clinical practice, and communication failings between health care professionals and patients.

Evidence from Europe indicates that there is variability in awareness among physicians of referral pathways and the availability of biomarker testing. Some physicians are uncertain about the interpretation and use of genomic data to guide treatment (Horgan et al., 2022). A lack of clinical standardisation aggravates this problem. Without proper validation of in-house biomarkers and consistent testing procedures between hospitals, physicians struggle to feel confident in incorporating genomic sequencing into routine clinical care. Guidance on evidence requirements to demonstrate clinical utility is currently insufficient, undermining the decisions made during treatment planning and limiting clarity when choosing the type of test (Horgan et al., 2022).

Many of the challenges described above can be observed in Spain, as demonstrated by the Spanish case study (see Box 4). In Spain, no standard procedures or nationally agreed guidelines are available for using NGS, leaving the responsibility of funding and implementing genomic testing to autonomous regions (Colàs-Campàs, 2021). NGS is available in specific centres and hospitals in Spain, and most NGS testing (78%) is done in public sector hospitals (Colàs-Campàs, 2021). Only two autonomous regions have reimbursed NGS and incorporated diagnostic tests for precision oncology in their healthcare practice: Cantabria and Catalonia (Hiris care & Amgen, 2021). Since biomarkers are not included in the basic standard of care decided nationally, individual regions are responsible for establishing guidelines around use and reimbursement. In some larger regions, such as Madrid, decisions are taken at hospital or borough level (Hiris care & Amgen, 2021). This lack of national guidance often leads to what has been referred to as a postcode lottery, with individuals living in more affluent areas potentially benefiting from greater access to these services and ultimately to inequality in access.

In Italy, there is no standard of practice for genetic testing, driving regions or individual hospitals to create their own guidelines. Members of our Advisory Group described how decision-making in this context has been slow in Italy and that the health system is sometimes slow in implementing directives once they have passed. It is notable, for example, that the DRG tariff was last reviewed in 2017, and Advisory Group members cited the lack of a DRG for NGS testing as a significant obstacle. Although geographical differences account for some variation in NGS testing availability, with the north of Italy generally having more capabilities (Marchetti et al., 2021), one of the main organisational barriers is the divide between small and large centres and the lack of established networks of communication between them. NGS is performed across numerous institutions, which vary in size and capability (Marchetti et al., 2021). The larger centres can generally manage increased

complexities and have greater productivity. This is linked to larger institutions benefiting from more staff members with specialised or diversified expertise. Additionally, they are more likely to be associated with a multi-disciplinary working group or molecular tumour board (MTB), which can provide further advice on interpreting the results of the genomic testing and guidance on the appropriate next steps in the treatment pathway. Marchetti et al. (2021) found that about two-thirds of surveyed centres communicated with MTBs or multi-disciplinary groups. The same research highlighted that diagnostic centres suffer from a lack of structure and national networks resulting in heterogeneity of laboratory characteristics and services provided. Furthermore, the study found that only 40% of the centres included a bioinformatician in their personnel, highlighting the variation in expertise in these centres (Marchetti et al., 2021). This problem disproportionately affects small centres, as the small number of tests performed provides little incentive for staff training—limited funding results in an inability to hire the appropriate experts, as derived from discussions with experts.

Variation in policy and guidance impacts funding but also directly influences the use of NGS. Variation leads to a lack of clarity on clinical pathways and undermines the development of the specialist capacity to conduct NGS testing.

Opportunities

Through the case studies, we have identified key opportunities across the four countries that could be important in driving the widespread uptake of NGS testing. These relate primarily to existing institutions and mechanisms, including patient organisations, multi-disciplinary clinical groups, education programmes, scientific societies, and industry funding.

Organisational capacities

Patient organisations act as the voice of patients and play an essential role in driving and enacting change. Lung Cancer Europe (LuCE) has led research demonstrating the disparities in access to diagnostic testing (Baird et al., 2021), and they regularly publish reports and provide guidance for patients and stakeholders. The European Cancer Patient Coalition (ECPC) is the leading overarching cancer patient organisation in Europe and a key stakeholder with significant influence, impact and involvement in cancer policy (de Lorenzo and Apostolidis, 2019). This is mirrored in countries such as Italy and Spain, where patient organisations are influential in cancer care. In Italy, Salute Donna, a voluntary, not-for-profit organisation focused on education and prevention of cancer, has launched the project *Health: an asset to defend, a right to promote*. Conducted in partnership with 46 organisations, this project aims to create a permanent dialogue with stakeholders to address the regional differences in cancer care across Italy (Salute Donna, 2017). Additionally, Women Against Lung Cancer Europe is another organisation allowing patients to access NGS testing locations through their website, supporting them to find and access their nearest NGS testing centre.

In addition to the national government, HTA agencies, and regional authorities, scientific societies are influential in providing guidelines. These guidelines inform and support clinicians in delivering optimal diagnosis and treatment practices. In Europe, ESMO was the first scientific society to give recommendations on the use of NGS for patients with metastatic cancer (ESMO, 2020). These recommendations were authored by European experts, including members of scientific societies from France, Italy, and Spain (Mosele et al., 2020). In Spain, the Spanish Lung Cancer Group (GECP) has launched the "Atlas" project that aims to provide NGS biomarker analysis to 1000 patients (GECP, 2022). Sociedad Espanola de Oncologia Medica (SEOM) and Sociedad Espanola de Anatomia Patologica (SEAP), two major Spanish scientific societies, performed a joint analysis of the NGS landscape in Spain (SEOM and SEAP, 2022). This highlighted areas of concern which can be addressed to improve the uptake of NGS in the country. As such, scientific societies continue to strengthen guidelines nationally and regionally to support optimal diagnosis for lung cancer, including the use of NGS.

Existing infrastructure

Adequate infrastructure is crucial to delivering equitable access to NGS testing. Our research and conversations with experts across the region indicate that countries fostering a centralised infrastructure, such as England and France, have provided more equitable access to these services than those with regional autonomy, such as Spain and Italy. In England, national genomic testing is performed via a network of seven Genomic Laboratory Hubs (GLHs) spread across the country and responsible for a particular region (HEE, 2022b). This centralised approach aims to simplify the care pathway for cancer patients and reduce geographical or social inequalities and was instrumental in improving the uptake of genomic testing for lung cancer patients (Snape, Wedderburn and Barwell,

2019). Similarly, molecular diagnostic tests in France are performed in a network of 28 platforms across the country with support from the French National Cancer Institute (INCa) and the Ministry of Health (Marino et al., 2018). This approach also aims to minimise the inequalities in access to molecular diagnostics (INCa, 2019). However, as the number of testing centres grows, they will need more stringent reporting guidelines to maintain standardisation.

Molecular tumour boards (MTBs) are multi-disciplinary groups comprising oncologists, pathologists, geneticists, pharmacologists, and bioinformaticians. They have played a crucial role in numerous countries, including France and Italy. Their purpose is to guide the selection of patients to receive appropriate personalised treatment based on the genomic profile results from NGS tests (Marchetti et al., 2021). Moreover, they have played a wider role in building local capacity to support NGS testing and build networks between stakeholders. In England, the NHS England Genomic Medicine Service Alliance aims to create networks among Genomic Laboratory Hubs and incorporate a more holistic approach to genomic testing. The project aims to bring together the essential multi-disciplinary groups which can help embed genomic testing into routine care (Hill, 2020).

Education and training

A lack of clinician awareness regarding the existence or availability of diagnostic tests can prevent patients from accessing the right treatment. Even if clinicians may be aware of these tools, poor understanding of referral pathways, time-to-results, and interpretation of reported results may deter healthcare professionals from using NGS. Hence, education and training play an essential role in supporting the uptake of NGS testing. In England, The Genomic Education Programme, supported by Health Education England (HEE), comprises various educational materials for healthcare professionals, including bitesize information on bioinformatics and short courses that teach and encourage the use of genomic testing (HEE, 2022a). In France, the rollout of whole-genome analysis is conducted by the France Medicine Genomique 2025 initiative (INCa, 2019). One of the offerings of this programme, launched in 2017, is education and training for those involved in genomic testing (France Medicine Genomique Plan 2025, 2022). At a European level, NEMHESYS (NGS Establishment in Multi-disciplinary Healthcare Education System) is an Erasmus+ initiative which aims to provide essential technical and bioinformatic training on NGS for qualified staff. The consortium includes several universities or academic centres from countries including Spain and France (NEMHESYS, 2022). Those investing more in training and education programmes from the countries investigated seem to benefit from greater uptake of NGS.

Industry support

Industry funding is a helpful steppingstone for regions at the beginning of their journey in NGS implementation and developing funding and reimbursement mechanisms. However, this model is not sustainable for long-term use, and countries should not rely on industry to provide resources to cover the cost of NGS testing.[1] Sponsorship from the pharmaceutical industry remains a requirement for reimbursement in some countries (IQNPath, ECPC, and EFPIA, 2021), and our Advisory Group members highlighted that industry-sponsored clinical trials were an important mechanism for the

[1] It is important to note that we are not discussing companion diagnostics, the reimbursement of which may rely on pricing agreements that include coverage of testing costs by pharmaceutical companies. NGS testing can be used to sequence thousands of genes and thus need not be considered with dependence on any specific corresponding drug therapy.

funding of tests in Italy. While this provides an avenue for increased patient access to these tests, albeit focusing on the trial's aims, it highlights the insufficient funding and necessity for outside support.

Objectives and recommendations

By synthesising the findings from the literature review, the Advisory Group meetings, and the in-depth case studies, we propose a set of recommendations to improve the uptake of NGS testing in lung cancer and achieve the efficiencies offered by this approach. These recommendations should be considered by policymakers and other stakeholders seeking to support more comprehensive access to NGS testing for lung cancer in Europe.

Learnings from the case studies have emphasised that different countries are at different stages of the pathway to full implementation of NGS testing as part of standard clinical care. For some countries, establishing reimbursement is the first necessary step. Other health care systems have established reimbursement processes but are restricted by infrastructural limitations. We propose six recommendations relating to three broad objectives designed to tackle the significant barriers to the widespread uptake of NGS testing for lung cancer across Europe.

Objective 1: pricing and reimbursement

In many countries, regions, and hospitals, reimbursement for NGS testing is insufficient to cover prevailing prices. As outlined above, there are distinct barriers and numerous opportunities in different settings, and the ideal model will differ for each setting. However, there are common challenges in personalised medicine and diagnostics, and generalisable strategies apply to the reimbursement of NGS testing for lung cancer across Europe.

Recommendation 1: reimburse NGS testing according to its value

There was a uniform agreement among the members of our Advisory Group that NGS tests should be priced and reimbursed according to their full health economic value. Given that healthcare systems vary in their comprehensiveness of what value entails and what elements of value are paid for, our (pragmatic) recommendation is to focus on clinical value initially. This would comprise the extent to which testing leads to improved patient outcomes such as survival and disease progression by identifying the optimal treatment for them. This would be compared to the direct medical cost and system efficiency implications, including testing and treatment costs along the patient pathway.

In countries such as Italy, we have observed that all but one of the regions are waiting for a national DRG to establish reimbursement of NGS testing at the regional level. Ensuring a well-designed comprehensive DRG is very important, as the flexibility of this system is often limited. As NGS comes with a high upfront cost, it may be that a specific DRG for NGS testing (as opposed to genomic testing in general) is required.

The potential clinical and economic gains from NGS testing are well documented in the literature. However, funding issues persist in many countries across Europe. HTA agencies, such as NICE and HAS, cite challenges surrounding the evaluation of the cost-effectiveness of NGS testing, of which there are many. Firstly, the value of the advanced diagnostic is often heavily anchored to the value of the targeted treatments it facilitates. These treatments are more expensive and have a much more limited pool of patients than traditional therapies such as chemotherapy. Secondly, establishing the value of NGS treatment is complicated as conventional frameworks do not capture many areas. Thirdly, the cost and the value of NGS testing are changing quickly. The budget impact in future is uncertain – it may increase (as more patients can be targeted) or decrease (if treatments bring cost

savings in the long term). Critically, NGS provides clearer information about who the population is for a new targeted treatment; NGS availability effectively supports the understanding of budget impact for future therapies.

Our investigation has revealed significant broader value elements, such as the value of knowing and scientific spill-overs that are not unique to NGS testing and are becoming key features of advanced diagnostic instruments (Towse and Garrison, 2017). In light of this, health care systems would benefit from reviewing standard value frameworks to understand how they might be adapted to capture the total value of innovative technologies. Where novel value frameworks are not adopted, these additional value elements should be considered by decision makers and should be a focus for future research.

Recommendation 2: include NGS in national minimum provision

We recommend that all European countries include NGS in their national minimum requirement, resulting in full reimbursement for the procedure. An important finding from our research and stakeholder engagement is that sustainable access requires national-level commitments and initiatives. Members of our Advisory Group stressed the value of not limiting test funding and reimbursement to specific indications. Given limited resources and the cost of the test, policymakers may opt for the gradual introduction of specific well-known biomarkers and indications to national 'minimum data sets'. This would enable healthcare systems to realise the clinical and efficiency gains from the intervention while benefiting patients. Decision-making opportunities for the realisation of this recommendation will arise in the future. For example, a discussion at the 2022 congress of the French Society of Predictive and Personalised Medicine (SFMPP) highlighted that, in France, a set of additional procedures is expected to be released from the RIHN envelope between 2023 and 2025 (SFMPP, 2022).

Objective 2: standardisation

The need for standardisation in testing pathways and biomarker analysis and reporting was repeatedly raised by members of our Advisory Group and evidenced in our case study investigations. Clinical guidelines are essential to harmonising the procedure, exploring when NGS testing is offered to patients and how its results are presented to clinicians. The development of international guidelines, such as those proposed by ESMO, should be encouraged, with individual countries contextualising these to their national frameworks.

Recommendation 3: issue national standards for sample analysis and reporting

The evidence suggests numerous potential efficiency gains could be realised with proper implementation of NGS testing, but a comprehensive infrastructure is needed to make this a reality. Standardisation is essential in ensuring that the entire testing process is precise, reliable, and quality controlled. Inconsistencies in reporting were highlighted as a barrier to the success of NGS testing in several countries. At the pathology level, result standardisation will help to ensure that laboratory reports are clinician- and patient-friendly. Additionally, national standards should include clear guidance regarding when NGS is offered to provide equitable access for all patients suitable for the intervention.

Recommendation 4: develop local clinical guidelines informed by international recommendations

If patients are to benefit from the breadth of information yielded during NGS testing, they must be supported by clear and comprehensive communication from their care giver. Patients place value on

the information itself and on knowing how their clinician is using this to create holistic treatment plans. There is value in international guidelines, such as those provided by ESMO. These guidelines should provide strong and coherent recommendations to support a consistent message across countries, directing clinical professionals and pathologists to incorporate NGS testing into standard clinical practice. Additionally, they should provide clear information on the potential benefits of genomic sequencing and how to communicate this to the patient. Finally, they should specify when to begin testing and the effect on the patient pathway, and explain how to avoid tissue wasting and get the most from the sample. However, both local and national priorities and contextual differences should be considered. Therefore, local guidelines should be developed that adopt the overarching principles from international guidelines and find the most effective ways to apply them to their local markets.

Objective 3: infrastructure

In many countries, a critical barrier to NGS testing is a lack of capacity in terms of physician knowledge and infrastructural support. There remains a need to develop capacity and expertise, focusing on informing clinicians and managers about clinical pathways and the role of NGS testing in lung cancer care.

Recommendation 5: introduce a national initiative to map patient referral pathways

Mapping the patient referral pathway may significantly streamline the diagnostic process for patients and clinicians. The national initiative should include a stepwise approach with details on how samples should be collected and handled, where and how to be transported, and how long it should take for the results to come back. This could help minimise the time taken for the investigation and enable earlier diagnosis, which could result in better clinical outcomes. Primary care practitioners should have strong relations with specialist clinics and foster collaboration for speedy referrals and direct access for suspected patients.

Recommendation 6: develop national education programmes

The potential clinical benefits of an NGS-informed treatment course are consistently validated in the literature. However, variable awareness among physicians leads to uncertainty in leveraging genomic data to guide treatment (de Alava et al., 2022; Tan et al., 2020; Horgan et al., 2022). Therefore, a comprehensive and practical education programme could ensure physicians feel comfortable delivering specialised care to patients who can benefit from targeted therapy. Hosting regional workshops for training and refreshing clinicians' knowledge could be one method to upkeep nationwide education and awareness towards NGS, complemented by national guidelines. MTBs have been successful in several countries and serve to build networks of specialists from different disciplines who can share knowledge and ensure that NGS testing pathways are managed effectively. MTBs are just one model for multi-disciplinary collaboration, which is vital to ensure buy-in from multiple stakeholders and increase uptake of NGS.

Conclusion

Throughout our research, the clinical case to support the use of NGS testing in lung cancer was framed as being settled. Its potential value is set to increase as the cost of testing falls and the number of patients who stand to benefit increases. However, our literature review highlighted a shortage of cost-effectiveness and economic evidence, a lack of clinical guidance, and significant shortcomings in the infrastructure needed to ensure widespread access across Europe.

We have set out the health economic case for NGS testing in lung cancer, specifying the areas in which it can deliver value to patients and health care systems across Europe. Our case study investigations reveal the heterogeneity in the access to NGS testing and significant differences in challenges faced by different health care systems in achieving widespread uptake. From here, we have developed a set of recommendations across three broad objectives. These recommendations have been designed to address the shortfall in uptake in Europe across reimbursement and funding, proper infrastructural implementation, and comprehensive clinical guidance. We urge researchers and policymakers to consider how advanced diagnostics in lung cancer can be appropriately valued and how treatment pathways in Europe can comprehensively implement NGS. We conclude that clinical and economic evidence supports NGS testing as part of the clinical management of lung cancer. It is time standardised comprehensive NGS testing in lung cancer becomes a reality.

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