RESEARCH ARTICLE

Understanding barriers to the introduction of precision medicine in non-small cell lung cancer: a qualitative interview study [version 1; peer review: 2 approved with reservations]

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Abstract

Background: While treatments targeting genetic mutations and alterations in non-small cell lung cancer (NSCLC) have been available since 2010, the adoption of such examples of precision medicine into clinical practice has historically been slow. This means that patients with NSCLC may not have received life improving and extending treatments which should have been available to them. The purpose of this qualitative interview study was to identify the barriers to the provision of examples of precision medicine for NSCLC.

Methods: This study used semi-structured telephone interviews with clinicians, test providers and service commissioners to identify the perceived barriers to providing historical, current, and future examples of precision medicine in NSCLC. Participants were identified through mailing list advertisements and snowball sampling. The qualitative data was analysed using a framework analysis.

Results: Interviews were conducted with 11 participants including: five oncologists; three pathologists; two clinical geneticists; and one service commissioner. A total of 17 barriers to the introduction of precision medicine for NSCLC were identified and these were grouped into five themes: the regulation of precision medicine and tests; the commissioning and reimbursement of tests and the testing process; the complexity of the logistics around providing tests; centralisation or localisation of test provision; and opinions about future developments in precision medicine for NSCLC.

Conclusions: A number of barriers exist to the introduction of precision medicine in NSCLC. Addressing these barriers may improve access to novel life improving and extending treatments for patients.

Keywords

Lung Cancer, Qualitative Interviews, Implementation, Precision Medicine

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Introduction

Advances in the treatment options for people with non-small cell lung cancer (NSCLC) have opened up the possibility of targeting specific mutations in a tumour. The first in class of such medicines to be recommended by the National Institute for Health and Care Excellence (NICE) was gefitinib in 2010¹. Gefitinib is an EGFR tyrosine kinase inhibitor (TKI). In patients with tumours that showed *EGFR* mutations, treatment with EGFR TKIs has been shown to extend the length of time a tumour takes to progress to a life-threatening size by two to five months^{2,3}. Furthermore, *EGFR* TKIs may offer greater improvements in quality of life and fewer severe side effects than standard chemotherapy^{2,4}.

Other targeted therapies have also been developed and introduced into practice, including crizotinib. For the approximately 5% of patients whose tumours exhibit *ALK* mutations, crizotinib can be used as a first line treatment⁵. Treatment with crizotinib has been shown to improve patient's progression free survival by over 4 months⁶ compared with standard chemotherapy. Treatments targeting a number of other biomarkers including PD-L1 overexpression of *ROS1* alterations have also been recommended by NICE and more are currently under evaluation^{7,8}.

These examples of precision medicine for NSCLC offer the potential to improve patients' quality and length of life. There is, however, some evidence that their uptake into practice in NHS England has been slower than anticipated. One factor affecting uptake, was raised during the NICE technology appraisals of the medicines targeting *EGFR* mutations. The issue raised was that that *EGFR* mutation testing was not current practice in the NHS before the medicines were available. In the 2010 appraisal of gefitinib, *EGFR* testing was not widely available in the NHS, although it was predicted that it could be quickly implemented with significant investment¹. In the 2012 appraisal of erlotinib it was stated during the NICE technology appraisal process that *EGFR* testing had become best practice. In 2013, the NICE Diagnostic Assessment Programme conducted an evaluation of testing methods for *EGFR*, which highlighted that there was heterogeneity in how testing was provided^{9,10}. A report published in 2014 by Cancer Research UK estimated that 48% of patients eligible for a targeted treatment for NSCLC were not receiving tests¹¹. As a result, 1,429 out of 3,007 patients who could have benefitted from targeted treatments were estimated to be missing out.

There is also evidence of variation in the turnaround time for tests meaning that some patients began treatment before receiving their results⁹. These concerns have been repeated in peer-reviewed published literature and NHS reports^{12,13} and a recent survey sponsored by the pharmaceutical company Boehringer-Ingelheim¹⁴.

When NICE recommends that a medicine should be used in the NHS, as part of the technology appraisal programme process, it becomes a legal requirement that it is made available for all members of the eligible patient group within three-months and paid for by service commissioners¹⁵. In contrast, when NICE appraises a diagnostic, guidance about its use is produced but there is no legal requirement to fund and provide the test¹⁶.

As a result there is evidence to support that testing is not immediately available for the entire patient population and complete uptake may require years¹¹. Even as testing is made available for all individuals, differences in the quality of testing and the turnaround time may have implications for treatment decisions meaning that the cost-effectiveness of test-treat interventions when used in NHS practice may differ from the cost-effectiveness estimated at the time of appraisal.

Previous research has shown that there have been issues with implementing examples of precision medicine for lung cancer but few have explored why this was the case for these test-treat interventions in particular¹⁷. One pilot study, conducted to inform a larger qualitative interview study, used face-to-face semi-structured interviews which explored how oncologist's perceptions and work environment affected their use of genomic-targeted medicines in clinical practice in the United States¹⁷. The published protocol for this study presents the results of a qualitative pilot study¹⁷. Approximately a third of the ten oncology fellows interviewed in the pilot study were uncertain about guidelines regarding the use of precision medicine as second or third-line treatments for lung cancer while a third of those interviewed were also uncertain regarding how to order testing¹⁷. Common barriers to performing tests included insufficient tissue samples, the inconvenience of testing and the cost of testing. Facilitators of tests were the ease of testing and deciphering results, as well as patients having health insurance. The cost of treatment was mentioned as a barrier by a smaller number of clinicians. These findings highlight how differences in financing arrangements may impact on the use of precision medicine in oncology.

A number of additional qualitative studies have sought to identify the barriers to precision medicine beyond NSCLC. In a 2013 study based in Canada, which used focus groups to explore the views of physicians about the future role of personalised medicine in health care, eight key relevant concerns about introducing personalised medicine were identified. These eight concerns were: insufficient knowledge; a need for training of physicians; lack of specific guidelines and protocols for using tests; unequal access to testing due to socioeconomic differences; the financial burden of testing on public funds; additional time pressures that precision medicine will put on clinical practice; need for geneticist support after testing¹⁸. In a qualitative study that used interviews to identify the barriers to introducing a test for the *BRCA* gene which significantly raises women's risk of breast cancer, clinicians highlighted potential issues with co-ordinating the receiving of test results with the timing of treatment decisions¹⁹. It was perceived by clinicians that the barriers to introducing *BRCA* testing could result in "postponement or avoidance of tests, delayed treatment decisions, and proceeding with decisions before test results [were received]".

Despite the number of studies investigating barriers to the uptake of precision medicine in general, there has been a paucity of research focussing on understanding the barriers to implementation of precision medicine for NSCLC into health care systems, in general, and in NHS England, specifically. This

study sought to create a typology of the organisational barriers to the introduction of examples of precision medicine in NSCLC. Organisational barriers are those that arise due to the way in which the health care system operates. These organisational barriers are in the control of the health system and so could be removed or reduced by taking actions to improve implementation.

Aims and objectives

This study aimed to understand and define the type and extent of barriers experienced by service providers and service commissioners when introducing precision medicine for NSCLC for relevant individuals within specific patient populations.

This study had four objectives to explore the views of stakeholders in the provision of examples of precision medicine for NSCLC to identify:

- the types of perceived organisational barriers to introduce examples of precision medicine for NSCLC in NHS England;
- the potential impact for NHS patients of the identified different barriers to the provision of licensed test-treat medicines indicated for the treatment of NSCLC;
- how the availability of existing licensed test-treat medicines indicated for the treatment of NSCLC has changed over time;
- a typology of barriers which may apply to introducing precision medicine beyond NSCLC.

Methods

This study used semi-structured telephone interviews with service providers (clinicians and test providers) and service commissioners to identify the barriers to introducing precision medicine for NSCLC in NHS England. This study was conducted between March 2018 and October 2018. A protocol for this study was published prior to the commencement of recruitment²⁰. This study was approved by The University of Manchester Proportionate Review Research Ethics Committee (Reference number: 2017-1885-3619; 25/08/2017). Participants were provided with an information sheet about the project and were asked to return a signed consent form by post or email prior to taking part in the study.

Telephone-based semi-structured interviews were used to collect qualitative data due to the focus of this work on capturing a geographically diverse sample to represent heterogeneity in health care provision. Telephone interviews offer similar advantages to face-to-face interviews while allowing more flexibility in arranging the timing of the interview.

Sample frame

The sampling frame aimed to identify stakeholders with experience of introducing precision medicine for NSCLC. The relevant stakeholders were identified by examining the NICE care pathway for patients with NSCLC. The relevant stakeholders were drawn from three groups: clinicians; test providers, for example pathologists and geneticists; and service commissioners

which may include individuals who are members of care commissioning groups or those involved in commissioning at the national level through NHS England. The principle service providers of interest were oncologists and respiratory physicians specialising in lung cancer but also geneticists and pathologists who are key in providing examples of precision medicine for NSCLC. Examples include *EGFR*, *ALK* and PD-L1 testing for medicines such as erlotinib, ceritinib and pembrolizumab.

While factors linked to demand for precision medicine by patients, such as uptake of testing or treatment or adherence to medicines treatment may also impede the implementation of precision medicine, the focus of these interviews was to identify potential barriers focussing on the perspective of the health care system (supply-side capacity constraints). This focus was taken because these capacity constraints in the supply of testing or treatments are within the control of the health system. For this reason, patients were not interviewed in this study.

Clinicians and test providers with over seven years of NHS experience were targeted as such individuals were more likely to have direct experience of the introduction of *EGFR* and *ALK* testing and treatment as they were working in clinical practice. Clinicians and test providers were recruited via the British Thoracic Oncology Group (BTOG) [15] and the Royal College of Pathologists (RCPATH) [16]. Details about the study and an invitation to participate were circulated via the BTOG mailing list which currently has 2083 members and the RCPATH list that has over 11,000 members.

The targeted service commissioner sample comprised hospital, regional and national level individuals involved with service commissioning and funding decisions. Examples of service commissioners may involve members of care commissioning groups, hospital finance staff and decision makers involved with national organisations, such as NICE. As service commissioners were likely to come from a range of organisations, there was no universal sampling frame available to reach them. Service commissioners were therefore recruited using existing links and collaborations within the supervisory team to identify an initial sample. As in recruitment for the clinician sample, geographical diversity was sought through purposive sampling and service commissioners were required to have been in a relevant position when *EGFR* and *ALK* mutation based testing and subsequent treatment were introduced.

Sample technique

Purposive sampling was used to gain a diverse sample in terms of the setting and geographical location of testing and treatment²¹. These characteristics were deemed likely to be important in the context of introducing examples of precision medicine as experiences may vary depending on the size and nature of hospitals. For example, mutation testing services may be more readily available in larger teaching hospitals with established links to laboratories. For smaller, general hospitals there may be a greater logistical challenge in sending samples for testing and receiving results in a timely manner.

Sample size

Calculating a target sample size based on defined rules is not relevant in the design of qualitative studies²². The target sample size in qualitative studies is informed by the aim of the analysis. In this study, interviews were used to identify the breadth of experiences, thoughts, or opinions on a given subject. This study therefore started with an approximate target sample of ten clinicians or test providers, and ten service commissioners. Inductive thematic saturation was then used that means sampling continued iteratively until no new themes arose from the collected data that were analysed alongside data collection²³.

Recruitment process

Information regarding the study was sent to clinicians and test providers using mailing lists, with contact details of the principal investigator provided for those interested in taking part. The individuals that expressed an interest in taking part were then subsequently sent more detailed information about the study. Service commissioners were directly sent an email including information about the study and the contact details of the principal investigator. Snowball sampling was used for both samples whereby participants were asked if they knew any other individuals who meet the inclusion criteria who may have been interested in taking part in the study²⁴.

Clinicians and service commissioners who were interested in taking part in the study were asked in the mailing list adverts to email or phone a named individual (SW) to express an interest in taking part. The researcher then emailed the potential participant a participant information sheet. After receiving an information sheet, potential participants were given at least 24 hours to consider taking part in the study. If they agreed to take part they were asked to complete a written consent form and to return a copy to the researchers by post or email.

Data collection

Semi-structured interview schedules were created for the two study samples. The interview schedule was piloted with two clinicians before study recruitment began. The interview schedule for service providers (see extended data²⁵), and service commissioners (see extended data²⁶) were, informed by a systematic review of previous economic evaluations of precision medicine (including health technology assessments)²⁷ and consultation with two expert clinical advisors who are lung oncologists. The core questions for each of the two interview schedules were similar. There were slight variations in the way some of the questions were asked depending on the particular role of the interviewee. For example, clinicians were asked primarily about their experience offering treatments to patients while for geneticists and pathologists the focus was on offering testing.

All telephone interviews were conducted by one researcher (SW) at The University of Manchester and were digitally-recorded. Phone calls and recording took place in an enclosed office. The recording device and memory card containing the interview recordings were stored in a locked draw in a secure university office. The recordings were saved onto an encrypted university computer and the files password protected. The lead researcher

(SW) transcribed the first three recordings from the interviews. The remaining recordings were transcribed verbatim by a contracted transcription company called 1st Class Secretarial Services²⁸. Recording were transferred using a secure, encrypted connection. Recorded interviews were deleted from recording devices after they were stored on a computer and anonymised and then destroyed completely at the end of the study. Interview transcripts will be stored for 10 years.

Data analysis

The objectives of data analysis were to: identify potential barriers; and create a typology of barriers that may prevent patients' access to precision treatments for NSCLC. The qualitative data were analysed using framework analysis²⁹.

In the initial data familiarisation stage, one researcher (SW) transcribed and read the first three interviews in order to gain an in-depth understanding of the initial themes emerging from the data. The initial key themes identified during the data familiarisation stage, alongside evidence from previous research formed an initial thematic framework against which the selection of data was sorted and collected³⁰. As semi-structured interviews were used for this study, many of the themes originated in the questions contained in the interview schedule. As new themes were identified in the data, they were added to the framework.

Each transcript, facilitated using NVivo software (version 10)³¹, was indexed against these identified themes, with sections from the text which support different themes annotated for later retrieval. In the context of this study, the identified themes were the range of barriers which occur in providing and accessing examples of precision medicine for NSCLC and views about which barriers were most significant in restricting the provision of precision medicines.

Results

The section reports the results from 11 interviews with participants including; five clinicians, three pathologists, two clinical geneticists, and one service commissioner. All of the clinicians were consultant oncologists. The pathologists comprised two consultant histopathologists and a biomedical scientist. The geneticists were clinical scientists and the service commissioner was a consultant in clinical genetics. Participants were based in a range of hospitals including city-based teaching hospitals and city-based general hospitals serving town and rural communities. The interviews took place between March 2018 and October 2018 and each interview lasted a mean of 23 minutes (range: 10 minutes to 39 minutes). Data saturation was achieved in the clinician sample but it was not possible to recruit sufficient numbers of test providers or service commissioner to achieve data saturation and as such results from this sample can only be viewed as indicative.

A total of 17 barriers to introducing precision medicine for NSCLC were identified. These 17 barriers were grouped into five key broad themes (see Table 1): the managed entry of precision medicine for NSCLC; the commissioning and reimbursement of precision medicine for NSCLC and specifically

Table 1. A typology of barriers to the introduction of examples of precision medicine for NSCLC.

Theme	Barrier	Description
Managed entry of precision medicines for NSCLC	Delays between the end of trials or early access to medicines programmes and NICE approval	While NICE is appraising whether a targeted treatment should be made available to all patients in the NHS, there is no funding available to make it available to new patients.
	Increasing number of targeted treatments being appraised by NICE	NICE is appraising an increasing number of targeted treatments for patients with NSCLC and this may lead to a slower appraisal process and delays in new patients accessing the medicines
Funding mechanisms and service commissioning	Withdrawal of pump-priming funding for biomarker testing	If pharmaceutical companies withdraw funding for testing before the NHS can provide enough tests, some patients may not receive treatments targeted to their mutations or may experience delays in receiving treatment
	Geographical inequalities in access to funding for testing	In the absence of a clear route for reimbursement of test costs, smaller or more rural hospitals may find it more difficult to provide testing than larger hospitals.
	No mandate for NHS England to fund testing when a targeted treatment was approved	Upon approval of a targeted treatment by NICE, the cost of the drug will be reimbursed to hospitals by NHS England. However, previously there was no such provision for the test required to target the treatment. As such hospitals often offered the test at a loss as they didn't know how the test was reimbursed. There was conflict between different service providers about who should pay for the test
	Lack of awareness of guidelines about test reimbursement	As of 2016, most biomarker tests required for a targeted treatment approved by NICE have a clear reimbursement route. However, there is still a lack of awareness of these guidelines
	Lack of funding for test validation	There is a lack of funding to validate the locally conducted immunohistochemical testing required for some targeted treatments. This may lead to heterogeneity in the quality and therefore ability to stratify of the biomarker testing in different areas
Logistics of Organising Testing to Guide Treatment	Delays occurring in pathology laboratories have knock on effects for other testing	Pathology laboratories are involved at the beginning of the testing pathway in preparing samples and conducting immunohistochemical screening. If there are delays at this stage, this causes delays for subsequent genomic testing and in returning results to patients
	Poor quality of samples sent by pathology	If the quality of samples sent by pathology to genomic laboratories is insufficient then there may be delays as an additional tumour sample will have to be requested and re-sent. Patients may refuse a second biopsy meaning that testing cannot take place
	Increasing workload for pathology laboratories	Pathology laboratories are required to process samples, provide a number of immunohistochemical tests and send samples to different laboratories for genomic testing. As the number of biomarker tests required, pathology laboratories may find it hard to keep up with this demand, resulting in a slower turnaround time for tests
	The quantitative nature of the PD-L1 test	When conducting the immunohistochemical test for PD-L1 overexpression, pathologists must estimate the percentage of the tumour sample showing overexpression. This introduces subjectivity into the result. If pathologists do not analyse many tests then they may be less effective at estimating this percentage
	Understaffing of pathology laboratories	Even when funding is available for testing, a shortage of staff in pathology laboratories may slow the turnaround times for tests.
	Sequential biomarker testing	Currently many hospitals run the tests in a sequence. This means that there is a delay in waiting for the initial test results to be returned before additional tests are requested. It is also possible for pathology laboratories to run out of tumour sample to be tested for the latter tests requiring additional samples to be taken.

Theme	Barrier	Description
	Tests conducted in different locations	For hospitals which do not conduct testing in-house, the samples may have to be sent to different hospitals for different tests. This when combined with the sequential testing of samples may further add delays to receiving results.
Providing Testing Locally or a Through A Centralised Service	Testing is centralised	Centralised testing may mean longer turnaround times for tests as they struggle to meet the demand from multiple hospitals
	Testing is localised	Localised testing may mean that testing is of poorer quality as pathologists do not get to see as many samples so have less opportunity for learning
Barriers to Introducing Future Barriers to Precision Medicine	Less accurate IHC screening	The IHC screening stain for <i>ROS1</i> mutations has a lower specificity than that of <i>ALK</i> and so more tests will have to be sent for more costly and complex FISH testing

the test component of precision medicine; the complexity of the logistics around providing tests; opinions about whether test provision should be localised or centralised; and opinions about future developments, including potential barriers to their introduction, in precision medicine for NSCLC. None of the participants identified any facilitators to the introduction of precision medicine for NSCLC.

Managed entry of precision medicine for NSCLC

Strategies to manage the entry of precision medicine for NSCLC, such as the process of technology appraisal by NICE, was an identified barrier to patients being able to access these test-treatment interventions. Some interviewees, mainly those from an oncology background, suggested that patients could previously access new medicines by enrolling in a trial or through Early Access to Medicines (EAM) programmes. For *EGFR* and *ALK* targeted medicines, there was now clearly a gap between the availability of the medicine through a trial and EAM programmes and in standard clinical. This gap was perceived to be the result of the appraisal process by NICE:

“but then there’s a delay between...with NICE approval or CDF (cancer drugs fund) approval and so it just means that there often windows of a few weeks to a small number of months where it’s not clear where you can get the stuff from” [C3, Oncologist, Town based hospital]

This interviewee pointed out that the length of this gap has been observed to be shortening in recent years:

“[NICE are] much more responsive than they were two or three years ago” [C1, Oncologist, City based teaching hospital]

This clinician believed that the observed responsiveness had been achieved by an improved process of “horizon scanning” and working with pharmaceutical companies to identify new examples of precision medicine that are currently being investigated in phase three (clinical development) clinical trials. However, the same clinician also warned that the increasing number of such

interventions may have consequences for NICE and hence patient access to precision medicine for NSCLC:

“because one of the problems we know is that there are lots of things happening, there are very exciting new treatments that are demonstrating efficacy and so we just need to be able to make sure that NICE can keep up with all of the new approvals that are coming through which will be an issue” [C1, Oncologist, City based teaching hospital]

Funding mechanisms and service commissioning

The most commonly discussed barrier across service providers was a lack of clarity in the commissioning process for precision medicine, with a particular focus on the availability of funding for testing. Due to the low availability of biomarker testing before and at the time of NICE approval for a precision medicine, it is common for the manufacturer of the medicine to provide initial (‘pump-priming’) funding to the NHS to help conduct testing. The process, while loss-leading for the manufacturer, allows clinicians to start using targeted medicines when testing does not exist in the health system. However, many participants highlighted the problems which occurred when companies withdrew funding for *EGFR* and *ALK* mutation testing before NHS funding for tests had been established:

“the pharma companies, of course, kind of, got wind to that [there was no existing testing] and started to fund the testing, either centrally or locally for a period of time, which then became time-limited. And at the end of that time-limited period, there was quite a lot of uncertainty about who would be paying for the tests, and where the bills should be sent” [C4, Oncologist, City based hospital, regarding *EGFR* testing]

Geographical inequity in access to testing arising from difficulties in receiving reimbursement for testing was a common theme in the interviews. While some service providers struggled to provide testing due to a lack of available funding, others used different strategies to ensure a continuity of test provision. Some clinicians believed that hospitals with bigger reputations

could provide more funds for testing. In some cases research funding was used to fund testing until NHS funding was made available:

“We didn’t set things up that way in [City based Hospital], so we didn’t have that situation because actually we were paying for it from research funds anyway. So [City based Hospital] have not had that sudden removal of testing because we were paying for it from our own funds in the first place and just continued to do so” [C1, Oncologist, City based teaching hospital].

After the removal of pump-priming funds for testing by pharmaceutical companies, there was a perceived need for the NHS to provide a clear commissioning route through which hospitals would be reimbursed for the tests they conduct. However, one problem identified by this participant was that:

“NICE, kind of, recommends the drug and then don’t really make any provisions for the test” [C4, Oncologist, City based hospital]

While service providers are mandated to provide a medicine for patients with specific biomarkers, there is no requirement for them to actually provide the stratifying tests. In addition, no formal reimbursement mechanism exists should they decide to fund the test¹⁶. This gap in the process for agreeing funding appears to have caused significant issues for each test for some service providers:

“And then there was the testing requirements for looking for EGFR mutations and ALK alterations, so that the main issue is that although these drugs became recommended for use, there was very little clarity about who would pay, who would pick up funding for the testing” [C4, Oncologist, City based hospital]

In this scenario, test providers would effectively be supplying testing for free:

“It all comes down to the funding. You see what happens is, in our experience, like NICE would approve the drug, but at no point are laboratories or the managers being supported of how they can recoup the costs of the test. So, like say for ALK, we found it costs £50 a day by immunohistochemistry but it’s about £120 if you do it by FISH So, we got that result but it’s about £50 for that and we’ve been doing ALK for about three years now and we still have not been able to get the money reimbursed” [TP2, Biomedical Scientist, City based teaching hospital]

The lack of service commissioning arrangements seems to have resulted in the cost of the tests not being reimbursed by NHS England. There were, however, clear negative consequences for hospitals in NHS England. Without the cost of testing being reimbursed, it was perceived that the pathology laboratory performing testing would experience a financial loss. No interviewee stated that patients weren’t receiving tests because of a lack of reimbursement for testing:

“I have to do what’s right by the patient and follow the guidelines as they’re set and it’s for the labs to fight with the CCG’s

[Clinical Commissioning Group] to try and clarify how they’re going to fund it, but I think in reality, they don’t have enough money and therefore they’re just going to get more in debt because there isn’t a way round it” [C3, Oncologist, Town based hospital]

For many interviewees, it was not clear who should take responsibility for the cost of testing given who accrues the potential benefits. This confusion in responsibility was because precision medicine involves a complex intervention comprising a test-treat strategy and involves processes using many different specialities including pathology, genomics, and oncology. As such while specialities such as pathology and genomics may be covering the cost of testing, the benefits are realised almost entirely in oncology:

“we are paying huge amounts still for sending tests for PD-L1 testing which is actually not our test. In a way it is a test for oncologists” [TP3, Histopathologist, City based teaching hospital]

If testing helps to prevent patients from receiving an intervention that will not benefit them, as was the case when *EGFR* testing for gefitinib was introduced, the expense paid for by pathology or genomics may even save money for oncology services. The complexity of the testing pathway and the lack of clarity about test commissioning appeared to create conflict between the stakeholders in the provision of the precision medicine:

“historically these sorts of things have perhaps been picked up in pathology departments but, you know, the more and more tests we do, the less and less they are willing to, kind of, handle those budgets and the more pushback there’s been” [C4, Oncologist, City based hospital]

“The actual doing of the work, it’s not been a problem at all and we’ve got a really good relationship with the clinic and they’re very grateful that we reflex test but now the managers are going, whose paying for this, whose approved this, that sort of thing” [TP2, Biomedical Scientist, City based teaching hospital]

Some test providers who were interviewed were aware of relevant guidelines for the introduction of precision medicine for NSCLC but for many there was still confusion about test reimbursement:

“So what I found was when the ALK testing was rolled out there is a tariff paid by NHS England which covers the cost of the test” [TP1, Histopathologist, Suburban hospital]

“...you just jump through hoops and everybody wants to know who is going to be pay for this test. So, we’re at the short-fall at the minute with ALK” [TP2, Biomedical Scientist, City based teaching hospital]

Even where funding for the day-to-day costs of testing was available, some participants in this study, particularly pathologists, struggled to find funding to validate the tests in their own laboratories. This problem emerged with the introduction of immunohistochemistry screening for *ALK*:

“So the reagent for the ALK test was £50 so if you wanted to check, say, 100 cases that would be £5,000 that needed to come from somewhere to validate it on before you could start running it clinically. So there was no funding laid out by the NHS for that, you’d have to try and just find it locally or source it within your lab itself” [TP1, Histopathologist, Suburban hospital]

For some test providers the barrier of a lack of funding for test validation was mitigated through the provision of grants by the manufacturers of the relevant precision medicine. This potentially mutually beneficial agreement helps laboratories to provide testing to patients while also ensuring the company increases the number of patients who are deemed eligible to receive the medicine. This solution was used by different providers for both ALK and PD-L1 testing. This interviewee gave the example for ALK mutation testing

“[Pharmaceutical Company] gave us a grant and because we were paying £120 to do the FISH and £50 for the immunohistochemistry, [pharmaceutical company] gave the Trust a grant to validate so we didn’t incur that cost to validate” [TP2, Biomedical Scientist, City based teaching hospital]

Other interviewees seem to believe that the NHS should be more involved in providing funding for test validation and development:

“...we’ve got one or two people who do work solely on development of tests. But, most departments don’t, I don’t think, have that. So, having more funds, or at least allocated time to do development of new tests, that’s the main, sort of, barrier that we have, I think” [TP4, Clinical Scientist, City based teaching hospital]

Failing to provide funding for genomic and pathology laboratories to validate their tests could lead to heterogeneity in the level of test validation and therefore quality of testing across England. This heterogeneity in test validation and quality in turn may result in patients missing out on treatments that would benefit them or receiving treatments which do not benefit them due to poor stratification. For example, one pathologist believed that other laboratories might not be as rigorous in assuring the quality of their test:

“I think it’s all very variable in that if someone else in another pathology departments sets up the same assay they might not necessarily ask the questions that we’re asking in exactly the same way” [TP1, Histopathologist, Suburban hospital]

Logistics of organising testing to guide treatment

Precision medicine for NSCLC involves the provision of diagnostic test that then informs whether a targeted medicine is appropriate and the logistics of organising this process involves the collaboration of multiple health service disciplines. These complex interactions between different departments can be a barrier to implementation. For example, pathologists are involved near the beginning of the precision medicine pathways for:

EGFR testing in preparing tumour samples, in ALK testing in conducting IHC screening to determine the need for follow up FISH testing, and in fully conducting PD-L1 testing. Clinicians and geneticists suggested that delays occurring in pathology laboratories could have knock-on effects for the rest of the clinical pathway:

“So, as soon as we receive the sample, we can get the results back very fast. But, sometimes, there’s a delay in receiving the actual sample from pathology, so that can delay things quite a bit sometimes” [TP4, Clinical Scientist, City based teaching hospital, regarding EGFR mutation testing]

“there’s a number of delays in that pathway. Partly it’s the pathologists remembering to do it, then the sample actually being physically sent, then the sample being received, then processed, then the result coming back” [C4, Oncologist, City based hospital, regarding ALK testing]

An additional barrier, which was highlighted by some participants, can be that the quality of the tumour sample is not sufficient for geneticists to conduct mutation testing:

“Quite often. It’s not very rare, actually. Or, it might even be that we do receive the sample on time, but the quality of the sample is not good enough for testing” [TP4, Clinical Scientist, City based teaching hospital]

These delays may be as a result of processing by pathologists or simply because it is difficult to extract a sufficient volume of tumour from patients who have advanced lung cancer³². In the former case, additional samples can be requested from those kept in storage or through re-biopsy. In the case of the latter, treatment options may be limited:

“it can happen that either the patient refuses to have the second biopsy or the patient can’t wait to have the second biopsy, because of deteriorating clinical conditions and it’s better to start chemotherapy instead of waiting for another biopsy” [C2, Oncologist, City based hospital serving rural community]

Potential barriers in the quality and speed of service provided by pathology laboratories may occur due to an increasing pressure on services due to the volume of samples processed and the increased workload involved in processing each sample. For example, pathologists first conduct haematoxylin and eosin stains that help to highlight abnormal cell structures to inform a cancer diagnosis. The pathologist then determine the type of lung cancer present by looking at the cells and potentially conducting additional immunohistochemistry tests. If the cancer is identified as NSCLC, the pathologist will then prepare part of the sample to send for EGFR mutation testing and potentially conduct a number of IHC tests on the remaining parts of the sample for other markers such as ALK or PD-L1.

An additional barrier presented in providing PD-L1 testing is that there is some subjectivity involved in the interpretation and reporting of the results of IHC stains:

“if there’s a little bit of tumour in a big resection slice like that might be a resection slice and you might have thousands of tumour cells in that. And then they’re asking you to say, well, is it one per cent of the tumour positive or less than one per cent? So if you have a little bit of staining in the tumour but it’s less than one per cent it will be taken as a negative result, but if it’s one per cent it’s taken as positive for second line therapy. So that can be really hard to decide sometimes” [TP1, Histopathologist, Suburban hospital]

The tumour samples sent for different tests often need to be prepared in different ways, adding an additional layer of complexity and a potential barrier to providing prompt results:

“what we do in our lab is cut sections and send the slides, but for tests like PD-L1 they want the whole block because they want to cut it fresh so that interpretation is not missed, not changed. So, we all needed to understand how we can do it best” [TP3, Histopathologist, City based teaching hospital]

Despite the increased workload, pathologists suggested that they struggled to find sufficient resources to support their services, therefore creating another barrier to returning test results promptly and allowing treatment to be started quickly. This problem did not seem to occur in genomics laboratories.

“that’s the major problem we are facing in our department because as we know, budget is available for PD-L1 testing and I get every time the pharmaceutical companies com[ing] to me. I say I can understand that, but we don’t have enough people so we just need to see how much we can do” [TP3, Histopathologist, City based teaching hospital]

“the genetics lab had the capacity there, they’ve had to increase their capacity to incorporate other tests but they had capacity for that test at the time they implemented it” [C5, Oncologist, City based teaching hospital, regarding EGFR mutation testing]

The increasing number of different tests that are now involved in the pathway for patients with advanced NSCLC can act as a barrier to patients receiving prompt access to a relevant targeted medicine. Delays in processing one test can cause delays in conducting and receiving results for others. This delay is because the mutation tests are currently done in sequence and it is common to wait for the results of EGFR or ALK before sending more of a tumour sample for PD-L1 testing:

“sometimes in the past what has happened is we have received a request for EGFR and ALK and then we’ll get a request, oh, can you do PD-L1? And by that time the sample has already gone for testing for ALK in a different place. So, we’ll have to ask for a block and then it causes time delays” [TP3, Histopathologist, City based teaching hospital]

In addition to the complexity caused by sequential testing, the different tests were often sent to different laboratories and potentially even different trusts for analysis:

“the additional issue is that our pathologists have to collect the sample and send part of it to Sheffield to perform the EGFR and ALK, and part of it to Birmingham. So two different places. And I understand an additional complication for the pathologists, because I think they want to wait and see if there is enough tissue for EGFR and ALK. And once they know there is enough tissue, then they send the request for the PD-L1” [C2, Oncologist, City based hospital serving rural community]

Providing testing locally or a through a centralised service

The size and location of the laboratory conducting ALK IHC or FISH testing was identified as a potential barrier to the timely use of precision medicine. However, there were significant differences in interviewee attitudes to whether testing should be conducted more locally or should be conducted in fewer, centralised laboratories. In addition, opinions on the issue of centralisation or localisation appeared to depend on the nature of the test and role of the service provider. For example, it was generally considered that as EGFR testing required specialist knowledge this test would need to be conducted in larger genomic medicine centres:

“Yeah, yeah. I think EGFR can’t be established in all places. It has to be where molecular tests can be done” [TP3, Histopathologist, City based teaching hospital]

There was substantially more disagreement about where ALK testing, when compared with EGFR testing, should be conducted. While ALK testing was originally conducted using centralised FISH (fluorescence *in situ* hybridisation)-based genomic testing, the move towards immunohistochemical screening for the mutation increased calls for the analysis to be moved into local pathology labs. Many participants believed that moving testing “in-house”, often in the same hospital that the patient was being treated at, would mean cheaper testing and a shorter turnaround time for tests leading to better outcomes for patients. This was seen to be particularly true of PD-L1 testing, another immunohistochemical-based test, which is currently only conducted by a small number of centralised pathology labs.

“So it’s a problem at the moment and when that comes in house in the next few weeks it will take away that terrible time delay that will take away the uncertainty of me having to say to the patient “well actually I’m not sure of what you’re initial treatments going to be”” [C1, Oncologist, City based teaching hospital]

“So, we’re getting good correlation, so I think we should be able to finish our validation in the next two weeks or so and fingers crossed, if we can get the money, we can do it in half because the turnaround time in-house is going to be a day, whereas with Liverpool currently it’s taking about two weeks” [TP2, Biomedical Scientist, City based teaching hospital]

Some test providers were more sceptical of the drive to localise pathology testing. Some pathologists believed that

policy makers were pushing for local testing because the large laboratories did not have the capacity to meet demand. Furthermore, these individuals highlighted the fact that they were being asked to set up testing without any funding being available.

"I find there's this huge pressure and bottleneck from the whole structure of the trust within the NHS because there's a drive to save money and they don't actually want you to set up a new test locally if they think another hospital can do it because they want to just save money within the trust" [TP1, Histopathologist, Suburban hospital]

"I think the main problem which the bigger hospitals are now finding is the turnaround time. They can't deal with it. They have the pressure of cases, so it's the balance between expertise and turnaround time" [TP3, Histopathologist, City based teaching hospital]

In addition to a trade-off between cost and turnaround time for IHC testing, questions were raised about whether localising testing would reduce quality. This is because large laboratories processing large volumes of tests would be able to learn from experience while small laboratories might be unfamiliar with test methodology.

"we'll have more local testing although it won't necessarily be done in every single lab because the pathologist needs to have a number of tests that they do on a regular basis in order to be confident in the scoring" [C1, Oncologist, City based teaching hospital]

Barriers to introducing future examples of precision medicine in NSCLC

Interviewees identified a number of new developments in the provision of precision medicine for patients with NSCLC as well as the potential barriers that were faced to support their implementation. During the time-scale of the interview process for this study, NICE approved the use of the drug crizotinib for patients with *ROS1* mutations. When asked about potential barriers to introducing testing for *ROS1* mutations, there was some optimism that implementation would be smoother than for previous tests. This perceived easier implementation was because many laboratories have set up *ROS1* testing for research purposes and as the testing process is similar to that of *ALK* testing, because it also uses an immunohistochemical-based test prior to FISH testing. This interviewee spoke about establishing *ROS1* testing before the approval of crizotinib:

"[Tertiary hospital] have the assay but we just do that, we just do ROS1 on some of the adenos, basically give ROS1 testing at [tertiary hospital] as an immunochemical test. And then if they're positive they'd get FISHed the same way you would for ALK." [C1, Oncologist, City based teaching hospital]

There were still deemed to be some potential barriers to introducing *ROS1* testing. Again, a lack of clear commissioning routes for the test was highlighted and one participant highlighted that the IHC screen for *ROS1* was not as good as that for *ALK*

meaning that more samples sent for the more expensive FISH test would be negative for the mutation.

"But I think ALK is the most straightforward interpretation of all of them. ROS1 will have more cases which will go for FISH so I think we'll have to be careful about the funding and budget about those should be there so, yeah" [TP3, Histopathologist, City based teaching hospital]

Given the increasing number of tests available to stratify treatment for patients with NSCLC and the current approach of running tests in sequence, there is a risk of delaying the start of treatment for patients while waiting for test results. However, a number of developments may help to reduce this risk by ensuring that some or all of the tests were conducted at the same time. Some genomics laboratories have begun offering panel tests in which all potentially relevant mutation tests were conducted at the same time. However, such panel tests can be technically difficult to set-up as the methods for testing for *EGFR* and *ALK* mutations are different. A further development, next generation sequencing (NGS), may counter this issue by allowing all mutations to be searched for using a single test rather than a group of individual tests:

"And ideally you need a panel that includes...that can cover the translocations as well and then you could actually test for ALK and ROS1 in the panel and you could have one test, more or less, except maybe PD-L1 as well, that's separate. Yeah, but I think that's what needs to be aimed for, that you just make one test, that just makes it easier" [TP1, Histopathologist, Suburban hospital]

At the time of the interviews, NGS-based testing was used only in research but not in clinical practice due to its high cost. However, as more mutations become relevant in clinical decision-making, the balance between the cost of NGS, and associated interpretation of the result, and the cost and interpretation of a number of individual tests may become more favourable. NGS-based testing also has the advantage of requiring less tissue from patients and may reduce the number of repeat biopsies that are required³³. However, as highlighted by one pathologist, NGS-based testing would not be able to guide treatment of PD-L1 targeting therapies as currently only immunohistochemical-based tests are available for PD-L1 overexpression.

Importantly, patients' tumour profiles can change over time, therefore, additional tests may be required regardless of how advanced the original test methods were. Such changes include the addition of resistance mutations such as *EGFR* T790M³⁴ and *ALK* G1269A³⁵ following treatment with *EGFR* TKIs and *ALK* inhibitors respectively. To identify these potential mutations in patients who stop responding to treatment, additional testing is required which in the past has required an additional invasive biopsy to be conducted. Recently circulating tumour DNA (ctDNA) testing has been introduced by some laboratories which allows such mutations to be identified from a blood sample rather than a tumour sample³⁶. Some participants suggested benefits to

using blood-based tests instead of tumour samples for initial identification of mutations:

"If anything, I think, I mean, obviously if you'd skipped the whole pathology step, then that would save a lot of money. Especially if you don't do the biopsies, but the actual test, the cost is very similar." [TP4, Clinical Scientist, City based teaching hospital]

"sometimes they're [the patient] too sick, sometimes you have multiple failed biopsies, sometimes you...yes so, we had a patient that we tried to repeatedly biopsy and we just couldn't get enough tissue to do it and we did a serum test and it was positive and that was our answer" [C3, Oncologist, Town based hospital].

Discussion

This qualitative interview study identified 17 barriers that may impede the introduction of examples of precision medicine for NSCLC. These barriers were grouped into five themes: the managed entry of precision medicine for NSCLC; the commissioning and reimbursement of precision medicine for NSCLC and specifically the test component of precision medicine; the complexity of the logistics around providing tests; opinions about whether test provision should be localised or centralised; and opinions about future developments, including potential barriers to their introduction, in precision medicine for NSCLC.

The existence of these barriers may explain the slow adoption of the test-treat interventions into the clinical practice for treating patients with NSCLC. Therefore, these barriers can also be identified as capacity constraints (bottlenecks) in the health care system (supply-side). The development of this typology of barriers, and associated supply-side capacity constraints, to the introduction of examples of precision medicine for NSCLC may aid in predicting the potential challenges that may be faced in introducing future examples of precision medicine in NSCLC, specifically, and other disease areas, generally. By being aware of the barriers and taking action to address them before the introduction of a new test-treat intervention, it may be possible to increase the speed of implementation of precision medicine into clinical practice and ensure that all patients receive appropriate, high quality testing and treatment.

Some of the specific barriers raised in this qualitative study were consistent with barriers mentioned in published reports and papers authored by institutions involved in the provision of examples of precision medicine. For example, a recent report by Cancer Research UK highlighted the strain on pathology laboratories in the NHS³⁷. In particular, this report highlighted increasing workloads for cytopathologists who diagnose cancer while the number of new professionals working in those roles was growing at a slower rate. The report suggested that while molecular pathologists who are involved in biomarker tests were currently able to manage their workloads, this was partly due to the

current underuse of these tests to guide treatment with precision medicine.

The potential barriers associated with localised testing have been recognised more broadly across pathology testing and there is currently a national strategy to create a national network of pathology laboratory hubs³⁸. It has been argued that "consolidating pathology services allows for the most consistent, clinically appropriate turnaround times, ensuring the right test is available at the right time"³⁹. Furthermore, it has been suggested that centralising testing could save the NHS £200million by 2020–2021 through economies of scale. The potential to benefit from economies of scale when centralising testing has also been highlighted by Buckell *et al.* (2015) who suggest potential efficiency savings of 13% or up to £390 million per year⁴⁰.

There were some limitations to this qualitative study. It transpired during interviewing that one of the targeted samples in this study, the service commissioners responsible for financing for tests and targeted treatments were not identifiable as an individual. This specific role is not part of NHS service commissioning processes. One service commissioner was interviewed, but their primary commissioning role was in the provision of germline genetic and genomic tests. The individual only had second-hand knowledge of the commissioning of the companion diagnostic tests required for precision medicine in NSCLC. It became apparent through this participant, and those working in other specialities, that in essence the role of service commissioner for such test-treat diagnostics does not exist and that commissioning arrangements were often laboriously discovered following conflict between hospital managers and test providers.

There were also difficulties in interviewing a sufficient number of participants in the test provider sample. Due to a national policy of restructuring NHS genetics and genomics services during the recruitment phase for this interview, it was difficult to recruit clinical geneticists who make up a sub-section of the test provider sample due to their excessive workload. It was possible that due to the small number of these participants who were interviewed that saturation was not reached in this sub-sample. It was therefore possible that other barriers to precision medicine in NSCLC exist which were not identified in this study. In addition, it was difficult to identify participants who had experienced the introduction of *EGFR* mutation testing and treatment with gefitinib. At the time of recruitment it had been over 8 years since this example of precision medicine had been approved by NICE and few participants were working in an NHS role at this time. As such, the coverage of the barriers to the introduction of *EGFR* mutation and targeted treatment appeared, in this study, to be less extensive than for *ALK* or *PD-L1* testing. This extensive length of time also created a greater risk of recall bias when compared to *ALK* testing (approved four years prior to the study), and *PD-L1* testing (approved two years prior to the study but still being implemented). However, the extent and

range of barriers that were identified in this study was sufficient for generating a typology of capacity constraints.

Conclusion

This qualitative study, that used semi-structured telephone interviews, has described and generated a typology for barriers that exist to the introduction of examples of precision medicine in NSCLC into the NHS in England. These barriers may result in patients not receiving access to potential beneficial testing and treatment, healthcare providers offering testing at a financial loss, and poorer quality testing leading to worse outcomes for patients. While some progress in addressing these barriers has been made, some have been faced in the introduction of all example of precision medicine currently available in the NHS.

Data availability

Underlying data

The interview transcripts created as part of this study contain a large amount of personal identifying information including names, job titles, workplaces, and references to colleagues and as such have not been provided alongside this manuscript. In addition, this data is not available to reviewers. Consent was

provided for the inclusion of anonymised quotes in this manuscript by participants.

Extended data

Figshare: Clinicians Interview Schedule Version 2_kp.docx. <https://doi.org/10.6084/m9.figshare.13625729.v1>²⁵

Qualitative interview schedule to explore the barriers that have been faced by clinicians in introducing examples of precision medicine for non-small cell lung cancer.

Figshare: Pathologists and Geneticists version 2.docx. <https://doi.org/10.6084/m9.figshare.13625738.v1>²⁶

Interview schedule from a study which sought to understand the barriers to introducing examples of precision medicine for non-small lung cancer

Data are available under the terms of the [Creative Commons Zero “No rights reserved” data waiver](#) (CC0 1.0 Public domain dedication).

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Vishal Vashistha

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Thank you for allowing me to review this paper. The authors conducted a qualitative study evaluating barriers to uptake of precision medicine among clinicians and pathologists in the UK. The authors should be commended for their work that used standard qualitative methods and provides insight into issues limiting precision oncology in the UK.

I only have a few concerns.

1. The significance and importance of this work should be accented further in the background. I would specifically comment on the randomized trial data supporting the approval of osimertinib, a third generation TKI for patients with activating EGFR mutations. Similarly, I would comment on the data for brigatinib and alectinib, second generation ALK inhibitors. The benefits of these drugs lead to improvement of years in survival compared to chemotherapy. These are critically important drugs for appropriate candidates.
2. The authors focused on discussing actionable variants within the most well-known genes with the greatest prevalence. The authors did not discuss issues surrounding activating variants in lesser common genes, such as BRAF, MET, RET, and KRAS. This is certainly reasonable as the authors wanted to focus on the most critical variants of interest; however, I would comment about how it is difficult for UK practitioners to try to advance the field with inability to complete comprehensive genomic profiling (it seems single gene evaluations using PCR and IHC are standard rather than comprehensive NGS allowing for 50+ genes to be sequenced concurrently).
3. The authors highlighted very important points regarding costs. They found that oncologists are concerned about the effects on NICE's overall financial structure, pathologists are stressed with overburdening budgets, and hospitals are unsure of how to assess the overall ballooning costs associated with precision medicine. I suggest dedicating a paragraph more clearly to this in the discussion. Clearly, at least streamlining the types of testing and timing

of testing seems most reasonable, even if testing is not centralized. Given that these points are most readily actionable from a policy standpoint, I would emphasize these issues in the discussion.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Not applicable

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: health services within the realm of medical oncology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 21 September 2021

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Robb Rowley

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Overall comment - Understanding barriers to somatic testing in NSCLC is an important topic to understand. The authors could be more descriptive and clearer about their intent which is finally explained on page 5 "The objectives of data analysis were to: identify potential barriers; and create

a typology of barriers that may prevent[limit] patients' access to precision treatments for NSCLC." Seems like the objective could be narrowed even more since this mostly pertains to barriers within NHS. Might be adaptable but that was the focus of this study.

Overall comment - The authors reference the limitations of the people interviewed. A table would be helpful about the final makeup of those surveyed. Especially since some of those surveyed were selected through snowballing which can skew their results.

Page 1 - The background needs to read more factual and less descriptive as to the benefit. For example, the authors state that "This means that patients with NSCLC may not have received life improving and extending treatments which should have been available to them." True but something like. "Despite these tests demonstrating a X reduction in morbidity and mortality, health systems are not adopting these practices..." What evidence do you have that they are not adopting the methods where appropriate?

Page 3 first paragraph first sentence – Believe this is backwards. Haven't advances in understanding the role of somatic mutations in NSCLC led to more effective treatment options.

Page 3 third paragraph – consider flipping the paragraph. "In 2014, Cancer Research UK estimated that ... The lack of uptake remains despite EGFR testing being recognized for implementation in 2010 and approved by NICE in 2012..."

Page 7 – can this quote be clarified "but then there's a delay..." Not sure about "stuff". A sentence interpreting might be helpful.

Page 11 – last two paragraphs on the page should be incorporated into the discussion. Does not seem part of the results.

Page 12 – seems like the 5 themes could be clarified into barriers. For example, "opinions about whether test..." doesn't seem like a barrier. Isn't lack of clear policy the barrier. Seems like the 5 themes are more like "lack of clear policy, procedures, and roles and responsibilities related to the transition from approval to clinical care, lack of funds to hire staff and pay for the test, lack of staff trained to perform the test." Consider framing these that help groups focus on how to overcome the barrier.

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

No

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

No

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Genomic medicine research using electronic medical records.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.