Greater Manchester Cancer

Non-small cell lung cancer reflex testing protocol

Update March 2023

Background to the 2023 protocol update:

Significant changes are occurring in the treatment paradigm for NSCLC with an ever-evolving role of systemic anti-cancer therapy in stage II, III, and IV NSCLC. Immune profiling (PD-L1) and genomic testing (EGFR, ALK, ROS-1 and extended gene testing with NGS) is becoming more and more important to define optimal treatment. Examples of new NICE-approved treatment regimens include:

- ✓ Neoadjuvant chemotherapy-immunotherapy followed by surgery for resectable NSCLC tumours >4cm or with lymph node metastases. Non-squamous tumours must be proven to be EGFR & ALK negative to be eligible for this treatment.
- ✓ Adjuvant chemotherapy-immunotherapy following surgical resection for stage II/III NSCLC with PD-L1 >50%
- ✓ Adjuvant immunotherapy following concurrent chemoradiotherapy in stage III NSCLC with PD-L1 >1%
- ✓ Adjuvant tyrosine kinase inhibitor treatment after surgical resection of stage IB-III EGFR positive NSCLC

There is a critical need, therefore, for the Greater Manchester (GM) Lung MDTs to have the results of genomic testing and immune profiling at the time of MDT discussion in order to make evidence-based recommendations and ensure the highest quality patient care.

A recent GM-wide audit of the NSCLC reflex testing protocol and genomic pathway demonstrated challenges in the pathway with a median turnaround time of 29 days from tissue acquisition to full genomic results. The audit also revealed that reflex testing saved an average of 8 days in the pathway.

To support the delivery of cancer waiting times and ensure the very best patient outcomes it is critical all teams involved in the lung cancer pathway in GM implement this updated protocol.

Key updates to the protocol:

- ✓ **All NSCLC samples will be reflex tested regardless of stage**
- ✓ New minimum dataset requirements in clinical details provided by clinical teams performing tissue sampling procedures
- ✓ New pathway for patients with adenocarcinoma/NOS/large cell NSCLC under consideration for neoadjuvant chemotherapy-immunotherapy (to facilitate rapid EGFR/ALK turnaround)

This update has been developed and agreed by the GM NSCLC multi-modality treatment working group with representatives from histopathology, NW Genomic laboratory hub, thoracic surgery, medical oncology, respiratory medicine and the GM cancer alliance.

The protocol has been reviewed & approved by:

- ✓ GM Lung Pathway Board
- ✓ GM Lung Pathway Pathology Sub-group
- ✓ GM Cancer Board

Further Information on the development of the protocol update:

1. The decision to reflex test all NSCLC samples was agreed across all members of the working group with pathology and GLH representation. There is a clear need for reflex testing to make clinical decisions in Stage II/III/IV and some cases of stage IB. This is likely to extend in the future and on the basis of making a simplified, future-proofed protocol it was agreed reflex testing across all NSCLC samples should become standard of care

2. The decision to create a dedicated indication for rapid EGFR processing for patients with non-squamous NSCLC under consideration for the neoadjuvant pathway is based on the national requirements for EGFR and ALK testing prior to neoadjuvant chemotherapy-immunotherapy.

3. In neoadjuvant therapy candidates, there is an urgency to start treatment as soon as possible therefore rapid EGFR and ALK testing is beneficial. However, rapid EGFR testing does not test the full spectrum of mutation and in such cases after neoadjuvant therapy, the sample may not be suitable for NGS panel due to treatment related changes and necrosis. Therefore, these cases will undergo dual testing at GLH, rapid EGFR testing (COBAS) to provide quick result to facilitate neoadjuvant treatment and full NGS panel which can be used for future reference and trials.

4. **The protocol is dependent upon clinicians performing tissue sampling procedures providing the required minimum dataset in the clinical information. All clinical teams across GM must work to deliver this standard of care and ensure adequate tissue alongside adequate clinical history is provided to facilitate complete biomarker testing.**

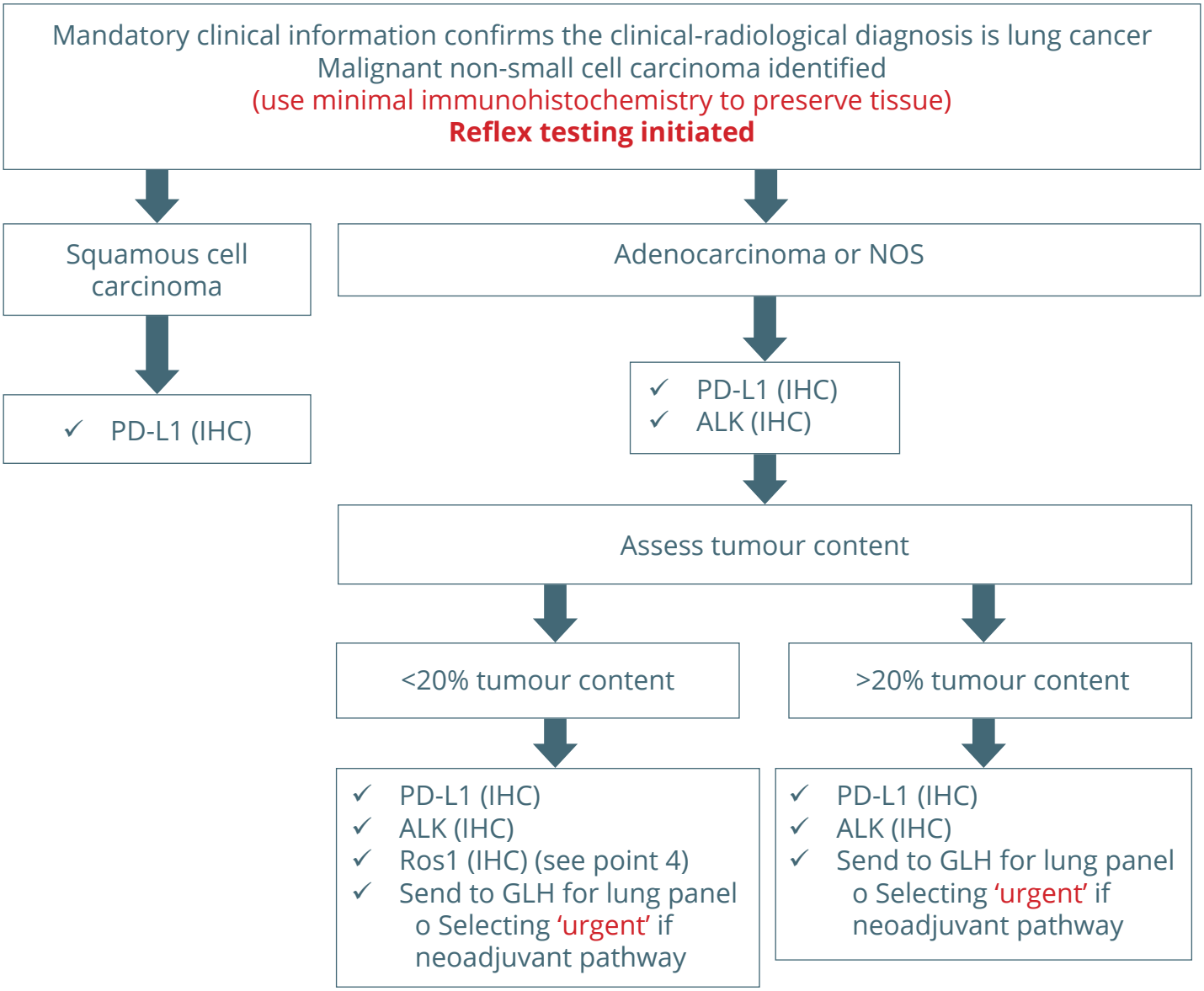
   4.a The GM Single queue programme is implementing a single digital platform for requesting EBUS, CT-guided lung biopsy, peripheral bronchoscopy, thoracoscopy. This system has been designed to capture the minimum dataset for the reflex testing protocol to support implementation of this pathway

The GM NSCLC Reflex testing Protocol

Definition of 'reflex testing' in this protocol – the immediate pathologist-led initiation of further testing for predictive markers on NSCLC samples to select anti-cancer systemic therapy (PDL1, EGFR, ALK, ROS-1, NGS) without waiting for an MDT discussion

Mandatory clinical information to be provided on all histology/cytology requests for patients with suspected lung cancer:

- The clinical-radiological diagnosis is primary lung cancer (yes/no/unsure)
  - If no, provide further details, including any previous cancers
- Inform the pathology team if the patient under assessment for neoadjuvant treatment using the phrase **'Urgent neoadjuvant pathway'** (this will allow pathology labs to select 'urgent' when sending to GLH)



Explanatory Notes:

1. Minimal immunohistochemistry should be performed in cases with clinical and radiological diagnosis of lung cancer to preserve tissue for biomarker testing.

2. All non-small cell carcinoma cases, where the clinical details confirm a clinical-radiological diagnosis of lung cancer, will undergo reflex testing beginning with immediate PD-L1 testing.

3. Adenocarcinoma and NSCLC-NOS cases will undergo immediate ALK IHC testing. ROS-1 IHC will be performed only when tumour content is <20%.

4. Fusion panel analysis (including ROS1) will be performed in all cases by GLH unless only Urgent EGFR is requested; however, for cases with low tumour content (<20%), where fusion analysis may be insensitive, parallel ROS1 IHC needs to be performed. If ROS1 immunohistochemistry result shows borderline or positive result, there needs to be consultation with GLH to attempt to confirm the result by ROS1 FISH or fusion analysis. If ROS1 immunohistochemistry result is negative, no further testing is required.

5. Samples sent to GLH (genomic laboratory hub) will be tested for lung panel depending on tumour content:

   - ✓ >20% tumour content will be tested for EGFR, BRAF, MET, KRAS, ROS1, RET, ALK, NTRK fusions
   - ✓ <20% tumour content will be tested for EGFR, BRAF, MET, KRAS
   - ✓ Cases with urgent neoadjuvant pathway will dual testing as described below (5)

6. Samples sent to the GLH that are selected as **'urgent'** on the GLH referral form will undergo rapid COBAS EGFR testing **AND** next generation sequencing (NGS) panel (dual testing) so that a rapid EGFR result is available as soon as possible.

7. Pathology teams will select 'urgent' on the GLH referral form when the clinical details state that this patient is on the **'Urgent neoadjuvant pathway'**.

8. **If the clinical details provided does not provide any information about the neoadjuvant pathway, 'Urgent' will not be selected on the GLH referral form.**

9. Clinical teams may specifically ask for genomic testing in the rare situation of a squamous cell carcinoma in a never or light smoker. This will be on a case-by-case basis and is outside the scope of the protocol.

10. There may be specific clinical scenarios in which 'Urgent' may be appropriate to select on the GLH referral form. This may be in a never smoker at significant risk of rapid deterioration and requiring rapid decision making. This is on a case-by case basis and is outside the scope of this protocol. This requires individual communication between clinicians and the pathology team (noting that is highly likely that ctDNA will support rapid genomic testing in advanced stage disease in the near future).

    - ✓ M4.4 on GLH form for urgent (clinical, non-neoadjuvant cases)

11. The type of lung panel testing at GLH depends on tumour content. Therefore, it is **essential that pathologists provide the information about tumour content to the GLH.**

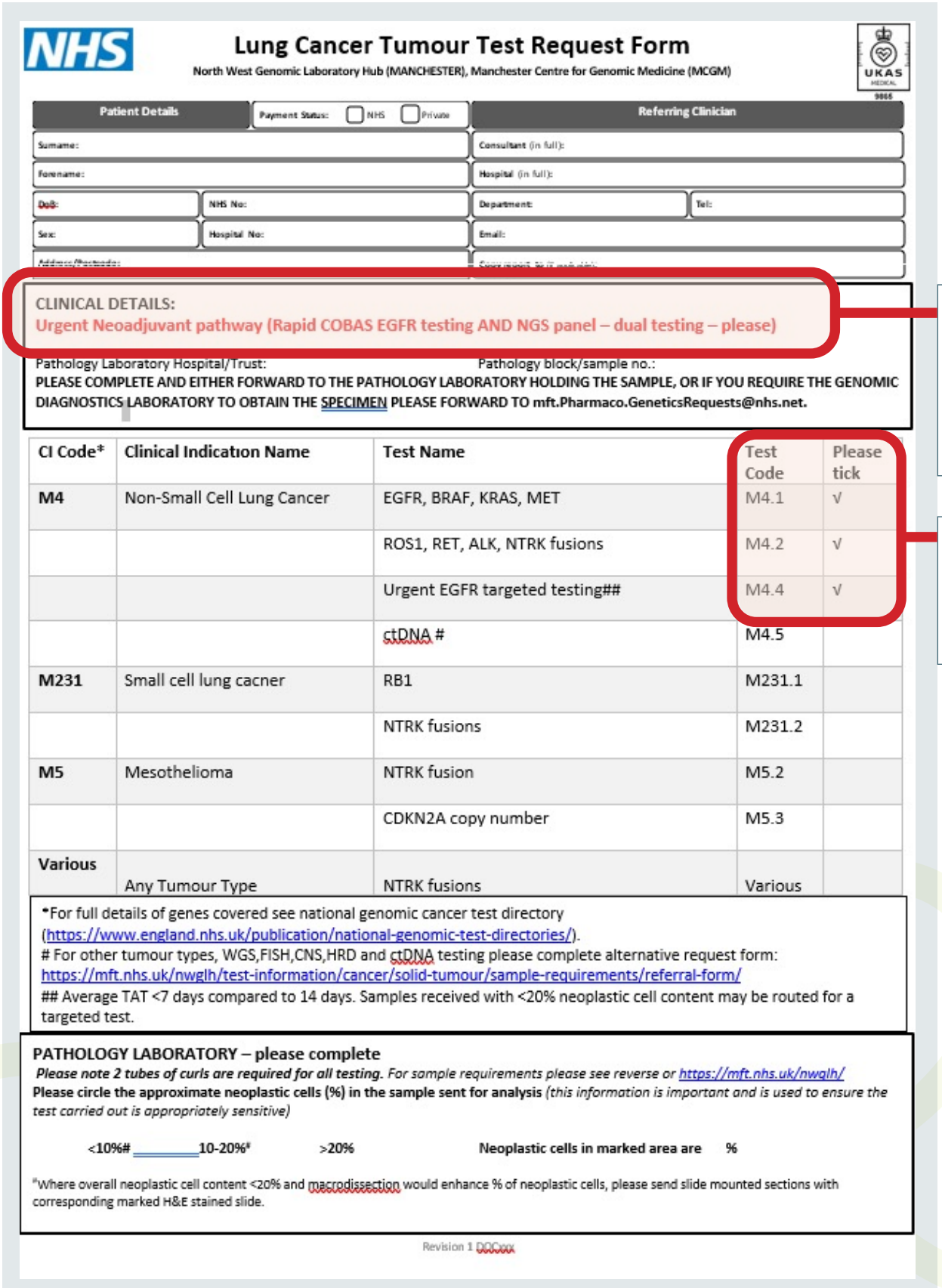
12. In cases with very low tumour content (less than 10%), sample should still be sent to GLH for panel testing but a discussion in the MDT may be beneficial to plan for repeat biopsy or sampling from other sites (or ensuring ctDNA has been completed when available).

13. Stating primary lung cancer as the clinical-radiological diagnosis is a **critical step** in this protocol and will help preserve tissue for reflex testing. It is important to inform the pathology teams if there are any previous cancers or an uncertain clinical-radiological diagnosis in which further IHC testing is appropriate. Therefore, only state that lung cancer is the clinical-radiological diagnosis when there is clear evidence for this.

14. Whilst taking samples for lung cancer, the clinician should try to provide ample tissue for diagnosis and biomarker testing.

Specific Instructions for referral to the NW Genomics Laboratory Hub for a patient on the 'Urgent Neoadjuvant Pathway'

Using the paper referral form:



NHS

Lung Cancer Tumour Test Request Form

North West Genomic Laboratory Hub (MANCHESTER), Manchester Centre for Genomic Medicine (MCGM)

UKAS MEDICAL 9865

Patient Details	Payment Status: ☐ NHS ☐ Private	Referring Clinician
Surname:		Consultant (in full):
Forename:		Hospital (in full):
DoB:	NHS No:	Department: Tel:
Sex:	Hospital No:	Email:
Address (Postcode):		Copy report to (in addition):

CLINICAL DETAILS:
Urgent Neoadjuvant pathway (Rapid COBAS EGFR testing AND NGS panel – dual testing – please)

Pathology Laboratory Hospital/Trust: Pathology block/sample no.:

PLEASE COMPLETE AND EITHER FORWARD TO THE PATHOLOGY LABORATORY HOLDING THE SAMPLE, OR IF YOU REQUIRE THE GENOMIC DIAGNOSTICS LABORATORY TO OBTAIN THE SPECIMEN PLEASE FORWARD TO mft.Pharmaco.GeneticsRequests@nhs.net.

CI Code*	Clinical Indication Name	Test Name	Test Code	Please tick
M4	Non-Small Cell Lung Cancer	EGFR, BRAF, KRAS, MET	M4.1	√
		ROS1, RET, ALK, NTRK fusions	M4.2	√
		Urgent EGFR targeted testing##	M4.4	√
		ctDNA #	M4.5	
M231	Small cell lung cacner	RB1	M231.1	
		NTRK fusions	M231.2	
M5	Mesothelioma	NTRK fusion	M5.2	
		CDKN2A copy number	M5.3	
Various	Any Tumour Type	NTRK fusions	Various	

*For full details of genes covered see national genomic cancer test directory (https://www.england.nhs.uk/publication/national-genomic-test-directories/).
For other tumour types, WGS,FISH,CNS,HRD and ctDNA testing please complete alternative request form: https://mft.nhs.uk/nwglh/test-information/cancer/solid-tumour/sample-requirements/referral-form/
Average TAT <7 days compared to 14 days. Samples received with <20% neoplastic cell content may be routed for a targeted test.

PATHOLOGY LABORATORY – please complete

Please note 2 tubes of curls are required for all testing. *For sample requirements please see reverse or https://mft.nhs.uk/nwglh/*
Please circle the approximate neoplastic cells (%) in the sample sent for analysis *(this information is important and is used to ensure the test carried out is appropriately sensitive)*

<10%# 10-20%* >20% Neoplastic cells in marked area are %

*Where overall neoplastic cell content <20% and macrodissection would enhance % of neoplastic cells, please send slide mounted sections with corresponding marked H&E stained slide.

Revision 1 DDCxxx

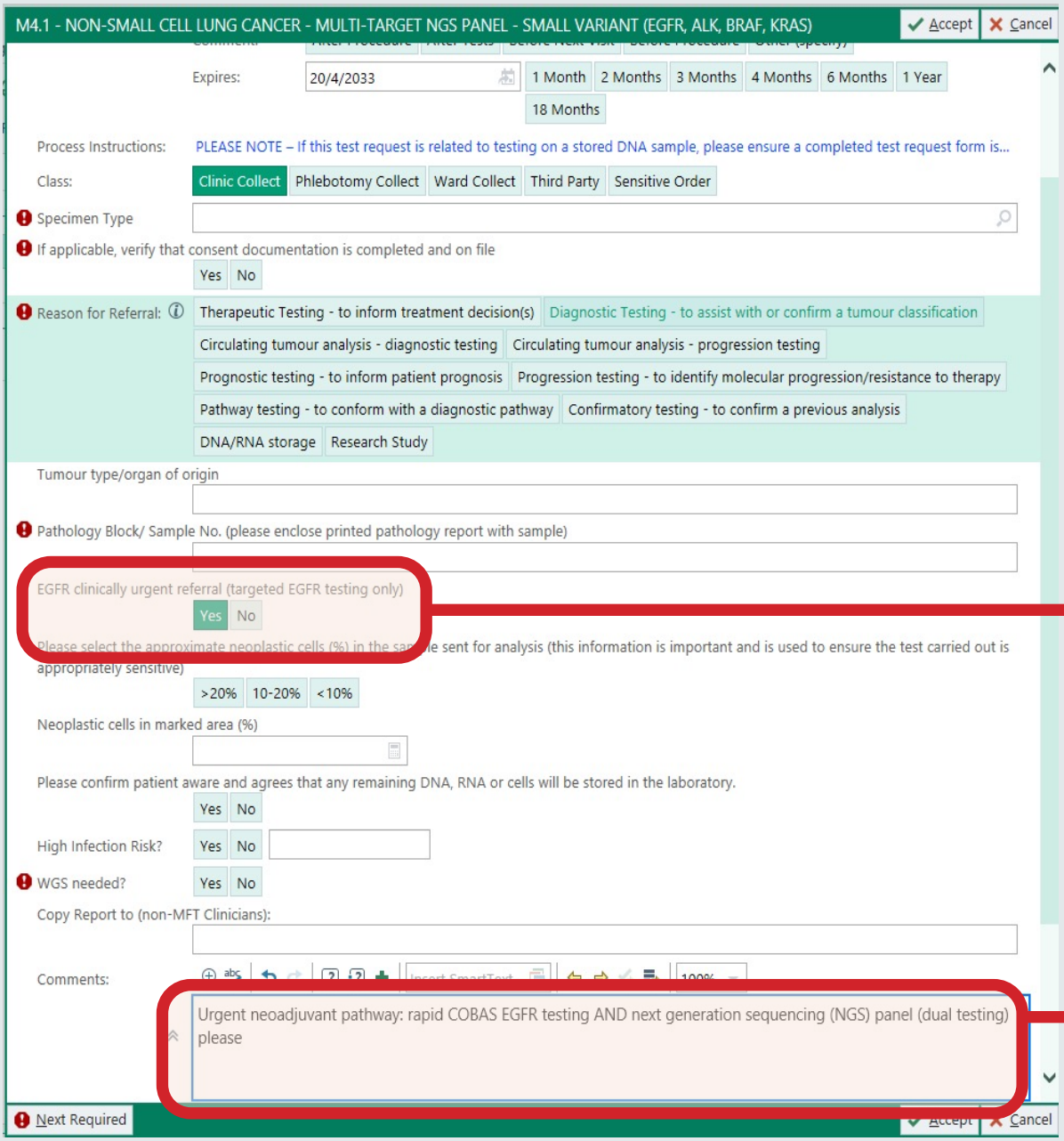
Ensure clinical details includes the phrase:

'Urgent neoadjuvant pathway'

Please tick:

- ✓ **M4.1**
- ✓ **M4.2**
- ✓ **M4.4**

For electronic referrals on HIVE at MFT



Select 'Yes' for 'EGFR clinically urgent referral')

Ensure clinical details includes the phrase:

'Urgent neoadjuvant pathway'