NHS
South East
Genomic Medicine Service

A Guide to

Synnovis Genetics Centre ctDNA Reports

Cancer Genetics | Guy's Hospital | Synnovis

This guide explains the structure, content, and clinical interpretation of ctDNA genomic analysis reports issued by Synnovis | South East Genomic Medicine Service

WHAT THIS GUIDE COVERS

Variants & Clinical Interpretation

Additional Findings

Methodology

Key Terms

MSK-ACCESS® powered with SOPHiA DDM™ | ctDNA Panel

South East Genomic Medicine Service: A Guide to the Lung Cancer ctDNA Report

Patient demographics:

Includes patient identifiers, referring physician, and sample dates (taken and received).

Verify patient identity against clinical request before reviewing results.

Sample and clinical details:

States sample type (e.g. blood/cfDNA) and reason for testing (e.g. M4.14 lung cancer ctDNA testing). ctDNA fraction is not determined by this assay (see end of report, page 1 of 3).

Aged sample: Indicates samples received >7 days after collection, with increased likelihood of low ctDNA fraction.

Summary of variants:

This table summarises genomic findings in essential target genes as defined by the **National Genomic Test Directory** for this clinical indication **(see Report page 3). It includes small variants** (SNVs and indels) and **copy number variants** (CNVs), classified as oncogenic, likely oncogenic, or variants of uncertain significance (VUS).

Columns show: Gene, CN (copy number), VAF (variant allele frequency), exon, and classification (see page 5 for definitions and HGVS nomenclature).

If analysis is incomplete, the following notation rows may also appear in the table:

Suboptimal coverage: Reported as 'No variants detected in the following genes with suboptimal coverage: [*GENE*] (e.g. BRAF; specific regions such as exons 11 and 15 are detailed on page 2). This means no variants were detected, but test quality was insufficient for confident assessment. This may be due to low DNA input, sample degradation (e.g. older samples), or technical variation. Variants at higher levels (≥1%) may still be detected, but variants below this level could be missed. A negative result should be interpreted with caution and is not fully reliable.

Analysis failure: Reported as 'Analysis of [*GENE*] has failed" . No result could be generated due to insufficient data quality, and the gene is uninformative. No variants can be assessed at any level. Likely causes include low DNA input, sample degradation, or technical issues.

Summary of fusions:

This table lists **gene fusions and oncogenic isoforms** detected in the fusion genes analysed in this test panel *ALK, ROS1, RET, MET, NTRK1, ETV6(::)NTRK3, NTRK2***

A **negative result row** indicates that these genes were successfully analysed and **no fusions were detected.**

**Fusion detection is DNA-based and has reduced sensitivity for some fusion events; further details are provided on page 3 of 3 of report.

synnovis
A SYNLAB pathology partnership

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CANCER GENETICS

GENETIC ANALYSIS REPORT — **ONCOLOGY**

NAME: PATIENT
: Example

DOB: 01/01/1970 Age: 56 Sex: Female

Referring Physician: Dr Referring Clinician
Hospital: Guy's Hospital

SPECIMEN No: 26/00000
PRU No: 123456:01
Date Taken: 05/01/2026
Date Rec'd: 08/01/2026
Hospital No: 12345678
NHS Number: 111 111 1111

Sample: Blood, cfDNA extracted from plasma (Sample ID, Hospital Sample Number)
Clinical details: **M4.14 (see targets below). Lung cancer**
ctDNA fraction: Unknown, **aged sample**

CIRCULATING TUMOUR DNA (ctDNA) FINAL REPORT

SUMMARY OF LIKELY/ONCOGENIC (and VUS) SMALL VARIANTS AND CNV ASSESSMENT

Gene	Description	CN	VAF	Exon	Classification
EGFR	c.2573T>G, p.(Leu858Arg)		0.9%	21	Oncogenic
No variants detected in *MET, ALK*					
No variants detected in the following genes with suboptimal coverage: *BRAF*					
Analysis of *KRAS* has failed					

SUMMARY OF FUSIONS	VAF
No fusions detected in *ALK, ROS1, RET, MET, NTRK1, ETV6(::)NTRK3, NTRK2***	

Please see page 2 for additional findings that may be relevant for clinical trial eligibility.

ACTIONABILITY

An EGFR sensitising variant was detected. Therefore, this patient may respond to treatment with EGFR tyrosine kinase inhibitor therapy.

However, analysis of BRAF was suboptimal and uninformative for variant detection below 1%; therefore, we cannot exclude the presence of a variant below this frequency. Additionally, analysis of KRAS is considered to have failed. Repeat testing using a suitable alternative specimen at this timepoint may be appropriate.

This sample was over 7 days old at receipt and, as such, there is an increased likelihood of low ctDNA fraction, and the possibility of a false negative findings for additional variants, cannot be determined. Repeat testing on a an FFPE specimen at this timepoint is highly recommended.

These ctDNA results should be interpreted in the context of any available immunohistochemistry, tissue genomics and additional ctDNA results that may be available for this patient.

Consideration should be given to tumor heterogeneity, potential germline findings and the possibility of malignancies incidental to the indicated diagnosis, and referral to GTAB should further discussion be required; email: gstt.gtabsoutheastglh@nhs.net

GTAB referral form: https://southeastgenomics.nhs.uk/wp-content/uploads/2024/09/Blank-GTAB-referral-form.pdf

ctDNA fraction is not quantifiable with this assay. False negative results and variants below the limit of detection cannot be excluded. Repeat testing at clinically appropriate timepoints is recommended when no actionable alterations are detected.

Associated results: current result is concordant with previously tested tissue GW 25/01234 authorised 10/10/2025.

Report Date : 19/01/2026
Authorised by : Senior Clinical Scientist

Actionability:

Provides **clinical interpretation** of detected variants in relation to the **tumour type tested,** including **therapeutic actionability** (e.g. EGFR tyrosine kinase inhibitor therapy) with reference to **NICE** or **Cancer Drugs Fund (CDF)** guidance.

Where present, limitations such as suboptimal coverage (e.g. *BRAF*) or analysis failure (e.g. *KRAS*) are flagged and may affect result completeness; repeat testing using an alternative specimen or method may be recommended.

Clinical Reminder
interpret alongside IHC and tissue genomic findings. **GTAB contact details** are provided for further advice if required.

Note:

Directs the reader to page 2 where information on additional findings including clinical trial targets can be found.

GENETIC ANALYSIS REPORT **ONCOLOGY**

NAME: PATIENT
: Example

SPECIMEN No: 26/00000
PRU No: 123456:01
Date Taken: 05/01/2026
Date Rec'd: 08/01/2026
Hospital No: 12345678
NHS Number: 111 111 1111

DOB: 01/01/1970 Age: 56 Sex: Female

Referring Physician: Dr Referring Clinician
Hospital: Guy's Hospital

ADDITIONAL FINDINGS OUTSIDE OF STANDARD OF CARE TESTING

Analysis has been performed in accordance with the National Genomic Test Directory. (https://www.england.nhs.uk/publication/national-genomic-test-directories/)

Additional findings reported here fall outside standard-of-care testing and these findings may represent variants of potential clinical relevance.

If considering clinical trials or further discussion is required regarding these results, then please refer to the Regional or National Genomic Tumour Advisory Board (GTAB).

For information on potential clinical trials please visit the ECMC trial finder (https://ecmctrialfinder.org) or Cancer Research UK clinical trials finder (https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial).

All additional variants meeting AMP/ASCO/CAP Tier 1 or Tier 2 clinical significance or variants classified as A or B according to SOPHiA DDM™ are reported.

These variants have not been assessed by the laboratory for clinical significance.

Additional findings:

Genetic variants detected in genes beyond the essential targets for the patient's clinical indication. These genes are included to support emerging therapies or clinical trials; therefore, the variants are reported for information only and have not been clinically interpreted by the laboratory.

If clinically appropriate, referral to the Genomic Tumour Advisory Board (GTAB) should be considered.

If no variants are reported in this section, it means the genes were successfully analysed but no clinically significant alterations were identified in the tested variant types.

SUMMARY OF LIKELY/ONCOGENIC FINDINGS

Gene	Description	CN	VAF	Exon
BRCA1	c.5145C>A, p.(Ser1715Arg)		0.87%	18
NF1	c.1198C>T, p.(Gln400*)		0.69%	9
STK11	c.291-1G>T, p.?		0.79%	2
FGFR3	Copy Number Gain	6.2		

Regions with insufficient coverage within essential gene targets

Variants cannot be excluded below 1% in the suboptimal regions described below.

GENE	Suboptimal regions	FAILED regions
BRAF	Exons 11 and 15	
KRAS	Exon 2	Exons 3 and 4

Please note that coverage has not been assessed for all reported additional findings, therefore, the possibility of false negatives cannot be excluded.

Coverage information:

Coverage refers to how many times a DNA region is read during sequencing; higher coverage increases confidence in variant detection. This table lists exons/regions within essential target genes with reduced or failed coverage.

Suboptimal regions indicate reduced (but not absent) coverage (e.g. *BRAF* exons 11 and 15): variants above ~1% VAF may still be detected, but lower-level variants cannot be excluded, so results are only partially informative. This applies only to the listed exons; other regions of the gene met required coverage.

FAILED regions indicate that sequencing data quality was insufficient to generate any result. Unlike suboptimal regions, failed regions yield no reportable result at any allele frequency. The failure of specific exons does not automatically constitute a whole-gene analysis failure; however, if the failed exons encompass clinically relevant hotspot positions (e.g. *KRAS* exons 3 and 4), the gene must be considered uninformative for those variants.

The **ACTIONABILITY** section (Report page 1) reflects this and repeat ctDNA or tissue-based testing should be considered where there are technical limitations.

Report Date : 19/01/2026
Authorised by : Senior Clinical Scientist

GENETIC ANALYSIS REPORT **ONCOLOGY**

NAME: PATIENT
: Example

SPECIMEN No: 26/00000
PRU No: 123456:01
Date Taken: 05/01/2026
Date Rec'd: 08/01/2026
Hospital No: 12345678
NHS Number: 111 111 1111

DOB: 01/01/1970 Age: 56 Sex: Female

Referring Physician: Dr Referring Clinician
Hospital: Guy's Hospital

MSK-ACCESS® powered with SOPHiA DDM™ ctDNA panel methodology:

ctDNA and gDNA extraction is performed on the QIAsymphony using the QIAsymphony DSP circulating DNA Maxi kit and DSP DNA Mini kit, respectively. MSK-ACCESS® powered with SOPHiA DDM™ is a decentralised assay collaboration between SOPHiA GENETICS and Memorial Sloan Kettering Cancer Center (MSK) involving the deep sequencing (~20,000x) of 147 key cancer-associated genes to inform nucleotide variants (SNVs), indels, splicing isoforms, and intra- and intergenic fusion rearrangement, and *TERT* promoter variants. Powered by the advanced features of the SOPHiA DDM Platform, the assay incorporates a paired tumour cfDNA and matched normal white blood cell DNA approach to enable CHIP filtering. Using the proprietary molecular barcoding approach CUMIN™ and a capture-based workflow either manually or automated, paired tumour-normal libraries are sequenced using Illumina NGS systems.
Data are uploaded securely to SOPHiA DDM™ Decision Support Software (DSS) for encrypted analysis and storage. Variants are additionally curated through SOPHiA DDM™ and OncoPortal™ Plus by integration of ClinVar, OncoKB, and JAXCKB.

Analysis is performed according to the requirements of the National Genomics Test Directory.
M4.14 Lung ctDNA: Small variants: ***EGFR, ALK, BRAF, KRAS, MET* exon 14 skipping**
Fusions/oncogenic isoforms: ***ALK, ROS1, RET, NTRK1/2/3***
Copy number variations: ***MET***
Additional findings (SNV & CNV): ***ERBB2***

The assay fully covers the coding sequences of the following 39 genes (hg19) and provides CNV detection (other than *HIST1H3B*):
APC (NM_000038.6), *AR* (NM_000044.6), *ARID1A* (NM_006015.6), *ASXL1* (NM_015338.6), *ATM* (NM_000051.4), *BAP1* (NM_004656.4), *BRCA1* (NM_007294.4), *BRCA2* (NM_000059.4), *CDH1* (NM_004360.5), *CDK12* (NM_016507.4), *CDK4* (NM_000075.4), *CDKN2A* (NM_000077.5, NM_058195.4), *CHEK2* (NM_007194.4), *DNMT3A* (NM_022552.5), *ERCC2* (NM_000400.4), *FBXW7* (NM_033632.3), *FOXL2* (NM_023067.4), *GATA3* (NM_002051.3), *HIST1H3B* (NM_003537.4, **no CNV**), *KDM6A* (NM_021140.4), *KEAP1* (NM_203500.2), *KRAS* (NM_033360.4), *MLH1* (NM_000249.4), *MSH2* (NM_000251.3), *MSH6* (NM_000179.3), *NF1* (NM_001042492.3), *PALB2* (NM_024675.4), *PMS2* (NM_000535.7), *PPM1D* (NM_003620.4), *PTCH1* (NM_000264.5), *PTEN* (NM_000314.8), *RB1* (NM_000321.3), *SMAD4* (NM_005359.6), *STK11* (NM_000455.5), *TET2* (NM_001127208.3), *TP53* (NM_000546.6), *TSC1* (NM_000368.5), *TSC2* (NM_000548.5), *VHL* (NM_000551.4).

The assay covers the following regions (hg19) and provides CNV and fusion* detection as indicated (*GENE* (reference sequence, exons, **CNV/fusions**)):
AKT1 (NM_001014431.2, 3, 6-12, **CNV**), *ALK* (NM_004304.5, 5, 9, 20-29, **CNV, fusions**), *ARAF* (NM_001654.5, 7, 10-16, **CNV**), *ARID2* (NM_152641.4, 8), *B2M* (NM_004048.4, 1), *BCL2* (NM_000633.3, 2), *BCOR* (NM_001123385.2, 10), *BRAF* (NM_004333.6, 11-18, **CNV, fusions**), *CARD11* (NM_032415.7, 13), *CBFB* (NM_022845.3, 2), *CBL* (NM_005188.4, 9), *CCND1* (NM_053056.3, 5), *CD79B* (NM_001039933.3, 5), *CIC* (NM_015125.5, 5), *CREBBP* (NM_015125.5, 26, 27, 30, **CNV**), *CTCF* (NM_006565.4, 6), *CTNNB1* (NM_001904.4, 3, 7, 8), *DICER1* (NM_030621.4, 27), *DIS3* (NM_014953.5, 10), *EGFR* (NM_005228.5, 3, 6, 7, 15, 18-24, **CNV, oncogenic isoform**), *EIF1AX* (NM_001412.4, 1, 2), *EP300* (NM_001429.4, 26, 27, **CNV**), *ERBB2* (NM_004448.4, 3, 6-8, 12, 16-25, 27, **CNV**), *ERBB3* (NM_001982.4, 3, 6-9, 18-24, **CNV**), *ESR1* (NM_001122740.2, 6-9, **CNV**), *ETV6* (, **fusions**), *EZH2* (NM_004456.5, 16), *FGFR1* (NM_001174067.2, 12-19, **CNV**), *FGFR2* (NM_000141.5, 3, 5, 7-9, 11-18, **CNV, fusions**), *FGFR3* (NM_000142.5, 7, 9, 11-18, **CNV, fusions**), *FGFR4* (NM_213647.3, 13), *FLT3* (NM_004119.3, 14, 20), *FOXA1* (NM_004496.5, 2, **CNV**), *FOXO1* (NM_002015.4, 1), *FOXP1* (NM_001244814.3, 14), *FUBP1* (NM_003902.5, 14), *GNA11* (NM_002067.5, 5), *GNAQ* (NM_002072.5, 5), *GNAS* (NM_000516.7, 6, 8, 9), *H3F3A* (NM_002107.7, 2), *HRAS* (NM_001130442.3, 2-4), *IDH1* (NM_005896.4, 4, 5), *IDH2* (NM_002168.4, 4), *IKZF1* (NM_006060.6, 8), *INPPL1* (NM_001567.4, 2), *JAK1* (NM_002227.4, 19), *JAK2* (NM_004972.4, 14), *KIT* (NM_000222.3, 8-21, **CNV**), *KNSTRN* (NM_033286.4, 1), *MAP2K1* (NM_002755.4, 2-11, **CNV**), *MAP2K2* (NM_030662.4, 2-11, **CNV**), *MAPK1* (NM_002745.5, 7), *MAX* (NM_002382.5, 2, 4), *MED12* (NM_005120.3, 2, 26), *MET* (NM_000245.4, 13-21, **CNV, fusions, oncogenic isoform**), *MSH3* (NM_002439.5, 7), *MTOR*
(NM_004958.4, 29-31, 39, 40, 43, 44, 46-50, 53, 56, 57, **CNV**), *MYC* (NM_002467.6, 2, **CNV**), *MYCN* (NM_005378.6, 2, **CNV**), *MYD88* (NM_002468.5, 5), *MYOD1* (NM_002478.5, 1), *NFE2L2* (NM_006164.5, 2), *NOTCH1* (NM_017617.5, 6, 8), *NPM1* (NM_002520.7, 11), *NRAS* (NM_002524.5, 2-4), *NTRK1* (NM_002529.4, 13-17, **CNV, fusions**), *NTRK2* (NM_006180.6, 15-19, **CNV**), *NTRK3* (NM_001012338.3, 15-20, **CNV**), *NUP93* (NM_014669.5, 2), *PAK5* (NM_177990.4, 4, **CNV**), *PDGFRA* (NM_006206.6, 5-7, 9-21, **CNV**), *PHF6* (NM_032458.3, 5, 9), *PIK3CA* (NM_006218.4, 2, 3, 5, 6, 8-12, 14, 19-21, **CNV**), *PIK3CB* (NM_006219.3, 24), *PIK3R1* (NM_181523.3, 10, 11, 13, 14, **CNV**), *PIK3R2* (NM_005027.4, 10), *PIM1* (NM_002648.4, 1), *POLE* (NM_006231.4, 1, 9, 13), *POT1* (NM_015450.3, 6), *PPP2R1A* (NM_014225.6, 5, 6), *PPP6C* (NM_002721.5, 7), *PRKCI* (NM_002740.6, 15), *PTPN11* (NM_002834.5, 3, 13), *RAC1* (NM_018890.4, 2), *RAD54L* (NM_001142548.2, 10), *RAF1* (NM_002880.4, 7, 10-17, **CNV**), *RET* (NM_020975.6, 8, 10-19, **CNV, fusions**), *RHOA* (NM_001664.4, 2, 3), *RIT1* (NM_006912.6, 5), *ROS1* (NM_002944.3, 36-42, **CNV, fusions**), *RRAS2* (NM_012250.6, 1, 3), *RXRA* (NM_002957.6, 10), *SETD2* (NM_014159.7, 7), *SF3B1* (NM_012433.4, 14, 15, 18, **CNV**), *SMAD3* (NM_005902.4, 6), *SMARCA4* (NM_003072.5, 19, 25, 26, **CNV**), *SMARCB1* (NM_003073.5, 9), *SOS1* (NM_005633.4, 5), *SPOP* (NM_001007228.2, 4, 5), *SRSF2* (NM_003016.4, 1), *STAT3* (NM_139276.3, 20), *STK19* (NM_004197.2, 1), *TERT* promoter (NM_198253.3), *TCF7L2* (NM_001146274.2, 14), *TGFBR1* (NM_004612.4, 4, 9), *TGFBR2* (NM_001024847.2, 8), *TP63* (NM_003722.5, 9, 14), *U2AF1* (NM_006758.3, 2, 6), *XPO1* (NM_003400.4, 15)
* MSK-ACCESS® powered with SOPHiA DDM™ is target agnostic and, as such, other fusions than those indicated may be present as off-target or low-quality calls.

Please note that *RAD51C/D* and *NF2* are not covered by this panel in the context of clinical trial targets.

Please note that coverage has not been assessed for all reported additional findings, therefore, the possibility of false negatives cannot be excluded.

The limit of detection (LoD) is stated as and validated to ≥0.1% with a minimum coverage of 3 supporting alt allele molecule counts, with target-specific LoD provided per sample. Variants which are described according to Human Genome Variation Society nomenclature.

****Please note the coverage for intronic regions at fusion breakpoints has not been determined, therefore fusion calling is limited and, as such, a false negative result cannot be excluded. RNA-based testing is recommended for improved sensitivity and accuracy. Scope of analysis of *NTRK2* fusions is limited and deep intronic breakpoints are not supported.**

Potential germline findings in six of the seven most actionable cancer susceptibility genes (*BRCA1, BRCA2, PALB2, MLH1, MSH2* and *MSH6*) as described by The European Society for Medical oncology1 will be reported and germline testing recommended for indels and SNV's >40% VAF.

[1]Kuzbari et al Ann Oncol, 2023 Mar;34(3):215-227

Please note: The QIAsymphony extraction assays and MSK-ACCESS® powered with SOPHiA DDM™ ctDNA testing are currently part of an Extension to Scope application to UKAS ISO 15189.

Report Date : 19/01/2026
Authorised by : Senior Clinical Scientist

Test Methodology:

This test analyses circulating tumour DNA (ctDNA) from plasma using the MSK-ACCESS® assay powered by the SOPHiA DDM™ platform. ctDNA from plasma and matched normal genomic DNA (gDNA) from white blood cells are extracted and analysed using targeted next-generation sequencing (NGS). The assay performs ultra-deep sequencing (approximately 20,000× coverage) across a panel of **147 cancer-associated genes**, enabling detection of several types of genomic alterations including single nucleotide variants (SNVs), small insertions and deletions (indels), splice variants, gene fusions, and selected copy number changes. Matched normal DNA is analysed alongside tumour-derived ctDNA to help filter non-tumour variants, including changes related to clonal haematopoiesis (CHIP; see glossary of terms). The genes and genomic regions covered by the assay are listed in the report.

Variant analysis and reporting:

Variant analysis and reporting are performed in accordance with the **National Genomic Test Directory.**

For the lung ctDNA pathway (M4.14), these include key actionable genes such as *EGFR, ALK, BRAF, KRAS,* and *MET*, as well as fusion targets involving *ALK, ROS1, RET,* and *NTRK1/2/3*. Variants identified in these genes are interpreted and reported because they have established clinical relevance for diagnosis, treatment selection, or eligibility for approved targeted therapies.

The panel also analyses a broader set of **clinical trial targets**. Variants detected in these genes are reported as **Additional Findings** and may provide information relevant to emerging therapies or clinical trial eligibility (see Report page 2).

Fusion detection limitations:

Detection of gene fusions may be limited because some intronic regions where fusion breakpoints occur are not fully covered by this assay. As a result, certain fusions (including some *NTRK2* fusions) may not be detected. RNA-based testing may be considered where more sensitive fusion detection is required.

Limit of detection:

The assay has a validated **limit of detection of approximately 0.10% variant allele frequency (VAF)** when sufficient sequencing coverage (~20,000x) and supporting molecular reads are present. Detection depends on the amount of tumour DNA present in the blood sample; therefore, a negative result does not exclude the presence of a tumour variant.

Potential germline findings:

Variants suggestive of possible **germline alterations** in highly actionable cancer susceptibility genes (including *BRCA1, BRCA2, PALB2, MLH1, MSH2,* and *MSH6*) may be identified when detected at high allele frequency. In such cases, confirmatory germline testing may be recommended.

Accreditation status:

This test is fully validated and accreditation to ISO 15189 by UKAS is underway.

South East Genomic Medicine Service: A Guide to the Breast Cancer ctDNA Report

Report | Page 1

Patient demographics:

Includes patient identifiers, referring physician, and sample dates (taken and received).
Verify patient identity against clinical request before reviewing results.

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CANCER GENETICS

GENETIC ANALYSIS REPORT — **ONCOLOGY**

NAME: PATIENT
: Example

DOB: 01/01/1970 Age: 56 Sex: Female

Referring Physician: Dr Referring Clinician
Hospital: Guy's Hospital

SPECIMEN No: 26/00000
PRU No: 123456:01
Date Taken: 05/01/2026
Date Rec'd: 08/01/2026
Hospital No: 12345678
NHS Number: 111 111 1111

Sample: Blood, cfDNA extracted from plasma (Sample ID.123456)
Clinical details: **M3.13 (see targets below). Breast cancer progression**
ctDNA fraction: Unknown

CIRCULATING TUMOUR DNA (ctDNA) FINAL REPORT

SUMMARY OF LIKELY/ONCOGENIC (and VUS) SMALL VARIANTS AND CNV ASSESSMENT

Gene	Description	CN	VAF	Exon	Classification
AKT1	c.49G>A, P.Glu17Lys		1.9%	4	Oncogenic
No variants detected in ***ESR1, PIK3CA*** and ***PTEN***					

Please see page 2 for additional findings that may be relevant for clinical trial eligibility.

ACTIONABILITY

An *AKT1* variant was detected. This patient may respond to treatment with an AKT inhibitor.

These ctDNA results should be interpreted in the context of any available immunohistochemistry, tissue genomics and additional ctDNA results that may be available for this patient.

Consideration should be given to tumor heterogeneity, potential germline findings and the possibility of malignancies incidental to the indicated diagnosis, and referral to GTAB should further discussion be required; email: gstt.gtabsoutheastglh@nhs.net

GTAB referral form: https://southeastgenomics.nhs.uk/wp-content/uploads/2024/09/Blank-GTAB-referral-form.pdf

ctDNA fraction is not quantifiable with this assay. False negative results and variants below the limit of detection cannot be excluded. Repeat testing at clinically appropriate timepoints is recommended when no actionable alterations are detected.

Report Date : 19/01/2026
Authorised by : Senior Clinical Scientist

Sample and clinical details:

States sample details: type (blood / cfDNA from plasma) and the reason for testing (e.g. M3.13 for breast cancer ctDNA testing).

ctDNA fraction is not determined by this assay. Further explanation is provided **at the end of the Report page 1)**.

Summary of variants:

This table summarises genomic findings in essential target genes as defined by the **National Genomic Test Directory** for this clinical indication **(see Report page 3). It includes small variants** (SNVs and indels) and **copy number variants** (CNVs), classified as oncogenic, likely oncogenic, or variants of uncertain significance (VUS).

Columns show: Gene, CN (copy number), VAF (variant allele frequency), exon, and classification (see page 5 for definitions and HGVS nomenclature).

Note on ctDNA testing in breast cancer (M3.13):

ctDNA testing in breast cancer (M3.13) does **not** include fusion gene analysis. Unlike ctDNA testing in lung cancer.

No Summary of Fusions table appears in this report. This is expected and does not represent a test limitation for this pathway.

Actionability:

Provides **clinical interpretation** of detected variants in relation to the **tumour type tested,** including **therapeutic actionability** (e.g. AKT inhibitor therapy) with reference to **NICE** or **Cancer Drugs Fund (CDF)** guidance.

Clinical Reminder
interpret alongside IHC and tissue genomic findings. **GTAB contact details** are provided for further advice if required.

Note:

Directs the reader to page 2 where information on additional findings including clinical trial targets can be found.

GENETIC ANALYSIS REPORT **ONCOLOGY**

NAME: PATIENT
: Example

DOB: 01/01/1970	Age: 56	Sex: Female	SPECIMEN No:	26/00000
			PRU No:	123456:01
			Date Taken:	05/01/2026
			Date Rec'd:	08/01/2026
			Hospital No:	12345678
Referring Physician:	Dr Referring Clinician		NHS Number:	111 111 1111
Hospital:	Guy's Hospital			

ADDITIONAL FINDINGS OUTSIDE OF STANDARD OF CARE TESTING

Analysis has been performed in accordance with the National Genomic Test Directory. (https://www.england.nhs.uk/publication/national-genomic-test-directories/)

Additional findings reported here fall outside standard-of-care testing and these findings may represent variants of potential clinical relevance.

If considering clinical trials or further discussion is required regarding these results, then please refer to the Regional or National Genomic Tumour Advisory Board (GTAB).

For information on potential clinical trials please visit the ECMC trial finder (https://ecmctrialfinder.org) or Cancer Research UK clinical trials finder (https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial).

All additional variants meeting AMP/ASCO/CAP Tier 1 or Tier 2 clinical significance or variants classified as A or B according to SOPHiA DDM™ are reported.

These variants have not been assessed by the laboratory for clinical significance.

Additional findings:

Genetic variants detected in genes beyond the essential targets for the patient's clinical indication. These genes are included to support emerging therapies or clinical trials; therefore, the variants are reported for information only and have not been clinically interpreted by the laboratory.

If clinically appropriate, referral to the Genomic Tumour Advisory Board (GTAB) should be considered.

If no variants are reported in this section, it means the genes were successfully analysed but no clinically relevant alterations were identified in the tested variant types.

SUMMARY OF LIKELY/ONCOGENIC SMALL VARIANTS AND CNV

Gene	Description	CN	VAF	Exon
TGFBR2	c.1136A>G, p.(Asp379Gly)		0.61%	6
NF1	c.1198C>T, p.(Gln400*)		0.69%	9

Regions with insufficient coverage within essential gene targets

Variants cannot be excluded below 1% in the suboptimal regions described below.

GENE	Suboptimal regions	FAILED regions
No target regions with suboptimal or failed coverage		

Please note that coverage has not been assessed for all reported additional findings, therefore, the possibility of false negatives cannot be excluded.

Coverage information:

Coverage refers to how many times a DNA region is read during sequencing; higher coverage increases confidence in variant detection. This section lists exons/regions within essential target genes with reduced or failed coverage.

Where the report states '**No target regions with suboptimal or failed coverage**', all assessed regions in the essential gene targets met the required coverage threshold for reliable variant detection.

If suboptimal or failed regions are present, further details are provided in this table and reflected in the ACTIONABILITY section (see lung cancer ctDNA report example).

Report Date : 19/01/2026
Authorised by : Senior Clinical Scientist

GENETIC ANALYSIS REPORT **ONCOLOGY**

NAME: PATIENT
: Example

SPECIMEN No: 26/00000
PRU No: 123456:01
Date Taken: 05/01/2026
Date Rec'd: 08/01/2026
Hospital No: 12345678
NHS Number: 111 111 1111

DOB: 01/01/1970 Age: 56 Sex: Female

Referring Physician: Dr Referring Clinician
Hospital: Guy's Hospital

MSK-ACCESS® powered with SOPHiA DDM™ ctDNA panel methodology:

ctDNA and gDNA extraction is performed on the QIAsymphony using the QIAsymphony DSP circulating DNA Maxi kit and DSP DNA Mini kit, respectively. MSK-ACCESS® powered with SOPHiA DDM™ is a decentralised assay collaboration between SOPHiA GENETICS and Memorial Sloan Kettering Cancer Center (MSK) involving the deep sequencing (~20,000x) of 147 key cancer-associated genes to inform nucleotide variants (SNVs), indels, splicing isoforms, and intra- and intergenic fusion rearrangement, and *TERT* promoter variants. Powered by the advanced features of the SOPHiA DDM Platform, the assay incorporates a paired tumour cfDNA and matched normal white blood cell DNA approach to enable CHIP filtering. Using the proprietary molecular barcoding approach CUMIN™ and a capture-based workflow either manually or automated, paired tumour-normal libraries are sequenced using Illumina NGS systems.
Data are uploaded securely to SOPHiA DDM™ Decision Support Software (DSS) for encrypted analysis and storage. Variants are additionally curated through SOPHiA DDM™ and OncoPortal™ Plus by integration of ClinVar, OncoKB, and JAXCKB.

Analysis is performed according to the requirements of the National Genomics Test Directory.
M3.13 breast ctDNA: *ESR1, PIK3CA, AKT1, PTEN (SNV & CNV)*

The assay fully covers the coding sequences of the following 39 genes (hg19) and provides CNV detection (other than *HIST1H3B*):
APC (NM_000038.6), ***AR*** (NM_000044.6), ***ARID1A*** (NM_006015.6), ***ASXL1*** (NM_015338.6), ***ATM*** (NM_000051.4), ***BAP1*** (NM_004656.4), ***BRCA1*** (NM_007294.4), ***BRCA2*** (NM_000059.4), ***CDH1*** (NM_004360.5), ***CDK12*** (NM_016507.4), ***CDK4*** (NM_000075.4), ***CDKN2A*** (NM_000077.5, NM_058195.4), ***CHEK2*** (NM_007194.4), ***DNMT3A*** (NM_022552.5), ***ERCC2*** (NM_000400.4), ***FBXW7*** (NM_033632.3), ***FOXL2*** (NM_023067.4), ***GATA3*** (NM_002051.3), ***HIST1H3B*** (NM_003537.4, **no CNV**), ***KDM6A*** (NM_021140.4), ***KEAP1*** (NM_203500.2), ***KRAS*** (NM_033360.4), ***MLH1*** (NM_000249.4), ***MSH2*** (NM_000251.3), ***MSH6*** (NM_000179.3), ***NF1*** (NM_001042492.3), ***PALB2*** (NM_024675.4), ***PMS2*** (NM_000535.7), ***PPM1D*** (NM_003620.4), ***PTCH1*** (NM_000264.5), ***PTEN*** (NM_000314.8), ***RB1*** (NM_000321.3), ***SMAD4*** (NM_005359.6), ***STK11*** (NM_000455.5), ***TET2*** (NM_001127208.3), ***TP53*** (NM_000546.6), ***TSC1*** (NM_000368.5), ***TSC2*** (NM_000548.5), ***VHL*** (NM_000551.4).

The assay covers the following regions (hg19) and provides CNV and fusion* detection as indicated (***GENE*** (reference sequence, exons, **CNV/fusions**)):
AKT1 (NM_001014431.2, 3, 6-12, **CNV**), ***ALK*** (NM_004304.5, 5, 9, 20-29, **CNV, fusions**), ***ARAF*** (NM_001654.5, 7, 10-16, **CNV**), ***ARID2*** (NM_152641.4, 8), ***B2M*** (NM_004048.4, 1), ***BCL2*** (NM_000633.3, 2), ***BCOR*** (NM_001123385.2, 10), ***BRAF*** (NM_004333.6, 11-18, **CNV, fusions**), ***CARD11*** (NM_032415.7, 13), ***CBFB*** (NM_022845.3, 2), ***CBL*** (NM_005188.4, 9), ***CCND1*** (NM_053056.3, 5), ***CD79B*** (NM_001039933.3, 5), ***CIC*** (NM_015125.5, 5), ***CREBBP*** (NM_015125.5, 26, 27, 30, **CNV**), ***CTCF*** (NM_006565.4, 6), ***CTNNB1*** (NM_001904.4, 3, 7, 8), ***DICER1*** (NM_030621.4, 27), ***DIS3*** (NM_014953.5, 10), ***EGFR*** (NM_005228.5, 3, 6, 7, 15, 18-24, **CNV, oncogenic isoform**), ***EIF1AX*** (NM_001412.4, 1, 2), ***EP300*** (NM_001429.4, 26, 27, **CNV**), ***ERBB2*** (NM_004448.4, 3, 6-8, 12, 16-25, 27, **CNV**), ***ERBB3*** (NM_001982.4, 3, 6-9, 18-24, **CNV**), ***ESR1*** (NM_001122740.2, 6-9, **CNV**), ***ETV6*** (, **fusions**), ***EZH2*** (NM_004456.5, 16), ***FGFR1*** (NM_001174067.2, 12-19, **CNV**), ***FGFR2*** (NM_000141.5, 3, 5, 7-9, 11-18, **CNV, fusions**), ***FGFR3*** (NM_000142.5, 7, 9, 11-18, **CNV, fusions**), ***FGFR4*** (NM_213647.3, 13), ***FLT3*** (NM_004119.3, 14, 20), ***FOXA1*** (NM_004496.5, 2, **CNV**), ***FOXO1*** (NM_002015.4, 1), ***FOXP1*** (NM_001244814.3, 14), ***FUBP1*** (NM_003902.5, 14), ***GNA11*** (NM_002067.5, 5), ***GNAQ*** (NM_002072.5, 5), ***GNAS*** (NM_000516.7, 6, 8, 9), ***H3F3A*** (NM_002107.7, 2), ***HRAS*** (NM_001130442.3, 2-4), ***IDH1*** (NM_005896.4, 4, 5), ***IDH2*** (NM_002168.4, 4), ***IKZF1*** (NM_006060.6, 8), ***INPPL1*** (NM_001567.4, 2), ***JAK1*** (NM_002227.4, 19), ***JAK2*** (NM_004972.4, 14), ***KIT*** (NM_000222.3, 8-21, **CNV**), ***KNSTRN*** (NM_033286.4, 1), ***MAP2K1*** (NM_002755.4, 2-11, **CNV**), ***MAP2K2*** (NM_030662.4, 2-11, **CNV**), ***MAPK1*** (NM_002745.5, 7), ***MAX*** (NM_002382.5, 2, 4), ***MED12*** (NM_005120.3, 2, 26), ***MET*** (NM_000245.4, 13-21, **CNV, fusions, oncogenic isoform**), ***MSH3*** (NM_002439.5, 7), ***MTOR***
(NM_004958.4, 29-31, 39, 40, 43, 44, 46-50, 53, 56, 57, **CNV**), ***MYC*** (NM_002467.6, 2, **CNV**), ***MYCN*** (NM_005378.6, 2, **CNV**), ***MYD88*** (NM_002468.5, 5), ***MYOD1*** (NM_002478.5, 1), ***NFE2L2*** (NM_006164.5, 2), ***NOTCH1*** (NM_017617.5, 6, 8), ***NPM1*** (NM_002520.7, 11), ***NRAS*** (NM_002524.5, 2-4), ***NTRK1*** (NM_002529.4, 13-17, **CNV, fusions**), ***NTRK2*** (NM_006180.6, 15-19, **CNV**), ***NTRK3*** (NM_001012338.3, 15-20, **CNV**), ***NUP93*** (NM_014669.5, 2), ***PAK5*** (NM_177990.4, 4, **CNV**), ***PDGFRA*** (NM_006206.6, 5-7, 9-21, **CNV**), ***PHF6*** (NM_032458.3, 5, 9), ***PIK3CA*** (NM_006218.4, 2, 3, 5, 6, 8-12, 14, 19-21, **CNV**), ***PIK3CB*** (NM_006219.3, 24), ***PIK3R1*** (NM_181523.3, 10, 11, 13, 14, **CNV**), ***PIK3R2*** (NM_005027.4, 10), ***PIM1*** (NM_002648.4, 1), ***POLE*** (NM_006231.4, 1, 9, 13), ***POT1*** (NM_015450.3, 6), ***PPP2R1A*** (NM_014225.6, 5, 6), ***PPP6C*** (NM_002721.5, 7), ***PRKCI*** (NM_002740.6, 15), ***PTPN11*** (NM_002834.5, 3, 13), ***RAC1*** (NM_018890.4, 2), ***RAD54L*** (NM_001142548.2, 10), ***RAF1*** (NM_002880.4, 7, 10-17, **CNV**), ***RET*** (NM_020975.6, 8, 10-19, **CNV, fusions**), ***RHOA*** (NM_001664.4, 2, 3), ***RIT1*** (NM_006912.6, 5), ***ROS1*** (NM_002944.3, 36-42, **CNV, fusions**), ***RRAS2*** (NM_012250.6, 1, 3), ***RXRA*** (NM_002957.6, 10), ***SETD2*** (NM_014159.7, 7), ***SF3B1*** (NM_012433.4, 14, 15, 18, **CNV**), ***SMAD3*** (NM_005902.4, 6), ***SMARCA4*** (NM_003072.5, 19, 25, 26, **CNV**), ***SMARCB1*** (NM_003073.5, 9), ***SOS1*** (NM_005633.4, 5), ***SPOP*** (NM_001007228.2, 4, 5), ***SRSF2*** (NM_003016.4, 1), ***STAT3*** (NM_139276.3, 20), ***STK19*** (NM_004197.2, 1), ***TERT*** promoter (NM_198253.3), ***TCF7L2*** (NM_001146274.2, 14), ***TGFBR1*** (NM_004612.4, 4, 9), ***TGFBR2*** (NM_001024847.2, 8), ***TP63*** (NM_003722.5, 9, 14), ***U2AF1*** (NM_006758.3, 2, 6), ***XPO1*** (NM_003400.4, 15)
* MSK-ACCESS® powered with SOPHiA DDM™ is target agnostic and, as such, other fusions than those indicated may be present as off-target or low-quality calls.

Please note that *RAD51C/D* and *NF2* are not covered by this panel in the context of clinical trial targets.

Please note that coverage has not been assessed for all reported additional findings, therefore, the possibility of false negatives cannot be excluded.

The limit of detection (LoD) is stated as and validated to ≥0.1% with a minimum coverage of 3 supporting alt allele molecule counts, with target-specific LoD provided per sample. Variants which are described according to Human Genome Variation Society nomenclature.

Potential germline findings in six of the seven most actionable cancer susceptibility genes (*BRCA1, BRCA2, PALB2, MLH1, MSH2* and *MSH6*) as described by The European Society for Medical oncology1 will be reported and germline testing recommended for indels and SNV's >40% VAF.

[1]Kuzbari et al Ann Oncol, 2023 Mar;34(3):215-227

Please note: The QIAsymphony extraction assays and MSK-ACCESS® powered with SOPHiA DDM™ ctDNA testing are currently part of an Extension to Scope application to UKAS ISO 15189.

Report Date : 19/01/2026
Authorised by : Senior Clinical Scientist

Test Methodology:

This test analyses circulating tumour DNA (ctDNA) from plasma using the MSK-ACCESS® assay powered by the SOPHiA DDM™ platform. ctDNA from plasma and matched normal genomic DNA (gDNA) from white blood cells are extracted and analysed using targeted next-generation sequencing (NGS). The assay performs ultra-deep sequencing (approximately 20,000× coverage) across a panel of **147 cancer-associated genes**, enabling detection of several types of genomic alterations including single nucleotide variants (SNVs), small insertions and deletions (indels), splice variants, gene fusions, and selected copy number changes. Matched normal DNA is analysed alongside tumour-derived ctDNA to help filter non-tumour variants, including changes related to clonal haematopoiesis (CHIP; see glossary of terms). The genes and genomic regions covered by the assay are listed in the report.

Variant analysis and reporting:

Variant analysis and reporting are performed in accordance with the **National Genomic Test Directory**.

For the breast ctDNA pathway (M3.13), these are: *ESR1, PIK3CA, AKT1,* and *PTEN*, assessed for small nucleotide variants (SNVs), insertions/deletions (indels), and copy number variants (CNVs). Variants identified in these genes are interpreted and reported because they have established clinical relevance for diagnosis, treatment selection, or eligibility for approved targeted therapies in breast cancer.

The panel also analyses a broader set of **clinical trial targets**. Variants detected in these genes are reported as **Additional Findings** and may provide information relevant to emerging therapies or clinical trial eligibility (see page 2 the report).

Test scope and limitations:

This assay does not provide complete coverage of all genes. In some genes analysis may be limited to selected exons or hotspot regions. Variants occurring outside the regions covered by the assay will not be detected.

For instance, *ESR1* is analysed in exons 6–9 only, which include clinically relevant ligand-binding domain mutations associated with endocrine resistance.

Limit of detection:

The assay has a validated **limit of detection of approximately 0.10% variant allele frequency (VAF)** when sufficient sequencing coverage (~20,000x) and supporting molecular reads are present. Detection depends on the amount of tumour DNA present in the blood sample; therefore, a negative result does not exclude the presence of a tumour variant.

Accreditation status:

This test is fully validated and accreditation to ISO 15189 by UKAS is underway.

Potential germline findings:

Variants suggestive of possible **germline alterations** in highly actionable cancer susceptibility genes (including *BRCA1, BRCA2, PALB2, MLH1, MSH2,* and *MSH6*) may be identified when detected at high allele frequency. In such cases, confirmatory germline testing may be recommended.

Glossary of Terms

ctDNA Fraction

The proportion of total cfDNA derived from tumour. Not determined by this assay - false negatives cannot be excluded if fraction is low or unknown.

VAF (Variant Allele Frequency)

Percentage of reads carrying the variant. Low VAF may indicate low tumour signal or minor clone. VAF > 40% may suggest germline origin.

Gene Fusions

Chromosomal rearrangements creating chimeric oncogenes. DNA-based detection has reduced sensitivity. RNA testing recommended if fusion status is critical.

CHIP (Clonal Haematopoiesis of Indeterminate Potential)

Haematopoietic clonal variants unrelated to the tumour have been filtered using matched white blood cell (WBC) DNA. However, variants arising from CHIP may still be detected at low VAF.

CNV (Copy Number Variant)

Gene amplification or deletion. CNV detection is gene-specific and depends on tumour fraction - check the methodology section for coverage.

Germline Risk

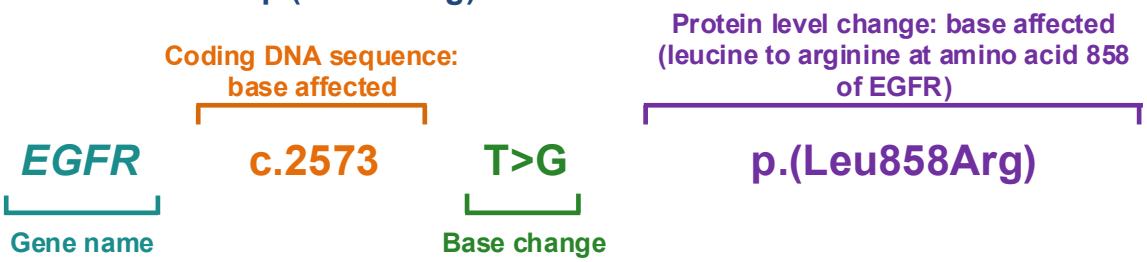
Flagged in *BRCA1/2, PALB2, MLH1, MSH2, MSH6* if SNV/indel >40% VAF. Constitutional germline testing should be arranged separately.

Variant Nomenclature

All variants use Human Genome Variation Society (HGVS) standard nomenclature for variant descriptions.

Example:

EGFR c.2573T>G p.(Leu858Arg)



Please note that in the **protein level** description, we apply the **3-letter amino acid abbreviations**. However, some clinical guidance, databases or alternative reports may refer to the variant with a **single-letter amino acid abbreviation**.

The above variant, *EGFR c.2573T>G p.(Leu858Arg)*, is also commonly referred to as *L858R* where **L** is equivalent to Leu (leucine) and **R** is equivalent to Arg (arginine). This can cause confusion, particularly for amino acids where single-letter and three-letter abbreviations are less intuitive.

For example, the *KRAS c.35G>A p.(Gly12Asp)* variant is also known as *KRAS G12D*, whereas *KRAS c.35G>C p.(Gly12Ala)* is known as *KRAS G12A*.

The table (shown right) provides a complete list of amino acids, including their three-letter and single-letter codes, to support interpretation of full HGVS descriptions.

Amino acid	3-letter	1-letter
Alanine	Ala	A
Arginine	Arg	R
Asparagine	Asn	N
Aspartic acid	Asp	D
Cysteine	Cys	C
Glutamine	Gln	Q
Glutamic acid	Glu	E
Glycine	Gly	G
Histidine	His	H
Isoleucine	Ile	I
Leucine	Leu	L
Lysine	Lys	K
Methionine	Met	M
Phenylalanine	Phe	F
Proline	Pro	P
Serine	Ser	S
Threonine	Thr	T
Tryptophan	Trp	W
Tyrosine	Tyr	Y
Valine	Val	V