Patient ID / MRN	Patient Name		Birth Date	Gender	Age
	LAST, FIRST		dd-0m-yyyy	Male	
Accession Number	Account Name		Ordering Physician		
	Clinic / Hospital		LAST, FIRST		
Sample Type	Collected	Received	Reported		
Formalin Fixed Paraffin Embedded (FFPE) tissue 10-SP-24-#####, Block A1	DD Mmm YYYY	DD Mmm YYYY	DD Mmm YYYY		
Test		Test Indication			
17243209 - KRAS Somatic Mutation, Tumor		Non-Small Cell Lung Cancer			

KRAS Somatic Mutation, Tumor

RESULT

Oncogenic/Tier I Variant Detected
KRAS: Chr12(GRCh38):g.25245351; NM_004985.5(KRAS):c.34G>T; p.Gly12Cys; exon 2/5

INTERPRETATION

Normal Gene/Protein Function: The KRAS gene encodes a small GTPase protein, K-Ras, which plays a pivotal role in cellular signal transduction. K-Ras acts as a molecular switch within the RAS/MAPK signaling pathway, regulating processes like cell growth, differentiation, and survival. It cycles between an active, GTP-bound state and an inactive, GDP-bound state in response to extracellular signals such as growth factors. Upon activation, K-Ras transmits signals to downstream effectors, including RAF kinases, to modulate gene expression and cellular responses. Under normal conditions, K-Ras activity is tightly controlled to maintain cellular homeostasis. Dysregulation, often through mutations, can lead to aberrant signaling and tumorigenesis.

Mutation Effect: A KRAS mutation c.34G>T; p.Gly12Cys, commonly known as G12C, was detected in this sample. Mutations in the KRAS gene often result in a constitutively active K-Ras protein that is locked in its GTP-bound state, bypassing normal regulatory controls. This leads to persistent activation of downstream signaling pathways, such as the MAPK/ERK and PI3K/AKT pathways, which drive uncontrolled cell proliferation, survival, and migration. The most frequent mutations occur at codons 12, 13, and 61, altering the protein's GTPase activity and contributing to oncogenesis.

Disease Associations: The presence of a KRAS G12C mutation is of therapeutic importance for a variety of human cancers, including Ampullary cancer, Anal cancer, Colorectal cancer, Esophagogastric cancer, Gastrointestinal neuroendocrine tumors of the esophagus/stomach, Non-small cell lung cancer, Hepatobiliary cancer, Pancreatic adenocarcinoma, and Small bowel cancer (OncoKB, data version v4.23, last accessed: December 18th, 2024). KRAS mutations are associated with poor prognosis and resistance to certain therapies.

Therapeutic Implications: Based on the clinical indication of this individual, Adagrasib or Sotorasib can be of therapeutic importance (OncoKB, data version v4.23, last accessed: December 18th, 2024; PMID: 34096690, 38157806, 38157806, 37098232, 36764316, 35658005; Gadgeel, S. et al., Abstract# MA06.04, Journal of Thoracic Oncology Vol. 18). This result should be interpreted in the context of clinical and other laboratory findings.

METHODOLOGY

The Idylla™ KRAS Mutation Test, performed on the Biocartis Idylla™ system, is an in vitro diagnostic test (IVD) that uses ready-to-use cartridges for the qualitative detection of 21 mutations in codons 12, 13, 59, 61, 117 and 146 of the KRAS gene. The test was conducted following the manufacturer's recommended protocol. In brief, a tumor-rich section of tissue was macrodissected from glass slides, or an FFPE curl/scroll was loaded into the Idylla cartridge. Inside the cartridge, a combination of chemical reagents, enzymes, heat, and high-intensity focused ultrasound facilitated deparaffinization, tissue disruption, and cell lysis. This process released nucleic acids, making them available for subsequent PCR amplification.

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Real-time PCR was then carried out using allele-specific primers, with simultaneous detection of an endogenous sample processing control. Specific targets were identified using fluorescent-labeled probes. The entire process within the cartridge was automated. This method has been previously described in the literature (PMID: 28114309).

Vendor-provided software automatically analyzed fluorescent signals and displayed results on the Idylla Console. The software evaluated PCR curve validity and calculated a cycle of quantification (Cq) value for each valid curve.
The presence of a mutant genotype was determined by comparing the Cq of the sample processing control to the Cq of the mutant signal, producing a ΔCq value. Mutant signals were considered valid if the ΔCq fell within a vendor-defined range, and any detected variants were reported. At the end of the run, a final report confirmed the presence or absence of specific codon mutations in the KRAS gene.

LIMITATIONS

KRAS mutation below the detection limit may not be detected. The test enables identifying the presence of a KRAS mutation with a limit of detection (LOD) of 5% allelic fraction except mutations p.Gly12Ala, p.Gly13Asp, and p.Ala146Pro/Thr/Val which show LOD values of 9%, 10%, and 16%, respectively. Rare polymorphisms in the primer-binding site could lead to false-negative or false-positive results. **The assay includes all major and some minor KRAS mutations, encompassing virtually 100% of KRAS mutations described in tumors**. The presence of codons 12, 13, and 61 mutations ensures coverage of the most clinically significant and commonly observed alterations. This assay does not detect KRAS mutations other than those listed in **Table 1**.

Table 1. List of KRAS Mutations Detectable by this Assay

No.	DNA change	Protein change	Location	No.	DNA change	Protein change	Location	No.	DNA change	Protein change	Location
1	c.34G>T	p.Gly12Cys	Codon 12 (exon 2)	8	c.175G>A	p.Ala59Thr	Codon 59 (exon 3)	15	c.183A>C	p.Gln61His	Codon 61(exon 3)
2	c.34G>C	p.Gly12Arg	Codon 12 (exon 2)	9	c.176C>A	p.Ala59Glu	Codon 59 (exon 3)	16	c.183A>T	p.Gln61His	Codon 61(exon 3)
3	c.34G>A	p.Gly12Ser	Codon 12 (exon 2)	10	c.176C>G	p.Ala59Gly	Codon 59 (exon 3)	17	c.351A>C	p.Lys117Asn	Codon 117(exon 4)
4	c.35G>C	p.Gly12Ala	Codon 12 (exon 2)	11	c.180_181delinsAA	p.Gln61Lys	Codon 61 (exon 3)	18	c.351A>T	p.Lys117Asn	Codon 117(exon 4)
5	c.35G>A	p.Gly12Asp	Codon 12 (exon 2)	12	c.181C>A	p.Gln61Lys	Codon 61 (exon 3)	19	c.436G>C	p.Ala146Pro	Codon 146(exon 4)
6	c.35G>T	p.Gly12Val	Codon 12 (exon 2)	13	c.182A>T	p.Gln61Leu	Codon 61 (exon 3)	20	c.436G>A	p.Ala146Thr	Codon 146(exon 4)
7	c.38G>A	p.Gly13Asp	Codon 13 (exon 2)	14	c.182A>G	p.Gln61Arg	Codon 61 (exon 3)	21	c.437C>T	p.Ala146Val	Codon 146(exon 4)

DISCLAIMER

This test was developed, and its performance characteristics were determined by the Molecular Diagnostics & Genomics Laboratory of NRL. This test is marked with In-Vitro Diagnostics (IVD) CE approval. "CE" stands for "Conformité Européenne" [European Conformity]. The IVD CE mark assures that the product meets quality and purity requirements according to the European IVD Regulation [2017/746 EU IVDR) and guarantees maximum reproducibility for analysis. At NRL, this test is used for

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Sample Type	Collected	Received	Reported		
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Test		Test Indication			
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clinical purposes and should not be regarded as investigational or for research. The test is currently not accredited by the Emirates International Accreditation Centre (EIAC) but will be added to the scope of accreditation in the next assessment cycle.

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