Patient ID	Patient Name		Birth Date	Sex	Age
SA00174995	TESTINGRNV, ABNORMAL		1955-02-14	F	70
Order Number	**Client Order Number**	**Ordering Physician**	**Report Notes**		
SA00174995	SA00174995	CLIENT,CLIENT			
Account Information		**Collected**			
C7028846 DLMP Rochester		28 Mar 2025 00:00			

MayoComplete Kidney Cancer Panel

Result

MCR

Provided diagnosis: kidney renal cell carcinoma

The following CLINICALLY RELEVANT VARIANT was detected:
Gene: TSC1
DNA Change: c.107–1G>A
Variant Allele Frequency: 20.1%

Microsatellite Instability (MSI) status: Stable (MSS)

The following VARIANT OF UNCERTAIN SIGNIFICANCE was detected:
Gene: PBRM1
DNA Change: c.1949A>C (Exon 18)
Amino Acid Change: p.K650T (Lys650Thr)
Variant Allele Frequency: 17.1%

No other reportable sequence variants were detected within the analyzed regions of the tested gene(s) listed in the method description.

Interpretation

MCR

1) TSC1 c.107–1G>A

TSC1 encodes hamartin, which forms a heterodimer with tuberin (encoded by TSC2) to act as a GTPase activating protein for Rheb, a potent activator of the mammalian target of rapamycin (mTOR) [PMID:12271141, PMID:12869586, PMID:12906785]. By converting Rheb from a GTP- to GDP-bound state, the hamartin/tuberin heterodimer inactivates Rheb and suppresses mTOR activity [PMID:18466115, PMID:21428921]. Inactivation of TSC1, mainly through deletions and mutations, leads to activation of the mTOR signaling pathway and contributes to tumorigenesis [PMID:12271141, PMID:16452213].

TSC1 mutations have been reported in 2–3% of renal tumor samples [COSMIC, cBioPortal for Cancer Genomics].

TSC1 mutations are described in the literature in new and emerging renal entities including renal cell carcinoma with fibromyomatous stroma, eosinophilic solid and cystic renal cell carcinoma, eosinophilic vacuolated tumor, low grade oncocytic tumor, and angiomyolipoma [PMID: 33526874, PMID: 34531523, PMID: 34521993]. The presence of this alteration in this specimen should be interpreted in correlation with histopathological and clinico-radiological findings.

The loss of TSC1 function has been reported to lead to activation of mTOR, suggesting that TSC1 loss or hamartin inactivation may predict sensitivity to mTOR inhibitors [PMID:12869586, PMID:12906785]. In a number of cancer types (including bladder, breast, thyroid, and PEComa), patients who have had exceptional responses to mTOR inhibitors have been found to harbor TSC1 or TSC2 inactivating alterations [PMID:22923433, PMID:25295501, PMID:20048174, PMID:22927055, PMID:26859683]. However, additional studies are needed to assess the efficacy of these therapies in solid tumors.

MSI: Stable (MSS)
NO evidence of microsatellite instability was detected suggesting the presence of normal DNA mismatch repair function within the tumor. Current data suggest that advanced stage solid tumors with intact mismatch repair (MSS) are less likely to be responsive to treatment with immunotherapies such as anti-PD-1 therapies [PMID 28596308, PMID 29355075].

VARIANT OF UNCERTAIN SIGNIFICANCE

One variant of uncertain significance was detected. The variant was not observed at significant frequency in population germline/cancer somatic variant databases nor predicted to be functionally significant based on variant type/in silico algorithm results. Additionally, there was no convincing published evidence of cancer association. Therefore, the clinical significance of the detected variant is unknown.

Performing Site Legend

Code	Laboratory	Address	Lab Director	CLIA Certificate
MCR	Mayo Clinic Laboratories - Rochester Main Campus	200 First Street SW, Rochester, MN 55905	Nikola Baumann Ph.D.	24D0404292

MAYO CLINIC LABORATORIES

Patient ID	Patient Name		Birth Date	Sex	Age
SA00174995	TESTINGRNV, ABNORMAL		1955-02-14	F	70
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Additional Information

MCR

CLINICAL TRIALS

Possible clinical trials of benefit for this patient can be found at the following sites:
1) ClinicalTrials.gov:
www.clinicaltrials.gov/ct2/search/advanced
2) Mayo Clinic: www.mayo.edu/research/clinical-trials/ 3) National Cancer Institute: www.cancer.gov/clinicaltrials/search

REFERENCE TRANSCRIPTS

Sequence variant nomenclature is based on the following RefSeq accession numbers (build GRCh37 (hg19)): PBRM1 NM_181042 and TSC1 NM_000368.

Specimen

MCR

Tissue, Tumor

Tissue ID

MCR

12345

Method

MCR

Microscopic examination is performed by a pathologist to identify areas of tumor for enrichment by macrodissection.

Next generation sequencing is performed to test for the presence of microsatellite instability and a mutation within most coding regions and exon/intron boundaries of the following genes: ATRX, BAP1, BRAF, CDKN2A, ELOC, FH, FLCN, KRAS, MET, MITF, MTOR, MLH1, MSH2, MSH6, NF2, PBRM1, PMS2, PTEN, RB1, SDHA, SDHB, SDHC, SDHD, SETD2, SMARCB1, TERT, TP53, TSC1, TSC2, and VHL

Variant nomenclature is based on build GRCh37 (hg19). For details about gene transcripts (RefSeq accession numbers), specific targeted regions of each gene, and additional information on this test, see www.mayocliniclabs.com (Test ID MCKCP).

Disclaimer

1 MCR

This test cannot differentiate between somatic and germline alterations. Additional testing may be necessary to clarify the significance of results if there is a potential hereditary risk.

DNA variants of uncertain significance may be identified.

A negative result does not rule out the presence of a variant that may be present but below the limits of detection of this assay. The analytical sensitivity of this assay for sequence reportable alterations is 5% mutant allele frequency with a minimum coverage of 500X in a sample with at least 20% tumor content.

Point mutations and small insertion/deletion mutations will be detected in the ATRX, BAP1, BRAF, CDKN2A, ELOC, FH, FLCN, KRAS, MET, MITF, MTOR, MLH1, MSH2, MSH6, NF2, PBRM1, PMS2, PTEN, RB1, SDHA, SDHB, SDHC, SDHD, SETD2, SMARCB1, TERT, TP53, TSC1, TSC2, and VHL genes only. This test may detect single exon deletions but does not detect multi-exon deletions, duplications, larger-scale genomic copy number variants, copy neutral loss of heterozygosity (LOH), or epigenetic modifications such as promoter methylation. DELINS of 1,000 bp or less are detectable with at least 50 or more supporting reads.

This test cannot reliably determine if a variant identified in PMS2 exons 11–15 originated from PMS2 or the highly homologous pseudogene PMS2CL. In the instance that a reportable variant is detected in PMS2 exons 11–15, additional testing will be recommended in the patient report.

Variant allele frequency (VAF) is the percentage of sequencing reads supporting a specific variant divided by the total sequencing reads at that position. In somatic testing, VAF should be interpreted in the context of several factors including, but not limited to: tumor purity/heterogeneity/copy number status (ploidy, gains/losses, loss of heterozygosity) and sequencing artifact/misalignment [PMID: 27144058, PMID: 29769535].

Rare polymorphisms may be present that could lead to false-negative or false-positive results.

The presence or absence of a variant may not be predictive of response to therapy in all patients.

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Test results should be interpreted in the context of clinical, tumor sampling, histopathological, and other laboratory data. If results obtained do not match other clinical or laboratory findings, contact the laboratory for discussion. Misinterpretation of results may occur if the information provided is inaccurate and/or incomplete.

Reliable results are dependent on adequate specimen collection and processing. This test has been validated on cytology slides and formalin-fixed, paraffin-embedded tissues; other types of fixatives are discouraged. Improper treatment of tissues, such as decalcification, may cause PCR failure.

Released By MCR

Ying-Chun Lo, M.D., Ph.D.

Received: 29 Mar 2025 15:21 **Reported:** 07 Apr 2025 17:12

Laboratory Notes

1 This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.

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