Patient ID	Patient Name		Birth Date	Gender	Age
SA00143935	TESTINGRNV, TPNUQ ABNORMAL		2008-10-16	M	12
Order Number	**Client Order Number**	**Ordering Physician**	**Report Notes**		
SA00143935	SA00143935	CLIENT,CLIENT			
Account Information		**Collected**			
C7028846 DLMP Rochester		05 Apr 2021 00:00			

Results

Analyte	Result	Performing Site
TPMT Genotype	*2/*2	MCR
TPMT Phenotype	⚠ Poor metabolizer	MCR
NUDT15 Genotype	*1/*1	MCR
NUDT15 Phenotype	✓ Normal metabolizer	MCR

Interpretation

MCR

High toxicity risk when treated with thiopurines. This individual most likely is a poor TPMT metabolizer. In non-malignant disease, treatment with thiopurine drugs is generally contraindicated for patients with poor TPMT activity and alternative agents should be considered. For malignant disease, drastically reduced doses may be used with subsequent dose adjustments based on degree of myelosuppression and according to published guidelines. Therapeutic drug monitoring may be considered if thiopurines are used. No variants in NUDT15 were identified in this individual.

Method

MCR

Genotyping is performed using a PCR-based 5'-nuclease assay. Fluorescently labeled detection probes anneal to the target DNA. PCR is used to amplify the segment of DNA that contains the polymorphism. If the detection probe is an exact match to the target DNA, the 5'-nuclease polymerase degrades the probe, the reporter dye is released from the effects of the quencher dye, and a fluorescent signal is detected. Genotypes are assigned based on the allele-specific fluorescent signals that are detected. (TaqMan(r) SNP Genotyping Assays User Guide, Applied Biosystems)

Disclaimer

1 MCR

Targeted analysis using a polymerase chain reaction (PCR)-based 5'-nuclease assay using fluorescently labeled detection probes is performed to detect the following variants in thiopurine methyl transferase (TPMT): *2 (c.238G>C), *3A (c.460G>A;c.719A>G), *3B (c.460G>A), *3C (c.719A>G,) *4 (c.626–1G>A), *5 (c.146T>C), *8 (c.644G>A), and *12 (c.374C>T) based on GRCh37 NM_000367.4; and nudix hydrolase 15 (NUDT15): *2 or *3 (c.415C>T), *4 (c.416G>A), and *5 (c.52G>A), based on NM_018283.3. TPMT*2, *3A, *3B, *3C, *4, and *5 are nonfunctional (null) alleles. TMPT*8 and *12 have reduced activity but retain some residual activity. The NUDT15 variants are nonfunctional (null) or have significantly reduced function alleles. If these alleles are not detected, a genotype of *1/*1 is assigned for both genes. However, this method may not detect all variants that result in altered TPMT or NUDT15 activity. Therefore, absence of a detectable variant does not rule out the possibility that a patient has altered TPMT or NUDT15 metabolism due to other TPMT or NUDT15 variants that cannot be detected with this method. Furthermore, when two or more variants are detected, the cis-/trans- status (whether the variants are on the same or opposite chromosomes) is not always known. Results are generally interpreted assuming the two variants are in trans (on opposite chromosomes) with the exception of the *3A allele as described below. There is a residual risk that other rarer alleles may be present which are not detected by this assay and which might affect the patient's response to thiopurine drugs.

This genotyping method will not distinguish between a TPMT*1/*3A genotype, which is associated with an intermediate TPMT activity, and the rare TPMT*3B/*3C genotype (estimated 1:120,890), which is associated with low TPMT activity. This is

Performing Site Legend

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

Patient ID	Patient Name		Birth Date	Gender	Age
SA00143935	TESTINGRNV, TPNUQ ABNORMAL		2008-10-16	M	12
Order Number	**Client Order Number**	**Ordering Physician**	**Report Notes**		
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C7028846 DLMP Rochester		05 Apr 2021 00:00			

because the *3A allele is a combination of the *3B and *3C variations in cis, and this assay cannot determine if the TPMT*3B and *3C variations are on the same or opposite chromosomes. At the discretion of the care provider, evaluation of enzyme activity can be done to definitively assign phenotype in this setting. Order Mayo Test ID TPMT3, Thiopurine Methyltransferase (TPMT) Activity Profile, Erythrocytes.

Since some adverse reactions to thiopurine drugs, including myelosuppression, are not always explained by TPMT or NUDT15, regular monitoring of complete blood count (CBC), liver function tests, and other signs of toxicity should be considered. Therapeutic drug monitoring may also be considered for patients with a TPMT variant, but no variant in NUDT15.

Inhibitors:
Concurrent treatment with allopurinol might inhibit TPMT activity. Other drugs that have been shown to inhibit TPMT activity include: naproxen, ibuprofen, ketoprofen, furosemide, sulfasalazine, mesalamine, olsalazine, mefenamic acid, thiazide diuretics, and benzoic acid inhibitors.

CAUTIONS:

Rare variants may be present that could lead to false negative or positive results. If results obtained do not match the clinical findings (phenotype), additional testing should be considered.

Samples may contain donor DNA if obtained from patients who have recently received non-leukoreduced blood transfusions or allogeneic hematopoietic stem cell transplantation. Results from samples obtained under these circumstances may not accurately reflect the recipient's genotype. For individuals who have received blood transfusions, the genotype usually reverts to that of the recipient within 6 weeks. For individuals who have received allogeneic hematopoietic stem cell transplantation, a pre-transplant DNA specimen is recommended for testing. TPMT and NUDT15 genetic test results in patients who have undergone liver transplantation may not accurately reflect the patient's TPMT and NUDT15 status.

Reviewed by MCR

Ann Marie Moyer, M.D., Ph.D.

Received: 07 Apr 2021 09:17 **Reported:** 07 Apr 2021 16:09

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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