Memorandum MolePath #34

To: UNC Healthcare System Attending Physicians, Housestaff, Nursing Coordinators, Department Heads and Supervisors

From: Karen Weck MD, Director, Molecular Genetics Laboratory

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Subject: *TPMT/NUDT15* genotyping recommended for thiopurine treatment

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Effective July 31, 2021, the UNC Molecular Genetics Laboratory recommends *TPMT/NUDT15* genotyping (LAB11186) over TPMT enzyme activity testing (LAB5769) (both ordered through Referral Testing and Mayo Laboratories) to screen for risk of toxicity to thiopurine medications (azathioprine, mercaptopurine, and thioguanine).

Rationale for TPMT/NUDT15 testing:
Both TPMT and NUDT15 are involved in converting active metabolites of thiopurines into inactive compounds. Deficiencies in these enzymes are associated with increased levels of active thioguanines and increased toxicity (including life-threatening myelosuppression). Patients who have inherited deficiencies in either or both of these enzymes should be evaluated for reduced starting doses of thiopurines and should be monitored more frequently for toxicity, specifically myelosuppression.

Rationale for use of *TPMT/NUDT15* genotyping over TPMT enzyme activity testing:
TPMT enzyme activity testing was previously preferred to *TPMT* genotyping due to the risk of missing rare genotypic variants that lead to reduced TPMT enzymatic activity. With the current *TPMT/NUDT15* genotyping test from Mayo laboratories, there is <0.5% chance that the patient will have an allele leading to loss of TPMT enzymatic activity that is not detected by the genotyping assay. TPMT deficiency due to inherited genotypes is a primary cause of thiopurine intolerance in European and African populations. TPMT enzyme activity testing may be appropriate in addition to therapeutic

drug monitoring in patients who have unexplained myelosuppression while on thiopurines.

Our understanding of NUDT15 activity as a predictor of myelosuppression has developed since 2015. There is no currently available assay to directly measure enzymatic activity of NUDT15. Measuring thioguanine metabolites does not identify NUDT15 insufficiency, as the assay does not distinguish tri- and di- phosphates from monophosphates. Therefore, the only currently available test to infer NUDT15 activity is genotyping. The presence of *NUDT15* risk alleles explains the majority of cases of thiopurine intolerance in Asians and Hispanics. By doing TPMT enzyme activity testing alone, there is the risk of missing patients with NUDT15 deficiency, with a multi ethnic allele frequency of 13.5%.

Specimen Requirements: 1-3 mL blood in purple top (EDTA) tube

Turn-around time: 5-7 days

Test Order (EAP) number in EPIC: LAB11186: TPMT AND NUDT15 GENOTYPING; TPNUV; TPMT GENOTYPING; NUDT15 GENOTYPING

References:

1. Relling MV, Schwab M, Whirl-Carrillo M, et al. Clinical Pharmacogenetics Implementation Consortium Guideline for Thiopurine Dosing Based on TPMT and NUDT15 Genotypes: 2018 Update. Clin Pharmacol Ther. 2019 May;105(5):1095-1105. Available at: https://cpicpgx.org/guidelines/guideline-for-thiopurines-and-tpmt/
2. Table of Pharmacogenetic Associations, US Food & Drug administration. Accessed: July 20,2021. Available at: https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations
3. gnomAD: Genome Aggregation Database. Available at: https://gnomad.broadinstitute.org/

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