TPMT TESTING IN THE TREATMENT OF INFLAMMATORY BOWEL DISEASE

WHY IS TPMT TESTING IMPORTANT?

- Detection of individuals with low thiopurine methyltransferase (TPMT) activity who are at risk for excessive myelosuppression or severe hematopoietic toxicity when taking thiopurine drugs.
- Detection of individuals with hyperactive TPMT activity who have therapeutic resistance to thiopurine drugs and may develop hepatotoxicity if treated with these drugs.

WHICH TESTS ARE AVAILABLE AND WHEN SHOULD I ORDER THEM?

<table>
<thead>
<tr>
<th>WHEN TO ORDER</th>
<th>PRIOR TO INITIATION OF THERAPY*</th>
<th>AFTER INITIATION THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>GENOTYPING ASSAY (MAYO ID: TPNUV)</td>
<td>Prior to initiation of therapy to predict risk of toxicity. If patient was previously tested and toxicity is encountered.</td>
<td>Prior to initiation of therapy to predict risk of toxicity. After initiation of therapy to optimize therapy and identify elevated metabolite concentrations that may result in toxicity. As needed for dose changes, flare-up, signs of toxicity, or suspicion of non-compliance. In patients that do not respond to therapy as expected. <strong>Recommended Timepoints</strong>: 4 weeks after starting treatment to ensure patient compliance and to look for early risk of toxicity. 12-16 weeks (after TGN metabolites have reached steady-state). Annually.</td>
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<td>ACTIVITY ASSAY (MAYO ID: TPMT3)</td>
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<tr>
<td>METABOLITE MONITORING (MAYO ID: FPMET)</td>
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ADVANTAGES

- Can identify patients at risk of myelotoxicity and start them on a reduced dose or alternate therapy.
- Test is not impacted by other medications.
- DNA is stable/specimen is less sensitive to transport conditions.
- Includes NUDT15 (three genetic variants).
- This data gives clinicians the confidence to prescribe an appropriate thiopurine dosage, as opposed to titrating at a low-starting dosage and risking ineffective therapy.

TPMT TESTING ALGORITHM

Initiation of thiopurine therapy for IBD

Has patient had RBC transfusion within past 6 weeks?*
OR
Does patient have low hematocrit or reticulocytosis?
OR
Is patient uremic?

NO

Is patient a bone marrow transplant recipient?

NO

Pre-transplant specimen required

TPMT/NUDT15 genotype testing

YES to any

TPMT Activity: normal
TPMT genotype: normal metabolizer
NUDT15 genotype: intermediate metabolizer****

OR

TPMT activity: heterozygote
TPMT genotype: normal metabolizer
NUDT15 genotype: normal metabolizer

OR

TPMT activity: heterozygote
TPMT genotype: intermediate metabolizer
NUDT15 genotype: intermediate metabolizer****

OR

TPMT activity: deficient
TPMT genotype: poor metabolizer
NUDT15 genotype: normal metabolizer

OR

TPMT activity: normal
TPMT genotype: normal metabolizer
NUDT15 genotype: poor metabolizer****

OR

TPMT activity: heterozygote
TPMT genotype: intermediate metabolizer
NUDT15 genotype: poor metabolizer

Reduce dose and monitor appropriately

Consider alternative medications**

Standard dose and monitoring

Consider alternative medications**

4 weeks after treatment initiation

12-16 weeks after treatment initiation

Annually, or as needed for dose changes, flare-up, signs of toxicity, suspicion of non-compliance, lack of response

TPMT Metabolite Monitoring

6-TGN 235-450 pmol/8x10^8 RBC

Low/absent 6-TGN and 6-MMP

Low 6-TGN and high 6-MMP*

High 6-TGN and low 6-MMP

High 6-TGN and 6-MMP

Continue therapy and monitoring

Noncompliance/underdosing

Consider allopurinol and drastic dose reduction

Dose reduction and close monitoring

Refractory; consider alternative medication

* Presence of donor DNA in products may influence genotyping results; however, genotype typically reverts to recipient within 6 weeks after a transfusion.
** If phenotype testing is preferred, recent research and Mayo Clinic strongly recommend ordering NUDT15 genotype testing in addition. Mayo Clinic Laboratories provides NUDT15 genotyping testing at no additional cost with its TPMT genotyping test (TPMUV).
*** Patients with high TPMT activity cannot achieve therapeutic levels with thiopurine drugs and prescribing higher doses may cause hepatotoxicity.
**** Metabolite monitoring assays would not be useful in cases where the patient has an NUDT15 genetic variant.