Implementation of Personalized Medicine at Moffitt Cancer Center

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Mission Health

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DeBartolo Family Personalized Medicine Institute
H. Lee Moffitt Cancer Center & Research Institute
Moffitt Cancer Center & Research Institute

• Established by Florida legislature in 1981

• Only NCI-designated Comprehensive Cancer Center based in FL

• Based on patient volumes, Moffitt is the fastest growing and 3rd largest cancer center in U.S
Moffitt Cancer Center Personalized Medicine Institute

- Established in 2012
- Revolutionize the discovery, delivery and effectiveness of cancer care at an international scale
  - Total Cancer Care (TCC) Study
  - Personalized Medicine Consult Service
  - Clinical Genomic Action Committee (CGAC)
  - Personalized Medicine Training Program
Personalized Medicine Consult Service

Purpose: Optimize the treatment of each patient through utilization of all clinically relevant methods of personalization

What stimulates a consult?
- Germline pharmacogenetic mutation analysis (i.e. TPMT, CYP2C19, etc.)
- Somatic (tumor) genetic results with treatment implications not clearly dictated by available practice guidelines or standards of care
  - Recommendations for clinical trials or off-label use of targeted treatment based on genomic findings

Output from the consult service: Formal consult note in patient’s chart and availability to discuss these results and implications for therapy with patients

Attendings: Dr. Christine Walko
Dr. Kevin Hicks
Dr. Todd Knepper (Fellow)
Clinical Pharmacogenetics Implementation Consortium Guidelines for Thiopurine Methyltransferase Genotype and Thiopurine Dosing

MV Relling¹, EE Gardner¹, WJ Sandborn², K Schmiegelow³,⁴, C-H Pui⁵, SW Yee⁶, CM Stein⁷, M Carrillo⁸, WE Evans¹ and TE Klein⁸

The assignment of likely TPMT phenotype is based on genotype

<table>
<thead>
<tr>
<th>Likely phenotype</th>
<th>Genotypes</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal or high activity (~90% of patients)</td>
<td>Homozygous wild-type: two or more wild-type/ functional alleles</td>
<td>*1/*1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>High or normal $TPMT$ activity</th>
<th>Intermediate $TPMT$ activity</th>
<th>Low or absent $TPMT$ activity</th>
</tr>
</thead>
</table>
| • Initiate normal starting doses  
• Allow 2 weeks to reach steady state after each dose adjustment  
• No special emphasis should be placed upon thiopurines | • Start at 30-70% of full dose MP and Azathioprine  
• Start at 30-50% of full dose of TG  
• Adjust dose based on myelosuppression and disease-specific guidelines  
• Emphasis on reducing thiopurines over other agents  
• Allow 2-4 weeks to reach steady state after each dose adjustment | • For non-malignant conditions, consider alternative non-thiopurine immunosuppressant therapy  
• Choose an alternative agent for Azathioprine  
• For malignancy, reduce daily doses by 10-fold and reduce frequency to 3X per week instead of daily  
• Allow 4-6 weeks to reach steady state after each dose adjustment |

TPMT implementation steps

- Determine timing and method of genotyping
  - Patient selection - All patients receiving POMP or other maintenance with MP
  - Determine timing for test ordering
  - In house vs. send out genotyping - Send out to ARUP Labs

- Formulate strategy for return of results
  - Create consensus on genotype-specific action – CPIC guidelines, met with heme malignancies MDs and PharmD
  - Create discrete entry into EHR – results will automatically populate, interface with ARUP
  - Create consults to accompany results – worked with Cerner App services
  - Design clinical decision support – worked with Cerner App services – presented to CDS subcommittee before going live

- Consensus on endpoints
  - Ensure mechanisms to capture the impact on drug ordering or monitoring – worked with Cerner App Services

- Education of clinicians and patients
  - Email announcement for clinicians – sent prior to go-live
TPMT genotype results from Reference Lab are interfaced into PowerChart within the Molecular Pathology Laboratory results flowsheet.

**Assay Name**: PROMETHEUS TPMT Genetics

**Reference Range**: TPMT*1/TPMT*1

**Result**: TPMT*1/TPMT*1

Alleles present are associated with NORMAL ENZYME ACTIVITY.

PROMETHEUS TPMT Genetics is an analysis to determine an ability to produce thiopurine methyltransferase (TPMT) activity. It is a method to identify patients at risk for acute toxicity from 6-MP or azathioprine. This profile provides a breakdown of a patient’s genetics. The distribution of TPMT activity is trimodal: homozygous normal (8%), heterozygous (11%) and homozygous recessive (0.3%). Approximately 1 in 1213 individuals may have a low TPMT enzyme activity (homozygous low) resulting from known and theoretical mutations that are not included in this panel.

Notes: Genetic testing results are reported above as the individual allele present on each chromosome for three different polymorphisms: G238C, G460A, and A719G within the TPMT gene on chromosome 6. The alleles are numbered based on order of discovery.
Laboratory Result for TPMT triggers a notification of a consult to a Multi-Patient Task List for personalized consult service members.
<table>
<thead>
<tr>
<th>TPMT Consult Language</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TPMT normal (high) activity</strong></td>
<td>This result signifies that this patient has two copies of a wild-type (high activity) allele. This patient is predicted to have high (normal) TPMT activity. Initiate standard starting doses of thiopurines (mercaptopurine, thioguanine, or azathioprine). In the setting of myelosuppression, adjust doses of thiopurines (and of any other myelosuppressive therapy) without special emphasis on thiopurines. Allow 2 weeks to reach steady state after each dose adjustment.</td>
</tr>
<tr>
<td><strong>TPMT intermediate</strong></td>
<td>This result signifies that this patient has one copy of a wild-type (high activity) allele and one copy of a non-functional allele. This patient is predicted to have intermediate TPMT activity and is at risk for myelosuppression with standard doses of medications in the thiopurine class (mercaptopurine, thioguanine, or azathioprine). Recommend starting with 65% of the target dose for mercaptopurine, 30-70% of the target dose of azathioprine and 30-50% of the target dose for thioguanine (or an alternative agent such as mercaptopurine). Adjust thiopurine doses based on degree of myelosuppression and disease-specific guidelines. In the setting of myelosuppression, and depending on other therapy, emphasis should be on reducing thiopurine doses over other agents. Allow 2-4 weeks to reach steady state after each dose adjustment.</td>
</tr>
<tr>
<td><strong>TPMT Low or absent activity</strong></td>
<td>This result signifies that this patient has two copies of a non-functional (low activity) allele. This patient is predicted to have low or absent TPMT activity and is at high risk for life-threatening myelosuppression with normal doses of drugs in the thiopurine class (mercaptopurine, thioguanine or azathioprine). For malignancy, reduce dose and frequency of mercaptopurine or thioguanine drastically. Recommend starting with 10% of the target dose for mercaptopurine and administering three times a week. For thioguanine, consider an alternative agent such as mercaptopurine or start with 10% of the target dose and administer three times a week. Azathioprine should be avoided, or if azathioprine is given, start with 10% of the target dose and administer three times a week instead of daily. Adjust thiopurine doses based on degree of myelosuppression and disease-specific guidelines. In the setting of myelosuppression, and depending on other therapy, emphasis should be on reducing thiopurine doses over other agents. Allow 2-4 weeks to reach steady state after each dose adjustment.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Phenotype</th>
<th>On-screen Clinical Decision Support Language</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>6MP</strong></td>
<td>TPMT Intermediate Activity</td>
<td>Based on the genotype result, this patient is predicted to have intermediate TPMT activity. The patient is at risk for myelosuppression with normal doses of 6-mercaptopurine. Recommend starting 6-mercaptopurine at 65% of the target dose. Please contact the personalized medicine consult service or review the pharmacogenetics consult for more information.</td>
</tr>
<tr>
<td></td>
<td>TPMT Low or absent activity</td>
<td>Based on the genotype result, this patient is predicted to have low or absent TPMT activity. The patient is at high risk for life-threatening myelosuppression with normal doses of 6-mercaptopurine and should receive greatly reduced doses. Recommend starting with 10% of the target dose for 6-mercaptopurine and administering three times a week instead of daily. Please contact the personalized medicine consult service or review the pharmacogenetics consult for more information.</td>
</tr>
<tr>
<td><strong>AZA</strong></td>
<td>TPMT Intermediate Activity</td>
<td>Based on the genotype result, this patient is predicted to have intermediate TPMT activity. The patient is at risk for myelosuppression with normal doses of azaTHIOprine. Recommend starting azaTHIOprine at 30-70% of the target dose. Please contact the personalized medicine consult service or review the pharmacogenetics consult for more information.</td>
</tr>
<tr>
<td></td>
<td>TPMT Low or absent activity</td>
<td>Based on the genotype result, this patient is predicted to have low or absent TPMT activity. The patient is at high risk for life-threatening myelosuppression with normal doses of azaTHIOprine. azaTHIOprine should be avoided, or if azaTHIOprine is given, start with 10% of the target azaTHIOprine dose and administer three times a week instead of daily. Please contact the personalized medicine consult service or review the pharmacogenetics consult for more information.</td>
</tr>
</tbody>
</table>

Consults for TPMT or other genetic results can be charted by using customized Powerform.
Personalized Medicine Consult for TPMT GENOTYPE

TPMT Genotype Result:
- TPMT*1/*1
- TPMT*1/*3A
- TPMT*2/*2

Sample Type: Whole Blood
Test Results: Reference Lab - for Reference Only

Clinical Notes

Wednesday, June 25, 2014 - Wednesday, July 02, 2014: 1 out of 2 documents are accessible. (Date Range) In Error Documents Filtered

Personalized Medicine Consultation

Result type: Personalized Medicine Consultation
Result date: 07/02/2014 7:16
Result status: Auth (Verified)
Result title: Personalized Medicine Consult
Performed by: Kelly, Kerry on 07/02/2014 7:16
Verified by: Kelly, Kerry on 07/02/2014 7:16
Encounter info: 6369245, HLM, Routine Outpatient, 06/16/2014

Personalized Medicine Consult Details:
Personalized Medicine Consult performed by: Kelly, Kerry
Date / Time of Consult: 07/02/2014 7:16
Type of Consultation Performed: TPMT Activity Consultation

TPMT Activity Consultation
TPMT Genotype Result: TPMT*1/*3B
TPMT Predicted phenotype: Low or absent activity
TPMT activity consult: TPMT predicted phenotype. Low or absent activity
This result signifies that this patient has two copies of a non-functional (low activity) allele. This patient is predicted to have low or absent TPMT activity and is at high risk for life-threatening myelosuppression with normal doses of drugs in the thiopurine class (mercaptopurine, thioguanine or azathioprine). For malignancy, reduce dose and frequency of mercaptopurine or thioguanine drastically. Recommend starting with 10% of the target dose for mercaptopurine and administering three times a week. For thioguanine, consider an alternative agent such as mercaptopurine or start with 10% of the targeted dose and administer three times a week. Azathioprine should be avoided, or if azathioprine is given, start with 10% of the target dose and administer three times a week instead of daily. Adjust subsequent thiopurine doses based on degree of myelosuppression and dose-specific guidelines. In setting of myelosuppression, and depending on other therapy, emphasis should be on reducing thiopurine doses over other agents. Allow 4-6 weeks to reach steady state after each dose adjustment.

Kelly, Kerry: 07/02/2014 7:16
Personalized medicine consults can be ordered by clinicians for any pharmacogenetic test.
Personalized medicine consults can also be completed through ad hoc charting.
A TPMT genotype test is recommended before using a thiopurine (mercaptopurine, thioguanine, and azathioprine).

A TPMT genotype test does not appear to have been ordered for XTEST, FALL. Laboratory services offers a reference lab test for genotyping.

More information can be obtained about TPMT activity by contacting the Personalized Medicine Group:
- Email: Personalized Med Consult (personalizedmedconsult@moffitt.org)
- Pager: Personalized Medicine Consult (256-4996)

mercaptopurine was just ordered on XTEST, DISCERN MR# 100028, however, a TPMT genotype test does not appear to have been ordered for this patient.

This email is sent to the Personalized Medicine Consult Service. If you are following this patient, please follow up to be certain a TPMT genotype test is ordered and used to guide thiopurine prescribing.

Please consider the environment before printing this email.
TPMT Post-test alerts

**WARNING - Patient at Risk**

Based on the genotype result, this patient is predicted to have intermediate TPMT activity.

**XTEST, DISCERN is at risk for myelosuppression with normal doses of 6-mercaptopurine.**

Recommend starting 6-mercaptopurine at 65% of the target dose. Please contact the personalized medicine consult service or review the personalized medicine consult for more information.

**WARNING - Patient at HIGH RISK**

Based on the genotype result, this patient is predicted to have low or absent TPMT activity.

**XTEST, DISCERN is at high risk for life-threatening myelosuppression with normal doses of 6-mercaptopurine and should receive greatly reduced doses.**

Recommend starting with 10% of the target dose for 6-mercaptopurine and administering three times a week instead of daily. Please contact the personalized medicine consult service or review the personalized medicine consult for more information.
Future Directions

• Review alert firings
  • Kept a spreadsheet off all alerts from emails
  • Most alerts were from patients already on drug
  • Institute a way to suppress alerts for those already on drug and after multiple firings
• Find a way to have a trigger to order test further upstream from medication prescribing
Personalized Cancer Medicine

Implementation of CYP2C19-Voriconaozle
Voriconazole Metabolism

Antifungal activity

CYP2C19, CYP3A4, CYP2C9

Less antifungal activity

Yanni et al. *Drug Metabolism and Disposition*. 38(1) 25-31; 2010
Evidence-based correlation between *CYP2C19* genotype and voriconazole plasma concentrations

<table>
<thead>
<tr>
<th>Major Findings</th>
<th>References</th>
</tr>
</thead>
</table>
| Significant association between *CYP2C19* genotype and voriconazole concentrations | • Weiss et al. *J Clin Pharmacol.* 49, 2009  
• Hassan et al. *Ther Drug Monit.* 33, 2011  
• Lee et al. *J Clin Pharmacol.* 52, 2012  
• Ikeda et al. *Clin Pharmacol Ther.* 75, 2004  
• Lei et al. *Ann Pharmacother.* 43, 2009  
• Wang et al. *J Antimicrob Chemother.* 69, 2014  
• Hicks et al. *Pharmacogenomics.* 15, 2014  
• Lamoureux et al. *Int J Antimicrob Agents.* In press |
Budget impact analysis of CYP2C19-guided voriconazole prophylaxis in AML

Neil T. Mason¹*, Gillian C. Bell¹, Rod E. Quilitz², John N. Greene² and Howard L. McLeod¹

<table>
<thead>
<tr>
<th>Marginal costs</th>
<th>Events</th>
<th>Cost</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening all patients for CYP2C19*17</td>
<td>100</td>
<td>($291.80)</td>
<td>($29180)</td>
</tr>
<tr>
<td>Voriconazole level for UMs</td>
<td>36</td>
<td>($18.68)</td>
<td>($675)</td>
</tr>
<tr>
<td>total</td>
<td></td>
<td></td>
<td>($29803)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Marginal savings</th>
<th>Events</th>
<th>Savings</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fungal infections avoided</td>
<td>2.3</td>
<td>$30 952</td>
<td>$71 270</td>
</tr>
<tr>
<td>total</td>
<td></td>
<td></td>
<td>$71 270</td>
</tr>
</tbody>
</table>

Total savings                         |        | $41 467  |
Total savings per patient             |        | $415     |
CYP2C19-Voriconazole

- Large inter-patient voriconazole concentration variability
- CYP2C19 activity may explain ~30-50% of voriconazole inter-patient plasma concentration variability

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Frequency</th>
<th>Metabolizer Phenotype</th>
<th>Voriconazole effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19*17/*17</td>
<td>2.5%</td>
<td>Ultra-rapid</td>
<td>High risk of subtherapeutic levels</td>
</tr>
<tr>
<td>CYP2C19*1/*17</td>
<td>20%</td>
<td>Rapid</td>
<td>Risk of subtherapeutic levels</td>
</tr>
<tr>
<td>CYP2C19*1/*1</td>
<td>50%</td>
<td>Normal</td>
<td>Therapeutic levels more likely</td>
</tr>
<tr>
<td>CYP2C19*2/*2, *1/*3,</td>
<td>25%</td>
<td>Intermediate</td>
<td>Therapeutic levels more likely</td>
</tr>
<tr>
<td>*2/*17, *3/*17</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP2C19*2/*2, *2/*3</td>
<td>2.5%</td>
<td>Poor</td>
<td>Risk of supratherapeutic levels</td>
</tr>
</tbody>
</table>

Obeng et al. *Pharmacotherapy*. 34(7) 703-718; 2014
Proposed CYP2C19-Voriconazole Clinical Workflow

1. **CYP2C19 test in AML PowerPlan**
   - **CYP2C19 Ultra-rapid or rapid metabolizer?**
     - No → **Usual prophylaxis therapy (Voriconazole 200 mg BID)**
     - Yes →
       - **Ultra-rapid metabolizer** → Isavuconazonium
       - **Rapid metabolizer** → Voriconazole 300 BID

2. **Voriconazole 300 BID**
   - **Trough Level in 5-7 days**
     - < 1 mcg/mL?
       - Yes → Increase dose and check levels x2
       - No → Continue therapy

3. **Continue therapy**
   - Switch to Isavuconazonium if still < 1mcg/mL
Proposed CYP2C19-Voriconazole Clinical Workflow

- Personalized Medication Consult placed into medical record
- Point-of-care decision support to assist in voriconazole dosing
  - Will be driven by lab results

AML PowerPlan initiated (CYP2C19 assay) → Vori ordered → *CYP2C19 result in EHR?*
  - Yes → Result Actionable?
    - Yes → CDS provides recommendation
    - No → Continue with order (No pharmacogenomic CDS required)
  - No → CDS recommending pharmacogenomic test

*Red boxes indicate where clinician action is required*
# Proposed CYP2C19-Voriconazole CDS Language

<table>
<thead>
<tr>
<th>CDS text, Relative to Genetic Testing</th>
<th>Trigger Condition</th>
<th>CDS Alert Text</th>
<th>Reasons for not ordering CYP2C19 genotype test</th>
</tr>
</thead>
</table>
| Pre-Pharmacogenetic Test            | AML diagnosis & voriconazole ordered in the context of no CYP2C19 test in the EHR  | RISK OF SUB-THERAPEUTIC LEVELS. CYP2C19 genotyping is recommended to help guide voriconazole dosing for the purpose of avoiding a breakthrough fungal infection due to low voriconazole levels.  
Please select the genotype test below OR select a reason for not ordering the test.  
Please click here for additional information about CYP2C19-voriconazole, or contact the Personalized Medicine Consultation service (pager number: 256-4996) | Previously achieved therapeutic levels  
History of allogeneic BMT  
History of liver transplant  
Voriconazole intolerance  
Prolonged QTc  
Patient declined test  
Other |
## Proposed CYP2C19-Voriconazole Clinical Workflow

<table>
<thead>
<tr>
<th>CDS text, Relative to Genetic Testing</th>
<th>Trigger Condition</th>
<th>CDS Alert Text</th>
<th>Reasons for not changing drug or dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-Pharmacogenetic Test</td>
<td>CYP2C19 ULTRA-rapid metabolizer &amp; vori ordered</td>
<td>HIGH RISK OF SUB-THERAPEUTIC LEVELS. The patient is predicted to be a CYP2C19 ultra-rapid metabolizer and is likely to have low voriconazole levels. To avoid a breakthrough fungal infection, consider prescribing isavuconazonium or another anti-fungal agent. Please click here for additional information about CYP2C19-voriconazole, or contact the Personalized Medicine Consultation service (pager number: 256-4996)</td>
<td>• Previously achieved therapeutic levels • Isavuconazonium intolerance • Other</td>
</tr>
<tr>
<td>Post-Pharmacogenetic Test</td>
<td>CYP2C19 rapid metabolizer &amp; vori ordered</td>
<td>RISK OF SUB-THERAPEUTIC LEVELS. The patient is predicted to be a CYP2C19 rapid metabolizer and is likely to have low voriconazole levels. To avoid a breakthrough fungal infection, consider increasing the voriconazole dose to 300 mg twice daily. Please click here for additional information about CYP2C19-voriconazole, or contact the Personalized Medicine Consultation service (pager number: 256-4996)</td>
<td>• Previously achieved therapeutic levels • Other</td>
</tr>
</tbody>
</table>
PURPOSE OF DOCUMENT: CYP2C19 metabolizes voriconazole to compounds with less anti-fungal activity. There is an increased risk of breakthrough fungal infections in those who are CYP2C19 ultra-rapid/rapid metabolizers due to low voriconazole plasma trough concentrations. CYP2C19 genotyping is offered at Moffitt Cancer Center (test name _____) to help identify those predicted to be CYP2C19 ultra-rapid/rapid metabolizers. The purpose of this document is to provide guidance for CYP2C19 test ordering, result interpretation, and gene-based pharmacotherapy recommendations.

CYP2C19 GENOTYPING AND TEST INTERPRETATION: It is recommended that consideration should be given to CYP2C19 genotyping for those prescribed voriconazole. Genetic variations may influence the enzymatic activity of CYP2C19, and dependent upon the test result individuals are assigned a predicted phenotype of ultra-rapid, rapid, normal, intermediate, or poor metabolizer. The current CYP2C19 genotyping assay utilized by Moffitt Cancer Center interrogates for the three most common variant alleles including the increased function allele *17 and two no function alleles *2 and *3. A list of all possible genotypes reported by this particular assay along with the corresponding phenotypes (enzyme activity) is found in Table 1. An algorithm is available for clinical decision making regarding CYP2C19 genotyping and voriconazole therapy (Figure 1). Drug selection and dosage may also depend on other clinical factors such as a history of drug intolerances or drug-drug interactions.

GENE BASED PHARMACOTHERAPY RECOMMENDATIONS: CYP2C19 ultra-rapid and rapid metabolizers are at an increased risk for breakthrough fungal infections due to low voriconazole concentrations. To prevent breakthrough fungal infections, there is strong evidence suggesting that ultra-rapid metabolizers should avoid voriconazole and that rapid metabolizers should be administered higher doses. Table 1 summarizes the pharmacotherapy recommendations based on CYP2C19 metabolizer status.

![Diagram](image.png)

**Table 1. Translation of CYP2C19 genotype to phenotype and corresponding pharmacotherapy recommendations**

<table>
<thead>
<tr>
<th>CYP2C19 genotype</th>
<th>CYP2C19 predicted</th>
<th>Dosing recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrasapid</td>
<td>fast</td>
<td>Increase dose and check levels x2</td>
</tr>
<tr>
<td>Rapid</td>
<td>rapid</td>
<td>Continue Therapy</td>
</tr>
<tr>
<td>Normal Intermediate or Poor metabolizer</td>
<td>intermediate or poor</td>
<td>Usual prophylaxis therapy (Voriconazole 200 mg BID)</td>
</tr>
<tr>
<td>Normal Intermediate or Poor metabolizer</td>
<td>intermediate or poor</td>
<td>Usual prophylaxis therapy (Voriconazole 200 mg BID)</td>
</tr>
<tr>
<td>Normal Intermediate or Poor metabolizer</td>
<td>intermediate or poor</td>
<td>Usual prophylaxis therapy (Voriconazole 200 mg BID)</td>
</tr>
</tbody>
</table>
FDA BLACK BOX WARNING: RISK OF A SERIOUS/FATAL HYPERSENSITIVITY REACTION. A HLA-B*57:01 genotype test is recommended before prescribing abacavir or reinitiating abacavir therapy, including for those who previously tolerated abacavir therapy. Please click 'accept' below to order the HLA-B*57:01 genotype test or a reason for not ordering the test.

Click here for additional information regarding HLA-B*57:01 - Abacavir

Acknowledge reason:  
- Test drawn and pending in lab  
- External result noted by clinician  
- External test result records requested  
- Other - Document in note  
- Patient declined test

Open order: HLA B5701

U.S. BOXED WARNING FOR ABACAVIR: Serious and sometimes fatal hypersensitivity reactions have occurred for patients testing positive for the presence of the HLA B5701 allele. Therapy is not recommended in patients testing positive for the HLA B5701 allele.

Click here for additional information regarding HLA-B*57:01 - Abacavir

Last HB5701=Positive on 2/25/2014

Acknowledge reason:  
- Med Update

Accept  Cancel
Pharmacogenomic Test Reporting in Drug Entry Screen

<table>
<thead>
<tr>
<th>Component</th>
<th>Time Elapsed</th>
<th>Value</th>
<th>Range</th>
<th>Status</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA B*1502 Typing</td>
<td>506 days (03/05/14 0700)</td>
<td>POSITIVE (NOTE) The allele HLA-B*1502 is associated with increased risk of developing severe skin reactions to carbamazepine therapy (Stevens-Johnson Syndrome and toxic epidermal necrolysis).</td>
<td></td>
<td>Final result</td>
<td></td>
</tr>
</tbody>
</table>

Reference Links:
1. HLA-B*15:02 Pharmacogenomic Summary Sheet
2. Drug Info - Adult
3. Drug Info - Peds

Dose: 200 mg
Administer Dose: 200 mg
Administer Amount: 1 tablet
Route: ORAL
Frequency: 2 TIMES DAILY
Personalized Medicine Consult Service

Purpose: Optimize the treatment of each patient through utilization of all clinically relevant methods of personalization

What stimulates a consult?
• Germline pharmacogenetic mutation analysis (i.e. TPMT, CYP2C19, etc.)
• Somatic (tumor) genetic results with treatment implications not clearly dictated by available practice guidelines or standards of care
  • Recommendations for clinical trials or off-label use of targeted treatment based on genomic findings

Output from the consult service: Formal consult note in patient’s chart and availability to discuss these results and implications for therapy with patients

Attendings: Dr. Christine Walko
Dr. Kevin Hicks
Dr. Todd Knepper (Fellow)
Implementation in Clinical Practice

Genetic Tumor Testing ordered and results returned

Personalized Medicine Consult Service discussion and review

Consult report generated and documented in EMR

Referral to Clinical Genomic Action Committee

Tumor Board discussion of patient with consideration of genetic results

Patient and Oncologist discussion
Translating Recommendations into Clinical Decision Making

- Researching and presenting available data to facilitate the decision making process
- Considering the interaction of all the mutations together
- Consideration of each patient’s unique characteristics
  - Desire for a clinical trial and ability to travel
  - Availability and ability to qualify for a clinical trial
  - Sequencing of treatment options
  - Insurance coverage and ability to afford off label therapy
  - Patient preference on treatment options
  - Where patient is in his/her treatment course
Patient Recommendations

**Recommendation Summary:** As detailed below, this patient has an FGFR amplification which would qualify him for the Phase I trial of a pan-FGFR inhibitor enrolling at Moffitt (MCC 17565) **(Level 3)**. Additionally, the multi-tyrosine kinase inhibitor *pazopanib*, inhibits FGFR and is FDA approved for soft tissue sarcoma **(Level 1)**. When choosing the order of these treatments, please consider the inclusion criteria of MCC 17565. Additionally, other phase I trials not enrolling at Moffitt are available based on the TP53 mutation **(Level 5)**. Use of a CDK 4/6 inhibitor is not recommended based on inactivation of Rb. Additionally, based on the presence of the TP53 and RB mutations, referral to the genetic risk assessment service is recommended.

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>FDA approved drug for patient's specific cancer</td>
</tr>
<tr>
<td>2</td>
<td>FDA approved drug for another cancer or indication</td>
</tr>
<tr>
<td>3</td>
<td>Clinical trial available at Moffitt for this gene</td>
</tr>
<tr>
<td>4</td>
<td>Clinical trial available at Moffitt based on pathway biology</td>
</tr>
<tr>
<td>5</td>
<td>Clinical trial available at a non-Moffitt site for this gene</td>
</tr>
<tr>
<td>6</td>
<td>Clinical trial available at a non-Moffitt site based on pathway biology</td>
</tr>
<tr>
<td>7</td>
<td>Human data available, no currently active clinical trial</td>
</tr>
<tr>
<td>8</td>
<td>In vitro or animal data available</td>
</tr>
<tr>
<td>9</td>
<td>No information available</td>
</tr>
</tbody>
</table>
Collecting Data and Future Analysis

• Bioinformatics collaboration essential for database development and evolution

• Utility of the database:
  – Tracking outcomes data
  – Informing clinical trial selection and design
  – Resource to aide with future clinical decision making

• Requires quality control measures and thoughtful design to maximize data integrity across numerous users
## CGAC Database

### List of Findings for patient **Foundation One**

<table>
<thead>
<tr>
<th>ID</th>
<th>Gene</th>
<th>Mutation</th>
<th>Significant</th>
<th>CNA</th>
<th>MAF</th>
<th>Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>4165</td>
<td>RET</td>
<td>NCOA4-RET fusion</td>
<td>YES</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4166</td>
<td>SMA04</td>
<td>W509*</td>
<td>YES</td>
<td></td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>4167</td>
<td>GNAS</td>
<td>K295K</td>
<td>NO</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4168</td>
<td>MAP3K1</td>
<td>S939C</td>
<td>NO</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4169</td>
<td>MLL2</td>
<td>P4454T</td>
<td>NO</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Add Gene and Mutation

- **Gene:**
- **Mutation (Change):**
- **Significant:**
- **CNA:**
- **MAF:**

[ADD]
Gene Information

Symbol: ATM
ID: CT
Alias: AT1, ATA, ATC, ATD, ATDC, ATE, TEL1, Telo1
Description: ataxia telangiectasia mutated

3. Mutation Frequency in TCC Samples

Tumor Samples vs. Normal Samples
- Tumor Samples (%): 0.18%
- Normal Samples (%): 0.84%

Across Different Tissue Types

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Protein</th>
<th>Sample with Mutation</th>
<th>Total Sample</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrium</td>
<td>G2023R</td>
<td>1</td>
<td>200</td>
<td>0.5</td>
</tr>
<tr>
<td>Esophagus</td>
<td>G2023R</td>
<td>1</td>
<td>44</td>
<td>2.27273</td>
</tr>
<tr>
<td>HEME-CLL</td>
<td>G2023R</td>
<td>2</td>
<td>94</td>
<td>2.12766</td>
</tr>
<tr>
<td>Kidney</td>
<td>G2023R</td>
<td>1</td>
<td>243</td>
<td>0.41152</td>
</tr>
<tr>
<td>Lung</td>
<td>G2023R</td>
<td>1</td>
<td>603</td>
<td>0.16584</td>
</tr>
</tbody>
</table>
Moffitt Cancer Center

- Howard McLeod
- Chris Walko
- Todd Knepper
- Jennifer Greenman
- Kerry Kelly
- Ashley Helms
- Sue Meservy
- Viet Ho
- Bijal Shah
- Jeffrey Lancet

- Kevin Hicks
- Neil Mason
- Rod Quillitz
- John Greene

QUESTIONS?
Extra Slides
Personalized Medicine Consultation Process

1. **TPMT genotype (reference lab) is ordered and results are directly uploaded to EHR**

2. **TPMT result triggers a notification of a consult to be completed via email to consult service and Multi-Patient Task List**

3. **Consultation completed and entered into EHR and is retrievable as “Personalized Medicine Consult”**

4. **Clinicians attempting to order 6MP or other thiopurines for patients with “high-risk” results will be presented with on-screen alert**
Define a location in EHR for pharmacogenetic results

Create a discrete result entry (TPMT *1/*3A)

Determine mechanism for knowing when results are back

Design a consult to accompany result

Create clinical decision support for high-risk phenotypes

Event logging of each alert occurrence for prescribing attempts