Clinical Information Systems to Support Personalized Medicine at the Bedside

March 2012

Mia Levy, MD, PhD
Director Cancer Clinical Informatics, Vanderbilt Ingram Cancer Center
Assistant Professor of Biomedical Informatics and Medicine
Agenda

• Vanderbilt Personalized Medicine Projects
  – Personalized Cancer Medicine Initiative
  – Diagnostic Management Team
  – Pharmaco-genomic Resource for Enhanced Decisions in Care & Treatment (PREDICT)

• Informatics Opportunities
  – Workflow and communication
  – Data integration and visualization
  – Actionable decision support
Biomarkers in the Clinical Continuum

- Diagnosis
  - Risk Biomarker
  - Diagnostic Biomarker
- Treatment Selection
  - Prognostic Biomarker
  - Predictive Biomarker
- Treatment Plan Management
- Treatment Response Assessment
  - Response Biomarker
Personalized Cancer Medicine Initiative

Genome directed cancer treatment selection

Diagnosis → Treatment Selection → Treatment Plan Management → Treatment Response Assessment

Predictive Biomarker
Traditional View of Cancer

Melanoma
- Arising from Skin Without Chronic Sun Damage
- Arising from Skin With Chronic Sun Damage
- Arising from Mucosal Surfaces
- Arising from Acral Surfaces

Lung Cancer
- Adenocarcinoma
- Squamous
- Large
- Small
Melanoma Panel: 538 patients
67% Patients with Actionable Mutation
33% No Mutation Identified

Lung Panel: 451 patients
46% Patients with Actionable Mutation
54% No Mutation Identified

12 ALK fusions
Old Method for Reporting Mutation Results in the Electronic Medical Record

Old Method:

- Report Template
- Scanned into Electronic Health Record as image file (not computable)

Challenges:

- How to report > 40 mutations in 8 genes?
- Whose role to curate knowledge regarding clinical significance?
- Lack clinical trial information
### Tumor Gene Mutations

<table>
<thead>
<tr>
<th>MR#</th>
<th>Patient Name</th>
<th>Actions</th>
<th>Tumor Gene Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>BRAF</td>
</tr>
<tr>
<td>03</td>
<td>81 A, B M.</td>
<td>Actions</td>
<td>Yellow</td>
</tr>
<tr>
<td>03</td>
<td>56 A, P</td>
<td>Actions</td>
<td>Yellow</td>
</tr>
<tr>
<td>03</td>
<td>35 B, J A</td>
<td>Actions</td>
<td>Yellow</td>
</tr>
<tr>
<td>01</td>
<td>80 B, S A</td>
<td>Actions</td>
<td></td>
</tr>
<tr>
<td>02</td>
<td>29 E, J E</td>
<td>Actions</td>
<td>Yellow</td>
</tr>
<tr>
<td>02</td>
<td>27 F, R M</td>
<td>Actions</td>
<td></td>
</tr>
<tr>
<td>02</td>
<td>77 G, T</td>
<td>Actions</td>
<td></td>
</tr>
<tr>
<td>02</td>
<td>73 H, A</td>
<td>Actions</td>
<td>Yellow</td>
</tr>
<tr>
<td>03</td>
<td>64 S, C</td>
<td>Actions</td>
<td></td>
</tr>
<tr>
<td>02</td>
<td>79 S, A S</td>
<td>Actions</td>
<td>Yellow</td>
</tr>
<tr>
<td>02</td>
<td>40 W, J E I</td>
<td>Actions</td>
<td></td>
</tr>
<tr>
<td>03</td>
<td>74 W, C L</td>
<td>Actions</td>
<td>Yellow</td>
</tr>
</tbody>
</table>

**Order Status**
- O = Order Received
- R = Outside Specimen Requested
- A = Outside Specimen Arrived
- v = Specimen Accessioned

**Result Status**
- Yellow = Gene Mutation Detected
- Grey = Gene Mutation Not Detected
- Red = No Result – Insufficient Specimen
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</tr>
<tr>
<td>03</td>
<td>56 A, P</td>
<td>Actions</td>
<td>BRAF, NRAS</td>
</tr>
<tr>
<td>03</td>
<td>35 B, J A</td>
<td>Actions</td>
<td>CTNNB1, GNAQ, KIT</td>
</tr>
<tr>
<td>01</td>
<td>80 B, S A</td>
<td>Actions</td>
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<td>Actions</td>
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</table>

**BRAF c.1798_1799GT>AG (V600R) Not Detected**

**BRAF c.1798_1799GT>AA (V600K) Not Detected**

**BRAF c.1799T>A (V600E) Detected**

**BRAF c.1799_1800TG>AA (V600E) Not Detected**

**BRAF c.1798G>A (V600M) Not Detected**

**BRAF c.1799T>G (V600G) Not Detected**

**BRAF c.1799_1800TG>AT (V600D) Not Detected**
BRAF V600E (c.1799T>A) mutation in Melanoma

The V600E mutation results in an amino acid substitution at position 600 in BRAF, from a Valine (V) to a glutamic acid (E). This mutation occurs within the activation segment of the kinase domain (Fig. 2). Approximately 70-90% of V600 BRAF mutations are V600E (Rubinstein, 2010). Mutant BRAF proteins have increased kinase activity and are transforming in vitro (Davies, 2002). BRAF mutations are usually found in tumors with a wild-type for NRAS, KIT, and other driver mutations.

In the initial phase trial, patients with metastatic melanoma whose tumor harbored a BRAF V600E mutation displayed an 81% response rate to vemurafenib (PLX4032), an orally available inhibitor of mutated BRAF. The estimated progression-free survival was > 7 months and overall survival had not been reached at the time of study publication (Ehaherty, 2010). In the follow-up randomized phase III trial comparing vemurafenib to dacarbazine in previously untreated, metastatic melanoma with the BRAF V600E mutation, vemurafenib improved rates of overall survival and progression-free survival (Chapman, 2011).

Pre-clinical data has correlated the presence of activating mutations in BRAF with sensitivity to non-ATP competitive MEK inhibitors, AZD6244 and CI-1040 (Davies, 2007; Solt, 2006). In a Phase II clinical trial of AZD6244 versus temozolomide, 5 of 42 melanoma patients with BRAF V600E mutation had confirmed partial responses (12% objective response rate) (Dummer, 2009).

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<tr>
<th>BRAF V600E mutation</th>
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<tbody>
<tr>
<td>Treatment Agent</td>
</tr>
<tr>
<td>vemurafenib (PLX4032)</td>
</tr>
<tr>
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</tr>
<tr>
<td>dacarbazine</td>
</tr>
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</table>
**BRAF V600E mutation**

**Properties**

<table>
<thead>
<tr>
<th>Location of mutation</th>
<th>Kinase domain (exon 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of BRAF V600E</td>
<td>~85-90% of BRAF mutant melanoma</td>
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**Implications for Targeted Therapeutics**

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<th>Response to BRAF inhibitors</th>
<th>Confers increased sensitivity*</th>
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</thead>
<tbody>
<tr>
<td>Response to MEK inhibitors</td>
<td>Uncertain at this time#</td>
</tr>
<tr>
<td>Response to KIT inhibitors</td>
<td>Uncertain at this time</td>
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AZD6244 versus temozolomide. 5 of 42 melanoma patients with BRAF V600E mutation had confirmed partial responses (12% objective response rate) (Durnam, 2006).
# BRAF V600E (c.1799T>A) mutation in Melanoma

## BRAF V600E mutation

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<th>Treatment Agent</th>
<th>Drug Class</th>
<th>Line of Treatment</th>
<th># pts in study</th>
<th>Response Rate</th>
<th>PFS (months)</th>
<th>OS (months)</th>
<th>Level of evidence</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>vemurafenib</td>
<td>Mutated BRAF TKI</td>
<td>1st to &gt;3rd</td>
<td>32^</td>
<td>81%</td>
<td>&gt; 7 months (estimated)</td>
<td>Not reached</td>
<td>II-1</td>
<td>(Flaherty, 2010)</td>
</tr>
<tr>
<td>(PLX4032)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>337</td>
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<td>5.3</td>
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**References:**
- Flaherty, 2010
- Chapman, 2011
- Dunnen, 2009
Inhibition of mutated, activated BRAF in metastatic melanoma.


Abstract

BACKGROUND: The identification of somatic mutations in the gene encoding the serine-threonine protein kinase B-RAF (BRAF) in the majority of melanomas offers an opportunity to test oncogene-targeted therapy for this disease.

METHODS: We conducted a multicenter, phase 1, dose-escalation trial of PLX4032 (also known as RG7204), an orally available inhibitor of mutated BRAF, followed by an extension phase involving the maximum dose that could be administered without adverse effects (the recommended phase 2 dose). Patients received PLX4032 twice daily until they had disease progression. Pharmacokinetic analysis and tumor-response assessments were conducted in all patients. In selected patients, tumor biopsy was performed before and during treatment to validate BRAF inhibition.

RESULTS: A total of 55 patients (49 of whom had melanoma) were enrolled in the dose-escalation phase, and 32 additional patients with metastatic melanoma who had BRAF with the V600E mutation were enrolled in the extension phase. The recommended phase 2 dose was 960 mg twice daily, with increases in the dose limited by grade 2 or 3 rash, fatigue, and arthralgia. In the dose-escalation cohort, among the 16 patients with melanoma whose tumors carried the V600E BRAF mutation and who were receiving 240 mg or more of PLX4032 twice daily, 10 had a partial response and 1 had a complete response. Among the 32 patients in the extension cohort, 24 had a partial response and 2 had a complete response. The estimated median progression-free survival among all patients was more than 7 months.

CONCLUSIONS: Treatment of metastatic melanoma with PLX4032 in patients with tumors that carry the V600E BRAF mutation resulted in complete or partial tumor regression in the majority of patients. (Funded by Plexxikon and Roche Pharmaceuticals.)
BRAF V600E (c.1799T>A) mutation in Melanoma

**BRAF c.1799T>A (V600E) mutation in Melanoma**

**Properties**
- Location of mutation: Kinase domain (exon 15)
- Frequency of BRAF V600E: ~85-90% of BRAF mutant melanoma

**Implications for Targeted Therapeutics**
- Response to BRAF inhibitors: Confers increased sensitivity*
- Response to MEK inhibitors: Uncertain at this time
- Response to KIT inhibitors: Uncertain at this time

The V600E mutation results in an amino acid substitution at position 600 in BRAF, from a Valine (V) to a glutamic acid (E). This mutation occurs within the activation segment of the kinase domain (Fig. 2). Approximately 70-90% of V600 BRAF mutations are V600E (Rubinstein, 2010). Mutant BRAF proteins have increased kinase activity and are transforming in vitro (Davies, 2002). BRAF mutations are usually found in tumors wildtype for NRAS, KIT, and other driver mutations.

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**BRAF V600E mutation**

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BRAF Mutation Directed Melanoma Clinical Trials

Great effort was made to include all clinical trials relevant for this mutation. However, the completeness of this information cannot be guaranteed.

- At Vanderbilt (4)

<table>
<thead>
<tr>
<th>Protocol No.</th>
<th>Title</th>
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</thead>
<tbody>
<tr>
<td>VICCPhi1075 06/01/2011</td>
<td>A Phase Ib, Open Label, Dose-Escalation, Study Evaluating the Safety, Tolerability and Pharmacokinetics of RO5185426 in Combination with GDC-0973 when Administered in Patients with BRAFV600E-Positive Metastatic Melanoma Who Have Progressed After Treatment with RO5185426</td>
</tr>
<tr>
<td>VICCMEL1091 Pending</td>
<td>BRF113929: A Phase II Open-Label, Two-Cohort, Multicentre Study of GS2118436 as a Single Agent in Treatment Naive and Previously Treated Subjects with BRAF Mutation-Positive Metastatic Melanoma to the Brain</td>
</tr>
<tr>
<td>VICCPhi1076 Pending</td>
<td>A Phase I, Randomized, Open-Label, Multi-Center, Two Period Crossover Study to Investigate the Effect of Food on the Pharmacokinetics of a Single Oral Dose of RO5185426, Followed by Administration of 960mg RO5195426 Twice Daily to BRAF-V600E Positive Metastatic Melanoma Patients</td>
</tr>
<tr>
<td>VICCMEL1083 Pending</td>
<td>An Open-Label, Dose-Escalation, Phase II Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics, and Clinical Activity of the BRAF Inhibitor GS2118436 in Combination with the MEK Inhibitor GSK1120212 in Subjects with BRAF Mutant Metastatic Melanoma</td>
</tr>
</tbody>
</table>

- Melanoma Clinical Trials at Vanderbilt (7)

- Tennessee (4)

- United States (13)

- Internationally (12)
### Clinical Trial VICCPHI1075

**Title**
A Phase Ib, Open Label, Dose-Escalation, Study Evaluating the Safety, Tolerability and Pharmacokinetics of RO5185426 in Combination with GDC-0973 when Administered in Patients with BRAFV600E-Positive Metastatic Melanoma Who Have Progressed After Treatment with RO5185426

**Principal Investigator(s)**
Igor Puzanov

**Description**
The purpose of this study is to test the combination of the investigational drugs RO5185426 (BRAF inhibitor) and GDC-0973/XL518 (MEK inhibitor) in order to find a safe and tolerated dose when taking these drugs together.

**Eligibility**

**Details**

**Learn more**
- Call toll-free number: 1-800-811-8480
- Use our [Online self-referral form](#)
- Print this page for your doctor

**Melanoma (5)**

**Tennessee (4)**

**United States (13)**

**Internationally (12)**
### United States (13)

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<td>NCT01271803</td>
<td>A Study of RO5185426 And GDC-0973 in Patients With BRAF-Mutation Positive Metastatic Melanoma</td>
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<td>NCT01350401</td>
<td>Phase I/II Study to Assess the Safety and Activity of Enhanced TCR Transduced Autologous T Cells in Metastatic Melanoma</td>
</tr>
<tr>
<td>NCT01390818</td>
<td>Trial of MEK Inhibitor and PI3K/mTOR Inhibitor in Subjects With Locally Advanced or Metastatic Solid Tumors</td>
</tr>
<tr>
<td>NCT01136967</td>
<td>An Open-Label, 2-Cohort, Multicenter, Study of E7080 in Previously Treated Subjects With Unresectable Stage III or Stage IV Melanoma</td>
</tr>
<tr>
<td>NCT00866177</td>
<td>Phase II Study of MEK Inhibitor AZD6244 in Patients With BRAF-Mutated or NRAS-Mutated, Unresectable Stage III or IV Melanoma</td>
</tr>
<tr>
<td>NCT00948467</td>
<td>Study of TAK-733 in Adult Patients With Advanced Nonhematologic Malignancies</td>
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<tr>
<td>NCT01248936</td>
<td>A Study of RO5185426 in Patients With Metastatic Melanoma</td>
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<tr>
<td>NCT01266967</td>
<td>A Study of GSK2118436 in BRAF Mutant Metastatic Melanoma to the Brain</td>
</tr>
<tr>
<td>NCT01072175</td>
<td>Investigate Safety, Pharmacokinetics and Pharmacodynamics of GSK2118436 &amp; GSK1120212</td>
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</tbody>
</table>

### Internationally (12)
Trial of MEK Inhibitor and PI3K/mTOR Inhibitor in Subjects With Locally Advanced or Metastatic Solid Tumors

This study is currently recruiting participants.
Verified on July 2011 by EMD Serono
First Received on April 18, 2011. Last Updated on July 8, 2011 History of Changes

Purpose
This research trial is testing a combination of two experimental drugs, MSC196368B (Mitogen-activated protein extracellular signal-regulated kinase (Mek) Inhibitor) and SAR245409 (Phosphatidylinositol 3-kinase (PI3K)/Mammalian Target of Rapamycin (mTOR) inhibitor), in the treatment of locally advanced or metastatic solid tumours. The primary purpose of the study is to determine the maximum tolerated dose of the drug combination.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Intervention</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Locally Advanced Solid Tumor</td>
<td>Drug: MSC196368B and SAR245409</td>
<td>Phase I</td>
</tr>
<tr>
<td>Metastatic Solid Tumor</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Study Type: Interventional
Study Design: Endpoint Classification: Safety/Efficacy Study
Intervention Model: Single Group Assignment
Masking: Open Label
Primary Purpose: Treatment

Official Title: An Open-Label, Phase Ib Dose Escalation Trial of Oral Combination Therapy With MSC196368B and SAR245409 in Subjects With Locally Advanced or Metastatic Solid Tumors

Resource links provided by NLM:
- MedicinePlus related topics: Cancer
- Drug Information available for: Sirolimus, Everolimus, CCI 779
- U.S. FDA Resources

Further study details as provided by EMD Serono:
7 Cancers
Lung
Melanoma
Breast
Colon
Thymic
GIST
Thyroid

22 Genes

203 Disease-Gene-Variant Relationships
NEW clinical trial search
- 135 Cancer Diagnoses
- 443 Cancer Genes
>1500 site visits per week

48,656 visits came from 119 countries and territories
This country/territory sent 30,500 visits via 52 regions
Worldwide Collaboration

30 Contributors
13 Institutions
6 Countries
Scale, Maintain & Sustain

Content Generation → My Cancer Genome → Content Dissemination
Decision Support as a Service

- Vanderbilt EHR
- Public Access
- Treatment Plan Selection
- Academic Medical Center EHR
- Laboratory Testing Facility
- Oncology Vendor EHR

Vanderbilt-Ingram Cancer Center
Scalability: Data Driven Approach

Assess clinical outcomes -> Select patient treatment

Compare treatment effectiveness

Implement new evidence for treatment prioritization

Learning Cancer System
DIRECT

- Collection of EGFR mutations in NSCLC
- 1596 patient level case reports
  - 1876 gene, drug, response instances
- 146 publications
- 150 unique primary EGFR mutations
- 47 unique secondary EGFR mutations

L Horn, H Chen, CM Lovly, J Andrews, P Yeh, MA Levy, W Pao
Vanderbilt-Ingram Cancer Center

Synthetic Derivative

Labs, notes, medications
Vanderbilt EHR
1.8M pt

De-identification
Synthetic Derivative

Tumor Registry
63K pt

Site, Stage, histology, vital status

>1000 pt with tumor gene mutation analysis And growing

Continuous extraction and integration with knowledge resources
Limitation: Biomarker Input to Treatment Selection Service

- Diagnosis
- Treatment Selection
- Treatment Plan Management
- Treatment Response Assessment

Risk Biomarker
Prognostic Biomarker
Diagnostic Biomarker
Predictive Biomarker
Response Biomarker
Algorithmic, intelligent, team oriented, and cost effective approach to biomarker testing and interpretation.

- Diagnosis
- Treatment Selection
- Treatment Plan Management
- Treatment Response Assessment

Risk Biomarker
Prognostic Biomarker
Response Biomarker

Diagnostic Biomarker
Predictive Biomarker
Traditional approach to testing bone marrow specimens

Bone Marrow Specimen

Specimen Acquired

Ala Carte Ordering

Patient

Physician

Review Results

Tx Decision

Multiple Asynchronous Reports

Hematopathology

Immunopathology

Cytogenetics

Molecular Pathology

Vanderbilt-Ingram Cancer Center
Diagnostic Management Team approach to testing bone marrow specimens

Bone Marrow Specimen

Orders BM testing Panel

Provides Clinical History

Patient

Physician

Diagnosis Specific Testing Algorithms (SOP’s)

Hematopathology

Immunopathology

Cytogenetics

Molecular Pathology

Comprehensive Report
Challenges & Opportunities

• Intelligent Test Ordering
  – Panel based ordering
  – Bidirectional communication
  – Disease specific testing algorithms (SOP’s)
  – Efficient longitudinal data aggregation

• Comprehensive Report
  – Consistent format
  – Integration of multiple reports
  – Structured reporting to enable clinical decision support & research
Intelligent Test Ordering

Orders BM testing Panel

Provides Clinical History

Patient

Physician
Bone Marrow Testing Panel Order Form
(retains ability to order a la carte)

Clinical Trial Patient: Yes

D&H Account: 999999

Clinical Trial Diagnosis Codes:
- V70.7 Participant in a Clinical Trial, procedures are CC
- V60.9 Participant in a Clinical Trial, procedures for...

Specimen Type:
- Blood
- Bone Marrow: Unilateral

Post-SCT:
125 days since transplant

Testing:
- Bone Marrow Testing Panel (morphology and clinical history)
- Bone Marrow (select ancillary)

Ancillary Testing:
Intelligent Test Ordering

Orders BM testing Panel

Provides Clinical History

Bone Marrow Specimen

Hematopathology

Day of Bone Marrow Biopsy Hematopathologist

• Reviews order form
• Reviews patient flow sheet
• Reviews preliminary aspirate and smears
• Orders appropriate ancillary tests based on:
  • Diagnosis & treatment history
  • Current state (preliminary review)
  • SOP’s (with ability to order al carte)
Hematopathology Flow Sheet

**HEMATOPATHOLOGY REPORT**

**Division of Hematopathology**

4601 TVC, 22nd & Pierce Avenue

Nashville, Tennessee 37232-5310

615.343.9167 office; 615.343.7961 fax

Mary Zutter, M.D., Director

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Accession number: S10-28075

**DIAGNOSIS:**

1-5) **BONE MARROW - BIOPSY, PARTICLE PREPARATION, ASPIRATE SMEAR, PERIPHERAL BLOOD SMEAR, AND FLOW CYTOMETRY:** HYPERCELLULAR MARROW WITH MYELOID HYPERPLASIA WITH NO DEFINITIVE INCREASE IN BLASTS (SEE PREVIOUS S10-15701 & MICROSCOPIC EVALUATION)

**MICROSCOPIC EVALUATION:**

1-2) Bone Marrow Biopsy and Particle Preparation: Sections of the biopsy and particle preparation are examined using H&E and PAS stains. The biopsy features hypercellular marrow. All three cell lines are present with normal maturation, normal distribution, and no increase in blasts. There are no focal lesions, lymphoid aggregates, or granulomas.

Paraffin immunoperoxidase studies using antibodies to CD34 and CD117 show no increase in immature cells.

**Bone Marrow Smears and Touch Preparations:** The aspirate smears and touch preparations are examined using Wright's stain. The aspirate features trilineage hematopoiesis with granulocytic hyperplasia, and no increase in blasts in the manual differential or in scanning multiple areas of marrow. The touch preparations show similar findings.

**A Prussian blue iron stain on the aspirate smear demonstrates iron present with no ringed sideroblasts.**

**Marrow Smear Differential**

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<th></th>
<th>NORMAL</th>
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<tbody>
<tr>
<td>Blast</td>
<td>0.3-5.0</td>
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<tr>
<td>Promyelocytes</td>
<td>1.0-8.0</td>
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<tr>
<td>Myelocytes</td>
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<tr>
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**Vanderbilt-Ingram Cancer Center**
# Secondary Testing Standards – MDS/AML

<table>
<thead>
<tr>
<th>Diagnosis or Morphologically Overt Disease</th>
<th>No Overt Disease (multiple encounters)</th>
<th>Pre-SCT</th>
<th>Post-SCT</th>
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<tr>
<td>Flow Cytometry</td>
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<tr>
<td>FISH</td>
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**AML or MDS**

- SOP’s Developed for:
  - Acute Myeloid Leukemia/Myelodysplastic Syndrome
  - Acute Lymphoblastic Leukemia
  - Myeloproliferative Disorders, including CML
  - Non-Hodgkin and Hodgkin Lymphoma
  - Multiple Myeloma
  - Bone Marrow Failure Syndrome

**AML**

**A**ML includes MDS in evolution to AML
SOPs- The Principles

• Evidence-based:
  – Published literature
  – Clinical guidelines (e.g., NCCN)
  – Best clinical practices
• Tests should be ordered at diagnosis if:
  – They are diagnostically useful
  – They can be used for monitoring response.
  – If they have prognostic value.
• Tests should be ordered at follow-up if:
  – They were positive at diagnosis.
  – They are sensitive for residual disease detection.
• If two tests measure the same abnormality, the more sensitive of the two should be used.
Intelligent Test Ordering

Orders
BM testing Panel

Provides Clinical History

Intelligent Testing of Bone Marrow now Exceeds 70%
# Dashboard with Indicators

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<tr>
<th>MR#</th>
<th>Patient Name</th>
<th>Actions</th>
<th>Heme Order</th>
<th>HEME</th>
<th>CNG</th>
<th>CNG(FISH)</th>
<th>PLO</th>
<th>MoleDiag</th>
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**Status indicators**

- v = pending
- green = all tests in category resulted
- yellow = some resulted, some pending

**Secure Messaging**
Vanderbilt-Ingram Cancer Center

Patient

Physician

Bone Marrow Specimen

Orders BM testing Panel

Provides Clinical History

Hematopathology

Immunopathology

Cytogenetics

Molecular Pathology

Diagnosis Specific Testing Algorithms (SOP’s)

Comprehensive Report
Structured->Prose Reports

Structured Data Fields

**Bone Marrow Report**

**Diagnosis:**
- biopsy
- particle
- aspirate
- blood
- flow

**Impression:** ("free text")

**Microscopic Evaluation**

1-2) Bone Marrow Biopsy and Particle Preparation

**Quality:**
- adequate
- limited
- blood clot
- crush artifact
- aspiration artifact
- small size

**Cellularity:**
- normocellular
- hypercellular
- hypoplastic
- acellular
- cellular
- other ("free text")

**Megakaryocytes:**
- adequate
- increased
- decreased
- no significant atypia
- with atypia
- with dysplasia
- small size
- "cloud-like" nuclei
- hyperlobated nuclei
- widely separated nuclear lobes
- present cytoplasm
- mild
- moderate
- marked
- other ("free text")

**Erythroid Elements:**
- adequate
- increased
- decreased
- left-shifted maturation
- geographic dyserythropoiesis
- no significant atypia
- with atypia
- with dysplasia
- mild
- moderate
- marked
- other ("free text")

**Myeloid Elements:**
- adequate
- increased
- decreased
- scattered
- left-shifted maturation
- increased immature cells
- no significant atypia
- with atypia
- with dysplasia
- mild

Prose Report

Accession Number: S10-XXXX

**Diagnosis:**

1-5) Bone marrow — Biopsy, Particle Preparation, Aspirate Smear, Peripheral Blood Smear, and Flow Cytometry: Normocellular Bone Marrow with Trilineage Hematopoiesis. (See Microscopic Evaluation).

**Impression:** Smears show a relative erythroid hyperplasia. However, in the context of a normocellular bone marrow, this likely represents approximately normal red cell mass. There is no abnormal myeloid or megakaryocytic proliferation and no significant reticulin fibrosis. In conjunction with a normal CBC and reported negative JAK2 mutation evaluation, these findings are not suggestive of a myeloproliferative neoplasm.

**Microscopic Evaluation:**

1-2) Bone Marrow Biopsy and Particle Preparation: Sections of the biopsy and particle preparation are examined using H&E and PAS stains. The biopsy is adequate and normocellular (30-40% cellularity). Megakaryocytes are adequate with no significant atypia. Erythroid elements are increased with orderly maturation and no significant atypia. Myeloid elements are increased with orderly maturation and no significant atypia. Plasma cells are not increased. Lymphoid aggregates are absent. A reticulin stain demonstrates no significant reticulin fibrosis.

3) Aspirate Smears and Touch Preparations: The aspirate and touch preparations are examined using Wright’s stain. The aspirate is normocellular and particulate. The M:E ratio is 0.8:1. Megakaryocytes are adequate with no significant atypia. Erythroid elements are increased with orderly maturation and atypia, including irregular nuclear contours and megakaryoblastic change. Myeloid elements are adequate with orderly maturation and no significant atypia. Blasts are not increased. Plasma cells are not increased. Lymphocytes are not increased.

A Prussian blue iron stain is performed on the aspirate smear and demonstrates adequate storage iron with no ringed sideroblasts.
Patient Name: XXXXXXXXXXX
MRN: XXXXXXXXXX
Accession number: S-10-XXXXX
Sample Date: XX/XX/2010

(1) Clinical History (see clinic note): The patient is a 15-year-old male with increased blasts in the peripheral blood smear, presenting for bone marrow evaluation. Prior pathology cases: S-10-XXXXX, S09-XXXXX

(2) Morphologic Evaluation (see report): B lymphoblastic leukemia.

(3) Flow Cytometry (see report): Gating on blasts (85% of total cells) identified on CD45/SS histograms, immature cells mark as lymphoid expressing CD19, CD10 bright, TdT, CD34, HLA-DR, CD9, CD38, CD58, and CD81. The blasts do co-express myeloid markers CD33 dim. The blasts do not express CD20 or CD13. This phenotype is similar to previous and consistent with a B-cell lineage of early lymphoid cells.

(4) Cytogenetics (see report): 26,XY,+14,+21[16]/46,XY[4].

(5) FISH (see report): nuc ish 9q34(ABLx1),22q11.2(BCRx1)[195/200]
                        nuc ish 11q23(MLLx1)[193/200]
                        nuc ish 12p13(ETV6x1),21q12(RUNX1x2)[182/200]
                        nuc ish 4cen(D4Z1x1)[194/200]
                        nuc ish 10cen(D10Z1x1)[194/200]
                        nuc ish 17cen(D17Z1x1)[194/200]

COMPREHENSIVE INTERPRETATION
This is a hypercellular bone marrow exhibiting replacement of normal hematopoietic elements by blasts, identified by flow cytometry as B-lineage lymphoblasts. Cytogenetic analysis reveals a near-haploid karyotype, which is supported by FISH studies indicating monosomy of chromosomes 4, 9, 10, 11, 12, 17, and 22. Taken together, these findings are indicative of B lymphoblastic leukemia with hypodiploidy. Hypodiploid ALL, particularly with a near-haploid karyotype, has a relatively poor prognosis.
Concordance with SOPs

By Clinical Stage

- Examining the concordance rate by clinical stage allows us to see in which clinical setting excessive testing is most common.
- By both percentage and total number, post-SCT is by far the least concordant.

![Graph showing concordance rates by clinical stage]

- Diagnosis/Overt: 84%
- Staging: 50%
- Follow-up: 64%
- Pre-SCT: 32%
- Post-SCT: 100%
Concordance with SOPs

<table>
<thead>
<tr>
<th>Tests</th>
<th>Number</th>
<th>Percent</th>
<th>Per Marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>335</td>
<td>100%</td>
<td>3.4</td>
</tr>
<tr>
<td>Concordant with SOP</td>
<td>188</td>
<td>56%</td>
<td>1.9</td>
</tr>
<tr>
<td>Non-concordant</td>
<td>147</td>
<td>44%</td>
<td>1.5</td>
</tr>
</tbody>
</table>

- Extrapolating to an estimated **1,700** adult bone marrow specimens per year, following the SOPs could potentially **eliminate approximately 2550 ancillary tests per year**.
PREDICT: Pharmaco-genomic Resource for Enhanced Decisions in Care & Treatment

Pilot in cath lab for post stent drug selection and dosing (September, 2010)

Diagnosis → Treatment Selection → Treatment Plan Management → Treatment Response Assessment

predict drug metabolism => drug & dose selection

Prospective testing of 184 SNPs in 34 pharmacogenomic genes
Genetic testing has been performed and indicates this patient may be at risk for inadequate anti-platelet response to clopidogrel (Plavix) therapy.

**Treatment modification is recommended if not contraindicated:**
- Prescribe prasugrel (EFFIENT) 10mg daily and stop clopidogrel (PLAVIX) startdate, 10 AM

**If prasugrel (EFFIENT) not selected, please choose desired action:**
- Increase maintenance dose of clopidogrel (PLAVIX) 150 mg daily, startdate, 10AM
- Maintain requested daily dose of clopidogrel (PLAVIX) 75 mg daily, startdate, 10AM

If not using prasugrel, please select a reason:
- Contraindicated for prasugrel
- Potential side effects
- Patient opts for clopidogrel
- Other (Specify)

NOTE: The Vanderbilt P&T Committee has recommended that prasugrel (if not contraindicated) should replace clopidogrel for poor metabolizers; if this is not possible consider doubling the standard dose of clopidogrel (or, use standard dose clopidogrel). However, there is not a national consensus on drug/dose guidance in this population.
Biomarkers in the Clinical Continuum

Diagnosis → Treatment Selection → Treatment Plan Management → Treatment Response Assessment

Risk Biomarker
Diagnostic Biomarker
Prognostic Biomarker
Predictive Biomarker
Response Biomarker
Acknowledgements

- **PCMI Team**
  - William Pao
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  - Claudio Mosse
  - Mary Ann Arildsen
  - Madan Jagasia

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