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

1. Diagnosis
2. Treatment Selection
3. Treatment Plan Management
4. 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

- Squamous
- Large
- Small
- Adenocarcinoma

Vanderbilt-Ingram Cancer Center
Vanderbilt-Ingram Cancer Center
Personalized Cancer Medicine Initiative

7/1/10-12/31/11

Melanoma Panel: 538 patients
67% Patients with Actionable Mutation
33% No Mutation Identified

- NRAS 19.0%
- GNAQ 2.5%
- BRAF 40.5%
- GNA11 1.0%
- CTNNB1 1.0%
- KIT 3.0%

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

- EGFR 17%
- ERBB2 1%
- KRAS 21%
- NRAS 0.25%
- PIK3CA 3%
- PTEN 0.25%
- MEK 0.5%

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
<table>
<thead>
<tr>
<th>MR#</th>
<th>Patient Name</th>
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<th>Tumor Gene Mutations</th>
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<td>Actions</td>
<td>BRCA1, VEGF, CTNNB1, CTNNB2, NRAS</td>
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**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>
<td>03</td>
<td>56 A, P</td>
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<td><strong>BRAF</strong> c.1798_1799GT&gt;AA (V600K) Not Detected</td>
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<tr>
<td>03</td>
<td>35 B, J A</td>
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<td>01</td>
<td>80 B, S A</td>
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<tr>
<td>02</td>
<td>29 E, J E</td>
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<td>02</td>
<td>27 F, R M</td>
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<td>02</td>
<td>77 G, T</td>
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<tr>
<td>02</td>
<td>73 H, A</td>
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</table>

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

**BRAF V600E (c.1799T>A) 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 \( (\text{Rubinstein, 2010}) \). Mutant BRAF proteins have increased kinase activity and are transforming in vitro \( (\text{Davies, 2002}) \). BRAF mutations are usually found in tumors with mutation 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 \( (\text{Flaherty, 2010}) \). 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 \( (\text{Chapman, 2011}) \).

*Pre-clinical data has correlated the presence of activating mutations in BRAF with sensitivity to non-ATP competitive MEK inhibitors, AZD6244 and CI-1040 \( (\text{Davies, 2007, Soll, 2006}) \). 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) \( (\text{Dummer, 2009}) \).

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**BRAF V600E mutation**

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<thead>
<tr>
<th>Treatment Agent</th>
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<th>Line of Treatment</th>
<th># pts in study</th>
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# BRAF V600E (c.1799T>A) mutation in Melanoma

## Properties

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| Frequency of BRAF V600E | ~85-90% of BRAF mutant melanoma |

## Implications for Targeted Therapeutics

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| Response to KIT inhibitors | Uncertain at this time |

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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, 2009](#)).

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*Preliminary results:* Partial responses (12% objective response rate) (Dunner, 2008).
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

BRAF V600E mutation

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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>
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<tbody>
<tr>
<td>VICCphi1075</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>
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<tr>
<td>VICCMel1091</td>
<td>BRF113929: A Phase II Open-Label, Two-Cohort, Multicentre Study of GSK2118436 as a Single Agent in Treatment Naive and Previously Treated Subjects with BRAF Mutation-Positive Metastatic Melanoma to the Brain</td>
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<tr>
<td>VICCphi1076</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</td>
<td>An Open-Label, Dose-Escalation, Phase I/II Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics, and Clinical Activity of the BRAF Inhibitor GSK2118436 in Combination with the MEK Inhibitor GSK1120212 in Subjects with BRAF Mutant Metastatic Melanoma</td>
</tr>
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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 (1)

Tennessee (4)

United States (13)

Internationally (12)
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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>
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<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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<td>NCT01266967</td>
<td>A Study of GSK2118436 in BRAF Mutant Metastatic Melanoma to the Brain</td>
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<tr>
<td>NCT01072175</td>
<td>Investigate Safety, Pharmacokinetics and Pharmacodynamics of GSK2118436 &amp; GSK1120212</td>
</tr>
</tbody>
</table>
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 6, 2011  History of Changes

Purpose

This research trial is testing a combination of two experimental drugs, MSC193635B (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>
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<tbody>
<tr>
<td>Locally Advanced Solid Tumor</td>
<td>Drug: MSC193635B and SAR245409</td>
<td></td>
</tr>
<tr>
<td>Metastatic Solid Tumor</td>
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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 MSC193635B and SAR245409 in Subjects With Locally Advanced or Metastatic Solid Tumors

Resource links provided by NLM:

MedlinePlus related topics: Cancer
Drug Information available for: Sirolimus, Everolimus, CCI 779
U.S. FDA Resources

Further study details as provided by EMD Serono:
Vanderbilt-Ingram Cancer Center

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
Country/Territory Detail:
United States

Comparing to: Site

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
- Academic Medical Center EHR
- Treatment Plan Selection
- Laboratory Testing Facility
- Oncology Vendor EHR
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
Synthetic Derivative

De-identification

Vanderbilt EHR
1.8M pt

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

Labs, notes, medications
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
Diagnostic Management Team

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
- Diagnostic Biomarker
- Predictive Biomarker
- Response Biomarker
Traditional approach to testing bone marrow specimens

Bone Marrow Specimen

- Hematopathology
- Immunopathology
- Cytogenetics
- Molecular Pathology

Multiple Asynchronous Reports

Specimen Acquired

Ala Carte Ordering

Review Results

Tx Decision

Patient

Physician
Diagnostic Management Team approach to testing bone marrow specimens

Orders BM testing Panel

Provides Clinical History

Bone Marrow Specimen

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  No
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

Post-SCT
125 days since transplant
  □ Auto  □ First  □ Second
  ✔ Allo
  □ Reduced Intensity Chemotherapy/ Mini
  ✔ Full

Specimen Type:
  □ Blood
  ✔ Bone Marrow
  □ Unilateral
  □ Bilateral
  □ Lymph Node
  □ Other:

Testing:
  ✔ Bone Marrow Testing Panel (morphology and clinical history)
  □ Bone Marrow (select ancillary
Ancillary Testing:
Intelligent Test Ordering

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 a la carte)
Hematopathology Flow Sheet

Hematopathology Report
Division of Hematopathology
4601 TCV, 22nd & Pierce Avenue
Nashville, Tennessee 37232-5310
615.343.9167 office; 615.343.7961 fax
Mary Zutter, M.D., Director

Accession number: S10-28075

Final Report

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 granulomata.

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

N13) Aspirate 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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<thead>
<tr>
<th>Cell Type</th>
<th>Normal</th>
<th>%</th>
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<tr>
<td>Promyelocytes</td>
<td>1.0-8.0</td>
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<tr>
<td>Myelocytes</td>
<td></td>
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<tr>
<td>Neutrophilic</td>
<td>5.0-19.0</td>
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<tr>
<td>Eosinophilic</td>
<td>0.5-3.0</td>
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<td>Basophilic</td>
<td>0-0.5</td>
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<td>Basophilic</td>
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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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<tbody>
<tr>
<td>Flow Cytometry</td>
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<td>Karyotype</td>
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<tr>
<td>FISH</td>
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<tr>
<td><strong>AML or MDS</strong></td>
<td>**AML includes MDS in evolution to AML</td>
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</table>

- **AML** includes MDS in evolution to AML
- 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
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

Bone Marrow Specimen

Patient

Physician

Hematopathology

Immunopathology

Cytogenetics

Molecular Pathology

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

### Status indicators
- **v** = pending
- **green** = all tests in category resulted
- **yellow** = some resulted, some pending

### Secure Messaging

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<thead>
<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>MolecDiag</th>
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Comprehensive Report

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
Structured Data Fields

Bone Marrow Report

Diagnosis: □ biopsy □ particle □ aspirate □ blood □ flow
(“free text”)

Impression: (“free text”)

Microscopic Evaluation

1-2) Bone Marrow Biopsy and Particle Preparations

Quality:
□ adequate □ periosteum and cortical bone only
□ limited □ blood clot
□ crush artifact □ aspiration artifact
□ small size

Cellularity:
□ normocellular □ hypercellular
□ hypocellular □ ameloblastoma
□ cellular □ other (“free text”)

Megakaryocytes:
□ adequate □ no significant atypia □ small size □ hyperchromatic nuclei:
□ increased □ with atypia □ large size □ “cloud-like” nuclei:
□ decreased □ with dysplasia □ hypolobated nuclei:
□ mild □ moderate □ widely separated nuclear lobes:
□ marked □ present cytoplasm:
□ other (“free text”)

Erythroblasts:
□ adequate □ orderly maturation □ no significant atypia:
□ increased □ left-shifted maturation □ with atypia:
□ decreased □ geographic dyserythropoiesis □ with dysplasia:
□ mild □ moderate □ marked
□ other (“free text”)

Myeloid elements:
□ adequate □ orderly maturation □ no significant atypia:
□ increased □ left-shifted maturation □ with atypia:
□ decreased □ increased immature cells □ with dysplasia:
□ scattered □ mild
□ other (“free text”)

Prose Report

Accession Number: S10-XXXX

Final Report

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 CR and reported negative JAK2 mutation evaluation, these findings are not suggestive of a myeloproliferative neoplasm.

Microscopic Evaluation:

1-2) Bone Marrow Biopsy and Particle Preparations: 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. 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 0:1. Megakaryocytes are adequate with no significant atypia. Erythroid elements are increased with orderly maturation and atypia, including irregular nuclear contours and megakaryoblastoid 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: XXXXXXXXXXXX
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/Side Scatter 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.
Retrospective Analysis
100 Bone Marrow Specimens

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.
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)

1. Diagnosis
2. Treatment Selection
3. Treatment Plan Management
4. 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

**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
- Prognostic Biomarker
- Diagnostic Biomarker
- Predictive Biomarker
- Response Biomarker
Acknowledgements

- **PCMI Team**
  - William Pao
  - Jennifer Pietenpol
  - Ashley Lamb
  - Christine Lovly
  - Leora Horn
  - Jeff Sosman

- **DMT Team**
  - Mary Zutter
  - Annette Kim
  - Adam Seegmiller
  - Claudio Mosse
  - Mary Ann Arildsen
  - Madan Jagasia

- **PREDICT**
  - Jill Pulley
  - Dan Masys
  - Josh Denny
  - Jim Jirgis

- **Molecular Diagnostics Laboratory**
  - Cindy Vnenacak-Jones

- **Informatics Teams**
  - Ed Shultz
  - Dario Giuse
  - Jonathan Grande
  - RuAnn Schleicher
  - Riyad Naser
  - Leslie Mackowiac
Thank you
Genome-based test results are expected to develop into an integral component of diagnostic clinical medicine and to provide the basis for individually tailored health care. The discipline of pathology is well positioned to implement genome-based testing and to interpret its results, but new knowledge and skills must be included in the training of pathologists to develop expertise in this area. Pathology residents should be trained in emerging technologies to integrate genomic test results appropriately with more traditional testing, to accelerate clinical studies using genomic data, and to help develop appropriate standards of data quality and evidence-based interpretation of these test results. The Department of Pathology at Stanford University has developed an annual course in Genomic Medicine for all of its residents and fellows, as part of its required core educational curriculum. The course provides an overview of fundamental principles of molecular biology, clinical genomics and personalized medicine, as well as current and evolving research and clinical applications. Ethical and legal ramifications as well as regulatory considerations pertaining to this increasingly comprehensive approach to diagnostic testing and predictive medicine are also being addressed. A curriculum in Advanced Genomic Medicine has also been developed. This second course is taught as an elective. The curriculum is specifically created to enable interactive learning in a small group setting, addressing topics such as computational and statistical methods relevant to analysis of DNA sequence data including genomic data.
Genomics and personalized medicine are revolutionizing patient care. Given their critical role in laboratory diagnostics, pathologists must understand genomic testing. Recognizing this need for training, in 2009, a genomics curriculum was implemented for pathology residents at Beth Israel Deaconess Medical Center (BIDMC). Taught by pathology faculty and hospital genetic counselors, the curriculum was incorporated into the major objective classes defined by Kern: cognitive; affective/attitudinal and skills-based. Based on resident feedback, the curriculum has been well-received. In addition, comparison of pre- and post-curriculum test results demonstrated an improvement in resident knowledge. The BIDMC model has also formed the basis for a curriculum designed by the Training Residents in Genomics (TRIG) Working Group of the Pathology Residency Directors Section of the Association of Pathology Chairs. Since being established in 2010, the TRIG Working Group has created a series of four genomic pathology lectures (available in a booklet at the 2012 USCAP Annual Meeting), promoted pathology resident genomics training at national meetings and assisted in creating, for the first time, genomics-related knowledge and survey questions for the pathology resident in-service exam (RISE).