Clinical Information Systems to Support Personalized Medicine at the Bedside

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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
- Treatment Selection
- Treatment Plan Management
- Treatment Response Assessment

- Risk Biomarker
- Prognostic Biomarker
- Diagnostic Biomarker
- Predictive Biomarker
- 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
- Lung Cancer

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

- Lung Panel: 451 patients
  - 40% Patients with Actionable Mutation
  - 54% No Mutation Identified

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Personalized Cancer Medicine Initiative

7/1/10-12/31/11
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

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R = Outside Specimen Requested
O = Order Received
A = Outside Specimen Arrived
v = Specimen Accessioned
Yellow = Gene Mutation Detected
Grey = Gene Mutation Not Detected
Red = No Result – Insufficient Specimen

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**Clinical Trial VICCI11075**

**Title:**
Phase II Study of Weekly Oral Doses of Alizaprevir in Combination with Pegylated Interferon Alpha-2b and Ribavirin to Treat Genotype 1 Chronic Hepatitis C

**Protocol No.:**
VICCI11075

**Design:**
Randomized, open-label, multicenter, 2-stage, 2-arm, phase II study with a primary endpoint of sustained virological response in the combination arm.

**Inclusion Criteria:**
- Age: 18 years or older
- HCV genotype 1
- Treatment-naïve
- Sustained virological response to prior treatment with interferon alpha and ribavirin

**Exclusion Criteria:**
- Active liver disease due to other causes
- Active cancer
- Active autoimmune disease

**Objectives:**
- To determine the efficacy of alizaprevir in combination with pegylated interferon alpha-2b and ribavirin for the treatment of chronic hepatitis C genotype 1.

**Safety:**
- No significant adverse events reported

**Conclusion:**
The study demonstrated the feasibility and safety of the combination therapy, warranting further investigation.

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**Clinical Trial VICCI11063**

**Title:**
Phase II Study of Weekly Oral Doses of Alizaprevir in Combination with Pegylated Interferon Alpha-2b and Ribavirin to Treat Genotype 1 Chronic Hepatitis C

**Protocol No.:**
VICCI11063

**Design:**
Randomized, open-label, multicenter, 2-stage, 2-arm, phase II study with a primary endpoint of sustained virological response in the combination arm.

**Inclusion Criteria:**
- Age: 18 years or older
- HCV genotype 1
- Treatment-naïve
- Sustained virological response to prior treatment with interferon alpha and ribavirin

**Exclusion Criteria:**
- Active liver disease due to other causes
- Active cancer
- Active autoimmune disease

**Objectives:**
- To determine the efficacy of alizaprevir in combination with pegylated interferon alpha-2b and ribavirin for the treatment of chronic hepatitis C genotype 1.

**Safety:**
- No significant adverse events reported

**Conclusion:**
The study demonstrated the feasibility and safety of the combination therapy, warranting further investigation.

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**Clinical Trial VICCI11053**

**Title:**
Phase II Study of Weekly Oral Doses of Alizaprevir in Combination with Pegylated Interferon Alpha-2b and Ribavirin to Treat Genotype 1 Chronic Hepatitis C

**Protocol No.:**
VICCI11053

**Design:**
Randomized, open-label, multicenter, 2-stage, 2-arm, phase II study with a primary endpoint of sustained virological response in the combination arm.

**Inclusion Criteria:**
- Age: 18 years or older
- HCV genotype 1
- Treatment-naïve
- Sustained virological response to prior treatment with interferon alpha and ribavirin

**Exclusion Criteria:**
- Active liver disease due to other causes
- Active cancer
- Active autoimmune disease

**Objectives:**
- To determine the efficacy of alizaprevir in combination with pegylated interferon alpha-2b and ribavirin for the treatment of chronic hepatitis C genotype 1.

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**Conclusion:**
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My Cancer Genome
Genetically informed cancer medicine - the next standard of care

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

Clinical Trials search displays lists of trials by Disease or Gene for all national and international trials registered within FDAtools.clinicaltrials.gov.
Enter the first few letters of the disease or gene you are interested in learning to begin.

Map Overlay
>1500 site visits per week
88,656 visits from 119 countries and territories

Country/Territory Detail:
United States
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
- Oncology Vendor EHR
- Academic Medical Center EHR
- Laboratory Testing Facility

**Scalability: Data Driven Approach**

- Assess clinical outcomes
- Select patient treatment
- Compute treatment effectiveness
- Implement best evidence for treatment prioritization

**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

**Synthetic Derivative**

- Labs, notes, medications
- Vanderbilt EHR
- 1.8M pt
- Tumor Registry
- 63K pt
- Site, Stage, histology, vital status
- Continuous extraction and integration with knowledge resources

**Limitation: Biomarker Input to Treatment Selection Service**

- Diagnostic Management Team

- Algorithmic, intelligent, team oriented, and cost effective approach to biomarker testing and interpretation

**Diagnostic Management Team**

- 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

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Traditional approach to testing bone marrow specimens

Specimen Acquired
Bone Marrow Specimen

Review
Patient
Physician

Results

Multiple Asynchronous Reports

Hematopathology
Immunopathology
Cytogenetics
Molecular Pathology

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Diagnostic Management Team approach to testing bone marrow specimens

Orders BM testing Panel

Bone Marrow Specimen

Diagnosis Specific Testing Algorithms (SOP's)

Hematopathology
Immunopathology
Cytogenetics
Molecular Pathology

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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

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

Bone Marrow Testing Panel Order Form

(remains ability to order a la carte)

Hematopathology

Bone Marrow Testing Panel

antigen

Testing:

Bone Marrow Testing Panel

Bone Marrow (select ancillary)

Ancillary Testing:

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Intelligent Test Ordering

Orders BM testing Panel

Provides Clinical History

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Intelligent Test Ordering

Orders BM testing Panel

Provides Clinical History

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

Secondary Testing Standards – MDS/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

Dashboard with Indicators

Comprehensive Report
Structured->Prose Reports

Structured Data Fields

Prose Report

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.

Report fields automatically populated by data from individual pathology reports.

Library of “canned comments” for common interpretations with free-text option for more complex cases.

Retrospective Analysis

100 Bone Marrow Specimens

Mallows (100)

Tests (335)

MDS/AML
Myeloma
BMF
Other
NHL
ALL
MPD

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.

Tests Number Percent Per Marrow

Concordant with SOP 188 56% 1.9
Non-concordant 147 44% 1.5

• 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
Medication Order Entry

Genetic testing has been performed and indicates this patient may be at risk for inadequate anti-angiogenic response to bevacizumab (Avastin) therapy.

**TREATMENT MODIFICATION IS RECOMMENDED IF NOT CONTRAINDICATED:**
- Prescribe prasugrel (Cordaptive) 10mg daily and stop clopidogrel (Plavix) starting 10 AM on Day 1.
- API dose may need to be adjusted according to platelet count.
- If patient develops rash, please consult the team.

**NOTES:**
- The Vanderbilt Clinicians have recommended that a second pair of anti-angiogenic agents be administered if the first is ineffective.
- The team recommends that patients be monitored closely for adverse effects.
- The drug interactions should be reviewed before initiating treatment.

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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 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).