Precision Medicine: Applying Predictive and Prognostic Indicators to Risk-Adapted Treatment Selection

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Conflicts of Interest

Ms. Kurtin has nothing to disclose.

Objectives

• Describe tumor specific diagnostic strategies
• Interpret prognostic indicators for common solid and liquid tumors
• Apply prognostic indicators in risk-adapted treatment selection
Personalized Precision Oncology Care
Using *predictive* biomarkers plus considering *prognostic* biomarkers and patient attributes to select therapy = *personalized* life-span approach

Requires
- Effective diagnostics
- Consider characteristics of individual patient
- Risk-adapted treatment selection
- Optimal sequencing and duration of therapy
- Understanding, applying response criteria
- Partnership with the patient and family

Biomarkers: Predictive vs. Prognostic
- *Prognostic* biomarker
  - Correlates to likely disease natural history in untreated individual
- *Predictive* biomarker
  - Identifies patients most likely to benefit from a given therapy
  - Guides selection of therapy
  - A biomarker can have both predictive and prognostic value; each has different clinical utility
  - Biomarker-driven therapy may be safer, more cost-effective
    - Newer, more costly targeted therapies administered to patients likely to benefit
    - Limits potential adverse events in patients not likely to benefit
    - May allow enrollment of selected patients into biomarker-driven clinical trials with tandem tissue analysis

Drug Development Then and Now
Then: One Size Fits All
- Cytotoxic drug development
- Evaluate response in patients with similar diagnosis or late-stage disease
- MTD based on AE profile
- Reduction in measurable disease
- PD and PK measures

Now: Made to Order
- Use of predictive biomarkers to match individual tumor genotype
- Dose-escalation studies are most appropriate
- Biomarker profile as part of the inclusion criteria
- Redefinition of clinical efficacy and clinical trial endpoints
  - Active biological dose range
  - Functional imaging
  - Molecular biomarker measures

Definitions

- Maximum tolerated dose
  Highest drug dose or treatment that does not cause unacceptable toxicity

- Pharmacodynamics
  Relationship between drug concentration and biological effect

- Pharmacokinetics
  Concentration of drug in the body over time, including absorption, metabolism, tissue penetration, and excretion

- Pharmacogenetics
  Coined in 1959, study of genetic factors that influence response to drugs and other chemicals


Definitions

- Pharmacogenomics
  Next generation of pharmacogenetics; studies of the entire spectrum of genes in the human genome

- Biologically active dose range
  Range of drug doses needed to modulate the cellular target and produce the desired effect

- Response Evaluation Criteria in Solid Tumors (RECIST)
  Define response, stable disease, progression

- Synthetic lethality
  Combination of two otherwise non-lethal mutations that results in cell death

http://www.recist.com/

Key Elements of Effective Diagnosis

- Asking key questions at the time of surgery/biopsy
  Adequate specimens: FNA vs. core biopsy, vs. excisional

- Complete diagnostics prior to initial therapy

- Appropriate baseline imaging for tumor type

- Analyzing individual risk
  - Predictive genetic testing
  - Personal attributes

Key Elements of Risk-Adapted Treatment Selection

- **Patient characteristics**
  - Comorbidities
  - Performance status
  - Lifestyle
  - Finances
  - Quality of life

- **Disease characteristics**
  - Prognostic biomarkers
  - Predictive biomarkers
  - Tissue type
  - Staging

- **Available treatment options**
  - Selection based on risk analysis and patient choice
  - Shift from safety and efficacy only to biomarker-driven therapy

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Recommended Imaging: Selected Solid Tumors

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Recommended Baseline Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>Contrast-enhanced diagnostic CT of chest, abdomen, and pelvis</td>
</tr>
<tr>
<td></td>
<td>New MRIs give crisp, detailed imaging of abdomen and pelvis</td>
</tr>
<tr>
<td></td>
<td>PET/CT scan not routine; consider for surgically curable M1 disease</td>
</tr>
<tr>
<td>Breast</td>
<td>Diagnostic bilateral mammography, US, or MRI as indicated</td>
</tr>
<tr>
<td></td>
<td>Disease stage and symptoms determined additional tests</td>
</tr>
<tr>
<td></td>
<td>- Stage III - bone scan, CT of the abdomen and pelvis, chest imaging</td>
</tr>
<tr>
<td></td>
<td>- Bone scan for localized bone pain or elevated alkaline phosphatase</td>
</tr>
<tr>
<td></td>
<td>- CT of the abdomen and pelvis for elevated LFTs, abnormal PE</td>
</tr>
<tr>
<td></td>
<td>- FDG PET/CT only in selected locally advanced or metastatic disease</td>
</tr>
<tr>
<td>NSCLC</td>
<td>Determined by size and location of tumor</td>
</tr>
<tr>
<td></td>
<td>- PET/CT findings require pathological confirmation</td>
</tr>
<tr>
<td></td>
<td>- Brain MRI</td>
</tr>
<tr>
<td></td>
<td>- Bronchoscopy: navigational</td>
</tr>
<tr>
<td></td>
<td>- Endobronchial ultrasound and biopsy</td>
</tr>
</tbody>
</table>

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Imaging Techniques for Selected Liquid Tumors

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Recommended Baseline Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myeloma</td>
<td>Skeletal survey (plain films)</td>
</tr>
<tr>
<td></td>
<td>CRP PA and lateral</td>
</tr>
<tr>
<td></td>
<td>MRI of the spine if findings on plain film or clinical signs/symptoms</td>
</tr>
<tr>
<td></td>
<td>PET/CT under some circumstances</td>
</tr>
<tr>
<td>AML</td>
<td>CRP</td>
</tr>
<tr>
<td></td>
<td>Echoangiogram or MUGA scan</td>
</tr>
<tr>
<td></td>
<td>Other imaging based on symptoms or clinical findings only</td>
</tr>
<tr>
<td>ALL</td>
<td>CRP</td>
</tr>
<tr>
<td></td>
<td>Other imaging based on symptoms or clinical findings only</td>
</tr>
<tr>
<td>MDS</td>
<td>CRP</td>
</tr>
<tr>
<td></td>
<td>Other imaging based on symptoms or clinical findings only</td>
</tr>
<tr>
<td>NHL, DLBCL, FL, MCL, CLL/SL, CML</td>
<td>CT, CRP, CRP and lateral, MUGA or echoangiogram</td>
</tr>
<tr>
<td></td>
<td>PET/CT is only indicated for mantle cell or DLBCL, not recommended for follicular or CLL/SL</td>
</tr>
<tr>
<td></td>
<td>MRI or CT of the brain for selected high-risk cases or with symptoms</td>
</tr>
<tr>
<td>CML</td>
<td>CRP PA and lateral</td>
</tr>
<tr>
<td></td>
<td>Abdominal US or CT of the abdomen with splenomegaly</td>
</tr>
</tbody>
</table>
Techniques: Molecular and Genetic Analysis

- Interphase cytogenetics
- Fluorescence in situ hybridization
- Polymerase chain reaction
- Gene expression profiling
  - Genoptix: Probes/panels for both solid and liquid tumors
- Oncotype DX: Microarray panel
  - 21-gene assay recurrence score in breast cancer
  - Both prognostic and predictive
- 12-gene assay recurrence score for colon cancer
  - Prognostic but not predictive
- Target Now (Caris)
  - 25 panel of IHC determined targets and a 55 panel RT-PCR based on gene expression profiling

The Ki67 rate is only used in the evaluation of solid tumors.
True or false?

A. True
B. False

Serum Tumor Markers for Breast Cancer: ASCO Clinical Guidelines

<table>
<thead>
<tr>
<th>Tumor Marker</th>
<th>2007 ASCO Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA 15-3</td>
<td>Insufficient evidence to recommend for screening, diagnosis, staging, or monitoring for recurrence after primary breast cancer therapy</td>
</tr>
<tr>
<td>CA 27-29</td>
<td>May be used with diagnostic imaging, H&amp;P for monitoring patients with metastatic disease during active therapy</td>
</tr>
<tr>
<td></td>
<td>Insufficient evidence to be used alone for monitoring unless no other strategies for measurable disease</td>
</tr>
<tr>
<td>CEA</td>
<td>May be useful for selected patients during active treatment with diagnostic imaging and other clinical evaluation</td>
</tr>
</tbody>
</table>

### Key Predictive and Prognostic Indices: Breast Cancer (BC)

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Technique</th>
<th>Clinical Significance</th>
</tr>
</thead>
</table>
| Hormone receptors (ER, PR) | Tissue analysis (IHC) | - Recommended: All patients with newly diagnosed invasive or recurrent BC  
- ER status: Significant predictive value for tumor response to hormone therapy (HT) in metastatic disease  
- Significance of PR status less clear  
- ER+ and PR+ tumors may respond better to HT  
- ER/PR status may change over course of disease |
| HER2 | Tissue analysis (IHC, FISH, HERmark) | - Recommended: All newly diagnosed BC patients  
- Overexpressed TK in 15%-30% of BC  
- 3+ HER2 expression associated with poor prognosis  
- HER2+ patients may benefit from trastuzumab and anthracyclines  
- Measurement of activated HER2 may be useful in evaluating disease progression |
| BRCA1 | Tissue analysis (IHC, serum) | - Tumor suppressor genes; mutation linked to lifetime risk of BC, ovarian, pancreatic cancer  
- Patients with documented mutations may benefit from increase surveillance |
| BRCA2 | Tissue analysis (IHC, serum) | - Tumor suppressor genes; mutation linked to lifetime risk of BC, ovarian, pancreatic cancer  
- Patients with documented mutations may benefit from increase surveillance |
| uPA PA-1 | Tissue analysis (IHC) | - Roles in extracellular matrix degradation, tissue remodeling, cell adhesion, migration  
- Elevated levels associated with poor outcomes in patients with node-negative BC  
- Recommended in risk assessment for N0 BC |
| CTC | Serum | - High CTC (≥5) at diagnosis R/T to poor prognosis  
- If CT number does not decrease during therapy, patient likely to progress on the current therapy |

### Selected Future Biomarkers: Breast Cancer

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Function</th>
<th>Clinical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclin D</td>
<td>Regulator of cell cycle progression</td>
<td>Overexpression linked to endocrine resistance development in BC</td>
</tr>
<tr>
<td>PTEN</td>
<td>Tumor suppressor</td>
<td>Mutation leading to PTEN loss may block tumorigenesis and sensitize BC to trastuzumab</td>
</tr>
<tr>
<td>IGF-IR</td>
<td>Cell proliferation and survival, drug resistance</td>
<td>May be an option for treating triple-negative BC</td>
</tr>
<tr>
<td>K67</td>
<td>Proliferation marker</td>
<td>Higher pre-treatment K67 may indicate improved response to K67-suppression treatment after initial neoadjuvant endocrine therapy and may be associated with improved overall survival</td>
</tr>
</tbody>
</table>

Application of Biomarkers in Treatment Selection for Breast Cancer

- Diagnostic staging: Tumor size, nodal status, tumor grade
- Tissue and serum testing for breast cancer
- ER+ Select best endocrine treatment
- HER2+ Select best anti-HER2 treatment
- Triple Negative Select best chemotherapy or clinical trial

Role of Biomarkers in the Selection of Adjuvant Therapy of Breast Cancer

- ER+ Trastuzumab Chemotherapy (anthracycline) Endocrine Tx
- ER- Trastuzumab Chemotherapy (anthracycline)

Triple Negative Breast Cancer (TNBC)

- ER-, PR-, HER2: 15% of all breast cancers
  - Common in women with BRCA1 mutations
  - Generally high proliferative index
  - Poorer survival than most other subtypes of breast cancer
  - Usually high-grade tumors; greatest recurrence risk years 1–5
  - More common in African Americans
- Approach to treatment:
  - Dose-dense anthracycline + taxane (AC-T) every 2 weeks
  - PARP inhibitors in clinical trials for patients with BRCA mutations or TNBC
  - Platinum agents are currently being investigated in clinical trials
    - CALGB 40603: Neoadjuvant paclitaxel, doxorubicin, cyclophosphamide plus carboplatin
    - Triple Negative Trial (NCT00532727), carboplatin against docetaxel in the metastatic setting
HER2 Overexpression in Other Tumor Types

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>HER2 Overexpression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastroesophageal cancer</td>
<td>34%</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>20% to 30%</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>20%</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>11% to 30%</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>11%</td>
</tr>
</tbody>
</table>

Traditional High-Risk Features in Colon Cancer

- Grade 3/4
- Lymphatic/vascular invasion
- Bowel obstruction
- < 12 lymph nodes examined
- Perineural invasion
- Localized perforation, or close, indeterminate or positive margins

Key Predictive and Prognostic Indices: Colorectal Cancer (CC)

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Technique</th>
<th>Clinical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEA</td>
<td>Serum</td>
<td>Used as a measure of tumor activity; Not elevated in all patients even with bulky disease; Not specific to CC; elevated in smokers</td>
</tr>
<tr>
<td>UGT1A1</td>
<td>Serum</td>
<td>Enzyme critical to inactivation of SN-38 (irinotecan metabolism); Polymorphism associated with hyperbilirubinemia; UGT1A1*28 allele may increase toxicity to irinotecan</td>
</tr>
<tr>
<td>DPD deficiency</td>
<td>Serum</td>
<td>DPD is important to 5-FU metabolism and deficiency associated with severe 5-FU toxicity</td>
</tr>
<tr>
<td>MSI</td>
<td>Tissue (IHC)</td>
<td>Microsatellites mutations in mismatch repair gene; Testing recommended for all patients &lt; 50 years; Stage II patients with MSI-high frequency (MSI-H) tumors have good prognosis; may not benefit from adjuvant 5-FU chemotherapy</td>
</tr>
</tbody>
</table>
**Key Predictive and Prognostic Indices: Colorectal Cancer (CC)**

<table>
<thead>
<tr>
<th>Biomarker, Technique</th>
<th>Clinical Significance</th>
</tr>
</thead>
</table>
| KRAS, tissue         | • KRAS mutations: Predictive of a negative response to anti-EGFR monoclonal antibodies (EGFR-I)  
                      • Mutations in codon 12 & 13 of exon 2 most common  
                      • WT-KRAS with low-level expression of amphiregulin and epiregulin (ligands for EGFR) have inferior response to EGFR-I  
                      • KRAS13 p.G13D mutation may have response to EGFR-I now (investigating in clinical trials) |
| BRAF, tissue (PCR)   | • BRAF mutation: Indicator of poor prognosis  
                      • V600E mutations predict negative response to EGFR-I; may have limited benefit in first-line chemo for metastatic disease |
| PI3KCA, tissue       | • Mutation stimulates AKT pathways, increasing CC tumor cell growth |
| PTEN, tissue         | • Negative regulator of PI3KCA  
                      • PTEN+ tumors may have more favorable outcomes  
                      • PTEN- tumors may not respond to EGFR-I |

**Application of Biomarkers in Treatment Selection for Colon Cancer**

Diagnostic Staging:
- Tumor size
- Nodal status
- Tumor grade
- High-risk features

Tissue and serum testing for colon cancer

Stage II KRAS
- No  
  - No adjuvant therapy  
  - EGFR-I therapy likely beneficial  
  - Chemotherapy, no EGFR-I therapy
- Yes  
  - No adjuvant therapy  
  - KRAS mutation likely to predict negative response to EGFR-I  
  - Chemotherapy, no EGFR-I therapy

Metastatic WT KRAS

Metastatic mutated KRAS

**Traditional Poor Prognostic Indices: Lung Cancer**
- Pulmonary symptoms present
- Large tumor (> 3 cm)
- Non-squamous histology
- Metastases to multiple lymph nodes within a TNM-defined nodal station
- Vascular invasion
- Poor performance status
- Weight loss of > 10%
- Advanced age alone not been shown to influence response to therapy or survival
**Precision Medicine: The Way Forward**

- Histology-directed therapy
  - Nonsquamous (bevacizumab, pemetrexed)
  - Squamous (nab-paclitaxel)
- Biomarker-directed therapy
  - Erlotinib, crizotinib, afatinib
- Clinical trials remain the standard of care for patients eligible for a trial

**Frequency of Mutations and Availability of Targeted Therapies in NSCLC**

<table>
<thead>
<tr>
<th>Gene Alteration</th>
<th>Frequency</th>
<th>Therapy</th>
<th>Approval</th>
<th>Targeted Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>AKT1 Mutation</td>
<td>1%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALK Rearrangement</td>
<td>3%–7%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRAF Mutation</td>
<td>1%–3%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DDR2 Mutation</td>
<td>4%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGFR Mutation</td>
<td>10%–35%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGFR1 Amplification</td>
<td>20%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HER2 Mutation</td>
<td>2%–4%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KRAS Mutation</td>
<td>15%–25%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MEX1 Mutation</td>
<td>1%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MET Amplification</td>
<td>12%–4%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NRAS Mutation</td>
<td>1%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PIK3CA Mutation</td>
<td>1%–3%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTEN Mutation</td>
<td>4%–8%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TET Rearrangement</td>
<td>1%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ROS1 Rearrangement</td>
<td>1%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Predictive and Prognostic Implications of Molecular Testing in NSCLC**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Predictive</th>
<th>Predictive and Prognostic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Crizotinib</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Afatinib</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Pemetrexed</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>
Application of Biomarkers in First-Line Treatment Selection for Advanced Stage NSCLC

**NSCLC stage III or IV**
- **EML4-ALK**
  - **EML4-ALK – EGFR –**
    - Platinum-based chemotherapy ± Bevacizumab
  - **EML4-ALK + EGFR –**
    - VEGF-I eligible
    - Crizotinib
  - **EML4-ALK – EGFR +**
    - VEGF-I ineligible
    - Platinum-based chemotherapy ± Bevacizumab
    - Crizotinib
  - **EML4-ALK + EGFR +**
    - VEGF-I eligible
    - Crizotinib
- **Non-squamous histology**
  - Platinum-based chemotherapy ± Bevacizumab
  - **EML4-ALK – EGFR –**
  - Crizotinib
- **Squamous histology**
  - Platinum-based chemotherapy ± Bevacizumab
  - **EML4-ALK – EGFR –**
  - Crizotinib
  - **EML4-ALK + EGFR –**
  - VEGF-I eligible
  - Crizotinib
  - **EML4-ALK + EGFR +**
  - VEGF-I ineligible
  - Platinum-based chemotherapy ± Bevacizumab
  - Crizotinib


High-Risk Features for Common Hematologic Malignancies

<table>
<thead>
<tr>
<th>Disease</th>
<th>High-Risk Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML</td>
<td></td>
</tr>
</tbody>
</table>
  - High-risk cytogenetics
  - Complex cytogenetics
  - Monosomal karyotype
  - Abnormalities of chromosome 5 or 7
  - 17p abnormality (17p16.1), inv(3), t(4;11), t(6;9), t(9;22), inv(3), t(12;13)
  - Intermediate cytogenetic risk ±8 |
| ALL     | 
  - BCR-ABL positive disease
  - Age > 35
  - WBC > 30 x 10^9/L at diagnosis
  - Null ALL
  - CD10+ (CALLA) mature B-cell ALL |


Which of the following are considered high-risk features for MDS?

A. 46XX, –Y  
B. 46XY, del5q  
C. 46XX, -7  
D. 46XY

**Kurtin, S. (2012).**
Risk-Adapted Therapy for MDS

- IWG-PM review of more than 7,000 cases
- Major clinical factors for prognostic risk categories:
  - Marrow blasts
  - Cytogenetics
  - Hemoglobin, neutrophil and platelet levels
  - Age
- "Advanced" IPSS-R calculator tool also includes 'differentiating features' (only applicable for survival, not AML evolution).
  - Performance status
  - Serum ferritin
  - LDH
  - Beta-2 microglobulin
  - Marrow fibrosis

IPSS-R Cytogenetic Risk Groups

<table>
<thead>
<tr>
<th>Cytogenetic Risk</th>
<th>Cytogenetic types</th>
<th>Estimated survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very good</td>
<td>del(11q), -Y</td>
<td>60.8 mo</td>
</tr>
<tr>
<td>Good</td>
<td>Normal, del(20q), del(5q) alone and double, del(12p)</td>
<td>48.5 mo</td>
</tr>
<tr>
<td>Intermediate</td>
<td>+8, 7q-, i(17q), +19, +21, any other single or double, independent clones</td>
<td>24 mo</td>
</tr>
<tr>
<td>Poor</td>
<td>del(3q), t(11q), t-, t, double including 7q, complex (3 abnormalities)</td>
<td>14 mo</td>
</tr>
<tr>
<td>Very poor</td>
<td>Complex (&gt; 3 abnormalities)</td>
<td>5.7 mo</td>
</tr>
</tbody>
</table>


IPSS-R Risk Categories

<table>
<thead>
<tr>
<th>Score/Attribute</th>
<th>0</th>
<th>1</th>
<th>1.5</th>
<th>1.5</th>
<th>2.5</th>
<th>3.5</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytogenetics</td>
<td>Very good</td>
<td>Good</td>
<td>Int</td>
<td>Poor</td>
<td>Very Poor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blasts</td>
<td>&lt; 5%</td>
<td>5%-10%</td>
<td>11%-30%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>≥ 10g/dL</td>
<td>&lt; 10g/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets</td>
<td>≥ 100,000</td>
<td>&lt; 100,000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANC</td>
<td>≥ 0.8</td>
<td>&lt; 0.8</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

IPSS-R: Survival and Risk of Leukemic Transformation

<table>
<thead>
<tr>
<th>Score</th>
<th>1 Very Low</th>
<th>2 Good</th>
<th>3 Intermediate</th>
<th>4 Poor</th>
<th>5 Very High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean overall survival</td>
<td>8.7 yr</td>
<td>5.3 yr</td>
<td>3.0 yr</td>
<td>1.6 yr</td>
<td>0.8 yr</td>
</tr>
<tr>
<td>Mean risk of AML in 25% of patients</td>
<td>Not reached</td>
<td>10.7 yr</td>
<td>4.0 yr</td>
<td>1.4 yr</td>
<td>0.8 yr</td>
</tr>
</tbody>
</table>

Biomarkers in MDS: TET 2 Mutations and 5q- in MDS

- **10-11 translocation-2 (TET-2)**
  - Most common gene mutation in MDS (16%-26%)
  - Thought to be involved in the regulation of gene expression
  - Improved response to azacitidine

- **5q deletion**
  - Predictive of increased sensitivity to lenalidomide

High-Risk Features for Common Hematologic Malignancies

<table>
<thead>
<tr>
<th>Disease</th>
<th>High-Risk Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHL:</td>
<td>Elevated LDH</td>
</tr>
<tr>
<td>CLL</td>
<td>Elevated B-cell DR</td>
</tr>
</tbody>
</table>

### Predictive and Prognostic Markers in Diffuse Large B-Cell Lymphoma (DLBCL)
- CD20 expression is predictive of response to rituximab
- Ki67 remains prognostic in DLBCL
- Addition of rituximab to standard chemotherapy improved the survival of patients with DLBCL in both GCB and non-GCB subgroups
- BCL-2 overexpression; most common in GCB
  - Associated with poor survival.
- Ruximab + anthracycline-based regimen overcame adverse influence of BCL-2 overexpression
- Additional biomarkers or molecular targets are being explored in clinical trials

### Key Prognostic Indices: Acute Myelogenous Leukemia (AML)

<table>
<thead>
<tr>
<th>Risk Status</th>
<th>Cytogenetics</th>
<th>Molecular Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Better risk</td>
<td>inv(16) or i(16;16)</td>
<td>Normal cytogenetics with NPM1 mutation or isolated CEBPA mutation in the absence of FLT3-ITD</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Normal cytogenetic</td>
<td>t(9;11) +8</td>
</tr>
<tr>
<td>Poor risk</td>
<td>Complex (≥ 3 clonal CA)</td>
<td>t(9;21), inv (16), i(16;16) with c-KIT mutation</td>
</tr>
<tr>
<td></td>
<td>(t(9;11), inv(3), i(3;3), t(6;9), t(9;22))</td>
<td>Normal cytogenetic with FLT3-ITD mutation</td>
</tr>
</tbody>
</table>

### Application of Prognostic Indices: Acute Myelogenous Leukemia

#### Age > 60
- Evaluate for antecedent MDS
- Induction Anthracycline and cytarabine
- Consider MDS therapy for Elderly AML or Modified Induction
- Favorable risk cytogenetics
- NPM1+/ FLT3- x3 cycles +/- HCT
- All HCT Clinical Trial

#### Age < 60
- Normal cytogenetics
- Unfavorable risk cytogenetics or BCR-ABL
- NQO1, HPC, FLT3
- Allo HCT Clinical Trial
Staging of MM: Key Components

<table>
<thead>
<tr>
<th>ISS Stage</th>
<th>Criteria</th>
<th>Median Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Serum β2-microglobulin &lt; 3.5 mg/dL AND Serum albumin ≥ 3.5 g/dL</td>
<td>62 mo</td>
</tr>
<tr>
<td>II*</td>
<td>Neither stage I nor stage II</td>
<td>44 mo</td>
</tr>
<tr>
<td>III</td>
<td>Serum β2-microglobulin ≥ 5.5 mg/dL</td>
<td>29 mo</td>
</tr>
</tbody>
</table>

Two categories for stage II:
- Serum β2-microglobulin <3.5 mg/dL, serum albumin <3.5 g/dL
- Serum β2-microglobulin <3.5 to >5.5 mg/dL, irrespective of serum albumin level


Risk-Stratification Based on Tumor Biology

<table>
<thead>
<tr>
<th>High Risk*</th>
<th>Intermediate Risk</th>
<th>Standard Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>17p deletion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>t(14;16) (C-MAF)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>t(14;20) (MAF-B)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GEP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>t(4;14) (FGFR3/MMSET)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All others including:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperdiploidy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>t(11;14) (CCND1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>t(6;14) (CCND3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Presence of trisomies ameliorates high risk

C-MAF = cellular musculoaponeurotic fibrosarcoma oncogene homolog; MAF-B = musculoaponeurotic fibrosarcoma oncogene homolog B; GEP = gene expression programming; FGFR3 = fibroblast growth factor receptor 3; MMSET = multiple myeloma set domain; CCND1 = cyclin D1; CCND3 = cyclin D3

Complete response appears critical

Bortezomib critical

Excellent outcome

Complete Response (CR) Is Critical in Patients With High-Risk Myeloma

Low-Risk MM (87%)

High-Risk MM (13%)

CR = complete response; NR = no response


Approach to Newly Diagnosed MM

**High Risk**
- Transplant Eligible
- ASCT, 2nd if not in CR or VGPR
- Continue VRD for 2 years
- Early ASCT (preferred) or Delayed ASCT
- Bortezomib-based maintenance

**Intermediate Risk**
- Transplant Ineligible
- ASCT if not in CR or VGPR
- Continue VCD for 1 year
- Continue Rd or if VCD continue for 1 year
- Bortezomib maintenance if not in CR, or VGPR following ASCT

**Standard Risk**
- Transplant Ineligible
- Rd (or VCD) x 4 cycles
- Continue Rd;
- or if VCD continue for 1 year
- Lenalidomide maintenance if not in CR or VGPR following ASCT

*ASCT = autologous stem cell transplant; CR = complete response; VGPR = very good partial response.*

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Cancer Occurs Most Often in Older Adults

- Effect of comorbidities
- Fit vs. frail
- Cost of treatment
- Self-care and caregiver support
- Proximity to the clinical setting
- Quality of life
- Personal choice

---

When to Change Therapy?

- Progression of disease
  - RECIST criteria for solid tumors
    - Need to look at films
    - What is it being compared to
    - Verify dates
  - Roles of tumor markers
  - Stable disease in setting of metastatic disease is a very good thing!
- Intolerance to current therapy
  - Reversible vs. potentially irreversible adverse events
  - Severity of symptoms despite optimal management

---
What Are the Advantages of Precision Medicine?

• Selecting the ‘best’ therapy early in the disease course offers the best treatment outcome
• Avoiding unnecessary exposure to potential toxicity in patients not likely to respond
• Up-front consideration of clinical trials for patients with high-risk disease is the way forward
• Continued refinement of predictive and prognostic indices needed

Future Challenges

• Genetic heterogeneity
• Limited oversight for microarray diagnostics
• Continued limited enrollment of patients into clinical trials
• Funding for early phase research in small populations

The Challenges of Drug Development

• Who will spend time and money to discover, design, and develop novel drugs to newly discovered targets?
• Who has the vision? Academia or pharma
  Academia is capable, but implementing a phase I trial does not often meet standard productivity requirements for faculty
• Will likely require innovative individuals who are motivated to work to get their discoveries to small biotech and finally to pharma for clinical trial evaluation