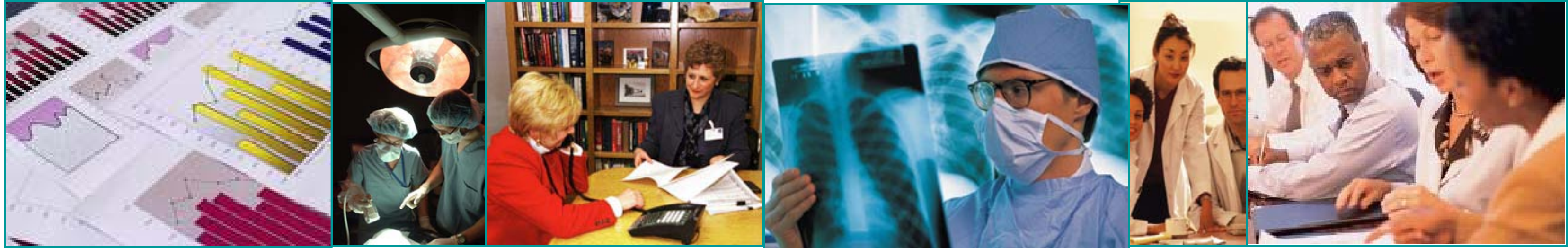

Molecular Markers in Solid Tumors:
Breast, Lung, and Colorectal Cancer

Dr. Linda W. Wilson
Board-Certified Hematologist-Oncologist

AllMed
HEALTHCARE MANAGEMENT

© AllMed Healthcare Management, Inc.

Speaker Introductions

Moderator:

Ann Correa, RN, OCN

- AllMed Healthcare Management

Presenters:

Dr. Linda W. Wilson

- Director of Medical Oncology, Pacific Cancer Institute, Maui, Hawaii

© AllMed Healthcare Management, Inc.

Overview

- Introduction to molecular tumor markers
  - Prognostic vs. predictive molecular markers
- Overview of specific tumor markers
  - Breast cancer
  - Lung cancer
  - Colorectal cancer
- The role of external independent medical review for molecular marker testing

AllMed HEALTHCARE MANAGEMENT

© AllMed Healthcare Management, Inc.

Oncology: A Rapidly Evolving Field

- Adoption of new molecular markers in oncology is challenging
  - Lack of a standardized validation process due to the many tumor types, treatments, and tests
- Clinical utility of predictive markers depends on the efficacy of available therapeutic agents

AllMed
HEALTHCARE MANAGEMENT

© AllMed Healthcare Management, Inc.

Molecular Markers in Solid Tumors

- **Predictive markers:** Associated with response to a particular treatment
- **Prognostic markers:** Baseline measurements that project disease trajectory
- *Static measurements* diagnose cancer and identify toxicity to chemotherapeutic agents
- *Dynamic measurements* correlate with tumor growth or regression over time

AllMed
Healthcare Management

© AllMed Healthcare Management, Inc.

Breast Cancer

- Estrogen receptor (ER) and progesterone receptor (PR)
- Human epidermal growth factor receptor-2 (HER2)
- Oncotype DX breast cancer assay
- MammaPrint
- Breast cancer susceptibility gene 1 (BRCA1) and 2 (BRCA2)

© AllMed Healthcare Management, Inc.

Hormone Receptors

- Estrogen receptor (ER) and progesterone receptor (PR)
  - 70% to 80% of tumors are ER and/or PR positive
  - Weakly prognostic of more indolent tumors
  - Strongly predictive of benefit from endocrine therapy

AllMed Healthcare Management

© AllMed Healthcare Management, Inc.

HER2

- Recommended in all new cases of invasive breast cancer
- HER2-positive breast cancer associated with higher-grade tumors that are more likely to metastasize

AllMed
HEALTHCARE MANAGEMENT

© AllMed Healthcare Management, Inc.

Oncotype DX Breast Cancer Assay

- Generates a 21-gene signature
- Refines assessment of recurrence risk in patients who have lymph-node-negative, ER-positive invasive breast cancer

AllMed
HEALTHCARE MANAGEMENT

© AllMed Healthcare Management, Inc.

MammaPrint

- Identifies a 70-gene signature for risk stratification in lymph-node-negative breast cancer
- Demonstrated prognostic value independent of conventional clinicopathologic features
- Not yet validated as a predictive marker of chemotherapy benefit

AllMed
HEALTHCARE MANAGEMENT

© AllMed Healthcare Management, Inc.

BRCA Mutations

BRCA1 Mutation	BRCA2 Mutation
Increased risk for breast and ovarian cancer in women 50% to 85% risk of developing breast cancer by age 70 40% to 60% risk of developing ovarian cancer by age 85	Increased risk for breast cancer in both men and women Increased risk for prostate cancer in men 16% to 27% risk of developing ovarian cancer by late age in women Increased risk for pancreatic cancer and melanoma in both men and women

Breast/Ovarian Cancer: BRCA1 & BRCA2. Memorial Sloan-Kettering Cancer Center Web site. http://wwwmskcc.org/mskcc/pring/8623.cfm#45826. Accessed November 8, 2010.

AllMed
Healthcare Management

© AllMed Healthcare Management, Inc.

Lung Cancer

- KRAS
- Epidermal growth factor receptor (EGFR)
- Echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK) fusion gene

© AllMed Healthcare Management, Inc.

KRAS

- Protein involved in cell growth
- Mutually exclusive with EGFR mutations
- KRAS mutations
  - Found in 20% to 30% of non-small cell lung cancer (NSCLC) tumors and adenocarcinomas, and smokers
  - Associated with worse prognosis
  - May not respond to adjuvant chemotherapy
  - Do not respond to tyrosine kinase inhibitors (TKIs) such as erlotinib
  - Response to cetuximab is unclear

Tsao et al. J Clin Oncol. 2007;25:5240-5247.

AllMed
Healthcare Management

© AllMed Healthcare Management, Inc.

Epidermal Growth Factor Receptor (EGFR)

- Receptor with growth-promoting effects
- EGFR mutation
  - 70% of patients with EGFR mutation respond to TKIs such as erlotinib
  - Progression-free survival of about 5 months
  - No overall survival benefit
- The National Comprehensive Cancer Network (NCCN) recommends erlotinib as first-line therapy for patients with EGFR mutation

Aggarwal et al. J Natl Compr Canc Netw. 2010;8:822-832.
NCCN Clinical Practice Guidelines in Oncology. Non-Small Cell Lung Cancer. 2011.

AllMed
Healthcare Management

© AllMed Healthcare Management, Inc.

Echinoderm Microtubule-Associated Protein-Like 4-Anaplastic Lymphoma Kinase (EML4-ALK)

- Fusion protein that produces a kinase with oncogenic activity
- EML4-ALK mutation
  - Found in only 3% to 5% of patients with NSCLC
  - More common in men and younger patients, in adenocarcinomas, and in never/light smokers
- ALK-positive patients do not have mutations in EGFR or KRAS and are resistant to TKIs

Aggarwal et al. J Natl Compr Canc Netw. 2010;8:822-832.

AllMed
HEALTHCARE MANAGEMENT

© AllMed Healthcare Management, Inc.

Colorectal Cancer

- KRAS
- BRAF V600E
- Microsatellite instability (MRI) and mismatch repair protein (MMR)
- Oncotype DX colon cancer assay

AllMed
HEALTHCARE MANAGEMENT

© AllMed Healthcare Management, Inc.

KRAS

- KRAS mutations predictive of nonresponse to monoclonal antibodies cetuximab and panitumumab, which target EGFR
- KRAS wild-type (nonmutated) patients will respond to cetuximab and panitumumab

© AllMed Healthcare Management, Inc.

BRAF V600E

- BRAF V600E mutation may be associated with poor prognosis
- KRAS wild-type tumors with mutated BRAF may not respond to cetuximab and panitumumab
- Testing optional for patients with newly diagnosed KRAS-nonmutated metastatic colorectal cancer
  - May help to determine patient's responsiveness to EGFR-targeted therapies

Di Nicolantonio et al. J Clin Oncol. 2008;26:5705-5712.
Laurent-Puig et al. J Clin Oncol. 2009;27:5924-5930.
Loupakis et al. Br J Cancer. 2009;101:715-721.
NCCN Clinical Practice Guidelines in Oncology. Colon Cancer. 2011.

© AllMed Healthcare Management, Inc.

Microsatellite Instability (MSI) and Mismatch Repair Protein (MMR)

- High levels of MSI indicate a deficiency in MMR function
  - Possible predictive marker for lower response rates to adjuvant fluorouracil-based (5-FU-based) chemotherapy in patients with stage II colon cancer
- MSI/MMR testing accepted for diagnosis of hereditary nonpolyposis colorectal cancer
  - Should be considered in patients diagnosed with colorectal cancer before the age of 50 years

Sargent et al. J Clin Oncol. 2010;28:3219-3226.

AllMed Healthcare Management

© AllMed Healthcare Management, Inc.

Oncotype DX Colon Cancer Assay

- Uses technology similar to Oncotype DX breast cancer assay
- Generates a 12-gene signature to assess the risk for recurrence in patients with stage II colorectal cancer following surgery

AllMed
HEALTHCARE MANAGEMENT

© AllMed Healthcare Management, Inc.

Oncology Case Management: External Review

- Specialty match critical
- Oncology specialist
  - Understands the emerging data on new molecular markers
  - Remains current on available therapeutic agents
  - Makes proactive decisions, based on true needs of the patient, that meet standard of care

© AllMed Healthcare Management, Inc.

The Role of Independent Review in Oncology

- An independent medical review:
  - Looks at whether or not a specific procedure or treatment was medically necessary
  - Avoids conflicts of interest, not having the appropriate specialists to review cases, or having the same physician who initially denied a claim also review an appeal
- Independent review organizations (IROs) provide specialty match
  - Especially important for molecular marker testing—results from ongoing clinical trials lead to the continual emergence of new diagnostic/prognostic tools, treatments, and therapeutic agents
  - Board-certified physician specialists who work with IROs keep up-to-date with the latest medical literature, the latest standard of care, and continually evolving technology and treatments

AllMed
HEALTHCARE MANAGEMENT

© AllMed Healthcare Management, Inc.

Conclusions

- Recent advances in the molecular biology of cancer allow physicians to:
  - Establish more accurate diagnoses
  - Gather information that can be used to guide therapy and predict response to various treatments
- Continually emerging molecular testing technologies offer the promise of increased personalization of cancer care
  - Presents physicians with the challenge of keeping up with rapidly evolving advances

© AllMed Healthcare Management, Inc.

Conclusions (cont'd)

- Independent review organizations (IROs):
  - Provide ready access to specialists, which healthcare plans may lack internally
  - Allow for timely determination of whether the requested tests and treatment falls under medical necessity guidelines
- Independent medical reviews:
  - Provide unbiased evaluation of medical need for molecular marker testing
  - Facilitate the optimization of care for patients with cancer

AllMed
HEALTHCARE MANAGEMENT

© AllMed Healthcare Management, Inc.

Questions and Answers

Please use the questions box within the GoToWebinar tool bar, usually located on the right side of your screen towards the bottom of the gray bar.

AllMed
Healthcare Management

© AllMed Healthcare Management, Inc.

Thank You

AllMed Healthcare Management, Inc.

(800) 400-9916

www.allmedmd.com

Ann Correa

ann@allmedmd.com