Rodger C. Haggitt GIPS Forum

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Evidence for Use of Molecular Testing

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Making Cancer History®

Components of personalized cancer care

- **Patient:** Germline genetics and pharmacogenetics
- **Tumor:** Somatic genomics and pharmacogenomics
- **Environment:** Lifestyle and exposures
- **Agents**

Deciding on what's ready for clinical use

Evaluation of evidence

- Levels
  - Green and Byar
  - TMUGS
- Depth
- Breadth
- Marketing
- Role of professional organizations

Considerations

- Individualized decisions
  - Physician requests
  - Patient population
  - Laboratory capabilities
  - Fiscal environment
  - Build or buy

Strength of evidence (therapy)

Evidence of treatment efficacy	Green & Byar 1984
Anecdotal case reports	1
Case series without controls	2
Series with literature controls	3
Analyses using computer databases	4
“Case-control” observational studies	5
Series based on historical control groups	6
Single randomized controlled clinical trials	7
Confirmed randomized controlled clinical trials	8

DEFINITIONS AND SPECIFICATIONS OF MARKER

Marker Designation/ Nomenclature (e.g. ER, P53, CEA, etc.)		**Molecule/Substance Assayed & Alteration Detected** (e.g. DNA/mutation/RNA/over expression, protein, increased level, etc.)		**Assay Format to Detect Marker** (e.g. EIA, ICA, SSCP, etc.)	
Reagents Used (e.g. MAb or probe, or commercial assay)			**Specimen Source** (e.g. frozen or fixed tissue, plasma, urine, circulating cells, etc.)		
Disease (e.g. breast cancer, colon cancer, etc)					

Utility

	Marker association with biologic:				**Use leads to decision in practice that results in a more favorable clinical outcome:**							
	Process		**Endpoint**		**Survival**		**Disease Free Survival**		**Quality of Life**		**Cost of Care**	
Uses	**Utility Score[1]**	**Level of Evidence[3]**	**Utility Score[1]**	**Level of Evidence[3]**	**Utility Score[2]**	**Level of Evidence[3]**	**Utility Score[2]**	**Level of Evidence[3]**	**Utility Score[2]**	**Level of Evidence[3]**	**Utility Score[2]**	**Level of Evidence[3]**
Determine Risk												
Screening												
Differential Diagnosis												
Prognostic: Predict Relapse/Progression												
Primary												
Metastatic												
Prognosis: Predict Response to Therapy												
Primary Metastatic												
Monitor Course												
Detect relapse in patient with no evidence of disease after therapy for primary or recurrent disease												
Follow Detectable Disease												

The Molecular Testing Evaluation Committee (MTEC)

Charge to the MTEC

- Standard of care
- Routine clinical ordering
- EMR order entry sets
- Investment of institutional funds
- Documentation for negotiations with third-party and second-party payers
- Advanced Beneficiary Notification (ABN)
- Documentation of medical necessity, billing compliance, and utilization

MTEC roster and governance

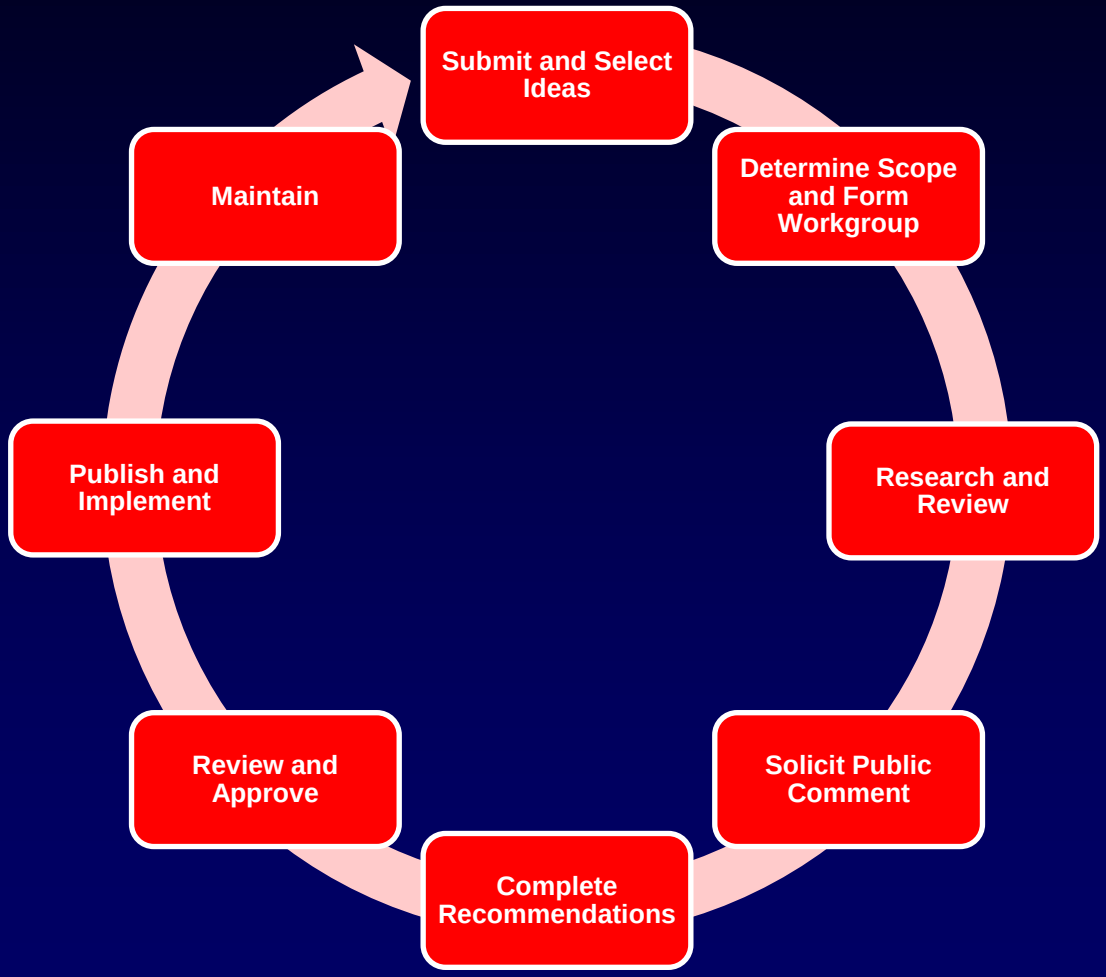
- Multidisciplinary clinical Division Heads, Department Chairs, and faculty
- Administrative personnel: Clinical activities, patient services, compliance, billing, and clinical research
- Patient data acquisition and analysis
- Patient advocacy
- Subcommittee of the Executive Committee of the Medical Staff and reports to the Medical Practice Committee

Professional organizations

- Review of literature
- Opinions of experts
- Published guidelines

- National Comprehensive Cancer Network (NCCN)
- Combined efforts of ASCP, CAP, AMP and ASCO

Guideline Development Process



Leadership

- Expert Panel Co-chairs
  - Wayne W. Grody, MD, ASCP Co-chair , University of California Los Angeles
  - Stan Hamilton, MD, CAP Co-chair, The University of Texas MD Anderson Cancer Center
  - Federico A. Monzon, MD, AMP Co-chair, Baylor College of Medicine,
  - Monica M. Bertagnolli, MD, ASCO Co-chair, Brigham and Women's Hospital
- Expert Panel
- Advisory Panel

Competition in molecular diagnostics

- Hospital labs
- Reference labs: Megalabs, niche labs
- Diagnostic assay companies
- Benefits management companies
- Direct-to-consumer or -physician companies
- Advisory and educational service companies
- Non-pathologist professionals
- Accountable Care Organizations

Commercialized Gene Expression Profiling

- **Colon Cancer Assay (January, 2010)**
- **ColoPrint**
- **Colon and Rectal Cancer Assay**
- **ColDx (available in 2012)**

Comparisons of commercial assays

	CCA	ColoPrint	CRCA	ColDx
Stage	II	II&III	I&II	II
Site	Colon	Colon	Colon, rectal (I)	Colon
Tissue	FFPE	Frozen	FFPE	FFPE
Genes	7	18	5	634
Report	3-yr DFS	5-yr RFS	5-yr OS	5-yr DFS
Val. hi-risk II	26%	37%	1/3	41%
Val. Surv. II	79%	74%	86%	60% (est.)
Val. HR II	1.47	3.29	N/A	2.21

Caveats

- **Assumption that worse prognosis equates to likelihood of benefit from adjuvant chemotherapy.**
- **Diverse chemotherapy options: modulated 5-FU, 5-FU + oxaliplatin, 6 months.**
- **Analytic validation**
- **Clinical validation**
- **Biologic plausibility of genes**

Caveats

- **Applicability to general patient population after development in clinical trial patients of younger age and good performance status**
- **Survival in T4N0M0 stage II worse than T1-2N1M0 stage IIIA**
- **Few studies in rectal cancer patients**
- **Marketed, including direct-to-patient, before convincing evidence**

Guidelines

- **Based upon opinion of panels of experts, including literature review**
- **Tumor gene expression profiling for prognosis of colon and rectal cancer**
  - **Colon Cancer Assay not recommended (National Comprehensive Cancer Network Guidelines Panel for Colon Cancer; Kelley RK et al. JNCCN 9: 13-25, 2011)**
  - **ColoPrint, Colon and Rectal Cancer Assay, and ColDx not evaluated and reported individually**

Summary

- Identification of subsets of stage II colon cancer patients who will develop recurrence is an important goal.
- Numerous studies have used tumor gene expression profiling to indicate high-risk patients, and four commercial assays will be available in the marketplace in 2012.
- High-level evidence is not yet available for any of the four assays, including the crucial information on whether or not the identified subsets will benefit from post-operative adjuvant chemotherapy.
- Use of these assays in not recommended at present.

Thanks for your attention.