These guidelines have been specifically developed for MD Anderson and are not intended to replace the independent medical or professional judgment of physicians or other health care providers.

The Molecular Testing Evaluation Committee (MTEC) is responsible for the review and approval of requests for biomarker testing based on evaluating published data and determining if there is sufficient scientific and clinical interest for their use in standard care of patients at MD Anderson. The committee reports up to Medical Practice and the Executive Committee for the Medical Staff. Biomarkers approved by MTEC and available through Pathology and Laboratory Medicine using CLIA-compliant molecular diagnostic tests that satisfy the institutionally defined criteria are included in this document.

The following exception criteria must be met for orders which are not included in this document; additionally, the request must be approved by the internal MDACC Single Use Order Set Committee.

Exception criteria:
- The test is clinically justifiable: Molecular test results will guide treatment decisions, and the results will identify treatment selection among currently available therapies.
- The patient is appropriate for such therapies: The patient has a performance status of ECOG of 0 or 1 and is expected to live for at least three months.
- The patient has locally advanced or metastatic disease not appropriate for other therapies.

Table of Contents

<table>
<thead>
<tr>
<th>Solid Tumors:</th>
<th>Suggested Readings .........................</th>
<th>Page 13 – 53</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Brain ..........................</td>
<td>Breast ......................................</td>
<td>Page 13-16</td>
</tr>
<tr>
<td>● Breast ..........................</td>
<td>Endocrine ..................................</td>
<td>Page 16-18</td>
</tr>
<tr>
<td>● Endocrine ........................</td>
<td>Gastrointestinal ..........................</td>
<td>Page 19-22</td>
</tr>
<tr>
<td>● Gastrointestinal .................</td>
<td>Genitourinary/Urology .....................</td>
<td>Page 23-24</td>
</tr>
<tr>
<td>● Genitourinary ......................</td>
<td>Gynecology .................................</td>
<td>Page 25-34</td>
</tr>
<tr>
<td>● Gynecology ...........................</td>
<td>Head &amp; Neck ................................</td>
<td>Page 35</td>
</tr>
<tr>
<td>● Head and Neck .......................</td>
<td>Leukemia ..................................</td>
<td>Page 36-45</td>
</tr>
<tr>
<td>● Melanoma ..........................</td>
<td>Lymphoma ..................................</td>
<td>Page 45-46</td>
</tr>
<tr>
<td>● Sarcoma .............................</td>
<td>Melanoma ..................................</td>
<td>Page 46</td>
</tr>
<tr>
<td>● Thoracic ............................</td>
<td>Myeloma ..................................</td>
<td>Page 47</td>
</tr>
<tr>
<td>● Unknown Primary ......................</td>
<td>Neurology ..................................</td>
<td>Page 47-50</td>
</tr>
<tr>
<td>Liquids:</td>
<td>Sarcoma ..................................</td>
<td>Page 51</td>
</tr>
<tr>
<td>● Leukemia ..........................</td>
<td>Thoracic ..................................</td>
<td>Page 51-54</td>
</tr>
<tr>
<td>● Lymphoma ..........................</td>
<td>Development Credits .....................</td>
<td>Page 55</td>
</tr>
<tr>
<td>● Myeloma ..........................</td>
<td>............................................</td>
<td></td>
</tr>
</tbody>
</table>

Biomarkers - MD Anderson Approved

Copyright 2017 The University of Texas MD Anderson Cancer Center

Approved by the Executive Committee of the Medical Staff on 12/13/2016
## Biomarkers - MD Anderson Approved

These guidelines have been specifically developed for MD Anderson and are not intended to replace the independent medical or professional judgment of physicians or other health care providers.

<table>
<thead>
<tr>
<th>DISEASE SITE</th>
<th>CELL TYPE</th>
<th>FISH</th>
<th>IMMUNOHISTOCHEMISTRY</th>
<th>MOLECULAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>Glioma</td>
<td>1p/19q co-deletion</td>
<td>EGFR</td>
<td>MGMT promoter methylation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PTEN</td>
<td>IDH1 mutation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>BRAF V600E</td>
<td>IDH2 mutation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PIK3CA mutation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BRAF mutation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PTEN mutation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>EGFR mutation</td>
</tr>
<tr>
<td></td>
<td>Primitive Neuroectodermal Tumors/</td>
<td>MYC</td>
<td></td>
<td>CTNNB1</td>
</tr>
<tr>
<td></td>
<td>Medulloblastoma</td>
<td></td>
<td></td>
<td>PDGFRA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MET mutation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>FGFR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TP53</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CDKN2A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NF1</td>
</tr>
<tr>
<td>Breast</td>
<td>All invasive Cancer types</td>
<td>HER2/neu&lt;sup&gt;1&lt;/sup&gt;</td>
<td>ER&lt;sup&gt;1, 2&lt;/sup&gt;</td>
<td>ESR1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PR&lt;sup&gt;1, 2&lt;/sup&gt;</td>
<td>FGFR1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ki-67 (MIB-1) labeling index&lt;sup&gt;2&lt;/sup&gt;</td>
<td>MammaPrint</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HER2/neu&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Oncotype DX</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PIK3CA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TP53</td>
</tr>
</tbody>
</table>

1 For DCIS specimens, ER and PR should be performed on the final surgical specimen and not the core biopsy since there may be invasive cancer in the surgical specimen in which case all biomarkers should be done on the invasive cancer (ER, PR, HER2/neu, Ki-67). If no invasive cancer seen, then ER and PR should be preformed on the DCIS specimen.

2 For metastatic breast cancer cases, ER, PR, HER2/neu and Ki-67 should be obtained if ordered by the requesting physician as clinically indicated.

3 HER2/neu by FISH will only be performed if a 2+ or greater result is obtained by HER2/neu IHC, or in select 1+ IHC results as judged by the pathologist on the case, or if requested by the ordering or treating physicians as clinically indicated.

Department of Clinical Effectiveness V3
Approved by the Executive Committee of the Medical Staff on 12/13/2016
<table>
<thead>
<tr>
<th>DISEASE SITE</th>
<th>CELL TYPE</th>
<th>FISH</th>
<th>IMMUNOHISTOCHEMISTRY</th>
<th>MOLECULAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine</td>
<td>Papillary Thyroid Carcinoma (all variants)</td>
<td>BRAF V600E</td>
<td></td>
<td>BRAF mutation, KRAS mutation, HRAS mutation, NRAS mutation, PIK3CA mutation</td>
</tr>
<tr>
<td></td>
<td>Follicular Thyroid Carcinoma / Hurthle Cell (oxyphilic) Thyroid Carcinoma</td>
<td>PTEN</td>
<td></td>
<td>KRAS mutation, HRAS mutation, NRAS mutation, PIK3CA mutation</td>
</tr>
<tr>
<td></td>
<td>Medullary Thyroid Carcinoma</td>
<td></td>
<td></td>
<td>RET mutation, KRAS mutation, HRAS mutation, NRAS mutation</td>
</tr>
<tr>
<td></td>
<td>Anaplastic Thyroid Carcinoma</td>
<td>PTEN</td>
<td></td>
<td>BRAF mutation, KRAS mutation, HRAS mutation, NRAS mutation, PIK3CA mutation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BRAF V600E</td>
<td></td>
<td>BRAG mutation, KRAS mutation, HRAS mutation, NRAS mutation, PIK3CA mutation</td>
</tr>
<tr>
<td></td>
<td>Adrenocortical Carcinoma</td>
<td>Ki-67 (MIB-1) labeling index</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Parathyroid Carcinoma</td>
<td>Ki-67 (MIB-1) labeling index</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pituitary Carcinoma</td>
<td>Ki-67 (MIB-1) labeling index, p53</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### BIOMARKER

<table>
<thead>
<tr>
<th>DISEASE SITE</th>
<th>CELL TYPE</th>
<th>FISH</th>
<th>IMMUNOHISTOCHEMISTRY</th>
<th>MOLECULAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastro-Intestinal</td>
<td>Stomach &amp; Esophagogastric Junction Adenocarcinoma</td>
<td>• HER2/neu</td>
<td>• HER2/neu</td>
<td>• Microsatellite Instability (MSI) by PCR</td>
</tr>
</tbody>
</table>
| | | • MET | | • MLH1 promoter hypermethylation analysis and BRAF mutation analysis (only if immunohistochemistry for DNA mismatch repair enzymes has already been performed and shows loss of MLH1)
| | | | | • KRAS mutation
| | | | | • BRAF mutation
| | | | | • NRAS mutation
| | | | | • PIK3CA mutation
| | Colorectal Adenocarcinoma | • HER2/neu | | • Microsatellite Instability (MSI) by PCR |
| | Small Intestinal Adenocarcinoma | | | • MLH1 promoter hypermethylation analysis and BRAF mutation analysis (only if immunohistochemistry for DNA mismatch repair enzymes has already been performed and shows loss of MLH1)
| | Appendiceal Adenocarcinoma | | | • KRAS mutation
| | PMP (Pseudomyxoma Peritonei) | | | • BRAF mutation
| | | | | • NRAS mutation
| | | | | • PIK3CA mutation
| | | | | • 18q LOH
| | | | | • MGMT methylation
| | | | | • RB1 mutation
| | | | | • TP53 mutation
| | | | | • TSC2 mutation
| Anal Carcinoma | | | • ATRX | • Microsatellite Instability (MSI) by PCR |
| | | | | • MGMT methylation
| | | | | • PTEN mutation
| | | | | • RB1 mutation
| | | | | • TP53 mutation
| | | | | • TSC2 mutation
| Neuroendocrine | | • TTF1 | • ATRX | • Microsatellite Instability (MSI) by PCR |
| | | • CDX2 | • CgA | • MLH1 methylation performed based on MSI |
| | | • Ki-67 (MIB-1) labeling index | • MENIN | • MLH1 methylation performed based on MSI and immunohistochemistry results |
| | | • DAXX | | • BRAF sequencing (V600E) if applicable for Colon (only) |
| Hepatic Adenoma | | | | CTNNB1 (β-catenin) mutation |
| Hepatocellular | MET | MET | | |
| Lynch Syndrome | | • Microsatellite Instability (MSI) (MLH1, MSH2, MSH6, PMS2) | • Microsatellite Instability (MSI) by PCR |
| | | MLH1 methylation performed based on MSI | | • MLH1 methylation performed based on MSI and immunohistochemistry results |
| | | • BRAF | | • BRAF sequencing (V600E) if applicable for Colon (only) |

¹ HER2/neu by FISH will only be performed if a 2+ or greater result is obtained by HER2/neu IHC.
### Genitourinary

#### Urothelial Carcinoma

- **HER2/neu**
- **Immunohistochemistry for DNA mismatch repair enzymes (MLH1, MSH2, MSH6, PMS2)**
  - Note: **MLH1** promoter hypermethylation analysis will also be performed if immunohistochemistry shows loss of **MLH1** and if sufficient tumor DNA is available for analysis.
  - **CK20**
  - **CK5/6**
  - **GATA3**
  - **MTAP**

#### MOLECULAR
- **BRAF** mutation
- **CDKN2A** mutation
- **FGFR1** mutation
- **FGFR3** mutation
- **KRAS** mutation
- **MTOR** mutation
- **MLH1** promoter hypermethylation analysis (only if immunohistochemistry for DNA mismatch repair enzymes has already been performed and shows loss of **MLH1**)
- **Microsatellite Instability (MSI)** by PCR

#### FISH
- **PTEN**
- **RB1**
- **TP53**

### Prostate

- **PSA**
- **AR**
- **RB**

### Testicular, Suspected Testicular

- **β HCG**
- **AFP**

### Lynch Syndrome

- **Microsatellite Instability (MSI)** (MLH1, MSH2, MSH6, PMS2)
- **MLH1** methylation performed based on MSI
- **BRAF**

- **Microsatellite Instability (MSI)** by PCR
- **MLH1** methylation performed based on MSI and immunohistochemistry results
## DISEASE SITE

### Gynecology

<table>
<thead>
<tr>
<th>CELL TYPE</th>
<th>FISH</th>
<th>IMMUNOHISTOCHEMISTRY</th>
<th>MOLECULAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovarian and Uterine Carcinoma</td>
<td>HER2/neu</td>
<td>HER2/neu, ER/PR, MSI (MLH1, MSH2, MSH6, PMS2), PTEN</td>
<td>Microsatellite Instability (MSI) by PCR, MLH1 promoter hypermethylation if applicable, KRAS mutation, BRAF mutation, TP53 mutation, PIK3CA mutation, AKT1 mutation, PTEN mutation</td>
</tr>
<tr>
<td>Lynch Syndrome</td>
<td></td>
<td>Microsatellite Instability (MSI) (MLH1, MSH2, MSH6, PMS2), MLH1 methylation performed based on MSI</td>
<td>Microsatellite Instability (MSI) by PCR, MLH1 methylation performed based on MSI and immunohistochemistry results</td>
</tr>
</tbody>
</table>

### Head and Neck

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>BIOMARKER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oropharynx Carcinoma</td>
<td>HPV for high risk (in situ hybridization)</td>
</tr>
<tr>
<td>Nasopharynx Carcinoma</td>
<td>HPV low risk (in situ hybridization)</td>
</tr>
<tr>
<td>Oral Cavity Carcinoma</td>
<td>HPV low risk (in situ hybridization)</td>
</tr>
<tr>
<td>Salivary Carcinoma</td>
<td>HER2/neu, KIT, EGFR, Androgen Receptor</td>
</tr>
<tr>
<td>Unknown Primary Carcinoma metastatic to cervical lymph node</td>
<td>Epstein-Barr Virus (in situ hybridization), HPV high risk (in situ hybridization), p16</td>
</tr>
<tr>
<td>BIOMARKER</td>
<td>CELL TYPE</td>
</tr>
<tr>
<td>-----------</td>
<td>-----------</td>
</tr>
<tr>
<td>Melanoma</td>
<td>Cutaneous</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acral</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mucosal</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Uveal</td>
</tr>
<tr>
<td></td>
<td>Unknown Primary</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Sarcoma</td>
<td>Neuroblastoma</td>
</tr>
<tr>
<td></td>
<td>Desmoid Fibromatosis</td>
</tr>
<tr>
<td></td>
<td>Soft Tissue and Bone</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal Stromal Tumor</td>
</tr>
<tr>
<td>DISEASE SITE</td>
<td>CELL TYPE</td>
</tr>
<tr>
<td>-------------------</td>
<td>----------------------------</td>
</tr>
<tr>
<td>Thoracic</td>
<td>Non Small Cell Lung Carcinoma</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown Primary</td>
<td>Breast, Gastric Profile</td>
</tr>
<tr>
<td></td>
<td>Lung Profile</td>
</tr>
<tr>
<td></td>
<td>Small Bowel, Colon Profile</td>
</tr>
<tr>
<td>DISEASE SITE</td>
<td>DIAGNOSIS</td>
</tr>
<tr>
<td>---------------------</td>
<td>----------------------------------------</td>
</tr>
</tbody>
</table>
| Leukemia            | ALL - New Patient Work-up for all patients | ● Conventional chromosome analysis  
 ● FISH - t(9;22) BCR/ABL1  
 ● FISH - MYC (8q24) | ● IGH clonality  
 ● TCRB clonality  
 ● TCGR clonality  
 ● t(9;22) BCR/ABL1  
   Major (p210; b2a2/e13a2, b3a2/e14a2)  
   Minor (p190; e1a2)  
 ● Multiplex PCR=|t(4;11), t(1;19), t(6;9), t(12;21),  
   t(9;22), t(15;17), t(8;21), inv(16)/t(16;16)  
 ● Ph-Like ALL Fusion Multiplex Panel (ABL1, JAK2, Kinase: ABL2, PDGFRB, CSF1R, TYK2, NTRK3) |
|                     | ALL - Peripheral Blood (Similar to Marrow) | FISH - MYC                                       | • ABL1 gene mutation (kinase domain) qualitative  
 • ABL1 gene mutation p.T315I quantitative  
 • TP53 mutation  
 • JAK2 mutation  
 • KRAS mutation  
 • NRAS mutation |
|                     | ALL - T Lineage                         | Conventional chromosome analysis                  | ● TCRB clonality  
 ● TCGR clonality                                      |
|                     | ALL – Philadelphia Negative             | Conventional chromosome analysis                  | ● TCRB clonality  
 ● TCGR clonality  
 ● IGH clonality                                      |
|                     | ALL – Philadelphia Positive             | ● Conventional chromosome analysis  
 ● FISH - t(9;22) BCR/ABL1 | ● TCRB clonality  
 ● TCRG clonality  
 ● IGH clonality  
 ● t(9;22) BCR/ABL1  
   Major (p210; b2a2/e13a2, b3a2/e14a2)  
   Minor (p190; e1a2)  
 ● ABL1 gene mutation (kinase domain) qualitative  
 ● ABL1 gene mutation p.T315I quantitative |
|                     | ALL - Relapsed                          |                                                 | Ph-Like ALL Fusion Multiplex Panel (ABL1, JAK2, Kinase: ABL2, PDGFRB, CSF1R, TYK2, NTRK3)  
 • JAK 1 and JAK2 Targeted Mutation Analysis |

KEY = ALL: acute lymphocytic/lymphoblastic leukemia  
AML/MDS: acute myelogenous leukemia /myelodysplastic syndrome
<table>
<thead>
<tr>
<th>DISEASE SITE</th>
<th>DIAGNOSIS</th>
<th>CYTOGENETICS</th>
<th>MOLECULAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemia – continued</td>
<td>AML/MDS</td>
<td>Conventional chromosome analysis</td>
<td>FLT3, EZH2, KIT (exon 17), MPL, NRAS, KRAS, IDH1, IDH2, NPM1, JAK2, DNMT3A, aCGH panel (chr 5, 7, 8, 17, 20)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>APL</td>
<td>Conventional chromosome analysis, FISH – PML/RARA t(15:17)</td>
<td>t(15:17) PML/RARA, FLT3, KIT (exon 17), KRAS, NPM1, NRAS, TP53</td>
</tr>
<tr>
<td></td>
<td>APL – Peripheral Blood</td>
<td>FISH – PML/RARA t(15:17)</td>
<td>t(15:17) PML/RARA</td>
</tr>
<tr>
<td></td>
<td>Aplastic Anemia</td>
<td></td>
<td>TCRB clonality (TCR-BETA chain gene), TCRG clonality (TCR-gamma chain gene)</td>
</tr>
<tr>
<td></td>
<td>Burkitt Leukemia</td>
<td>Conventional chromosome analysis, FISH - MYC</td>
<td>IGH clonality, TP53</td>
</tr>
<tr>
<td></td>
<td>Burkitt Leukemia Peripheral Blood</td>
<td>FISH - MYC</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CLL - Peripheral Blood with or without Bone Marrow</td>
<td>Conventional chromosome analysis, FISH – CLL Panel</td>
<td>Somatic Hypermutation, Mutation Analysis for (EndCLL Assay V1): ATM, BTK, PLG2, TP53, BIRC3, NOTCH1, SF3B1, IGH Clonality, aCGH panel (chr 5, 7, 8, 17, 20)</td>
</tr>
</tbody>
</table>

**KEY:**
- APL: acute promyelocytic leukemia
- CLL: chronic lymphoblastic leukemia

These guidelines have been specifically developed for MD Anderson and are not intended to replace the independent medical or professional judgment of physicians or other health care providers.

Copyright 2017 The University of Texas MD Anderson Cancer Center

Approved by the Executive Committee of the Medical Staff on 12/13/2016
### Leukemia – continued

<table>
<thead>
<tr>
<th>DISEASE SITE</th>
<th>DIAGNOSIS</th>
<th>CYTOGENETICS</th>
<th>MOLECULAR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CML</strong></td>
<td>Conventional chromosome analysis</td>
<td></td>
<td><strong>ABL1</strong> gene mutation (kinase domain) qualitative</td>
</tr>
<tr>
<td></td>
<td>FISH – BCR/ABL1 t(9;22)</td>
<td></td>
<td><strong>ABL1</strong> gene mutation p.T315I quantitative</td>
</tr>
<tr>
<td><strong>CML - Peripheral Blood</strong></td>
<td>FISH – BCR/ABL1 t(9;22)</td>
<td></td>
<td><strong>ABL1</strong> gene mutation (kinase domain) qualitative</td>
</tr>
<tr>
<td></td>
<td>Conventional chromosome analysis</td>
<td></td>
<td><strong>ABL1</strong> gene mutation p.T315I quantitative</td>
</tr>
<tr>
<td><strong>CML – Blast Phase</strong></td>
<td>Conventional chromosome analysis</td>
<td><strong>t(9;22) BCR/ABL1</strong> Major (p210; b2a2/e13a2, b3a2/e14a2) Minor (p190; e1a2)</td>
<td><strong>ABL1</strong> gene mutation p.T315I quantitative</td>
</tr>
<tr>
<td><strong>CMML</strong></td>
<td>Conventional chromosome analysis</td>
<td><strong>t(9;22) BCR/ABL1</strong> Major (p210; b2a2/e13a2, b3a2/e14a2) Minor (p190; e1a2)</td>
<td><strong>ABL1</strong> gene mutation p.T315I quantitative</td>
</tr>
<tr>
<td><strong>Hairy Cell Leukemia</strong></td>
<td>Conventional chromosome analysis</td>
<td><strong>IGH</strong> clonality Exon 17</td>
<td><strong>KIT</strong> exon 17</td>
</tr>
<tr>
<td><strong>HES, Mastocytosis</strong></td>
<td>Conventional chromosome analysis</td>
<td>Somatic Hypermutation</td>
<td><strong>BRAF</strong></td>
</tr>
<tr>
<td><strong>MPN</strong></td>
<td>Conventional chromosome analysis</td>
<td><strong>TCRG</strong> clonality</td>
<td><strong>KIT</strong> p.D816V for mast cell disease (Hypereosinophilic Syndrome)</td>
</tr>
</tbody>
</table>

**KEY**
- CML: chronic myeloid leukemia
- HES: hypereosinophilic syndrome
- CMML: chronic myelomonocytic leukemia
- MPN: myeloproliferative neoplasms
### Biomarkers - MD Anderson Approved

These guidelines have been specifically developed for MD Anderson and are not intended to replace the independent medical or professional judgment of physicians or other health care providers.

<table>
<thead>
<tr>
<th>DISEASE SITE</th>
<th>DIAGNOSIS</th>
<th>CYTOGENETICS</th>
<th>MOLECULAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemia – continued</td>
<td>MF - Peripheral Blood</td>
<td>Conventional chromosome analysis</td>
<td>JAK2, MPL</td>
</tr>
<tr>
<td></td>
<td>PV, ET, MF</td>
<td>t(9,22) BCR/ABL1, JAK2, CALR</td>
<td>MPL, ASXL1, TET2, EZH2</td>
</tr>
<tr>
<td></td>
<td>T Cell Disorders - Peripheral Blood</td>
<td>EBV</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T Cell Disorders</td>
<td>Conventional chromosome analysis, TCRB clonality, TCRG clonality</td>
<td></td>
</tr>
<tr>
<td>Lymphoma</td>
<td>Burkitt Lymphoma</td>
<td>Conventional chromosome analysis, IGH clonality, TP53</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Burkitt Lymphoma Peripheral Blood</td>
<td>FISH - MYC</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diffuse Large B-Cell Lymphoma</td>
<td>TP53, EZH2 (codon 646), MYD88 (codon 265), CARD11, CD79A, CD79B</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mantle Cell Lymphoma</td>
<td>NOTCH1 – Exons 26, 27, 34, TP53</td>
<td></td>
</tr>
<tr>
<td>Myeloma</td>
<td>Plasma Cell Myeloma</td>
<td>KRAS mutation, BRAF mutation, FGFR3 mutation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Waldenstrom’s Macroglobulinemia</td>
<td>MYD88 (codon 265), CXCR4</td>
<td></td>
</tr>
</tbody>
</table>

**KEY** = MF: Mycosis fungoides  PV: Polycythemia Vera  ET: Essential thrombocytopenia
Biomarkers - MD Anderson Approved

These guidelines have been specifically developed for MD Anderson and are not intended to replace the independent medical or professional judgment of physicians or other health care providers.

SUGGESTED READINGS

Breast

Immunohistochemistry/ER and Immunohistochemistry/PR:


Immunohistochemistry/Ki67:

Immunohistochemistry/HER2/NEU and Immunohistochemistry/FISH/HER2/NEU:


Continued on next page
Breast - continued

**Molecular/ESR1:**


**Molecular/FGFR1:**


Continued on next page
Biomarkers - MD Anderson Approved

These guidelines have been specifically developed for MD Anderson and are not intended to replace the independent medical or professional judgment of physicians or other health care providers.

SUGGESTED READINGS - continued

Breast – continued

Molecular/MammaPrint:


Molecular/Oncotype:


Molecular/PIK3CA:


Department of Clinical Effectiveness V3
Approved by the Executive Committee of the Medical Staff on 12/13/2016
Biomarkers - MD Anderson Approved

These guidelines have been specifically developed for MD Anderson and are not intended to replace the independent medical or professional judgment of physicians or other health care providers.

**Breast – continued**

**Molecular/TP53:**


**Endocrine**

**Adrenocortical Neoplasm**

**Immunohistochemistry/Ki67:**


**Medullary Thyroid Carcinoma**

**Molecular/RET mutation status:**


**Molecular/HRAS KRAS & NRAS mutation status:**


Sherman et al. (2013). Demonstrating patients with somatic RAS or RET mutation in MTC have better response to TKI therapy with cabozantinib than those lacking mutations. *ASCO* presentation #6000.

*SUGGESTED READINGS - continued*

*Continued on next page*
These guidelines have been specifically developed for MD Anderson and are not intended to replace the independent medical or professional judgment of physicians or other health care providers.

**Endocrine – continued**

**Papillary, Follicular, Anaplastic Thyroid Carcinoma**

**Molecular/BRAF:**


**Immunohistochemistry/PTEN:**


**Molecular/KRAS HRAS NRAS:**


CMS SUPERSEDED Local Coverage Determination (LLCD): [https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=35396&ContrId=338&ver=20&ContrVer=1&Keyword=biomarker&KeywordSearchType=Or&PolicyType=Both&ArticleType=SAD%7cEd&Cntrrt=338*1&Date=&KeyWordLookUp=Doc&SearchType=Advanced&CoverageSelection=Both&q=true&bc=IAAAABAAAAAAA%3d%3d&](https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=35396&ContrId=338&ver=20&ContrVer=1&Keyword=biomarker&KeywordSearchType=Or&PolicyType=Both&ArticleType=SAD%7cEd&Cntrrt=338*1&Date=&KeyWordLookUp=Doc&SearchType=Advanced&CoverageSelection=Both&q=true&bc=IAAAABAAAAAAA%3d%3d&)

**SUGGESTED READINGS - continued**

---

Continued on next page
These guidelines have been specifically developed for MD Anderson and are not intended to replace the independent medical or professional judgment of physicians or other health care providers.

**Endocrine – continued**

**Papillary, Follicular, Anaplastic Thyroid Carcinoma**

**Molecular/PK3CA:**


**SUGGESTED READINGS - continued**

**Parathyroid Carcinoma**

**Immunohistochemistry/Ki67:**


**Pituitary Neoplasm**

**Immunohistochemistry/Ki67:**


**Immunohistochemistry/p53:**


**Continued on next page**
Gastrointestinal

Stomach and Esophagogastric Junction Adenocarcinoma

Immunohistochemistry/HER2/neu and FISH/HER2/neu:


Small Intestinal Adenocarcinoma

Immunohistochemistry/DNA mismatch repair enzymes and Molecular/MSI PCR, MLH1 promoter methylation, KRAS, BRAF:

Small bowel and appendiceal adenocarcinoma may be treated with systemic chemotherapy according to the NCCN Guidelines for Colon Cancer. *NCCN Guidelines*, Version 3.2013, Colon Cancer, Page COL-1.


Colorectal Adenocarcinoma

Immunohistochemistry/IHC mmr enzymes and Colorectal Adenocarcinoma/Molecular/MSI PCR:


The panel recommends that MMR protein testing be performed for all patients younger than 50 years old with colon cancer, based on an increased likelihood of Lynch syndrome in this population. MMR testing should also be considered for all patients with stage II disease, because stage II MSH-H patients may have a good prognosis and do not benefit from 5-FU adjuvant therapy. *NCCN Guidelines*, Version 3.2013, Colon Cancer, Page COL-A 4 of 5.


Continued on next page
These guidelines have been specifically developed for MD Anderson and are not intended to replace the independent medical or professional judgment of physicians or other health care providers.

Gastrointestinal - continued

Colorectal Adenocarcinoma

Molecular/KRAS:

Molecular/BRAF:

Carcinoma of the Anal Canal

Immunohistochemistry/p16:

Immunohistochemistry/HPV:

Continued on next page
Gastrointestinal - continued

Neuroendocrine

Immunohistochemistry/TTF:


Immunohistochemistry/CDX2:


Immunohistochemistry/Ki67:


Molecular/18Q LOH:

Continued on next page
**Biomarkers - MD Anderson Approved**

These guidelines have been specifically developed for MD Anderson and are not intended to replace the independent medical or professional judgment of physicians or other health care providers.

**Gastrointestinal – continued**

**Neuroendocrine**

**MGMT Methylation:**

**Immunohistochemistry/DAXX, ATRX:**


**DAXX, ATRX, MEN1, PIK3CA, TSC2:**

**Immunohistochemistry/MEN1:**

**Molecular/PTEN, TSC2:**

**TP53:** Liu et al., *Asian Pac J Cancer Prev*. 2013;14(1):419-22

**Pseudomyxoma Peritonei**

**Molecular/1KRAS:**

*SUGGESTED READINGS - continued*
### Genitourinary/Urology

#### Hepatic Adenoma

**Molecular/Beta Catenin:**

#### Prostate

**Immunohistochemistry/PSA:**

**Immunohistochemistry/PAP:**

**Immunohistochemistry/CgA:**

**Molecular/RB1, TP53, PTEN, AR:**

**Molecular/RB1, TP53, AR:**

**Molecular/RB1, TP53:**

**Use of platinum-based chemotherapy in aggressive variant prostate carcinomas:**

*Continued on next page*
GU/Urology – continued

Testicular, Suspected Testicular

Immunohistochemistry/βHCG and AFP:

Upper Urinary Tract and Renal Pelvis Urothelial Carcinoma

FISH/HER2/neu:

Immunohistochemistry and Molecular/MSI panel and MLH1 promoter methylation assay and PCR based MSI testing:

SUGGESTED READINGS - continued
Gynecology

Ovarian and Uterine

**FISH/Her2/neu:**


Continued on next page
Gynecology – continued

Ovarian and Uterine

Immunohistochemistry/Her2/neu:


Continued on next page
Ovarian and Uterine

Immunohistochemistry/MSI:


Murphy, M. A., & Wentzensen, N. (2011). Frequency of mismatch repair deficiency in ovarian cancer: a systematic review This article is a US Government work and, as such, is in the public domain of the United States of America. *International Journal of Cancer*, 129(8), 1914-1922. doi: http://dx.doi.org/10.1002/ijc.25835.


Continued on next page
These guidelines have been specifically developed for MD Anderson and are not intended to replace the independent medical or professional judgment of physicians or other health care providers.

SUGGESTED READINGS - continued

Gynecology - continued

Ovarian and Uterine

Immunohistochemistry/PTEN:


Continued on next page
Gynecology - continued

Ovarian and Uterine

Molecular/BRAF:


Continued on next page
Gynecology - continued

Ovarian and Uterine

Molecular/KRAS:


Continued on next page
**Gynecology - continued**

**Ovarian and Uterine**

**Molecular/MLH1 promoter methylation:**


Continued on next page
These guidelines have been specifically developed for MD Anderson and are not intended to replace the independent medical or professional judgment of physicians or other health care providers.

**Gynecology - continued**

**Ovarian and Uterine**

**Molecular/MSI PCR:**


Continued on next page
**Ovarian and Uterine**

**Molecular/P13K AKT:**


Continued on next page
SUGGESTED READINGS - continued

Gynecology - continued

Ovarian and Uterine

Molecular/PTEN:


Continued on next page
Head and Neck
Oropharynx/Nasopharynx/Oral Cavity

HPV and P16:


Nasopharynx Cancer and Salivary Cancer

EBV and erB-2 and HER2/neu:


Salivary Cancer

c-kit and EGFR and Androgen Receptor:


SUGGESTED READINGS - continued
SUGGESTED READINGS - continued

ALL Burkitts

Cytogenetics/Multiplex PCR (all subtypes):


Molecular-Genetics (Overview):

Molecular-Genetics (Philadelphia negative - all types):

Molecular-Genetics (Philadelphia negative B-lineage):

Burkitt subtype (c-myc):

Philadelphia positive subtype (BCR-ABL1) - Overlap CML:

Continued on next page
Leukemia – continued

ALL Burkitts

Philadelphia positive subtype (Mutations) - Overlap CML:

IgH/TCR (all subtypes):

TP53 Mutations:
Chiaretti S, Brugnoletti F, Tavolaro, S et al. TP53 mutations are frequent in adult acute lymphoblastic leukemia cases negative for recurrent fusion genes and correlate with poor response to induction therapy. Haematologica 2013 May;98(5):e59-61

AML/MDS/CMML/Aplastic Anemia

Cytogenetics:

Continued on Next Page
**Biomarkers - MD Anderson Approved**

These guidelines have been specifically developed for MD Anderson and are not intended to replace the independent medical or professional judgment of physicians or other health care providers.

---

**Leukemia – continued**

**AML/MDS/CMML/Aplastic Anemia**

**Molecular/FLT3:**


**Molecular/DNMT3A:**


Continued on next page
AML/MDS/CMML/Aplastic Anemia

KIT:

IDH1/IDH2:

RAS:

Continued on next page
SUGGESTED READINGS - continued

LEUKEMIA – continued

AML/MDS/CMML/Aplastic Anemia

CEBPA:


NPM1:


JAK2/MPL:

Continued on next page
Additional CMML:

APL

Cyto/FISH:

FLT3:

KIT:
Leukemia – continued

IDH1/IDH2:

RAS:

NPM1:

Continued on next page
Biomarkers - MD Anderson Approved

These guidelines have been specifically developed for MD Anderson and are not intended to replace the independent medical or professional judgment of physicians or other health care providers.

SUGGESTED READINGS - continued

Leukemia – continued

CLL  Blood or bone marrow can be used for any of these tests. There are leukemia cells sampled by blood draw or bone marrow aspirate.

Metaphase karyotype:


FISH for 11q del, 17p del, +12, 13q del:


IGHV mutation status:


Continued on next page
SUGGESTED READINGS - continued

**Leukemia – continued**

**CLL**

**TP53 sequencing and ATM sequencing:**


**CML**


**Hairy Cell Leukemia**


*Continued on next page*
Leukemia – continued

HES, Mastocytosis, MF, PV, ET


T-Cell Disorders


Lymphoma

Diffuse Large B-Cell Lymphoma


Continued on next page
These guidelines have been specifically developed for MD Anderson and are not intended to replace the independent medical or professional judgment of physicians or other health care providers.

Lymphoma – continued

Mantle Cell


Melanoma


Continued on next page

SUGGESTED READINGS - continued
**Myeloma – continued**

**Plasma Cell**

**Neuro-Oncology**

**Diffuse Glioma**

**FISH/1p19q:**


**Immunohistochemistry/BRAF:**


**Immunohistochemistry/EGFR528:**


**Continued on next page**
Neuro-Oncology – continued

Diffuse Glioma

Molecular/IDH1/IDH2:
Capper, D., Sahm, F., Hartmann, C., et al. (2010). Application of mutant IDH1 antibody to differentiate diffuse glioma from nonneoplastic central nervous system lesions and therapy-induced changes. American Journal of Surgical Pathology, 34(8), 1199-1204. doi: http://dx.doi.org/10.1097/PAS.0b013e3181e7740d.

Continued on next page
These guidelines have been specifically developed for MD Anderson and are not intended to replace the independent medical or professional judgment of physicians or other health care providers.

**Neuro-Oncology – continued**

**Diffuse Glioma**

**Molecular/IDH1/Multigene predictor:**


**Molecular/PIK3CA:**


**Immunohistochemistry/PTEN:**


**Molecular/CIMP:**


Continued on next page
**Neuro-Oncology – continued**

**Low Grade Glioma**

**Molecular/BRAF:**


**Molecular/MGMT:**


**FISH/1p/19q:**


**SUGGESTED READINGS - continued**

Continued on next page
SUGGESTED READINGS - continued

**Sarcoma**

**Neuroblastoma**

**FISH/NMYC:**


**Desmoid fibromatosis**

**Molecular/CTNNBI:**


**Gastrointestinal stromal tumor**

**Molecular/CKIT and PDGFR:**


**Thoracic**

**Non Small Cell Lung Cancer**

**Immunohistochemistry/PD-L1 22C3:**


Continued on next page
Non Small Cell Lung Cancer

Molecular/EGFR:


Molecular/KRAS:


Continued on next page
SUGGESTED READINGS - continued

**Thoracic – continued**

**Non Small Cell Lung Cancer**

**Molecular/BRAF V600E:**


**Molecular/ELM4-ALK:**


**Molecular/BRAF V600E:**


Continued on next page
**Thoracic – continued**

**Non Small Cell Lung Cancer**

**FISH/ROS1:**


**FISH/Non Small Cell Lung Cancer/BRAF:**
This practice consensus document was reviewed in conjunction with disease site representatives listed below. It was approved by the Molecular Testing Evaluation Committee (MTEC) at the University of Texas MD Anderson Cancer Center. The information is updated at least every two years or as new evidence emerges and is presented to MTEC for review and approval.

MTEC Members, 2015:

- Aman U. Buzdar, MD: MTEC Co-Chair, Clinical Research
- Stanley R. Hamilton, MD: MTEC Co-Chair, Pathology/Laboratory Medicine
- Keith A. Baggerly, PhD: Bioinformatics and Computational Biology
- Russell Broaddus, MD, PhD: Pathology
- Ernest Hawk, MD: Cancer Prevention
- Dimitrios P. Kontoyiannis, MD: Infectious Diseases
- Scott Kopetz, MD, PhD: GI Medical Oncology
- Raja Luthra, PhD: Hematopathology
- Funda Meric-Bernstam, MD: Investigational Cancer Therapeutics
- Vali Papadimitrakopoulos, MD: Thoracic/Head & Neck Med Oncology
- Keyur Pravinchandra Patel, MD, PhD: Hematopathology
- Donald A. Podoloff, MD: Nuclear Medicine
- Victor A. Prieto, MD, PhD: Pathology
- Elizabeth Rebello, MD: Anesthesiology and Critical Care
- Ellen J. Schlette, MD: Hematopathology
- Kenna R. Shaw, PhD: Institute for Personalized Cancer Therapy
- Heath Skinner, MD, PhD: Radiation Oncology
- Stephen G. Swisher, MD: Surgery
- Robert J. Wells, MD: Pediatrics
- W.K. Alfred Yung, MD: Neuro-Oncology

Disease Site Representatives:

- Brain - W.K. Alfred Yung, MD
- Breast – Debub Tripathy, MD
- Endocrine – Steven I. Sherman, MD
- GI – Stanley R. Hamilton, MD
- GU – Suren Matin, MD
- Neema Navai, MD
- Gyn - Anil K. Sood, MD
- Head & Neck – Randal S. Weber, MD
- Leukemia – William G. Wierda, MD
- Lymphoma – William G. Wierda, MD

Pauline Koinis, BSMT - Clinical Effectiveness Development Team

These guidelines have been specifically developed for MD Anderson and are not intended to replace the independent medical or professional judgment of physicians or other health care providers.