Multiple Myeloma by FISH

Multiple myeloma (MM) is a plasma cell dyscrasia that can evolve from a premalignant monoclonal gammopathy. Prognosis often depends on the presence or absence of particular genetic markers. Fluorescence in situ hybridization (FISH) testing for relevant markers should be performed upon diagnosis and in low-risk individuals at time of relapse to aid in risk stratification.1

TEST DESCRIPTION

Plasma cells are isolated from a bone marrow (BM) aspirate using CD138+ microbeads. CD138+ cells (plasma cells) are then analyzed by FISH using specific probes for the following:

- **CCND1/IGH** fusion t(11;14)
- **CKS1B** (1q gain)
- **IGH** rearrangement (14q32)
- **ASS1** (+9)
- **PML** (+15)
- **TP53** (17p deletion)

If IGH rearrangement detected does not involve CCND1, additional probes are added:

- **FGFR3/IGH** fusion t(4;14)
- **MAF/IGH** fusion t(14;16)

DISEASE OVERVIEW

Incidence
1.8% of all cancers in the U.S.2

Age of Onset
Most frequently diagnosed between ages 65 and 74 years (median age 69 years)2

Symptoms
Presenting clinical features include symptoms of1,2:

- Hypercalcemia
- Impaired renal function
- Anemia
- Bone disease (lesions)

FISH Testing and Prognostic Issues

Abnormalities are detected by conventional cytogenetics in ~30% of MMs. FISH testing increases this number to >90%.1 Cytogenetic abnormalities affect the prognosis of patients with MM. Because most genetic subtypes in MM are primary, ploidy state, IGH translocation, and genetic status need only be assessed once at diagnosis. However, repeat testing is justified in cases of gain/amplification of CKS1B (1q21) and deletion of TP53 (17p13), as these markers occur in disease progression and confer a worse prognosis.1,3

<table>
<thead>
<tr>
<th>Genetic Markers and Resulting Prognostic Issues</th>
<th>Characteristics and Prognostic Value</th>
<th>Recurrent Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Cytogenetic Abnormalities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperdiploidy</td>
<td>Presence: 40-60% of MM1,4</td>
<td>Test only once</td>
</tr>
<tr>
<td>Usually gains (trisomies) of three or more odd-numbered chromosomes (3, 5, 7, 9, 11, 15, 19, 21)1</td>
<td>Standard risk1</td>
<td></td>
</tr>
<tr>
<td>Infrequently occurs with IGH translocations1,4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Panel tests most commonly gained chromosomes (9, 11, 15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>14q32 (IGH) rearrangement</strong></td>
<td>Presence: 45-70% of MM1</td>
<td>Test only once</td>
</tr>
<tr>
<td>7 major oncogenes involved: 11q13 [CCND1], 16q23 [MAF], 4p16 [FGFR3/MMSET], 6p21 [CCND3], 20q11 [MAF8], 8q24 [MAFA], 12p13 [CCND2]</td>
<td>Prognosis varies depending on translocation partner:</td>
<td></td>
</tr>
<tr>
<td>Main translocations are t(11;14), t(4;14), t(14;16), and t(14:20)2</td>
<td>t(11;14)/q13;q14</td>
<td>Generally associated with poor prognosis</td>
</tr>
<tr>
<td>t(4;14)(p16;q32) IGH-FGFR3/MMSET1</td>
<td>Presence: 5% of MM1,3</td>
<td>Test only once</td>
</tr>
<tr>
<td>High to intermediate risk3,4</td>
<td>Detectable only by FISH (cytogenetically cryptic)</td>
<td></td>
</tr>
</tbody>
</table>
### Secondary Cytogenetic Abnormalities

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Characteristics and Prognostic Value</th>
<th>Recurrent Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>t(11;14)(q13;q32) IGH-CCND1</td>
<td>Presence: 15% of MM&lt;br&gt;Standard risk</td>
<td>3 Test only once</td>
</tr>
<tr>
<td>t(14;16)(q32;q23) IGH-MAF</td>
<td>Presence: 5% of MM&lt;br&gt;High risk</td>
<td>3 Test only once</td>
</tr>
<tr>
<td>Gain/amplification of 1q21 (CKS1B)</td>
<td>Presence: 30-70% of MM&lt;br&gt;Presence higher in disease progression&lt;br&gt;High risk&lt;br&gt;May be observed in hypodiploid, hyperdiploid, and IGH translocation-positive MM&lt;br&gt;Confers a poor prognosis in all subtypes</td>
<td>4, 5 Repeat testing justified</td>
</tr>
<tr>
<td>Deletion 17p (TP53)</td>
<td>Presence: 5-10% of MM&lt;br&gt;Presence higher in disease progression&lt;br&gt;High risk&lt;br&gt;May be observed in hypodiploid, hyperdiploid, and IGH translocation-positive MM&lt;br&gt;Confers a poor prognosis in all subtypes</td>
<td>1, 4 Repeat testing justified</td>
</tr>
</tbody>
</table>

### TEST INTERPRETATION

**Analytical Sensitivity/Specificity**

>95%

**Results**

- Abnormal: gain/loss/rearrangement/translocation detected; percentage of cells affected (out of 200) reported
- Normal: no evidence of gains, deletions, rearrangements, or translocations of loci tested

**Limitations**

Only detects aberrations specific to probes used

### REFERENCES


### RELATED INFORMATION

- Plasma Cell Dyscrasias
- Plasma Cell Dyscrasias Testing Algorithm

### RELATED TESTS

- Chromosome Analysis, Bone Marrow 2002292
  Method: Giemsa Band
- Chromosome FISH, Multiple Myeloma Panel Process and Hold 2006270
  Method: Cell culture/Fluorescence in situ Hybridization