**IGH-CCND1 Fusion, t(11;14) by FISH**

**Indications for Ordering**
Diagnosis of mantle cell lymphoma (MCL) particularly when individual presents with
- Atypical morphology
- Aberrant immunophenotype
- Unusual clinical presentation
- Equivocal cyclin D1 staining

**Test Description**
Cyclin D1
- Immunohistochemistry

**IGH-CCND1 Fusion, t(11;14) by FISH**
- Fluorescence in situ hybridization (FISH)
- Dual color, dual fusion probes detect t(11;14)

**Tests to Consider**

**Typical Testing Strategy**
Lymph node biopsy with morphologic and immunohistochemical evaluation
- Cyclin D1
  - Surrogate marker for t(11;14)
  - Present in 97% of MCL cases
Leukemia/lymphoma phenotyping by flow cytometry
- CD5+, CD10- in combination with bright CD20, CD23-, and high light-chain intensity suggests MCL
Detect cytogenetic abnormalities, if necessary
- IGH-CCND1 fusion, t(11;14) by FISH
Bone marrow (BM) evaluation for staging
Chromosome analysis – sometimes necessary

**Primary Tests**
**Cyclin D1, SP4 by Immunohistochemistry 2003842**
- Diagnosis of MCL in conjunction with morphology and immunohistochemical studies
- Formalin-fixed, paraffin-embedded (FFPE) tissue specimens only

**IGH-CCND1 Fusion, t(11;14) by FISH 3001306**
- Aid in diagnosis of MCL if cyclin testing is noninformative
- FFPE tissue specimens

**Related Tests**
- **Leukemia/Lymphoma Phenotyping by Flow Cytometry 2008003**
  - Aid in evaluation of hematopoietic neoplasms
  - Monitor therapy in patients with established diagnosis of hematopoietic neoplasms
- **Chromosome FISH, Interphase 2002298**
  - Specific FISH probe for t(11;14)(q13;q32) must be requested
  - Fresh tissue specimens only
- **Chromosome Analysis, Bone Marrow 2002292**
  - Diagnosis, prognosis, and monitoring of hematopoietic neoplasms (eg, lymphoma in BM)
- **Chromosome Analysis, Solid Tumor 2002296**
  - May identify additional, useful cytogenetic abnormalities in tissues that are not targeted by FISH assays

**Disease Overview**
**Incidence** – 3-10% of all non-Hodgkin B-cell lymphomas

**Symptoms**
- Majority present at advanced stage
- Lymphadenopathy – usually widespread
- Extranodal sites most commonly include
  - Gastrointestinal tract
  - Waldeyer’s ring

**Diagnostic Criteria**
- Morphology
  - Small- to medium-sized lymphoid cells with irregular nuclear contours (centrocyte-like) with dispersed chromatin and inconspicuous nuclei
  - Nodular, diffuse, mantle zone pattern has been described
  - Associated hyalinized small vessels are common
- Flow cytometry immunoprofile
  - Bright CD20, monoclonal light chains, CD5+, CD10-, CD23-
- Immunohistochemistry
  - Cyclin D1 expression is present in the majority of cases
Diagnostic Issues
MCL is often diagnosed using combination of morphology, immunohistochemistry (cyclin D1), immunophenotyping, and clinical presentation
• Variants of MCL (small cell, marginal-zone-like) that phenotypically resemble other non-Hodgkin lymphomas, such as chronic lymphocytic leukemia/small lymphocytic lymphoma may present problems for diagnosis in atypical cases
  ○ *IGH-CCND1* fusion, t(11;14) FISH testing is most useful in this setting

Genetics
Gene – *IGH-CCND1*
Structure/Function
• The translocation juxtaposes the *CCND1* gene located on the long arm of chromosome 11 (q13) with the *IGH* gene located on the long arm of chromosome 14 (q32)
• *IGH-CCND1* fusion causes overexpression of cyclin D1
  ○ Overexpression is oncogenic and defines disease
• Cyclin D1 promotes cell division and growth

Test Interpretation
*IGH-CCND1* Fusion, t(11;14) by FISH
Sensitivity
• Analytical sensitivity – 20%
Results
• Positive – presence of the t(11;14) translocation supports a diagnosis of MCL
• Negative – absence of the t(11;14) translocation
Limitations
• *IGH-CCND1* Fusion, t(11;14) by FISH has not been validated for
  ○ Tissue fixed in alcohol-based or nonformalin fixatives
  ○ Decalcified tissue
• Negative result does not exclude the possibility of translocations involving other partners
• Variant is not specific for MCL
  ○ Results need to be analyzed in conjunction with morphology, immunohistochemistry, and immunophenotyping results