



May 10, 2018

Proposed Contact
Part B Policy
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RE: MoIDX: MDS FISH (DL37602)

Dear Dr. Almas,

Thank you for the opportunity to review and comment on Palmetto GBA's proposed coverage policy for MoIDX: MDS FISH (DL37602). The Association for Molecular Pathology (AMP) is an international medical and professional association representing approximately 2,300 physicians, doctoral scientists, and medical technologists who perform or are involved with laboratory testing based on knowledge derived from molecular biology, genetics, and genomics. Membership includes professionals from the government, academic medicine, private and hospital-based clinical laboratories, and the in vitro diagnostics industry.

As the world's largest organization of board-certified pathologists and leading provider of laboratory accreditation and proficiency testing programs, the College of American Pathologists (CAP) serves patients, pathologists, and the public by fostering and advocating excellence in the practice of pathology and laboratory medicine worldwide.

We are submitting joint comments because at this time both of our organizations share the same perspective regarding this draft LCD. We appreciate the effort that has gone into the creation of this proposed LCD, and we offer the following recommendations for Palmetto's consideration.

FISH testing detects alterations in 5-10% of cases negative by conventional karyotyping that inform diagnosis, prognosis, and/or therapy. In cases that are positive by conventional karyotyping, FISH testing detects additional alterations that may impact clinical management above and beyond those that are detected by conventional karyotyping alone.^{5,6,7,8}

FISH testing is utilized to monitor the patient's clinical course over time and there are many alterations that are required to establish a diagnosis of MDS or acute myeloid leukemia above and beyond the 4 probes referenced in the draft LCD. For example according to the 2016 WHO classification for hematologic disorders, in high grade MDS, detection of an aberration typically seen in acute myeloid leukemia would necessitate upgrading a diagnosis of MDS to acute myeloid leukemia.⁴ This has very significant diagnostic, prognostic, and treatment implications.

Patients who are treated for other malignancies including plasma cell disorders may subsequently develop myeloid disorders such as MDS. This is outlined in the WHO book.⁴

As a result, the draft LCD is overly restrictive and will negatively impact patient access to medically necessary FISH testing.

Summary of Evidence

1. *dLCD statement, third paragraph*: These include the number of cell lineages (i.e., platelets, red blood cells, white blood cells) affected by dysplasia, the percentage of immature "blast" cells, and the presence or absence of a characteristic pattern of iron deposition in immature red blood cells called ringed sideroblasts.

Recommendation: Change the language to, "the dysplastic changes on one or more cell lineages of megakaryocytes, erythrocytes and granulocytes; increased myeloblasts; and/or presence of ringed sideroblasts."

2. *dLCD statement, third paragraph*: Low risk MDS is associated with dysplasia affecting only one cell lineage, with or without ringed sideroblasts, and isolated large deletions involving the short arm of chromosome 5 (5q-). High risk disease is associated with dysplasia across multiple lineages, increased blast percentages, and complex karyotype.

Recommendation: Change "large deletions" to "deletions", and change "short arm" to "long arm."

Cytogenetic Testing (Chromosome Analysis)

1. *dLCD statement, first paragraph*: "The identification of a chromosomal abnormality strongly supports the diagnosis of MDS and has important prognostic implications.

Recommendation: Change the language to, "The identification of clonal cytogenetic abnormalities, except for +8, del(20q) and -Y, can serve as presumptive evidence of MDS."

2. *dLCD statement, first paragraph*: "In decreasing order of frequency, the most frequent chromosomal abnormalities associated with MDS are: +8, -7 or del(7q), -5 or del(5q), and del(20q)."

Recommendation: Change the chromosomal abnormalities to "-7 or del(7q), -5 or del(5q), +8 and del(20q)."

3. *dLCD statement, second paragraph*: "Depending on the application, detection of structural chromosome changes, resulting in a loss or gain of genetic material by these methods, is estimated to be limited to those of 4-6 mb (megabase) in size."

Recommendation: We recommend changing the language to, "Depending on the application, detection of structural chromosome changes, such as deletion or translocation, is limited to those of 5-10 mb (megabase) or above in size."

FISH Testing

1. *dLCD statement, first paragraph*: "FISH testing is a method by which an assessment is made for the presence, absence, relative position and/or copy number of specific DNA segments by fluorescence microscopy."

Recommendation: We recommend changing the language to, "FISH testing is a method that can be used to detect gene location, copy number changes, and/or gene rearrangement by fluorescence microscopy."

Indications and Limitations of Coverage

1. *dLCD statement*: "FISH (fluorescent in situ hybridization) testing is indicated in the evaluation of patients whose bone marrow examination are suggestive of myelodysplasia (MDS) and who have had a failed or inadequate cytogenetic assessment (conventional karyotype)."

Recommendation: We recommend modifying the first sentence to read, "FISH testing is indicated in the evaluation of patients whose bone marrow examination is suggestive of a myeloid disorder such as MDS and/or when there is clinical suspicion of MDS by the treating oncologist."

Limitations

1. *dLCD statement, bullet #6*: "FISH testing for MDS and a plasma cell disorder are not reasonable and necessary and not a Medicare benefit."

Recommendation: We recommend this item be modified to state, "FISH testing should be limited to MDS or plasma cell disorder based on clinical and pathologic findings, but not both."

2. As the only CPT codes specifically mentioned in this dLCD are those within the "Cytogenetic Studies" category,

it would appear that Palmetto's intent is that this particular dLCD should not address the "side issue" of the appropriateness of molecular mutation testing in the evaluation of MDS – and we certainly agree with that intent. Had Palmetto indeed intended to address mutation testing for MDS in this particular dLCD (often done by next-generation sequencing), some "Molecular Pathology" CPT codes (such as 81450) would undoubtedly have been included – and they were not.

Recommendation: Given this universal intent to not extend this FISH-specific payment policy to other non-cytogenetic testing modalities, we strongly recommend the deletion of specific statements that may be misconstrued as a possible formal Medicare payment policy for mutation-based molecular testing in MDS. In particular, we recommend that the "Limitations" section of the dLCD be revised to delete the statement: **"Molecular NGS testing alone (for myeloid mutations) or in combination with FISH testing is not reasonable and necessary for the diagnosis of MDS and is not a Medicare benefit"**.

3. Medicare will only cover up to four 4 FISH studies (+8, -7 or del(7q), -5 or del(5q), and del(20q)) on initial evaluation. This decision is inconsistent with established guidelines. NCCN guidelines specify MDS-associated karyotype to include del(5q), del(20q), +8, or -7/del(7q). WHO guidelines specify an MDS diagnosis to include both 1) an abnormal karyotype +8, del(20q) with dysplasia or increased blast count or 2) a specific MDS-associated karyotype [eg, del(5q), -7/del(7q), isochromosome 17q or t(17p)]. The choice of FISH probes may be different based on the clinical background of the patient. For example, therapy-related MDS (t-MDS) comprises 10-20% of all MDS. Unlike primary MDS, +8 and del(20q) is very rarely present in t-MDS as a sole abnormality, so FISH for +8 and del(20q) has a very limited or no value in t-MDS, neither diagnostic or prognostic. On the other hand, TP53 deletion is a common finding in t-MDS (in 25-30% of t-MDS patients) and is also a very important prognostic marker

Recommendation: We recommend the coverage of 4 FISH studies (+8, -7 or del(7q), -5 or del(5q), del(20q) or isochromosome 17q or t(17p)) on initial evaluation with the choice of probes based on the patient's clinical history.

Additional Recommendation to Proposed Policy

1. Although this dLCD does not mention the role of FISH-based testing in the post-diagnostic setting for monitoring responses to therapy, we recommend that such repeat testing of post-treatment follow-up samples be specifically covered (when standard cytogenetic testing is inadequate). The clinical utility of FISH-based testing for monitoring the "cytogenetic response" to therapy in MDS patients is specifically endorsed by NCCN guidelines³ and the MDS International Working Group.

ICD-10 Codes

The proposed policy lists 12 ICD-10 codes for MDS. We agree that an specific diagnosis and ICD-10 should be known for a patient with pathologically-confirmed MDS. However the ICD10 codes listed in the policy do not accommodate MDS/MPN diseases such as CMML which demonstrate features of both MDS and MPN. In addition, given that the clinical presentation of MDS, and thus the clinical justification for a bone marrow biopsy, is quite often very non-specific (cytopenias of various lineages), FISH-based testing is often necessary (when conventional cytogenetic karyotyping is inadequate) to distinguish MDS from benign/toxicologic/immunologic causes of cytopenias. As the treatment of a patient with a confirmed MDS diagnosis is radically different from that of a patient with a non-malignant etiology of cytopenias, the ability to rule out an MDS diagnosis is of great clinical relevance. We therefore strongly recommend that this MDS-FISH dLCD specifically include additional ICD10 codes corresponding to clinical conditions (cytopenias) that mimic MDS – and would thus be the appropriate diagnostic code in a patient in whom the bone marrow biopsy does not confirm a specific MDS diagnosis. The use of an "MDS" ICD10 code in a patient who did meet MDS diagnostic criteria – but did need bone marrow FISH to "rule out" MDS (after an inadequate conventional cytogenetic study) - would obviously be inappropriate.

We recommend inclusion of additional ICD-10 codes for MDS-mimic conditions that would fulfill criteria for this policy. These additional codes include, but may not be limited to, those listed below:

C96	Other and unspecified malignant neoplasms of lymphoid, hematopoietic and related tissue
C96.9	Malignant neoplasm of lymphoid, hematopoietic and related tissue, unspecified
C96.Z	Other specified malignant neoplasms of lymphoid, hematopoietic and related tissue
D46	Myelodysplastic syndromes
D46.2	Refractory anemia with excess of blasts [RAEB]
D46	Myelodysplastic syndromes

D46.2	Refractory anemia with excess of blasts [RAEB]
D61.818	Other pancytopenia
D64.9	Anemia, unspecified
D69	Purpura and other hemorrhagic conditions
D69.4	Other primary thrombocytopenia
D69.42	Congenital and hereditary thrombocytopenia purpura
D69.49	Other primary thrombocytopenia
D69.59	Other secondary thrombocytopenia
D69.6	Thrombocytopenia, unspecified
D69.8	Other specified hemorrhagic conditions
D69.9	Hemorrhagic condition, unspecified
D70.8	Other neutropenia
D70.9	Neutropenia, unspecified
D72	Other disorders of white blood cells
D72.8	Other specified disorders of white blood cells
D72.81	Decreased white blood cell count
D72.810	Lymphocytopenia
D72.818	Other decreased white blood cell count
D72.819	Decreased white blood cell count, unspecified
D75	Other and unspecified diseases of blood and blood-forming organs
D75.89	Other specified diseases of blood and blood-forming organs
D77	Other disorders of blood and blood-forming organs in diseases classified elsewhere
D77	Other disorders of blood and blood-forming organs in diseases classified elsewhere

MPN/MDS (Myelodysplastic/myeloproliferative neoplasms) as defined by the WHO

C93.1	Chronic myelomonocytic leukemia (CMML)
C93.10	CMML not having achieved remission
C93.12	CMML in relapse
C95.1	Chronic leukemia of unspecified cell type
C95.10	Chronic leukemia of unspecified cell type not having achieved remission
C95.12	Chronic leukemia of unspecified cell type in relapse

Thank you again for the opportunity to review and comment on this proposed policy. We are happy to be of assistance in providing additional clinical or other information to assist you with this draft LCD. Please direct your correspondence to Tara Burke, AMP Director of Public Policy, at tburke@amp.org or Nonda Wilson, CAP's Manager, Economic and Regulatory Affairs, at nwilson@cap.org.

Association for Molecular Pathology
College of American Pathologists

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