Local Coverage Determination (LCD): MolDX: MDS FISH (L37622)

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Noridian Healthcare Solutions, LLC	A and B MAC	02102 - MAC B	J - F	Alaska
Noridian Healthcare Solutions, LLC	A and B MAC	02201 - MAC A	J - F	Idaho
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LCD Information

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L37622

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MolDX: MDS FISH

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CMS National Coverage Policy

Title XVIII of the Social Security Act, §1862(a)(1)(A). Allows coverage and payment for only those services that are considered to be reasonable and necessary.

Title XVIII of the Social Security Act, §1833(e). Prohibits Medicare payment for any claim which lacks the necessary information to process the claim.

42 Code of Federal Regulations (CFR) 410.32(a). Diagnostic x-ray tests, diagnostic laboratory tests, and other diagnostic tests: Conditions.

CMS On-Line Manual, Publication 100-02, Medicare Benefit Policy Manual, Chapter 15, §§80.0, 80.1.1, 80.2. Clinical Laboratory services.

CMS Internet-Only Manuals, Publication 100-04, Medicare Claims Processing Manual, Chapter 16, §50.5 Jurisdiction of Laboratory Claims, 60.12 Independent Laboratory Specimen Drawing, 60.2. Travel Allowance.

CMS Internet Online Manual Pub. 100-04 (Medicare Claims Processing Manual), Chapter 23 (Section 10) "Reporting ICD Diagnosis and Procedure Codes."

Coverage Guidance

Coverage Indications, Limitations, and/or Medical Necessity

This policy provides coverage for indicated fluorescent in situ hybridization (FISH) probes for patients whose bone marrow examination is suggestive of myelodysplasia (MDS) and who have an inadequate cytogenetic assessment by conventional karyotyping. In general, conventional karyotype analysis is sufficient for confirmation for the diagnosis of MDS. MDS FISH studies should only be performed when there are fewer than 20 metaphases available for analysis, or an unresolved karyotype. Medicare will only cover up to four 4 FISH studies (-7 or del(7q), -5 or del(5q), +8 and del(20q)) on initial evaluation to diagnose MDS. Reflex testing for additional FISH markers to diagnose MDS is only reasonable and necessary when the initial 4 studies are negative, or the diagnosis remains uncertain following the initial 4 probes.

Generally, FISH testing is not reasonable and necessary for diagnosing MDS and provides little if any additional information to conventional karyotyping.

Summary of Evidence

The myelodysplastic syndromes (MDS) represent a spectrum of clonal bone marrow diseases with heterogeneous presentations. The classic triad for MDS includes one or more cytopenias, defective differentiation (dysplasia) of one or more blood cell lines and marrow hypercellularity. Over time, there is an increased rate of progression to acute myeloid leukemia (AML). These secondary AML cases carry a worse prognosis than de novo AML cases. Furthermore, there are myeloid neoplasms that share overlapping characteristics with both MDS and myeloproliferative neoplasms (MPNs), such as chronic myelomonocytic leukemia (CMML). The World Health Organization (WHO) has designated these diseases separately as MDS/MPNs, distinct from either MDS or MPNs.[(1)]

According to the 2016 National Comprehensive Cancer Network (NCCN) Guidelines, the overall incidence of MDS is approximately 5/100,000 per year, primarily in adults. MDS is rare in patients under the age of 40, but much more common in older patients. The incidence of MDS among patients 70-79 years of age is 30/100,000, and in patients > 80 years the incidence is 60/100,000.[(2)]

MDS has historically been classified by a combination of traditional laboratory techniques, such as demonstration of stable cytopenias by complete blood count, microscopic examination of a bone marrow biopsy, and bone marrow cytogenetic (conventional karyotype) studies. Other than the clinical feature of the number of cytopenias and specific cytogenetic changes found recurrently in MDS, all other diagnostic criteria in MDS rely upon light microscopy findings. These include the dysplastic changes on one or more cell lineages of megakaryocytes, erythrocytes and granulocytes; increased myeloblasts; and/or presence of ringed sideroblasts. Low risk MDS is associated with dysplasia affecting only one cell lineage, with or without ringed sideroblasts, and isolated deletions involving the long arm of chromosome 5 (5q-). High risk disease is associated with dysplasia across multiple lineages, increased blast percentages, and complex karyotype.

Neither the 2016 WHO Classification of MDS, the International Prognostic Scoring System (IPSS) nor the Revised IPSS (IPSS-R) require the use of additional MDS-associated mutations to establish a diagnosis of MDS. As noted in NCCN 2017 Guidelines, "Bone marrow or peripheral blood cells may be assayed for MDS-associated gene mutations. These can establish the presence of clonal hematopoiesis which can help exclude benign causes of cytopenia with non-diagnostic morphology but do not establish the diagnosis of MDS in the absence of clinical diagnostic criteria."

Cytogenetic Testing (Chromosome Analysis)

Conventional cytogenetic testing (routine chromosome analysis) is also referred to as karyotyping and is the most important special study for the diagnosis of MDS. The identification of clonal cytogenetic abnormalities, except for +8, del(20q) and -Y, can serve as presumptive evidence of MDS. In decreasing order of frequency, the most frequent chromosomal abnormalities associated with MDS are: -7 or del(7q), -5 or del(5q), +8 and del(20q). A more comprehensive list of chromosomal abnormalities associated with MDS is available from the World Health Organization (WHO).[3]

Cytogenetic studies are used to detect numerical and/or structural chromosome abnormalities in metaphase cells in constitutional conditions such as congenital conditions (Down's syndrome) and acquired conditions associated with neoplastic or cancer processes. Conventional chromosome analyses require some form of cell culture, followed by chromosome harvesting, chromosome banding, analysis and karyotype production. 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.

FISH Testing

Molecular cytogenetic testing (aka fluorescence in-situ hybridization (FISH)) may be utilized to address specific, focused clinical questions and is available for a variety of clinical application including the assessment of both constitutional and acquired chromosomal aberrations. 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. FISH involves hybridization of a fluorochrome-labeled DNA probe to an in situ chromosomal target. Metaphase preparations from cultured cells that are routinely used for cytogenetic analysis are considered the "gold standard" because morphology and position of the fluorescent signals can be visualized directly. A major advantage of FISH is that it can be performed on non-dividing interphase cells, affording a rapid screen for specific chromosome rearrangements or numerical abnormalities associated with hematologic malignancies. Interphase analysis can be performed on bone marrow cell suspensions routinely used for conventional cytogenetics, paraffin-embedded tissue sections, or disaggregated cells from paraffin blocks, bone marrow, blood smears and touch-preparations of cells from lymph nodes or solid tumors.

The majority of probes used for clinical FISH testing are considered analyte-specific reagents, i.e., reagents that are produced under good manufacturing practice guidelines set forth by the FDA, but their safety and efficacy must be established by the user. When a new analyte-specific reagent probe is introduced in the lab, specific validation of the probe itself (probe validation) and validation of the procedures using the probe (analytical validation) is needed. Known normal and abnormal cases are used to validate a FISH test. A variety of FISH probes are available:

- Enumeration probes (e.g., one color chromosome 8 a-satellite centromere probe; two color X/Y probes)
- Dual-color, dual-fusion probes (e.g., BCR/ABL1; IGH/BCL2; PML/RARA)
- Single-fusion, extra signal (ES) probes (e.g., ETV6/RUNX1; BCR/ABL1 ES)
- Break-apart probes (e.g., CBFB, MLL)

Interpretation of the various groups of probes requires significant experience. Most labs require two technologists to score routine FISH evaluations. For metaphase FISH, it is recommended that clinical FISH tests include control probes to tag the chromosomes of interest. Such probes provide a limited level of quality control by providing an internal control of hybridization efficiency. The interpretation of FISH results should include consideration of the reason for referral for testing and, when available, additional laboratory findings including conventional cytogenetic analysis, histology and immunophenotype.

FISH probes are available for the common chromosomal abnormalities associated with MDS as FISH panels. Advantages of FISH over standard cytogenetics are:

- FISH testing can be performed on archived paraffin-embedded clot bone marrow clot sections,
- Results are available more quickly, and
- Sensitivity is superior

However, cytogenetics is sufficiently sensitive to detect these abnormalities in most instances, such that FISH is rarely indicated.

Diagnostic Report

The diagnostic report should clearly indicate both the diagnostic and prognostic significance of the FISH findings. It should also contain a statement as to the normalcy/abnormalcy of a FISH result, as well as the percentage of abnormal and normal cells, and whether the results are from metaphase or interphase cells or from both. Specific naming of the probes used to obtain results, including the name of the manufacturer, MUST be included in the written report. Any specific limitations of the assay, some of which may be described in the probe manufacturer's package insert, should be included in the patient report.

MDS Testing Algorithm

Many laboratories adhere to a MDS testing algorithm to determine the necessity for FISH testing. More than 20 metaphases and a resolved karyotype preclude FISH testing. Mayo Medical Laboratories (MML) specifies that "MDS FISH does not increase the detection of MDS if chromosome analysis is successful and >20 metaphases are analyzed."[7] They specify that MDS FISH studies should be ordered at the discretion of the cytogeneticist if <20 metaphases are identified, if there is an unresolved karyotype, or if only 1 abnormal metaphases is indicated. MML also supports use of a FISH study with a specific probe but without chromosome analysis for follow-up of a bone marrow for a previously diagnosed MDS with a specific genetic anomaly.

A number of studies support a MDS testing algorithm that a conventional karyotype is often all that is needed in the diagnostic process[3,4,5,6,] and that MDS FISH studies should only be performed when there are fewer than 20 metaphases available for analysis.

The Mayo Clinic has used a diagnostic algorithm in its practice and it supports this approach. A recent published article by Mayo[7] concludes "…supports this assumption and showed that MDS-FISH studies provide little additional value beyond conventional karyotype studies if that study is adequate (defined by at least 20 metaphases available for analysis).

The American Society of Clinical Pathology (ASCP) has endorsed this practice pattern in its practice recommendations in its "Choosing Wisely" program.[8] The ASCP notes that the added value of MDS FISH on bone marrow is extremely low when a satisfactory karyotype is obtained (=20 interpretable metaphases). They also note that MDS FISH can be performed post hoc in the event of an unsatisfactory karyotype.

Coding for FISH Testing

There are two sets of codes that describe in situ hybridization (ISH). Although the laboratory methods are similar, one distinguishes between the two sets of codes based on whether the ISH test is an adjunct to a surgical or cytopathology case, versus whether it is part of a clinical, chromosomal analysis. Specifically, the CPT codes 88271-88291 must be used when the laboratory performs **ISH as an ancillary analysis to cytogenetic studies for oncologic or inherited disorders.**

When a pathologist performs **ISH techniques as an adjunct to a surgical pathology or cytopathology case,** CPT codes 88365-88377 should be used to distinguish qualitative versus quantitative analysis (computer assisted versus manual). These codes must never be used by a pathologist when ISH is performed as an ancillary analysis to cytogenetic studies.

Indications and Limitations of Coverage

Indications

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

Limitations

- When the results of conventional cytogenetics are adequate, FISH testing is not reasonable and necessary and not a Medicare benefit.
- When conventional karyotyping is inadequate, Medicare will limit initial FISH testing to 4 probes (studies, as specified above in this policy.
- Reflex FISH testing may be indicated when the initial 4 probes are negative.
- 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.
- When a patient has a bone marrow suggestive of another disorder (e.g., a plasma cell disorder), MDS-FISH is not indicated.
- Delay in diagnosis is not a legitimate reason for performing more than 4 initial FISH studies followed by step-wise reflex testing.
- Repeat FISH testing by another laboratory on the same specimen is not reasonable and necessary.

Analysis of Evidence

(Rationale for Determination)

Level of Evidence:

Quality – Moderate to High
Strength – Moderate
Weight – Moderate

This Medicare contractor supports the use of conventional karyotyping in patients being evaluated for MDS (myelodysplastic) syndromes and related disorders as being reasonable and necessary. It is not reasonable and necessary to perform MDS FISH studies when the conventional karyotype is adequate (20 or more metaphases are available for analysis) since the evidence suggests that even when FISH does not agree with conventional karyotyping, it does not meaningfully alter the diagnosis. When a karyotype is inadequate, FISH testing is limited to up to four (4) FISH studies (+8, -7 or del(7q), -5 or del(5q), and del(20q)). Only when the initial FISH studies are negative, or there is still diagnostic uncertainty, will subsequent studies be considered on an individual basis.

Coding Information

Bill Type Codes:

Contractors may specify Bill Types to help providers identify those Bill Types typically used to report this service. Absence of a Bill Type does not guarantee that the policy does not apply to that Bill Type.Complete absence of all Bill Types indicates that coverage is not influenced by Bill Type and the policy should be assumed to apply equally to all claims.

N/A

Revenue Codes:

Contractors may specify Revenue Codes to help providers identify those Revenue Codes typically used to report this service. In most instances Revenue Codes are purely advisory. Unless specified in the policy, services reported under other Revenue Codes are equally subject to this coverage determination. Complete absence of all Revenue Codes indicates that coverage is not influenced by Revenue Code and the policy should be assumed to apply equally to all Revenue Codes.

N/A

CPT/HCPCS Codes

Group 1 Paragraph:

N/A

Group 1 Codes:

CODE	DESCRIPTION
88271	MOLECULAR CYTOGENETICS; DNA PROBE, EACH (EG, FISH)

CODE	DESCRIPTION
88273	MOLECULAR CYTOGENETICS; CHROMOSOMAL IN SITU HYBRIDIZATION, ANALYZE 10-30 CELLS (EG, FOR MICRODELETIONS)
88274	MOLECULAR CYTOGENETICS; INTERPHASE IN SITU HYBRIDIZATION, ANALYZE 25-99 CELLS
88275	MOLECULAR CYTOGENETICS; INTERPHASE IN SITU HYBRIDIZATION, ANALYZE 100-300 CELLS
88291	CYTOGENETICS AND MOLECULAR CYTOGENETICS, INTERPRETATION AND REPORT

ICD-10 Codes that Support Medical Necessity

Group 1 Paragraph:

N/A

Group 1 Codes:

ICD-10 CODE	DESCRIPTION
C94.6	Myelodysplastic disease, not classified
D46.0	Refractory anemia without ring sideroblasts, so stated
D46.1	Refractory anemia with ring sideroblasts
D46.20	Refractory anemia with excess of blasts, unspecified
D46.21	Refractory anemia with excess of blasts 1
D46.22	Refractory anemia with excess of blasts 2
D46.A	Refractory cytopenia with multilineage dysplasia
D46.B	Refractory cytopenia with multilineage dysplasia and ring sideroblasts
D46.C	Myelodysplastic syndrome with isolated del(5q) chromosomal abnormality
D46.4	Refractory anemia, unspecified
D46.Z	Other myelodysplastic syndromes
D46.9	Myelodysplastic syndrome, unspecified

ICD-10 Codes that DO NOT Support Medical Necessity

N/A

Additional ICD-10 Information

N/A

General Information

Associated Information

N/A

Sources of Information

N/A

Bibliography

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2. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Myeloproliferative Neoplasms. Version 2.2017. Available at https://www.nccn.org/professionals/physician_gls/pdf/mpn.pdf. Accessed: Dec 21, 2016.

3. Coleman JF, Theil KS, Tubbs RR, et al. Diagnostic yield of bone marrow and peripheral blood FISH panel testing in clinically suspected myelodysplastic syndromes and/or acute myeloid leukemia: a prospective analysis of 433 cases. American Journal of Clinical Pathology 2011;135:915-920.

4. Jiang H, Xue Y, Wang Q, et al. The utility of fluorescence in situ hybridization analysis in diagnosing myelodysplastic syndromes is limited to cases with karyotype failure. Leukemia Research 2012;36:448-452.

5. Pitchford CW, Hettinga AC, Reichard KK. Fluorescence in situ hybridization testing for -5/5q, -7/7q, +8, and del(20q) in primary myelodysplastic syndrome correlates with conventional cytogenetics in the setting of an adequate study. American Journal of Clinical Pathology 2010;133:260-264.

6. Seegmiller AC, Wasserman A, Kim AS, et al. Limited utility of fluorescence in situ hybridization for common abnormalities of myelodysplastic syndrome at first presentation and follow-up of myeloid neoplasms. Leukemia & Lymphoma 2014;55:601-605.

7. He R, et al. Bone marrow conventional karyotyping and fluorescent in situ hybridization: Defining an effective utilization strategy for evaluation of myelodysplastic syndromes. American Journal of Clinical Pathology 2016;146:86-94.

8. http://www.choosingwisely.org/societies/american-society-for-clinical-pathology/

Revision History Information

N/A

Associated Documents

Attachments

N/A

Related Local Coverage Documents

Article(s)

A56447 - Response to Comments: MolDX: MDS FISH

LCD(s)

DL37622 - MolDX: MDS FISH

Related National Coverage Documents

N/A

Public Version(s)

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- 88291