Microarray-Based Gene Expression Profile Testing for Multiple Myeloma Risk Stratification

Policy # 00461
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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Hematopoietic Stem-Cell Transplantation for Plasma Cell Dyscrasias, Including Multiple Myeloma and POEMS Syndrome is addressed separately in medical policy 00060.

Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers microarray-based gene expression profile (GEP) testing for multiple myeloma for all indications to be **investigational.***

Policy Guidelines

According to Mayo Clinic recommendations, a large number of prognostic factors have been validated and categorized into 3 main groups: tumor biology, tumor burden, and patient-related factors. These factors must be considered to individualize the choice of therapy in multiple myeloma patients (see Table PG1) (see Mikhael et al, 2013).

Table PG1. Prognostic Factors in Multiple Myeloma (Mikhael et al, 2013)

Tumor Biology	Tumor Burden	Patient-Related
• Ploidy • 17p (p53 deletion) • t(14;16) • t(14;20) • t(4;14) • Deletion 13 on conventional cytogenetics • Alterations in chromosome 1 • t(11;14) • t(6;14) • Lactate dehydrogenase levels • Plasma cell proliferative rate • Presentation as plasma cell leukemia • High-risk GEP signature	• Durie-Salmon stage • International Staging System stage • Extramedullary disease	• ECOG Performance Status • Age • Renal function

ECOG: Eastern Cooperative Oncology Group; GEP: gene expression profile.
[a] The Mayo Clinic does not currently recommend or routinely perform GEP analysis in a nonresearch setting. However, Mikhael et al (2013) have suggested GEP analysis will likely play a greater role in the management of multiple myeloma as evidence develops.

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Background/Overview

MULTIPLE MYELOMA

Multiple myeloma is a genetically complex—and invariably fatal—neoplasm of plasma cells.

Disease Description

Multiple myeloma is a malignant plasma cell dyscrasia characterized by clonal proliferation of plasma cells derived from B cells in the bone marrow. It accounts for about 1 in every 100 cancers and 13% of hematologic cancers. The American Cancer Society has estimated 21,700 new cases of multiple myeloma will occur in the United States in 2012, and some 10,200 deaths will occur due to the disease. The annual age-adjusted incidence is about 6 cases per 100,000 persons, with a median age-at-diagnosis of about 70 years. Before the advent of current treatment protocols, most patients with multiple myeloma succumbed to their disease within 5 to 10 years; in the prechemotherapy era, median survival was less than 1 year. Among patients who present at an age younger than 60 years, 10-year overall survival with current treatment protocols may now exceed 30%.

Criteria for the diagnosis, staging, and response assessment of multiple myeloma have been reported by the International Myeloma Working Group and are in widespread use. The decision to treat is based on criteria set forth in the diagnosis of multiple myeloma, which includes calcium elevation; renal insufficiency; anemia; and bone disease (CRAB). Patients with monoclonal gammopathy of undetermined significance (MGUS) or smoldering myeloma do not require therapy, irrespective of any associated risk factors—except on specifically targeted protocols.

Pathogenesis and Genetic Architecture of Multiple Myeloma

Multiple myeloma is a complex disease that presents itself in distinct clinical phases and risk levels. They include MGUS and smoldering multiple myeloma (also known as asymptomatic myeloma). MGUS is a generally benign condition, with a transformation rate to symptomatic plasma cell disorders of about 1% to 2% annually. Smoldering multiple myeloma represents a progression from MGUS to frank multiple myeloma; the risk of the disease transforming to multiple myeloma is about 10% for the first 5 years. Although both of these entities lack many clinical features of multiple myeloma, they may ultimately share characteristics that necessitate therapy. By contrast, symptomatic multiple myeloma is defined by specific clinical symptoms, accumulation of monoclonal immunoglobulin proteins in the blood or urine, and associated organ dysfunction (including nephropathy and neuropathy). The acronym CRAB is used to reflect the hallmark features of multiple myeloma. Premyeloma plasma cells initially require interaction with the bone marrow microenvironment; however, during disease progression, the cells develop the ability to proliferate outside the bone marrow, manifesting as extramedullary myeloma and plasma cell leukemia. These “bone marrow independent” cells represent the end stages in a multistep transformation process from normal to multiple myeloma.

As outlined below in this evidence review, complex genetic abnormalities, commonly identified in multiple myeloma plasma cells, are considered to play major roles in disease initiation, progression, and pathogenesis; further, these abnormalities are used in conjunction with laboratory and radiographic studies to stratify patients for therapeutic decisions.

Diagnosis
Cytogenetic and other laboratory tests identify markers to classify newly diagnosed multiple myeloma patients into high, intermediate, and standard clinical risk categories. The level of risk reflects the aggressiveness of the disease, and ultimately dictates the intensity of initial treatment. Thus, a risk-adapted approach provides optimal therapy to patients, ensuring intense treatment for those with aggressive disease; further, this approach minimizes toxic effects, thereby delivering sufficient—but less-intense—therapy for those with lower risk of disease. However, it should be noted that clinical outcomes can vary substantially, using even the most standard of methods, among patients with the same estimated risk who undergo a similar intensity of treatment.

A microarray-based GEP analysis estimates the underlying activity of cellular biological pathways, and these pathways control a host of mechanisms such as cell division, cell proliferation, apoptosis, metabolism, and other signaling pathways. Relative over- or underexpression of these pathways is considered to mirror disease aggressiveness, independent of cytogenetics and other laboratory measures. GEP analysis has been proposed as a means to more finely stratify multiple myeloma patients into risk categories for two purposes: (1) to personalize therapy selection according to tumor biology; and (2) to avoid over- or undertreating patients. Moreover, GEP analysis could be used as a supplement to existing stratification methods, or as a stand-alone test; however, further study is needed to confirm that the analysis has the capability to perform those roles.

The term *gene expression* refers to the process by which the coded information of genes, deoxyribonucleic acid (DNA), is transcribed into messenger ribonucleic acid (mRNA) and translated into proteins. A GEP assay simultaneously examines the patterns of multiple genes in a single tissue sample; it does this to assess those that are actively producing mRNA or not, ultimately producing proteins or not. By concurrently measuring the cellular levels of mRNA of thousands of genes, a GEP test creates a picture of the rate at which those genes are expressed in a tissue sample.

GEP tests are not “genetic” tests. Genetic tests measure an individual DNA signature to identify genetic changes or variants that remain constant in the genome. Gene expression tests measure the activity of mRNA in a tissue or bodily fluid at a single point, reflecting an individual’s current disease state (or the likelihood of developing a disease). However, because mRNA levels are dynamic and change as a result of disease processes or environmental signals, dynamic changes in these processes can be studied over time. This information thus reflects the pathogenic process, and in theory, can be used to assess the effects of therapeutic interventions or select therapy based on specifically expressed gene targets.

Gene Expression Analysis of Cancer Using Microarray Technology
GEP analysis using microarray technology is based on the Watson-Crick pairing of complementary nucleic acid molecules. A collection of DNA sequences, referred to as “probes,” are “arrayed” on a miniaturized solid support (the “microarray”). These are used to determine the concentration of the corresponding complementary mRNA sequences, called “targets,” isolated from a tissue sample. Laboratory advancements in attaching nucleic acid sequences to solid supports, combined with robotic technology,

have allowed investigators to miniaturize the scale of the reactions. As a result of these advances, it is possible to assess the expression of thousands of different genes in a single reaction.

A basic microarray GEP analysis uses mRNA targets that have been both harvested from a patient's tissue sample and labeled with a fluorescent dye. These samples are hybridized to the DNA probe sequences attached to the microarray medium, then incubated in the presence of mRNA from a different sample labeled with a different fluorescent dye. In a 2-color experimental design, samples can be directly compared with one another or with a common reference mRNA, and their relative expression levels can be quantified. After hybridization, grayscale images corresponding to fluorescent signals are obtained by scanning the microarray with dedicated instruments; the fluorescence intensity corresponding to each gene is then quantified by specific software. After normalization, the intensity of the hybridization signals can be compared to detect differential expression by using sophisticated computational and statistical techniques.

Technical variability is a major concern with microarray technologies for clinical management; e.g., the source of mRNA is a technical variable that can affect test results. A typical biopsy sample from a solid tumor contains a mixture of malignant and normal (stromal) cells that, in turn, will yield total RNA that reflects all the cells contained in the specimen. To address this, tissue samples may be macro- or microdissected (prior to RNA extraction) to ensure that the specimens contain a sufficiently representative percentage of cancer cells to reflect the disease. For analysis of hematologic cancers, including multiple myeloma, immunomagnetic cell separation technology is used to isolate and enrich cancerous cells from bone marrow aspirates that contain a mixture of cell types.

The instability of mRNA relative to DNA complicates GEP analysis studies, especially when comparing the method against genomic analyses. Two factors that affect RNA quality include preanalysis storage time and the reagents used to prepare mRNA. Moreover, pH changes in the storage media can trigger mRNA degradation, as can ribonucleases that are present in cells and can remain active in the RNA preparation if not stringently controlled.

As noted above, Watson-Crick hybridization of complementary nucleic acid moieties in the sequences of mRNA and DNA is the basis of any microarray-based GEP test. For this reason, sequence selection and gene annotation are among the most important factors that can contribute to analytical variability, hence validity, in results. Different technologic platforms, protocols, and reagents can affect the analytic variability of the results, and therefore affect reproducibility within and across laboratories. Gene expression measures are virtually never used as raw output but undergo sequential steps of mathematical transformation; thus, data preprocessing and analysis may increase variability in results. Moreover, different levels of gene expression can be further processed and combined, according to complex algorithms, to obtain composite summary measurements that are associated with the phenotype(s) under investigation. A statistical analytic technique known as "unsupervised clustering analysis" is applied to the data to produce a visual display, known as a "dendrogram," that shows a hierarchy of similar genes, differentially expressed as mRNA.

International standards have been developed to address the quality of microarray-based GEP analysis. These standards focus on documentation of experimental design, details, and results. Additional topics of

interest include interplatform and interlaboratory reproducibility. Quality control efforts emphasize the importance of minimizing the sources of variability in gene expression analysis, thus ensuring that the information derived from such analyses is specific and does not represent accidental associations.

Prognosis and Risk Stratification
Two validated clinical systems have been in widespread use to assess prognosis in newly diagnosed multiple myeloma patients: the Durie-Salmon Staging System and the International Staging System. The Durie-Salmon Staging System provides a method to measure multiple myeloma tumor burden, according to multiple myeloma cell numbers and clinical, laboratory, and imaging studies; however, the system has significant shortcomings due to its use of observer-dependent studies (e.g., radiographic evaluation of bone lesions), primarily focused on tumor mass—not behavior. The International Staging System, incorporating serum albumin and β_2-microglobulin measures, is considered valuable because it permits comparison of outcomes across clinical trials; it is even more reproducible than the Durie-Salmon Staging System. However, the International Staging System is useful only if a diagnosis of multiple myeloma has already been made; it has no role in MGUS, smoldering multiple myeloma, or other related plasma cell dyscrasias. Further, the International Staging System does not provide a good estimate of tumor burden—nor is it generally useful for therapeutic risk stratification; in fact, it may not retain prognostic significance in the era of novel drug therapies.

Although multiple myeloma cells may appear morphologically similar across risk levels, the disease exhibits substantial genetic heterogeneity that may change with progression or at relapse. Investigators have used conventional cytogenetic methods (karyotyping) and fluorescence in situ hybridization to prognostically stratify multiple myeloma patients according to a host of recurrent chromosomal changes (immunoglobulin heavy chain translocations, chromosome deletions, or amplifications). This stratification forms the basis of the Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART), an evidence-based algorithm to facilitate treatment decisions for patients with newly diagnosed multiple myeloma (see Table 1).

Table 1. Mayo Clinic Stratification of Multiple Myeloma and Risk-Adapted Therapy (mSMART)

Variables	High Risk	Intermediate Risk	Standard Risk
Variants	Any of the following: • Del 17p • t(14;16) by FISH • t(14;20) by FISH • GEP high-risk signature	• t(4;14) by FISH • Cytogenetic del 13 • Hypodiploidy • Plasma cell labeling index >3.0	All others including: • t(11;14) by FISH • t(6;14) by FISH
Incidence	2%	20%	60%
Median overall survival	3 y	4-5 y	8-10 y

FISH: fluorescence in situ hybridization; GEP: gene expression profile.

In addition to the cytogenetic characteristics noted in Table 1, other findings are typically considered in this model. Although GEP analysis is included in Table 1, the Mayo Clinic does not currently recommend or routinely perform GEP analysis in a nonresearch setting.

The risk-stratification model outlined in Table 1 is meant to prognosticate and to determine the treatment approach; it is not used to decide whether to initiate therapy (see Therapy Synopsis subsection). Furthermore, therapeutic outcomes among individuals in these categories may vary significantly, to the effect that additional means of subdividing patients into response groups are under investigation—in particular, molecular profiling using microarray-based methods (see Rationale section).

Therapy Synopsis
Asymptomatic (smoldering) multiple myeloma and MGUS currently require only ongoing clinical observation (this is because early treatment with conventional chemotherapy has shown no benefit). However, for symptomatic patients diagnosed with multiple myeloma, prompt induction therapy is indicated. For patients younger than age 65 years who have adequate heart, liver, and lung function, this will comprise combinations that may include melphalan, dexamethasone, cyclophosphamide, or doxorubicin with thalidomide, lenalidomide, or bortezomib. Next, the therapy includes autologous hematopoietic cell transplantation (HCT). Older patients (or those with underlying liver, lung, or cardiovascular dysfunction) may be candidates for induction followed by reduced-intensity conditioning allogeneic HCT.

A program referred to as Total Therapy, developed primarily at the University of Arkansas for Medical Science and at the Mayo Clinic, uses all available agents as induction, followed by 2 cycles of high-dose melphalan and autologous HCT support, with a 4-year event-free survival as high as 78%. Despite the achievement of complete remission and apparent eradication of disease, the clinical response is transitory in all cases, and multiple myeloma is considered incurable with current approaches.

GEP Test
The MyPRS™‡/MyPRS *Plus*™‡GEP70 test analyzes all of the "nearly 25,000 genes" in the human genome to determine the level of aggressiveness of diagnosed multiple myeloma based on 70 of the most relevant genes involved in cellular signaling and proliferation.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. The MyPRS/MyPRS *Plus*GEP70 test was acquired by Quest Diagnostics in December 2016. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. FDA has chosen not to require any regulatory review of this test.

Centers for Medicare and Medicaid Services (CMS)
Medicare does not have a national coverage determination for this testing.

In 2012, Novitas Solutions, the Medicare contractor over Jurisdiction H (which includes Arkansas), issued a Medicare local coverage decision for the MyPRS test. Because all MyPRS tests are processed through

Signal Genetics Clinical Laboratory Improvement Act–certified laboratory in Little Rock, Arkansas, the local coverage determination applies to all Medicare patients in the United States.

This test is used only after the initial diagnosis of multiple myeloma has been made and will be available to help stratify therapeutic interventions. The coverage is set to include only 2 clinical settings (https://www.novitas-solutions.com/policy/jh/l32636-r1.html):

1) Once after initial diagnosis is made (ICD-9-CM 203.00). In the event MyPRS was not tested at diagnosis of myeloma and there is ongoing initial therapy with persistent disease, MyPRS can be done still as an initial test.
2) If relapse has occurred and a change in the therapeutic modalities is contemplated (ICD-9-CM 203.02).

Rationale/Source

Validation of the clinical use of any genetic test focuses on 3 main principles: (1) analytic validity, which refers to the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent; (2) clinical validity, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and (3) clinical utility (i.e., how the results of the diagnostic test will be used to change management of the patient, and whether these changes in management lead to clinically important improvements in health outcomes). The following is a summary of the key findings to date.

MULTIPLE MYELOMA

Multiple myeloma is a genetically complex—and invariably fatal—disease. A host of well-characterized factors related to tumor biology, tumor burden, and patient-centered characteristics are used to stratify patients into high, intermediate, and standard clinical risk categories for prognostication purposes, as well as determining treatment intensity. However, clinical outcomes have varied among patients in the same risk category who received similar therapy. Thus, more specific methods have been sought to classify multiple myeloma; one such method being proposed is the utilization of a microarray-based GEP analysis, which serves to reveal the underlying activity of cellular biological pathways.

The MyPRS/MyPRS *Plus* test, which is currently under evaluation, was developed primarily using microarray-based technology described in the Background section. Two key publications have reported that the application of this method can do two things: (1) construct molecular profiles of multiple myeloma in newly diagnosed patients; and (2) retrospectively associate treatment outcomes with specific GEPs.

Analytical Validity

Published data on analytic performance characteristics of the MyPRS test was not found. Information available online from the manufacturer of the microarray chip used in this test (Human Genome U133Plus 2.0; Affymetrix, Santa Clara, CA) have shown a detection call sensitivity of 1.5 pM, a concentration of mRNA that corresponds to approximately 1 transcript in 100,000, or 3.5 copies per cell. The false-positive

rate of making a present call for an expressed gene was reported to be about 10%, noted by 90% of clone sequences being called absent when not spiked into the test sample (0 pM concentration).

Clinical Validity
In a widely cited validation paper by Shaughnessy et al (2007), GEP data were reported for 523 newly diagnosed patients (training group n=351, validation group n=181) who underwent similar treatments for multiple myeloma on National Institutes of Health–sponsored clinical trials (UARK 98-026 and UARK 03-033, respectively). Both protocols used induction regimens followed by melphalan-based tandem autologous HCT, consolidation chemotherapy, and maintenance treatment. Plasma cells were purified from bone marrow aspirates using a fully automated ROBOSEP cell separation system that uses immunomagnetic technology to positively select for CD138+ cells from which mRNA was isolated. These preparations were hybridized to total human genome DNA using Affymetrix U133Plus2.0 microarrays; they were then processed to identify 19 underexpressed and 51 overexpressed prognostic genes (GEP70 test) that mapped primarily to chromosome 1 and were linked to short survival among the multiple myeloma patients. A high-risk GEP score, defined by the mean expression levels of up-regulated to down-regulated genes, was observed in 13% of patients who had significantly shorter durations of overall survival at 5 years (28%) than those with a low risk score (78%; $p<0.001$; hazard ratio, 5.16). The absence of a high risk score identified a favorable subset of patients with a 5-year continuous complete remission of 60%, as opposed to a 3-year rate of only 20% in those with a high-risk GEP70 score. Multivariate analyses suggested significant correlations between overall survival and event-free survival, the presence of a high-risk GEP70 score, and laboratory parameters associated with a poor prognosis, including lactate dehydrogenase, albumin, and β_2-microglobulin as used in the International Staging System (see Background/Overview section). This evidence suggests a potential connection between a GEP70 test result indicative of high-risk multiple myeloma; moreover, the evidence suggests that survival is higher when patients are treated on the same intensity protocol. However, this validation study was performed retrospectively on multiple myeloma plasma cells obtained prior to therapy; further, the study is associated with the clinical outcomes from a small number of patients treated at a single center in the United States, primarily in the context of autologous HCT.

A study published by Kumar et al in 2011 examined the utility of the GEP70 risk-stratification test among patients undergoing initial therapy with lenalidomide in a phase 3 trial. Patients with previously untreated multiple myeloma who enrolled in the E4A03 trial were randomized to lenalidomide plus either standard-dose dexamethasone (40 mg on days 1-4, 9-12, and 17-21) or low-dose dexamethasone (40 mg/wk). After the first 4 cycles of therapy, patients could discontinue therapy to pursue HCT or continue on protocol until progression. Overall, 445 patients were randomized: 222 to the low-dose arm and 223 to the high-dose arm. As in the GEP70 validation study, CD138-positive plasma cells were isolated from bone marrow aspirates of consenting patients. Total mRNA was isolated from those cells and analyzed by high-density oligonucleotide microarrays containing probes for 50,000 transcripts and variants including 14,500 known human genes (Affymetrix U133Plus2.0 array). The GEP70 signature was determined as described by Shaughnessy in the 2007 report and compared with overall survival data and other variables. Overall, 7 (15.6%) of 45 patients with adequate mRNA samples were considered high risk by the GEP70 test, similar to the proportion described previously. Among patients who had fluorescence in situ hybridization (FISH)

cytogenetic data available, 10 (22.7%) of 44 were considered high risk by the presence of t(4;14), t(14;16), t(14;20) or del17p. Six of the FISH high-risk patients and two of the standard-risk patients were reclassified into the low- and high-risk categories by GEP70, respectively. Median overall survival was 19 months for the 7 GEP70 high-risk patients; overall survival did not reach median for the standard-risk group. For 10 high-risk FISH patients, median overall survival was 39 months; overall survival did not reach median for the standard-risk group. The predictive ability of the GEP70 test, which was estimated using the C-statistic for the GEP70 score dichotomously, was 0.74 (95% confidence interval [CI], 0.61 to 0.88), a value conventionally considered as reflecting a prediction model with good discriminatory ability. The C-statistic for FISH-based risk stratification was 0.70 (95% CI, 0.55 to 0.84), very similar to the GEP70 finding. These results suggest the GEP70 high-risk results are inversely associated with overall survival among patients treated outside the context of HCT, in a cohort of patients treated primarily with novel agents. The small number of patients and the retrospective nature of the association between GEP70 scores and survival rates preclude conclusions on the clinical utility of the test in risk stratification and therapeutic decisions, as well as assessment of the incremental value of GEP70 compared with FISH.

Papanikolaou et al (2015) analyzed predictive factors for survival in patients with multiple myeloma. Clinical and demographic factors were combined with cytoplasmic immunoglobulin and the GEP70 model. Cytoplasmic immunoglobulin is a new prognostic factor being tested in conjunction with other known predictors of survival. The outcome variables used were overall survival and progression-free survival. Both cytoplasmic immunoglobulin and GEP70 score were independent predictors of survival. The multivariate predictive model derived included the GEP70 score, the cytoplasmic immunoglobulin index, and the albumin level.

Clinical Utility
In our 2014 literature search update of this evidence review, we did not identify any systematic reviews or meta-analyses that addressed clinical data on GEP70 for risk analysis of multiple myeloma. Several review articles on risk stratification of multiple myeloma reported on the use of GEP70; however, reviewers uniformly stated this technology has not yet been proven to have clinical utility for this purpose.

SUMMARY OF EVIDENCE
For individuals who have multiple myeloma who received risk stratification using a gene expression profiling, the evidence includes retrospective series that correlate risk scores with survival. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and other test performance measures. The microarray-based GEP70 test (MyPRS/MyPRS *Plus*) has been reported to risk-stratify multiple myeloma patients. Patients with a high GEP70 risk score have a substantially increased risk of mortality than patients without a high score. However, there is no evidence (from available studies) that this test would add incremental value to existing risk-stratification methods; nor have any studies demonstrated the need to prospectively allocate patients to risk-based therapies based on GEP70 score. The evidence is insufficient to determine the effects of the technology on health outcomes.

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Policy History

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01/08/2015	Medical Policy Committee review
01/21/2015	Medical Policy Implementation Committee approval. New policy.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
01/07/2016	Medical Policy Committee review
01/22/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
01/05/2017	Medical Policy Committee review
01/18/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/04/2018	Medical Policy Committee review
01/17/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/29/2018	Coding update
Next Scheduled Review Date:	01/2019

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2017 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Microarray-Based Gene Expression Profile Testing for Multiple Myeloma Risk Stratification

Policy # 00461
Original Effective Date: 01/21/2015
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CPT is a registered trademark of the American Medical Association.
Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	81479, 81406, 81599, 86849
HCPCS	No codes
ICD-10 Diagnosis	C90.00-C90.02

*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

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