



BlueCross BlueShield
of Alabama

Name of Policy:

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

Policy #: 551
Category: Laboratory

Latest Review Date: October 2018
Policy Grade: B

Background/Definitions:

As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

- 1. The technology must have final approval from the appropriate government regulatory bodies;*
- 2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
- 3. The technology must improve the net health outcome;*
- 4. The technology must be as beneficial as any established alternatives;*
- 5. The improvement must be attainable outside the investigational setting.*

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

- 1. In accordance with generally accepted standards of medical practice; and*
- 2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
- 3. Not primarily for the convenience of the patient, physician or other health care provider; and*
- 4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.*

Description of Procedure or Service:

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-risk categories for prognostic 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 gene expression profile (GEP) analysis, which serves to reveal the underlying activity of cellular biologic pathways. This method lends itself to a variety of benefits including the ability to risk-stratify patients with multiple myeloma, as well as guide treatment decisions.

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 one in every 100 cancers, and 13% of hematologic cancers. The American Cancer Society has estimated 30,770 new cases of multiple myeloma will occur in the U.S. in 2018, and some 12,770 deaths due to the disease. The annual age-adjusted incidence is about six cases per 100,000 persons, with 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 five to ten years; in the pre-chemotherapy era, median survival was less than one year. Among patients who present at age younger than 60 years, ten-year overall survival with current treatment protocols now may 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 five years. Although both of these conditions 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. Pre-myeloma 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 Policy, 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 that undergo a similar intensity of treatment.

A microarray-based gene expression profile (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 (DNA) is transcribed into messenger RNA (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 two-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 pre-analysis 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, 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 inter-platform 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 (DSS) and the International Staging System (ISS). 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 (FISH) 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

Variables	High Risk	Intermediate Risk	Standard Risk
Variants	Any of the following: <ul style="list-style-type: none"> • Del 17p • t(14;16) by FISH • t(14;20) by FISH • GEP high-risk signature 	<ul style="list-style-type: none"> • t(4;14) by FISH • Cytogenetic del 13 • Hypodiploidy • Plasma cell labeling index >3.0 	All others including: <ul style="list-style-type: none"> • 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

Adapted from Mikhael et al (2013).

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 below). 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.

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, induction therapy is comprised of 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 Mayo Clinic, uses all available agents as induction, followed by two cycles of high-dose melphalan and autologous HCT support, with a four-year event-free survival as high as 78%. Despite 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 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.

Policy:

Microarray-based gene expression profile testing for multiple myeloma does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational for all indications.**

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member's contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

The most recent literature review was performed through August 6, 2018.

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

MyPRS™/MyPRS Plus™

Multiple myeloma is a 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 gene expression profile (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 of this Policy. 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 gene expression profiles (GEPs).

Clinical Context and Therapy Purpose

The purpose of a microarray-based GEP test (e.g., MyPRS™/MyPRS Plus™) in patients who have multiple myeloma is to provide risk stratification information that can be used to guide treatment decisions.

The question addressed in this evidence review is: Does the use of a microarray-based GEP test improve the net health outcome in patients with multiple myeloma?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest are patients with multiple myeloma.

Interventions

The therapy being considered is a microarray-based GEP test (e.g., MyPRS™/MyPRS Plus™) which provides risk stratification information. The level of risk reflects the aggressiveness of the disease, and ultimately dictates the intensity of initial treatment. The MyPRS™/MyPRS Plus™ GEP70 test analyzes 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.

Comparators

Tests such as the following may be used to perform standard clinical risk evaluation for multiple myeloma. Some of these tests may also be part of the diagnostic evaluation.

- complete blood count and differential examination of peripheral blood smear
- chemistry screen plus serum calcium, albumin, lactate dehydrogenase, and β -2 microglobulin
- serum creatinine and glomerular filtration rate estimate
- serum free light chain assay
- serum protein electrophoresis, routine urinalysis, and 24-hour urine collection
- bone marrow aspiration and biopsy with immunophenotyping and fluorescence in situ hybridization
- cross-sectional imaging (eg, computed tomography, positron emission tomography with computed tomography, or magnetic resonance imaging).

Outcomes

Long-term outcomes involve overall survival as well as disease-specific morbidity and mortality.

Timing

Measurement of long-term outcomes requires follow-up over years; multiple myeloma has a 5-year overall survival (OS) rate of 50%.

Setting

Clinical laboratories licensed by the Clinical Laboratory Improvement Amendment for high-complexity testing perform this test.

Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Randomized Controlled Trials (RCTs)

A phase 3 trial by Kumar et al (2011) examined the utility of the GEP70 risk stratification test among patients undergoing initial therapy with lenalidomide. 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 four cycles of therapy, patients could discontinue therapy to pursue hematopoietic cell transplantation (HCT) or continue on protocol until progression. Overall, 445 patients were randomized: 222 to the lowdose arm and 223 to the high-dose arm. As in the GEP70 validation study, CD138-positive plasma cells were isolated using bone marrow aspirates of consenting patients. Total messenger RNA was isolated from those cells and analyzed by high-density oligonucleotide microarrays containing probes for 50000 transcripts and variants including 14500 known human genes (Affymetrix U133Plus2.0 array). The GEP70 signature was determined as described by the Shaughnessy et al (2007) report and compared with OS data and other variables. Overall, 7 (15.6%) of 45 patients with adequate messenger RNA 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 the following translocations and deletions: t(4;14), t(14;16), t(14;20), and del(17p). 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 OS was 19 months for the 7 GEP70 high-risk patients; OS did not reach median for the standard-risk group. For 10 high-risk FISH patients, median OS was 39 months; OS 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, 0.61 to 0.88), a value conventionally considered to reflect a prediction model with good discriminatory ability. The C-statistic for FISH-based risk stratification was 0.70 (95% confidence interval, 0.55 to 0.84), very similar to the GEP70 finding. These results would suggest the GEP70 high-risk results are inversely associated with OS 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 precluded conclusions on the clinical utility of the test in risk stratification and therapeutic decisions, as well as an assessment of the incremental value of GEP70 compared with FISH.

Prospective and Retrospective Studies

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 OS 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.

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 hematopoietic cell transplantation (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 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.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

In our 2018 literature search of this evidence review for this policy, 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.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of this test for multiple myeloma has not been established, a chain of evidence cannot be constructed to support the test's clinical utility.

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 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 compared 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.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) practice guidelines (V.2.2019) for multiple myeloma state that “although GEP [gene expression profiling] is not currently routinely used in clinical practice during diagnostic workup, GEP is a useful tool and may be helpful in selected patients to estimate the aggressiveness of the disease and individualize treatment”. The Network offered no specific recommendation for the use of the MyPRS™ GEP70 test.

Mayo Clinic Stratification of Multiple Myeloma and Risk-Adapted Therapy

Guidelines from the Mayo Clinic (2017) have stated that “if indicated, gene expression profiling may be performed to further understand the behavior of the disease and guide therapy.”

U.S. Preventive Services Task Force Recommendations

Not applicable.

Key Words:

Gene expression profiling, myeloma, myPRS™, MyPRS Plus™, multiple myeloma, GEP, gene expression profile testing, gene expression, microarray-based gene expression profile, microarray technology, GEP70

Approved by Governing Bodies:

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. Food and Drug Administration has chosen not to require any regulatory review of this test.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

ITS: Home Policy provisions apply.

FEP: Special benefit consideration may apply. Refer to member's benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

Current Coding:

CPT Codes:

81479	Unlisted molecular pathology procedure
81599	Unlisted multianalyte assay with algorithmic analysis
86849	Unlisted immunology procedure

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Policy History:

Medical Policy Panel, July 2014,

Medical Policy Group, July 2014 **(1)** New Policy, previously only listed on Investigational Listing; remains investigational

Medical Policy Administration Committee, August 2014

Available for comment August 21 through October 4, 2014

Medical Policy Panel, October 2015

Medical Policy Group, October 2015 **(3)**: 2015 Updates to Key Points & References; no change in policy statement.

Medical Policy Panel, October 2017

Medical Policy Group, October 2017 **(3)**: 2017 Updates to Description, Key Points & Approved by Governing Bodies; no new references added; no change in policy statement.

Medical Policy Panel, October 2018

Medical Policy Group, October 2018 **(9)**: 2018 Updates to Description, Key Points, References; added key words: MyPRS Plus™, multiple myeloma, GEP, gene expression profile testing, gene expression, microarray-based gene expression profile, microarray technology, GEP70; no change to policy statement.

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plan contracts.