BlueCross BlueShield of Alabama

Name of Blue Advantage Policy:

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

Policy #: 551
Category: Laboratory

Latest Review Date: November 2019
Policy Grade: B

BACKGROUND:

Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
   - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
   - *Furnished in a setting appropriate to the patient's medical needs and condition;*
   - *Ordered and furnished by qualified personnel;*
   - *One that meets, but does not exceed, the patient's medical need; and*
   - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

POLICY:

Blue Advantage will treat **microarray-based gene expression profile testing for multiple myeloma** as a **non-covered benefit** and as **investigational** for all indications

Blue Advantage 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 Advantage administers benefits based on the members' contract and 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.

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 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 micro-dissected (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 β2-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: 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

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.

KEY POINTS:
The most recent literature review was performed through August 6, 2019.

Summary of Evidence
For individuals who have multiple myeloma who received risk stratification using a gene expression profiling test, the evidence includes retrospective series that correlate risk scores with survival. The 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.3.2019) 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".

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, 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.

CURRENT CODING:
CPT Codes:

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

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POLICY HISTORY:

Adopted for Blue Advantage, July 2014
Available for comment August 21 through October 4, 2014
Medical Policy Group, October 2015
Medical Policy Group, October 2017
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.
Medical Policy Group, November 2019
Medical Policy Group, February 2020: removed CPT code 86849.