Corporate Medical Policy

Microarray-Based Gene Expression Profile Testing for Multiple Myeloma Risk Stratification AHS-B0002

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Description of Procedure or Service

Microarray-based gene expression profile analysis has been proposed as a means to risk-stratify patients with multiple myeloma to guide treatment decisions.

Background

Multiple myeloma is a genetically complex, invariably fatal, neoplasm of plasma cells. 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 thus dictates the intensity of initial treatment. Thus, a risk-adapted approach is considered to provide optimal therapy to patients, ensuring intense treatment for those with aggressive disease and minimizing toxic effects delivers sufficient but less-intense therapy for lower-risk disease. However, clinical outcomes may vary substantially, using standard methods, among patients with the same estimated risk who undergo a similar intensity of treatment.

Microarray-based gene expression profile (GEP) analysis estimates the underlying activity of cellular biological pathways that control, for example, cell division or proliferation, apoptosis, metabolism, or other signaling pathways. Relative over- or under-expression 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 to personalize therapy selection according to tumor biology, with the goal of avoiding over- or under-treating patients. It could be used as a supplement to existing stratification methods or as a stand-alone test, but further study is necessary to establish its role.

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 gene expression profile (GEP) assay examines the patterns of many genes in a tissue sample at the same time to assess those that are actively producing mRNA or not, ultimately producing proteins or not. By simultaneously 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 mutations 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

This section of the Background comprises a generalized description of microarray-based technology. It also addresses laboratory issues that potentially affect the technical variability, hence reliability and interpretation, of GEP tests in cancer, including MyPRS™.

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 harvested from a patient's tissue sample and labeled with a fluorescent dye. These 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 to one another or to a common reference mRNA, and their relative expression levels can be quantified. After hybridization, gray-scale images corresponding to fluorescent signals are obtained by scanning the microarray with dedicated instruments, and the fluorescence intensity corresponding to each gene is 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 in the use of microarray technologies for clinical management. For example, the source of mRNA is one 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 relative instability of mRNA compared to DNA complicates GEP analysis studies compared to genomic analyses. Factors that affect RNA quality include pre-analysis storage time and the reagents used to prepare mRNA, including specific lots or batches of reagents. 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 technological platforms, protocols, and reagents can affect the analytical variability of the results, and thus 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 pre-processing 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 focus on documentation of experimental design, details, and results. Inter-platform and interlaboratory reproducibility also are topics of interest. 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.

Multiple Myeloma

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 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 6 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 5 to 10 years; in the pre-chemotherapy era, median survival was less than one year. Among patients who present at age younger than 60 years, 10-year overall survival with current treatment protocols now may reach more than 30%.

Pathogenesis and Genetic Architecture of Multiple Myeloma

Multiple myeloma is a complex disease that presents in distinct clinical phases and risk levels. These include monoclonal gammopathy of undetermined significance (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; it has an annual risk for transformation to multiple myeloma of about 10% for the first 5 years. Although both 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: calcium elevation; renal insufficiency; anemia; and, bone disease. Pre-myeloma plasma cells initially require interaction with the bone marrow microenvironment, but during disease progression, 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, and are used in conjunction with laboratory and radiographic studies to stratify patients for therapeutic decisions.

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 more than 30-years old DSS provides a method to measure multiple myeloma tumor burden, according to multiple myeloma cell numbers and clinical, laboratory and imaging studies, but is recognized to have significant shortcomings due to the use of observer-dependent studies (e.g., radiographic evaluation of bone lesions) primarily focused on tumor mass, not behavior. The ISS, incorporating serum albumin and β2-microglobulin measures, is considered valuable to permit comparison of outcomes across clinical trials and is more reproducible than the DSS. However, the ISS 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. It also does not provide a good estimate of tumor burden; is not generally useful for therapeutic risk stratification; and, 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 make treatment decisions for patients with newly diagnosed multiple myeloma.

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

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

In addition to the cytogenetic characteristics noted in Table 1, other findings are typically considered in this model (Table 2, Policy Guidelines). Although GEP analysis is included in Tables 1 and 2, the Mayo Clinic does not currently recommend nor routinely performs GEP analysis in a non-research setting. However, the investigators suggest GEP analysis will likely play a greater role in management of multiple myeloma as evidence develops.

The risk stratification model outlined in Table 1 is meant for prognostication and to determine the treatment approach; it is not utilized to decide whether to initiate therapy, but to guide the type of 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, as 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, followed by autologous hematopoietic stem-cell transplantation (HSCT). Older patients or those with underlying liver, lung, or cardiovascular dysfunction may be candidates for induction followed by reduced-intensity conditioning allogeneic HSCT.

A program referred to as Total Therapy, developed primarily at the University of Arkansas for Medical Science and Mayo Clinic, utilizes all available agents as induction, followed by 2 cycles

of high-dose melphalan and autologous HSCT support, with a 4-years 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.

Regulatory Status

The MyPRS™/MyPRS Plus™ GEP70 test (Signal Genetics LLC, Little Rock, AR) is being offered as a laboratory-developed test. The laboratory performing this test is accredited by the Centers for Medicare and Medicaid (CMS) under the Clinical Laboratory Improvement Amendments of 1988 (CLIA). The test will be performed by Signal Genetics and offered commercially through certain specialty commercial labs (e.g., Caris Life Sciences, Phoenix, AZ)

Related Policy:
Hematopoietic Cell Transplantation

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

Microarray-based gene expression profile testing for multiple myeloma is considered investigational for all applications. BCBSNC does not provide coverage for investigational services or procedures.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Microarray-Based Gene Expression Profile Testing for Multiple Myeloma is covered

Not applicable.

When Microarray-Based Gene Expression Profile Testing for Multiple Myeloma is not covered

Microarray-based gene expression profile testing for multiple myeloma is considered **investigational** for all indications.

Policy Guidelines

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 serum hypercalcemia, renal dysfunction, anemia and bone lesions (i.e., CRAB). Patients with MGUS or

smoldering myeloma do not require therapy, irrespective of any associated risk factors, except on specifically targeted protocols.

For individuals who have multiple myeloma who received risk stratification using a GEP test, the evidence includeds a 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 than patients without a high score. No evidence is available from studies that report the incremental value that this test would add to existing risk-stratification methods, nor have any studies prospectively allocated patients to risk-based therapies by GEP70 score. The evidence is insufficient to determine the effects of the technology on health outcomes.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable codes: *There is no specific code for this service.*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.97

Mikhael JR, Dingli D, Roy V et al. Management of Newly Diagnosed Symptomatic Multiple Myeloma: Updated Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) Consensus Guidelines 2013. Mayo Clin Proc 2013; 88(4):360-76.

Senior Medical Director – 8/2013

Specialty Matched Consultant Advisory Panel – 3/2014

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.97, 7/10/14

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BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.97, 10/27/17

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BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.97, 10/10/18

Specialty Matched Consultant Advisory Panel- 3/2019

Specialty Matched Consultant Advisory Panel- 3/2020

Medical Director review 3/2020

Specialty Matched Consultant Advisory Panel- 3/2021

Medical Director review 3/2021

Medical Director review 8/2023

Policy Implementation/Update Information

9/10/13 New policy. "Microarray-based gene expression profile testing for multiple myeloma is considered investigational for all indications." Senior Medical Director review 8/29/2013. (btw)

4/15/14 Specialty Matched Consultant Advisory Panel review 3/25/2014. No change to policy. (btw)

10/28/14 Reference added. (lpr)

4/28/15 Specialty matched consultant advisory panel review 3/25/2015. No change to policy intent. (lpr)

11/24/15 Reference added. No change to policy statement. (lpr)

4/29/16 Updated Policy Guidelines section. Specialty Matched Consultant Advisory Panel review 3/30/2016. No change to policy intent. (lpr)

4/28/17 Specialty Matched Consultant Advisory Panel review 3/29/2017. No change to policy statement. (lpr)

11/10/17 Reference added. (lpr)

4/27/18 Specialty Matched Consultant Advisory Panel review 3/28/2018. No change to policy statement. (lpr)

11/9/18 Reference added. (lpr)

4/1/19 Specialty Matched Consultant Advisory Panel review 3/20/2019. No change to policy statement. (lpr)

3/31/20 Specialty Matched Consultant Advisory Panel review 3/18/2020. No change to policy statement. (lpr)

4/6/21 Specialty Matched Consultant Advisory Panel review 3/17/2021.No change to policy statement. (lpr)

8/29/23 General review per Avalon CAB Q2 2023. Medical Director review 8/2023. No change to policy statement. (lpr)