CLINICAL UM POLICY FOR COVERAGE DETERMINATION

Policy Title:	Policy – BCR-ABL Genetic Testing (Qualitative or Quantitative)	Number & Version:	UM-Gene BCR-ABL
Functional Unit:	Utilization Management	Effective Date:	07/10/2023
Policy Owner (Title):	Director, Utilization Management	Page Number:	1 of 7

I. POLICY STATEMENT and PURPOSE

The purpose of this policy is to describe the circumstances under which BCR-ABL(1) (Qualitative or Quantitative) Genetic Testing would or would not be considered medically necessary for members under the guidelines used for clinical review of organizational determinations.

II. BACKGROUND

BCR (breakpoint cluster region)-ABL (non-receptor tyrosine kinase Abelson)1 refers to a gene sequence found in an abnormal chromosome 22 of some people with certain forms of leukemia. Unlike most cancers, the cause of chronic myelogenous leukemia (CML) and some other leukemias can be traced to a single, specific genetic abnormality in one chromosome (Testing.com, 2020). Nearly all cases of CML and a minority of cases of acute lymphocytic leukemia (ALL) are caused by a piece of one chromosome breaking off and attaching to another chromosome. This is known as the Philadelphia chromosome – which fuses 2 genes: BCR and ABL (NIBSC, 2022). The presence of the gene sequence known as BCR-ABL1 confirms the diagnosis of CML and a form of ALL, specifically a type of B-lymphoblastic leukemia/lymphoma (Testing.com, 2020). Acute myeloid leukemia (AML) with BCR-ABL1 is rare, but does occur (Takeuchi, 2021).

The BCR-ABL1 fusion acts as an oncogene, which can cause cancer, and promotes genomic instability. In the late 1990's, effective chemotherapy was developed for CML. This treatment and others that followed for other leukemias created the need for accurate measurement of the amount of the abnormal clone remaining in the patient. This is known as the measurement of minimal residual disease (MRD) and it has become the most useful measurement in monitoring the effectiveness of treatment in individual patients. Measurement of MRD is routinely performed quantifying levels of BCR-ABL1 mRNA transcripts in peripheral blood and bone marrow samples. The technique can determine accurately the response to treatment and is particularly valuable for patients who have achieved complete chromosomal remission (NIBSC, 2022).

A BCR-ABL test is usually obtained by a blood test or a bone marrow aspiration and biopsy. It is most often used to diagnose or rule out chronic myeloid leukemia (CML) or a specific form of acute lymphoblastic leukemia (ALL) called Ph-positive ALL. It can also be used for diagnosis and monitoring of AML. BCR-ABL testing is ALSO used to see if treatment is working as desired, or if the patient has become resistant to certain treatments, aka, pharmacogenomic testing (NIH, Sept., 2021) (ASCO, 2018) (CRO, 2015).

III. SCOPE

This Policy applies to BCR-ABL Genetic Testing (Qualitative or Quantitative), which may also be referred to as BCR-ABL1, BCR-ABL1 fusion, or Philadelphia (Ph) chromosome testing (MedlinePlus, Sept. 2021).

IV. DEFINITIONS

ALL – ALL is an abbreviation for Acute Lymphocytic Leukemia, which is a cancer of B or T lymphoblasts characterized by uncontrolled production of abnormal, immature lymphocytes and their antecedents. This leads to the replacement of bone marrow elements and other lymphoid organs resulting symptoms related to anemia, thrombocytopenia, and neutropenia due to the replacement of the bone marrow with the tumor. Symptoms that may present include fatigue, easy or spontaneous bruising and/or bleeding, and infections. Additionally, B-symptoms, such as fever, night sweats, and unintentional weight loss may occur. About half of the adults also experience hepatomegaly, splenomegaly, and lymphadenopathy. Central nervous system (CNS) involvement is common and can results in symptoms related to increased intracranial pressure (Puckett, 2022).

AML – AML is an abbreviation for Acute Myeloid Leukemia, which is a fast-growing cancer in which too many myeloblasts (a type of immature white blood cell) are found in the bone marrow and blood. Acute myeloid leukemia usually progresses quickly if it is not treated. It is known to spread outside the blood to other parts of the body, including the lymph nodes, spleen, liver, central nervous system (brain and spinal cord), skin, gums, and testicles. AML is is most often diagnosed in older adults. It is also known as acute myelogenous leukemia, acute nonlymphocytic leukemia, AML, and ANLL (NCI, 2023).

CML – CML is an abbreviation for Chronic Myeloid Leukemia, which is a myeloproliferative neoplasm predominantly made up of proliferating granulocytes. Almost half of the patients with CML have no symptoms and are diagnosed on routine complete blood count. In the chronic phase, patients with CML will frequently present with symptoms related to anemia and splenomegaly (Eden, 2023).

DNA - DNA is an abbreviation for deoxyribonucleic acid, which contains hereditary information (NIH, June 2021).

Genetic Testing - A medical test that looks for changes in DNA. Genetic tests analyze cells or tissue to look for any changes in genes, chromosomes, and proteins (MedlinePlus, June 2021).

Medically Necessary - Covered Services rendered by a Health Care Provider that the Plan determines are:

1) Safe and effective
2) Not experimental or investigational
3) Appropriate for patients,
   a) including the duration and frequency that is considered appropriate for the item or service, in terms of whether it is—
      i) 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,
      ii) furnished in a setting appropriate to the patient's medical needs and condition,
      iii) ordered and furnished by qualified personnel,
      iv) one that meets, but does not exceed, the patient's medical need; and
      v) is at least as beneficial as existing and available medically appropriate alternatives.

Minimal Residual Disease (MRD) – (sometimes referred to as Minimal Measurable Disease) refers to low-level disease detected in a variety of clinical conditions. It is used to describe residual disease after suboptimal induction chemotherapy, but at the same time refers to the lowest levels of disease potentially compatible with cure or to molecularly defined relapse after long-term remission (Paietta, 2002).

Pharmacogenomic testing - Testing used to help determine a course of treatment for a patient based either on the patient's genotype or on the genetic characteristics of their specific condition. It can be useful before the administration of a medication to determine potential effectiveness, dosing levels, or potential adverse interactions or events. It may be used after medication administration to determine an outcome in the patient. This type of testing is a key component of personalized, or precision, medicine (CRO, 2015).

V. OWNERSHIP & TRAINING

The Director of Utilization Management is responsible for administration, oversight, and training regarding performance under this Policy.

VI. PROTOCOLS / COVERAGE POLICY

A. BCR-ABL testing / analysis is considered **medically necessary** in the following circumstances:

i. in the diagnosis of individuals with suspected CML, ALL, or AML, and
ii. in the evaluation of individuals with CML or BCR-ABL positive ALL or AML to monitor response to therapy (MRD) (pharmacogenomic testing), and/or
iii. for the identification of recurrence or progression of disease within the intended use population as identified in the National Comprehensive Cancer Network (NCCN) or other established guidelines as a condition that requires a definitive change in patient management. (NCCN-ALL, 2022) (NCCN-AML, 2023) (NCCN-CML, 2023)

VII. REGULATORY REFERENCES / CITATIONS

CMS National Coverage Determination (NCD) none
CMS Local Coverage Determinations (LCDs) see table below
CMS Articles * available online

*https://www.cms.gov/medicare-coverage-database (keyword "BCR" and "Minimal Residual Disease Testing for Cancer)

L38822	MolDX: Minimal Residual Disease Testing for Cancer	LCD	CGS Administrators, LLC
L38814	MolDX: Minimal Residual Disease Testing for Cancer	LCD	Noridian Healthcare Solutions, LLC
L38816	MolDX: Minimal Residual Disease Testing for Cancer	LCD	Noridian Healthcare Solutions, LLC
L38779	MolDX: Minimal Residual Disease Testing for Cancer	LCD	Palmetto GBA
L38835	MolDX: Minimal Residual Disease Testing for Cancer	LCD	WPS Insurance Corporation

PROFESSIONAL REFERENCES / CITATIONS

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5. National Cancer Institute (NCI). NCI Dictionary of Cancer Terms. Accessed at: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/acute-myeloid-leukemia on April 26, 2023.

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9. National Institute for Biologic Standards and Control (NIBSC). WHO International Genetic Reference Panel for the quantitation of BCR-ABL1 translocation. Accessed at: https://www.nibsc.org/science_and_research/advanced_therapies/genomic_reference_materials/bcr-abl_(who).aspx on April 26, 2023.

10. National Institutes of Health (NIH). MedlinePlus. Bethesda (MD): National Library of Medicine (US). Updated September 14, 2021. Medical Test. BCR-ABL Genetic Test. Accessed at: https://medlineplus.gov/lab-tests/bcr-abl-genetic-test/ on April 26, 2023.

11. National Institutes of Health (NIH). MedlinePlus. Bethesda (MD): National Library of Medicine (US). Updated June 11, 2021. Medical Test. Genetic Testing. Accessed at: https://medlineplus.gov/genetictesting.html on April 26, 2023.

12. Paietta, E. Assessing minimal residual disease (MRD) in leukemia: a changing definition and concept?. Bone Marrow Transplant 29, 459–465 (2002). https://doi.org/10.1038/sj.bmt.1703388. Accessed at: https://www.nature.com/articles/1703388 on April 26, 2023.

13. Puckett Y, Chan O. Acute Lymphocytic Leukemia. June 27, 2022. StatPearls Publishing. National Institutes of Health. National Library of Medicine. Accessed at: https://www.ncbi.nlm.nih.gov/books/NBK459149/#:~:text=Acute%20lymphocytic%20leukemia%20(ALL)%20is,in%20a%20characteristic%20disease%20pattern on April 26, 2023.

14. Testing.com. BCR-ABL1. November 6, 2020. Accessed at: https://www.testing.com/tests/bcr-abl1/#:~:text=Breaks%20in%20the%20minor%20breakpoint,breakpoints%20in%20the%20fusion%20gene on April 26, 2023.

VIII. RELATED POLICIES / PROCEDURES

None

IX. ATTACHMENTS

See Section VII.

APPROVALS:

	Printed Name	Signature
Senior Medical Director, UM:	Michael Fusco, MD	
Corporate Chief Medical Officer (QMMC Chair):	Debbie Zimmerman, MD	

VERSION HISTORY:

Version #	Date	Author	Purpose/Summary of Major Changes
01	05/03/2023	Gina Vehige	Original; FINAL Approved by MMC 6/30/2023; Effective 07/10/2023

Medicare Administrative Contractors (MACs)
As of June 2021

MAC Jurisdiction	Processes Part A & Part B Claims for the following states/territories:	MAC
DME A	Connecticut, Delaware, District of Columbia, Maine, Maryland, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, Vermont	Noridian Healthcare Solutions, LLC
DME B	Illinois, Indiana, Kentucky, Michigan, Minnesota, Ohio, Wisconsin	CGS Administrators, LLC
DME C	Alabama, Arkansas, Colorado, Florida, Georgia, Louisiana, Mississippi, New Mexico, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Virginia, West Virginia, Puerto Rico, U.S. Virgin Islands	CGS Administrators, LLC
DME D	Alaska, Arizona, California, Hawaii, Idaho, Iowa, Kansas, Missouri, Montana, Nebraska, Nevada, North Dakota, Oregon, South Dakota, Utah, Washington, Wyoming, American Samoa, Guam, Northern Mariana Islands	Noridian Healthcare Solutions, LLC
5	Iowa, Kansas, Missouri, Nebraska	Wisconsin Physicians Service Government Health Administrators
6	Illinois, Minnesota, Wisconsin ****HH + H for the following states:** Alaska, American Samoa, Arizona, California, Guam, Hawaii, Idaho, Michigan, Minnesota, Nevada, New Jersey, New York, Northern Mariana Islands, Oregon, Puerto Rico, US Virgin Islands, Wisconsin and Washington	National Government Services, Inc.
8	Indiana, Michigan	Wisconsin Physicians Service Government Health Administrators
15	Kentucky, Ohio ****HH + H for the following states:** Delaware, District of Columbia, Colorado, Iowa, Kansas, Maryland, Missouri, Montana, Nebraska, North Dakota, Pennsylvania, South Dakota, Utah, Virginia, West Virginia, and Wyoming	CGS Administrators, LLC
E	California, Hawaii, Nevada, American Samoa, Guam, Northern Mariana Islands	Noridian Healthcare Solutions, LLC
F	Alaska, Arizona, Idaho, Montana, North Dakota, Oregon, South Dakota, Utah, Washington, Wyoming	Noridian Healthcare Solutions, LLC
H	Arkansas, Colorado, New Mexico, Oklahoma, Texas, Louisiana, Mississippi	Novitas Solutions, Inc.
J	Alabama, Georgia, Tennessee	Palmetto GBA, LLC
K	Connecticut, New York, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont ****HH + H for the following states:** Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, and Vermont	National Government Services, Inc.
L	Delaware, District of Columbia, Maryland, New Jersey, Pennsylvania (includes Part B for counties of Arlington and Fairfax in Virginia and the city of Alexandria in Virginia)	Novitas Solutions, Inc.
M	North Carolina, South Carolina, Virginia, West Virginia (excludes Part B for the counties of Arlington and Fairfax in Virginia and the city of Alexandria in Virginia) ****HH + H for the following states:** Alabama, Arkansas, Florida, Georgia, Illinois, Indiana, Kentucky, Louisiana, Mississippi, New Mexico, North Carolina, Ohio, Oklahoma, South Carolina, Tennessee, and Texas	Palmetto GBA, LLC
N	Florida, Puerto Rico, U.S. Virgin Islands	First Coast Service Options, Inc.

**Also Processes Home Health and Hospice claims