Clinical Policy: Genetic Testing – Gene Expression

Reference Number: WNC.CP.295
Last Review Date:

Coding Implications
Revision Log

See Important Reminders at the end of this policy for important regulatory and legal information.

Note: When state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Description

Gene expression refers to the mechanism through which the genetic information stored in a gene is transformed into a functional outcome. This predominantly transpires by transcribing RNA molecules that encode proteins or non-coding RNA molecules with alternative roles. Gene expression can be likened to an "on/off switch," determining the timing and location of RNA molecules and proteins production, and a "volume control," dictating the quantity of these products generated. The process of gene expression is meticulously regulated and undergoes significant changes based on various conditions and cell types. Numerous RNA and protein products derived from genes play a role in governing the expression of other genes. The extent, timing, and manner in which a gene is expressed can be evaluated by assessing the functional activity of its product or observing the phenotype associated with the gene.

Policy/Criteria[1]

I. WellCare of North Carolina® **shall cover** Genetic Testing – Gene Expression, when Member meets the following specific criteria:

A. WellCare of North Carolina shall cover Gene Expression profiling with the Oncotype DX® Breast Recurrence Score, EndoPredict®, Prosigna® Breast Cancer Prognostic Gene Signature Assay, the Breast Cancer Index℠ or MammaPrint® as a method for managing the treatment of breast cancer when ALL of the following criteria are met:

1. Member underwent surgery and comprehensive pathological evaluation of the specimen has been finalized;
2. Histology is ductal, lobular, mixed, or metaplastic;
3. Estrogen receptor positive (ER+), or progesterone receptor positive (PR+), or both;
4. HER2 (human epidermal growth factor receptor-2) receptor negative;
5. pN0 (node negative) or pN1mi with axillary lymph node micrometastasis less than or equal to 2 mm;
6. T1b to T3 (tumor size greater than 0.5 cm and less than or equal to 5.0 cm);

7. The Member and their healthcare provider are contemplating the utilization of chemotherapy as a potential therapeutic approach; **AND**
8. No additional gene expression profiling for breast cancer has been performed on the same tumor (such as a metastatic focus) or on multiple sites when the primary tumor is multifocal; **OR**

B. WellCare of North Carolina® **shall cover** the use of gene expression profiling with the Oncotype DX Breast Recurrence Score for postmenopausal individuals with one (1)- three (3) positive lymph nodes (pN1a, pN1b or pN1c) when the criteria in Subsection 3.2.1(a)(1-4; 6-8) are also met; **OR**

C. WellCare of North Carolina® **shall cover** the use of gene expression profiling with EndoPredict, Prosigna Breast Cancer Prognostic Gene Signature Assay, or the Breast Cancer Index as a genetic indicator employed to aid in determining whether to prolong adjuvant hormonal therapy beyond a five (5)-year treatment period when **ALL** of the following criteria are met:
1. When the criteria in Subsection 3.2.1(a)(1-6) have been met;
2. When the Oncotype DX Breast Recurrence Score was the initial gene expression profiling test used; **AND**
3. The Member is a candidate for additional cancer therapy; **OR**

D. WellCare of North Carolina® **shall cover** the use of gene expression profiling with the Breast Cancer Index as a genetic indicator employed to aid in determining whether to prolong adjuvant hormonal therapy beyond a five (5)-year treatment period for members with one (1)-three (3) positive lymph nodes (pN1a, pN1b or pN1c) when **ALL** of the following criteria are met:
1. When the criteria in Subsection 3.2.1(a) (1-4) have been met; **AND**
2. When the Oncotype DX Breast Recurrence Score was the initial gene expression profiling test used; **AND**
3. The Member is a candidate for additional hormonal or chemotherapy. **OR**

E. WellCare of North Carolina® **shall cover** gene expression profiling tests for evaluation of a thyroid nodule when **ALL** of the following criteria are met:
1. Member is age 21 years of age and older; **AND**
2. Thyroid nodule is indicated by ALL of the following:
    a. A diameter measuring one (1) cm or more on ultrasound; **AND**
    b. Uncertain cytology (also known as cytopathology) results from an initial fine needle aspirate biopsy, as indicated by **one or more** of the following:
        i. Atypia of undetermined significance;
        ii. Follicular lesion of undetermined significance;
        iii. Follicular neoplasm;
        iv. Suspicious for follicular neoplasm; **OR**
        v. Suspicious for malignancy

II. Additional Criteria Covered

In addition to the specific criteria covered in Criteria I., of this policy, for **ALL** covered Gene Expression profiling tests discussed in this policy, **ALL** of the following additional criteria must be met:

- **A.** A certified genetic counselor or ordering provider shall evaluate and counsel the Member pre- and post-test. Refer to Criteria IV.E. and Background I.E.;
- **B.** After genetic counseling has been provided, informed consent is obtained prior to, and Member agrees to testing;
- **C.** The test must not be duplicative of another performed test;
- **D.** The test must be performed by a certified Clinical Laboratories Improvement Amendment (CLIA) laboratory;
- **E.** The test must be clinically valid, based on published peer-reviewed literature, and available for the suspected diagnosis; **and**
- **F.** The test must be proven scientifically valid for the identification of a specific genetically linked disease or clinical condition.

III. WellCare of North Carolina® **shall NOT cover** gene expression profiling tests with the Oncotype DX Breast Recurrence Score, EndoPredict, Prosigna Breast Cancer Prognostic Gene Signature Assay, the Breast Cancer Index or MammaPrint as a technique of managing the treatment of breast cancer when the criteria in Criteria I or II, have not been met, or for **ANY** of the following indications:

- **A.** To predict response to specific chemotherapy regimens;
- **B.** For a Member with known metastatic cancer;
- **C.** Gene expression profiling as a technique of managing the treatment of ductal carcinoma in situ (DCIS) (when DCIS is the sole breast cancer histology);
- **D.** Gene expression profiling for the same tumor (such as a metastatic focus) or from more than one (1) site when the primary tumor is multifocal;
- **E.** Use of gene expression profiling to determine risk in a Member with primary breast cancer who meets the criteria in Section 3.0 but who has made the decision to undergo or forego chemotherapy; **OR**
- **F.** Oncotype DX Breast Recurrence Score, EndoPredict, Prosigna Breast Cancer Gene expression profiling as a technique of managing the treatment of breast cancer when a gene expression profiling test other than the Prognostic Gene Signature Assay, the Breast Cancer Index or MammaPrint is being used.

Note: WellCare of North Carolina® **shall NOT cover** Gene Expression profiling tests for evaluation of a thyroid nodule when the criteria in Criteria II are not met.

IV. Additional Limitations on Coverage

- **A.** WellCare of North Carolina® requires prior approval for certain Gene Expression profiling tests. Please see WellCare North Carolina Provider Authorization Lookup for specific service code prior authorization requirements. For services that require prior authorization, providers shall follow the requirements documented in Criteria IV.B, below.

B. The provider(s) **shall submit** to WellCare of North Carolina® the following:
1. The prior approval request; and
2. All health records and any other records that support the Member has met the specific criteria in Criteria I or II of this policy.

C. Testing Limitations
Refer to CPT Code boxes, listed below, for testing limitations for CPT codes covered in this policy.

D. Documentation Requirements
When the provider requests additional units for the CPT Codes found in CPT Code boxes, listed below, then, in addition to the prior approval requirements found in Criteria IV.B., the following supporting documentation is required to justify the request:
1. The reason for the test(s);
2. Previous related lab results;
3. How the test results contribute to improved health outcomes; **AND**
4. How the test results alter the Member's treatment and management.

E. Provider Certifications
1. Genetic counseling must be provided by a medical (licensed) provider or genetic counselor that is certified by the American Board of Genetic Counseling or has an Active Candidate Status. A genetic counselor shall be employed by or under contract to hospitals or other entities that employ licensed physicians. Licensed physicians shall be responsible for providing on-site clinical supervision and be directly involved in the care of an NC Medicaid Member for whom the counseling service is billed. The services of the Genetic Counselor are billed by the supervising physician. See Definitions D. and E. below for additional requirements for genetic counselors and licensed providers.
2. Clinical laboratory services must be rendered only by medical care entities that are issued certifications that are in compliance with the Clinical Laboratories Improvement Amendment (CLIA) [Public Law 100-578, amended §353 of the Public Health Service Act (PHSA)].

Background[1]

I. Definitions:

A. Adjuvant Therapy
Adjuvant therapy refers to an additional treatment approach employed after the primary treatment (such as surgery or radiation therapy) for a specific condition, typically cancer. It is administered with the intention of eliminating any remaining cancer cells that may not have been removed by the primary treatment or to reduce the risk of cancer recurrence. Adjuvant therapy aims to improve long-term outcomes

and enhance the chances of cure or disease control. It is often used in conjunction with the primary treatment to provide a comprehensive and more effective approach to managing the condition.

B. Estrogen Receptor (ER)

Estrogen receptor (ER) is a protein that responds to estrogen and influences cell growth and gene expression. It is relevant in cancer treatment decisions and hormone therapies.

C. Genetics

Genetics involves investigating the impact of genes on an individual's characteristics and traits.

D. Genetic Counselor

Genetic counselors are health professionals with specialized education, training, and experience in medical genetics and counseling. They are certified by the American Board of Genetic Counseling or have an Active Candidate Status for certification. They help a Member understand and adapt to the implications of genetic contributions to disease.

E. Genetic Counseling

Genetic counseling is a process of communication that allows members and their families to make informed medical decisions. These services include obtaining a structured family medical and genetic history, constructing a multiple-generation genetic pedigree, performing an analysis of available medical information for genetic risk assessment, and counseling the Member and family. This counseling includes natural history of disease, recurrence risk to family members, and availability of testing, screening and monitoring options. (Criteria IV.E.)

A licensed provider may provide genetic counseling when there is no access to a fellowship-trained genetic subspecialty physician or a certified genetic counselor. Similar to other genetic counselors, the licensed provider shall discuss and document in the Member's health record the following:

1. Likelihood of developing disease;
2. Impact of the disease;
3. Possibility of modification of either the impact or likelihood of disease;
4. Anticipated future developments in diagnosis or treatment; **AND**
5. Informed consent to testing was obtained after the Member verbalized understanding of the testing procedure, the benefits and limitations of the test, and the possible consequences of the test results.

F. Genomics

Genomics is all a person's DNA. Genomics is the study of a person's genes (the genome) explores the entirety of DNA, encompassing genes, by investigating its structure, function, mapping, and evolutionary aspects.

G. Histology
Histology is the study of tissues, focusing on their microscopic structure and composition.

H. Hormonal Therapy
Hormonal therapy is a treatment that modifies hormone levels or activity to manage hormone-sensitive conditions, such as certain types of cancer.

I. Human Epidermal Growth Factor Receptor 2 (HER2)
HER2 (Human Epidermal Growth Factor Receptor 2) is a protein receptor found on certain cells, including cancer cells. It influences cell growth and is used as a biomarker in cancer diagnosis and treatment decisions.

J. Phenotype
Phenotype refers to a person's observable traits resulting from the interaction between genes and the environment.

K. Primary Cancer
Primary cancer refers to the initial site where a cancerous tumor originates within the body before it potentially spreads to other locations.

L. Progesterone Receptor (PR)
Progesterone receptor (PR) is a protein that responds to progesterone and regulates gene expression and cellular functions, particularly in the female reproductive system. It is relevant in reproductive processes and can impact hormone-based treatments.

Coding Implications
This clinical policy references Current Procedural Terminology (CPT®). CPT® is a registered trademark of the American Medical Association. All CPT codes and descriptions are copyrighted 2024, American Medical Association. All rights reserved. CPT codes and CPT descriptions are from the current manuals and those included herein are not intended to be all-inclusive and are included for informational purposes only. Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

BREAST CANCER		
CPT®* Codes	**Description**	**Unit Limitations**
81518	Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 11 genes (7 content and 4 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithms reported as percentage risk for metastatic recurrence and likelihood of benefit from extended endocrine therapy	Once each primary cancer occurrence

BREAST CANCER		
CPT®* Codes	**Description**	**Unit Limitations**
81519	Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 21 genes, utilizing formalin-fixed paraffin embedded tissue, algorithm reported as recurrence score	Once each primary cancer occurrence
81520	Oncology (breast), mRNA gene expression profiling by hybrid capture of 58 genes (50 content and 8 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a recurrence risk score	Once each primary cancer occurrence
81521	Oncology (breast), mRNA, microarray gene expression profiling of 70 content genes and 465 housekeeping genes, utilizing fresh frozen or formalin-fixed paraffin-embedded tissue, algorithm reported as index related to risk of distant metastasis	Once each primary cancer occurrence
81522	Oncology (breast), mRNA, gene expression profiling by RT-PCR of 12 genes (8 content and 4 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence risk score	Once each primary cancer occurrence
81523	Oncology (breast), mRNA, next-generation sequencing gene expression profiling of 70 content genes and 31 housekeeping genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as index related to risk to distant metastasis	Once each primary cancer occurrence

THYROID CANCER		
CPT®* Codes	**Description**	**Unit Limitations**
81546	Oncology (thyroid), mRNA, gene expression analysis of 10,196 genes, utilizing fine needle aspirate, algorithm reported as a categorical result (e.g., benign or suspicious)	Once each primary cancer occurrence
0018U	Oncology (thyroid), microRNA profiling by RT-PCR of 10 microRNA sequences, utilizing fine needle aspirate, algorithm reported as a positive or negative result for moderate to high risk of malignancy	Once each primary cancer occurrence
0026U	Oncology (thyroid), DNA and mRNA of 112 genes, next-generation sequencing, fine needle aspirate of thyroid nodule, algorithmic analysis reported as a categorical result ("Positive, high probability of malignancy" or "Negative, low probability of malignancy")	Once each primary cancer occurrence
0204U	Oncology (thyroid), mRNA, gene expression analysis of 593 genes (including BRAF, RAS, RET, PAX8, and NTRK) for	Once each primary cancer occurrence

THYROID CANCER		
CPT®* Codes	Description	Unit Limitations
	sequence variants and rearrangements, utilizing fine needle aspirate, reported as detected or not detected	
0245U	Oncology (thyroid), mutation analysis of 10 genes and 37 RNA fusions and expression of 4 mRNA markers using next-generation sequencing, fine needle aspirate, report includes associated risk of malignancy expressed as a percentage	Once each primary cancer occurrence
0287U	Oncology (thyroid), DNA and mRNA, next-generation sequencing analysis of 112 genes, fine needle aspirate or formalin-fixed paraffin-embedded (FFPE) tissue, algorithmic prediction of cancer recurrence, reported as a categorical risk result (low, intermediate, high)	Once each primary cancer occurrence

GENETIC COUNSELING		
CPT®* Codes	Description	Unit Limitations
96040	Medical genetics and genetic counseling services, each 30 minutes face-to-face with patient/family	3 units (1 unit = 30 minutes) 90 minutes total: Refer to Criteria II.A.

Reviews, Revisions, and Approvals	Reviewed Date	Approval Date
Original approval date		

References

1. State of North Carolina Medicaid Clinical Coverage Policy No:1S-11 Genetic Testing – Gene Expression. Program Specific Clinical Coverage Policies | NC Medicaid (ncdhhs.gov). Published July 1, 2024. Accessed July 2, 2024.

North Carolina Guidance

Eligibility Requirements

1. An eligible beneficiary shall be enrolled in the NC Medicaid Program (Medicaid is NC Medicaid program, unless context clearly indicates otherwise);
2. Provider(s) shall verify each Medicaid beneficiary's eligibility each time a service is rendered.
3. The Medicaid beneficiary may have service restrictions due to their eligibility category that would make them ineligible for this service.

EPSDT Special Provision: Exception to Policy Limitations for a Medicaid Beneficiary under 21 Years of Age

- 42 U.S.C. § 1396d(r) [1905(r) of the Social Security Act]

Early and Periodic Screening, Diagnostic, and Treatment (EPSDT) is a federal Medicaid requirement that requires the state Medicaid agency to cover services, products, or procedures for Medicaid beneficiary under 21 years of age if the service is medically necessary health care to correct or ameliorate a defect, physical or mental illness, or a condition [health problem] identified through a screening examination (includes any evaluation by a physician or other licensed practitioner).

This means EPSDT covers most of the medical or remedial care a child needs to improve or maintain his or her health in the best condition possible, compensate for a health problem, prevent it from worsening, or prevent the development of additional health problems.

Medically necessary services will be provided in the most economic mode, as long as the treatment made available is similarly efficacious to the service requested by the beneficiary's physician, therapist, or other licensed practitioner; the determination process does not delay the delivery of the needed service; and the determination does not limit the beneficiary's right to a free choice of providers.

EPSDT does not require the state Medicaid agency to provide any service, product or procedure:

I. that is unsafe, ineffective, or experimental or investigational.
II. that is not medical in nature or not generally recognized as an accepted method of medical practice or treatment.

Service limitations on scope, amount, duration, frequency, location of service, and other specific criteria described in clinical coverage policies may be exceeded or may not apply as long as the provider's documentation shows that the requested service is medically necessary "to correct or ameliorate a defect, physical or mental illness, or a condition" [health problem]; that is, provider documentation shows how the service, product, or procedure meets all EPSDT criteria, including to correct or improve or maintain the beneficiary's health in the best condition possible, compensate for a health problem, prevent it from worsening, or prevent the development of additional health problems.

EPSDT and Prior Approval Requirements

- If the service, product, or procedure requires prior approval, the fact that the beneficiary is under 21 years of age does NOT eliminate the requirement for prior approval.
- **IMPORTANT ADDITIONAL INFORMATION** about EPSDT and prior approval is found in the *NCTracks Provider Claims and Billing Assistance Guide*, and on the EPSDT provider page. The Web addresses are specified below:
  NCTracks Provider Claims and Billing Assistance Guide:
  https://www.nctracks.nc.gov/content/public/providers/provider-manuals.html
  EPSDT provider page: https://medicaid.ncdhhs.gov/

Provider(s) Eligible to Bill for the Procedure, Product, or Service
To be eligible to bill for the procedure, product, or service related to this policy, the provider(s)

shall:

i. meet Medicaid qualifications for participation;
ii. have a current and signed Department of Health and Human Services (DHHS) Provider Administrative Participation Agreement; and
iii. bill only for procedures, products, and services that are within the scope of their clinical practice, as defined by the appropriate licensing entity.

Compliance

Provider(s) shall comply with the following in effect at the time the service is rendered:

A. All applicable agreements, federal, state and local laws and regulations including the Health Insurance Portability and Accountability Act (HIPAA) and record retention requirements; and
B. All NC Medicaid's clinical (medical) coverage policies, guidelines, policies, provider manuals, implementation updates, and bulletins published by the Centers for Medicare and Medicaid Services (CMS), DHHS, DHHS division(s) or fiscal contractor(s).

Claims-Related Information

Provider(s) shall comply with the NC Tracks Provider Claims and Billing Assistance Guide, Medicaid bulletins, fee schedules, NC Medicaid's clinical coverage policies and any other relevant documents for specific coverage and reimbursement for Medicaid:

- Claim Type - as applicable to the service provided:
  Professional (CMS-1500/837P transaction)
  Institutional (UB-04/837I transaction)
  Unless directed otherwise, Institutional Claims must be billed according to the National Uniform Billing Guidelines. All claims must comply with National Coding Guidelines.
- International Classification of Diseases and Related Health Problems, Tenth Revisions, Clinical Modification (ICD-10-CM) and Procedural Coding System (PCS) - Provider(s) shall report the ICD-10-CM and Procedural Coding System (PCS) to the highest level of specificity that supports medical necessity. Provider(s) shall use the current ICD-10 edition and any subsequent editions in effect at the time of service. Provider(s) shall refer to the applicable edition for code description, as it is no longer documented in the policy.
- Code(s) - Provider(s) shall report the most specific billing code that accurately and completely describes the procedure, product or service provided. Provider(s) shall use the Current Procedural Terminology (CPT), Health Care Procedure Coding System (HCPCS), and UB-04 Data Specifications Manual (for a complete listing of valid revenue codes) and any subsequent editions in effect at the time of service. Provider(s) shall refer to the applicable edition for the code description, as it is no longer documented in the policy. If no such specific CPT or HCPCS code exists, then the provider(s) shall report the procedure, product or service using the appropriate unlisted procedure or service code.
  Unlisted Procedure or Service
  CPT: The provider(s) shall refer to and comply with the Instructions for Use of the CPT Codebook, Unlisted Procedure or Service, and Special Report as documented in the current CPT in effect at the time of service.

HCPCS: The provider(s) shall refer to and comply with the Instructions For Use of HCPCS National Level II codes, Unlisted Procedure or Service and Special Report as documented in the current HCPCS edition in effect at the time of service

- Modifiers - Providers shall follow applicable modifier guidelines.
- Billing Units - Provider(s) shall report the appropriate code(s) used which determines the billing unit(s).
- Co-payments -
  For Medicaid refer to Medicaid State Plan:
  https://medicaid.ncdhhs.gov/get-involved/nc-health-choice-state-plan

- Reimbursement - Provider(s) shall bill their usual and customary charges. For a schedule of rates, refer to: https://medicaid.ncdhhs.gov/.

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members/enrollees. This clinical policy is not intended to recommend treatment for members/enrollees. Members/enrollees should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members/enrollees and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members/enrollees and their representatives agree to be bound by such terms and conditions by providing services to members/enrollees and/or submitting claims for payment for such services.