DRAFT

To all beneficiaries enrolled in a Prepaid Health Plan (PHP): for questions about benefits and services available on or after implementation, please contact your PHP.

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1.0 Description of the Procedure, Product, or Service

Next-generation sequencing, also referred to as next-gen sequencing, has revolutionized genetic research and healthcare by enabling the identification of genetic variations. This innovative technique involves determining the sequence of nucleotides, the building blocks of DNA, in a beneficiary's genetic code, which is known as DNA sequencing. Two commonly employed methods, namely **whole exome sequencing** and **whole genome sequencing**, leverage advanced technologies that enable the rapid sequencing of substantial amounts of DNA. These approaches have significantly propelled the field of genetics and serve as invaluable tools in the detection of genetic disorders.

1.1 Definitions

1.1.1 Checkpoint Inhibition Immunotherapy

Immune checkpoint inhibitors are drugs that target certain proteins known as checkpoints, present on specific immune system cells like T cells, as well as on certain cancer cells. These checkpoints play a role in regulating immune responses to prevent them from becoming overly aggressive and can sometimes hinder T cells from effectively eliminating cancer cells. By blocking these checkpoints, immune checkpoint inhibitors enable T cells to enhance their ability to kill cancer cells more effectively. Immune checkpoint inhibitors are utilized in cancer treatment.

1.1.2 Close Relatives (First-, Second- and Third-Degree Relatives)

a. A **first-degree relative** is a close blood relative which includes the beneficiary's parents, full siblings, and children.
b. A **second-degree relative** is a blood relative which includes the beneficiary's grandparents, grandchildren, aunts, uncles, nephews, nieces, and half-siblings.
c. A **third-degree relative** is a blood relative which includes the beneficiary's first cousins, great-grandparents, great-grandchildren on the same side of the family.

1.1.3 Consanguinity

Consanguinity is a term used to describe a close biological relationship between individuals who share a common ancestor. It signifies a blood tie or kinship among family members, particularly those closely related by descent from the same forebear, such as parents, siblings, grandparents, or cousins.

1.1.4 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 beneficiary understand and adapt to the implications of genetic contributions to disease.

1.1.5 Genetic Counseling

Genetic counseling is a process of communication that allows a beneficiary and their family 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 beneficiary and family. This counseling includes natural history of disease, recurrence risk to family members, and availability of testing, screening and monitoring options. (Refer to **Subsection 6.2**)

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 beneficiary's health record the following:

a. Likelihood of developing disease;
b. Impact of the disease;
c. Possibility of modification of either the impact or likelihood of disease;
d. Anticipated future developments in diagnosis or treatment; and
e. Informed consent to testing was obtained after the beneficiary verbalized understanding of the testing procedure, the benefits and limitations of the test, and the possible consequences of the test results.

1.1.6 Molecular Profiling

Molecular profiling, also known as comprehensive genomic profiling, is a technique used to detect various biomarkers within cancerous tumor of beneficiary with cancer. These biomarkers provide valuable information to identify potential treatment options.

1.1.7 Phenotype

Phenotype refers to a beneficiary's observable characteristics resulting from the interaction between an organism's genes and the environment.

1.1.8 Tumor Mutation Burden (TMB)

Tumor Mutation Burden (TMB) refers to the overall count of somatic mutations (changes) detected in the DNA of cancer cells. Understanding the TMB can aid in devising the most effective treatment strategy. For instance, tumors with a high mutation count are believed to be more responsive to certain forms of immunotherapy. TMB serves as a valuable biomarker in this context.

1.1.9 Whole Exome Sequencing

Whole exome sequencing (WES) is a laboratory technique employed to identify the nucleotide sequence of a beneficiary's genome, focusing mainly on the exonic regions that code for proteins. These regions, which comprise around 1% of the entire DNA sequence, and their associated sequences are analyzed during this process.

1.1.10 Whole Genome Sequencing

Whole genome sequencing (WGS) is a laboratory process utilized to ascertain nearly all of a beneficiary's complete DNA sequence, encompassing

approximately 3 billion nucleotides. This comprehensive analysis contains both coding and non-coding sequences within the genome.

2.0 Eligibility Requirements

2.1 Provisions

2.1.1 General

(*The term "General" found throughout this policy applies to all Medicaid policies*)

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

2.1.2 Specific

(***The term "Specific" found throughout this policy only applies to this policy***)

a. Medicaid
None Apply.

2.2 Special Provisions

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

a. **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:

1. that is unsafe, ineffective, or experimental or investigational.
2. 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.

b. **EPSDT and Prior Approval Requirements**

1. 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.
2. **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/

3.0 When the Procedure, Product, or Service Is Covered

Note: Refer to Subsection 2.2.1 regarding EPSDT Exception to Policy Limitations for a Medicaid Beneficiary under 21 Years of Age.

3.1 General Criteria Covered

Medicaid shall cover the procedure, product, or service related to this policy when medically necessary, and:

a. the procedure, product, or service is individualized, specific, and consistent with symptoms or confirmed diagnosis of the illness or injury under treatment, and not in excess of the beneficiary's needs;
b. the procedure, product, or service can be safely furnished, and no equally effective and more conservative or less costly treatment is available statewide; and
c. the procedure, product, or service is furnished in a manner not primarily intended for the convenience of the beneficiary, the beneficiary's caretaker, or the provider.

3.2 Specific Criteria Covered

3.2.1 Medicaid Specific Criteria Covered

Medicaid shall cover Genetic Testing – Next Generation Sequencing (NGS) when the beneficiary meets the following specific criteria:

a. Medicaid shall cover whole exome sequencing (WES) (CPT 81415) for the evaluation of unexplained congenital anomalies or neurodevelopmental disorders in a beneficiary 21 years of age and younger when **ALL** of the following criteria are met:
   1. The beneficiary has **one** of the following:
      A. A severe global developmental delay or intellectual disability;
      B. A family history that strongly indicates a genetic etiology, including consanguinity; or
      C. A period of developmental regression without a clear explanation, unrelated to autism or epilepsy;
      and
   2. The clinical presentation does not match any well-defined syndrome for which single-gene or targeted panel testing (such as comparative genomic hybridization or chromosomal microarray analysis) is available;
   3. A genetic etiology is the most probable explanation for the phenotype or clinical scenario regardless of previous genetic testing (such as chromosomal microarray analysis or targeted single gene testing), or when previous genetic testing has failed to produce a diagnosis and the affected beneficiary faces invasive procedures or testing as the next diagnostic step (such as a muscle biopsy);
   4. The symptoms cannot be attributed to any other etiologies such as environmental exposures, injury, or infection; **and**
   5. The results of WES have the potential to significantly influence beneficiary's management and improve the clinical outcome for the beneficiary undergoing testing.

b. Medicaid shall cover comparator exome sequence analysis (CPT 81416) when the criteria in **Subsection 3.2.1(a)** have been met and WES is being performed simultaneously or has been previously performed.

c. Medicaid shall cover whole exome reanalysis (CPT 81417) of previously acquired uninformative whole exome sequence when **one** of the following criteria is met:
   1. The onset of additional symptoms has emerged, expanding the phenotype assessed during the initial exome evaluation; **or**
   2. There has been the birth or diagnosis of a similarly affected first-degree relative added to the clinical picture.

d. Medicaid shall cover whole genome sequencing (WGS) (CPT 81425) for the assessment of unexplained congenital anomalies or neurodevelopmental disorders in newborns when **ALL** of the following criteria are met:
   1. The beneficiary is 12 months of age and younger and currently admitted to or recently discharged from a Neonatal Intensive Care Unit (NICU) or Pediatric Intensive Care Unit (PICU);
   2. When standard clinical workup does not lead to a definitive diagnosis;

3. When the beneficiary's phenotype lacks clear identification of a specific disease with an established single gene or multi-gene panel, or the beneficiary exhibits phenotypic characteristics that extend beyond or differ from what is known for the disease;
4. A genetic etiology is the most probable explanation for the phenotype or clinical scenario regardless of previous genetic testing (such as chromosomal microarray analysis or targeted single gene testing), or when previous genetic testing has failed to produce a diagnosis and the affected beneficiary faces invasive procedures or testing as the next diagnostic step (such as a muscle biopsy);
5. The symptoms cannot be attributed to any other causative factors, such as environmental exposures, injury, or infection; **and**
6. A confirmed diagnosis will lead to clinical utility, resulting in improved net health outcomes.

e. Medicaid shall cover comparator genome sequence analysis (CPT 81426) when the criteria in **Subsection 3.2.1(d)** have been met and WGS is being performed simultaneously or has been previously performed.

f. Medicaid shall cover whole genome reanalysis (CPT 81427) of previously acquired uninformative whole genome sequence when **one** of the following criteria is met:
   1. The onset of additional symptoms has emerged, expanding the phenotype assessed during the initial genome evaluation; **or**
   2. There has been the birth or diagnosis of a similarly affected first-degree relative added to the clinical picture.

g. Medicaid shall cover molecular profiling for the evaluation of malignancies when **ALL** of the following criteria are met:
   1. The beneficiary has a solid tumor that is inoperable or has spread to other parts of the body (metastatic);
   2. The purpose of the test is to evaluate the tumor mutation burden (TMB);
   3. The test is employed to identify a beneficiary eligible for checkpoint inhibition immunotherapy; **and**
   4. There are no viable alternative treatment options available for the beneficiary.

h. Medicaid shall cover the use of a circulating tumor DNA (ctDNA) test to direct precise cancer treatments for a beneficiary with a solid tumor when the criteria in **Subsection 3.2.1(g)** are met and when formalin-fixed paraffin-embedded tumor tissue (FFPET) lacks sufficient quality or quantity or is unavailable for analysis.

3.2.2 Medicaid Additional Criteria Covered

In addition to the specific criteria covered in **Subsection 3.2.1** of this policy, Medicaid shall cover next generation sequencing testing when ALL of the following criteria is met:

a. A certified genetic counselor or ordering provider shall evaluate and counsel the beneficiary pre- and post-test. Refer to **Subsections 1.1.5** and **6.2;**

b. After genetic counseling has been provided, informed consent is obtained prior to, and beneficiary agrees to testing;
c. The test must guide treatment;
d. The test must not be duplicative of another performed test;
e. The test must be performed by a certified Clinical Laboratory Improvement Amendment (CLIA) laboratory;
f. The test must be clinically valid, based on published peer-reviewed literature, and available for the suspected diagnosis; **and**
g. The test must be proven scientifically valid for the identification of a specific genetically linked disease or clinical condition.

4.0 When the Procedure, Product, or Service Is Not Covered

Note: Refer to Subsection 2.2.1 regarding EPSDT Exception to Policy Limitations for a Medicaid Beneficiary under 21 Years of Age.

4.1 General Criteria Not Covered

Medicaid shall not cover the procedure, product, or service related to this policy when:
a. the beneficiary does not meet the eligibility requirements listed in **Section 2.0;**
b. the beneficiary does not meet the criteria listed in **Section 3.0;**
c. the procedure, product, or service duplicates another provider's procedure, product, or service; or
d. the procedure, product, or service is experimental, investigational, or part of a clinical trial.

4.2 Specific Criteria Not Covered

4.2.1 Medicaid Specific Criteria Not Covered

a. Medicaid shall not cover whole exome sequencing (WES) or whole genome sequencing (WGS) for **ANY** of the following scenarios:
   1. When the criteria in **Subsection 3.2.1** are not met;
   2. For uncomplicated autism spectrum disorder, developmental delay, and mild to moderate global developmental delay;
   3. For screening during pregnancy to diagnose fetal conditions;
   4. For testing an embryo before implantation;
   5. For screening genetic carriers;
   6. Genetic disorders in every other circumstance; **or**
   7. The test is used to determine ancestry.
b. Medicaid shall not cover molecular profiling when the criteria in **Subsection 3.2.1(g)** are not met.

4.2.2 Medicaid Additional Criteria Not Covered

None Apply.

5.0 Requirements for and Limitations on Coverage

Note: Refer to Subsection 2.2.1 regarding EPSDT Exception to Policy Limitations for a Medicaid Beneficiary under 21 Years of Age.

5.1 Prior Approval

Medicaid shall require prior approval for Genetic Testing – Next Generation Sequencing (NGS). The provider shall obtain prior approval before rendering Genetic Testing – Next Generation Sequencing (NGS). Medicaid shall require prior approval for all codes associated with Whole Genome Sequencing (WGS) found in **Attachment A, Section C**. The provider shall obtain prior approval before rendering Whole Genome Sequencing (WGS).

Medicaid shall not require prior approval for Whole Exome Sequencing (WES) or Molecular Profiling, however, Medicaid shall require prior approval when exceeding the limitations found in **Attachment A, Section C.** Providers must follow Prior Approval requirements found in **Subsection 5.2.1**.

5.2 Prior Approval Requirements

5.2.1 General

The provider(s) shall submit to the Department of Health and Human Services (DHHS) Utilization Review Contractor the following:

a. the prior approval request; and
b. all health records and any other records that support the beneficiary has met the specific criteria in **Subsection 3.2** of this policy.

5.2.2 Specific

None Apply.

5.3 Additional Limitations or Requirements

5.3.1 Testing Limitations

Refer to **Attachment A, Section C**, for testing limitations for CPT codes covered in this policy.

5.3.2 Documentation Requirements

When the provider requests additional units for the CPT Codes found in **Attachment A, Section C**, then, in addition to the prior approval requirements found in **Subsection 5.2.1**, the provider shall submit all of the following supporting documentation is required to justify the request:

a. The reason for the test(s);
b. Previous related lab results;
c. How the test results contribute to improved health outcomes; **and**
d. How the test results alter the beneficiary's treatment and management.

6.0 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:

a. meet Medicaid qualifications for participation;
b. have a current and signed Department of Health and Human Services (DHHS) Provider Administrative Participation Agreement; and

c. bill only for procedures, products, and services that are within the scope of their clinical practice, as defined by the appropriate licensing entity.

6.1 Provider Qualifications and Occupational Licensing Entity Regulations

None Apply.

6.2 Provider Certifications

Genetic counseling must be provided by a medical 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 beneficiary for whom the counseling service is billed. The services of the Genetic Counselor are billed by the supervising physician.

Clinical laboratory services must be rendered only by medical care entities that are issued certifications that are in compliance with the Clinical Laboratory Improvement Amendment (CLIA) of 1988 [Public Law 100-578, amended §353 of the Public Health Service Act (PHSA)].

7.0 Additional Requirements

Note: Refer to Subsection 2.2.1 regarding EPSDT Exception to Policy Limitations for a Medicaid Beneficiary under 21 Years of Age.

7.1 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).

8.0 Policy Implementation and History

Original Effective Date: Month Day, Year

History:

Date	Section or Subsection Amended	Change
	All Sections and Attachment(s)	CCP 1S-4 terminated and coverage for WES absorbed into this policy. Added new coverage for WGS and molecular profiling, including liquid biopsy.

Attachment A: Claims-Related Information

Provider(s) shall comply with the, *NCTracks 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:

A. Claim Type

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.

B. 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.

C. 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.

Molecular Profiling:

CPT Code	Unit Limitations
81457	Once per primary cancer occurrence
81458	Once per primary cancer occurrence
81459	Once per primary cancer occurrence
81462	Once per primary cancer occurrence
81463	Once per primary cancer occurrence
81464	Once per primary cancer occurrence
0037U	Once per primary cancer occurrence
0048U	Once per primary cancer occurrence
0211U	Once per primary cancer occurrence
0242U	Once per primary cancer occurrence
0244U	Once per primary cancer occurrence
0250U	Once per primary cancer occurrence
0326U	Once per primary cancer occurrence

0329U	Once per primary cancer occurrence
0334U	Once per primary cancer occurrence
0364U	Once per primary cancer occurrence
0379U	Once per primary cancer occurrence
0388U	Once per primary cancer occurrence
0391U	Once per primary cancer occurrence
0395U	Once per primary cancer occurrence
0409U	Once per primary cancer occurrence
0414U	Once per primary cancer occurrence

Whole Exome Sequencing/Whole Genome Sequencing:

CPT Code	Unit Limitations
81415	Once in a lifetime
81416	Once per comparator per lifetime
81417	Once in a lifetime
81425	Once in a lifetime
81426	Once per comparator per lifetime
81427	Once in a lifetime
0094U	Once in a lifetime
0212U	Once in a lifetime
0213U	Once in a lifetime
0417U	Once in a lifetime

Genetic Counseling:

CPT Code	Unit Limitations
96040	3 units (1 unit = 30 minutes) 90 minutes total: Refer to **Subsection 3.2.2(a)**

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.

D. Modifiers

Provider(s) shall follow applicable modifier guidelines.

E. Billing Units

Provider(s) shall report the appropriate code(s) used which determines the billing unit(s).

F. Place of Service

Inpatient, Outpatient, Office, Laboratory

G. Co-payments

For Medicaid refer to Medicaid State Plan:
https://medicaid.ncdhhs.gov/meetings-notices/medicaid-state-plan-public-notices

H. Reimbursement

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