Healthy Blue

Medical Policy

Subject:	Proteogenomic Testing for the Evaluation of Malignancies		
Document#:	GENE.00025	**Publish Date:**	12/16/2020
Status:	Reviewed	**Last Review Date:**	11/05/2020

Description/Scope

This document addresses proteogenomic testing for the evaluation of malignancies in persons who have been diagnosed with cancer.

Proteogenomic tests include, but may not be limited to:

- DarwinOncoTarget™ (Darwin Health, New York, NY)
- Genomic Proteomic Spectrometry, or GPS Cancer™ test (NantHealth, Culver City, CA)

Position Statement

Investigational and Not Medically Necessary:

Proteogenomic testing is considered **investigational and not medically necessary** for all indications.

Rationale

Proteogenomics refers to the complex integration of genomic, proteomic, and transcriptomic data to provide a more comprehensive picture of the function of the genome. Proteogenomic testing differs from proteomic testing in that proteomic testing is typically limited to the measurement of protein products alone without the inclusion of genomic and transcriptomic information.

Research on the use of proteogenomic testing for individuals with oncologic conditions is in the early stages of development and has primarily focused on the diagnostic, prognostic, and predictive value of proteogenomics in various cancers. Examples of proteogenomic tests in the United States include the GPS Cancer test and the DarwinOncoTarget test. At the time of this review, no peer-reviewed published evidence on the clinical validity or utility of these tests and no guidelines or recommendations by professional medical societies or governmental organizations were identified.

Several studies have been published in the past few years on whole exome and tumor-normal sequencing, which may be applicable to one component of the GPS cancer test (Beltran, 2015; Jones, 2015; Mandelker, 2017; Teer, 2017). These studies have described the ability of whole exome and tumor-normal sequencing to identify individuals within a population with inheritable genetic mutations with potential clinical ramifications, including the identification of mutations for which specific pharmacological therapies are available, in a rare percentage of

the time. However, the methods used are not the same as the GPS test and these studies do not provide any data related to clinical or health-related outcomes that may result from the use of whole exome and tumor-normal sequencing, let alone the GPS test. These remain outstanding questions that need to be addressed in properly designed and conducted trials.

Conclusion

There is insufficient information to draw conclusions regarding the clinical validity or utility of commercial proteogenomic tests in the diagnosis, prognosis, or management of individuals with oncologic conditions. Additional research is needed to determine if these tests result in improved health outcomes and which population of individuals with oncologic conditions might benefit.

Background/Overview

Cancer is a significant health problem in the United States (US), and according to the American Cancer Society (2020) cancer is the second most common cause of death in the US. Prognosis and therapeutic approach are determined using tumor location, stage, grade, and the individual's underlying physical condition.

Genomic study examines all of the genes of an organism, proteomic study addresses all of the proteins expressed by those genes. Proteogenomics combines proteomic and genomic data. In this approach, customized protein sequence databases employ genomic and transcriptomic information to help identify novel peptides not found in reference protein sequence databases. The proteomic data provides protein-level evidence of gene expression and helps to refine gene models. Due in large part to the emergence of next generation sequencing technologies such as RNA sequencing and improvements in the depths and throughput of mass spectrometry-based proteomics, the pace of proteogenomics research has greatly accelerated (Nesvizhskii, 2014).

Proteogenomics may someday provide a detailed analysis of the molecular components and underlying mechanisms associated with the development of various cancers. This work is driven in part by the hypothesis that a better understanding of both proteomics and genomics will improve diagnosis and treatment decisions in individuals with oncologic conditions. Potential clinical applications of proteogenomics include, but are not limited to:

- Detecting diagnostic, prognostic, and predictive biomarkers;
- Identifying cancer by proteomic signatures (also referred to as proteomic profiles);
- Quantitatively measuring and monitoring protein levels over time to identify cancer activity and early resistance to targeted tumor therapy;
- Linking protein profiles with specific disease states.

According to information on the NantHealth website, the GPS Cancer test integrates quantitative targeted proteomics detected by mass spectrometry with whole transcriptome and whole genome sequencing, of both cancer tissue and normal tissue. The GPS Cancer test is marketed as a tool to diagnose molecular alterations in an individual's cancer, and to identify personalized therapeutic regimens.

DarwinOncoTarget is described as a diagnostic platform that "detects and assesses the full repertoire of aberrantly active and pharmacologically actionable proteins" in a tumor sample that is independent of the DNA mutational state. A report is generated that identifies the proteins and target drugs/investigational compounds that may be used.

The White House Office of the Vice President of the United States has announced an international collaboration between the National Cancer Institute (NCI) at the National Institutes of Health in the United States, and Macquarie University, Children's Medical Research Institute, Garvan Institute of Medical Research, and Bioplatforms Australia Limited in Australia, to facilitate scientific collaborations in the field of clinical proteogenomic studies and their translation to cancer care. Additionally, the State governments of New South Wales and Victoria have signed separate agreements with the NCI that will construct a general framework of collaboration for promoting and conducting high-quality research and data-sharing to strengthen the evidence base necessary for cancer prevention, treatment, and management. As part of the Cancer Moonshot, it is hoped that this international partnership will break down silos and allow scientists to work together and share information, with the goal of cancer prevention, earlier detection, and widely available therapies. In December 2016, congress passed the 21st Century Cures Act, which authorized $1.8 billion in funding for the Cancer Moonshot over 7 years. (NCI, 2019).

As a result of the interest in proteogenomic research, several databases are under construction. These databases include but are not limited to the Human Protein Reference Database, Human Cancer Proteome Variation Database and the Cancer Mutant Proteome Database.

Definitions

Cancer Moonshot: A collaborative effort between the public and private sectors (including but not limited to the governments, researchers, healthcare providers, data and technology experts, patients, families, and patient advocates) to make a decade's worth of advances in the understanding, prevention, diagnosis, treatment, and care of cancer.

Genome: The total genetic composition of an organism.

Genomic data: Information derived from the sequencing of DNA or RNA fragments.

Proteome: The complete set of proteins expressed by a genome.

Proteomic data: Data related to the functioning of protein; generally obtained using a combination of liquid chromatography and tandem mass spectrometry.

Proteomics: The comprehensive and integrative study of proteins and their biological functions.

Transcriptome: The sum total of all the messenger RNA molecules expressed from the genes in a specified cell population or organism. May also be defined as the array of mRNA transcripts expressed in a particular cell or tissue type.

Whole transcriptome (RNA) sequencing: A next-generation sequencing technique used to identify and measure RNA in a biological sample at a given moment in time. Also known as RNA sequencing and whole transcriptome shotgun sequencing.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services are Investigational and Not Medically Necessary:
When the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

CPT

81479	Unlisted molecular pathology procedure [when specified as proteogenomic testing, such as the GPS Cancer test]
0019U	Oncology, RNA, gene expression by whole transcriptome sequencing, formalin-fixed paraffin embedded tissue or fresh frozen tissue, predictive algorithm reported as potential targets for therapeutic agents OncoTarget/OncoTreat, Columbia University Department of Pathology and Cell Biology, Darwin Health

ICD-10 Diagnosis

	All diagnoses, including but not limited to the following:
C00.0-C80.2	Malignant neoplasms
C81.00-C86.6	Hodgkin and non-Hodgkin lymphomas

References

Peer Reviewed Publications:

1. Ansong C, Purvine SO, Adkins JN, et al. Proteogenomics: needs and roles to be filled by proteomics in genome annotation. Brief Funct Genomic Proteomic. 2008; 7(1):50-62.
2. Armengaud J. A perfect genome annotation is within reach with the proteomics and genomics alliance. Curr Opin Microbiol. 2009; 12(3):292-300.
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4. Keshava Prasad TS, Goel R, Kandasamy K, et al. Human Protein Reference Database--2009 update. Nucleic Acids Res. 2009; 37(Database issue):D767-772.

5. Nesvizhskii AI. Proteogenomics: concepts, applications and computational strategies. Nat Methods. 2014; 11(11):1114-1125.
6. Renuse S, Chaerkady R, Pandey A. Proteogenomics. Proteomics. 2011; 11(4):620-630.
7. Rivers RC, Kinsinger C, Boja ES, et al. Linking cancer genome to proteome: NCI's investment into proteogenomics. Proteomics. 2014; 14(23-24):2633-2636.
8. Subbannayya Y, Pinto SM, Gowda H, et al. Proteogenomics for understanding oncology: recent advances and future prospects. Expert Rev Proteomics. 2016; 13(3):297-308.

Websites for Additional Information

1. American Cancer Society. Available at: http://www.cancer.org. Accessed on September 29, 2020.
2. Office of Cancer Clinical Proteomics Research, National Cancer Institute. Proteomics and Proteogenomics. https://proteomics.cancer.gov/. Accessed on September 29, 2020.

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DarwinOncoTarget
GPS Cancer Test
Proteogenomic Test

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
Reviewed	11/05/2020	Medical Policy & Technology Assessment Committee (MPTAC) review. Updated Background/Overview and Websites for Additional Information sections.
Revised	11/07/2019	MPTAC review. Title changed to "Proteogenomic Testing for the Evaluation of Malignancies." Molecular profiling content removed and transferred to GENE.00052 Whole Genome Sequencing, Whole Exome Sequencing, Gene Panels, and Molecular Profiling. Websites section updated. Updated Coding section; removed associated CPT code 88363.
Reviewed	06/06/2019	MPTAC review. Description/Scope, Rationale, References and Websites sections updated. Updated Coding section with 07/01/2019 CPT changes; removed 0057U deleted 06/30/2019.
	12/27/2018	Updated Coding section; added 0019U.
Revised	07/26/2018	MPTAC review.

Revised	07/25/2018	Hematology/Oncology Subcommittee review. Added MN statement for molecular profiling. The Description/Scope, Rationale, Background, Coding, References, Websites, and Index sections updated.
Reviewed	05/03/2018	MPTAC review.
Reviewed	05/02/2018	Hematology/Oncology Subcommittee review. Updated Description/Scope, Rationale, Background, References, and Websites sections. Updated Coding section with 07/01/2018 CPT changes; added 0048U, 0050U, 0056U, 0057U.
	03/29/2018	Updated Coding section with 04/01/2018 CPT changes; added PLA codes 0036U, 0037U.
Reviewed	11/02/2017	MPTAC review.
Reviewed	11/01/2017	Hematology/Oncology Subcommittee review. The document header wording updated from "Current Effective Date" to "Publish Date." Updated Rationale and References sections.
	08/01/2017	Updated Coding section with 08/01/2017 CPT PLA code changes
Revised	11/03/2016	MPTAC review.
Revised	11/02/2016	Hematology/Oncology Subcommittee review. Investigational and NMN statement added for proteogenomic testing. Description, Rationale, Background, Definitions, Coding, References and Index sections updated.
Reviewed	11/05/2015	MPTAC review.
Reviewed	11/04/2015	Hematology/Oncology Subcommittee review. Description, Background and Reference sections updated. Updated Coding section with 01/01/2016 CPT descriptor changes, and also removed ICD-9 codes.
Reviewed	11/13/2014	MPTAC review.
Reviewed	11/12/2014	Hematology/Oncology Subcommittee review. Rationale, Background, Reference and Index sections updated. Updated Coding section with 01/01/2015 CPT changes.
Revised	11/14/2013	MPTAC review.
Revised	11/13/2013	Hematology/Oncology Subcommittee review. Brand names removed from position statement. Description, Rationale, Background, Definition, and Reference sections updated.
Revised	05/09/2013	MPTAC review.
Revised	05/08/2013	Hematology/Oncology Subcommittee review. Position statement updated to include "Molecular Intelligence Service". Description, Rationale, Background, Definition, Reference, and Index Sections updated.
	01/01/2013	Updated Coding section with 01/01/2013 CPT changes; removed 88384-88386 deleted 12/31/2012.
New	05/10/2012	MPTAC review.
New	05/09/2012	Hematology/Oncology Subcommittee review. Initial document development.