Protocol

General Approach to Evaluating the Utility of Genetic Panels

(20492)

Medical Benefit		**Effective Date**: 01/01/17	**Next Review Date**: 09/20
Preauthorization	Yes	**Review Dates**: 09/13, 09/14, 09/15, 09/16, 09/17, 09/18, 09/19	

Preauthorization is required.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: • Who are symptomatic with a suspected genetically associated disease	Interventions of interest are: • Genetic panel testing for a suspected genetically associated disorder	Comparators of interest are: • Standard clinical management without genetic panel testing	Relevant outcomes include: • Test accuracy • Test validity • Disease-specific survival • Overall survival • Changes in disease status • Morbid events • Functional outcomes • Changes in reproductive decision making
Individuals: • Who are asymptomatic and have a close relative diagnosed with a genetically associated disease	Interventions of interest are: • Genetic panel testing for a genetically associated disorder	Comparators of interest are: • Standard clinical management without genetic panel testing	Relevant outcomes include: • Test accuracy • Test validity • Disease-specific survival • Overall survival • Changes in disease status • Morbid events • Functional outcomes • Changes in reproductive decision making

DESCRIPTION

Genetic panel testing offers potential advantages and disadvantages compared with direct sequence analysis. This conceptual framework outlines a structure for evaluating the utility of genetic panels, by classifying them into clinically relevant categories and developing criteria for evaluating panels in each category.

SUMMARY OF EVIDENCE

Genetic panels using next-generation technology or chromosomal microarray analysis are available for many clinical conditions. The major advantage of panels is the ability to analyze many genes simultaneously, potentially improving the breadth and efficiency of the genetic workup. A potential disadvantage of panels is

that they provide a large of amount of ancillary information whose significance may be uncertain. Limited published evidence has reported that the analytic validity of panels approaches that of direct sequencing. The clinical validity and clinical utility of panels are condition-specific. The clinical validity of panels will reflect the clinical validity of the underlying individual variants. The clinical utility of panels will depend on the context in which they are used, i.e., whether the advantages of panel testing outweigh the disadvantages for the specific condition under consideration.

Panels can be classified into categories based on their intended use and composition. For each category of panels, specific criteria can be used to evaluate medical necessity. When all criteria for a given category are met, that panel may be considered medically necessary.

POLICY

Genetic panels that use next generation sequencing or chromosomal microarray analysis, and are classified in one of the categories below, may be considered **medically necessary** when all criteria are met for each category, as outlined in the Policy Guidelines Section:

- Panels for hereditary or genetic conditions
  - Diagnostic testing of an individual's germline to benefit the individual
  - Testing of an asymptomatic individual to determine future risk of disease
- Cancer panels
  - Testing of an asymptomatic individual to determine future risk of cancer
  - Testing cancer cells from an individual to benefit the individual by identifying targeted treatment
- Reproductive panels
  - Preconception testing - Carrier testing of the parent(s)
  - Prenatal testing
    - Carrier testing of the parent(s)
    - In utero testing of a fetus, including testing for aneuploidy or familial variants
  - Preimplantation genetic testing.

Genetic panels that use next generation sequencing or chromosomal microarray analysis that do not meet the criteria for a specific category are considered **investigational**.

**Refer to the Genetic Cancer Susceptibility Panels Using Next Generation Sequencing Protocol for the following panels: CancerNext™, BreastNext™, ColoNext™, and OvaNext™

POLICY GUIDELINES

CRITERIA FOR EVALUATING GENETIC PANELS

The following are all criteria that can be applied to evaluating genetic panels, with an explanation of the way the criteria are to be defined and applied. Not all criteria will apply to all panels.

Test is performed in a Clinical Laboratory Improvement Amendments (CLIA)-Licensed lab

- Testing is performed in a laboratory licensed under CLIA for high-complexity testing. This requires delivery of a reproducible set of called, quality filtered variants from the sequencing platform.

- These calculations should occur prior to variant annotation, filtering, and manual interpretation for patient diagnosis.

Technical Reliability of Panels Approaches That of Direct Sequencing

- The technical reliability for detecting individual variants, compared with the criterion standard of conventional direct Sanger sequencing, is reported.
    - The testing methods are clearly described, and the overall analytic validity for that type of testing is defined.
- Any decrease in analytic sensitivity and specificity is not large enough to result in a clinically meaningful difference in diagnostic accuracy (clinical valid).

All individual components of the panel have demonstrated clinical utility for the condition being evaluated OR the implications and consequences of test results that have not demonstrated clinical utility are clear AND there is no potential for incidental findings to cause harm.

- For each panel, if each mutation in the panel would be indicated for at least some patients with the condition, then the criterion is met.
    - If there are individual variants that do not have clinical utility, then the potential to cause harm might occur.
- For incidental findings, the potential for harm may be due to:
    - Incorrect diagnosis due to false-positive or false-negative results
        - False positive - Unnecessary treatment that may have adverse effects
        - False negative - Effective treatment not provided
    - Incorrect risk assessment
        - Unnecessary surveillance tests that may lead to further confirmatory tests that may be invasive
        - Effective surveillance/screening not provided to patients at risk
        - Incorrect decision made on reproductive decision making
            - Alteration made in reproductive planning that would not have been made with correct information
            - No alteration made in reproductive planning, where alteration would have been made with correct information

Panel Testing Offers Substantial Advantages in Efficiency Compared to Sequential Analysis of Individual Genes

- The composition of the panel is sufficiently complex such that next generation sequencing, or chromosomal microarray analysis, is expected to offer considerable advantages. Complexity of testing can be judged by:
    - The number of genes tested.
    - The size of the genes tested.
    - The heterogeneity of the genes tested.

The Impact of Ancillary Information is Well-Defined

- If a panel contains both mutations that are medically necessary and mutations that are investigational (or not medically necessary), the impact of results for investigational (or not medically necessary) variants is considered, taking into account the following possibilities:

- The information may be ignored (no further impact).
- The information may result in further testing or changes in management.
  - Positive impact
  - Negative impact
- It is more likely that the results of tests that are not medically necessary cause a negative, rather than a positive, impact on the patient. This is because additional tests and management changes that follow are not evidence-based, and because additional testing and treatment generally involves risks.

Decision Making Based on Genetic Results is Well-Defined

- Results of genetic test will lead to changes in diagnosis and/or treatment.
- The potential changes in treatment are defined prior to testing and accord with current standard of care.
- Changes in diagnosis or management are associated with improvements in health outcomes.
- For prenatal and preconception testing:
  - Alterations in reproductive decision making are expected, depending on the results of testing.

Yield of Testing is Acceptable for the Target Population

- The number of individuals who are found to have a pathogenic variant, in relation to the total number of individuals tested, is reasonable given the underlying prevalence and severity of the disorder, and the specific population that is being tested.
  - It is not possible to set an absolute threshold for acceptable yield across different clinical situations. Some guidance can be given from clinical precedence as follows:
    - For diagnosis of hereditary disorders, genetic testing is generally performed when signs and symptoms of disease are present, including family history. The likelihood of a positive genetic test depends on the accuracy of the signs and symptoms (pre-test probability of disorder), and the clinical sensitivity of genetic testing. For disorders such as testing for congenital long QT syndrome and Duchenne muscular dystrophy, the likelihood of a positive result in patients with signs and symptoms of disease is greater than 10%.
    - For cancer susceptibility, testing is recommended for genetic abnormalities such as BRCA and Lynch syndrome when the likelihood of a positive result is in the range of 2% to 10%.
    - For a clinical syndrome that has multiple underlying etiologies, such as developmental delay in children, chromosomal microarray testing is recommended when the likelihood of a positive result is in the 5% to 20% range.
- There is Increase in yield over alternate methods of diagnosis, and this increase is clinically significant.

Other Issues to Consider

- Most tests will not, and possibly should not, be ordered by generalists.
  - Guidance for providers is appropriate on the expertise necessary to ensure that test ordering is done optimally.
- Many tests, particularly those for inherited disorders, should be accompanied by patient counseling, preferably by certified genetic counselors.

- Counseling may be needed both before and after testing, depending on the specific condition being tested.

Criteria for Evaluating Panels by Type and Intent of Panel

Panel Category	Examples of Panels	Criteria for Evaluating Utility of Panel
1. Diagnosis of hereditary, single-gene disorders		• All individual components of the panel have demonstrated clinical utility OR test results that have not demonstrated clinical utility do not have a potential to cause harm • Testing is performed in a CLIA-approved lab • Analytic validity of panel approaches that of direct sequencing • Panel testing offers substantial advantages in efficiency compared to sequential analysis of individual genes
Category 1a – Diagnostic testing Panels that include variants for a single condition	• Retinitis Pigmentosa Panel • Leigh Disease Panel	• Includes all criteria for criterion 1 (Diagnosis of hereditary, single-gene disorders)
Category 1b – Diagnostic testing Panels that include variants for multiple conditions (indicated plus non-indicated conditions)	• Retinitis Pigmentosa/Leber Congenital Amaurosis Panel • Noonan Syndrome and Related Disorders Panel	• Includes all criteria for criterion 1 (Diagnosis of hereditary, single-gene disorders) PLUS • The impact of ancillary information is well-defined
Category 1c – Diagnostic testing Panels that include variants for multiple conditions (clinical syndrome for which clinical diagnosis not possible)	• X-linked Intellectual Disability Panel • Marfan, Aneurysm and Related Disorders Panel • Epilepsy Panel	• Includes all criteria for criterion 1 (Diagnosis of hereditary, single-gene disorders) PLUS • The impact of ancillary information is well-defined • Yield of testing is acceptable for the target population
Category 1d – Risk Assessment Risk assessment panels for at-risk individuals	• Most panels for hereditary conditions can be used for this purpose when there is not a known variant in the family	• Includes all criteria for criterion 1 (Diagnosis of hereditary, single-gene disorders) PLUS • Yield of testing is acceptable for the target population
2. Cancer panels		• All individual components of the panel have demonstrated clinical utility, OR test results that have not demonstrated clinical utility do not have a potential to cause harm • Testing is performed in a CLIA-approved lab • Analytic validity of panel approaches that of direct sequencing • Panel testing offers substantial advantages in efficiency compared with sequential analysis of individual genes
Category 2a – Risk assessment Risk assessment panels for at-risk individuals	• Hereditary colon cancer syndromes panel • BreastNext Panel	• Includes all criteria for criterion 2 (Cancer panels) PLUS • Yield of testing is acceptable for the target population
Category 2b – Targeted treatment	• None identified	• Includes all criteria for criterion 2 (Cancer

Panel Category	Examples of Panels	Criteria for Evaluating Utility of Panel
based on variant analysis • Panels with multiple variants intended to direct treatment – all indicated tests • Effective targeted treatment based on variant analysis is available		panels) PLUS • Yield of testing is acceptable for the target population
Category 2c – Targeted treatment based on variant analysis • Panels with multiple variants intended to direct treatment (indicated plus non-indicated tests) • Effective targeted treatment based on variant analysis has not been established	• CancerNext panels, when there is an effective targeted treatment for the specific type of cancer	• Includes all criteria for criterion 2 (Cancer panels) PLUS • Impact of ancillary information is defined
Category 2d • Panels with multiple variants intended to direct treatment – no indicated tests for that particular cancer • Effective targeted treatment based on variant analysis has not been established	• CancerNext panels, when there is no known effective treatment for the specific type of cancer	• Includes all criteria for criterion 2 (Cancer panels) PLUS • Decision-making based on potential results is defined • Yield of testing is acceptable for the target population • Impact of ancillary information is defined • Probability that ancillary information leads to further testing or management changes
3. Reproductive panels		• All individual components of the panel have demonstrated clinical utility, OR test results that have not demonstrated clinical utility do not have a potential to cause harm • Testing is performed in a CLIA-approved lab • Analytic validity of panel approaches that of direct sequencing • Panel testing offers substantial advantages in efficiency compared to sequential analysis of individual genes
Category 3a – Preconception testing of at-risk individuals Panels that include only variants associated with increased risk	• Ashkenazi Jewish Carrier Test Panel • GoodStart Panel (customized)	• Includes all criteria for criterion 3 (Reproductive panels) PLUS • Decision-making based on genetic results is well-defined
Category 3b – Preconception testing of at-risk individuals Panels that include variants associated with increased risk plus other variants	• GoodStart Panel (full panel, not customized)	• Includes all criteria for criterion 3 (Reproductive panels) PLUS • Decision-making based on genetic results is well-defined • Impact of ancillary information is defined
Category 3c – Preconception screening Panels intended for preconception testing – screening panels for different populations	• Counsyl Panel	• Includes all criteria for criterion 3 (Reproductive panels) PLUS • Yield of testing is acceptable for the target population • Decision-making based on genetic results is well-defined
Category 3d – Prenatal screening	• Signature Prenatal Microarray	• Includes all criteria for criterion 3

Panel Category	Examples of Panels	Criteria for Evaluating Utility of Panel
Panels that include only variants associated with increased risk	Panel (customized)	(Reproductive panels) PLUS • Decision-making based on genetic results is well-defined
Category 3e – Prenatal screening Panels that include variants associated with increased risk plus other variants	• Signature Prenatal Microarray Panel (full panel, not customized)	• Includes all criteria for criterion 3 (Reproductive panels) PLUS • Yield of testing is acceptable for the target population • Decision-making based on genetic results is well-defined
Category 3f – Preimplantation testing Panels that include only variants associated with increased risk	• Signature Prenatal Microarray Panel (customized)	• Includes all criteria for criterion 3 (Reproductive panels) PLUS • Decision-making based on genetic results is well-defined
Category 3g – Preimplantation testing Panels that include variants associated with increased risk plus other variants	• Signature Prenatal Microarray Panel (full panel, not customized)	• Includes all criteria for criterion 3 (Reproductive panels) PLUS • Yield of testing is acceptable for the target population • Decision-making based on genetic results is well-defined

GENETICS NOMENCLATURE UPDATE

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the HUman Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"—to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

GENETIC COUNSELING

Experts recommend formal genetic counseling for patients who are at-risk for inherited disorders and who wish

to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

MEDICARE ADVANTAGE

Medicare generally only covers tests that are medically necessary for diagnosis and treatment, panels that are risk assessment testing may be considered **not medically necessary**.

The above policy and policy guidelines content is applicable for Medicare Advantage for diagnostic testing, prognostic testing and testing for genetic variants that alter response to treatment or to an environmental factor which meet medically necessary criteria.

BACKGROUND

This conceptual framework applies if there is not a separate protocol that outlines specific criteria for testing. If a separate protocol does exist, then the criteria for medical necessity therein supersede the guidelines herein.

REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer LDTs must be licensed by the CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

An exhaustive list of commercially available panel tests is impractical. For example, the EGL Genetics offers 243 different genetic panels, of a total of 929 molecular genetics tests.[11] Table 1 provides a sample of panels that use NGS or chromosomal microarray technologies.

Table 1. Panels Using Next-Generation Sequencing or Chromosomal Microarray Analysis (as of December 2017)

Test Name	Laboratory
Agammaglobulinemia Panel	ARUP Laboratories
Ashkenazi Jewish Diseases Panel	ARUP Laboratories
Mitochondrial Disorders Panel	ARUP Laboratories
Amyotrophic Lateral Sclerosis Pane	ARUP Laboratories
Aortopathy Panel	ARUP Laboratories
Autism Panel	ARUP Laboratories
Brugada Syndrome Panel	ARUP Laboratories
Vascular Malformation Syndromes	ARUP Laboratories
Retinitis Pigmentosa/Leber Congenital Amaurosis Panel	ARUP Laboratories
Cardiomyopathy and Arrhythmia Panel	ARUP Laboratories
Periodic Fever Syndromes Panel	ARUP Laboratories
Arrhythmias Sequencing Panel	EGL Genetics
Arrhythmias Deletion/Duplication Panel	EGL Genetics
Autism Spectrum Disorders	EGL Genetics
Cardiomyopathy Panel	EGL Genetics
Ciliopathies Panel	EGL Genetics
Congenital Glycosylation Disorders	EGL Genetics

Test Name	Laboratory
ACOG/ACMG Carrier Screen Targeted Mutation Panel	EGL Genetics
Epilepsy	EGL Genetics
Eye Disorders	EGL Genetics
Neuromuscular Disorders	EGL Genetics
Noonan Syndrome and Related Disorders	EGL Genetics
Short Stature Panel	EGL Genetics
Sudden Cardiac Arrest Panel	EGL Genetics
X-linked Intellectual Disability	EGL Genetics
CancerNext™	Ambry Genetics
BreastNext™	Ambry Genetics
ColoNext™	Ambry Genetics
OvaNext™	Ambry Genetics
RhythmNext®	Ambry Genetics
X-linked Intellectual Disability	Ambry Genetics
TAADNext®	Ambry Genetics
Cobalamin Metabolism Comprehensive Panel	Baylor College of Medicine
Progressive External Ophthalmoplegia Panel	Baylor College of Medicine
CoQ10 Comprehensive Panel	Baylor College of Medicine
Usher Syndrome Panel	Baylor College of Medicine
Retinitis Pigmentosa Panel	Baylor College of Medicine
Pyruvate Dehydrogenase Deficiency and Mitochondrial Respiratory Chain Complex V Deficiency Panel	Baylor College of Medicine
Myopathy/Rhabdomyolysis Panel	Baylor College of Medicine
Mitochondrial Disorders Panel	Baylor College of Medicine
Low Bone Mass Panel	Baylor College of Medicine
Glycogen Storage Disorders Panel	Baylor College of Medicine
Leigh Disease Panel	Medical Neurogenetics
Pan Cardiomyopathy Panel	Partners Healthcare
Isolated Non-syndromic Congenital Heart Defects Panel	Partners Healthcare
Noonan Spectrum Panel	Partners Healthcare
Usher Syndrome Panel	Partners Healthcare
Hereditary Colon Cancer Syndromes	Mayo Medical Laboratories
Hypertrophic Cardiomyopathy Panel	Mayo Medical Laboratories
Dilated Cardiomyopathy Panel	Mayo Medical Laboratories
Arrhythmogenic Right Ventricular Cardiomyopathy Panel	Mayo Medical Laboratories
Noonan Syndrome Panel	Mayo Medical Laboratories
Marfan Syndrome Panel	Mayo Medical Laboratories
Long QT Syndrome	Mayo Medical Laboratories
Brugada Syndrome	Mayo Medical Laboratories
Signature Prenatal Microarray	Signature Genomics
Counsyl™ Panel	Counsyl Genomics
GoodStart Select™	GoodStart Genetics

RELATED PROTOCOLS

General Approach to Genetic Testing

Genetic Cancer Susceptibility Panels Using Next-Generation Sequencing

Molecular Testing of Cancers to Identify Targeted Therapies

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

REFERENCES

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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