Genetic Testing by Multigene Panels

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Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
Genomic Sequencing Procedures	81410-81471
Molecular Proprietary Laboratory Analyses (PLA)	Various Molecular* PLA codes (ending in U)
Tier 1 Molecular Pathology Procedures	81161-81383
Tier 2 Molecular Pathology Procedures	81400-81408
Unlisted Molecular Pathology Procedure	81479

What are multigene panels?

Various methodologies can be used to identify potential disease-causing gene mutations. Gene sequencing involves evaluating each DNA nucleotide along the length of a gene. Full gene sequencing is the best approach when many different mutations in the same gene can cause the disorder.

- There are two main ways to sequence a gene:
  - Sanger sequencing methodology, originally developed in the 1970s, sequences DNA from one gene at a time in several independent assays. Sanger sequencing is labor intensive and did not lend itself to high-throughput applications.[1]
  - Next generation sequencing (NGS), also called massively parallel sequencing, was developed to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence.[1]
- The efficiency of NGS has led to an increasing number of large, multigene testing panels.

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  - NGS panels are particularly well-suited to conditions caused by more than one gene or where there is considerable clinical overlap between conditions making it difficult to reliably narrow down likely causes.
  - Panels including genes associated with a high risk of a condition are of greatest value since these mutation-positive results often lead to changes in medical management.
  - Panels may also include genes believed to be associated with a particular condition, but with a more modest impact on risk. Results for such genes are of less clear value because there often are not clear management recommendation for mutation-positive individuals.
- Laboratories offer panel testing for multiple genes at the same time in an effort to increase the likelihood of finding a causative gene mutation in a more efficient manner. Such testing may be performed for diagnostic or predictive purposes.
  - Diagnostic testing is performed in patients with clinical signs or symptoms of a genetic condition. The genetic test may confirm or rule out a clinical diagnosis. However, many genetic conditions have overlapping features, which can make determining appropriate genetic testing difficult. The use of clinical and family history information may not always lead to a likely diagnosis for an individual. In some cases, many genes may be candidates for an individual's symptoms. In these cases, testing one gene at a time may be time-consuming and costly.
  - Predictive genetic testing is performed in people known to be at increased risk of developing an inherited condition based on their family history. For some conditions, a positive genetic test predicts with certainty that the individual will eventually develop signs and symptoms of a condition. For other conditions, a positive genetic test result indicates an increased risk (susceptibility) for a condition. Without a specific known mutation running in the family, a negative result rarely rules out a condition. Having test results may improve medical management through improved screening, preventive measures (e.g., prophylactic medication, surgery) and other means. In order to better define an individual's risk, it is preferable to first test someone in the family who is affected.

Test information

- Multigene panel tests, even for similar clinical scenarios, vary considerably in the genes that are included and in technical specifications (e.g., depth of coverage, extent of intron/exon boundary analysis, methodology of large deletion/duplication analysis). Therefore, technologies used in multigene testing may fail to identify mutations that might be identifiable through single-gene testing.

- If high clinical suspicion remains for a particular syndrome after negative multigene test results, consultation with the testing lab and/or additional targeted genetic testing may be warranted.
- Results may be obtained that cannot be adequately interpreted based on the current knowledgebase. When a sequence variation is identified that has not been previously characterized or shown to cause the disorder in question, it is called a variant of uncertain clinical significance (VUS). VUSs are relatively common findings when sequencing large amounts of DNA with NGS.[2]
- Since genes can be added or removed from multigene tests over time by a given lab, medical records must document which genes were included in the specific multigene test used for each patient, and in which labs they were performed.
- Tests should be chosen to:
  - maximize the likelihood of identifying mutations in the genes of interest
  - contribute to alterations in patient management
  - minimize the chance of finding variants of uncertain significance.

Guidelines and evidence

American College of Medical Genetics and Genomics

The American College of Medical Genetics and Genomics (ACMG, 2021) revised technical standard for clinical NGS stated:[3]

- "Choosing an appropriate NGS-based test is the responsibility of the ordering health-care provider. Given the large number of tests (https://www.ncbi.nlm.nih.gov/gtr/) available to the clinician, the clinical laboratory often provides critical advice in test selection. Ordering providers must weigh considerations of sensitivity, specificity, cost, and turnaround time for each clinical situation."
- "Diagnostic gene panels are optimal for well-defined clinical presentations that are genetically heterogeneous (e.g., congenital hearing loss), for which pathogenic variants in disease-associated genes account for a significant fraction of cases. Secondary/ incidental findings should not be encountered, although broad panels (e.g., epilepsy, or pan-cancer panels) may identify clinically significant findings unrelated to the test indication. By limiting the test to those genes relevant to a given disease, the panel can be optimized to maximize coverage of relevant regions of the gene(s).[Bean et al. 2020]"
- "Test development must consider the variant types that will be detected in the genes or regions of the genome interrogated."

The ACMG (2020) technical standard on diagnostic gene panels stated:[4]

- "Gene panels developed by clinical molecular laboratories assess multiple potential genetic causes of a suspected disorder(s) simultaneously and reduce the cost and time of diagnostic testing. Gene panels are useful to diagnose disorders with genetic

and clinical heterogeneity. Panels for phenotypically related disorders can increase the likelihood of identifying an underlying genetic cause and may be preferred to exome or genome sequencing to maximize target coverage and avoid secondary findings."

- "The goal of a diagnostic gene panel is to maximize clinical sensitivity and minimize the clinical burden from analysis of inappropriate or unnecessary genes that may result in variants of uncertain clinical significance (VUS)."
- "While it may be technically possible to sequence all genes related to a phenotype, the power of a gene panel is the ability to match a patient's specific clinical features to genes associated with that phenotype, thereby increasing clinical specificity and limiting the number of VUS."
- "While it is technically feasible to include genes with low-penetrance pathogenic variants on gene panels, the penetrance and the factors affecting penetrance are generally not known, thus limiting clinical utility. "

In an earlier Points to Consider document, ACMG (2012) offered general guidance on the clinical application of large-scale sequencing focusing primarily on whole exome and whole genome testing. However, some of the recommendations regarding counseling around unexpected results and variants of unknown significance and minimum requirements for reporting apply to many applications of NGS sequencing applications.[5]

National Society of Genetic Counselors

The National Society of Genetic Counselors position statement on the use of multigene panels (NSGC, 2023) stated:[6]

- "The National Society of Genetic Counselors (NSGC) endorses the use of multi-gene panel tests when clinically warranted and appropriately applied. These tests can provide a comprehensive and efficient route to identifying the genetic causes of disease. Before ordering a multi-gene panel test, providers should thoroughly evaluate the analytic and clinical validity of the test, as well as its clinical utility. Additional factors to consider include, but are not limited to: clinical and family history information, gene content of the panel, limitations of the sequencing and informatics technologies, and variant interpretation and reporting practices."
- "Panels magnify the complexities of genetic testing and underscore the value of experts, such as genetic counselors, who can educate stakeholders about appropriate utilization of the technology to mitigate risks of patient harm and unnecessary costs to the healthcare system. NSGC supports straightforward and transparent pricing so that patients, providers, laboratories, and health plans can easily weigh the value of genetic testing in light of its cost."

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the policy, following EviCore's criteria for genetic testing by multigene panels will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic/management strategies are considered. However, it is possible that some members who would benefit from the testing, but do not meet criteria, will not receive an immediate approval for testing.

Criteria

This guideline applies to multigene panel testing, which is defined as any assay that simultaneously tests for more than one gene associated with a condition. The testing may focus on sequence variants and/or deletions/duplications of those genes. Panels vary in scope, and may include:

- Multiple genes that are associated with one specific genetic condition (e.g., Noonan syndrome, Stickler syndrome, etc.)
- Multiple genes that are associated with a symptom or non-specific presentation (e.g., epilepsy, intellectual disability, hearing loss, retinal disorders, etc.)
- Coverage determinations generally rely on the medical necessity of the components of a panel. A panel approach to testing is most compelling when:
  - Multiple genes are known to cause the same condition and a limited subset of genes does not account for the majority of disease-causing mutations.
  - The clinical presentation is highly suspicious for a genetic disorder, but the constellation of findings in the personal or family history does not suggest a specific diagnosis or limited set of conditions.
- The following general principles apply:
  - Broad symptom-based panels (e.g., comprehensive ataxia panel) are not medically necessary when a narrower panel is available and more appropriate based on the clinical findings (e.g., autosomal dominant ataxia panel).
  - More than one multigene panel should not be necessary at the same time. Multigene panel testing should be performed in a tiered fashion with independent justification for each panel requested.
  - If more than ten units of any combination of procedure codes will be billed as part of a panel with no stated differential, the panel will be deemed excessive and not medically necessary.
  - Germline genetic testing is only medically necessary once per lifetime. Therefore, a single gene included in a panel or a multigene panel may not be reimbursed if testing has been performed previously. Exceptions may be considered if technical advances in testing demonstrate significant advantages that would support a medical need to retest.

- This guideline may not apply to multigene panel testing for indications that are addressed in test-specific guidelines.

Other Considerations

- All requested procedures must follow correct coding practices. Any procedure codes that do not meet these standards will not be reimbursable, even if medical necessity criteria for the associated test(s) are met. For general coding requirements, please refer to the guideline *Laboratory Billing and Reimbursement*.
- Multiple guidelines may apply to multigene panel testing, including test-specific guidelines, where they exist, or the clinical use guidelines *Genetic Testing to Diagnose Non-Cancer Conditions* or *Genetic Testing to Predict Disease Risk*.

References

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