Clinical Use Guidelines

Genetic Testing by Multigene Panels

MOL.CU.116.A
v1.0.2023

Procedures Addressed

The inclusion of any procedure code in this table is provided for informational purposes and is not a guarantee of coverage nor an indication that prior authorization is required.

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?

Definition

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:
  - Until recently, most sequencing tests used the Sanger sequencing methodology that was originally developed in the 1970s. 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 in 2005 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.

- **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 a person'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 person 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 a person'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 significance (VUS). VUSs are relatively common findings when sequencing large amounts of DNA with NGS.[2]
- Since genes can be easily 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 from 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. [Klein et al, 2017; Bevilacqua et al, 2017]."**
- **"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]

Centers for Medicare and Medicaid Services

For laboratory procedures that include multiple molecular/genomic components the CMS National Correct Coding Initiative Policy Manual (CMS, updated 2022) provides the following coding guidance:[6]

- **"If one laboratory procedure evaluates multiple genes using a next generation sequencing procedure, the laboratory shall report only one unit of service of one genomic sequencing procedure, molecular multianalyte assay, multianalyte assay with algorithmic analysis, or proprietary laboratory analysis CPT code. If no CPT code accurately describes the procedure performed, the laboratory may report CPT code 81479 (Unlisted molecular pathology procedure) with one unit of service or may report multiple individual CPT codes describing the component test results when medically reasonable and necessary. Procedures reported together must be both medically reasonable and necessary (e.g., sequencing of procedures) and ordered by the physician who is treating the beneficiary and using the results in the management of the beneficiary's specific medical problem."**
- **"All genomic sequencing procedures and molecular multianalyte assays (e.g., CPT codes 81410-81471), many multianalyte assays with algorithmic analyses (e.g., CPT codes 81490-81599, 0004M-XXXXM), and many Proprietary**

Laboratory Analyses (PLA) (e.g., CPT codes 0001U-XXXXU) are DNA or RNA analytic methods that simultaneously assay genes or genetic regions. A provider/supplier shall not additionally separately report testing for the same gene or genetic region by a different methodology (e.g., CPT codes 81105-81408, 81479, 88364-88377). CMS payment policy does not allow separate payment for multiple methods to test for the same analyte."

National Society of Genetic Counselors

The National Society of Genetic Counselors position statement on the use of multigene panels (NSGC, 2020) stated:[7]

- "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."

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, such as:
  - Panels consisting of multiple genes that are associated with one specific genetic condition (e.g. Noonan syndrome, Stickler syndrome, etc.)
  - Panels consisting of 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.

- Multiple policies may apply, including test-specific policies where they exist or the following clinical use policies:
  - Genetic Testing to Diagnose Non-Cancer Conditions
  - Genetic Testing to Predict Disease Risk
- 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 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.

Billing and Reimbursement 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. See the guideline *Laboratory Procedure Code Requirements* for general coding requirements.
- If a panel was previously performed and an updated, larger panel is being requested, only testing for the medically necessary, previously untested genes will be reimbursable. Therefore, only the most appropriate procedure codes for those additional genes will be considered for reimbursement.
- Panel coding and billing should reflect the efficiency gains for the laboratory in testing multiple candidate genes simultaneously. Currently, laboratories are billing for panels in a variety of ways. When a panel approach to testing is determined to be medically necessary, the following billing guidelines will apply:

- If a panel is billed with multiple procedure codes representing individual genes analyzed, the panel will be redirected to an appropriate panel code. If the laboratory will not accept redirection to a single code, the medical necessity of each billed component procedure will be assessed independently. Only the individual panel components that meet medical necessity criteria as a first tier of testing will be reimbursed. The remaining individual components will not be reimbursable.
- Examples of appropriate panel codes include:
  - An appropriate proprietary laboratory analyses (PLA) code, or
  - An appropriate genomic sequencing procedure (GSP) code (if there are two different GSP codes to describe the sequencing and deletion/duplication analysis components of the test, both codes will be reimbursable as long as medical necessity is established for both methodologies), or
  - If no more specific code exists, the panel will be redirected to a single unit of the unlisted molecular pathology code 81479, which can be used to represent a panel in total.
- The billed amount should not exceed the list price of the test.

- If the member meets medical necessity, billing of the deletion/duplication portion of the panel with a microarray code (typically billed with 81228 or 81229) is allowed when at least 3 genes are included on the panel. Panels with less than 3 genes are more appropriately billed with individual CPT codes.

References

1. Roy S, LaFramboise WA, Nikiforov YE, et al. Next-generation sequencing informatics: challenges and strategies for implementation in a clinical environment. *Arch Pathol Lab Med*. 2016;140(9):958-975. doi: 10.5858/arpa.2015-0507-RA
2. Robson M. Multigene panel testing: planning the next generation of research studies in clinical cancer genetics. *J Clin Oncol*. 2014;32(19):1987-1989. doi: 10.1200/JCO.2014.56.0474
3. Rehder C, Bean LJH, Bick D, et al. Next-generation sequencing for constitutional variants in the clinical laboratory, 2021 revision: a technical standard of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2021 Apr 29. doi: 10.1038/s41436-021-01139-4 [Epub ahead of print]
4. Bean LJH, Funke B, Carlston CM, et al. Diagnostic gene sequencing panels: from design to report—a technical standard of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2020;22(3):453-461. doi: 10.1038/s41436-019-0666-z

5. **ACMG Board of Directors. Points to consider in the clinical application of genomic sequencing. *Genet Med*. 2012 Aug;14(8):759-61. doi: 10.1038/gim.2012.74**
6. **CMS. NCCI Policy Manual for Medicare. Available at: https://www.cms.gov/medicare/national-correct-coding-initiative-edits/ncci-policy-manual-medicare**
7. **The National Society of Genetic Counselors. Position statement: Use of multi-gene panel tests. Released March 2017; Reaffirmed 2020. Available at: https://www.nsgc.org/Policy-Research-and-Publications/Position-Statements/Position-Statements/Post/use-of-multi-gene-panel-tests**