Genetic Testing by Multigene Panels

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.

<table>
<thead>
<tr>
<th>Procedures addressed by this guideline</th>
<th>Procedure codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genomic Sequencing Procedures</td>
<td>81410-81471</td>
</tr>
<tr>
<td>Tier 1 Molecular Pathology Procedures</td>
<td>81161-81383</td>
</tr>
<tr>
<td>Tier 2 Molecular Pathology Procedures</td>
<td>81400-81408</td>
</tr>
<tr>
<td>Unlisted Molecular Pathology Procedure</td>
<td>81479</td>
</tr>
</tbody>
</table>

What are multi-gene 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, has been developing since about 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, multi-gene 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. It may also lead to a situation where a mutation is missed in another gene that was not tested.

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

Multi-gene 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 multi-gene 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 multi-gene 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.\(^3\)

- Since genes can be easily added or removed from multi-gene tests over time by a given lab, medical records must document which genes were included in the specific multi-gene test used from each patient, and in which labs they were performed.
- Tests should be chosen that maximize the likelihood of identifying mutations in the genes of interest.

### Guidelines and evidence

- The National Society of Genetic Counselors states the following regarding the use of multi-gene panels:\(^4\)
  
  o "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."

  o "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."

- The American College of Medical Genetics has a policy statement that offers 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.\(^5\)

### Criteria

- This guideline applies to multi-gene 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

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.

- Panel is to be billed with a single panel-specific code (e.g., Genomic Sequencing Procedure or GSP) or single unit of the unlisted molecular pathology code 81479:
  - The billed amount should not exceed the list price of the test.

- Panel is to be billed with multiple procedure codes representing individual genes analyzed:
  - If a more specific code exists that adequately describes the requested panel, the panel will be redirected to the more specific code (e.g., a genomic sequencing procedure code), 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, or
  - 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, and
The billed amount should not exceed the list price of the test.

- 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 multi-gene panel should not be necessary at the same time. Multi-gene 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.
  - Genetic testing is only necessary once per lifetime. Therefore, a single gene included in a panel or a multi-gene 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 multi-gene panel testing for indications that are addressed in test-specific guidelines.

Billing and reimbursement considerations

- 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.

- 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


2. Memorial Sloan Kettering Cancer Center. When to consider multigene panels. April 23, 2015. Available at: https://www.mskcc.org/blog/should-i-consider-multigene-panel-testing.


