**General Approach to Genetic Testing**

**DISCLAIMER**

Our medical policies are designed for informational purposes only and are not an authorization, explanation of benefits or a contract. Receipt of benefits is subject to satisfaction of all terms and conditions of the coverage. Medical technology is constantly changing, and we reserve the right to review and update our policies periodically.

**POLICY**

Genetic testing classified in one of the categories below may be considered **medically necessary** when all criteria are met for each category, as outlined in the Rationale section:

1. Testing of an affected (symptomatic) individual’s germline DNA to benefit the individual (excluding reproductive testing)
   a. Diagnostic
   b. Prognostic
   c. Therapeutic
2. Testing cancer cells of an affected individual to benefit the individual
   a. Diagnostic
   b. Prognostic
   c. Therapeutic
3. Testing an asymptomatic individual to determine future risk of disease.

Genetic testing that does not meet the criteria for a specific category is considered **investigational** or **not medically necessary**, according to the standard definitions used for these terms (see Policy Guidelines section).

**POLICY GUIDELINES**

For the following category of testing, the benefit of testing is for a family member rather than the individual being tested. In this category, the criteria developed are for clinical utility.

- Testing of an affected individual’s germline to benefit family member(s).

Genetic testing is considered not medically necessary when:

- testing is not considered standard of care, such as when the clinical diagnosis can be made without the use of a genetic test.
MP 2.04.91
General Approach to Genetic Testing

- Testing is not clinically appropriate for the patient’s condition (e.g., when it would not change diagnosis and/or management). Other situations where testing is not clinically appropriate include, but are not limited to:
  - Testing performed entirely for nonmedical (e.g., social) reasons;
  - Testing not expected to provide a definitive diagnosis that would obviate the need for further testing.
- Testing is performed primarily for the convenience of the patient, physician, or other health care provider;
- Testing would result in outcomes that are equivalent to outcomes using an alternative strategy, and the genetic test is more costly.

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

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

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.

**CODING**

If the specific analyte is listed in codes 81200-81355 or 81400-81408, that CPT code would be reported. If the specific analyte is not listed in the more specific CPT codes, unlisted code 81479 would be reported.

**BENEFIT APPLICATION**

**BLUECARD/NATIONAL ACCOUNT ISSUES**

Some Plans may have contract or benefit exclusions for genetic testing.

**BACKGROUND**

The purpose of this conceptual framework is to assist evaluation of the utility of genetic tests. In providing a framework for evaluating genetic tests, this review will not determine the clinical utility of genetic testing for specific disorders. Rather, it provides guidelines that can be applied to a wide range of tests.

This conceptual framework applies only if there is not a separate evidence review that outlines specific criteria for testing. If a separate review exists, then the criteria for medical necessity in that evidence review supersede the guidelines herein.

This conceptual framework does not include cytogenetic testing (karyotyping), biochemical testing, or molecular testing for infectious disease.

This conceptual framework also does not address reproductive genetic testing. There are separate evidence reviews for genetic testing in the reproductive setting, addressing, eg, carrier testing for genetic diseases (2.04.107), invasive prenatal (fetal) diagnostic testing (2.04.116), and preimplantation genetic testing (4.02.05).

The following categories of genetic testing are addressed herein (see Appendix 1):

1. Testing of an affected (symptomatic) individual’s germline to benefit the individual
   a. Diagnostic
   b. Prognostic
   c. Therapeutic
2. Testing cancer cells of an affected individual to benefit the individual
   a. Diagnostic
   b. Prognostic
   c. Therapeutic
3. Testing an asymptomatic individual to determine future risk of disease
4. Testing of an affected individual’s germline to benefit family members.

BCBSA genetic testing category 5 (Reproductive testing) is not addressed herein.

**DEFINITIONS**

**Genetic Testing**

Genetic testing involves the analysis of chromosomes, DNA, RNA, genes, or gene products to detect inherited (germline) or non-inherited (somatic) genetic variants related to disease or health.
General Approach to Genetic Testing

Carrier Testing
A carrier of a genetic disorder has 1 abnormal allele for a disorder. When associated with an autosomal recessive or X-linked disorder, carriers of the causative variant are typically unaffected. When associated with an autosomal dominant disorder, the person has 1 normal copy of the gene and 1 mutated copy of the gene; such a person may be affected with the disorder, may be unaffected but at high risk of developing the disease later in life, or may remain unaffected because of the sex-limited nature of the disease.

Carrier testing may be offered to people: (a) who have family members with a genetic condition; (b) who have family members who are identified carriers; and (c) who are members of ethnic or racial groups known to have a higher carrier rate for a particular condition.

Germline Variants
Germline variants are present in the DNA of every cell of the body, from the moment of conception. They include cells in the gonads (testes or ova) and could, therefore, be passed on to offspring.

Somatic Variants
Somatic variations occur with the passage of time and are restricted to a specific cell or cells derived from it. If these variants are limited to cells that are not in the gonads, they will not be passed on to offspring.

Pharmacogenomics
Pharmacogenomics studies how a person’s genetic makeup affects his or her body’s response to drugs.

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

RATIONALE
This conceptual framework was created in May 2013 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through November 7, 2017.

GENERAL PRINCIPLES OF GENETIC TESTS
A test should be cleared or approved by the U.S. Food and Drug Administration or performed in a Clinical Laboratory Improvement Amendments–certified laboratory.

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The following rubric outlines the steps in assessing a medical test. The first step is to formulate the clinical context and purpose of the test. Then the evidence is reviewed to determine whether the test is technically reliable, clinically valid, and clinically useful. However, as noted below, technical reliability is outside the scope of evidence reviews.1,2
TYPES OF GENETIC TESTS ADDRESSED IN THIS CONCEPTUAL FRAMEWORK

1. Testing of an affected (symptomatic) individual’s germline to benefit the individual (excluding reproductive testing)
   a. Diagnostic: To confirm or exclude genetic or heritable variants in a symptomatic person. This refers to a molecular diagnosis supported by the presence of a known pathogenic variant. For genetic testing, a symptomatic person is defined as an individual with a clinical phenotype correlated with a known pathogenic variant.
   b. Prognostic: To determine or refine estimates of disease natural history or recurrence in patients already diagnosed with disease in order to predict natural disease course (e.g., aggressiveness, recurrence, risk of death). This type of testing may use gene expression of affected tissue to predict the course of disease (e.g., testing breast cancer tissue with Oncotype DX).
   c. Therapeutic: To determine that a particular therapeutic intervention is effective (or ineffective) for an individual. To determine the probability of favorable or adverse response to medications. To detect genetic variants that alter risk of treatment response, adverse events, drug metabolism, drug effectiveness, etc. (e.g., cytochrome P450 testing). To detect genetic variants that adversely affect response to exposures in the environment that are ordinarily tolerated (e.g., G6PD deficiency, genetic disorders of immune function, aminoacidopathies).

2. Testing cancer cells of an affected individual to benefit the individual
   a. Diagnostic: To determine the origin of a cancer or to determine a clinically relevant subgroup into which a cancer is classified.
   b. Prognostic: To determine the risk of progression, recurrence, or mortality for a cancer that is already diagnosed.
   c. Therapeutic: To determine the likelihood that a patient will respond to a targeted cancer therapy that is based on the presence or absence of a specific variant.

3. Testing an asymptomatic individual to determine future risk of disease. To detect genetic variants associated with disorders that appear after birth, usually later in life. Such testing is intended for individuals with a family history of a genetic disorder, but who themselves have no features of the disorder, at the time of testing, in order to determine their risk for developing the disorder.

4. Testing of an affected individual’s germline to benefit family member(s). To focus and direct family testing of asymptomatic relatives, by testing an individual with known disease but in whom the presence or absence of a pathogenic variant has not been determined.

MEDICAL NECESSITY CRITERIA
The criteria listed below for medical necessity represent minimum criteria that must be met in each category to conclude that a test is medically necessary. Alternative approaches to grouping these factors are presented in Appendix 2. The tables in Appendix 2 list all factors considered for clinical utility, and the figures in Appendix 2 group the factors into a branching logic schematic that facilitates a decision whether the test does or does not meet clinical utility.

Genetic testing is considered medically necessary for a genetic or heritable disorder when the following are met.

For ALL genetic testing, the condition being tested for must have either:

- Reduced life expectancy OR
- At least moderate-to-severe morbidity.

3
For the specific categories of testing, the following criteria must also be met:

1. Testing of an affected (symptomatic) individual’s germline to benefit the individual (excluding reproductive testing)
   a. Diagnostic
      i. An association between the marker and the disorder has been established AND
      ii. Symptoms of the disease are present AND
      iii. A definitive diagnosis cannot be made based on history, physical examination, pedigree analysis, and standard diagnostic studies/tests AND
      iv. The clinical utility of identifying the variant has been established (see Appendix 2):
         1) Leads to changes in clinical management of the condition that improve outcomes OR
         2) Eliminates the need for further clinical workup or invasive testing OR
         3) Leads to discontinuation of interventions that are unnecessary and/or ineffective,
   b. Prognostic
      i. An association between the marker and the natural history of the disease has been established AND
      ii. Clinical utility of identifying the variant has been established (see Appendix 2):
         1) Provides incremental prognostic information above that of standard testing AND
         2) Reclassifies patients into clinically relevant prognostic categories for which there are different treatment strategies AND
         3) Reclassification leads to changes in management that improve outcomes.
   c. Therapeutic
      i. Genetic testing identifies variants of a phenotype/metabolic state that relate to different pharmacokinetics, drug efficacy, or adverse drug reactions AND
      ii. Clinical utility of identifying the variant has been established (see Appendix 2):
         1) Leads to initiation of effective medication(s) OR
         2) Leads to discontinuation of medications that are ineffective or harmful OR
         3) Leads to clinical meaningful change in dosing of medication that is likely to improve outcomes.

2. Testing cancer cells of an affected individual to benefit the individual
   a. Diagnostic
      i. Genetic testing can establish the cell origin of a cancer when the origin is uncertain following standard workup AND
      ii. Clinical utility of identifying the variant has been established (see Appendix 2):
         1) Start effective treatment OR
         2) Discontinue ineffective or harmful treatment
   b. Prognostic
      i. An association between the marker and the natural history of the disease has been established AND
      ii. Clinical utility of identifying the variant has been established (see Appendix 2):
         1) Provides incremental prognostic information above that of standard testing AND
         2) Reclassifies patients into clinically relevant prognostic categories for which there are different treatment strategies AND
         3) Reclassification leads to changes in management that improve outcomes.
c. Therapeutic
   i. Association between a variant and treatment response to a particular drug has been established AND
   ii. Clinical utility has been established (see Appendix 2):
      1) The patient is a candidate for targeted drug therapy associated with a specific variant AND
      2) There is a clinically meaningful improvement in outcomes when targeted therapy is given for the condition.

3. Testing an asymptomatic individual to determine future risk of disease
   i. An association between the marker and future disorder has been established AND
   ii. Clinical utility has been established (see Appendix 2):
      1) There is a presymptomatic phase for this disorder and interventions or surveillance are available AND
      2) Interventions in the presymptomatic phase are likely to improve outcomes:
         a. Prevent or delay onset of disease OR
         b. Detect disease at an earlier stage during which treatment is more effective OR
         c. Discontinuation of ineffective or unnecessary interventions.

CLINICAL UTILITY CRITERIA
For the following category, focusing on the benefit of testing for another individual, the definition of medical necessity may not apply. When an individual is tested to benefit a family member, and there is no benefit for the individual being tested, eligibility for coverage depends on individual plan benefit language. Individual plans may differ whether benefit structure allows testing of an individual to benefit an unaffected family member.

For these reasons, the following criteria are considered for clinical utility of testing and not for medical necessity.

4. Testing of an affected individual’s germline to benefit family members
   i. An association between the genetic variant and clinical disease has been established AND
   ii. Family members are available who may be at risk for the disorder AND
   iii. The individual tested has a clinical diagnosis of the condition (or represents the family member who is most likely to harbor the pathogenic variant), but genetic testing has not been performed AND
   iv. There is a presymptomatic phase for the disorder in which interventions are available AND
   v. Interventions in the presymptomatic phase are likely to improve outcomes in one of the following ways:
      1) Prevent or delay onset of disease;
      2) Detect disease at an earlier stage during which treatment is more effective;
      3) Discontinuation of interventions that is ineffective or unnecessary.

LIMITATIONS OF GENETIC TESTING
- The testing methods may not detect all variants that may occur in a gene.
- Genetic testing may identify variants of uncertain significance.
- Genetic testing may not necessarily determine the clinical outcome.
- Different genes can cause the same disease (genetic heterogeneity).
- A variant in a gene may cause different phenotypes (phenotypic heterogeneity).
- Some disease-causing genes may not yet be identified.
General Approach to Genetic Testing

- Genetic testing is subject to laboratory error.

SUMMARY OF EVIDENCE
This conceptual framework addresses genetic testing in non-reproductive settings. Genetic testing in reproductive settings is addressed separately (e.g., evidence reviews 2.04.107, 2.04.116, 4.02.05). For categories of genetic testing for which the benefit of testing is the individual, criteria for medical necessity apply. When the benefit of testing is not for the individual, but for a family member, medical necessity criteria may not apply, and the criteria are developed for clinical utility.

SUPPLEMENTAL INFORMATION

PRACTICE GUIDELINES AND POSITION STATEMENTS
No guidelines or statements were identified.

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS
Not applicable.

MEDICARE NATIONAL COVERAGE
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

ONGOING AND UNPUBLISHED CLINICAL TRIALS
A search of ClinicalTrials.gov in November 2017 did not identify any ongoing or unpublished trials that would likely influence this review.

REFERENCES

CODES

<table>
<thead>
<tr>
<th>Codes</th>
<th>Number</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>CPT</td>
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<td>See Policy Guidelines</td>
</tr>
<tr>
<td>ICD-10-CM</td>
<td></td>
<td>Diagnosis coding would depend on the condition for which the testing is being performed, if the test is being performed as screening or carrier testing, and any family history of the condition.</td>
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<tr>
<td>ICD-10-PCS</td>
<td></td>
<td>Not applicable. ICD-10-PCS codes are only used for inpatient services.</td>
</tr>
<tr>
<td>Type of Service</td>
<td></td>
<td>There are no ICD procedure codes for laboratory tests.</td>
</tr>
<tr>
<td>Place of Service</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
POLICY HISTORY

<table>
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<th>Date</th>
<th>Action</th>
<th>Description</th>
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<tr>
<td>05/22/14</td>
<td>Replace policy</td>
<td>Policy statements unchanged. No new literature has been identified for this concept policy update. Expanded framework for determining clinical utility has been added as an appendix for the categories of diagnostic testing, risk assessment, prognostic testing, and pharmacogenomics.</td>
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<td>03/12/15</td>
<td>Replace policy</td>
<td>Policy updated with new categories of genetic testing. No new references added. Medical necessity criteria revised for each new category of testing; for the category of testing an individual for the benefit of a family member, criteria are for clinical utility rather than medical necessity.</td>
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<td>01/14/16</td>
<td>Replace policy</td>
<td>Policy updated with literature review through December 31, 2015; references redone with references 1 and 3 added. Branching schematic diagrams for determining clinical utility added. Policy statements unchanged.</td>
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<td>02/24/17</td>
<td>Replace policy</td>
<td>Blue Cross of Idaho policy review, no change to the policy.</td>
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<tr>
<td>12/27/17</td>
<td>Replace policy</td>
<td>Blue Cross of Idaho adopted changes as noted. Policy updated with literature review through November 7, 2017; on new references added. Policy statements unchanged.</td>
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<td>02/21/19</td>
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<td>Blue Cross of Idaho annual review; no change to policy.</td>
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APPENDIX

APPENDIX 1. CATEGORIZATION OF TYPES OF TESTING ADDRESSED IN EVIDENCE REVIEWS

<table>
<thead>
<tr>
<th>Category</th>
<th>Addressed</th>
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</thead>
<tbody>
<tr>
<td>1. Testing of an affected individual's germline to benefit the individual</td>
<td></td>
</tr>
<tr>
<td>1a. Diagnostic</td>
<td></td>
</tr>
<tr>
<td>1b. Prognostic</td>
<td></td>
</tr>
<tr>
<td>1c. Therapeutic</td>
<td></td>
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<tr>
<td>2. Testing cancer cells from an affected individual to benefit the individual</td>
<td></td>
</tr>
<tr>
<td>2a. Diagnostic</td>
<td></td>
</tr>
<tr>
<td>2b. Prognostic</td>
<td></td>
</tr>
<tr>
<td>2c. Therapeutic</td>
<td></td>
</tr>
<tr>
<td>3. Testing an asymptomatic individual to determine future risk of disease</td>
<td></td>
</tr>
<tr>
<td>4. Testing an affected individual's germline to benefit family members</td>
<td></td>
</tr>
<tr>
<td>5. Reproductive testing</td>
<td></td>
</tr>
<tr>
<td>5a. Carrier testing: preconception</td>
<td></td>
</tr>
<tr>
<td>5b. Carrier testing: prenatal</td>
<td></td>
</tr>
<tr>
<td>5c. In utero testing: aneuploidy</td>
<td></td>
</tr>
<tr>
<td>5d. In utero testing: familial variants</td>
<td></td>
</tr>
<tr>
<td>5e. In utero testing: other</td>
<td></td>
</tr>
<tr>
<td>5f. Preimplantation testing with in vitro fertilization</td>
<td></td>
</tr>
</tbody>
</table>
APPENDIX 2. APPROACH TO DETERMINING CLINICAL UTILITY FOR GENETIC TESTING

Direct Evidence
If direct evidence is available on the impact of testing on outcomes, this evidence takes precedence. Examples of direct evidence are:

- Trial comparing outcomes with and without use of the test
- Associational study of genetic testing with outcomes.

Indirect Evidence
When direct evidence is not available, indirect evidence should be evaluated. Indirect evidence addresses one or more components of a chain of evidence but does not connect the intervention with the outcome.

An example of indirect evidence is the accuracy of the genetic test for diagnosing the clinical condition (i.e., clinical sensitivity and specificity). If improved accuracy leads to improved diagnosis of the disorder, and if more accurate diagnosis leads to management changes that improve outcomes, then clinical utility has been established.

Many disorders are rare, and high-quality evidence on the efficacy of treatment is often lacking. This is particularly true for aspects of management such as increased surveillance for complications, ancillary treatments (e.g., physical therapy, occupational therapy), and referrals to specialists. When evidence on outcomes is lacking, consideration may be given to whether these aspects of care are considered standard of care for that disorder, especially when they are part of guidelines by authoritative bodies.

A number of factors influence the strength of indirect evidence that is needed to determine whether health outcomes are improved. No single factor by itself is determinative of whether genetic testing should be performed, but the factors may be important determinants of the potential clinical utility of testing. We enumerate 4 factors below, each with an accompanying table (see Appendix Tables 1-4).

1. Factors impacting the strength of indirect evidence for diagnostic testing (categories 1a, 2a)

Disease Characteristics
- Is life expectancy reduced with this disorder?
- What is the level of physical and/or psychosocial morbidity (disability) associated with the disorder?
  - Severe morbidity/disability
  - Moderate morbidity/disability
  - Minor or no morbidity/disability

Impact of Genetic Testing on Diagnosis
- Can genetic testing confirm the suspected diagnosis?
- Can the diagnosis be confirmed by alternative methods without genetic testing?
  - Disorder is defined by the presence of genetic variant
  - Genetic testing is one of several factors contributing to diagnosis
  - Unable to make diagnosis without genetic testing in some patients
- Can genetic testing rule out the disorder?
- Can genetic testing eliminate further clinical workup?
  - Is disorder one for which a diagnosis can be difficult, and the patient may be subjected to long and complicated workups?
Impact of Genetic Testing on Clinical Management

- Does confirmation of diagnosis by genetic testing lead to improved outcomes?
  - Initiation of effective treatment
  - Discontinuation of ineffective treatment
- Does confirmation of diagnosis by genetic testing lead to initiation of other management changes with uncertain impact on outcomes (e.g., referrals to specialists and/or ancillary care, initiate screening)?
- Does confirmation of diagnosis by genetic testing lead to initiation of other management changes that are considered “standard of care” treatment for disorder?

Impact on Health Outcomes

- Is there a definite improvement in health outcomes with genetic testing? For example:
  - Diagnosis cannot be made without genetic testing, and confirmation of diagnosis leads to initiation of effective treatment.
- Is there a possible, but not definite, improvement in health outcomes with genetic testing? For example:
  - Diagnosis cannot be made without genetic testing, and confirmation of diagnosis leads to management changes with uncertain impact on outcomes.
- Are there significant barriers to research, such as rarity of the disorder?
- What is the impact of genetic testing on lifestyle factors?
  - Employment/occupational decision making
  - Leisure activities
  - Reproductive decision-maker

Appendix Table 1. Factors Influencing the Strength of Indirect Evidence on Clinical Utility (Categories 1a, 2a)

<table>
<thead>
<tr>
<th>Disorder Characteristics</th>
<th>Impact on Diagnosis</th>
<th>Impact on Management</th>
<th>Impact on Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shortened life expectancy</td>
<td>Confirms diagnosis</td>
<td>Eliminates need for other clinical workup</td>
<td>Change in management with improved health outcomes</td>
</tr>
<tr>
<td>Severe morbidity/disability</td>
<td>Confirms diagnosis, otherwise unable to make clinically</td>
<td>Initiate effective treatment for disorder</td>
<td>Provide “standard of care” treatment for disorder</td>
</tr>
<tr>
<td>Moderate morbidity/disability</td>
<td>Rules out disorder</td>
<td>Discontinue ineffective treatment</td>
<td>Change in management with uncertain impact on outcomes</td>
</tr>
<tr>
<td>Minor or no morbidity/disability</td>
<td>Contributes to ability to make</td>
<td>Initiate other management changes</td>
<td>Barriers to research</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Impact on lifestyle factors</td>
</tr>
</tbody>
</table>
2. Factors impacting the strength of indirect evidence for assessing risk of future disease in asymptomatic individuals (category 3)

Disease Characteristics
- Is life expectancy reduced with this disorder?
- What is the level of physical and/or psychosocial morbidity (disability) associated with the disorder?
  - Severe morbidity/disability
  - Moderate morbidity/disability
  - Minor or no morbidity/disability
- Is there a presymptomatic phase during which a clinical diagnosis cannot be made?

Impact of Genetic Testing on Defining Risk of Disease
- Can genetic testing determine the risk of subsequent disease in at least a substantial proportion of the population tested?
- Is there a known variant in the family?
- Is the penetrance of the genetic variant known?
- Are there other factors that impact the clinical expression of disease?

Impact of Genetic Testing on Management
- Does confirmation of risk lead to interventions that are indicated for this condition in the presymptomatic phase?
  - Interventions that prevent or delay disease onset
  - Surveillance for manifestations or complications of disease
- Does confirmation of risk by a positive genetic testing result lead to the initiation of other management changes that may or may not lead to improved outcomes (e.g., referrals to specialists and/or ancillary care, initiate screening)?
- Does a negative test confirm a lack of risk for the disease, and does this lead to discontinuation of interventions (e.g., surveillance) that would otherwise be performed?
- Is it likely that knowledge of variant status will lead to alterations in reproductive decision making?

Impact on Health Outcomes
- Is there a definite improvement in health outcomes with genetic testing? For example:
  - Risk assessment cannot be made without genetic testing, and confirmation of risk leads to initiation of effective preventive interventions that delay onset of disease
- Is there a possible, but not definite, improvement in health outcomes with genetic testing? For example:
  - Risk assessment cannot be made without genetic testing, and confirmation of risk leads to management changes with uncertain impact on outcomes.
- Are there significant barriers to research, such as rarity of the disorder?
- What is the impact of genetic testing on lifestyle factors?
  - Employment/occupational decision making
  - Leisure activities
  - Reproductive decision-maker
Appendix Table 2. Factors Influencing the Strength of Indirect Evidence for Risk Assessment Testing (Category 3)

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Disease Characteristics</th>
<th>Impact on Defining Risk</th>
<th>Impact on Management</th>
<th>Impact on Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Shortened life expectancy</td>
<td>Determines risk in substantial proportion of patients</td>
<td>Initiate effective interventions in presymptomatic phase</td>
<td>Likely to impact reproductive outcomes</td>
</tr>
<tr>
<td></td>
<td>Severe morbidity/disability</td>
<td>Has presymptomatic stage</td>
<td>Other factors impact clinical management</td>
<td>Negative test leads to discontinuation of interventions</td>
</tr>
<tr>
<td></td>
<td>Moderate morbidity/disability</td>
<td>Known variant in family</td>
<td>Other management changes with uncertain impact</td>
<td>Definite improved health outcomes</td>
</tr>
<tr>
<td></td>
<td>Minor or no morbidity/disability</td>
<td>Penetrance is well known</td>
<td>Other factors impact clinical management</td>
<td>Possible impact on outcomes, data lacking</td>
</tr>
</tbody>
</table>

3. Factors influencing the strength of indirect evidence for prognosis testing (categories 1b, 2b)

**Disease Characteristics**
- Is life expectancy reduced with this disorder?
- What is the level of physical and/or psychosocial morbidity (disability) associated with the disorder?
  - Severe morbidity/disability
  - Moderate morbidity/disability
  - Minor or no morbidity/disability

**Impact of Genetic Testing on Prognosis**
- Does the genetic test have an association with prognosis of disease?
- Does genetic testing lead to an incremental improvement in prognosis above that which can be done by usual testing?
- Does the genetic testing allow classification of patients into clinically credible prognostic groups?
  - Have these prognostic groups been defined clinically a priori?

**Impact of Genetic Testing on Management**
- Are different prognostic groups associated with different treatment interventions?
  - Type of intervention
  - Timing of intervention
- Has treatment according to risk category been demonstrated to improve outcomes?
- Is treatment according to risk category considered standard of care for this disorder?

**Impact on Health Outcomes**
- Is there a definite improvement in health outcomes with genetic testing? For example:
MP 2.04.91
General Approach to Genetic Testing

- Reclassification by prognosis leads to change in management that is known to be effective for the condition
- Is there a possible, but not definite, improvement in health outcomes with genetic testing? For example:
  - Reclassification by prognosis leads to changes in management with uncertain impact on outcomes
- Are there significant barriers to research, such as rarity of the disorder?
- What is the impact of testing on lifestyle factors?
  - Employment/occupational decision making
  - Leisure activities
  - Reproductive decision-maker

Appendix Table 3. Factors Influencing the Strength of Indirect Evidence for Prognosis Testing (Categories 1b, 2b)

<table>
<thead>
<tr>
<th>Disorder Characteristics</th>
<th>Impact on Prognosis</th>
<th>Impact on Management</th>
<th>Impact on Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shortened life expectancy</td>
<td>Variant associated with</td>
<td>Clinically credible prognostic</td>
<td>Definite improved health</td>
</tr>
<tr>
<td>Severe morbidity/disability</td>
<td>Incremental improvement above clinical measures</td>
<td>Treatment by prognostic group is standard of care</td>
<td>Possible impact on outcomes</td>
</tr>
<tr>
<td>Moderate morbidity/disability</td>
<td></td>
<td>Treatment by prognostic group improves outcomes</td>
<td>Barriers to research</td>
</tr>
<tr>
<td>Minor or no morbidity/disability</td>
<td></td>
<td></td>
<td>Impact on lifestyle factors</td>
</tr>
</tbody>
</table>

4. Factors influencing the strength of indirect evidence for genetic variants that alter response to treatment (categories 1c, 2c)

Disease Characteristics
- Is life expectancy reduced with this disorder?
- What is the level of physical and/or psychosocial morbidity (disability) associated with the disorder?
  - Severe morbidity/disability
  - Moderate morbidity/disability
  - Minor or no morbidity/disability
- Is there effective pharmacologic therapy for this disorder?

Impact of Genetic Testing on Assessing Response to Treatment
- Can genetic testing define variants associated with different pharmacokinetics of drug metabolism?
- Are these changes in drug metabolism clinically important?
  - Variants have been associated with clinically significant differences in outcomes of treatment
**General Approach to Genetic Testing**

- Are there genetic variants associated with increased risk for adverse effects?

**Impact of Genetic Testing on Pharmacologic Management**
- Does identification of genetic variants lead to changes in pharmacologic management?
  - Initiation of alternate agents
  - Discontinuation ineffective agents
  - Changes in dosing

**Impact on Health Outcomes**
- Is there a definite improvement in health outcomes with genetic testing? For example:
  - Identification of variants leads to initiation of medications known to be effective.
- Is there a possible, but not definite, improvement in health outcomes with genetic testing? For example:
  - Identification of variants leads to change in pharmacologic management with uncertain impact on outcomes.
- Are there significant barriers to research, such as rarity of the disorder?

**Appendix Table 4. Factors Influencing the Strength of Indirect Evidence for Genetic Variants That Alter Response to Treatment (Categories 1c, 2c)**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Disease Characteristics</th>
<th>Impact on Response to Treatment</th>
<th>Impact on Management</th>
<th>Impact on Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Define variants with different pharmacokinetics are clinically important</td>
<td>Variants lead to differences in response</td>
<td>Discontinue ineffective treatment</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Disease Characteristics</th>
<th>Impact on Response to Treatment</th>
<th>Impact on Management</th>
<th>Impact on Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Effective pharmacologic therapy may be altered</td>
<td>Variants with increased risk for adverse effects</td>
<td>Initiation of alternate agents</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Different pharmacokinetics are clinically important</td>
<td>Variants lead to differences in response</td>
<td>Discontinue ineffective treatment</td>
</tr>
</tbody>
</table>
Appendix Figure 1. Diagnostic Testing Schematic of an Affected Individual’s Germline to Benefit the Individual (Category 1a)

CU: clinical utility
Appendix Figure 2. Prognostic Testing Schematic of an Affected Individual’s Germline to Benefit the Individual (Category 1b)

1. Testing an affected individual’s germline to benefit the individual
   
   1b. Prognostic
   
   Does this disorder have reduced life expectancy?
   
   Yes ────► Does this disorder have at least moderate or severe morbidity?
   
   Yes ───► Does genetic testing provide incremental prognostic information above that provided by standard testing?
   
   Yes ───► Does testing reclassify patients into clinically relevant prognostic categories for which there are different treatment strategies?
   
   Yes ───► Does treatment according to the defined prognostic categories improve outcomes?
   
   Yes ───► Meets CU Criteria
   
   No ───► Uncertain impact on outcomes, but standard of care
   
   Indeterminate, consider clinical vetting
   
   Does not meet CU Criteria
   
   No ───► Does not meet CU Criteria

CU: clinical utility
Appendix Figure 3. Therapeutic Testing Schematic of an Affected Individual's Germline to Benefit the Individual (Category 1c)

1. Testing an affected individual's germline to benefit the individual

1c. Therapeutic

Does this disorder have reduced life expectancy?

- Yes
  - Does this disorder have at least moderate or severe morbidity?
    - Yes
      - Does genetic testing identify variants which have different drug sensitivities or pharmacokinetics?
        - Yes
          - Are the differences in sensitivity or metabolism clinically important?
            - Yes
              - Are there clinically credible management changes associated with identification of genetic variants?
                - Yes
                  - Meets CU Criteria
                - No
                  - Does not meet CU Criteria
            - No
              - Does not meet CU Criteria
        - No
          - Does not meet CU Criteria
    - No
      - Does not meet CU Criteria
- No

Discontinue ineffective drug

Start effective drug

Change dose of drug

Do these changes in drug dosages improve health outcome?

- Yes
  - Meets CU Criteria
- No
  - Does not meet CU Criteria

CU: clinical utility.
Appendix Figure 4. Diagnostic Testing Schematic of DNA From Cancer Cells of an Affected Individual to Benefit the Individual (Category 2a)

CU: clinical utility.
Appendix Figure 5. Prognostic Testing Schematic of DNA From Cancer Cells of an Affected Individual to Benefit the Individual (Category 2b)

CU: clinical utility.
Appendix Figure 6. Therapeutic Testing Schematic of DNA From Cancer Cells of an Affected Individual to Benefit the Individual (Category 2c)

2. Testing of DNA from cancer cells of an affected individual to benefit the individual
   2c. Predictive testing for treatment response

   Does this disorder have reduced life expectancy?
   - Yes
     - Does this disorder have at least moderate or severe morbidity?
       - Yes
         - Does not meet CU Criteria
       - No
         - Does not meet CU Criteria
   - No
     - Does not meet CU Criteria

   Can genetic testing identify markers associated with treatment response?
   - Yes
     - Are there targeted drugs aimed at the specific genetic markers?
       - Yes
         - Is there a clinically meaningful improvement in outcomes for targeted treatment?
           - Yes
             - Meets CU Criteria
           - No
             - Does testing "turn off" ineffective treatment
               - Yes
                 - Meets CU Criteria
               - No
                 - Does not meet CU Criteria
         - Does not meet CU Criteria
       - No
         - Does not meet CU Criteria
   - No
     - Does not meet CU Criteria

CU: clinical utility.
Appendix Figure 7. Testing Schematic of an Asymptomatic Individual to Determine Future Risk of Disease (Category 3)

3. Testing an asymptomatic individual to determine future risk of disease

Does this disorder have reduced life expectancy?
- Yes
  - Does this disorder have at least moderate or severe morbidity?
    - Yes
      - Does testing identify genetic markers indicating future risk of disease?
        - Yes
          - Is penetrance for these markers known, and are other factors that affect clinical expression well understood?
            - Yes
              - Is there a presymptomatic phase for this disorder in which interventions are available?
                - Yes
                  - Does testing improve outcomes: Prevent/delay onset of disease
                    - Yes: Meets CU Criteria
                    - No: Indeterminate, consider clinical vetting
                  - Does not meet CU Criteria
                - No
                  - Does not meet CU Criteria
            - No: Does not meet CU Criteria
          - Does not meet CU Criteria
        - No: Does not meet CU Criteria
    - No
      - Does not meet CU Criteria
  - No: Does not meet CU Criteria
- No
  - Does not meet CU Criteria

CU: clinical utility.
Appendix Figure 8. Testing Schematic of an Affected Individual’s Germline DNA to Benefit Family Members (Category 4)

4. Testing of an affected individual’s germline DNA to benefit family member(s)

Does this disorder have reduced life expectancy?

Yes

Does this disorder have at least moderate or severe morbidity?

Yes

Can testing identify a mutation that has a hereditary pattern and is likely to be passed on to offspring?

Yes

Is penetrance for these markers known, and are other factors that affect clinical expression well understood?

Yes

Interventions that improve outcomes:
- Prevent/delay onset of disease
- Detect disease at earlier stage that has more effective treatment
- Discontinue surveillance or screening interventions

Means CU Criteria

Interventions with uncertain impact on outcomes but are standard of care

Indeterminate, consider clinical weighting

Interventions that are unlikely to improve outcomes

Does not meet CU Criteria

No

No

Does not meet CU Criteria

No

Does not meet CU Criteria

No

Does not meet CU Criteria

CU: clinical utility.