Medical Policy

General Approach to Genetic Testing

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Policy Number: 735
BCBSA Reference Number: 2.04.91
NCD/LCD: N/A

Related Policies
- General Approach to Evaluating the Utility of Genetic Panels, #734
- Carrier Testing for Genetic Diseases, #666
- Invasive Prenatal (Fetal) Diagnostic Testing, #708
- Preimplantation Genetic Testing, #088

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO BlueSM and Medicare PPO BlueSM Members

The purpose of this policy is to provide assistance in evaluating the utility of genetic tests. This policy applies only if there is not a separate BCBSMA policy that outlines specific criteria for testing. If a separate BCBSMA policy does exist, then the criteria for medical necessity in that policy supersede the guidelines in this 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 of DNA from cancer cells of an affected individual to benefit the individual
   a. Diagnostic
   b. Prognostic
   c. Testing to predict treatment response
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.
Rationale
General Principles of Genetic Tests
The test should be cleared or approved by the U.S. Food and Drug Administration or performed in a Clinical Laboratory Improvement Amendment-certified laboratory.

Peer-reviewed literature on the performance and indications for the test should be available. This evaluation of a genetic test focuses on 3 main principles: (1) analytic validity (technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent); (2) clinical validity, (diagnostic performance of the test [sensitivity, specificity, positive and negative predictive values] in detecting clinical disease); and (3) clinical utility (ie, how results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

Types of Genetic Tests Addressed in This Policy
1. Testing of an affected (symptomatic) individual's germline DNA to benefit the individual (excluding reproductive testing)
   a. Diagnostic. To confirm or exclude genetic or heritable mutations in a symptomatic person. This refers to a molecular diagnosis supported by the presence of a known pathologic mutation. For the purposes of genetic testing, a symptomatic person is defined as a person with a clinical phenotype that is correlated with a known pathologic mutation.
   b. Prognostic. To determine or refine estimates of disease natural history or recurrence in patients already diagnosed with disease. To predict natural disease course, eg, aggressiveness, recurrence, risk of death. This type of testing may use gene expression of affected tissue to predict the course of disease, eg, testing breast cancer tissue with Oncotype DX.
   c. Therapeutic. To determine that a particular therapeutic intervention is effective (or ineffective) for an individual patient. 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. (eg, cytochrome p450 testing). To detect genetic mutations that adversely affect response to exposures in the environment that are ordinarily tolerated, such as G6PD deficiency, genetic disorders of immune function, and aminoacidopathies.
2. Testing of DNA from 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 that a cancer falls into.
   b. Prognostic. To determine the risk of progression, recurrence, mortality for a cancer that is already diagnosed.
   c. Predictive testing for treatment response. 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 mutation.
3. Testing an asymptomatic individual to determine future risk of disease. To detect genetic mutations associated with disorders that appear after birth, usually later in life. 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 DNA 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 pathologic mutation has not been determined.

Medical Necessity Criteria
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.
For the specific categories of testing, the following criteria must also be met:

1. Testing of an affected (symptomatic) individual's germline DNA to benefit the individual (excluding reproductive testing)
   a. Diagnostic
      i. An association of the marker with 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, standard diagnostic studies/tests AND
      iv. The clinical utility of identifying the mutation has been established (see Appendix):
         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 of the marker with the natural history of the disease has been established AND
      ii. Clinical utility of identifying the mutation has been established (see Appendix),
         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 mutation has been established (see Appendix),
         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 of DNA from 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 work-up; AND
      ii. Clinical utility of identifying the mutation has been established (see Appendix)
         1) Start effective treatment; OR
         2) Discontinue ineffective or harmful treatment
   b. Prognostic
      i. An association of the marker with the natural history of the disease has been established AND
      ii. Clinical utility of identifying the mutation has been established (see Appendix),
         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. Testing to predict treatment response
      i. Association of a mutation with treatment response to a particular drug has been established AND
      ii. Clinical utility has been established (see Appendix),
         1) The patient is a candidate for targeted drug therapy associated with a specific mutation; 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 of the marker with future disorder has been established AND
Clinical utility has been established (see Appendix)

1. There is a presymptomatic phase for this disorder in which interventions/surveillance are available; AND

2. Interventions in the presymptomatic phase are likely to improve outcomes:
   a. Prevent/delay onset of disease OR
   b. Detect disease at an earlier stage for which treatment is more effective OR
   c. Discontinuation of interventions that are ineffective or unnecessary.

Clinical Utility Criteria
For the following category, in which the benefit of testing is 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 is dependent on individual plan benefit language. Individual plans may differ as to whether benefit structure allows testing of an individual to benefit an unaffected family member.

Because of these concerns, the following criteria are considered to be criteria for clinical utility of testing and not for medical necessity.

4. Testing of an affected individual’s germline DNA to benefit family member(s)
   i. An association of the genetic mutation with 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 mutation), 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/delay onset of disease
      2) Detect disease at an earlier stage for which treatment is more effective;
      3) Discontinuation of interventions that are ineffective or unneeded.

Genetic Counseling
Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual’s family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Limitations of Genetic Testing
- The testing methods may not detect all of the mutations that may occur in a gene
- Genetic testing may identify variants of unknown clinical significance
- Genetic testing may not necessarily determine the clinical outcome
- Different genes can cause the same disease (genetic heterogeneity)
- A mutation in a gene may cause different phenotypes (phenotypic heterogeneity)
- Some disease-causing genes may not be identified as of yet
- Genetic testing is subject to laboratory error

Prior Authorization Information
Pre-service approval is required for all inpatient services for all products. See below for situations where prior authorization may be required or may not be required. Yes indicates that prior authorization is required. No indicates that prior authorization is not required.
N/A indicates that this service is primarily performed in an inpatient setting.

<table>
<thead>
<tr>
<th>Commercial Managed Care (HMO and POS)</th>
<th>Outpatient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial PPO and Indemnity</td>
<td>No</td>
</tr>
<tr>
<td>Medicare HMO BlueSM</td>
<td>No</td>
</tr>
<tr>
<td>Medicare PPO BlueSM</td>
<td>No</td>
</tr>
</tbody>
</table>

CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

CPT Codes

There is no specific CPT code for this service.

Description

The purpose of this policy is to provide assistance in evaluating the utility of genetic tests. In providing a framework for evaluating genetic tests, this policy will not attempt to determine the clinical utility of genetic testing for specific disorders. Rather, it provides guidelines that can be applied to a wide range of different tests.

This policy applies only if there is not a separate BCBSMA policy that outlines specific criteria for testing. If a separate BCBSMA policy does exist, then the criteria for medical necessity in that policy supersede the guidelines in this policy.

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

This policy does not address reproductive genetic testing. There are separate BCBSMA policies for genetic testing in the reproductive setting: Carrier Testing for Genetic Diseases (Policy #666); Invasive Prenatal (Fetal) Diagnostic Testing (Policy #708); and Preimplantation Genetic Testing (Policy #088).

The following categories of genetic testing are addressed in this policy:

1. Testing of an affected (symptomatic) individual’s germline DNA to benefit the individual
   d. Diagnostic
   e. Prognostic
   f. Therapeutic
2. Testing of DNA from cancer cells of an affected individual to benefit the individual
   d. Diagnostic
   e. Prognostic
   f. Testing to predict treatment response
   g. Testing an asymptomatic individual to determine future risk of disease
3. Testing of an affected individual's germline DNA to benefit family member(s).

Definitions

Genetic Testing

Genetic testing involves the analysis of chromosomes, DNA (deoxyribonucleic acid), RNA (ribonucleic acid), genes or gene products to detect inherited (germline) or noninherited (somatic) genetic variants related to disease or health.
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 mutation are typically unaffected. When associated with an autosomal dominant disorder, the person has 1 normal and 1 mutated copy of the gene and may be affected with the disorder, may be unaffected but at high risk of developing the disease later in life, or the carrier 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 Mutations
Mutations that are present in the DNA of every cell of the body, present from the moment of conception. These include cells in the gonads (testes or ova) and could, therefore be passed on to offspring.

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

Pharmacogenomics
Study of how a person’s genetic makeup affects the body’s response to drugs.

Summary
There are numerous commercially available genetic tests, including those used to guide intervention in symptomatic or asymptomatic people, to identify people at risk for future disorders, to predict the prognosis of diagnosed disease, and to predict treatment response. This concept policy offers a framework for evaluating the utility of genetic tests, by classifying the types of genetic tests into clinically relevant categories and developing criteria that can be used for evaluating tests in each category.

This policy addresses genetic testing in nonreproductive settings. Genetic testing in reproductive settings is addressed in separate policies. For categories of genetic testing in which the benefit of testing is for 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.

Policy History

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>8/2015</td>
<td>Rationale and appendix added. 8/21/2015</td>
</tr>
<tr>
<td>8/2015</td>
<td>New medical policy describing medically necessary, not medically necessary or investigational indications. Effective 8/1/2015.</td>
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</tbody>
</table>

Information Pertaining to All Blue Cross Blue Shield Medical Policies
Click on any of the following terms to access the relevant information:
- Medical Policy Terms of Use
- Managed Care Guidelines
- Indemnity/PPO Guidelines
- Clinical Exception Process
- Medical Technology Assessment Guidelines
References

APPENDIX
Appendix 1. Table for Categorizing Which Type of Testing Is Being Addressed in MPRM Policies

The following table will be used on individual genetic MPRM policies to indicate which categories are addressed in the policy, including both general genetic testing and reproductive genetic testing.

<table>
<thead>
<tr>
<th>Category</th>
<th>Addressed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Testing of an affected individual's germline to benefit the individual</td>
<td>Yes</td>
</tr>
<tr>
<td>1a. Diagnostic</td>
<td>Yes</td>
</tr>
<tr>
<td>1b. Prognostic</td>
<td>No</td>
</tr>
<tr>
<td>1c. Therapeutic</td>
<td>Yes</td>
</tr>
<tr>
<td>2. Testing cancer cells from an affected individual to benefit the individual</td>
<td>Yes</td>
</tr>
<tr>
<td>2a. Diagnostic</td>
<td>Yes</td>
</tr>
<tr>
<td>2b. Prognostic</td>
<td>No</td>
</tr>
<tr>
<td>2c. Therapeutic</td>
<td>Yes</td>
</tr>
<tr>
<td>3. Testing an asymptomatic patient to determine future risk of disease</td>
<td>Yes</td>
</tr>
<tr>
<td>4. Testing of an affected individual's germline to benefit family members</td>
<td>Yes</td>
</tr>
<tr>
<td>5. Reproductive testing</td>
<td>Yes</td>
</tr>
<tr>
<td>5a. Carrier testing: preconception</td>
<td>Yes</td>
</tr>
<tr>
<td>5b. Carrier testing: prenatal</td>
<td>Yes</td>
</tr>
<tr>
<td>5c. In utero testing: aneuploidy</td>
<td>Yes</td>
</tr>
<tr>
<td>5d. In utero testing: mutations</td>
<td>Yes</td>
</tr>
<tr>
<td>5e. In utero testing: other</td>
<td>Yes</td>
</tr>
<tr>
<td>5f. Preimplantation testing with IVF</td>
<td>Yes</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 would be:
- Trial comparing outcomes with use of the test versus outcomes 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 is evidence that addresses one or more components of a chain of evidence, but does not itself connect the intervention with the outcome.

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

There are a number of factors that influence the strength of indirect evidence that is needed to determine whether health outcomes are improved. None of these factors are by themselves determinative of whether genetic testing should be performed, but they may be important determinants of the potential clinical utility of testing. Some of these considerations are as follows:

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 Test on Diagnosis**
   - Can genetic testing confirm the suspected diagnosis?
   - Can the diagnosis be confirmed by alternate methods without genetic testing?
   - Disorder is defined by the presence of genetic mutation
   - Genetic test is one of several factors contributing to diagnosis
   - Unable to make diagnosis without genetic test in some patients
   - Can genetic testing rule out the disorder?
   - Can genetic testing eliminate the need for further clinical work-up?
   - Is this a disorder in which the diagnosis can be difficult, and the patient may be subjected to long and complicated work-ups?

   **Impact of Genetic Test on 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 the Initiation of other management changes with uncertain impact on outcomes (referrals to specialists and/or ancillary care, initiate screening, etc.)
   - 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 an Indirect Chain of Evidence on Clinical Utility: Testing 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 LE</td>
<td>Confirm diagnosis</td>
<td>Initiate effective treatment for disorder</td>
<td>Change in management with uncertain impact on outcomes</td>
</tr>
<tr>
<td>Severe morbidity/disability</td>
<td>Condition defined by</td>
<td>Discontinue ineffective treatment</td>
<td>Change in management with improved health outcomes</td>
</tr>
<tr>
<td>Moderate morbidity/disability</td>
<td>Confirms diagnosis, o/w unable to make clinically</td>
<td>Initiate other management changes</td>
<td>Barrier to research</td>
</tr>
<tr>
<td>Minor or no morbidity/disability</td>
<td>Eliminates need for other clinical workup</td>
<td>Provide standard of care treatment for disorder</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 Test 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 mutation in the family?
Is the penetrance of the genetic mutation known?
Are there other factors that impact the clinical expression of disease?

**Impact of Genetic Test 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 test lead to the initiation of other management changes that may or may not lead to improved outcomes (referrals to specialists and/or ancillary care, initiate screening, etc.)
Does a negative test confirm a lack of risk for the disease, and does this lead to “turning off” interventions, such as surveillance, that would otherwise be performed?
Is it likely that knowledge of mutation 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: 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>
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</table>

<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>Shortened LE</td>
<td>Severe</td>
<td>Moderate</td>
<td>Minor or no</td>
<td>Has presymptomatic stage</td>
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</table>

3. Factors influencing the strength of indirect evidence for prognosis testing (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 Test 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 Test 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:
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: Testing Categories 1b, 2b

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Disease Characteristics</th>
<th>Impact on Prognosis</th>
<th>Impact on Management</th>
<th>Impact on Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shortened LE</td>
<td>Severe morbidity/disability</td>
<td>Mutation associated with prognosis</td>
<td>Clinically credible prognostic groups</td>
<td>Treatment by prognostic groups is standard of care</td>
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<tr>
<td></td>
<td>Moderate morbidity/disability</td>
<td>Incremental improvement above clinical measures</td>
<td>Treatment by prognostic groups improve outcomes</td>
<td>Possible impact on outcomes, data lacking</td>
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<tr>
<td></td>
<td>Minor or no morbidity/disability</td>
<td>Contributes to ability to make diagnosis</td>
<td>Treatment by prognostic group is standard of care</td>
<td>Barriers to research</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Impact on lifestyle factors</td>
</tr>
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</table>

4. Factors influencing the strength of indirect evidence for genetic variants that alter response to treatment (Testing 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 that are 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
Are there genetic variants that are associated with increased risk for adverse effects?

**Impact of Genetic Test 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 that are 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: Genetic Variants That Alter Response to Treatment (Testing 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>
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</thead>
<tbody>
<tr>
<td>Shortened LE</td>
<td>Severe morbidity/disability</td>
<td>Define variants with different pharmacokinetics</td>
<td>Initiation of alternate agents</td>
<td>Definite improved health outcomes</td>
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<tr>
<td></td>
<td>Moderate morbidity/disability</td>
<td>Different pharmacokinetics are clinically important</td>
<td>Discontinue ineffective treatment</td>
<td>Possible impact on outcomes, data lacking</td>
</tr>
<tr>
<td></td>
<td>Minor or no morbidity/disability</td>
<td>Variants lead to differences in outcomes</td>
<td>Changes in dosing</td>
<td>Barriers to research</td>
</tr>
<tr>
<td></td>
<td>Effective pharmacologic therapy</td>
<td>Variants with increased risk for adverse effects</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>