2.04.91	General Approach to Genetic Testing		
Original Policy Date:	December 18, 2009	**Effective Date:**	October 1, 2025
Section:	2.0 Medicine	**Page:**	Page 1 of 25

Policy Statement

I. 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:
   A. Testing of an affected (symptomatic) individual's germline DNA to benefit the individual (excluding reproductive testing)
      1. Diagnostic
      2. Prognostic
      3. Therapeutic
   B. Testing cancer cells of an affected individual to benefit the individual
      1. Diagnostic
      2. Prognostic
      3. Therapeutic
   C. Testing an asymptomatic individual to determine future risk of disease.

II. 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).

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

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;
- 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

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

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

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

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.

Description

Commercially available genetic tests can perform a host of functions, such as providing a guided intervention in both symptomatic or asymptomatic people, identifying people at risk for future disorders, predicting the prognosis of a diagnosed disease, and predicting the appropriate treatment response.

The conceptual framework provided herein offers an outline 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 conceptual framework addresses genetic testing in nonreproductive settings. Genetic testing in reproductive settings is addressed separately (e.g., Blue Shield of California Medical Policy: Invasive Prenatal (Fetal) Diagnostic Testing, Blue Shield of California Medical Policy: Preimplantation Genetic Testing). 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.

Related Policies

- General Approach to Evaluating the Utility of Genetic Panels
- Invasive Prenatal (Fetal) Diagnostic Testing
- Preimplantation Genetic Testing

Benefit Application

Benefit determinations should be based in all cases on the applicable member health services contract language. To the extent there are conflicts between this Medical Policy and the member health services contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal law may prohibit health plans from denying FDA-approved Healthcare Services as investigational or experimental. In these instances, Blue Shield of California may be obligated to determine if these FDA-approved Healthcare Services are Medically Necessary.

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

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, e.g., 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.

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 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 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.

Literature Review

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

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:

- 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. 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.
- 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.

- 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.

- 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 are ineffective or unneeded.

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.
- Genetic testing is subject to laboratory error.

Summary of Evidence

This conceptual framework addresses genetic testing in nonreproductive settings. Genetic testing in reproductive settings is addressed separately (e.g., Blue Shield of California Medical Policy: Invasive Prenatal (Fetal) Diagnostic Testing, Blue Shield of California Medical Policy: Preimplantation Genetic Testing). 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.

Appendix 1

Appendix 1. Categorization of Types of Testing Addressed in Evidence Reviews

Category	Addressed
1. Testing of an affected individual's germline to benefit the individual	
1a. Diagnostic	
1b. Prognostic	
1c. Therapeutic	
2. Testing cancer cells from an affected individual to benefit the individual	
2a. Diagnostic	
2b. Prognostic	
2c. Therapeutic	
3. Testing an asymptomatic individual to determine future risk of disease	
4. Testing of an affected individual's germline to benefit family members	
5. Reproductive testing	
5a. Carrier testing: preconception	
5b. Carrier testing: prenatal	
5c. In utero testing: aneuploidy	
5d. In utero testing: variants	
5e. In utero testing: other	
5f. Preimplantation testing with in vitro fertilization	

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 an Indirect Chain of Evidence on Clinical Utility: Categories 1a, 2a

Disorder	Disease Characteristics				Impact on Diagnosis					Impact on Management				Impact on Outcomes			
	Shortened life expectancy	Severe morbidity/disability	Moderate morbidity/disability	Minor or no morbidity/disability	Confirms diagnosis Condition defined by variant	Confirms diagnosis, otherwise unable to make clinically	Contributes to ability to make diagnosis	Rules out disorder	Eliminates need for other clinical workup	Initiate effective treatment for disorder	Discontinue ineffective treatment	Initiate other management changes	Provide " standard of care" treatment for disorder	Change in management with improved health outcomes	Change in management with uncertain impact on outcomes	Barriers to research	Impact on lifestyle factors

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

Disorder	Disease Characteristics					Impact on Defining Risk				Impact on Management				Impact on Outcomes			
	Shortened life expectancy	Severe morbidity/disability	Moderate morbidity/disability	Minor or no morbidity/disability	Has presymptomatic stage	Determines risk in substantial proportion of patients	Known mutation in family	Penetrance is well known	Other factors impact clinical expression	Initiate effective interventions in presymptomatic phase	Other management changes with uncertain impact	Negative test leads to discontinuation of interventions	Likely to impact reproductive decision making	Definite improved health outcomes	Possible impact on outcomes, data lacking	Barriers to research	Impact on lifestyle factors

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:
  - 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: Categories 1b, 2b

Disorder	Disease Characteristics				Impact on Prognosis				Impact on Management			Impact on Outcomes			
	Shortened life expectancy	Severe morbidity/disability	Moderate morbidity/disability	Minor or no morbidity/disability	Variant associated with prognosis	Incremental improvement above clinical measures	Contributes to ability to make diagnosis	Clinically credible prognostic groups	Prognostic groups have different treatment	Treatment by prognostic groups improve outcomes	Treatment by prognostic group is standard of care	Definite improved health outcomes	Possible impact on outcomes, data lacking	Barriers to research	Impact on lifestyle factors

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
- 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

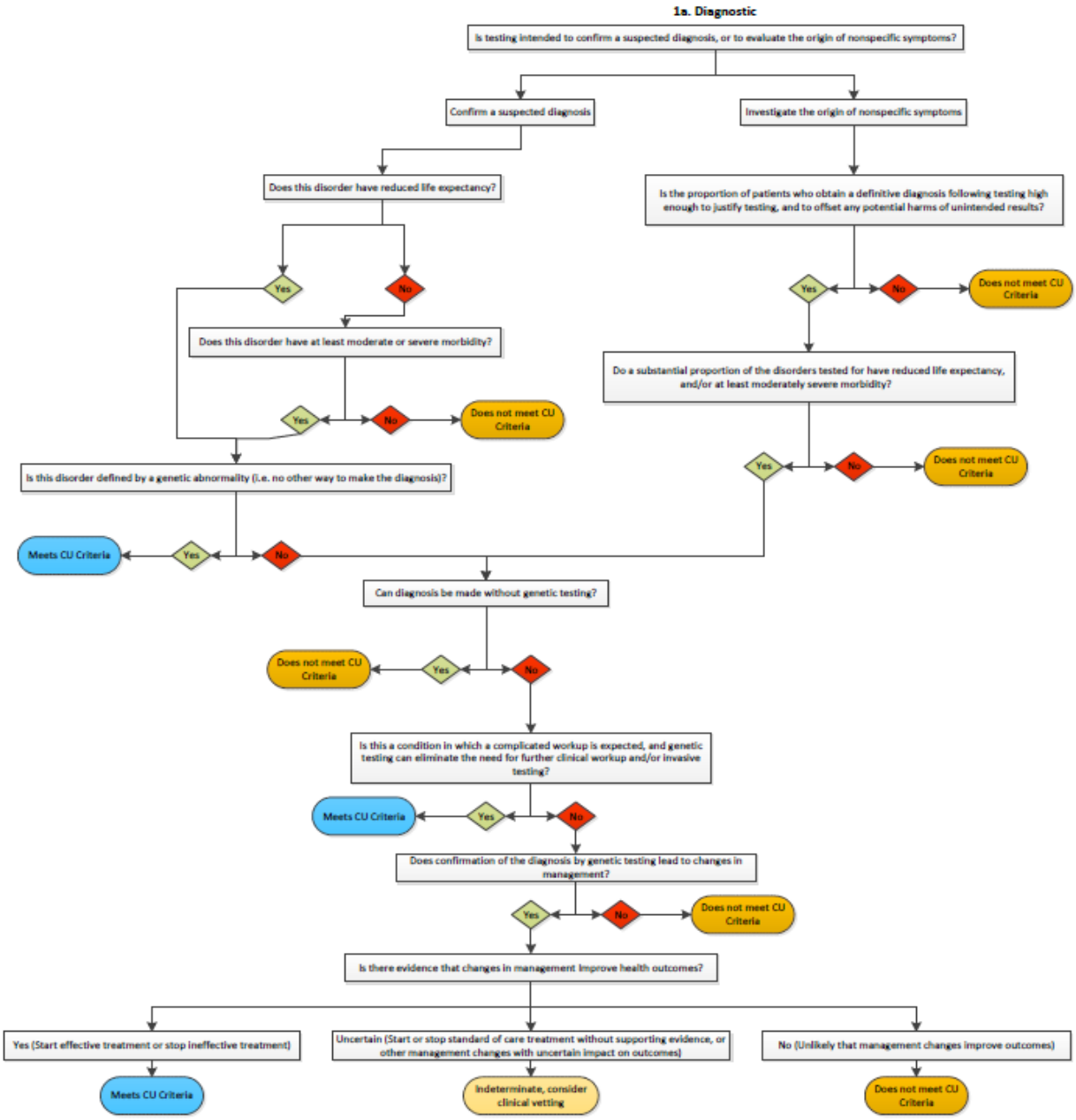
Impact on Health Outcomes

- 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: Genetic Variants That Alter Response to Treatment (Categories 1c, 2c)

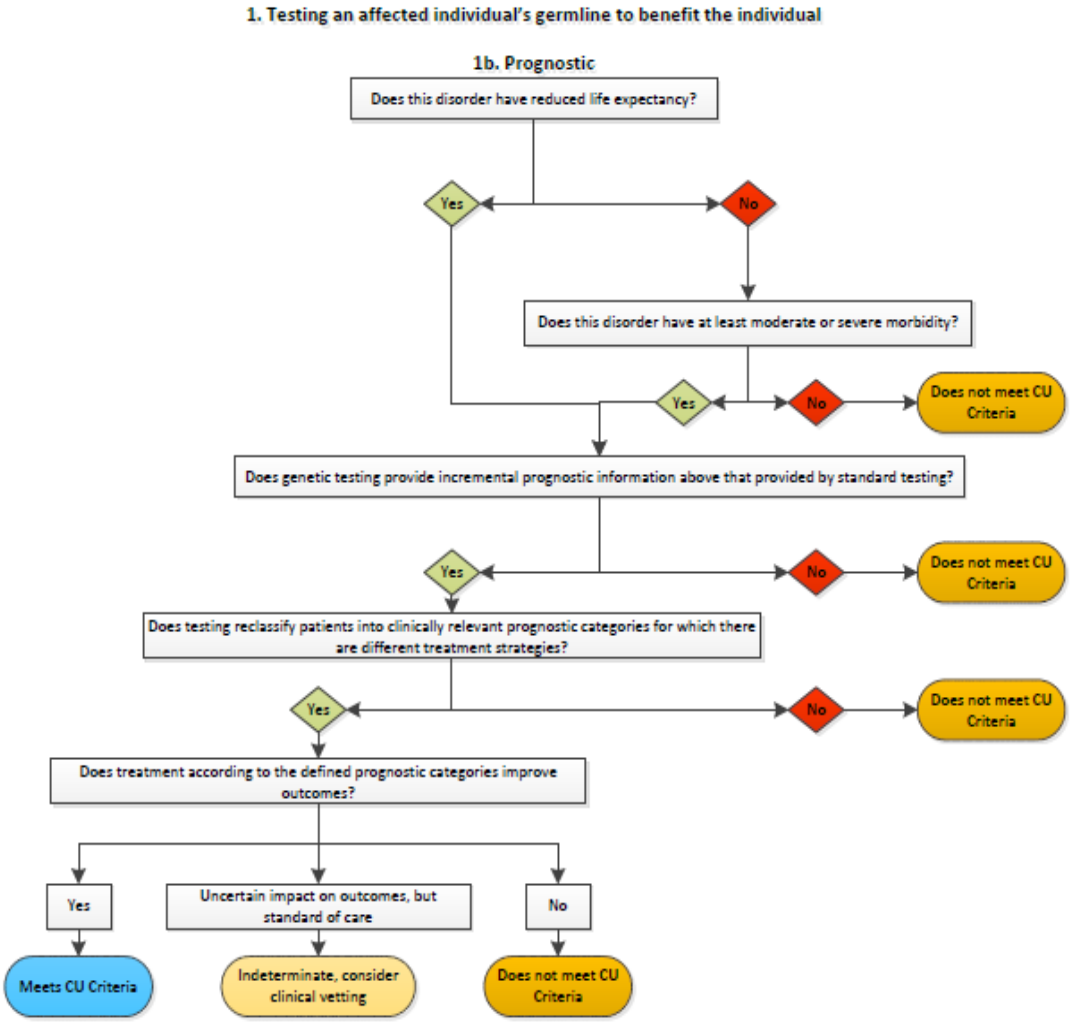
Disorder	Disease Characteristics					Impact on Response to Treatment				Impact on Management			Impact on Outcomes		
	Shortened life expectancy	Severe morbidity/disability	Moderate morbidity/disability	Minor or no morbidity/disability	Effective pharmacologic therapy	Define variants with different pharmacokinetics	Different pharmacokinetics are clinically important	Variants lead to differences in outcomes	Variants with increased risk for adverse effects	Initiation of alternate agents	Discontinue ineffective treatment	Changes in dosing	Definite improved health outcomes	Possible impact on outcomes, data lacking	Barriers to research

Appendix Figure 1. Diagnostic Testing Schematic of an Affected Individual's Germline to Benefit the Individual (category 1a)



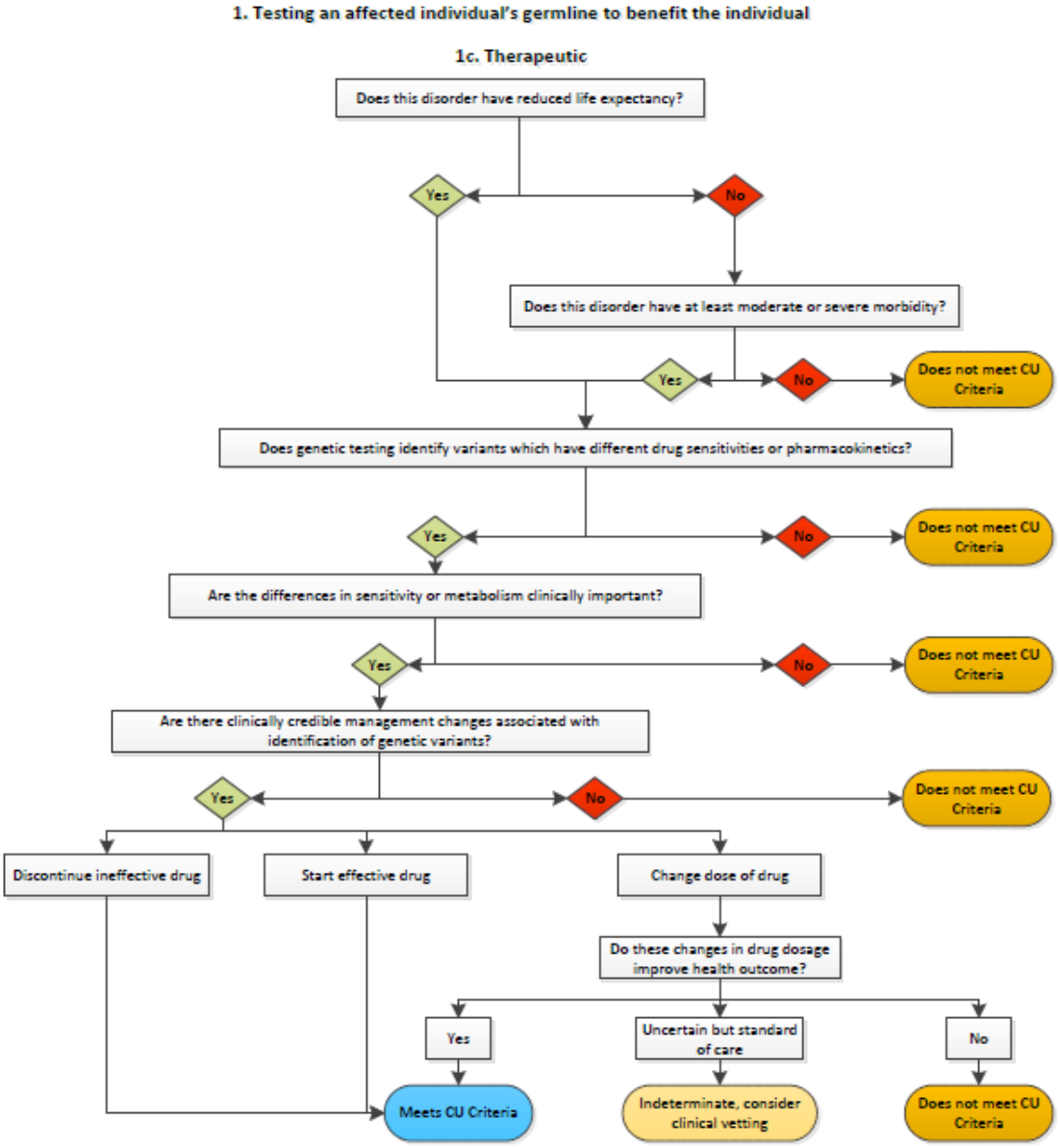
CU: clinical utility.

Appendix Figure 2. Prognostic Testing of an Affected Individual's Germline to Benefit the Individual (category 1b)



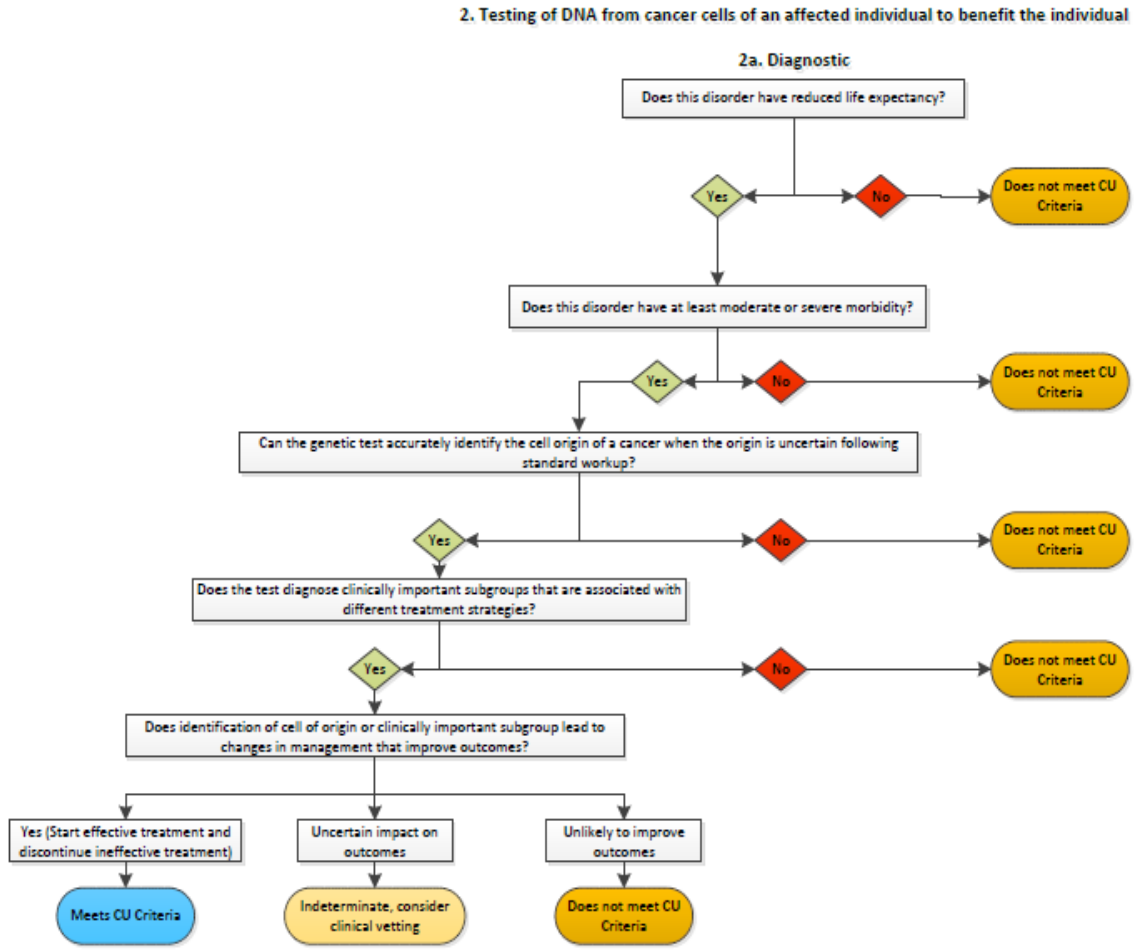
CU: clinical utility.

Appendix Figure 3. Therapeutic Testing of an Affected Individual's Germline to Benefit the Individual (category 1c)



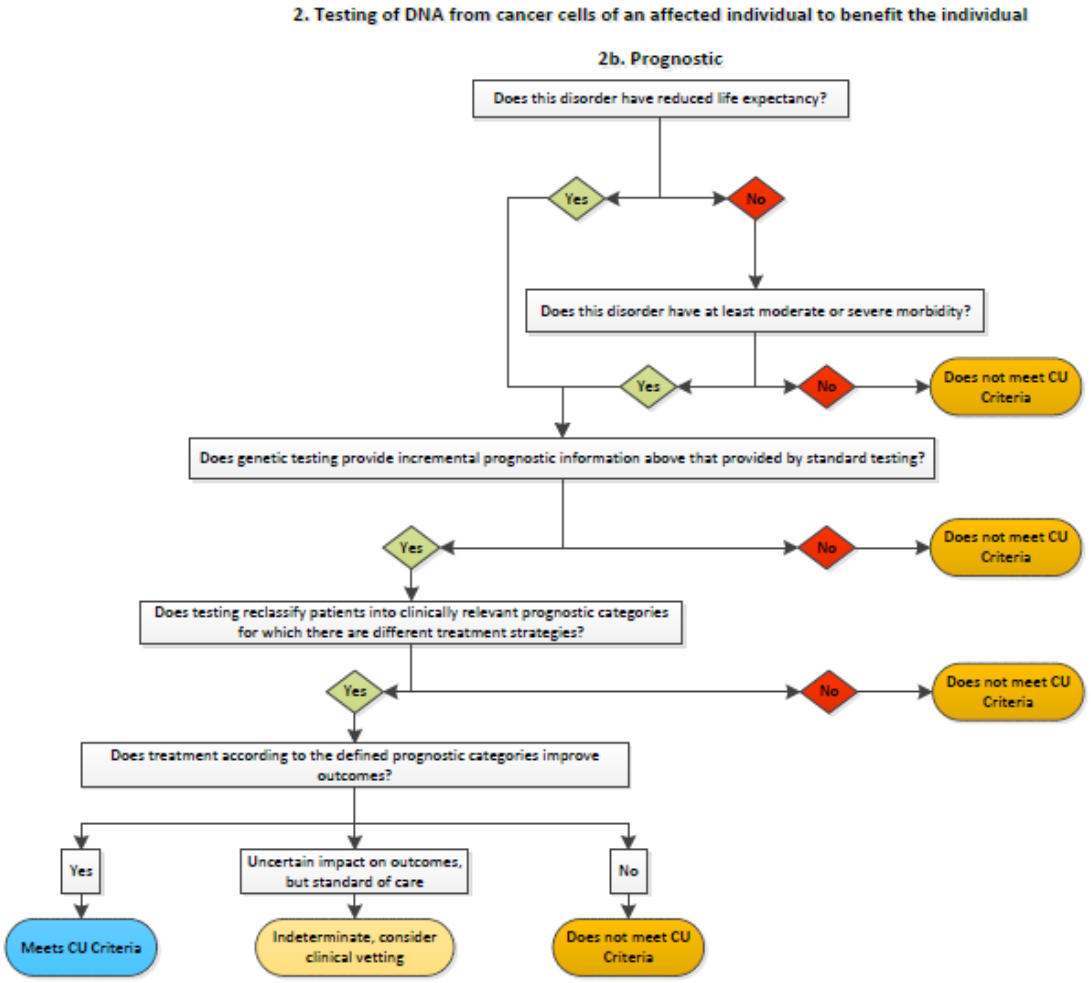
CU: clinical utility.

Appendix Figure 4. Diagnostic Testing of DNA Cells from Cancer Cells of an Affected Individual to Benefit the Individual (category 2a)



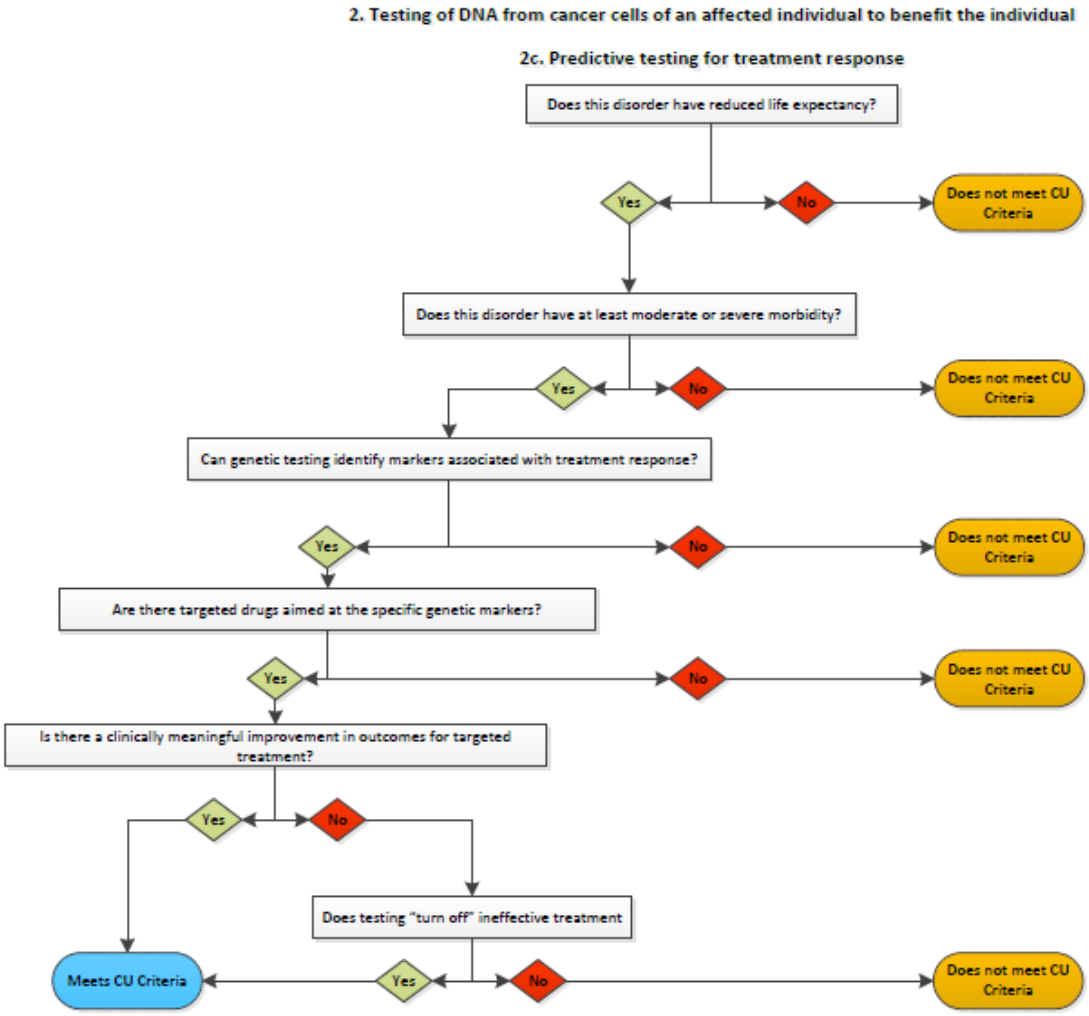
CU: clinical utility.

Appendix Figure 5. Prognostic Testing of DNA from Cancer Cells of an Affected Individual to Benefit the Individual (category 2b)



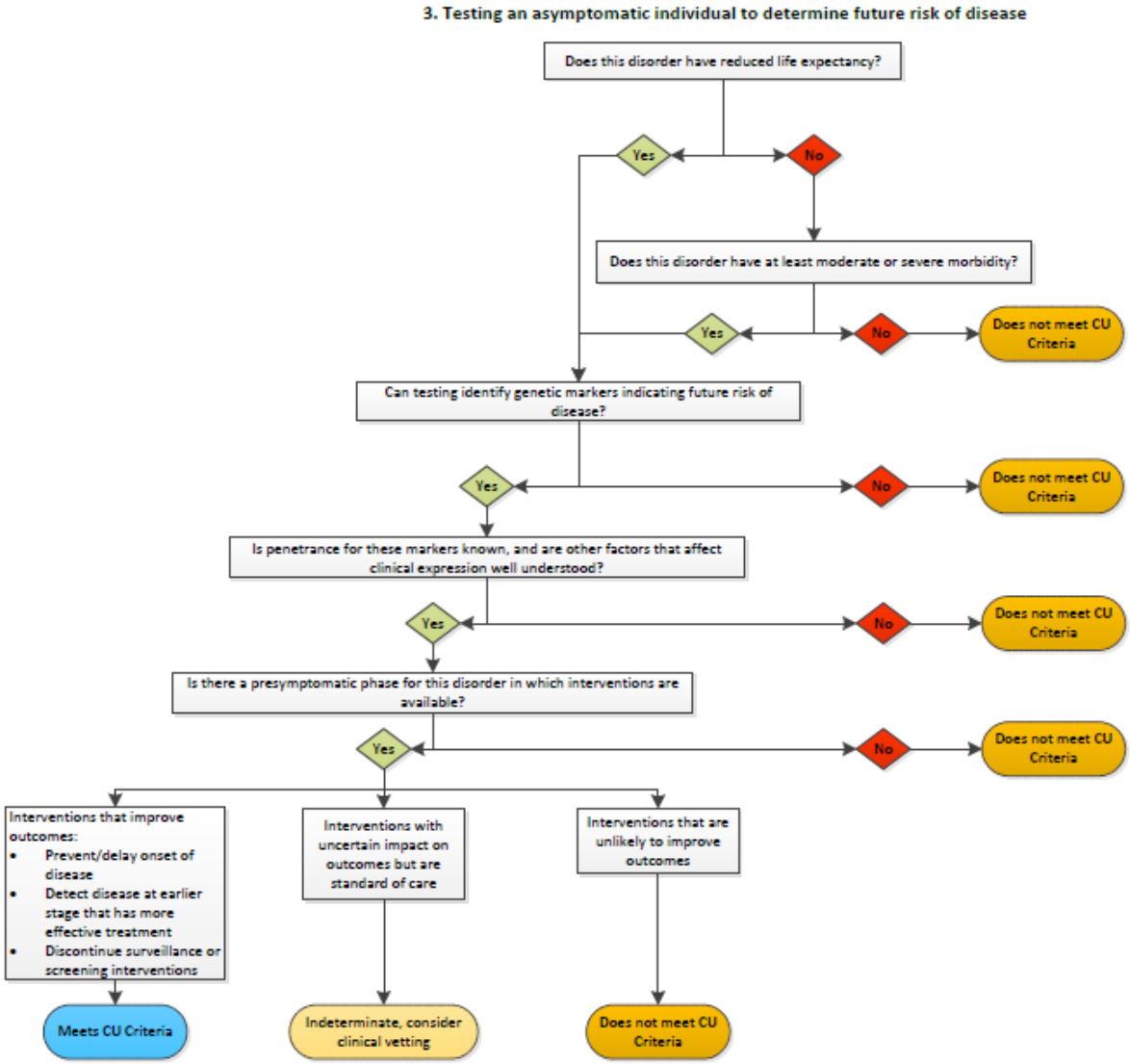
CU: clinical utility.

Appendix Figure 6. Therapeutic Testing of Cancer Cells of an Affected Individual to Benefit the Individual (category 2c)



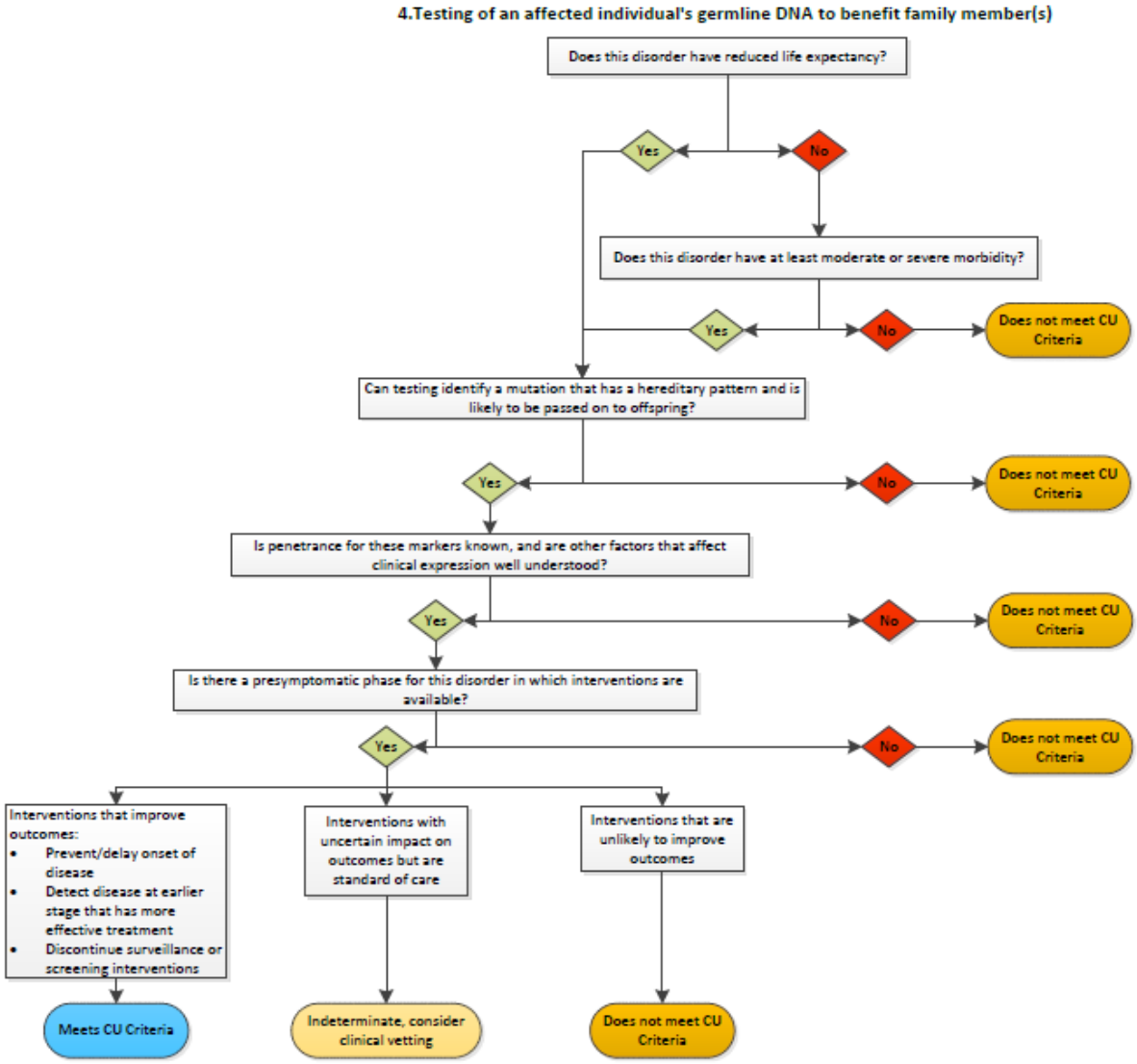
CU: clinical utility.

Appendix Figure 7. Testing an Asymptomatic Individual to Determine Future Risk of Disease (category 3)



CU: clinical utility.

Appendix Figure 8. Testing an Affected Individual's Determine DNA to Benefit Family Members (category 4)



CU: clinical utility.

References

1. ACMG Board of Directors. Clinical utility of genetic and genomic services: a position statement of the American College of Medical Genetics and Genomics. Genet Med. Jun 2015;17(6):505-507. PMID 25764213
2. Teutsch SM, Bradley LA, Palomaki GE, et al. The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Initiative: methods of the EGAPP Working Group. Genet Med. Jan 2009;11(1):3-14. PMID 18813139
3. Beltran-Sanchez H, Razak F, Subramanian SV. Going beyond the disability-based morbidity definition in the compression of morbidity framework. Glob Health Action. Sep 2014;7:24766. PMID 25261699

Documentation for Clinical Review

Please provide the following documentation:

- Provider order for genetic test
- Name and description of genetic test

- Name of laboratory performing the test
- Any available evidence supporting the clinical validity/utility of the specific test
- CPT codes to be billed for the particular genetic test
- History and physical and/or consultation notes including:
  - Reason for performing test
  - Signs/symptoms/test results related to reason for genetic testing
  - Family history if applicable
  - How test result will impact clinical decision making

Post Service (in addition to the above, please include the following):

- Results/reports of tests performed

Coding

The list of codes in this Medical Policy is intended as a general reference and may not cover all codes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy.

Type	Code	Description
CPT®	81200-81355	
	81400	Molecular pathology procedure, Level 1 (e.g., identification of single germline variant [e.g., SNP] by techniques such as restriction enzyme digestion or melt curve analysis)
	81401	Molecular pathology procedure, Level 2 (e.g., 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)
	81402	Molecular pathology procedure, Level 3 (e.g., >10 SNPs, 2-10 methylated variants, or 2-10 somatic variants [typically using non-sequencing target variant analysis], immunoglobulin and T-cell receptor gene rearrangements, duplication/deletion variants of 1 exon, loss of heterozygosity [LOH], uniparental disomy [UPD])
	81403	Molecular pathology procedure, Level 4 (e.g., analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)
	81404	Molecular pathology procedure, Level 5 (e.g., analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)
	81405	Molecular pathology procedure, Level 6 (e.g., analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)
	81406	Molecular pathology procedure, Level 7 (e.g., analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons)
	81407	Molecular pathology procedure, Level 8 (e.g., analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of >50 exons, sequence analysis of multiple genes on one platform)
	81408	Molecular pathology procedure, Level 9 (e.g., analysis of >50 exons in a single gene by DNA sequence analysis)

Type	Code	Description
	81479	Unlisted molecular pathology procedure
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
12/18/2009	New Policy Adoption
01/25/2010	Coding Update
09/27/2013	Policy revision with position change
07/31/2015	Coding Update Policy revision without position change
02/01/2016	Coding update
05/01/2016	Policy revision without position change
02/01/2017	Coding update
06/01/2017	Policy revision without position change
08/01/2017	Coding update
02/01/2018	Policy revision without position change Coding update
01/01/2019	Coding update
07/01/2019	Policy revision without position change Coding Update
04/01/2020	Annual review. No change to policy statement.
01/01/2021	Coding update.
04/01/2021	Annual review. No change to policy statement.
02/01/2022	Coding update.
04/01/2022	Annual review. Policy guidelines updated.
10/01/2022	Administrative update.
11/01/2022	Coding update.
04/01/2023	Annual review. Policy guidelines updated.
10/01/2025	Policy reactivated. Previously archived from 12/01/2023 to 09/30/2025.

Definitions of Decision Determinations

Healthcare Services: For the purpose of this Medical Policy, Healthcare Services means procedures, treatments, supplies, devices, and equipment.

Medically Necessary: Healthcare Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield of California, are: (a) consistent with Blue Shield of California medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the member; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the member's illness, injury, or disease.

Investigational or Experimental: Healthcare Services which do not meet ALL of the following five (5) elements are considered investigational or experimental:

A. The technology must have final approval from the appropriate government regulatory bodies.
   - This criterion applies to drugs, biological products, devices and any other product or procedure that must have final approval to market from the U.S. Food and Drug Administration ("FDA") or any other federal governmental body with authority to regulate the use of the technology.
   - Any approval that is granted as an interim step in the FDA's or any other federal governmental body's regulatory process is not sufficient.
   - The indications for which the technology is approved need not be the same as those which Blue Shield of California is evaluating.

B. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.
   - The evidence should consist of well-designed and well-conducted investigations published in peer-reviewed journals. The quality of the body of studies and the consistency of the results are considered in evaluating the evidence.
   - The evidence should demonstrate that the technology can measure or alter the physiological changes related to a disease, injury, illness, or condition. In addition, there should be evidence, or a convincing argument based on established medical facts that such measurement or alteration affects health outcomes.

C. The technology must improve the net health outcome.
   - The technology's beneficial effects on health outcomes should outweigh any harmful effects on health outcomes.

D. The technology must be as beneficial as any established alternatives.
   - The technology should improve the net health outcome as much as, or more than, established alternatives.

E. The improvement must be attainable outside the investigational setting.
   - When used under the usual conditions of medical practice, the technology should be reasonably expected to satisfy Criteria C and D.

Feedback

Blue Shield of California is interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration. Our medical policies are available to view or download at www.blueshieldca.com/provider.

For medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as member health services contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member health services contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE	**AFTER**
Reactivated Policy **Policy Statement:** N/A	**General Approach to Genetic Testing 2.04.91** **Policy Statement:** I. 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: A. Testing of an affected (symptomatic) individual's germline DNA to benefit the individual (excluding reproductive testing) 1. Diagnostic 2. Prognostic 3. Therapeutic B. Testing cancer cells of an affected individual to benefit the individual 1. Diagnostic 2. Prognostic 3. Therapeutic C. Testing an asymptomatic individual to determine future risk of disease. II. 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).