PHP_2.04.91	General Approach to Genetic Testing		
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State Guidelines

Applicable Medi-Cal guidelines as of the publication of this policy (this guideline supersedes the criteria in the Policy Statement section below):

I. Department of Managed Health Care (DMHC) All Plan Letter (APL) Guideline:
- N/A

II. Department of Health Care Services (DHCS) Provider Manual Guideline:
- TAR and Non-Standard Benefits List: Codes 80000 thru 89999 (tar and non cd8)
- Pathology: Molecular Pathology (path molec)

***Due to the broad range of testing/codes that can apply to this policy, please see above link(s) for the specific criteria related to the code(s) being billed.*

Below is an excerpt of the Molecular Pathology guideline language. Please refer to the specific Provider Manual in the link above for the complete guideline.

Biomarker and Pharmacogenetic Testing
Medi-Cal covers medically necessary biomarker and pharmacogenomic testing, as described in the manual section Proprietary Laboratory Analyses (PLA). Medi-Cal may not cover all CPT and HCPCS codes associated with a particular biomarker or pharmacogenomic test. As such, the particular biomarker or pharmacogenomic test code may be covered with an approved Treatment Authorization Request (TAR) if medical necessity is established, as described in the TAR and Non-Benefit: Introduction to List section of the Provider Manual.

Biomarker Testing
Biomarker testing is used to diagnose, treat, manage, or monitor a Medi-Cal member's disease or condition to guide treatment decisions. As defined by Section 14132.09 of the Welfare and Institutions Code, biomarker testing is the analysis of an individual's tissue, blood or other biospecimen for the presence of a biomarker. Biomarker testing includes, but is not limited to, single-analyte tests, multiplex panel tests and whole genome sequencing. Biomarkers are a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic responses to a specific therapeutic intervention. A biomarker includes, but is not limited to, gene mutations or protein expression. Medically necessary biomarker testing is subject to utilization controls and evidence-based clinical practice guidelines.

When testing for biomarkers, all Medi-Cal providers must ensure that they are provided in a manner that limits disruptions to care. As with all Medi-Cal benefits, restricted or denied use of biomarker testing for the purpose of diagnosis, treatment or ongoing monitoring of any medical condition is subject to Medi-Cal's grievance, appeal and State Fair Hearing processes, as well as any additional processes established specifically for Medi-Cal managed care plans.

Pharmacogenomic Testing
Pharmacogenomic testing is defined as a laboratory genetic testing that includes, but is not limited to, a panel test to identify how a person's genetics may impact the efficacy, toxicity and safety of medications. Medically necessary pharmacogenomic testing is covered subject to utilization controls and evidence-based clinical practice guidelines.

III. Department of Health Care Services (DHCS) All Plan Letter (APL) Guideline:
- APL 22-010 – Cancer Biomarker Testing

Below is an excerpt of the guideline language. Please refer to the specific All Plan Letter in the link above for the complete guideline.

For the purposes of this APL, "Biomarker test" is defined as a diagnostic test, single or multigene, of an individual's biospecimen, such as tissue, blood, or other bodily fluids, for DNA or RNA alterations, including phenotypic characteristics of a malignancy, to identify an individual with a subtype of cancer, in order to guide treatment. Biomarkers, also called tumor markers, are substances found in higher-than-normal levels in the cancer itself, or in blood, urine, or tissues of some individuals with cancer. Biomarkers can determine the likelihood some types of cancer will spread. They can also help doctors choose the best treatment.

Medi-Cal managed care health plans (MCPs) are required to cover medically necessary biomarker testing for members with:
- Advanced or metastatic stage 3 or 4 cancer.
- Cancer progression or recurrence in the member with advanced or metastatic stage 3 or 4 cancer.

MCPs are prohibited from imposing prior authorization requirements on biomarker testing that is associated with a federal Food and Drug Administration (FDA)-approved therapy for advanced or metastatic stage 3 or 4 cancer. If the biomarker test is not associated with an FDA-approved cancer therapy for advanced or metastatic stage 3 or 4 cancer, MCPs may still require prior authorization for such testing.

Policy Statement

Any criteria that are not specifically addressed in the above APL and Provider Manuals, please refer to the criteria below.

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).

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.

Coding

See the Codes table for details.

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. 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

Benefit Application

Blue Shield of California Promise Health Plan is contracted with L.A. Care Health Plan for Los Angeles County and the Department of Health Care Services for San Diego County to provide Medi-Cal health benefits to its Medi-Cal recipients. In order to provide the best health care services and practices, Blue Shield of California Promise Health Plan has an extensive network of Medi-Cal primary care providers and specialists. Recognizing the rich diversity of its membership, our providers are given training and educational materials to assist in understanding the health needs of their patients as it could be affected by a member's cultural heritage.

The benefit designs associated with the Blue Shield of California Promise Medi-Cal plans are described in the Member Handbook (also called Evidence of Coverage).

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.

Health Equity Statement

Blue Shield of California Promise Health Plan's mission is to transform its health care delivery system into one that is worthy of families and friends. Blue Shield of California Promise Health Plan seeks to advance health equity in support of achieving Blue Shield of California Promise Health Plan's mission.

Blue Shield of California Promise Health Plan ensures all Covered Services are available and accessible to all members regardless of sex, race, color, religion, ancestry, national origin, ethnic group identification, age, mental disability, physical disability, medical condition, genetic information, marital status, gender, gender identity, or sexual orientation, or identification with any other persons or groups defined in Penal Code section 422.56, and that all Covered Services are provided in a culturally and linguistically appropriate manner.

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.

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. 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

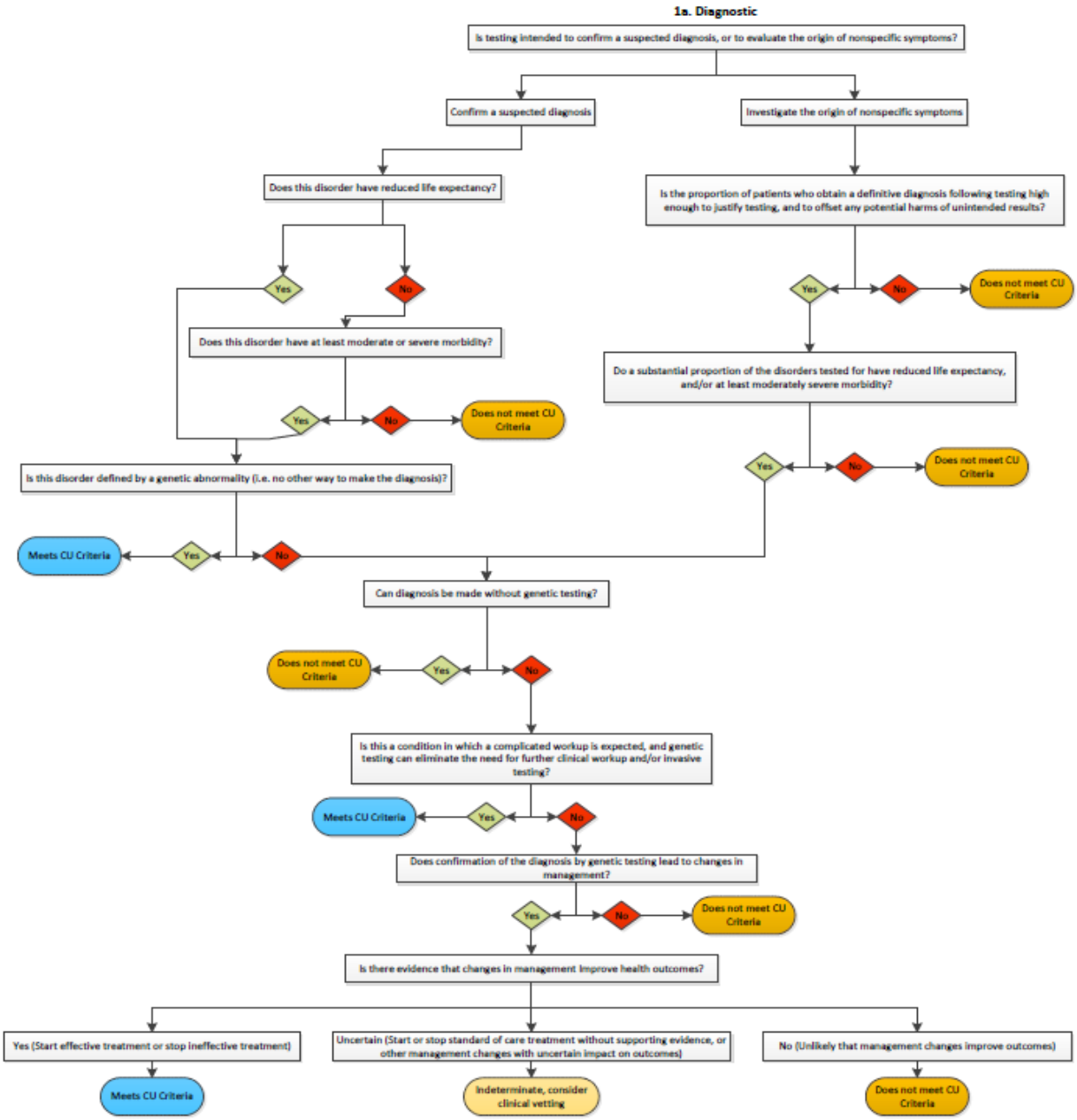
Impact on Health Outcomes

- 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)

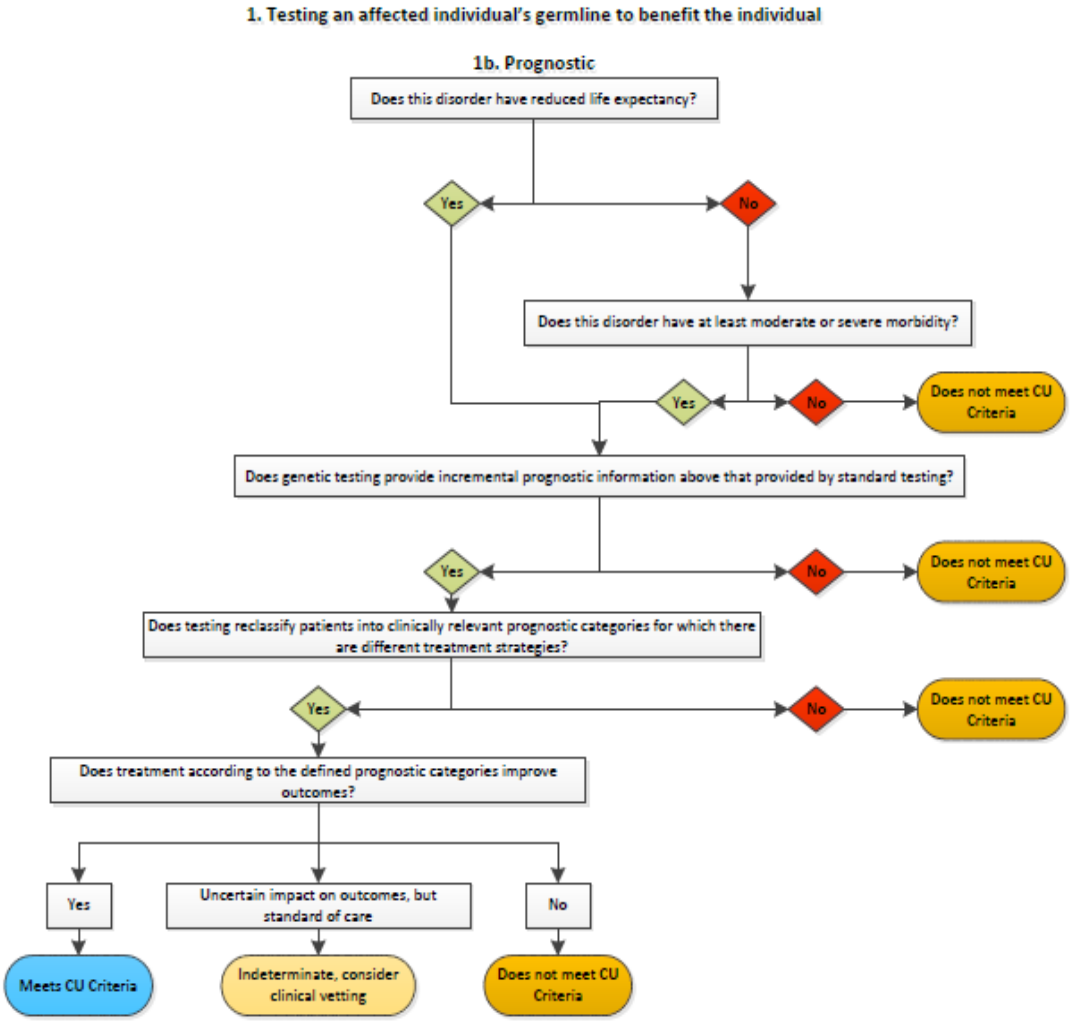
Disorder	Disease Characteristics					Impact on Response to Treatment				Impact on Management			Impact on Outcomes		
	Shortened life expectancy	Severe morbidity/disability	Moderate morbidity/disability	Minor or no morbidity/disability	Effective pharmacologic therapy	Define variants with different pharmacokinetics	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)



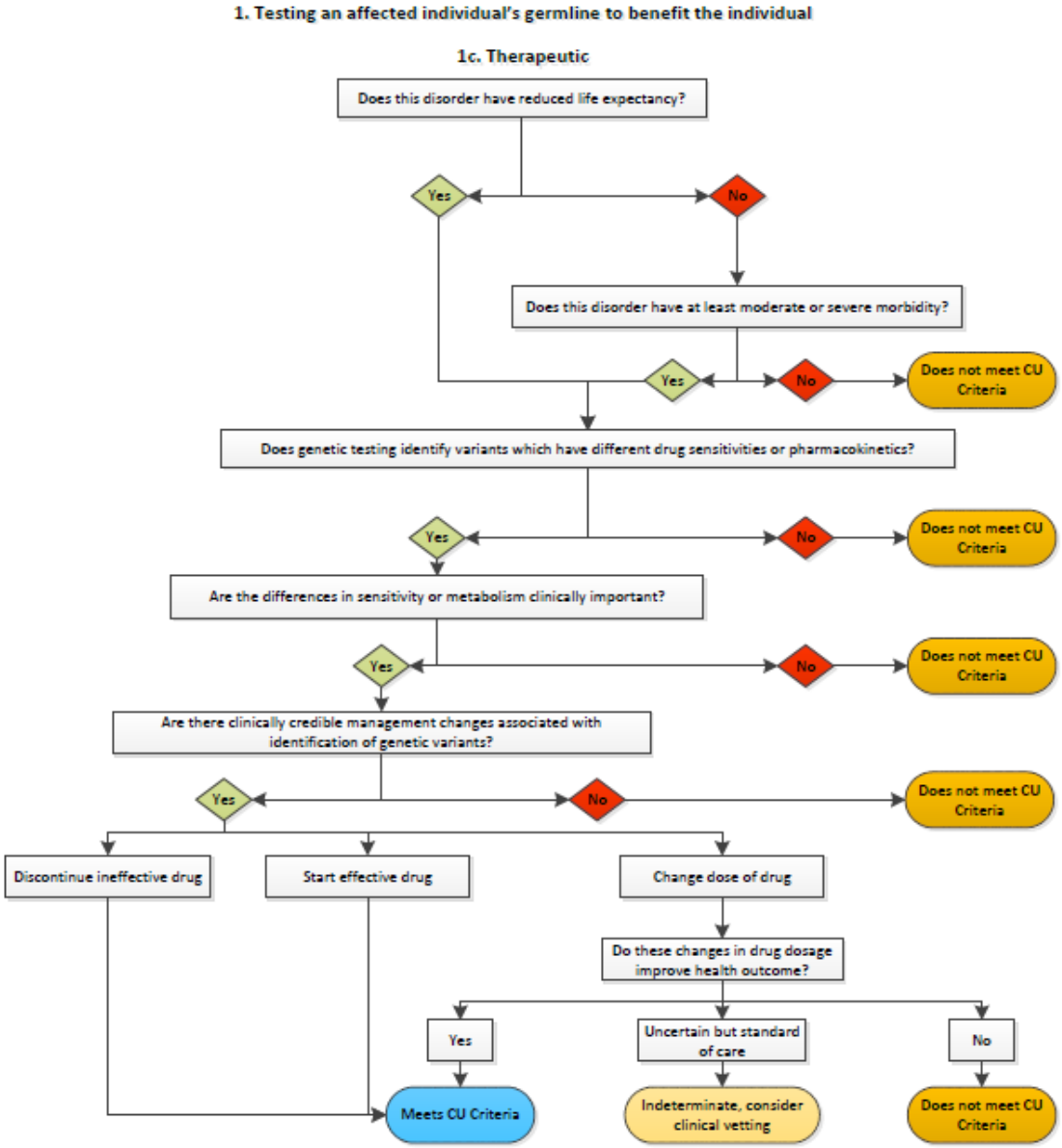
CU: clinical utility.

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



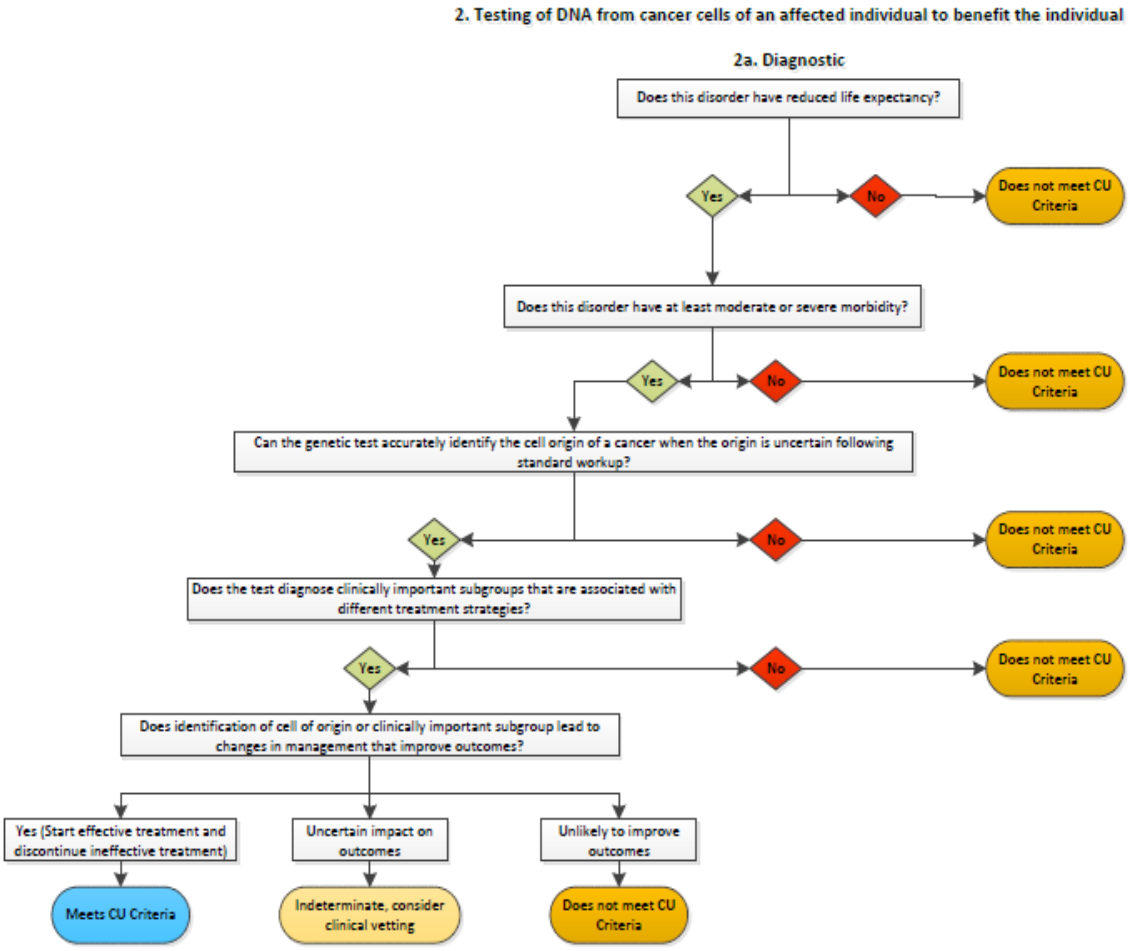
CU: clinical utility.

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



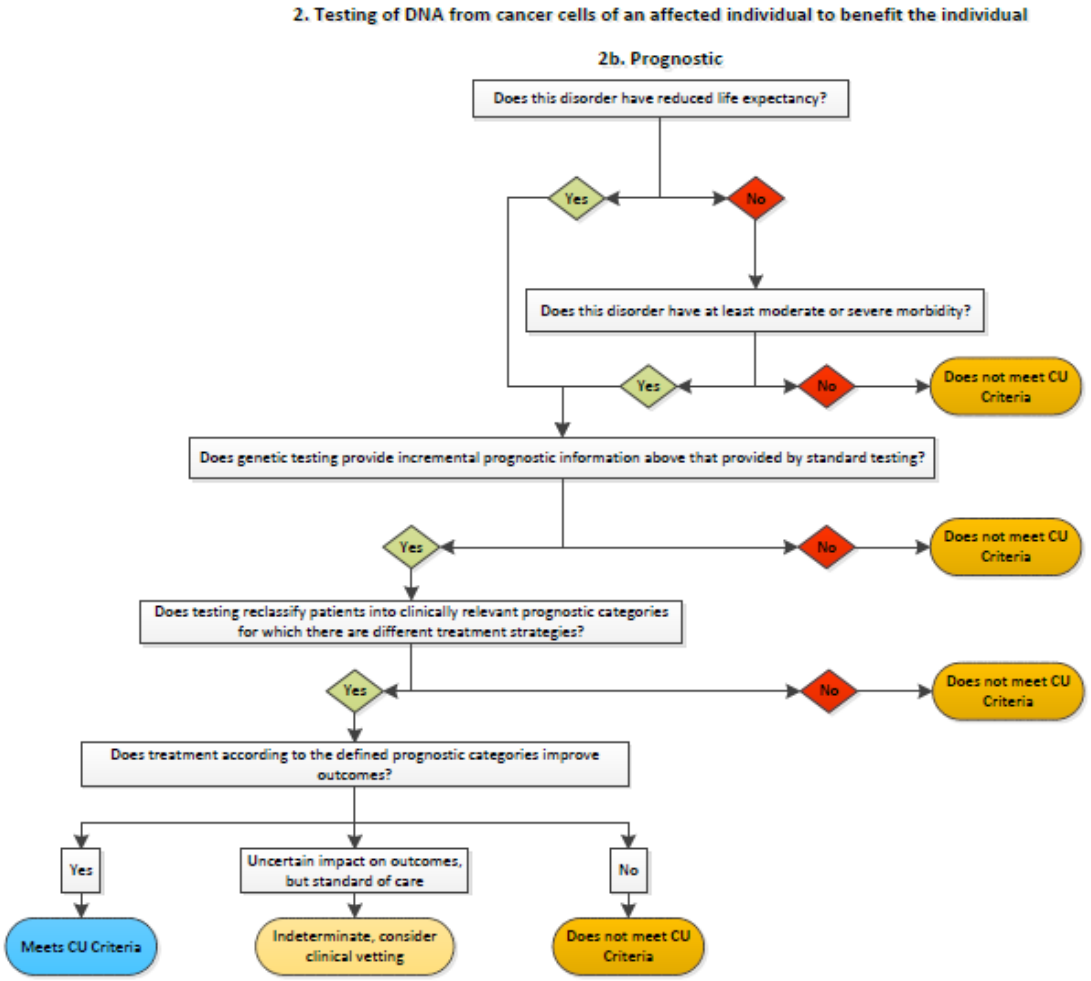
CU: clinical utility.

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



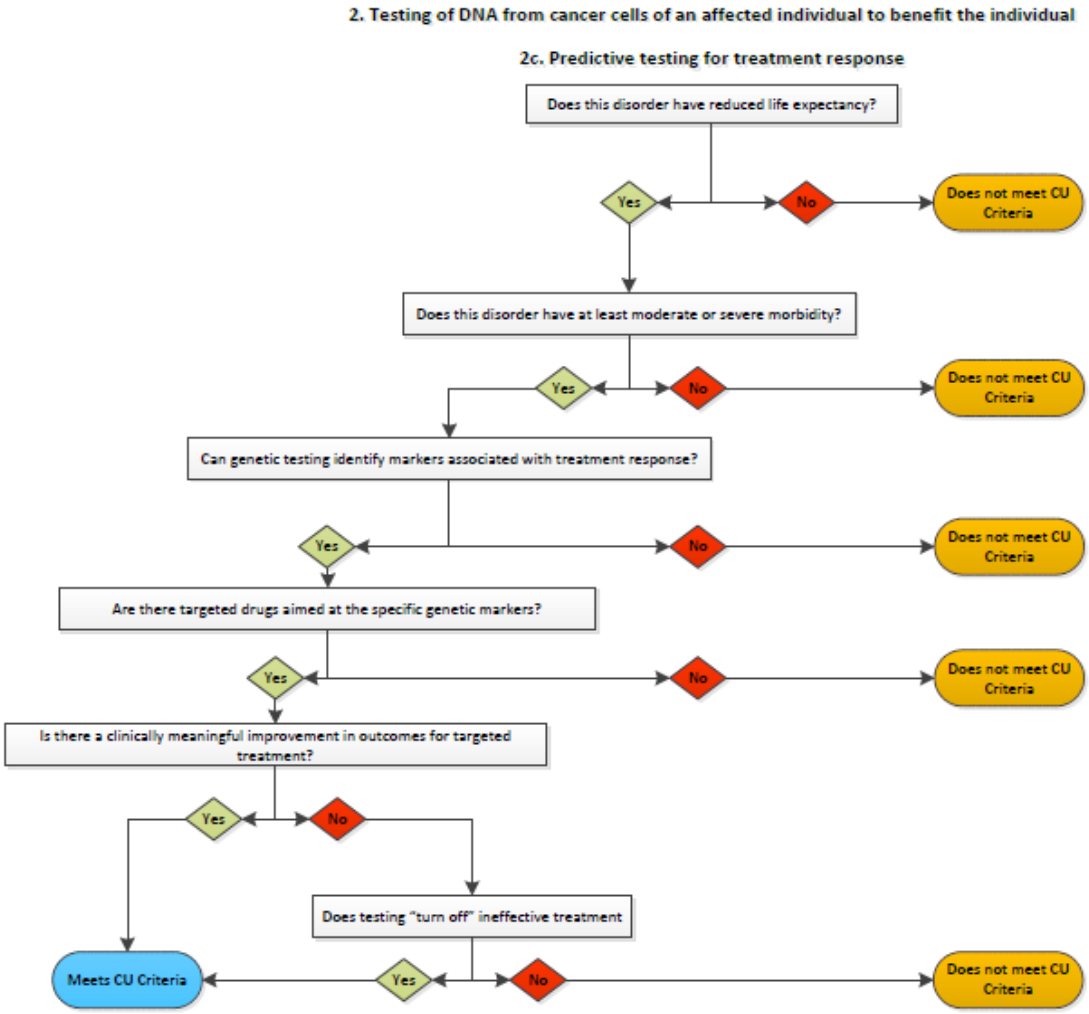
CU: clinical utility.

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



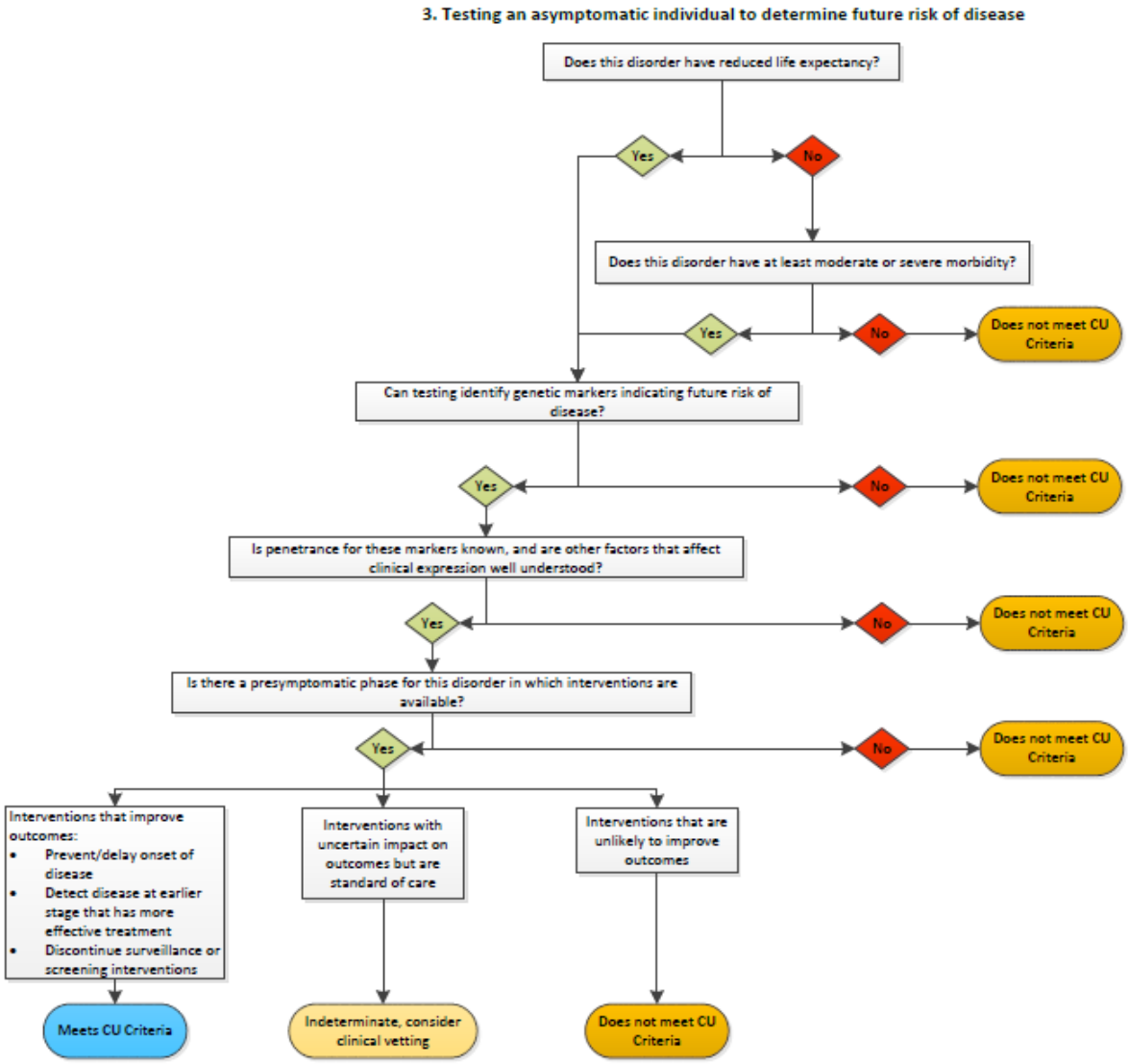
CU: clinical utility.

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



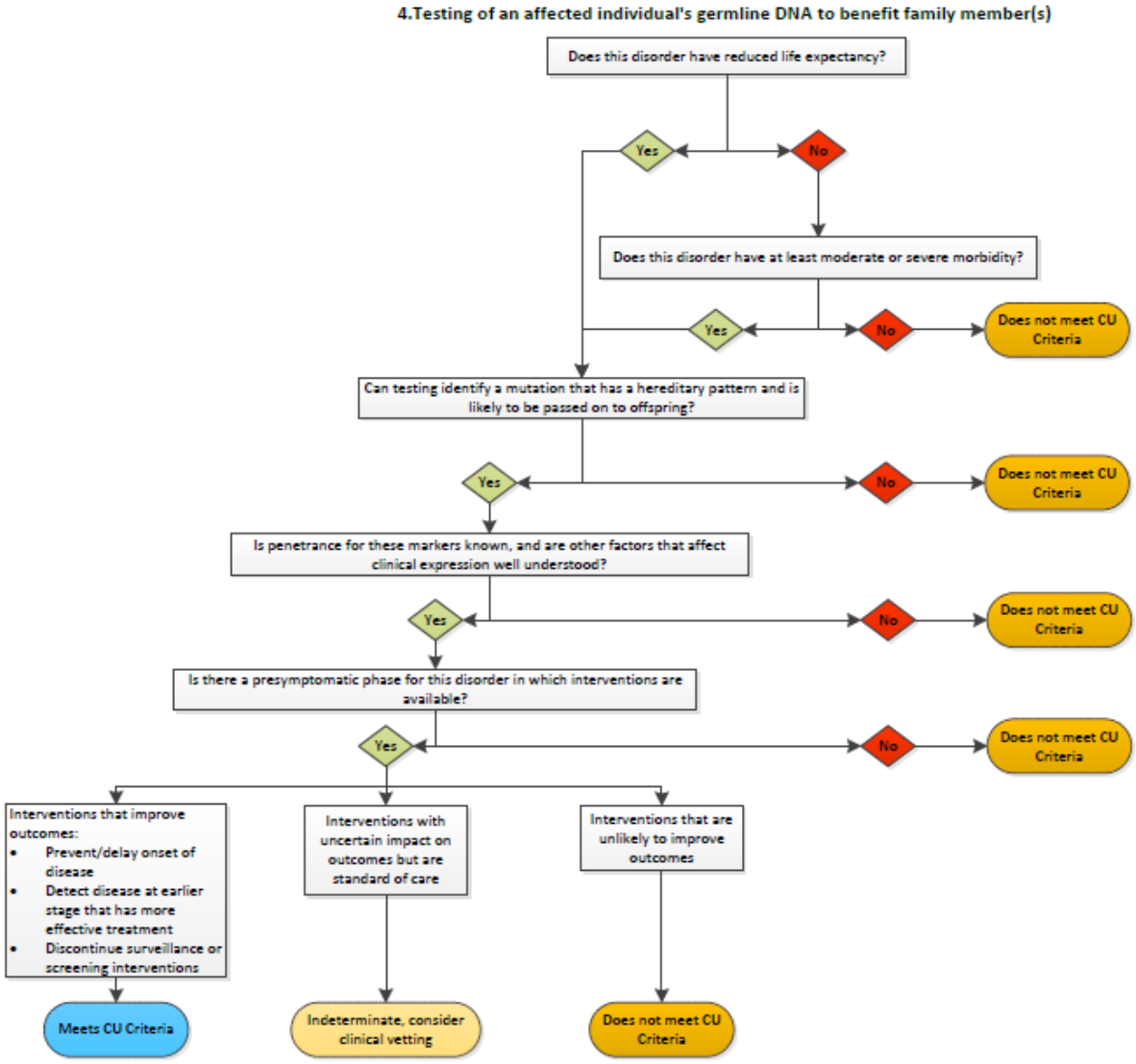
CU: clinical utility.

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.

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6. Department of Healthcare Services All Plan Letter. All Plan Letter APL 22-010: Cancer Biomarker Testing. Accessed January 22, 2026, from https://www.dhcs.ca.gov/formsandpubs/Documents/MMCDAPLsandPolicyLetters/APL2022/APL22-010.pdf

Documentation for Clinical Review

Please provide the following documentation:

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

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

Type	Code	Description
		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)
	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
03/01/2026	New policy.

Definitions of Decision Determinations

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

Medically Necessary or **Medical Necessity** means reasonable and necessary services to protect life, to prevent significant illness or significant disability, or alleviate severe pain through the diagnosis or treatment of disease, illness, or injury, as required under W&I section 14059.5(a) and 22 CCR section 51303(a). Medically Necessary services must include services necessary to achieve age-appropriate growth and development, and attain, maintain, or regain functional capacity.

For Members less than 21 years of age, a service is Medically Necessary if it meets the Early and Periodic Screening, Diagnostic, and Treatment (EPSDT) standard of Medical Necessity set forth in 42 USC section 1396d(r)(5), as required by W&I sections 14059.5(b) and 14132(v). Without limitation, Medically Necessary services for Members less than 21 years of age include all services necessary to achieve or maintain age-appropriate growth and development, attain, regain or maintain functional capacity, or improve, support, or maintain the Member's current health condition. Contractor must determine Medical Necessity on a case-by-case basis, taking into account the individual needs of the Child.

Criteria Determining Experimental/Investigational Status
In making a determination that any procedure, treatment, therapy, drug, biological product, facility, equipment, device, or supply is "experimental or investigational" by the Plan, the Plan shall refer to evidence from the national medical community, which may include one or more of the following sources:

1. Evidence from national medical organizations, such as the National Centers of Health Service Research.
2. Peer-reviewed medical and scientific literature.
3. Publications from organizations, such as the American Medical Association (AMA).
4. Professionals, specialists, and experts.
5. Written protocols and consent forms used by the proposed treating facility or other facility administering substantially the same drug, device, or medical treatment.
6. An expert physician panel selected by one of two organizations, the Managed Care Ombudsman Program of the Medical Care Management Corporation or the Department of Managed Health Care.

Feedback

Blue Shield of California Promise Health Plan 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 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/en/bsp/providers.

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

Questions regarding the applicability of this policy should be directed to the Blue Shield of California Promise Health Plan Prior Authorization Department at (800) 468-9935, or the Complex Case Management Department at (855) 699-5557 (TTY 711) for San Diego County and (800) 605-2556 (TTY 711) for Los Angeles County or visit the provider portal at www.blueshieldca.com/en/bsp/providers.

Disclaimer: Blue Shield of California Promise Health Plan 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 of California Promise Health Plan reserves the right to review and update policies as appropriate.