

## Medical Policy



### Title: General Approach to Genetic Testing

Related Policies:	▪ <i>General Approach to Evaluating the Utility of Genetic Panels</i>
-------------------	---

Professional	Institutional
Original Effective Date: February 7, 2014	Original Effective Date: February 7, 2014
Revision Date(s): February 7, 2014; March 25, 2016; January 1, 2017; February 10, 2021; January 1, 2022; August 11, 2022	Revision Date(s): February 7, 2014 March 25, 2016; January 1, 2017; February 10, 2021; January 1, 2022; August 11, 2022
Current Effective Date: February 10, 2021	Current Effective Date: February 10, 2021

**State and Federal mandates and health plan member contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. To verify a member's benefits, contact [Blue Cross and Blue Shield of Kansas Customer Service](#).**

**The BCBSKS Medical Policies contained herein are for informational purposes and apply only to members who have health insurance through BCBSKS or who are covered by a self-insured group plan administered by BCBSKS. Medical Policy for FEP members is subject to FEP medical policy which may differ from BCBSKS Medical Policy.**

**The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents of Blue Cross and Blue Shield of Kansas and are solely responsible for diagnosis, treatment and medical advice.**

**If your patient is covered under a different Blue Cross and Blue Shield plan, please refer to the Medical Policies of that plan.**

Populations	Interventions	Comparators	Outcomes
<b>Individuals:</b> <ul style="list-style-type: none"> <li>Who are symptomatic with a suspected genetically associated disease</li> </ul>	<b>Interventions of interest are:</b> <ul style="list-style-type: none"> <li>Genetic testing for a suspected genetically associated disorder</li> </ul>	<b>Comparators of interest are:</b> <ul style="list-style-type: none"> <li>Standard clinical management without genetic testing</li> </ul>	<b>Relevant outcomes include:</b> <ul style="list-style-type: none"> <li>Test accuracy</li> <li>Test validity</li> <li>Disease-specific survival</li> <li>Overall survival</li> <li>Change in disease status</li> <li>Morbid events</li> <li>Functional outcomes</li> </ul>

Populations	Interventions	Comparators	Outcomes
			<ul style="list-style-type: none"> <li>Changes in reproductive decision making</li> </ul>
<p><b>Individuals:</b></p> <ul style="list-style-type: none"> <li>Who are asymptomatic and have a close relative diagnosed with a genetically associated disease</li> </ul>	<p><b>Interventions of interest are:</b></p> <ul style="list-style-type: none"> <li>Genetic testing for a genetically associated disorder</li> </ul>	<p><b>Comparators of interest are:</b></p> <ul style="list-style-type: none"> <li>Standard clinical management without genetic testing</li> </ul>	<p><b>Relevant outcomes include:</b></p> <ul style="list-style-type: none"> <li>Test accuracy</li> <li>Test validity</li> <li>Disease-specific survival</li> <li>Overall survival</li> <li>Change in disease status</li> <li>Morbid events</li> <li>Functional outcomes</li> <li>Changes in reproductive decision making</li> </ul>

**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.

**OBJECTIVE**

The objective of this review is to outline the conceptual framework to assess the clinical utility of genetic tests.

**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.

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.

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.

**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.

## POLICY

- A. Genetic testing classified in one of the categories below may be considered **medically necessary** when all criteria are met for each category, as outlined in the Rationale Section:
1. Testing of an affected (symptomatic) individual's germline DNA to benefit the individual (excluding reproductive testing)
    - a. Diagnostic
    - b. Prognostic
    - c. Therapeutic
  2. Testing cancer cells of an affected individual to benefit the individual
    - a. Diagnostic
    - b. Prognostic
    - c. Therapeutic
  3. Testing an asymptomatic individual to determine future risk of disease
- B. Genetic testing that does not meet the criteria for a specific category is considered **experimental / investigational** or **not medically necessary**, according to the standard definitions used for these terms (see Policy Guidelines section).

## POLICY GUIDELINES

- A. 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.
1. Testing of an affected individual's germline DNA to benefit family member(s).
- B. Genetic testing is considered not medically necessary when:
1. testing is not considered standard of care, such as when the clinical diagnosis can be made without the use of a genetic test
  2. testing is not clinically appropriate for the patient's condition, (eg, when it would not change diagnosis and/or management). Other situations where testing is not clinically appropriate include, but are not limited to:
    - a. testing is performed entirely for nonmedical (eg, social) reasons
    - b. testing is not expected to provide a definitive diagnosis that would obviate the need for further testing
  3. testing is performed primarily for the convenience of the patient, physician or other health care provider
  4. 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.

**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.**

## RATIONALE

This conceptual framework been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through November 7, 2017.

### General Principles of Genetic Tests

The test should be cleared or approved by the U.S. Food and Drug Administration or performed in a Clinical Laboratory Improvement Amendment-certified laboratory.

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.<sup>1,2</sup>

### 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 pathologic variant. For genetic testing, a symptomatic person is defined as an individual with a clinical phenotype correlated with a known pathologic 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, (eg, aggressiveness, recurrence, risk of death). This type of testing may use gene expression of affected tissue to predict the course of disease (eg, testing breast cancer tissue with Oncotype DX).
  - c. Therapeutic. To determine that a particular therapeutic intervention is effective (or ineffective) for an individual patient. To determine the probability of favorable or adverse response to medications. To detect genetic variants that alter risk of treatment response, adverse events, drug metabolism, drug effectiveness, etc. (eg, cytochrome p450 testing). To detect genetic variants that adversely affect response to exposures in the environment that are ordinarily tolerated (eg, *G6PD* deficiency, genetic disorders of immune function, and 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 pathologic variant has not been determined.

### **Medical Necessity Criteria**

The criteria listed below for medical necessity represent the minimum criteria that must be met in each category to determine that a test is medically necessary. Alternate 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<sup>3</sup>

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

1. Testing of an affected (symptomatic) individual's germline to benefit the individual (excluding reproductive testing)
  - a. Diagnostic
    - i. An association of the marker with the disorder has been established AND
    - ii. Symptoms of the disease are present AND
    - iii. A definitive diagnosis cannot be made based on history, physical examination, pedigree analysis, standard diagnostic studies/tests AND
    - iv. The clinical utility of identifying the mutation has been established (see Appendix 2):
      - 1) Leads to changes in clinical management of the condition that improve outcomes; OR
      - 2) Eliminates the need for further clinical workup or invasive testing; OR
      - 3) Leads to discontinuation of interventions that are unnecessary and/or ineffective,
  - b. Prognostic
    - i. An association between the marker and the natural history of the disease has been established AND
    - ii. Clinical utility of identifying the variant has been established (see Appendix 2),
      - 1) Provides incremental prognostic information above that of standard testing; AND
      - 2) Reclassifies patients into clinically relevant prognostic categories for which there are different treatment strategies; AND



- 3) Reclassification leads to changes in management that improve outcomes.
- c. Therapeutic
    - i. Genetic testing identifies variants of a phenotype/metabolic state that relate to different pharmacokinetics, drug efficacy or adverse drug reactions; AND
    - ii. Clinical utility of identifying the mutation has been established (see Appendix 2),
      - 1) Leads to initiation of effective medication(s) OR
      - 2) Leads to discontinuation of medications that are ineffective or harmful OR
      - 3) Leads to clinical meaningful change in dosing of medication that is likely to improve outcomes.
2. Testing cancer cells of an affected individual to benefit the individual
    - a. Diagnostic
      - i. Genetic testing can establish the cell origin of a cancer when the origin is uncertain following standard work-up; AND
      - ii. Clinical utility of identifying the variant has been established (see Appendix 2)
        - 1) Start effective treatment; OR
        - 2) Discontinue ineffective or harmful treatment
    - b. Prognostic
      - i. An association between the marker and the natural history of the disease has been established AND
      - ii. Clinical utility of identifying the variant has been established (see Appendix 2),
        - 1) Provides incremental prognostic information above that of standard testing; AND
        - 2) Reclassifies patients into clinically relevant prognostic categories for which there are different treatment strategies; AND
        - 3) Reclassification leads to changes in management that improve outcomes.
    - c. Therapeutic
      - i. Association between a variant and treatment response to a particular drug has been established AND
      - ii. Clinical utility has been established (see Appendix 2),
        - 1) The patient is a candidate for targeted drug therapy associated with a specific variant; AND
        - 2) There is a clinically meaningful improvement in outcomes when targeted therapy is given for the condition
3. Testing an asymptomatic individual to determine future risk of disease
    - i. An association between the marker and future disorder has been established AND
    - ii. Clinical utility has been established (see Appendix 2)
      - 1) There is a presymptomatic phase for this disorder in which 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 for 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 is dependent on individual plan benefit language. Individual plans may differ whether benefit structure allows testing of an individual to benefit an unaffected family member.

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

4. Testing of an affected individual's germline to benefit family members
  - i. An association of 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 for 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. 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.

**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.

**CODING**

**The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.**

**Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.**

**The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.**

<b>CPT/HCPCS</b>	
<b>Tier 1 Molecular Pathology Procedure Codes</b>	
81200	ASPA (aspartoacylase) (eg, Canavan disease) gene analysis, common variants (eg, E285A, Y231X)
81201	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; full gene sequence
81202	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; known familial variants
81203	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; duplication/deletion variants
81205	BCKDHB (branched-chain keto acid dehydrogenase E1, beta polypeptide) (eg, Maple syrup urine disease) gene analysis, common variants (eg, R183P, G278S, E422X)
81206	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; major breakpoint, qualitative or quantitative
81207	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; minor breakpoint, qualitative or quantitative
81208	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; other breakpoint, qualitative or quantitative
81209	BLM (Bloom syndrome, RecQ helicase-like) (eg, Bloom syndrome) gene analysis, 2281del6ins7 variant
81210	BRAF (BRAF proto-oncogene serine/threonine kinase) (eg, colon cancer, melanoma), gene analysis, V600E variant(s)
81211	BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and common duplication/deletion variants in BRCA1 (ie, exon 13 del 3.835kb, exon 13 dup 6kb, exon 14-20 del 26kb, exon 22 del 510bp, exon
81212	BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants
81213	BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; uncommon duplication/deletion variants
81214	BRCA1 (breast cancer 1) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and common duplication/deletion variants (ie, exon 13 del 3.835kb, exon 13 dup 6kb, exon 14-20 del 26kb, exon 22 del 510bp, exon 8-9 del 7.1kb)

<b>CPT/HCPCS</b>	
81215	BRCA1 (breast cancer 1) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant
81216	BRCA2 (breast cancer 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81217	BRCA2 (breast cancer 2) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant
81218	CEBPA (CCAAT/enhancer binding protein [C/EBP], alpha) (eg, acute myeloid leukemia), gene analysis, full gene sequence)
81219	CALR (calreticulin) (EG, myeloproliferative disorders), gene analysis, common variants in exon 9
81220	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; common variants (eg, ACMG/ACOG guidelines)
81221	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; known familial variants
81222	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; duplication/deletion variants
81223	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; full gene sequence
81224	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; intron 8 poly-T analysis (eg, male infertility)
81225	CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *8, *17)
81226	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *5, *6, *9, *10, *17, *19, *29, *35, *41, *1XN, *2XN, *4XN)
81227	CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *5, *6)
81228	Cytogenomic constitutional chromosomal abnormalities (genome-wide) chromosomal abnormalities analysis; interrogation of genomic regions for copy number variants (eg, Bacterial Artificial Chromosome [BAC] or oligo-based comparative genomic hybridization [CGH] microarray analysis)
81229	Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities
81235	EGFR (epidermal growth factor receptor) (eg, non-small cell lung cancer) gene analysis, common variants (eg, exon 19 LREA deletion, L858R, T790M, G719A, G719S, L861Q)
81240	F2 (prothrombin, coagulation factor II) (eg, hereditary hypercoagulability) gene analysis, 20210G>A variant
81241	F5 (coagulation Factor V) (eg, hereditary hypercoagulability) gene analysis, Leiden variant
81242	FANCC (Fanconi anemia, complementation group C) (eg, Fanconi anemia, type C) gene analysis, common variant (eg, IVS4+4A>T)
81243	FMR1 (Fragile X mental retardation 1) (eg, fragile X mental retardation) gene analysis; evaluation to detect abnormal (eg, expanded) alleles

<b>CPT/HCPCS</b>	
81244	FMR1 (Fragile X mental retardation 1) (eg, fragile X mental retardation) gene analysis; characterization of alleles (eg, expanded size and methylation status)
81245	FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia), gene analysis, internal tandem duplication (ITD) variants (ie, exons 14, 15)
81246	FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia), gene analysis; tyrosine kinase domain (TKD) variants (eg, D835, I836)
81250	G6PC (glucose-6-phosphatase, catalytic subunit) (eg, Glycogen storage disease, Type 1a, von Gierke disease) gene analysis, common variants (eg, R83C, Q347X)
81251	GBA (glucosidase, beta, acid) (eg, Gaucher disease) gene analysis, common variants (eg, N370S, 84GG, L444P, IVS2+1G>A)
81252	GJB2 (gap junction protein, beta 2, 26kDa, connexin 26) (eg, nonsyndromic hearing loss) gene analysis; full gene sequence
81253	GJB2 (gap junction protein, beta 2, 26kDa; connexin 26) (eg, nonsyndromic hearing loss) gene analysis; known familial variants
81254	GJB6 (gap junction protein, beta 6, 30kDa, connexin 30) (eg, nonsyndromic hearing loss) gene analysis, common variants (eg, 309kb [del(GJB6-D13S1830)] and 232kb [del(GJB6-D13S1854)])
81255	HEXA (hexosaminidase A [alpha polypeptide]) (eg, Tay-Sachs disease) gene analysis, common variants (eg, 1278insTATC, 1421+1G>C, G269S)
81256	HFE (hemochromatosis) (eg, hereditary hemochromatosis) gene analysis, common variants (eg, C282Y, H63D)
81257	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis, for common deletions or variant (eg, Southeast Asian, Thai, Filipino, Mediterranean, alpha3.7, alpha4.2, alpha20.5, and Co)
81260	IKBKAP (inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein) (eg, familial dysautonomia) gene analysis, common variants (eg, 2507+6T>C, R696P)
81261	IGH@ (Immunoglobulin heavy chain locus) (eg, leukemias and lymphomas, B-cell), gene rearrangement analysis to detect abnormal clonal population(s); amplified methodology (eg, polymerase chain reaction)
81262	IGH@ (Immunoglobulin heavy chain locus) (eg, leukemias and lymphomas, B-cell), gene rearrangement analysis to detect abnormal clonal population(s); direct probe methodology (eg, Southern blot)
81263	IGH@ (Immunoglobulin heavy chain locus) (eg, leukemia and lymphoma, B-cell), variable region somatic mutation analysis
81264	IGK@ (Immunoglobulin kappa light chain locus) (eg, leukemia and lymphoma, B-cell), gene rearrangement analysis, evaluation to detect abnormal clonal population(s)
81265	Comparative analysis using Short Tandem Repeat (STR) markers; patient and comparative specimen (eg, pre-transplant recipient and donor germline testing, post-transplant non-hematopoietic recipient germline [eg, buccal swab or other germline tissue sample])
81266	Comparative analysis using Short Tandem Repeat (STR) markers; each additional specimen (eg, additional cord blood donor, additional fetal samples from different cultures, or additional zygosity in multiple birth pregnancies) (List separately in addition to code for primary procedure)

<b>CPT/HCPCS</b>	
81267	Chimerism (engraftment) analysis, post transplantation specimen (eg, hematopoietic stem cell), includes comparison to previously performed baseline analyses; without cell selection
81268	Chimerism (engraftment) analysis, post transplantation specimen (eg, hematopoietic stem cell), includes comparison to previously performed baseline analyses; with cell selection (eg, CD3, CD33), each cell type
81270	JAK2 (Janus kinase 2) (eg, myeloproliferative disorder) gene analysis, p.Val617Phe (V617F) variant
81272	KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (eg, mastocytosis), gene analysis, D816 variant(s)
81273	KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (eg, gastrointestinal stromal tumor [GIST], acute myeloid leukemia, melanoma), gene analysis, targeted sequence analysis (eg, exons 8, 11, 13, 17, 18)
81275	KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; variants in exon 2 (eg, codons 12 and 13)
81276	KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; additional variant(s) (eg, codon 61, codon 146)
81287	MGMT (O-6-methylguanine-DNA methyltransferase) (eg, glioblastoma multiforme), methylation analysis
81288	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; promoter methylation analysis
81290	MCOLN1 (mucolipin 1) (eg, Mucopolipidosis, type IV) gene analysis, common variants (eg, IVS3-2A>G, del6.4kb)
81291	MTHFR (5,10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)
81292	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81293	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
81294	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
81295	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81296	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
81297	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
81298	MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81299	MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
81300	MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants

<b>CPT/HCPCS</b>	
81301	Microsatellite instability analysis (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (eg, BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed
81302	MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome) gene analysis; full sequence analysis
81303	MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome) gene analysis; known familial variant
81304	MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome) gene analysis; duplication/deletion variants
81310	NPM1 (nucleophosmin) (eg, acute myeloid leukemia) gene analysis, exon 12 variants
81311	NRAS (neuroblastoma RAS viral [v-ras] oncogene homolog) (eg, colorectal carcinoma), gene analysis, variants in exon 2 (eg, codons 12 and 13) and exon 3 (eg, codon 61)
81313	PCA3/KLK3 (prostate cancer antigen 3 [non-protein coding]/kallikrein-related peptidase 3 [prostate specific antigen]) ratio (eg, prostate cancer)
81314	PDGFRA (platelet-derived growth factor receptor, alpha polypeptide) (eg, gastrointestinal stromal tumor [GIST]), gene analysis, targeted sequence analysis (eg, exons 12, 18)
81315	PML/RARalpha, (t(15;17)), (promyelocytic leukemia/retinoic acid receptor alpha) (eg, promyelocytic leukemia) translocation analysis; common breakpoints (eg, intron 3 and intron 6), qualitative or quantitative
81316	PML/RARalpha, (t(15;17)), (promyelocytic leukemia/retinoic acid receptor alpha) (eg, promyelocytic leukemia) translocation analysis; single breakpoint (eg, intron 3, intron 6 or exon 6), qualitative or quantitative
81317	PMS2 (postmeiotic segregation increased 2 [ <i>S. cerevisiae</i> ]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81318	PMS2 (postmeiotic segregation increased 2 [ <i>S. cerevisiae</i> ]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
81319	PMS2 (postmeiotic segregation increased 2 [ <i>S. cerevisiae</i> ]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
81321	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis
81322	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; known familial variant
81323	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; duplication/deletion variant
81324	PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; duplication/deletion analysis
81325	PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; full sequence analysis
81326	PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; known familial variant
81330	SMPD1(sphingomyelin phosphodiesterase 1, acid lysosomal) (eg, Niemann-Pick disease, Type A) gene analysis, common variants (eg, R496L, L302P, fsP330)



<b>CPT/HCPCS</b>	
81331	SNRPN/UBE3A (small nuclear ribonucleoprotein polypeptide N and ubiquitin protein ligase E3A) (eg, Prader-Willi syndrome and/or Angelman syndrome), methylation analysis
81332	SERPINA1 (serpin peptidase inhibitor, clade A, alpha-1 antiproteinase, antitrypsin, member 1) (eg, alpha-1-antitrypsin deficiency), gene analysis, common variants (eg, *S and *Z)
81340	TRB@ (T cell antigen receptor, beta) (eg, leukemia and lymphoma), gene rearrangement analysis to detect abnormal clonal population(s); using amplification methodology (eg, polymerase chain reaction)
81341	TRB@ (T cell antigen receptor, beta) (eg, leukemia and lymphoma), gene rearrangement analysis to detect abnormal clonal population(s); using direct probe methodology (eg, Southern blot)
81342	TRG@ (T cell antigen receptor, gamma) (eg, leukemia and lymphoma), gene rearrangement analysis, evaluation to detect abnormal clonal population(s)
81349	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities (effective 01-01-22)
81350	UGT1A1 (UDP glucuronosyltransferase 1 family, polypeptide A1) (eg, irinotecan metabolism), gene analysis, common variants (eg, *28, *36, *37)
81355	VKORC1 (vitamin K epoxide reductase complex, subunit 1) (eg, warfarin metabolism), gene analysis, common variant(s) (eg, -1639G>A, c.173+1000C>T)
<b>Tier 2 Molecular Pathology Procedure Codes</b>	
81400	Molecular pathology procedure, Level 1(eg, identification of single germline variant [eg, SNP] by techniques such as restriction enzyme digestion or melt curve analysis)
81401	Molecular pathology procedure, Level 2 (eg, 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 (eg, >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 (eg, 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 (eg, 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 (eg, 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 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia)
81407	Molecular pathology procedure, Level 8 (eg, 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)

<b>CPT/HCPCS</b>	
81408	Molecular pathology procedure, Level 9 (eg, analysis of >50 exons in a single gene by DNA sequence analysis)
81479	Unlisted molecular pathology procedure

<b>ICD-10 DIAGNOSES</b>
Diagnosis coding would depend on the condition for which the testing is being performed, if the test is being performed as screening or carrier testing, and any family history of the condition.

<b>REVISIONS</b>	
02-07-2014	Policy added to the bcbsks.com web site on 01-08-2014 for an effective date of 02-07-2014.
03-25-2016	Policy published 02-24-2016. Policy effective 03-25-2016.
	Description section updated
	In Policy section: <ul style="list-style-type: none"> <li>▪ In Item A removed "1. Diagnostic testing, 2. Risk assessment, 3. Prognostic testing, 4. Genetic variants that alter response to treatment or to an environmental factor"</li> <li>▪ In Item A added <ol style="list-style-type: none"> <li>"1. Testing of an affected (symptomatic) individual's germline DNA to benefit the individual (excluding reproductive testing) <ol style="list-style-type: none"> <li>a. Diagnostic b. Prognostic c. Therapeutic</li> </ol> </li> <li>2. Testing of DNA from cancer cells of an affected individual to benefit the individual <ol style="list-style-type: none"> <li>a. Diagnostic b. Prognostic c. Testing to predict treatment response</li> </ol> </li> <li>3. Testing an asymptomatic individual to determine future risk of disease"</li> </ol> </li> </ul>
	Rationale section updated
	In Coding section: <ul style="list-style-type: none"> <li>▪ Added CPT Codes: 81162, 81170, 81218, 81219, 81272, 81273, 81276, 81311, 81314 (Effective January 1, 2016)</li> <li>▪ Added CPT Codes: 81161, 81246, 81287, 81288, 81313, 81479</li> <li>▪ Revised CPT Codes: 81210, 81275, 81355 (Effective January 1, 2016)</li> <li>▪ Updated Coding notations</li> </ul>
	Appendix section added to reflect the categories of diagnostic testing, risk assessment, prognostic testing, and pharmacogenomics.
01-01-2017	Updated Coding section: <ul style="list-style-type: none"> <li>▪ Removed CPT Codes: 81280, 81281, 81282 (Effective December 31, 2016)</li> </ul>
02-10-2021	Updated Description section
	Updated Policy section <ul style="list-style-type: none"> <li>• Item A.2.c replaced "Testing to predict treatment response" with "Therapeutic"</li> <li>• Policy Guideline #2 was removed</li> <li>• Policy Guideline #3 was reformatted, however position statement was unchanged</li> <li>• "Genetic Nomenclature Update, Table PG1 and PG2, and Genetic Counseling" sections were added to the Policy Guidelines.</li> </ul>
	Rationale section updated
	References section updated
01-01-2022	Updated Coding section: <ul style="list-style-type: none"> <li>• Added CPT 81349</li> <li>• Revised nomenclature 81228</li> </ul>

<b>REVISIONS</b>	
	"Constitutional" and "microarray" removed and "constitutional chromosomal abnormalities" added.
08-11-2022	Updated Coding Section <ul style="list-style-type: none"> <li>▪ Removed CPT Codes: 81161, 81162, 81170</li> <li>▪ Removed Coding bullets               <ul style="list-style-type: none"> <li>• Effective in 2013, if a specific analyte is listed in codes 81200-81355 or 81400-81408, that CPT code would be reported.</li> <li>• If the specific analyte is not listed in the more specific CPT codes, unlisted code 81479 would be reported.</li> </ul> </li> </ul>

## 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

## APPENDIX

### Appendix 1. Categorizing of Types of Testing Addressed in Evidence Reviews

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

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: familial 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 (ie, clinical sensitivity and specificity). If improved accuracy leads to improved diagnosis of the disorder, and if more accurate diagnosis leads to management changes that improve outcomes, then clinical utility has been established.

Many 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 (eg, 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. 4 factors below are enumerated, 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 alternate methods without genetic testing?
  - ✓ Disorder is defined by the presence of genetic variant
  - ✓ Genetic test 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 work-up?
  - ✓ Is disorder one for which the diagnosis can be difficult, and the patient may be subjected to long and complicated work-ups?

### 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 the Initiation of other management changes with uncertain impact on outcomes (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: Testing Categories 1a, 2a**

Disorder	Disease Characteristics				Impact on Diagnosis				Impact on Management				Impact on Outcomes				
	Shortened LE	Severe morbidity/disability	Moderate morbidity/disability	Minor or no morbidity/disability	Confirms diagnosis Condition defined by variant	Confirms diagnosis, o/w 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 (eg, 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, (eg, 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: Testing Category 3**

Disorder	Disease Characteristics					Impact on Defining Risk				Impact on Management				Impact on Outcomes			
	Shortened LE	Severe morbidity/disability	Moderate morbidity/disability	Minor or no morbidity/disability	Has presymptomatic stage	Determines risk in substantial proportion of patients	Known variant 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 (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 for Prognosis Testing (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 that are associated with increased risk for adverse effects?

Impact of Genetic Test on Pharmacologic Management

- Does identification of genetic variants lead to changes in pharmacologic management?
  - ✓ Initiation of alternate agents
  - ✓ Discontinuation ineffective agents
  - ✓ Changes in dosing

Impact on Health Outcomes

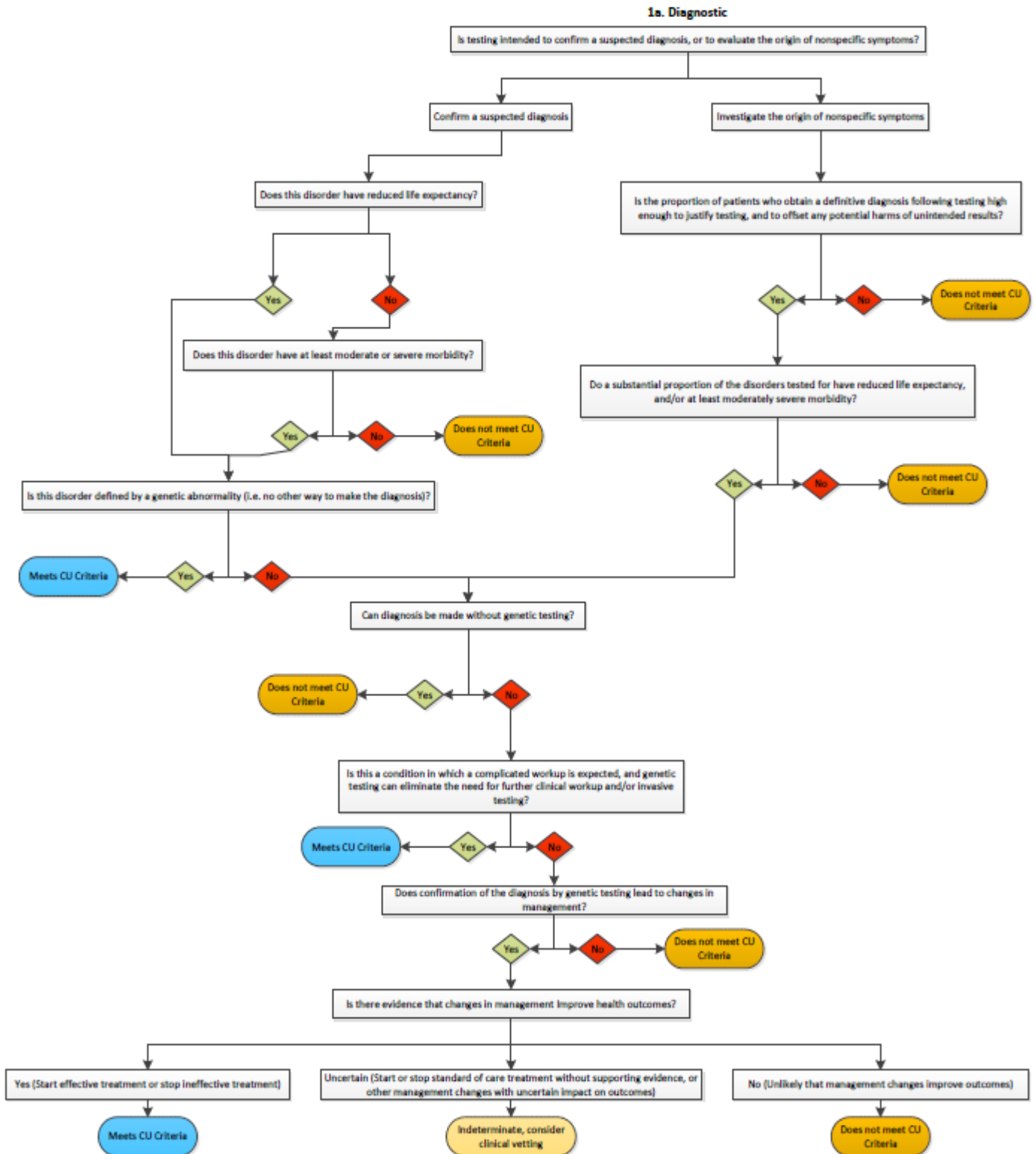
- Is there a definite improvement in health outcomes with genetic testing? For example:
  - ✓ Identification of variants leads to initiation of medications known to be effective

- Is there a possible, but not definite, improvement in health outcomes with genetic testing? For example:
  - ✓ Identification of variants leads to change in pharmacologic management with uncertain impact on outcomes
- Are there significant barriers to research, such as rarity of the disorder?

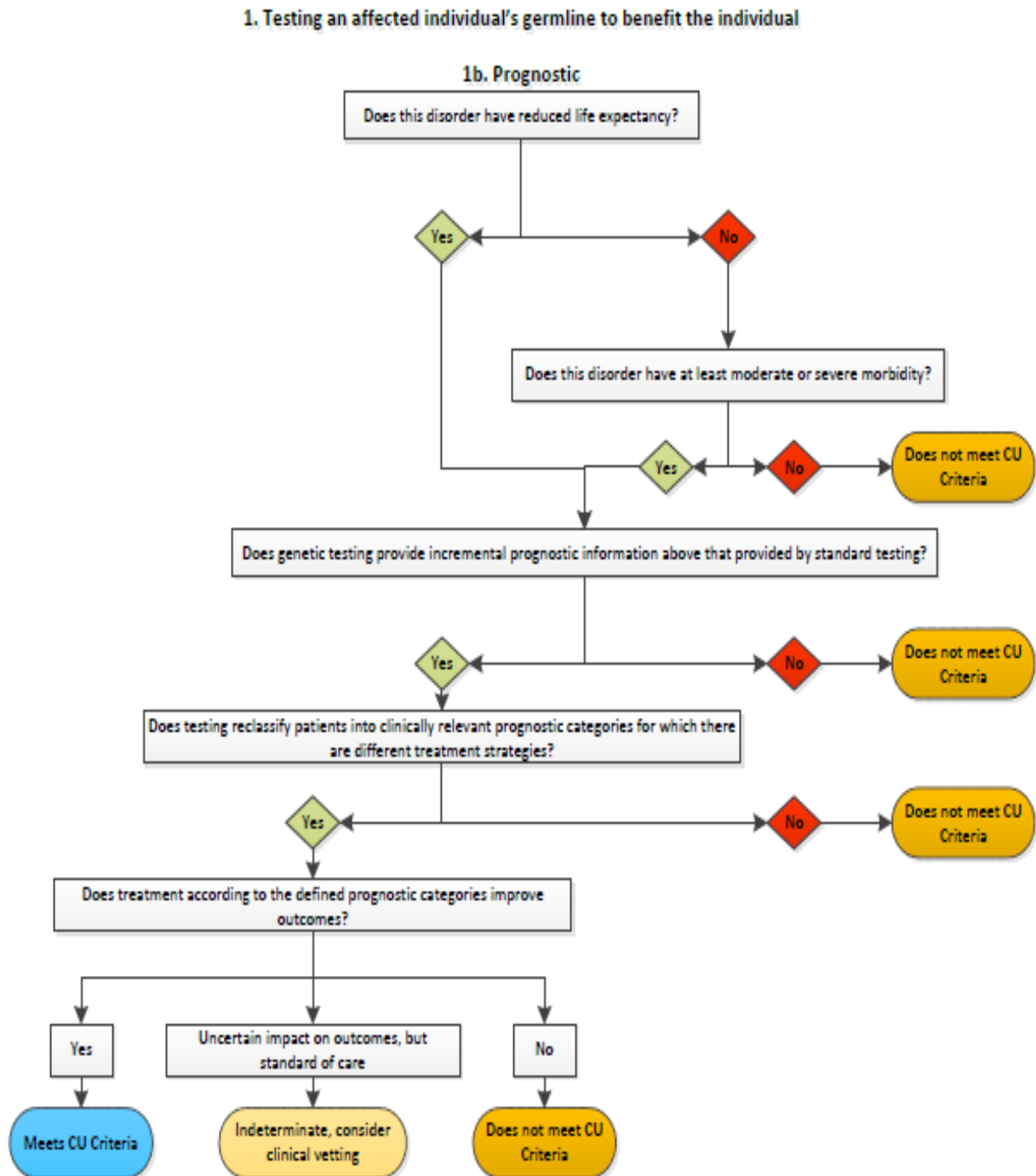
**Appendix Table 4. Factors Influencing the Strength of Indirect Evidence: Genetic Variants That Alter Response to Treatment (Testing Categories 1c, 2c)**

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

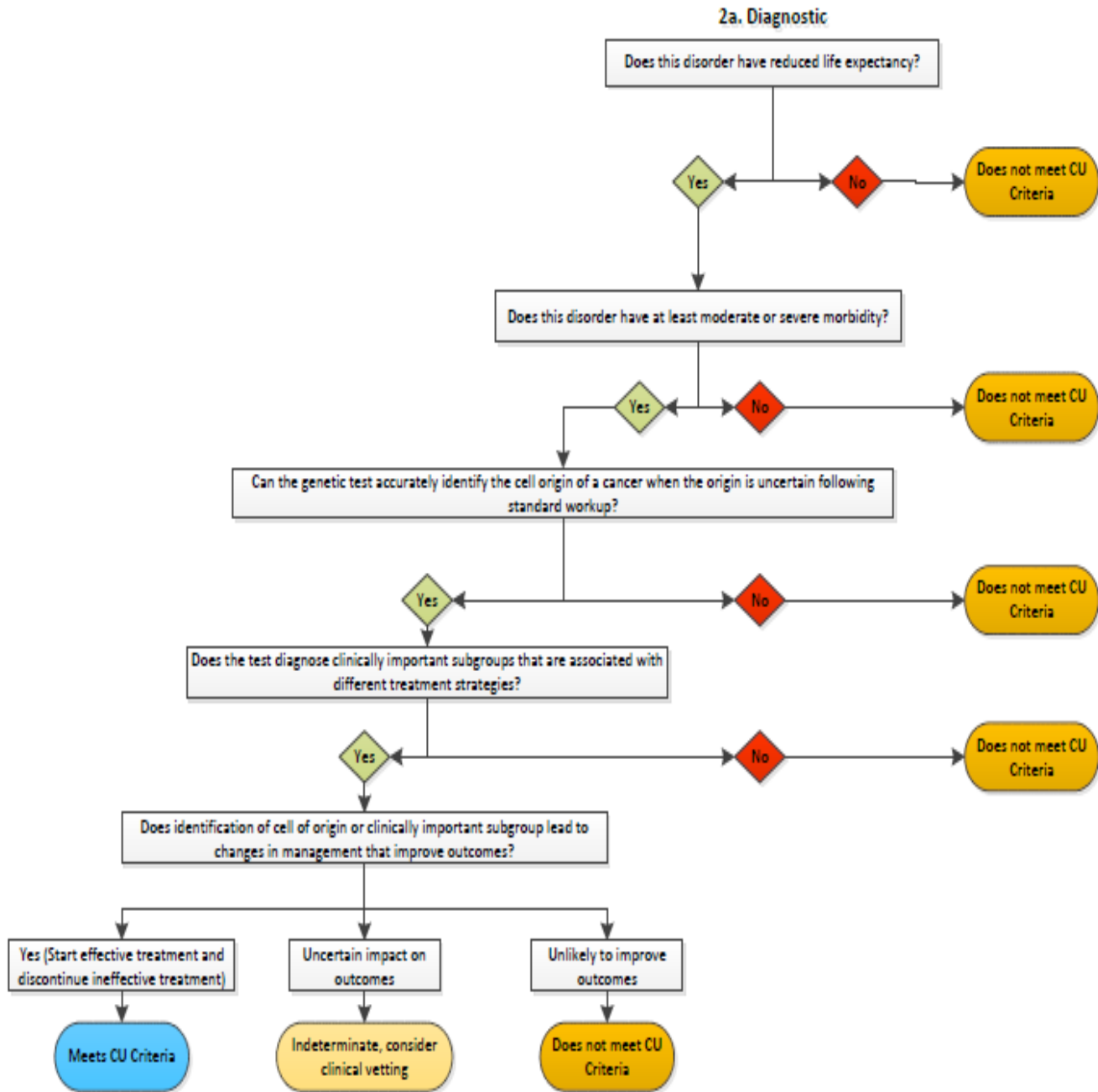


**Appendix Figure 1b. Prognostic Testing of an Affected Individual’s Germline to Benefit the Individual**



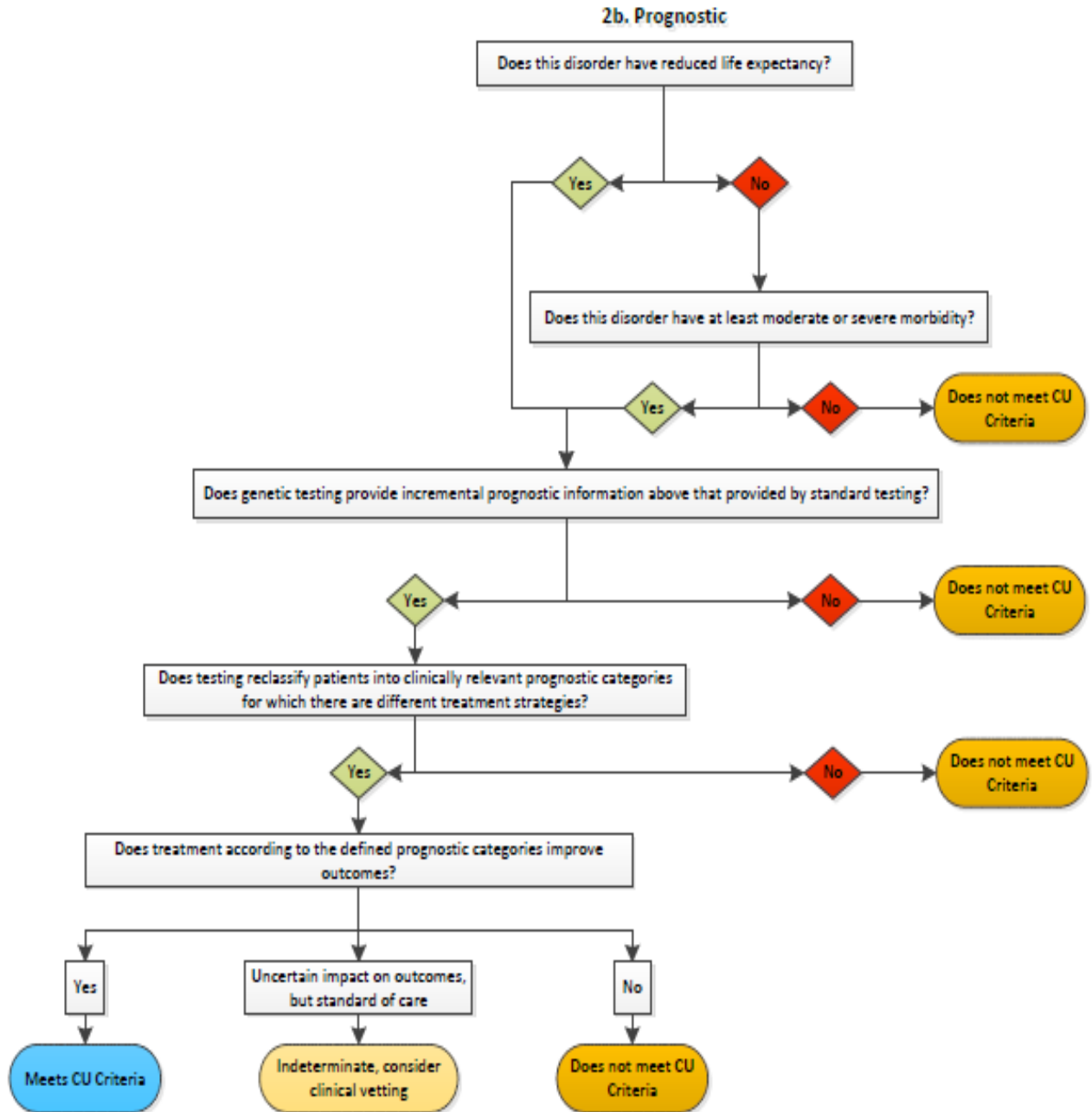
**Appendix Figure 2a. Diagnostic Testing of DNA Cells From Cancer Cells of an Affected Individual to Benefit the Individual**

2. Testing of DNA from cancer cells of an affected individual to benefit the individual



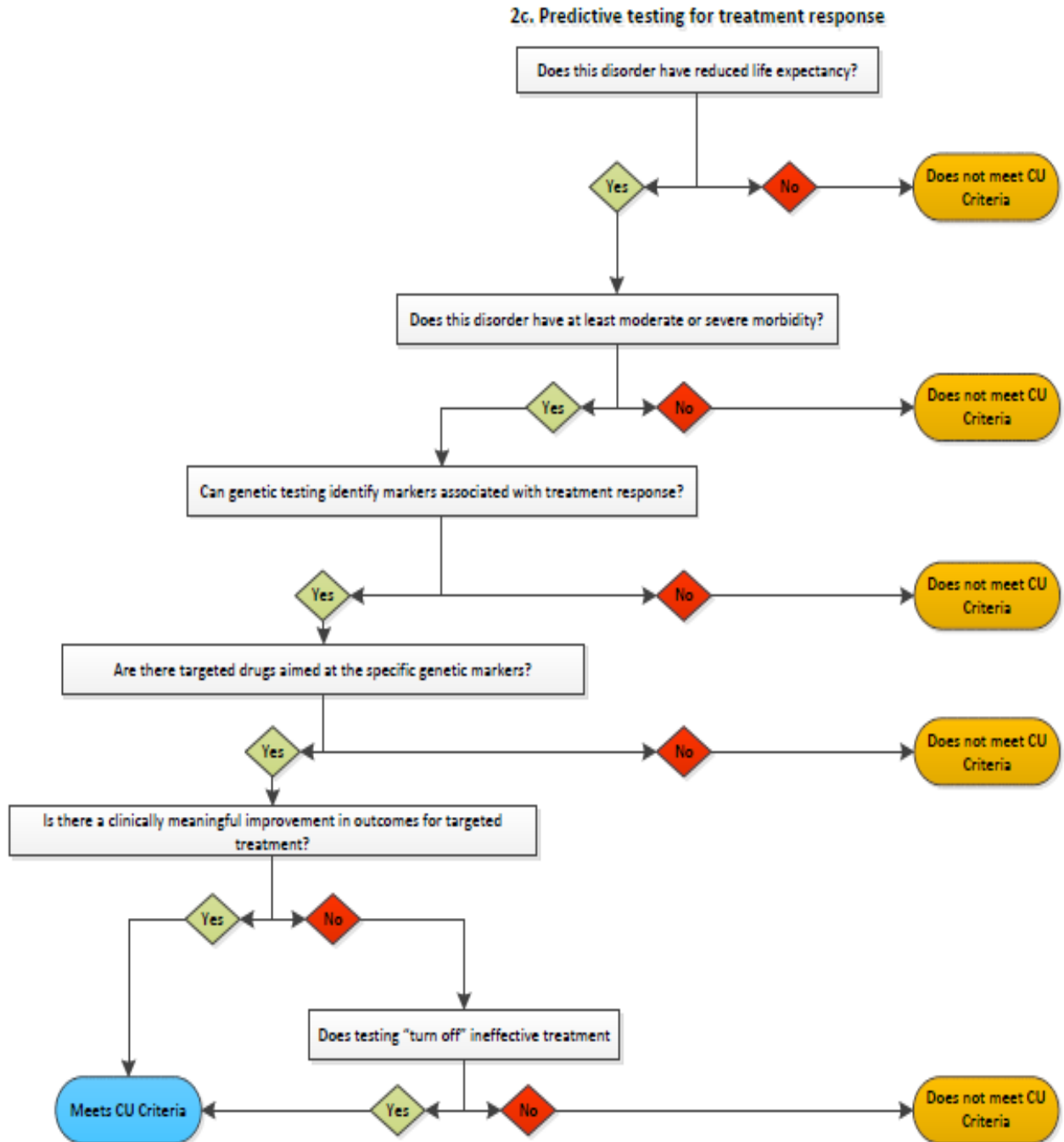
**Appendix Figure 2b. Prognostic Testing of DNA From Cancer Cells of an Affected Individual to Benefit the Individual**

**2. Testing of DNA from cancer cells of an affected individual to benefit the individual**



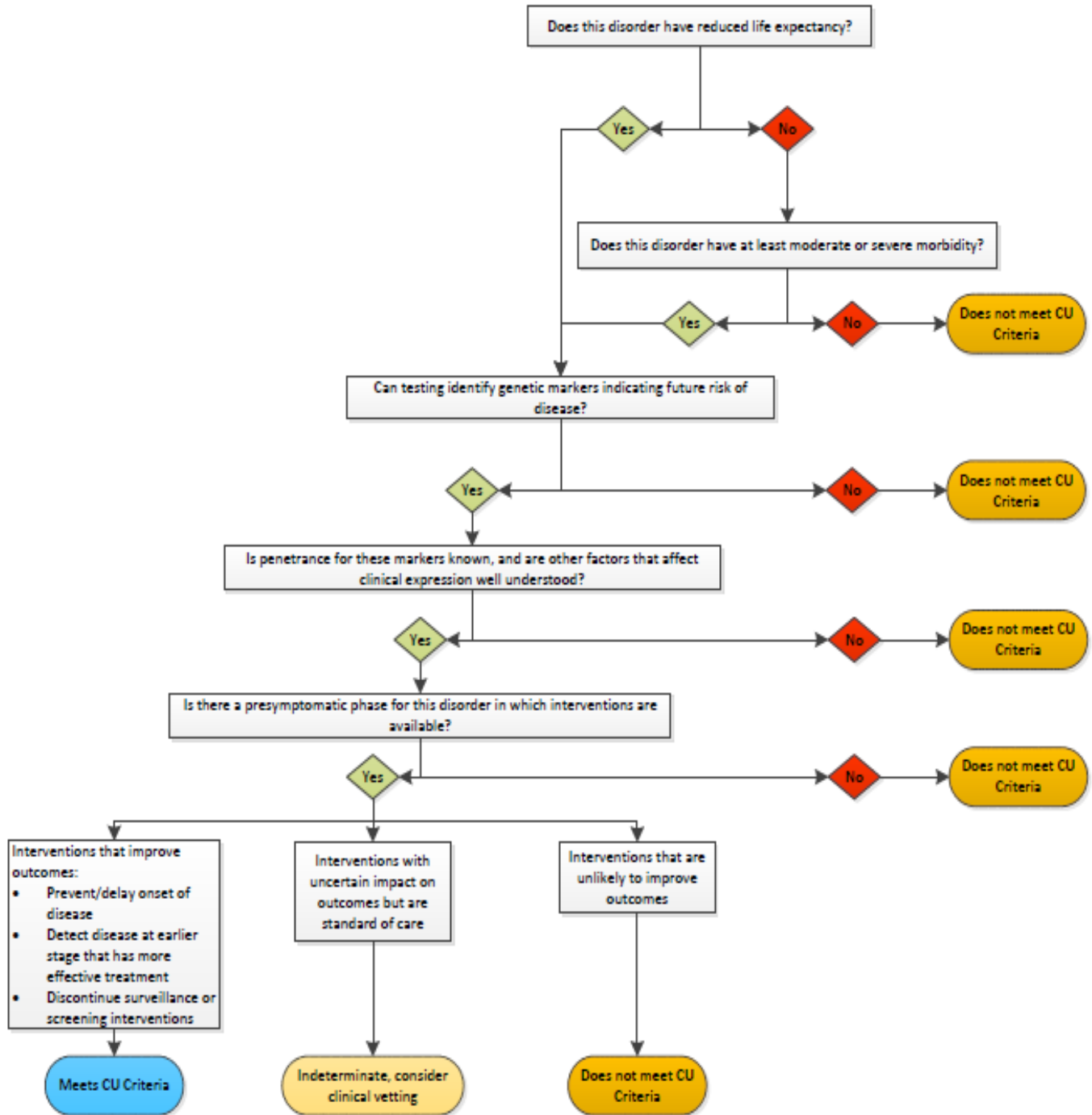
**Appendix Figure 2c. Therapeutic Testing of Cancer Cells of an Affected Individual to Benefit the Individual**

**2. Testing of DNA from cancer cells of an affected individual to benefit the individual**



**Appendix Figure 3. Testing an Asymptomatic Individual to Determine Future Risk of Disease**

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





**Appendix Figure 4. Testing an Affected Individual's Determine DNA to Benefit Family Member(s)**

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

