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General Approach to Genetic Testing

| | |
|-------------------------|--|
| Number | 12.04.91 |
| Effective Date | April 1, 2016 |
| Revision Date(s) | 05/04/16; 03/08/16; 05/12/15; 12/01/14; 07/14/14; 05/23/14; 02/27/14; 01/16/14; 01/03/14; 12/19/13; 11/20/13; 10/17/13; 09/16/13; 08/12/13; 06/04/13; 05/13/13 |
| Replaces | 2.04.91 |

Policy

[\[TOP\]](#)

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
 - Therapeutic
2. Testing of DNA from cancer cells of an affected individual to benefit the individual
 - a. Diagnostic
 - b. Prognostic
 - c. Testing to predict treatment response
3. Testing an asymptomatic individual to determine future risk of disease

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

4. When testing of an affected individual's germline DNA is done to benefit family member(s), rather than to benefit the individual being tested, see Rationale for clinical utility criteria.

Genetic testing is considered **not medically necessary** when performed entirely for non-medical reasons (e.g., a general interest in genetic test results).

Note: This policy applies only if there is not a separate policy that outlines specific criteria for testing. If a separate policy does exist, then the criteria for medical necessity in that policy supersede the guidelines in this policy. (See [Related Policies](#))

Related Policies

[\[TOP\]](#)

[12.04.121](#) [Miscellaneous Genetic and Molecular Diagnostic Tests](#)

Policy Guidelines

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Definitions

Experimental or Investigative Definition

Experimental or Investigational services include a treatment, procedure, equipment, drug, drug usage, medical device, or supply that meets one or more of the following criteria as determined by the Company:

- A drug or device, which cannot be lawfully marketed without the approval of the U. S. Food and Drug Administration (FDA), and has not been granted such approval on the date the service is provided.
- The service is subject to oversight by an Institutional Review Board.
- No credible scientific evidence demonstrates that the service is effective in clinical diagnosis, evaluation, management, or treatment of identified condition.
- The service is the subject of ongoing clinical trials to determine its maximum tolerated dose, toxicity, safety, or efficacy.
- Evaluation of credible scientific evidence indicates that additional research is necessary before the service can be classified as equally or more effective than conventional therapies.

Credible scientific evidence includes, but is not limited to, reports and articles published in authoritative peer-reviewed medical and scientific literature generally recognized by the relevant medical community, and assessments and coverage recommendations published by the Technology Evaluation Center (TEC).

Medical Necessity/Medically Necessary Definition

Those covered services and supplies that a Physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

1. In accordance with generally accepted standards of medical practice;
2. Clinically appropriate, in terms of type, frequency, extent, site and duration, and considered effective for the patient's illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician, or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "generally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

The fact that services were furnished, prescribed, or approved by a physician or other qualified provider does not in itself mean that services were medically necessary.

NOTE: A small number of member contracts may contain differing definitions of investigational or medically necessary services. The member booklet should be consulted for the definitions of investigational and/or medically necessary for that group.

Effective in 2013, 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

| CPT | |
|-------------|--|
| 81200-81355 | Molecular diagnostics, code range |
| 81400-81408 | Molecular pathology procedure code range |
| 81479 | Unlisted molecular pathology procedure |

Description

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

This policy review addresses genetic testing in nonreproductive settings. Genetic testing in reproductive settings is addressed in separate policies. For categories of genetic testing in which the benefit of testing is for the individual, criteria for medical necessity apply. When the benefit of testing is not for the individual, but for a family member, medical necessity criteria may not apply and the criteria are developed for clinical utility.

Background

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

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

The following categories of genetic testing will be addressed in this evidence review:

1. Testing of an affected (symptomatic) individual's germline DNA to benefit the individual
 - a. Diagnostic
 - b. Prognostic
 - c. Therapeutic
2. Testing of DNA from cancer cells of an affected individual to benefit the individual
 - a. Diagnostic
 - b. Prognostic
 - c. Testing to predict treatment response
3. Testing an asymptomatic individual to determine future risk of disease
4. Testing of an affected individual's germline DNA to benefit family member(s)

Definitions

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

Carrier testing: A carrier of a genetic disorder has *one abnormal allele for a disorder*. When associated with an

autosomal recessive or X-linked disorder, carriers of the causative mutation are typically unaffected. When associated with an autosomal dominant disorder, the person has one normal and one mutated copy of the gene and may be affected with the disorder, may be unaffected but at high risk of developing the disease later in life, or the carrier may remain unaffected because of the sex-limited nature of the disease.

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

Germline mutations: Mutations that are present in the DNA of every cell of the body, *present from the moment of conception*. These include cells in the gonads (testes or ova) and could, therefore be passed on to offspring.

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

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

Scope

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Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.

Benefit Application

[\[TOP\]](#)

N/A

Rationale

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This evidence review was created in May 2013 and has been updated periodically. The most recent update covers the period through December 31, 2015.

General principles of genetic tests

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

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

Types of genetic tests addressed in this policy

1. Testing of an affected (symptomatic) individual's germline DNA to benefit the individual (excluding

reproductive testing)

- a. Diagnostic. To confirm or exclude genetic or heritable mutations in a symptomatic person. This refers to a molecular diagnosis supported by the presence of a known pathologic mutation. For the purposes of genetic testing, a symptomatic person is defined as a person with a clinical phenotype that is correlated with a known pathologic mutation.
 - b. Prognostic. To determine or refine estimates of disease natural history or recurrence in patients already diagnosed with disease. to predict natural disease course, 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 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. e.g., cytochrome p450 testing). to detect Genetic mutations that adversely affect response to exposures in the environment that are ordinarily tolerated, such as G6PD deficiency, genetic disorders of immune function, and aminoacidopathies.
2. Testing of DNA from cancer cells of an affected individual to benefit the individual.
 - a. Diagnostic. To determine the origin of a cancer or to determine a clinically relevant subgroup that a cancer falls into.
 - b. Prognostic. To determine the risk of progression, recurrence, mortality for a cancer that is already diagnosed.
 - c. Predictive testing for treatment response. To determine the likelihood that a patient will respond to a targeted cancer therapy that is based on the presence or absence of a specific mutation.
 3. Testing an asymptomatic individual to determine future risk of disease. To detect genetic mutations associated with disorders that appear after birth, usually later in life. Intended for individuals with a family history of a genetic disorder, but who themselves have no features of the disorder at the time of testing, in order to determine their risk for developing the disorder.
 4. Testing of an affected individual's germline DNA to benefit family member(s). To focus and direct family testing of asymptomatic relatives, by testing an individual with known disease but in whom the presence or absence of a pathologic mutation has not been determined.

Medical Necessity Criteria

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 the Appendix. The Appendix tables list all of the factors that are considered for clinical utility, and the Appendix figures group the factors into a branching logic schematic that leads to a decision that the test does or does not meet clinical utility.

Genetic testing is considered **medically necessary** for a genetic or heritable disorder when the following are met: For ALL genetic testing, the condition being tested for must have either:

- Reduced life expectancy; OR
- At least moderate to severe morbidity(3)

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

1. Testing of an affected (symptomatic) individual's germline DNA to benefit the individual (excluding reproductive testing)
 - a. Diagnostic
 - An association of the marker with the disorder has been established AND
 - Symptoms of the disease are present AND
 - A definitive diagnosis cannot be made based on history, physical examination, pedigree analysis, standard diagnostic studies/tests AND
 - The clinical utility of identifying the mutation has been established (see Appendix):
 1. Leads to changes in clinical management of the condition that improve outcomes; OR
 2. Eliminates the need for further clinical workup or invasive testing; OR
 3. Leads to discontinuation of interventions that are unnecessary and/or ineffective,

- b. Prognostic
 - o An association of the marker with the natural history of the disease has been established AND
 - o Clinical utility of identifying the mutation has been established (see Appendix),
 - 1. Provides incremental prognostic information above that of standard testing: AND
 - 2. Reclassifies patients into clinically relevant prognostic categories for which there are different treatment strategies; AND
 - 3. Reclassification leads to changes in management that improve outcomes.
 - c. Therapeutic
 - o Genetic testing identifies variants of a phenotype/metabolic state that relate to different pharmacokinetics, drug efficacy or adverse drug reactions; AND
 - o Clinical utility of identifying the mutation has been established (see Appendix),
 - 1. Leads to initiation of effective medication(s) OR
 - 2. Leads to discontinuation of medications that are ineffective or harmful OR
 - 3. Leads to clinical meaningful change in dosing of medication that is likely to improve outcomes.
2. Testing of DNA from cancer cells of an affected individual to benefit the individual
- a. Diagnostic
 - o Genetic testing can establish the cell origin of a cancer when the origin is uncertain following standard work-up; AND
 - o Clinical utility of identifying the mutation has been established (see Appendix)
 - 1. Start effective treatment; OR
 - 2. Discontinue ineffective or harmful treatment
 - b. Prognostic
 - o An association of the marker with the natural history of the disease has been established AND
 - o clinical utility of identifying the mutation has been established (see Appendix),
 - 1. Provides incremental prognostic information above that of standard testing: AND
 - 2. Reclassifies patients into clinically relevant prognostic categories for which there are different treatment strategies; AND
 - 3. Reclassification leads to changes in management that improve outcomes.
 - c. Testing to predict treatment response
 - o Association of a mutation with treatment response to a particular drug has been established AND
 - o Clinical utility has been established (see [Appendix](#)),
 - 1. The patient is a candidate for targeted drug therapy associated with a specific mutation; AND
 - 2. There is a clinically meaningful improvement in outcomes when targeted therapy is given for the condition
3. Testing an asymptomatic individual to determine future risk of disease
- o An association of the marker with future disorder has been established AND
 - o Clinical utility has been established (see [Appendix](#))
 - 1. There is a presymptomatic phase for this disorder in which interventions/surveillance are available; AND
 - 2. Interventions in the presymptomatic phase are likely to improve outcomes:
 - a. Prevent/delay onset of disease OR
 - b. Detect disease at an earlier stage for which treatment is more effective OR
 - c. Discontinuation of interventions that are ineffective or unnecessary.

Clinical Utility Criteria

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

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

for medical necessity.

1. Testing of an affected individual's germline DNA to benefit family member(s)
 - a. An association of the genetic mutation with clinical disease has been established; AND
 - b. Family members are available who may be at risk for the disorder; AND
 - c. The individual tested has a clinical diagnosis of the condition (or represents the family member who is most likely to harbor the pathogenic mutation), but genetic testing has not been performed; AND
 - d. There is a presymptomatic phase for the disorder in which interventions are available; AND
 - e. Interventions in the presymptomatic phase are likely to improve outcomes in one of the following ways:
 - Prevent/delay onset of disease
 - Detect disease at an earlier stage for which treatment is more effective;
 - Discontinuation of interventions that are ineffective or unneeded.

Genetic Counseling

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

Limitations of Genetic Testing

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

References

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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.* 2014;7:24766. PMID 25261699

Appendix

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Appendix 1. Table for Categorizing Which Type of Testing Is Being Addressed in Separate Medical Policies

The following table will be used on individual genetic medical 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: mutations | |
| 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 would be:

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

Indirect Evidence

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

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

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

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

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

Disease Characteristics

- o Is life expectancy reduced with this disorder?

- What is the level of physical and/or psychosocial morbidity (disability) associated with the disorder?
 - Severe morbidity/disability
 - Moderate morbidity/disability
 - Minor or no morbidity/disability

Impact of genetic test on diagnosis

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

Impact of genetic test on management

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

Impact on Health Outcomes

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

Appendix Table 1. Factors influencing the strength of an indirect chain of evidence on clinical utility: Testing Categories 1a, 2a

| 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 mutation | 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 |
|--------------|-----------------------------|-------------------------------|----------------------------------|---|--|---|--------------------|--|--|-----------------------------------|--------------------------------------|--|---|---|----------------------|-----------------------------|

II. Factors impacting the strength of indirect evidence for assessing risk of future disease in asymptomatic individuals (Category 3)

Disease Characteristics

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

Impact of genetic test on defining risk of disease

- Can genetic testing determine the risk of subsequent disease in at least a substantial proportion of the population tested?
- Is there a known mutation in the family?
- Is the penetrance of the genetic mutation known?
- Are there other factors that impact the clinical expression of disease?

Impact of genetic test on management

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

Impact on Health Outcomes

- Is there a definite improvement in health outcomes with genetic testing? For example:
 - risk assessment cannot be made without genetic testing, and confirmation of risk leads to initiation of effective preventive interventions that delay onset of disease
- Is there a possible, but not definite, improvement in health outcomes with genetic testing? For example:
 - Risk assessment cannot be made without genetic testing, and confirmation of risk leads to management changes with uncertain impact on outcomes

- Are there significant barriers to research, such as rarity of the disorder?
- What is the impact of genetic testing on lifestyle factors?
 - Employment/occupational decision making
 - Leisure activities
 - Reproductive decision maker

Appendix Table 2. Factors influencing the strength of indirect evidence for risk assessment testing: Testing Category 3

| 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 mutation in family Penetrance is well known There are other factors that impact clinical expression | Initiate effective interventions in presymptomatic phase Other management changes with uncertain impact Negative test turns off interventions Likely to impact reproductive decision making | Definite improved health outcomes Possible impact on outcomes, data lacking Barriers to research Impact on lifestyle factors |

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

Disease Characteristics

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

Impact of genetic test on prognosis

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

Impact of genetic test on management

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

Impact on Health Outcomes

- Is there a definite improvement in health outcomes with genetic testing? For example:
 - Reclassification by prognosis leads to change in management that is known to be effective for the condition
- Is there a possible, but not definite, improvement in health outcomes with genetic testing? For example:

- Reclassification by prognosis leads to changes in management with uncertain impact on outcomes
- Are there significant barriers to research, such as rarity of the disorder?
- What is the impact of testing on lifestyle factors?
 - Employment/occupational decision making
 - Leisure activities
 - Reproductive decision maker

Appendix Table 3. Factors influencing the strength of indirect evidence: Testing Categories 1b, 2b

| Disorder | Disease Characteristics | Impact on Prognosis | Impact on Management | Impact on Outcomes |
|----------|--|--|--|---|
| | Shortened LE Severe morbidity/disability Moderate morbidity/disability Minor or no morbidity/disability | Mutation 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 |

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

Disease Characteristics

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

Impact of genetic testing on assessing response to treatment

- Can genetic testing define variants that are associated with different pharmacokinetics of drug metabolism?
- Are these changes in drug metabolism clinically important?
 - Variants have been associated with clinically significant differences in outcomes of treatment
- Are there genetic variants that are associated with increased risk for adverse effects?

Impact of genetic test on pharmacologic management

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

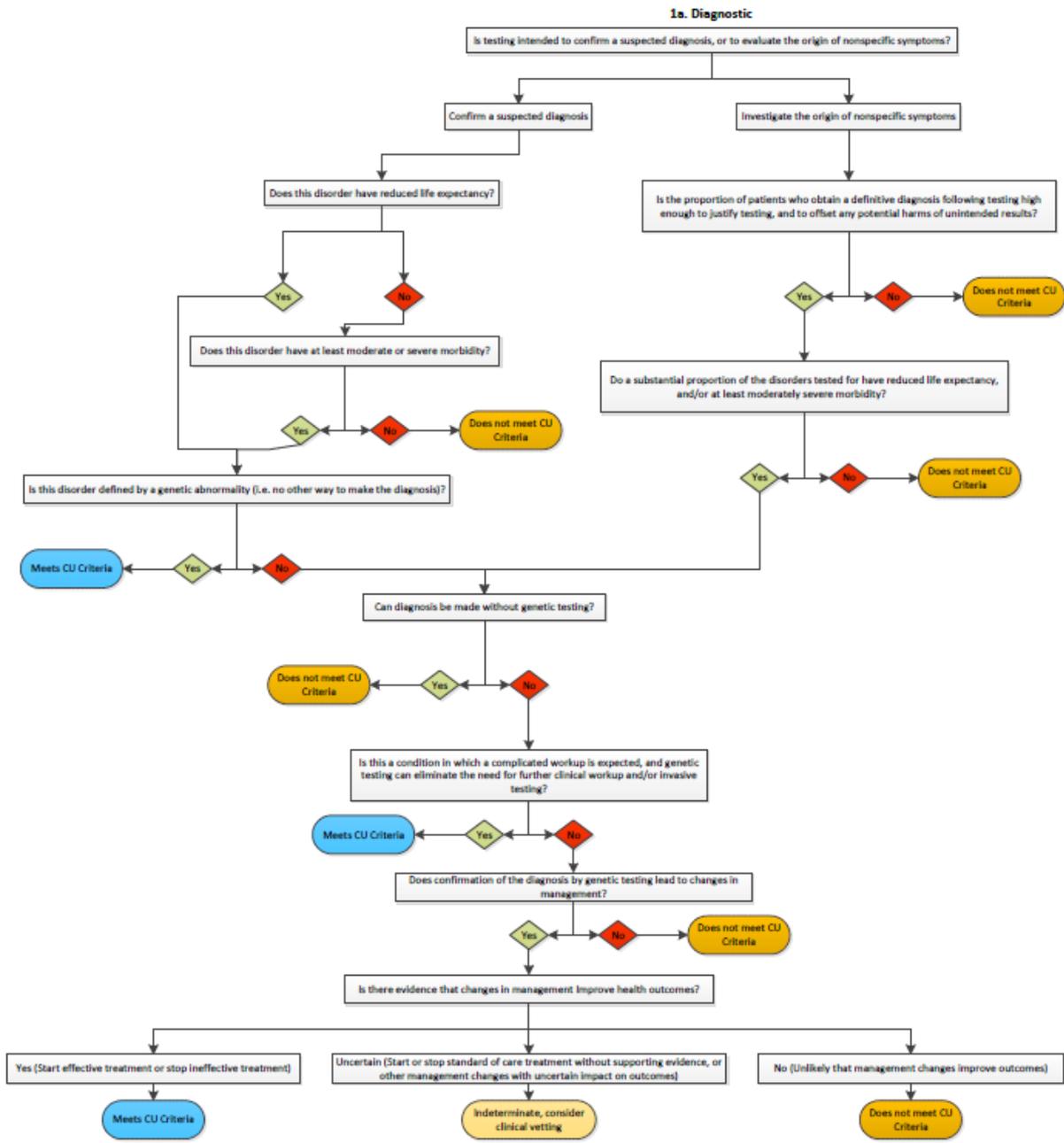
Impact on Health Outcomes

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

Appendix Table 4. Factors influencing the strength of Indirect Evidence: genetic variants that alter response to treatment (Testing Categories 1c, 2c)

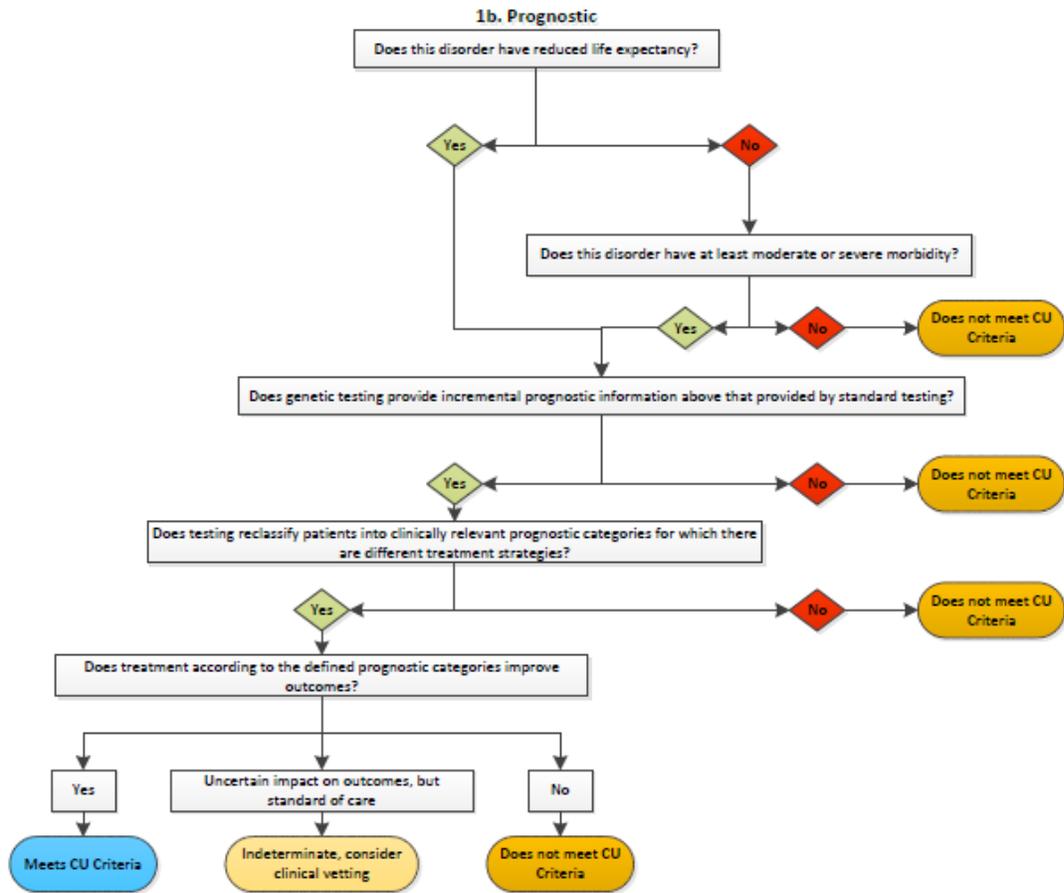
| Disorder | Disease Characteristics | Impact on response to treatment | Impact on Management | Impact on outcomes |
|----------|---|--|--|--|
| | Shortened LE Severe morbidity/disability Moderate morbidity/disability Minor or no morbidity/disability Effective pharmacologic therapy | Define variants 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



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

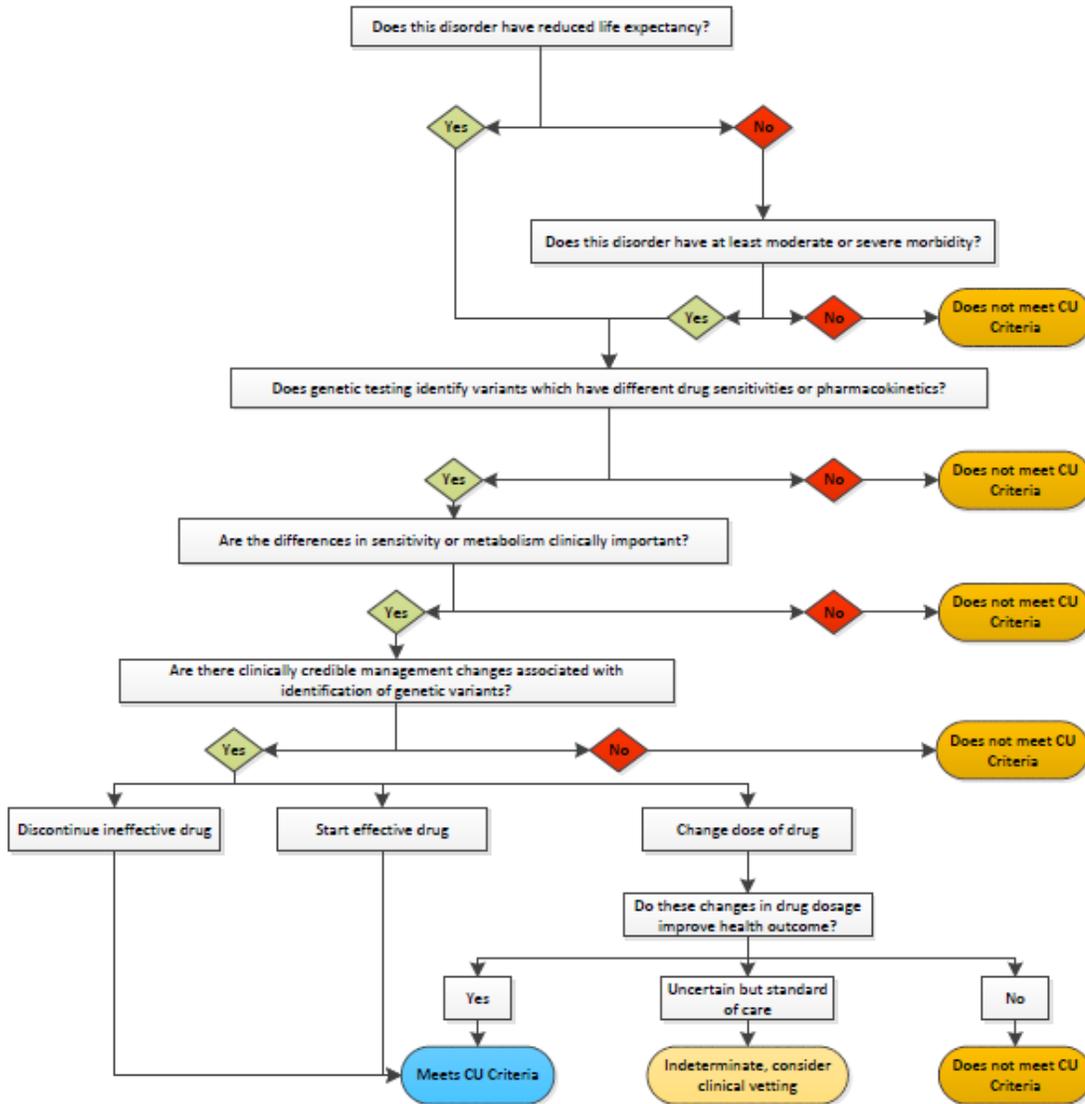
1. Testing an affected individual's germline to benefit the individual



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

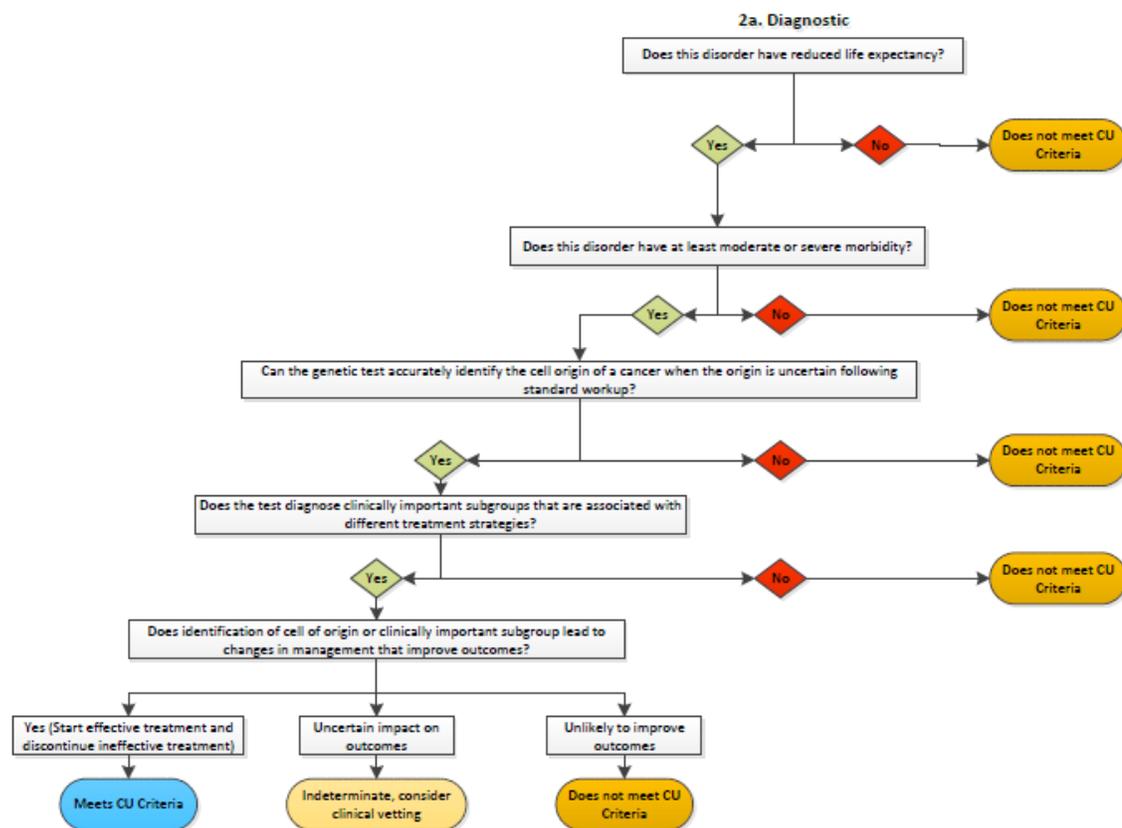
1. Testing an affected individual's germline to benefit the individual

1c. Therapeutic



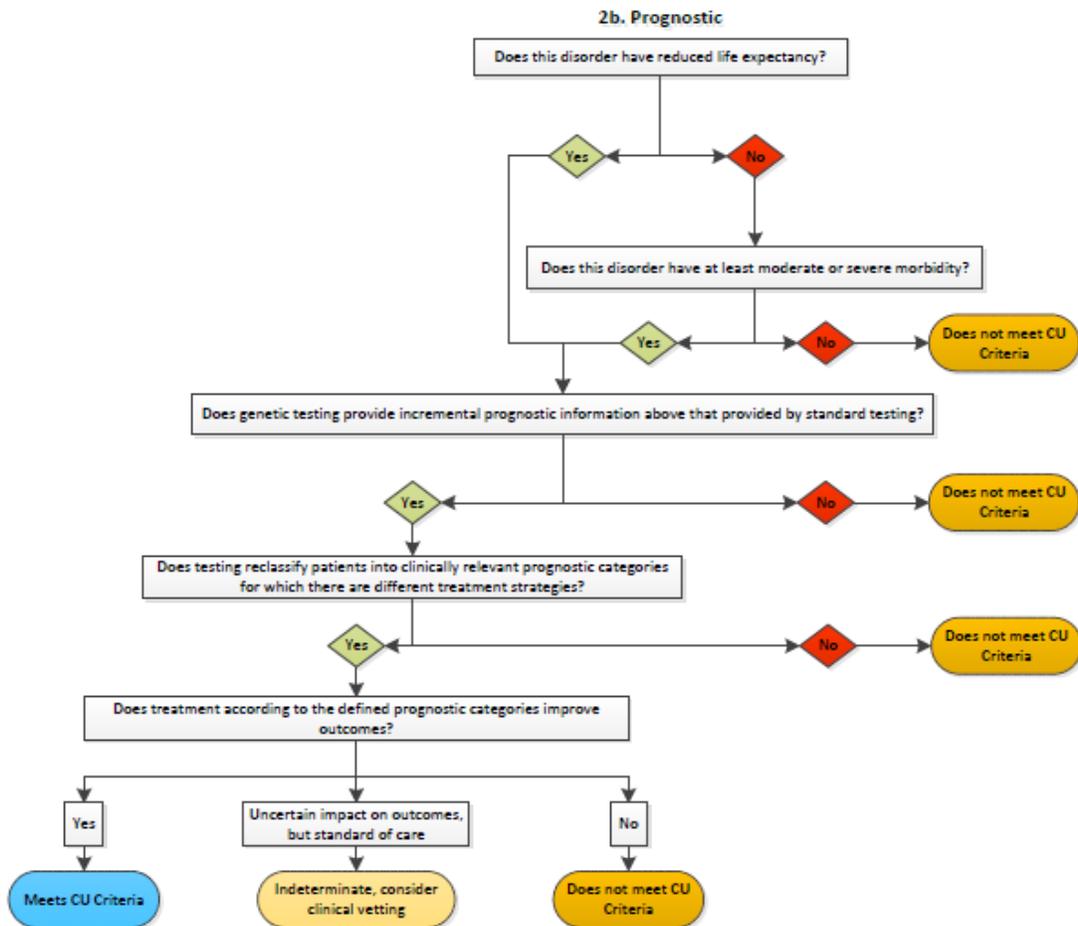
Appendix Figure 2a. Diagnostic Testing of DNA Cells From Cancer Cells of an Affected Individual to Benefit the Individual

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

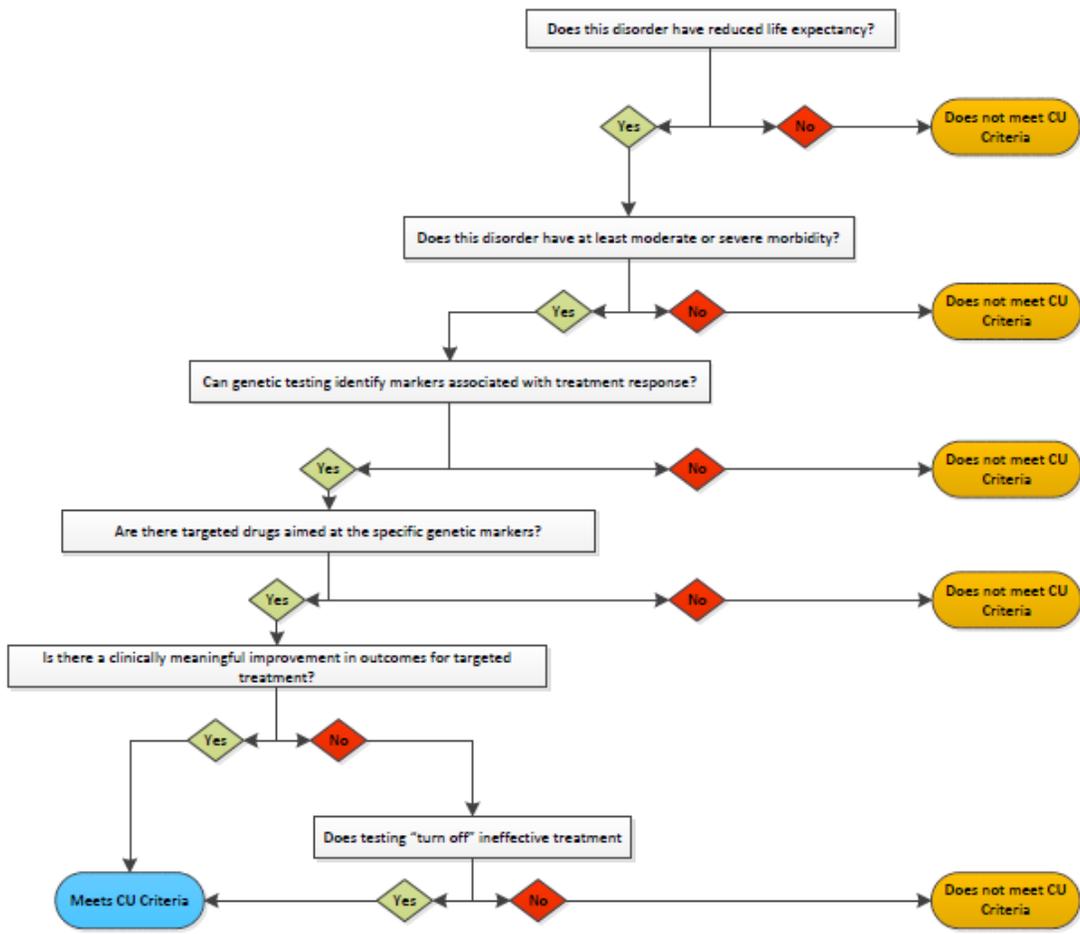
2. Testing of DNA from cancer cells of an affected individual to benefit the individual



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

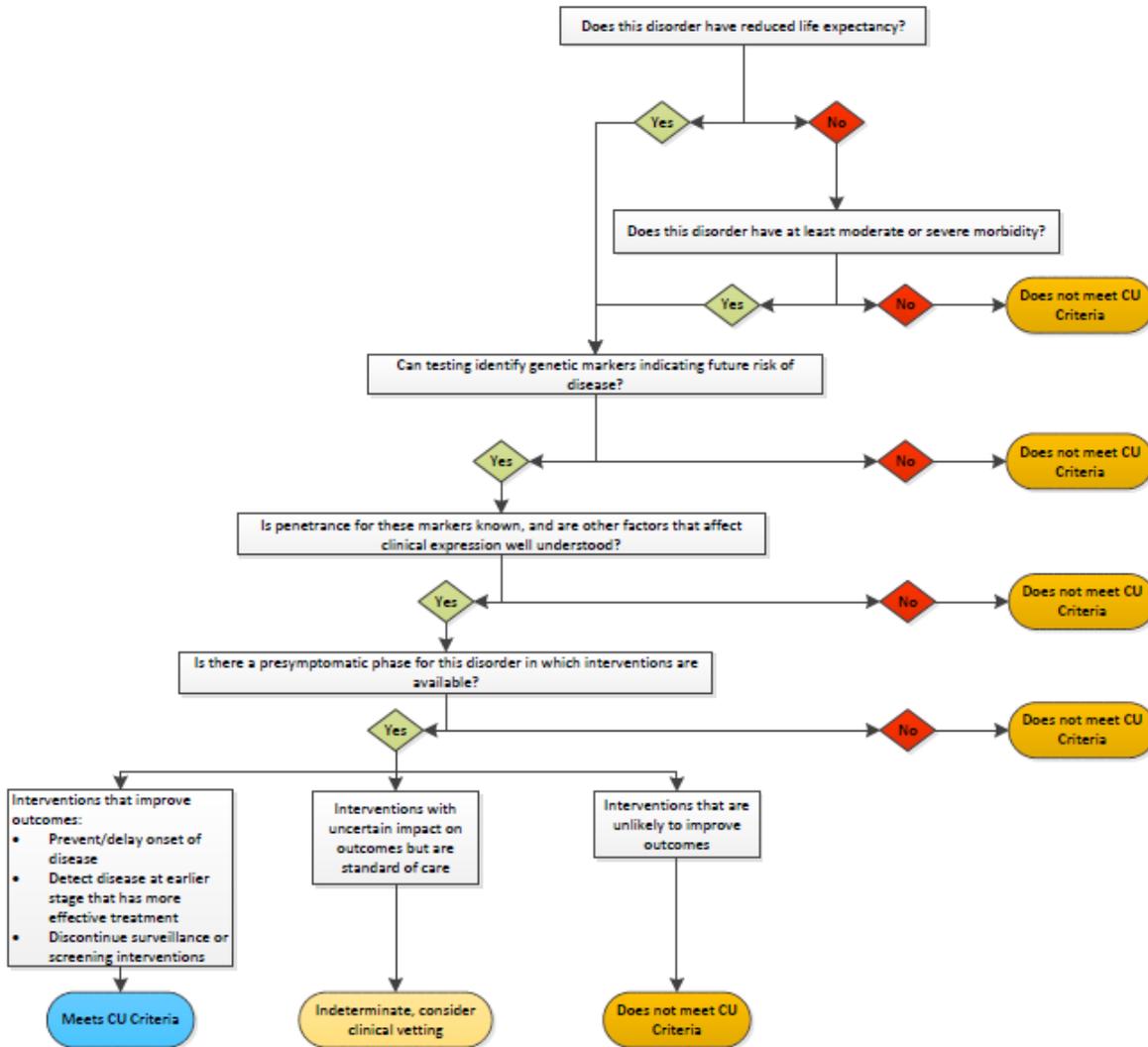
2. Testing of DNA from cancer cells of an affected individual to benefit the individual

2c. Predictive testing for treatment response



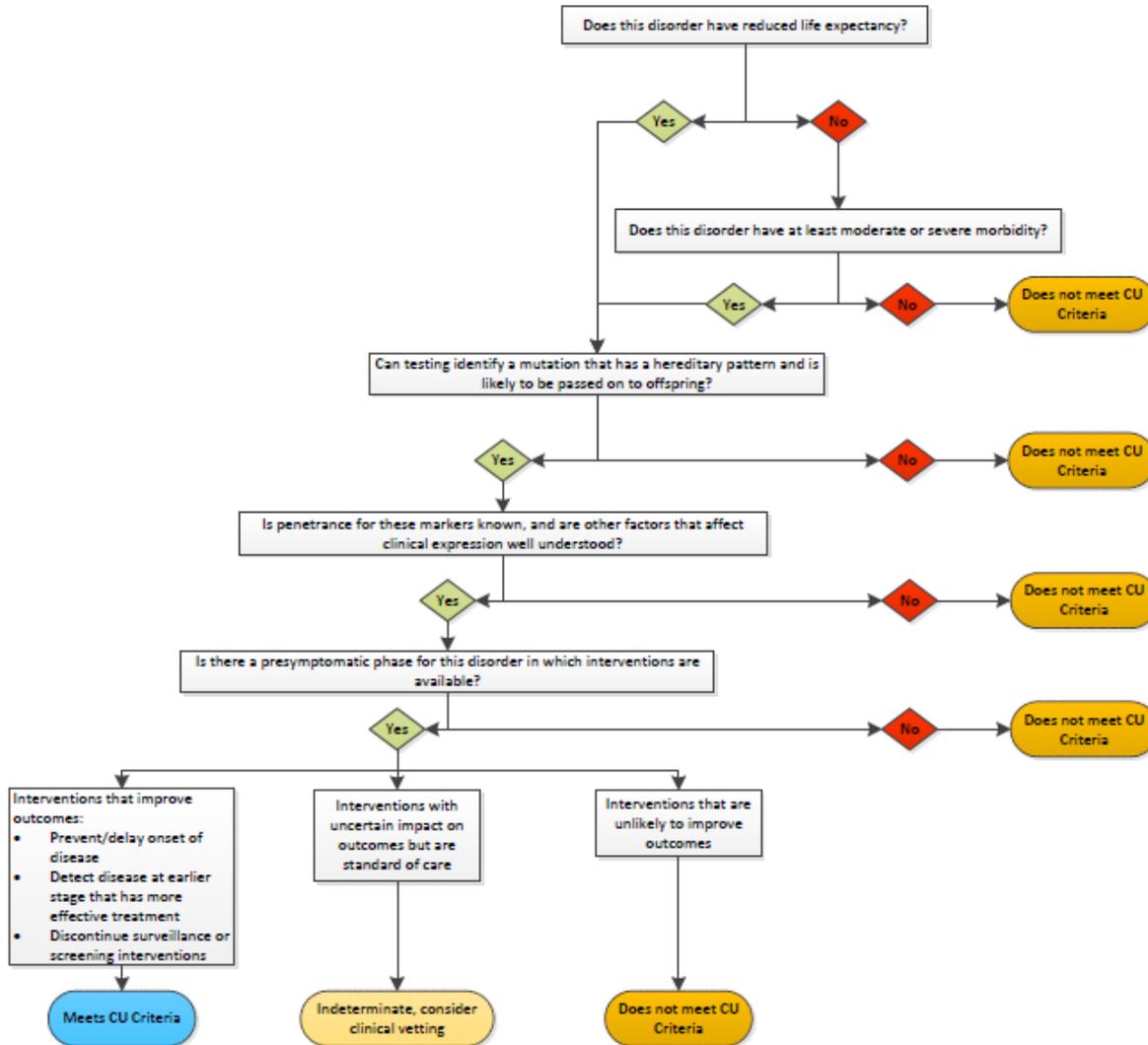
Appendix Figure 3. Testing an Asymptomatic Individual to Determine Future Risk of Disease

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)



History

[\[TOP\]](#)

| Date | Reason |
|----------|--|
| 05/13/13 | New Policy. Policy created with literature search through February 2013 |
| 06/04/13 | Update Related Policies. Add 12.04.86 and 4.01.21. |
| 08/12/13 | Replace policy. Additional bullet added to clarify what is meant by environmental factors ("Genetic mutations that adversely affect response to exposures in the environment that are ordinarily tolerated, such as G6PD deficiency, genetic disorders of immune function, and aminoacidopathies."). |
| 09/16/13 | Update Related Policies; new policy 12.04.97 added. |
| 10/17/13 | Update Related Policies. Add 12.04.99, 12.04.104, 12.04.105 and 12.04.106. |
| 11/20/13 | Update Related Policies. Add 12.04.102. |
| 12/19/13 | Update Related Policies. Change title to 12.04.75. |
| 01/03/14 | Update Related Policies; add new policies 12.04.103, 12.04.107, 12.04.108, 12.04.109, 12.04.110 and 12.04.111, all effective 12/9/13. |
| 01/16/14 | Update Related Policies. Change title to 12.04.504. |
| 02/27/14 | Update Related Policies. Change title to 12.04.48, add 12.04.113, and 12.04.114. |
| 05/23/14 | Update Related Policies. Add 2.04.115, 2.04.118, 2.04.119 and 12.04.509. Remove 12.04.82 as it |

- was deleted.
- 07/14/14 Annual Review. Policy statements unchanged. No new literature has been identified for this concept policy update. Expanded framework for determining clinical utility has been added as an appendix for the four categories of diagnostic testing, risk assessment, prognostic testing, and pharmacogenomics.
- 12/01/14 Update Related Policies. Add 12.04.121.
- 05/12/15 Annual Review. Policy updated with new categories of genetic testing. No new references added. Medical necessity criteria revised for each new category of testing; for the category of testing an individual for the benefit of a family member, criteria are for clinical utility rather than medical necessity and this category has been moved back to the policy statement. Company definitions of medical necessity and investigative added.
- 03/08/16 Annual Review. Policy updated with literature review through December 31, 2015; references redone with references 1 and 3 added. Branching schematic diagrams for determining clinical utility added. Policy statements unchanged.
- 05/04/16 Update related policies. Removed 12.04.92 as it was deleted and replace with 12.04.520.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2016 Premera All Rights Reserved.