Medical Policy

MP 2.04.95
Human Leukocyte Antigen Testing for Celiac Disease

BCBSA Ref. Policy: 2.04.95
Last Review: 11/30/2017
Effective Date: 11/30/2017
Section: Medicine

Related Policies
6.01.33 Wireless Capsule Endoscopy to Diagnose Disorders of the Small Bowel, Esophagus, and Colon

DISCLAIMER

Our medical policies are designed for informational purposes only and are not an authorization, explanation of benefits or a contract. Receipt of benefits is subject to satisfaction of all terms and conditions of the coverage. Medical technology is constantly changing, and we reserve the right to review and update our policies periodically.

POLICY

HLA-DQ2 and HLA-DQ8 testing may be considered medically necessary to rule out celiac disease in:

- patients with discordant serologic and histologic (biopsy) findings; or
- patients with persistent symptoms despite negative serology and histology.

HLA-DQ2 and HLA-DQ8 testing for celiac disease is considered investigational in all other situations.

POLICY GUIDELINES

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

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td></td>
<td>Change in the DNA sequence</td>
</tr>
<tr>
<td>Familial variant</td>
<td></td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
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</table>
### GENETIC COUNSELING

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

### CODING

There is specific coding for human leukocyte antigen gene testing in CPT (81370-81383).

One laboratory that performs this testing lists the following coding online:

- 81377 x 2 HLA Class II typing, low resolution (e.g., antigen equivalents); one antigen equivalent, each
- 81383 HLA Class I typing, high resolution (i.e., alleles or allele groups); one allele or allele group (e.g., HLA-DBQ1*06:02P), each

Other laboratory websites suggest that the testing be reported with code 81383 x 2 alone or with 81377 x 2.

### BENEFIT APPLICATION

#### BLUECARD/NATIONAL ACCOUNT ISSUES

Serologic diagnosis of celiac disease may be offered by reference laboratories specializing in the evaluation of gastrointestinal diseases.

### BACKGROUND

#### CELIAC DISEASE

Celiac disease (CD), also referred to as celiac sprue or gluten-sensitive enteropathy, CD is a relatively common disorder with variable clinical expression. Population-based screening surveys suggest a prevalence of 1 in 250 to 500 in most countries, including the United States. However, this prevalence may vary widely depending on how the disease is defined, i.e., whether only clinically apparent cases are considered, as opposed to including all people with any serologic or histologic evidence of disease.

#### Diagnosis

CD is characterized by inflammation of the small intestine resulting from an immunologic intolerance to gluten (i.e., proteins derived from wheat, barley, and rye). The symptoms of the disease are markedly variable and can be broadly subdivided into intestinal and extraintestinal manifestations; the latter is thought to be related to nutrient malabsorption. For example, osteopenia and osteoporosis, which are
commonly seen in adults with untreated CD, are related to the impaired absorption of vitamin D and binding of intraluminal calcium and magnesium to unabsorbed dietary fatty acids, forming insoluble soaps. The only treatment for CD is lifelong adherence to a gluten-free diet.

Many of the symptoms of CD (e.g., diarrhea, abdominal pain, weight loss) are nonspecific and are often overlooked. In addition, the disease may develop at any time in life, from infancy to very old age. In children, the disease typically presents following weaning between 6 and 24 months and is characterized by abnormal stools, poor appetite, and irritability. In adults, diarrhea is the main presenting symptom, but presenting symptoms may be entirely nonspecific, such as anemia or infertility. Typical or classical CD refers to the presence of malabsorption, while atypical CD consists primarily of extraintestinal manifestations.

CD is associated with the human leukocyte antigen (HLA). Approximately 90% to 95% of patients with CD carry the HLA-DQ2 allele, and the remaining 5% to 10% carry the HLA-DQ8 allele. However, not all people with one of these 2 alleles will develop CD. It is believed that approximately 25% to 40% of the general population of the United States carries either the HLA-DQ2 or HLA-DQ8 allele but only about 3% of people carrying the DQ2 or DQ8 alleles will develop gluten intolerance.\textsuperscript{1,2}

Given the nonspecific nature of the symptoms, the definitive diagnosis has been based on the results of small intestinal biopsies showing a flattened intestinal mucosa in association with an inflammatory infiltrate. Diagnostic criteria were first established in 1969 by the European Society of Paediatric Gastroenterology, Hepatology and Nutrition and consisted of a series of 3 intestinal biopsies: at diagnosis, after institution of a gluten-free diet, and the third after a repeat gluten challenge. This cumbersome method of diagnosis was revised in 1990 by simplifying the diagnostic criteria to a positive biopsy at a presentation in conjunction with consistent history and serologic results, followed by a clinical response to a gluten-free diet.\textsuperscript{3}

Testing

While a positive biopsy result is considered the criterion standard for diagnosis, serologic evaluation of patients with possible CD, together with a consistent clinical history and a positive response to a gluten-free diet, can sometimes be adequate for diagnosis. Serologic studies are also useful in triaging the large numbers of patients with nonspecific symptoms for biopsy. In approximately 10% of cases in which clinical suspicion suggests CD, serologic testing, and intestinal biopsy are nondiagnostic, either because the results of serology and biopsy are discordant, or because both tests are negative, despite persistent symptoms suggestive of CD. In these cases, HLA testing may be useful for ruling out a diagnosis of CD.

National guidelines and position statements recommend serologic testing as the first step in diagnosing CD and recommend the immunoglobulin (Ig) A antibody to human recombinant tissue transglutaminase (tTG) test.\textsuperscript{4-6} Guidelines have indicated that the IgA antibody to antiendomysium antibody test has similar sensitivity and specificity as the tTG IgA test, but national organizations have indicated that the antiendomysium antibody test is more prone to interpretation error. For subjects with known selective IgA deficiency, testing with tTG IgG and/or antiendomysium antibody IgG is recommended. The national organizations also concur that when test results are indeterminate, testing for the genetic markers HLA-DQ2 or HLA-DQ8 is recommended.

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. HLA typing for CD is offered by several laboratories such as Quest, LabCorp, and Prometheus. Several methods are used for HLA typing, including simple sequence-specific-primer,
polymerase chain reaction, reverse dot blot hybridization and real-time polymerase chain reaction. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

RATIONALE

This evidence review was created in May 2013 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through September 11, 2017 (see Appendix Table 1 for genetic testing categories).

Validation of the clinical use of any diagnostic test focuses on 3 main principles: (1) analytic validity, which refers to the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent; (2) clinical validity, which refers to the diagnostic performance of the test (sensitivity, specificity, positive [PPV] and negative predictive values [NPV]) in detecting clinical disease; and (3) clinical utility (ie, how the 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). The following is a summary of the key findings to date.

GENETIC TESTING FOR SIGNS OR SYMPTOMS SUGGESTIVE OF CELIAC DISEASE

Clinical Context and Test Purpose
The purpose of genetic testing of individuals with signs or symptoms suggestive of celiac disease (CD) is to rule out CD in:

- those with discordant serologic and histologic (biopsy) findings; or
- those with persistent symptoms despite negative serology and histology.

The questions addressed in this evidence review are: (1) Is there evidence that genetic testing of individuals with signs or symptoms suggestive of CD with discordant serologic and histologic (biopsy) findings or individuals with persistent symptoms despite negative serology and histology to rule out CD has clinical validity?; and (2) Does genetic testing of such individuals change patient management in a way that improves outcomes as a result of diagnostic testing?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant populations of interest are individuals with discordant serologic and histologic (biopsy) findings; and those with persistent symptoms despite negative serology and histology.

Interventions
The relevant intervention is genetic testing for the human leukocyte antigen (HLA) genes HLA-DQ2 and HLA-DQ8. Commercial testing is available from numerous companies.

Comparators
The comparator of interest is clinical management without genetic testing.

Outcomes
The potential beneficial outcomes of primary interest would be the avoidance of all downstream consequences that occur with lack of correct diagnoses such as the use of ineffective disease management options or gain of benefits that occur with a correct diagnosis such as the use of appropriate and effective disease management options. Implementation of an empirical gluten-free diet
in individuals with clinical ambiguity may not only be ineffective but may also lead to inconvenience without any benefit. An early confirmed diagnosis can avoid delayed treatment of appropriate treatment and lifestyle changes and subsequent avoidance of morbidity associated with the disease. False-positive or -negative test results can lead to the initiation of unnecessary treatment and adverse events from that treatment or under-treatment.

**Timing**
Genetic testing for HLA-DQ2 and HLA-DQ8 alleles may be performed at any point during a lifetime.

**Setting**
Ordering and interpreting genetic testing may be complex and is best done by experienced specialists such as gastroenterologists. Most patients are likely to be tested in an outpatient setting. Referral for genetic counseling is important for the explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

**Analytic Validity**
Limited relevant primary data on analytic validity were identified. The test is generally done by several methods that are used for HLA typing including simple sequence-specific-primer, polymerase chain reaction, reverse dot blot hybridization, and real-time polymerase chain reaction.

**Clinical Validity**
Clinical validity is the diagnostic performance of the test (sensitivity, specificity, PPV, NPV) in detecting clinical disease.

Several studies have established that HLA typing has a high sensitivity and a high NPV for the diagnosis of CD. For example, a 2007 prospective study by Hadithi et al included a total of 463 patients who were referred for evaluation of CD. Sixteen (3.5%) of the 463 patients met European Society of Paediatric Gastroenterology, Hepatology and Nutrition diagnostic criteria for CD (ie, characteristic histologic findings) (Marsh III) on small bowel biopsy and unequivocal symptom resolution after initiating a gluten-free diet. All 16 patients were positive for HLA-DQ2 and/or HLA-DQ8. In contrast, 192 (43%) of 227 patients who did not meet diagnostic criteria for CD were positive for one or both of these alleles. Testing positive for HLA-DQ2 or HLA-DQ8 had a PPV of 7.7% (95% confidence interval [CI], 4.5% to 12%) and a NPV of 100% (95% CI, 98.6% to 100%).

In 2014, Pallav et al retrospectively assessed HLA testing in 256 patients with known or suspected CD. Taking into account all available clinical and laboratory data, 44 patients were diagnosed with CD and, in 173 patients, CD was ruled out. A final diagnosis could not be obtained in 39 (15%) of 256 patients. HLA-DQ2 or -DQ8 was absent in 40% of non-CD patients and 2 CD patients. The NPV was 98%. A total of 154 patients were found to carry HLA-DQ2 or -DQ8 alleles. Forty-two of the 44 patients diagnosed with CD tested positive for one or both of the HLA alleles, with a test sensitivity of 95.5%. The diagnostic accuracy data are somewhat limited by the 15% of patients without a definitive diagnosis.

In 2017, Werkstetter et al reported on the results of a large, international prospective study to validate a biopsy free approach for diagnosis of CD in symptomatic children plus 10 times the upper limit of normal levels of immunoglobulin A against tissue transglutaminase (TGA-IgA) (aka serologic marker) and positive finding for HLA-DQ2 and -DQ8. The primary aim was to determine whether the nonbiopsy approach would identify children with CD with a PPV above 99% in clinical practice. Data on symptoms, total IgA, TGA, endomysium antibodies, and biopsy findings (reference standard) was collected from 803 consecutive pediatric patients (≤18 years) on a gluten-containing diet. When results were concordant, cases were classified as proven CD. Those with TGA-IgA levels of 3 times or below the upper limit of
normal low but without other features of CD were classified no CD. Biopsy analyses were performed and reviewed in a blinded manner. Inconclusive cases were regarded as not having CD. Data were analyzed for 707 children (65.1% girls; median age, 6.2 years) 645 were diagnosed with CD, 46 were found not to have CD, and 16 had inconclusive results. Use of test results including TGA-IgA 10 times or more the upper limit of normal, a positive result for endomysium antibodies, and any symptom identified children with CD (n=399) yielded a PPV of 99.75% (95% CI, 98.61% to 99.99%); the PPV was 100% (95% CI, 98.68% to 100%) when only malabsorption symptoms were used instead of any symptom (n=278). The inclusion of HLA analyses did not increase accuracy.

A 2016 report by Agency of Healthcare Research and Quality indicated that HLA testing could be used to rule out CD with close to 100% sensitivity. The report cited the 2013 American College of Gastroenterology estimates of NPV of the HLA-DQ2 and -DQ8 combination test at over 99%. In the Agency report, 2 studies were cited on the accuracy of HLA testing, a large 2013 prospective cohort found that HLA testing had a sensitivity of 100% and specificity of 18.2% and a 1999 cohort also reported a sensitivity of 100% and a specificity of 33.3%.

Section Summary: Clinical Validity
More than 99% of patients with CD have HLA-DQ2 and/or -DQ8 compared with about 40% of the general population. Thus, CD is highly unlikely in patients without these haplotypes. Testing positive for HLA-DQ2 or HLA-DQ8 had a PPV of 7.7% (95% CI, 4.5% to 12%) and a NPV of 100% (95% CI, 98.6% to 100%).

Clinical Utility
Clinical utility is how the results of a diagnostic test will be used to change management of a patient and whether these changes in management lead to clinically important improvements in health outcomes.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Preferred evidence comes from randomized controlled trials. Such information is not available.

Chain of Evidence
HLA-DQ2 and HLA-DQ8 genotype testing in patients who are suspected of CD with discordant serologic and histologic results or in those who are symptomatic of CD but test negative for serologic and histologic tests has clinical utility based on a chain of evidence. Confirming exclusion of a diagnosis of CD in clinically ambiguous patients may lead to avoidance of improper or ineffective interventions and implementation of appropriate diagnostic strategies to ascertain etiologies of their symptoms.

SUMMARY OF EVIDENCE
For individuals who are suspected of having CD and have discordant serologic and biopsy findings or who are symptomatic for CD and have negative serologic and biopsy findings, the evidence includes several retrospective and prospective cohort studies. Relevant outcomes are test accuracy and validity, other test performance measures, and change in disease status. Several studies have reported that the sensitivity and negative predictive value of HLA-DQ2 and HLA-DQ8 genotype testing for CD approached 100%, meaning that this test is highly accurate for ruling out CD. In contrast, a substantial number of patients who do not have CD carry the HLA-DQ2 and/or HLA-DQ8 alleles, resulting in suboptimal specificity, meaning that this test is less accurate for confirming the diagnosis. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.
SUPPLEMENTAL INFORMATION

PRACTICE GUIDELINES AND POSITION STATEMENTS

American College of Gastroenterology
The 2013 guidelines from the American College of Gastroenterology addressing the diagnosis and management of celiac disease (CD) stated the following on human leukocyte antigen (HLA) gene testing:

“1. HLA-DQ2/DQ8 testing should not be used routinely in the initial diagnosis of CD [celiac disease] (Strong recommendation, moderate level of evidence).
2. HLA-DQ2/DQ8 genotyping testing should be used to effectively rule out the disease in selected clinical situations (Strong recommendation, moderate level of evidence).
3. Examples of such clinical situations include but are not limited to:
   - Equivocal small-bowel histological finding (Marsh I-II) in seronegative patients
   - Evaluation of patients on a gluten-free diet in whom no testing for CD was done before gluten-free diet
   - Patients with discrepant celiac-specific serology and histology
   - Patients with suspicion of refractory CD where the original diagnosis of celiac remains in question
   - Patients with Down’s syndrome.”

European Society of Paediatric Gastroenterology, Hepatology and Nutrition
The 2012 guidelines from the European Society of Paediatric Gastroenterology, Hepatology and Nutrition addressed the diagnosis of CD; the guidelines indicated that HLA-DQ2 and HLA-DQ8 testing should be offered to patients with an uncertain diagnosis of CD, e.g., those with negative CD-specific antibodies and mild infiltrate changes in small bowel specimens. A negative finding renders CD highly unlikely in these people.

National Institute for Health and Care Excellence
The 2009 guidance, which was updated in 2015, from the National Institute for Health and Care Excellence on CD included the following statement on HLA typing:

“Do not use human leukocyte antigen (HLA) DQ2 (DQ2.2 and DQ2.5)/DQ8 testing in the initial diagnosis of coeliac disease in non-specialist settings.

Only consider using HLA DQ2 (DQ2.2 and DQ2.5)/DQ8 testing in the diagnosis of coeliac disease in specialist settings (for example, in children who are not having a biopsy, or in people who already have limited gluten ingestion and choose not to have a gluten challenge).”

American Gastroenterological Association
In 2006, the American Gastroenterological Association issued a position statement on the diagnosis and management of CD. Regarding serologic testing, the association concluded that, in the primary care setting, the transglutaminase immunoglobulin (Ig) A antibody test is the most efficient single serologic test for diagnosing CD. The guidelines indicated that the antiendomysial antibodies IgA test is more time-consuming and operator dependent than the tissue transglutaminase (tTG). If IgA deficiency is strongly suspected, testing with IgG antiendomysium antibody (EMA) and/or tTG IgG antibody test is recommended. If serologic test results are negative and CD is still strongly suspected, providers can test for the presence of the disease-associated HLA alleles and, if present, perform a small intestinal mucosal...
biopsy. Alternatively, if signs and symptoms suggest that small intestinal biopsy is appropriate, patients can proceed to biopsy without testing for HLA alleles.

**National Institutes of Health**

National Institutes of Health issued a consensus statement in 2004 based on a meeting and an independent literature review. The National Institutes of Health considered serologic testing as the first step in pursuing a diagnosis of CD and stated that the best tests are the tTG IgA and EMA IgA tests, which they considered to be of equivalent accuracy. In patients with suggestive symptoms and negative tTG IgA or EMA tests, consider an IgA deficiency and, if identified, it is recommended that a tTG IgG or EMA IgG be performed. When the diagnosis is uncertain because of indeterminate test results, an option according to the National Institutes of Health statement is to test for the genetic markers HLA-DQ2 or HLA-DQ8. Biopsy of the proximal small bowel is indicated in those with a positive CD antibody test, except those with biopsy-proven dermatitis herpetiformis. No specific approach was suggested when there are positive serology and normal biopsy findings. Options include additional biopsies, repeat serology testing and a trial of a gluten-free diet. Testing is indicated in patients with gastrointestinal tract symptoms and other signs and symptoms suggestive of CD.

**U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS**

No U.S. Preventive Services Task Force recommendations for screening for CD in children or adults have been identified.

**MEDICARE NATIONAL COVERAGE**

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

**ONGOING AND UNPUBLISHED CLINICAL TRIALS**

A search of ClinicalTrials.gov in October 2017 did not identify any ongoing or unpublished trials that would likely influence this review.

**REFERENCES**


### CODES

<table>
<thead>
<tr>
<th>Codes</th>
<th>Number</th>
<th>Description</th>
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</thead>
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<tr>
<td>CPT</td>
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<td>See Policy Guidelines</td>
</tr>
<tr>
<td>ICD-10-CM</td>
<td>K90.0</td>
<td>Celiac disease</td>
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<tr>
<td></td>
<td>R10.0-R10.13; R10.3- R10.829; R10.84-R10.9</td>
<td>Abdominal pain code range</td>
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<td></td>
<td>R14.0</td>
<td>Abdominal distension (gaseous) (includes bloating)</td>
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<td>ICD-10-PCS</td>
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<td>Not applicable. ICD-10-PCS codes are only used for inpatient services.</td>
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<td>There are no ICD procedure codes for laboratory tests</td>
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### POLICY HISTORY

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<td>Blue Cross of Idaho adopted changes noted. Policy updated with literature review through September 11, 2017; reference 9-10 added; references 11 and 14 updated. Policy statements unchanged. Rationale section reorganized.</td>
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### APPENDIX

**Appendix Table 1. Categories of Genetic Testing Addressed in 2.04.95**

<table>
<thead>
<tr>
<th>Category</th>
<th>Addressed</th>
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<tr>
<td>1. Testing of an affected individual’s germline to benefit the individual</td>
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### MP 2.04.95
Human Leukocyte Antigen Testing for Celiac Disease

<table>
<thead>
<tr>
<th>Category</th>
<th>Example</th>
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<tbody>
<tr>
<td>1a. Diagnostic</td>
<td>X</td>
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<tr>
<td>1b. Prognostic</td>
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<tr>
<td>1c. Therapeutic</td>
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<tr>
<td>2. Testing cancer cells from an affected individual to benefit the individual</td>
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</tr>
<tr>
<td>2a. Diagnostic</td>
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<tr>
<td>2b. Prognostic</td>
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<tr>
<td>2c. Therapeutic</td>
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<tr>
<td>3. Testing an asymptomatic individual to determine future risk of disease</td>
<td>X</td>
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<tr>
<td>4. Testing of an affected individual’s germline to benefit family members</td>
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<tr>
<td>5. Reproductive testing</td>
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<td>5a. Carrier testing: preconception</td>
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<td>5b. Carrier testing: prenatal</td>
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<td>5c. In utero testing: aneuploidy</td>
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<td>5d. In utero testing: familial variants</td>
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<td>5e. In utero testing: other</td>
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<td>5f. Preimplantation testing with in vitro fertilization</td>
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